DEFEAT DEGENERATION

CORPORATE OVERVIEW
MARCH 2024




DISCLAIMERS

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OUR PURPOSE: DEFEAT DEGENERATION

LYSOSOMAL STORAGE DISEASES

Dominic, living with MPS II

ALS/FTD

Seth, living with ALS

PARKINSON'S DISEASE

Allan, living with PD

ALZHEIMER'S DISEASE

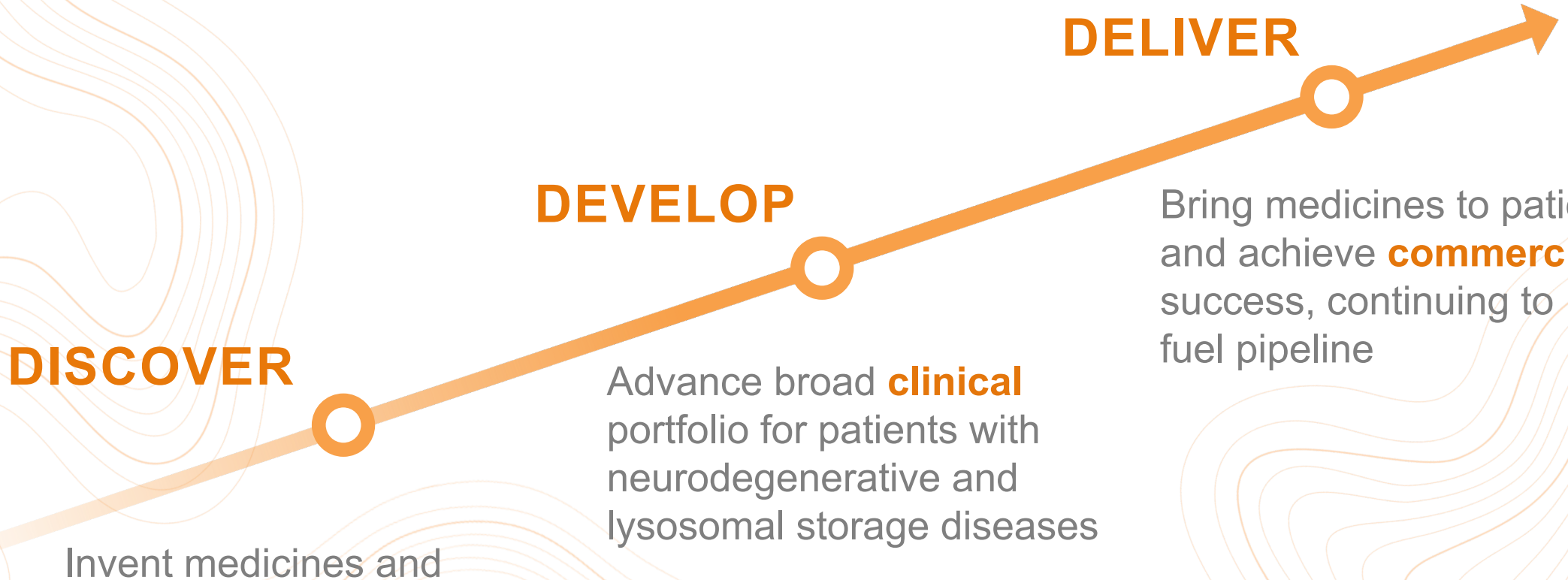
Denali Team at AD Walk 2023

Denali

The name captures the formidable challenges in fighting neurodegenerative diseases but also the unprecedented opportunities enabled by new scientific insights and technologies. With a relentlessly committed team and rigorous effort, breakthroughs appear to be within reach.

ALS – amyotrophic lateral sclerosis; **FTD** – frontotemporal dementia

PATH TO DEFEAT DEGENERATION



APPROACH TO DEFEAT DEGENERATION

Rigorously applying our scientific principles to increase the likelihood of success

DEGENOGENES
Genetic Pathway Realization

BRAIN DELIVERY
Validation & Optionality

BIOMARKERS
Biomarker-Driven Approval

DEVELOPMENT PORTFOLIO: COMMON & RARE DISEASES

DRUG CANDIDATE*	DISEASE INDICATION	DEVELOPMENT STAGE				PARTNER
		IND-ENABLING	EARLY	MID	LATE	
Neurodegeneration and Lysosomal Storage Diseases						
Tividenofusp alfa / DNL310 (ETV:IDS)	MPS II (Hunter)					
DNL343 (eIF2B activator)	ALS					
BIIB122 / DNL151 (LRRK2 inhibitor)	Parkinson's disease					Biogen
SAR443820 / DNL788 (RIPK1 inhibitor)	Multiple sclerosis					sanofi
TAK-594 / DNL593 (PTV:PGRN)	FTD-GRN					Takeda
DNL126 (ETV:SGSH)	MPS IIIA (Sanfilippo)					
DNL622 (ETV:IDUA)	MPS I (Hurler)					
ATV:Abeta	Alzheimer's disease					Biogen
OTV:MAPT	Alzheimer's disease					
OTV:SNCA	Parkinson's disease					
Peripheral Inflammatory Disease						
SAR443122 / DNL758 (RIPK1 inhibitor)	Ulcerative colitis					sanofi

Transport Vehicle Programs · Small Molecule Programs · 50/50 US Commercial · Royalty

Broad, diverse, and differentiated portfolio, including multiple TV-enabled programs in discovery

*Investigational – not approved for treatment; **MPS** – Mucopolysaccharidoses; **ALS** – Amyotrophic lateral sclerosis; **FTD-GRN** – Frontotemporal dementia-granulin

SUSTAINABLE VALUE GENERATION: MULTIPLE OPPORTUNITIES

Peak 1

Potential to Reach $10B in Peak Sales* 7 Current Clinical Programs

Peak Sales	Program	Indication
>$5B	**DNL151**	PD
$1-5B	**DNL788**	ALS/MS
	DNL343	ALS
	DNL758	UC
Up to $1B	**DNL310**	MPS II
	DNL126	MPS IIIA
	DNL593	FTD-GRN

● TV-Enabled ● Small Molecule

Peak 2

Potential to Reach >$10B in Peak Sales* 5 Discovery Programs in AD and PD

Peak Sales	Program	Indication
>$5B	**ATV:Abeta**	AD
	OTV:MAPT	AD
	OTV:SNCA	PD
	ETV:GCase	Gaucher/PD
	ATV:TREM2	AD
$1-5B	**Additional ETV/OTV**	Various
Up to $1B	–	–

Portfolio evolution to focus on TV-enabled programs in common neurodegenerative diseases

* Denali estimates of potential peak sales; **PD** – Parkinson's disease; **ALS** – amyotrophic lateral sclerosis; **MS** – multiple sclerosis; **UC** – ulcerative colitis; **MPS** – Mucopolysaccharidosis; **FTD-GRN** – Frontotemporal dementia-granulin; **AD** – Alzheimer's disease

TRANSPORT VEHICLE (TV) PLATFORM

PIONEERING BBB-CROSSING TECHNOLOGY FOR BRAIN DELIVERY

Discovery Milestones

2011: Impact of TfR affinity on BBB crossing[1]

2013: Addressing liabilities of targeting TfR[2]

2016: CD98hc characterization as BBB target[3]

2020: TV publication of invention (**ATV**)[4]

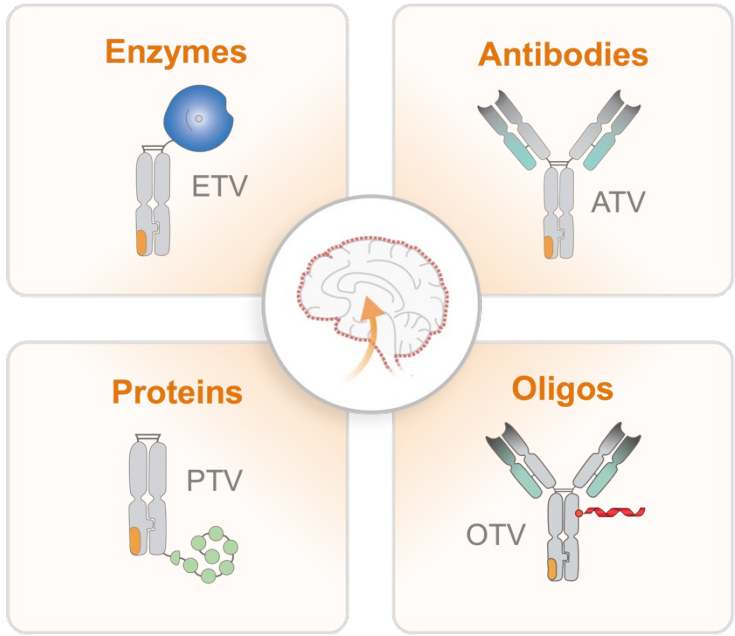
2020: TV-enabled enzyme delivery (**ETV**)[5]

2021: TV-enabled protein delivery (**PTV**)[6]

2022: ETV differentiated brain delivery[7]

2023: TV-enabled oligo delivery (**OTV**)[8]

Our Transport Vehicle (TV)



Key TV Achievements

392 Patents and Applications

8 Top-Tier Publications

3 Clinical Programs

13 Preclinical Programs

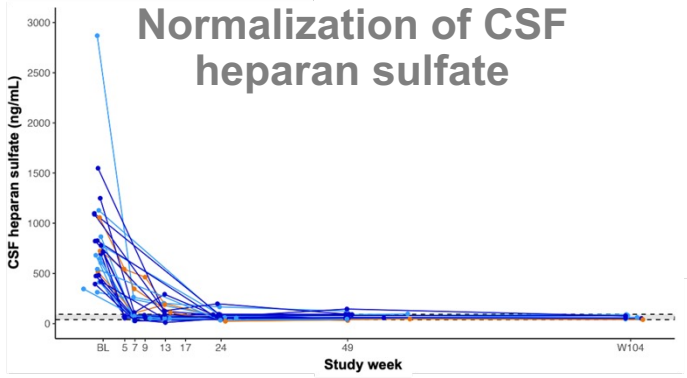
We are leading the field in discovery and development of BBB-crossing technology to revolutionize the treatment of neurodegenerative diseases

