Wave Life Sciences

Research Day

October 30, 2024

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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.

Agenda

Presentation		Speaker
Welcome & Introduction		**Kate Rausch** Vice President, Investor Relations & Corporate Affairs
Reimagining RNA Medicines		**Paul Bolno, MD, MBA** President and Chief Executive Officer
PRISM Platform: Best-in-Class Oligonucleotide Chemistry		**Chandra Vargeese, PhD** Chief Technology Officer
Lead Program Spotlights		
HD	Caudate Volume and Clinical Trials in Huntington's Disease	**Jeffrey Long, PhD** Professor of Psychiatry & Biostatistics at the University of Iowa
Obesity	Obesity: Current Treatment Landscape and Unmet Needs	**Mehmet Furkan Burak, MD** Instructor in Medicine at Harvard Medical School and Endocrinologist and Obesity Specialist at Brigham and Women's Hospital Center for Weight Management and Wellness
	WVE-007: Novel Obesity Therapeutic for Healthy, Sustainable Weight Loss	**Ginnie Yang, PhD** Senior Vice President, Translational Medicine
AATD	WVE-006: First-ever RNA Editor Unlocking New Wholly Owned Programs	**Erik Ingelsson, MD, PhD** Chief Scientific Officer
New RNA Editing Programs		
Building the Pipeline: New Programs Informed by Human Genetics		**Erik Ingelsson, MD, PhD** Chief Scientific Officer
Closing Remarks		**Paul Bolno, MD, MBA** President and Chief Executive Officer
Q&A		**All**

Reimagining RNA Medicines

Paul Bolno, MD, MBA
President and CEO

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Wave today: Making history in oligonucleotides

- Best-in-class, clinically differentiated oligonucleotide platform (PRISM®)
  - Proprietary chemistry
  - Multi-modal (editing, silencing and splicing)
- First-ever to unlock RNA editing- enabled by unique and proprietary capabilities
- HD and DMD clinical data support engagement with regulators on potential accelerated pathways to registration and commercialization
- Strong financial position with resources to deliver

Three clinical updates in 2024 demonstrate continued translation

Proprietary PRISM platform

- Stereopure oligonucleotides
- Novel backbone modifications (including PN chemistry)
- Novel base and sugar chemistry modifications

Strong and broad IP

Therapeutic modalities	Preclinical publication	Clinical translation	Clinical trial results
Splicing (WVE-N531 for DMD)	✓	✓ 53% exon skipping, 42 µg/g muscle tissue concentrations in 6 weeks	✓ *9.0% mean muscle-adjusted dystrophin; safe and tolerable* FORWARD-53
Allele-selective silencing (WVE-003 for HD)	✓	✓ 35% allele-selective mHTT silencing with single dose	✓ 46% allele-selective mHTT silencing; correlation with slowing of caudate atrophy SELECT HD
GalNAc-RNA editing (WVE-006 for AATD)	✓	✓ First ever RNA editing achieved; 11 µM total AAT protein, >60% (6.9 µM) M-AAT with single dose	*Multidose data expected in 2025* RESTORAATION
GalNAc-RNAi (WVE-007 for obesity)	✓	*Clinical trial initiation expected 1Q 2025*	

The future of Wave: Leader in oligonucleotide therapeutics

- Multiple late-stage clinical programs:
  - Potential for significant milestones and royalties from first-in-class RNA editing therapeutic for AATD
  - Opportunity for accelerated paths to registration for HD and DMD
- Robust, differentiated emerging pipeline, supported by human genetics
  - Best-in-class, clinical-stage GalNAc-siRNA obesity program with efficient path to proof-of-concept
  - Near-term expansion to include multiple cardiometabolic GalNAc-RNA editing programs, offering synergies in science and development
- Core focus on liver-targeted indications, with expansion opportunities in other tissue types
- Resourced to deliver, with continued news flow and catalysts to drive value into 2027

Five GalNAc clinical programs expected in 2026

2025

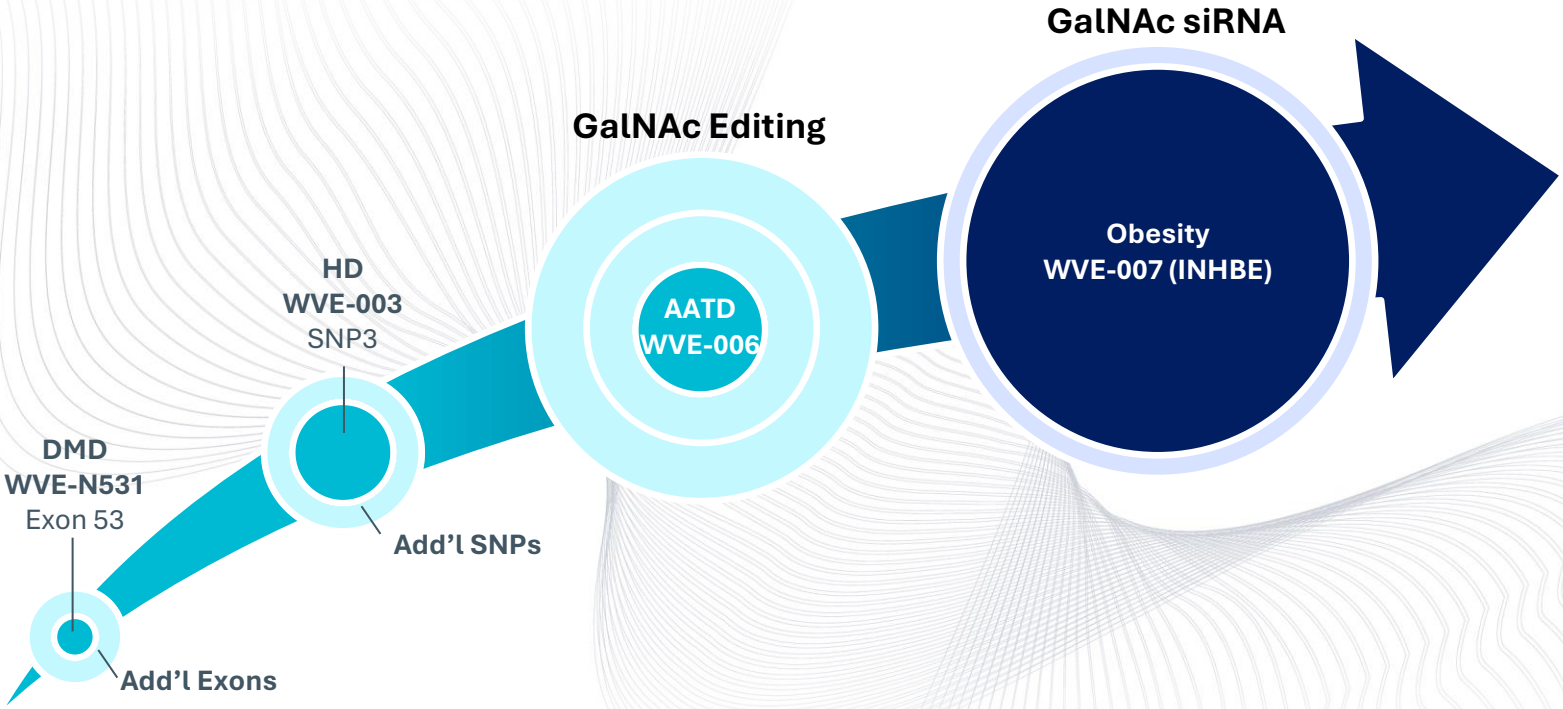
- WVE-006 for AATD
- WVE-007 for Obesity

- Multidose data from AATD further derisking AIMer portfolio
- Dosing in obesity clinical trial
- Synergies in cardiometabolic indications

2026

- WVE-006 for AATD (GalNAc-AIMer)
- PNPLA3 (GalNAc-AIMer)
- LDLR (GalNAc-AIMer)
- APOB (GalNAc-AIMer)
- WVE-007 for Obesity (GalNAc-siRNA)

Poised for significant and sustained growth driven by GalNAc editing and siRNA



Wave's platform is translating in the clinic and has potential to treat >90M patients in the US and Europe

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Note: Bubble size illustrative of size of total addressable US market (assuming 100% share of addressable patients)

PRISM Platform: Best-in-Class Oligonucleotide Chemistry

Chandra Vargeese, PhD
Chief Technology Officer

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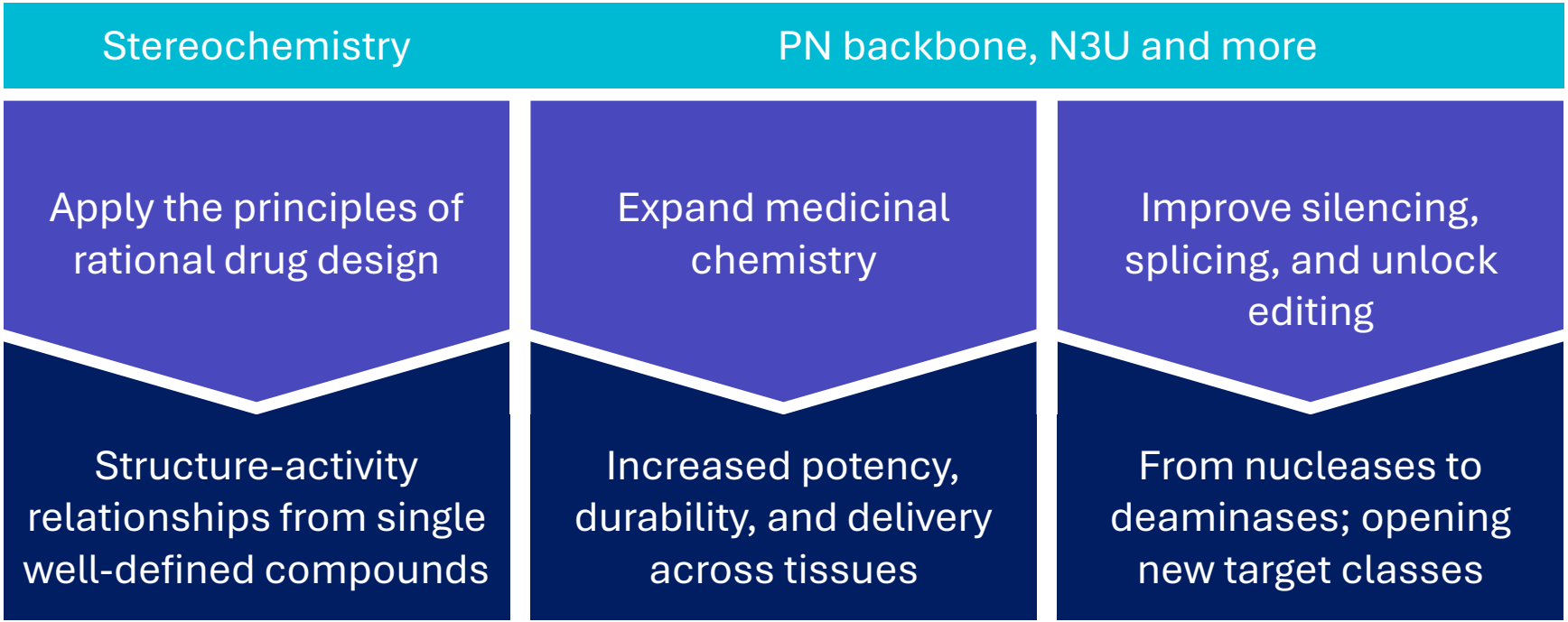
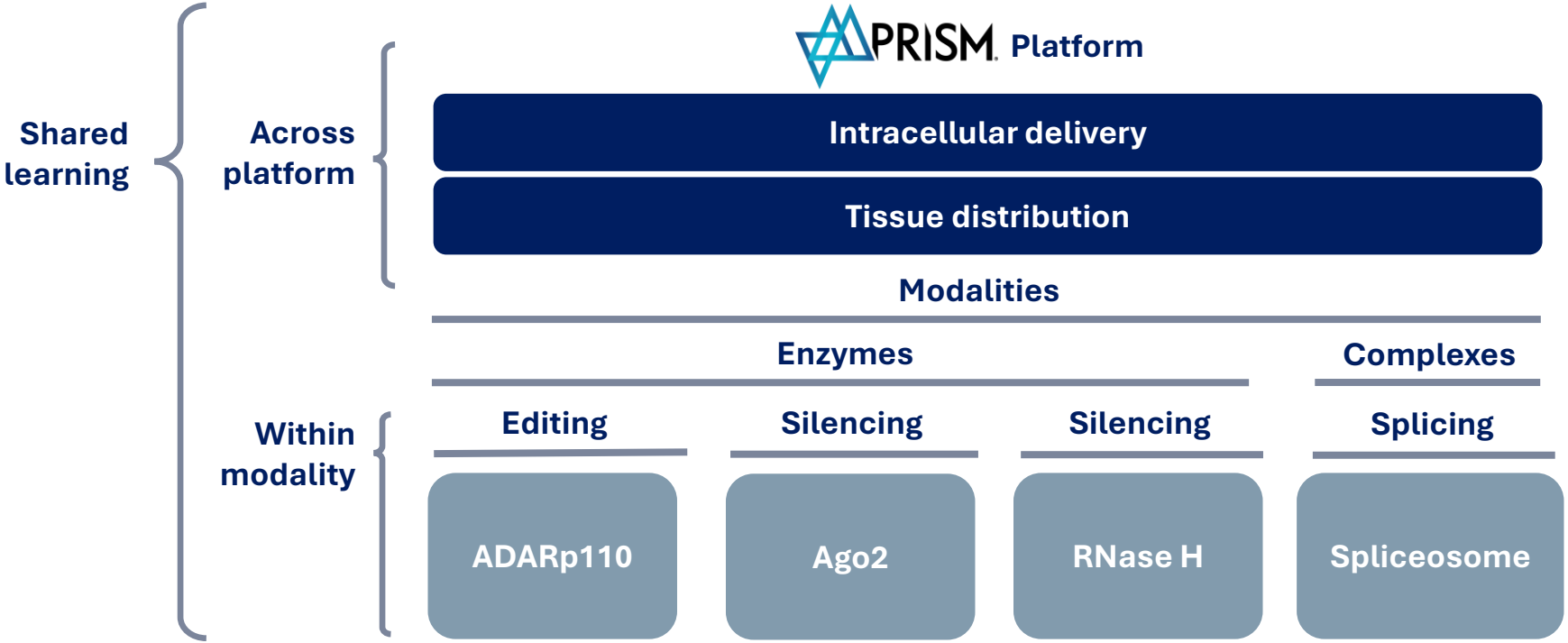
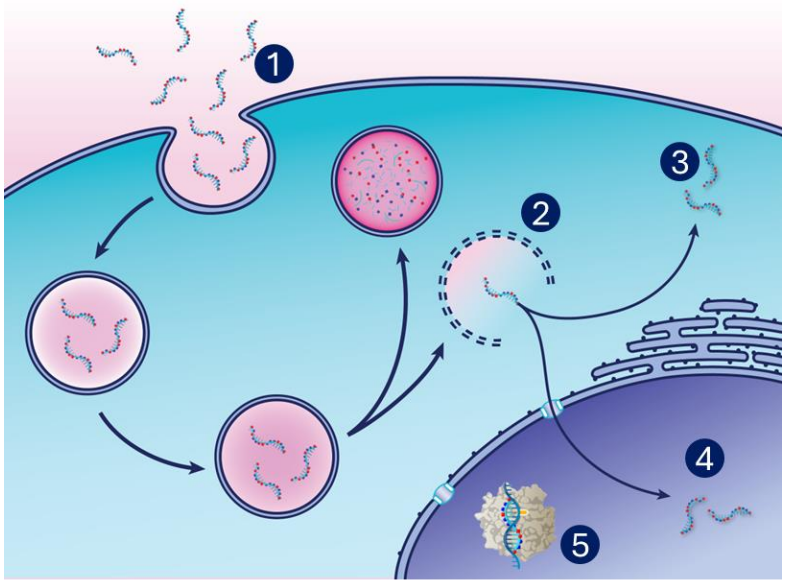
Building the best-in-class oligonucleotide platform



Shared learning enables rapid, predictable and efficient clinical translation



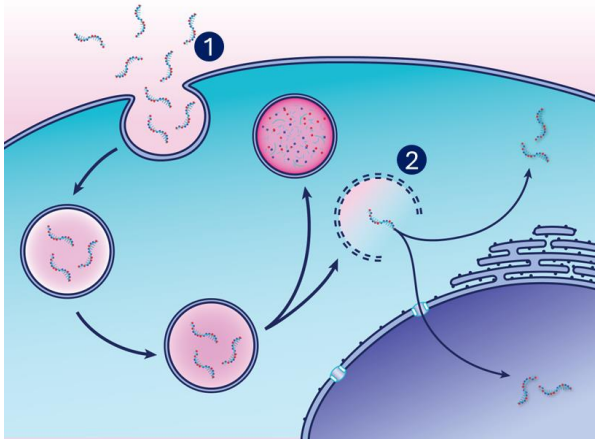
Wave's chemistry is a breakthrough for intracellular delivery



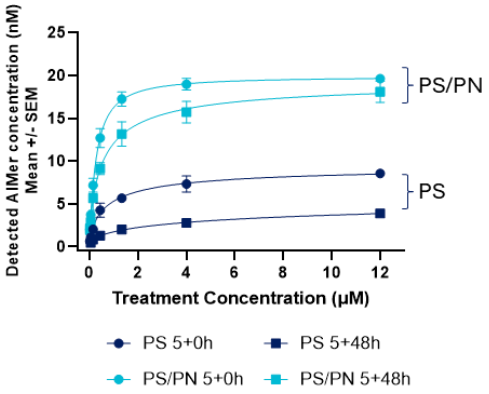
Addition of PN modification increases:

1. Cellular uptake
2. Endosomal release
3. Cellular residency
4. Nuclear uptake
5. Target engagement

PN modifications increase cellular uptake and endosomal release

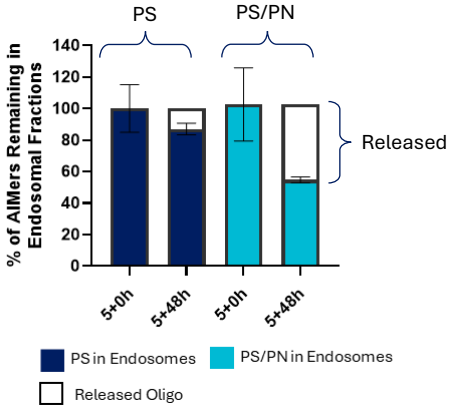


1 Cellular Uptake



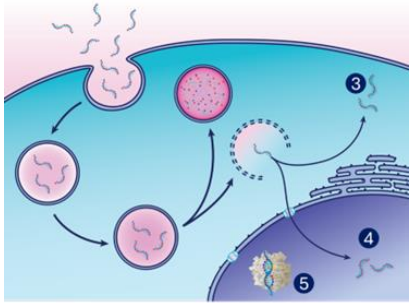
>2-fold increase in uptake after 5-hour dose pulse

2 Endosomal Release

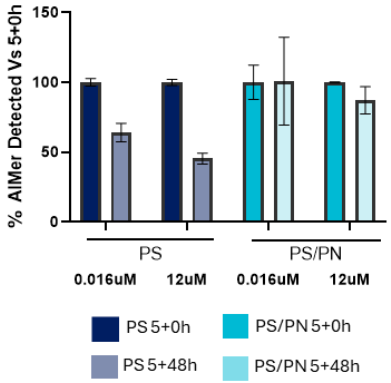


~4-fold increase in endosomal release

PN modifications increase cellular residency, nuclear uptake and target engagement

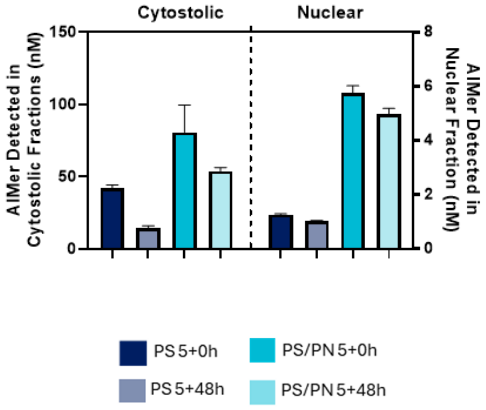


3 Cellular Residency



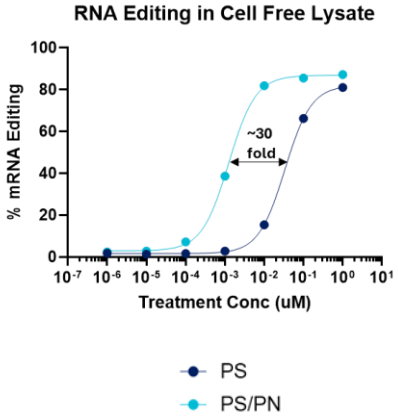
~2-fold increase in cellular residency

4 Nuclear Uptake



~5-fold increase in nuclear uptake

5 Target Engagement



30-fold increase in target engagement

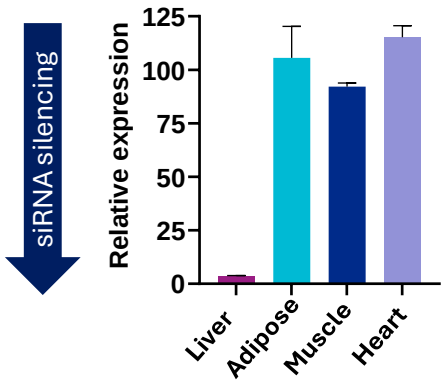
Directing silencing to high priority extrahepatic tissues

