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): March 3, 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 March 3, 2022, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter and year ended December 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 March 3, 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 March 3, 2022
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated March 3, 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: March 3, 2022

Wave Life Sciences Reports Fourth Quarter and Full Year 2021 Financial Results and Provides Business Update

Clinical data from multiple novel, PN-modified stereopure oligonucleotides for ALS/FTD, DMD, and HD expected in 2022

GalNAc-AIMers restore therapeutically relevant levels of AAT for lung protection and reduce liver-damaging aggregates in preclinical study; IND enabling toxicology studies expected to initiate in 3Q 2022

FY2021 year-end cash total of $150.6 million providing runway into 2Q 2023

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

CAMBRIDGE, Mass., March 3, 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 fourth quarter and full year ended December 31, 2021 and provided a business update.

“Wave achieved multiple significant milestones in 2021, including successfully bringing PN chemistry into the clinic with the initiation of three new clinical trials with our next-generation RNA silencing and exon-skipping therapeutics, as well as demonstrating the first successful protein restoration expression with AIMers in preclinical *in vivo* models for the treatment of alpha-1 antitrypsin deficiency, also known as AATD. These accomplishments have positioned us to deliver several key datasets in 2022 to inform the potential of our novel oligonucleotides across tissues and modalities,” said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences.

“We continue to rapidly advance our AIMer RNA editing capabilities and are poised to deliver a first-in-class novel modality to address both lung and liver manifestations of AATD. We remain on track to select our first GalNAc-AIMer development candidate in the third quarter of this year, and we are leading the way with RNA base editing to address a wide array of genetic diseases, with potentially even more expansive applications through protein modulation. Lastly, our decade of investment in our PRISM platform has resulted in a robust and diverse pipeline, as well as internal GMP manufacturing capabilities that can be scaled to support our needs as well as potential new partners,” continued Dr. Bolno.

Recent Business Highlights and Upcoming Milestones

Clinical silencing and exon skipping therapeutic programs:

Scientific publications

- In February 2022, Wave announced two publications in the journal *Nucleic Acids Research (NAR)* supporting the incorporation of PN backbone chemistry modifications (PN chemistry) in stereopure oligonucleotides as a significant advancement for the therapeutic oligonucleotide field. In the multitude of *in vitro* and *in vivo* (animal) studies highlighted in Wave’s papers, PN chemistry was shown to dramatically improve potency, distribution, and durability of effect. The papers explore the use of PN chemistry in stereopure silencing oligonucleotides (publication link) for central nervous system (CNS) diseases – designated as a Breakthrough Article by NAR — and stereopure splicing oligonucleotides (publication link) for neuromuscular diseases.

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

- WVE-N531 (PN-modified splicing oligonucleotide) is being evaluated in an open-label, intra-patient dose escalation 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.
- When comparing PN-modified compounds, including WVE-N531, to first-generation PS/PO (non-PN-modified) compounds, PN chemistry consistently leads to increased exon-skipping activity, increases in muscle exposure, longer half-life, and more durable effects in preclinical mouse and non-human primate studies. Based on an analysis of initial plasma PK from the starting single dose of WVE-N531 in Wave's ongoing clinical trial, there was a substantial increase in plasma concentrations and a clear increase in plasma half-life as compared to suvodirsen, Wave's first-generation PS/PO exon-skipping compound.

WVE-004 for C9orf72-associated amyotrophic lateral sclerosis (C9-ALS) and frontotemporal dementia (C9-FTD):

- FOCUS-C9, is an ongoing, double-blind, adaptive, Phase 1b/2a clinical trial of WVE-004. WVE-004 is an investigational stereopure PN-modified silencing oligonucleotide 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.
- In January 2022, the Alzheimer's Drug Discovery Foundation (ADDF) and The Association for Frontotemporal Degeneration (AFTD) announced they had partnered to support Wave's FOCUS-C9 clinical trial, specifically the evaluation of fluid biomarkers, functional assessments, and digital biomarkers used in the study, potentially leading to clinically meaningful endpoints to inform drug development for FTD. The decision to support the FOCUS-C9 trial was made following a review by members of the Treat FTD Fund Joint Steering Committee of Wave's Phase 1b/2a study plan, preclinical data supporting the program and expertise of the study team.

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

- SELECT-HD is an ongoing, double-blind, adaptive, Phase 1b/2a clinical trial of WVE-003. WVE-003 is an investigational stereopure PN-modified silencing oligonucleotide designed to selectively target the mutant allele of the *huntingtin* (mHTT) gene, while leaving the wild-type (healthy) HTT (wtHTT) protein relatively intact.
- In March 2022, Wave presented at the CHDI Foundation's 17th Annual HD Therapeutics Conference, including a poster titled "A novel quantitative wild-type huntingtin (wtHTT) protein biomarker method for human cerebrospinal fluid" that highlights Wave's wtHTT assay, which is intended to assess preservation of wtHTT protein in CSF in the setting of mHTT targeting, including in the ongoing SELECT-HD clinical trial.

Upcoming clinical milestones:

- Wave expects to share clinical data in 2022 for WVE-004, WVE-003, and WVE-N531 to provide insight into the clinical effects of PN chemistry and enable decision-making for each program.

ADAR editing therapeutic programs (RNA editing using endogenous ADAR enzymes)

Scientific presentations:

- In January 2022, Wave gave an oral presentation titled "*Towards the development of a therapeutic RNA editing platform*" at the 3rd International Conference on Base Editing – Enzymes and Applications Deaminet 2022, which highlighted Wave's RNA editing platform, the ability of AIMers to restore expression of functional protein in preclinical models *in vivo* and modulate protein-protein interactions *in vitro*.
- Wave leadership will present at the upcoming 3rd RNA Editing Summit on April 5 – 7, 2022 in Boston.

AATD program updates and upcoming milestones:

- Wave today announced new preclinical data demonstrating restoration of functional AAT protein in a transgenic mouse model with GalNAc-conjugated SERPINA1 AIMers. At 19 weeks, AIMer treatment resulted in approximately 60% RNA editing of SERPINA1 transcript and circulating serum AAT levels (18.5 uM) in AIMer treated mice that were approximately 5-fold greater than PBS-treated controls.

- Today, Wave also shared histological analysis that indicates reduction of liver aggregates in a transgenic mouse model at 19 weeks with AIMer treatment.
- In November 2021, Wave presented a poster at AASLD: The Liver Meeting, that included data demonstrating SERPINA1 AIMers achieve highly specific RNA editing *in vivo*, resulting in wild-type, M-AAT protein circulating in serum that was functional in a neutrophil elastase inhibition assay.
- Wave expects to select an AATD AIMer development candidate and initiate IND-enabling toxicology studies in the third quarter of 2022.

Fourth Quarter and Full Year 2021 Financial Results and Financial Guidance

Wave reported a net loss of $34.8 million in the fourth quarter of 2021, as compared to $28.8 million in the same period in 2020. Wave reported a net loss of $122.2 million for the year ended December 31, 2021, as compared to $149.9 million for the year ended December 31, 2020.

Revenue earned under the Takeda Collaboration in the fourth quarter of 2021 was $1.8 million, as compared to $9.4 million for the same period in 2020. The decrease in revenue year-over-year is mainly due to the amendment of Wave's collaboration with Takeda, which discontinued the Category 2 discovery research component of the Takeda Collaboration in exchange for an additional $22.5 million, which Wave received in October 2021 and accounted for in the third quarter of 2021. The Category 1 late-stage component of the Takeda Collaboration remains in effect and was unchanged by the amendment. During the year ended December 31, 2021, Wave earned $41.0 million under the Takeda Collaboration, as compared to $20.1 million earned under the Takeda Collaboration and the Pfizer Collaboration during the year ended December 31, 2020. The year-over-year increase is primarily driven by recognition of revenue related to the $22.5 million related to the Takeda Amendment.

Research and development expenses were $25.8 million in the fourth quarter of 2021 as compared to $30.0 million in the same period in 2020. Research and development expenses were $121.9 million in 2021, as compared to $130.9 million in 2020. The decrease in research and development expenses in the fourth quarter and full year 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 WVE-004, PRISM, including ADAR editing, and other ongoing programs.

General and administrative expenses were $12.1 million in the fourth quarter of 2021 as compared to $9.7 million in the same period in 2020. General and administrative expenses were $46.1 million in 2021, as compared to $42.5 million in 2020. The increase in general and administrative expenses in the fourth quarter of 2021 and full year was driven by increases in compensation-related and other external general and administrative expenses.

As of December 31, 2021, Wave had $150.6 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 of $122.2 million, partially offset by the receipt of $54.9 million in net proceeds under Wave's ATM equity program and funds of $52.5 million received from our collaboration with Takeda.

Wave expects that its existing cash and cash equivalents 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 fourth quarter and full year 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: 7694386. 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 initiation, site activation, patient recruitment, patient enrollment, dosing, generation of data for decision-making 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 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)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 150,564	$ 184,497
Current portion of accounts receivable	—	30,000
Prepaid expenses	6,584	10,434
Other current assets	5,416	5,111
Total current assets	162,564	230,042
Long-term assets:		
Property and equipment, net	22,266	29,198
Operating lease right-of-use assets	18,378	16,232
Restricted cash	3,651	3,651
Other assets	148	115
Total long-term assets	44,443	49,196
Total assets	$ 207,007	$ 279,238
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 7,281	$ 13,795
Accrued expenses and other current liabilities	14,861	11,971
Current portion of deferred revenue	37,098	91,560
Current portion of operating lease liability	4,961	3,714
Total current liabilities	64,201	121,040
Long-term liabilities:		
Deferred revenue, net of current portion	77,479	41,481
Operating lease liability, net of current portion	24,955	25,591
Other liabilities	—	474
Total long-term liabilities	102,434	67,546
Total liabilities	$ 166,635	$ 188,586
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at December 31, 2021 and 2020	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 59,841,116 and 48,778,678 shares issued and outstanding at December 31, 2021 and 2020, respectively	749,851	694,085
Additional paid-in capital	87,980	71,573
Accumulated other comprehensive income	181	389
Accumulated deficit	(805,514)	(683,269)
Total shareholders' equity	32,498	82,778
Total liabilities, Series A preferred shares and shareholders' equity	$ 207,007	$ 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 December 31,		Twelve Months Ended December 31,	
	2021	2020	2021	2020
Revenue	$ 1,765	$ 9,439	$ 40,964	$ 20,077
Operating expenses:				
Research and development	25,761	30,033	121,875	130,944
General and administrative	12,114	9,719	46,105	42,510
Total operating expenses	37,875	39,752	167,980	173,454
Loss from operations	(36,110)	(30,313)	(127,016)	(153,377)
Other income, net:				
Dividend income and interest income, net	5	24	30	568
Other income, net	1,116	659	4,537	2,058
Total other income, net	1,121	683	4,567	2,626
Loss before income taxes	(34,989)	(29,630)	(122,449)	(150,751)
Income tax benefit	204	841	204	841
Net loss	$ (34,785)	$ (28,789)	$ (122,245)	$ (149,910)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (0.61)	$ (0.59)	$ (2.36)	$ (3.82)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	57,190,742	48,777,001	51,825,566	39,227,618
Other comprehensive income (loss):				
Net loss	$ (34,785)	$ (28,789)	$ (122,245)	$ (149,910)
Foreign currency translation	(77)	88	(208)	122
Comprehensive loss	$ (34,862)	$ (28,701)	$ (122,453)	$ (149,788)

