December 4, 2025

Welcome to Denali Therapeutics 2025 Investor Day

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 2025 and beyond; Denali’s ability to execute on its tailored commercial strategies and accelerate commercial launch readiness; the potential for Denali's product candidates to treat various neurodegenerative diseases including MPS I (Hurler Syndrome), MPS II (Hunter Syndrome), MPS IIIA (Sanfilippo Syndrome), PD, ALS, AD, FTD-*GRN*, UC, Gaucher's Disease, Pompe Disease, 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 related to Denali's TransportVehicle™ (TV) platform, including the Enzyme TV (ETV), Antibody TV (ATV), Protein TV (PTV), and Oligonucleotide TV (OTV), and its therapeutic and commercial opportunities; plans, timelines, and expectations related to the ETV platform and ETV-enabled programs, including ETV:GAA, ETV:GCase, and ETV:IDUA, their therapeutic and commercial potential, and the timing and likelihood of planned regulatory filings; plans, timelines, and expectations relating to DNL310, including the ongoing Phase 1/2 study and Phase 2/3 COMPASS study, the timing of planned regulatory filings, and the timing, likelihood, and scope of regulatory approvals and commercial launch; plans, timelines, and expectations related to DNL126, including the timing and availability of data from the Phase 1/2 study and likelihood and pathway of regulatory approval; plans, timelines, and expectations related to the OTV and OTV-enabled programs, including OTV:MAPT and OTV:SNCA, their therapeutic and commercial potential, and the timing and likelihood of planned regulatory filings; plans, timelines, and expectations relating to ATV:Abeta, including its therapeutic potential and the timing of planned regulatory filings; plans, timelines, and expectations relating to DNL151, including enrollment in the Ph2B LUMA study and Ph2A BEACON study; plans and expectations regarding DNL593, including enrollment of Cohort B in the Ph1/2 study; plans, timelines, and expectations related to DNL758 and enrollment in the Ph2 RESOLUTE study; plans and expectations regarding Denali's global organization and clinical and manufacturing 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, and forward-looking statements regarding potential outcomes should not be interpreted as guarantees of future performance.

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 but not limited to: the risk of the occurrence of any circumstance that could give rise to the termination of Denali’s agreements with its collaborators; Denali’s and its collaborators’ ability to complete the development and, if approved, commercialization of its product candidates; Denali’s and its collaborators’ ability to enroll patients in its ongoing and future clinical trials; Denali’s reliance on third parties for the manufacture and supply of its product candidates for clinical trials; Denali’s dependence on successful development of its blood-brain barrier platform technology and TV-enabled product candidates; Denali’s and its collaborators’ ability to conduct or complete clinical trials on expected timelines; the predictive value of Denali's biomarker selection; the occurrence of significant adverse events, toxicities or other undesirable side effects; the potential for clinical trials of Denali’s product candidates to differ from preclinical, early clinical, preliminary or expected results; the uncertainty that product candidates will receive regulatory approval or be commercialized; Denali’s ability to continue to create a pipeline of product candidates or develop commercially successful products; Denali’s ability to obtain, maintain, or protect intellectual property rights related to its product candidates; Denali's achievement of planned milestones and realization of value; implementation of Denali’s strategic plans for its business, product candidates, and blood-brain barrier platform technology; and other risks. In light of these risks, uncertainties and assumptions, the forward-looking statements in this press release are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali’s most recent quarterly and annual reports filed with the Securities and Exchange Commission on Forms 10-Q and 10-K, respectively, as well as Denali’s future reports to be filed with the SEC. Denali does not undertake any obligation to update or revise any forward-looking statements, to conform these statements to actual results or to make changes in Denali’s expectations, except as required by law.

The product candidates being developed by Denali are investigational and their safety and efficacy profiles remain unestablished. Denali's product candidates have not been approved by any health authority for any use.

Accuracy of Data. This presentation contains statistical data based on independent industry publications or other publicly available information, as well as other information based on Denali’s internal sources. Denali has not independently verified the accuracy or completeness of the data contained in these industry publications and other publicly available information. Accordingly, Denali makes no representations as to the accuracy or completeness of that data.