Achieved by changes in physicochemical properties without requirement for LNP or other delivery agents

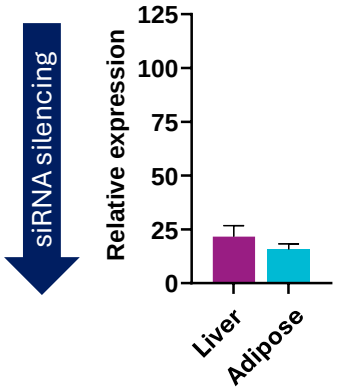
GalNAc + PN

Non-GalNAc + PN variants

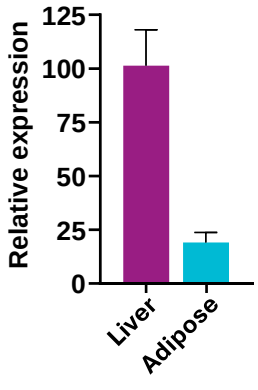
Liver Targeting (siRNA 1)



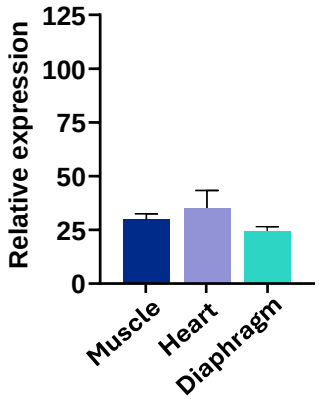
Liver and Adipose Targeting (siRNA 2)



Adipose Targeting (siRNA 3)



Muscle Targeting (siRNA 4)



***In vivo* silencing at 8 weeks following single dose of non-GalNAc siRNAs**

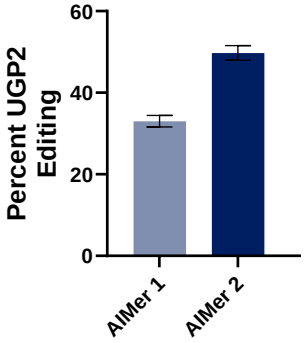
In mice

Directing editing across high priority extrahepatic tissues

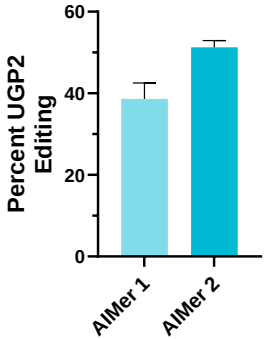
Achieved by changes in physicochemical properties without requirement for LNP or other delivery agents

Editing

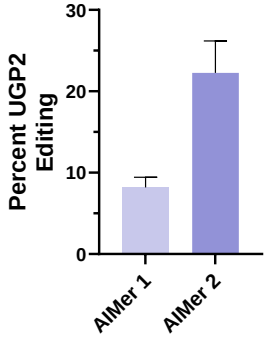
Lung



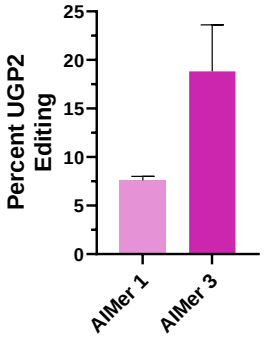
Adipose



Heart



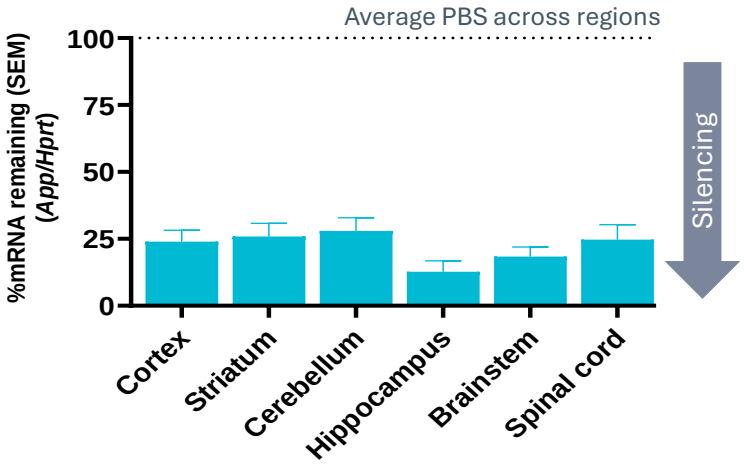
Pancreas

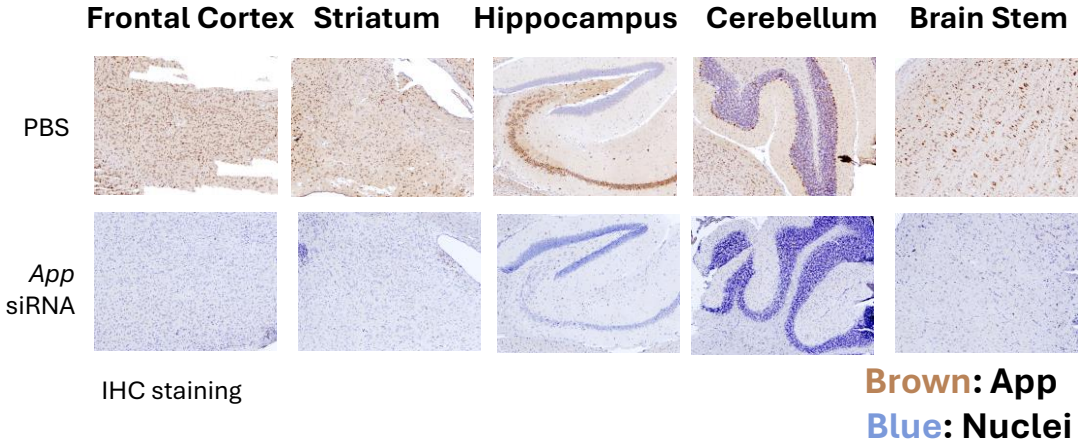


High levels of systemic RNA editing achieved across extrahepatic tissues

In mice

Potent and durable silencing across regions of the CNS

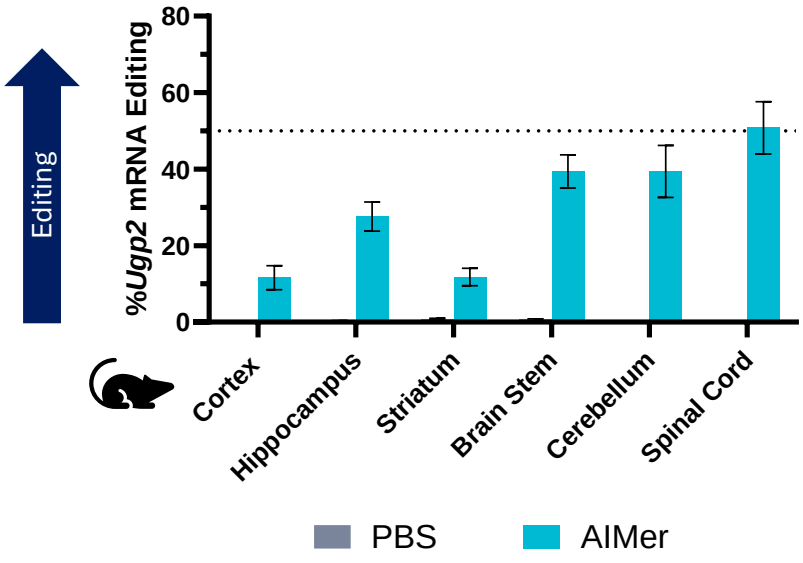




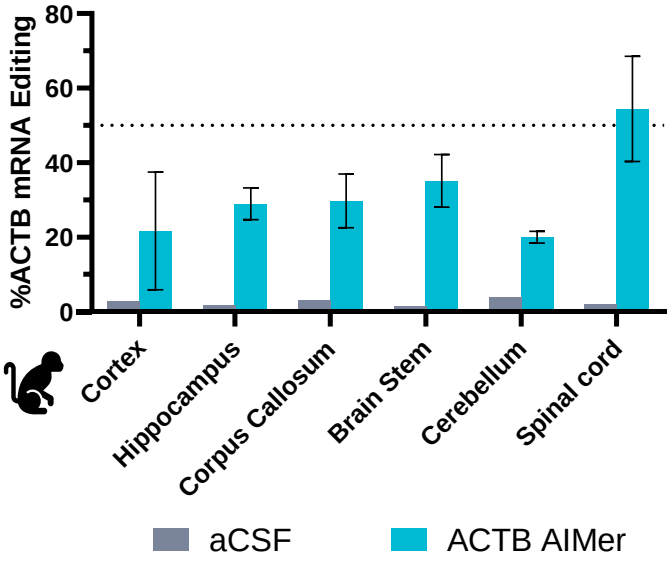
***In vivo* silencing in CNS at 16 weeks following single dose of APP siRNA**

Broad RNA editing in CNS observed following a single dose in mouse and NHP

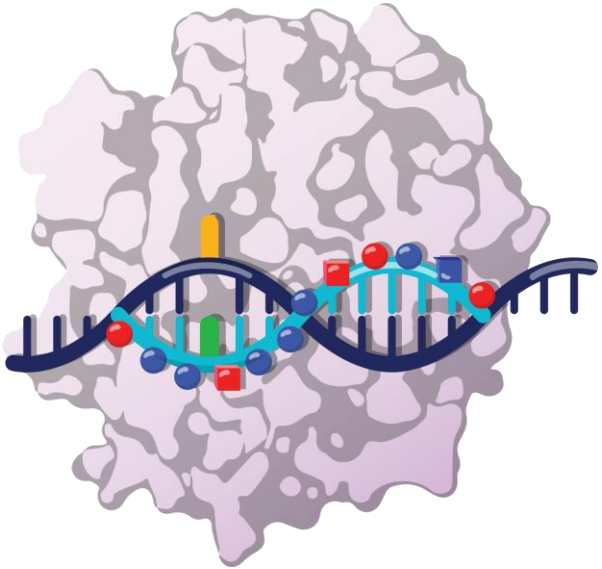
ICV injection



IT delivery



Wave has unique and proprietary chemistry space to drive potent, specific and durable RNA editing

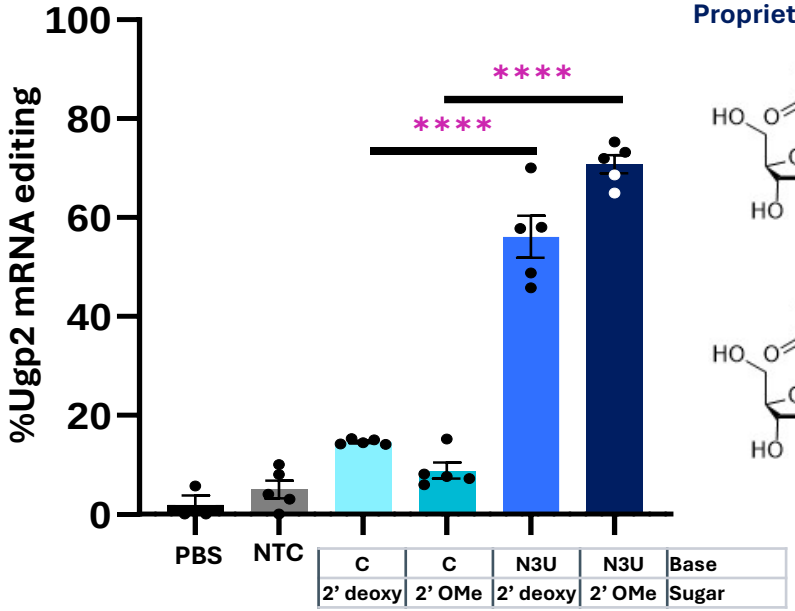


- Removal of any hairpin ADAR recruiting domain
- Pioneered the use of fully modified short oligonucleotides for highly efficient RNA editing including in human
- Proprietary base modifications (including N3U)
  - Enable multiple types of sugars across edit site (including 2'-OMe modified sugar)
  - Increase flexibility for chemistry at neighboring sites
- Asymmetric designs
- Incorporation of proprietary backbone modifications (including PN)

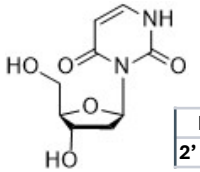
Multifaceted IP portfolio that protects Wave's leading oligonucleotide design

Proprietary N3U chemistry substantially enhances AIMer editing efficiency in a sequence independent manner

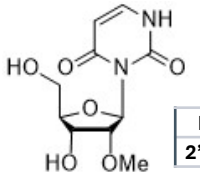
Enhanced RNA Editing with N3U Base



Proprietary Base



N3U	Base
2' deoxy	Sugar



N3U	Base
2' OMe	Sugar

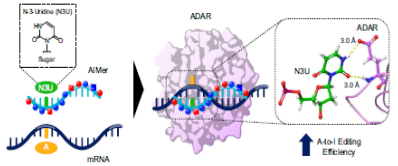
Nucleic Acids Research

Rational design of base, sugar and backbone modifications improves ADAR-mediated RNA editing

Abstract

AIMers are short, chemically modified oligonucleotides that induce A-to-I RNA editing through interaction with endogenous adenosine deaminases acting on RNA (ADAR) enzymes. Here, we describe the development of new AIMer designs with base, sugar and backbone modifications that improve RNA editing efficiency over our previous design. AIMers incorporating a novel pattern of backbone and 2' sugar modifications support enhanced editing efficiency across multiple sequences. Further efficiency gains were achieved through incorporation of an N-3-uridine (N3U), in place of cytidine (C), in the 'orphan base' position opposite the edit site. Molecular modeling suggests that N3U might enhance ADAR catalytic activity by stabilizing the AIMer-ADAR interaction and potentially reducing the energy required to flip the target base into the active site. Supporting this hypothesis, AIMers containing N3U consistently enhanced RNA editing over those containing C across multiple target sequences and multiple nearest neighbor sequence combinations. AIMers combining N3U and the novel pattern of 2' sugar chemistry and backbone modifications improved RNA editing both *in vitro* and *in vivo*. We provide detailed N3U synthesis methods and, for the first time, explore the impact of N3U and its analogs on ADAR-mediated RNA editing efficiency and targetable sequence space.

Graphical abstract



Introduction

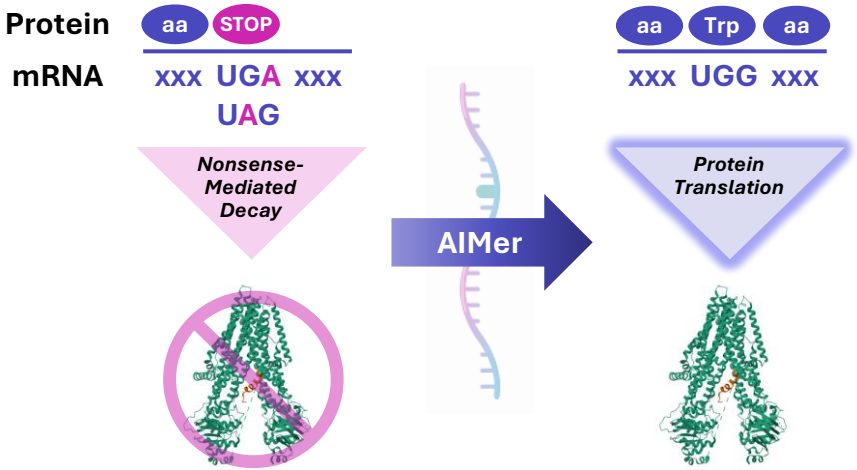
The class of nucleic acid medicines known as RNA medicines has risen in prominence considerably over the last decade. RNA medicines are chemically modified RNA-based molecules that are used to alter the properties or function of specific genes, transcripts, or proteins. One of the more promising emerging RNA medicine modalities is RNA editing, in which synthetic oligonucleotides direct enzymes to alter

Received: April 19, 2024. Revised: July 20, 2024. Editorial Decision: July 22, 2024. Accepted: July 25, 2024

Lu et al., 2024 *Nuc Acid Res* https://doi.org/10.1093/nar/gkae681 NTC: Non-targeting control, targeting *ACTB*. **** p<0.0001

RNA editing can address an unmet need for patients with nonsense mutation-induced diseases

Protein Restoration with RNA Editing



By converting termination codons (**UGA**, **UAG**) into tryptophan (**UGG**), ADAR editing can rescue full-length protein expression

Rett Syndrome → MECP2

- Female-dominant neurodevelopmental disorder affecting walking, talking, breathing and intellectual capability
- Nonsense mutations account for 35% of the disease population[2]

Cystic Fibrosis → CFTR

- Multi-organ disease that ultimately leads to respiratory failure due to an imbalance in epithelial ion transport
- No approved therapies for nonsense mutations, which occur in ~10% of CFTR patients[3]

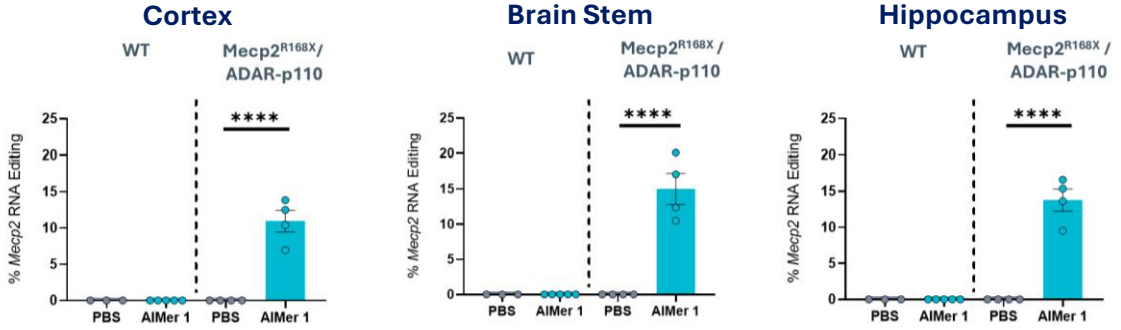
Nonsense mutations account for ~11% of all genetically inherited disease; 79% of these diseases can be addressed with a single A-to-G RNA edit[1]

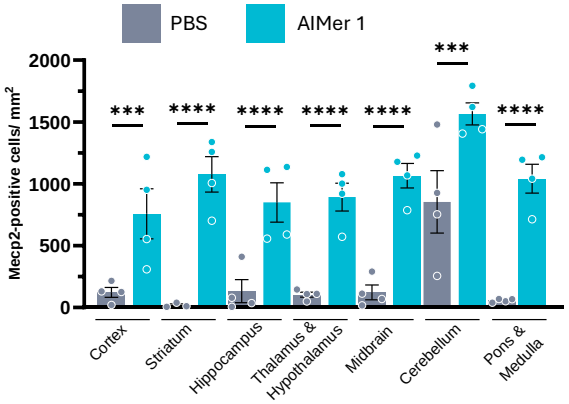
1. Mort, Matthew, et al. "A meta-analysis of nonsense mutations causing human genetic disease." Human mutation 29.8 (2008): 1037-1047.
2. Percy, Alan K., et al. "Rett syndrome: north American database." Journal of child neurology 22.12 (2007): 1338-1341.
3. Fajac and Sermet. 2021 Cells; 2. Bobadilla, JL, et al. 2002 Hum. Mutat.