[1]Yu et al. 2011 *STM*; [2]Couch et al. 2013 *STM;* [3]Zuchero et al. 2016 *Neuron*; [4]Kariolis et al. 2020 *STM*; [5]Ullman et al. 2020 *STM;* [6]Logan et al. *Cell* 2021; [7]Arguello et al. 2022 *JEM*; [8]Barker et al. 2023 *BioRxiv*

TRANSPORT VEHICLE (TV): SOLVING THE BBB CHALLENGE

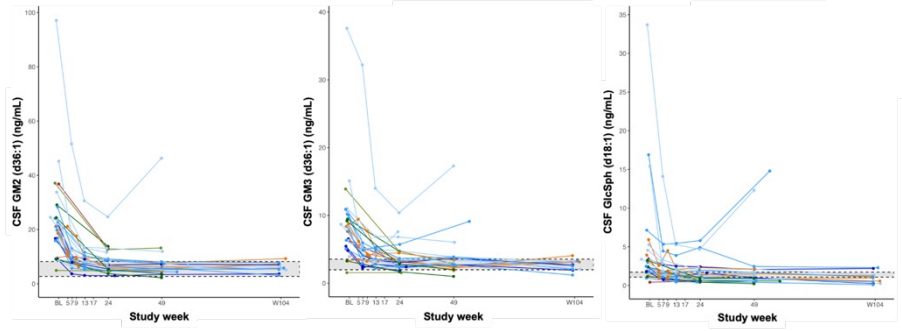
Substrate Correction

Normalization of CSF heparan sulfate



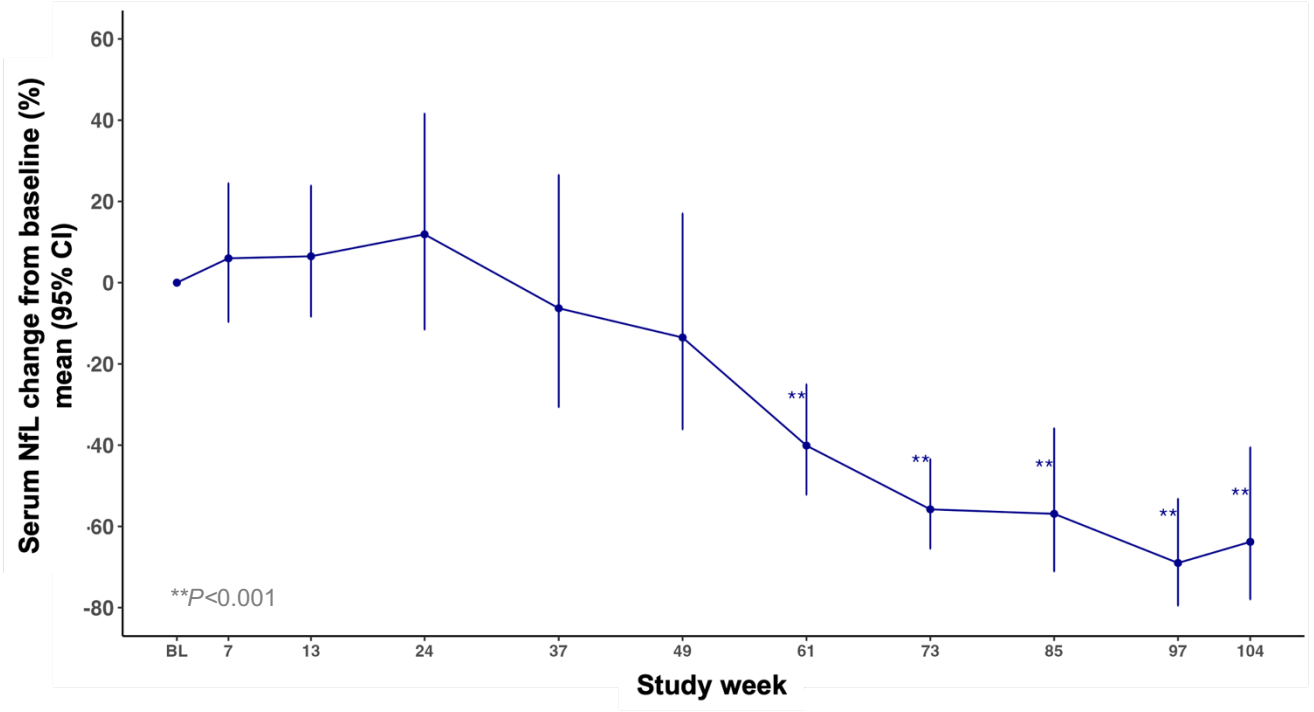
Cellular Correction

Near Normalization of Biomarkers of Lysosomal Function



Neurodegeneration Correction

Robust Reduction in Neurofilament Light (NfL), a Key Marker of Neurodegeneration

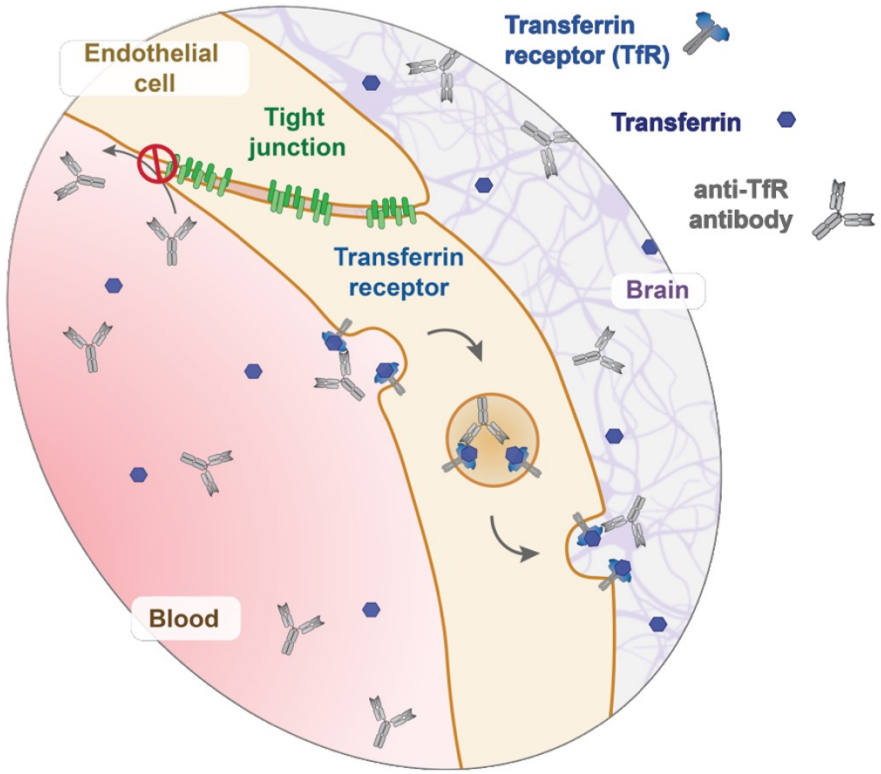


TV proof of concept for targeting TfR achieved in DNL310 Phase 1/2 study for MPS II

Source: Burton et al. SSIEM 2023
Bars represent 95% confidence intervals

LEADERSHIP IN THE BBB DELIVERY SPACE

TV Technology Leverages Receptor Mediated Transcytosis Into the Brain



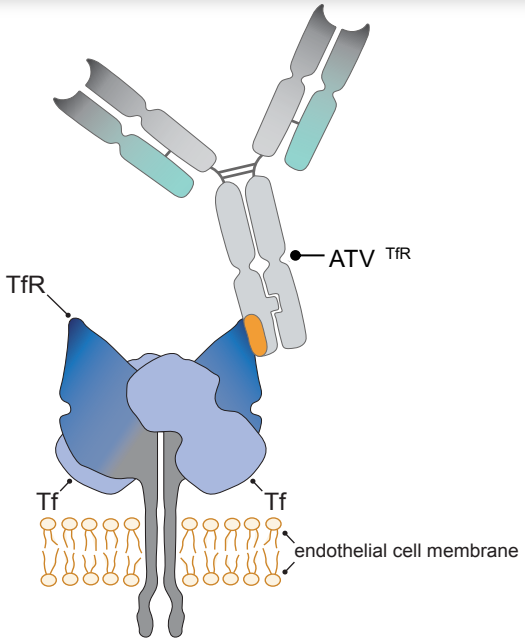
Transferrin Receptor (TfR)
Most Clinically Advanced

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

BLOOD-BRAIN BARRIER

Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys

May 2020



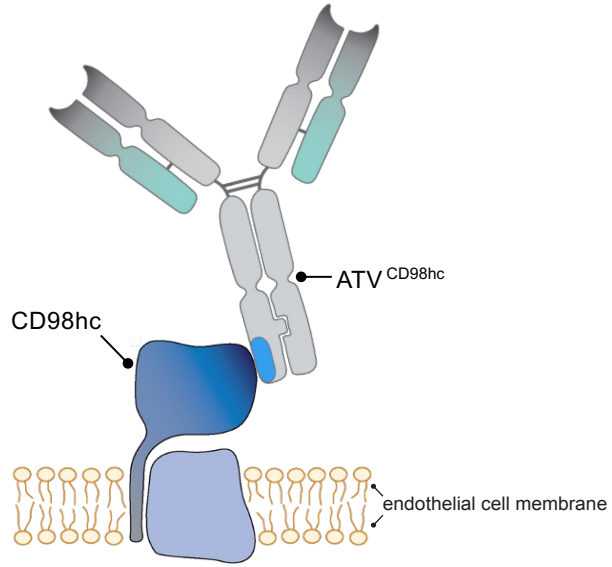
CD98hc Amino Acid Transporter
TV Platform Expansion