Leading a New Era of BBB-Crossing Therapeutics

Key Messages

Ryan Watts, Ph.D.
Chief Executive Officer

Our Purpose

Deliver the power of biotherapeutics to the whole body, including the brain, transforming life for people living with serious diseases

Key Messages for Today

Best-in-Class Blood-Brain Barrier (BBB) Platform

- TransportVehicle™ is the most validated, differentiated, and clinically proven technology enabling systemic delivery of biologics to the brain and other hard to target tissues

Ready to Capture $1B+ Market Opportunity with Two Near-Term Launches

- Launch of tividenofusp alfa (DNL310) in 2026 and DNL126 in 2027 lay the commercial foundation for ETV franchise and leadership in next-generation enzyme replacement therapy

Deep Pipeline Across High-Value Therapeutic Areas

- Broad clinical stage pipeline, including two potential best-in-class TfR-enabled programs for Alzheimer's disease, provides several near-term high-value milestones

Efficient Execution and Capital Allocation

- Well-capitalized and increasingly efficient capital allocation and execution timelines for long-term value creation

ETV – Enzyme Transport Vehicle™; **TfR –** Transferrin receptor

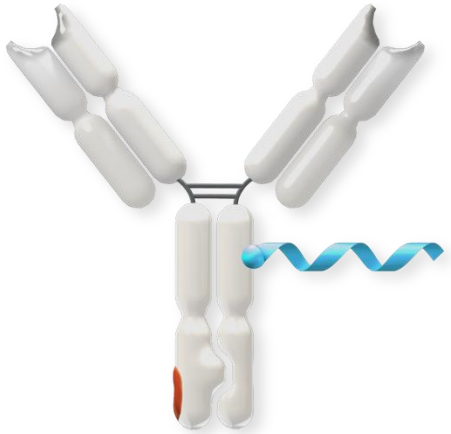
A New Class of Biotherapeutics for the Whole Body, Including the Brain

Enzyme TV
(ETV)

Enzyme replacement therapy for the body and brain

/

Oligonucleotide TV
(OTV)



Genetic medicines for the brain, delivered systemically

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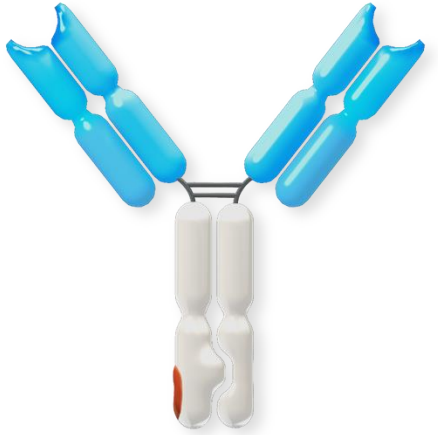
Antibody TV
(ATV)



Brain-penetrant immunotherapy for a wide range of diseases

Our TransportVehicle™ (TV) Platform enables TfR-mediated brain biodistribution and enhanced tissue delivery of biotherapeutics throughout the body with systemic administration

TfR – Transferrin receptor

Our Broad Therapeutic Portfolio

Lysosomal Storage Disorders

Molecule	Indication	Stage
tividenofusp alfa (ETV:IDS)	MPS II	Regulatory Filing
DNL126 (ETV:SGSH)	MPS IIIA	Phase 1/2
DNL593 (PTV:PGRN)	FTD-*GRN*[1]	Phase 1/2
DNL952 (ETV:GAA)	Pompe	Phase 1[2,3]
DNL111 (ETV:GCase)	Gaucher	IND-Enabling
DNL622 (ETV:IDUA)	MPS I	IND-Enabling

>30,000 Patients WW[4]

$500M-$1B+ per Indication

Common Neurodegenerative Diseases

Molecule	Indication	Stage
BIIB122 LRRK2 Inhibitor	PD	Phase 2b
DNL628 OTV:MAPT (tau)	AD	Phase 1b[2]
DNL921 ATV:Abeta	AD	IND-Enabling
DNL111 ETV:GCase	PD	IND-Enabling
DNL422 OTV:SNCA	PD	IND-Enabling

