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): November 10, 2021

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

Singapore	**001-37627**	**00-0000000**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

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

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

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

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

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

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

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

Emerging growth company ☐

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

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

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

Item 2.02 Results of Operations and Financial Condition.

On November 10, 2021, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter ended September 30, 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 November 10, 2021, the Company updated its corporate presentation, which is available on the "For Investors & Media" section of the Company's website at http://ir.wavelifesciences.com/. This presentation is also furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information in these Items 2.02 and 7.01 are being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, nor shall they be deemed incorporated by reference into any registration statement or other filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

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

Exhibit No.	Description
99.1	Press Release issued by Wave Life Sciences Ltd. dated November 10, 2021
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated November 10, 2021
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

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

WAVE LIFE SCIENCES LTD.

By: */s/ Paul B. Bolno, M.D.*

Paul B. Bolno, M.D.
President and Chief Executive Officer

Date: November 10, 2021

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

Strengthened balance sheet with approximately $52 million; focusing additional investment in RNA editing programs led by hepatic editing

Optimized AIMers for AATD program demonstrate potent, highly specific RNA editing and restoration of functional AAT protein substantially above therapeutic threshold; potential for best-in-class, potent and durable RNA editing in vivo in multiple preclinical models and tissues

Dosing ongoing in three clinical programs (WVE-004, WVE-003, WVE-N531); data being generated through 2022 to enable decision-making

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

CAMBRIDGE, Mass., November 10, 2021 (GLOBE NEWSWIRE) — Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced financial results for the third quarter ended September 30, 2021 and provided a business update.

“In the third quarter, we achieved several important milestones including providing a comprehensive update on our potentially best-in-class ADAR editing capability and the initiation of dosing in three clinical trials evaluating our next-generation stereopure PN-modified oligonucleotides,” said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. “RNA editing is a novel therapeutic modality that greatly expands our landscape of addressable genetically defined diseases. We are leading the way in this new field and quickly working toward announcing our first ADAR editing development candidate for our alpha-1 antitrypsin deficiency program next year. With this program, we are on a path to generate proof of principle that we can harness human biological machinery to edit RNA for the treatment of genetic diseases of the liver, CNS, and beyond.”

“Our robust and diversified pipeline is driven by our PRISM platform, which enables a unique ability to design and optimize oligonucleotides with novel, stereopure backbone modifications, including PN chemistry. We expect data being generated from our three ongoing clinical trials will enable us to make decisions on next steps for the programs next year. Finally, we recently strengthened our balance sheet via our at-the-market facility and funds received from Takeda under the terms of the amendment, leaving us well-capitalized to deliver on our portfolio, including advancing our first ADAR editing program toward the clinic and expanding our AIMer pipeline to include additional indications.”

ADAR editing capability recent events and upcoming milestones

Leading RNA editing capability using AIMers to harness endogenous ADAR enzymes

- Wave’s RNA editing capability leverages widely expressed endogenous ADAR enzymes to achieve highly specific A-to-I (G) RNA editing using stereopure oligonucleotides, called “AIMers,” with and without GalNAc conjugation, to edit RNA in the liver, central nervous system (CNS), and other tissues.

- In September 2021, during its Analyst and Investor Research Webcast, Wave presented new preclinical data that demonstrated potent and durable editing of UGP2 mRNA out to at least four months post-dose in multiple regions of mouse CNS. Wave is applying ADAR editing to multiple therapeutic targets in the CNS, including restoring functional MECP2 protein for the treatment of Rett Syndrome.
- Wave also presented preclinical data demonstrating up to 50% editing of UGP2 mRNA in the posterior of the eye of mice at one-month post-single intravitreal injection and ACTB RNA editing in non-human primates (NHPs) using systemic administration, including in the kidneys, liver, lungs, and heart, as well as editing of ACTB in multiple immune cell types *in vitro*.
- Wave expects to share additional ADAR editing data using AIMers in scientific publications and presentations in 2022.

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

- Wave's AATD program, its first therapeutic ADAR editing program, uses stereopure oligonucleotides to correct the single base mutation in mRNA coded by the *SERPINA1* Z allele. Restoring circulating levels of healthy alpha-1 antitrypsin (M-AAT) protein and reducing aggregation in the liver of mutant protein (Z-AAT) with RNA editing could potentially address both the lung and liver manifestations of the disease simultaneously.
- In September 2021, during its Analyst and Investor Research Webcast, Wave shared new *in vivo* data demonstrating durable restoration of M-AAT protein in the liver of transgenic mice with human SERPINA1 and human ADAR following initial doses of a GalNAc-conjugated SERPINA1 AIMer. Using PRISM chemistry optimization, Wave AIMers can achieve highly specific editing of up to 50% of SERPINA1 mRNA *in vivo* and restore AAT protein in serum to a level four-fold higher than phosphate-buffered saline (PBS) control (or more than 15 micromolar).
- Ongoing and planned preclinical studies are assessing durability, dose response, pharmacokinetics, and pharmacodynamics. Wave also plans to assess reduction of Z-AAT aggregates in the liver and changes in liver pathology in its transgenic mouse model, with data expected in 2022.
- Wave expects to announce its AATD AIMer development candidate in 2022.

Clinical silencing and exon skipping programs and upcoming milestones

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

- WVE-004 is an investigational stereopure antisense oligonucleotide designed to selectively target transcript variants containing a hexanucleotide repeat expansion (G_4C_2) associated with the *C9orf72* gene, which is one of the most common genetic causes of the sporadic and inherited forms of ALS and FTD. WVE-004 uses Wave's novel PN backbone chemistry modifications (PN chemistry).
- In July 2021, Wave announced the initiation of dosing in the Phase 1b/2a FOCUS-C9 clinical trial, which is adaptive, with an independent committee to guide dose level and dosing frequency.

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

- WVE-003, Wave's first HD candidate to use PN chemistry and leverage transgenic models to assess target engagement *in vivo*, is designed to selectively target the mutant allele of the *huntingtin* (mHTT) gene, while leaving the wild-type (healthy) HTT (wtHTT) protein relatively intact. Wave's approach to HD is guided by the recognition that people with HD have less wtHTT protein compared to unaffected individuals and a growing body of scientific evidence suggests that preserving as much of this essential protein as possible, when in the setting of stress from toxic mHTT protein, may be important for favorable clinical outcomes.
- In September 2021, Wave announced the initiation of dosing in the Phase 1b/2a SELECT-HD clinical trial of WVE-003 in patients with early manifest HD. The SELECT-HD trial is adaptive, with an independent committee to guide dose level and dosing frequency.

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

- WVE-N531 is Wave's first stereopure splicing candidate and first systemically administered candidate to incorporate PN chemistry.
- In September 2021, Wave announced the initiation of dosing in an open-label clinical trial of WVE-N531 dosed intravenously bi-weekly in patients with DMD amenable to exon 53 skipping. Dose level and dosing frequency will be guided by tolerability and plasma PK, with possible cohort expansion driven by an assessment of drug distribution in muscle and biomarkers, including dystrophin.

Upcoming clinical milestones:

- Wave expects to generate clinical data through 2022 from WVE-004, WVE-003, and WVE-N531 to provide insight into the clinical effects of PN chemistry and enable decision-making regarding next steps for each program.

Corporate developments

- In October 2021, Wave issued and sold an aggregate block of approximately $30 million in ordinary shares through its at-the-market (ATM) equity program, based on interest received from new and existing shareholders following its Analyst and Investor Research Webcast in September 2021. Wave intends to use the additional capital to accelerate its RNA editing capability, led by its AATD program.
- In October 2021, Wave announced an amendment to its ongoing collaboration with Takeda, which streamlined the collaboration and allows Wave to advance or partner early-stage CNS programs, including those using ADAR editing. Wave received $22.5 million from Takeda under the terms of the amendment. The amendment did not impact the late-stage component of the collaboration, including Takeda's option to co-develop and co-commercialize WVE-004 and WVE-003. Should Takeda opt in on any of these programs, Wave would receive an opt-in payment, global costs and potential profits would be shared 50:50, and Wave would be eligible to receive development and commercial milestone payments.

Third quarter 2021 financial results and financial guidance

Wave reported a net loss of $6.2 million in the third quarter of 2021 as compared to $33.1 million in the same period in 2020.

Revenue earned during the three months ended September 30, 2021 was $36.4 million, as compared to $3.4 million for the three months ended September 30, 2020. The increase in revenue year-over-year is primarily driven by the $22.5 million paid as part of the amendment to Wave's collaboration agreement with Takeda, which was recognized as revenue in the three months ended September 30, 2021, as well as the recognition of the remaining revenue related to Category 2 research support payments previously paid by Takeda.

Research and development expenses were $31.1 million in the third quarter of 2021 as compared to $28.3 million in the same period in 2020. The increase in research and development expenses in the third quarter was primarily due to increased external expenses related to preclinical programs and compensation-related expenses, partially offset by decreased external expenses related to our discontinued programs.

General and administrative expenses were $12.9 million in the third quarter of 2021 as compared to $9.6 million in the same period in 2020. The increase in general and administrative expenses in the third quarter of 2021 was driven by increases in compensation-related and other external general and administrative expenses.

As of September 30, 2021, Wave had $123.9 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 $87.5 million, partially offset by the receipt of $21.2 million in proceeds under Wave's ATM equity program through September 30, 2021.

Subsequently, in October 2021 Wave received an additional $52.1 million in cash, including $22.5 million from Takeda under the terms of the amendment to Wave's collaboration agreement with Takeda, and $29.6 million in proceeds under its ATM equity program from a block sale of ordinary shares based on interest received from new and existing shareholders following its Analyst and Investor Research Webcast in September 2021.

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 third quarter and 2021 financial results and provide a business update. The conference call may be accessed by dialing (866) 220-8068 (domestic) or (470) 495-9153 (international) and entering conference ID: 6995569. 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; 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; our ability to maintain the company infrastructure and personnel needed to achieve our goals; the clinical results of our programs, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials, including their receptiveness to our adaptive trial designs; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM, including our novel PN backbone chemistry modifications; the effectiveness of our novel ADAR-mediated RNA editing platform capability 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; the severity and duration of the COVID-19 pandemic and its negative impact on the conduct of, and the timing of enrollment, completion and reporting with respect to our clinical trials; and any other impacts on our business as a result of or related to the COVID-19 pandemic, as well as the information under the caption “Risk Factors” contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. We undertake no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED BALANCE SHEETS

(In thousands, except share amounts)

	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 123,896	$ 184,497
Accounts receivable	22,500	30,000
Prepaid expenses	7,627	10,434
Other current assets	3,964	5,111
Total current assets	157,987	230,042
Long-term assets:		
Property and equipment, net	24,020	29,198
Operating lease right-of-use assets	14,639	16,232
Restricted cash	3,651	3,651
Other assets	215	115
Total long-term assets	42,525	49,196
Total assets	$ 200,512	$ 279,238
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 7,443	$ 13,795
Accrued expenses and other current liabilities	11,364	11,971
Current portion of deferred revenue	8,736	91,560
Current portion of operating lease liability	4,097	3,714
Total current liabilities	31,640	121,040
Long-term liabilities:		
Deferred revenue, net of current portion	107,606	41,481
Operating lease liability, net of current portion	22,477	25,591
Other liabilities	1,014	474
Total long-term liabilities	$ 131,097	$ 67,546
Total liabilities	$ 162,737	$ 188,586
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at September 30, 2021 and December 31, 2020	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 51,998,032 and 48,778,678 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively	$ 716,118	$ 694,085
Additional paid-in capital	84,254	71,573
Accumulated other comprehensive income	258	389
Accumulated deficit	(770,729)	(683,269)
Total shareholders' equity	$ 29,901	$ 82,778
Total liabilities, Series A preferred shares and shareholders' equity	$ 200,512	$ 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 September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Revenue	$ 36,423	$ 3,450	$ 39,199	$ 10,638
Operating expenses:				
Research and development	31,086	28,275	96,114	100,911
General and administrative	12,944	9,590	33,991	32,791
Total operating expenses	44,030	37,865	130,105	133,702
Loss from operations	(7,607)	(34,415)	(90,906)	(123,064)
Other income, net:				
Dividend income and interest income, net	6	23	25	544
Other income, net	1,371	1,292	3,421	1,399
Total other income, net	1,377	1,315	3,446	1,943
Loss before income taxes	(6,230)	(33,100)	(87,460)	(121,121)
Income tax provision	—	—	—	—
Net loss	$ (6,230)	$ (33,100)	$ (87,460)	$ (121,121)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (0.12)	$ (0.86)	$ (1.75)	$ (3.36)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	50,709,877	38,364,224	50,017,521	36,021,256
Other comprehensive income (loss):				
Net loss	$ (6,230)	$ (33,100)	$ (87,460)	$ (121,121)
Foreign currency translation	(11)	23	(131)	34
Comprehensive loss	$ (6,241)	$ (33,077)	$ (87,591)	$ (121,087)

