



Wave Life Sciences

Research Day

October 30, 2024

WAVE[™]
LIFE SCIENCES

Forward-looking statements

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

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



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 
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 
GaINAc-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 
GaINAc-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)**

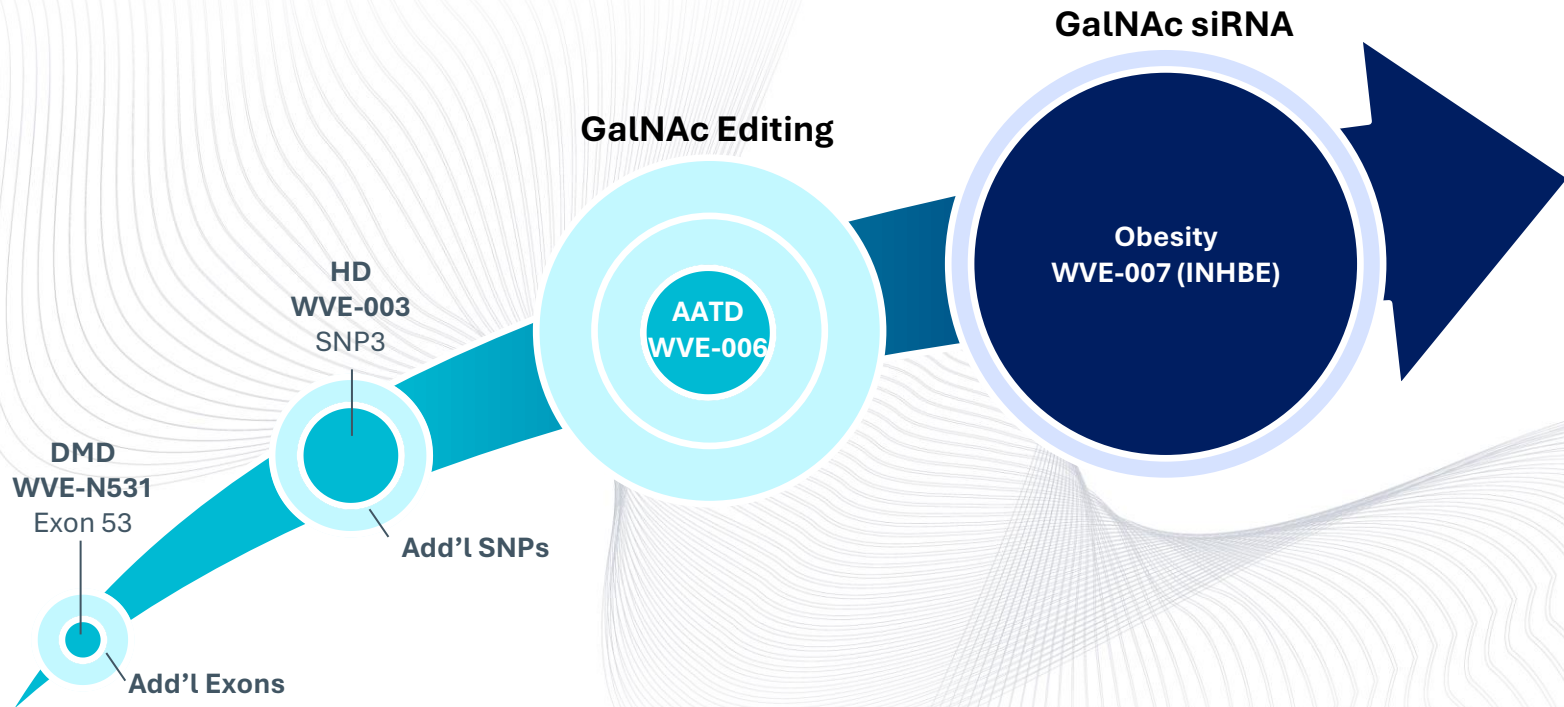
PNPLA3 (GalNAc-AIMER)

LDLR (GalNAc-AIMER)

APOB (GalNAc-AIMER)

**WVE-007 for Obesity
(GalNAc-siRNA)**

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



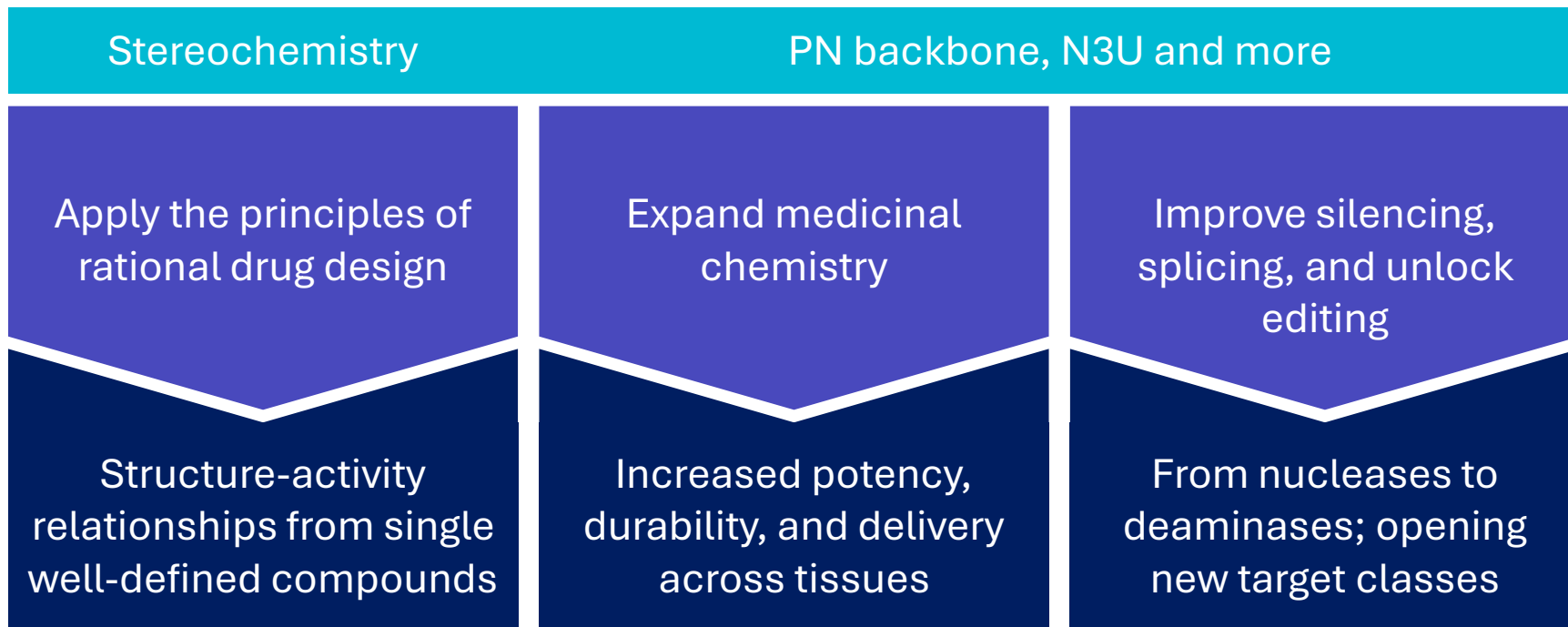
Wave's platform is translating in the clinic and has potential to treat >90M patients in the US and Europe

PRISM Platform: Best-in-Class Oligonucleotide Chemistry

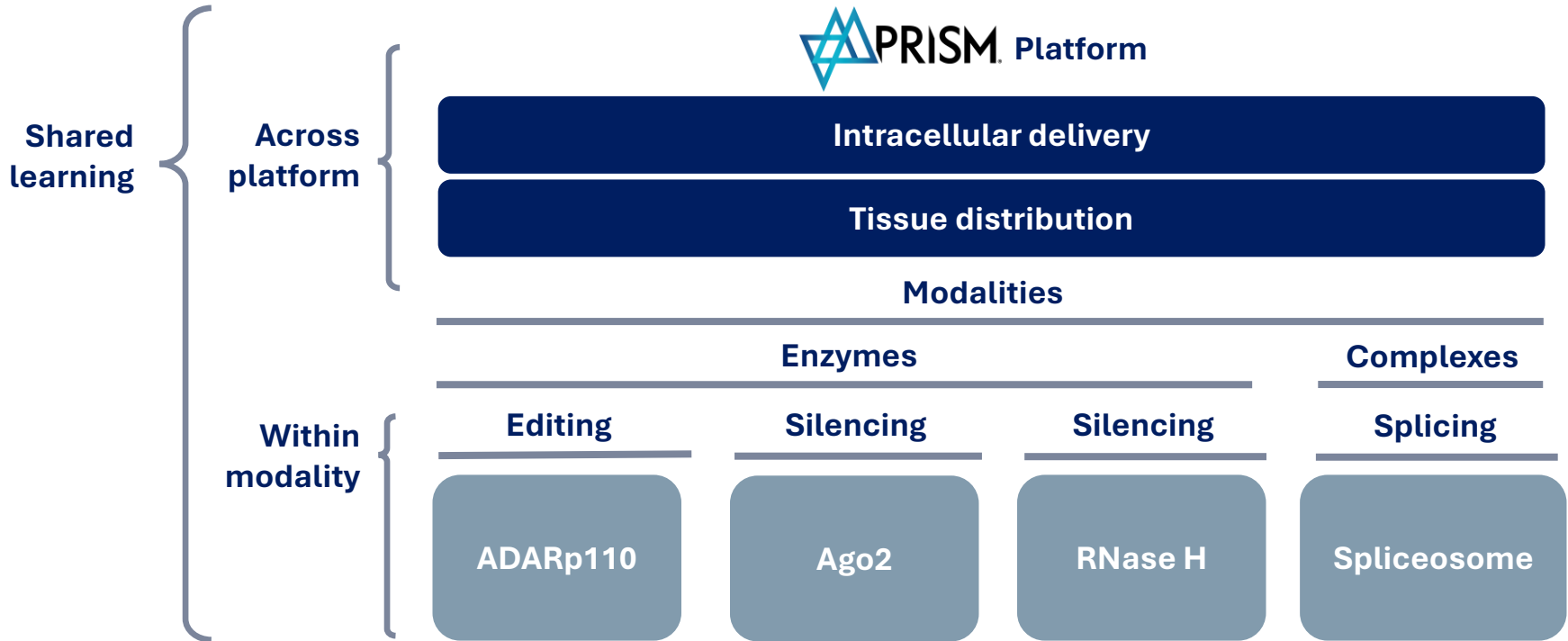
Chandra Vargeese, PhD
Chief Technology Officer



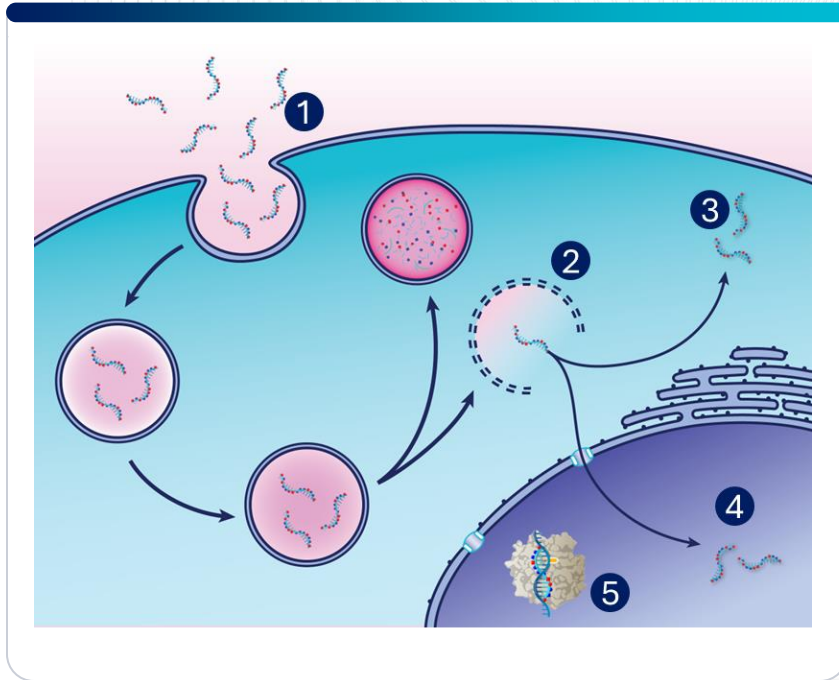
Building the best-in-class oligonucleotide platform



Shared learning enables rapid, predictable and efficient clinical translation



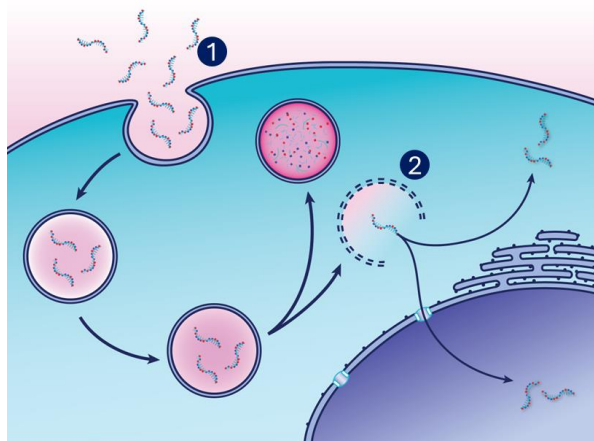
Wave's chemistry is a breakthrough for intracellular delivery



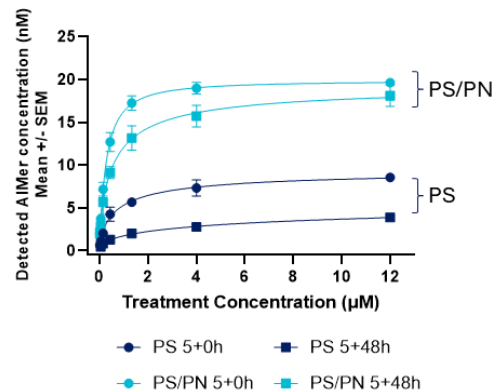
Addition of PN modification increases:

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

PN modifications increase cellular uptake and endosomal release

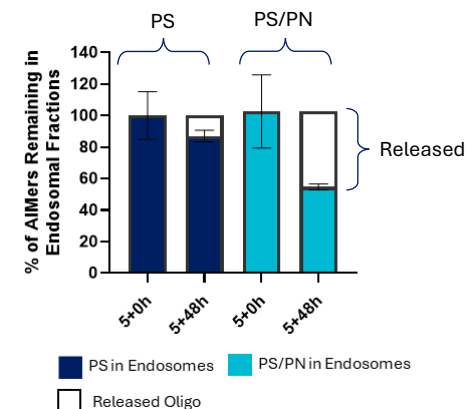


1 Cellular Uptake



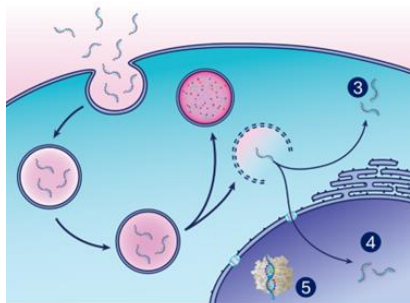
>2-fold increase in uptake after 5-hour dose pulse

2 Endosomal Release

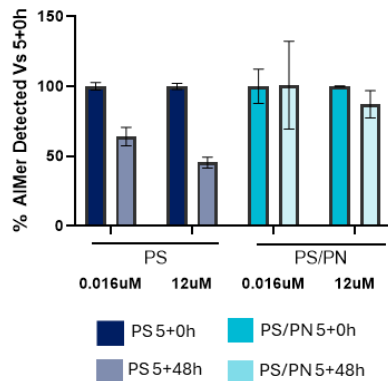


~4-fold increase in endosomal release

PN modifications increase cellular residency, nuclear uptake and target engagement

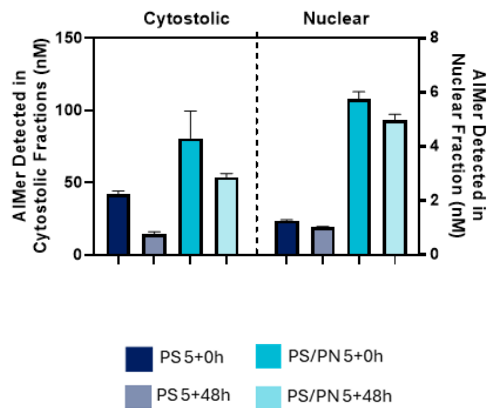


3 Cellular Residency



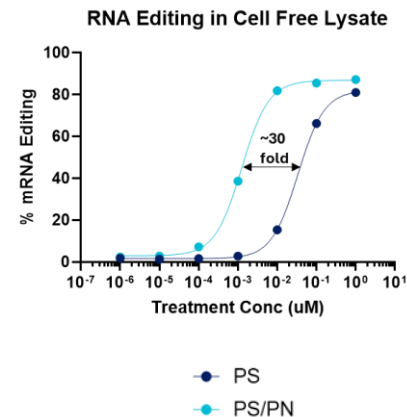
~2-fold increase in cellular residency

4 Nuclear Uptake



~5-fold increase in nuclear uptake

5 Target Engagement



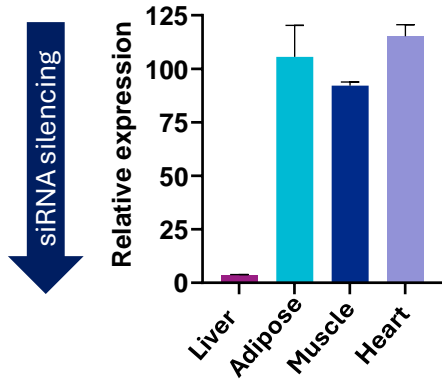
30-fold increase in target engagement

Directing silencing to high priority extrahepatic tissues

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

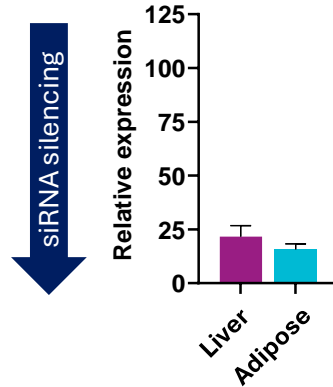
GalNAc + PN

Liver Targeting (siRNA 1)