nature communications

Article https://doi.org/10.1038/s41467-023-40681-4

CD98hc is a target for brain delivery of biotherapeutics

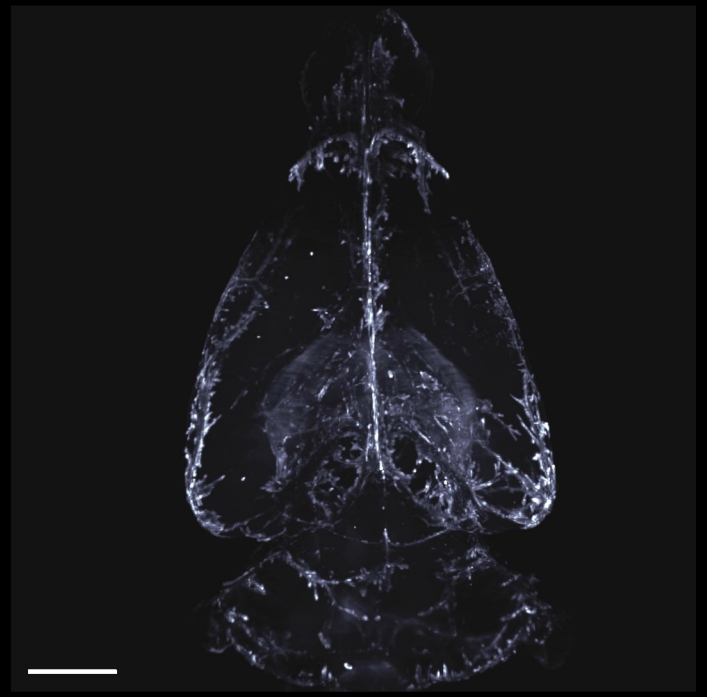
August 2023



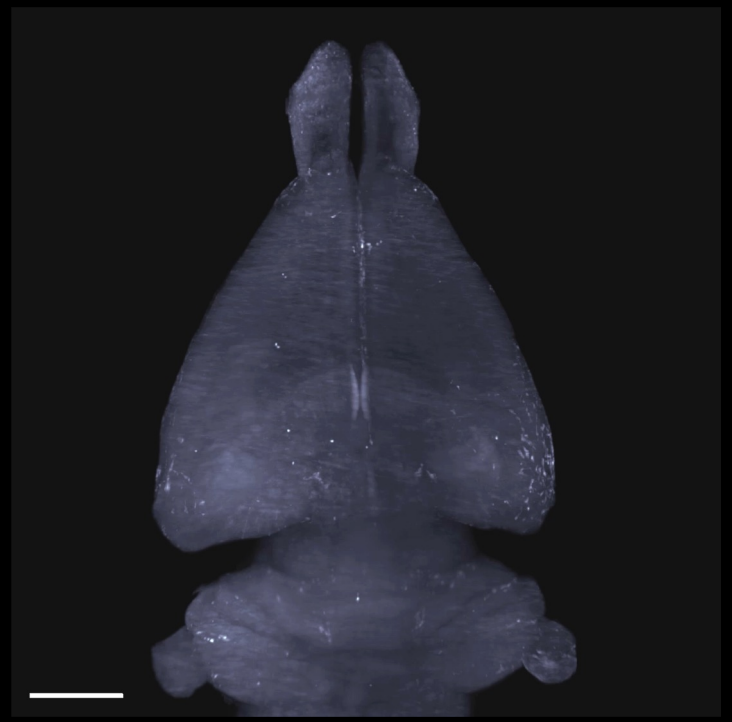
We continue to invent differentiated BBB-crossing technologies that have the potential to optimize the target space

ATV ENABLES BROAD DISTRIBUTION THROUGHOUT THE BRAIN

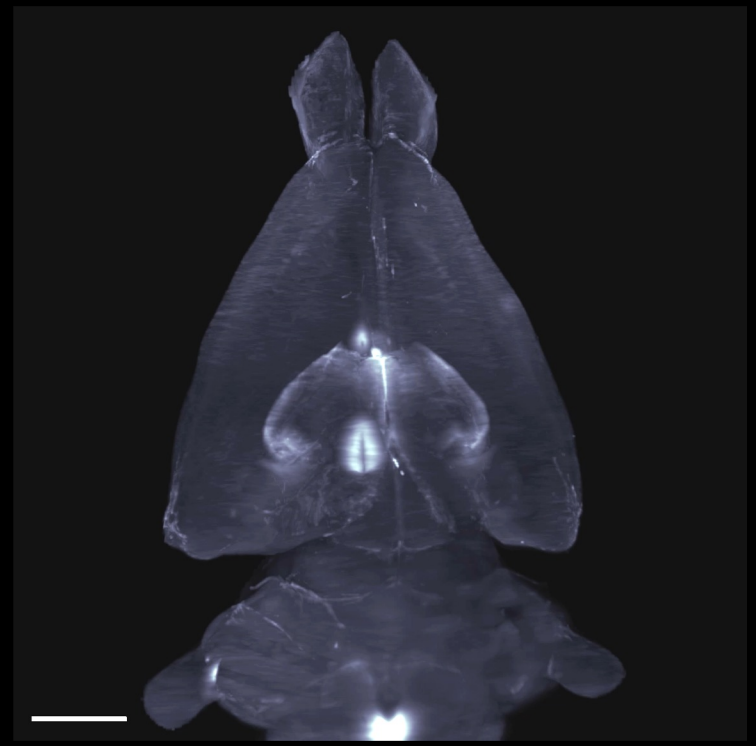
Control IgG



ATV with TfR



ATV with CD98hc



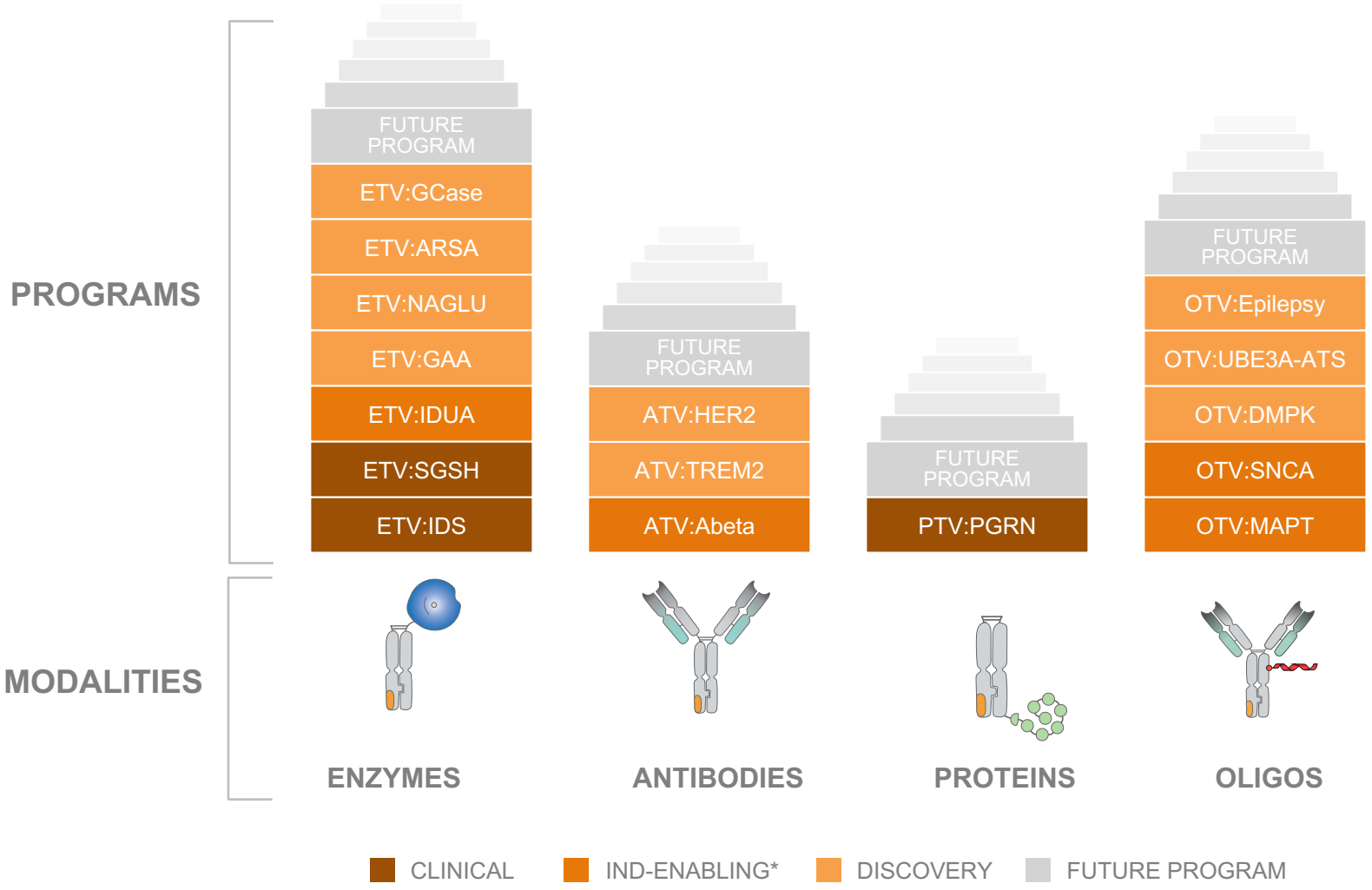
Tissue cleared brain movies

We continue to invent differentiated BBB-crossing technologies that have the potential to optimize the target space

DeepPiction
INTELLIGENCE IN MEDICINE

DRIVING SUSTAINABLE VALUE CREATION WITH THE TV TECHNOLOGY

TRANSPORT VEHICLE (TV) PROGRAMS AND MODALITIES TARGETING THE TRANSFERRIN RECEPTOR (TfR)



- Each TV modality is a platform opportunity
- Current focus on neurodegeneration and lysosomal storage diseases
- Future opportunities in oncology, infectious diseases, neuropsychiatry and pain
- New BBB receptors (CD98hc) further optimize the target space

*Includes programs planned to enter IND-enabling studies

PEAK 1
Current Clinical Pipeline

FOCUS ON CLINICAL EXECUTION AND COMMERCIAL READINESS

Three Late-Stage Clinical Trials

COMPASS

- Tividenofusp alfa (DNL310, ETV:IDS)*
- MPS II (Hunter syndrome)
- Complete enrollment in Phase 2/3 COMPASS in 2024

Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

- DNL343 (eIF2B activator)*
- Amyotrophic lateral sclerosis (ALS)
- Complete enrollment in Phase 2/3 HEALEY in 2024

Luma 201 STUDY

- BIIB122/DNL151 (LRRK2 inhibitor)
- Parkinson's disease
- Phase 2b LUMA study enrolling

Biogen

 *Denali-led programs covered in more detail in this presentation

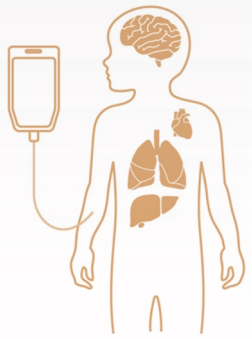
ENZYME TRANSPORT VEHICLE (ETV) FRANCHISE OPPORTUNITY

Lysosomal Storage Diseases (LSDs)

- Monogenic diseases (enzyme deficiency)
- 30,000 people with LSDs worldwide
- High likelihood (~90%) of historical ERT approvals[1]
- Up to $1B per indication[2]

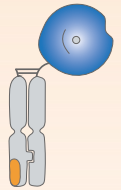
Large Unmet Need to Treat CNS Manifestations

- Approved ERTs partially address somatic symptoms and do not address CNS symptoms of LSDs
- Unmet need for ERTs that can treat body and brain



ETV Has the Potential to Treat the Body and Brain

- DNL310 clinical proof of concept achieved in MPS II[3]
- Apply learnings to accelerate development in other LSDs[4]

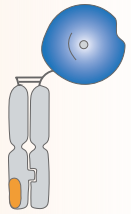


MPS IIIA DNL126 ETV:SGSH	PD, Gaucher ETV:Gcase	MLD ETV:ARSA
MPS IIIB ETV:NAGLU	MPS I ETV:IDUA	POMPE ETV:GAA

1. Denali estimates based on historical approvals of ERTs without a blood-brain crossing technology and designed to treat somatic manifestations of LSDs; **2.** Denali estimates of potential peak sales; **3.** Includes interim biomarker and other data from open-label Phase 1/2 study of DNL310 (ETV:IDS); 4. DNL310 (ETV:IDS) and DNL126 (ETV:SGSH) are in clinical development; other ETV programs are in earlier stages of development; **ERTs** – Enzyme Replacement Therapies; **CNS** – Central Nervous System; **ETV:IDS** – Enzyme Transport Vehicle: Idursulfase

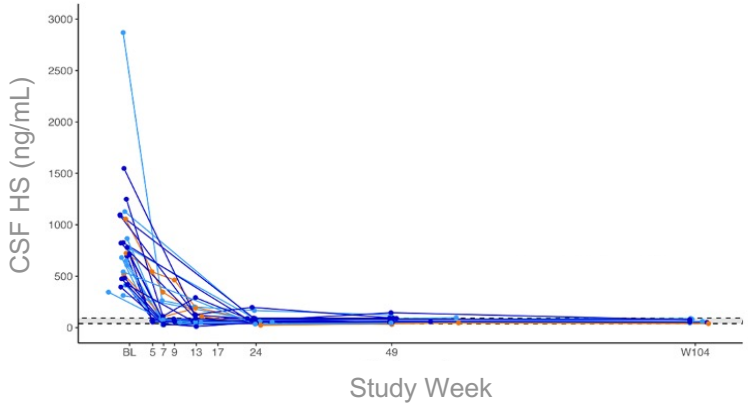
DNL310 (ETV:IDS): KEY INTERIM, OPEN-LABEL, PHASE 1/2 RESULTS

- Generally well tolerated; safety profile based on 33 participants (median treatment duration 100 wks)
- First and only therapy in development shown to normalize CSF HS and reduce NfL in MPS II
- Improvement in measures of hearing and behaviors most important to families



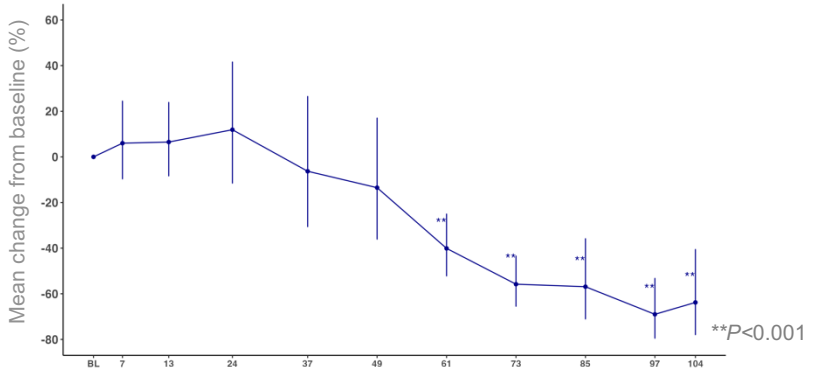
Normalization of CSF HS

Biomarker of neuronopathic disease



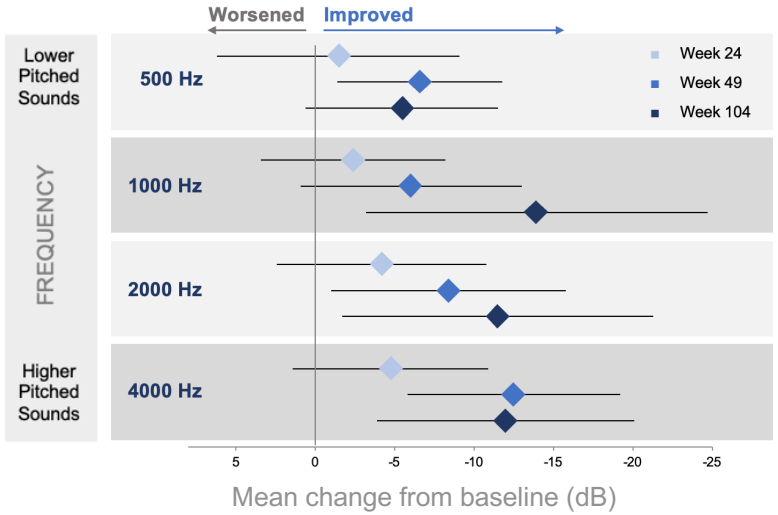
Robust Reduction in Serum NfL

Biomarker of neuronal damage



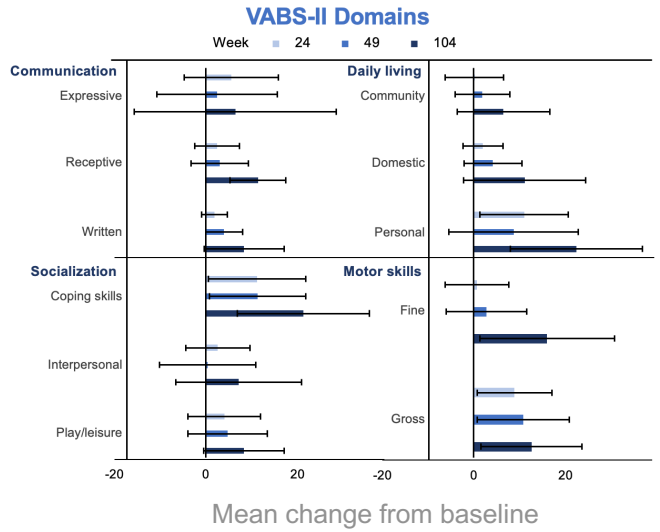
Improvement in Hearing

Auditory brainstem response



Improvement in Adaptive Behavior

VABS-II raw score



All bars represent 95% confidence intervals
Source: Muenzer, J et al. 2024 WORLD*Symposium*™

DEVELOPMENT AND REGULATORY PATH FOR DNL310 IN MPS II

Global Phase 1/2 (enrolling)

- Open-label study
- Up to 18 years of age
- 14 participants with more than 2 years of DNL310 treatment[1]
- Measuring biomarkers, safety and exploratory clinical outcomes

>40
participants[2]

Global Phase 2/3 (enrolling)

- Randomized, double blind, controlled study
- Ages ≥2 to <6 y.o. (Cohort A, neuronopathic)
- ≥6 to <17 y.o. (Cohort B, non-neuronopathic)
- Co-primary endpoints: CSF HS and VABS-III
- Peripheral endpoints: liver/spleen volume, 6MWT, ABR and others

54
participants[2]
COMPASS

Regulatory Path and Target Indication

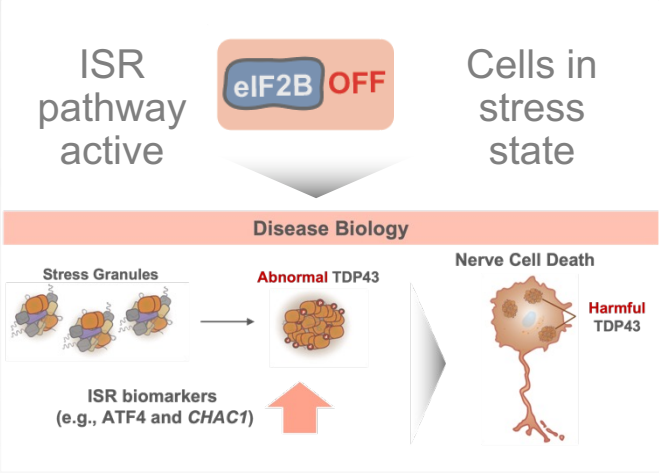
- Executing the Phase 2/3 COMPASS study; continue to generate Phase 1/2 data
- Ongoing regulatory interactions; prepared to pursue a faster path to approval
- Target indication – the full MPS II phenotype spectrum

~100
participants[2]
robust data package

1. As of March 2023 data cut; 2. Expected number of participants

DNL343 (eIF2B AGONIST): AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Targeting the Integrated Stress Response (ISR)

