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 12, 2022

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 12, 2022, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter ended March 31, 2022. 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 12, 2022, 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 12, 2022
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated May 12, 2022
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 12, 2022

Wave Life Sciences Reports First Quarter 2022 Financial Results and Provides Business Update

Delivered first clinical data demonstrating target engagement and translation of PN chemistry's impact in clinic; Adapting ongoing Phase 1b/2a FOCUS-C9 clinical trial to optimize dose level and frequency, with additional single and multidose data expected throughout 2022

Clinical data also expected in 2022 from Huntington's disease (WVE-003) and Duchenne muscular dystrophy (WVE-N531) trials

Robust preclinical datasets for first-in-class AATD program demonstrate restoration of levels of AAT relevant for potential lung protection and reduction of liver-damaging aggregates with GalNAc AIMers; IND enabling toxicology studies for lead AATD candidate on-track to initiate in 3Q 2022

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

CAMBRIDGE, Mass., May 12, 2022 – 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, 2022 and provided a business update.

"Thus far in 2022, Wave has achieved several important milestones, with the highlight being our first clinical data demonstrating successful target engagement with WVE-004 in the ongoing FOCUS-C9 clinical trial for C9-ALS and C9-FTD. We observed potent and durable reductions of the poly(GP) biomarker with low single doses of WVE-004, demonstrating that our preclinical data for PN-containing oligonucleotides are beginning to translate in the clinic," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "These initial results are compelling and reinforce the potential of our unique oligonucleotide platform and our expectation to see the advantages of PN chemistry manifest in our other pipeline programs. We also continue to rapidly advance our WVE-003 program for HD and WVE-N531 program for DMD towards initial data updates later this year. We are also pleased with the recognition we are receiving with our endogenous RNA editing modality, which is being highlighted through scientific presentations and our recent Nature Biotechnology publication. Alpha-1 antitrypsin deficiency (AATD) is uniquely suited for an RNA editing therapeutic, and our AATD program is rapidly advancing towards clinical development with IND enabling studies on track to initiate in the third quarter of this year."

Recent Pipeline and Business Highlights

Announced first clinical data from ongoing FOCUS-C9 trial of WVE-004 for C9-ALS and C9-FTD demonstrating potent and durable target engagement with low, single doses

- In April 2022, Wave announced a positive update to its ongoing FOCUS-C9 trial of WVE-004 (stereopure, PN-modified silencing oligonucleotide) for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD). The update was driven by the observation of potent and durable reductions of poly(GP) dipeptide repeat proteins in cerebrospinal fluid (CSF), a C9-ALS/C9-FTD disease biomarker that, when reduced in CSF, indicates WVE-004's engagement of target in the brain and spinal cord. Based on the poly(GP) reduction data, the observation period for single dose cohorts is being extended and additional

patients are being enrolled into the trial to further characterize depth of knockdown, durability and longer-term safety profile. Wave plans to share this recently announced clinical data in an oral presentation at the upcoming European Network to Cure ALS (ENCALS) Meeting in Edinburgh, Scotland, which is taking place June 1 – 3, 2022.

- FOCUS-C9 (NCT04931862) is an adaptive trial that was designed to rapidly optimize dose level and frequency based on early indicators of target engagement. WVE-004 is designed to selectively target transcript variants containing a hexanucleotide repeat expansion (G_4C_2) associated with the C9orf72 gene for the treatment of C9-ALS and C9-FTD, thereby reducing pathological mRNA products and toxic DPR proteins, including poly(GP). Planning is underway to initiate an open-label extension (OLE) clinical trial in mid-2022.

Continued to advance clinical trials evaluating WVE-003 targeting SNP3 for Huntington's disease (HD) and WVE-N531 for Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping

- WVE-003 for HD (PN-modified silencing oligonucleotide) is being evaluated in the ongoing, adaptive, double-blind Phase 1b/2a SELECT-HD (NCT05032196) clinical trial. WVE-003 is designed to selectively target the mutant allele of the huntingtin (mHTT) gene, while leaving the wild-type (healthy) HTT (wtHTT) protein relatively intact.
- WVE-N531 for DMD (PN-modified splicing oligonucleotide) is being evaluated in an open-label, intra-patient dose escalation (NCT04906460) clinical trial. Dose escalation is ongoing and being guided by tolerability and plasma PK, with possible cohort expansion informed by an assessment of drug distribution in muscle and biomarkers, including dystrophin, following multiple doses of WVE-N531.

Presented preclinical AIMer data for AATD program supporting the potential for a novel, first-in-class, subcutaneous therapeutic to address both lung and liver manifestations of disease

- In March 2022, preclinical data for Wave's Alpha-1 antitrypsin deficiency (AATD) AIMer program demonstrating restoration of functional AAT protein and reduction of liver aggregates in a transgenic mouse model was shared in a Featured Session at the 7th Annual Oligonucleotide & Precision Therapeutics (OPT) Congress. At 19 weeks, GalNAc-conjugated SERPINA1 AIMers resulted in approximately 60% RNA editing of SERPINA1 transcript and circulating serum AAT levels (18.5 uM) in AIMer administered mice that were approximately 5-fold greater than PBS-administered controls.
- Today, May 12, 2022, at the TIDES USA: Oligonucleotide & Peptide Therapeutics Conference, Wave is presenting additional preclinical data that confirmed restored AAT protein in serum was functional at week 19, as measured by a 3-fold increase in neutrophil elastase inhibition over placebo control. A histological analysis indicated reduction of liver aggregates in a transgenic mouse model at 19 weeks with AIMers. Wave will also share these data in an oral presentation at the American Society of Gene and Cell Therapy (ASGCT) 25th Annual Meeting taking place May 16 – 19, 2022 in Washington, D.C.

Scientific publications highlight breadth and potential of Wave's therapeutic oligonucleotide platform, including novel PN-chemistry and RNA editing modality

- In March 2022, preclinical proof-of-concept data for Wave's novel ADAR-mediated RNA base editing modality was published in the journal *Nature Biotechnology* – the first scientific publication to report that RNA base editing in NHPs can be achieved with a simplified oligonucleotide approach. Data reported include an *in vivo* study where Wave's GalNAc-conjugated A-to-I(G) RNA base editing oligonucleotides ("AIMers") yielded up to 50% editing of ACTB (Beta-actin) transcript in the liver of non-human primates (NHPs), with editing levels persisting as high as 40% for more than one month.
- In February 2022, two papers were published in the journal *Nucleic Acids Research* (NAR) that reported a multitude of preclinical *in vitro* and *in vivo* studies demonstrating the incorporation of PN backbone chemistry modifications (PN chemistry) in stereopure silencing oligonucleotides (publication link) and stereopure splicing oligonucleotides (publication link) significantly improves potency, distribution, and durability of effect.
- Wave has published a total of eight peer-reviewed papers thus far in 2022.

Key Anticipated 2022 Milestones

WVE-004 for C9-ALS and C9-FTD:

- Additional single and multidose clinical data for WVE-004 expected throughout 2022. Wave expects to use these data to optimize WVE-004 dose level and frequency, as well as to enable discussions with regulatory authorities regarding the next phase of development later in 2022.
- Planning underway to initiate an open-label extension (OLE) clinical trial in mid-2022.

WVE-003 for HD:

- Clinical data expected in 2022 for WVE-003 to provide further insight into the clinical effects of PN chemistry and enable decision-making for this program.

WVE-N531 for DMD:

- Clinical data, including muscle biopsies, expected in 2022 for WVE-N531 to provide further insight into the clinical effects of PN chemistry and enable decision-making for this program.

AIMer GalNAc-conjugated program for AATD:

- Wave expects to select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in the third quarter of 2022.

First Quarter 2022 Financial Results and Financial Guidance

Wave reported a net loss of $37.8 million in the first quarter of 2022, as compared to $42.5 million in the same period in 2021.

Wave recorded revenue of $1.8 million for the first quarter of 2022, primarily under the Takeda Collaboration. Wave did not record any revenue under the Takeda Collaboration in the first quarter of 2021.

Research and development expenses were $27.5 million in the first quarter of 2022 as compared to $33.4 million in the same period in 2021. The decrease in research and development expenses in the first quarter was primarily due to decreased external expenses related to our previously disclosed discontinued PRECISION-HD programs, partially offset by increased internal and external expenses related to PRISM, including ADAR editing, and other ongoing programs.

General and administrative expenses were $12.4 million in the first quarter of 2022 as compared to $10.1 million in the same period in 2021. The increase in general and administrative expenses in the first quarter of 2022 was primarily due to increases in compensation-related expenses, as well as increases in professional services expenses and other general and administrative operating expenses.

As of March 31, 2022, Wave had $111.7 million in cash, cash equivalents and short-term investments. As of December 31, 2021, Wave had $150.6 million in cash and cash equivalents. This decrease was mainly due to Wave's year-to-date net loss of $37.8 million.

Wave expects that its existing cash, cash equivalents and short-term investments 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 2022 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: 092347. 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 the FOCUS-C9 Clinical Trial

The FOCUS-C9 trial is an ongoing, global, multicenter, randomized, double-blind, placebo-controlled Phase 1b/2a clinical trial to assess the safety and tolerability of single- and multiple-ascending intrathecal doses of WVE-004 for people with C9-ALS and/or C9-FTD. Additional objectives include measurement of poly(GP) DPR proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics (PK), and exploratory biomarkers and clinical outcomes. The FOCUS-C9 trial is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent committee.

In an initial data analysis, reductions in poly(GP) were observed across all active treatment groups (10 mg, n=2 patients; 30 mg, n=4 patients; 60 mg, n=3 patients), reaching statistical significance versus placebo (n=3 patients) after single 30 mg doses, with a 34% reduction in poly(GP) at day 85 (p=0.011). At the time of analysis, none of the patients dosed with 60 mg had reached day 85. As the poly(GP) reduction in the 30 mg single dose cohort does not appear to have plateaued, Wave will extend the observation period from approximately three months (85 days) to approximately six months to identify the maximum reduction of poly(GP) and duration of effect of low single doses. Based on the durability and potency observed in the 30 mg cohort, FOCUS-C9 has been adapted to include additional patients receiving 20 mg and 30 mg single doses of WVE-004. Adverse events (AEs) were balanced across treatment groups, including placebo, and were mostly mild to moderate in intensity. Four patients (including one on placebo) experienced severe and/or serious adverse events; three were reported by the investigators to be related to ALS or administration, and one was reported by the investigator to be related to study drug. There were no treatment-associated elevations in CSF white blood cell counts or protein and no other notable laboratory abnormalities were observed.

Support for FOCUS-C9 is provided by the Alzheimer's Drug Discovery Foundation.

About Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease in which the progressive degeneration of motor neurons in the brain and spinal cord leads to the inability to initiate or control muscle movement. People with ALS may lose the ability to speak, eat, move and breathe. ALS affects as many as 20,000 people in the United States.

Frontotemporal dementia (FTD) is a fatal neurodegenerative disease in which progressive nerve cell loss in the brain's frontal lobes and temporal lobes leads to personality and behavioral changes, as well as the gradual impairment of language skills. It is the second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65. FTD affects as many as 70,000 people in the United States.

A hexanucleotide repeat expansion (G4C2) is the most common known genetic cause of the sporadic and inherited forms of ALS and FTD. The expansion leads to production of modified sense and antisense transcripts that can form nuclear RNA foci and encode dipeptide protein repeats (DPRs), which are believed to drive disease pathology. Additionally, the G4C2 expansion can decrease expression of C9orf72 protein, affecting regulation of neuronal function and the immune system.

In the United States, mutations of the C9orf72 gene are present in approximately 40% of familial ALS cases and ~8-10% of sporadic ALS cases. In FTD, the mutations appear in 38% of familial cases and 6% of sporadic cases.

About Huntington's Disease

Huntington's disease (HD) is a debilitating and ultimately fatal autosomal dominant neurological disorder, characterized by cognitive decline, psychiatric illness, and chorea. HD causes nerve cells in the brain to deteriorate over time, affecting thinking ability, emotions, and movement. HD is caused by an expanded cytosine-adenine-guanine (CAG) triplet repeat in the huntingtin (HTT) gene that results in production of mutant HTT (mHTT) protein. Accumulation of mHTT causes progressive loss of neurons in the brain. Wild-type, or healthy, HTT (wtHTT) protein is critical for neuronal function and suppression may have detrimental long-term consequences. Approximately 30,000 people in the United States have symptomatic HD and more than 200,000 others are at risk for developing the disease. There are currently no approved disease-modifying therapies available.