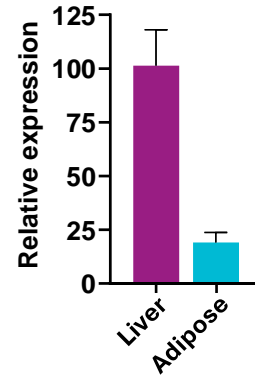


Non-GalNAc + PN variants

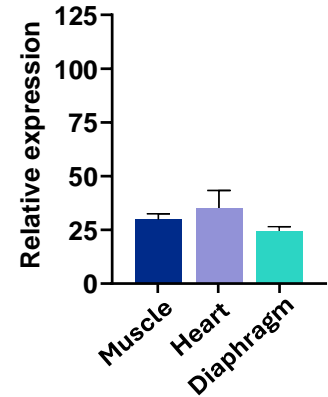
Liver and Adipose Targeting (siRNA 2)



Adipose Targeting (siRNA 3)



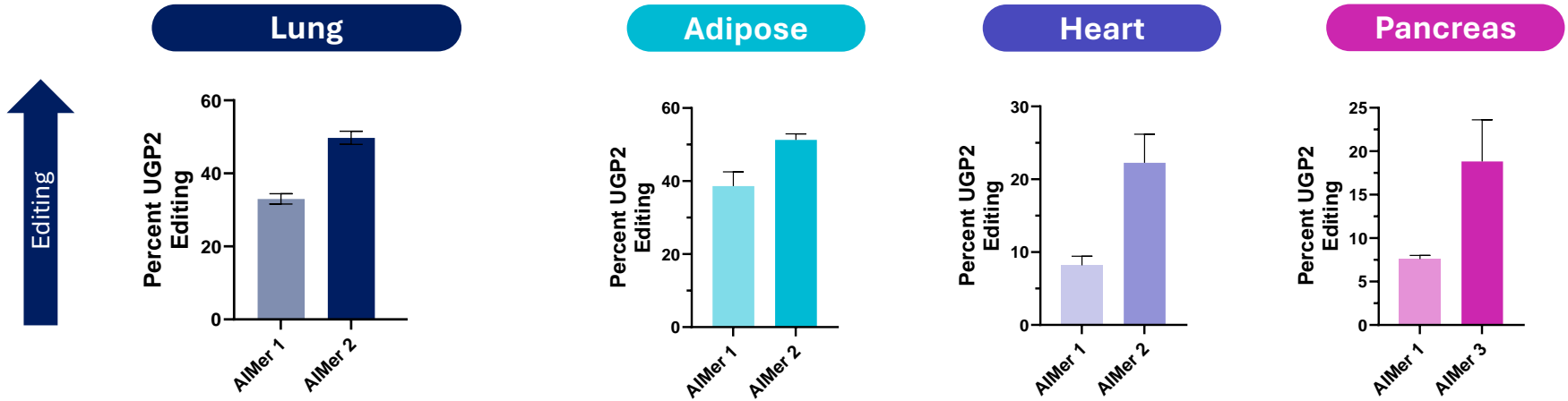
Muscle Targeting (siRNA 4)



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

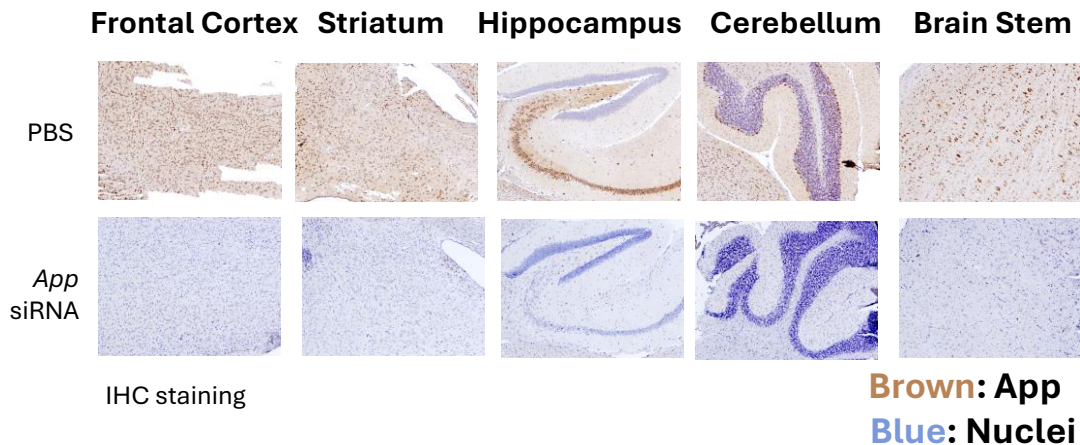
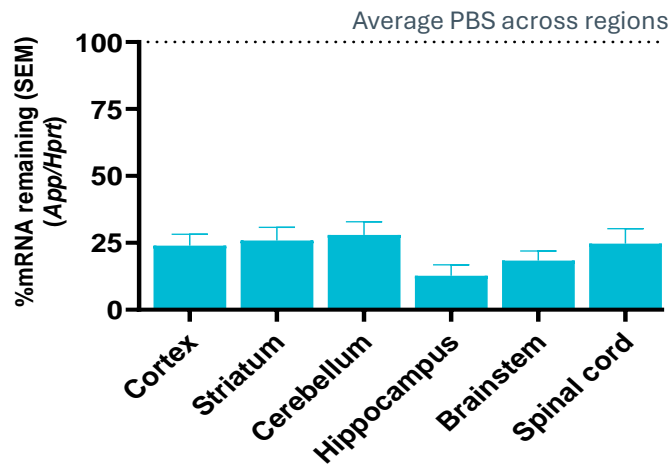
Directing editing across high priority extrahepatic tissues

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



High levels of systemic RNA editing achieved across extrahepatic tissues

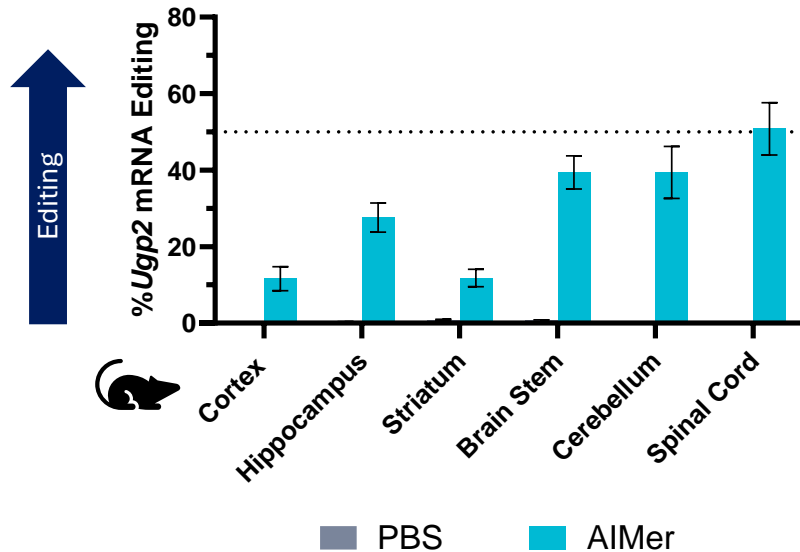
Potent and durable silencing across regions of the CNS



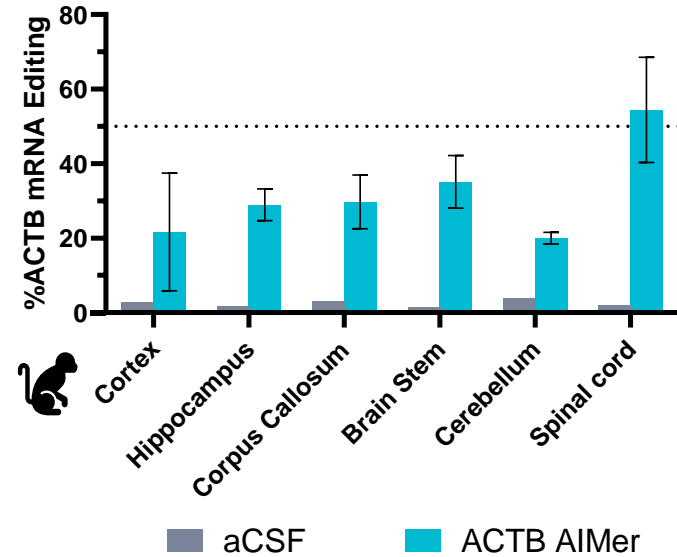
In vivo silencing in CNS at 16 weeks following single dose of APP siRNA

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

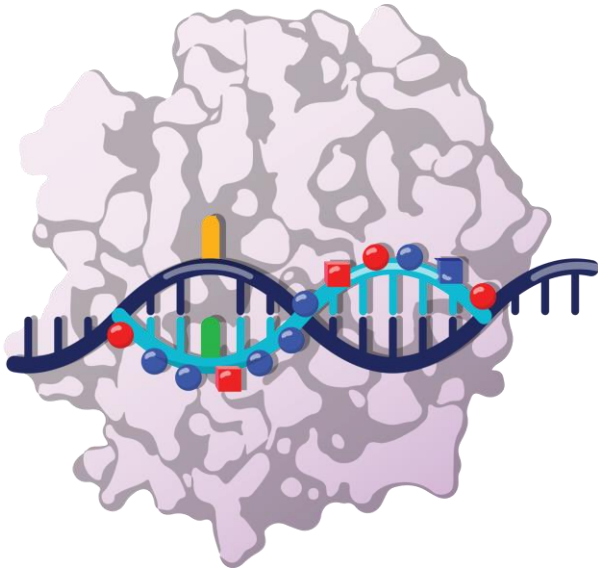
ICV injection



IT delivery



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

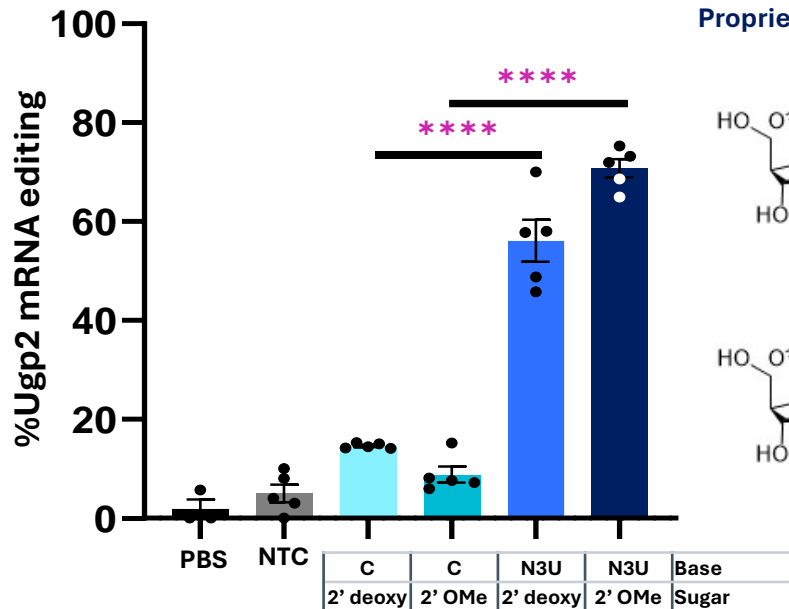


- Removal of any hairpin ADAR recruiting domain
- Pioneered the use of fully modified short oligonucleotides for highly efficient RNA editing including in human
- Proprietary base modifications (including N3U)
 - Enable multiple types of sugars across edit site (including 2'-OMe modified sugar)
 - Increase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

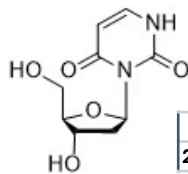
Multifaceted IP portfolio that protects Wave's leading oligonucleotide design

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

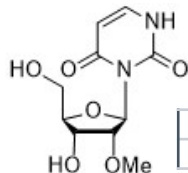
Enhanced RNA Editing with N3U Base



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 cytosine 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.

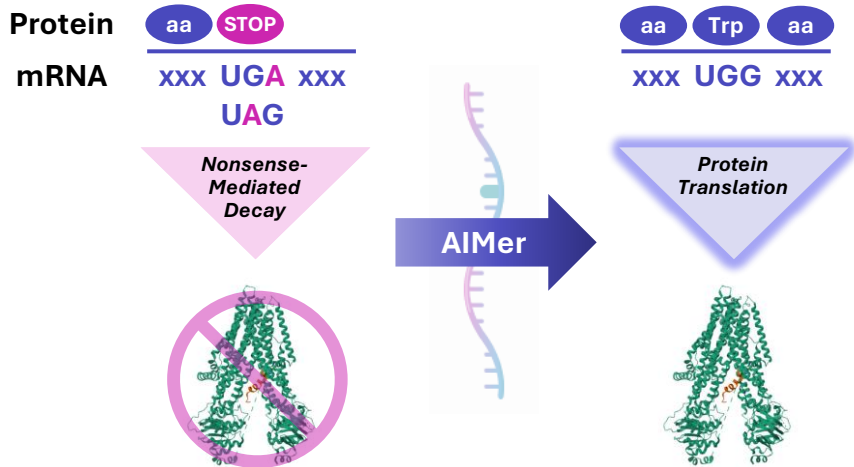
Graphical abstract

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

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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 population²

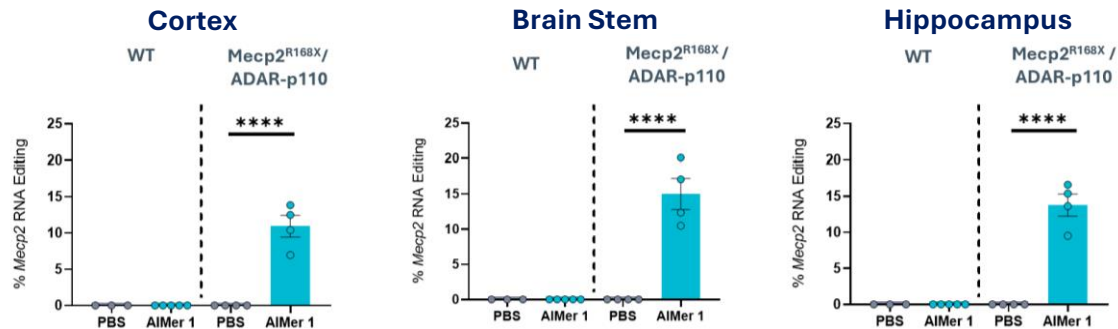
Cystic Fibrosis → CFTR

- 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 patients³

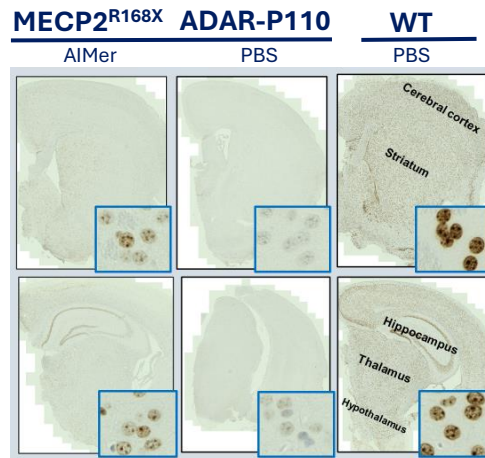
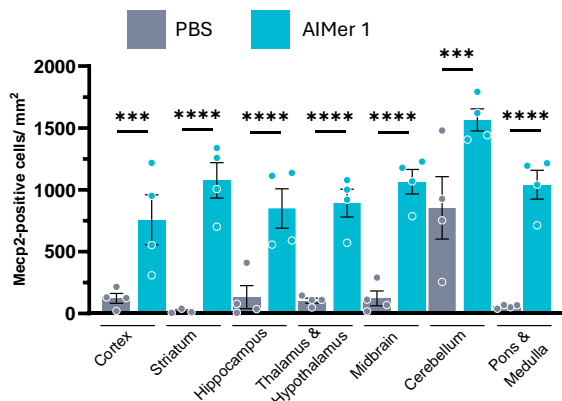
Nonsense mutations account for ~11% of all genetically inherited disease; 79% of these diseases can be addressed with a single A-to-G RNA edit¹

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

MECP2
RNA
Editing

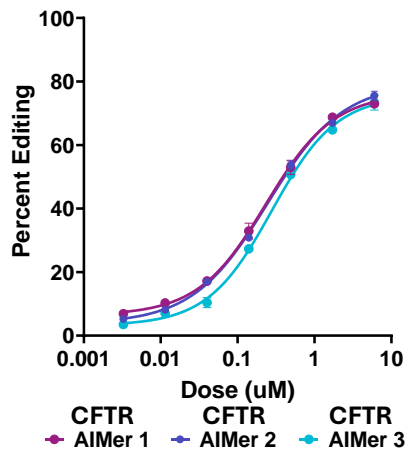


MECP2
Protein
Rescue

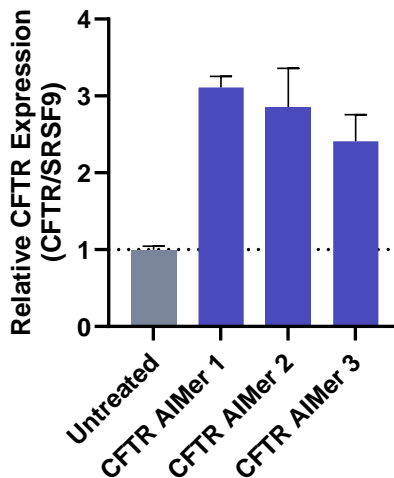


AIMer treatment in bronchial epithelial cells produces up to 75% editing, translating to a 50% recovery of wild-type CFTR protein

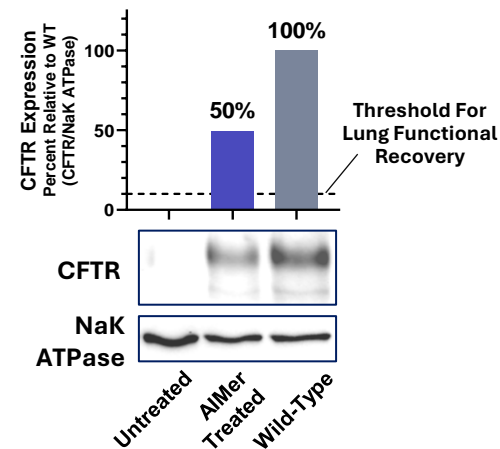
75% W1282X editing in human bronchial epithelial cells (gymnotic delivery)