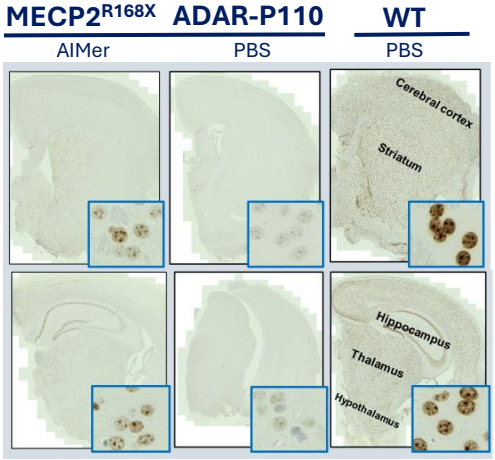
MECP2 RNA editing and protein rescue detected *in vivo* 6 weeks post single neonatal ICV injection

MECP2 RNA Editing

MECP2 Protein Rescue

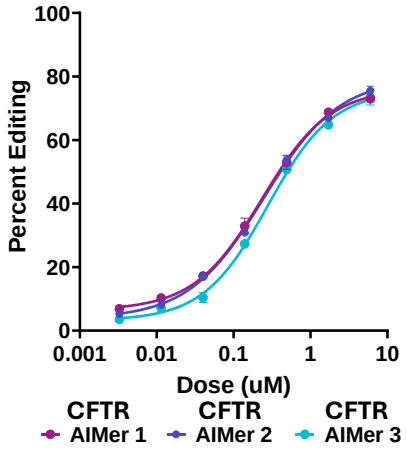




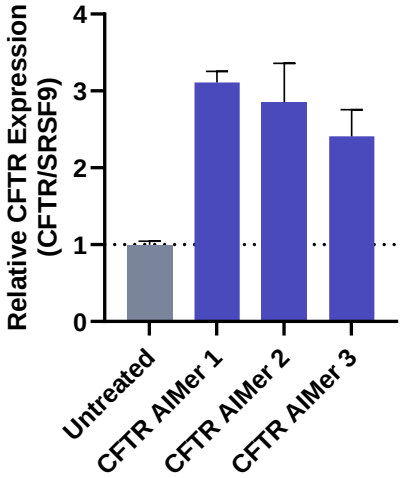


AIMer treatment in bronchial epithelial cells produces up to 75% editing, translating to a 50% recovery of wild-type CFTR protein

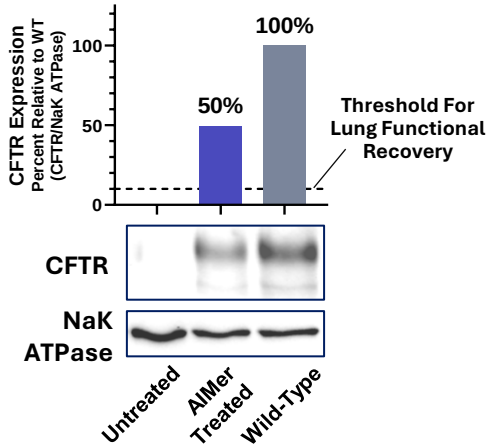
75% W1282X editing in human bronchial epithelial cells (gymnotic delivery)



3-fold increase in CFTR transcript expression

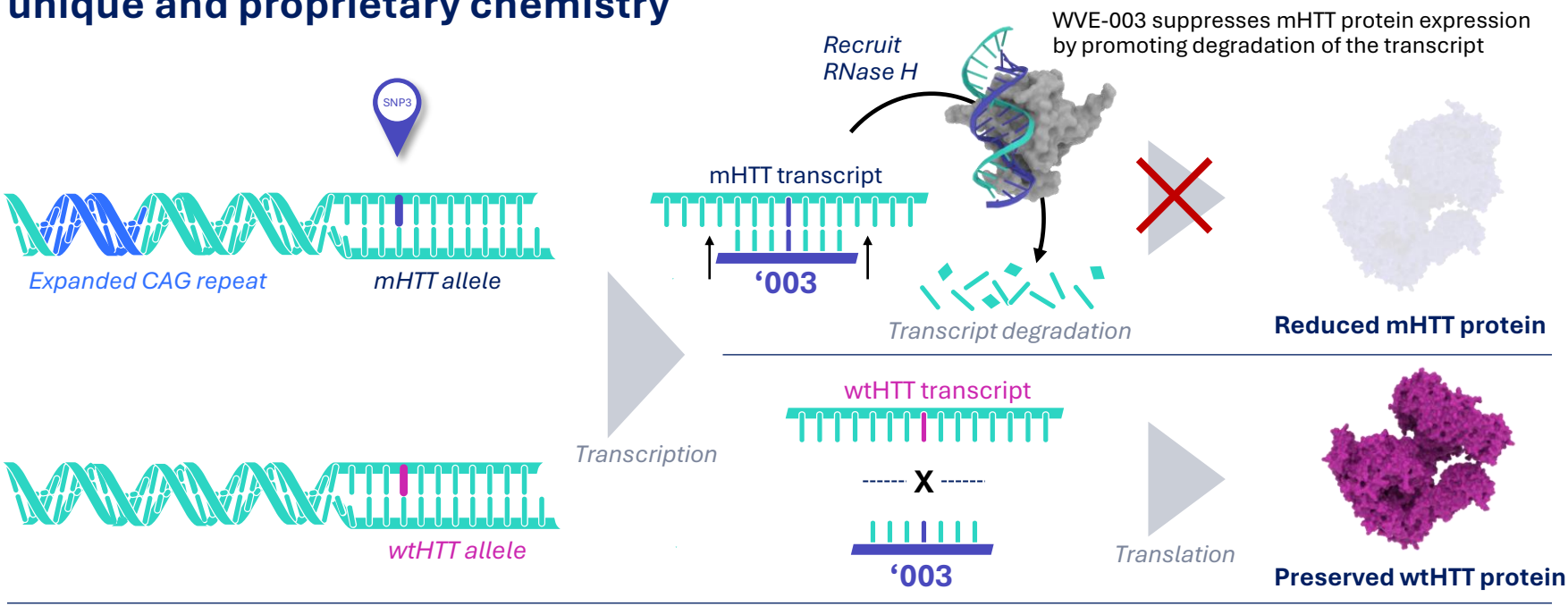


50% recovery of wild-type CFTR protein



Spotlight:
WVE-003: Allele-Selective Treatment for Huntington's Disease

WVE-003: First-in-class allele-selective oligonucleotide, enabled by Wave's unique and proprietary chemistry



An allele-selective, wtHTT-sparing approach is uniquely suited to address HD across all stages of disease; >200,000 patients with HD with pre-symptomatic and symptomatic disease in US and Europe

Iwamoto *et al.*, *Mol Ther Nuc Acids* 2024 DOI: 10.1016/j.omtn.2024.102246

SELECT-HD results: WVE-003 led to allele-selective mHTT reduction, correlating with slowing of caudate atrophy

Allele-Selective mHTT KD with wtHTT Preservation

- mHTT reduction of up to 46% vs. placebo
- wtHTT preserved/increased throughout study

Slowing of Caudate Atrophy

- WVE-003 trended towards less caudate atrophy vs. placebo (4.68% vs. 5.10%, not significant)

Functional Benefit

- Caudate atrophy is an imaging biomarker expected to predict clinical outcomes, including clinically meaningful worsening of Total Motor Score (TMS)

SELECT HD

Greater allele-selective mHTT reduction correlated with the slowing of caudate atrophy at 24 weeks (R = -0.50, p=0.047)

Expect feedback from regulators on path to accelerated approval by year-end 2024

Liu et al., 2023 Brain Comm

Guest speaker: Jeffrey D. Long, PhD

Professor of Psychiatry & Biostatistics at the University of Iowa

- Dr. Long is Professor in the departments of Psychiatry and Biostatistics at the University of Iowa and works primarily in Huntington's disease (HD).
- He is the co-chair of the C-PATH HD Regulatory Science Consortium Modeling Working Group, and a member of the Coordinating Committee.
- He has over 15 years of experience in analyzing data from large HD observational studies, including Enroll-HD, Predict-HD, and Track-HD.
- He and his collaborators have developed several progression indices that are used for clinical trial enrichment, such as the Huntington's Disease Integrated Staging System, which is intended to facilitate the conduct of new clinical trials.

Caudate Volume and Clinical Trials in Huntington's Disease

JEFFREY D. LONG, PHD

PROFESSOR, PSYCHIATRY AND BIOSTATISTICS, UNIVERSITY OF IOWA

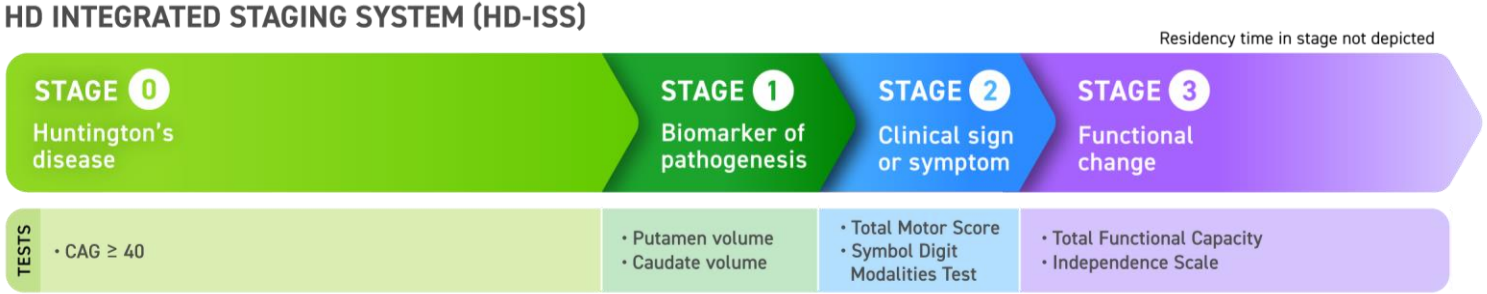
Wave Research Day, October 30, 2024

Overview

- Why consider caudate volume in HD clinical trials?
  - Sample size considerations
- Caudate volume and the prediction of clinical variables
  - Tutorial
- Ongoing research

Why Consider Caudate Volume?

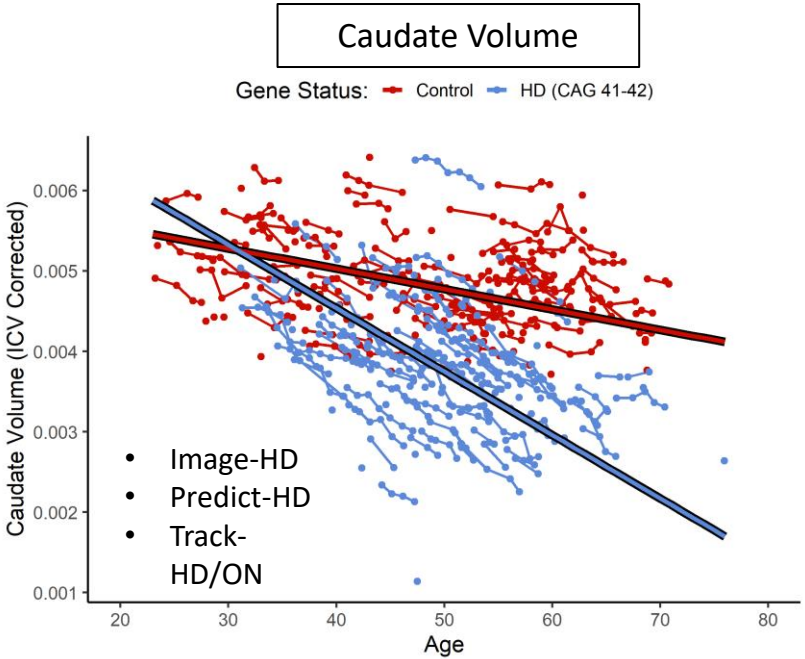
- (1) HD-specific biomarker
  - HD is caused by a CAG expansion on *HTT* gene
  - Loss of medium spiny neurons in the striatum
- (2) Enables earlier clinical trials

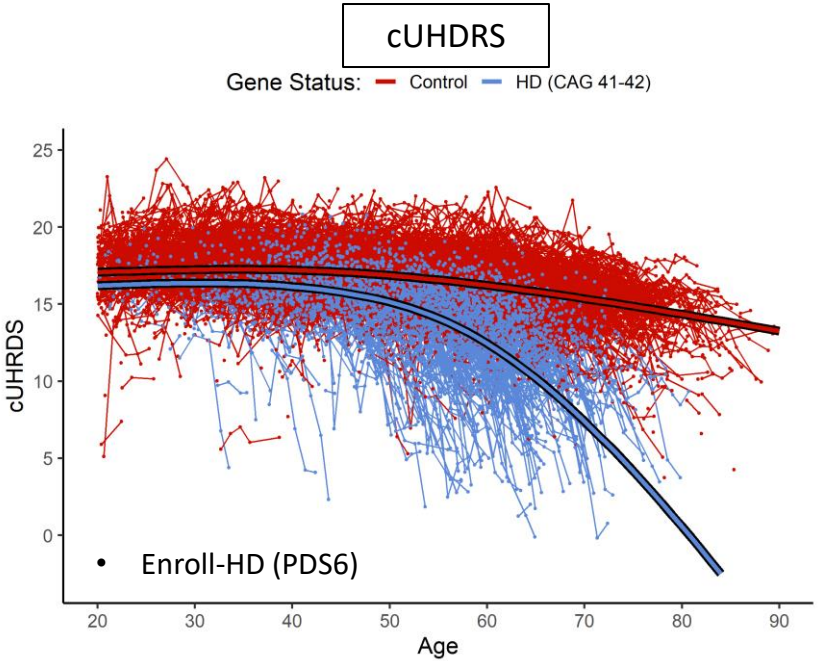


- (3) Enables smaller clinical trials
  - Due to favorable characteristics

Regularity of Caudate Change

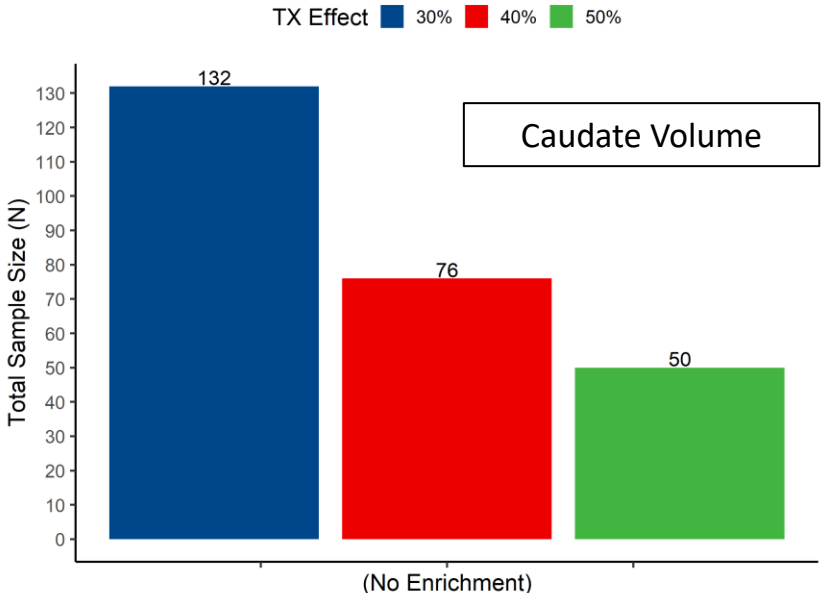
- HD-ISS Stage 2

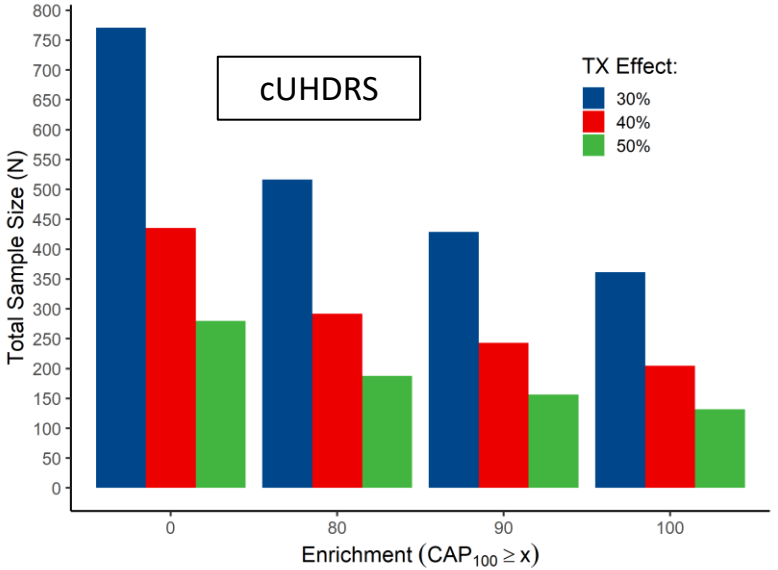




Required Sample Size

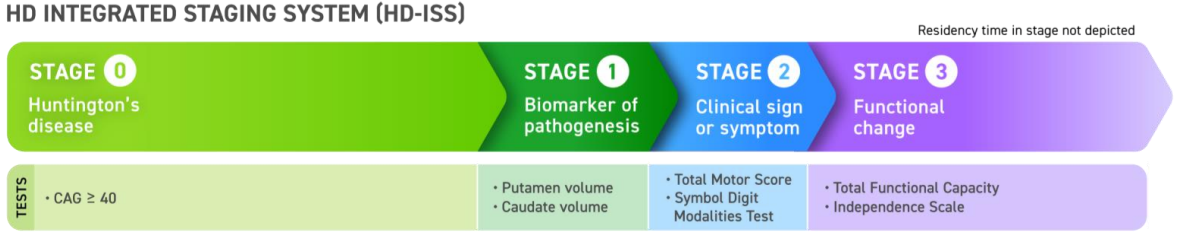
- HD-ISS Stage 2 inclusion
- Standard 2-year randomized controlled trial (2 arms)





Caudate Volume & Clinical Variables

- Regulators: does caudate volume predict clinical change?
  - Time precedence is important (caudate → clinical change)
- HD-ISS based on associations in the extent HD literature

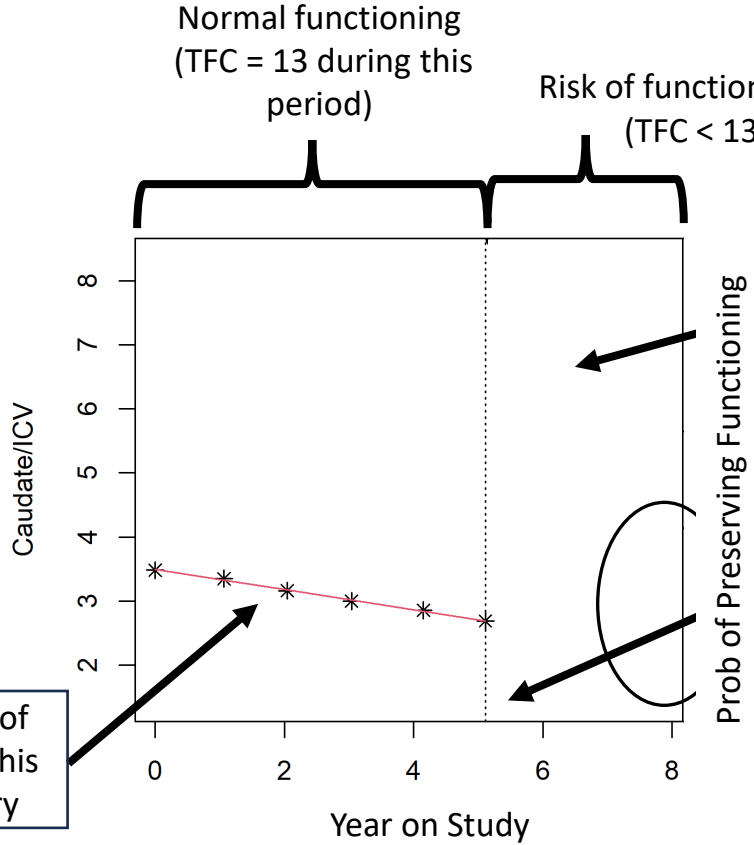


- Prediction analysis (in collaboration with Jim Mills, University of Iowa)
  - Use *earlier* caudate volume to predict *later* functional loss (TFC)
  - TFC is favored by regulators
  - Sophisticated statistical modeling using Predict-HD and Track-HD/ON

Tutorial Slides

- Earlier caudate volume predicting later functioning
  - Level of caudate volume
  - **Rate of atrophy**
- Total Functional Capacity (TFC)
  - TFC = 13 is normal functioning
  - TFC < 13 is functional loss
- First loss in TFC
  - Job modification: some change in occupation due to disease
  - Considered clinically meaningful
- Predict the probability of preserving functioning
  - Delaying function loss

Caudate Change and TFC Loss



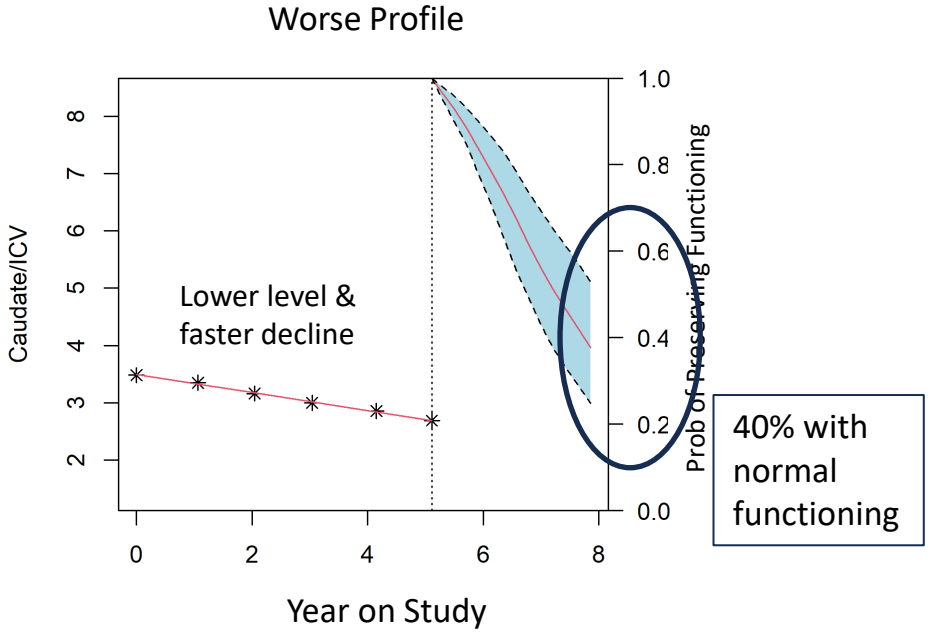
Probability of preserving functioning (with 95% CI)