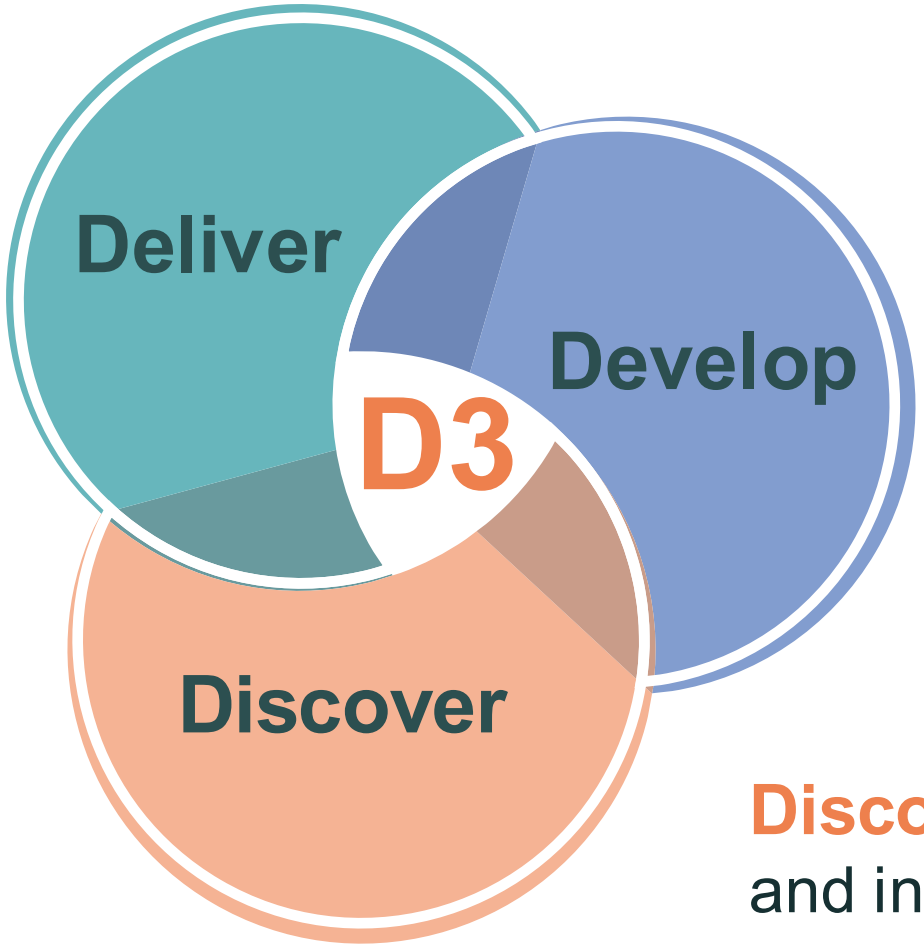
>40M Patients WW[4]

>$5B per AD/PD Indication

1. FTD-*GRN* has a lysosomal phenotype and can be considered a rare lysosomal storage disease; **2.** Regulatory applications filed to begin human clinical studies; **3.** Protocol amended and response to FDA submitted regarding clinical hold; **4.** Denali estimates of worldwide aggregate prevalence, excluding China and India for the lysosomal storage disorders; **MPS –** Mucopolysaccharidosis; **PD –** Parkinson's disease; **AD** – Alzheimer's disease

Our D3 Strategy for Sustainable Value Creation

Deliver the blockbuster potential of **ETV, ATV, OTV** franchises



Develop first or best-in-class **TV therapeutics**

Discover new **TV** targets and indications

D3 Strategy: Discover, Develop and Deliver on the TransportVehicle™ platform opportunity

D3 – Deliver, Develop, Discover; **ETV –** Enzyme Transport Vehicle™; **ATV –** Antibody TransportVehicle™; **OTV –** Oligonucleotide TransportVehicle™; **TV –** TransportVehicle™

On Track to Deliver Denali's D3X3 Goals: 3-Year Outlook

2 Growing Brands

- Tividenofusp Alfa
- DNL126 (ETV:SGSH)

4-6 New Clinical Programs

- Continued leadership and invention on BBB technologies

5 Clinical Proof of Concepts

Alzheimer's Disease

- DNL628 (OTV:MAPT)
- DNL921 (ATV:Abeta)

Pompe Disease

- DNL952 (ETV:GAA)

FTD-*GRN*

- DNL593 (PTV:PGRN)

