DEFEAT DEGENERATION

CORPORATE OVERVIEW
NOVEMBER 2024




DISCLAIMERS

Forward-Looking Statements. This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements do not relate strictly to historical or current facts and they may be accompanied by such words as “anticipate,” “believe,” “could,” “estimate,” “expected,” “forecast,” “intend,” “may,” “plan,” “potential,” “possible,” "future," “will” and other words and terms of similar meaning. All statements other than statements of historical facts contained in this presentation, including, without limitation, statements regarding future results of operations and financial position of Denali Therapeutics Inc. (“Denali” or the “Company”); Denali’s business strategy and business plans, expected progress and expansion, and expected key milestones for Denali's therapeutic portfolio in 2024 and beyond; Denali’s ability to execute on its tailored commercial strategies and accelerate commercial launch readiness; expectations relating to the potential for Denali's product candidates to treat various neurodegenerative diseases including MPS I, MPS II (Hunter Syndrome), MPS IIIA (Sanfilippo Syndrome), ALS, MS, PD, AD, FTD-GRN, UC, and related peripheral inflammatory diseases; planned preclinical studies and clinical trials and the expectations regarding the timing and availability of results and data from such studies and trials; plans, timelines, expectations, breadth of indications, and current and future therapeutic and commercial opportunities related to Denali's Transport Vehicle (TV) platform, including its Enzyme Transport Vehicle (ETV), Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV), and Oligonucleotide (OTV) technologies, and other programs enabled by these platforms, as well as potential targets and differentiation strategies; plans, timelines, and expectations relating to DNL310, including the timing and availability of data from the ongoing Phase 1/2 study and enrollment in the Phase 2/3 COMPASS study, as well as the timing of regulatory approval; plans, timelines, and expectations related to DNL343, including enrollment in the ongoing Phase 2/3 HEALEY ALS platform trial; plans, timelines, and expectations relating to ATV:Abeta, its therapeutic potential, and its potential impact on ARIA risk; plans, timelines, and expectations related to Denali's OTV programs, including OTV:MAPT and OTV:SNCA; plans, timelines, and expectations related to DNL126, including the timing and availability of data from the Phase 1/2 study; plans and expectations regarding DNL593; plans, timelines, and expectations relating to the Biogen-led development of DNL151, including enrollment in the Phase 2b LUMA trial; Denali's and Sanofi's plans, timelines, and expectations related to DNL788 and DNL758; the potential benefits and results of the collaborations with Denali’s partners, including Biogen, Sanofi, and Takeda, and expected milestone payments; Company priorities, regulatory approvals, timing and likelihood of success and expectations regarding collaborations; expected use of proceeds from Denali's PIPE offering; and plans and expectations regarding Denali's global organization and clinical operations, the expected timing and likelihood of success of its commercial growth, and the potential value of Denali's programs, are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events.

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OUR PURPOSE: CROSS BARRIERS AND 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

OUR TEAM AND VISION

SCIENTISTS AND DRUG DEVELOPERS

~400 BASED IN SOUTH SAN FRANCISCO, SLC & ZURICH

BUILDING A GLOBAL BIOTECHNOLOGY COMPANY

- **Scale** to successfully discover, develop, and ultimately commercialize therapeutics
- **Well-capitalized** (raised >$3B) through equity sales and strategic partnerships

SENIOR LEADERSHIP

RYAN J WATTS, PHD – CEO
- Previously built and led Genentech's neuroscience strategy, portfolio and research department
- Stanford, PhD Biological Sciences

ALEXANDER SCHUTH, MD – COO & CFO
- Formerly head of Genentech's BD groups for neuroscience and discovery technologies; former Merrill Lynch ECM (London)
- Charite (Berlin) MD, Wharton MBA

JOE LEWCOCK, PHD – CSO
- Formerly director of the department of neuroscience, Genentech
- Johns Hopkins PhD, Salk Institute Postdoc

CAROLE HO, MD – CMO
- Formerly VP Early Clinical Development, Genentech
- Previously medical director at J&J and staff neurologist at Stanford
- Cornell MD, Harvard Neurology Residency

DANA ANDERSEN, PHD – CTMO
- Formerly VP of Global Technical Development Project & Portfolio Mgmt Genentech/Roche
- Stanford, PhD ChemEng

CINDY DUNKLE – CPO
- Formerly led HR at Avalanche
- Previously Genentech

KATIE PENG – CCO
- Formerly SVP, Head of OMNI Business Unit, Genentech
- Previously GM of Singapore & Taiwan, Roche
- UC Berkeley BA, Indiana MBA

CHRIS WALSH, PHD, JD –GC
- Previously Genentech
- George Washington, JD
- Univ of Illinois, Chemistry PhD

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
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					
OTV:MAPT	Alzheimer's disease					
OTV:SNCA	Parkinson's disease					
Peripheral Inflammatory Disease						
SAR443122 / DNL758 (RIPK1 inhibitor)	Ulcerative colitis					sanofi

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	**DNL343** **DNL758**	ALS UC
Up to $1B	**DNL310** **DNL126** **DNL593**	MPS II MPS IIIA FTD-GRN

● TV-Enabled ● Small Molecule

Peak 2

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

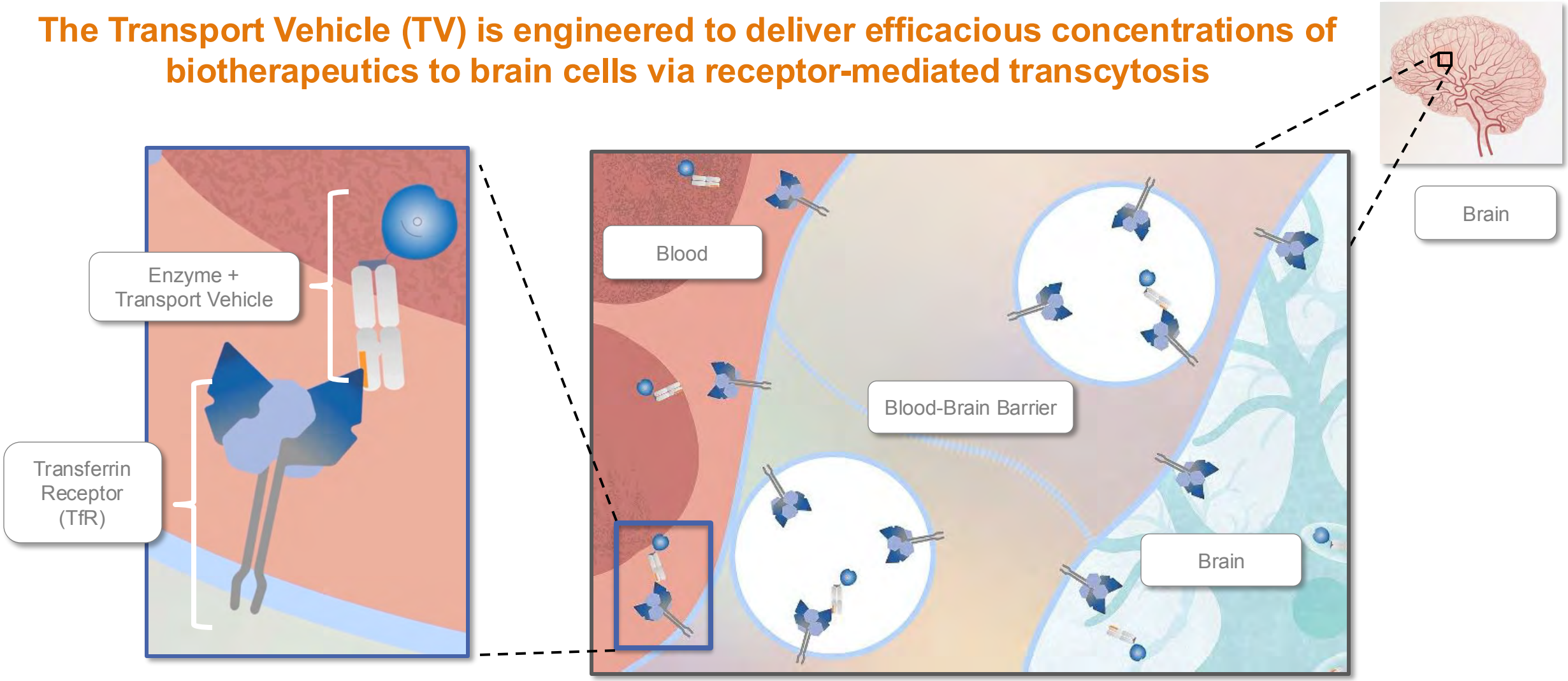
Peak Sales	Program	Indication
>$5B	**ATV:Abeta** **OTV:MAPT** **OTV:SNCA** **ETV:GCase** **ATV:TREM2**	AD AD PD Gaucher/PD AD
$1-5B	**Additional ETV/OTV**	Various
Up to $1B	–	–