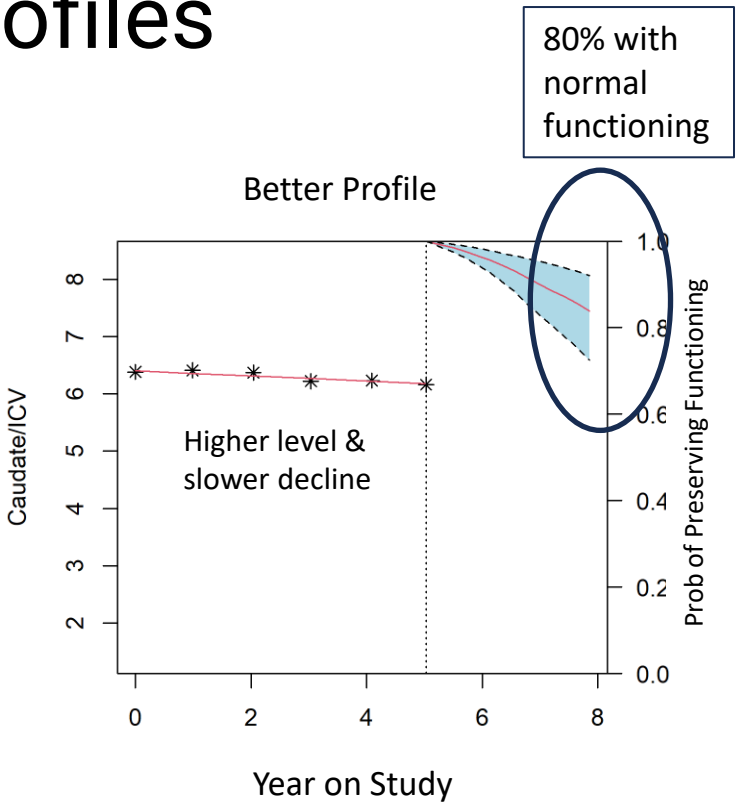
After 5th year is when TFC starts to decrease for at least one patient

Imagine a cohort of HD patients with this average trajectory

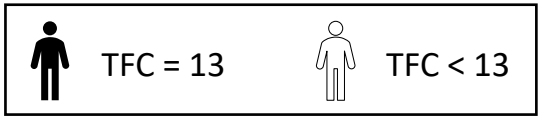
After 3 years of risk
- 40% normal
- 60% loss

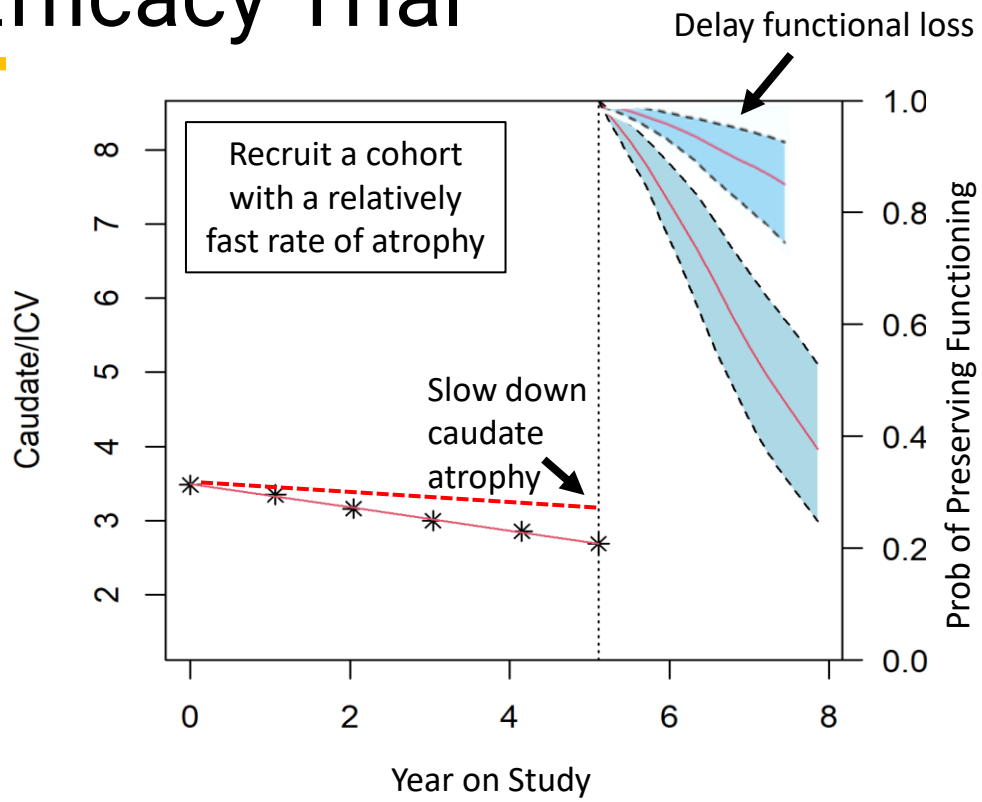
Comparing Caudate Profiles



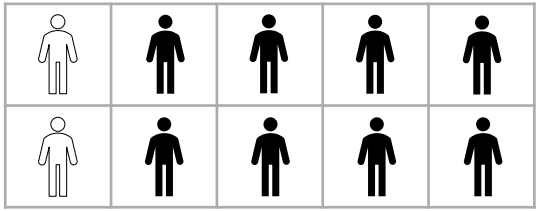


Efficacy Trial

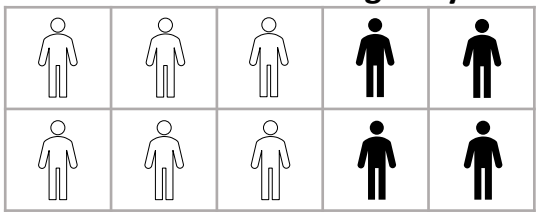




80% normal functioning at 8y



40% normal functioning at 8y



Ongoing Research

- **Determine how much slowing in caudate atrophy is required for a meaningful delay in HD onset**
- Clinical meaningfulness
  - Delay functioning loss by 1 year, for example
- Define the treatment effect
  - 1 year delay in functioning loss requires 40% slowing of caudate atrophy, for example
- This information can be used to plan an efficacy study

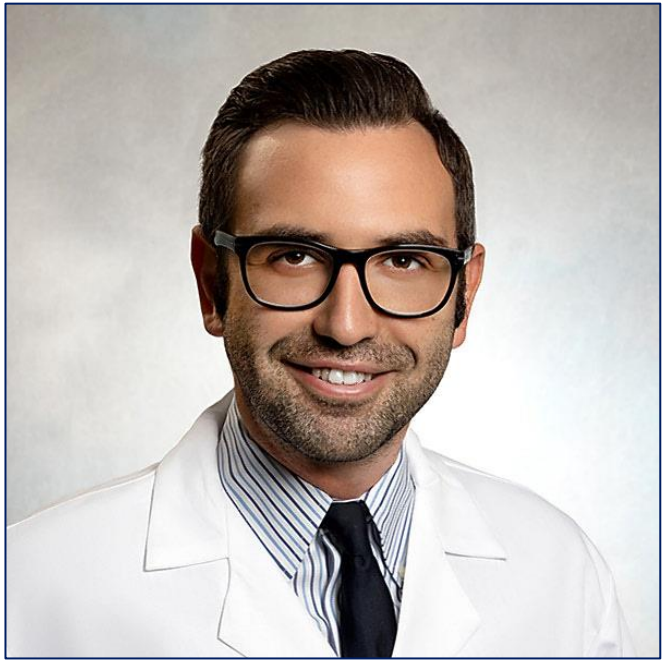
Thanks!

Spotlight:
WVE-007: GalNAc-siRNA for obesity

Guest speaker: Mehmet Furkan Burak, MD

Instructor in Medicine, Harvard Medical School & Endocrinologist and Obesity Specialist, Brigham and Women's Hospital

- Dr. Burak is an endocrinologist and faculty member, leading translational immunometabolism research group at Brigham and Women's Hospital / Harvard Medical School and basic science researcher at Harvard Chan School of Public Health (HSPH), Department of Molecular Metabolism.
- His research is focused on the role of adipose tissue-derived molecules in obesity and development of new therapeutic strategies in obesity related immunometabolic diseases such as diabetes, fatty liver disease and asthma.
- He has numerous high impact publications (such as in Science Translational Medicine, JCEM, Cell Metabolism, Nature Drug Discovery, Nature Endocrinology), a book chapter on 'Drug mechanism of actions in obesity' and has licensed U.S patents in the obesity field.
- He has received many prestigious awards and was selected as one of the 'Top Doctors' of America by the Castle Connolly and Boston Magazine in 2023 and 2024.
- He is the obesity section editor of the Journal of Endocrine Society.
- He is triple board certified in Internal Medicine and Endocrinology, Diabetes and Metabolism (ABIM) and Obesity Medicine (ABOM). His clinical practice focuses on obesity, diabetes and immunometabolism.

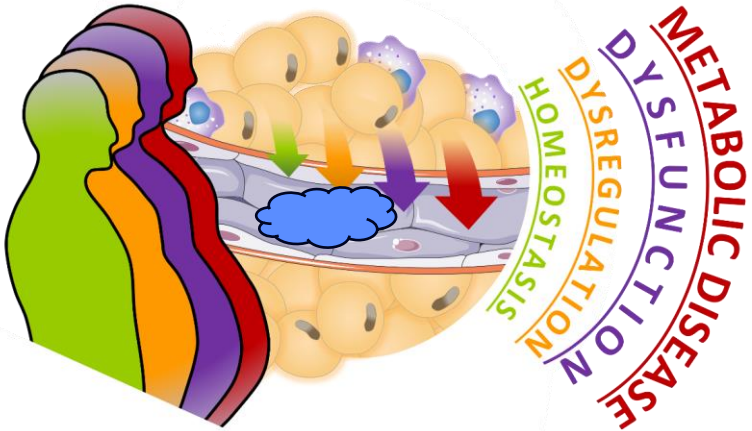


Paradigm Shift in Obesity Treatment

Dr. Mehmet Furkan Burak

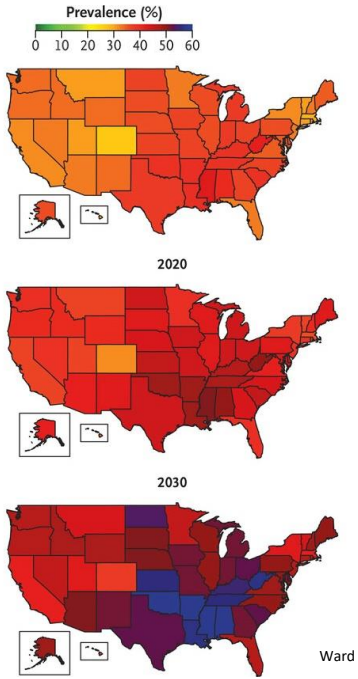
Division of Endocrinology, Diabetes and Hypertension
Brigham and Women's Hospital
Harvard Medical School

Department of Molecular Metabolism
Harvard T.H. Chan School of Public Health

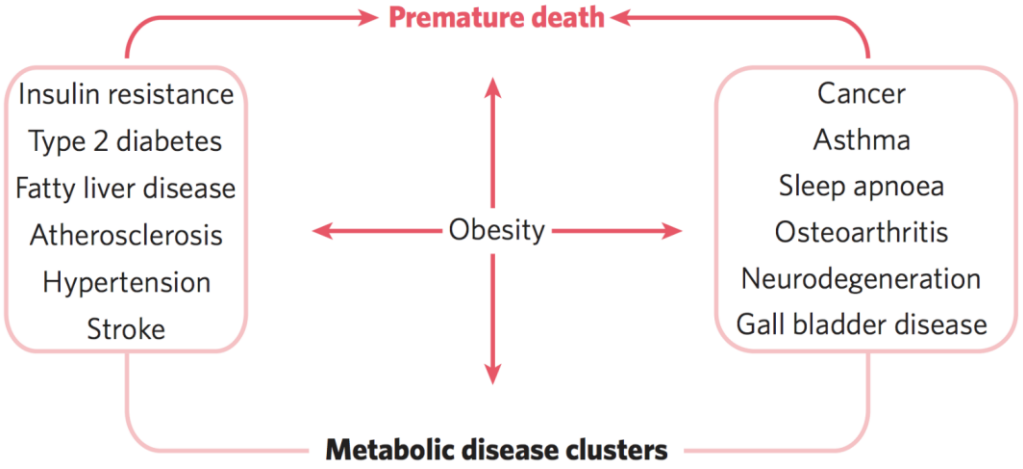


Obesity and Dysmetabolism

Prevalence of Overall Obesity (BMI ≥ 30)



Ward et al. N Engl J Med, 2019



Hotamisligil et al. Nature, 2006

History, Revolution of the Biologics!

August 23, 1947

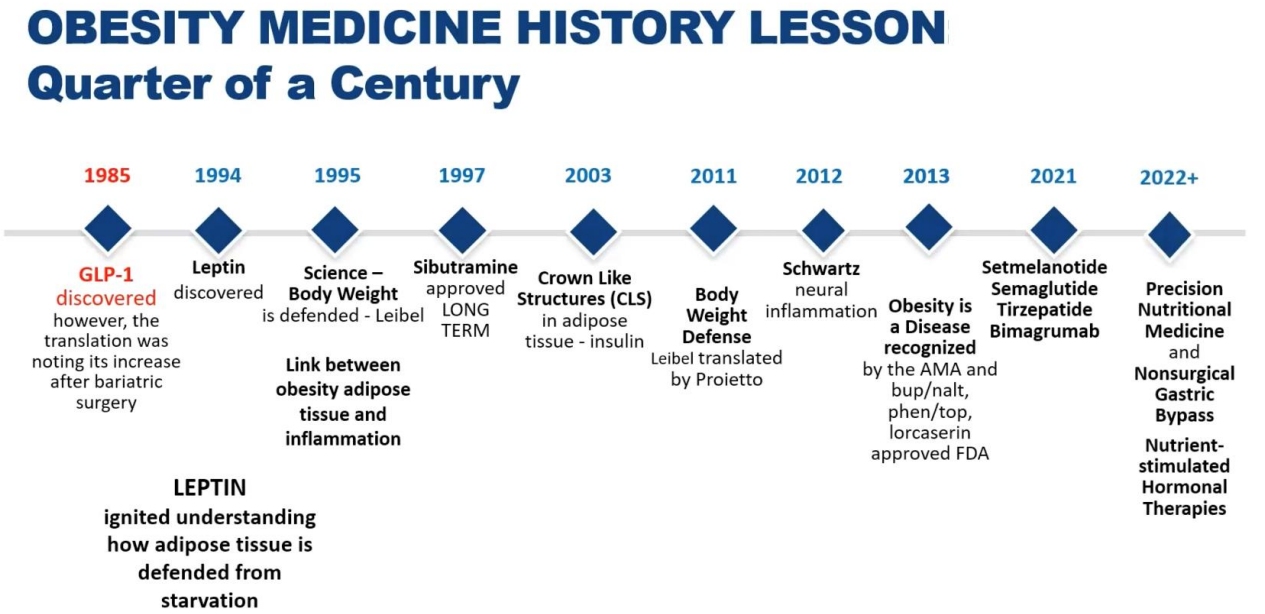
THE MECHANISM OF AMPHETAMINE-INDUCED LOSS OF WEIGHT

A Consideration of the Theory of Hunger and Appetite

STANLEY C. HARRIS, Ph.D.; A. C. IVY, Ph.D., M.D.; LAUREEN M. SEARLE, B.S.

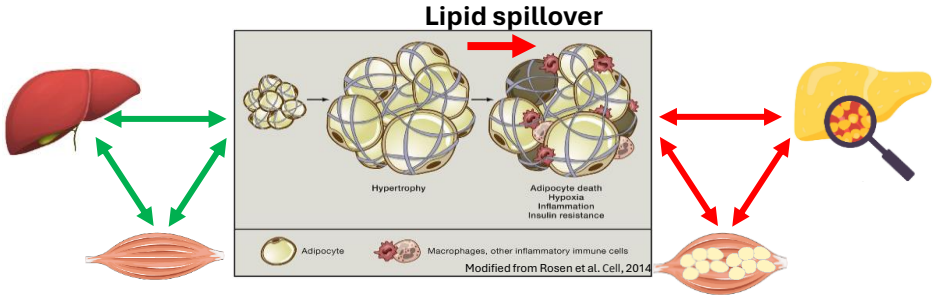
» Author Affiliations

JAMA. 1947;134(17):1468-1475. doi:10.1001/jama.1947.02880340022005



Courtesy of Caroline Apovian, modified

Energy Regulation and Current Anti-Obesity Medications

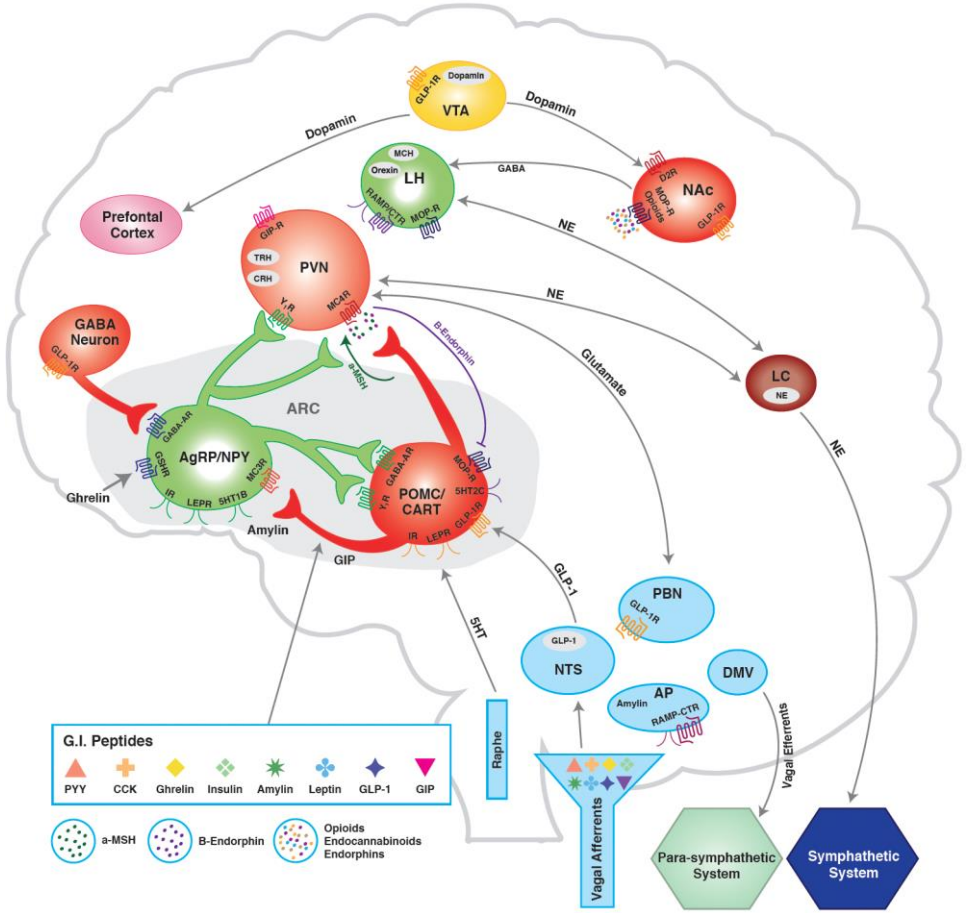


Adipogenic peripheral pathways become pathological in obesity

-INHBE

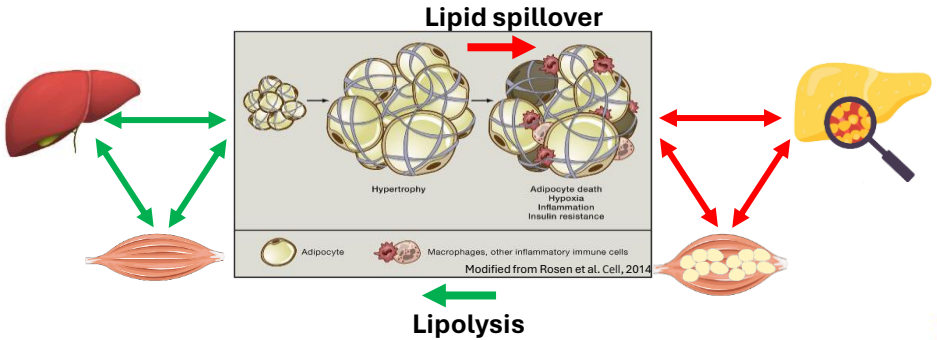
-GPR75

-Myostatin (GDF8), ALK7



Burak et al. 2023. Handbook of Obesity –
Volume 2: Clinical Applications (5th ed.) CRC Press.

