# 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): June 2, 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))

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

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

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

Emerging growth company ☐

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

**Item 7.01 Regulation FD Disclosure.**

On June 2, 2021, Wave Life Sciences Ltd. (the "Company") issued a press release announcing the first *in vivo* data from the Company's ADAR editing discovery program for alpha-1 antitrypsin deficiency ("AATD"). A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

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 June 2, 2021, the Company updated its corporate presentation to include the first *in vivo* data from the Company's ADAR editing discovery program for AATD. The presentation is available on the "For Investors & Media" section of the Company's website at http://ir.wavelifesciences.com/ and is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

*The information in this Item 7.01 is 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 it 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 Item 7.01 are furnished and not filed:

| Exhibit No. | Description |
|---|---|
| 99.1 | Press Release issued by Wave Life Sciences Ltd. dated June 2, 2021 |
| 99.2 | Corporate Presentation of Wave Life Sciences Ltd. dated June 2, 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: June 2, 2021

**Wave Life Sciences Announces Proof-of-Concept Preclinical Data for ADAR Editing Program in Alpha-1 Antitrypsin Deficiency**

*First proof-of-concept in vivo data for RNA editing using endogenous ADAR enzymes in alpha-1 antitrypsin deficiency*

*ADAR editing resulted in therapeutically meaningful restoration of circulating functional AAT protein*

*Wave's program in alpha-1 antitrypsin deficiency aims to correct the single base mutation in mRNA derived from the SERPINA1 Z allele, thereby addressing both lung and liver manifestations of the disease*

**CAMBRIDGE, Mass., June 2, 2021** – 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 the first proof-of-concept preclinical data for its ADAR (adenosine deaminases acting on RNA)-mediated RNA editing ("ADAR editing") program in alpha-1 antitrypsin deficiency (AATD). Up to 40 percent editing of human *SERPINA1* Z-allele mRNA in the liver was observed at a single timepoint, which resulted in a therapeutically meaningful increase in circulating functional wild-type AAT protein. This initial *in vivo* study utilized Wave's proprietary transgenic mouse model, which has both the human *SERPINA1* Z-allele as well as human ADAR that is expressed comparably to human cells.

"These findings are a critical contribution to the genetic medicines field, as they represent the first proof-of-concept *in vivo* data for RNA editing using endogenous ADAR enzymes in AATD. They also reinforce Wave's leadership position in the RNA editing field, as we continue to observe meaningful and significant levels of editing in animal models, including in mice and NHPs, which paves the way for translating this technology to the clinic," said Paul Bolno, President and Chief Executive Officer of Wave Life Sciences. "Wave's approach to RNA editing using endogenous ADAR and our AATD program have advanced quickly, with the team demonstrating immense creativity and tenacity to reach this important milestone. We look forward to presenting additional *in vivo* data in the second half of this year and continuing our progress towards the clinic."

Wave's AATD program, the first to utilize its ADAR editing modality, uses GalNAc-conjugated oligonucleotides to correct the single base mutation in mRNA derived from the *SERPINA1* Z allele. ADAR editing provides a simple and efficient approach to treating AATD by simultaneously reducing aggregation of mutated, misfolded alpha-1 antitrypsin protein (Z-AAT) and increasing circulating levels of wild-type protein (M-AAT), thus having the potential to address both the lung and liver manifestations of the disease while avoiding risk from permanent off-target changes to the DNA. Wave is initially focusing on homozygous "ZZ" patients who have the highest risk of disease and where RNA editing may result in a heterozygous "MZ" phenotype, which would result in a substantially lower risk of disease.

The goals of Wave's first *in vivo* proof-of-concept study were: 1) achieve editing of *SERPINA1* Z allele mRNA in the liver at levels that approach the MZ phenotype; 2) restore human M-AAT protein in serum; and 3) demonstrate functionality of the restored human M-AAT protein. Results were analyzed at a single timepoint (day 7) and demonstrated:

- Up to 40 percent editing of Z allele mRNA was observed in the liver of Wave's transgenic human ADAR mice, correlating with levels nearing correction to an MZ phenotype.
- Editing was highly specific with no bystander edits.

- A three-fold increase in circulating human AAT compared with placebo was observed, similar to the fold difference seen between ZZ and MZ patients.
- 75% of circulating AAT protein was confirmed as M-AAT. This also suggests a reduction of Z-AAT in the liver and serum.
- Confirmation of functionality of the M-AAT protein using a neutrophil elastase inhibition assay.

Wave's preclinical studies for its AATD program are ongoing and additional data on durability and dose response are expected in the second half of 2021. Wave also continues to evaluate ADAR editing compounds for other disease targets, leveraging its proprietary mouse model which expresses human ADAR and is crossed with disease-specific mouse models.

These proof-of-concept preclinical data were also presented at the Jefferies Virtual Healthcare Conference on June 2, 2021 and the presentation can be viewed by visiting the investor relations page of the Wave Life Sciences corporate website at http://ir.wavelifesciences.com.

**About ADAR Editing**

Wave's novel RNA editing platform capability uses endogenous ADAR (adenosine deaminases acting on RNA) enzymes via free uptake of A-to-I (G) RNA editing oligonucleotides. ADAR editing may provide an attractive alternative to DNA editing, as the effects of RNA editing are both reversible and titratable, and avoid potential long-term risks associated with permanent off-target genome edits. Wave's ADAR editing modality also offers potential advantages over other RNA editing approaches, including the use of short oligonucleotides that are freely taken up by cells and do not require viral or nanoparticle delivery. Wave's design also reduces the risk of immunogenicity from exogenous proteins and off-target effects.

**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 within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, the potential significance of Wave's first proof-of-concept *in vivo* data for RNA editing with respect to AATD and the genetic medicines field; the anticipated plans, type of data and timing from Wave's ongoing preclinical studies for its AATD program; Wave's evaluation of additional ADAR-amenable disease targets. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to

a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, the risks and uncertainties described in the section entitled “Risk Factors” in Wave’s most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as amended, and in other filings Wave makes with the SEC from time to time. Wave undertakes no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

# # #

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Exhibit 99.2

# Wave Life Sciences

## Corporate Presentation

June 2, 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.

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# Building a leading genetic medicines company

## INNOVATIVE PLATFORM

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

## FOUNDATION OF NEUROLOGY PROGRAMS

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

PRISM
Wave's discovery and drug development platform

## CLINICAL DEVELOPMENT EXPERTISE

- Multiple global clinical trials
- Innovative trial designs

## MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

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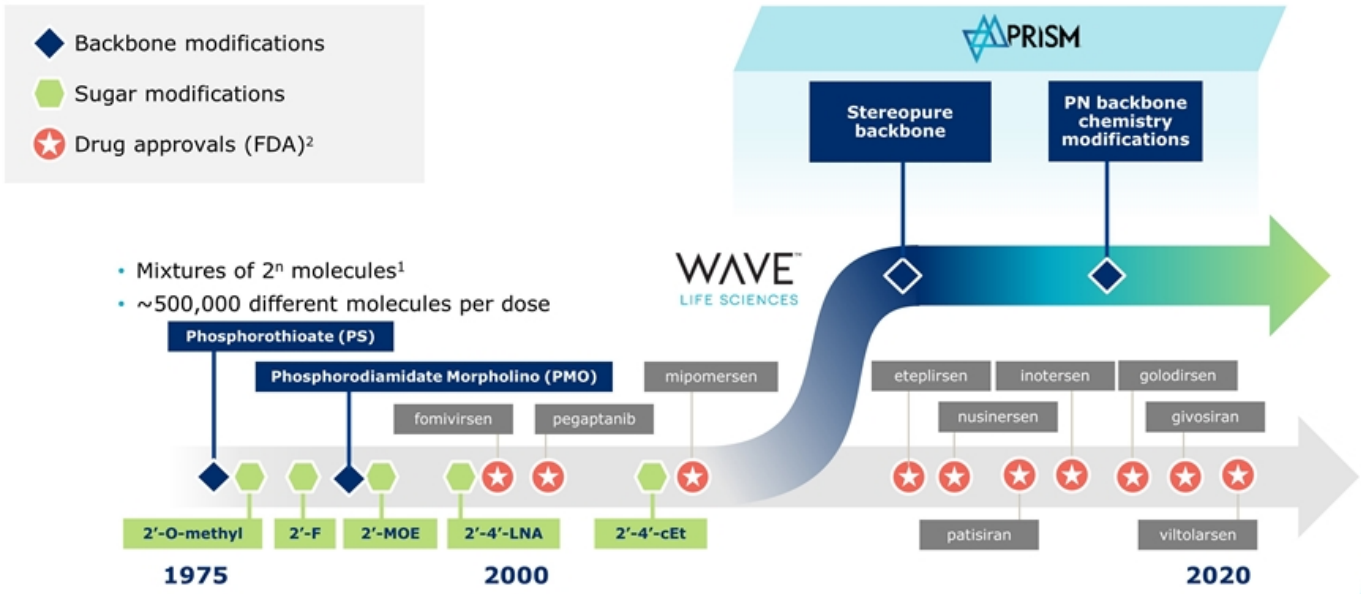
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
[1]stereopure oligonucleotides and novel backbone chemistry modifications

# PRISM has unlocked novel and proprietary advances in oligonucleotide design

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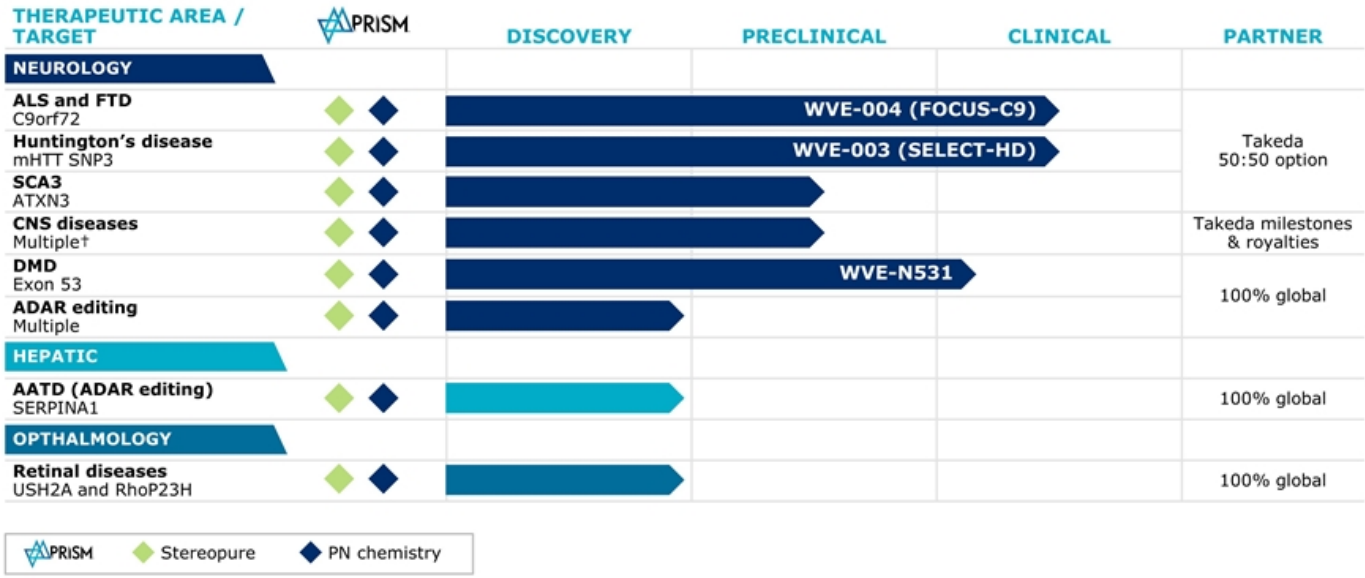
[1]n=number of chiral centers