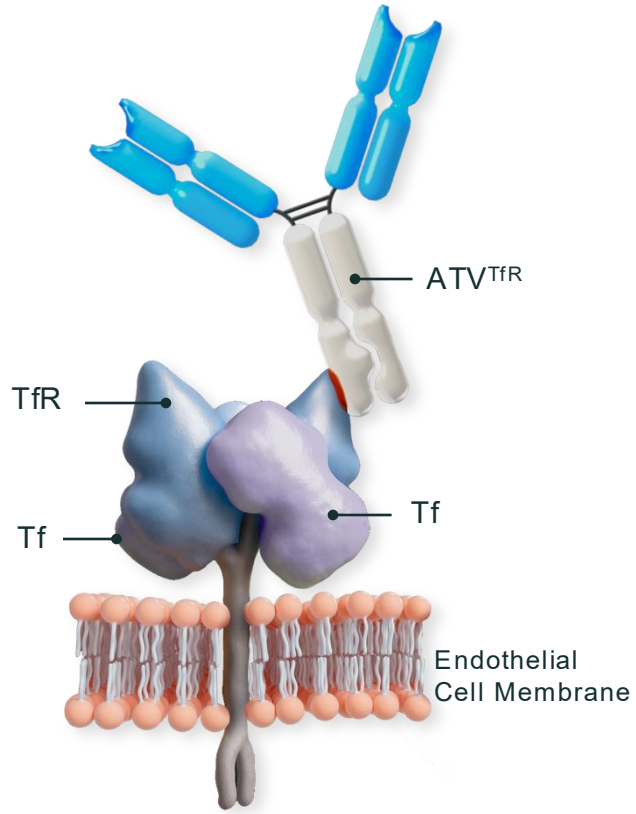
Parkinson's Disease

- DNL151 (LRRK2 inhibitor)

Delivering near-term value from planned product launches, advancing a robust pipeline and capturing the full potential of the TransportVehicle™

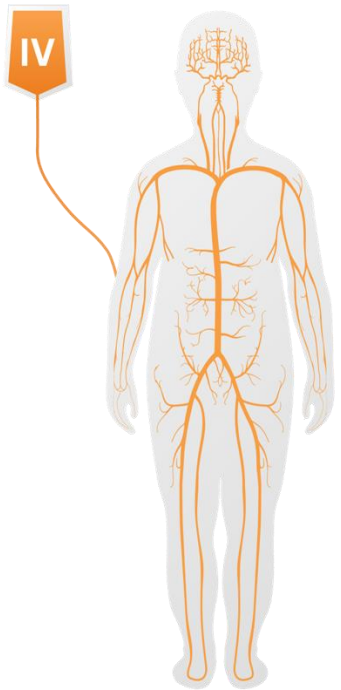
D3 – Deliver, Develop, Discover; **BBB –** Blood-brain barrier

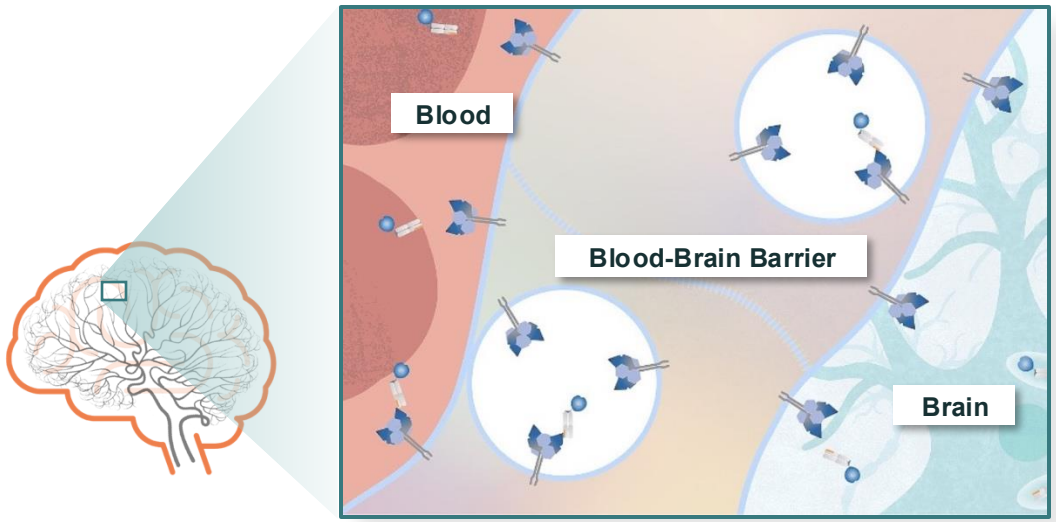
Treating the Whole Body, Including the Brain