About Duchenne Muscular Dystrophy

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

and lungs. Worldwide, DMD affects approximately one in 5,000 newborn boys. Approximately 8%-10% of DMD patients have mutations amenable to treatment with an exon 53 skipping therapy. Exon skipping aims to address the underlying cause of DMD by promoting the production of dystrophin protein to stabilize or slow disease progression

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 initiation, site activation, patient recruitment, patient enrollment, dosing, generation of data 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 preclinical data to predict the behavior of our compounds in humans; our identification and expected timing 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 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, including our AIMers, compared to others; anticipated benefits of our proprietary manufacturing processes and our internal manufacturing capabilities; the benefit of nucleic acid therapeutics generally; the strength of our intellectual property; our assumptions based on our balance sheet and the anticipated duration of our cash runway; our intended uses of capital; 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; the clinical results of our programs and the timing thereof, 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 and our AIMers; 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; our ability to maintain the company infrastructure and personnel needed to achieve our goals; the severity and duration of the COVID-19 pandemic and variants thereof, 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, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 61,713	$ 150,564
Short-term investments	50,000	—
Prepaid expenses	6,940	6,584
Other current assets	5,730	5,416
Total current assets	124,383	162,564
Long-term assets:		
Property and equipment, net	21,046	22,266
Operating lease right-of-use assets	17,594	18,378
Restricted cash	3,651	3,651
Other assets	685	148
Total long-term assets	42,976	44,443
Total assets	$ 167,359	$ 207,007
Liabilities, Series A preferred shares and shareholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 9,853	$ 7,281
Accrued expenses and other current liabilities	7,087	14,861
Current portion of deferred revenue	36,426	37,098
Current portion of operating lease liability	5,120	4,961
Total current liabilities	58,486	64,201
Long-term liabilities:		
Deferred revenue, net of current portion	76,567	77,479
Operating lease liability, net of current portion	23,617	24,955
Other liabilities	868	—
Total long-term liabilities	$ 101,052	$ 102,434
Total liabilities	$ 159,538	$ 166,635
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at March 31, 2022 and December 31, 2021	$ 7,874	$ 7,874
Shareholders' equity (deficit):		
Ordinary shares, no par value; 60,859,968 and 59,841,116 shares issued and outstanding at March 31, 2022 and December 31, 2021, respectively	$ 751,229	$ 749,851
Additional paid-in capital	91,951	87,980
Accumulated other comprehensive income	95	181
Accumulated deficit	(843,328)	(805,514)
Total shareholders' equity (deficit)	$ (53)	$ 32,498
Total liabilities, Series A preferred shares and shareholders' equity (deficit)	$ 167,359	$ 207,007

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,	
	2022	2021
Revenue	$ 1,750	$ —
Operating expenses:		
Research and development	27,470	33,393
General and administrative	12,374	10,078
Total operating expenses	39,844	43,471
Loss from operations	(38,094)	(43,471)
Other income, net:		
Dividend income and interest income, net	26	11
Other income, net	254	996
Total other income, net	280	1,007
Loss before income taxes	(37,814)	(42,464)
Income tax provision	—	—
Net loss	$ (37,814)	$ (42,464)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (0.62)	$ (0.86)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	60,516,616	49,101,606
Other comprehensive loss:		
Net loss	$ (37,814)	$ (42,464)
Foreign currency translation	(86)	(120)
Comprehensive loss	$ (37,900)	$ (42,584)

Investor Contact:

Kate Rausch
617-949-4827
krausch@wavelifesci.com

Media Contact:

Alicia Suter
617-949-4817
asuter@wavelifesci.com

Exhibit 99.2

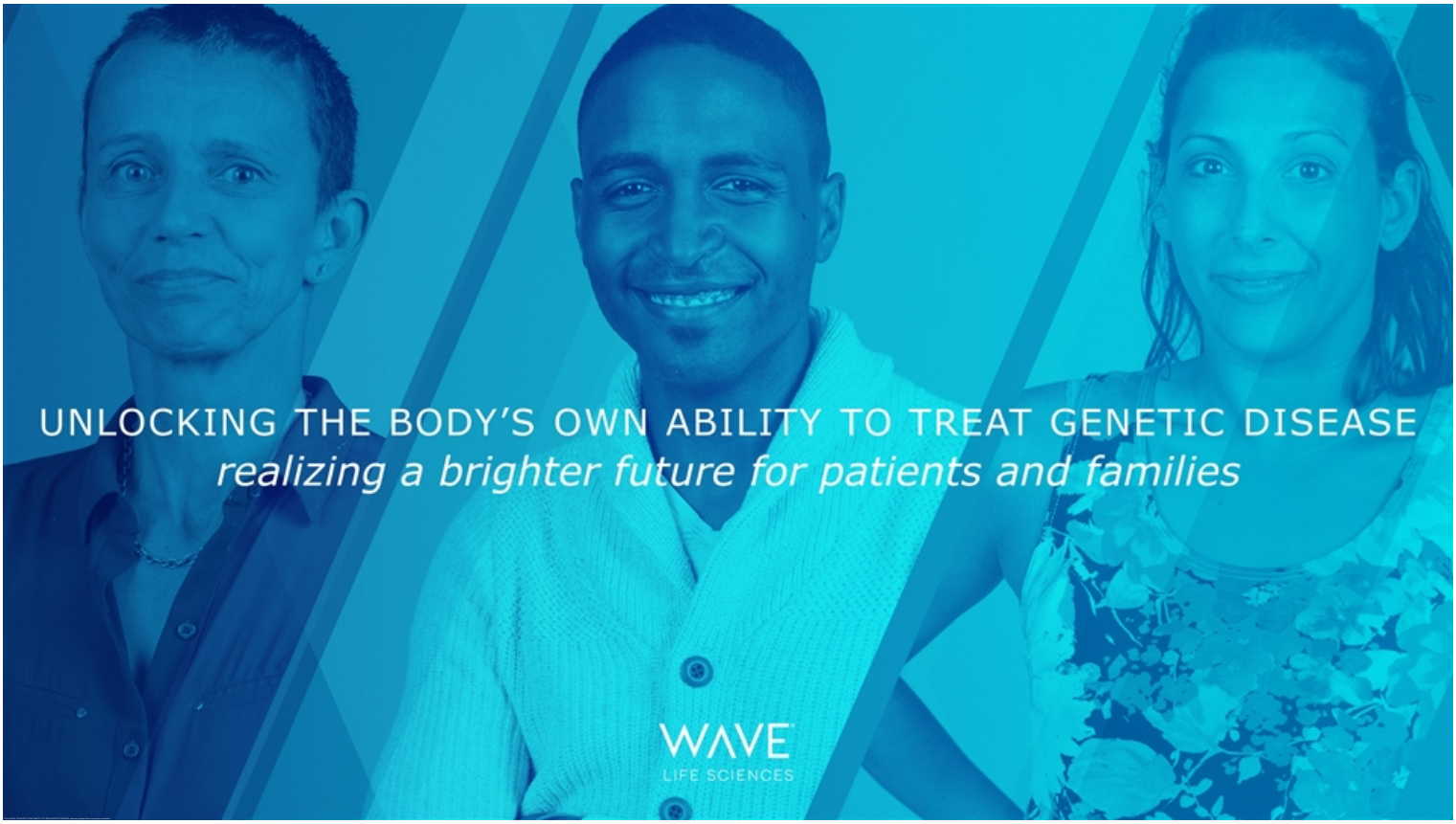
Wave Life Sciences
Corporate Presentation

May 12, 2022

WAVE
LIFE SCIENCES

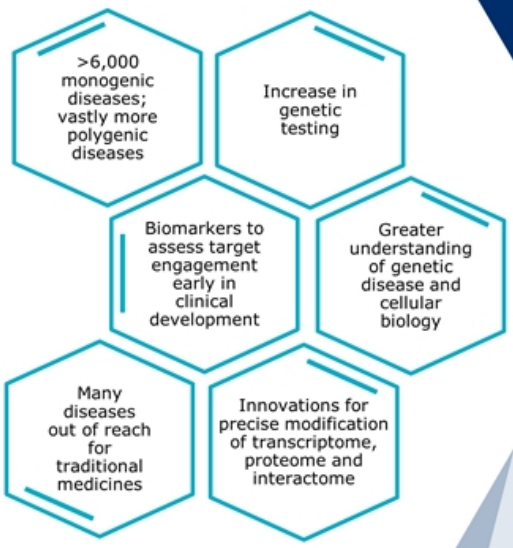
Forward-looking statements

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.


UNLOCKING THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE
realizing a brighter future for patients and families
WAVE
LIFE SCIENCES

Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



WAVE LIFE SCIENCES

TARGETING THE TRANSCRIPTOME TO UNLOCK THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE

PRISM

Innovative Platform

Stereopure oligonucleotides

Novel backbone modifications (PN chemistry)

Silencing, splicing, and editing modalities

Strong and broad IP position[1]

Diversified Pipeline

CNS: ALS, FTD, HD

Muscle: DMD

Hepatic diseases: AATD

Clinical Expertise

Multiple global clinical trials

Innovative trial designs

GMP Manufacturing

Internal manufacturing capable of producing oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; HD: Huntington's disease; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

[1]stereopure oligonucleotides and novel backbone chemistry modifications

Strategic focus on intervening at RNA level

RNA-targeting therapeutics offer ideal balance of precision, durability, potency, and safety

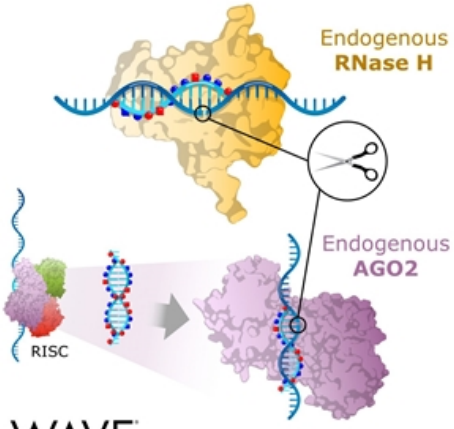
Address underlying genetic drivers of disease	Changes erroneous messages, not erroneous code
Simplified delivery	Freely taken up by cells in multiple tissues or compatible with simple ligands – no need for complex delivery vehicles
Durable effects	Continued progress towards longer dosing intervals while still being reversible and titratable
Defined path to commercialization	Established regulatory, manufacturing, access and reimbursement pathways

WAVE LIFE SCIENCES

Harnessing the biological machinery in our cells to treat genetic diseases

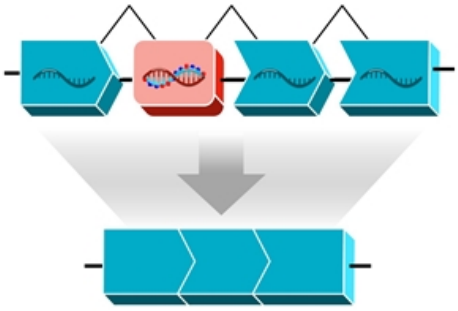
Silencing

- Degradation of RNA transcripts to **turn off** protein production



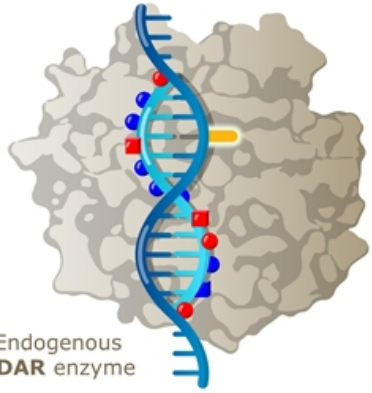
Splicing

- Restore RNA transcripts and **turn on** protein production



RNA Base Editing

- Efficient editing of RNA bases to **restore** or **modulate** protein production

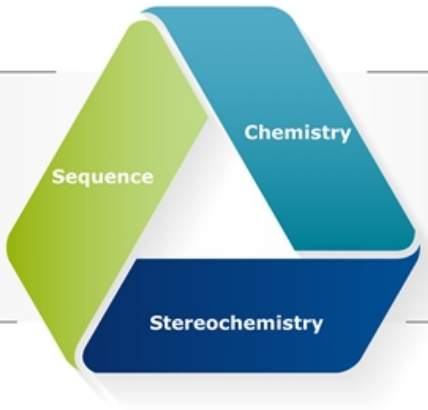


WAVE
LIFE SCIENCES

PRISM Unlocking the body's own ability to treat genetic disease

DESIGN

Unique ability to construct stereopure oligonucleotides and control three structural features to efficiently engage biological machinery



OPTIMIZE

Provides the resolution to observe this structural interplay and understand how it impacts key pharmacological properties

Built-for-Purpose Candidates to Optimally Address Disease Biology

Silencing | Splicing | RNA Editing

WAVE LIFE SCIENCES

Robust portfolio of stereopure, PN-modified oligonucleotides

Therapeutic modality: Silencing; Splicing; ADAR editing (AIMers)

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system; DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

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

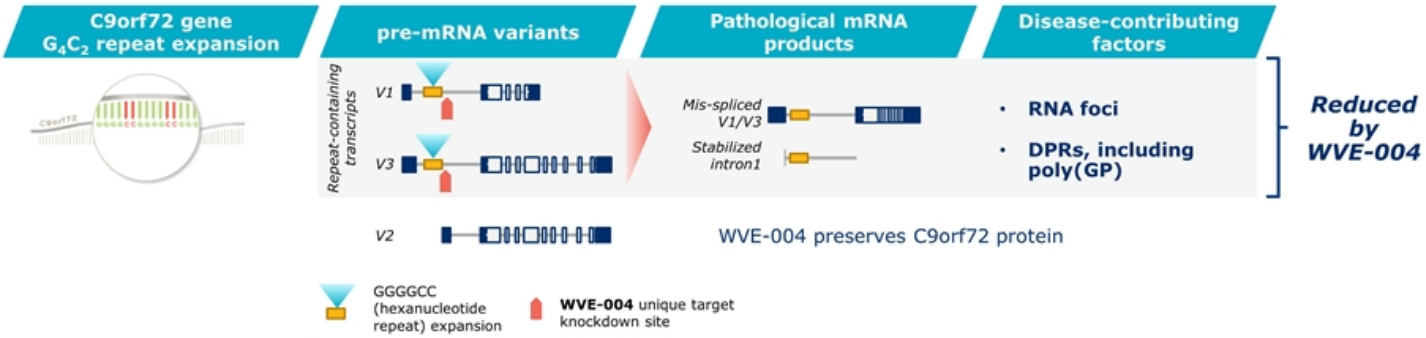
Amyotrophic Lateral Sclerosis (ALS)	Frontotemporal Dementia (FTD)
• Fatal neurodegenerative disease	• Progressive neuronal degeneration in frontal / temporal cortices
• Progressive degeneration of motor neurons in brain and spinal cord	• Personality and behavioral changes, gradual impairment of language skills
• C9-specific ALS: ~2,000 patients in US	• C9-specific FTD: ~10,000 patients in US

Including patients with C9-associated ALS, FTD or both

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

WVE-004 selectively targets repeat-containing transcripts to address multiple drivers of toxicity