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

# Innovative pipeline led by neurology programs

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

# Platform evolution reflected in clinical pipeline

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

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

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

C9orf72

**WVE-004**

Variant-selective silencing candidate in ALS and FTD

SNP3

**WVE-003**

Allele-selective silencing candidate in HD

Exon 53

**WVE-N531**

Exon skipping candidate in DMD

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

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# WVE-004

## Amyotrophic Lateral Sclerosis (ALS)

## Frontotemporal Dementia (FTD)

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

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


*Different manifestations across a clinical spectrum*

## Amyotrophic Lateral Sclerosis (ALS)

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

## Frontotemporal Dementia (FTD)

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

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

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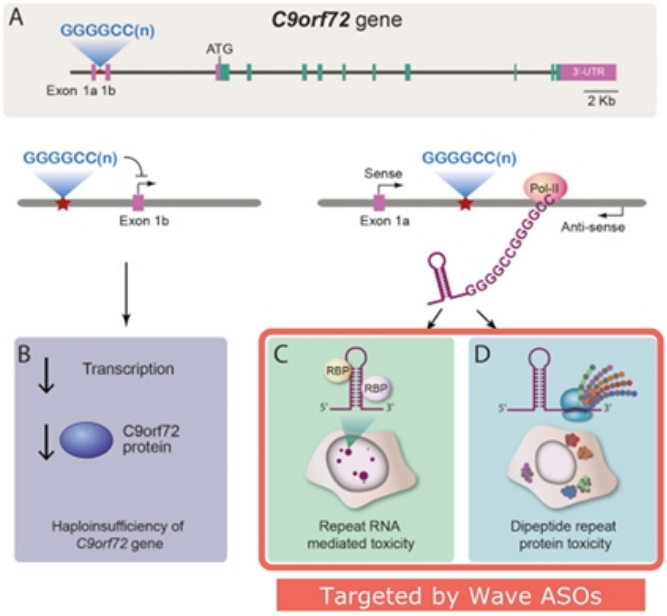
Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

# C9orf72 repeat expansions: Mechanisms of cellular toxicity

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

**Variant-selective targeting could address multiple potential drivers of toxicity**

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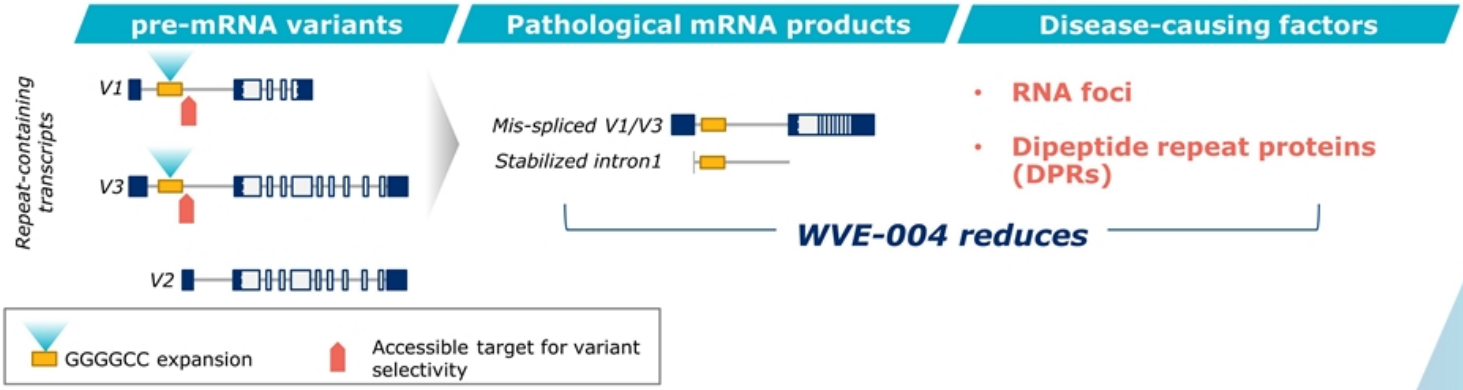
Sources: Gitler et al, Brain Research, September 2016. Zhu et al, Nature Neuroscience, May 2020

# C9orf72 targeting strategy spares C9orf72 protein

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




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

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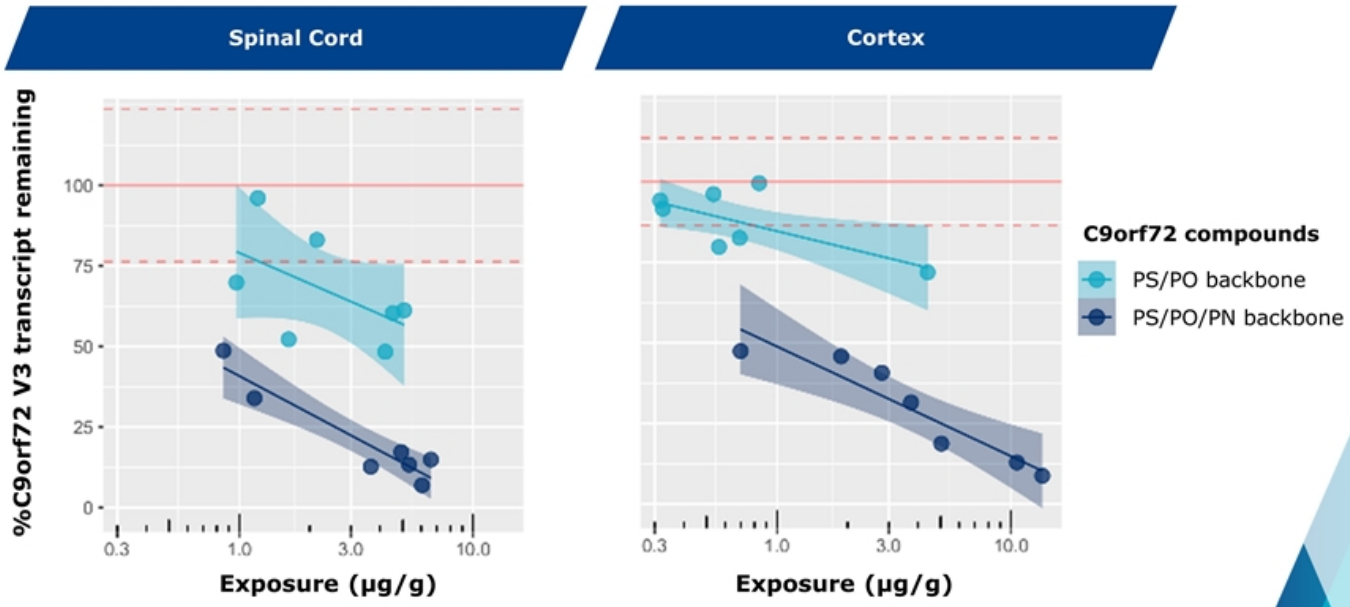
# PN backbone chemistry modifications: Improved potency among C9orf72-targeting oligonucleotides *in vivo*

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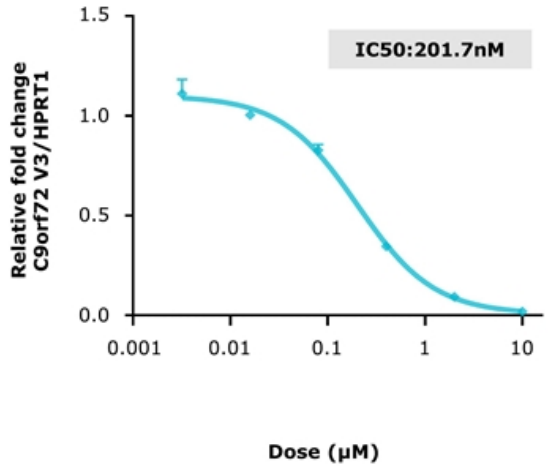
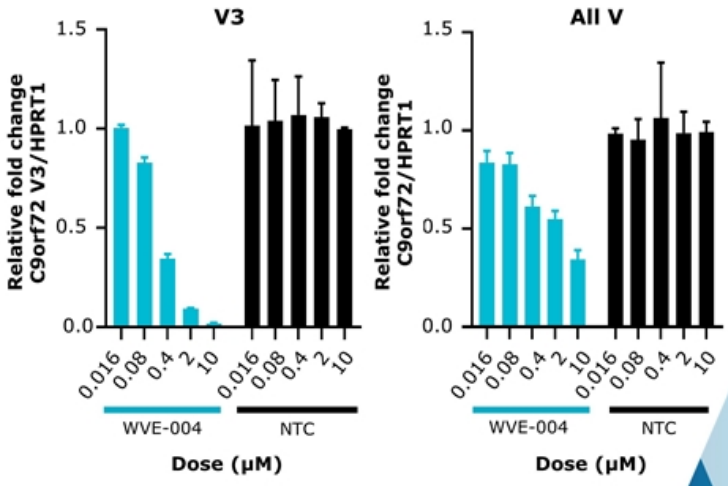
Mice received 2 x 50 ug ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.

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

**_In vitro_ activity in C9 patient-derived neurons**




**_In vitro_ selectivity in C9 patient-derived neurons**

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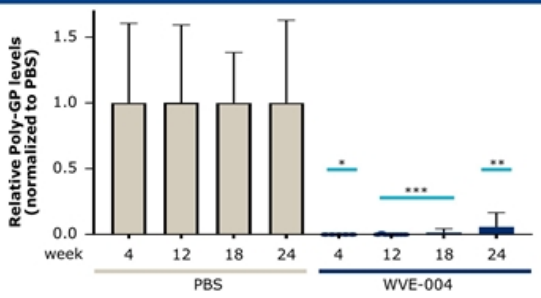
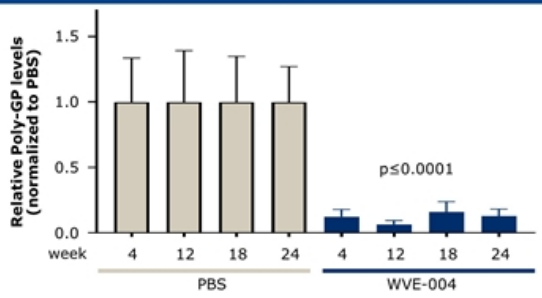
C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gymnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC- non-targeting control.