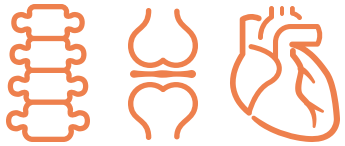


Transferrin receptor (TfR) is highly expressed at the blood–brain barrier for natural iron transport

Our **TransportVehicle™** leverages TfR to enable **brain delivery** of biotherapeutics







TfR may also facilitate delivery into tissues such as **bone**, **cartilage**, and the **heart**

TfR – Transferrin receptor

TransportVehicle™ Distributes to Whole Body, Including Brain

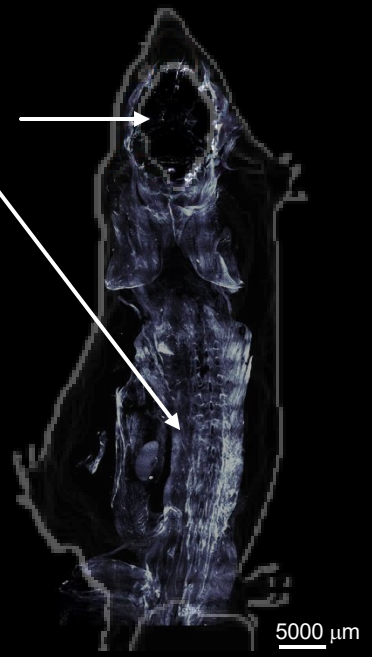
Standard Antibody (IgG)

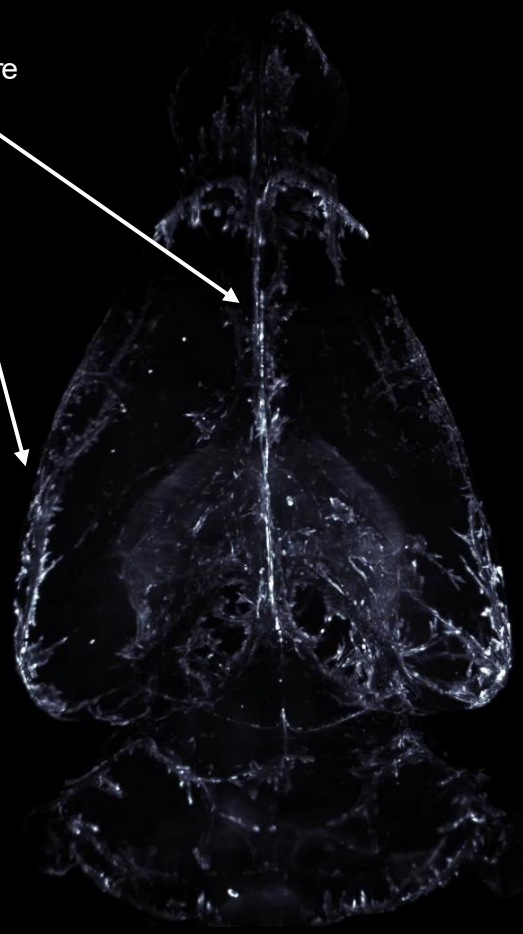
Brain

Surface vasculature accumulation

Whole Body

Minimal or limited distribution in brain and bone

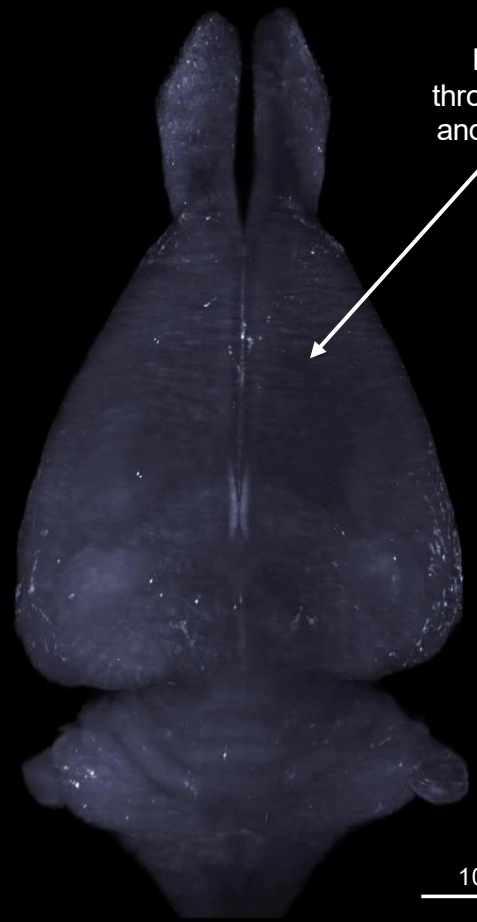




TV-enabled Antibody (TfR)