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

March 3, 2022

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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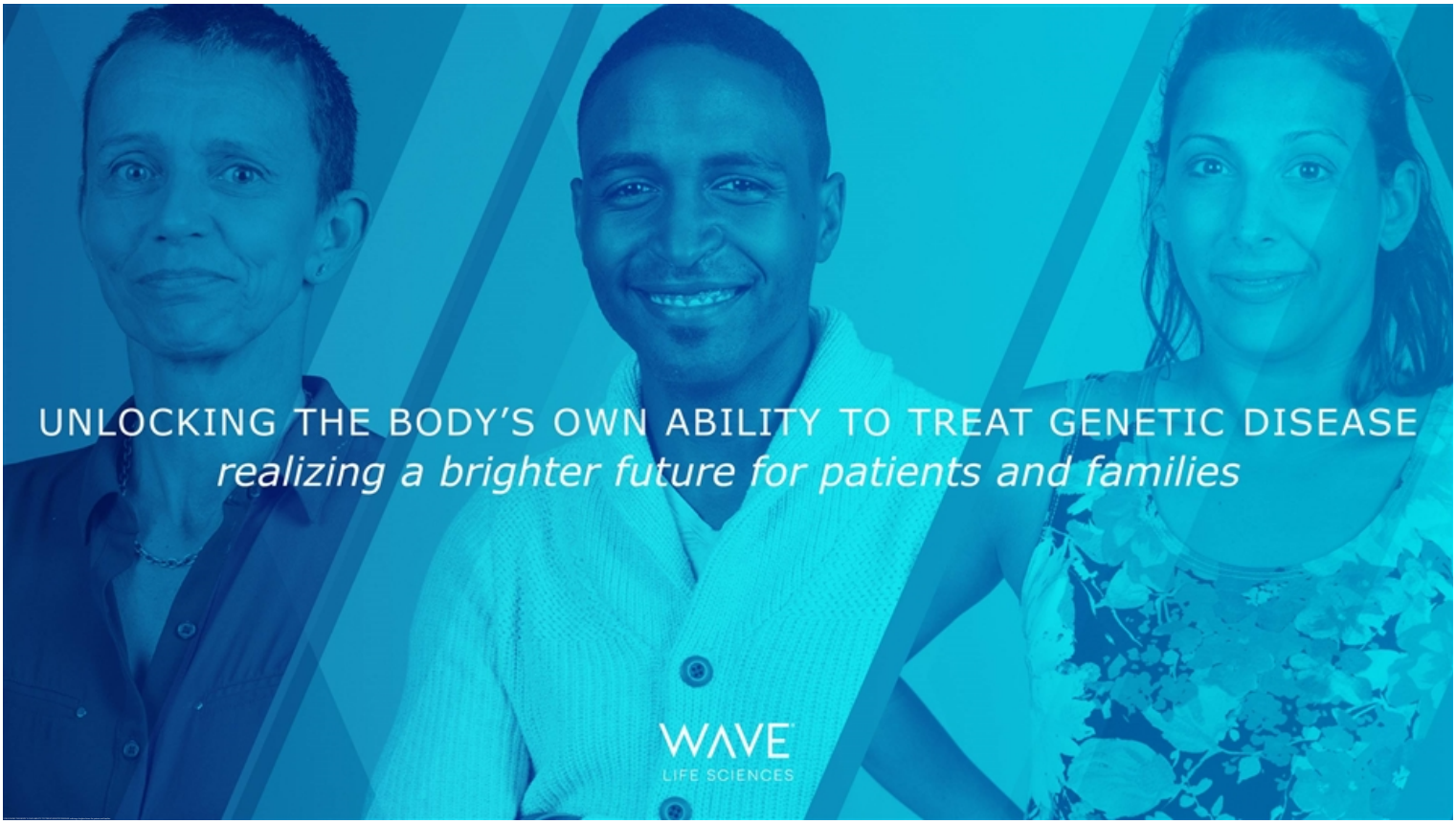
UNLOCKING THE BODY'S OWN ABILITY TO TREAT GENETIC DISEASE
realizing a brighter future for patients and families
WAVE
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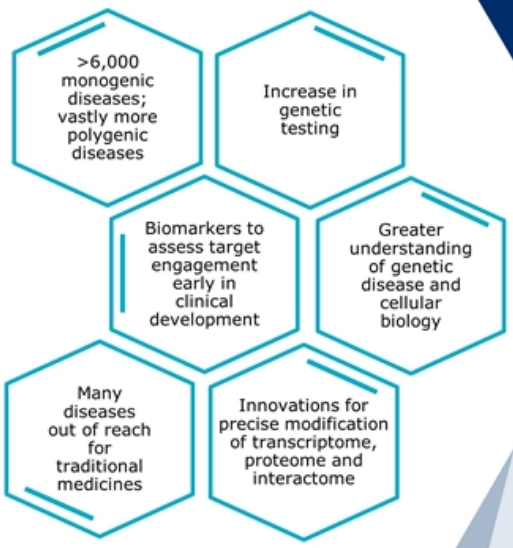
Building a leading genetic medicines company

LEVERAGING THE ONGOING GENETIC REVOLUTION



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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

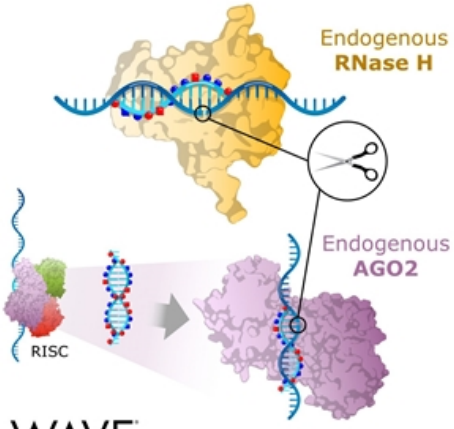
Address underlying genetic drivers of disease	Changes erroneous messages, not erroneous code
Simplified delivery	Freely taken up by cells in multiple tissues or compatible with simple ligands – no need for complex delivery vehicles
Durable effects	Continued progress towards longer dosing intervals while 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

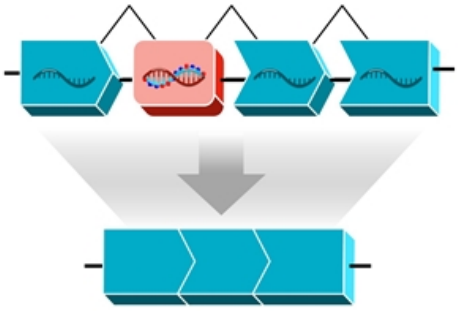
Silencing

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



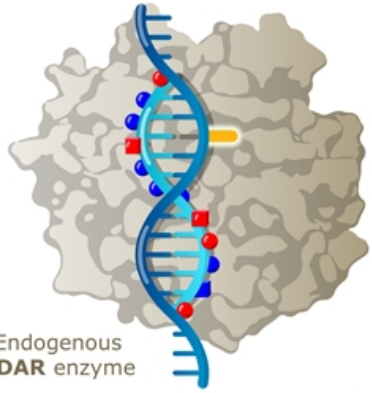
Splicing

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



RNA Base Editing

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



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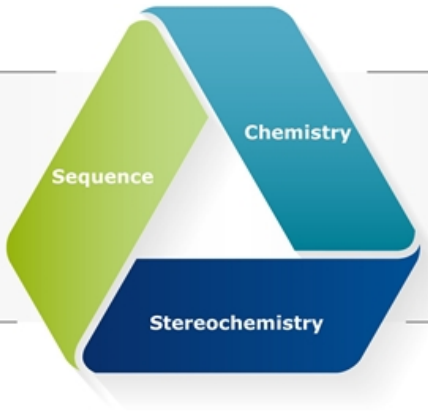
PRISM Unlocking the body's own ability to treat genetic disease

DESIGN

Unique ability to construct single isomers and control three structural features of oligonucleotides 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

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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*

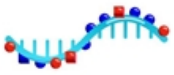
PRISM controls stereochemistry throughout drug discovery and development process

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, **single-isomer** RNA therapeutics



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

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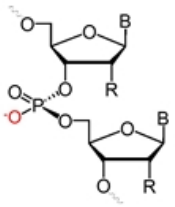
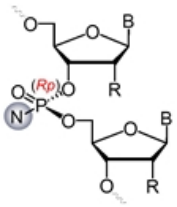
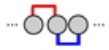
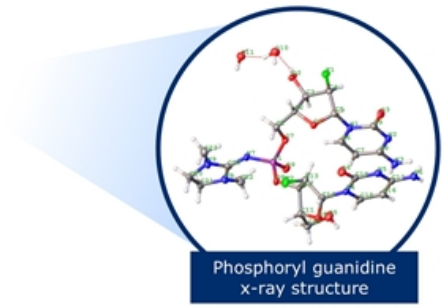
[1]Jahns et al., NAR, 2021; Hansen, et al. 2021; Funder, Albaek et al. 2020

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

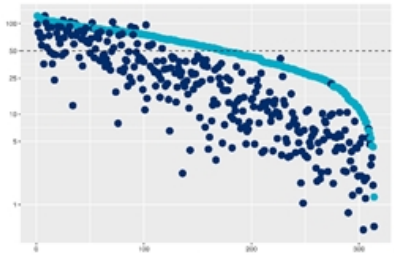
WAVE LIFE SCIENCES

PO: phosphodiester PS: phosphorothioate

Potency is enhanced with addition of PN modifications across modalities

Silencing

Target knockdown (% remaining)

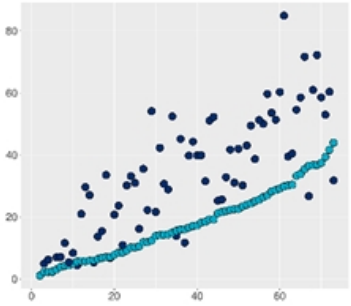


Ranked by potency of reference PS/PO compound

Improved knockdown

Splicing

% Skipping

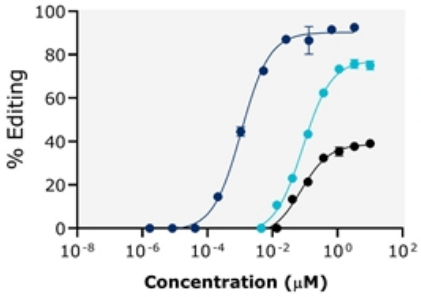


Ranked by potency of reference PS/PO compound

Improved skipping

Editing

% Editing



Improved editing

PS/PO/PN
PS/PO (Stereopure)
PS/PO (Stereorandom)

PS/PO reference compound
PS/PN modified compound

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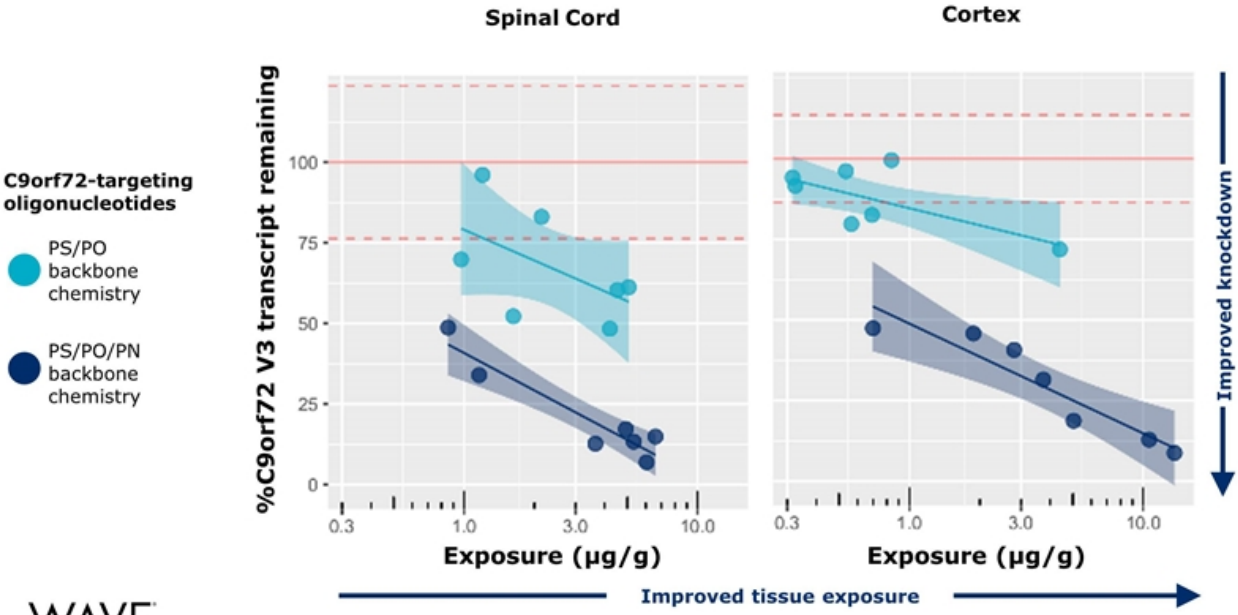
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake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