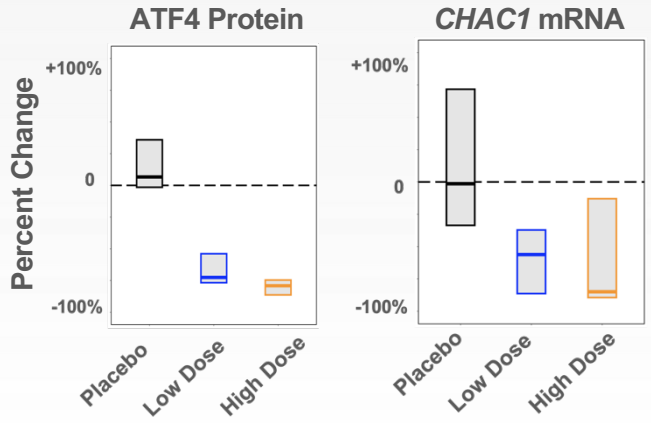


- ISR is implicated in stress granule formation and TDP43 aggregation, a hallmark of ALS
- DNL343 is designed to inhibit ISR & slow disease progression

DNL343 Inhibits the ISR

- Phase 1/1b studies in 95 healthy and 27 participants with ALS
- DNL343 was generally well tolerated
- DNL343 inhibited ISR biomarkers (shown in blood)

ALS Participant Data



Phase 2/3 HEALEY Study

Healey & AMG Center
Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital

- Platform trial in ALS
- 240 participants expected to enroll in DNL343 regimen
- Randomized 3:1 (DNL343:placebo)
- Primary endpoint ALSFRS-R at 24 weeks

Source: Sun L, et al., AAN abstract P8.8.010, 2023; ALSFRS-R, ALS Functional Rating Scale-Revised

PEAK 2
Focus on TV Programs in Alzheimer's Disease and Parkinson's Disease

OPPORTUNITY IS BREAKING OPEN IN ALZHEIMER'S DISEASE (AD)

Recent Advances Bring New Hope to People Living with AD

- New anti-amyloid therapies are the first disease modifying treatments
- New biomarkers and imaging tools
- New targets show promise in clinical testing, e.g., tau
- TfR-based targeting technology shows promise in clinical testing

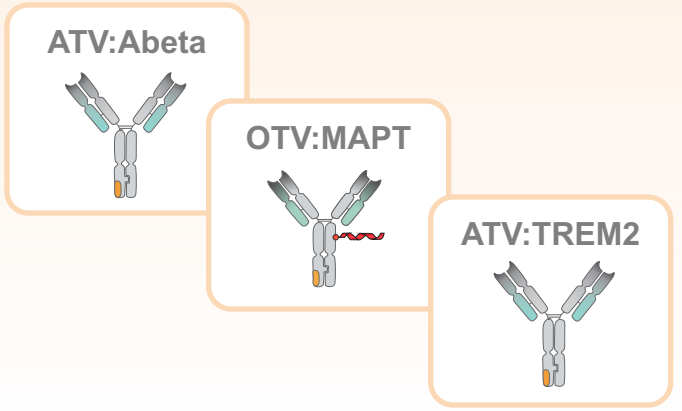
Opportunity for New Therapies to Improve Efficacy and Safety

Unmet Needs Include:

- Faster plaque reduction
- Lower doses
- More convenient delivery
- Reduced risk of ARIA

Denali is Positioned to Deliver the Next Generation of AD Therapies

- Discovery programs for multiple AD targets
- Best in class opportunities to improve efficacy and safety



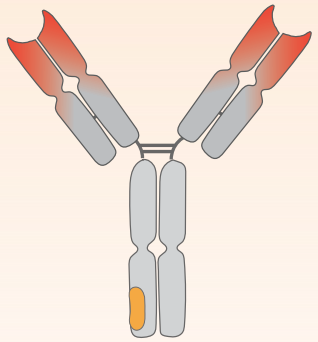
55 Million People Live with AD and Other Forms of Dementia

We Aim to Deliver Effective Medicines with Broad Societal Impact

TfR, transferrin receptor; ARIA, amyloid-related imaging abnormalities

ATV:Abeta: SUPERIOR AMYLOID PLAQUE BINDING AND REDUCTION

Optimally Engineered to Reduce Plaque & Improve Safety



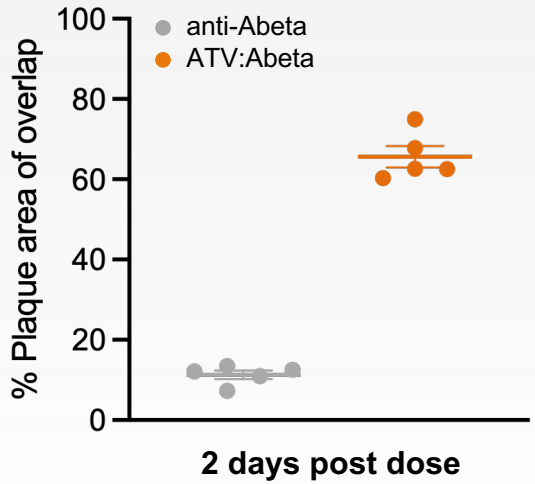
ATV:Abeta

Biogen leads development and commercialization

Greater Plaque Binding with ATV:Abeta

Aβ and huIgG colocalization

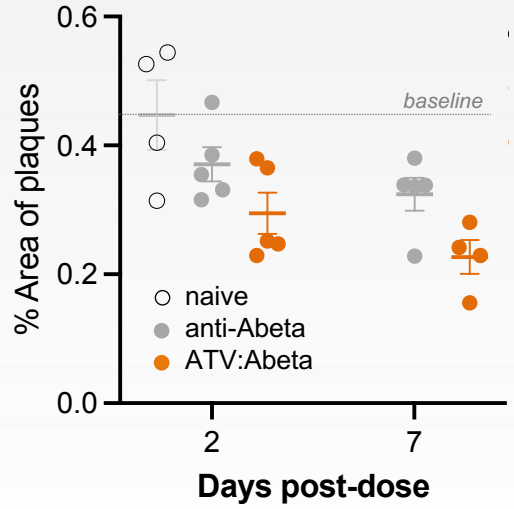
Single, mid dose, APP^{SAA} KI[1]



Greater Plaque Reduction with ATV:Abeta

Aβ Plaque Load

Single, mid dose, APP^{SAA} KI



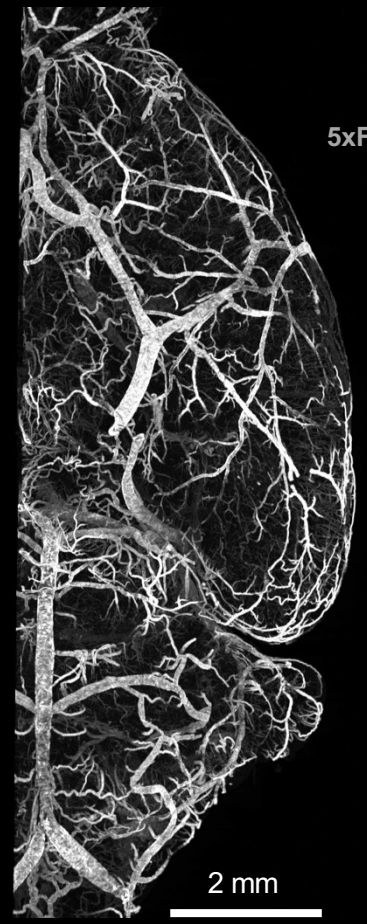
ATV:Abeta may enable a wider therapeutic window in treating AD as compared to conventional anti-Abeta therapy

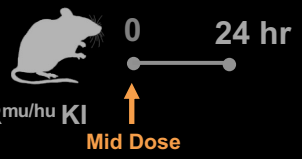
1. Xia et al., *Molecular Neurodegeneration* 2022; **ATV** – Antibody Transport Vehicle; **Aβ** – Amyloid beta; **huIgG** – Human immunoglobulin G

3D IMAGING SHOWS SUPERIOR AND DIFFERENTIATED ATV:Abeta BIODISTRIBUTION

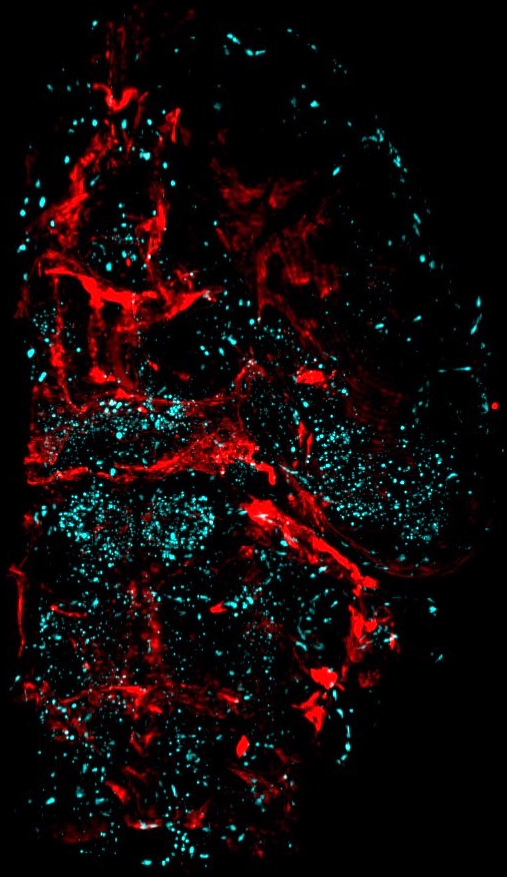
gubra

Brain Arteries





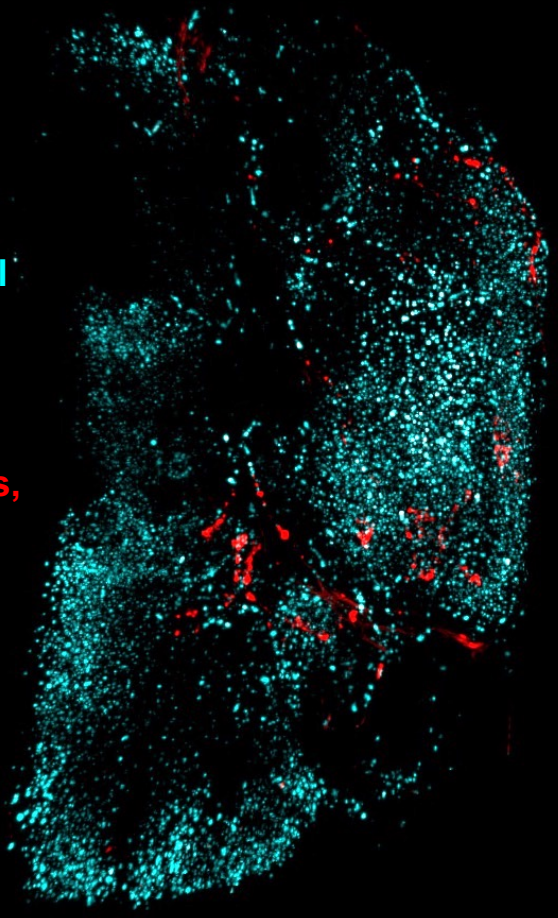
Anti-Abeta



huIgG, parenchymal (on plaques)

huIgG, associated with perivascular spaces, CSF cisterns, leptomeninges

ATV:Abeta



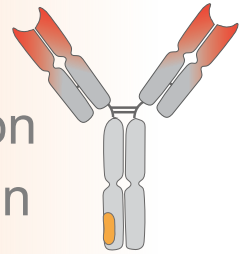
ATV leads to higher parenchymal plaque binding and lower perivascular localization compared to standard antibody