3-fold increase in CFTR transcript expression

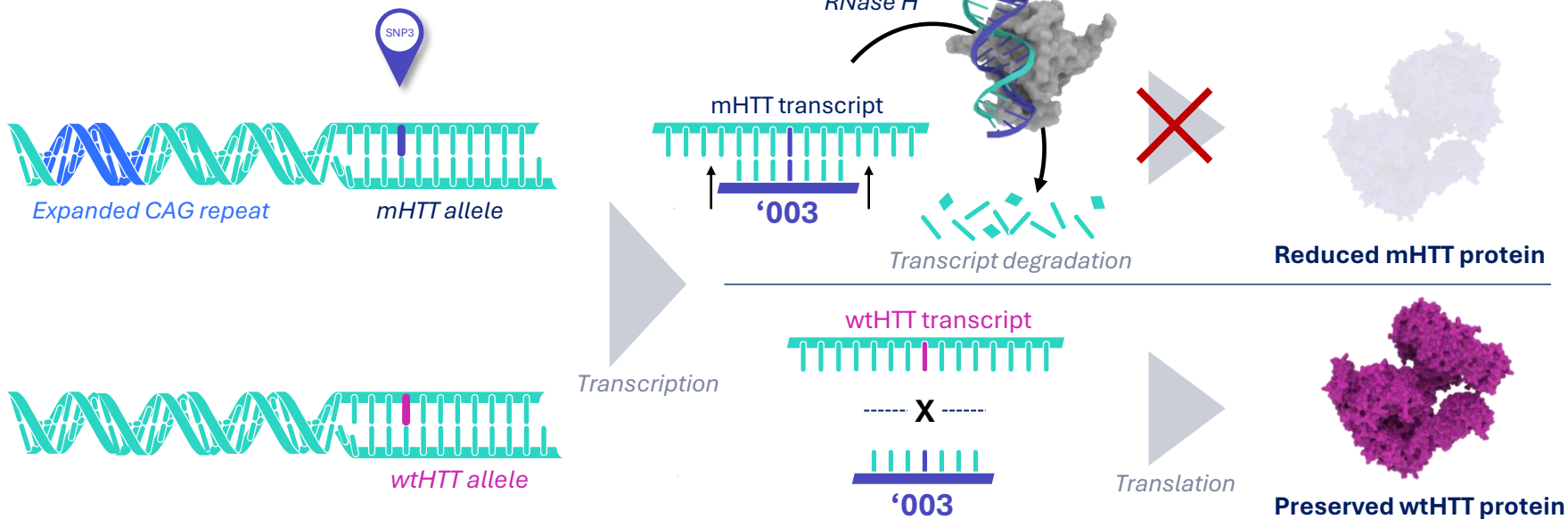


50% recovery of wild-type CFTR protein



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

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)



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

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

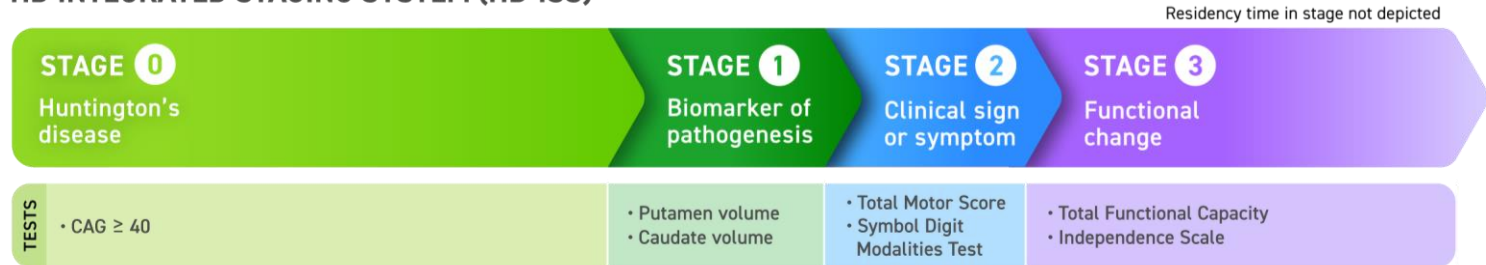
Overview

- 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

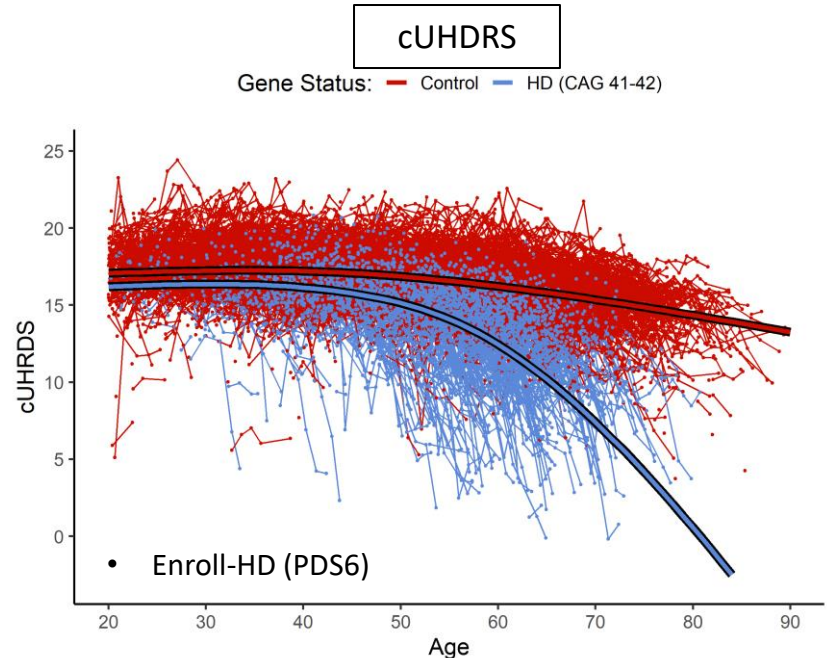
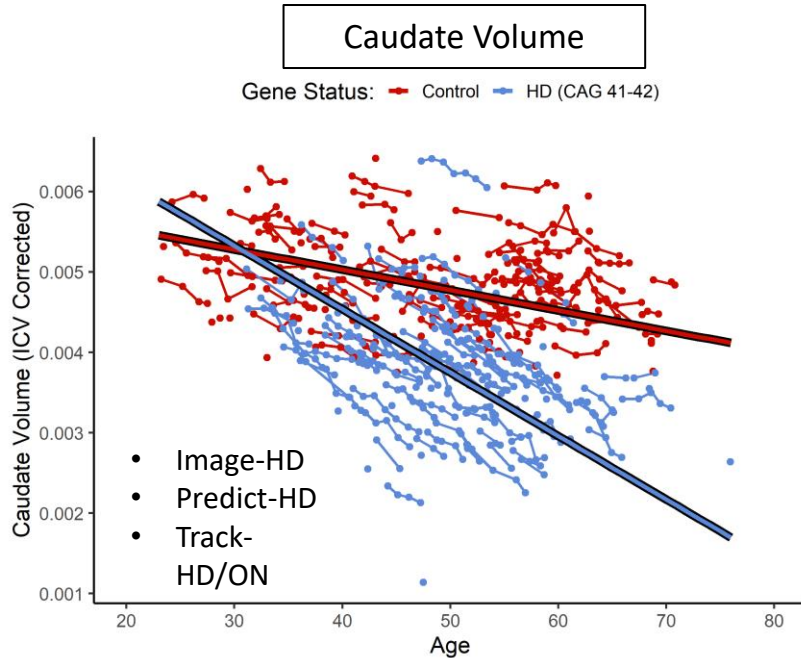
HD INTEGRATED STAGING SYSTEM (HD-ISS)



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

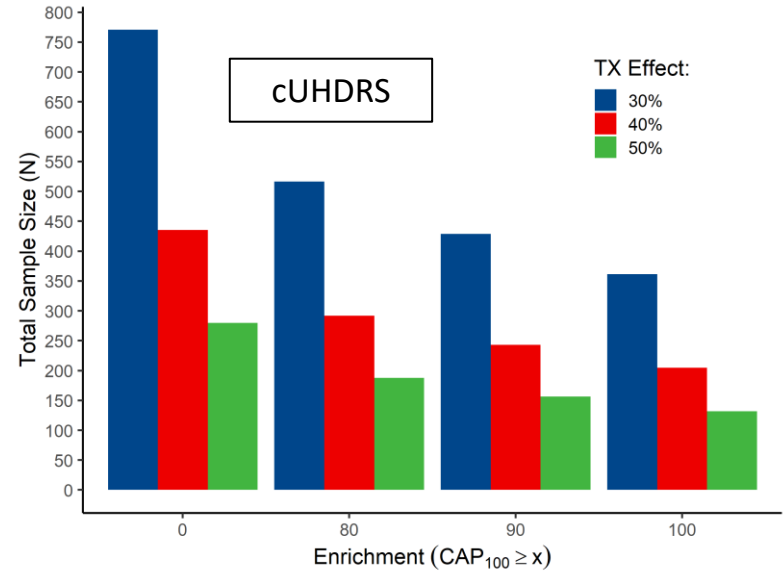
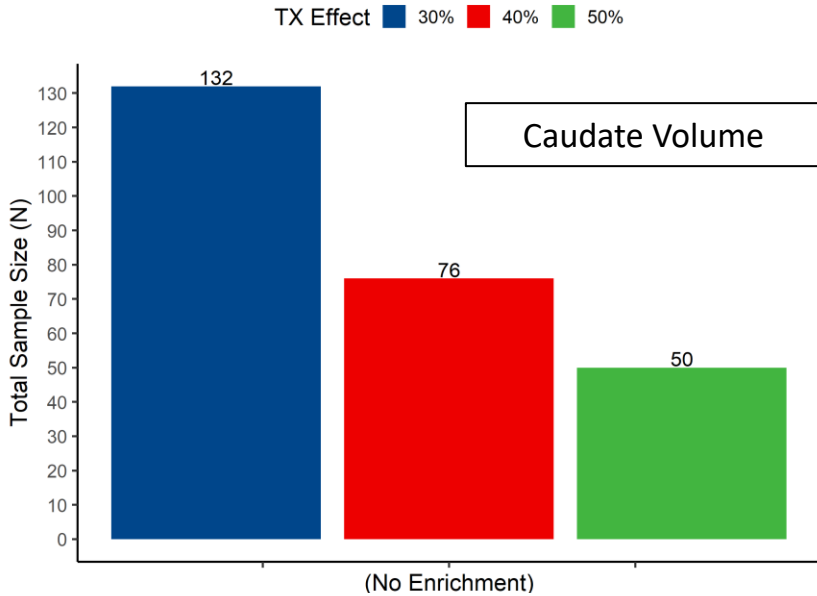
Regularity of Caudate Change

- HD-ISS Stage 2



Required Sample Size

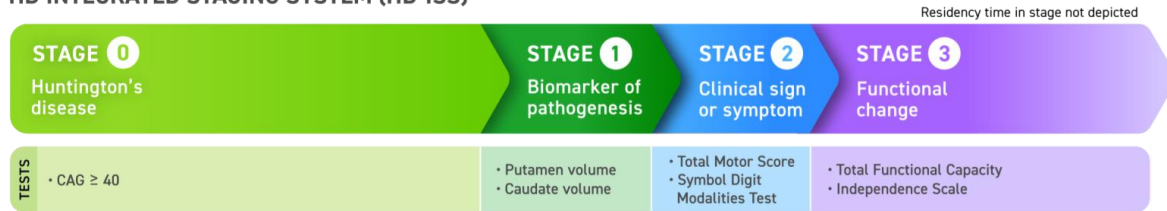
- HD-ISS Stage 2 inclusion
- Standard 2-year randomized controlled trial (2 arms)



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

HD INTEGRATED STAGING SYSTEM (HD-ISS)

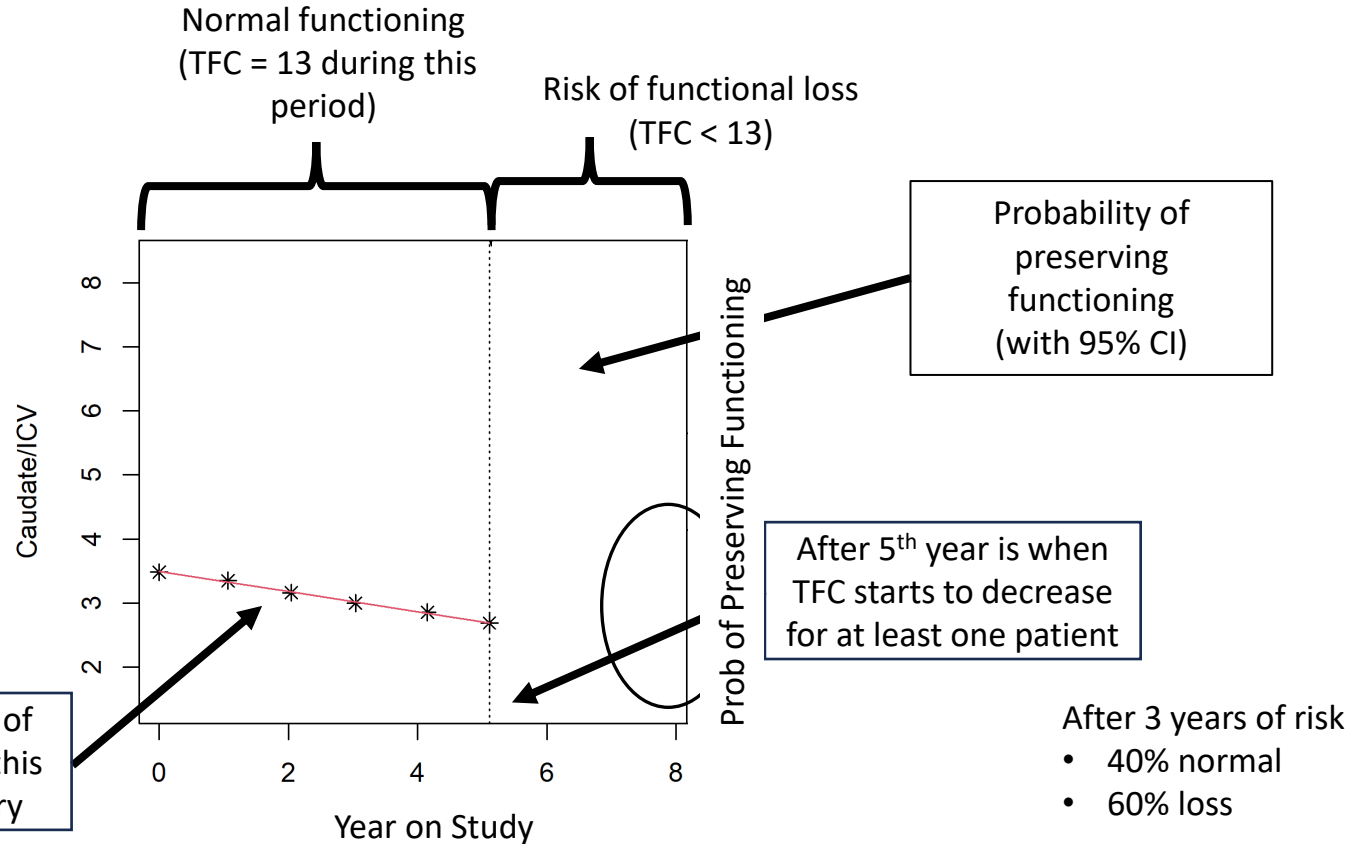


- Prediction analysis (in collaboration with Jim Mills, University of Iowa)
 - Use *earlier* caudate volume to predict *later* functional loss (TFC)
 - TFC is favored by regulators
 - Sophisticated statistical modeling using Predict-HD and Track-HD/ON