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Exhibit 99.2

WAVE
LIFE SCIENCES

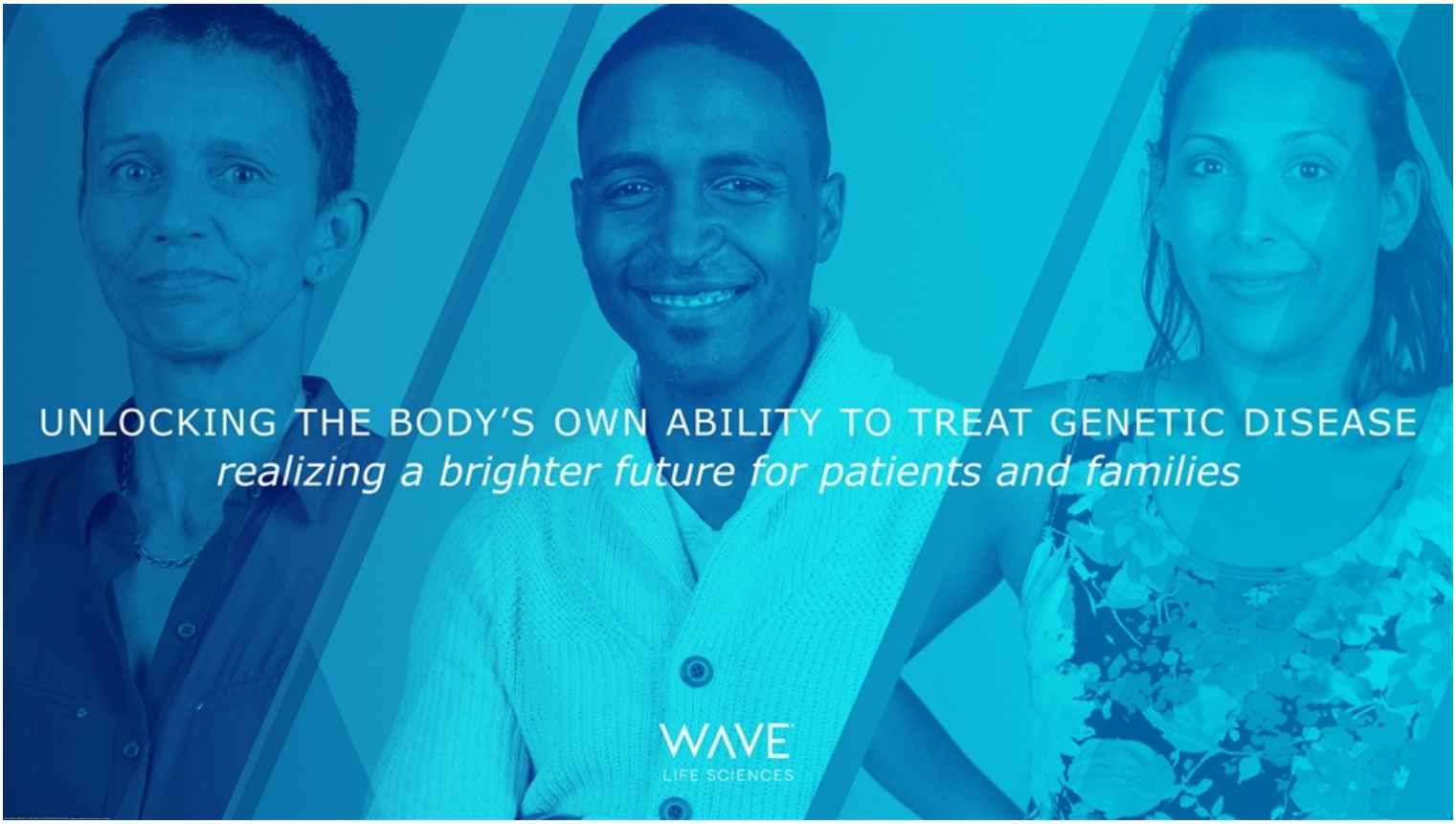
Wave Life Sciences

Corporate Presentation

November 10, 2021

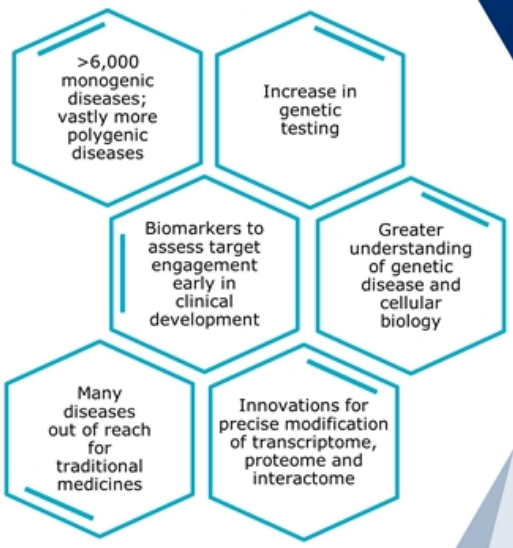
Forward-looking statements

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


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

DRUGGING 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

Ophthalmology

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

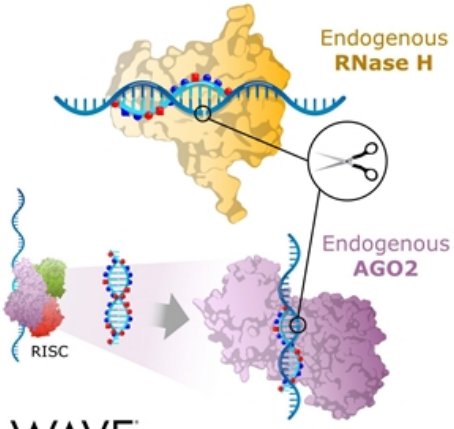
Address underlying genetic drivers of disease	Changes erroneous messages, not erroneous code
Simplified delivery	Freely taken up by cells in multiple tissues or compatible with simple ligands – no need for complex delivery vehicles
Durable effects to enable infrequent dosing	Continued progress towards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

WAVE LIFE SCIENCES

Biological machinery in our cells can be harnessed to treat genetic diseases

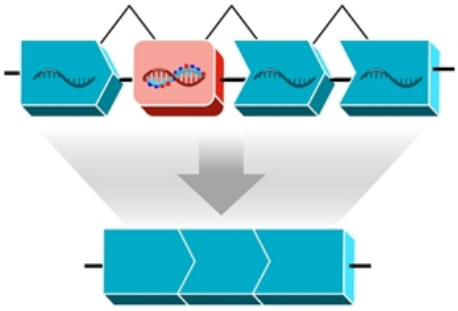
Silencing

- **Oligonucleotide-directed delivery** of RNA to regulate enzymes



Splicing

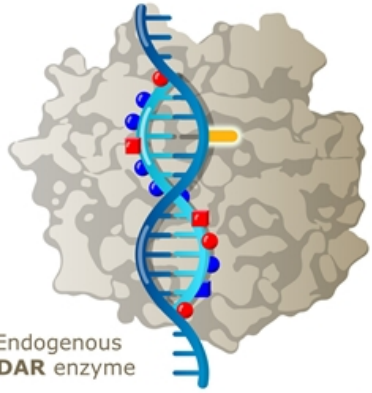
- Leverages **exon skipping machinery** to restore a working transcript



Restored **Reading Frame**

Editing

- Efficient editing of RNA bases using **endogenous ADAR**



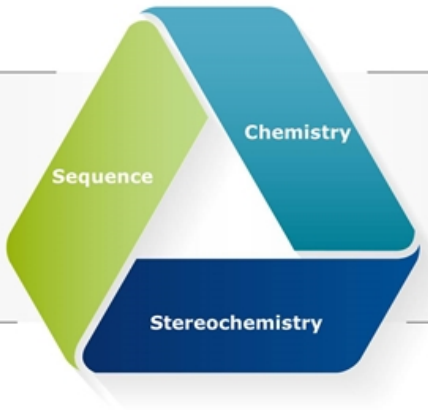
Endogenous **ADAR** enzyme

WAVE LIFE SCIENCES

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

WAVE LIFE SCIENCES

Wave is the leader in rationally designed stereopure oligonucleotides

Stereochemistry is a reality of chemically-modified nucleic acid therapeutics

Current therapeutics with chiral backbone modifications:

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

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

Seminal 2017 publication from Wave, increasingly recognized by leaders in nucleic acid

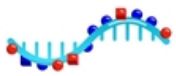

ARTICLES

nature biotechnology

Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides

PRISM controls stereochemistry throughout drug discovery and development process

Enables design and optimization of fully-characterized, **single-isomer** RNA therapeutics



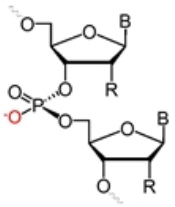
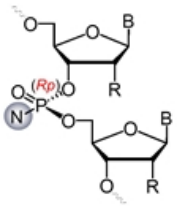
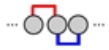
WAVE LIFE SCIENCES

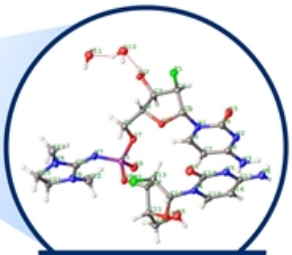
Strong and broad IP portfolio and unique ability to manufacture and screen stereopure oligonucleotides

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

Innovating stereopure backbone chemistry modifications

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**



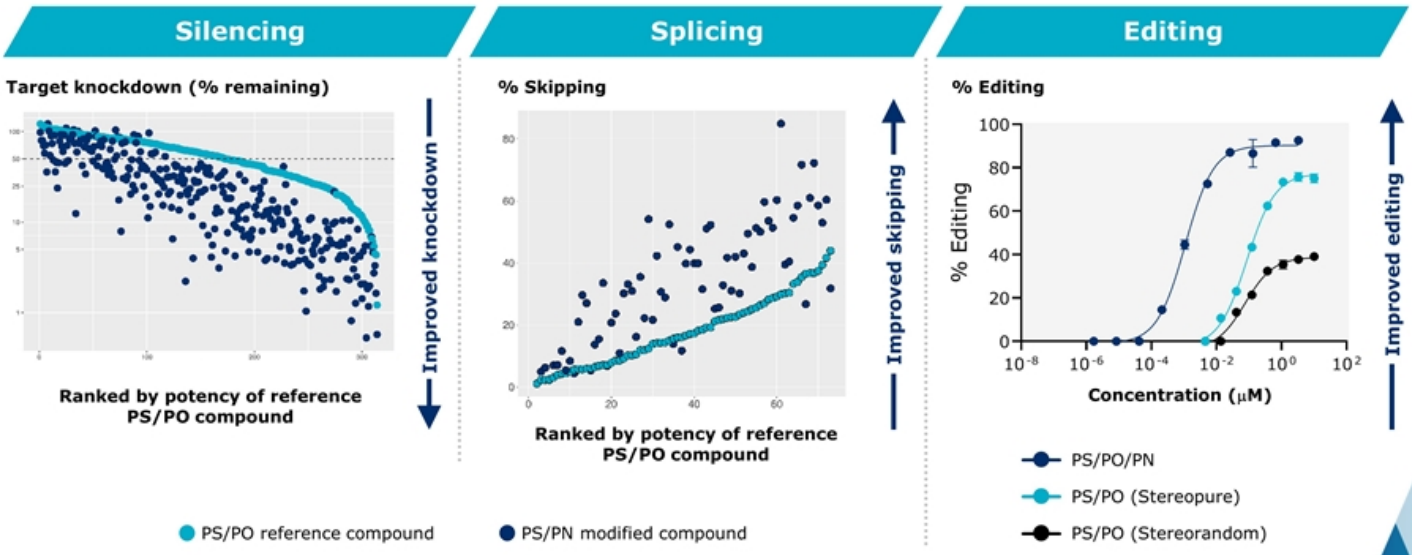
Phosphoryl guanidine x-ray structure

example

WAVE LIFE SCIENCES

PO: phosphodiester PS: phosphorothioate

Potency is enhanced with addition of PN modifications across modalities



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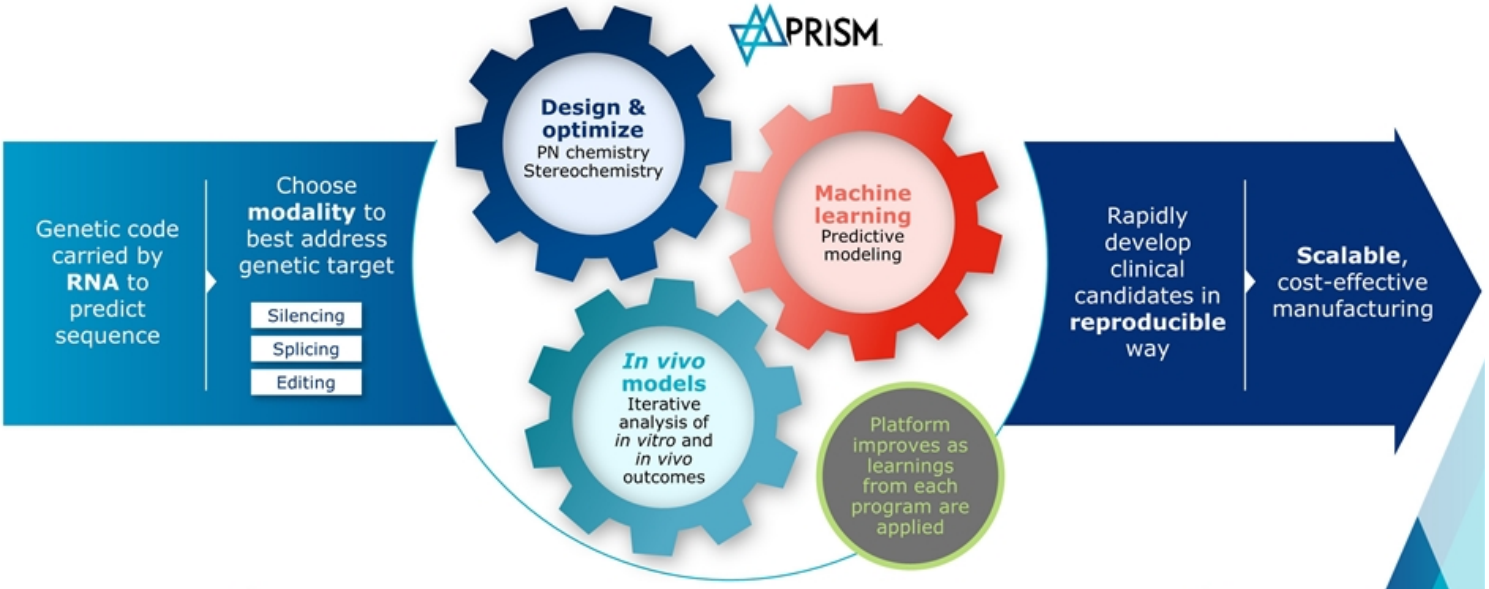
Left: Experiment was performed in iPSC-derived neurons *in vitro*; target mRNA levels were monitored using qPCR against a control gene (HPRT1) using a linear model equivalent of the ΔΔCt method; Middle: DMD patient-derived myoblasts treated with PS/PO or PS/PO/PN stereopure oligonucleotide under free-uptake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

PRISM platform is continuously improving



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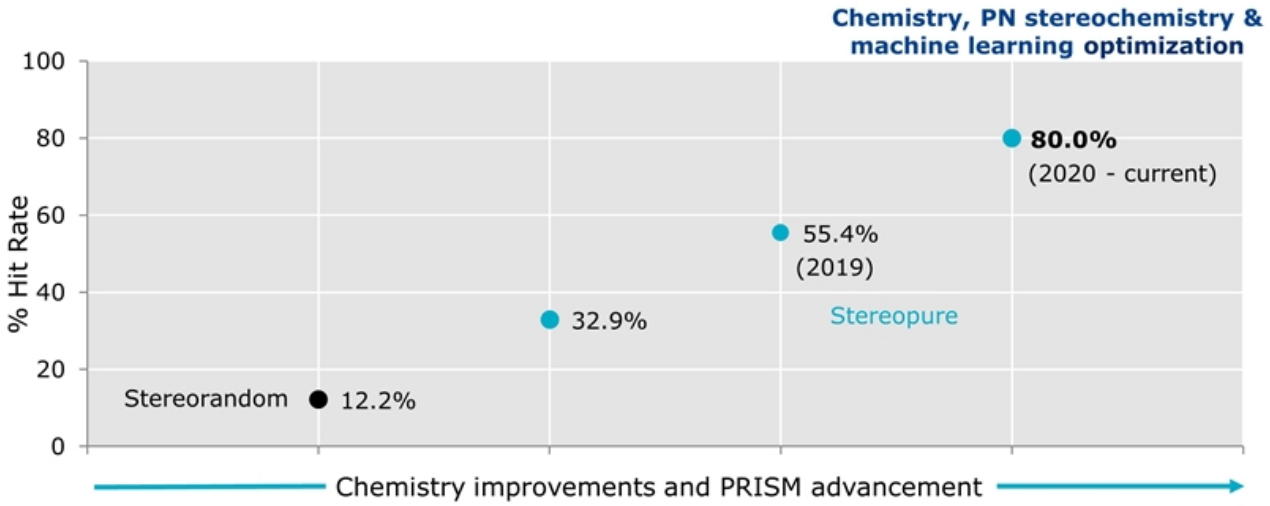
Continuous definition of design principles deployed across programs