Energy Regulation and Current Anti-Obesity Medications



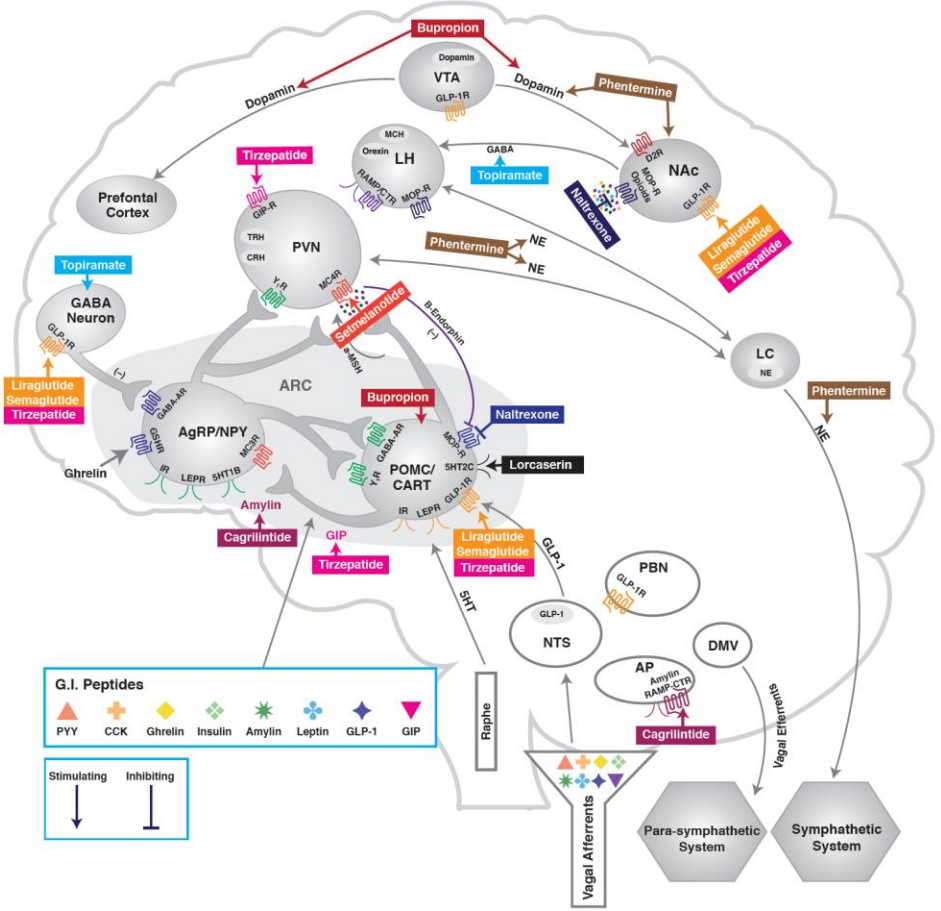
Adipogenic peripheral pathways become pathological in obesity

Inhibition of these pathways would be beneficial with switching back to more lipolysis and less muscle breakdown

-INHBE

-GPR75

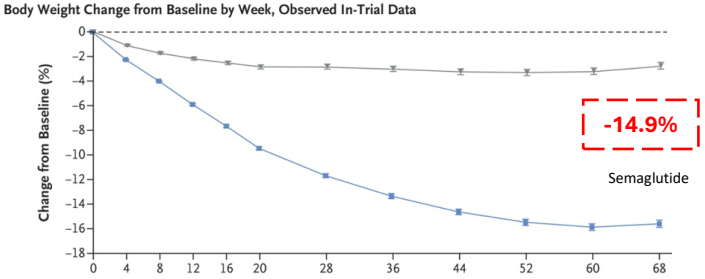
-Myostatin (GDF8), ALK7



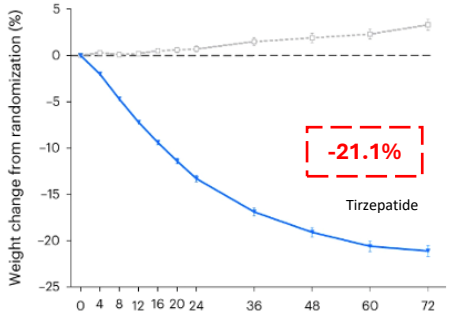
Burak et al. 2023. Handbook of Obesity –
Volume 2: Clinical Applications (5th ed.) CRC Press.

GLP-1 Agonists: Pros

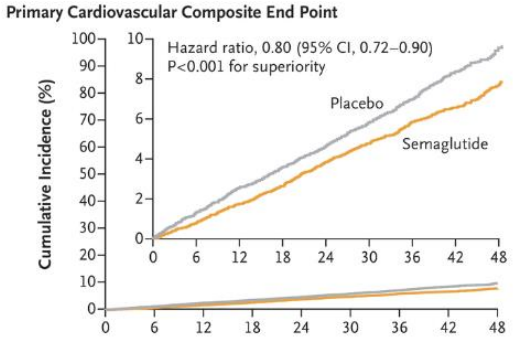
- Paradigm shift in obesity treatment
- The efficacy of weight loss medications is closing the gap with bariatric surgery
- Cardiovascular benefits

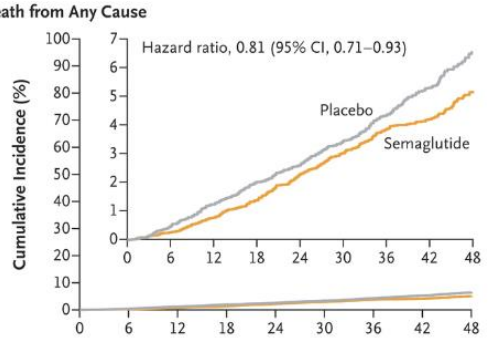


Wilding et al. NEJM, 2021



Wadden et al. Nat Med, 2023

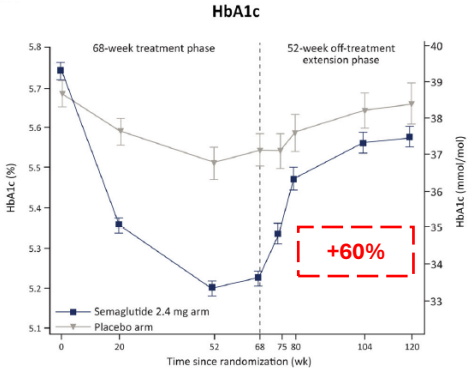


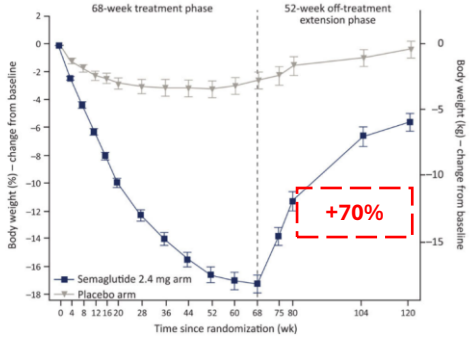


Lincoff et al. NEJM, 2023

GLP-1 Agonists: Cons

- Despite high obesity rate, only 2-3% is getting obesity treatment
- Discontinuation is high, only ~35% continues treatment over 1 year
- Decrease in energy expenditure
- Weight regain after discontinuation
- GI side effects, anhedonia
- Muscle mass loss





Wilding et al. Diabetes Obes Metab, 2022

Adverse Event	Semaglutide (N = 1306)
	No. of participants (%)
Nausea	577 (44.2)
Diarrhea	412 (31.5)
Vomiting	324 (24.8)
Constipation	306 (23.4)

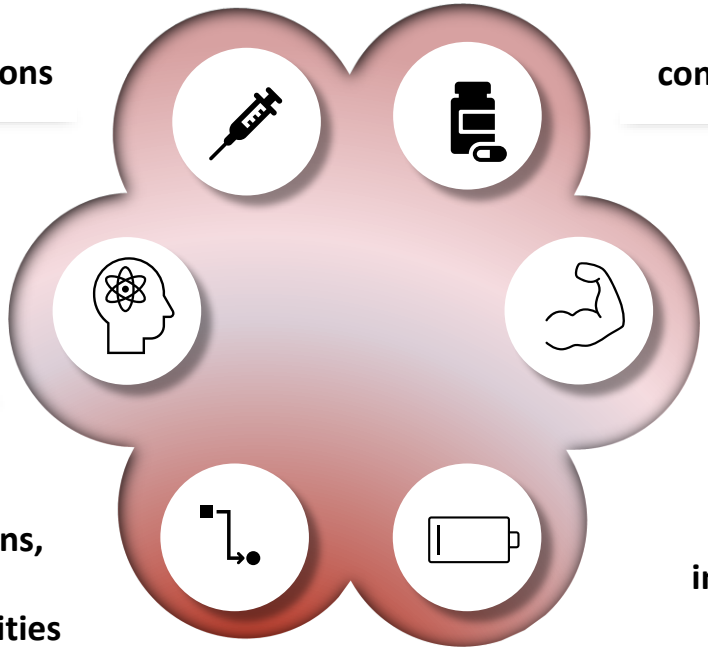
Changes in Body Weight	Changes in Skeletal Muscle Mass
−15.3 kg semaglutide vs −2.6 kg placebo	−5.26 kg vs −1.83 kg

Wilding et al. NEJM, 2021

Current Unmet Needs in Era of GLP-1 Agonists

Access to medications

Oral form of medications & convenient dosing for chronic treatment



Novel biological MoA for GLP-1 intolerant patients, Gentle drugs for maintenance

Prevention of muscle mass loss and weight regain

Higher efficacy drug combinations, including peripheral effects for severe obesity and comorbidities

Novel medications that safely increase energy expenditure rather than decrease food intake

MoA: mechanism of action

WVE-007: A Novel Obesity Therapeutic for Healthy, Sustainable Weight Loss

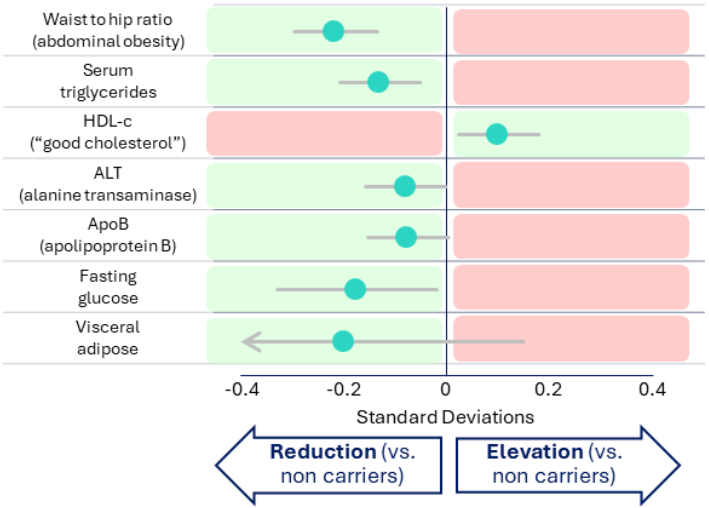
Ginnie Yang, PhD

SVP, Translational Medicine

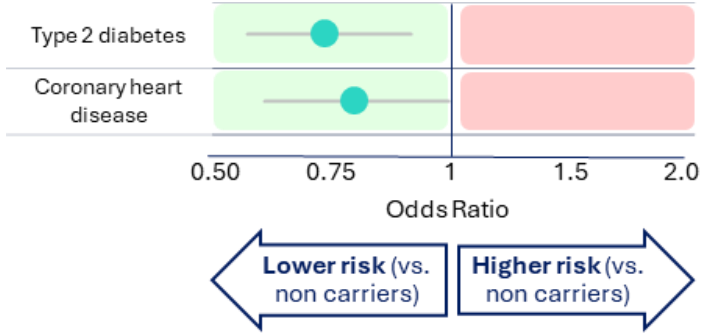
WAVE™ LIFE SCIENCES

Human genetic data demonstrate that INHBE heterozygous carriers have a healthy metabolic profile

Heterozygous INHBE LoF carriers have favorable traits: lower abdominal obesity, lower triglycerides, higher HDL-c



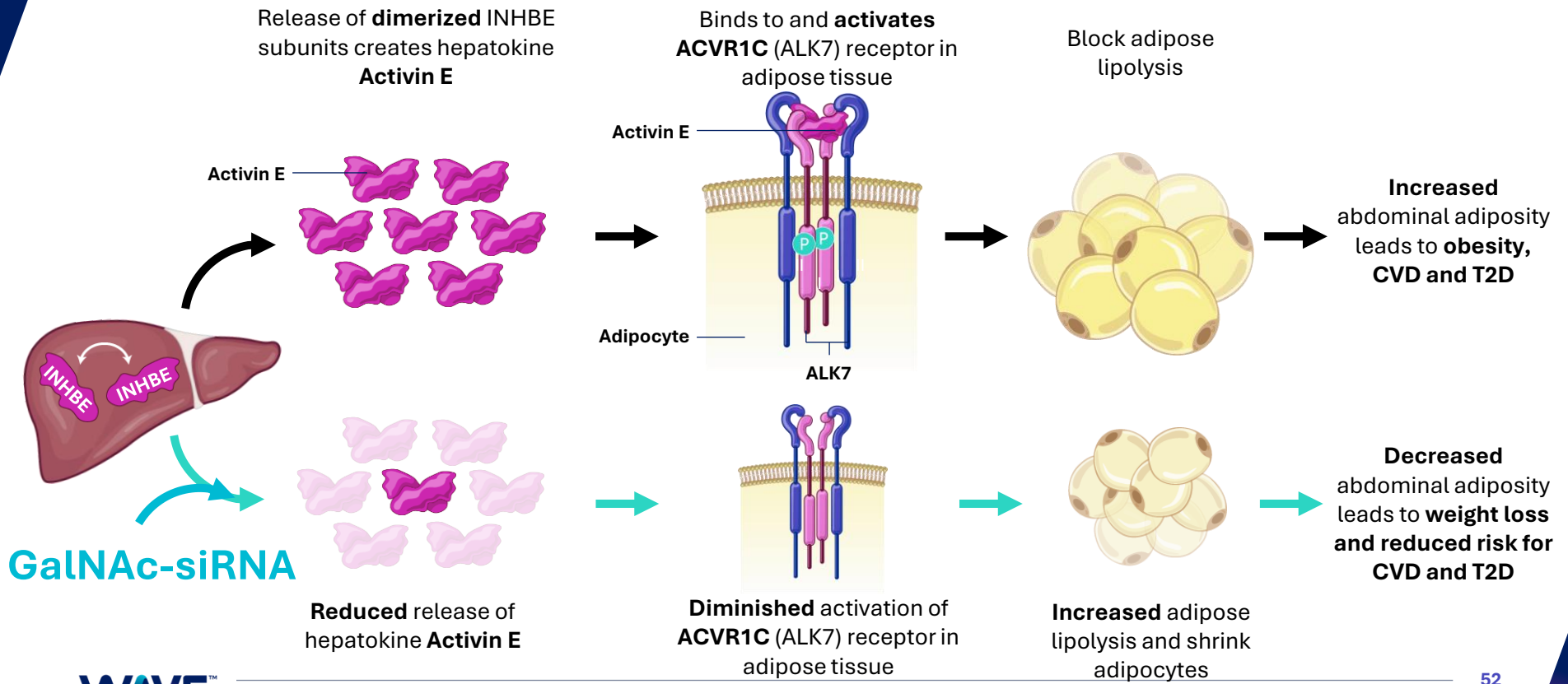
Heterozygous INHBE LoF carriers have lower risk of Type 2 diabetes and CHD



Silencing INHBE mRNA by ≥50% is expected to recapitulate the healthy metabolic profile of heterozygous INHBE loss of function (LoF) carriers

Akbari et al. Nat Commun. 2022 Aug 23;13(1):4844; Deaton et al. Nat Commun. 2022 Jul 27

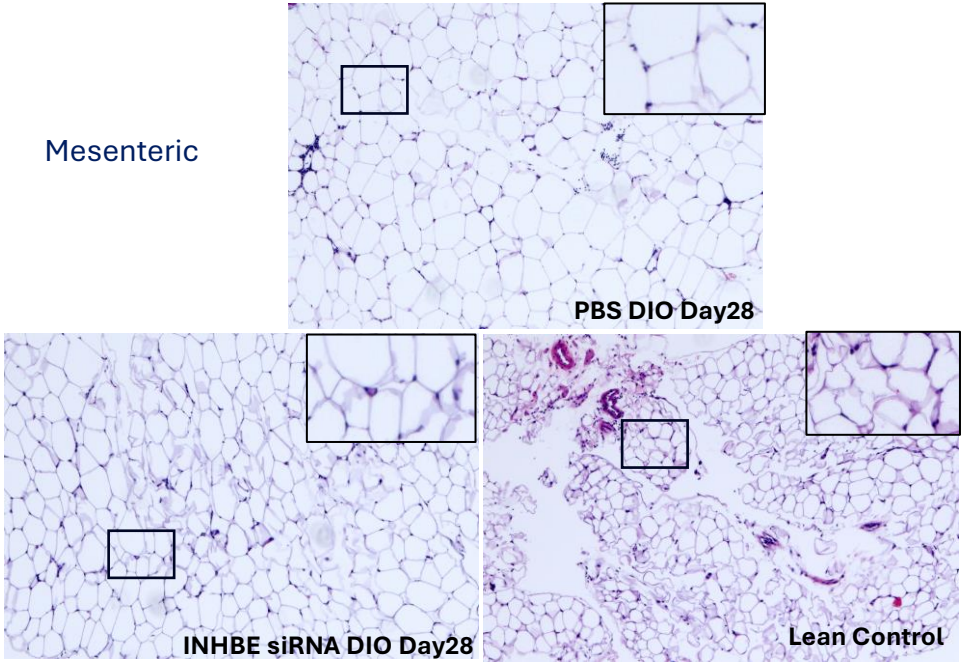
Role of INHBE in the pathogenesis of obesity associated metabolic diseases and how INHBE GalNAc-siRNA would address these health issues

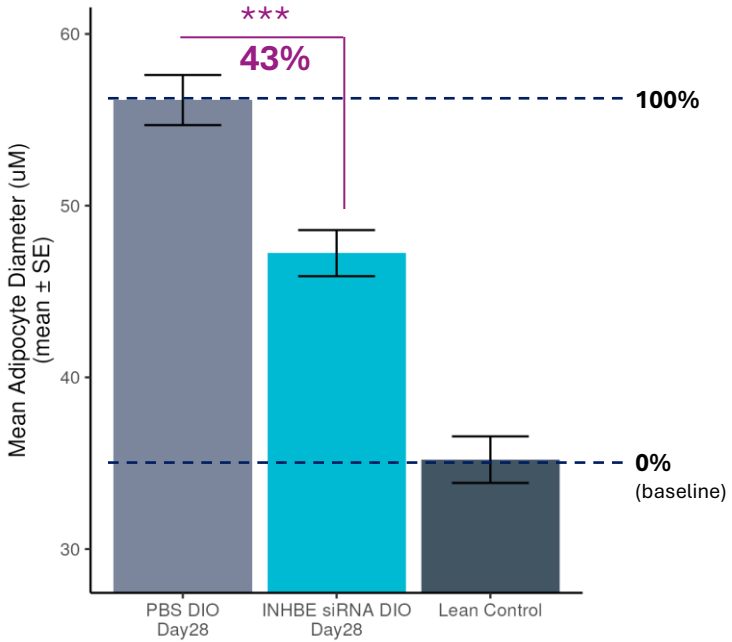


1. Cell Reports (2018) 25, 1193–1203; 2. Biochemical Journal (2024) 481 547–564; 3. PNAS 2023 Vol. 120 No. 32 e2309967120; 4. Nat Commun 2022. https://doi.org/10.1038/s41467-022-32398-7; 5. Nat Commun 2022. https://doi.org/10.1038/s41467-022-31757-8

Significant ~43% decrease of adipocyte size in mesenteric adipose tissues with INHBE siRNA treatment

Mesenteric



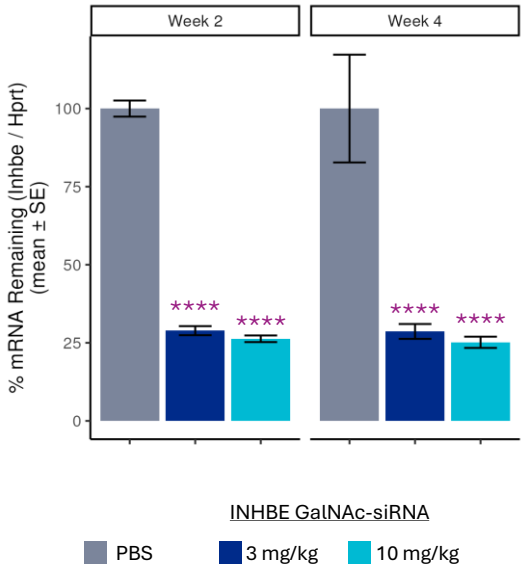


Supports peripheral mechanism of WVE-007 – distinct from GLP-1s with central mechanism