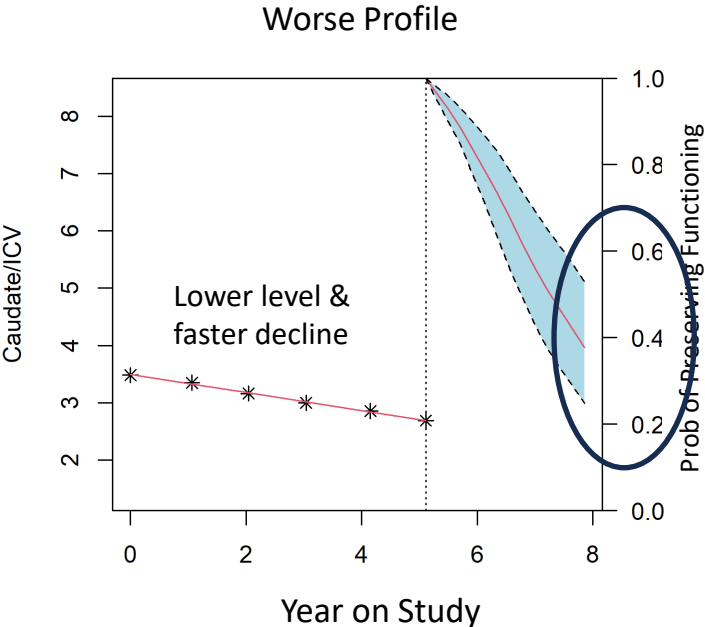
Tutorial Slides

- 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

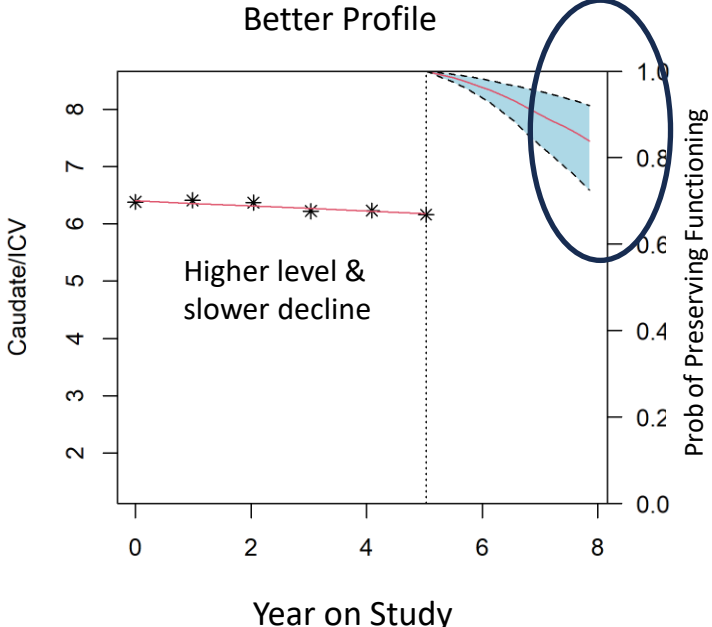
Caudate Change and TFC Loss



Comparing Caudate Profiles

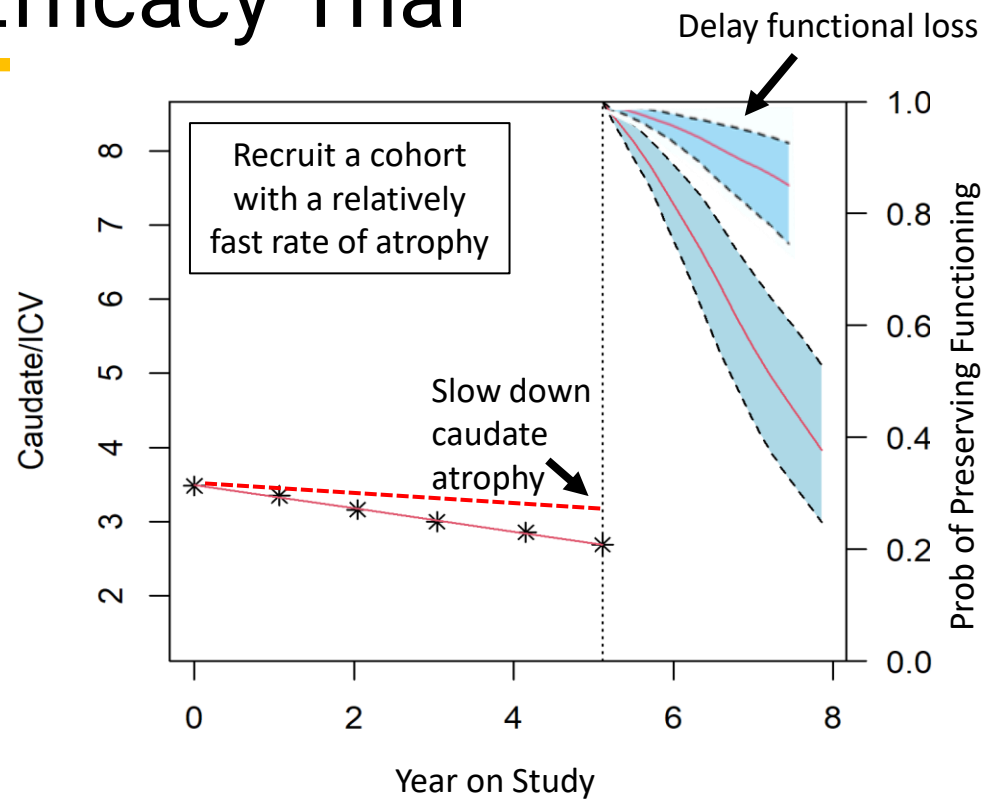
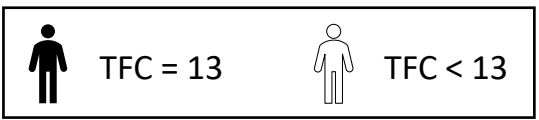


40% with normal functioning

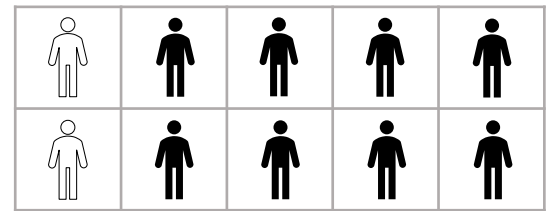


80% with normal functioning

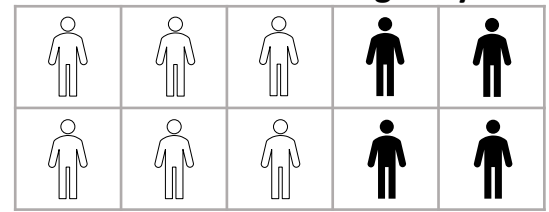
Efficacy Trial



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

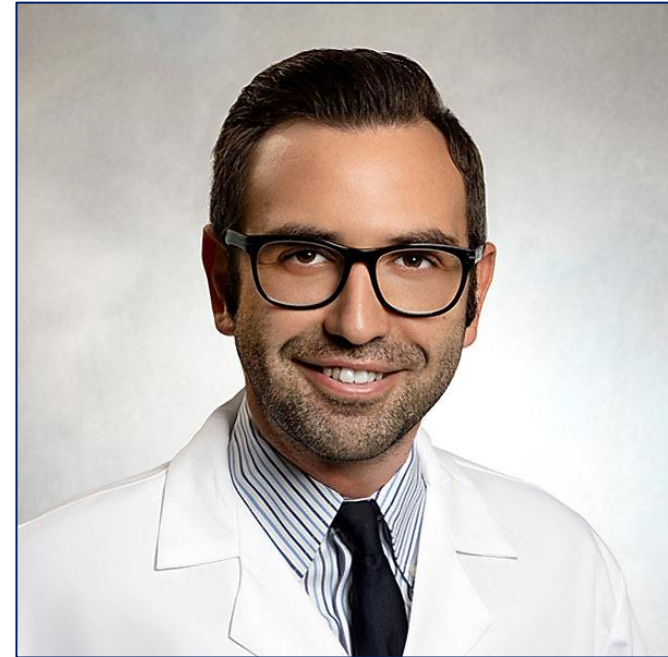
Thanks!

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.

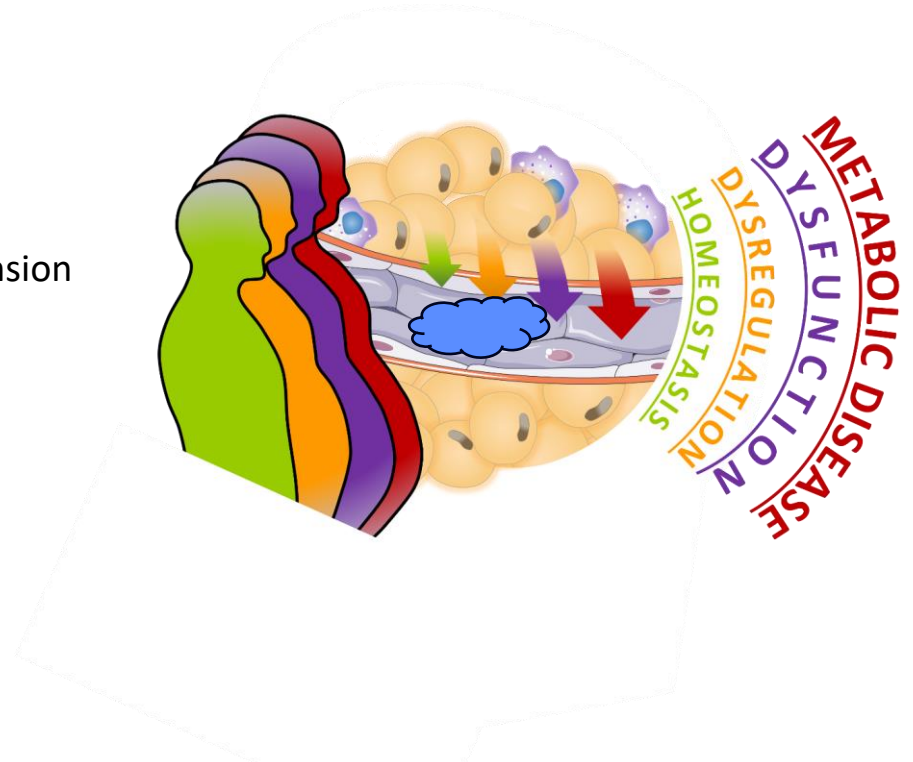


Paradigm Shift in Obesity Treatment

Dr. Mehmet Furkan Burak

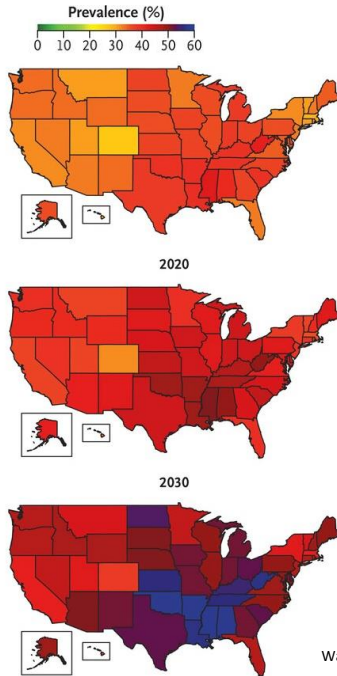
Division of Endocrinology, Diabetes and Hypertension
Brigham and Women's Hospital
Harvard Medical School

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

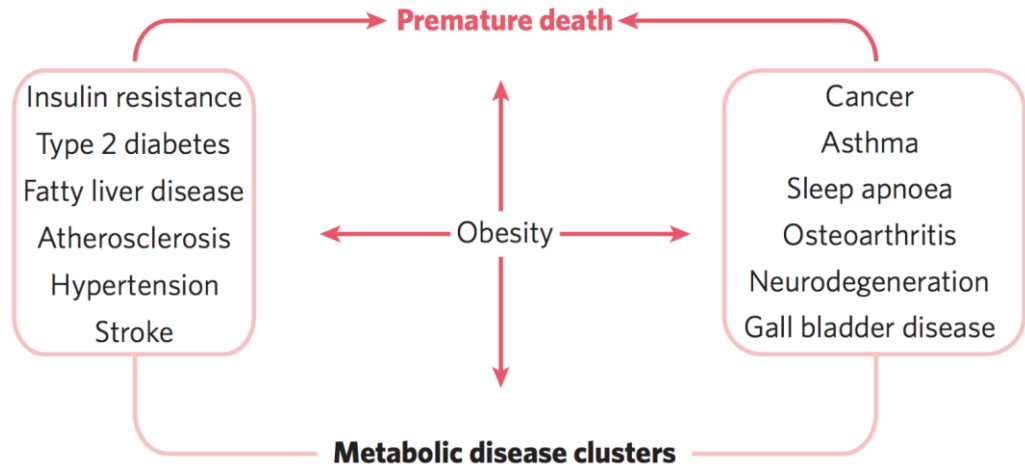


Obesity and Dysmetabolism

Prevalence of Overall Obesity (BMI \geq 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

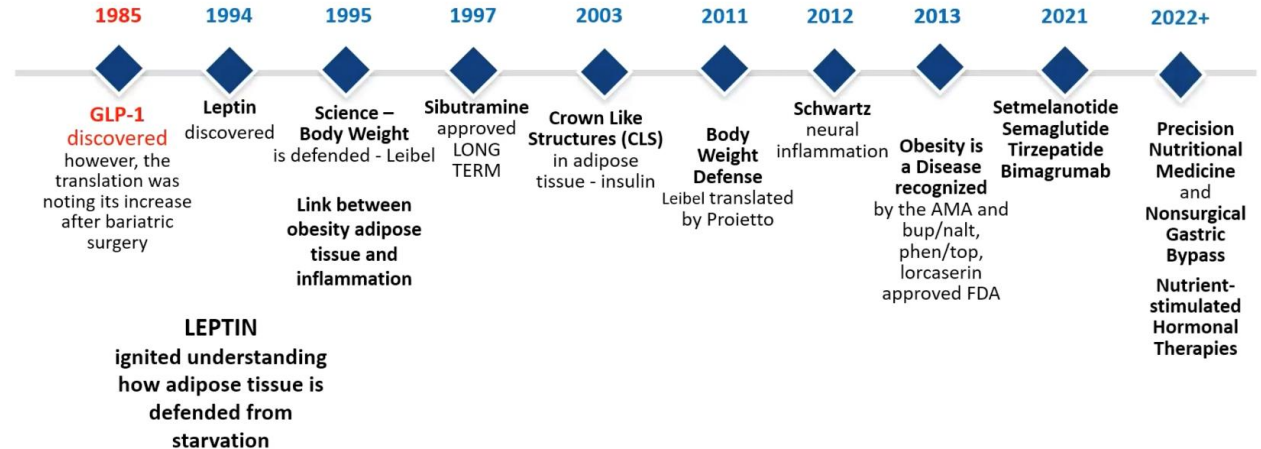
A Consideration of the Theory of Hunger and Appetite

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

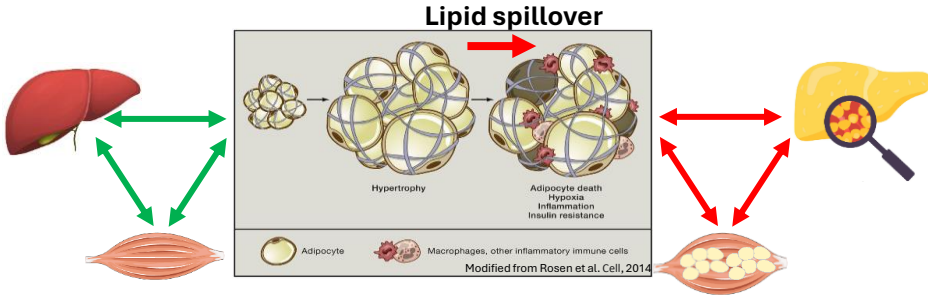
» Author Affiliations

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

OBESITY MEDICINE HISTORY LESSON Quarter of a Century

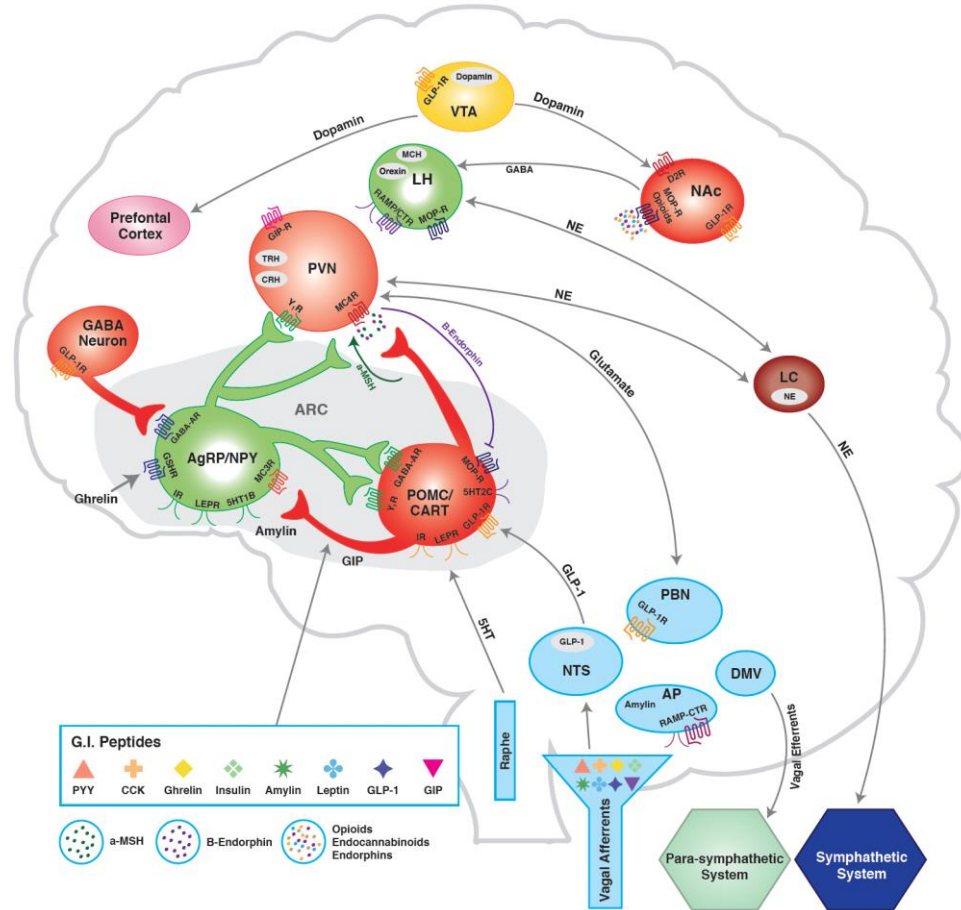


Energy Regulation and Current Anti-Obesity Medications

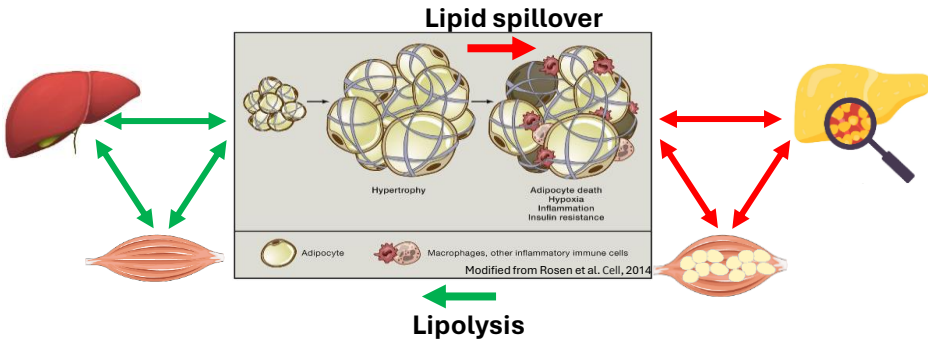


Adipogenic peripheral pathways become pathological in obesity

- INHBE
- GPR75
- Myostatin (GDF8), ALK7



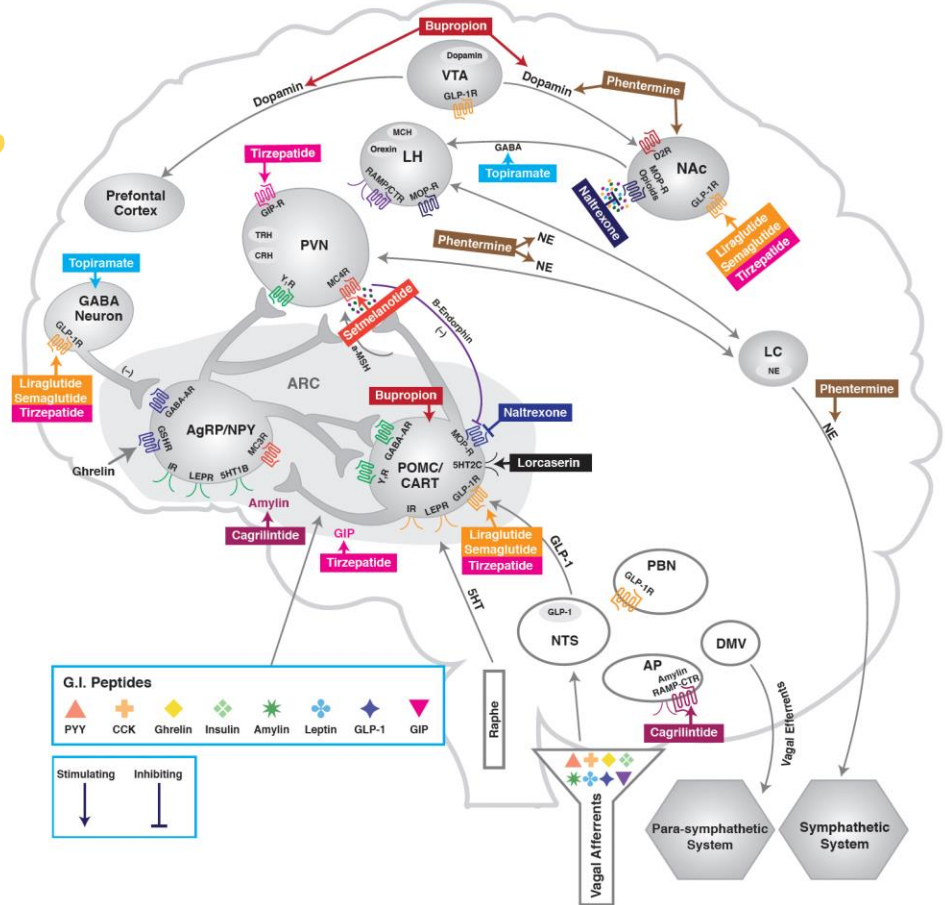
Energy Regulation and Current Anti-Obesity Medications