Improvements in PRISM primary screen hit rates accelerate drug discovery

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

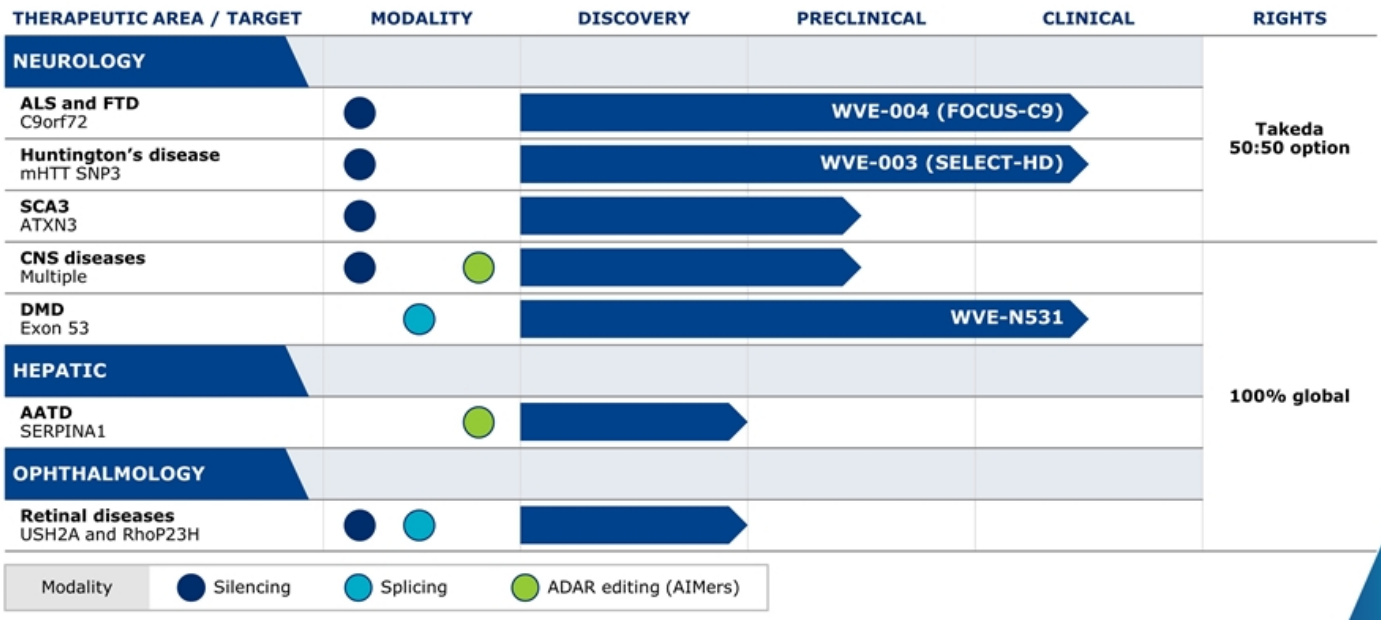


WAVE LIFE SCIENCES

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

PRISM

Robust portfolio of stereopure, PN-modified oligonucleotides



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 disease across phenotypes

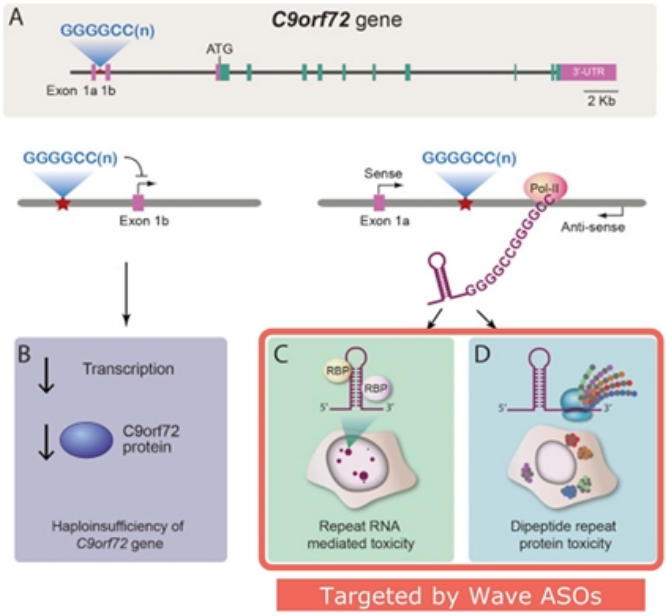
WAVE LIFE SCIENCES

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

Variant-selective targeting could address multiple potential drivers of toxicity

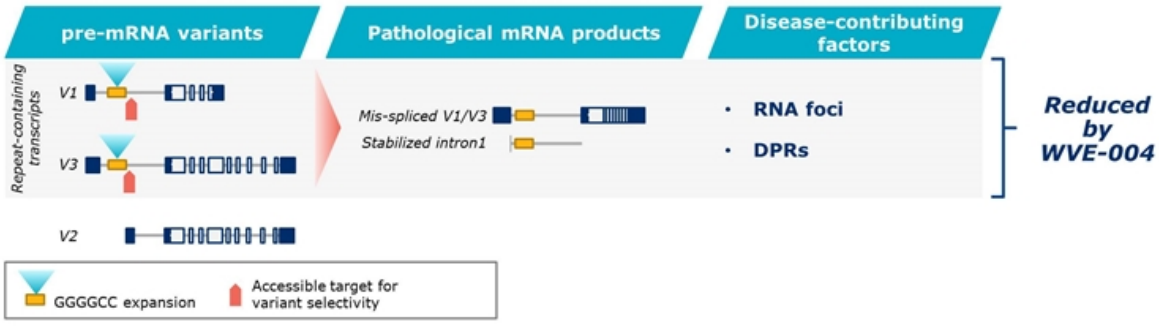


WAVE LIFE SCIENCES

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

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

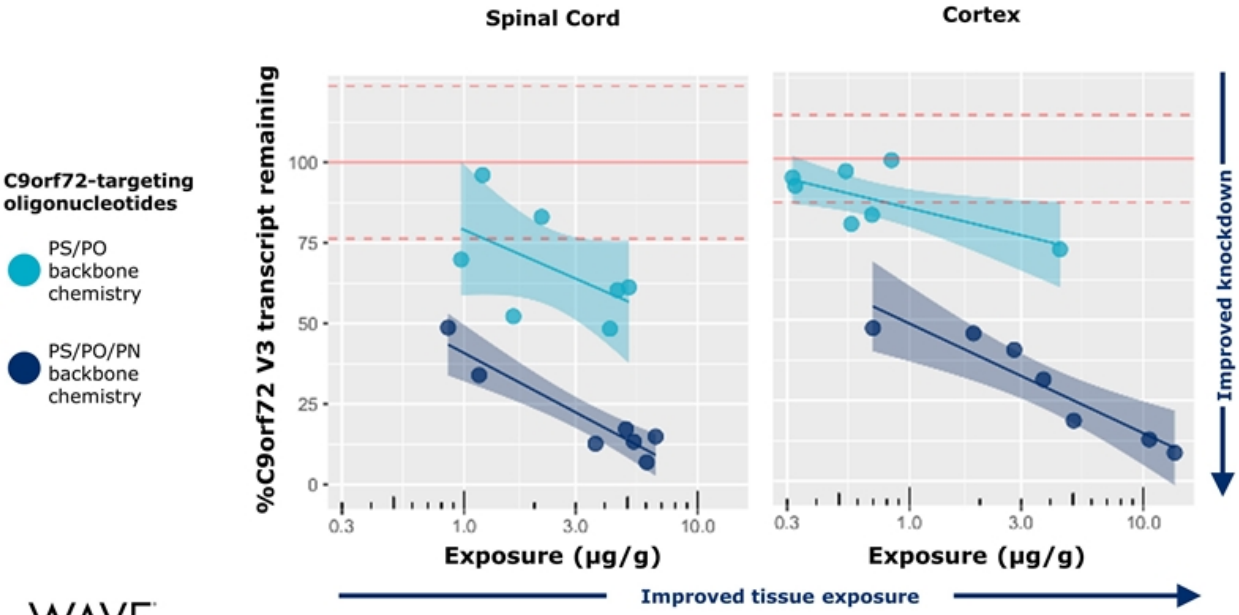
- C9orf72 protein is important for normal regulation of neuronal function and the immune system
- WVE-004 targets hexanucleotide repeat containing transcript variants that lead to loss of normal C9orf72 function and production of pathological mRNA products and toxic dipeptide repeat (DPR) proteins
- 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



WAVE LIFE SCIENCES

Liu et al, Nature Communications, 2021

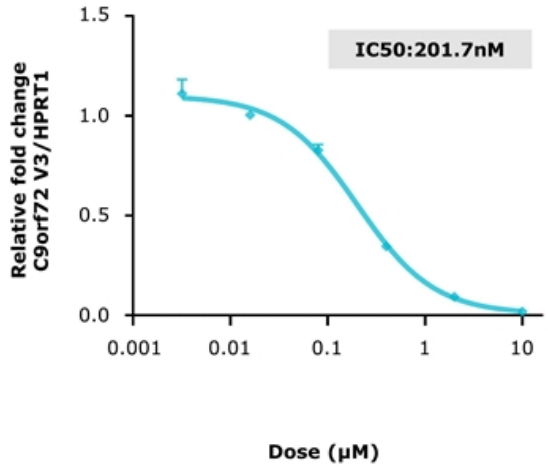
Adding PN chemistry modifications to C9orf72-targeting oligonucleotides improved potency *in vivo*



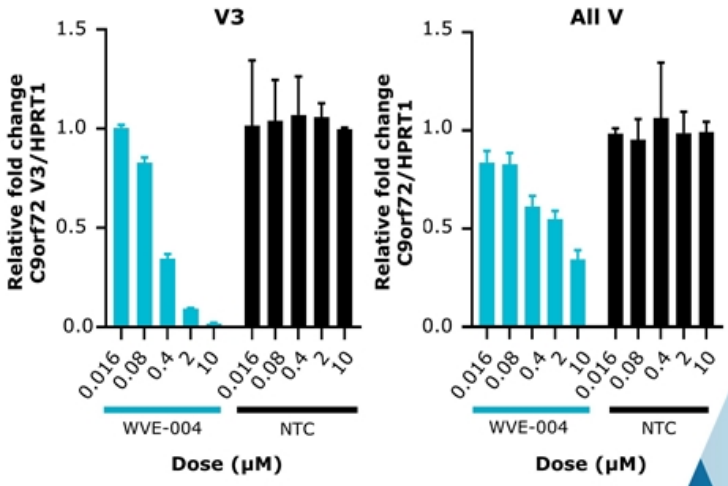
Target knockdown: Liu, TIDES poster 2021; Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis. Manuscript submitted.

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

In vitro activity in C9 patient-derived neurons



In vitro selectivity in C9 patient-derived neurons



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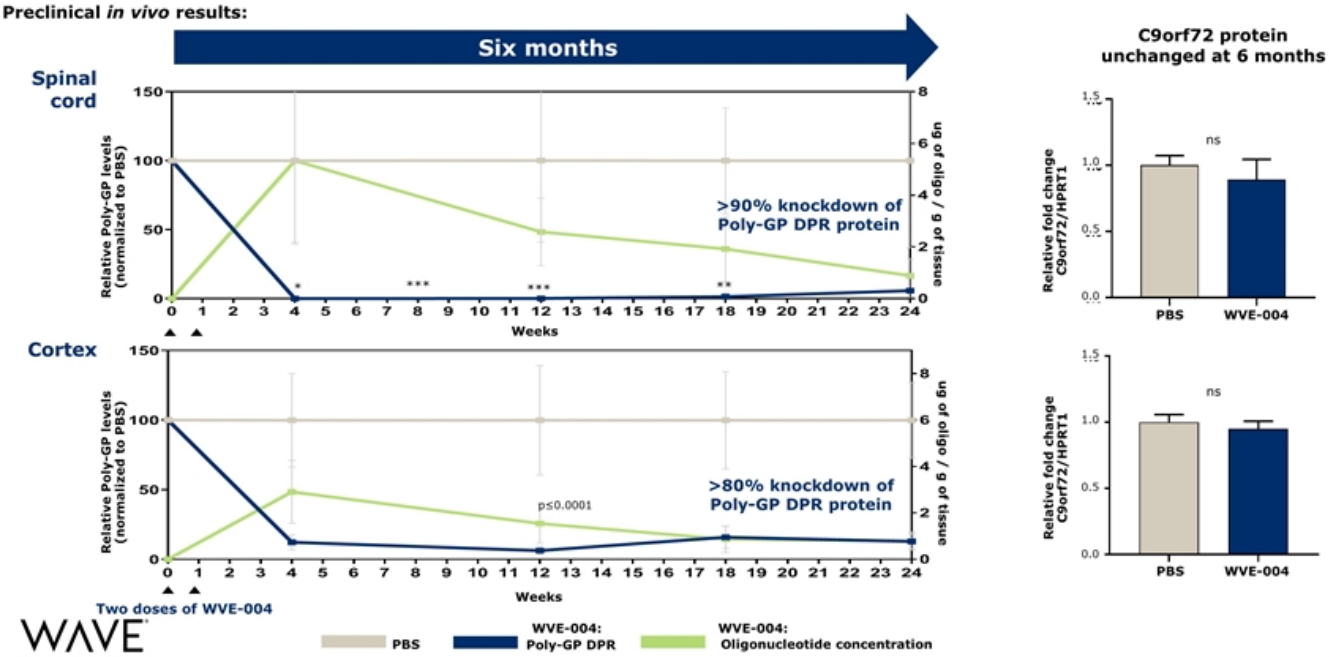
C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gymnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC- non-targeting control.