ATV:Abeta HAS POTENTIAL TO REDUCE ARIA RISK IN AD TREATMENT

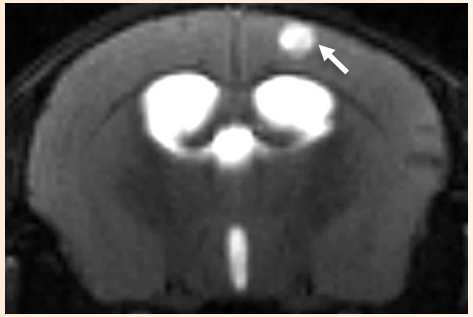
Optimally Engineered to Reduce Plaque & Improve Safety

Preclinical profile:

- Superior plaque reduction
- Less vascular localization
- Fewer ARIA events

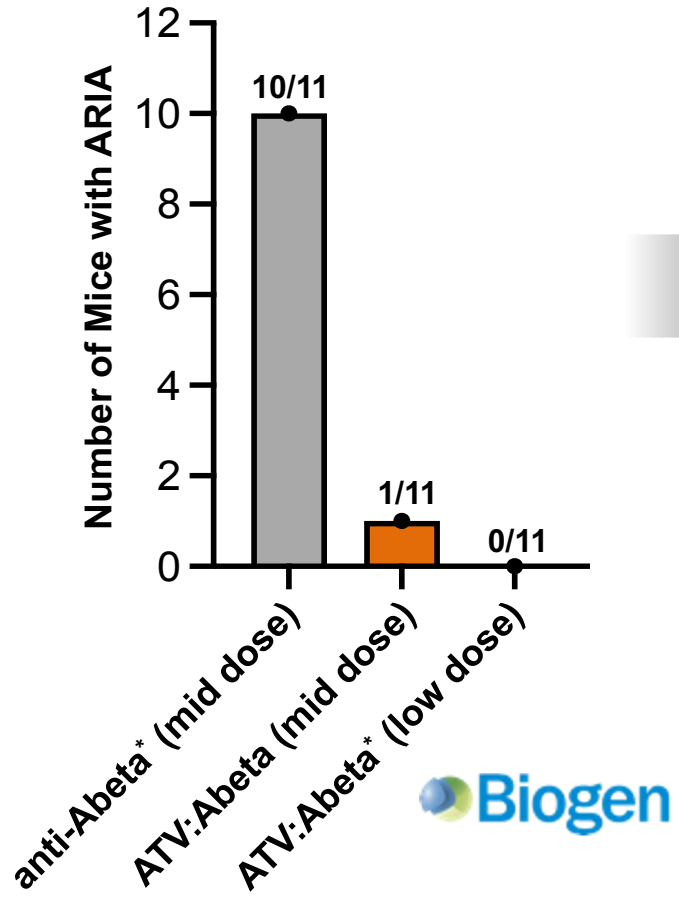


ARIA as Seen in a Mouse Model of AD



ARIA-like MRI events

Weekly dosing x 11 wks, 5xFAD TfR$^{mu/hu}$ KI



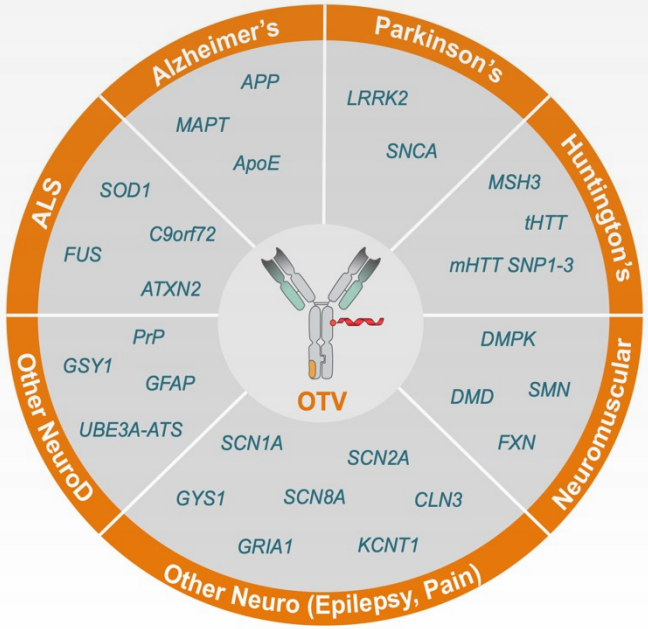
Fewer/no ARIA events observed with ATV:Abeta compared to a conventional Abeta antibody

Source: Biogen data on file; *At experimental doses selected to yield equivalent brain exposure and plaque reduction
ARIA – amyloid related imaging abnormalities; **MRI** – magnetic resonance imaging

OLIGONUCLEOTIDE TRANSPORT VEHICLE (OTV) OPPORTUNITY

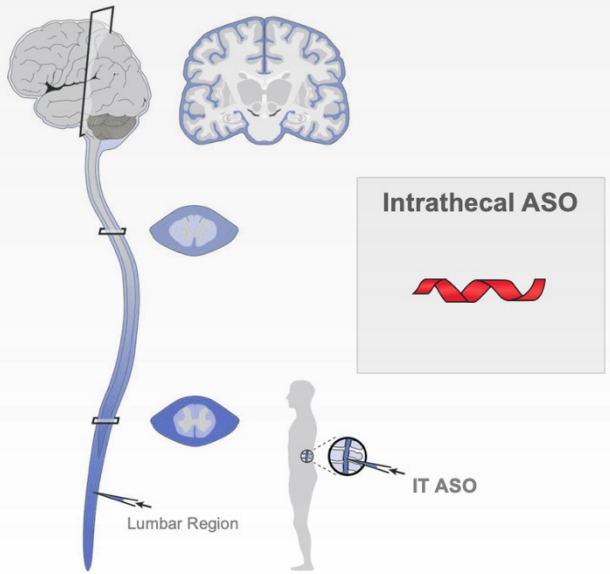
Oligonucleotide Therapies Enable New Disease Targets

- Oligonucleotides open a large potential indication space in neurodegeneration and beyond



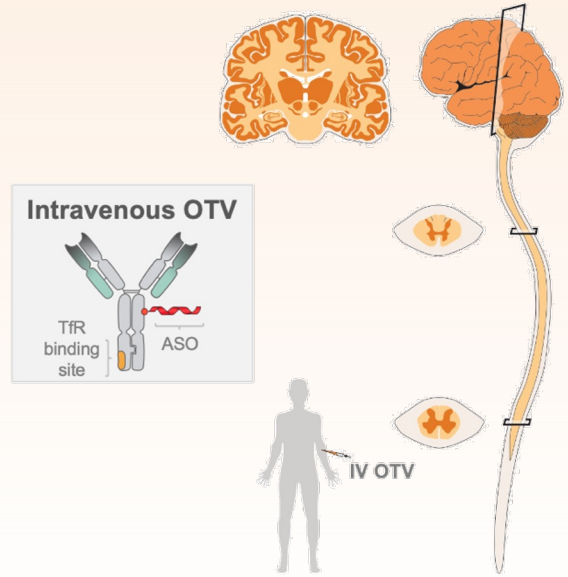
Opportunity for Improving Oligo Delivery and Therapeutic Profile

- Limited biodistribution with intrathecal ASO
- Sharp gradient limits biodistribution in brain and along the spinal cord