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

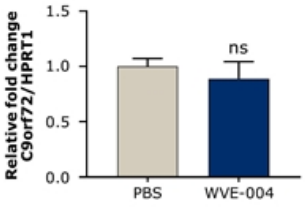
**Spinal cord**

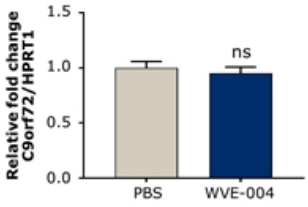



**Cortex**




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

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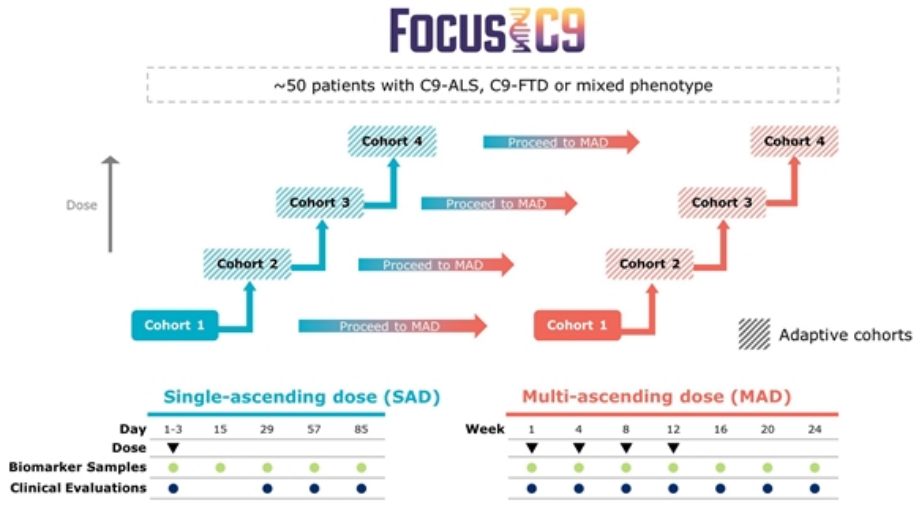
Full results presented at the 31st International Symposium on ALS/ MND (December 2020)
Top: 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. ICV: intracerebroventricular; DPR: Dipeptide repeat protein; Bottom: C9 BAC transgenic mice administered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

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

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




### Primary objectives

- Safety and tolerability

### Secondary objectives

- Plasma and CSF PK profile
- PolyGP in CSF

### Exploratory objectives

Biomarkers:

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

Clinical endpoints:

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

**Dose escalation and MAD dosing frequency guided by independent committee**

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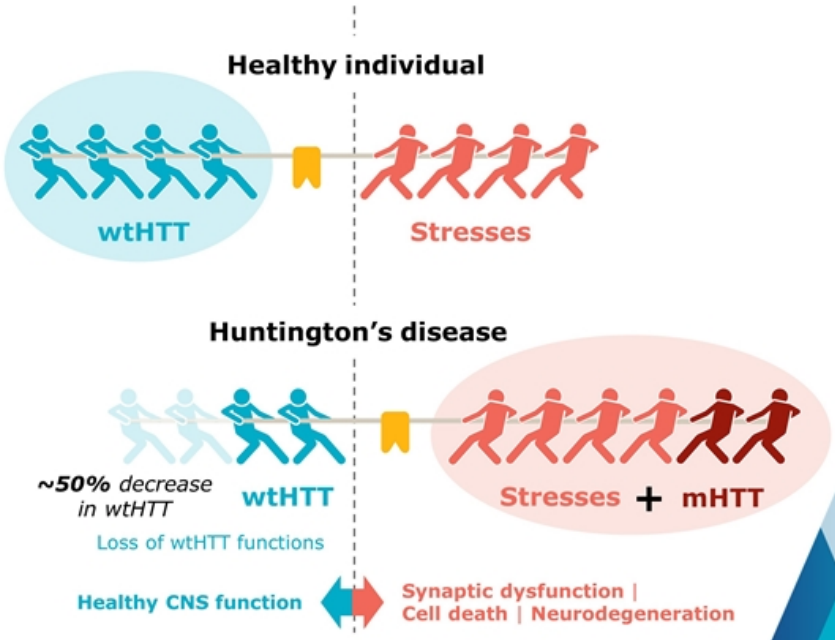
# WVE-003

## 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]

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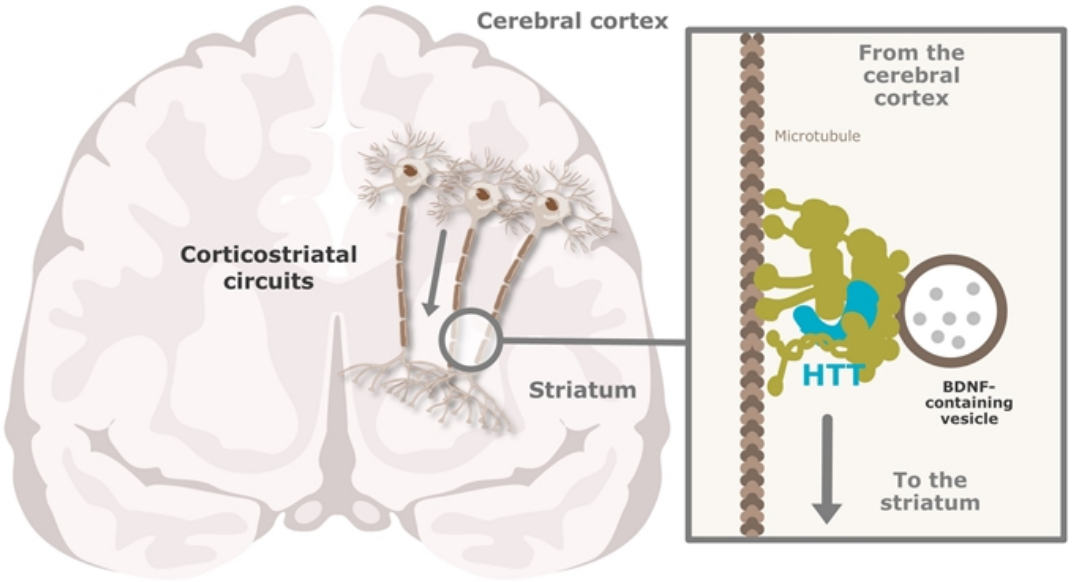
BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 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]**

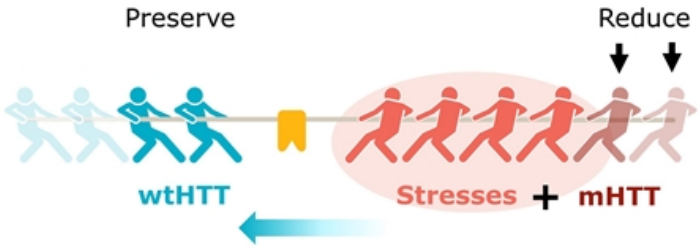
BDNF, brain-derived neurotrophic factor; HD, Huntington's disease; HTT, huntingtin protein.

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

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[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
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Check for updates

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

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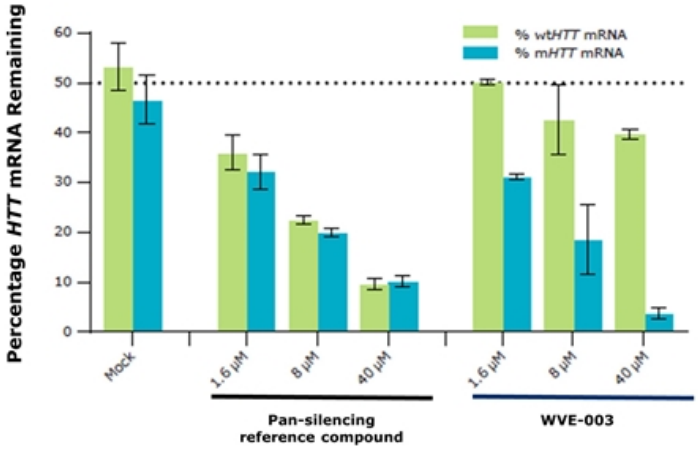
Source: Poplawski et al., *Nature*, April 2019
Htt: Huntingtin protein

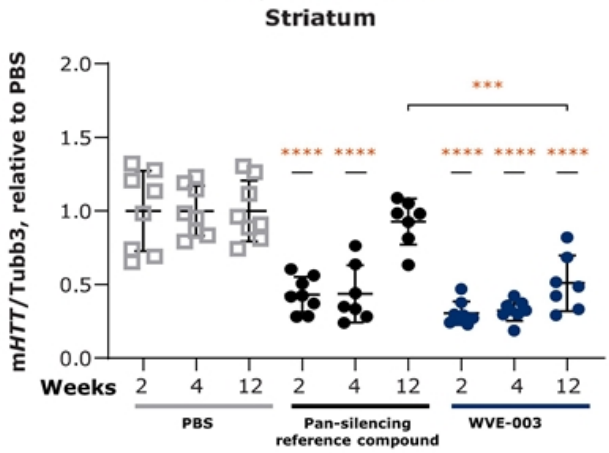
# WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

## 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

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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**

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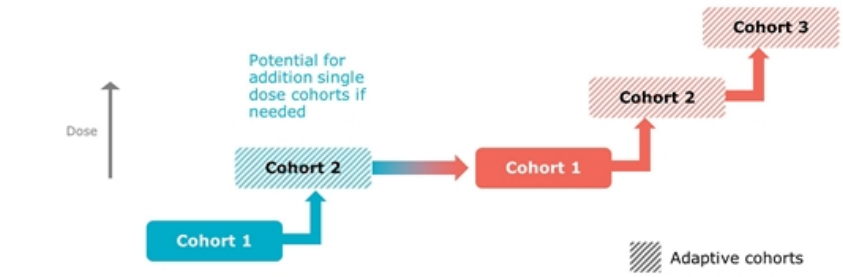
PK: pharmacokinetic PD: pharmacodynamic $IC_{50}$: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