Durable reduction *in vivo* of Poly-GP in spinal cord and cortex after 6 months

Preclinical *in vivo* results:



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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

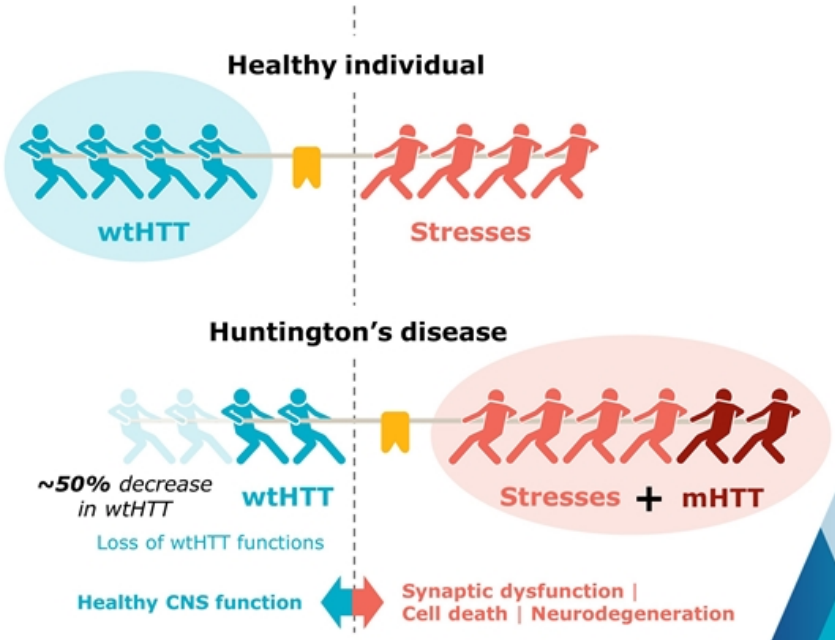
Adaptive cohorts

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



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

NEURON

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

SYNAPSE

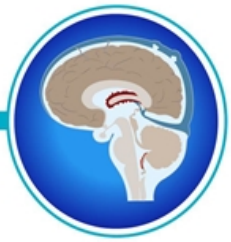
Plays an essential role in the transport of synaptic proteins—including neurotransmitters and receptors—to their correct location at synapses[9-12]

BRAIN CIRCUITS

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

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

CSF CIRCULATION

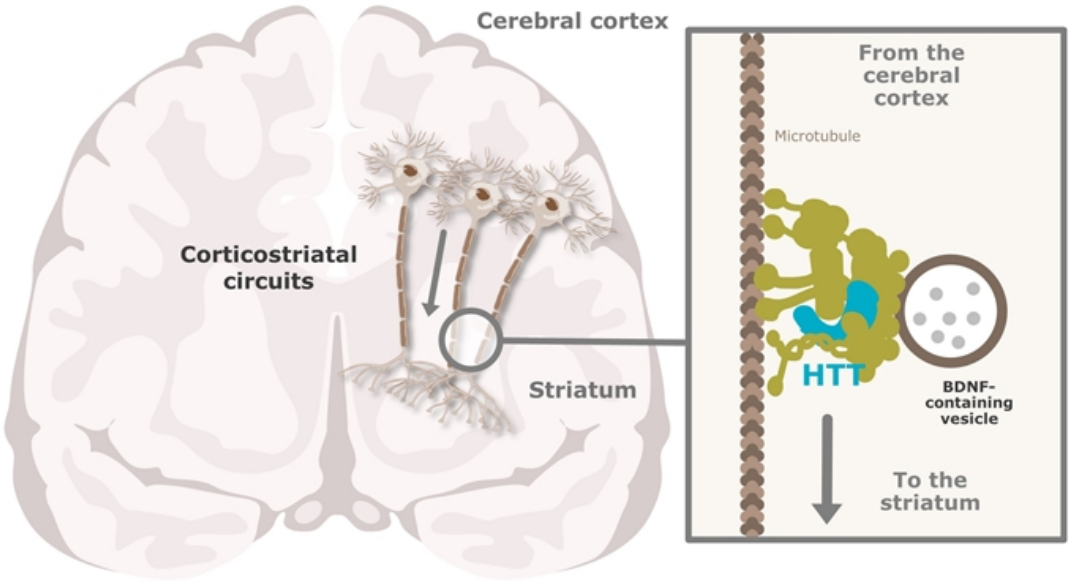


Plays a critical role in formation and function of cilia—sensory organelles that control the flow of CSF—which are needed to clear catabolites and maintain homeostasis[23]

WAVE LIFE SCIENCES

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

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



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

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

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

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

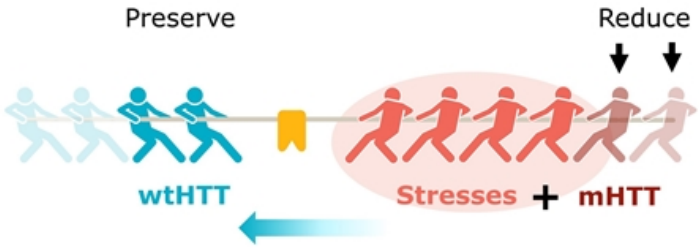
BDNF, brain-derived neurotrophic factor; HD, Huntington's disease; HTT, huntingtin protein.

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

Allele-selective approach to treating HD

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

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



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

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Allele-selective approach to treating HD

~40% of HD Patients Carry SNP3

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

Personalized approach to wtHTT sparing opens possibility of early treatment

WAVE LIFE SCIENCES

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

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

nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

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

Gunnar H. D. Poplawski[1,2], Riki Kawaguchi[1,3], Erna Van Niekerk[1], Paul Lu[1,4], Neil Mehta[1], Philip Canete[5], Richard Lie[5], Ioannis Dragatsis[6], Jessica M. Meves[1], Binhai Zheng[1,4], Giovanni Coppola[3,7] & Mark H. Tuszynski[1,4,8]

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

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

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

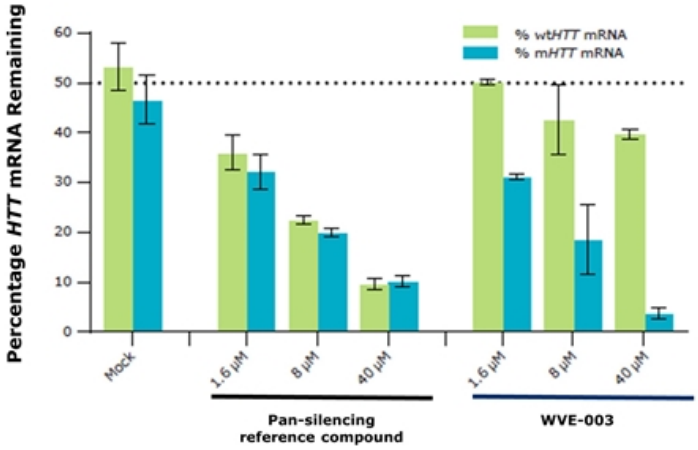
WAVE LIFE SCIENCES

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

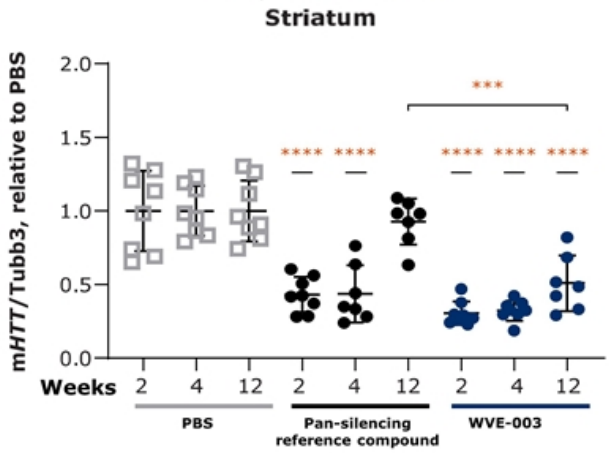
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

Incorporates PN backbone chemistry modifications

Selectively reduces mHTT mRNA in HD iPSC neurons in vitro



Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model



WAVE LIFE SCIENCES

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

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

BACHD model

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

NHP

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

Human

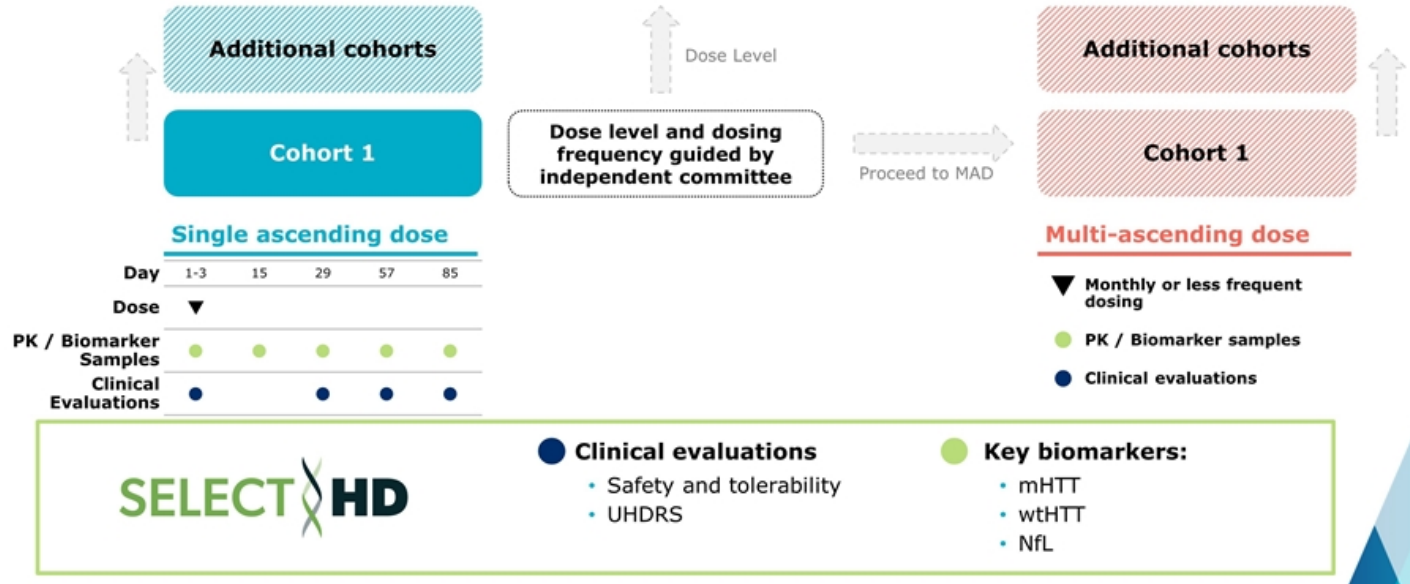
Anticipated mHTT knockdown in **cortex** and **striatum** based on PK-PD modeling

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

WAVE LIFE SCIENCES

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

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



SELECT HD

Clinical evaluations
- Safety and tolerability
- UHDRS

Key biomarkers:
- mHTT
- wtHTT
- NfL

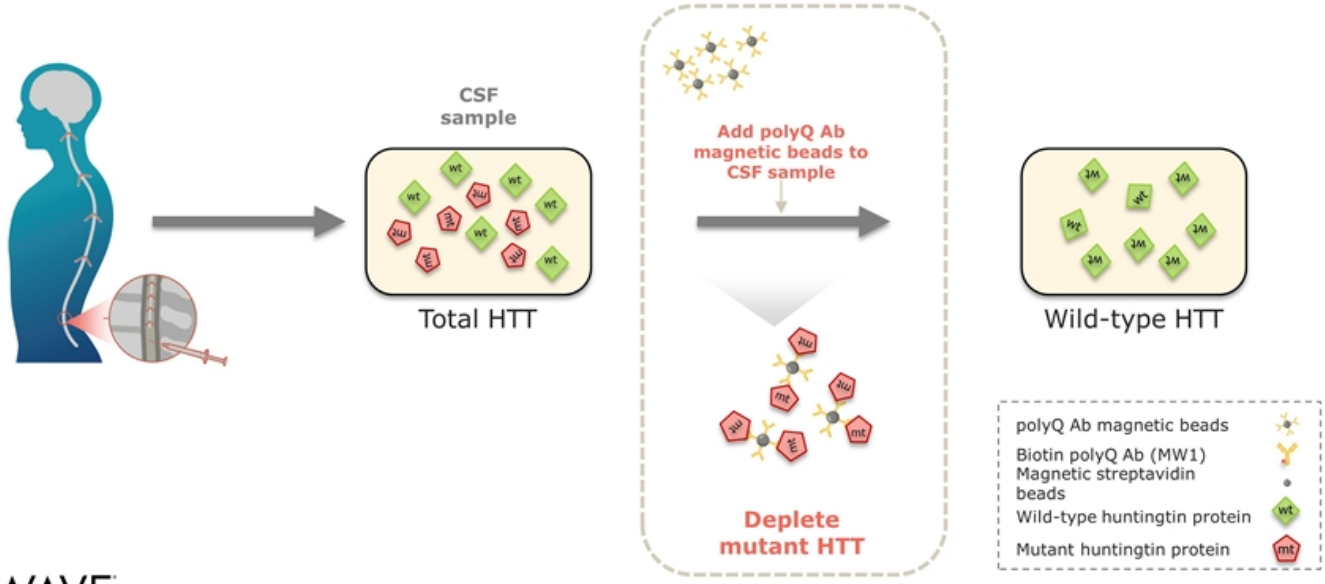
WAVE LIFE SCIENCES

PK: pharmacokinetic

Adaptive cohorts

Assessment of wild-type protein in CSF

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



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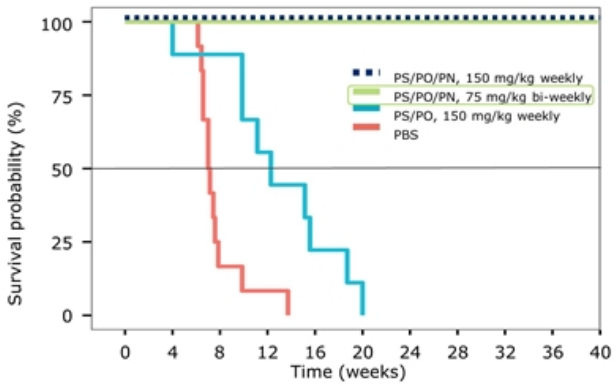
Ab: antibody CSF: cerebrospinal fluid HTT: huntingtin protein MW1: Wild et al. JCI 2015

WVE-N531

Duchenne muscular dystrophy

Dramatic increase in effect with PN-modified splicing oligonucleotide in dKO mouse model

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

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

WVE-N531: First splicing candidate to use PN chemistry

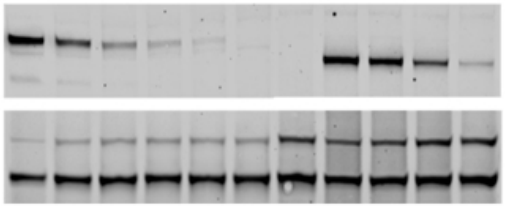
Duchenne muscular dystrophy

- 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

Clinical trial of WVE-N531 underway

- Unmet need in DMD remains high
- Open-label clinical trial of up to 15 boys with DMD amenable to exon 53 skipping
  - Powered to evaluate change in dystrophin production
  - Includes assessment of drug concentration in muscle and initial safety
  - Study planned for every-other-week administration
- Potential to apply PN chemistry to other exons if successful