OTV has Potential to Revolutionize Oligos for Treating CNS Disease

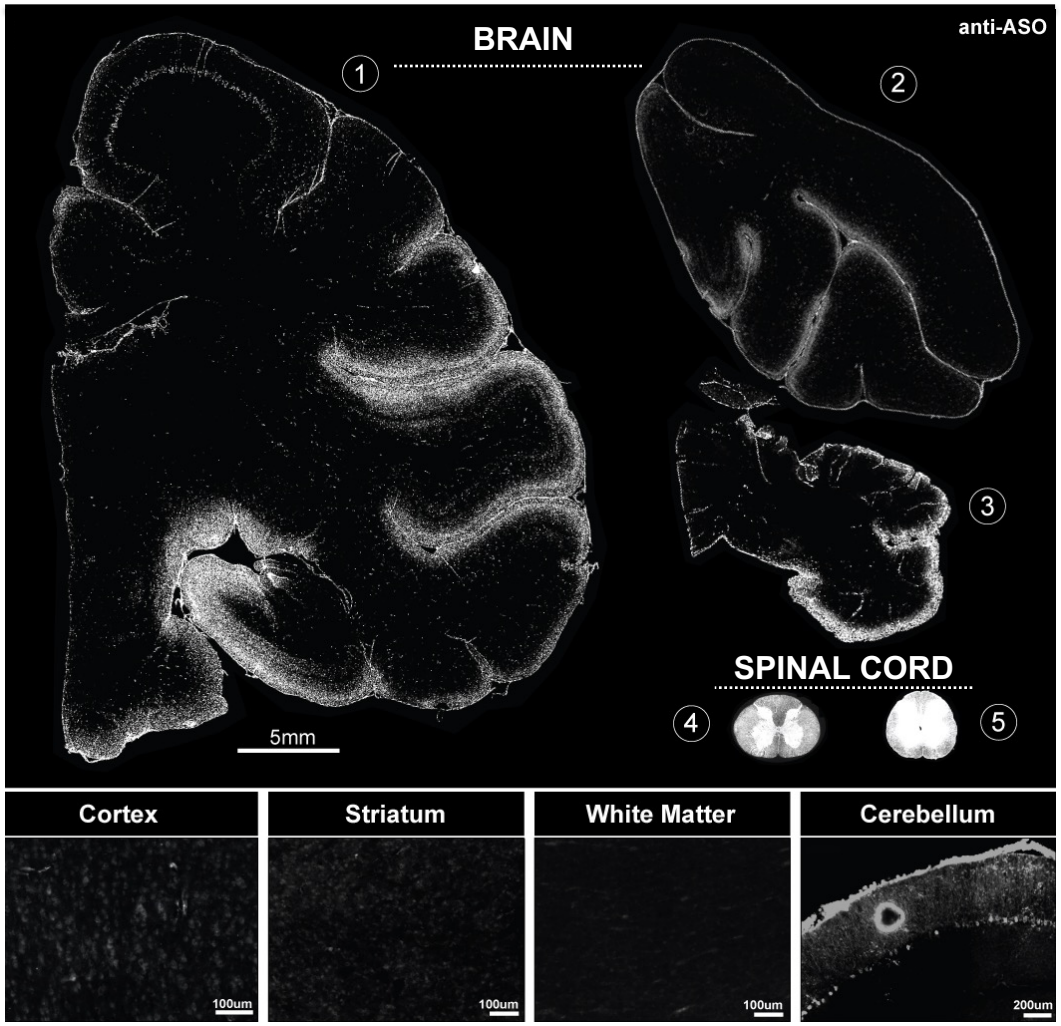
- Homogenous biodistribution of ASOs across brain regions
- Superior knockdown of target gene expression across all brain regions and cell types



OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

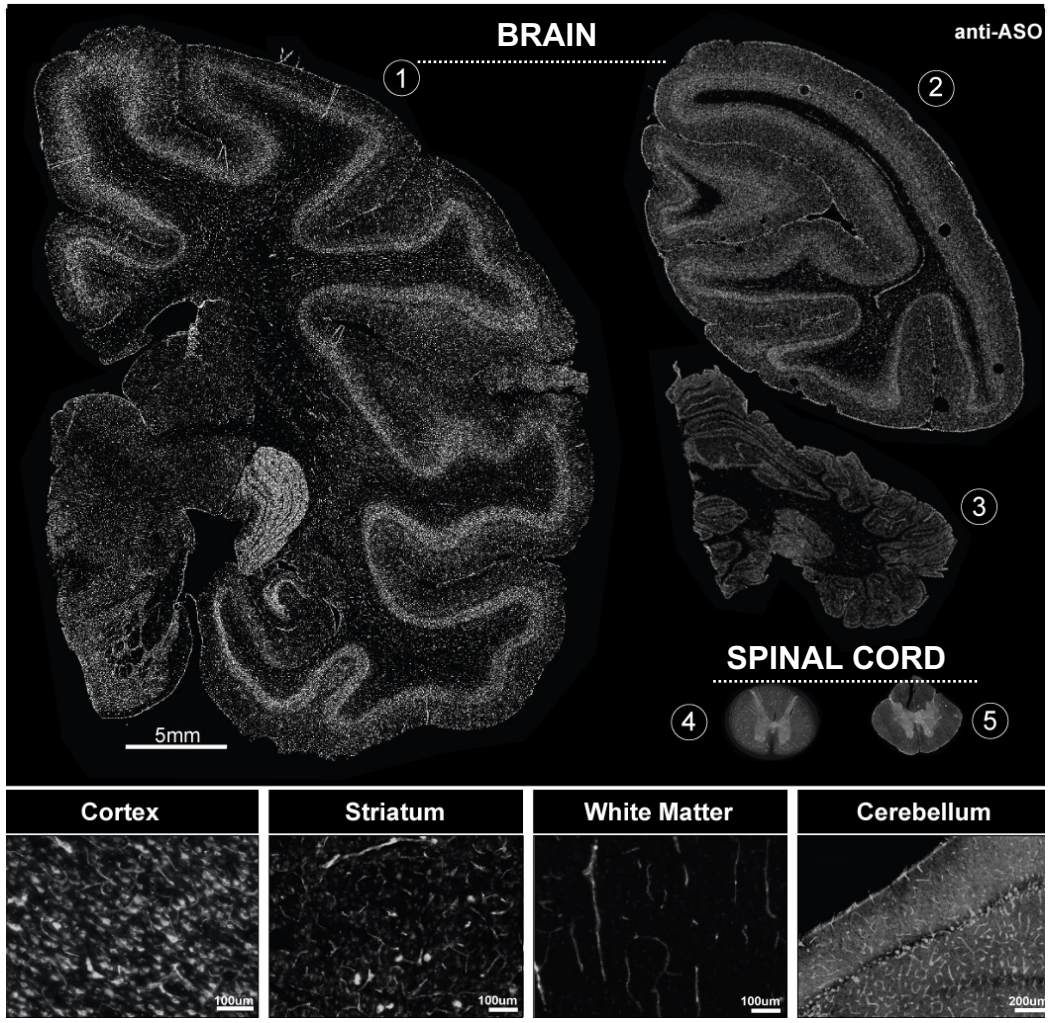
NAKED ASO INTRATHECAL (IT) DELIVERY

Limited ASO Biodistribution



OTV INTRAVENOUS (IV) DELIVERY

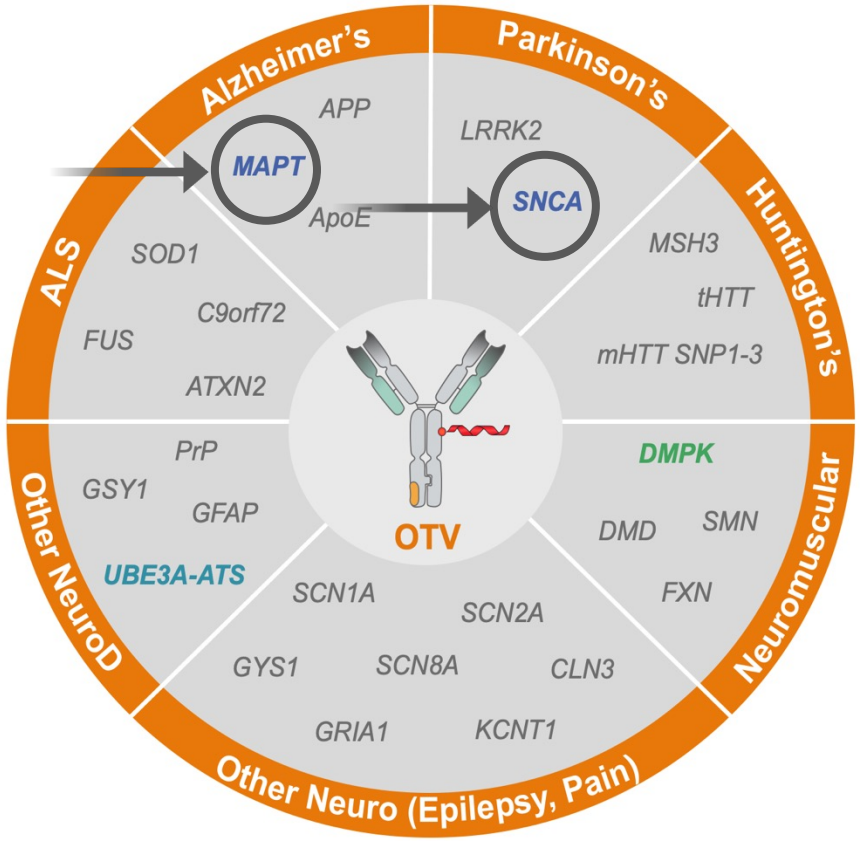
Widespread ASO Biodistribution



(1) Full Hemibrain Section (2) Posterior Cortex overlaying Cerebellum (3) Cerebellum (4) Cervical Spinal Cord (5) Lumbar Spinal Cord

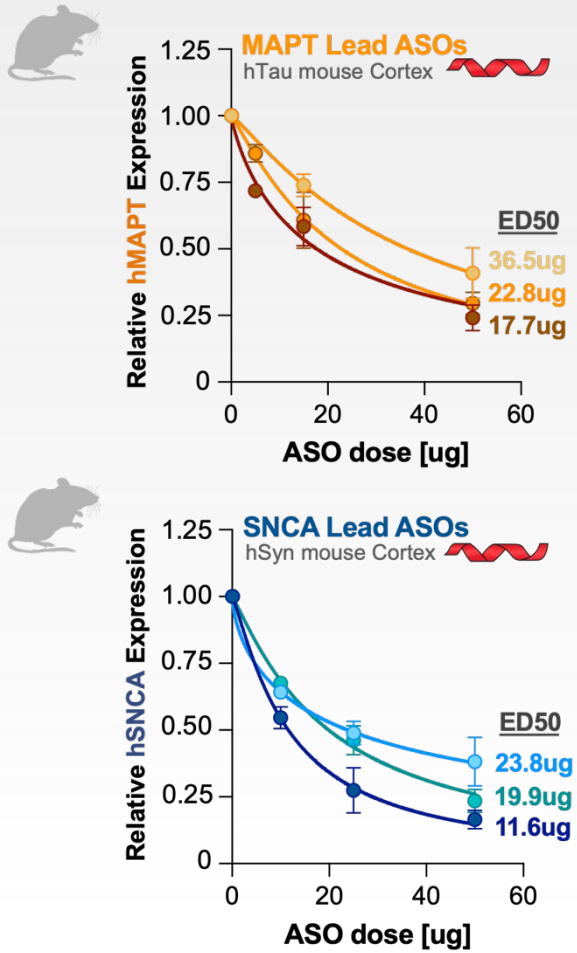
 Barker et al. 2023 *BioRxiv*

MAPT AND SNCA ARE LEAD IND-ENABLING OTV PROGRAMS



- MAPT (tau) and SNCA (α synuclein) are lead OTV programs in IND-Enabling stage
- Discovery programs include UBE3A-ATS, DMPK, and an epilepsy target