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; **UC** – ulcerative colitis; **MPS** – Mucopolysaccharidosis; **FTD-GRN** – Frontotemporal dementia-granulin; **AD** – Alzheimer's disease

ADDRESSING THE CHALLENGE OF DELIVERING THERAPY TO THE BRAIN

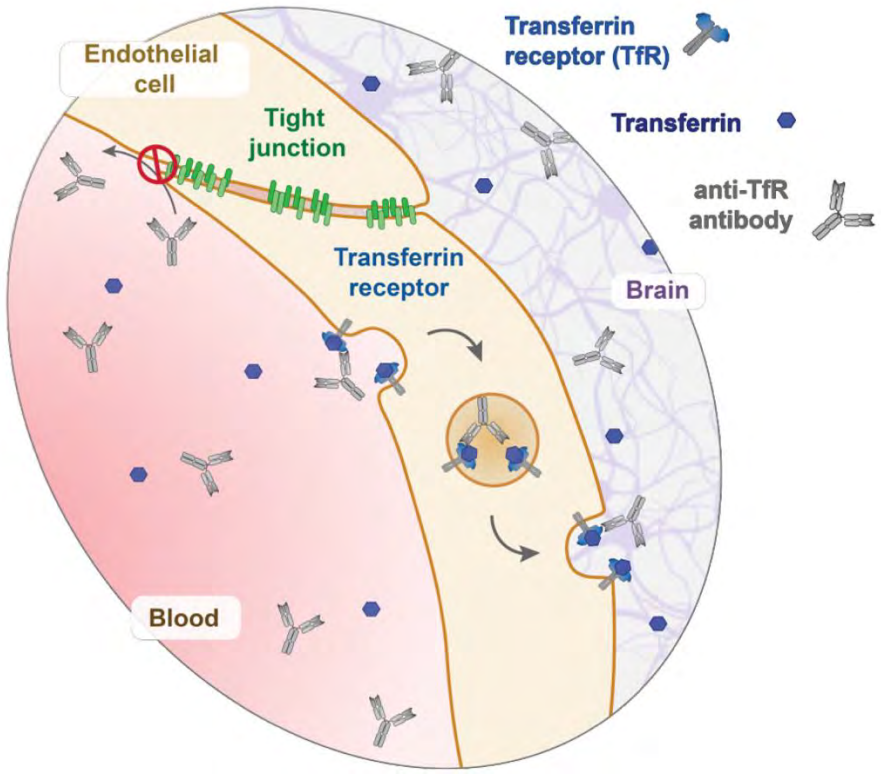
The Transport Vehicle (TV) is engineered to deliver efficacious concentrations of biotherapeutics to brain cells via receptor-mediated transcytosis



https://www.denalitherapeutics.com/patients

LEADERSHIP IN THE BBB DELIVERY SPACE

TV Technology Leverages Receptor Mediated Transcytosis Into the Brain



Transferrin Receptor (TfR)

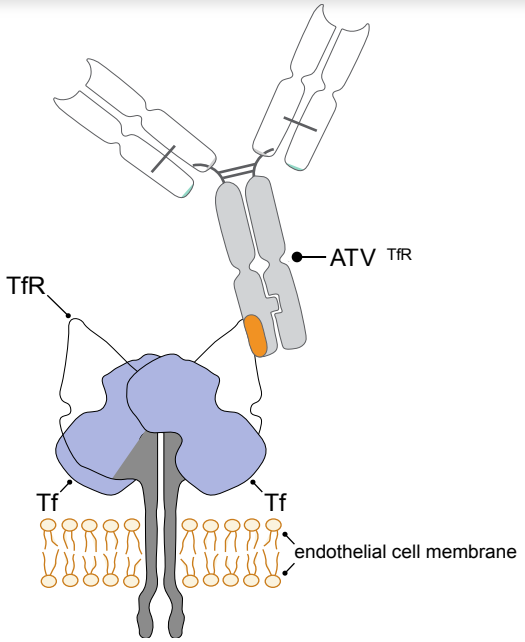
Most Clinically Advanced

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

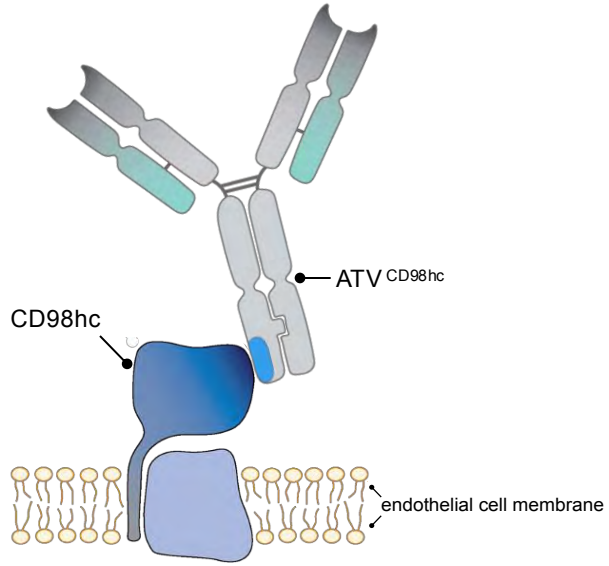
nature communications

Article

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

CD98hc is a target for brain delivery of biotherapeutics

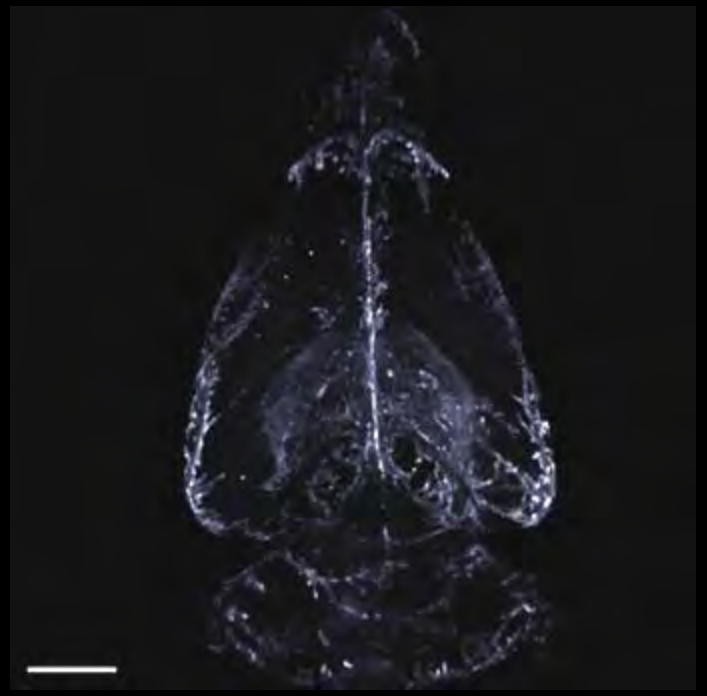
August 2023



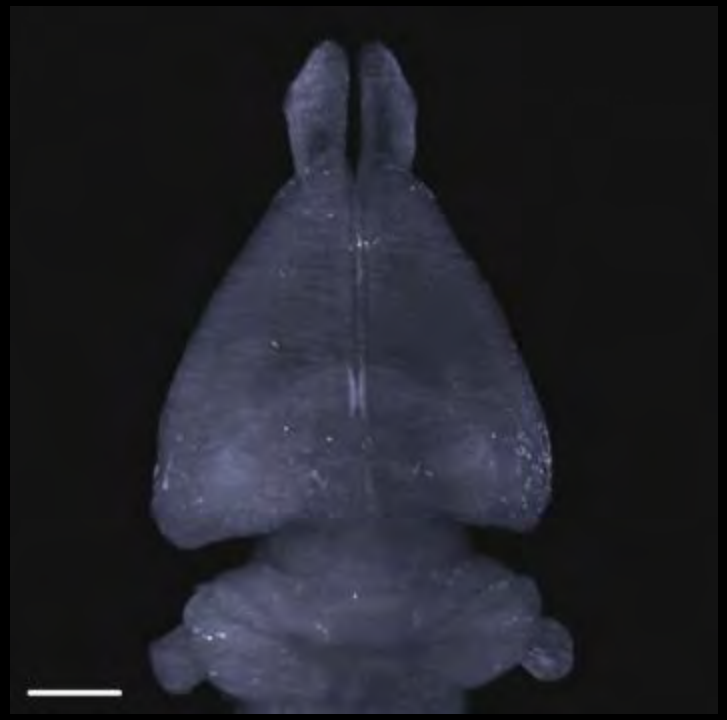
We continue to invent differentiated BBB-crossing technologies that have the potential to optimize the target space