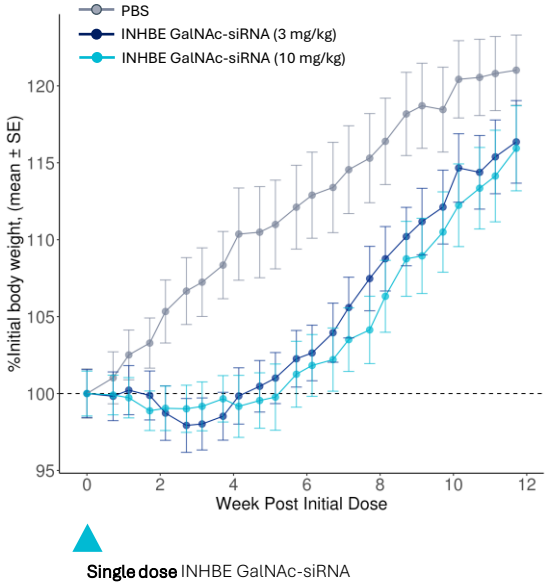
10 m/kg INHBE siRNA, Stats: One-way ANOVA with Tukey HSD post hoc comparisons *** $p < 0.001$ (only PBS vs. INHBE comparison shown)

Potent and sustained change in body weight up to 12 weeks with a single dose of INHBE GalNAc-siRNA, supporting 1-2x a year dosing

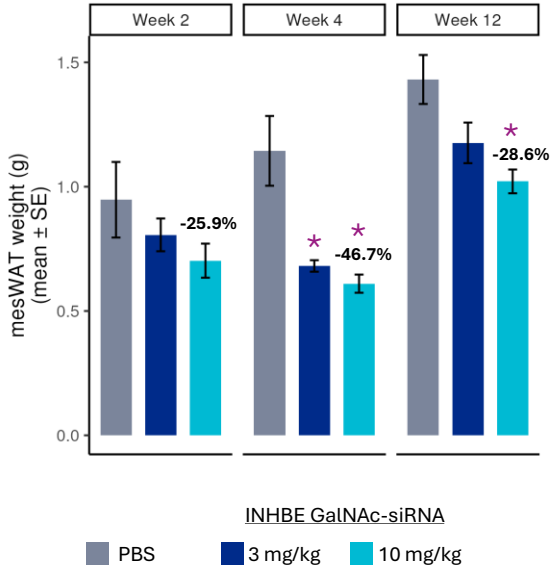
Potent knockdown of INHBE mRNA with a single dose



Potent and durable effect on body weight



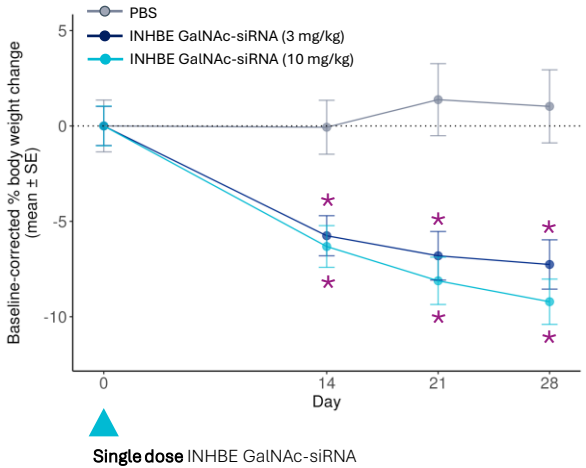
Sustained reductions of mesenteric fat mass at 12 weeks



Study conducted in rapid weight gain model. Stats: (left) Two-way ANOVA with Bonferroni-adjusted post hoc comparisons to PBS per time point **** $p < 0.0001$; (middle) Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects vs. PBS per time point * $p < 0.05$, 3 mg/kg and 10 mg/kg groups significantly different vs. PBS from days 12-82 and 8-82, respectively; (right) Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects per time point * $p < 0.05$

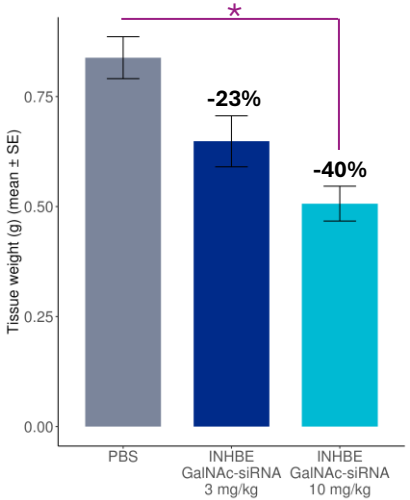
Single doses of INHBE GalNAc-siRNA result in dose-dependent weight loss and reduction of visceral fat, without affecting muscle mass

Reduction in body weight



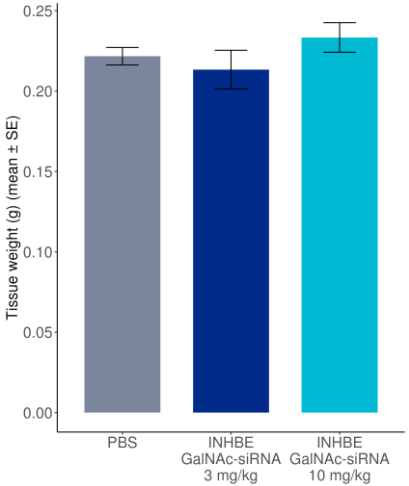
Reduction in visceral fat

Epididymal fat weight (Day 28)



No muscle loss

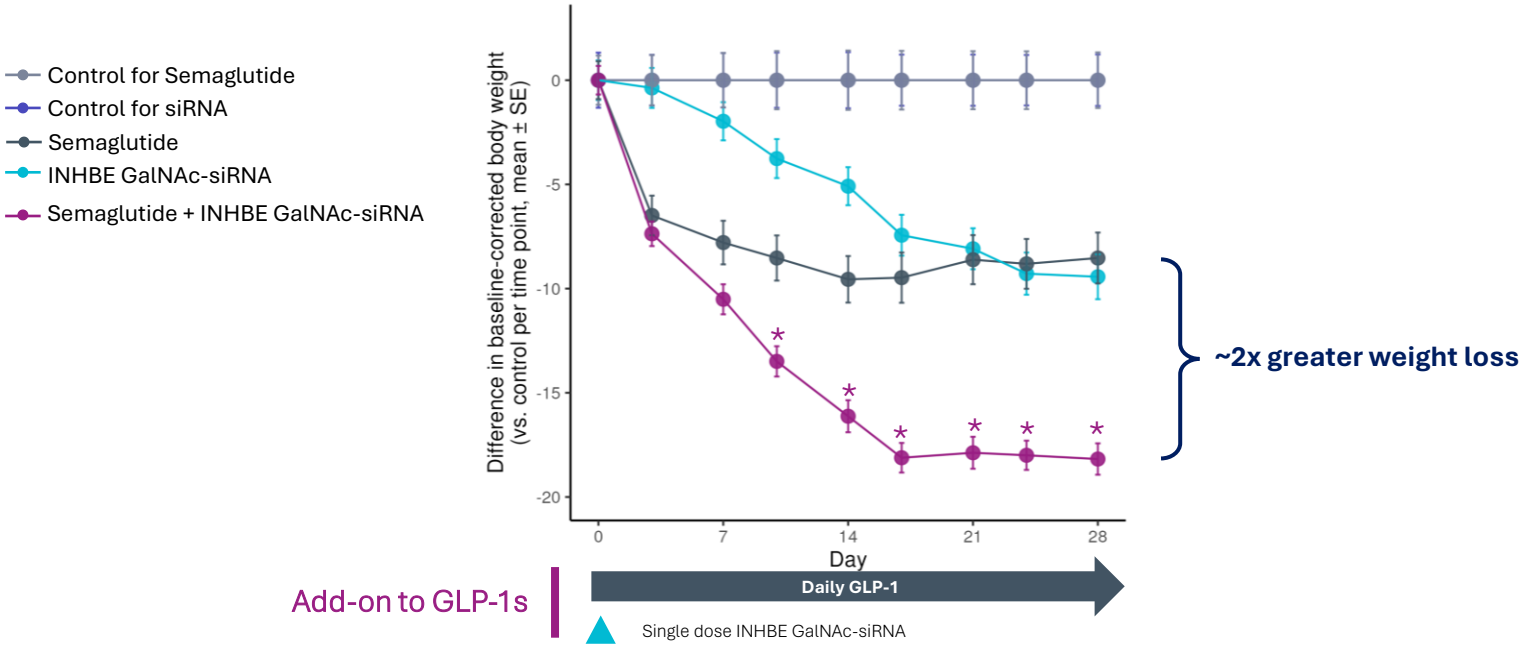
Quadricep weight (Day 28)



INHBE GalNAc-siRNA has potential as monotherapy weight loss therapeutic

Stats: (left, middle, right) Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects vs. PBS per timepoint (left) or per tissue (middle, right) * $p < 0.05$

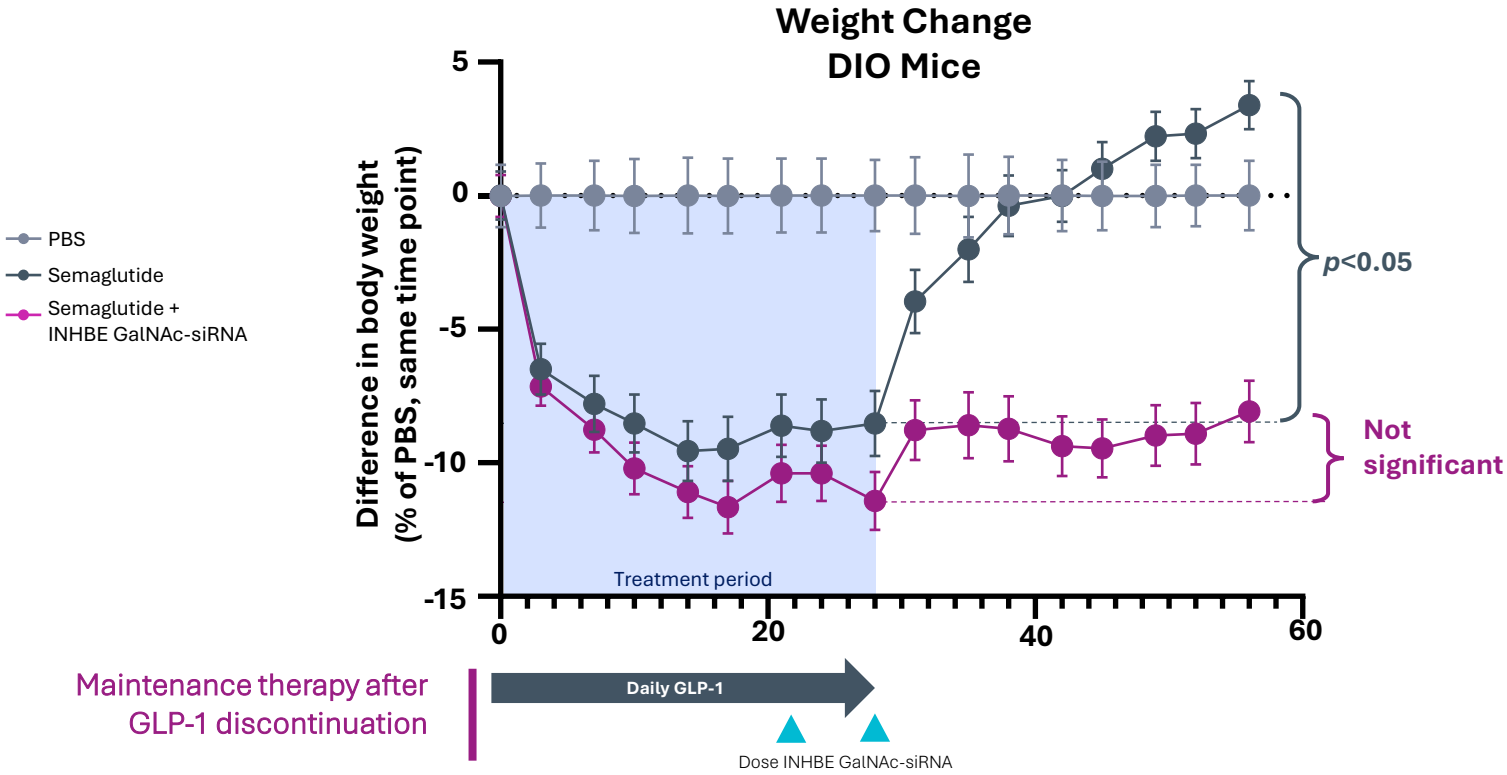
Single dose INHBE GalNAc-siRNA added to daily GLP-1 drives a synergistic effect on weight loss, resulting in ~2x greater overall weight loss



Adding INHBE GalNAc-siRNA to GLP-1 may enhance efficacy or enable reduction of GLP-1 dose

10nmol/kg in mouse is equivalent to therapeutic dose of GLP-1s in human. Stats: Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects of Semaglutide vs. Semaglutide + INHBE GalNAc-siRNA per time point * $p < 0.05$

Adding INHBE siRNA to GLP-1 treatment course prevents weight regain after the cessation of GLP-1



Stats: Linear Mixed Effects ANOVA with post hoc comparison of Day 28 vs. Day 56 marginal effects per treatment * $p < 0.05$

Preclinical data support best-in-class profile and potential to use WVE-007 across multiple treatment settings with 1-2x a year dosing

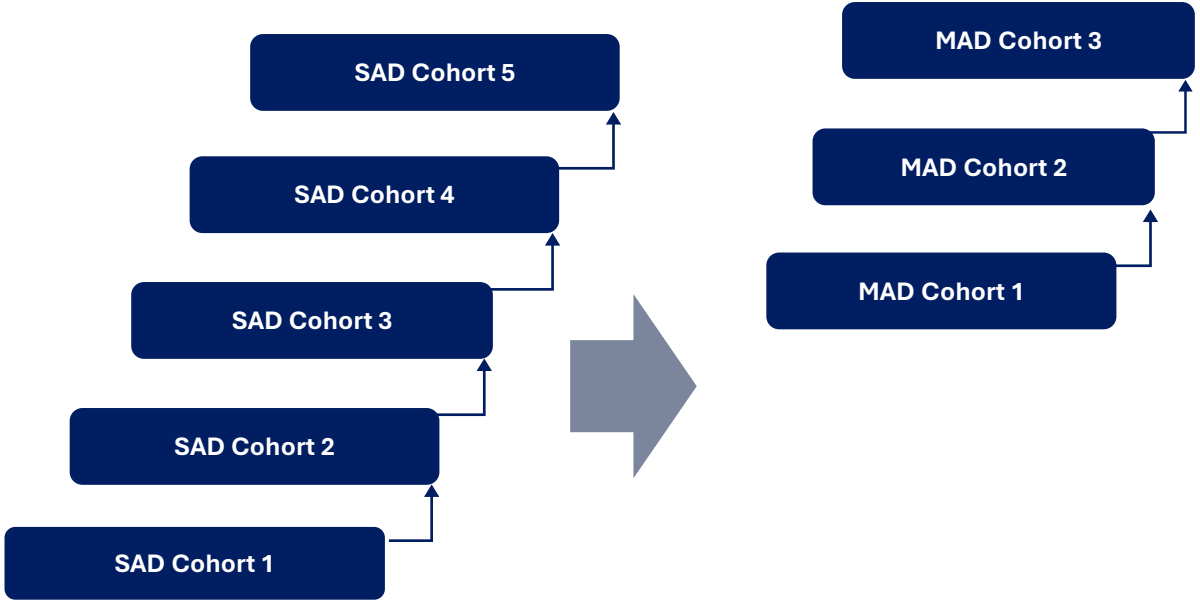
- ✓ **Monotherapy: as a single agent.** Weight loss similar to semaglutide with no loss of muscle mass and a reduction in fat mass with preferential effect to the visceral fat, and without suppressing food intake
- ✓ **Add-on to GLP-1s: WVE-007 in addition to GLP-1 therapy.** When administered as an add-on with semaglutide, a single dose of Wave's INHBE GalNAc-siRNA doubled the weight loss observed with semaglutide alone
- ✓ **Maintenance: for patients who stop treatment with GLP-1 therapy.** Curtailed rebound weight gain upon cessation of semaglutide and prevention of weight cycling, which worsens the outcomes of various metabolic diseases

CTA expected before year-end for Phase 1 trial of WVE-007 in adults living with overweight or obesity, otherwise healthy

Randomized, double-blind, placebo-controlled study of ascending doses of WVE-007

Trial Design

- **Objective**: Assess dose safety, tolerability, PK and PD
- **Key measurements**
  - **Primary:** Safety and Tolerability
  - **Secondary:** PK, Activin E
  - **Exploratory PD:**
    - Body Weight
    - Body compositions
    - Metabolic health
    - Biochemical markers



Expect to initiate clinical trial for WVE-007 in 1Q 2025

Spotlight:
WVE-006: First-ever RNA Editor Unlocking New Wholly Owned Programs

Erik Ingelsson, MD, PhD
Chief Scientific Officer

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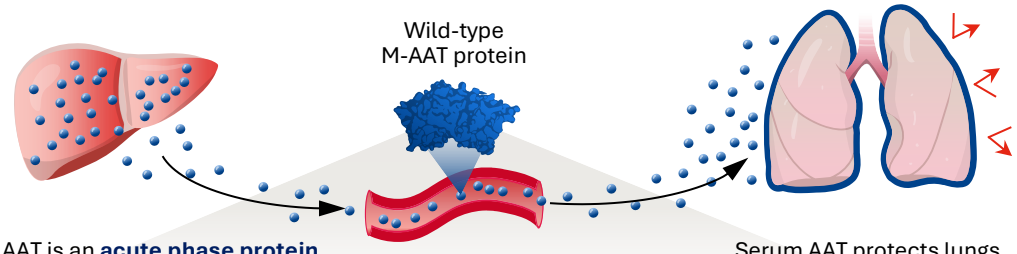
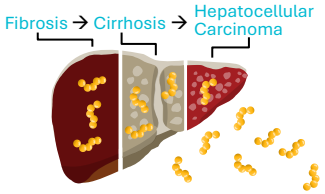
WVE-006: GalNAc-conjugated AIMer designed to correct mutant SERPINA1 transcript to address both liver and lung manifestations of AATD

Healthy

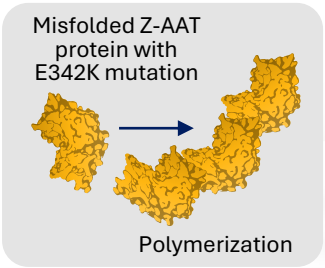


AATD

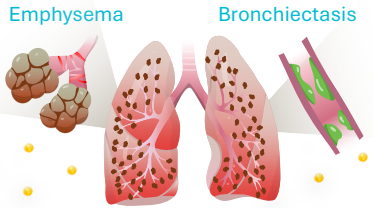
Gain of Function: Liver Disease



Z protein causes AAT proteotoxic stress, leading to progressive liver disease



Loss of Function: Lung Disease



Low serum AAT leads to lung disease

WVE-006 for AATD

SERPINA1 Z allele mRNA encodes Z-AAT protein with E342K mutation

Edited *SERPINA1* mRNA enables wild-type M-AAT protein production

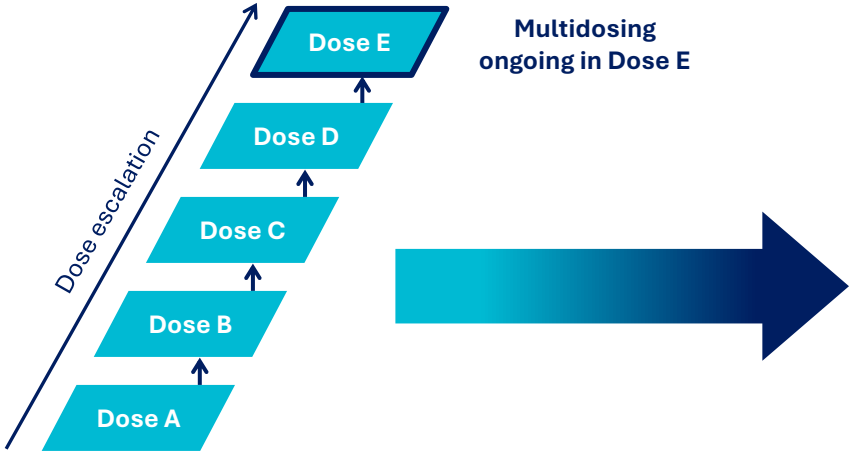
- ✓ Subcutaneous injection (GalNAc)
- ✓ Infrequent dosing
- ✓ Highly specific (No bystanders)

Strnad et al., 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 Alpha-1 Antitrypsin Deficiency GeneReviews.