Adipogenic peripheral pathways become pathological in obesity

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

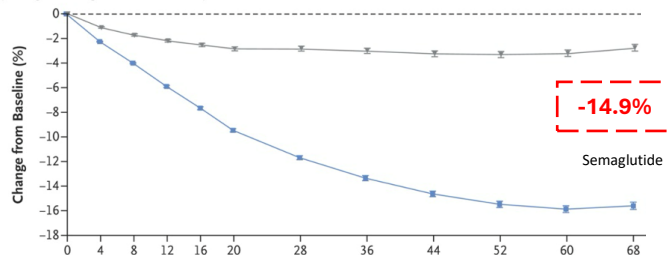
- INHBE
- GPR75
- Myostatin (GDF8), ALK7



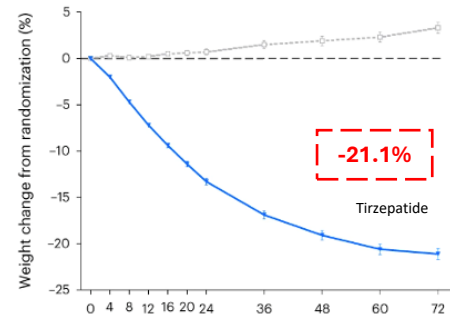
GLP-1 Agonists: Pros

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

Body Weight Change from Baseline by Week, Observed In-Trial Data

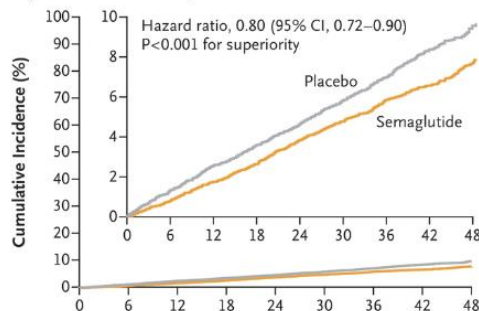


Wilding et al. NEJM, 2021

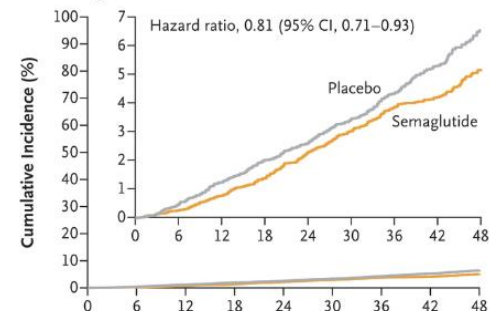


Wadden et al. Nat Med, 2023

Primary Cardiovascular Composite End Point



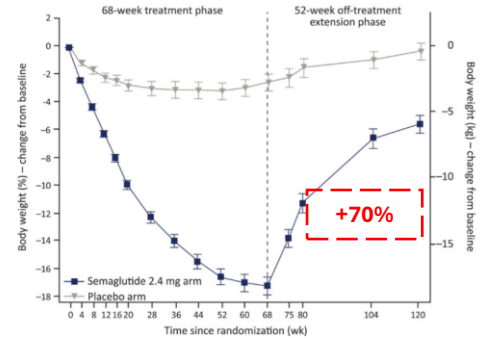
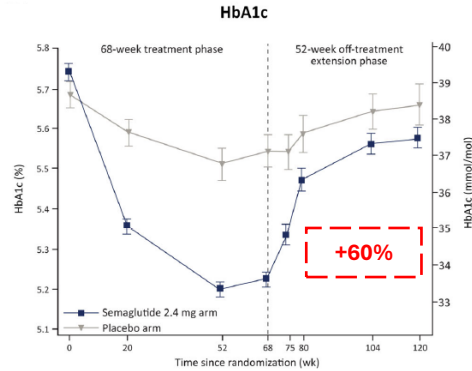
Death from Any Cause



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

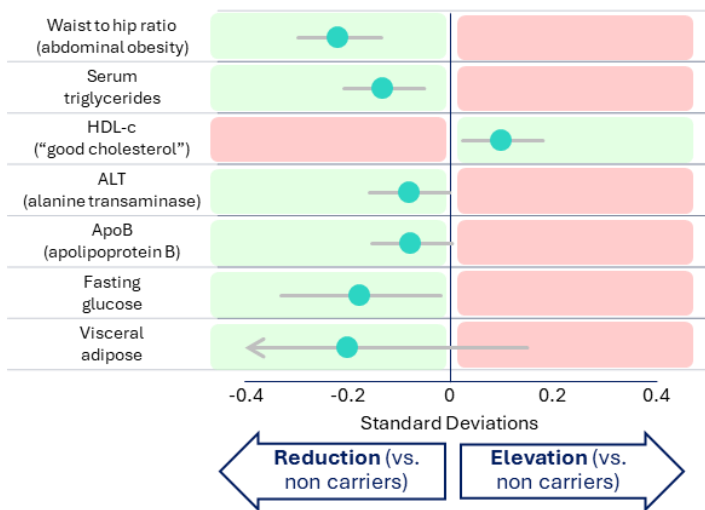
WVE-007: A Novel Obesity Therapeutic for Healthy, Sustainable Weight Loss

Ginnie Yang, PhD
SVP, Translational Medicine

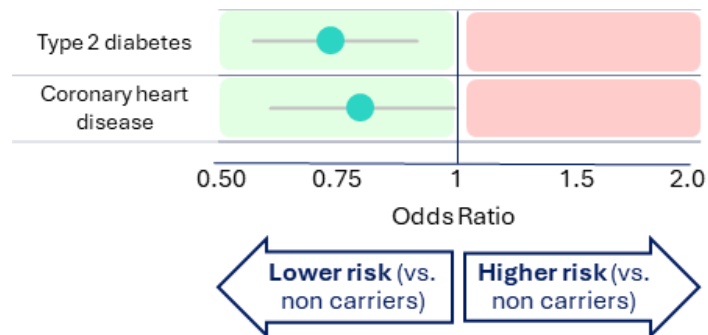


Human genetic data demonstrate that INHBE heterozygous carriers have a healthy metabolic profile

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

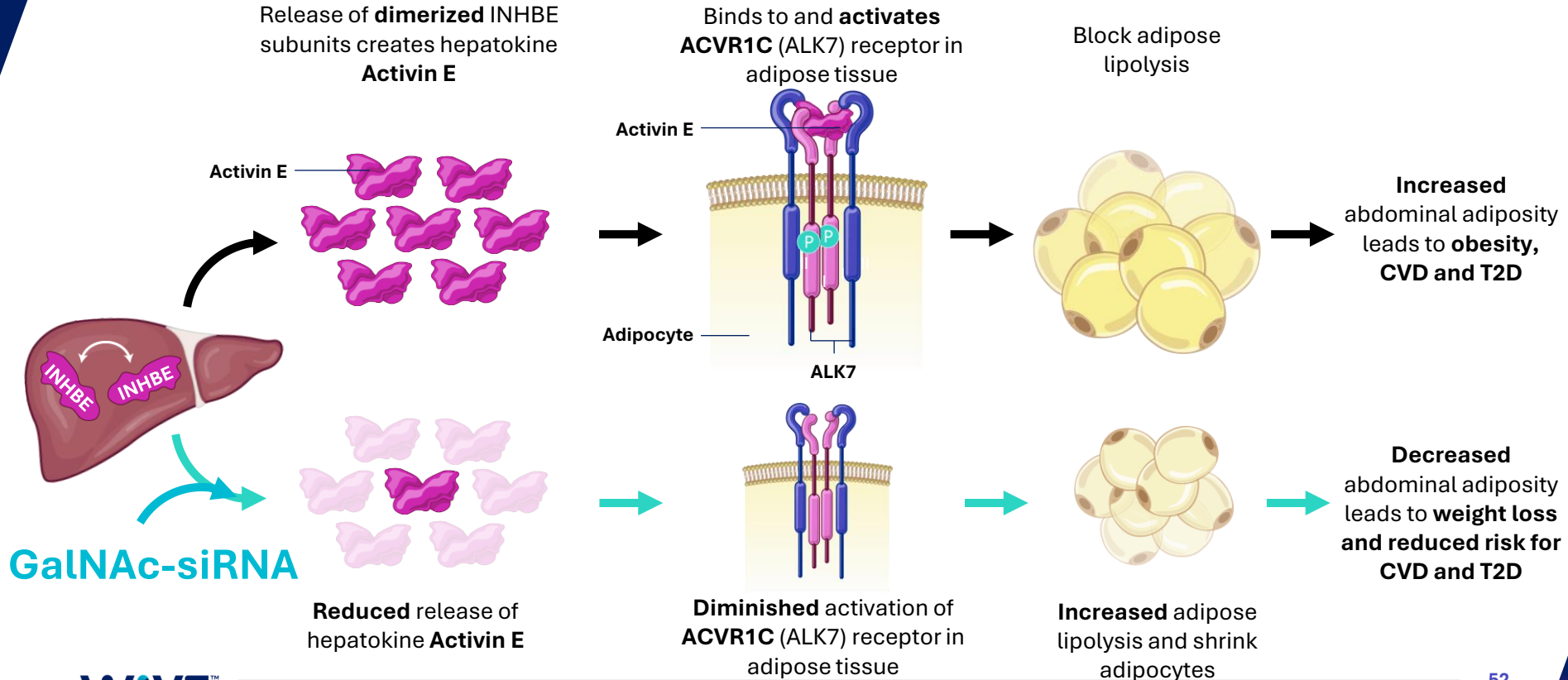


Heterozygous INHBE LoF carriers have lower risk of Type 2 diabetes and CHD



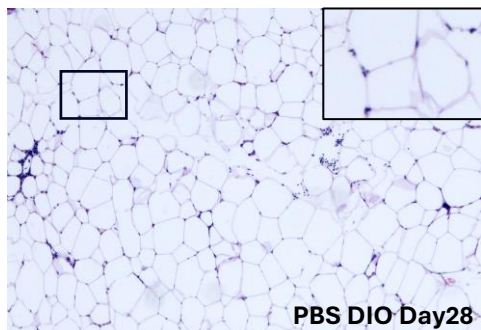
Silencing INHBE mRNA by $\geq 50\%$ is expected to recapitulate the healthy metabolic profile of heterozygous INHBE loss of function (LoF) carriers

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

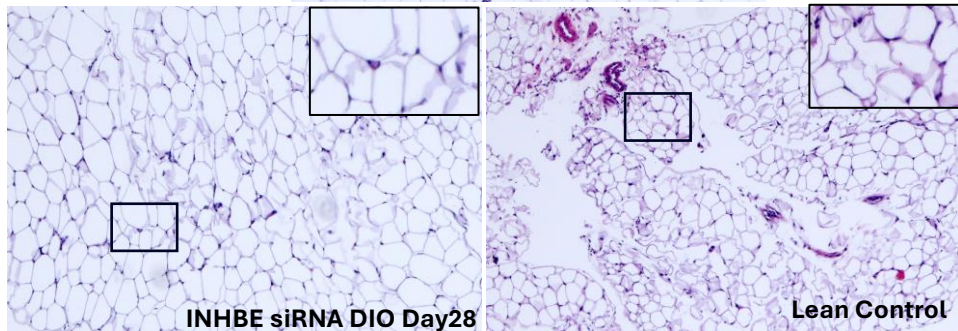


Significant ~43% decrease of adipocyte size in mesenteric adipose tissues with INHBE siRNA treatment

Mesenteric

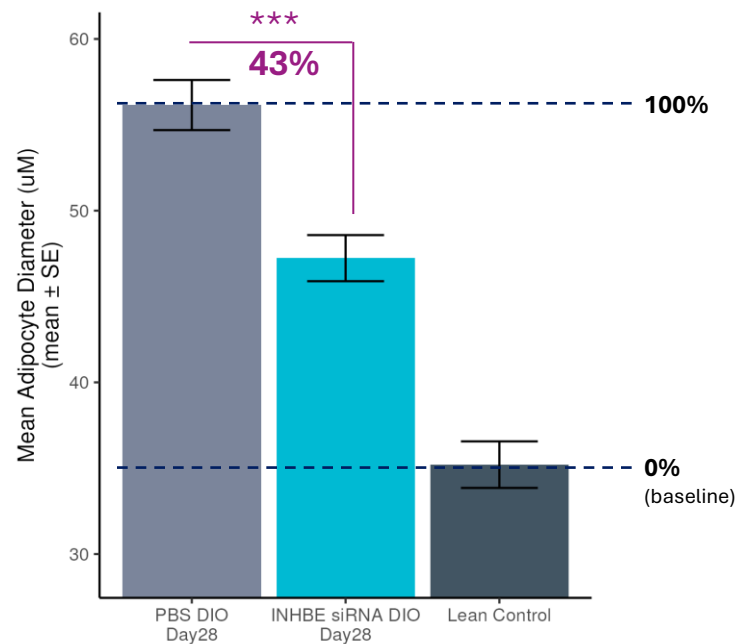


PBS DIO Day28



INHBE siRNA DIO Day28

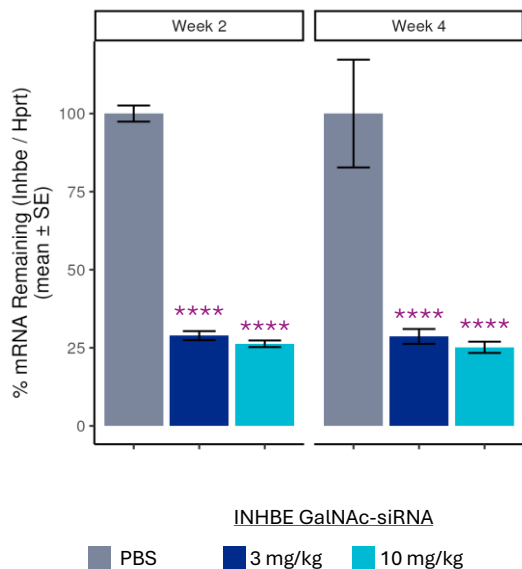
Lean Control



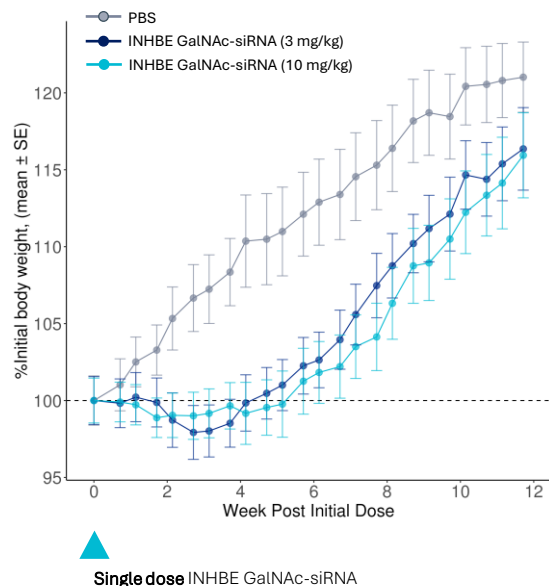
Supports peripheral mechanism of WVE-007 – distinct from GLP-1s with central mechanism

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

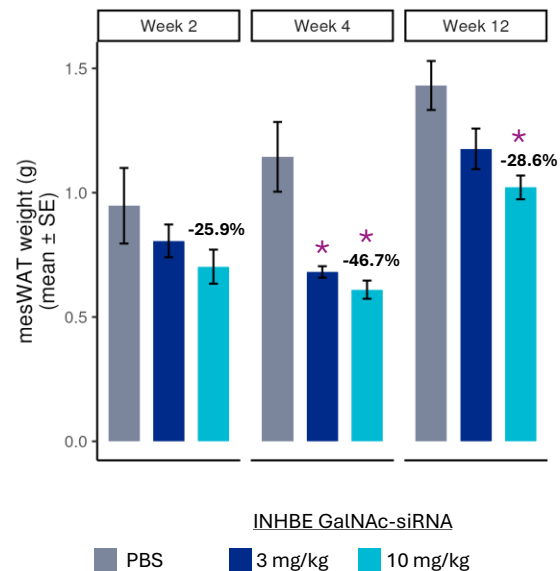
Potent knockdown of INHBE mRNA with a single dose