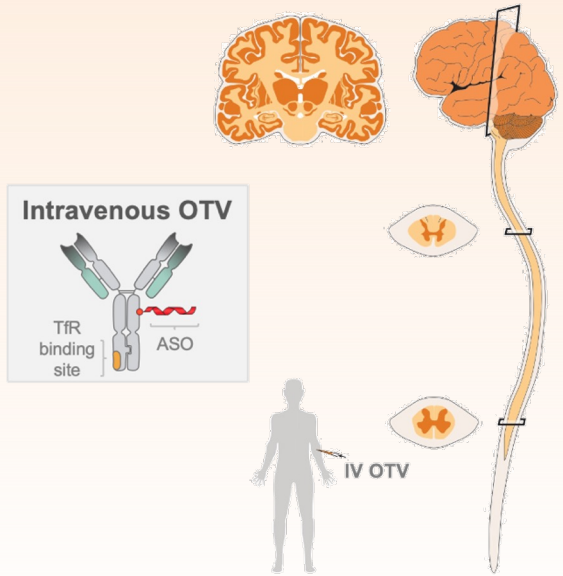
Highly Potent ASO Leads



ICV bolus in transgenic mice, 1.5wk after dose
Data shown as Mean +/- SEM; n=2-5/group
Relative gene expression normalized to Gapdh (housekeeping gene); expression relative to Vehicle Control

Optimize on OTV Format

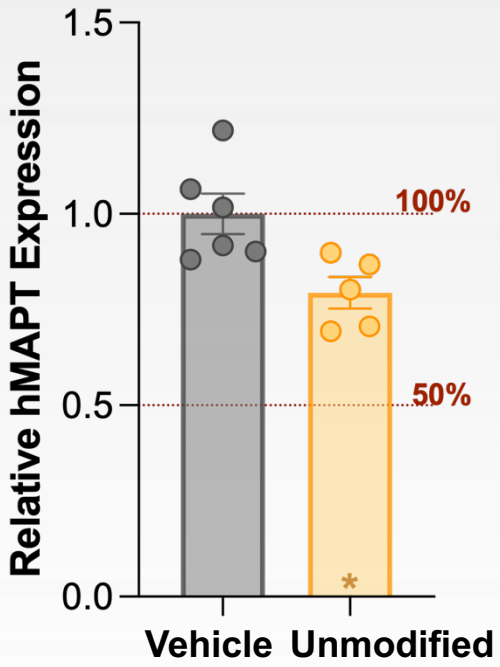
- Enables brain delivery of ASOs via intravenous (IV) administration



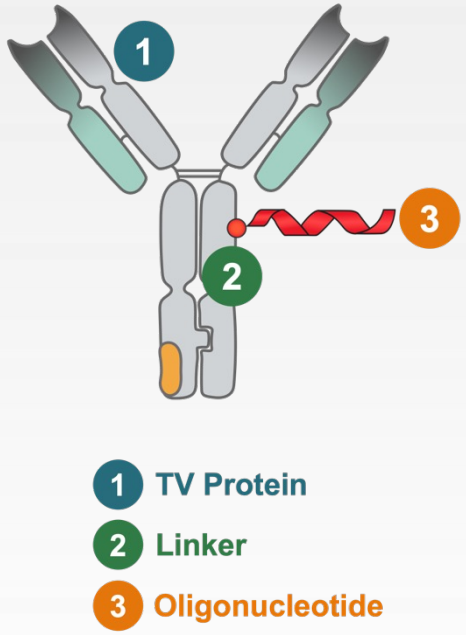
 ASO – antisense oligonucleotide

OPTIMIZING GENE KNOCKDOWN IN BRAIN WITH OTV PLATFORM

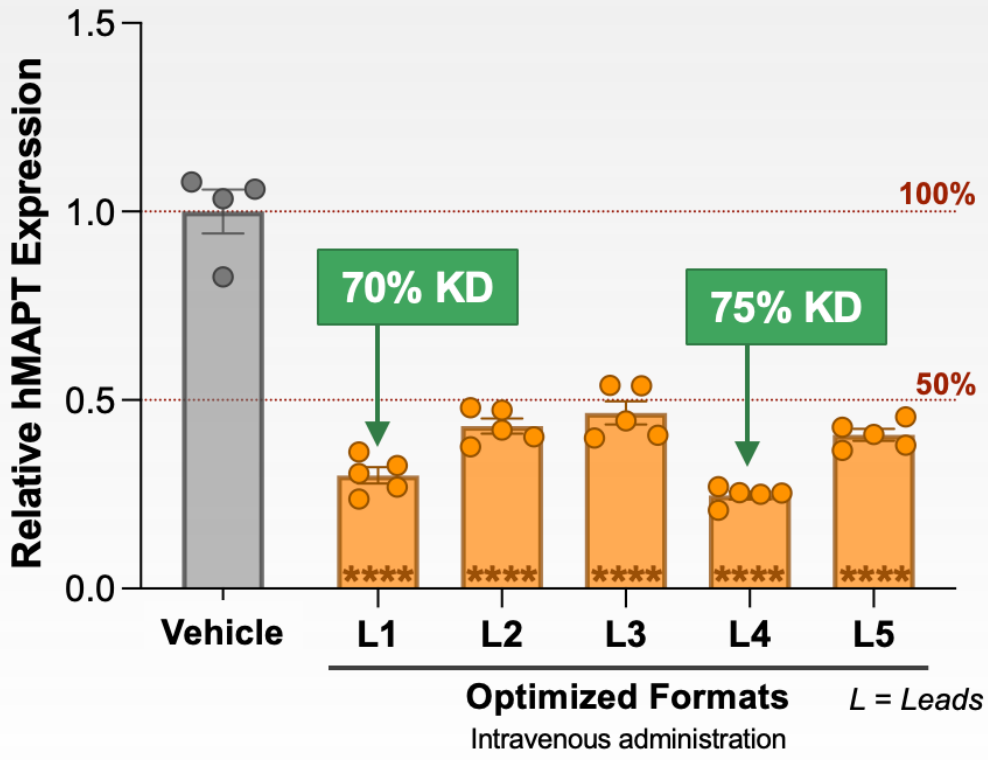
Unmodified OTV Format



Optimization of OTV Format



OTV Optimization Enables Enhanced Brain MAPT Knockdown



hTau x TfR$^{mu/hu}$ KI mice dosed IV at 1mg/kg ASO eq. on d1, d8, d15, d22; Collect d29. Data shown as Mean +/- SEM; Student t-test (left), One-way ANOVA w/ Dunnett's multiple comparisons test (right)
Relative gene expression normalized to Gapdh (housekeeping gene); expression relative to Vehicle Control
KD – knockdown

LOOKING AHEAD

POSITIONED TO DELIVER ON OUR GOALS

PLATFORM

- Proven and **expanding Transport Vehicle (TV)** platform for brain delivery

PEAK 1

- **Commercial readiness** for MPS II and ALS
- **Clinical execution** on PD, FTD-GRN, and MPS IIIA programs

PEAK 2

- Focus on **solving AD and PD** with TV-enabled programs

Capitalized to Achieve Value Creating Milestones in Peaks 1 & 2

$1.03 B (as of 12/31/23) + $500 M Anticipated Proceeds from PIPE with Runway into 2028

2024 MILESTONES

Expected 2024 Key Milestones for Denali-Led Programs

PROGRAM	MILESTONE	TIMING
DNL310 (ETV:IDS)	• Additional interim Phase 1/2 data at WORLD	Feb 4-9
	• Additional Interim Phase 1/2 data at SSIEM	Sept 3-6
	• Complete enrollment of global Phase 2/3 COMPASS study in MPS II	2024
DNL593 (PTV:PGRN)	• Continue Part B of Phase 1/2 study in FTD-GRN	2024
DNL126 (ETV:SGSH)	• Preclinical data at WORLD	Feb 4-9
	• Initiate dosing in Phase 1/2	Early 2024
	• Biomarker proof of concept and safety data from Phase 1/2 study in MPS IIIA	Late 2024
DNL343 (eIF2B activator)	• Complete enrollment of Regimen G in Phase 2/3 HEALEY ALS Platform Trial	2024
OTV:MAPT	• IND enabling studies	2024
OTV:SNCA	• IND enabling studies	2024

Expected 2024 Key Milestones for Partner-Led Programs

PROGRAM	MILESTONE	STRATEGIC PARTNER
BIIB122/DNL151 (LRRK2 inhibitor)	• Continue Phase 2b LUMA study in early-stage PD	Biogen
ATV:Abeta	• IND-enabling studies	Biogen
SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor)	• Topline results of the Phase 2 HIMALAYA study in ALS (1H 2024)	sanofi
	• Continue Phase 2 K2 study in MS	
SAR443122/DNL758 (Peripherally-restricted RIPK1 inhibitor)	• Continue Phase 2 UC study	sanofi

Early 2024 – Q1/Q2; **Late 2024** – Q3/Q4

OUR PURPOSE: DEFEAT DEGENERATION

LYSOSOMAL STORAGE DISEASES

Dominic, living with MPS II

ALS/FTD

Seth, living with ALS

PARKINSON'S DISEASE

Allan, living with PD

ALZHEIMER'S DISEASE

Denali Team at AD Walk 2023

Denali

The name captures the formidable challenges in fighting neurodegenerative diseases but also the unprecedented opportunities enabled by new scientific insights and technologies. With a relentlessly committed team and rigorous effort, breakthroughs appear to be within reach.

ALS – amyotrophic lateral sclerosis; **FTD** – frontotemporal dementia

THANK YOU

www.denalitherapeutics.com