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

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

~36 patients with early manifest HD diagnosis with SNP3 variant




**Single-ascending dose (SAD)**

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

**Multi-ascending dose (MAD)**

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

### Primary objectives

- Safety and tolerability

### Secondary objectives

- Plasma PK profile
- CSF exposure

### Exploratory objectives

Biomarkers:
- mHTT
- wtHTT
- NfL

Clinical endpoints:
- UHDRS

**Dose escalation and MAD dosing frequency guided by independent committee**

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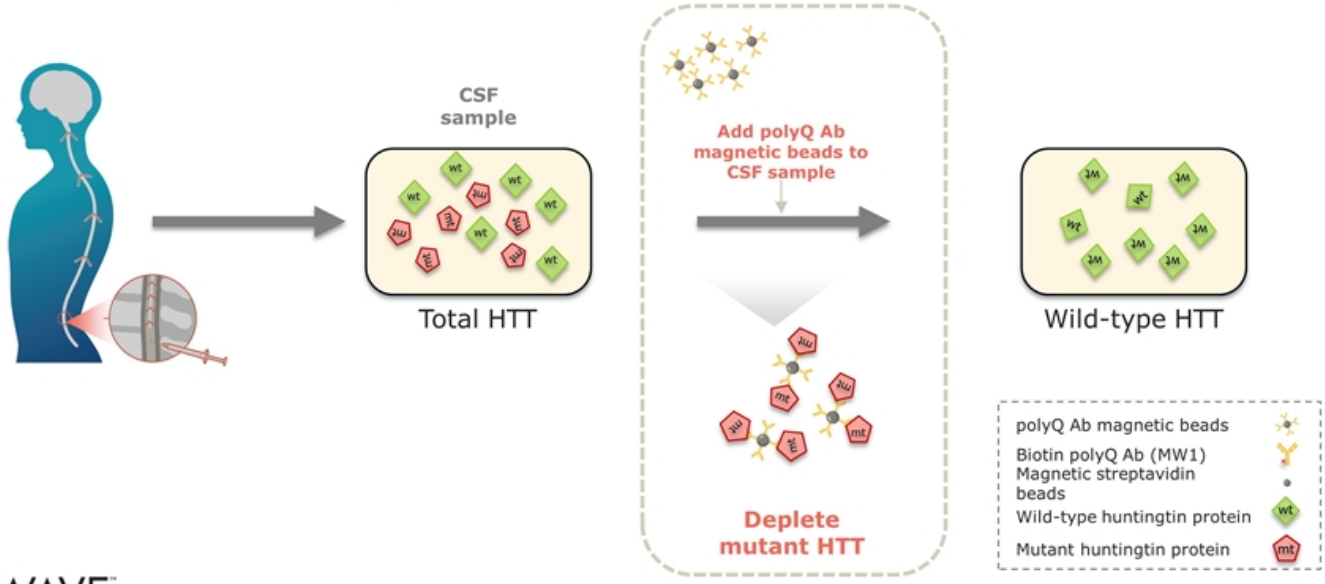
mHTT: mutant huntingtin; wtHTT: wild-type huntingtin; NfL: neurofilament light

# Assessment of wild-type protein in CSF

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

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

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# WVE-N531

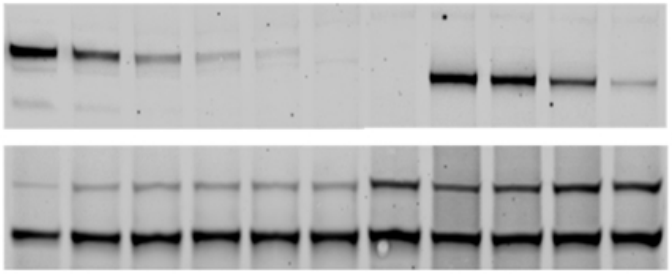
## Duchenne muscular dystrophy

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

## Dystrophin protein restoration of up to 71%

**Western Blot normalized to primary healthy human myoblast lysate**

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




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

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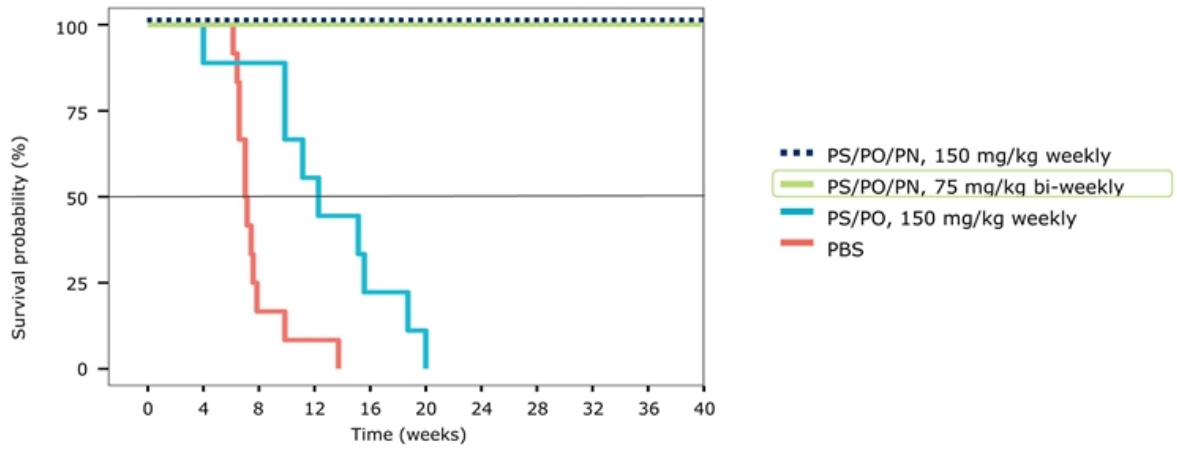
Experimental conditions: Δ45-52 (D45-52) patient myoblasts were treated with oligonucleotide for 6d under free-uptake conditions in differentiation media. Protein harvested in RIPA buffer and dystrophin restoration analyzed by Western Blot. Signal normalized to vinculin loading control and to primary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

# PN chemistry led to overall survival benefit in dKO model

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




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

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

# Clinical trial of WVE-N531 to initiate in 2021

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

**Dosing in clinical trial expected to initiate in 2021**

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Wave's discovery and drug development platform

# Rational drug design: Evolution of PRISM platform

## Addressing the reality of stereochemistry


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

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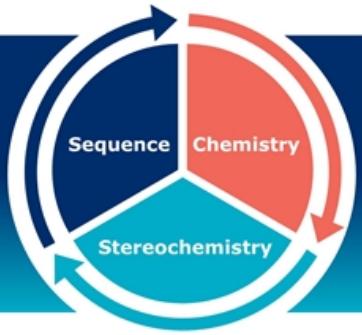
# PRISM

**Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities**

**DESIGN**

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile




**OPTIMIZE**

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

**Through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles**

Multiple modalities
Silencing | Splicing | ADAR editing

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# PRISM platform enables rational drug design

## Sequence

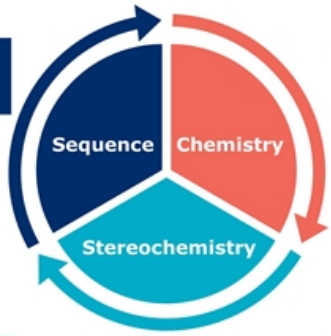
**B**: bases

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

## Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



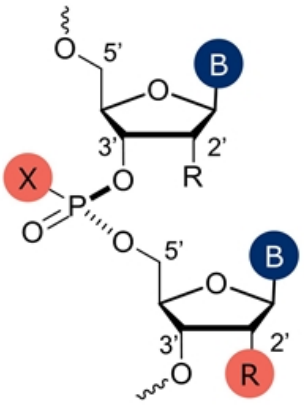

## Chemistry

**R**: 2′ modifications

OMe, MOE, F,
other modifications

**X:** backbone chemistry

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

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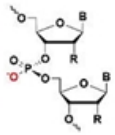
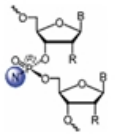
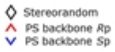
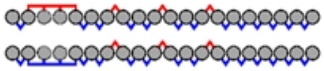
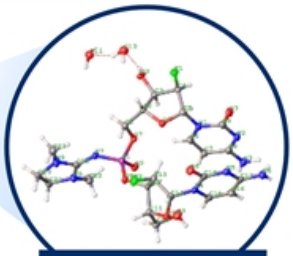
# Expanding repertoire of backbone modifications with novel PN backbone chemistry

## Backbone linkages

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



Phosphoryl guanidine x-ray structure

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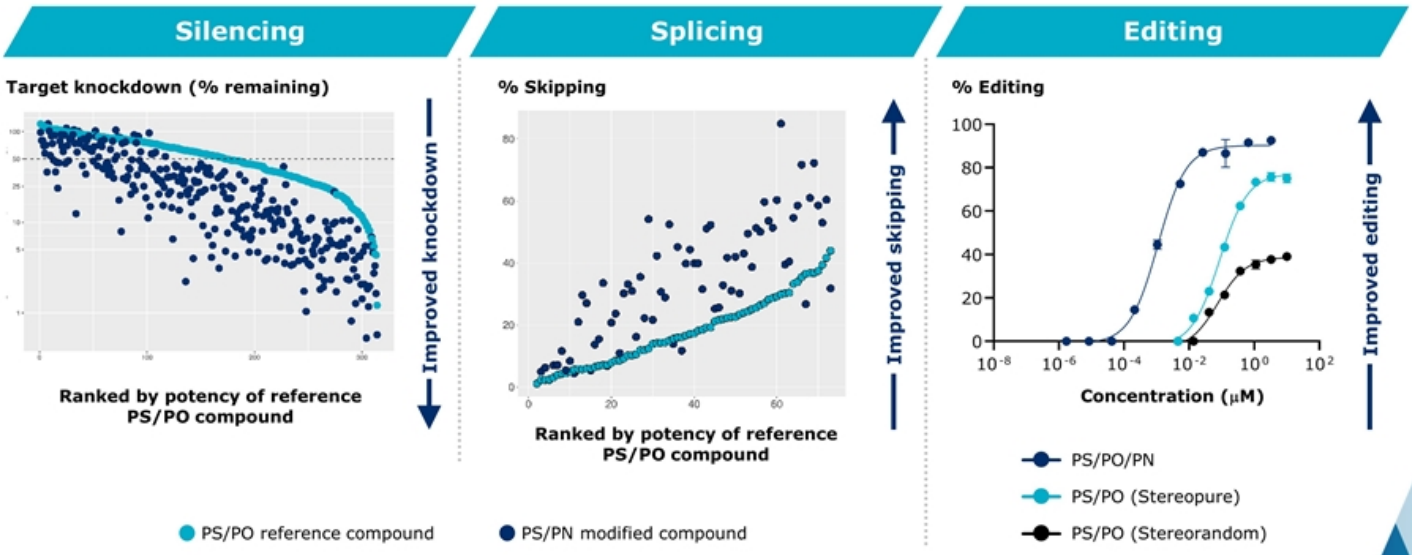
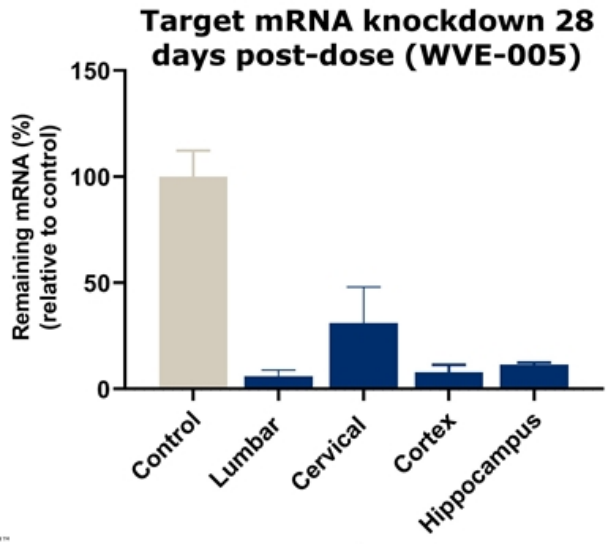
Molecule structure illustrative of backbone modification patterns