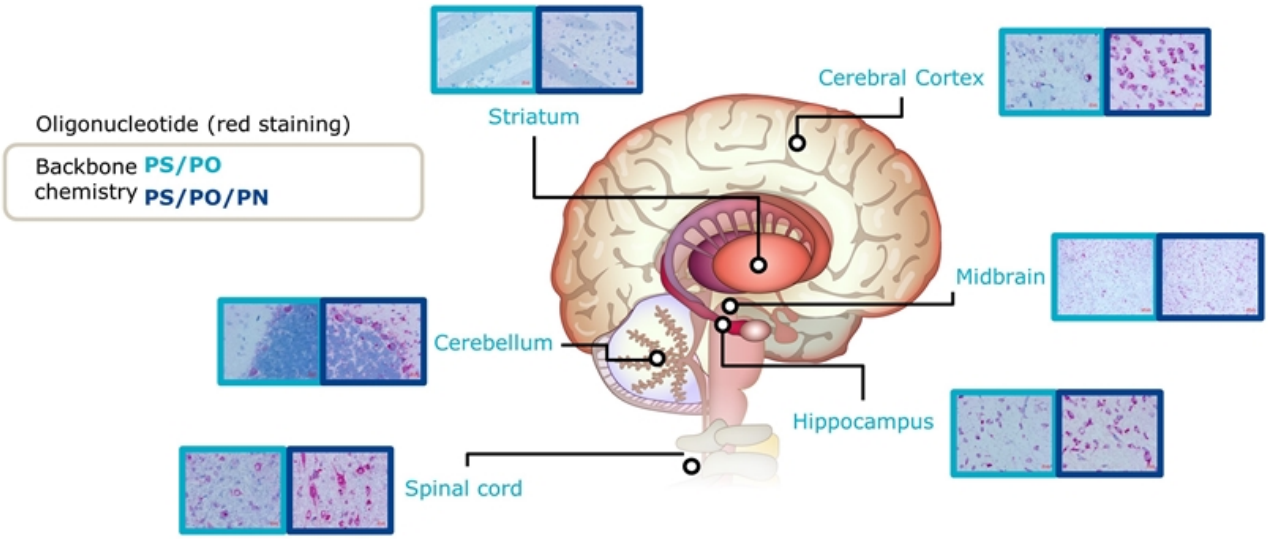
Adding PN chemistry modifications to C9orf72-targeting oligonucleotides improved potency *in vivo*



Target knockdown: Liu, TIDES poster 2021; Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis. Manuscript submitted.

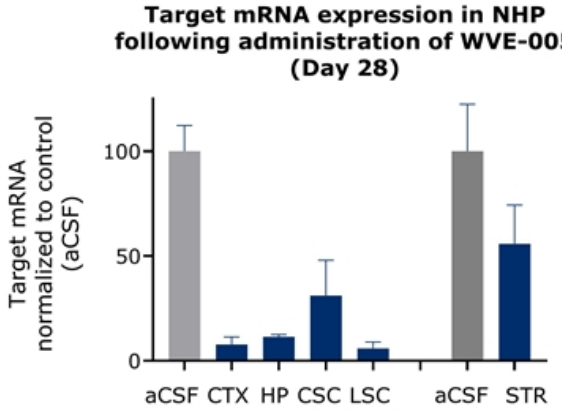
PN chemistry improves distribution to CNS

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



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.

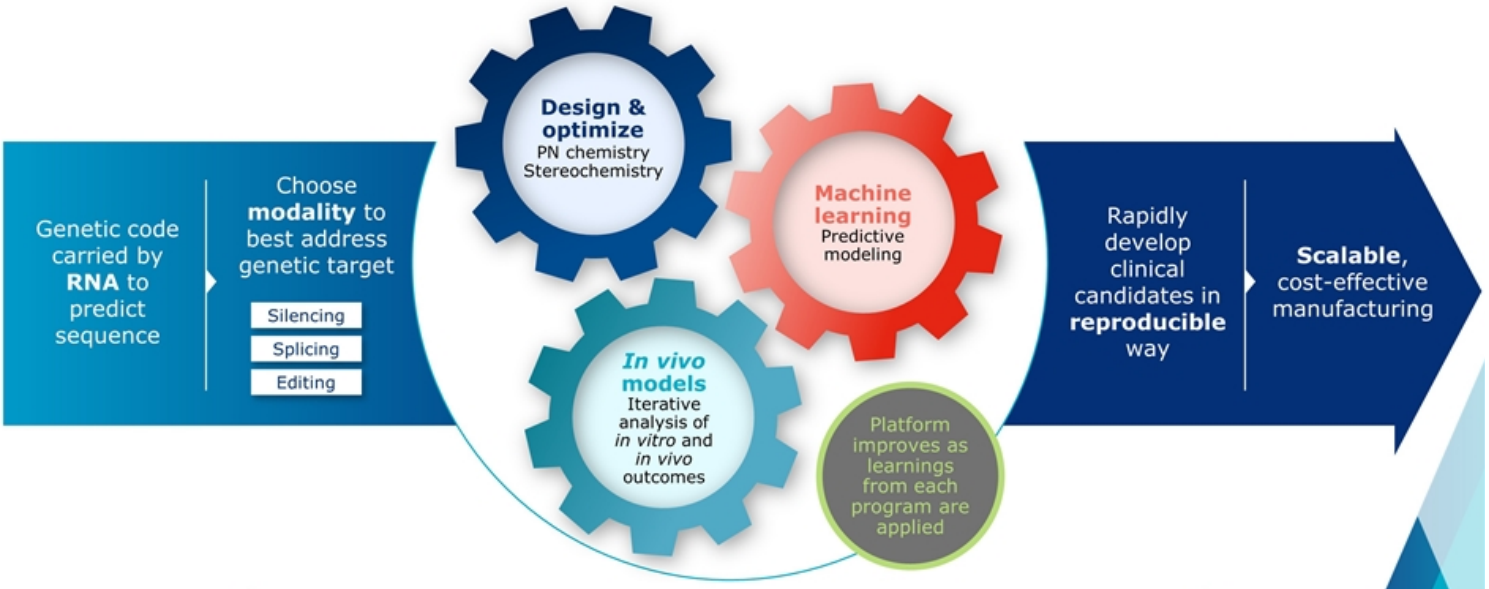
Single intrathecal dose in NHP leads to substantial and widespread target mRNA reduction throughout the CNS



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

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 platform is continuously improving



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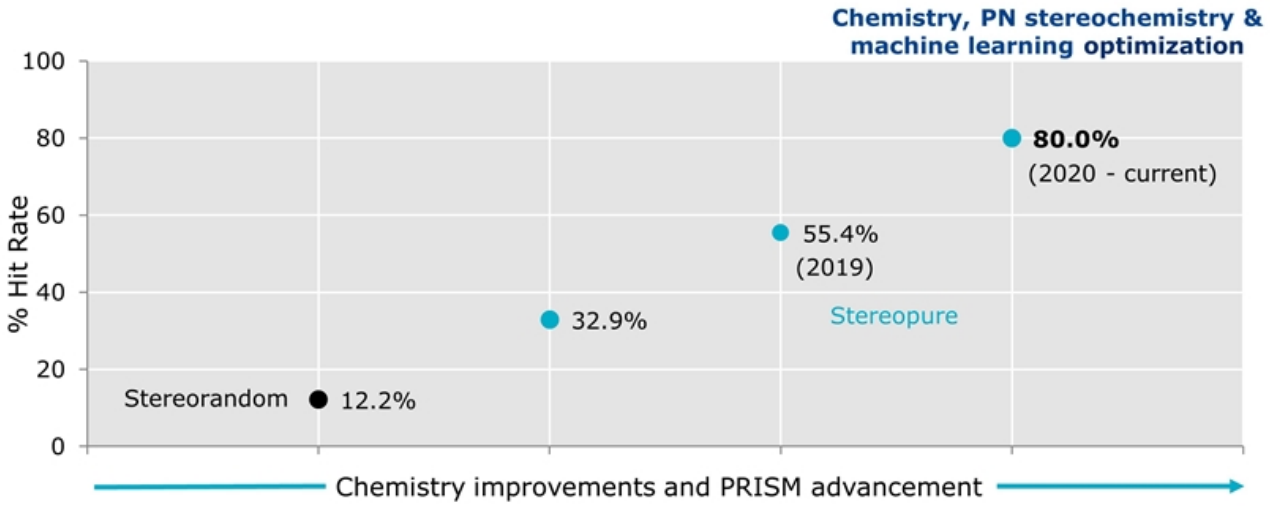
Continuous definition of design principles deployed across programs

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

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



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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

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

Robust portfolio of stereopure, PN-modified oligonucleotides

WAVE LIFE SCIENCES

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)

- 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

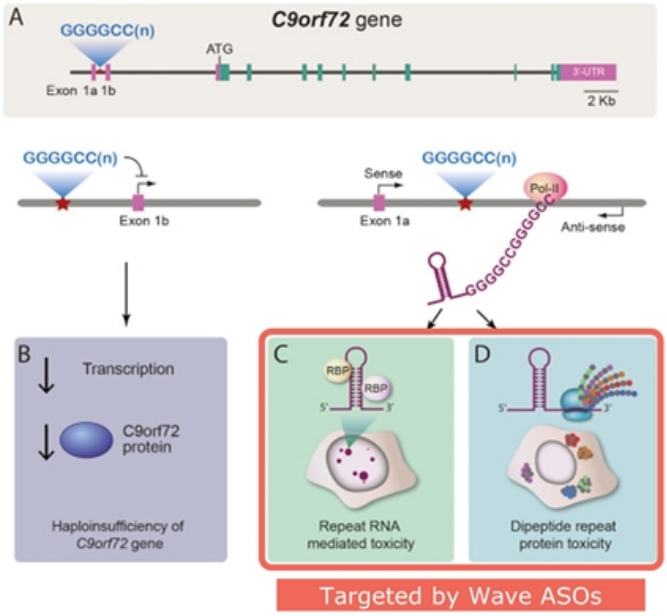
Including patients with C9-associated ALS, FTD or both

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

C9orf72 repeat expansions: Mechanisms of cellular toxicity in ALS and FTD

- 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



WAVE LIFE SCIENCES

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

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

- C9orf72 protein is important for normal regulation of neuronal function and the immune system
- WVE-004 targets hexanucleotide repeat containing transcript variants that lead to loss of normal C9orf72 function and production of pathological mRNA products and toxic dipeptide repeat (DPR) proteins
- Poly-GP is an important DPR transcribed from sense and antisense toxic mRNA transcripts
- Poly-GP is a sensitive biomarker of target engagement and reductions of mRNA transcripts and other toxic proteins by WVE-004
- Neurofilament Light-Chain (NfL) measurements will provide important insight into potential for neuroprotection

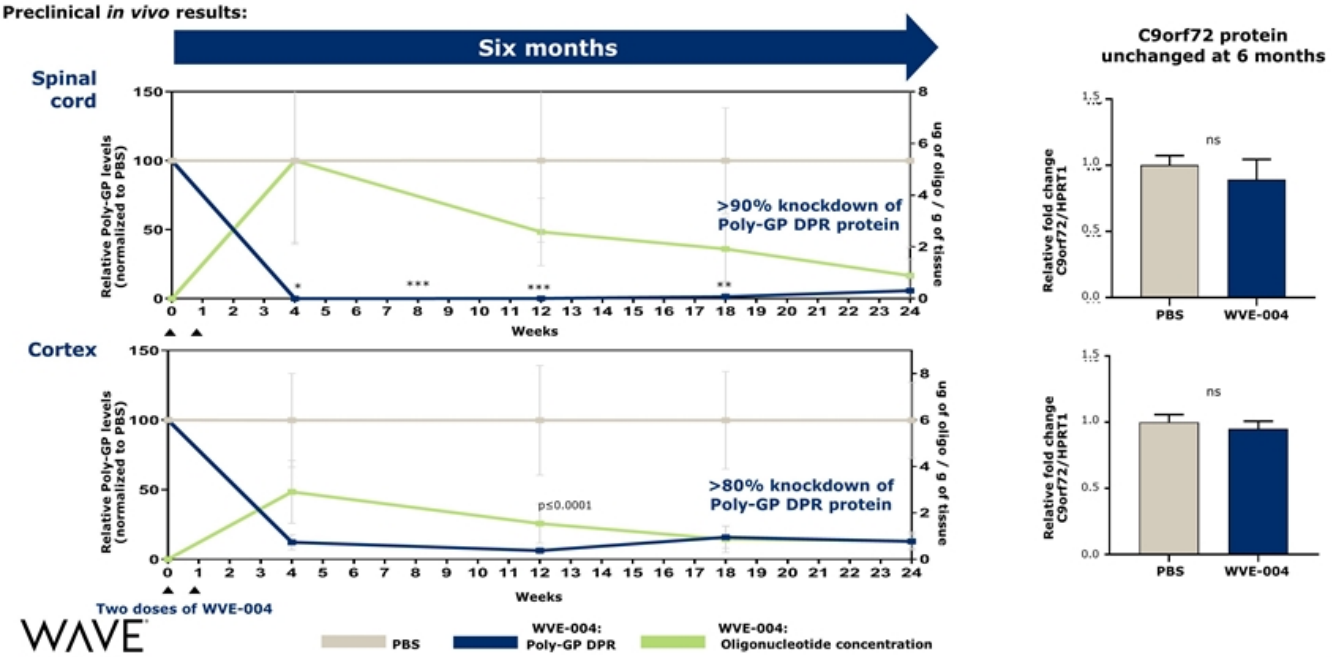
Variant-selective targeting could address multiple potential drivers of toxicity