ATV ENABLES BROAD DISTRIBUTION THROUGHOUT THE BRAIN

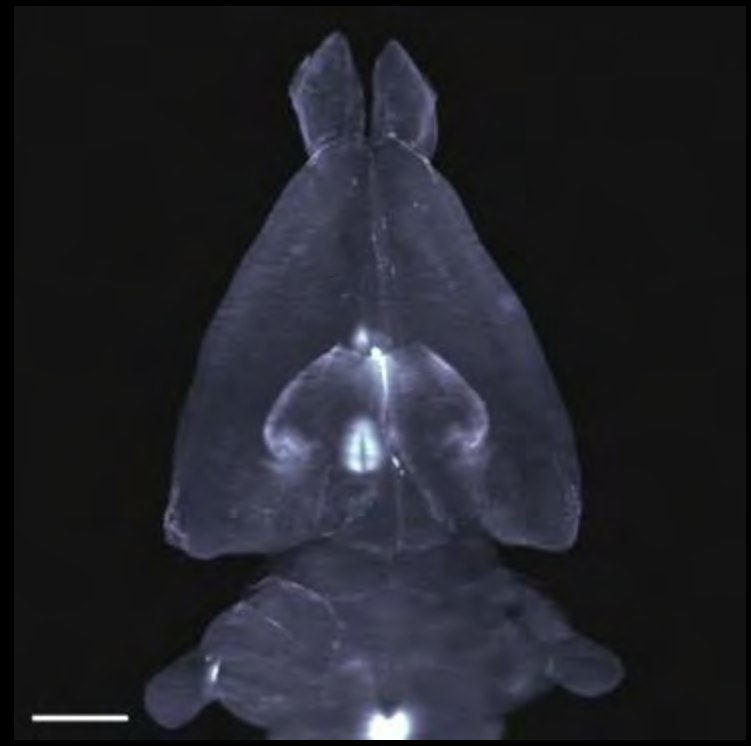
Control IgG



ATV with TfR



ATV with CD98hc



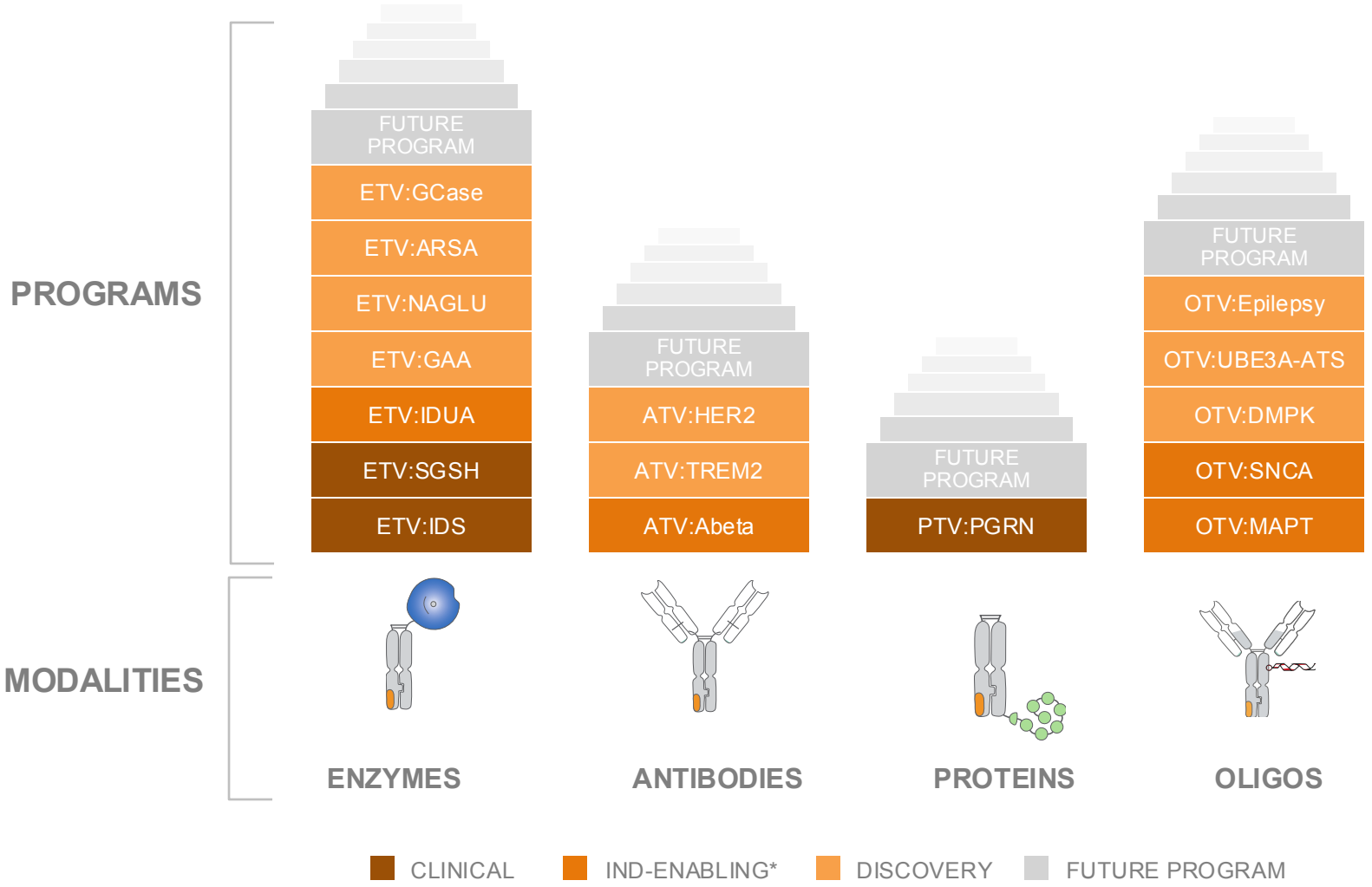
Tissue cleared brain movies

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

DeepPiction

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

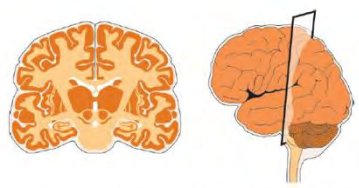
PEAK 1
TV-Enabled Clinical Programs

DEVELOPING A THERAPY FOR MPS II (HUNTER SYNDROME)

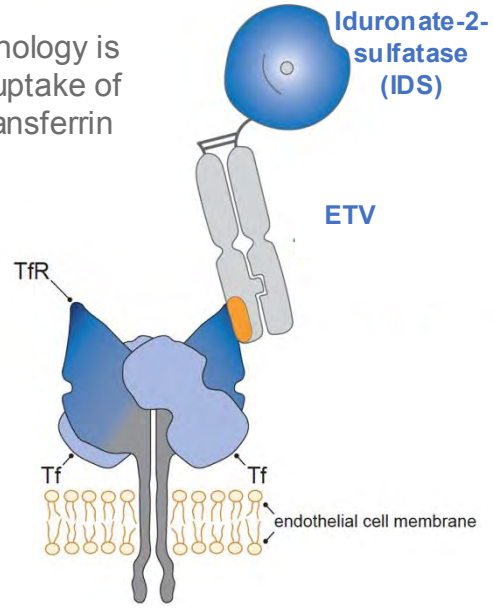
DNL310 (tividenofusp alfa, ETV:IDS) is an investigational iduronate-2-sulfatase (IDS) fusion protein engineered to treat the brain and somatic manifestations of mucopolysaccharidosis type II (MPS II) with a **single weekly IV infusion**

Enzyme Transport Vehicle (ETV)

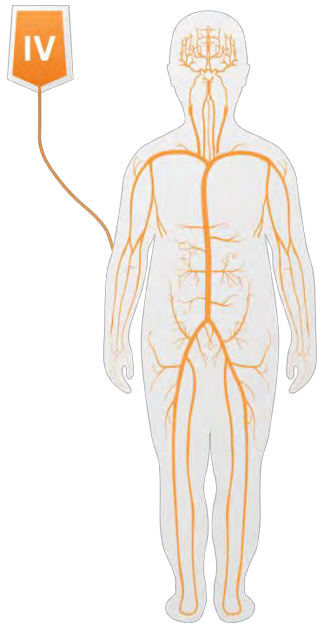
Transport Vehicle (TV) technology is optimized to improve brain uptake of biotherapeutics using the transferrin receptor (TfR)



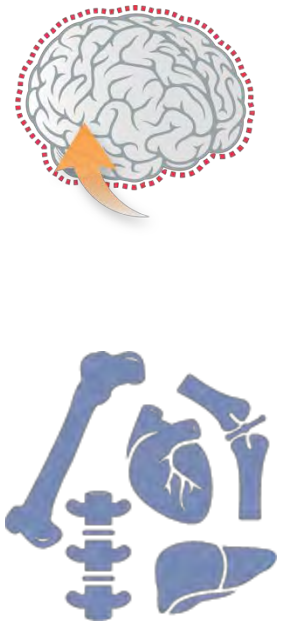
Capillary TfR expression in the brain facilitates widespread biodistribution of TV and enzyme