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



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

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

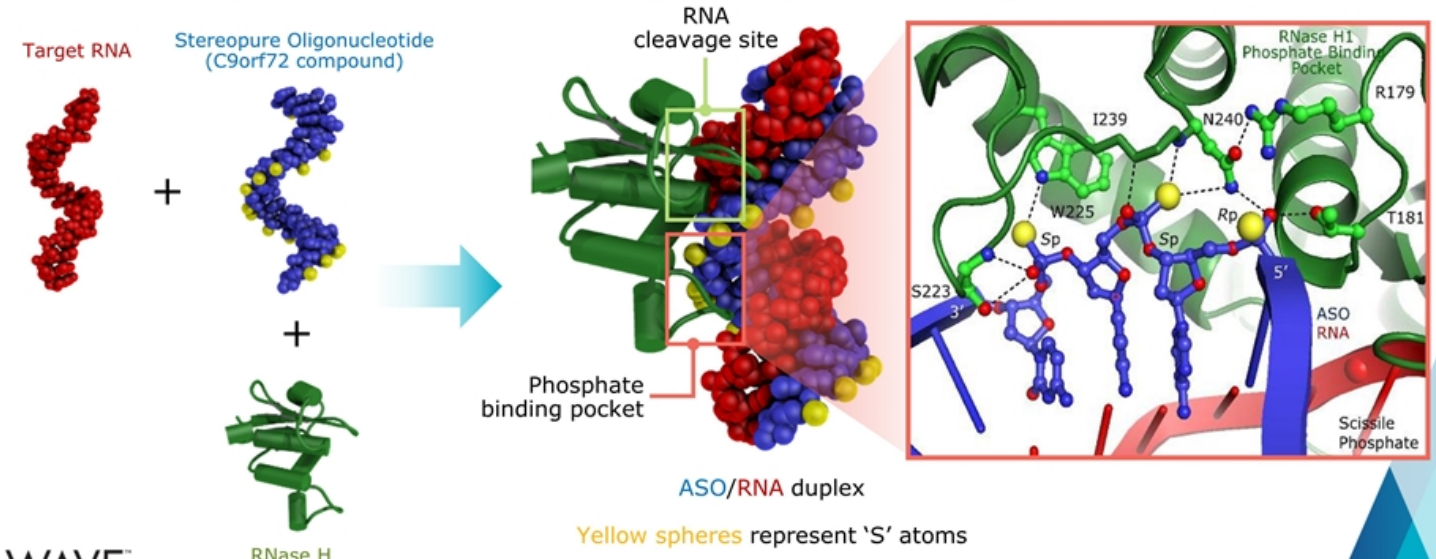



- Single IT dose of 12 mg (n=3)
- Therapeutic candidate widely distributed across brain and spinal cord
- ~90% mRNA knockdown one-month following single dose

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

# PRISM enables optimal placement of backbone stereochemistry

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

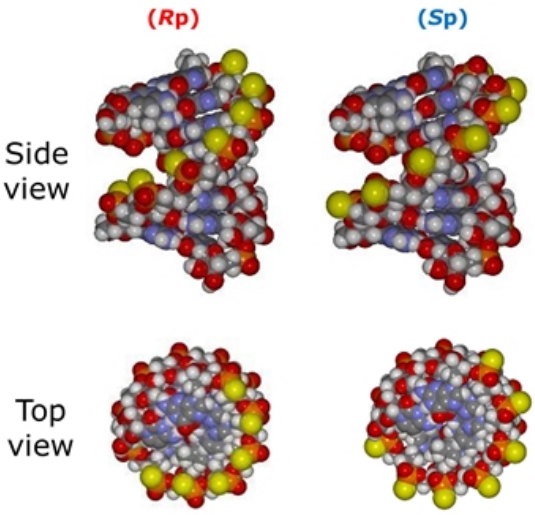



ASO/RNA duplex

Yellow spheres represent 'S' atoms

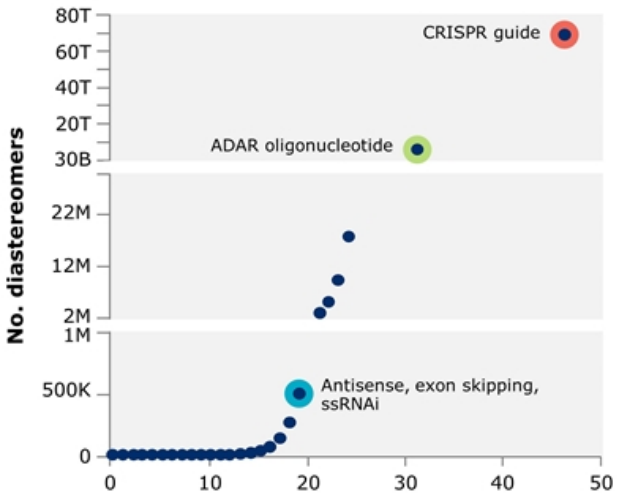
# Importance of controlling stereochemistry

**Stereochemical diversity**




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

**Exponential diversity arises from uncontrolled stereochemistry**




Number of PS linkages in oligonucleotide backbone

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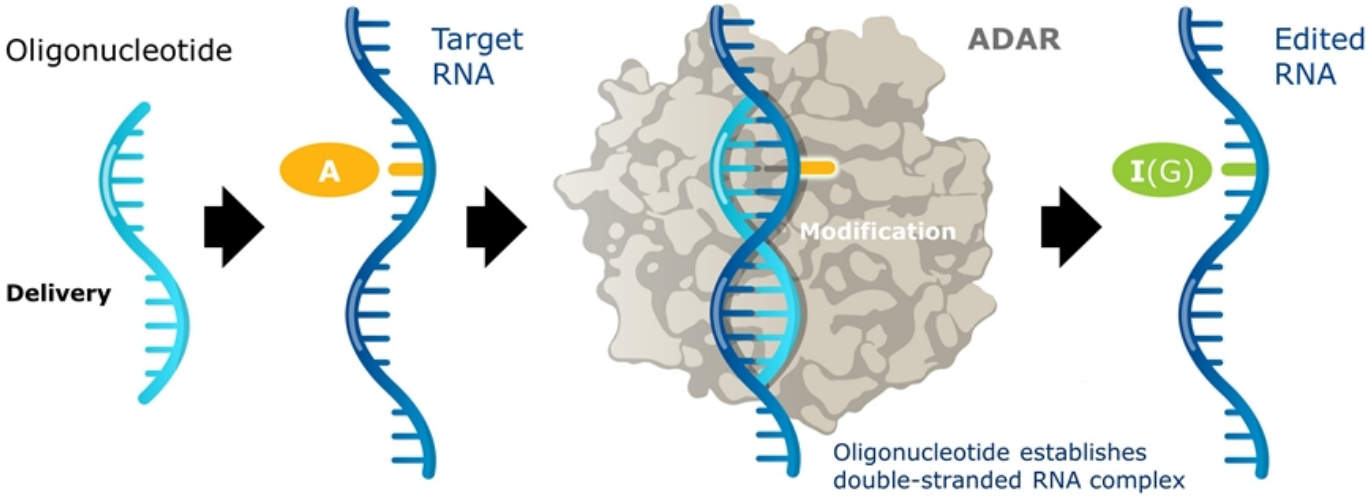
# ADAR editing

## Platform capability and Alpha-1 antitrypsin deficiency

# PRISM platform has unlocked ADAR editing




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

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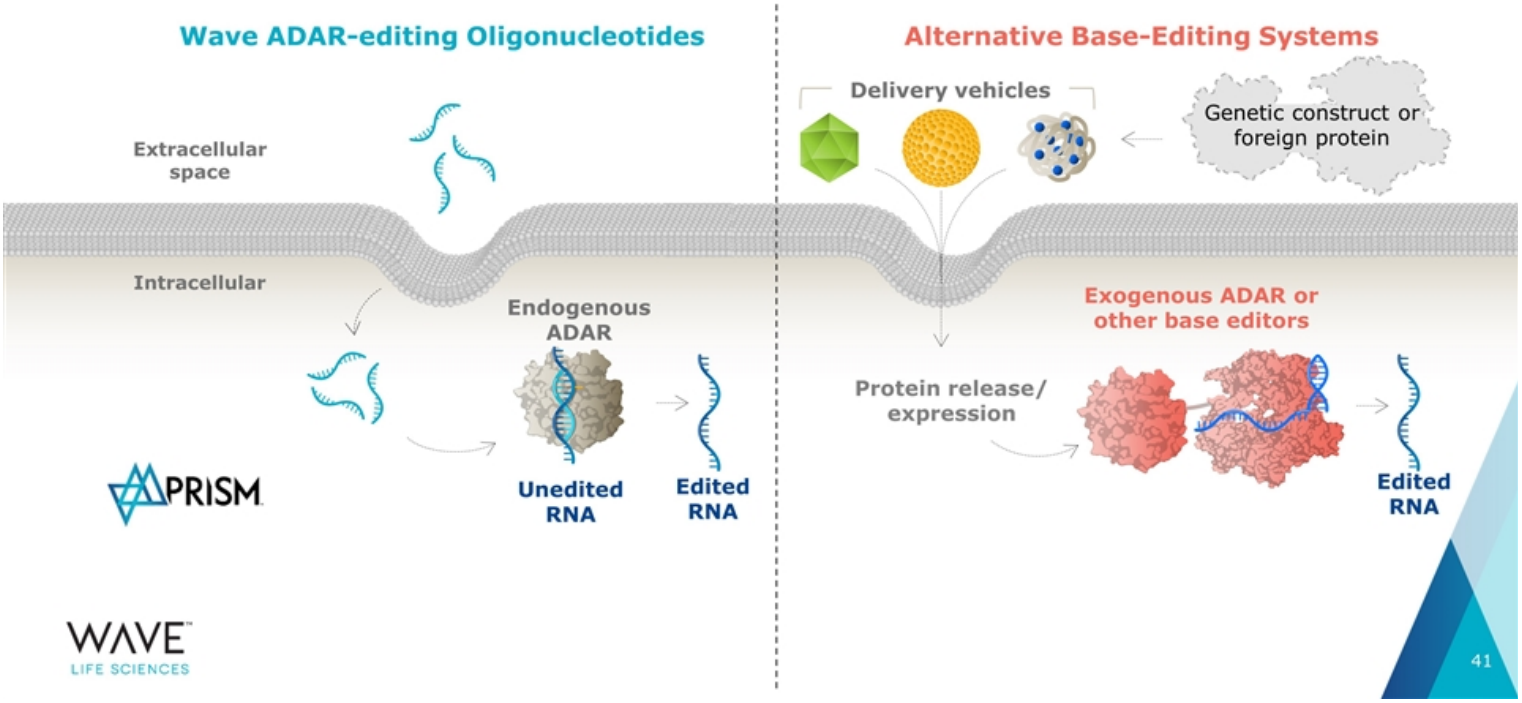
A: adenosine; I: inosine; G: guanosine; Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