WAVE LIFE SCIENCES

Liu et al, Nature Communications, 2021

WVE-004 treatment resulted in durable reduction of Poly-GP in spinal cord and cortex after 6 months

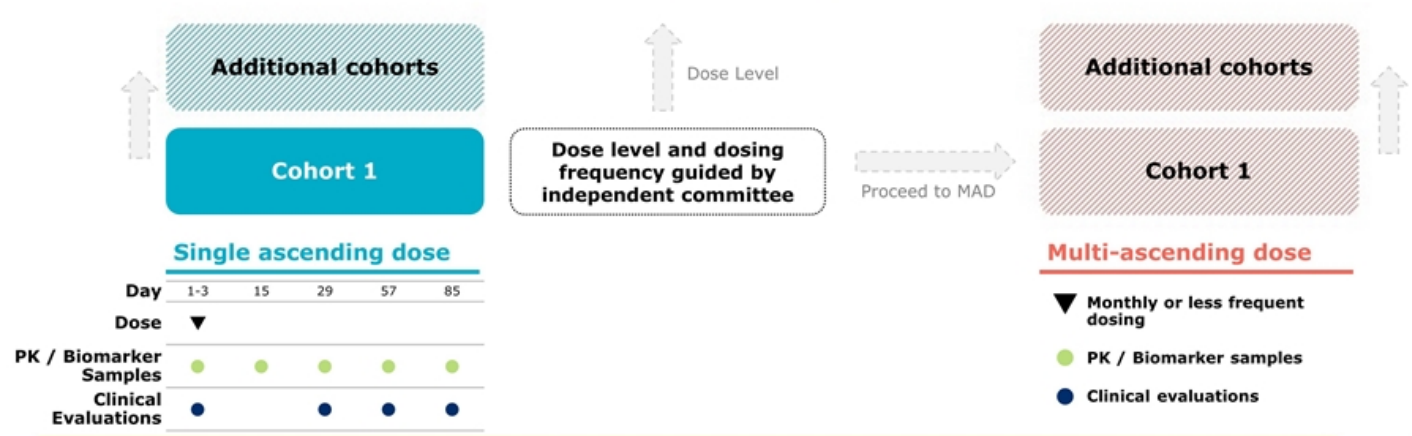
Preclinical *in vivo* results:



WAVE LIFE SCIENCES

Full results presented at the 31st International Symposium on ALS/ MND (December 2020); 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

FOCUS-C9 clinical trial: Dose level and dosing frequency guided by independent committee



FOCUS C9

Clinical evaluations
- Safety and tolerability
- ALSFRS-R
- CDR-FTDLD
- FVC
- HHD

Key biomarkers:
- PolyGP DPR in CSF
- p75NTRECD in urine
- NfL in CSF

WAVE LIFE SCIENCES

PK: pharmacokinetic

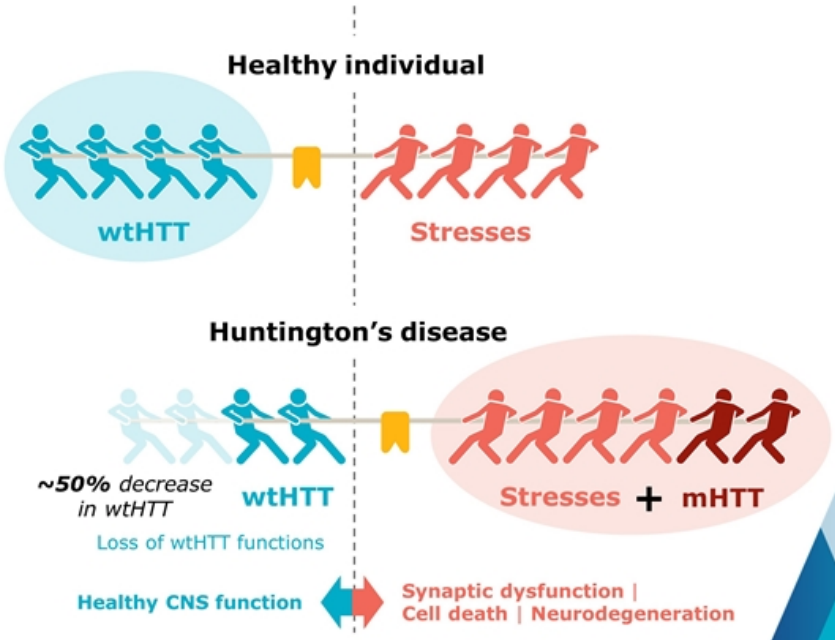
Adaptive cohorts

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]

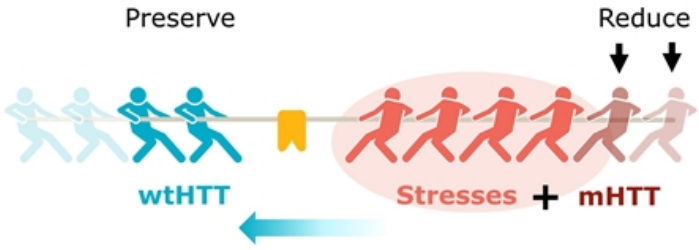
WAVE LIFE SCIENCES

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

WVE-003: Allele-selective approach to treating HD

Wave has the 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



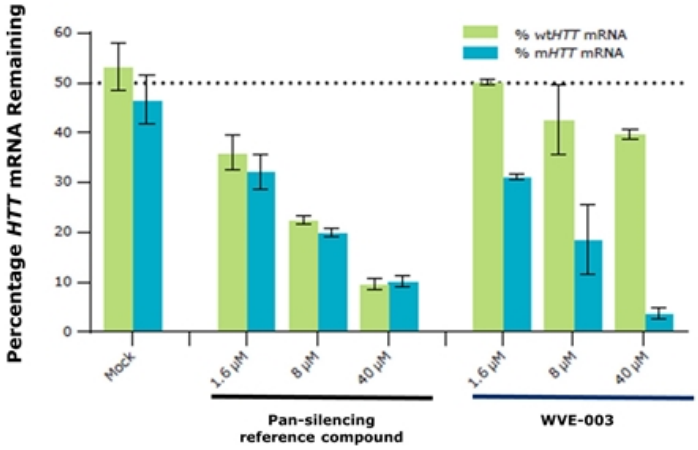
Only an allele-selective approach is designed to address <u>both</u> toxic gain of function and toxic loss of function drivers of HD

WAVE LIFE SCIENCES

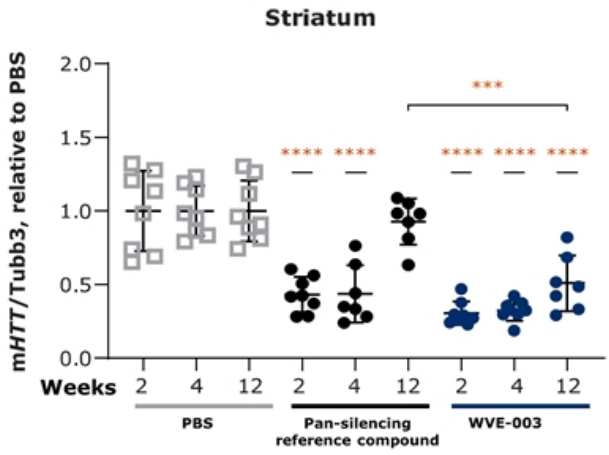
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

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 BACHD 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

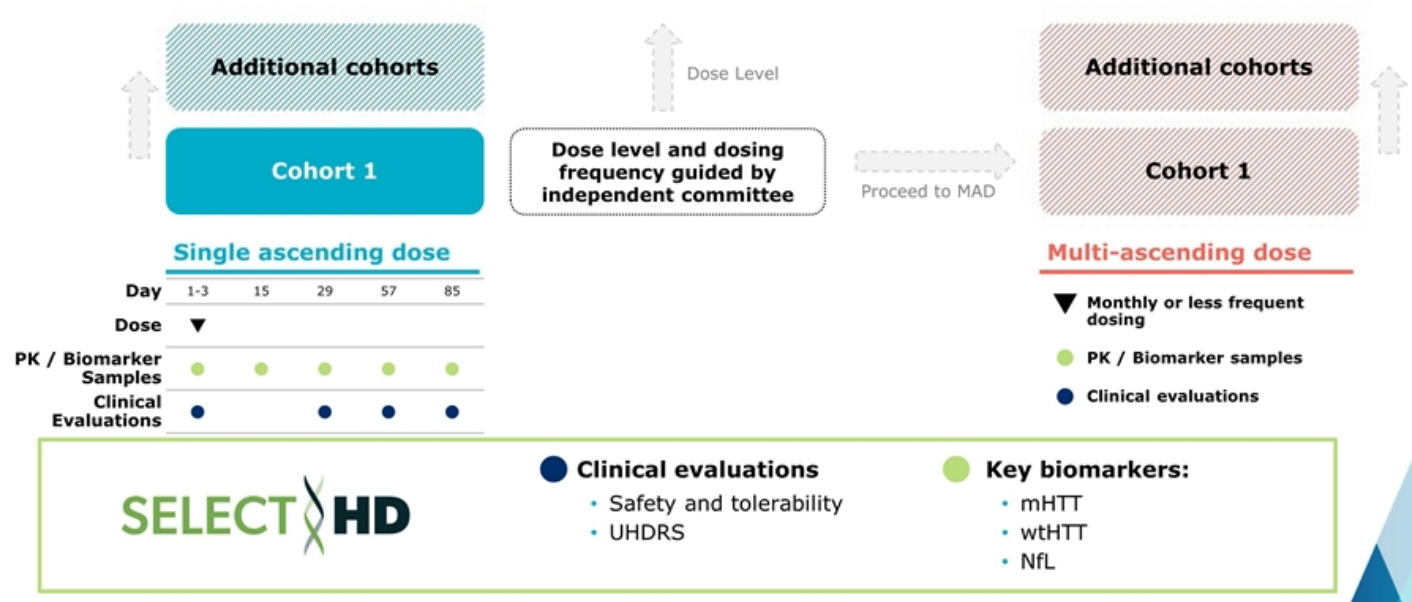
Anticipated mHTT knockdown in **cortex** and **striatum** based on PK-PD modeling

Clinical 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
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