Weekly IV infusion



Extensive tissue penetration



TfR is highly expressed at the blood-brain barrier. Design of the TV is optimized to enable DNL310 to cross the blood-brain barrier[1-5]

TfR may also facilitate IDS delivery into tissues such as bone, cartilage, and the heart[2,6-8]

DNL310 has the potential to treat neuronopathic and somatic manifestations of MPS II

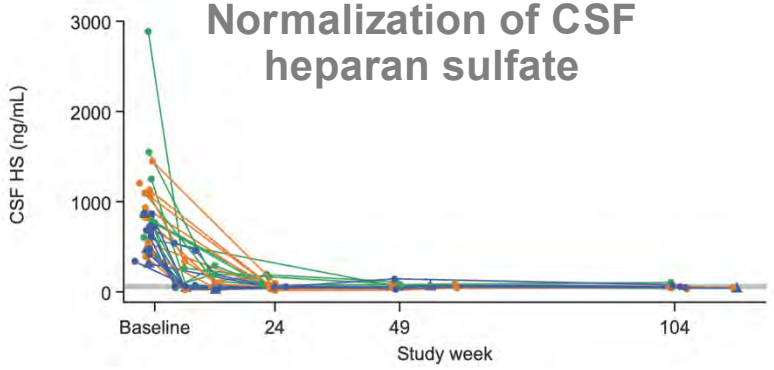
IV, intravenous; Tf, transferrin.

1. Jefferies WA, et al. *Nature*. 1984;312:162-163; 2. Qian ZM, et al. *Pharmacol Rev*. 2002;54(4):561-587; 3. Arguello A, et al. *JCI Insight*. 2021;6(19):e145445; 4. Arguello A, et al. *J Exp Med*. 2022;219(3):e20211057; 5. Ullman JC, et al. *Sci Transl Med*. 2020;12(545):eaay1163; 6. Wang S, et al. *Haematologica*. 2020;105(8):2071-2082; 7. Gammella E, et al. *Metallomics*. 2017;9(10):1367-1375; 8. Carlevaro MF, et al. *J Cell Biol*. 1997;136(6):1375-1384.

TIVIDENOFUSP ALFA ROBUSTLY IMPACTS DISEASE RELEVANT BIOMARKERS

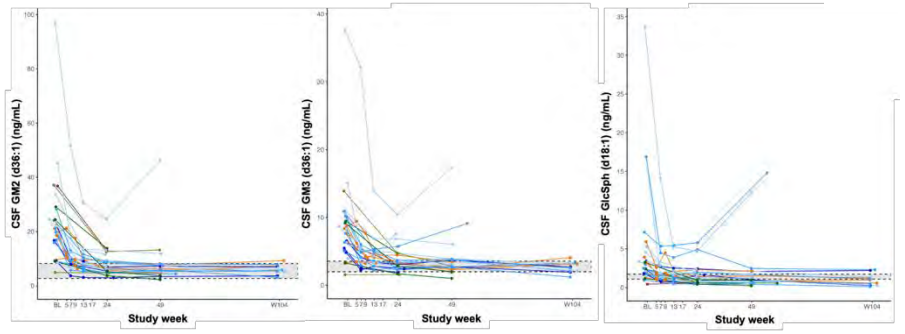
Substrate Correction

Normalization of CSF heparan sulfate



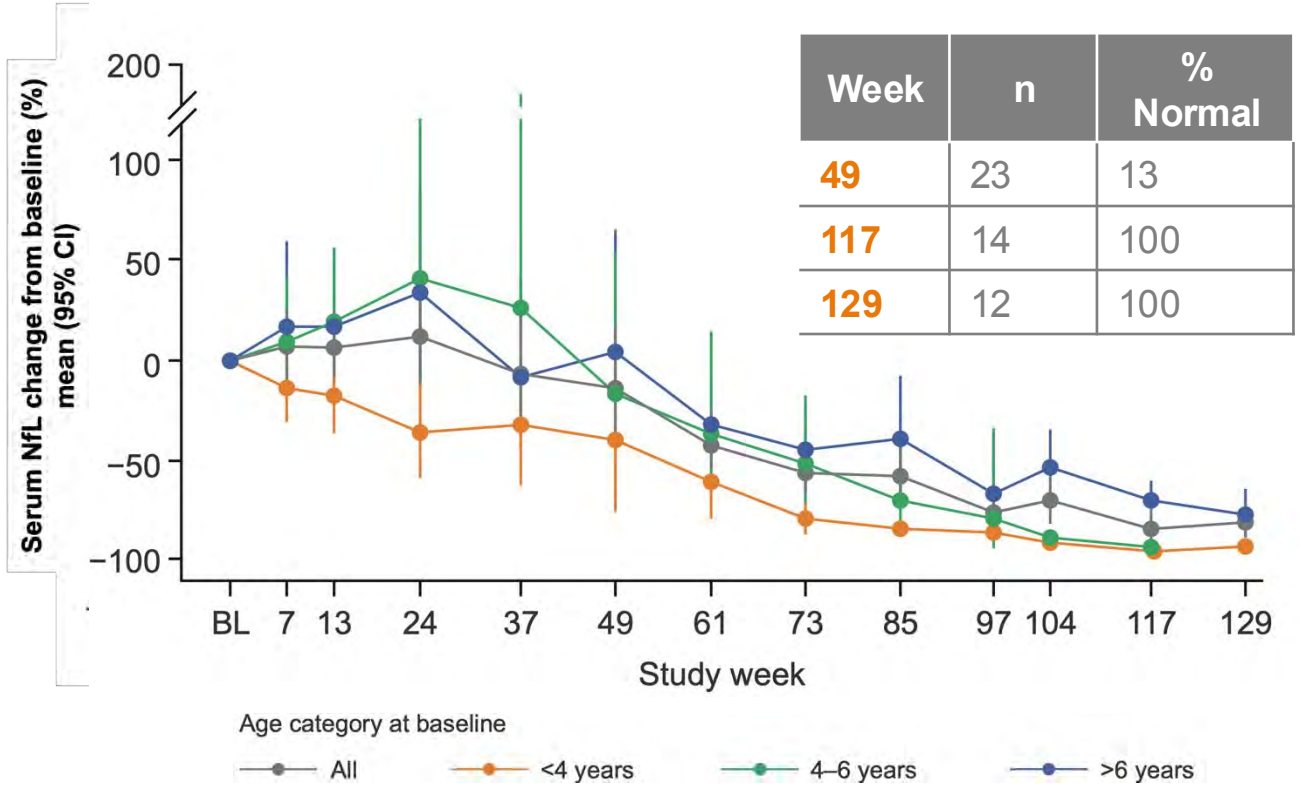
Cellular Correction

Near Normalization of Biomarkers of Lysosomal Function



Neurodegeneration Correction

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



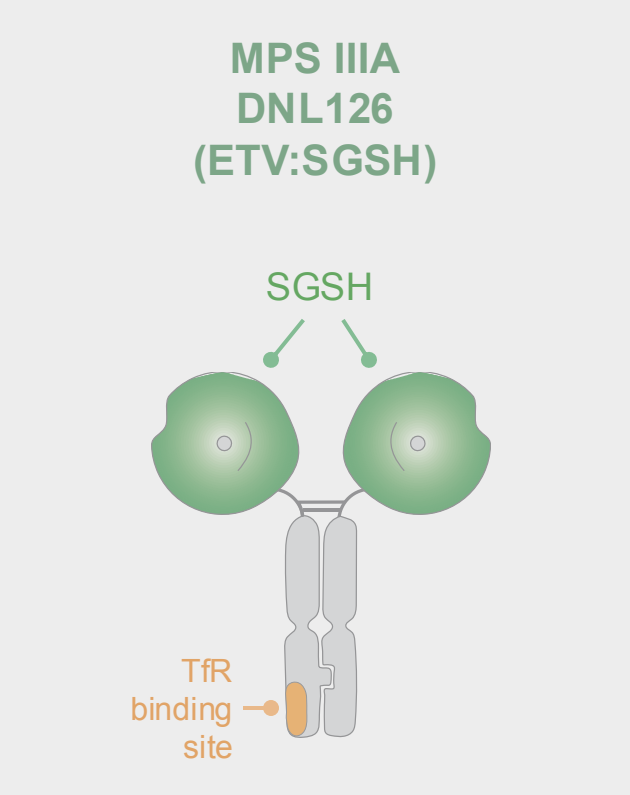
Week	n	% Normal
49	23	13
117	14	100
129	12	100

Plan to file BLA under the accelerated approval pathway in early 2025

Bars represent 95% confidence intervals; **BLA** – biologics license application; Sources: WORLD*Symposium* 2024 and SSIEM 2024