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

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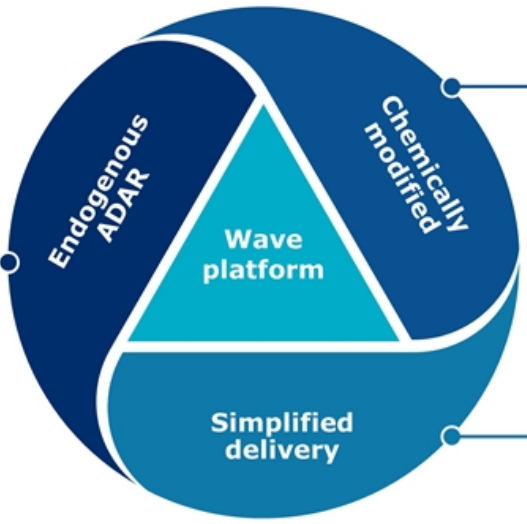
# Advantages of Wave ADAR editing platform

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




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

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

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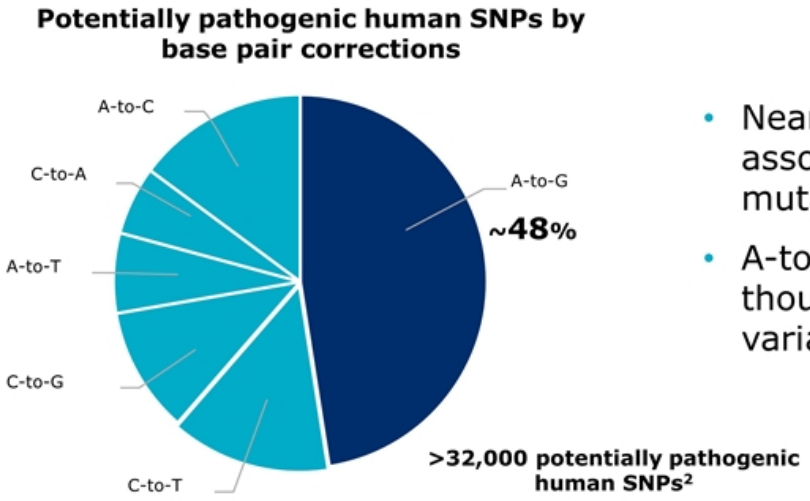
Sources: Chen Biochemistry 2019

# ADAR amenable diseases represent a sizeable opportunity




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

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

# RNA editing opens many new therapeutic applications

## Restore protein function

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

*Examples:*

**Recessive or dominant genetically defined diseases**

## Modify protein function

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

*Examples:*

**Ion channel permeability**

## Protein upregulation

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

*Examples:*

**Haploinsufficient diseases**

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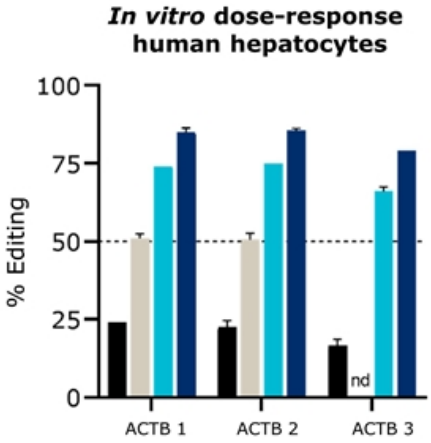
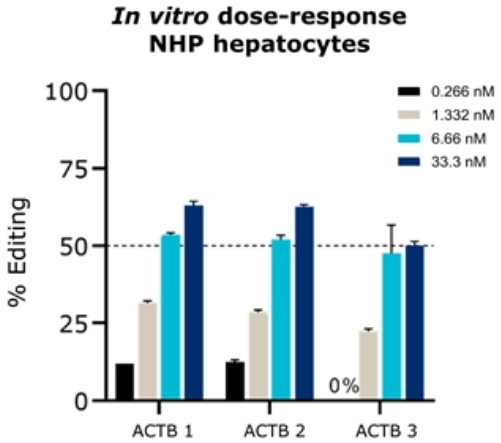
# Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

## ACTB GalNAc-conjugated oligonucleotides with stereopure PN backbone chemistry modifications

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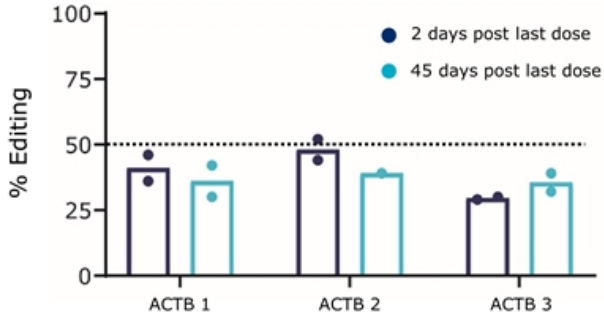
NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

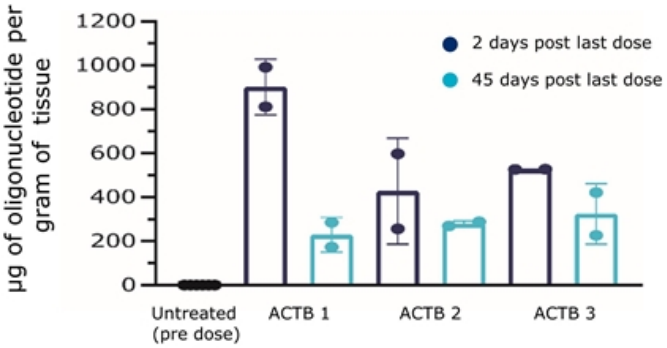
# Efficient ADAR editing translated *in vivo* in non-human primate study

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

**_In vivo_ editing in NHP following subcutaneous administration**

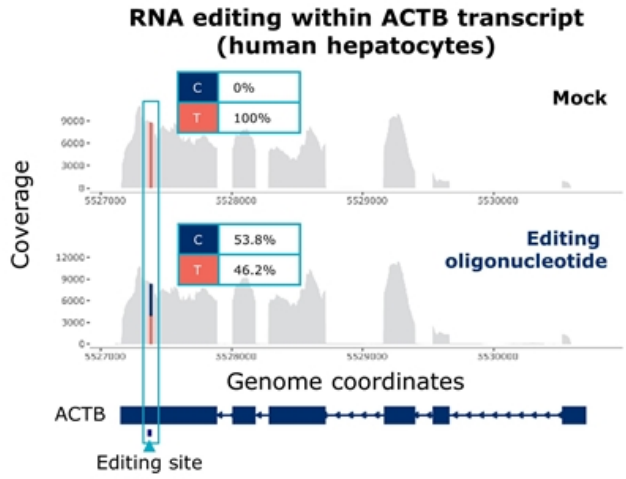



**Oligonucleotide quantification in NHP following subcutaneous administration**




NHP: non-human primate; ACTB: Beta-actin; Left: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing) & eASO Exposure: Day 7

# Wave ADAR editing oligonucleotides are highly specific





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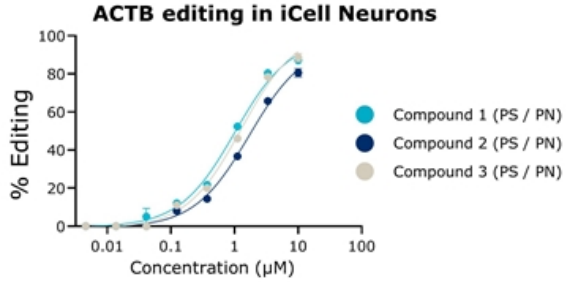
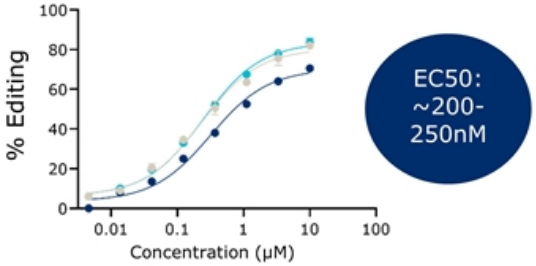
Human hepatocytes were dosed with 1um oligonucleotide, 48 hours later RNA was collected and sent for RNA sequencing. RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing in primary human hepatocytes; plotted circles represent sites with LOD>3

# Multiple opportunities for ADAR editing in neurology

**ACTB editing in iCell Neurons**

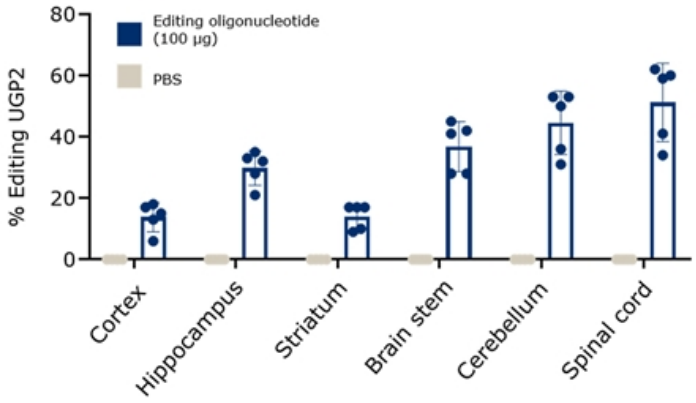



**ACTB editing in human iCell Astrocytes**



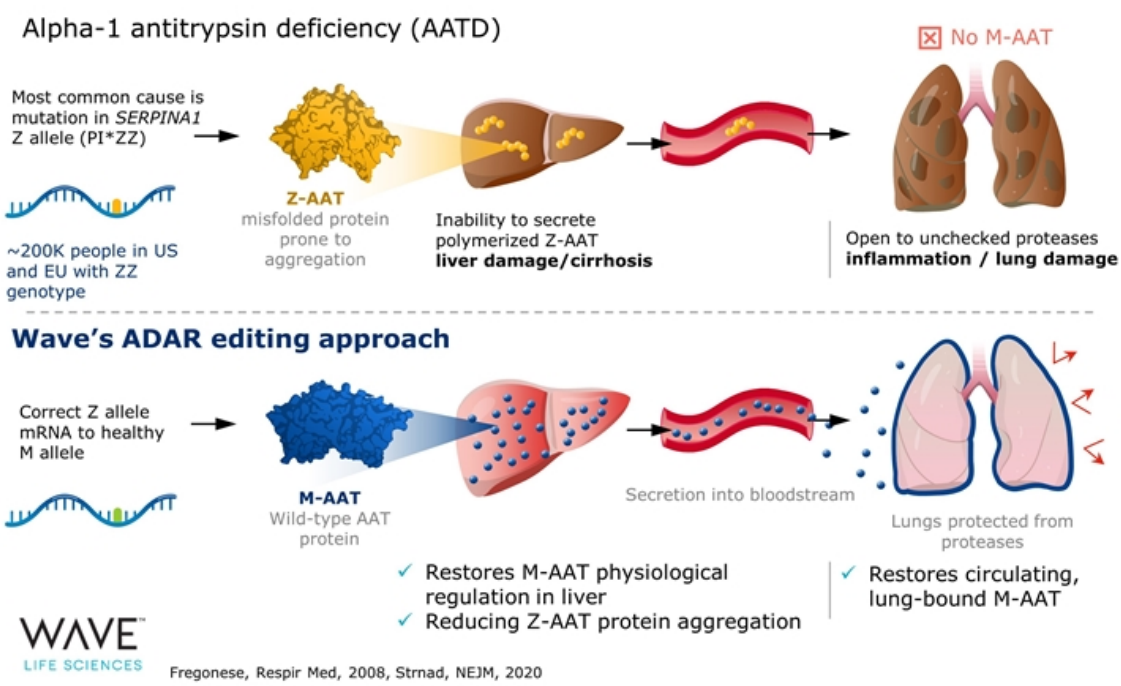

Gymnotic uptake; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

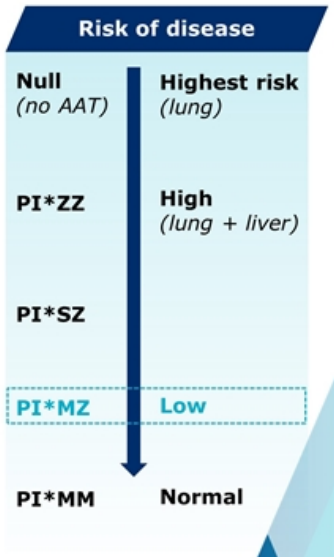
***In vivo* CNS editing in proprietary hADAR transgenic mouse (1 week)**