Potent and durable effect on body weight



Sustained reductions of mesenteric fat mass at 12 weeks

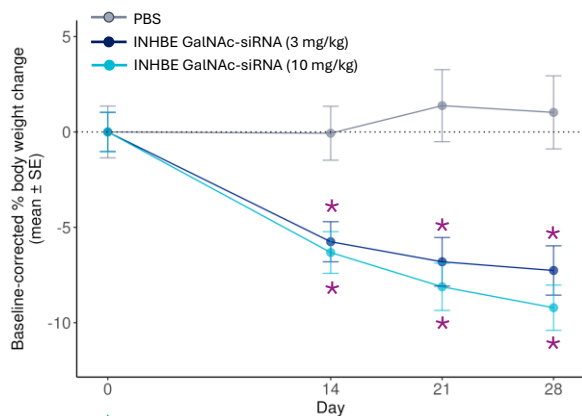


Single doses of INHBE GalNAc-siRNA result in dose-dependent weight loss and reduction of visceral fat, without affecting muscle mass

✓ Reduction in body weight

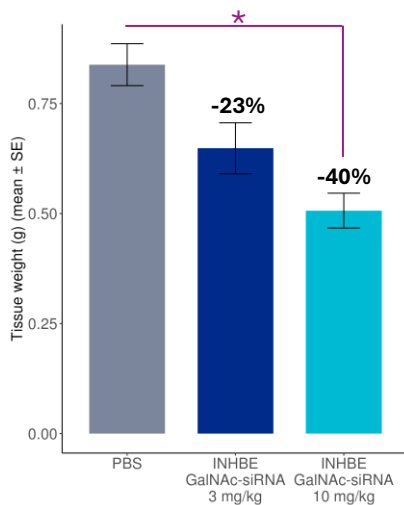
✓ Reduction in visceral fat

✓ No muscle loss

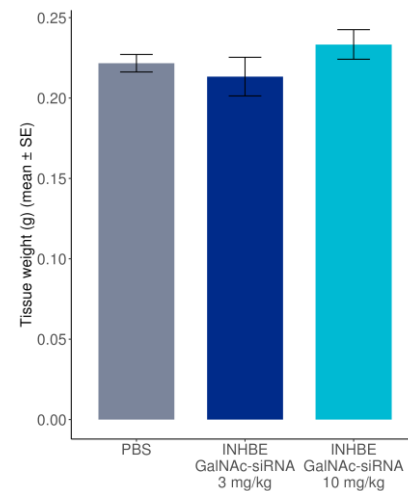


Single dose INHBE GalNAc-siRNA

Epididymal fat weight (Day 28)

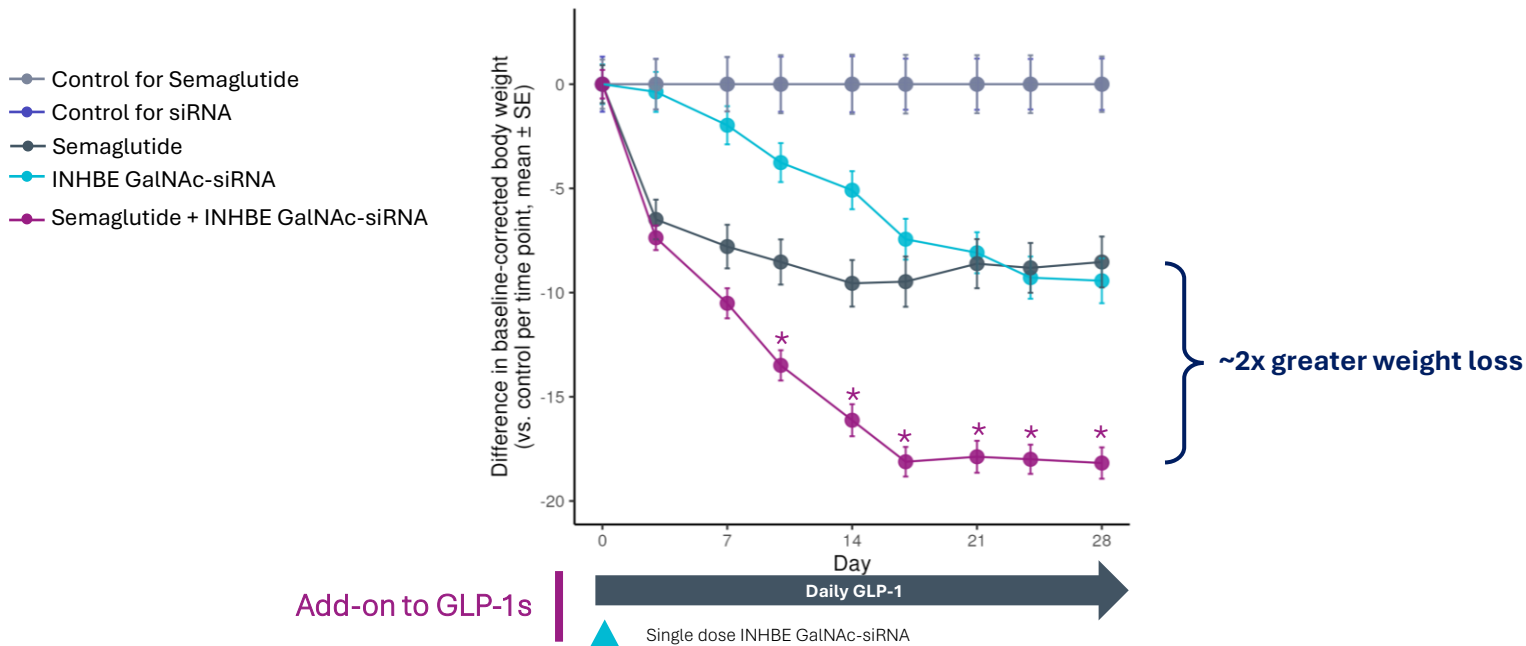


Quadriceps weight (Day 28)



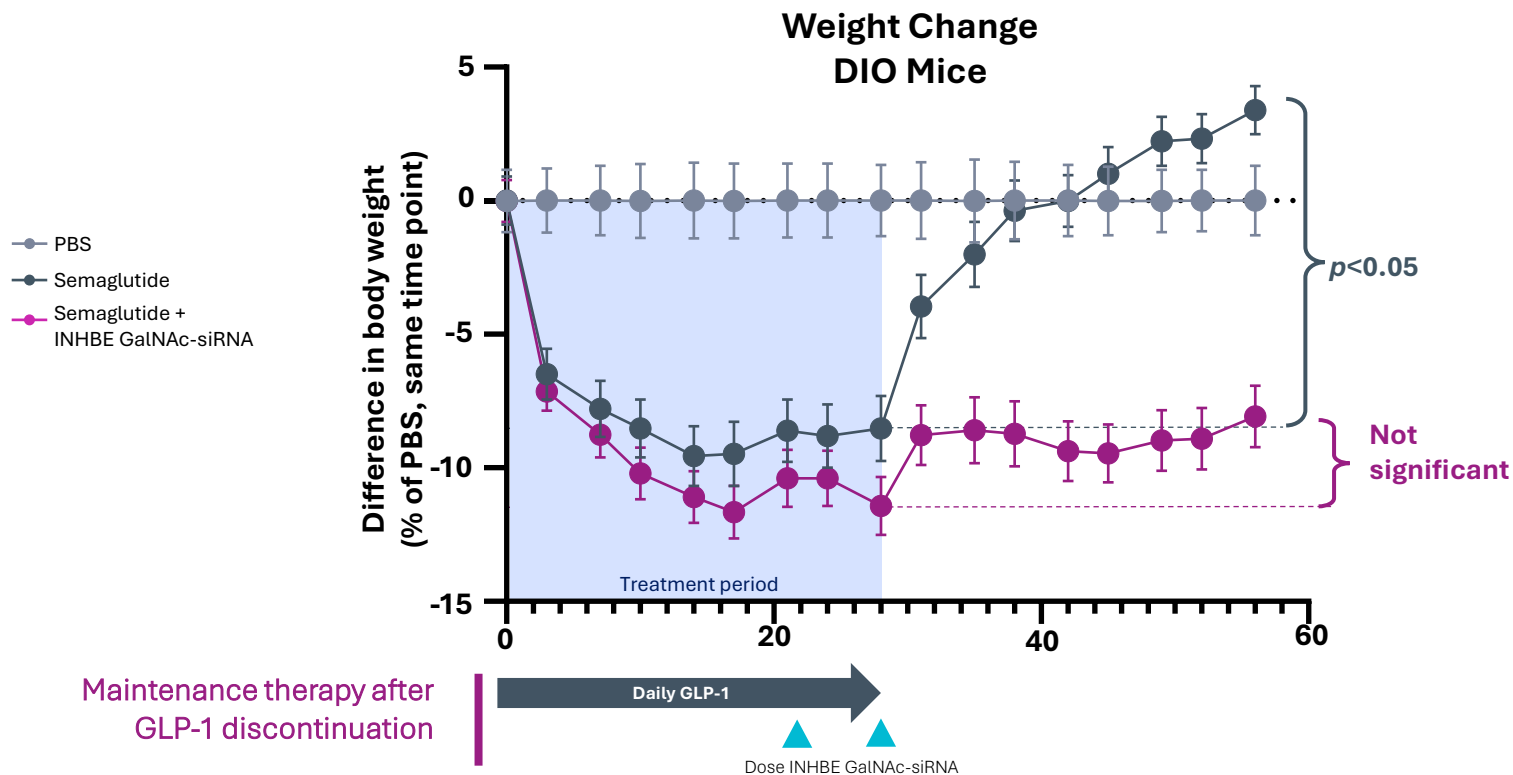
INHBE GalNAc-siRNA has potential as monotherapy weight loss therapeutic

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

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



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

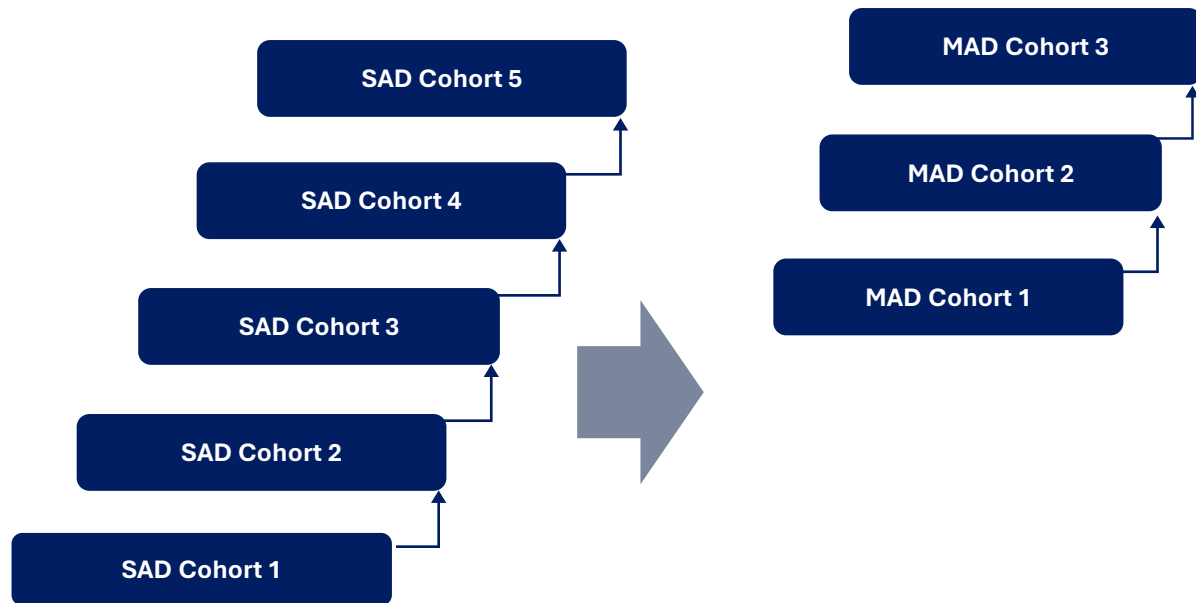
- ✓ **Monotherapy: as a single agent.** Weight loss similar to semaglutide with no loss of muscle mass and a reduction in fat mass with preferential effect to the visceral fat, and without suppressing food intake
- ✓ **Add-on to GLP-1s: WVE-007 in addition to GLP-1 therapy.** When administered as an 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

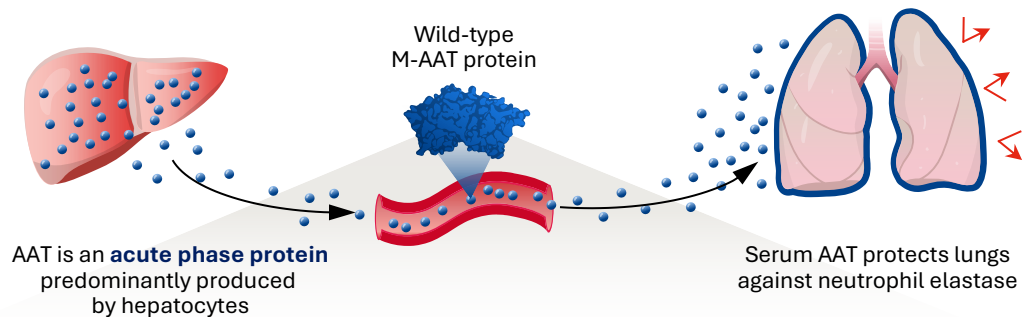
Spotlight:
WVE-006: First-ever RNA Editor
Unlocking New Wholly Owned
Programs

Erik Ingelsson, MD, PhD
Chief Scientific Officer



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

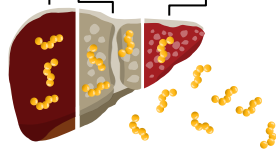
Healthy



AATD

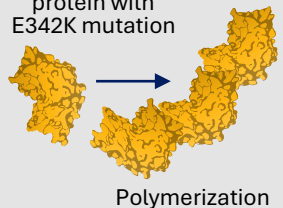
Gain of Function: Liver Disease

Fibrosis → Cirrhosis → Hepatocellular Carcinoma



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

Misfolded Z-AAT protein with E342K mutation



Loss of Function: Lung Disease

Emphysema Bronchiectasis



Low serum AAT leads to lung disease

WVE-006 for AATD

A

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



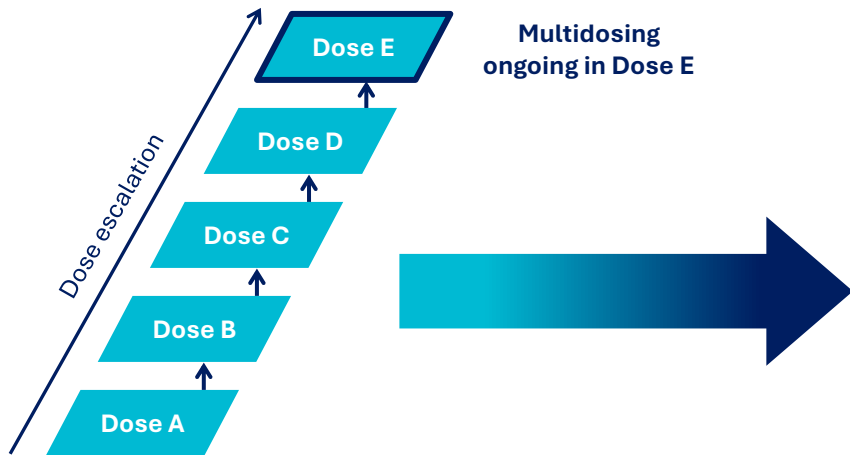
✓ Highly specific (No bystanders)

RestorAATion-1 and RestorAATion-2 ongoing

RestorAATion-1: Healthy Volunteers

RestorAATion-2: AATD Patients

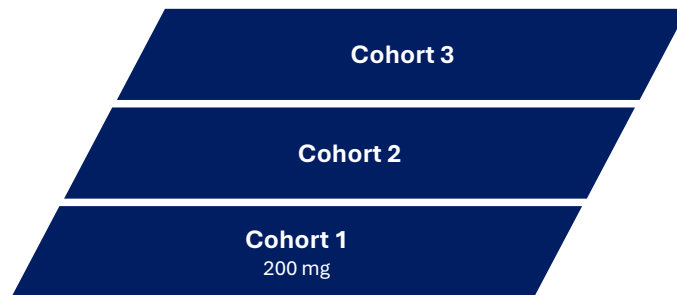
Single ascending dose (SAD) → Multiple-ascending dose (MAD) cohorts



Multidosing ongoing in Dose E



Up to 7 doses



Study key objectives

- Safety and tolerability
- Pharmacokinetics
- Serum M-AAT levels

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

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

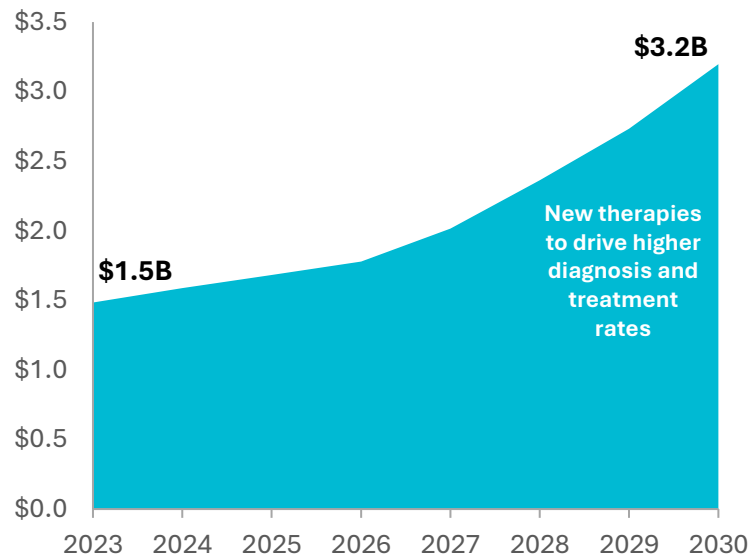
Wave expects to share multidose data from RestorAATion-2 in 2025