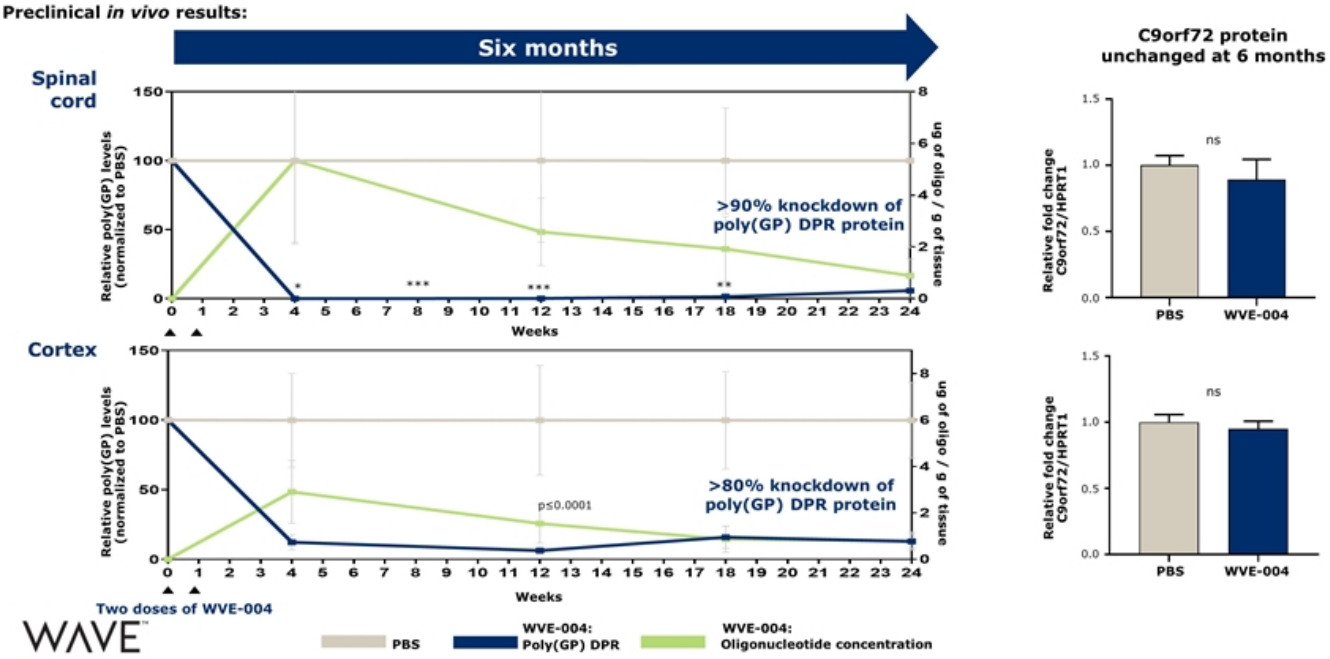
- WVE-004 targets repeat-containing transcript variants that lead to production of pathological mRNA products and toxic DPR proteins and loss of normal C9orf72 function, which is important for normal regulation of neuronal function and the immune system
- Wave selected the poly(GP) DPR because it is a sensitive biomarker of target engagement and reductions of mRNA transcripts and other toxic proteins

WAVE LIFE SCIENCES

Liu et al, Nature Communications, 2021; DPRs: dipeptide repeat proteins

Preclinical studies with WVE-004 demonstrated durable reduction of poly(GP) in spinal cord and cortex 6 months after two doses

Preclinical *in vivo* results:



WAVE LIFE SCIENCES

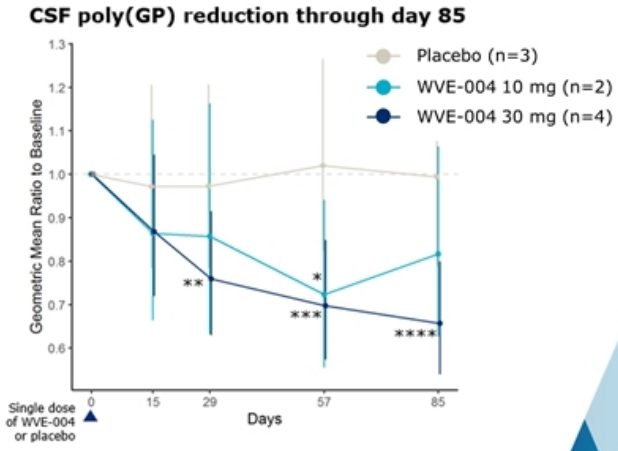
Liu *et al., 2022 Molecular Therapy Nucleic Acids* doi: 10.1016/j.omtn.2022.04.007; 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by poly(GP) MSD assay.
*: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. DPR: Dipeptide repeat protein

WVE-004 clinical data demonstrate successful translation of preclinical models to clinic

PK/PD modeling using preclinical *in vivo* models predicted pharmacodynamically active starting dose

- ✓ Poly(GP) reduction in cortex and spinal cord in transgenic mice with WVE-004
- ✓ Sufficient concentrations of WVE-004 in cortex and spinal cord of NHP for target engagement

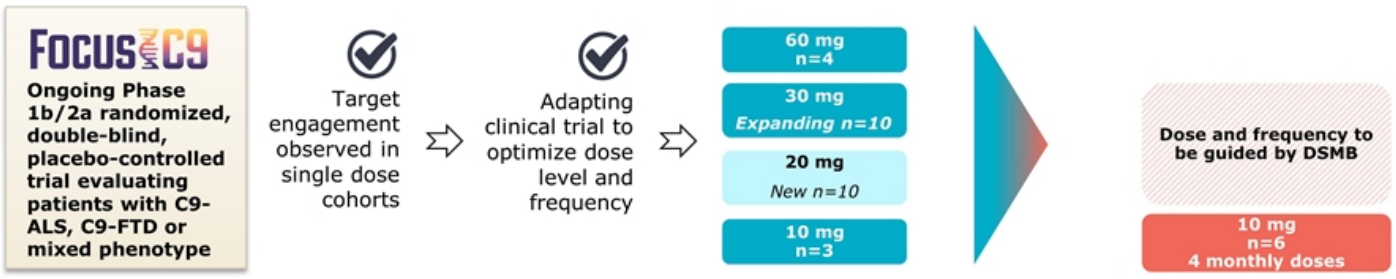
Target engagement confirmed in patients supports advancing FOCUS-C9 clinical study



WAVE LIFE SCIENCES

PK: pharmacokinetic PD: pharmacodynamic; Right: *p=0.020, **p=0.008, ***p=0.001, ****p<0.001, % change from baseline. Mixed model for repeated measures used for all statistical testing

Optimizing dose level and frequency to enable discussions with regulatory authorities later in 2022



- Given poly(GP) reduction with single 30 mg doses that does not appear to have plateaued at day 85, extending observation period and adding additional patients to FOCUS-C9 clinical trial
- Dosing in a multidose cohort (monthly) at 10 mg is well underway
- Planning underway for initiation of an open-label extension (OLE) clinical trial in mid-2022
- Data planned to be presented in oral presentation at ENCALS Meeting (June 1-3, 2022)

Additional single and multidose data for WVE-004 expected throughout 2022

WAVE LIFE SCIENCES

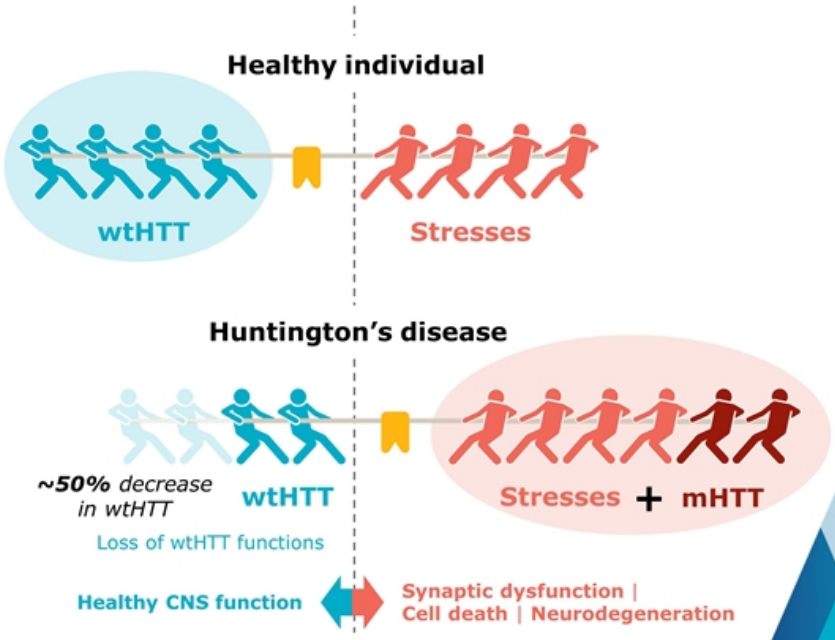
ENCALS: European Network to Cure ALS

WVE-003

Huntington's Disease

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

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



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]

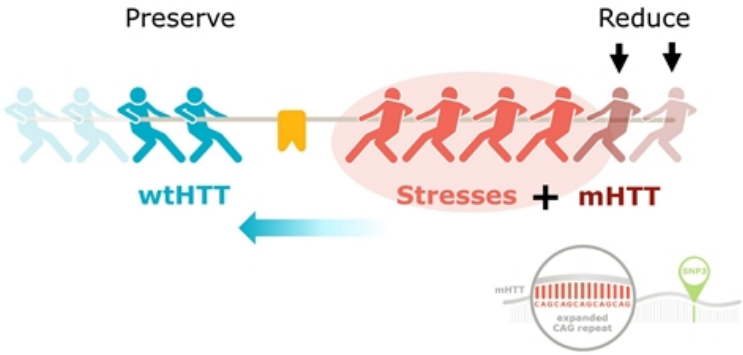
WAVE LIFE SCIENCES

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

WVE-003: Allele-selective approach to treating HD

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

- ✓ Target SNP3 on mutant mRNA HTT transcript to potentially reduce mutant HTT protein
- ✓ Potential to reserve wild-type HTT protein reservoir in brain



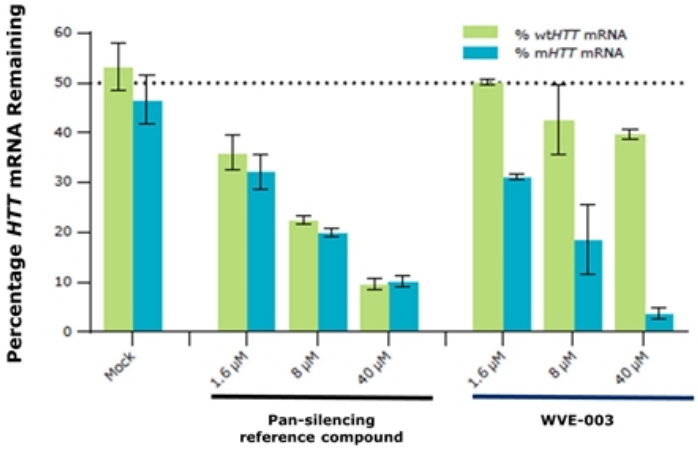
Only an allele-selective approach is designed to address <u>both</u> toxic gain of function and toxic loss of function drivers of HD

WAVE LIFE SCIENCES

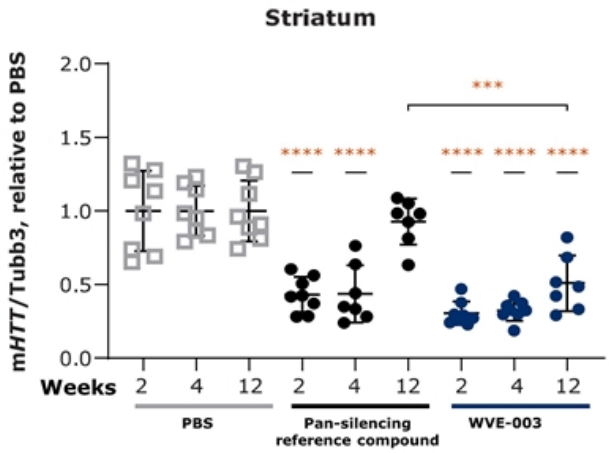
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

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



Similar results in cortex

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 cannula on days 1, 3, 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 mice and NHPs

BACHD mouse 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

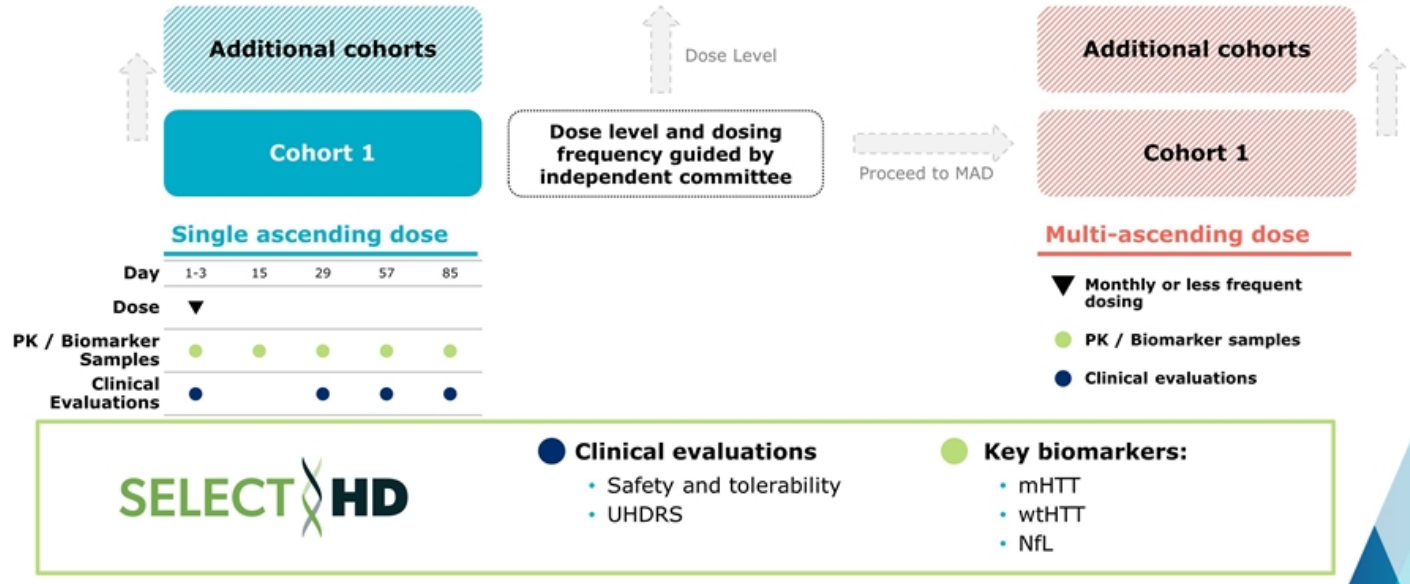
Anticipated mHTT knockdown in **cortex** and **striatum** based on PK-PD modeling

Clinical data to enable decision making expected in 2022

WAVE LIFE SCIENCES

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

SELECT-HD clinical trial: Dose level and dosing frequency guided by independent committee



SELECT HD

Clinical evaluations
- Safety and tolerability
- UHDRS

Key biomarkers:
- mHTT
- wtHTT
- NfL

WAVE LIFE SCIENCES

PK: pharmacokinetic

Adaptive cohorts

WVE-N531

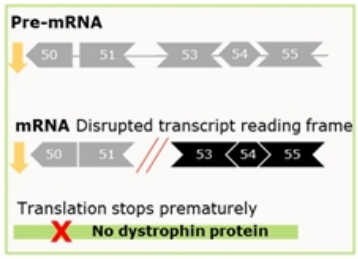
Duchenne muscular dystrophy

Duchenne muscular dystrophy

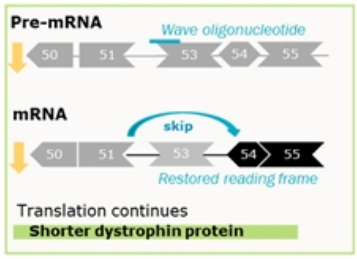
Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function.
- Dystrophin protein established by FDA as surrogate endpoint reasonably likely to predict benefit in patients[1] for accelerated approval in DMD
  - Confirmatory studies ongoing
  - Increasing amount of functional dystrophin expression over minimal amount shown with approved therapies is expected to result in greater benefit for patients
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide.