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

# An ADAR editing approach to correct alpha-1 antitrypsin deficiency

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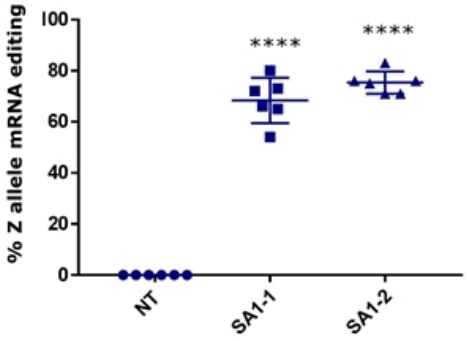
Fregonese, Respir Med, 2008, Strnad, NEJM, 2020

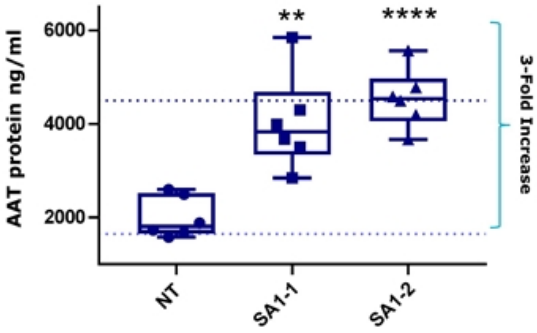
# *SERPINA1* Z allele mRNA editing restores wild-type M-AAT protein concentration *in vitro*

## Editing Z allele mRNA back to wild-type prevents protein misfolding and restores secretion of wild-type M-AAT protein from hepatocytes

**SERPINA1 Z allele mRNA editing**




**AAT protein concentration in media**




**Wild-type M-AAT protein analysis**

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

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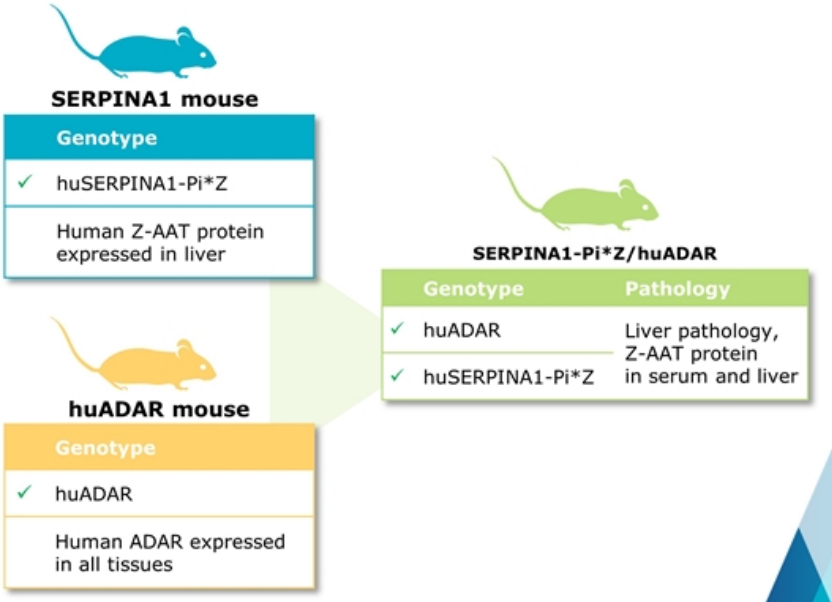
AAT (alpha-1 anti-trypsin); Mouse primary hepatocytes that express SERPINA1 Z allele mRNA were transfected with 25 nanomolar (nM) of SERPINA1 (SA1-1 and SA1-2) targeting antisense oligonucleotides (ASOs) and a control non-targeting (NT) ASO. Media and RNA was collected at 5 days post transfection. AAT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

# First proof-of-concept study to restore M-AAT protein with ADAR editing *in vivo*

- Goals of first *in vivo* proof-of-concept study:
  - Editing of SERPINA1 Z allele mRNA in liver to approach heterozygous (MZ) phenotype
  - Restore wild-type human M-AAT protein in serum
  - Demonstrate functionality of wild-type human M-AAT protein

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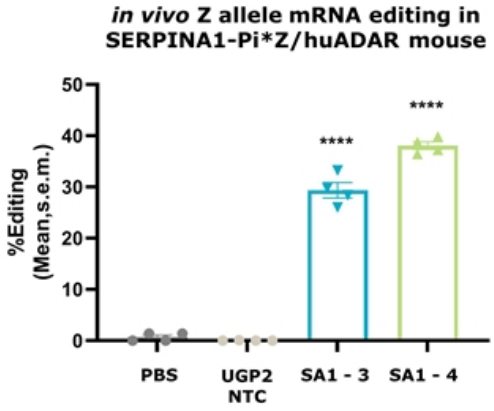
# Achieving 40% editing of Z allele mRNA at single timepoint

## *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
- Highly specific editing (no bystander edits)

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

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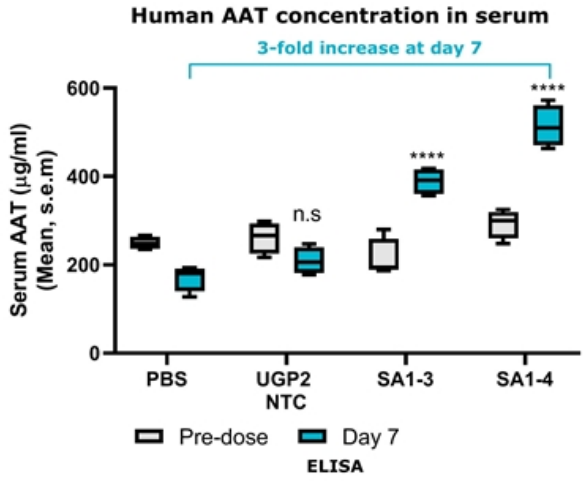
Statistics: One-way ANOVA with correction for multiple comparisons (Dunnett's) was used to test for differences SERPINA1-Z allele editing in treated vs. PBS groups; 10 mg/kg dose administered day 0, 2, 4, sample collected on day 7; NTC: non-targeting control

# Achieving therapeutically meaningful increases in circulating human AAT protein

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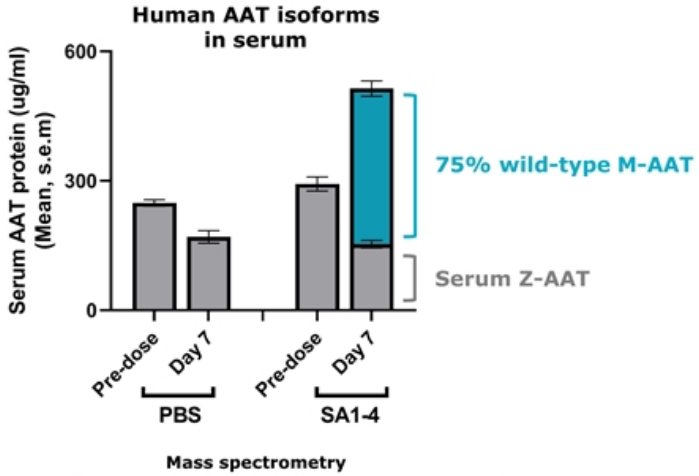
Statistics (ELISA): Matched 2-way ANOVA with correction for multiple comparisons (Bonferroni) was used to test for differences in AAT abundance in treated samples compared to PBS Statistics; de Serres et al., J Intern Med. 2014; NTC: non-targeting control

# Restoring circulating wild-type M-AAT

## ADAR editing restores wild-type M-AAT, suggesting reduction of Z-AAT in liver and serum




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

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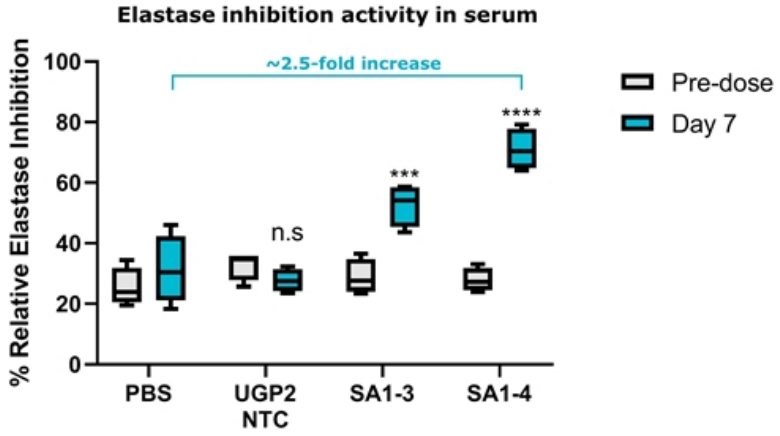
# Secreted wild-type M-AAT protein is functional

## Significant increase in neutrophil elastase inhibition with wild-type M-AAT protein




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

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(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

# ADAR editing successfully corrects Z allele mRNA *in vivo* to restore functional M-AAT protein

- Results support use of human transgenic mouse model to evaluate ADAR editing compounds for additional targets
- Up to 40% editing of *SERPINA1* Z allele mRNA in liver at single timepoint, nearing correction to heterozygotes (MZ)
- Initial Z allele mRNA editing resulted in therapeutically meaningful increase in circulating functional wild-type M-AAT protein *in vivo*
- Restoration of wild-type M-AAT suggests reduction of mutant Z-AAT protein in liver and serum
- Ongoing studies to assess duration of activity, dose response, PK/PD, reduction in Z-AAT protein aggregates to provide insight into wild-type M-AAT secretion levels over time and changes in liver pathology