Dose level and dosing frequency guided by independent committee

WAVE LIFE SCIENCES

DMD: Duchenne muscular dystrophy

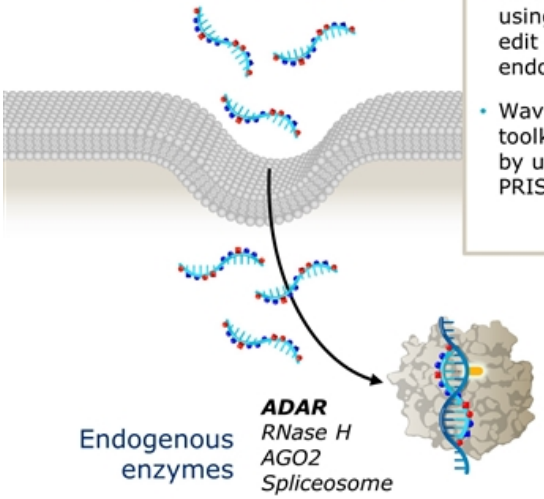
WAVE
LIFE SCIENCES

ADAR editing

RNA editing capability

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

Free-uptake of chemically modified oligonucleotides



Endogenous enzymes

ADAR
RNase H
AGO2
Spliceosome

- 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

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

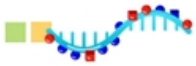
WAVE LIFE SCIENCES

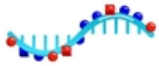
[1]Woolf et al., PNAS Vol. 92, pp. 8298-8302, 1995

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**

WAVE LIFE SCIENCES

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] – ~50% ADAR amenable
- 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]

Modulate protein interactions with AIMers

Upregulate expression

Modify function

Modulate protein-protein interaction

Post-translational modification

Alter folding or processing

Examples

Haploinsufficient diseases

Loss of function Neuromuscular

Dementias

Familial epilepsies

Neuropathic pain

- 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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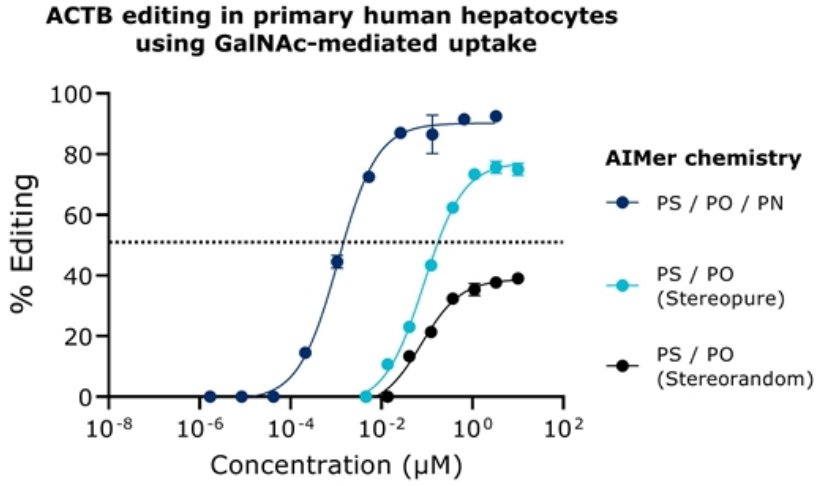
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine

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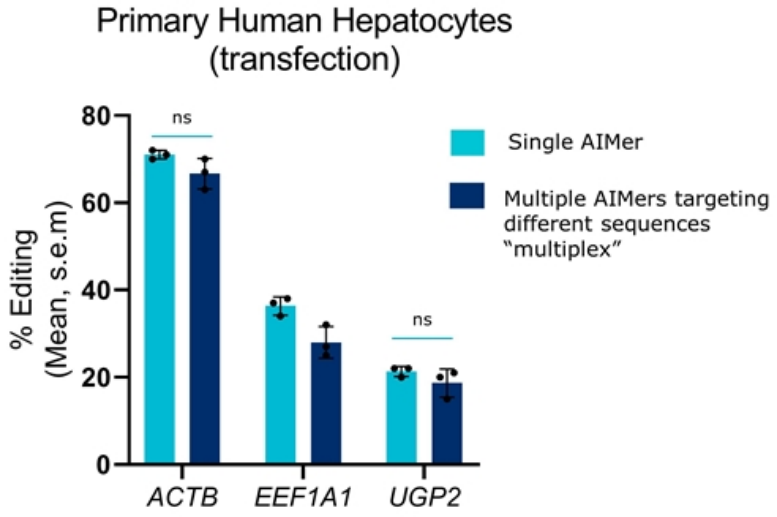
Data from independent experiments; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

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

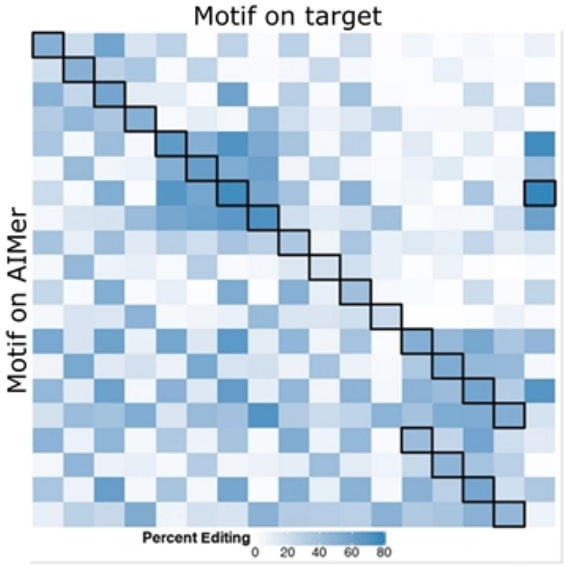
Example: Sequence is one of multiple dimensions for optimization

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



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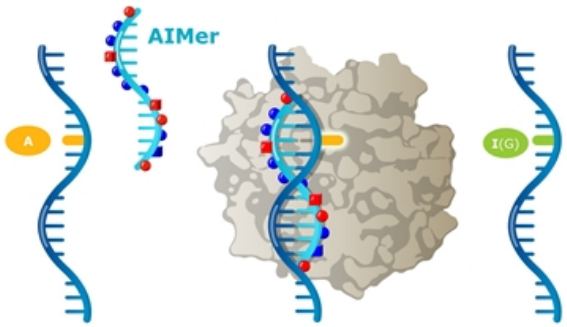
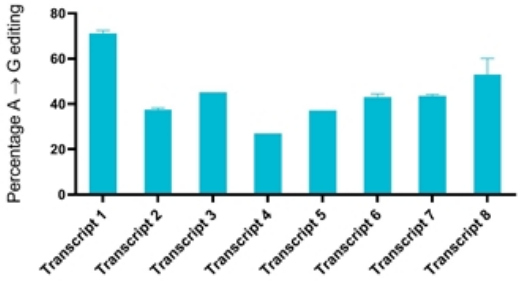
Learnings inform design principles deployed across future targets

ADAR interacts with double-stranded RNA duplex in a sequence independent way



- The intrinsic function of ADAR is to recognize dsRNA **independent of sequence**

RNA-editing design applicable across targets *in vitro* in primary human hepatocytes



- Editing achieved across several distinct RNA transcripts
- Supports potential for technology to be applied across variety of disease targets

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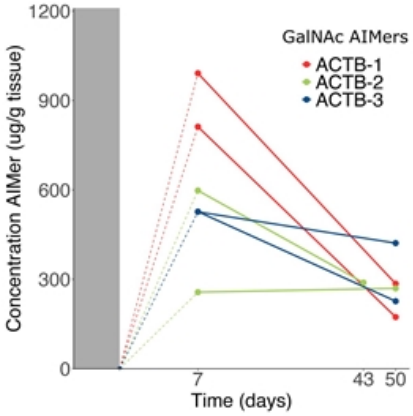
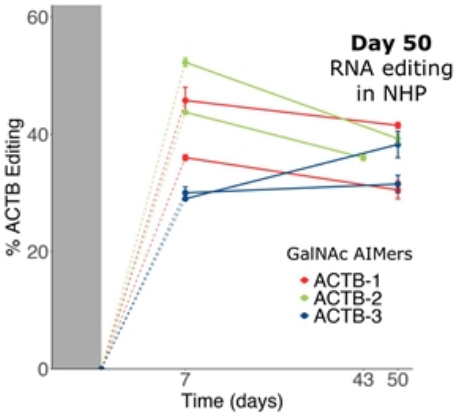
Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020). Manuscript submitted.

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

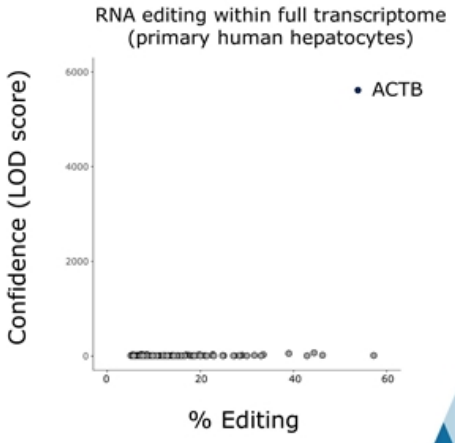
AIMers detected in liver of NHP at Day 50 (PK)



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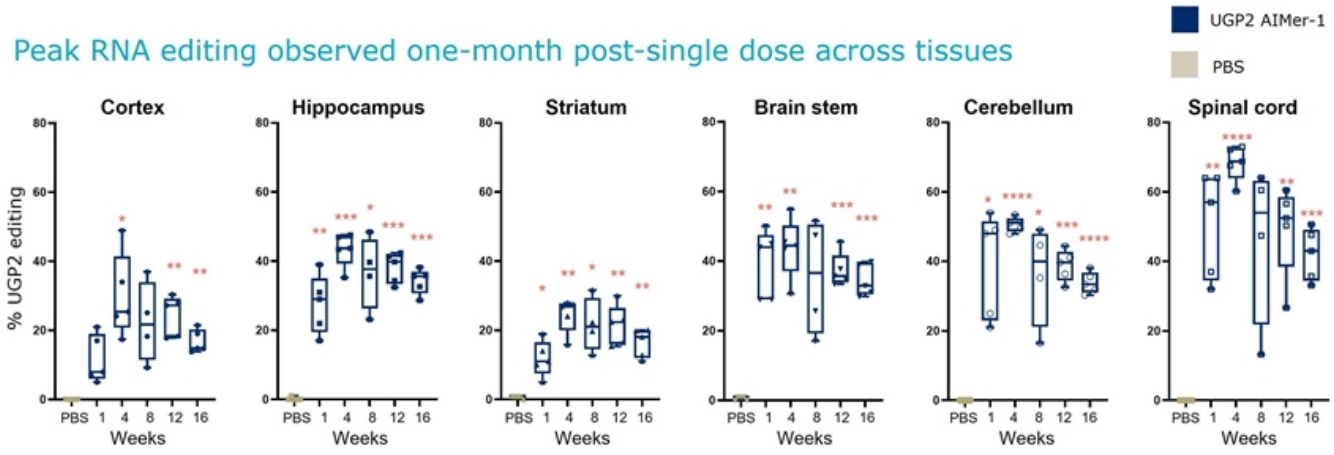
Left: AIMer PK C: 5mg/kg SC: Day 1,2,3,4,5; Liver biopsy; Right: Dosed 1um AIMer, 48 hrs later RNA collected, RNAseq conducted using strand-specific libraries to quantify on / off-target editing; plotted circles represent sites with LOD>3. Manuscript submitted. NHP: non-human primate; ACTB: Beta-actin

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

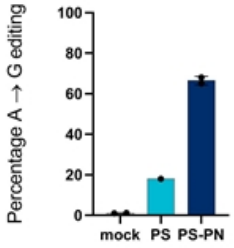
Variant base

ADAR editing site

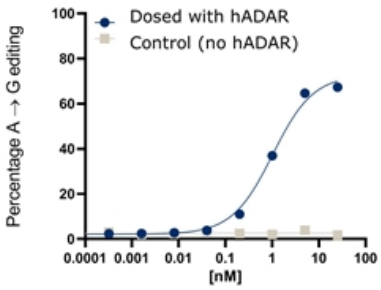
Nonsense mutations found in Rett Syndrome can occur in multiple locations on RNA transcript:

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

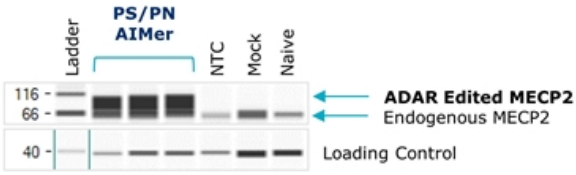
PN chemistry improved editing efficiency *in vitro*