Dysfunctional splicing (Disease)



Exon skipping (Partial Restoration)

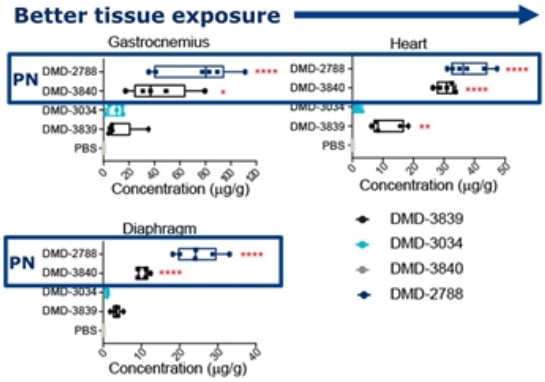


WAVE LIFE SCIENCES

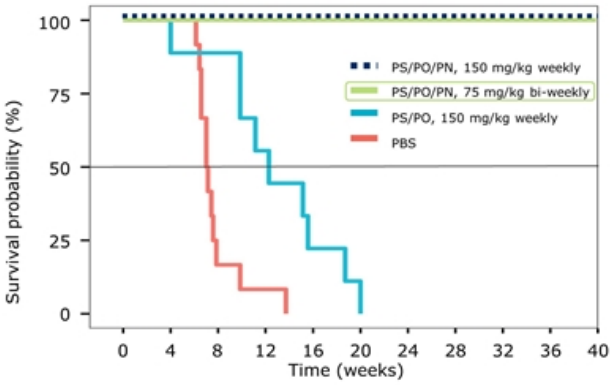
[1]Vyondys: www.fda.gov; viltepso; www.fda.gov; Exondys; www.fda.gov; Amondys: www.fda.gov

PN chemistry improved muscle exposure and survival in preclinical mouse models

PN boosted muscle concentrations after single dose, which correlated with exon-skipping activity



Treatment with PN-modified molecules led to 100% survival of dKO mice at time of study termination

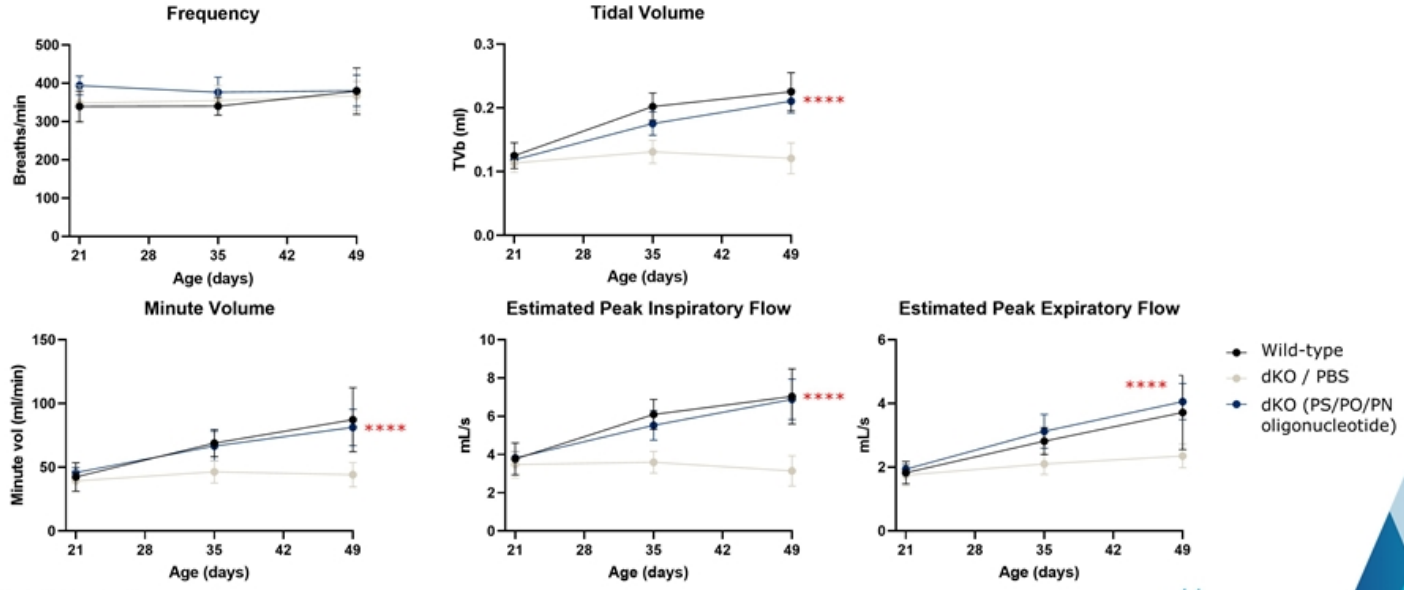


Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

WAVE LIFE SCIENCES

Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

PS/PO/PN splicing compound restores respiratory function to wild-type levels in dKO mice

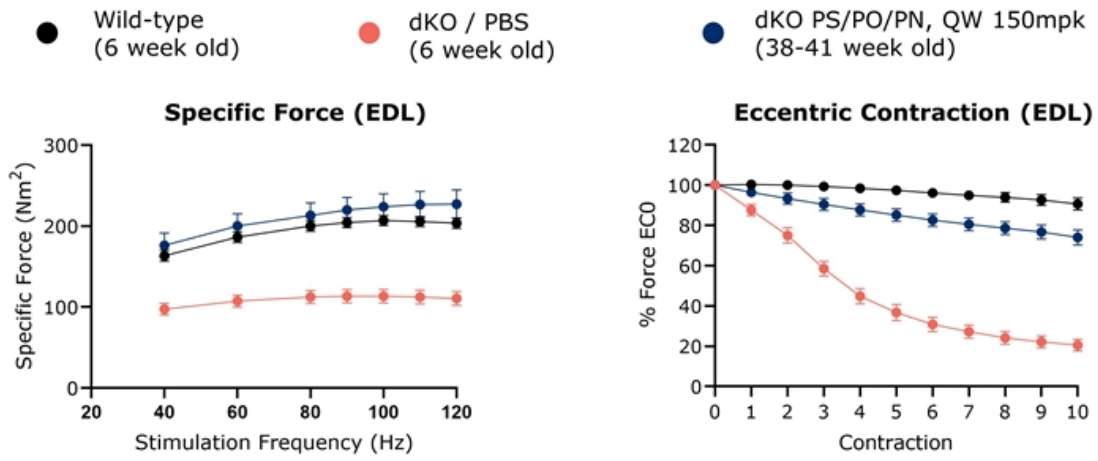


WAVE LIFE SCIENCES

Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

PRISM

PS/PO/PN compound restores muscle function to wild-type levels in dKO mice



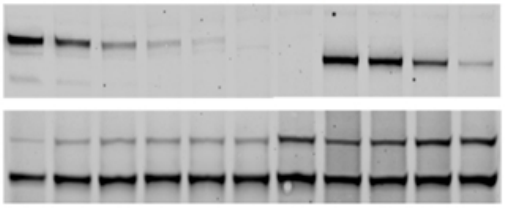
Mdx/utr-/- mice received weekly subQ 150 mpk dose of PS/PO/PN stereopure oligonucleotide beginning at postnatal day 10. Age-matched *mdx/utr-/-* littermates were treated with PBS, and *wild-type C57BL10* mice were not treated. Electrophysiology to measure specific force and eccentric contraction performed at Oxford University based on Goyenvalle et al., 2010 Mol Therapy 18(1), 198-205.

WVE-N531: Dystrophin restoration *in vitro* and enhanced muscle distribution in NHPs

Dystrophin protein restoration of up to 71% *in vitro*

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



Enhanced muscle distribution in NHPs

Plasma and tissue concentrations of WVE-N531 (PS/PO/PN) significantly higher than suvodirsen (1st-gen PS/PO) in multiple NHP studies

- ✓ Substantially higher muscle concentrations (including heart and diaphragm) as compared to suvodirsen
- ✓ Higher plasma Cmax, AUC and Ctrough

WAVE LIFE SCIENCES

Dose escalation ongoing in clinical trial of WVE-N531

- Open-label clinical trial of boys with DMD amenable to exon 53 skipping
- Dose level and dosing frequency guided by tolerability and plasma PK

Initial cohort

- Ascending intra-patient doses of WVE-N531
- Up to 4 dose levels (administered ≥4 weeks apart) evaluated to select dose level for multidose
- Up to 3 additional doses given every-other-week at selected dose level, followed by muscle biopsy

Cohort expansion to be guided by assessment of muscle biopsies: (drug distribution in muscle and biomarkers)

Possible cohort expansion (up to 15 boys)

- Additional patients enrolled and dosed every other week at selected dose level
- Up to 7 total doses to be given followed by a minimum 8-week safety monitoring period
- Powered to evaluate change in dystrophin expression

Clinical data, including muscle biopsies, expected in 2022

WAVE LIFE SCIENCES

DMD: Duchenne muscular dystrophy

WVE-N531 plasma concentrations at starting dose significantly improved over suvodirsen

WVE-N531 Phase 1b/2a open-label clinical trial starting dose
Dose escalation is ongoing

	WVE-N531 (PN chemistry) fold increase over suvodirsen at the same dose level
Plasma:	
C_{max}	**~2.5x**
AUC	**~4x**
Muscle:	*Patient muscle biopsies expected in 2022*

Increase in plasma concentrations with single dose

WVE-N531 plasma half-life estimated to be >1 week
(vs. less than 24 hours for suvodirsen)

WAVE LIFE SCIENCES

WVE-N531 is designed with PN chemistry backbone modifications. Suvodirsen (first-generation Exon 51 candidate) did not include PN chemistry.
NHP: non-human primates; AUC: Area under curve; C_{max}: Maximum plasma concentration

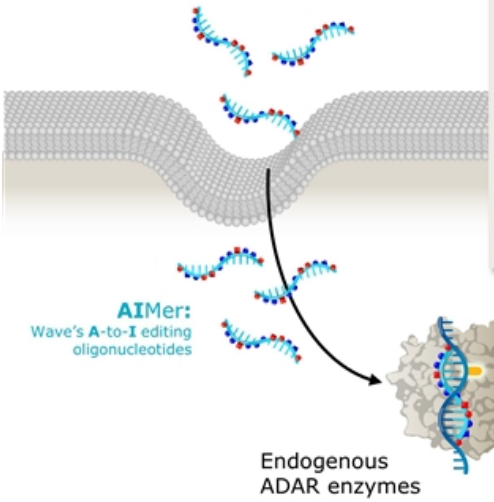
WAVE
LIFE SCIENCES

AIMers

RNA base editing capability

Unlocking RNA editing with PRISM platform to develop AIMers: A-to-I editing oligonucleotides

Free-uptake of chemically modified oligonucleotides
(No need for LNPs or viral vectors)



AIMer:
Wave's **A**-to-**I** editing oligonucleotides

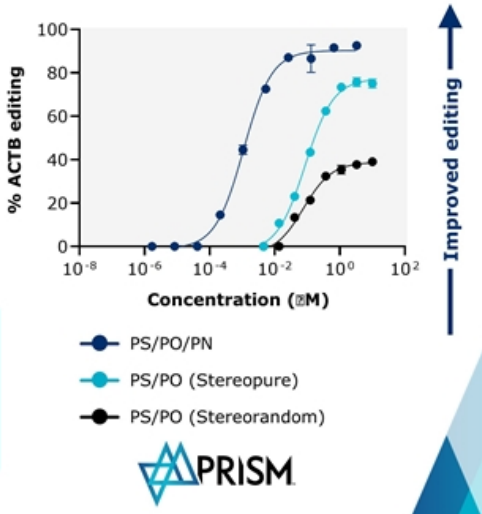
Endogenous ADAR enzymes

ADAR enzymes

- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- Catalyze conversion of A-to-I (G) in double-stranded RNA substrates
- A-to-I (G) edits are one of the most common post-transcriptional modifications
- ADAR1 is ubiquitously expressed across tissues, including liver and CNS

- ✓ Learnings from biological concepts
- ✓ Applied to ASO structural concepts
- ✓ Applied PRISM chemistry

Stereochemistry and PN chemistry enhance potency and editing efficiency of GalNAc AIMers in primary human hepatocytes



PRISM

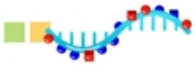
WAVE LIFE SCIENCES

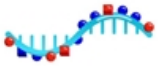
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995; Right: Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

AIMers: Realizing potential of therapeutic RNA editing by harnessing endogenous ADAR

Solved for key therapeutic attributes for potential best-in-class RNA editing therapeutics

Efficient ADAR recruitment	Stability	Delivery and intracellular trafficking	Beyond liver
• AIMer design principles • SAR developed to design AIMers for different targets	• Decade of investment and learnings to improve stability of single-stranded RNAs	• GalNAc compatible for targeted liver delivery • Endosomal escape and nuclear uptake	• AIMer design also works for delivery to CNS and other tissue types
Potent and specific editing *in vivo*	**Potential for infrequent dosing**	**Subcutaneous dosing**	**IT, IVT, systemic dosing**