DEVELOPING A THERAPY FOR MPS IIIA (SANFILIPPO SYNDROME)

DNL126 (ETV:SGSH) is an investigational N-sulfoglucosamine sulfohydrolase (SGSH) fusion protein engineered to treat the brain manifestations of mucopolysaccharidosis type IIIA (MPS IIIA) (Sanfilippo syndrome Type A)



- Preliminary data from up to 25 weeks of dosing with DNL126 in the ongoing open-label Phase 1/2 study in MPS IIIA participants demonstrate:
  - A significant reduction in cerebrospinal fluid heparan sulfate (CSF HS) levels from baseline, including normalization
  - The most frequent treatment emergent adverse events were infusion related reactions of mild and moderate severity in all participants
  - There was one serious adverse event considered by the investigator not related to drug
- DNL126 was selected in June 2024 for the FDA's Support for clinical Trials Advancing Rare disease Therapeutics (START) program to accelerate the development of rare disease therapeutics

Denali recently expanded the Phase 1/2 study and continues to assess development plans including an accelerated approval path

MPS IIIA: mucopolysaccharidosis type IIIA
ETV: Enzyme Transport Vehicle
SGSH: N-sulfoglucosamine sulfohydrolase
TfR: transferrin receptor

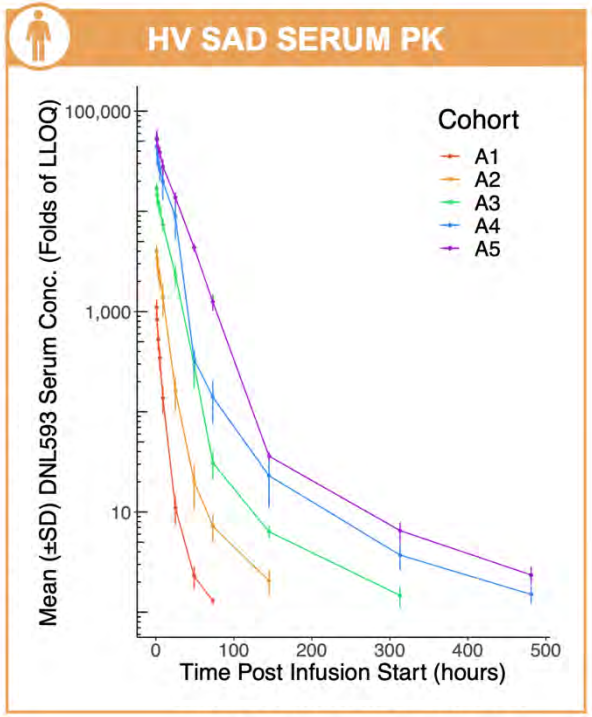
DNL593 (PTV:PGRN): PGRN BRAIN DELIVERY FOR FTD-GRN

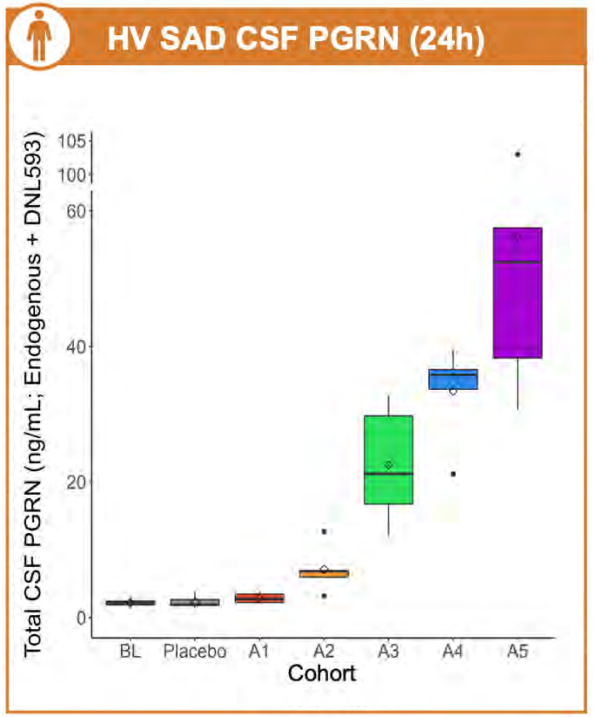
Brain delivery of progranulin (PGRN) designed to treat FTD-GRN

- FTD is the most common dementia in people under 60; no approved therapies
- FTD-GRN is associated with PGRN deficiency; accounts for 5-10% of FTD
- Single doses of DNL593 in HVs led to dose-dependent increases in CSF PGRN and were generally well tolerated
- Recruitment of participants with FTD-GRN in Part B (ascending multiple doses) of the Phase 1/2 study is ongoing

PTV:PGRN – Protein Transport Vehicle:Progranulin; **FTD-GRN** – frontotemporal dementia granulin; **CSF** – cerebrospinal fluid; **HVs** – healthy volunteers; **IRR** – infusion-related reactions

Dose-dependent increase in CSF PGRN in HV with IV DNL593 further validates TV for BBB crossing





ENZYME TRANSPORT VEHICLE (ETV) OPPORTUNITY IN LSDs

Lysosomal Storage Diseases (LSDs)

30,000
patients worldwide

DNL310
MPS II
Ph 2/3

DNL126
MPS IIIA
Ph 1/2

Brain delivery
clinical proof of concept achieved[1]

Accelerate
development with experience from DNL310

Blazing the trail to deliver the next generation of
Enzyme Replacement Therapies
designed to treat the body and brain

MPS II DNL310 ETV:IDS	**MPS IIIA** DNL126 ETV:SGSH	**POMPE** ETV:GAA	**PD, Gaucher** ETV:Gcase
MLD ETV:ARSA	**MPS IIIB** ETV:NAGLU	**MPS I** ETV:IDUA	**FTD-GRN** PTV:PGRN[2]

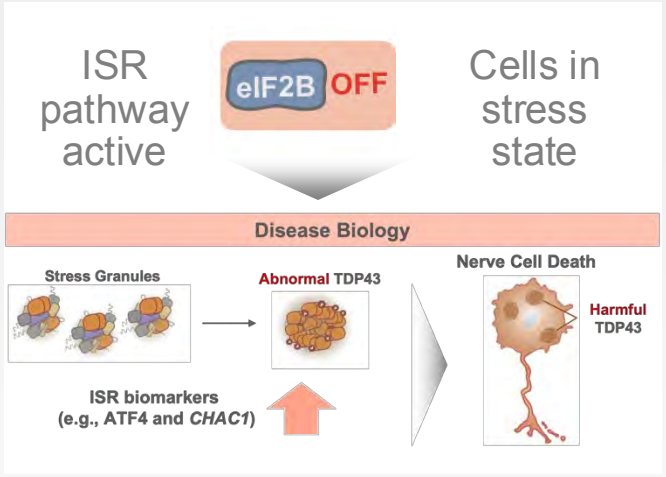
up to **$500M-$1B+**
market potential per indication

1. Includes interim biomarker and other data from open-label Phase 1/2 study of DNL310 (ETV:IDS); DNL310 (ETV:IDS) and DNL126 (ETV:SGSH) are in clinical development; other ETV programs are in earlier stages of development. **2.** FTD-GRN has a similar market and mechanism (Logan T et al., Cell. 2021) as broader ETV opportunities.

PEAK 1
Small Molecule Clinical Programs

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

Targeting the Integrated Stress Response (ISR)

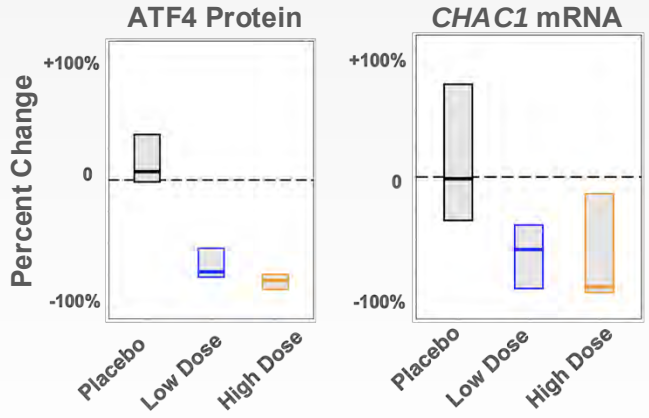


- ISR is implicated in stress granule formation and TDP43 aggregation, a hallmark of ALS
- DNL343 is designed to inhibit ISR & slow disease progression