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



Full length MECP2 protein is expressed following ADAR editing



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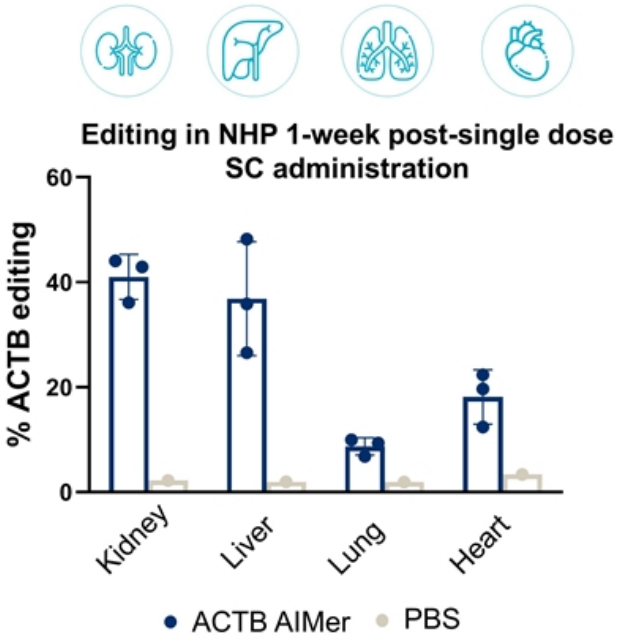
293T cells transfected with both nonsense mutation on MECP2 (GFP-fusion construct) and ADAR plasmids. AIMers transfected for 48h prior to RNA extraction and sequencing. Percentage editing determined by Sanger sequencing. Left: Single dose (25nM) treatment Middle: Full dose response curve (25nM, 5-fold 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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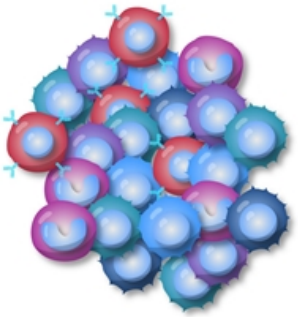
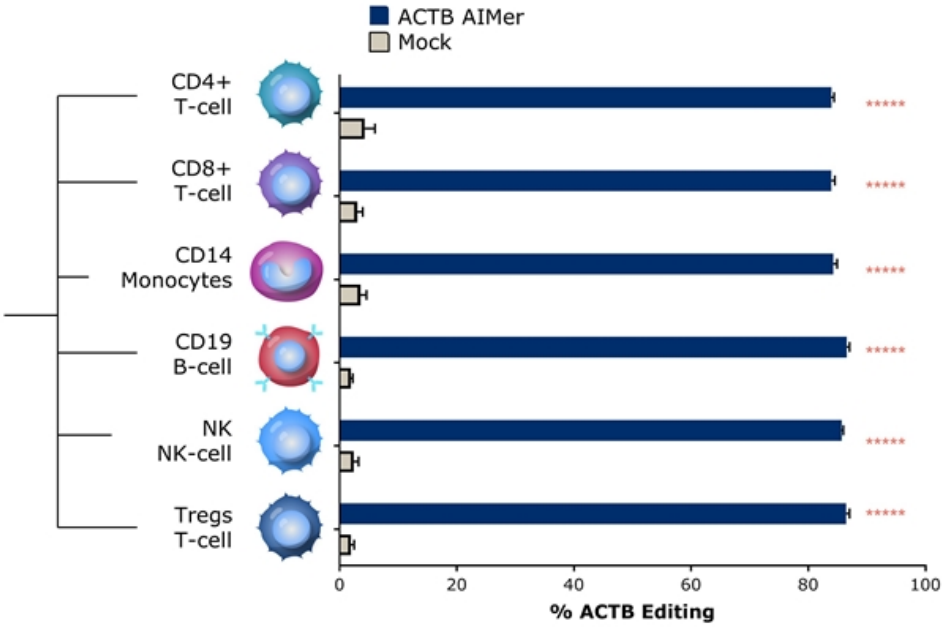
NHP: non-human primate; ACTB: Beta-actin
Dose: 50 mg/kg SC on Day 1 Necropsy for mRNA (ACTB Editing) Day 8

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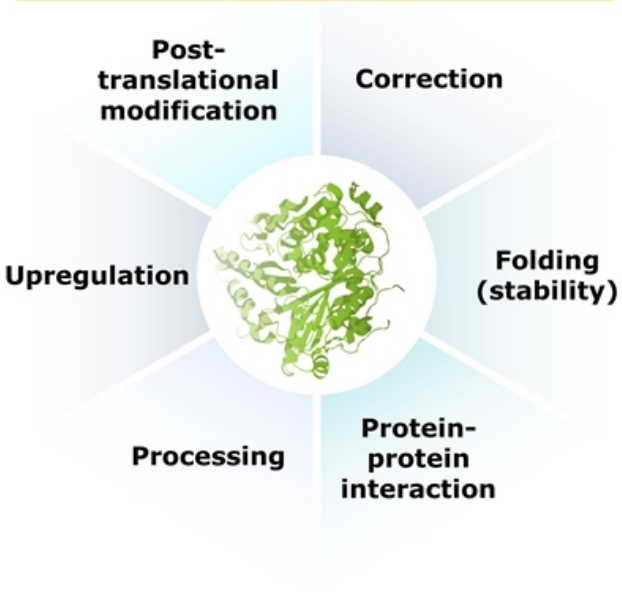
Human PBMCs dosed with 10 uM ACTB AIMers, under activating conditions (PHA). After 4 days, different cell types isolated, quantitated for editing %. ACTB: Beta-actin; Two-way ANOVA followed by post hoc comparison per cell line. P values were Bonferroni-corrected for multiple hypotheses

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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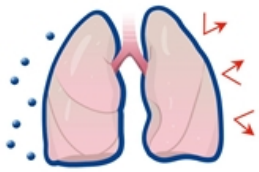
Alpha-1 antitrypsin deficiency

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

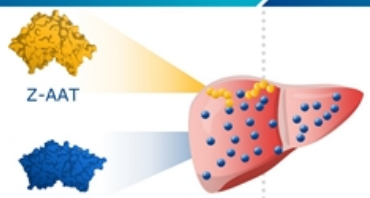
Wave ADAR editing approach addresses all goals of treatment:

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



M-AAT reaches lungs to protect from proteases

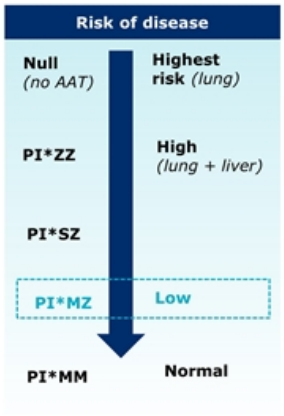
2) Reduce Z-AAT protein aggregation in liver



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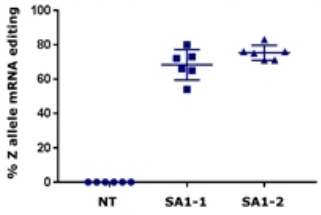
AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017; Remih 2021

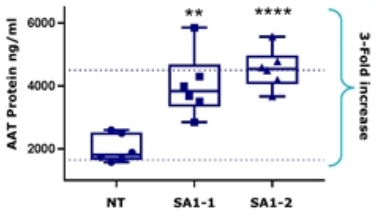
Focused on restoring wild-type M-AAT *in vivo*

In vitro proof of concept

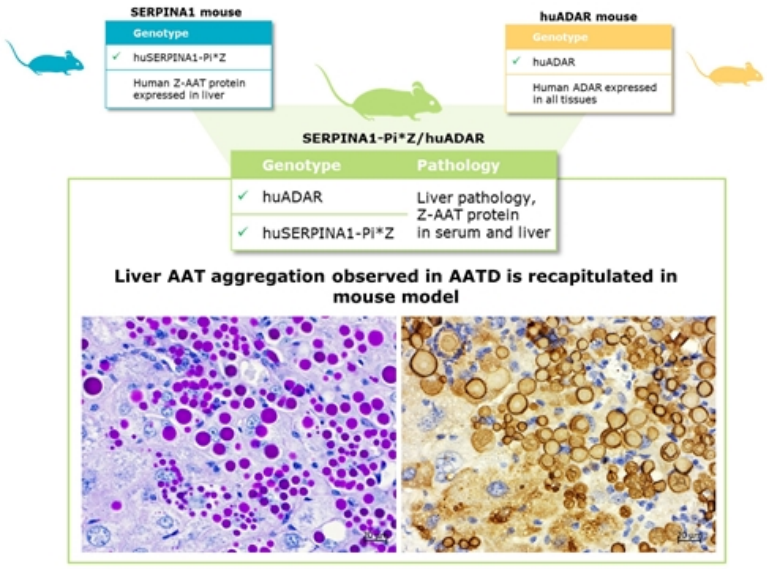
SERPINA1 Z allele mRNA editing



AAT protein concentration in media



In vivo proof of concept



Liver AAT aggregation observed in AATD is recapitulated in mouse model

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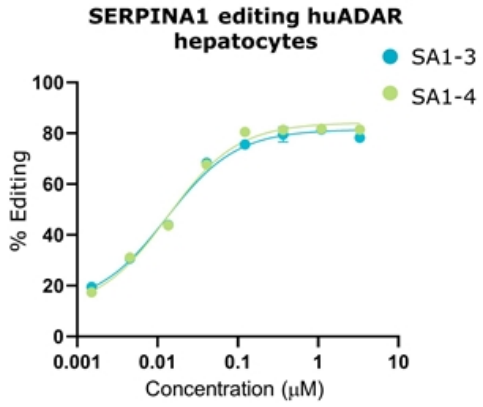
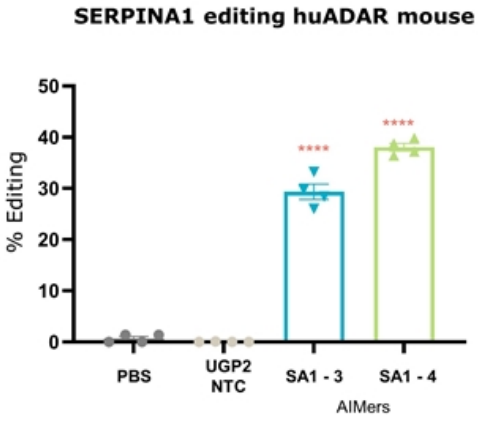
AATD: Alpha-1 antitrypsin deficiency, Z-AAT: mutated protein, M-AAT: wild-type human AAT protein
(Left) Hematoxylin and PAS stain and (Right) immunohistochemistry for AAT protein with hematoxylin counterstain in the huADAR/AATD mouse liver

Achieving 40% editing of Z allele mRNA at single time point

SERPINA1 Z allele mRNA editing levels nearing correction to heterozygote (MZ)





- GalNAc-conjugated compounds
- Up to 40% editing of Z allele mRNA in liver of transgenic human ADAR mice at day 7

✓ **Z allele mRNA editing *in vivo*** | **AAT protein increase** | **Wild-type M-AAT functional**

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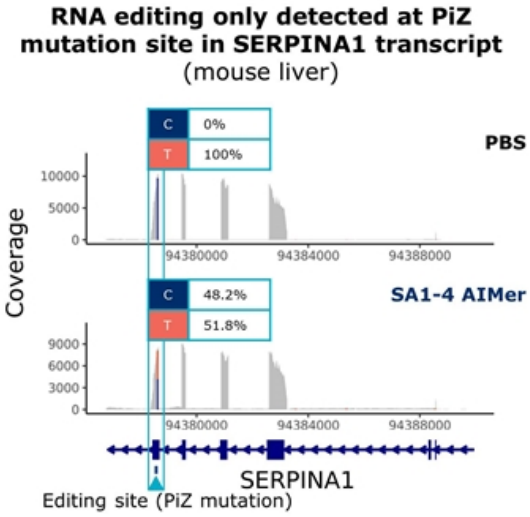
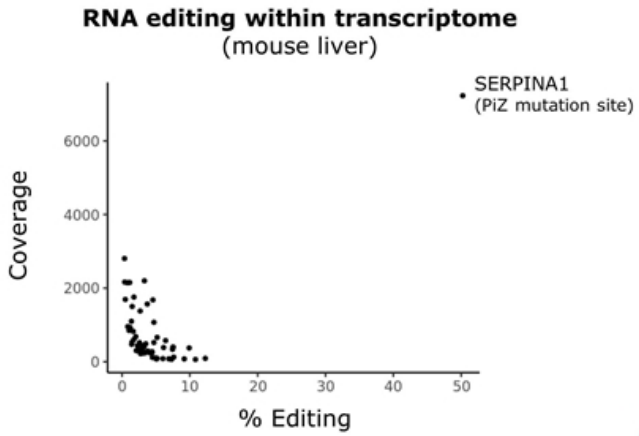
hu*ADAR*/*SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. Samples collected day 7. Stats: One-way ANOVA; NTC: non-targeting control

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





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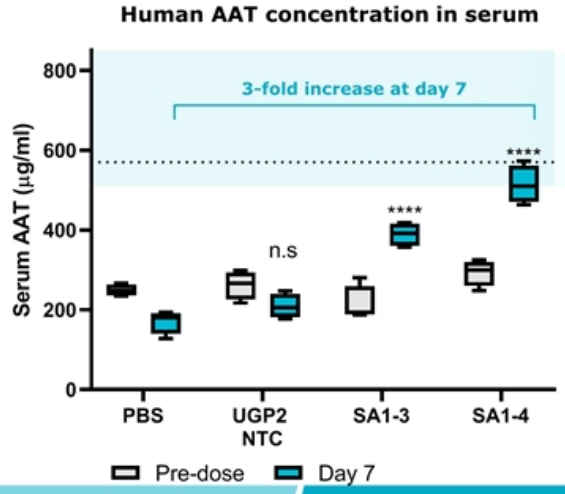
Dose 3 x 10mg/kg days (0, 2, 4) SC. Liver biopsies day 7. RNAseq, To quantify on-target SERPINA1 editing reads mapped to human SERPINA1, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4); Analyst and Investor Research Webcast September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

PRISM

Achieving therapeutically meaningful increases in circulating human AAT protein

3-fold increase in circulating human AAT as compared to PBS at initial timepoint



AAT serum levels by genotype

PI*MZ	~3 to 5-fold increase
PI*SZ	~2-fold increase
PI*ZZ	~3 – 7 uM

✓ Z allele mRNA editing *in vivo* | ✓ AAT protein increase | Wild-type M-AAT functional

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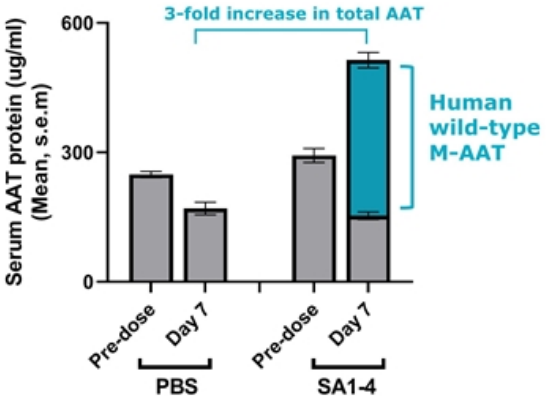
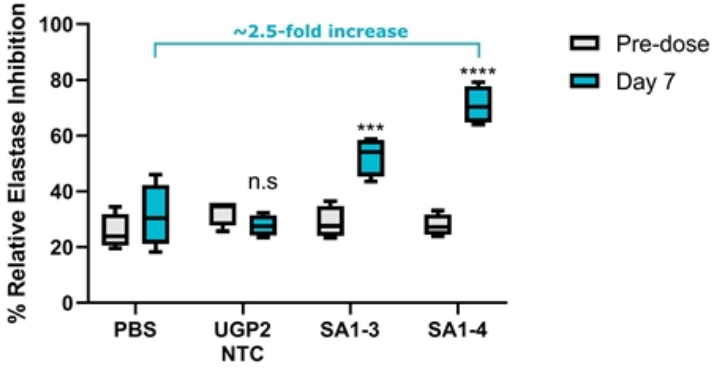
Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

ADAR editing restores circulating, functional M-AAT

Wild-type M-AAT detected with ADAR editing



Significant increase in neutrophil elastase inhibition with ADAR editing



✓ Z allele mRNA editing *in vivo* | ✓ AAT protein increase | ✓ Wild-type M-AAT functional