- **Systematized AIMer design enables rapid advancement of new targets**
- **Strong and broad IP in chemical and backbone modifications, stereochemistry patterns, novel and proprietary nucleosides**

WAVE LIFE SCIENCES

Wave's AIMers have potential to uniquely address wide array of genetically-defined diseases

PRISM

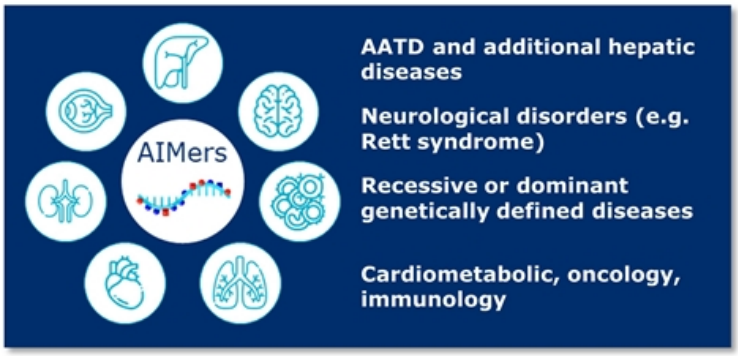
Editing: Potent, durable, specific A → I (G) RNA editing

Delivery: Efficient RNA editing in preclinical *in vivo* models:

- ✓ Targeted delivery (GalNAc)
- ✓ Systemic delivery
- ✓ Local delivery (IT, IVT, others)

AIMer opportunity

- **Correct** tens of thousands of pathogenic human SNPs potentially amenable to ADAR editing correction[1]
- **Modulate** protein interactions, e.g. **upregulation** of protein expression and **disruption** of protein-protein interactions



Potential to accelerate timelines to candidate with AIMer pipeline expansion

WAVE LIFE SCIENCES

Monian *et al.*, 2022 *Nature Biotech* published online Mar 7, 2022 doi: 10.1038.s41587-022-01225-1; SNP: single nucleotide polymorphism
A: Adenosine; I: Inosine; G: Guanosine; AATD: alpha-1 antitrypsin disease; [1]ClinVar database

Proof-of-concept preclinical RNA editing data published in *Nature Biotechnology* (March 2022)

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-022-01225-1

Check for updates

Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

Prashant Monian [1,2], Chikdu Shivalila [1,2], Genliang Lu [1], Mamoru Shimizu [1], David Boulay [1], Karley Bussow [1], Michael Byrne [1], Adam Bezigian [1], Arindom Chatterjee [1], David Chew [1], Jigar Desai [1], Frank Favaloro [1], Jack Godfrey [1], Andrew Hoss [1], Naoki Iwamoto [1], Tomomi Kawamoto [1], Jayakanthan Kumarasamy [1], Anthony Lamattina [1], Amber Lindsey [1], Fangjun Liu [1], Richard Looby [1], Subramanian Marappan [1], Jake Metterville [1], Ronelle Murphy [1], Jeff Rossi [1], Tom Pu [1], **Bijay Bhattarai** [1], Stephany Standley [1], Snehlata Tripathi [1], Hailin Yang [1], Yuan Yin [1], Hui Yu [1], **Cong Zhou** [1], Luciano H. Apponi [1], Pachamuthu Kandasamy [1] **and Chandra Vargeese** [1]✉

Technologies that recruit and direct the activity of endogenous RNA-editing enzymes to specific cellular RNAs have therapeutic potential, but translating them from cell culture into animal models has been challenging. Here we describe short, chemically modified oligonucleotides called AIMers that direct efficient and specific A-to-I editing of endogenous transcripts by endog - enous adenosine deaminases acting on RNA (ADAR) enzymes, including the ubiquitously and constitutively expressed ADAR1 p110 isoform. We show that fully chemically modified AIMers with chimeric backbones containing stereopure phosphorothio - ate and nitrogen-containing linkages based on phosphoryl guanidine enhanced potency and editing efficiency 100-fold com - pared with those with uniformly phosphorothioate-modified backbones in vitro. In vivo, AIMers targeted to hepatocytes with N-acetylgalactosamine achieve up to 50% editing with no bystander editing of the endogenous ACTB transcript in non-human primate liver, with editing persisting for at least one month. These results support further investigation of the therapeutic potential of stereopure AIMers.

Recruiting endogenous RNA-editing enzymes using chemi cally modified oligonucleotides holds promise for treating human disease. The most common mutation in human genes is transition from cytosine (C) to thymine (T) [1], and CpG dinucleo- tides are well established hot spots for disease-causing mutations The ADAR family of enzymes catalyze adenine (A)-to-inosine (I) changes in the transcriptome[2]. Because I is read as guanine (G) vehicles, such as viral vectors or lipid nanoparticles, for application beyond cell culture. So far, these technologies have yielded nominal editing in vivo[3].

Leveraging our oligonucleotide chemistry platform, we devel oped relatively short oligonucleotides that elicit A-to-I RNA editing with high efficiency using endogenous ADAR enzymes. These oligo nucleotides, called AIMers, are short and fully chemically modified

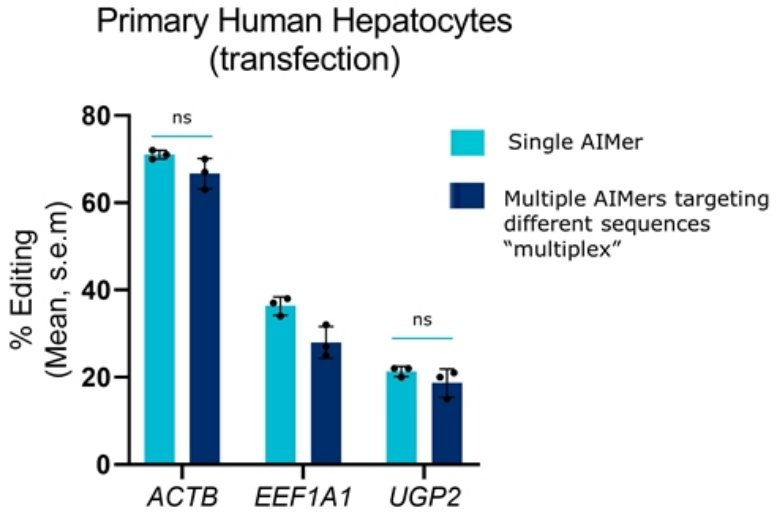
- Specificity *in vitro* & *in vivo* (NHPs)
- *In vitro-in vivo* translation (NHPs)
- GalNAc conjugation
- Foundational AIMer SAR

WAVE LIFE SCIENCES

Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1

SAR structure-activity relationship

Levels of endogenous ADAR enzyme are not rate limiting for editing



- Endogenous ADAR enzyme supports editing on multiple independent targets
- Editing efficiency comparable even when additional AIMers targeting different sequences are added, suggesting there is a more than sufficient reservoir of ADAR enzyme

WAVE LIFE SCIENCES

Percentage A-to-I editing detected on the indicated transcripts in presence of 20 nM each of a single (Isolated) or multiple (Multiplex) AIMers after transfection of primary human hepatocytes (left). Data are presented as mean ± SEM, n=3. P values as determine by two-tailed Welch's t-test are indicated. NTC non-targeting control. Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1

Optimization of every dimension to inform future rational design of AIMers

Heat map for sequence impact on SAR

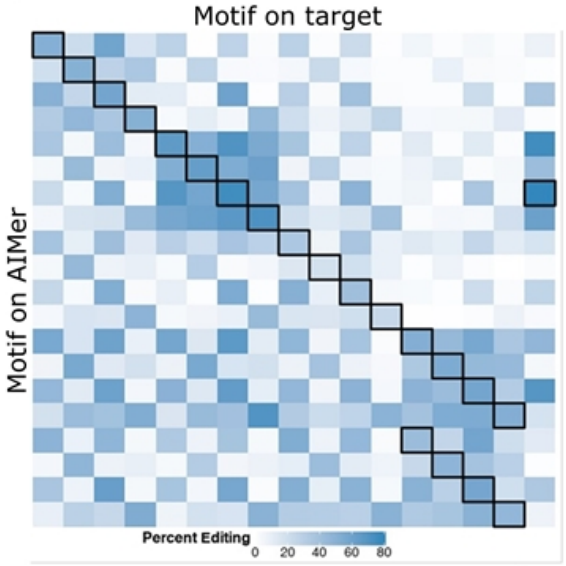
Example: Sequence is one of multiple dimensions for optimization

Sequence space is defined

NNN AIMer

XAX mRNA target

- >300 unique AIMers tested containing different base pair combinations
- Identified base modification combinations with high editing efficiency to optimize sequence

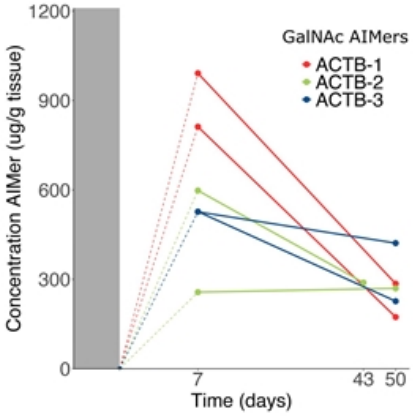


WAVE LIFE SCIENCES

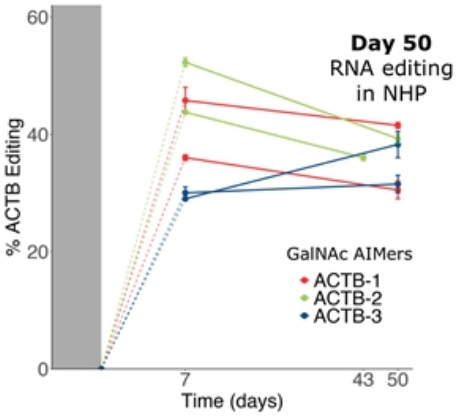
Learnings inform design principles deployed across future targets

Stability of AIMers enables durable and specific editing out to Day 50 in liver of NHPs

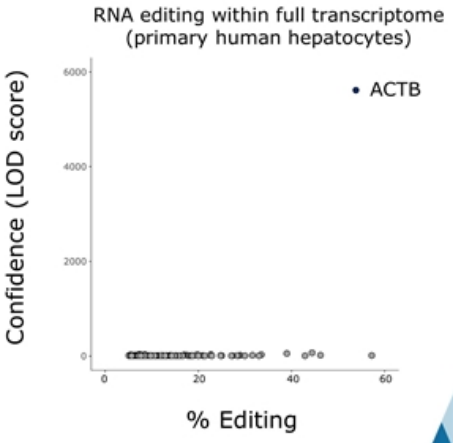
AIMers detected in liver of NHP at Day 50 (PK)



Substantial and durable editing in NHP liver *in vivo* (PD)



ADAR editing with ACTB AIMer is highly specific



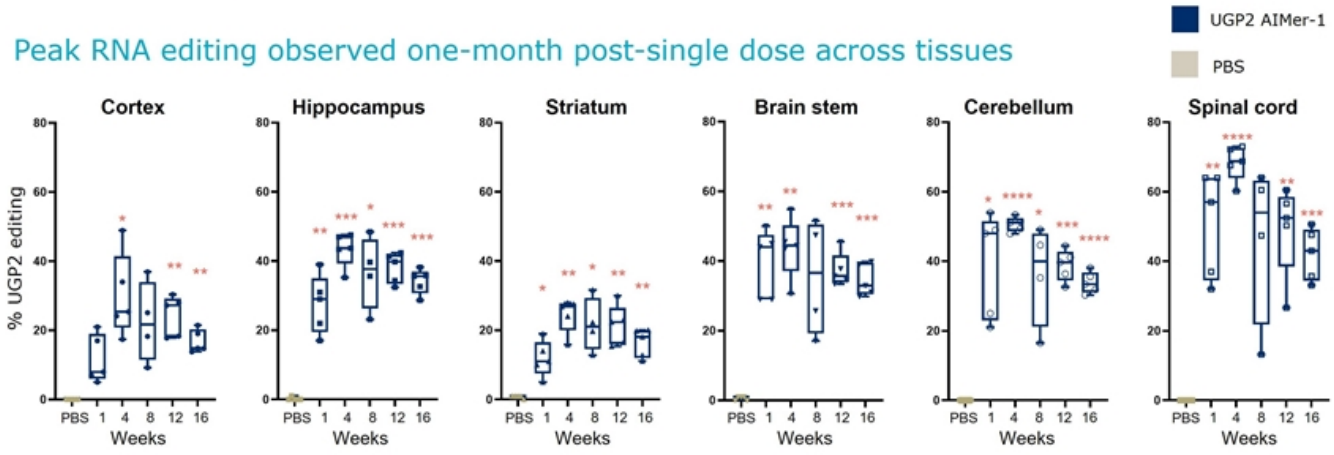
RNA editing only detected at editing site in ACTB transcript

WAVE LIFE SCIENCES

Monian et al., 2022 published online Mar 7, 2022; doi: 10.1038.s41587-022-01225-1 Left: AIMer PK C: 5mg/kg SC: Day 1,2,3,4,5; Liver biopsy; Right: Dosed 1um AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify on / off-target editing; plotted circles represent sites with LOD>3. NHP: non-human primate; ACTB: Beta-actin

Substantial *in vivo* RNA editing out to at least 4 months post-single dose in CNS tissues

Peak RNA editing observed one-month post-single dose across tissues



Peak editing	**30%**	**>40%**	**25%**	**>40%**	**50%**	**>65%**

WAVE LIFE SCIENCES

Transgenic huADAR mice administered 100 mg AIMer or PBS on day 0 and evaluated for UGP2 editing across CNS tissues at 1, 4, 8, 12, and 16-weeks post dose. Percentage UGP2 editing determined by Sanger sequencing. Stats: 2-way ANOVA compared to PBS (n=5 per time point per treatment) *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. ICV intracerebroventricular; PBS phosphate buffered saline

RNA editing of nonsense mutation found in MECP2 (Rett Syndrome) restores functional protein

Normal: ... CGA... wild type protein
Rett Syndrome: ... TGA... premature stop codon
ADAR editing: ... TGG... restored protein