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

AATD Market Overview

- **AATD market today is estimated at ~\$1.5B worldwide¹ 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 2030¹ 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

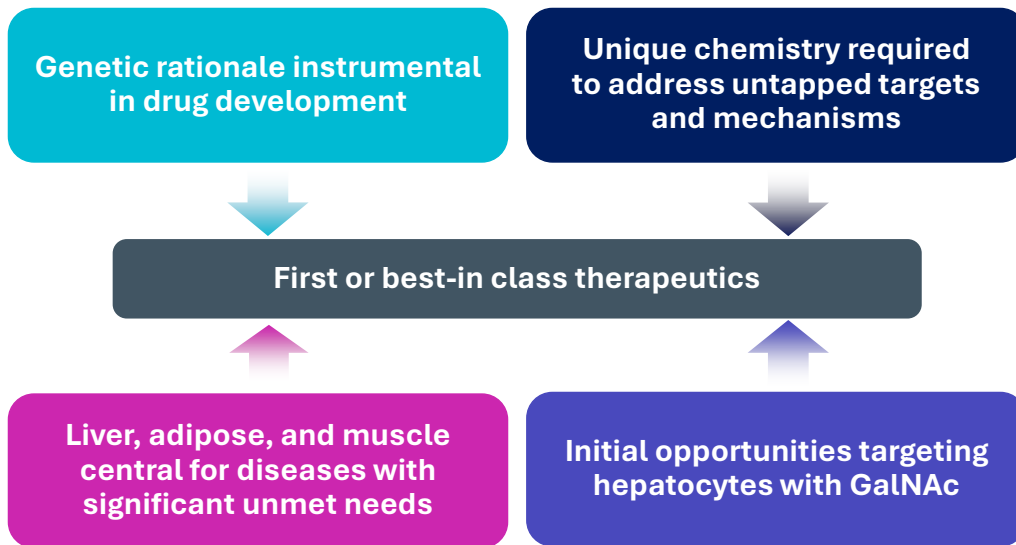


Building the pipeline: New programs informed by human genetics

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

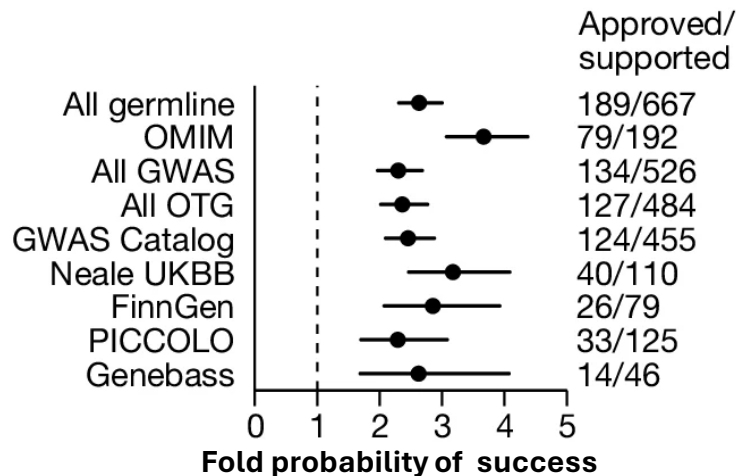


- ✓ Strong foundation in human genetics
- ✓ Proprietary chemistry: potency, durability, and delivery
- ✓ Clinically validated platform

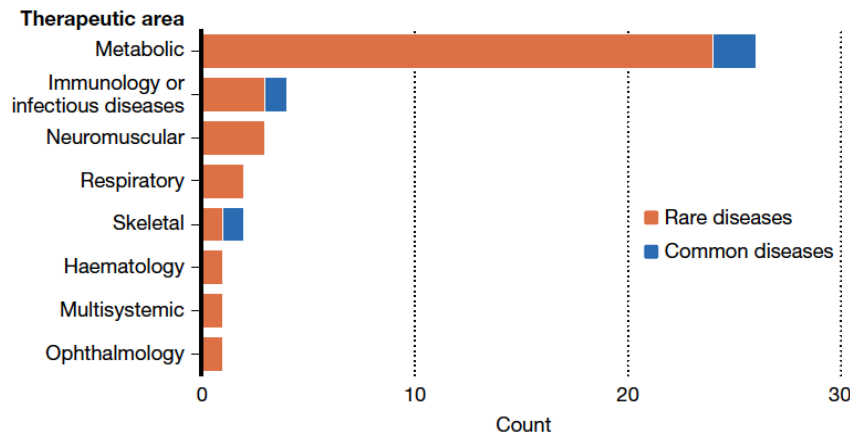


Human genetics dramatically increases probability of success in drug development and can accelerate development of new medicines

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

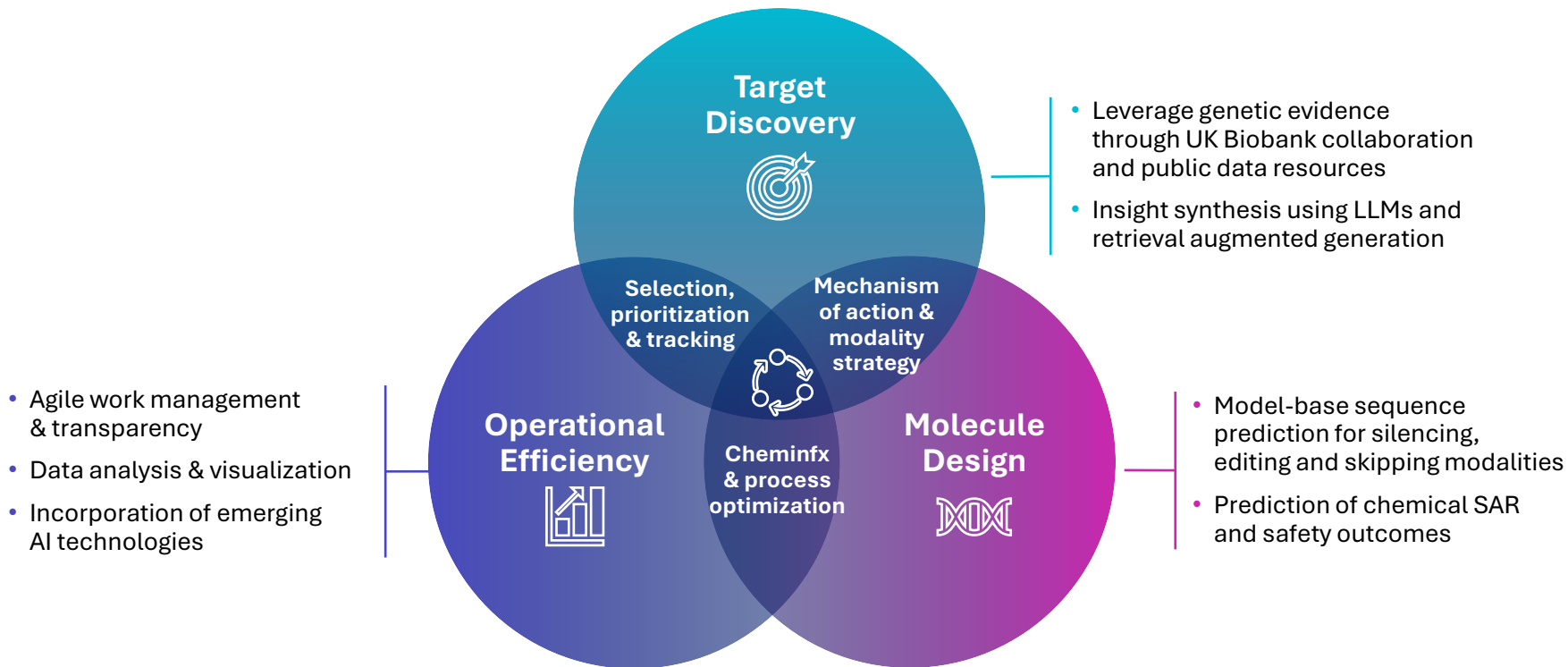


50 approved medicines driven by human genetics



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

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



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



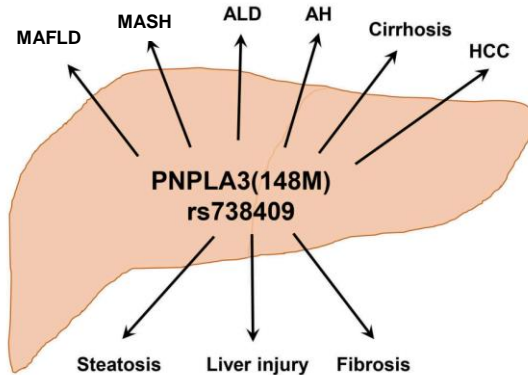
Correction of APOB
Familial hypercholesterolemia



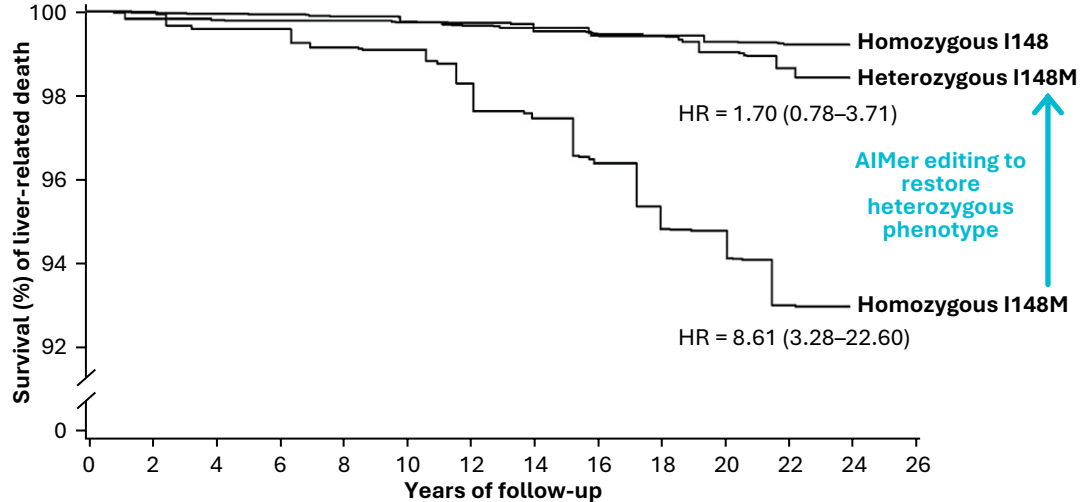
Homozygous PNPLA3 I148M are at high-risk for liver diseases

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 patients²

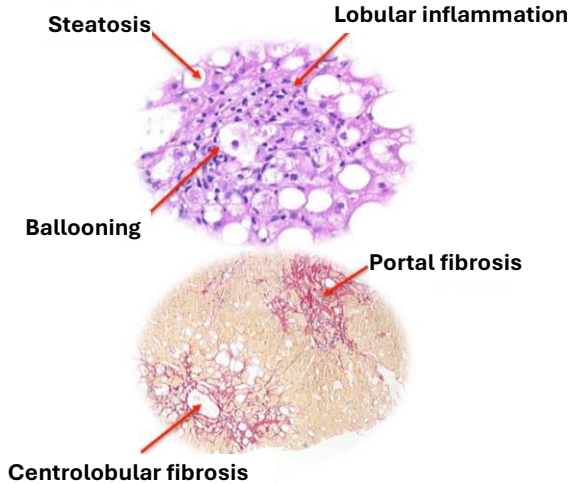


>50% RNA editing would support restoration of heterozygous phenotype with lower risk of liver diseases

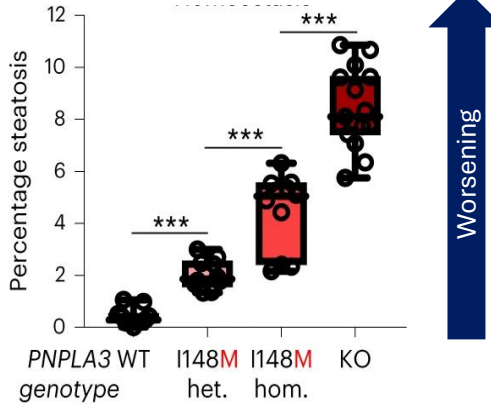
Functional PNPLA3 is imperative for liver health beyond improvements in steatosis

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

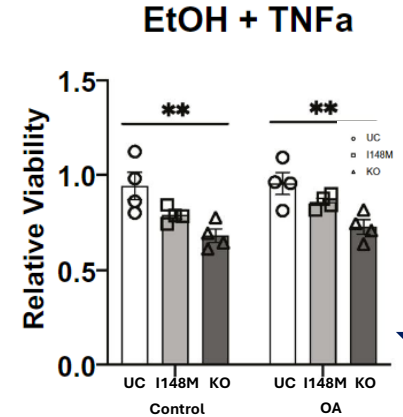
Multiple histological endpoints of liver disease



Silencing PNPLA3 worsens steatosis in iPSC-derived human liver organoids



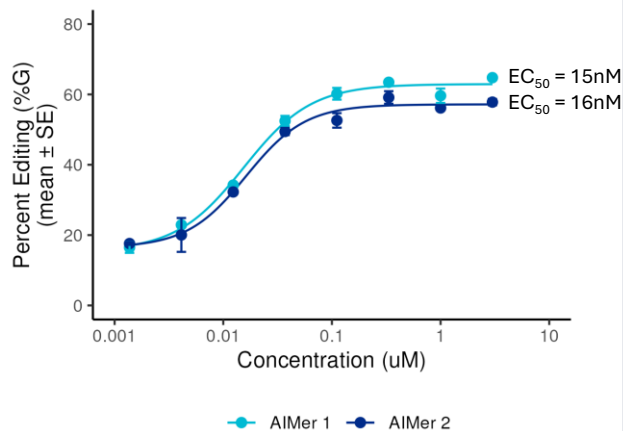
Silencing PNPLA3 increases inflammation-induced liver cell death in human primary hepatocytes



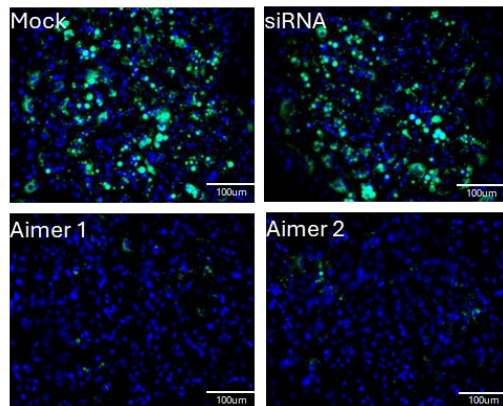
RNA editing offers an optimal approach to generate functional PNPLA3 and improve liver health

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

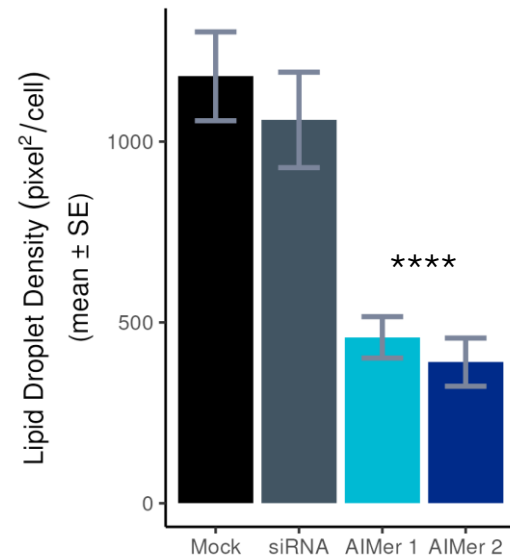
Potent editing of PNPLA3 in homozygous I148M human primary hepatocytes



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



AIMer



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

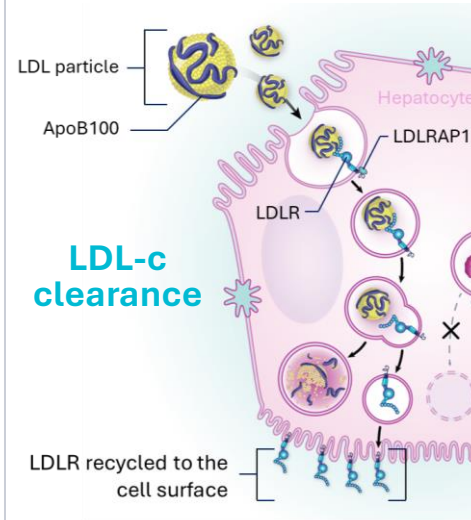
GaINAc-AIMer LDLR (upregulation)
GaINAc-AIMer APOB (correction)
Heterozygous familial hypercholesterolemia