**Additional data on durability and dose response expected in 2H 2021**

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# Ophthalmology

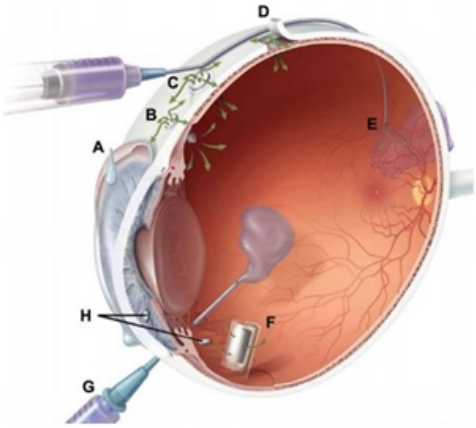
# Stereopure oligonucleotides for inherited retinal diseases (IRDs)

## 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

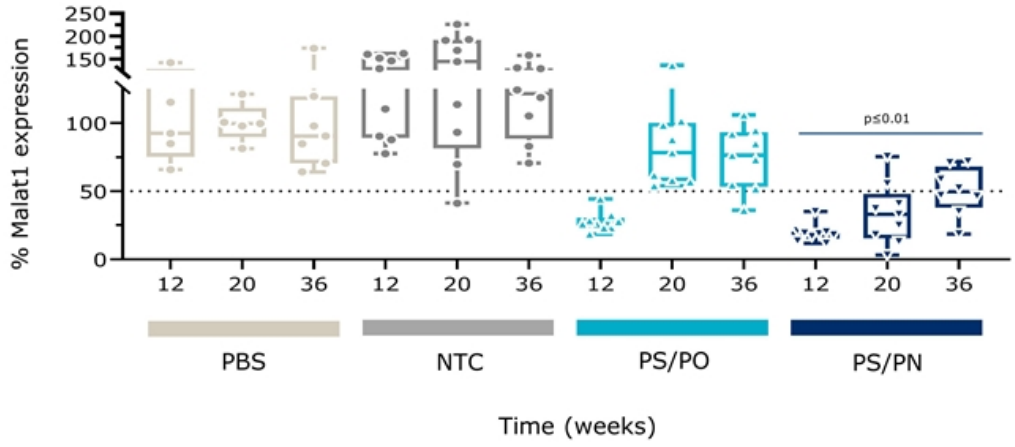



Intravitreal injection

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

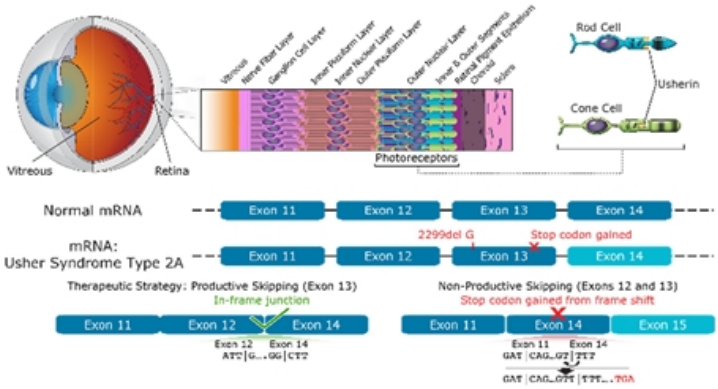
## ~50% Malat1 knockdown at 36 weeks in the posterior of the eye




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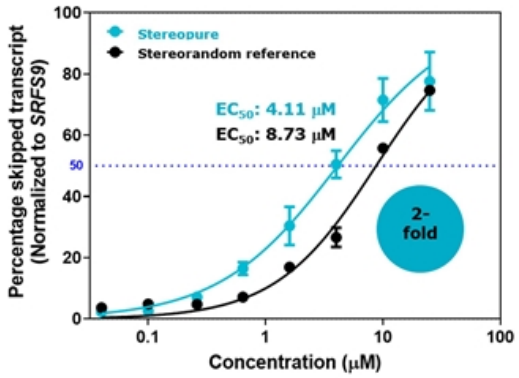
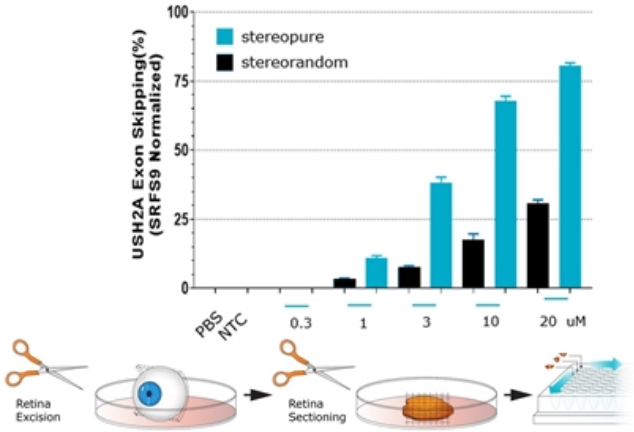
Sources: Boughman et al., 1983. *J Chron Dis.* 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

# 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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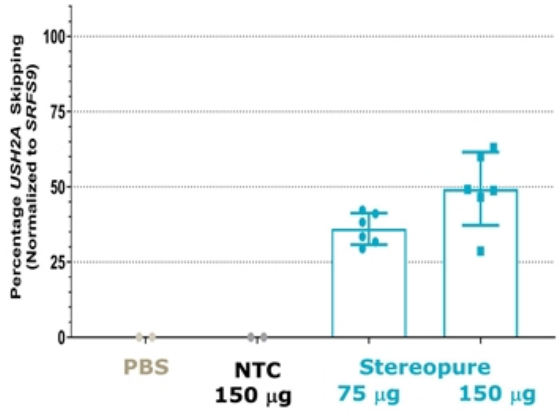
Oligonucleotides were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. USH2A transcripts were normalized to SRSF9. Data are mean±s.d., n=2. Stereorandom: Compound identified in van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. 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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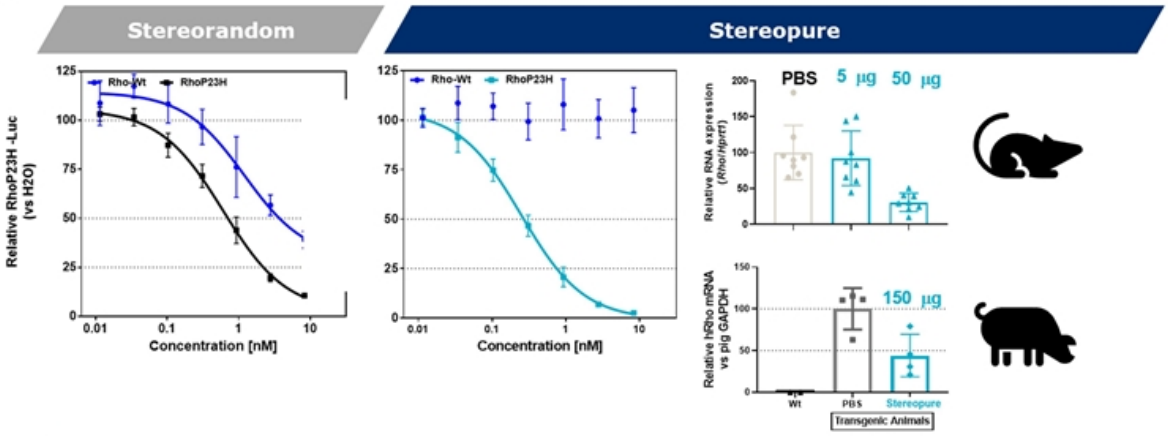
Stereopure *USH2A* skipping oligonucleotide, PBS or NTC antisense oligonucleotide was delivered to NHP by single IVT injection. One-week post-injection, retina was isolated and exon skipping was evaluated by Taqman assays. *USH2A* skipped transcript levels were normalized to *SRSF9*. Data are mean± s.e.m. 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

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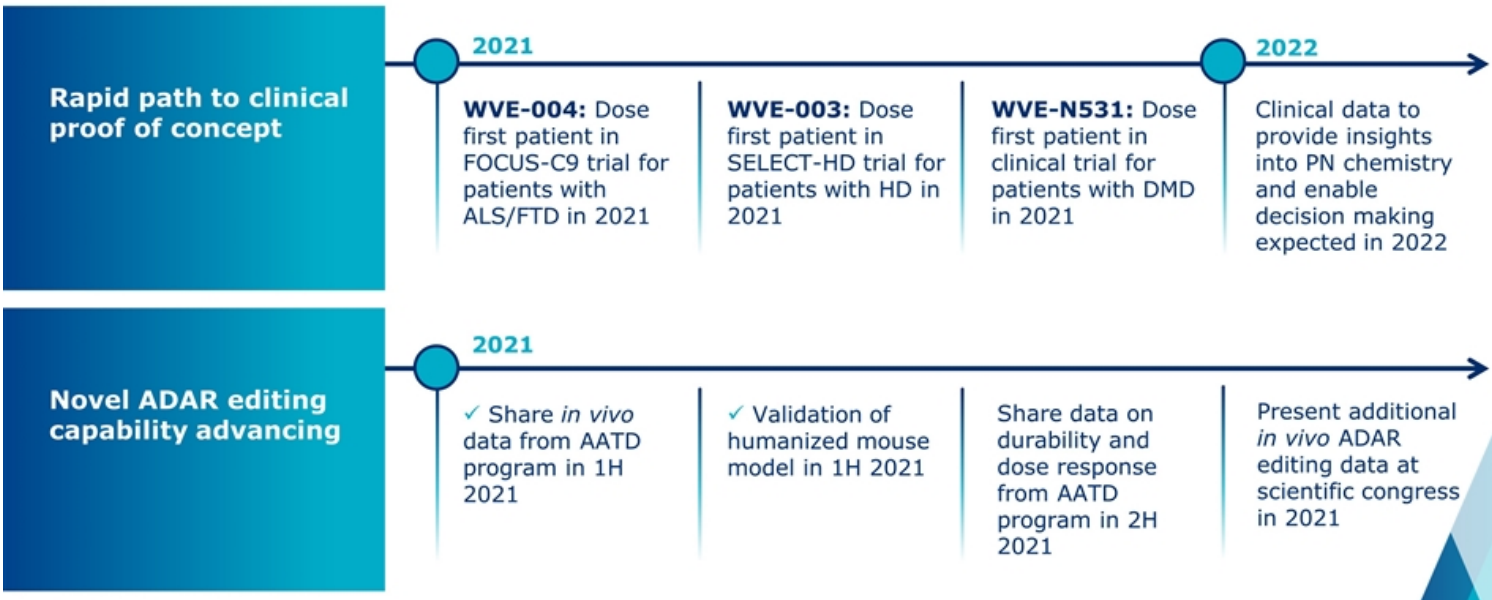
Left: Reporter assays on a sequence described in WO2016138353A1. Oligonucleotide and luciferase reporter plasmids (wild-type and mutant RHO) are transfected into Cos7 cells. Cells are harvested after 48 hrs, and relative luminescence is measured. Right: Single IVT injection (1 mL) in mouse Rho P23H mouse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

# Continuous flow of data to enable program decisions through 2022

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AATD: Alpha-1 antitrypsin deficiency

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# Realizing a brighter future for people affected by genetic diseases


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