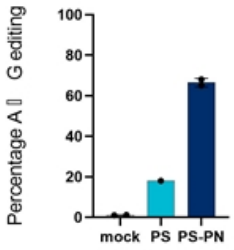
Variant base

ADAR editing site

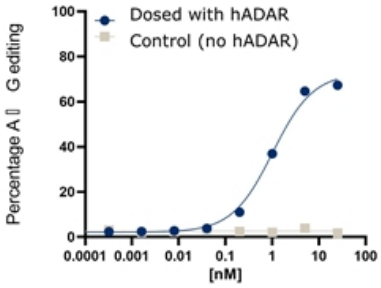
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

in vitro ADAR editing of over 60% targeting MECP2 disease transcript

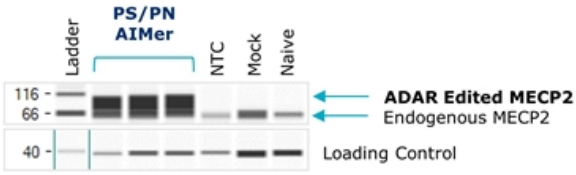
PN chemistry improved editing efficiency *in vitro*



Dose-dependent RNA editing of MECP2 mutation with PS/PN AIMer



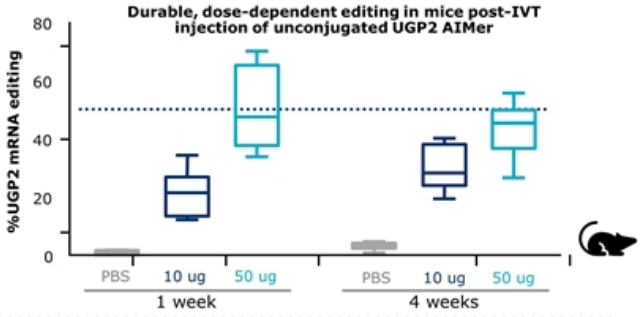
Full length MECP2 protein is expressed following ADAR editing



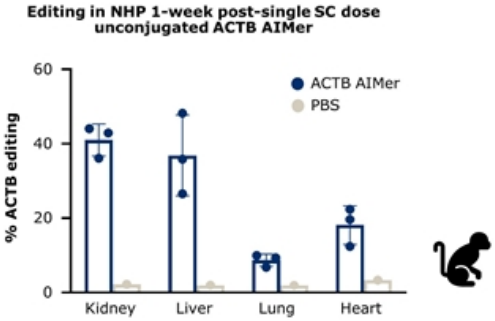
293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold dilution, 48h treatment) in presence or absence of hADAR Right: Western blot for MECP2 protein. Three biological replicates, NTC AIMer, mock and naïve 293T cells probed for fusion protein.

Productive editing beyond liver and CNS with unconjugated AIMers

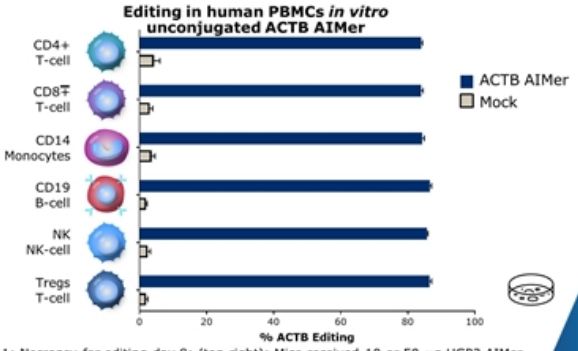
Ophthalmology



Kidney, liver, lung, heart



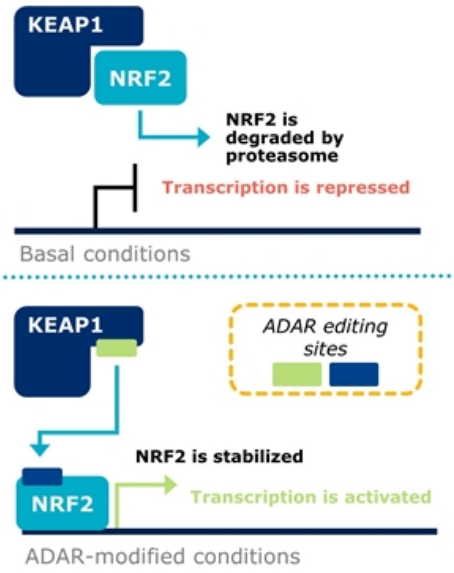
Immune cells



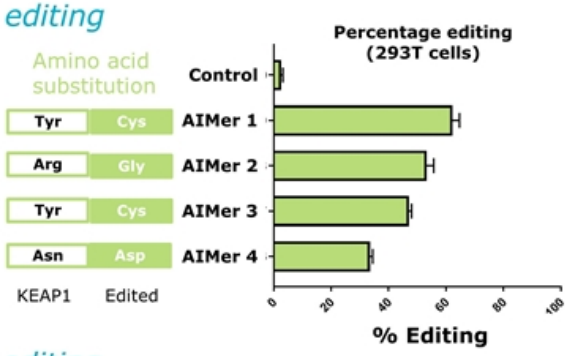
WAVE LIFE SCIENCES

(left): non-human primate (NHP) 50 mg/kg beta-Actin (ACTB) AIMer, SC (subcutaneous) on day 1; Necropsy for editing day 8; (top right): Mice received 10 or 50 mg UGP2 AIMer intravitreal (IVT), eye collected for analysis 1 or 4 weeks later. (lower right): Human PBMCs dosed with 10 mM ACTB AIMers, under activating conditions (PHA). After 4 days, different cell types isolated, quantitated for editing.

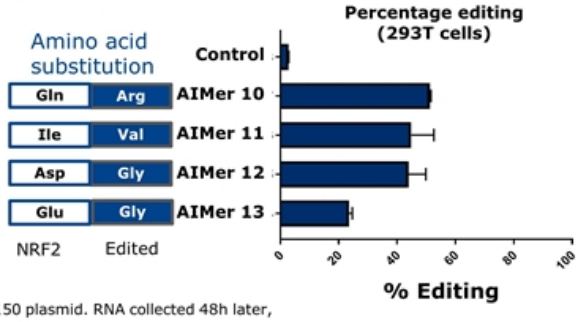
Apply AIMers to modify protein-protein interactions



KEAP1 editing



NRF2 editing

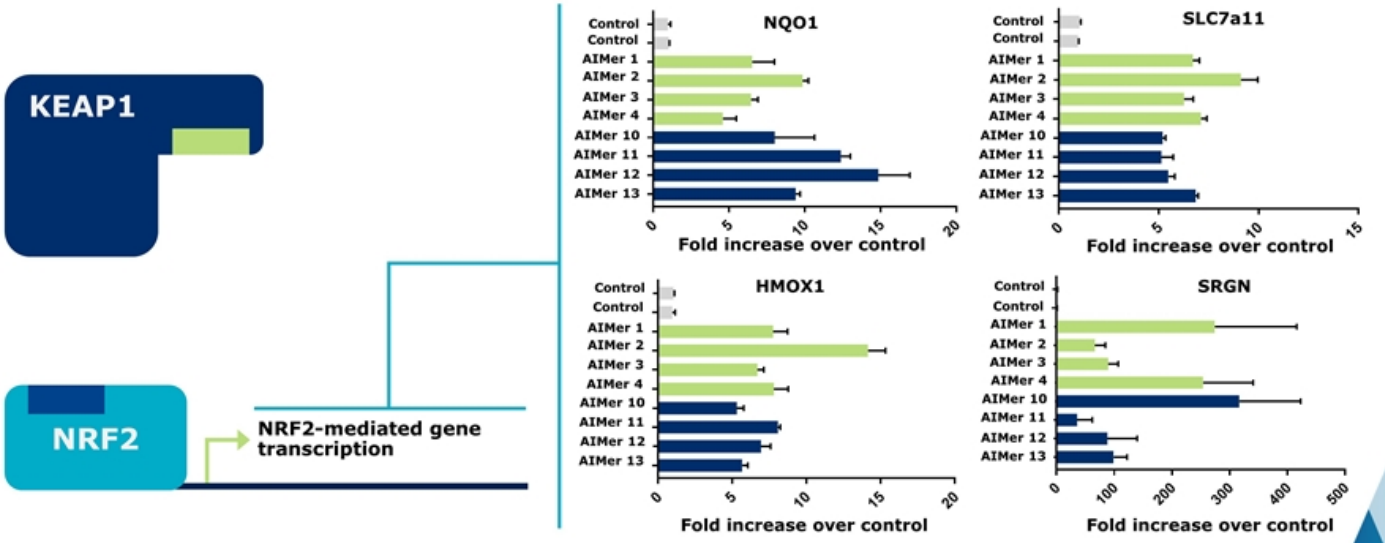


WAVE LIFE SCIENCES

293T cells transfected with 20 nM of AIMer, ADAR-p110 or ADAR-p150 plasmid. RNA collected 48h later, editing quantified by PCR and Sanger (n=2).

ADAR editing activates multiple genes, confirming disrupted protein-protein interaction *in vitro*

ADAR editing of either KEAP1 or NRF2 directs gene activation



Gene expression quantified by PCR (n=2) after transfection into 293T cells

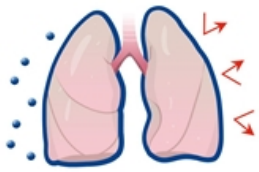
WAVE
LIFE SCIENCES

Alpha-1 antitrypsin deficiency (AATD)

RNA editing is uniquely suited to address the therapeutic goals for AATD

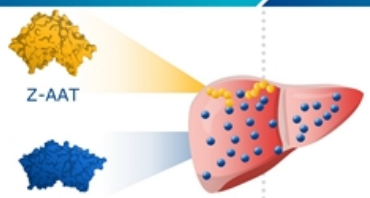
Wave ADAR editing approach addresses all goals of treatment:

1) Restore circulating, functional wild-type M-AAT



M-AAT reaches lungs to protect from proteases

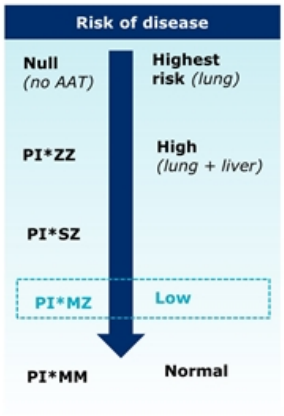
2) Reduce Z-AAT protein aggregation in liver



Wild-type M-AAT protein replaces Z-AAT with RNA correction

3) Retain M-AAT physiological regulation

M-AAT secretion into bloodstream



Alternative approaches address only a subset of treatment goals:

*Current **protein augmentation** addresses only lung manifestations*

***siRNA** approaches only address the liver disease*

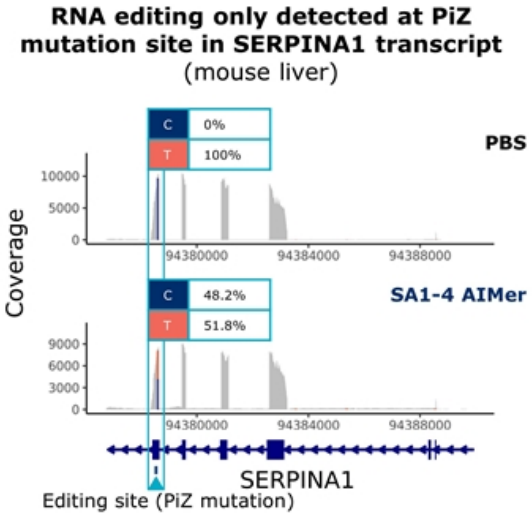
***Small molecule** approaches may address the lung and liver but do not generate wildtype M-AAT*

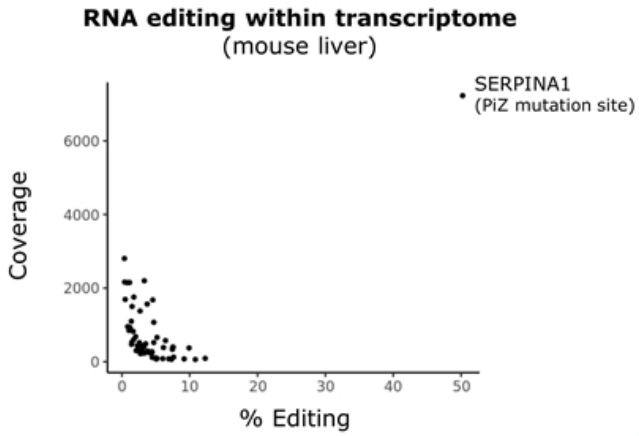
~200K people in US and EU with mutation in *SERPINA1* Z allele (PI*ZZ)

WAVE LIFE SCIENCES

AAT: Alpha-1 antitrypsin Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.*, 2021 *Curr Opin Pharmacol* 59:149-56.