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

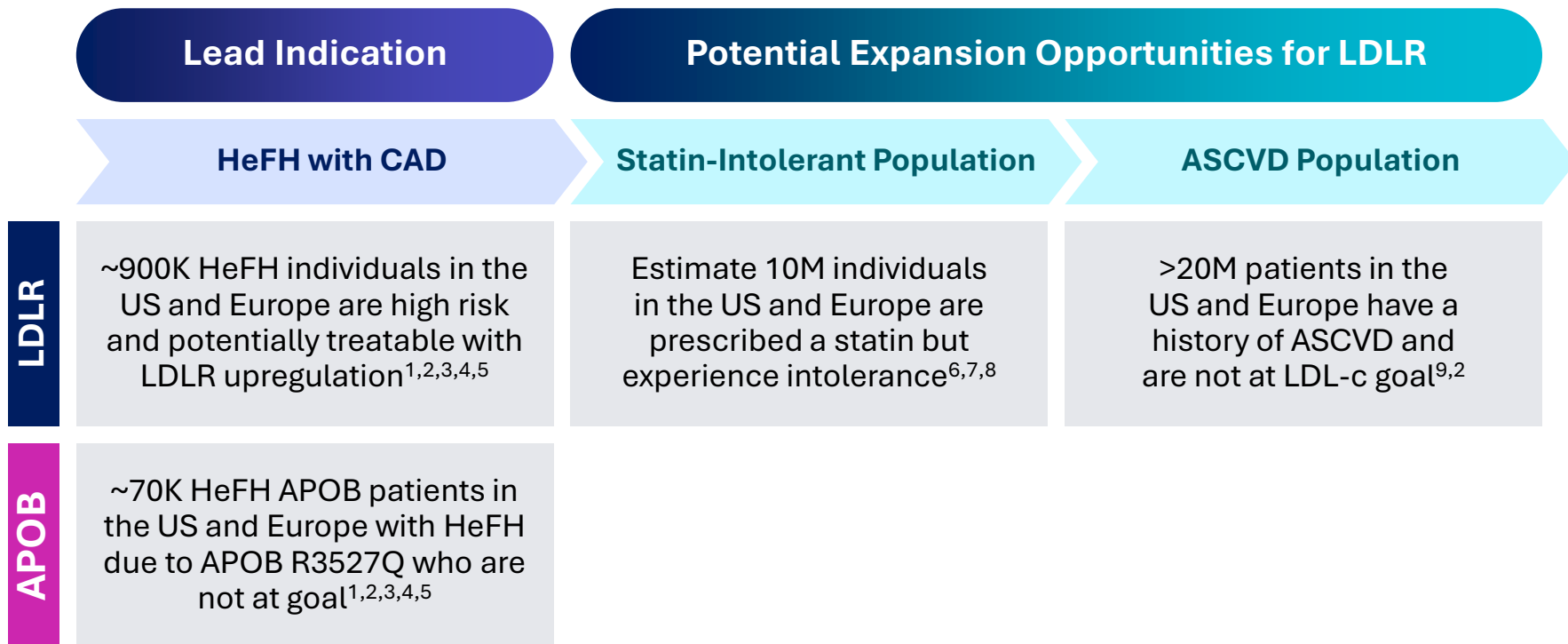
- Cardiovascular disease is the leading cause of death
- Familial hypercholesterolemia (FH) is a genetic disorder that leads to very high levels of LDL-cholesterol¹
- FH patients at **high risk for major cardiovascular events**¹ and **~50%** have need for more effective therapies^{2,3,4}

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

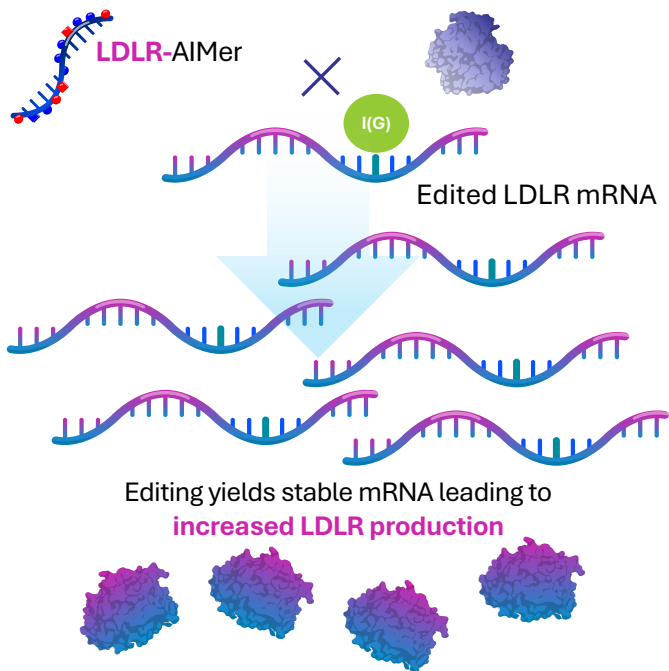


- ~90% heterozygous FH (HeFH) patients carry **LDLR** LoF mutations¹ which are amenable to **AIMer upregulation**
- ~5% - 10% of HeFH patients have mutations in **APOB**¹ amenable to **AIMer correction**

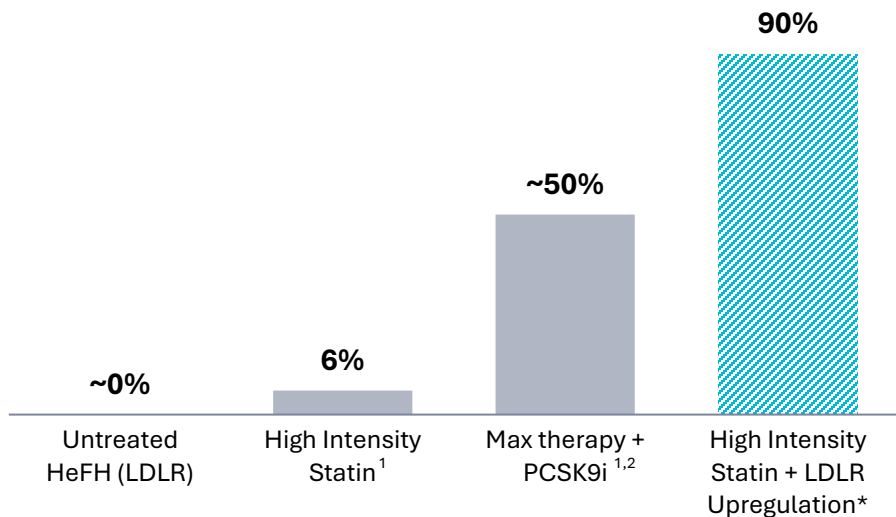
Initially focused on comprehensive treatment approach for HeFH, with multiple potential opportunities for expansion with LDLR upregulation



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



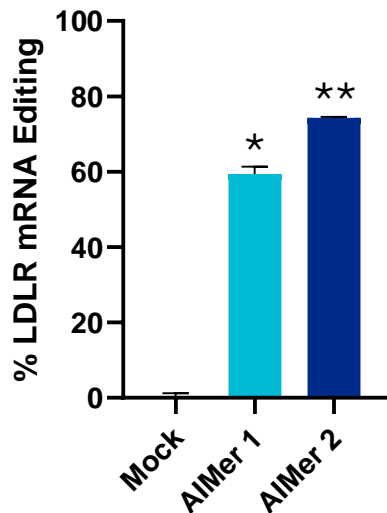
Proportion HeFH (LDLR) patients achieving goal LDL-c levels



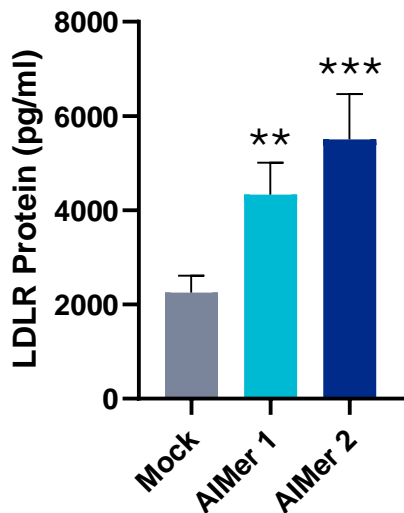
2-fold+ upregulation expected to result in best-in-class 75%+ LDL-c reduction

~2.5-fold upregulation of LDLR protein exceeds target threshold

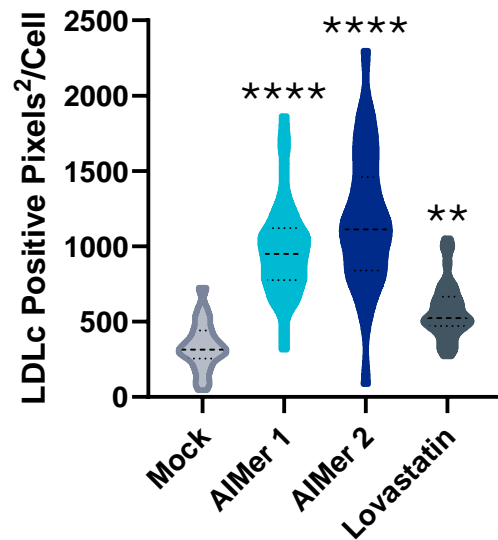
Up to 70% LDLR mRNA editing in primary human hepatocytes



~2.5x increase LDLR protein in primary human hepatocytes



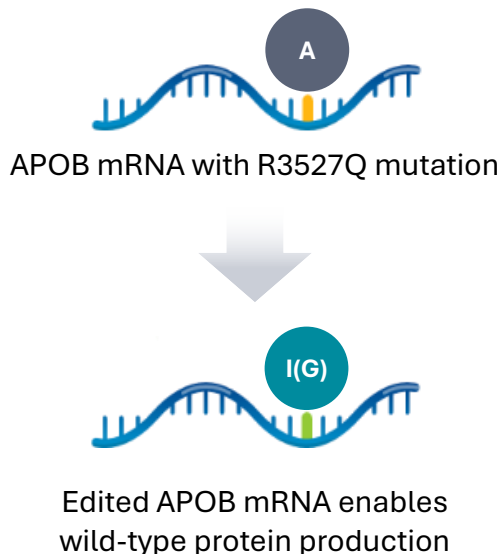
~4-fold increase LDL-c uptake to hepatocytes by AIMers



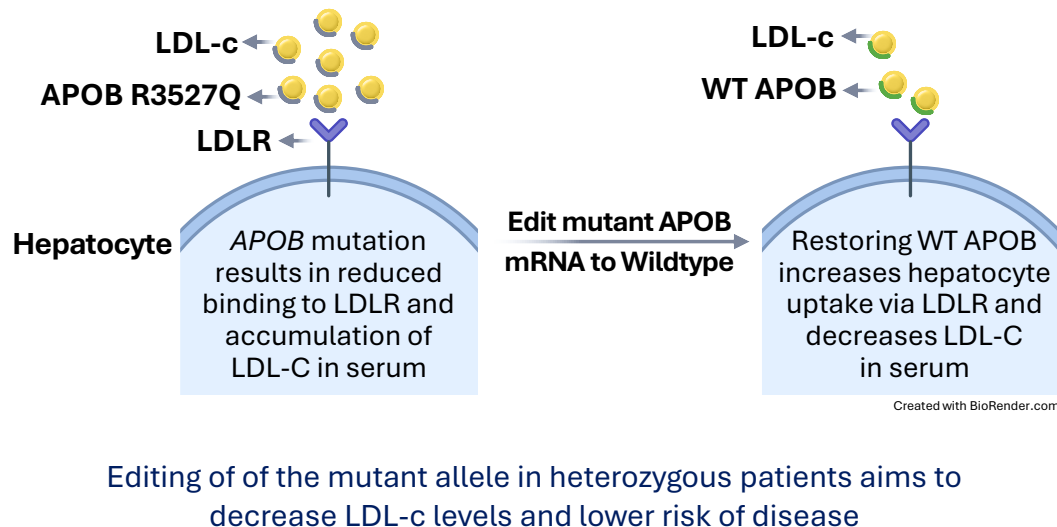
LDLR upregulation levels expected to translate into reductions in LDL-c of up to 85%

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

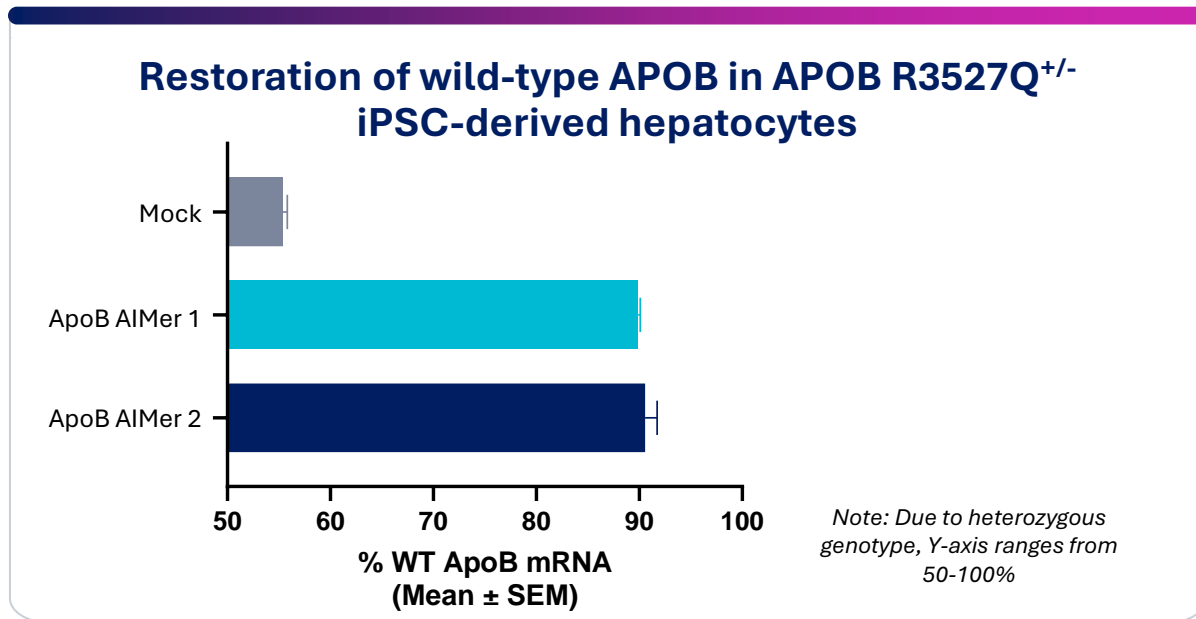
APOB AIMER for HeFH



APOB editing approach



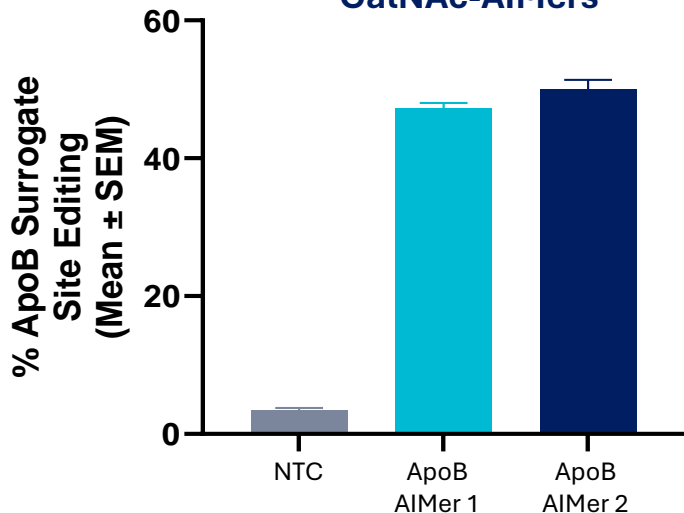
Increasing amount of wild type APOB from 50% in heterozygous patients to 75% is expected to provide therapeutic benefit



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

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

Potent *in vivo* editing with GalNAc-AIMers



- ~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



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)

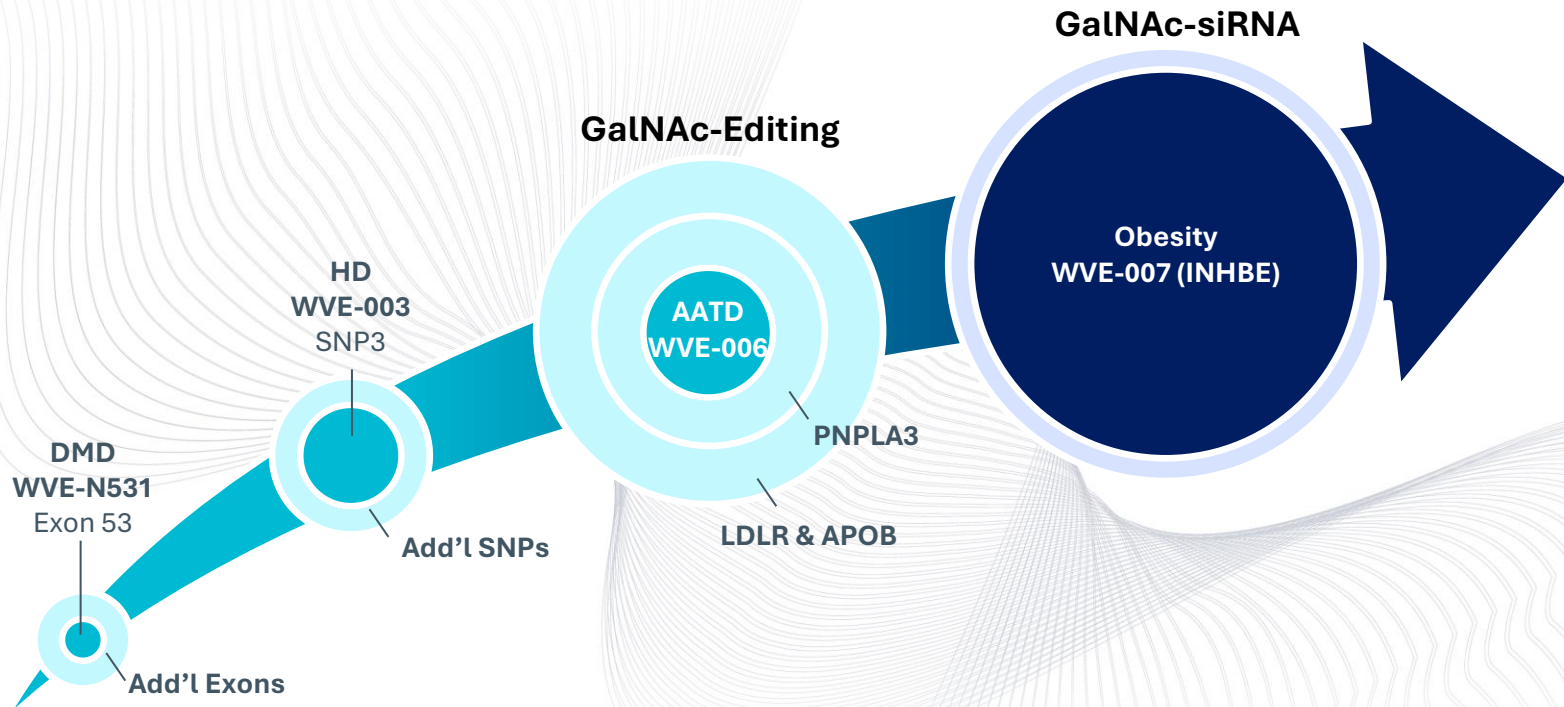


Editing for correction



Editing for upregulation

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

Q&A



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