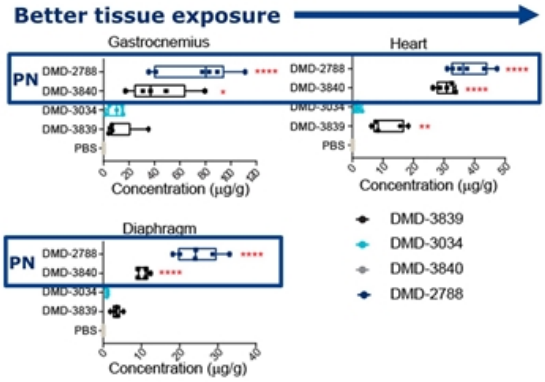
Adaptive cohorts

WVE-N531

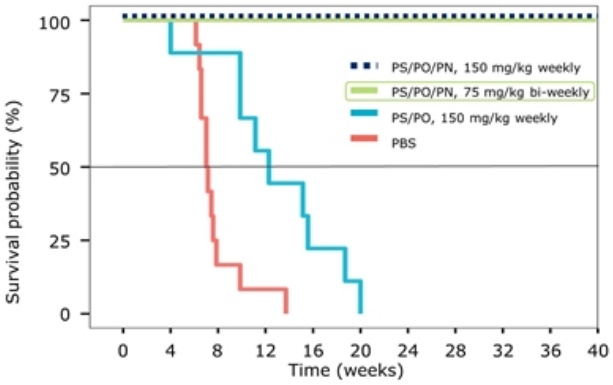
Duchenne muscular dystrophy

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

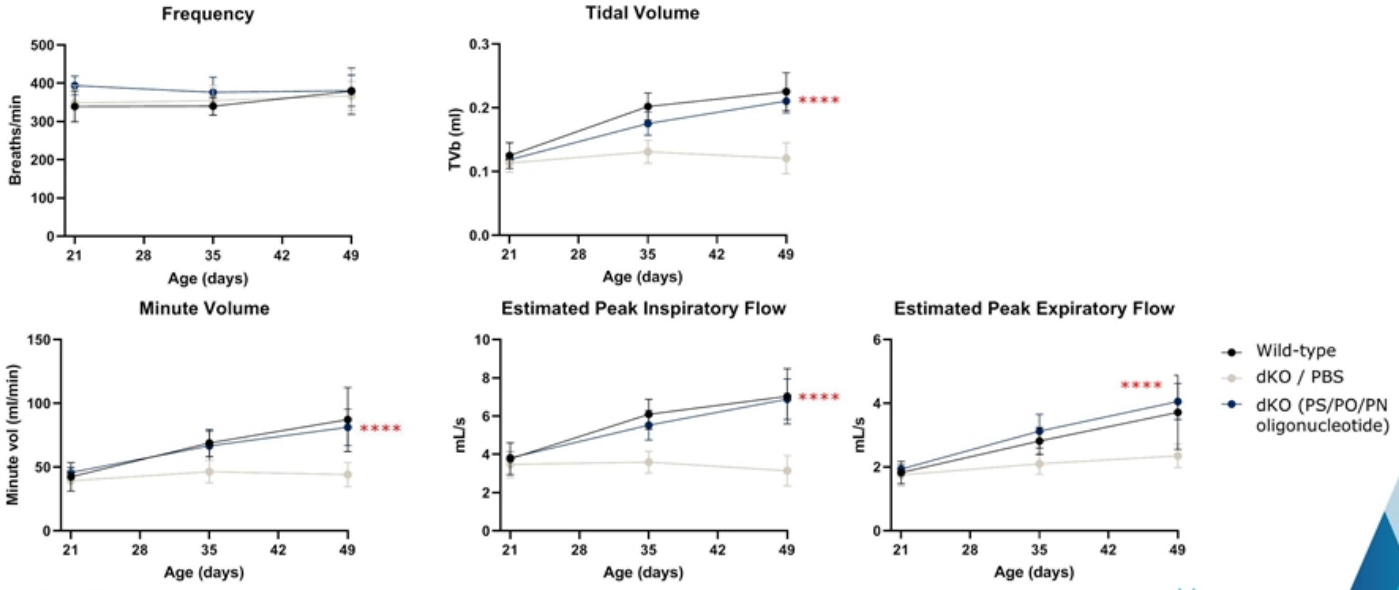


Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

WAVE LIFE SCIENCES

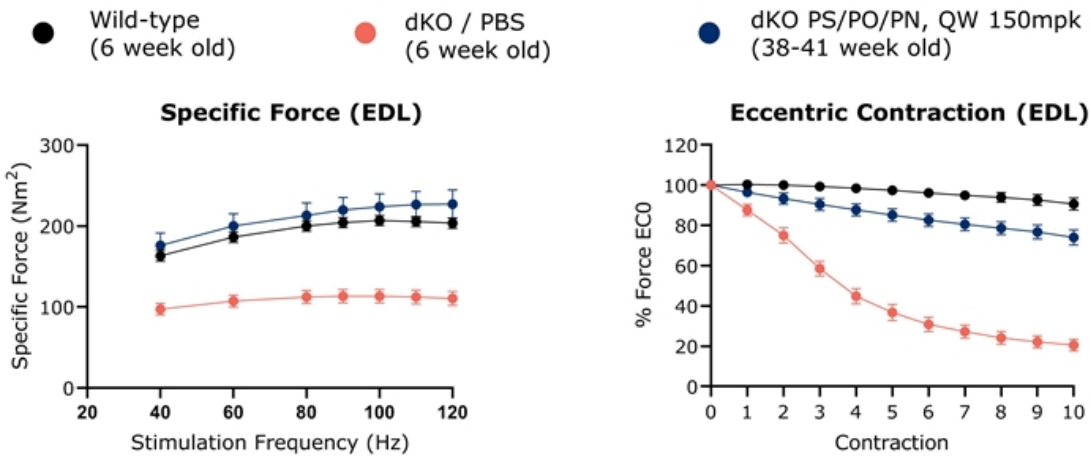
Kandasamy et al., 2022; doi: 10.1093/nar/gkac018

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



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

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: First splicing candidate to use PN chemistry

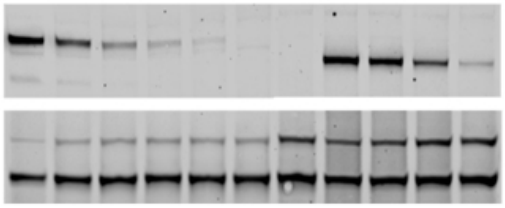
Duchenne muscular dystrophy

- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function.
- Current disease modifying treatments have demonstrated minimal dystrophin expression and clinical benefit has not been established.
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide.

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



WAVE LIFE SCIENCES

WVE-N531: PN chemistry enhances muscle distribution and exon-skipping 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

WVE-N531 leads to exon-skipping in NHPs at doses significantly lower than suvodirsen

6 weekly doses of 3 mg/kg

Healthy NHPs have normal levels of dystrophin, but target engagement can be assessed by detection of skipped transcript

WAVE LIFE SCIENCES

Non-human primates (NHPs) received 6 x weekly IV infusions of PBS or 3, 7, or 25 mg WVE-N531 (n=2 per dose); necropsied on day 38.
Exon 53 skipping quantified by RT-PCR; W, week; HED: Human equivalent dose

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

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

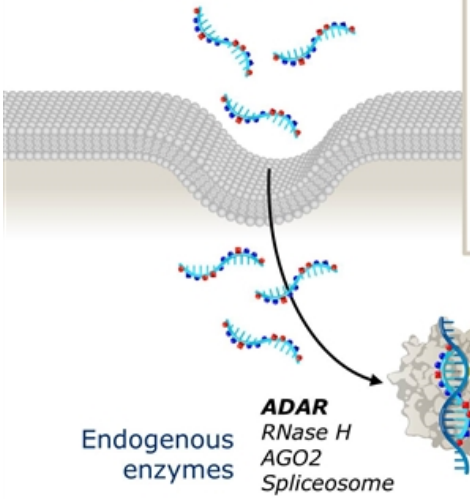
WAVE
LIFE SCIENCES

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



- First publication (1995) using oligonucleotide to edit RNA with endogenous ADAR[1]
- Wave goal: Expand toolkit to include editing by unlocking ADAR with PRISM oligonucleotides

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

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

Endogenous enzymes

ADAR
RNase H
AGO2
Spliceosome

ADAR enzymes

- 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

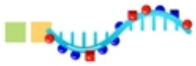
WAVE LIFE SCIENCES

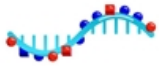
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995

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**

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Opportunity for novel and innovative AIMer therapeutics

Correct driver mutations with AIMers

Examples

AATD

Rett syndrome

Recessive or dominant genetically defined diseases

Restore or correct protein function

- >32,000 pathogenic human SNPs[2]; Tens of thousands of potential amenable disease variants[1]
- ~12% of all reported disease-causing mutations are single point mutations that result in a premature stop codon[3]
- Initial focus on correcting driver mutations of genetic hepatic diseases with clinically-proven GalNAc-mediated delivery

Modulate protein interactions with AIMers

Upregulate expression

Modify function

Modulate protein-protein interaction

Post-translational modification

Alter folding or processing

Examples

Cardiometabolic
Oncology
Immunology
Neurological disorders

- Large patient populations
- Human Reference Interactome documents >50K protein-protein interactions involving >8K proteins[4]
- >90K Post-translational modifications across ~30K proteins mapped,[5] thousands associated with disease[6]

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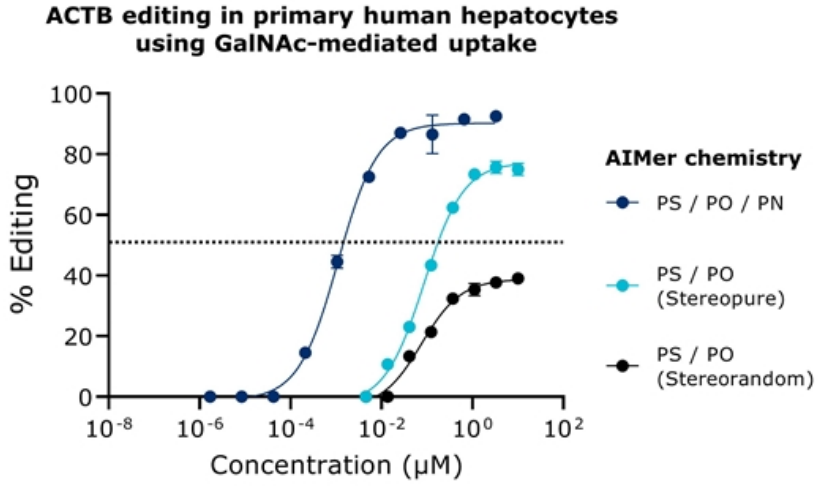
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1]ClinVar database [2]Gaudeli NM et al. *Nature* (2017) [3]Keeling KM et al., Madame Curie Bioscience Database 2000-2013 [4]Luck, K et al. *Nature* (2020)
[5]Prasad, TSK et al. *Nucleic Acids Research* (2009) [6]Huang, K et al. *Nucleic Acids Research* (2016)

Stereochemistry and PN chemistry enhance potency and editing efficiency of AIMers



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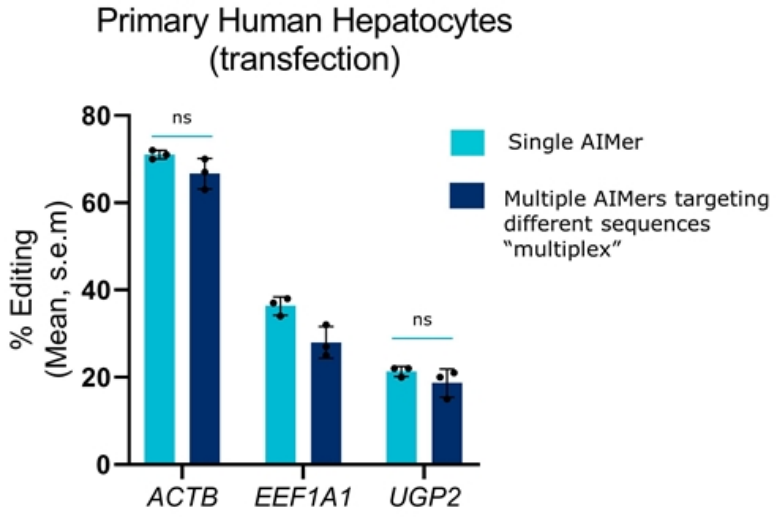
Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

PRISM

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

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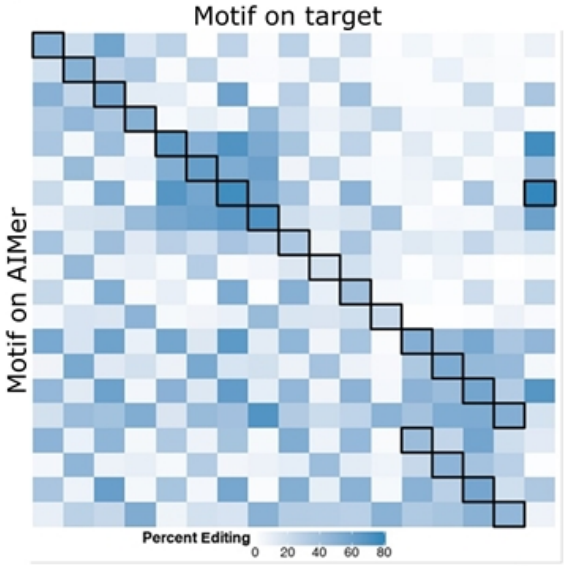
Percentage A-to-I editing detected on the indicated transcripts in presence of 20 nM each of a single (Isolated) or multiple (Multiplex) AIMers after transfection of primary human hepatocytes (left). Data are presented as mean ± SEM, n=3. P values as determine by two-tailed Welch's t-test are indicated. NTC non-targeting control. Manuscript submitted.