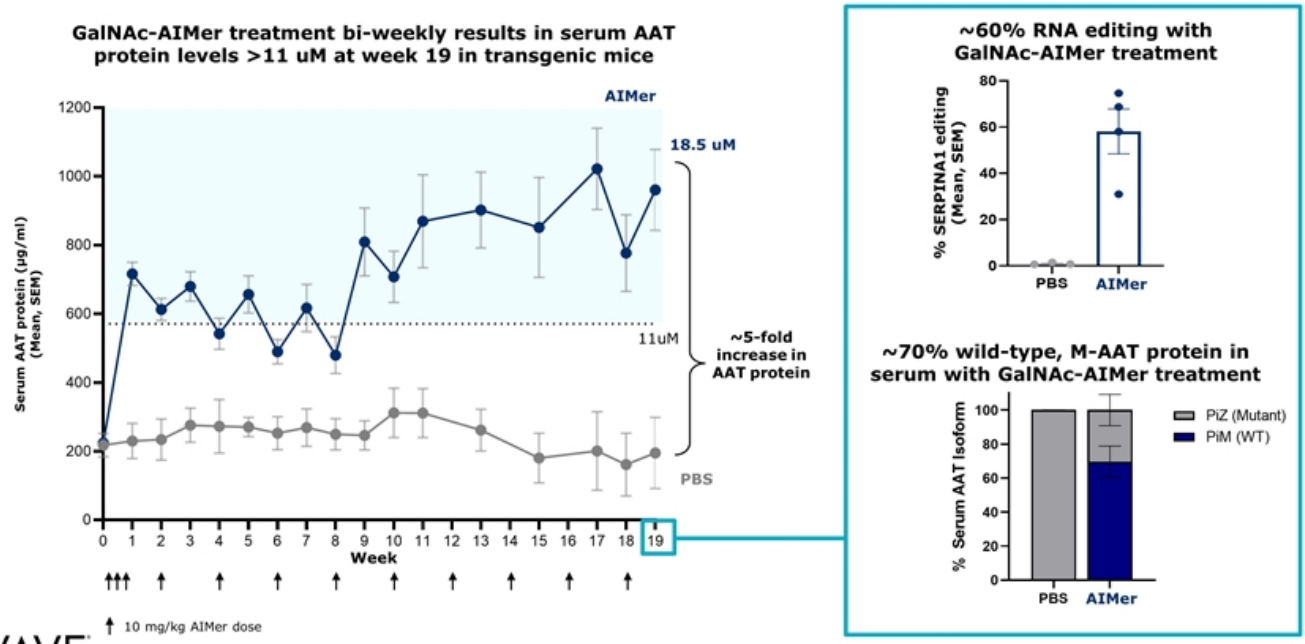
ADAR editing is highly specific; no bystander editing observed on SERPINA1 transcript





Dose 3 x 10mg/kg days (0, 2, 4) SC. Liver biopsies day 7. RNAseq, To quantify on-target SERPINA1 editing reads mapped to human SERPINA1, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4); Analyst and Investor Research Webcast September 28, 2021

Preclinical AIMer treatment results in circulating AAT protein levels well above anticipated therapeutic threshold



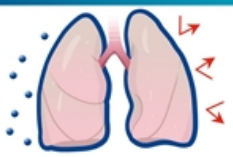
WAVE LIFE SCIENCES

AIMers (SA1-5) administered in hu*ADAR/SERPINA1* mice (8 – 10 weeks old) Left : Total AAT protein quantified by ELISA. Right: Liver biopsies collected at week 19 (one week after last dose) and SERPINA1 editing was quantified by Sanger sequencing

AATD AIMer restores functional M-AAT protein and alleviates liver aggregation in preclinical model

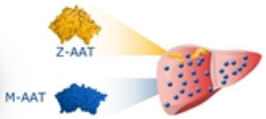
Correction of loss-of-function phenotypes

Restored M-AAT reaches lungs to protect from proteases



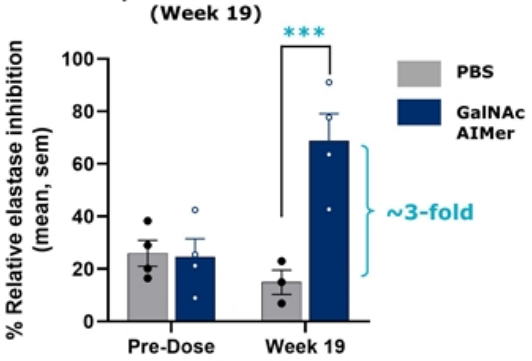
HYBRID EVENT TIDES USA | Oligonucleotide & Peptide Therapeutics

Correction of gain-of-function phenotypes

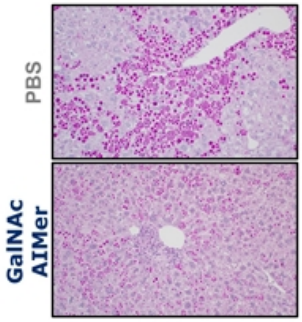


Wild-type M-AAT protein replaces Z-AAT with RNA correction

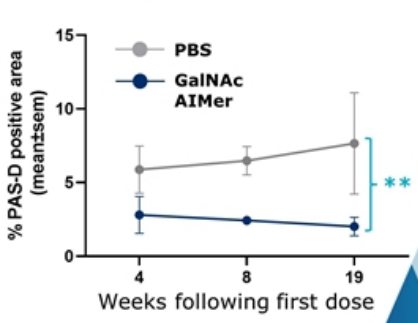
Neutrophil elastase inhibition (Week 19)



PAS-D staining (19 weeks)



PAS-D-positive area declines with AIMer treatment



WAVE LIFE SCIENCES

GalNAc AIMer (SA1-5) administered bi-weekly (10 mg/kg) following initial loading dose (3 x 10 mg/kg) in hu*ADAR/SERPINA1* mice (8–10 weeks old); Left: Neutrophil elastase inhibition assay (pre-dose, week 19 serum samples), Stats: Mixed effects analysis P<0.001; Right: 20x images from liver stained with PAS-D at 19 weeks ** p<0.01

GalNAc-AIMers are uniquely suited to address the key treatment goals for AATD

- ✓ Recruit endogenous ADAR enzyme to edit SERPINA1 Z mRNA with high specificity
- ✓ Restore circulating, functional M-AAT protein above expected therapeutic threshold (11 mM)
- ✓ Reduce Z-AAT protein aggregation in liver

	AIMers	RNAi	AAT augmentation therapy
Restore circulating functional wild-type AAT	✓		✓
Reduce Z-AAT protein aggregation in liver	✓	✓	
Retain M-AAT physiological regulation	✓		

Expect to select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in 3Q 2022

WAVE LIFE SCIENCES

https://www.labiotech.eu


WAVE
LIFE SCIENCES
PRISM
Wave's discovery and drug development platform

Wave is the leader in rationally designed stereopure oligonucleotides

Stereochemistry is a reality of chemically-modified nucleic acid therapeutics

Chirality matters: affects pharmacology of oligonucleotides *in vitro* and *in vivo*

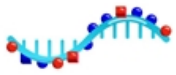
PRISM controls stereochemistry throughout drug discovery and development process

Current therapeutics with chiral backbone modifications:

- **Antisense oligonucleotides**
- **siRNA**
- **Exon-skipping oligonucleotides**
- **RNA guide strands**

Wave publications:

Enables rational design and optimization of fully-characterized, **stereopure** RNA therapeutics



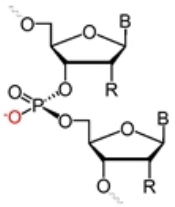
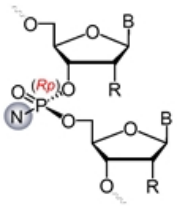
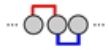
Strong and broad IP portfolio and unique ability to manufacture and screen stereopure oligonucleotides

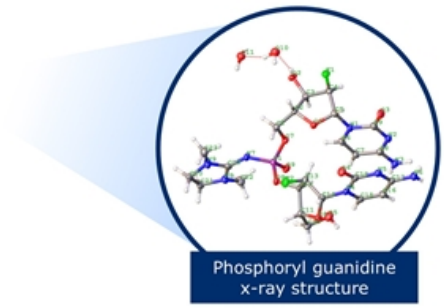
WAVE LIFE SCIENCES

[1]Jahns et al., NAR, 2021; Hansen, et al. 2021; Funder, Albaek et al. 2020

Innovating stereopure backbone chemistry modifications: PN chemistry

PRISM backbone linkages

PO	PS	PN
		
		
Chirality None	**Chirality** PS backbone *Rp* PS backbone *Sp*	**Chirality** PN backbone *Rp* PN backbone *Sp*
Negative charge	**Negative charge**	**Neutral charge**



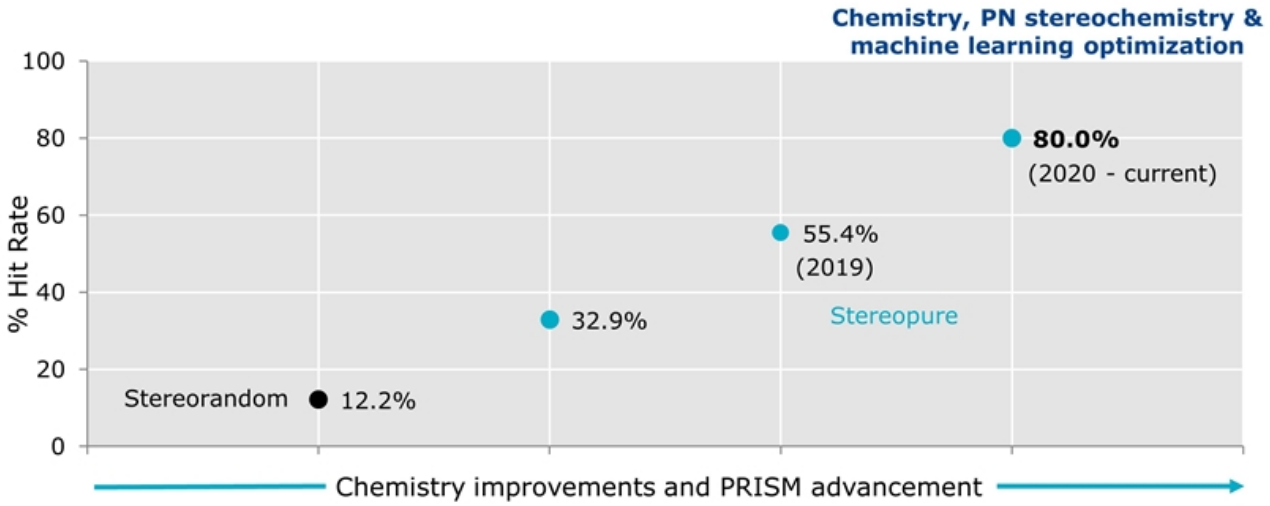
example

WAVE LIFE SCIENCES

PO: phosphodiester PS: phosphorothioate

Improvements in PRISM primary screen hit rates accelerate drug discovery over time

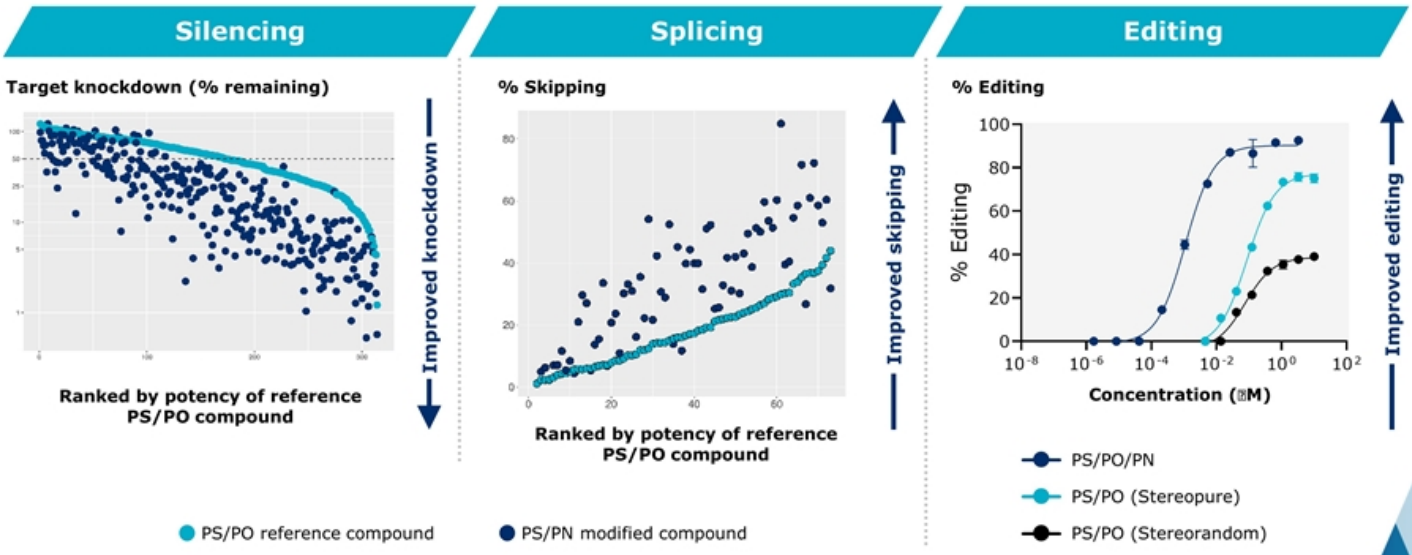
Primary screen hit rates with silencing far above industry standard hit rates



WAVE LIFE SCIENCES

All screens used iPSC-derived neurons; Data pipeline for improved standardization. Hit rate = % of oligonucleotides with target knockdown greater than 50%. Each screen contains >100 oligonucleotides. ML: machine learning

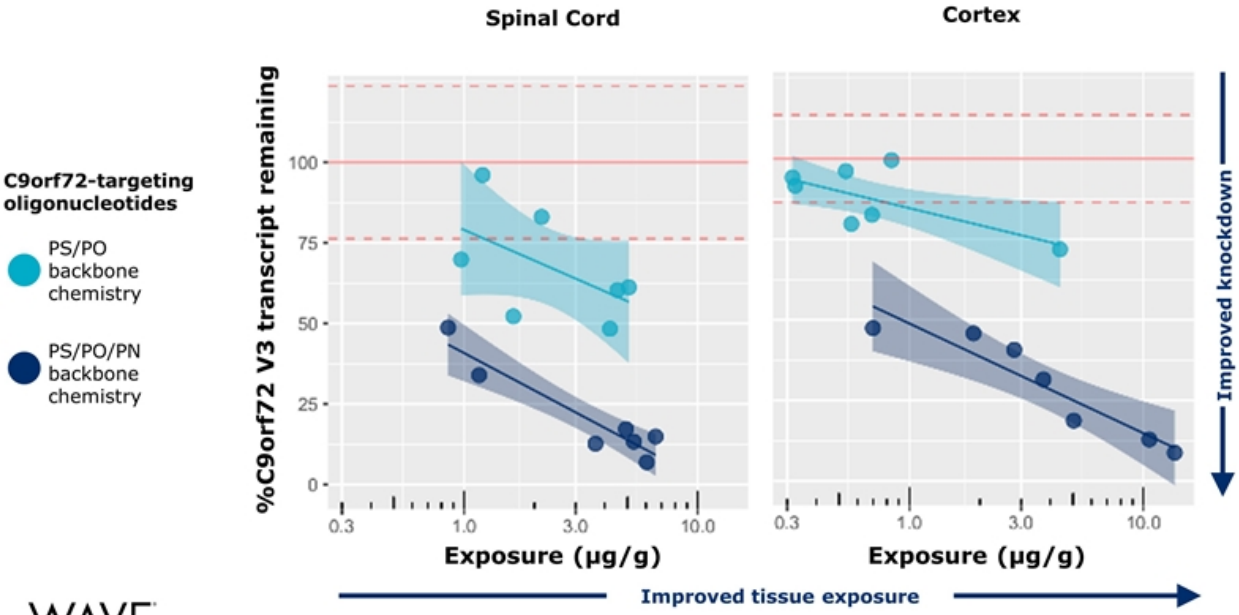
Potency is enhanced with addition of PN modifications across modalities