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

BIIB122 (LRRK2 INHIBITOR) CLINICAL STUDIES IN HEALTHY AND PD PARTICIPANTS

	Phase 1/1b Healthy & PD Participant Study	Phase 2a BEACON Study in LRRK2-PD Participants	Phase 2b LUMA Study in PD Participants
Participants	186 healthy and 36 PD participants	50 participants with PD associated with a pathogenic LRRK2 mutation	640 participants with early-stage PD
Treatment	Single and multiple oral daily dosing over 28-day treatment period	Oral daily dosing over a 12-week treatment period	Oral daily dosing over a 48-week treatment period
Endpoints	• Safety • BIIB122 levels (pharmacokinetics) • Biomarkers of lysosomal pathway engagement	• Safety • BIIB122 levels (pharmacokinetics) • Biomarkers of lysosomal pathway engagement	• Primary endpoint assessed using MDS-UPDRS
Status	Completed	Recruiting Study operationalized by Denali	Recruiting Study operationalized by Biogen

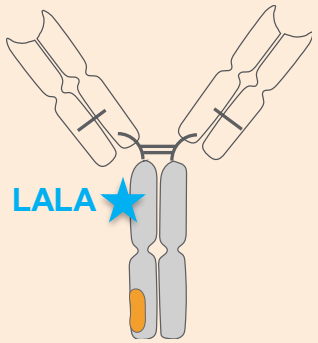
DENALI THERAPEUTICS

Biogen

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

ATV:Abeta: DEVELOPING A BEST-IN-CLASS ANTI-AMYLOID THERAPY

ATV:Abeta

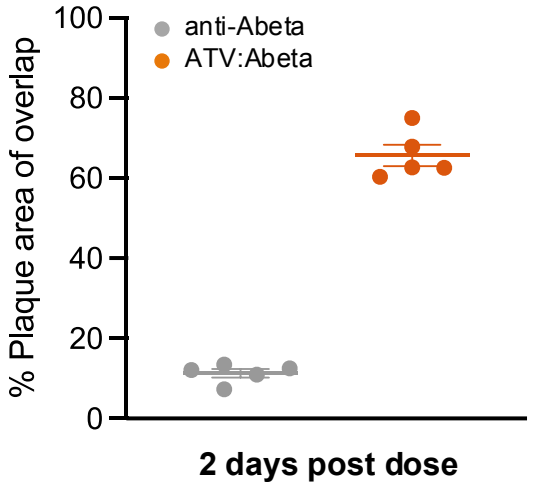


- Optimally engineered to reduce plaque and improve safety
- cisLALA mutation enables immune activation only when bound to plaque

Greater Plaque Binding, Plaque Reduction & Less ARIA with ATV:Abeta

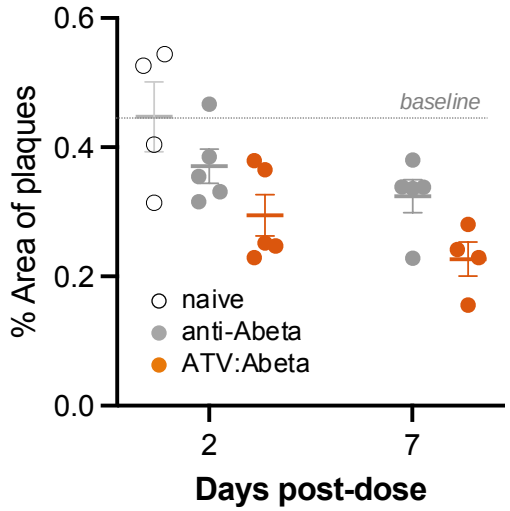
Aβ and huIgG colocalization

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



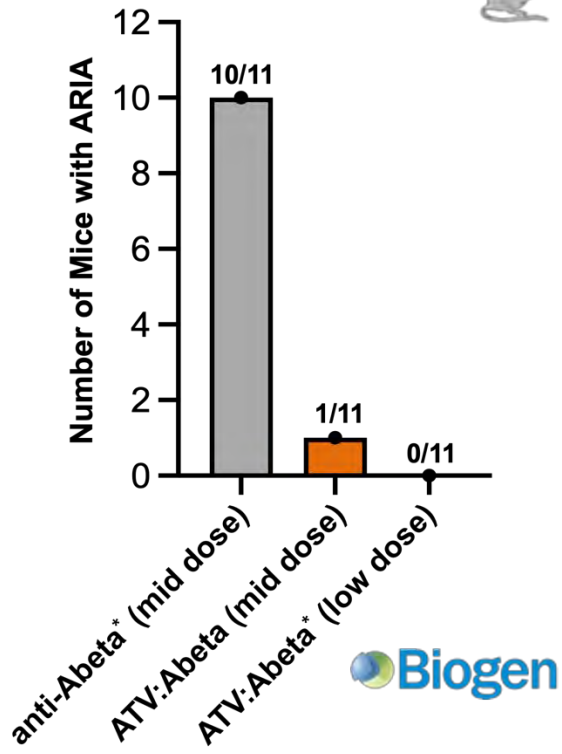
Aβ Plaque Load

Single, mid dose, APP^{SAA} KI



ARIA-like MRI events

Weekly dosing x 11 wks, 5xFAD TfR$^{mu/hu}$ KI[2]



Biogen

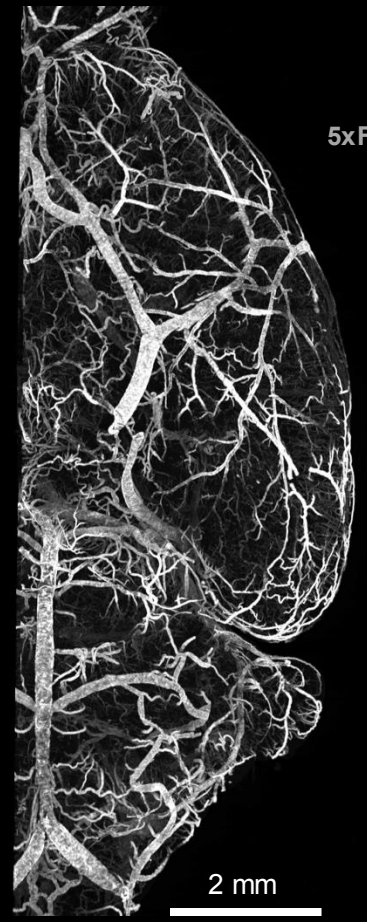
ATV:Abeta may enable a wider therapeutic window in treating AD as compared to conventional anti-Abeta therapy

1. Xia et al., *Molecular Neurodegeneration* 2022; 2. Biogen data on file; *At experimental doses selected to yield equivalent brain exposure and plaque reduction
ATV – Antibody Transport Vehicle; **Aβ** – Amyloid beta; **huIgG** – Human immunoglobulin G; **ARIA** – amyloid related imaging abnormalities; **MRI** – magnetic resonance imaging

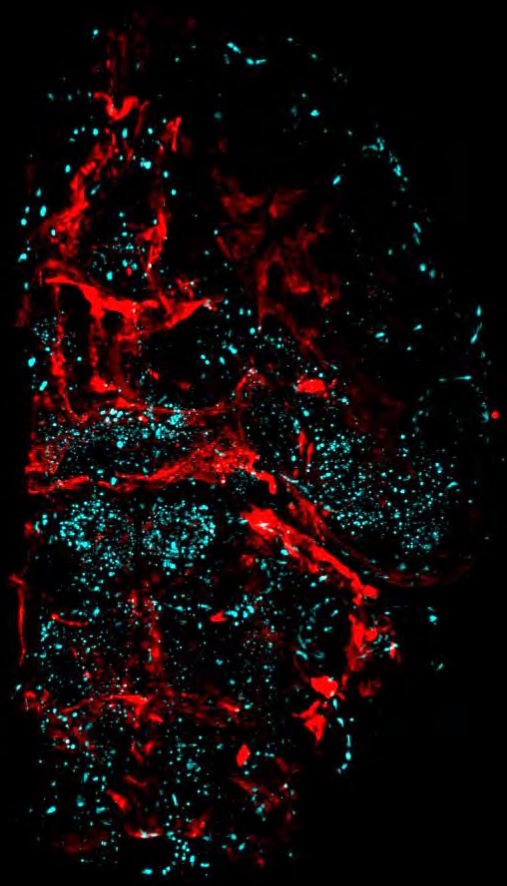
3D IMAGING SHOWS SUPERIOR AND DIFFERENTIATED ATV:Abeta BIODISTRIBUTION