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

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



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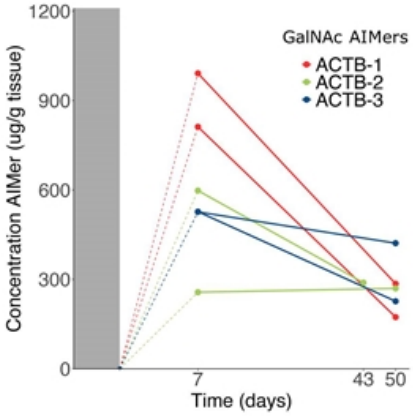
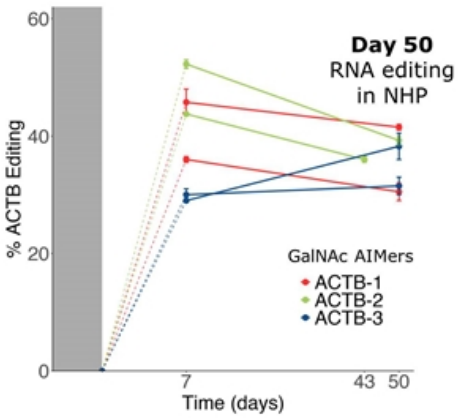
Learnings inform design principles deployed across future targets

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

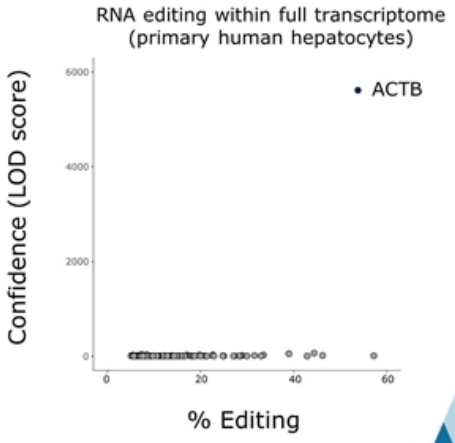
AIMers detected in liver of NHP at Day 50 (PK)



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

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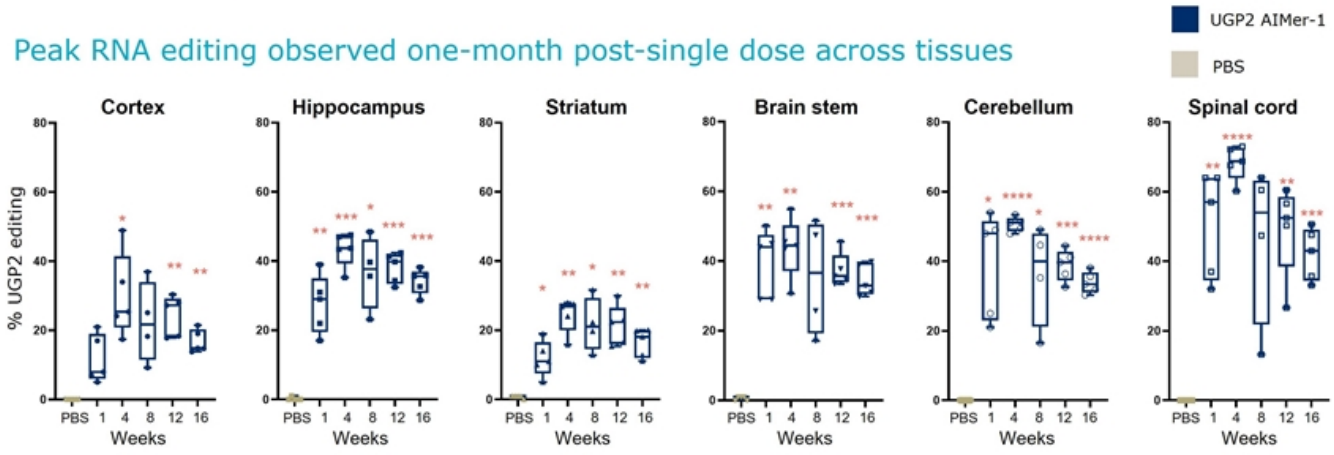
Manuscript in press. Left: AIMer PK C: 5mg/kg SC: Day 1,2,3,4,5; Liver biopsy; Right: Dosed 1um AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify on / off-target editing; plotted circles represent sites with LOD>3. NHP: non-human primate; ACTB: Beta-actin

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%**

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Transgenic huADAR mice administered 100 μg 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

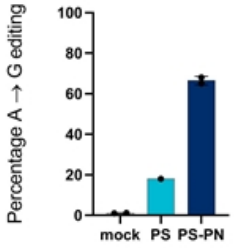
Variant base

ADAR editing site

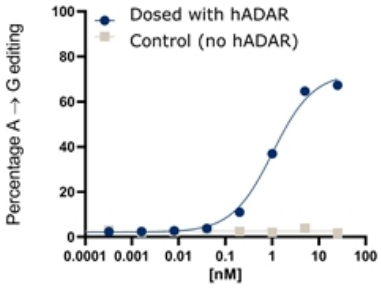
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

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

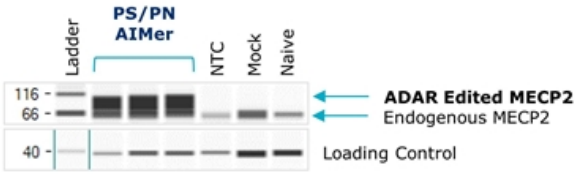
PN chemistry improved editing efficiency *in vitro*



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



Full length MECP2 protein is expressed following ADAR editing



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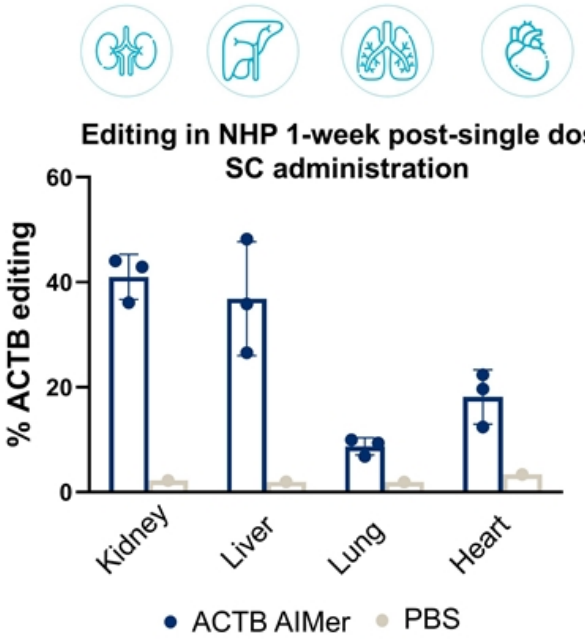
293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold 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.

Achieving productive editing in multiple NHP tissues with unconjugated systemic AIMer delivery

- ✓ GalNAc-conjugated *(Targeted - subcutaneous)*
- ✓ Unconjugated *(Local – IVT, IT)*
- ✓ **Unconjugated *(Systemic)***

- NHP study demonstrated productive editing in kidney, liver, lung and heart with single subcutaneous dose



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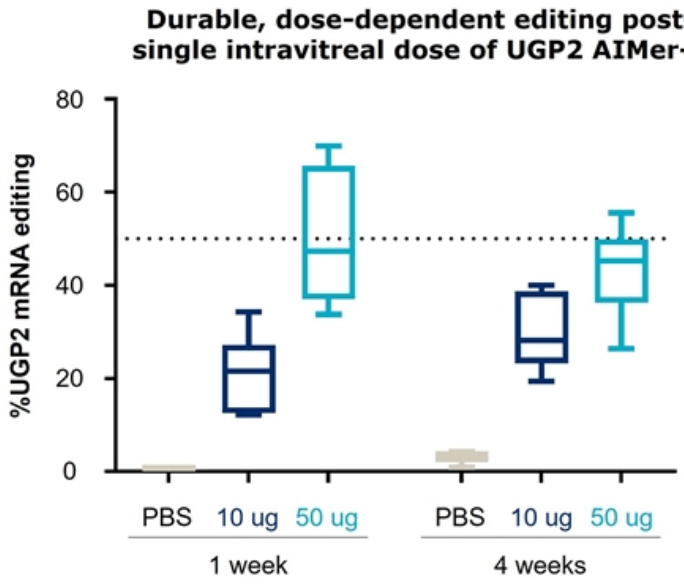
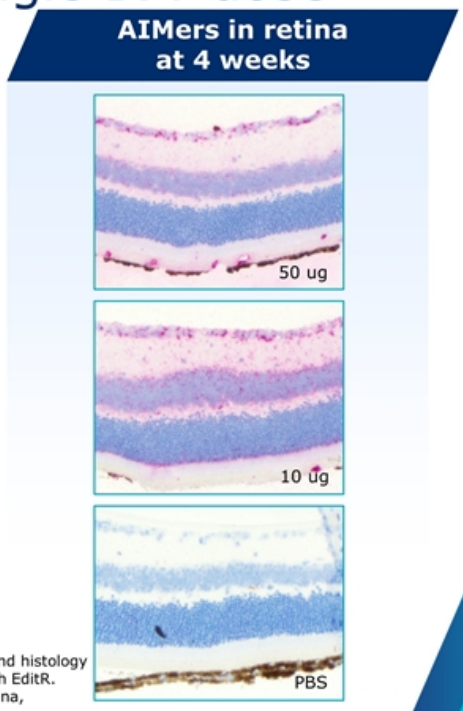
NHP: non-human primate; ACTB: Beta-actin
Dose: 50 mg/kg SC on Day 1 Necropsy for mRNA (ACTB Editing) Day 8

ADAR editing: Up to 50% editing *in vivo* in posterior of eye one month post-single IVT dose





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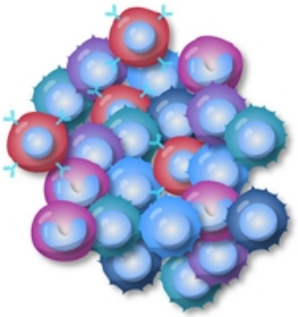
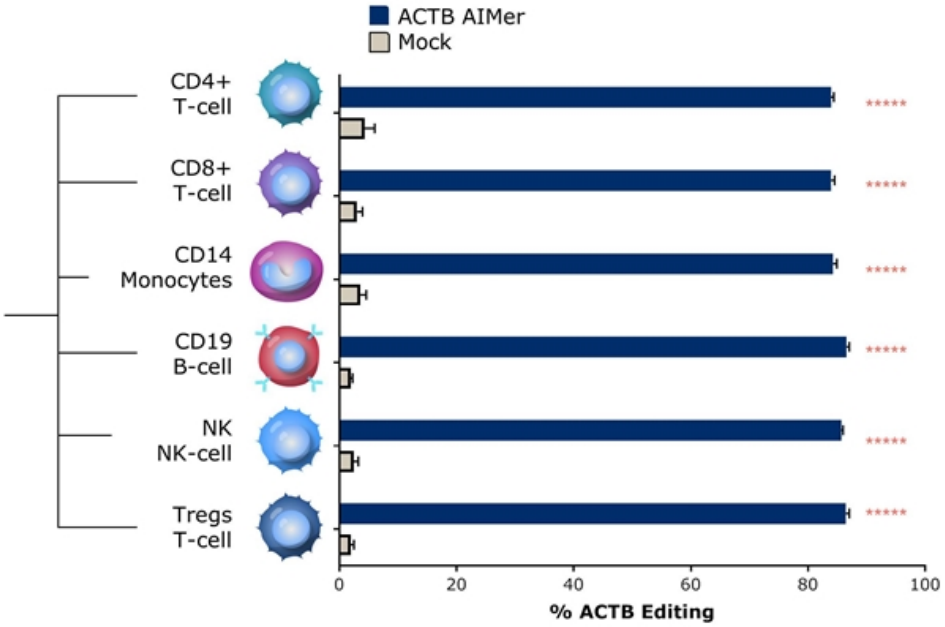
Mice received a single IVT injection (10 or 50 ug AIMer), and eyes were collected for RNA analysis and histology 1 or 4 weeks later. Left: editing evaluated by Sanger sequencing, and % RNA editing calculated with EditR. Right: FFPE and RNA scope assay specific for AIMer, red = oligo, blue = nuclei. Posterior region: retina, choroid, sclera.