RestorAATion-1 and RestorAATion-2 ongoing

RestorAATion-1: Healthy Volunteers → **RestorAATion-2: AATD Patients**

Single ascending dose (SAD) → Multiple-ascending dose (MAD) cohorts



Multidosing ongoing in Dose E

Up to 7 doses

Cohort 3

Cohort 2

Cohort 1
200 mg

Study key objectives

Safety and tolerability
Pharmacokinetics
Serum M-AAT levels

HV: healthy volunteer; SAD: single-ascending dose; MAD: multi-ascending dose

WVE-006 has been well-tolerated with a favorable safety profile to date

RestorAATion-1: Healthy Volunteers	RestorAATion-2: AATD Patients
Single ascending dose (SAD) → Multiple-ascending dose (MAD) cohorts	

- WVE-006 has been well-tolerated with a favorable safety profile to date
- Adverse events in RestorAATion-2, as well as in the ongoing RestorAATion-1 trial of healthy volunteers, are mild to moderate
- No Serious Adverse Events reported

Dosing ongoing in RestorAATion-1 at dose levels greater than those planned for Cohort 3 in RestorAATion-2

HV: healthy volunteer; SAD: single-ascending dose; MAD: multi-ascending dose

Achieved proof-of-mechanism for Wave's RNA editing platform

First two patients among first dose cohort in RestorAATion-2 with "ZZ" AATD (Pi*ZZ AATD) to reach day 57:

- Circulating wild-type M-AAT protein in plasma reached a mean of 6.9 micromolar at day 15, representing more than 60% of total AAT
- Increases in neutrophil elastase inhibition from baseline were consistent with production of functional M-AAT
- Mean total AAT protein increased from below the level of quantification at baseline to 10.8 micromolar at day 15, meeting the level that has been the basis for regulatory approval for AAT augmentation therapies.
- Increases in total AAT from baseline and M-AAT protein were observed as early as day 3 and through day 57

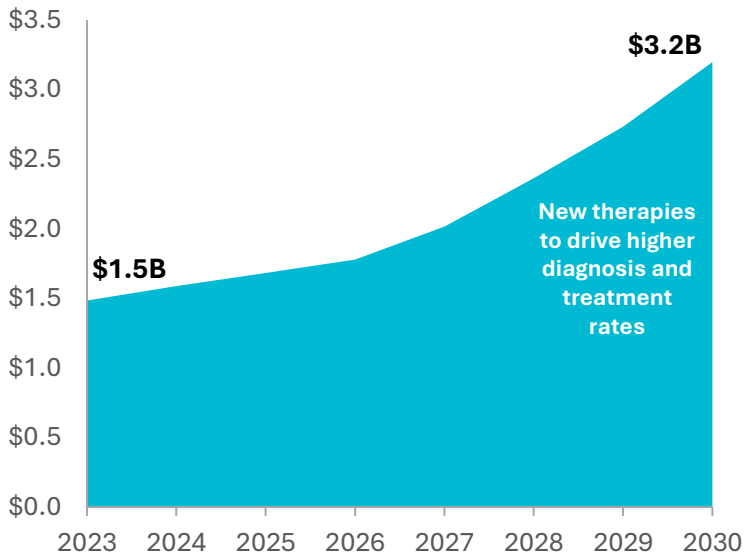
Wave expects to share multidose data from RestorAATion-2 in 2025

AATD market estimated to grow to ~$3B by 2030

AATD Market Overview

- **AATD market today is estimated at ~$1.5B worldwide[1] despite limitations of current treatment**
  - Market consists entirely of plasma-derived augmentation therapy for AATD-lung disease
  - Augmentation therapy requires weekly IV and is not reimbursed in some markets
- **The AATD market is forecasted to grow to ~$3.2B by 2030[1] driven by multiple factors**
  - Increased disease awareness and diagnosis rates (including consumer genetics)
  - Increased uptake arising from improved administration (subcutaneous) and durability
  - Treatments that impact both AATD-liver and lung-disease
- **Potential for additional opportunities in MZ patients with poorly controlled respiratory disease**

Global AATD Market Value ($, Billions) (2023 – 2030)[1]



1. AATD Market Report from Evaluate (October 2024)

Building the pipeline: New programs informed by human genetics

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Wave is uniquely positioned to develop first- and best-in-class therapies that leverage growing insight in human genetics

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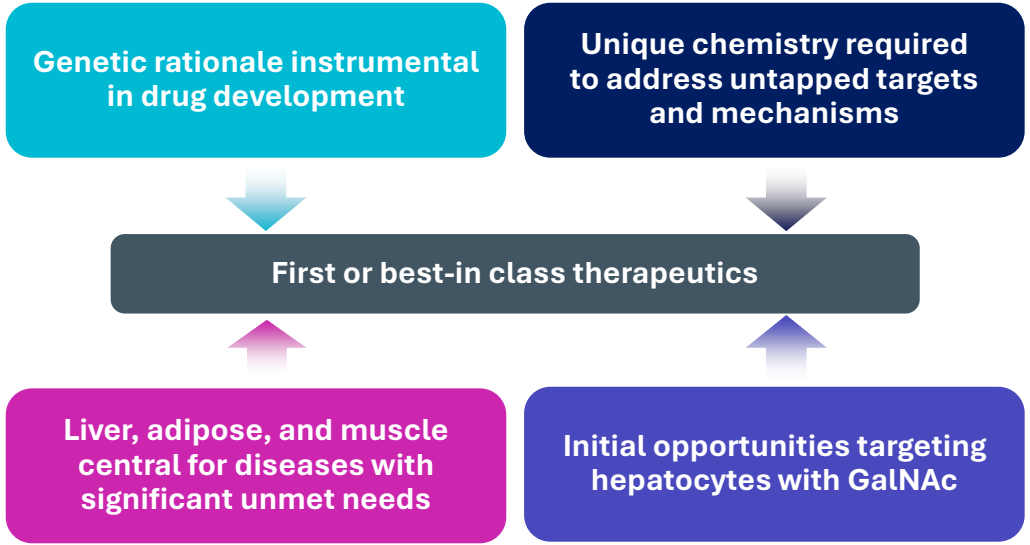
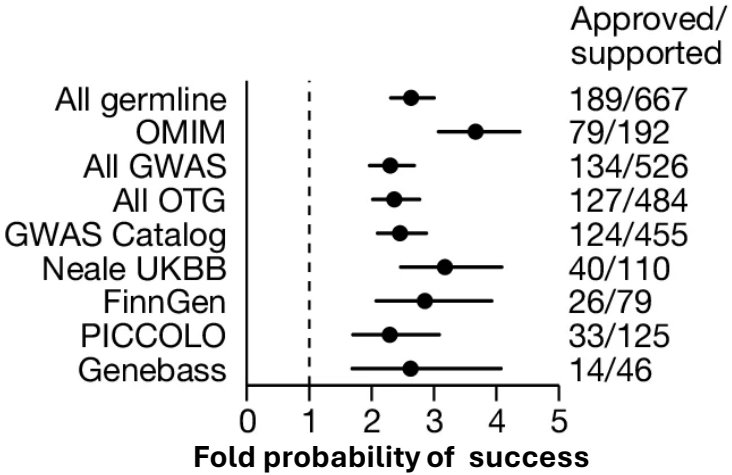
- Strong foundation in human genetics
- Proprietary chemistry: potency, durability, and delivery
- Clinically validated platform

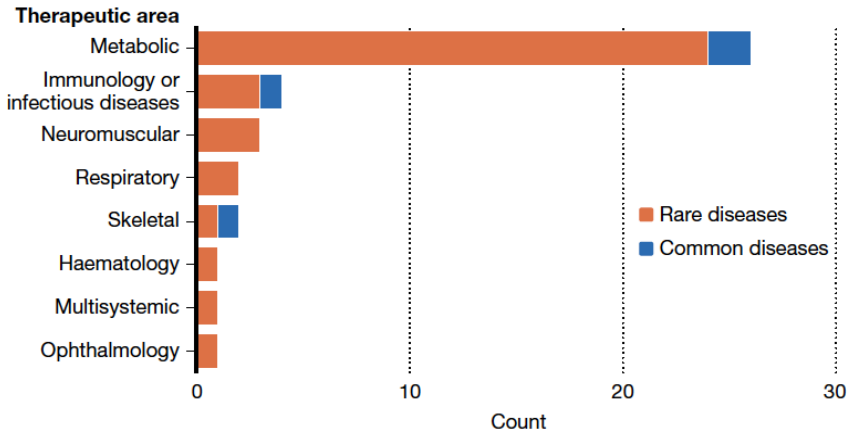


Human genetics dramatically increases probability of success in drug development and can accelerate development of new medicines

Evidence from human genetics increases probability of successful drug development at least 2x



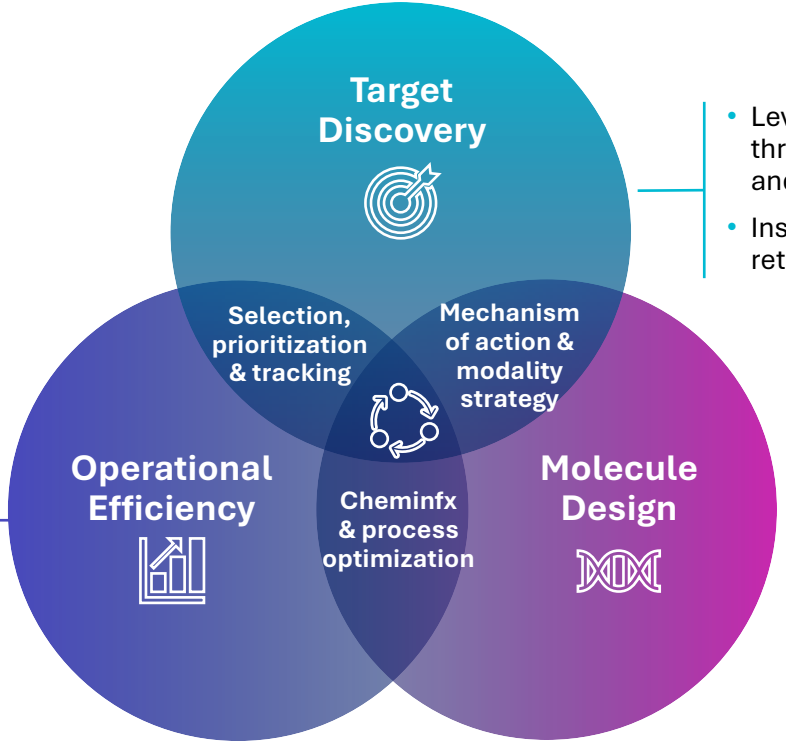
50 approved medicines driven by human genetics



Wave is poised to rapidly translate genetic insights into high impact medicines

Left: Vallabh Minikel et al., Nature 2024; 629(8012):624-629; Right: Drug Discovery & Development (https://www.drugdiscoverytrends.com/best-selling-pharmaceuticals-2023/); Trajanoska et al. Nature 2023;620(7975):737-745.

Wave's AI-driven approach to pipeline growth, quality & sustainability



- Leverage genetic evidence through UK Biobank collaboration and public data resources
- Insight synthesis using LLMs and retrieval augmented generation

- Agile work management & transparency
- Data analysis & visualization
- Incorporation of emerging AI technologies

- Model-base sequence prediction for silencing, editing and skipping modalities
- Prediction of chemical SAR and safety outcomes

Wave's data-driven drug discovery identifies high-quality drug targets with optimized design

Introducing new, wholly-owned GalNAc-AIMer programs

New targets meet key criteria, expected to improve probability of success:

- Strongly supported by human genetics
- Leverage unique platform capabilities; GalNAc-AIMers building on learnings of WVE-006
- Completely novel ways of treating diseases with high unmet need
- Readily accessible biomarkers and approaches to assess PD, defined regulatory paths

Correction of PNPLA3
Genetically defined liver disease

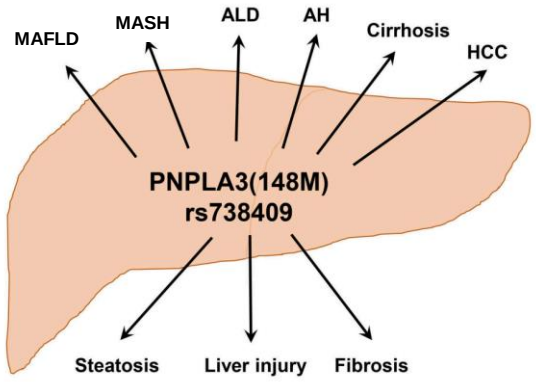
Upregulation of LDLR
Familial hypercholesterolemia

Correction of APOB
Familial hypercholesterolemia

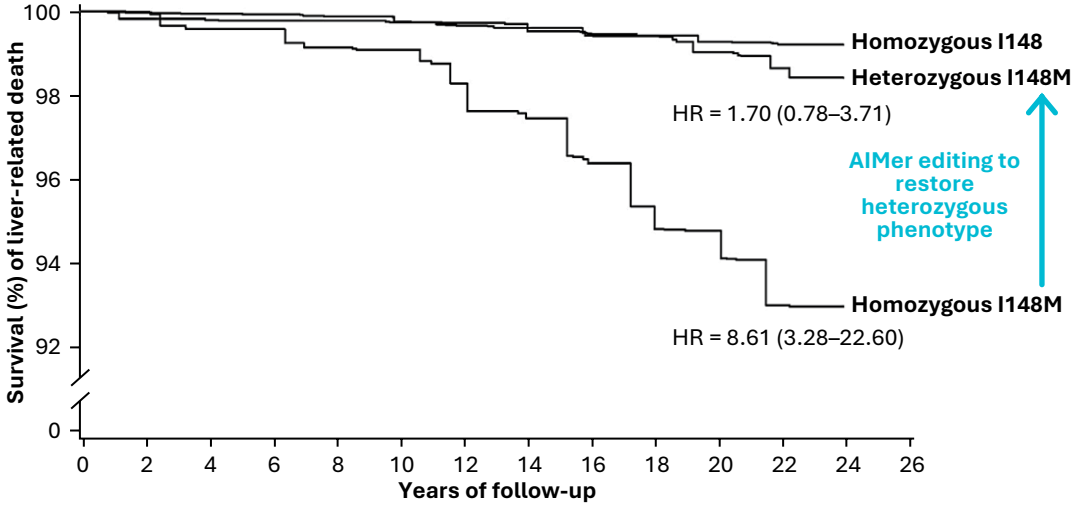
Homozygous PNPLA3 I148M are at high-risk for liver diseases

Over 9 million homozygous PNPLA3-I148M patients who are predisposed to liver diseases in US and Europe

Homozygous PNPLA3-I148M patients have significantly higher risk of multiple liver diseases



Heterozygous I148M patients have lower risk of liver diseases and a >5-fold increase in survival as compared to homozygous patients[2]



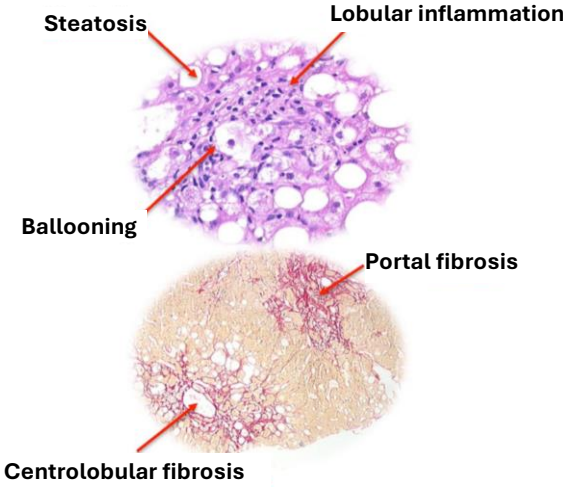
>50% RNA editing would support restoration of heterozygous phenotype with lower risk of liver diseases

1. Carlsson, B., et al. 2020 *Aliment Pharmacol Ther.*; 2. Unalp-Arida and Ruhl 2020 *Hepatology*; 3. Dong, XC, 2019 *Front. Med*.
MAFLD, Metabolic dysfunction-associated fatty liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; ALD, alcoholic liver disease; AH, Alcohol-associated hepatitis; HCC, hepatocellular carcinoma

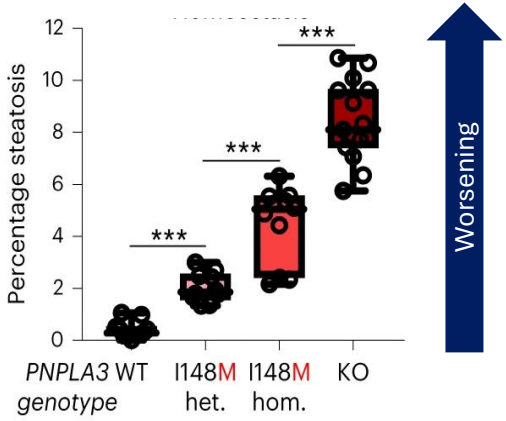
Functional PNPLA3 is imperative for liver health beyond improvements in steatosis

Knockout (KO) of PNPLA3 in normal liver may worsen basal physiological functions, i.e. steatosis or inflammation-induced cell death

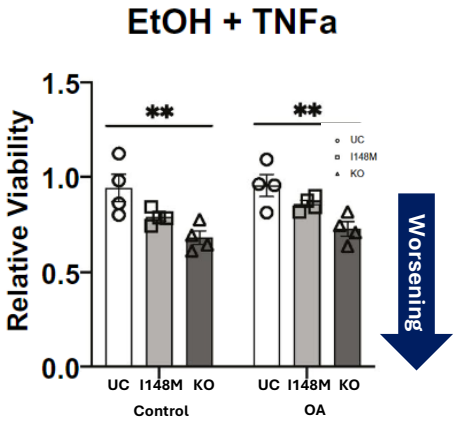
Multiple histological endpoints of liver disease



Silencing PNPLA3 worsens steatosis in iPSC-derived human liver organoids



Silencing PNPLA3 increases inflammation-induced liver cell death in human primary hepatocytes

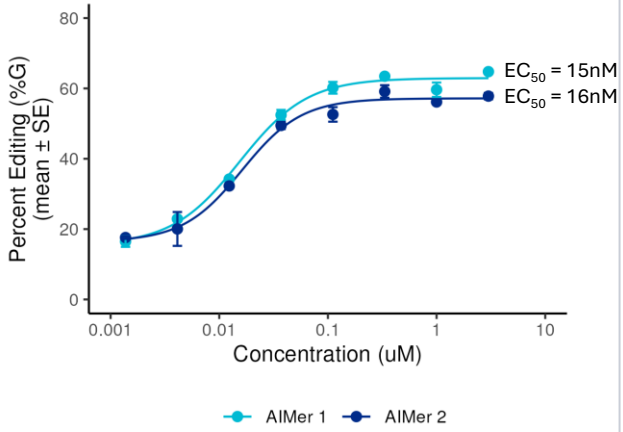


RNA editing offers an optimal approach to generate functional PNPLA3 and improve liver health

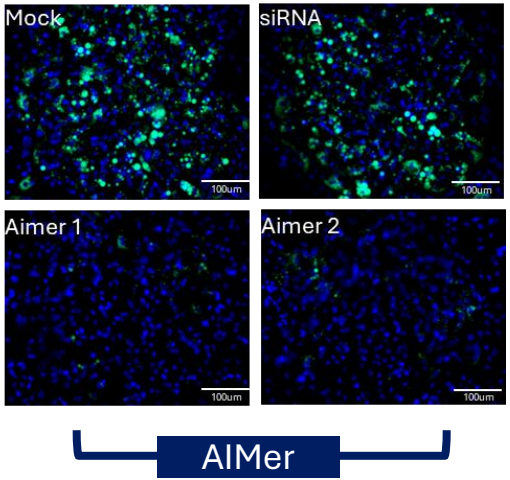
1. Dufour J-F, et al. 2022 Gut; 2. Hendriks, D, et al. 2023 Nat Biotechnol; 3. Tilson, SG, et al. 2021 Hepatology

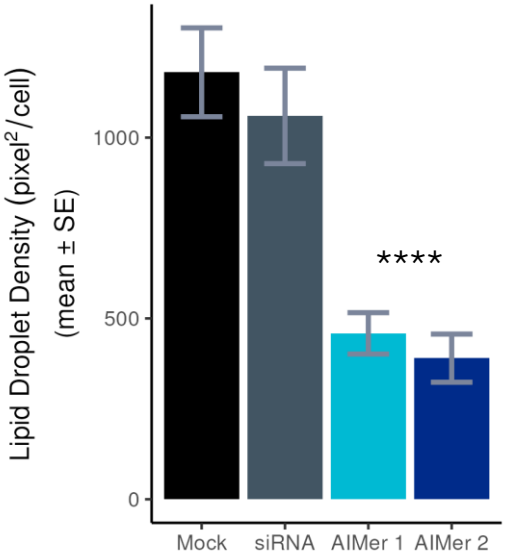
AIMers achieve efficient editing of PNPLA3, leading to reduction of liver fat

Potent editing of PNPLA3 in homozygous I148M human primary hepatocytes



Significant decrease in liver fat with PNPLA3 editing in human HEPATOPAC® with homozygous I148M





Significant reduction of liver droplets with PNPLA3 editing. Stats: (left) 4-parameter log-logistic curve fits, (right) One-way ANOVA with Dunnett post hoc test comparisons to Mock **** P < 0.0001

PNPLA3 I148M AIMer candidate selection expected in 2025

- PNPLA3 preclinical data demonstrates ability to restore functional PNPLA3, decreasing lipid uptake for improvement of liver health
- *In vivo* studies ongoing to support candidate selection in 2025
- Clinical development planning underway for a first-in-human clinical study
  - Leveraging previously genotyped populations to identify homozygous I148M carriers
  - Initial proof-of-concept study to enroll MASH patients to assess safety, tolerability, pharmacokinetics and pharmacodynamic endpoints (including steatosis)

Potential best-in-class treatment for patients with homozygous PNPLA3 I148M mutations at risk for liver disease