WAVE LIFE SCIENCES

Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the DDCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake conditions. Exon-skipping efficiency evaluated by qPCR. Right: Data from independent experiments

Adding PN chemistry modifications to C9orf72-targeting oligonucleotides improved potency *in vivo*

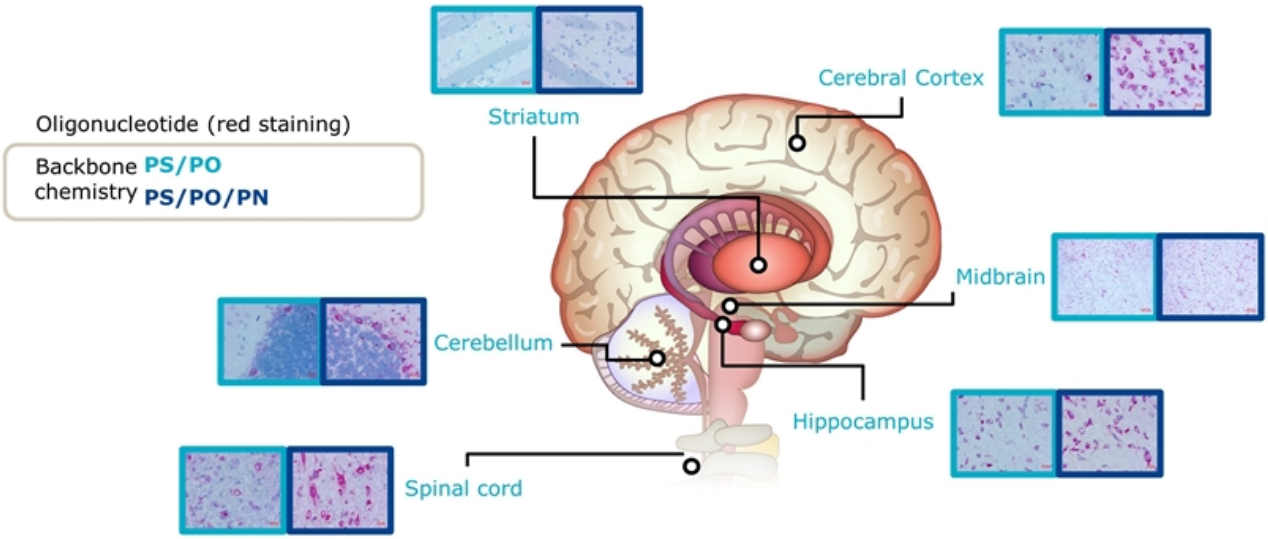


WAVE LIFE SCIENCES

Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis; Liu et al. Molecular Therapy Nucleic Acids 2022; Kandasamy et al., Nucleic Acids Research, 2022, doi: 10.1093/nar/gkac037

PN chemistry improves distribution to CNS

Distribution of oligonucleotides in non-human primate CNS 1-month post single IT dose



WAVE LIFE SCIENCES

NHPs administered 1x12 mg oligonucleotide or PBS by intrathecal injection/lumbar puncture (IT). CNS tissue evaluated 11 or 29 days after injection (n=6 per group). Oligonucleotide was visualized by ViewRNA (red), and nuclei are counterstained with hematoxylin. Images from day 29.

Rational design to achieve target engagement and preclinical tolerability

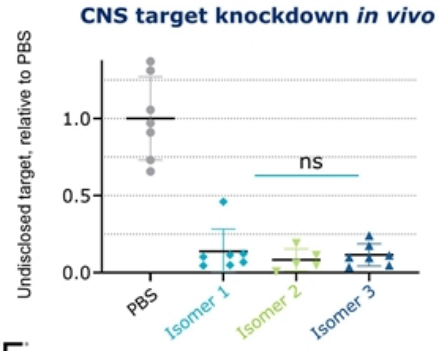
Unconjugated oligonucleotide administered **ICV**

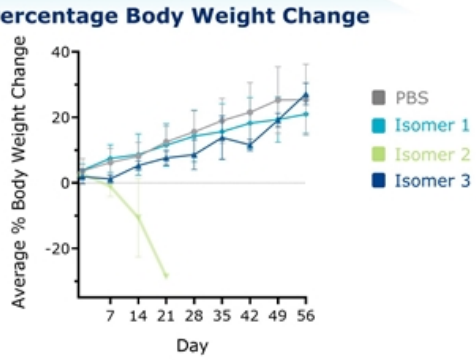
Isomer 1
Isomer 2
Isomer 3

Same sequence, but different backbone stereochemistry

Stereoisomers have **similar** pharmacodynamic effects *in vivo*

Changing backbone stereochemistry leads to **different** tolerability profiles *in vivo*

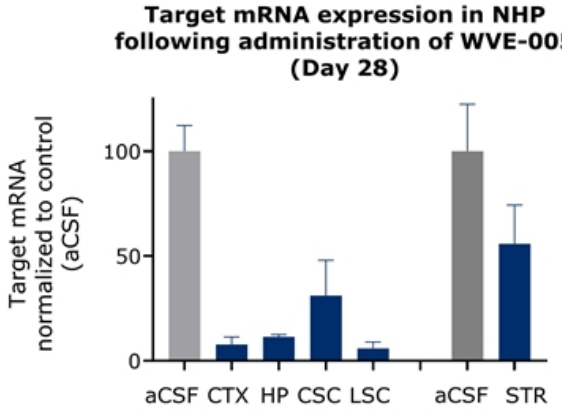




WAVE LIFE SCIENCES

Left: In a target engagement study, 7 mice administered 2 x 50 ug oligonucleotide or PBS by ICV on days 0 and 7. Tissue collected on day 14. Target mRNA normalized to Tubb3 and plotted relative to PBS. Data presented as mean ± SD (n=7). Stats: One-way ANOVA ns not significant, PBS phosphate buffered saline. Right: wt mouse tolerability study, n=4 administered 100 ug oligonucleotide or PBS by ICV on day 0 and monitored for 8 weeks.

Single intrathecal dose in NHP leads to substantial and widespread target mRNA reduction throughout the CNS



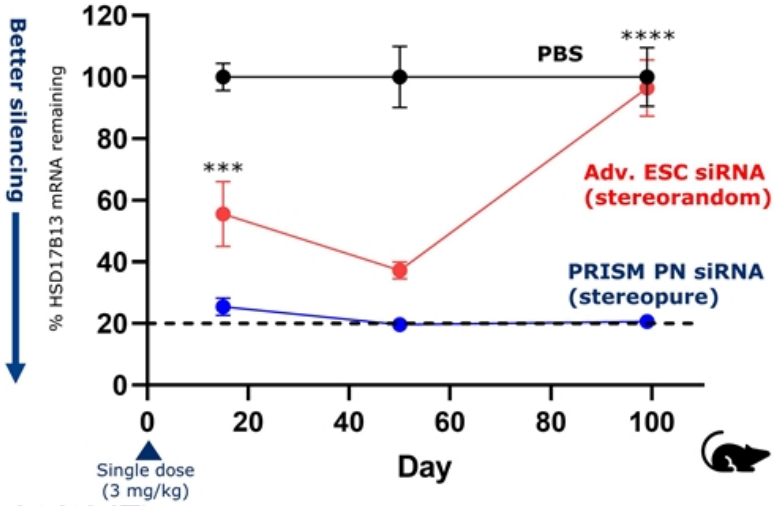
Potential for infrequent IT administration, widespread CNS distribution of PN modified oligonucleotides, and availability of disease biomarkers facilitates development of differentiated CNS portfolio

WAVE LIFE SCIENCES

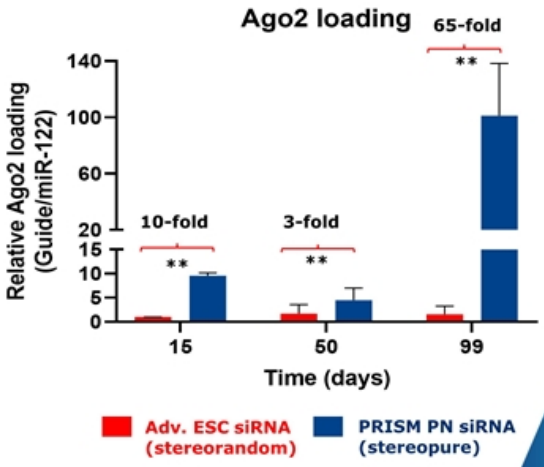
NHPs: Non-human primates; NHPs (n=3) received a single 12 mg IT dose of WVE-005. ASO and mRNA quantified by ELISA and qPCR, respectively. Striatum was evaluated in a separate experiment. CTX cortex; HP hippocampus; CSC cervical spinal cord; LSC lumbar spinal cord; STR striatum; aCSF artificial cerebrospinal fluid

PRISM PN siRNA led to unprecedented silencing as compared to state-of-art >3 months after single dose

~80% silencing HSD17B13 mRNA *in vivo* with GalNAc-conjugated PRISM PN siRNA 14 weeks post single dose



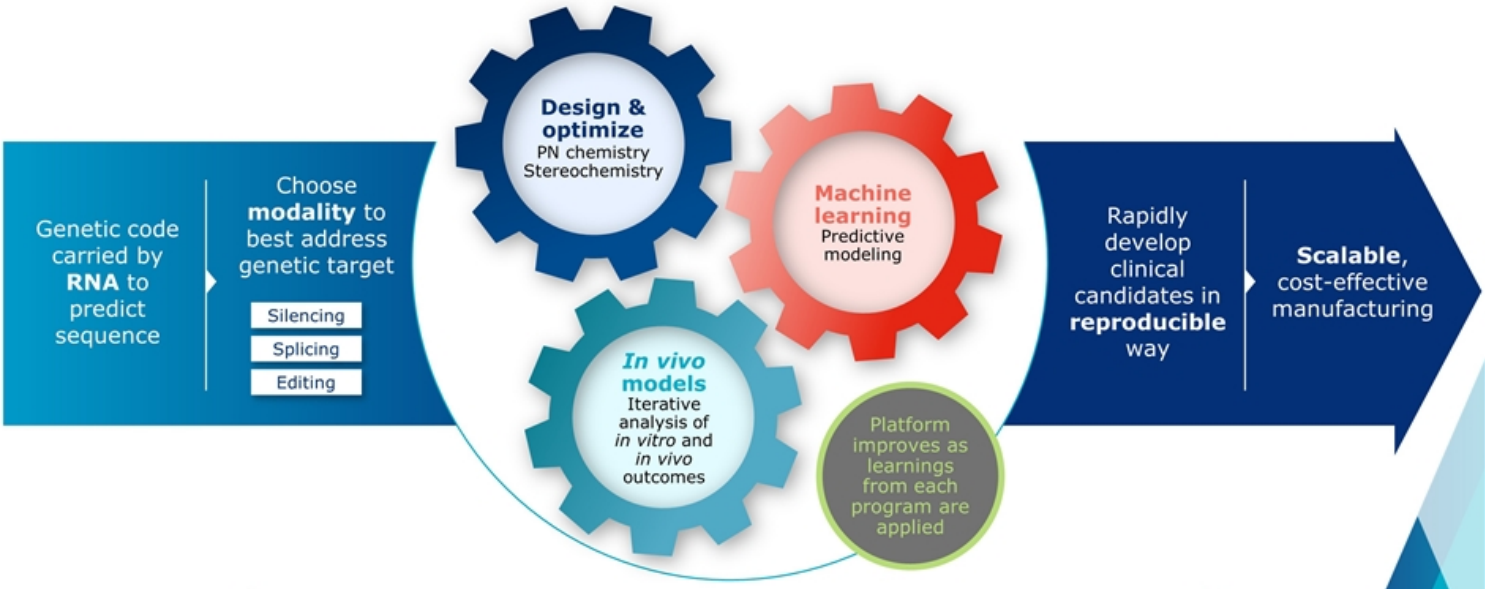
PRISM PN siRNA loaded in RISC is significantly greater than Adv. ESC siRNA



WAVE LIFE SCIENCES

(Left) Proprietary human transgenic mouse model, Post hoc tests derived from Linear Mixed Effects Model with Random subject effects;
(Right) ** P<0.01, 2-way ANOVA

PRISM platform is continuously improving



WAVE LIFE SCIENCES

Continuous definition of design principles deployed across programs

Established internal GMP manufacturing for multiple oligonucleotide modalities

Strong technical knowhow and operating expertise

- Experienced team led by Sridhar Vaddeboina, PhD (SVP Chemistry, Manufacturing, Controls)
- Experts in oligonucleotide synthesis (ASOs, DNAs, RNAs, siRNAs)
- Proven track record scaling complex chemistries; delivered clinical supply for six programs at Wave

Established infrastructure

- State of the art facilities (90,000 sq ft) and expansion space
- Process and analytical development labs
- GMP oligonucleotide (API) manufacturing
- Established Quality and GMP systems (QA, supply chain, logistics, QC testing)

Scalable to support Wave's GMP manufacturing needs, as well as potential new partners

WAVE LIFE SCIENCES

WAVE LIFE SCIENCES

Upcoming milestones

Key anticipated upcoming milestones

WVE-004 C9orf72 ALS & FTD	✓ Delivered clinical target engagement data with single doses • Additional single and multidose data throughout 2022 • Discussions with regulatory authorities regarding next phase of development later in 2022
WVE-003 HD SNP3	• Clinical data to enable decision making in 2022
WVE-N531 DMD Exon 53	• Clinical data to enable decision making in 2022
AATD program SERPINA1	• Select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in 3Q 2022

Silencing	**CNS** *(Intrathecal)*
Splicing	**Muscle** *(IV)*
ADAR editing	**Targeted delivery liver** *(Subcutaneous)*

Additional data generated in 2022 expected to further inform future opportunities and unlock value

WVE LIFE SCIENCES

WVE-004 FOCUS-C9 clinical trial (NCT04931862); WVE-003 SELECT-HD clinical trial (NCT05032196); WVE-N531 open-label clinical trial (NCT04906460)

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