gubra

Brain Arteries



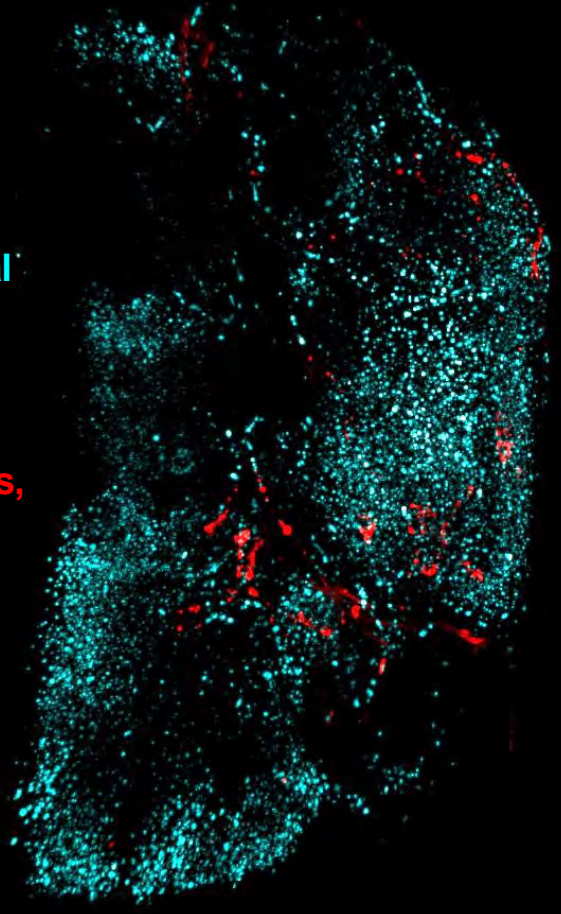
Anti-Abeta



huIgG, parenchymal (on plaques)

huIgG, associated with perivascular spaces, CSF cisterns, leptomeninges

ATV:Abeta

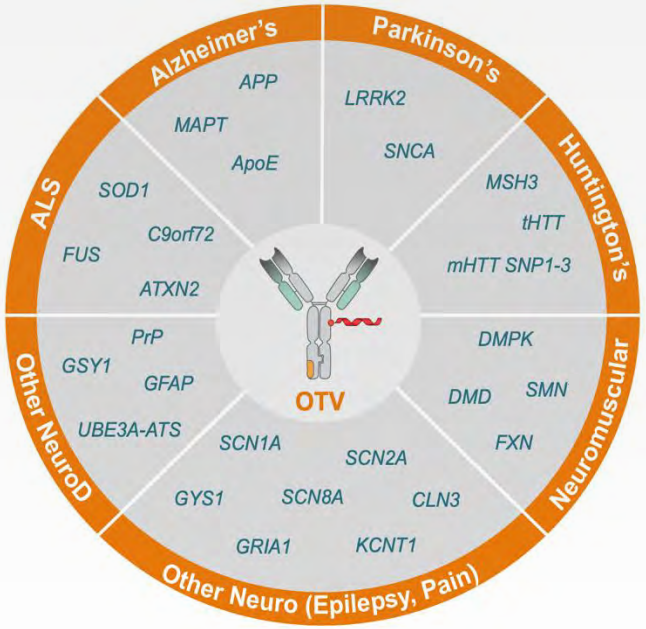


ATV leads to higher parenchymal plaque binding and lower perivascular localization compared to standard antibody

OLIGONUCLEOTIDE TRANSPORT VEHICLE (OTV) OPPORTUNITY

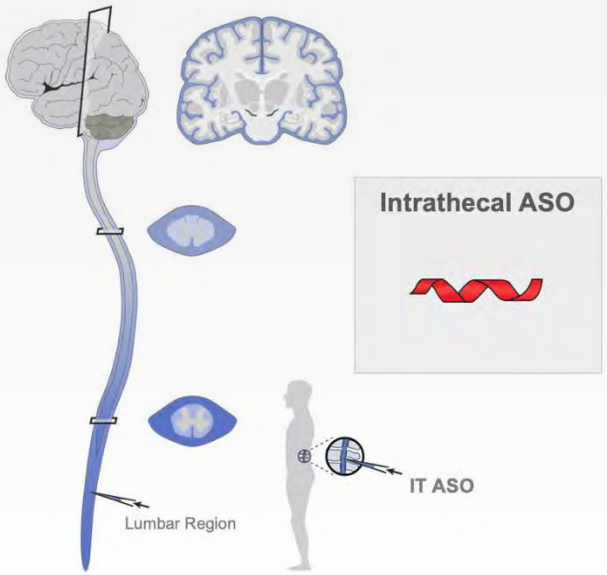
Oligonucleotide Therapies Enable New Disease Targets

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



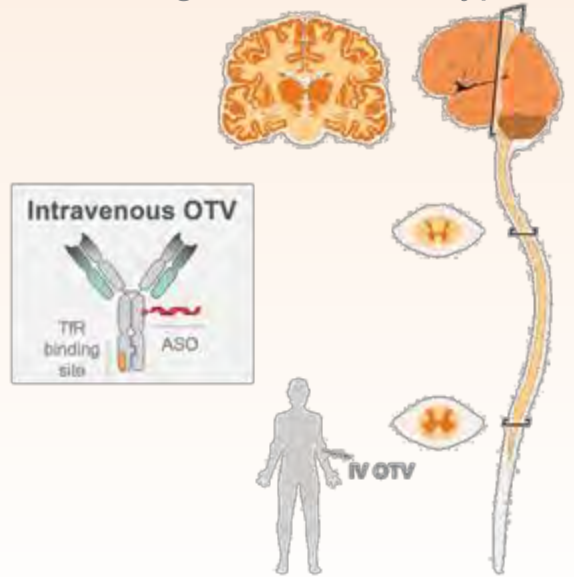
Opportunity for Improving Oligo Delivery and Therapeutic Profile

- 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

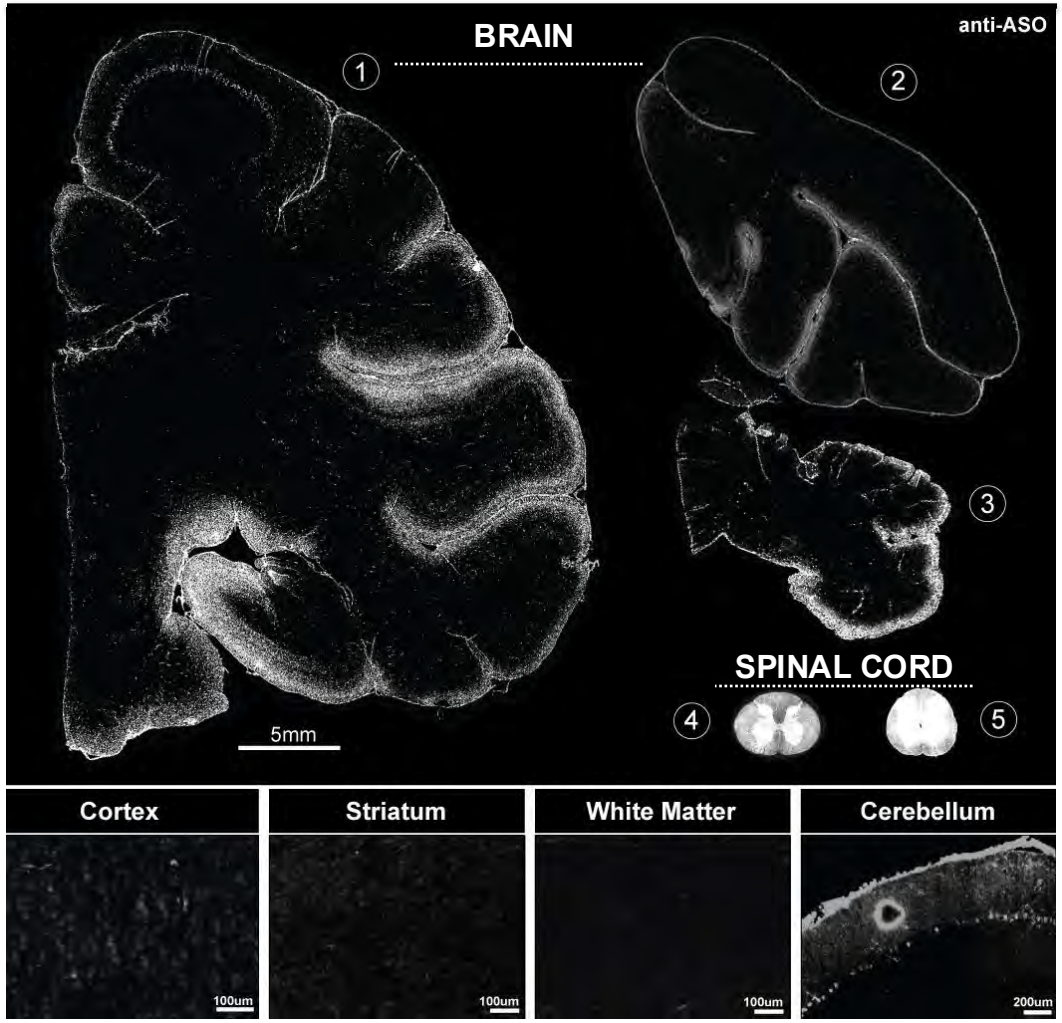
- Homogenous biodistribution of ASOs across brain regions
- Superior knockdown of target gene expression across all brain regions and cell types



OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

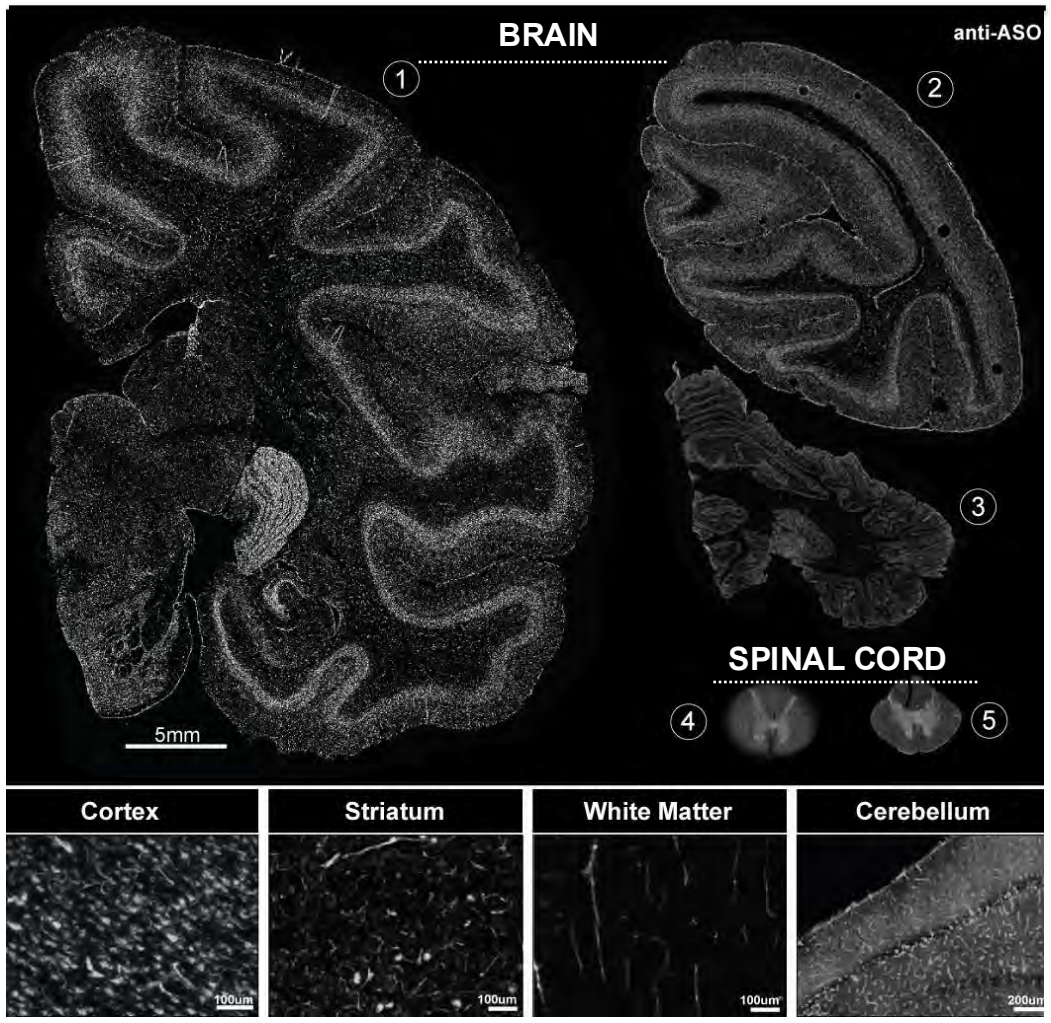
NAKED ASO INTRATHECAL (IT) DELIVERY

Limited ASO Biodistribution



OTV INTRAVENOUS (IV) DELIVERY

Widespread ASO Biodistribution

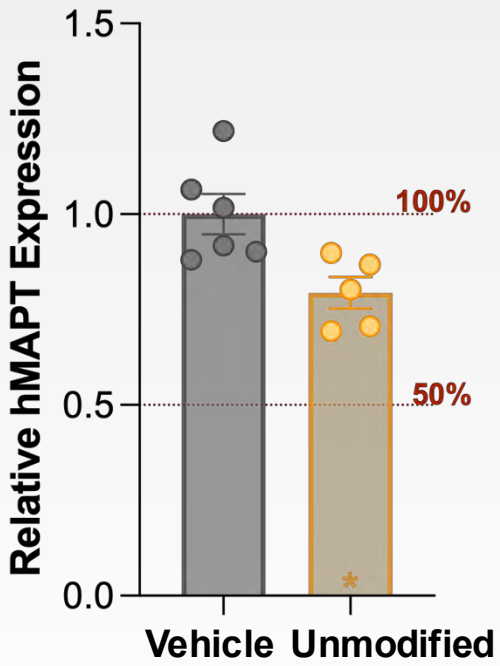


(1) Full Hemibrain Section (2) Posterior Cortex overlaying Cerebellum (3) Cerebellum (4) Cervical Spinal Cord (5) Lumbar Spinal Cord

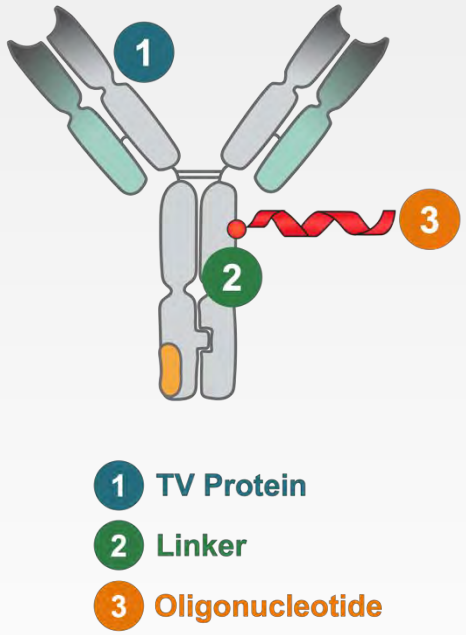
 Barker et al. 2023 *BioRxiv*

OPTIMIZING GENE KNOCKDOWN IN BRAIN WITH OTV PLATFORM

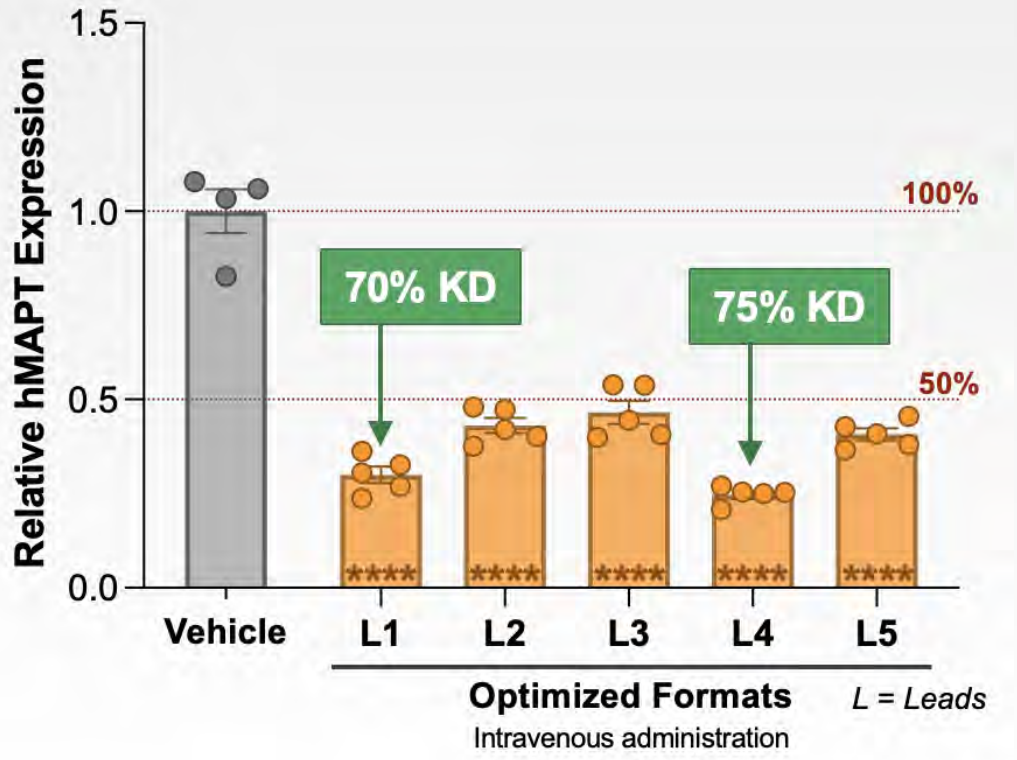
Unmodified OTV Format



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

$1.28 B (as of 9/30/24)

THANK YOU

www.denalitherapeutics.com