GalNAc-AIMer LDLR (upregulation)
GalNAc-AIMer APOB (correction)
Heterozygous familial hypercholesterolemia

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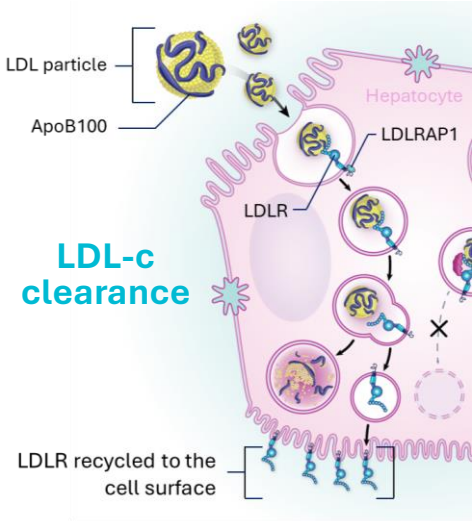
AIMer editing unlocks opportunity to deliver best-in-class LDL-c lowering with first-in-class LDLR and APOB RNA editing approaches

High unmet need remains for effective LDL-c lowering therapies

- Cardiovascular disease is the leading cause of death
- Familial hypercholesterolemia (FH) is a genetic disorder that leads to very high levels of LDL-cholesterol[1]
- FH patients at **high risk for major cardiovascular events**[1] and **~50%** have need for more effective therapies[2,3,4]

AIMer editing to enhance clearance and lower LDL-c through two different approaches



- ~90% heterozygous FH (HeFH) patients carry **LDLR** LoF mutations[1] which are amenable to **AIMer upregulation**
- ~5% - 10% of HeFH patients have mutations in **APOB**[1] amenable to **AIMer correction**

1. Chemello, K., et al. 2021 *J. Lipid Res*; 2. Duell, PB, et al. 2019 *Atherosclerosis*; 3. Alonso, R, et al. 2021 *J Clin Lipidol.*; 4. Arca, M, et al. 2023 *J Am Heart Assoc*

Initially focused on comprehensive treatment approach for HeFH, with multiple potential opportunities for expansion with LDLR upregulation

	Lead Indication	Potential Expansion Opportunities for LDLR	
	HeFH with CAD	**Statin-Intolerant Population**	**ASCVD Population**
LDLR	~900K HeFH individuals in the US and Europe are high risk and potentially treatable with LDLR upregulation[1,2,3,4,5]	Estimate 10M individuals in the US and Europe are prescribed a statin but experience intolerance[6,7,8]	>20M patients in the US and Europe have a history of ASCVD and are not at LDL-c goal[9,2]
APOB	~70K HeFH APOB patients in the US and Europe with HeFH due to APOB R3527Q who are not at goal[1,2,3,4,5]		

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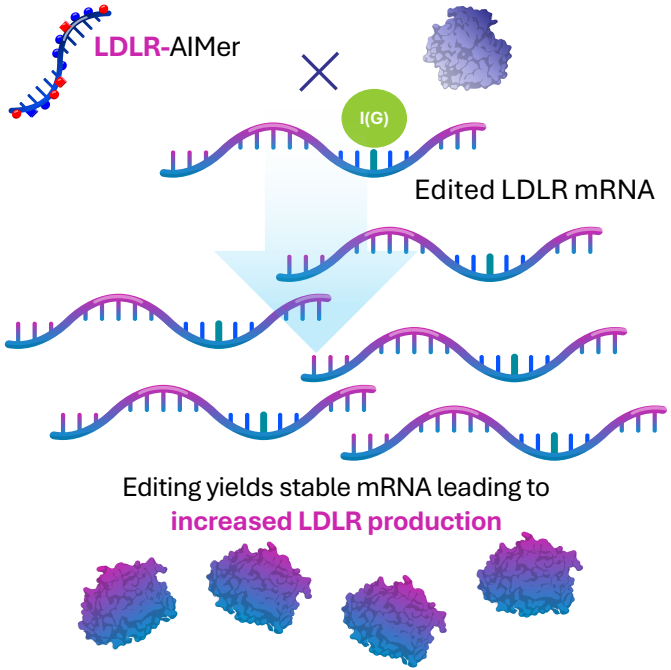
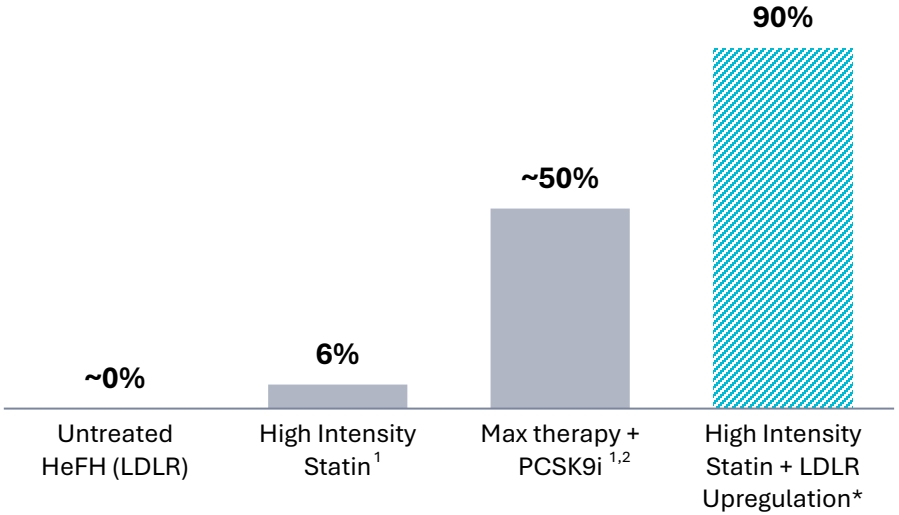
CAD: Coronary artery disease; ASCVD: Atherosclerotic Cardiovascular Disease

1. Joynt Maddox, KE, et al. 2024 *Circulation*; 2. Khan, MAB, et al. 2020 *Cureus*; 3. Hu, P, et al. 2020 *Circulation*; 4. Arca, M, et al. 2023 *J Am Heart Assoc;* 5. Alonso, R, et al. 2021 *J Clin Lipidol.*; 6. Thompson-Paul, AM, et al. 2022 *J Clin Lipidol*; 7. Mortensen, MB, et al. 2022 *JAMA Cardiol.*; 8. Bytci, I, et al. 2022 *Eur Heart J*; 9. Alanaeme, C, et al. 2022 *Am Heart J Plus*

Opportunity to directly upregulate LDLR with AIMers to bring majority of HeFH patients to goal



Proportion HeFH (LDLR) patients achieving goal LDL-c levels



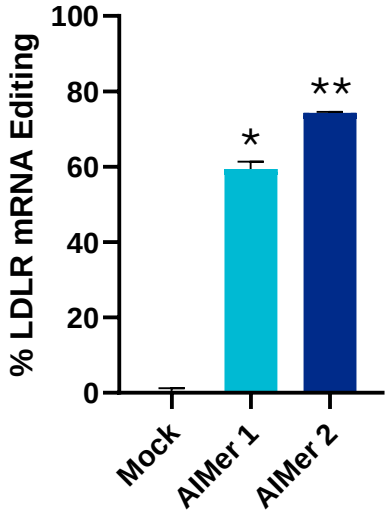
2-fold+ upregulation expected to result in best-in-class 75%+ LDL-c reduction

*Assumes 2x LDLR Upregulation

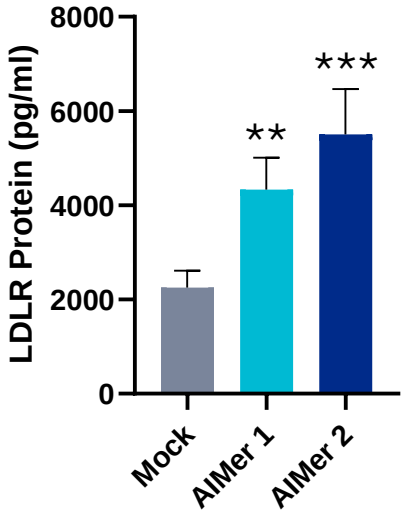
1. Rizos, CV, et al. 2021 *Int J Cardiol*; 2. Alonso, R, et al. 2021 *J Clin Lipidol.*

~2.5-fold upregulation of LDLR protein exceeds target threshold

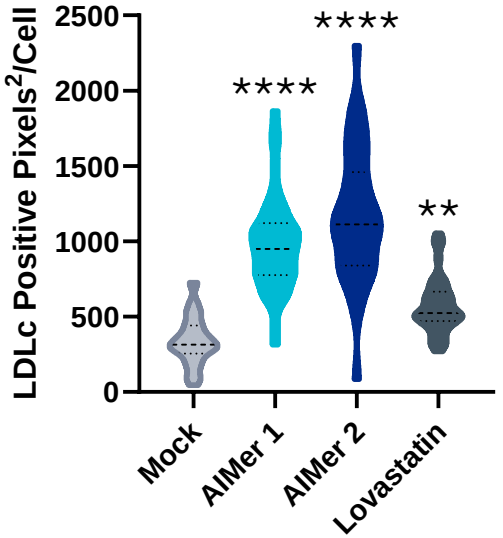
Up to 70% LDLR mRNA editing in primary human hepatocytes



~2.5x increase LDLR protein in primary human hepatocytes



~4-fold increase LDL-c uptake to hepatocytes by AIMers



LDLR upregulation levels expected to translate into reductions in LDL-c of up to 85%

Primary human hepatocytes were treated with 3uM of LDLR targeting AIMer for 96 hours before total RNA and protein were extracted. Editing was quantified using Sanger sequencing. LDLR protein concentration was quantified using an ELISA. LDLc uptake was measured using BODIPY labeled LDLc which was incubated with cells for 24 hours. LDLc positive signal was quantified using microscopy.

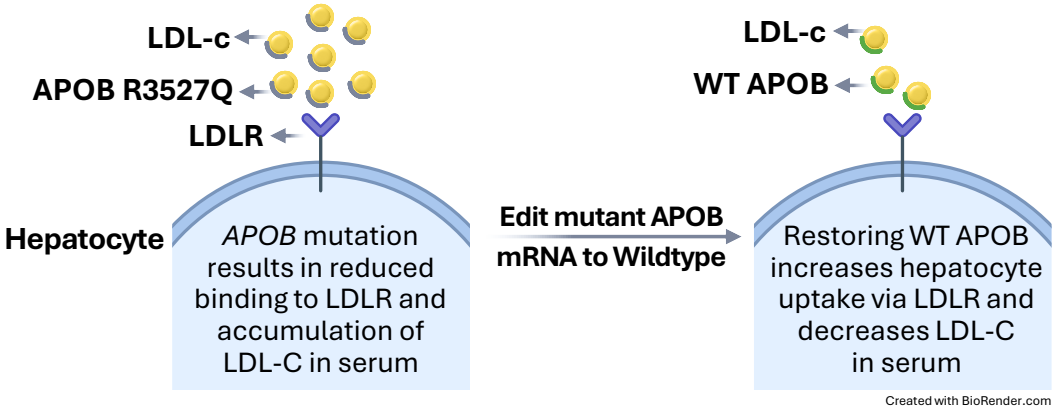
Correction of APOB point mutation with AIMer editing to address genetically-defined subset of familial hypercholesterolemia patients

APOB AIMer for HeFH

APOB mRNA with R3527Q mutation

Edited APOB mRNA enables wild-type protein production

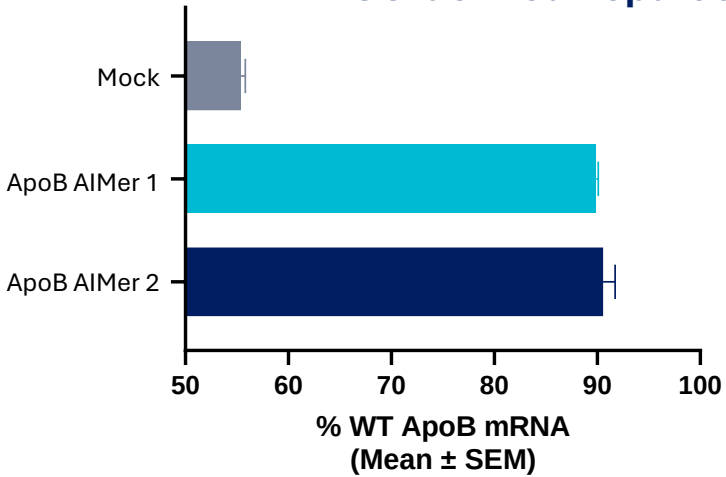
APOB editing approach



Editing of of the mutant allele in heterozygous patients aims to decrease LDL-c levels and lower risk of disease

Increasing amount of wild type APOB from 50% in heterozygous patients to 75% is expected to provide therapeutic benefit

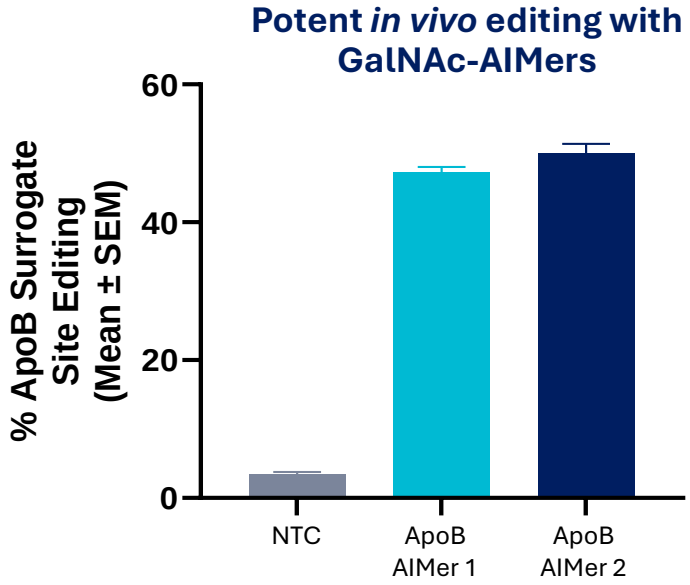
Restoration of wild-type APOB in APOB R3527Q$^{+/-}$ iPSC-derived hepatocytes



Note: Due to heterozygous genotype, Y-axis ranges from 50-100%

Restored wild-type APOB mRNA levels to ~90% *in vitro*

Potent editing *in vivo* support potential to provide therapeutic benefit to FH patients



- ~50% *in vivo* editing in transgenic mouse model expressing human ApoB, which would translate to ~75% circulating functional protein in heterozygous patients
- Similar levels of editing of mutant ApoB in heterozygous patients is expected to provide therapeutic benefit

LDLR and APOB clinical candidates expected in 2025

- LDLR and APOB are first-in-class approaches to achieve best-in-class LDL-c lowering
- HeFH patients offer a genetically-defined population to address a high unmet need with AIMers and represent ~1M patients in US and Europe
- *In vivo* studies underway to support selection of LDLR and APOB clinical candidates in 2025
- Clinical development planning underway for an umbrella study (single study with both LDLR and APOB arms) to enroll FH patients

Potential to offer a comprehensive treatment solution to ensure all FH patients reach LDL-c goals

Closing remarks

Paul Bolno, MD, MBA
President and CEO

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Wave is reimagining RNA medicines

- ✓ **Best-in-class, clinically validated platform:** Breakthroughs in oligonucleotide chemistry with shared learnings that enable rapid and predictable clinical translation
- ✓ **Clinical programs with potential paths to accelerated approval:** Caudate atrophy is a promising biomarker expected to predict clinical outcomes in HD
- ✓ **Novel approach to obesity:** WVE-007 has potential to address multiple unmet needs with a unique profile that leads to fat loss with muscle sparing and dosing 1-2x per year
- ✓ **RNA editing validated with unique and proprietary capabilities:** WVE-006 clinical data in AATD unlocks new therapeutic class and wholly owned pipeline for Wave
- ✓ **Pipeline of GalNAc-AIMers:** PNPLA3, LDLR, and APOB are supported by strong human genetics – potential first- and best-in-class approaches for cardiometabolic diseases

Robust, diversified RNA medicines pipeline including first-in-class RNA editing programs

Program	Discovery	IND / CTA Enabling Studies	Clinical	Rights	Patient population (US & Europe)
RNA EDITING					
WVE-006 SERPINA1 (AATD)			RestorAATion Clinical Program	GSK exclusive global license	200K
GalNAc-AIMer PNPLA3 (liver disease)				100% global	9M
GalNAc-AIMer LDLR (HeFH)				100% global	900K (30M expansion)
GalNAc-AIMer APOB (HeFH)				100% global	70K
RNAi					
WVE-007 (GalNAc) INHBE (Obesity and other metabolic disorders)				100% global	47M
GalNAc-siRNA Undisclosed				100% global	--
SPLICING					
WVE-N531 Exon 53 (DMD)			FORWARD-53 Trial (Phase 2)	100% global	2.3K
Other exons (DMD)				100% global	Up to 18K
ALLELE-SELECTIVE SILENCING					
WVE-003 mHTT (HD)			SELECT-HD Trial (Phase 1b/2a) - *Trial Completed*	100% global	25K Symptomatic (SNP3) 60K Pre-Symptomatic (SNP3)

Editing for correction Editing for upregulation

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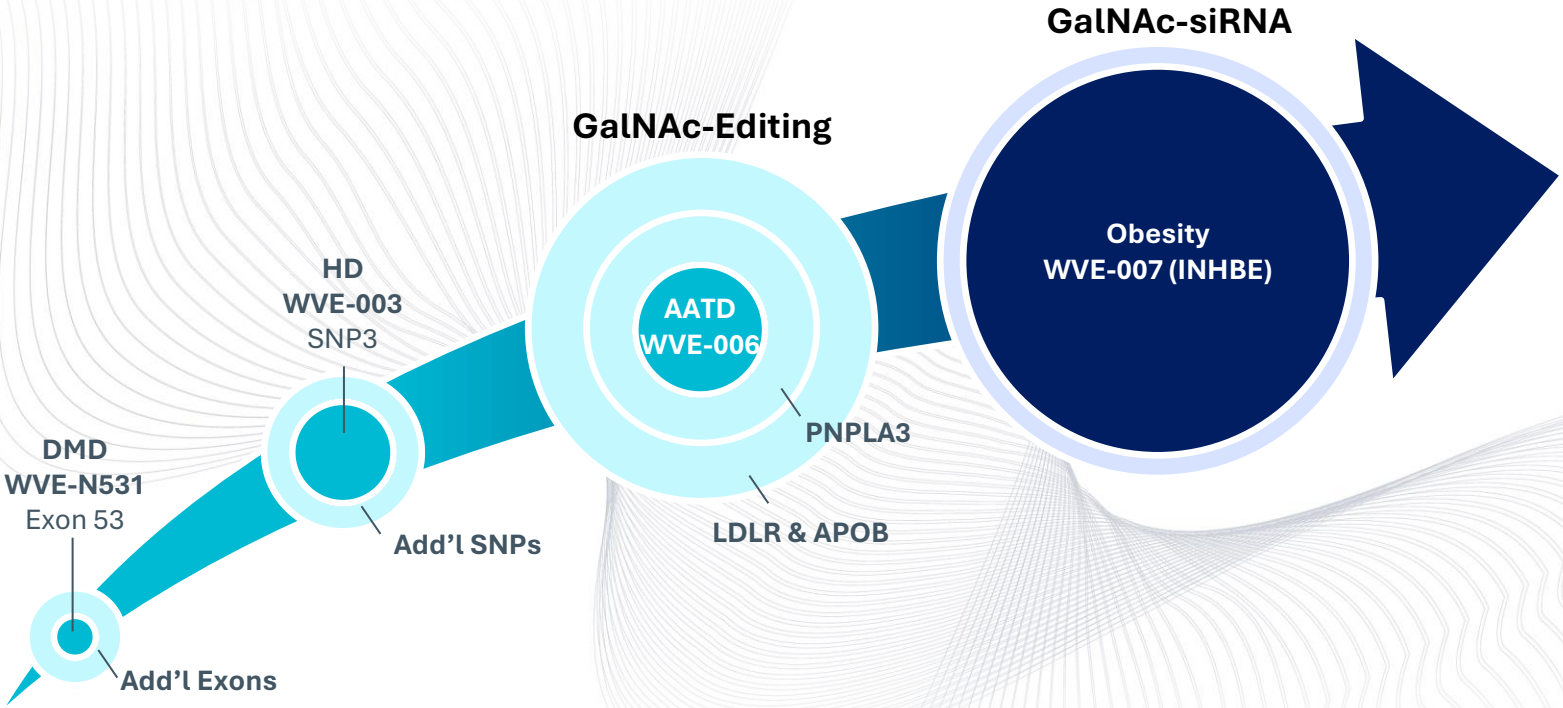
AATD: Alpha-1 antitrypsin deficiency; DMD: Duchenne muscular dystrophy; HD: Huntington's disease; HeFH: heterozygous familial hypercholesterolemia

Poised for significant and sustained growth driven by editing and siRNA



Wave's platform is translating in the clinic and has potential to treat >90M patients in the US and Europe

Note: Bubble size illustrative of size of total addressable US market (assuming 100% share of addressable patients)

Q&A

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