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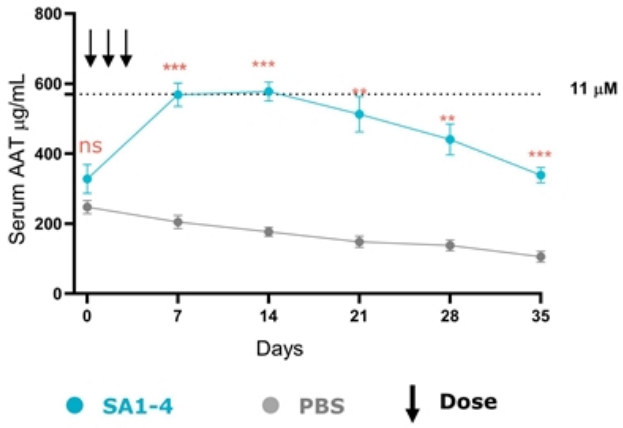
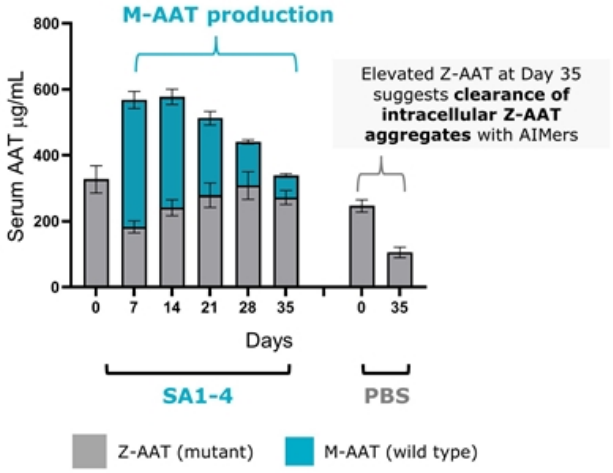
Left: Mass spectrometry and ELISA Right: (Elastase inhibition): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in elastase inhibition activity in serum collected at day 7 vs pre-dose for each treatment group; NTC: non-targeting control

Increase in circulating human AAT is durable, with restored M-AAT detected one month post last dose

Human AAT serum concentration ≥3-fold higher over 30 days post-last dose



Restored wild-type M-AAT detected over 30 days post-last dose



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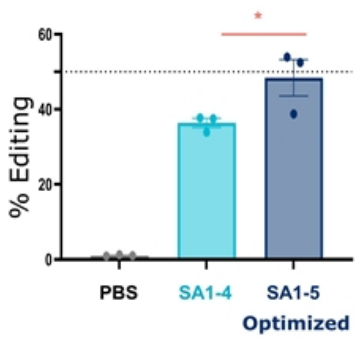
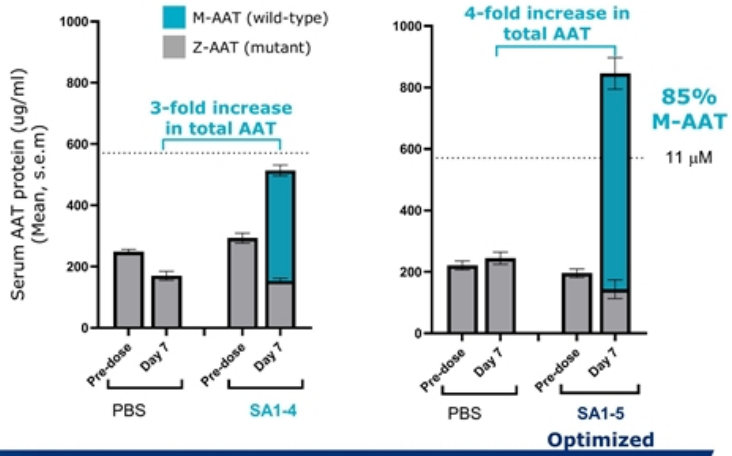
SA1-4: GalNAc AIMer (Left) hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. AAT levels quantified by ELISA. Data presented as mean ± sem. Stats: Matched 2-way ANOVA ns nonsignificant, ** P<0.01, *** P<0.001. (Right) Proportion of AAT in serum, Z type (mutant) or M type (wild type), measured by mass spectrometry, total AAT levels quantified by ELISA

Optimized AIMers achieve ~50% mRNA editing and restore AAT protein well above therapeutic threshold

SERPINA1 RNA editing huADAR mouse
(3x5 mg/kg, SC)



AAT protein concentration in serum
(3x10 mg/kg, SC)



- **Additional preclinical data expected in 2022, including reduction in Z-AAT aggregates and changes in liver pathology**
- **AATD AIMer development candidate expected in 2022**

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Left: AIMers administered hu*ADAR/SERPINA1* mice (3x5 mg/kg) on days 0, 2, and 4. Livers collected on day 7, and SERPINA1 editing was quantified by Sanger sequencing (shown as mean ±. sem) Stats: One-way ANOVA was used to test for differences in editing between SA1-4 and other oligos * P<0.05
Right: hu*ADAR/SERPINA1* mice administered PBS or 3 x 10 mg/kg AIMer (days 0, 2, and 4) SC. Proportion of AAT protein in serum, Z type or M type, measured by mass spectrometry, total AAT protein levels quantified by ELISA.

AATD development candidate expected in 2022

Demonstrate restoration of functional M-AAT	Assess specificity and duration of effect	Chemistry optimization to improve potency	Path to development candidate
✓ GalNAc-conjugated AIMers restore therapeutically meaningful levels of functional, wild-type M-AAT	✓ ADAR editing is highly specific ✓ Restored, circulating wild-type M-AAT in serum at 1-month post-last dose	✓ Chemistry optimization of AIMers further increases potency ✓ Optimized AIMers restore AAT in serum by 4-fold (>15uM) at Day 7 ✓ Restored wild-type M-AAT at 85% of total AAT	• Ongoing and planned preclinical studies assessing durability, dose response and PK/PD • Assessment of reduction in Z-AAT aggregates and changes in liver pathology

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Ophthalmology

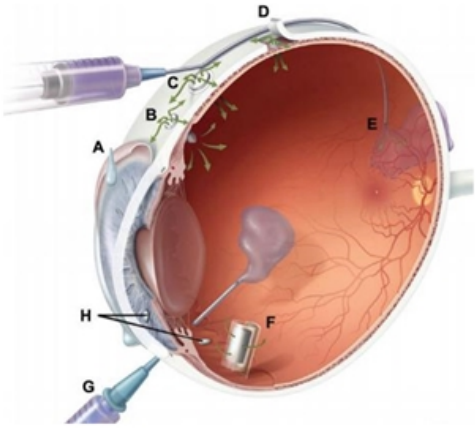
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus

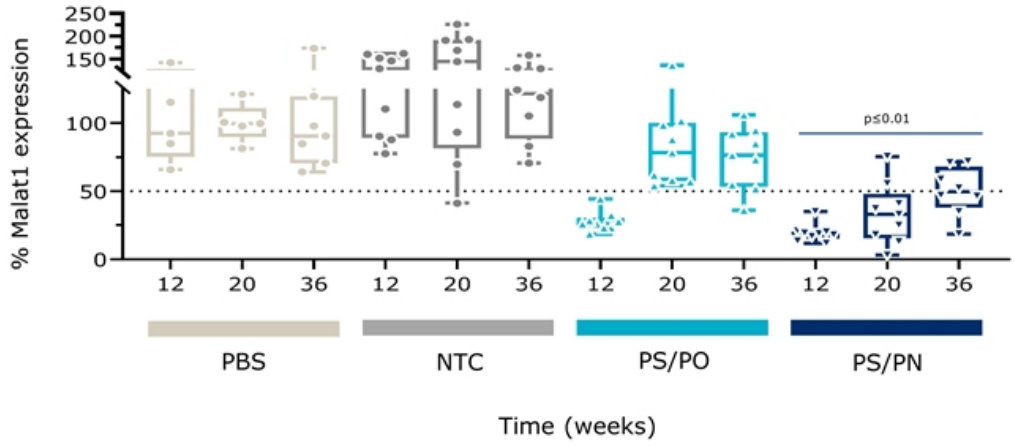


Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Durable Malat1 knockdown through 9 months with PN backbone chemistry modifications

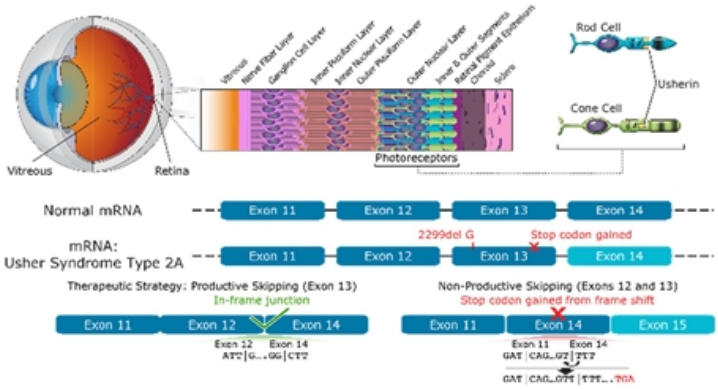
~50% Malat1 knockdown at 36 weeks in the posterior of the eye



Compound or PBS (1 x 50 ug IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control

Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



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

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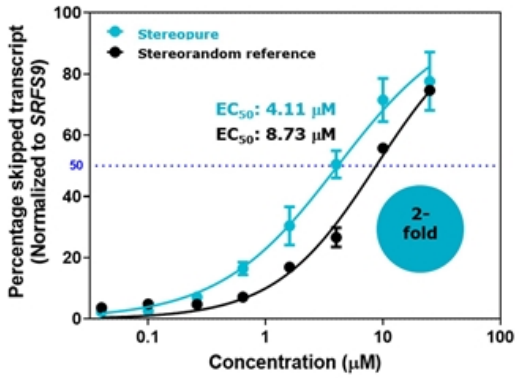
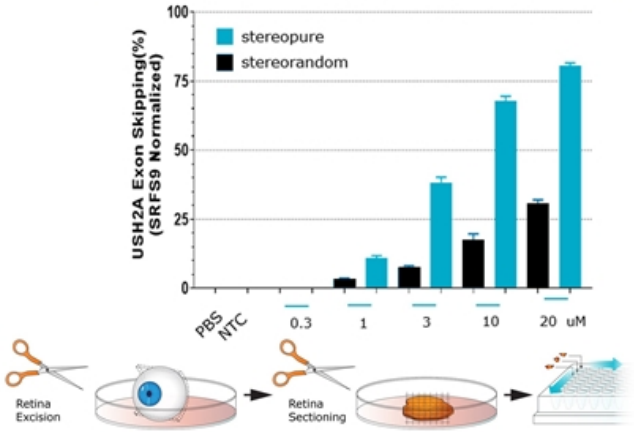
Sources: Boughman et al., 1983. *J Chron Dis.* 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

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

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



Target engagement in NHP retinas



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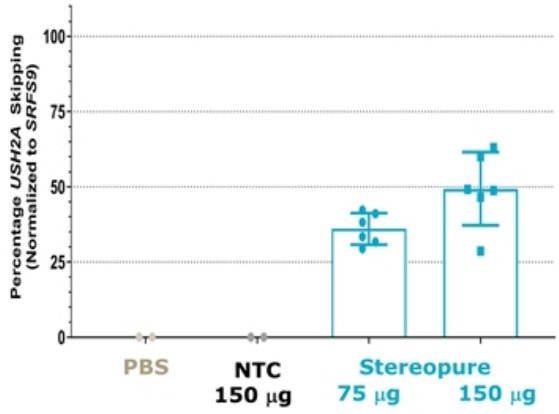
Oligonucleotides were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. USH2A transcripts were normalized to SRSF9. Data are mean±s.d., n=2. Stereorandom: Compound identified in van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Stereopure: is a stereopure antisense oligonucleotide. Right: Whole NHP were enucleated (n=4) and compounds (1–20 mM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m. stereorandom compound is from van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide.

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

Dose-dependent and specific exon skipping in NHP eye



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

*NHP exon 12 = human exon 13

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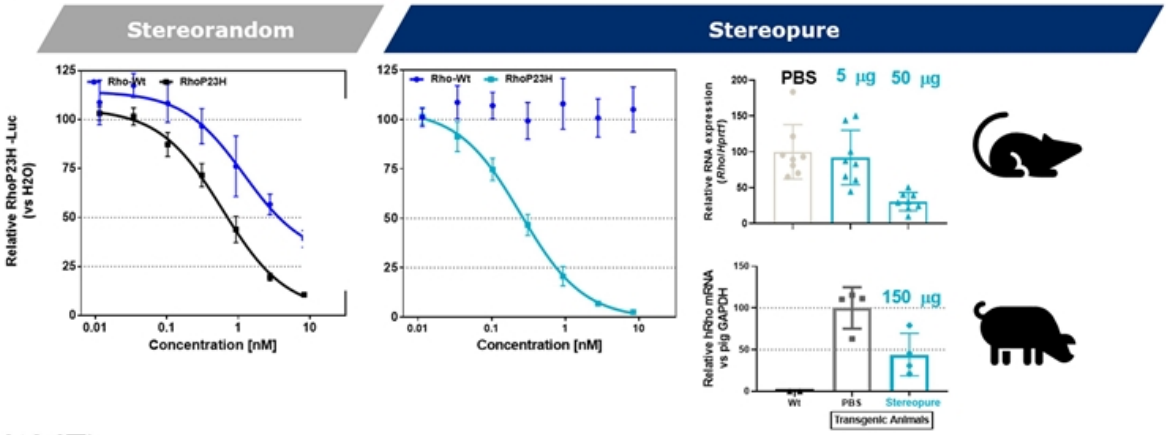
Stereopure *USH2A* skipping oligonucleotide, PBS or NTC antisense oligonucleotide was delivered to NHP by single IVT injection. One-week post-injection, retina was isolated and exon skipping was evaluated by Taqman assays. *USH2A* skipped transcript levels were normalized to *SRSF9*. Data are mean± s.e.m.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

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

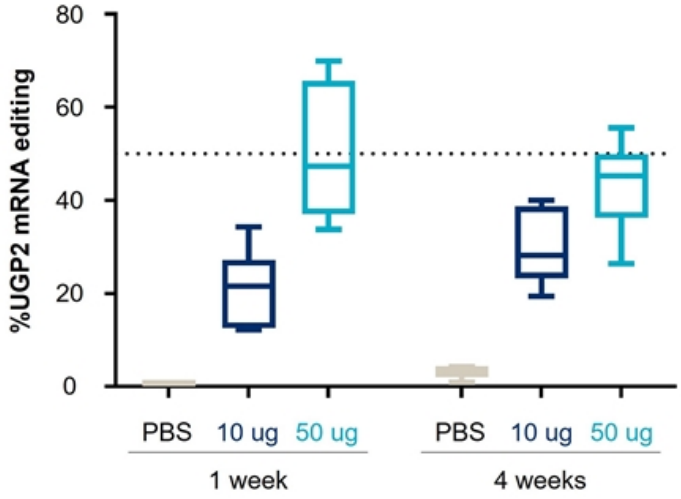
- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is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



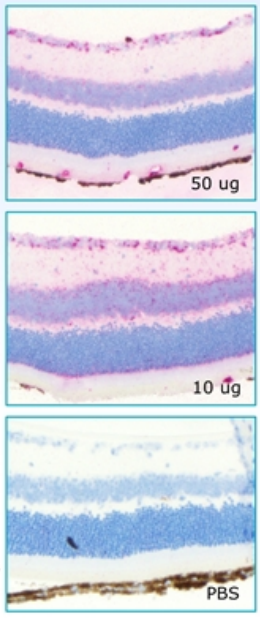
Left: Reporter assays on a sequence described in WO2016138353A1. Oligonucleotide and luciferase reporter plasmids (wild-type and mutant RHO) are transfected into Cos7 cells. Cells are harvested after 48 hrs, and relative luminescence is measured. Right: Single IVT injection (1 mL) in mouse Rho P23H mouse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

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

Durable, dose-dependent editing post-single intravitreal dose of UGP2 AIMer-1



AIMers in retina at 4 weeks



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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.