Achieving productive editing in multiple immune cell types with AIMers *in vitro*

Human peripheral blood mononuclear cell (PBMC)



Activate (PHA) → Dose → Sort



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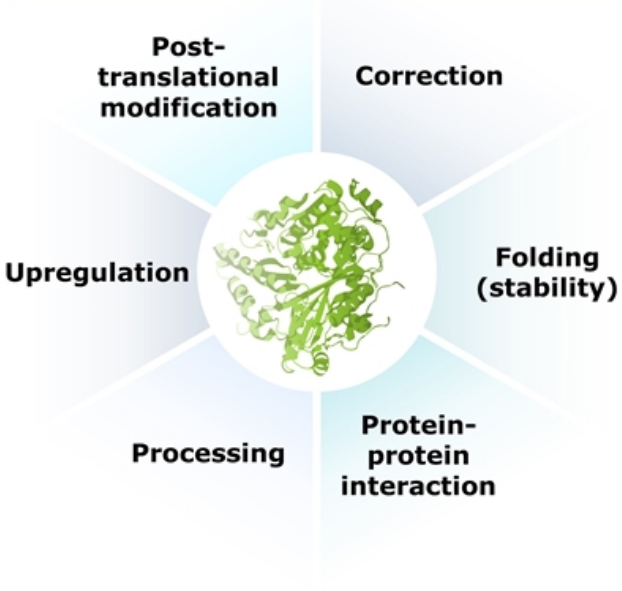
Human PBMCs dosed with 10 uM ACTB AIMers, under activating conditions (PHA). After 4 days, different cell types isolated, quantitated for editing %. ACTB: Beta-actin; Two-way ANOVA followed by post hoc comparison per cell line. P values were Bonferroni-corrected for multiple hypotheses

Expanding addressable disease target space using ADAR editing to modulate proteins

ADAR editing of mRNA

Restore or modify protein function



Impact diseases

Examples:

- Familial epilepsies
- Neuropathic pain
- Neuromuscular disorders
- Dementias
- Haploinsufficient diseases
- Loss of function

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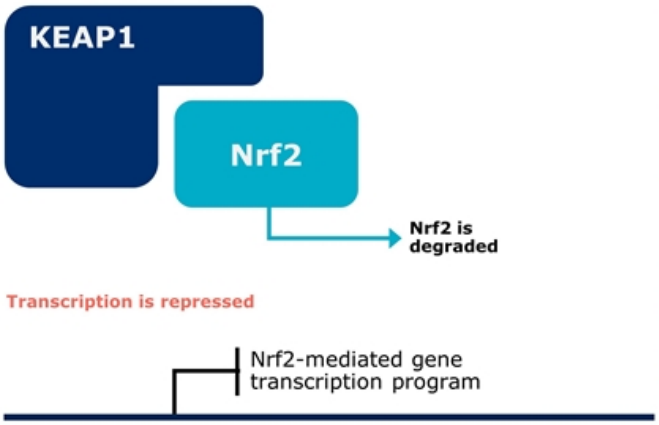
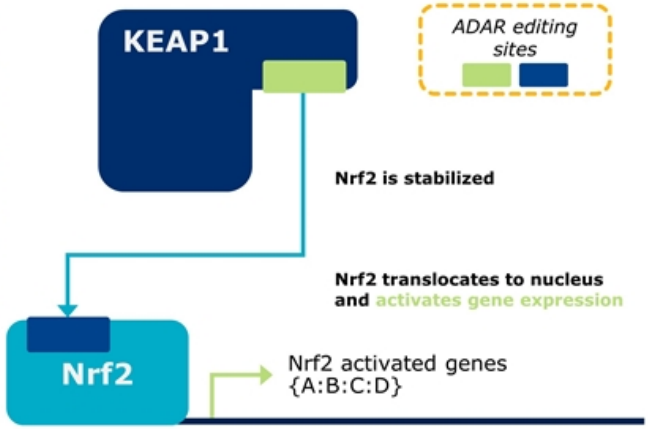
ADAR to modify protein-protein interactions

Basal conditions



KEAP1 binds Nrf2, targeting Nrf2 for proteosomal degradation and repressing Nrf2 mediated gene transcription

ADAR modified pathway



ADAR editing to change one amino acid in KEAP1 or Nrf2 could allow for stabilization of Nrf2 and activation of Nrf2 mediated gene transcription

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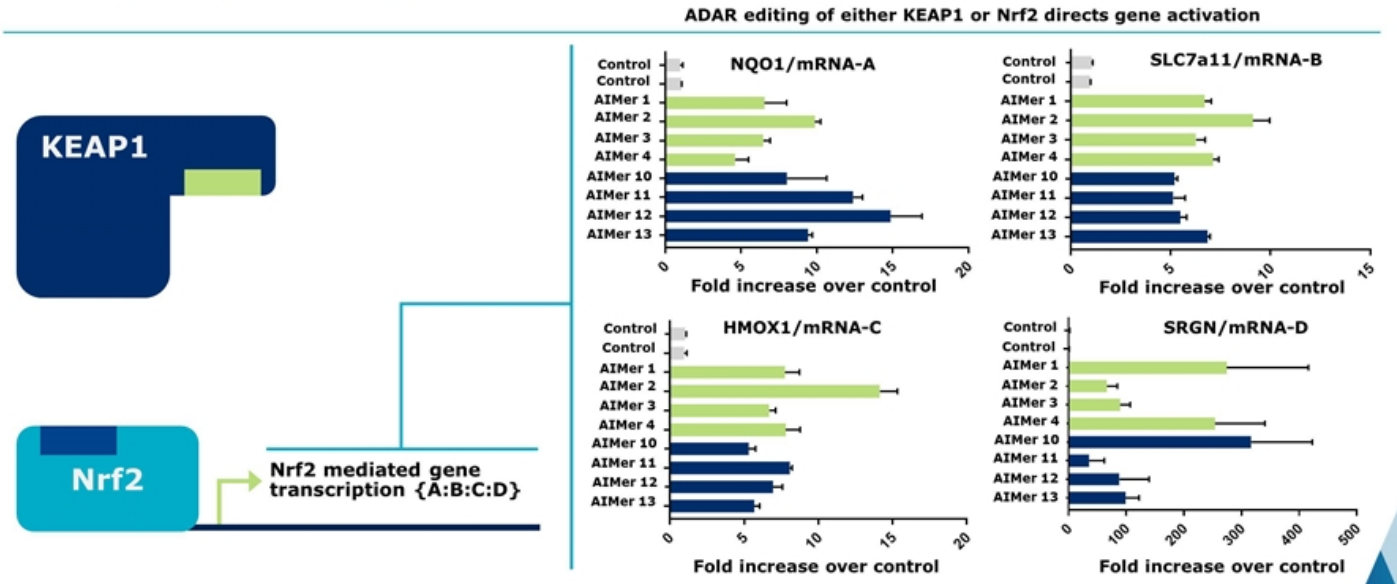
ADAR editing activates multiple genes confirming disrupted protein-protein interaction *in vitro*



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Gene expression quantified by PCR (n=2)

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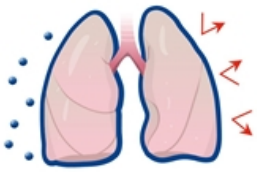
Alpha-1 antitrypsin deficiency

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

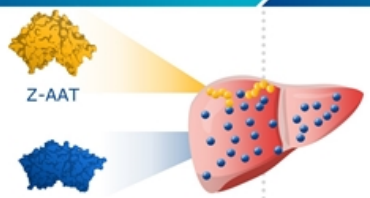
Wave ADAR editing approach addresses all goals of treatment:

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



M-AAT reaches lungs to protect from proteases

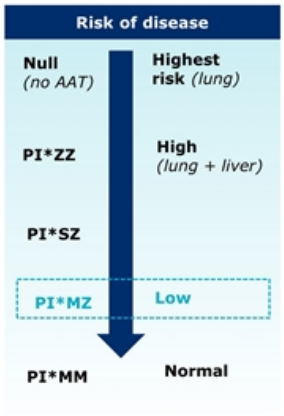
2) Reduce Z-AAT protein aggregation in liver



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)

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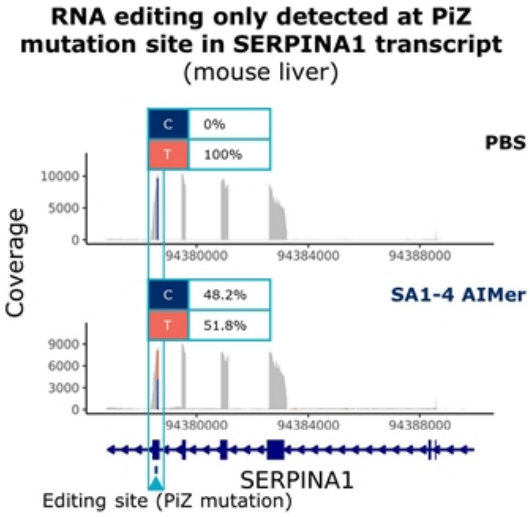
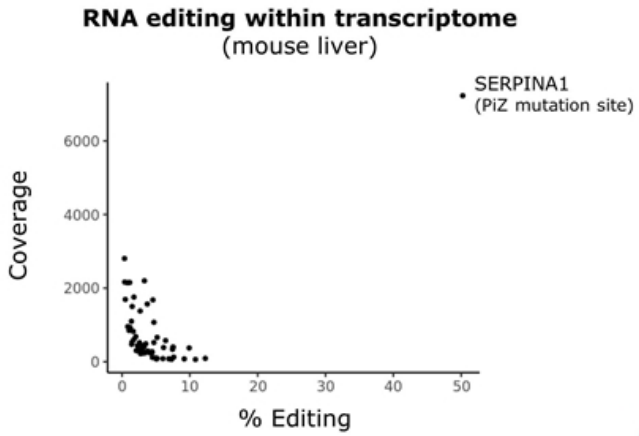
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017; Remih 2021

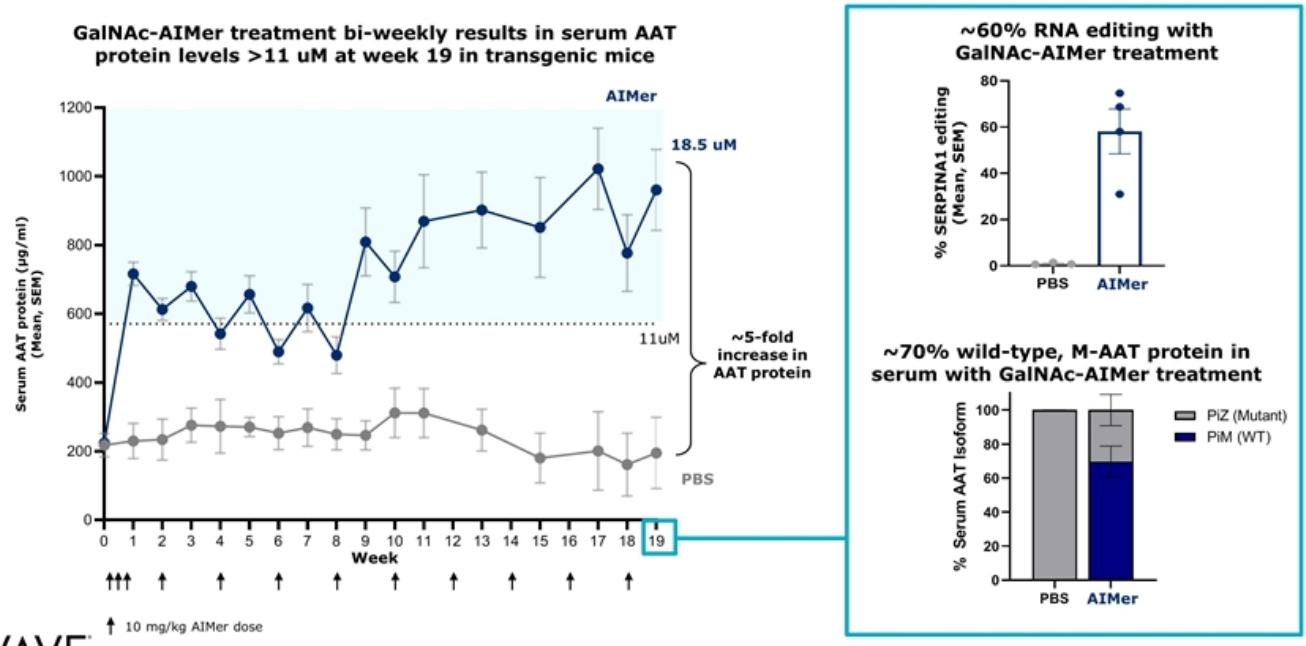
ADAR editing is highly specific; no bystander editing observed on SERPINA1 transcript