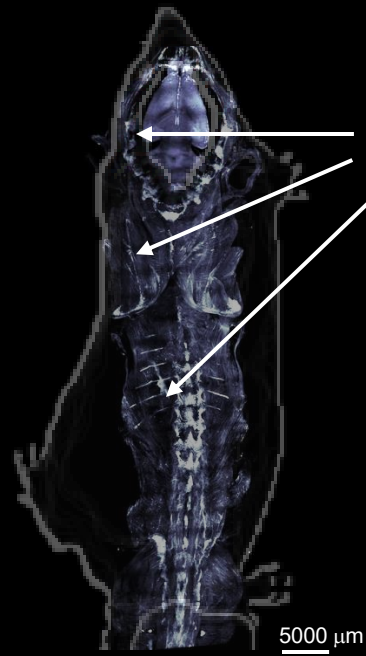
Brain

Broad distribution throughout parenchyma and deep brain regions



Whole Body

Increased signal in brain, muscle, bone

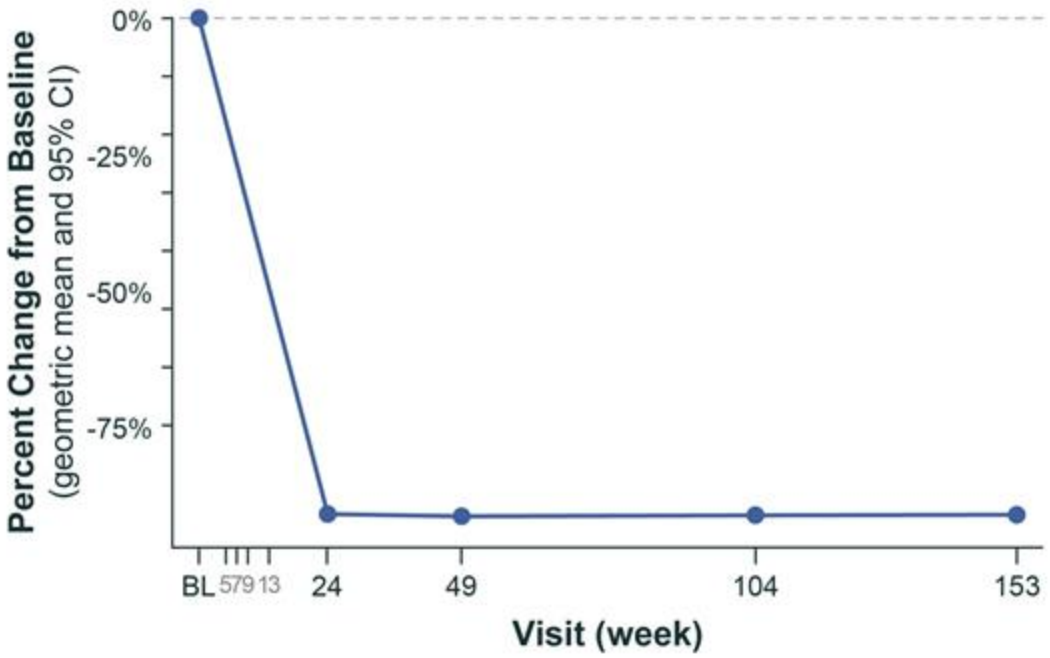


TransportVehicle™ Clinical Effects: MPS II Phase 1/2 Study

Brain

CSF Heparan Sulfate

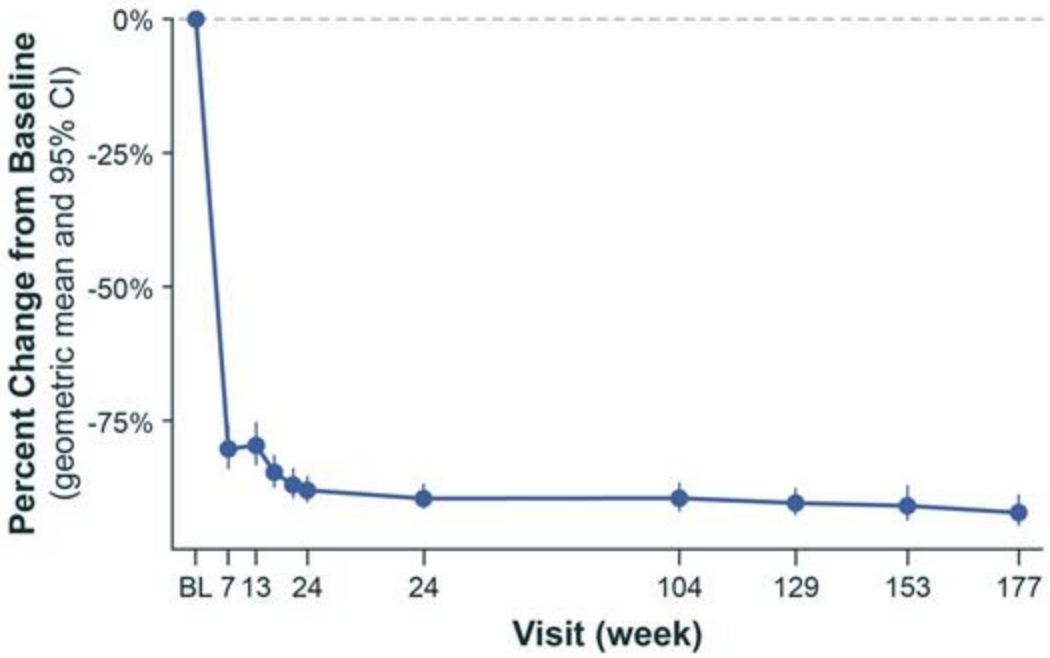
Biomarker of CNS disease



Body

Urine Heparan Sulfate

Biomarker of peripheral disease



Our ETV franchise is clinically validated, derisking the broader TV platform

Source – WORLD 2025; **MPS II** – Mucopolysaccharidosis Type II; **CSF** – Cerebrospinal fluid; **CNS –** Central nervous system; **ETV –** Enzyme Transport Vehicle™

Our TransportVehicle™ Platform Sets the Bar for BBB Delivery

Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery

BBB receptor binding site engineered into the **Fc for optimal properties and modularity**

Modularity — Enables broad ability to transport range of therapeutics, such as enzymes, oligos and antibodies