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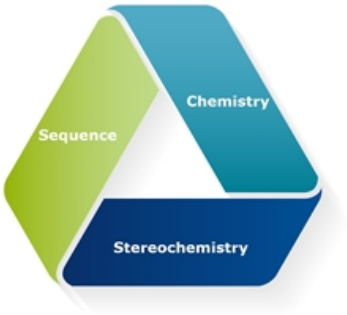
PRISM
Wave's discovery and drug development platform

PRISM enables precision modulation of RNA therapeutic properties using unique chemistry toolkit

PRISM

Bases	A, T, C, mC, G, U, other modified bases
2′ modifications	OMe, MOE, F, other modifications
Backbone chemistry	PO, PS, PN
Chiral control of any stereocenter	5′ modifications, backbone modifications



- Potency
- Tissue exposure
- Duration of activity

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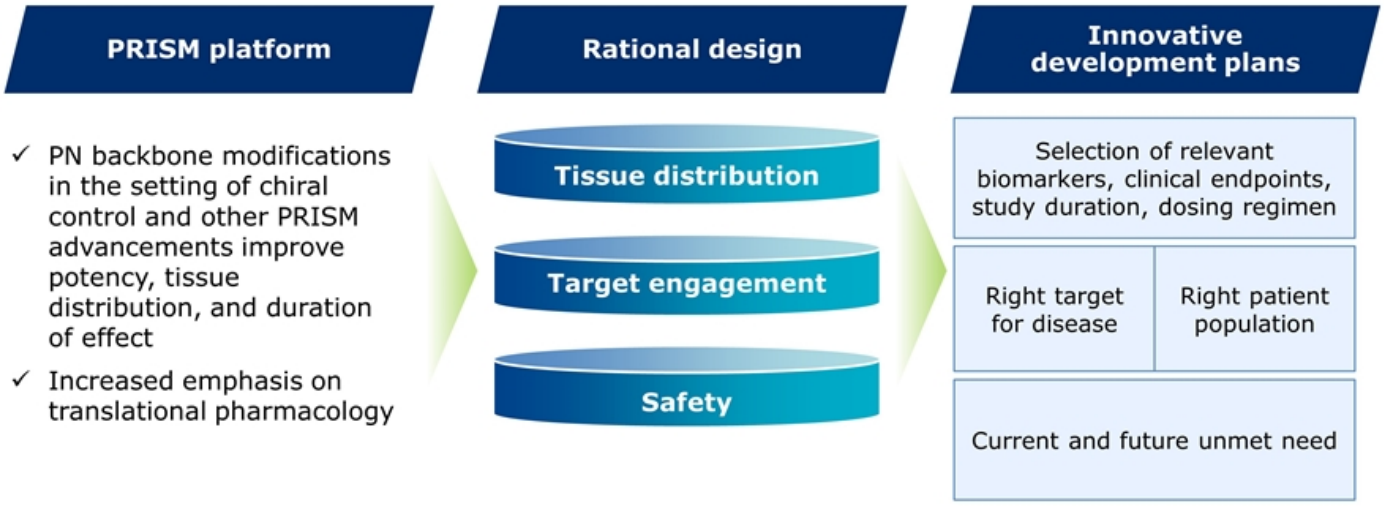
Keys to delivering therapeutic success in CNS



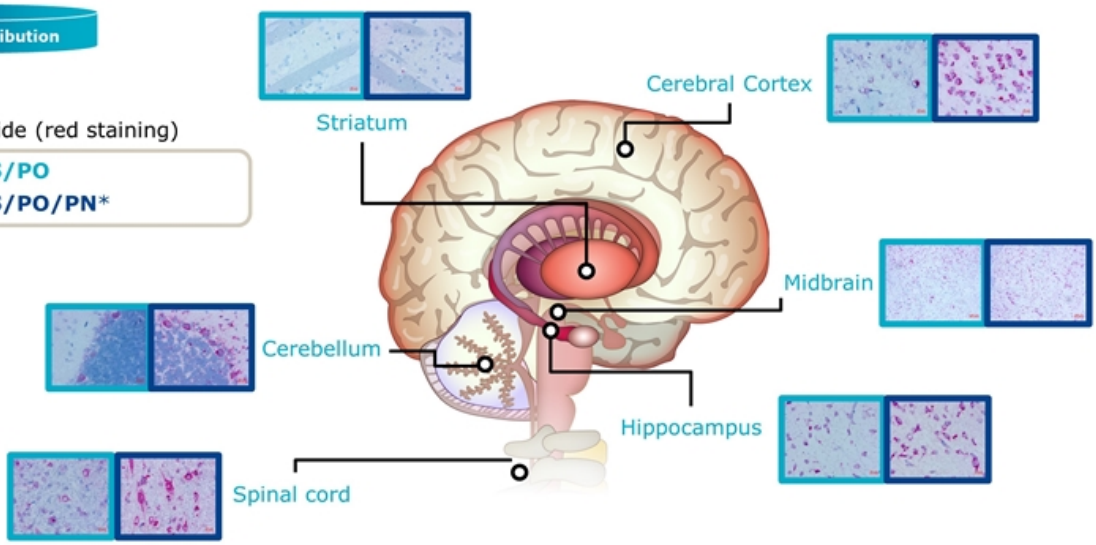
PN chemistry improves distribution to CNS

Distribution of oligonucleotides in NHP CNS 1-month post single IT dose

Tissue distribution

Oligonucleotide (red staining)

Backbone chemistry **PS/PO** **PS/PO/PN***



*Isomer 3; 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**

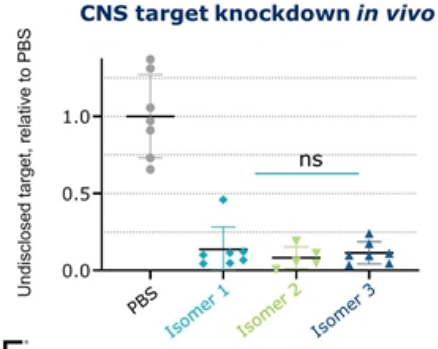
Isomer 1
Isomer 2
Isomer 3

Same sequence, but different backbone stereochemistry

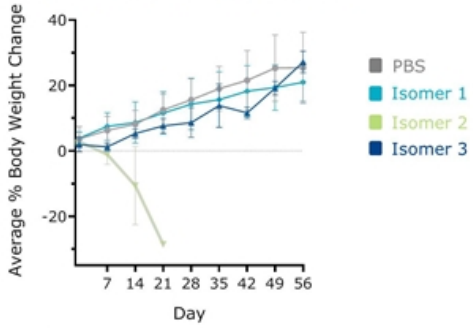
Stereoisomers have **similar** pharmacodynamic effects *in vivo*

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

CNS target knockdown *in vivo*



Percentage Body Weight Change



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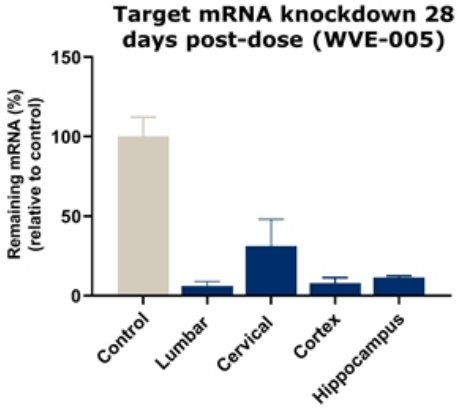
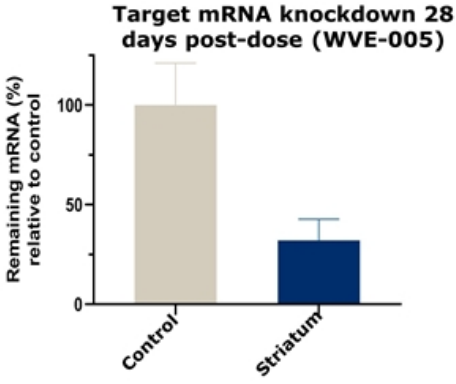
Left: In a target engagement study, 7 mice administered 2 x 50 ug oligonucleotide or PBS by ICV on days 0 and 7. Tissue collected on day 14. Target mRNA normalized to Tubb3 and plotted relative to PBS. Data presented as mean ± SD (n=7). Stats: One-way ANOVA ns not significant, PBS phosphate buffered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



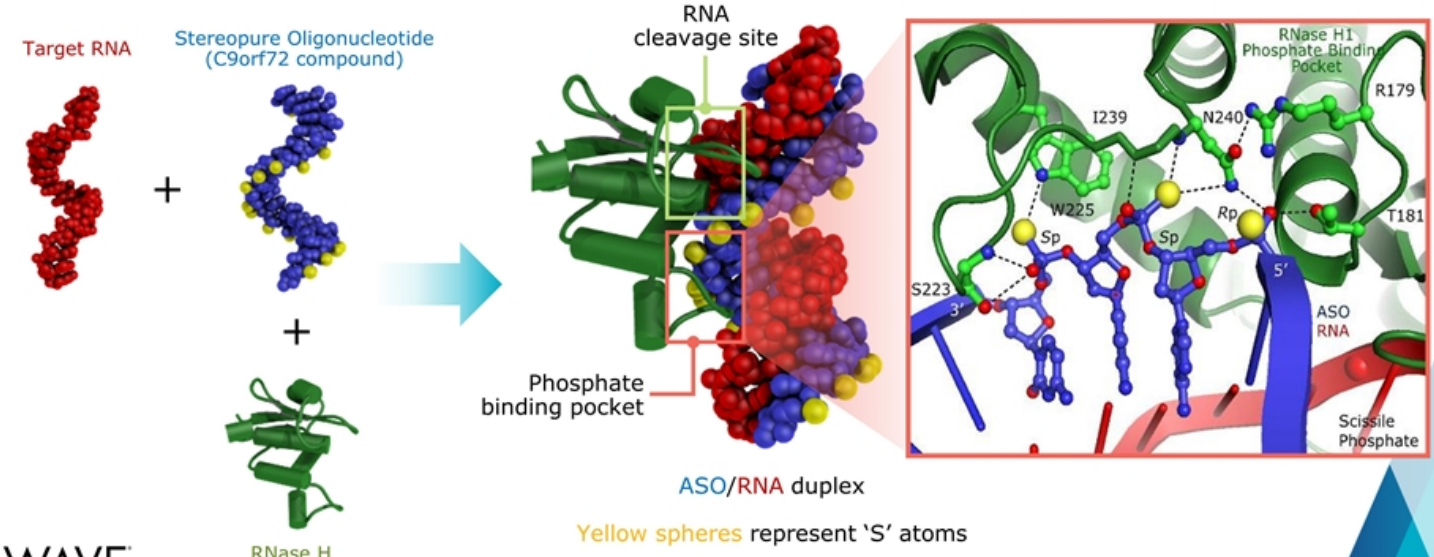


Potential for infrequent IT administration, widespread CNS distribution of PN modified oligonucleotides, and availability of disease biomarkers facilitates development of differentiated CNS portfolio

NHPs: Non-human primates
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.

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

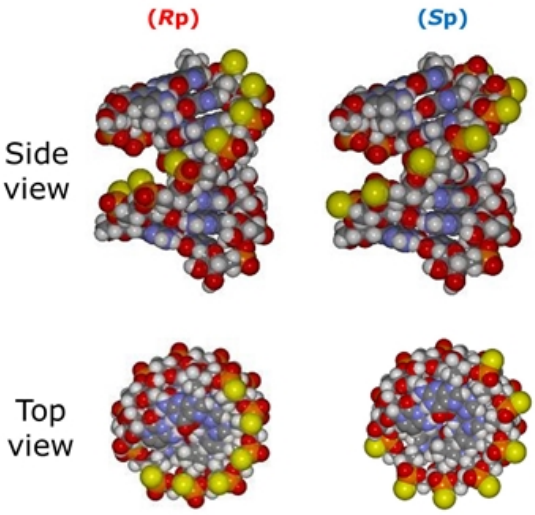


ASO/RNA duplex

Yellow spheres represent 'S' atoms

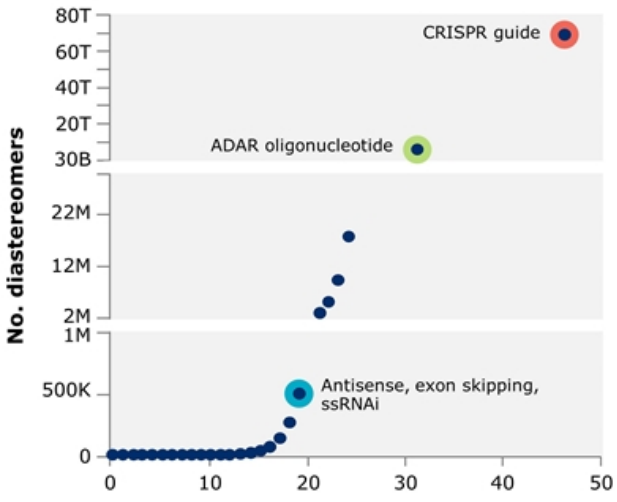
Importance of controlling stereochemistry

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

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Upcoming milestones

Upcoming milestones throughout 2022 will unlock opportunities

WVE-004 C9orf72 ALS & FTD	• Clinical data being generated to enable decision making	**Silencing**	**CNS** *(Intrathecal)*
WVE-003 HD SNP3	• Clinical data being generated to enable decision making	**Splicing**	**Muscle** *(IV)*
WVE-N531 DMD Exon 53	• Clinical data being generated to enable decision making		
AIMer AATD SERPINA1	• Additional preclinical data, including reduction in Z-AAT aggregates and changes in liver pathology • AATD AIMer development candidate expected	**ADAR editing**	**Liver** *(Subcutaneous GalNAc)*

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

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