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



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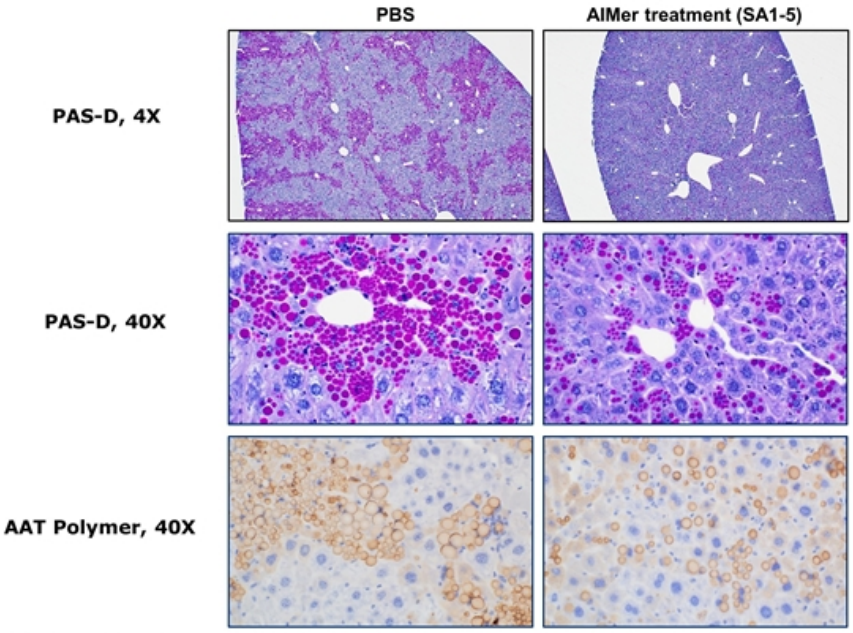
AIMers (SA1-5) administered in hu*ADAR/SERPINA1* mice (8 – 10 weeks old) Left : Total AAT protein quantified by ELISA. Right: Liver biopsies collected at week 19 (one week after last dose) and SERPINA1 editing was quantified by Sanger sequencing

Histological analysis indicates reduction of liver aggregates at 19 weeks with AIMer treatment

Preliminary histological analysis of transgenic mouse liver aggregates (Week 19)



Representative images from liver biopsies stained with PAS-D (top, middle) or AAT-polymer specific antibody (bottom)

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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 μM)
- ✓ 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

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https://www.labiotech.eu


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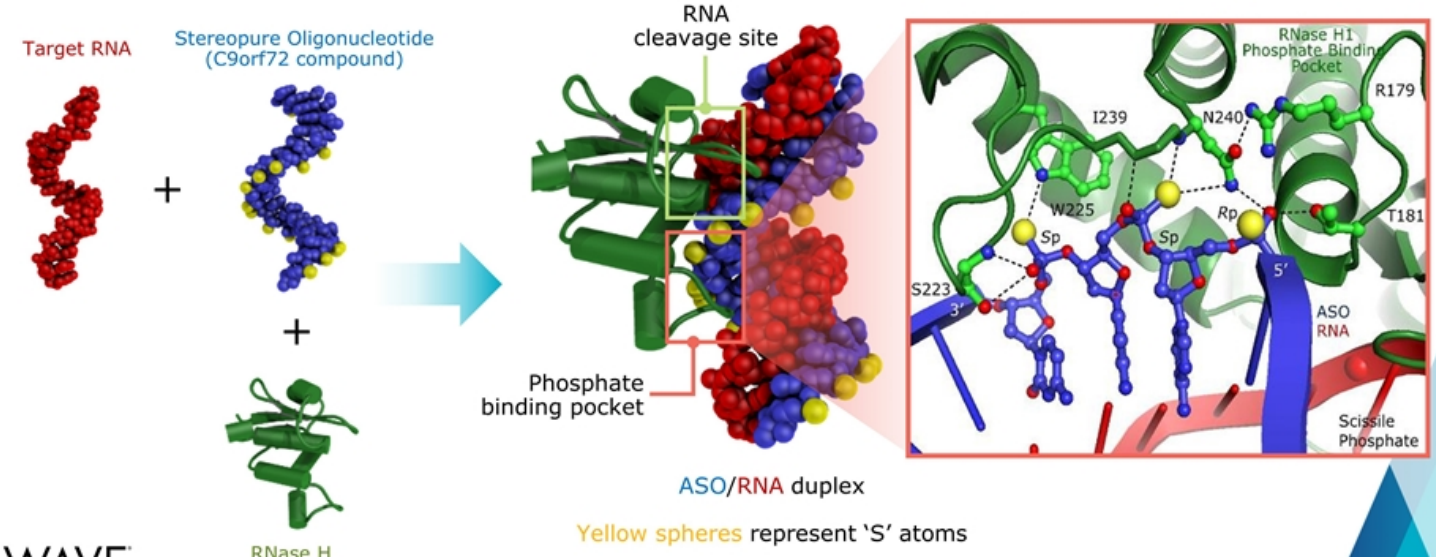
PRISM
Wave's discovery and drug development platform

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

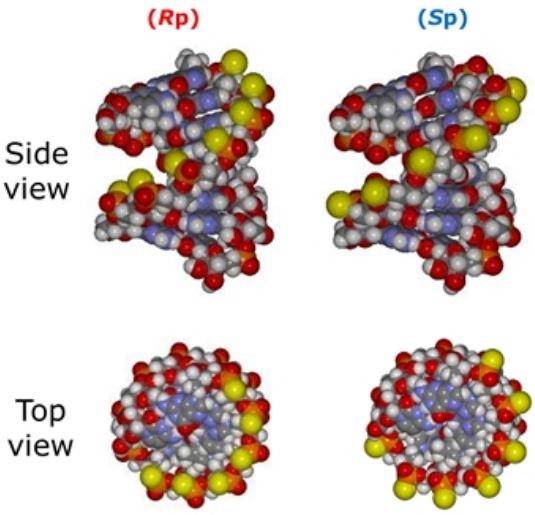


ASO/RNA duplex

Yellow spheres represent 'S' atoms

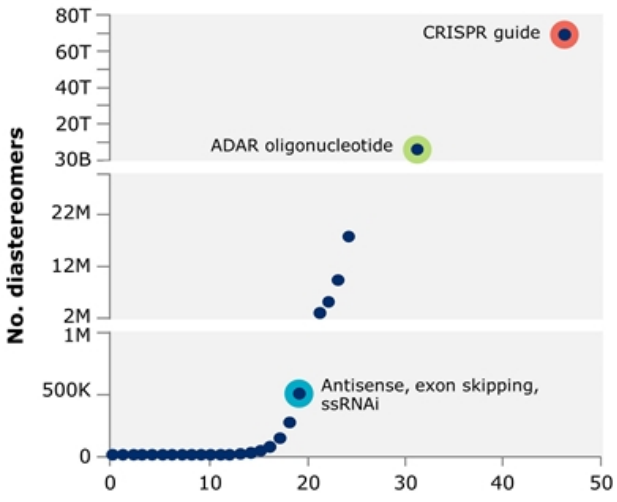
Importance of controlling stereochemistry

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

Rational design to achieve target engagement and preclinical tolerability

Unconjugated oligonucleotide administered **ICV**

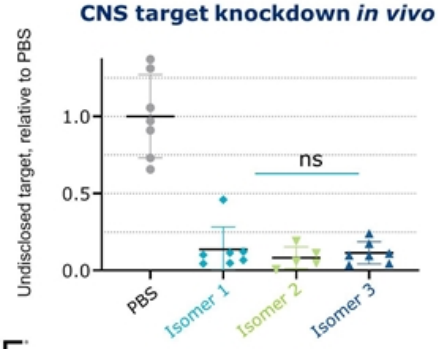
Isomer 1
Isomer 2
Isomer 3

Same sequence, but different backbone stereochemistry

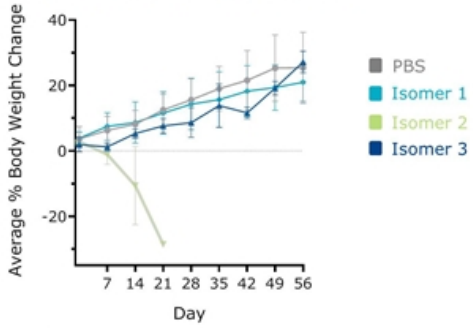
Stereoisomers have **similar** pharmacodynamic effects *in vivo*

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

CNS target knockdown *in vivo*



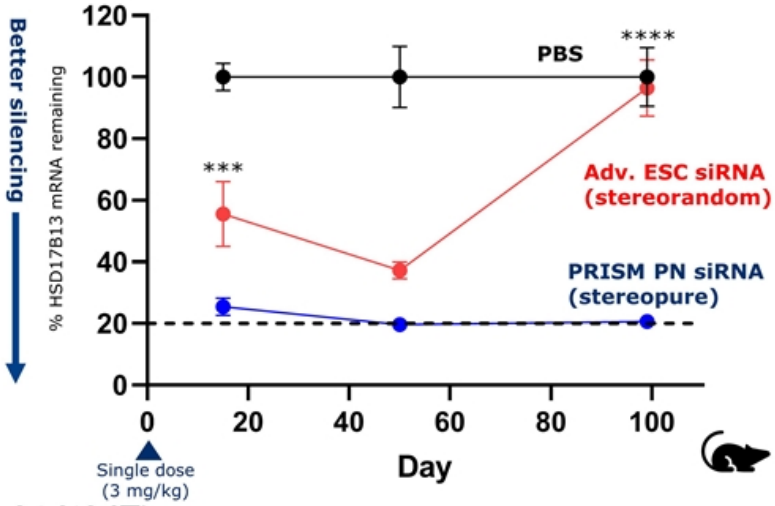
Percentage Body Weight Change



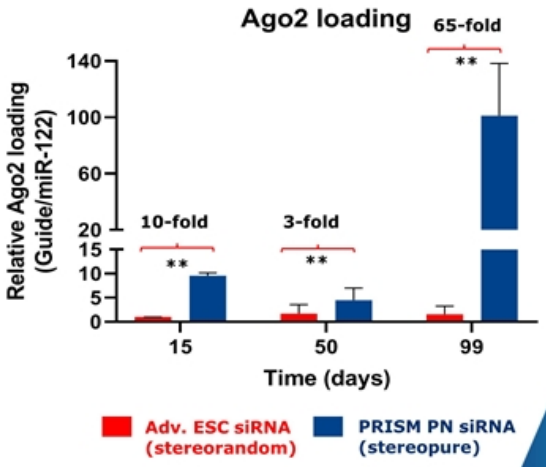
Left: In a target engagement study, 7 mice administered 2 x 50 ug oligonucleotide or PBS by ICV on days 0 and 7. Tissue collected on day 14. Target mRNA normalized to Tubb3 and plotted relative to PBS. Data presented as mean ± SD (n=7). Stats: One-way ANOVA ns not significant, PBS phosphate buffered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

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



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(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

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Upcoming milestones

Data generated in 2022 expected to inform future opportunities and unlock value

WVE-004 C9orf72 ALS & FTD	• Clinical data to enable decision making 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
AIMer AATD 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)*

Success with any current program validates platform and unlocks modalities and tissues

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Realizing a brighter future for people affected by genetic diseases

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