Brain Uptake — Optimized affinity and epitope enhance brain delivery while limiting receptor degradation

Safety — Conditional effector function avoids reticulocyte loss and minimizes anemia liability potential

Architecture — High fidelity to natural protein (e.g., no appended sequences) improves stability, limits immunogenicity and improves ease of manufacturing

Industry Leading Platform

- 1st Potential FDA-approved TfR therapeutic to cross the BBB
- 5 Clinical programs*
- Demonstrated ability to correct neurodegeneration (e.g., NfL)
- >10 Preclinical programs
- >200 Subjects dosed
- >11,000 Doses administered
- >20 Publications in last 5 years
- >350 Patents/Applications

*includes regulatory applications to begin clinical studies for DNL628 and DNL952; **BBB –** Blood-brain barrier; **TfR**– Transferrin receptor; **NfL –** Neurofilament light chain

TransportVehicle™ has Demonstrated Best-in-Class Properties

Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery

Modularity

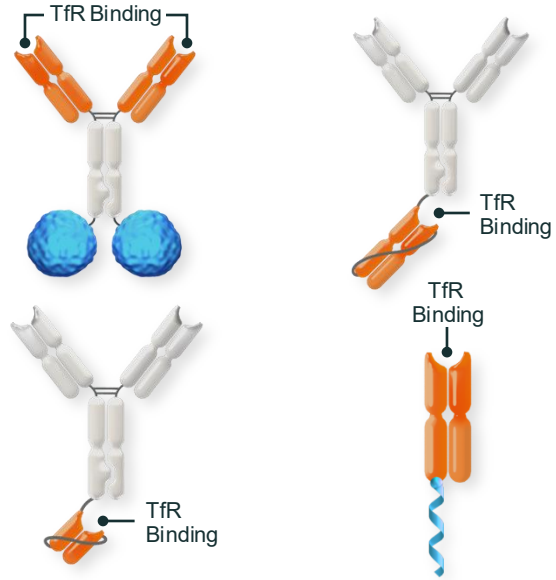
Brain Uptake

BBB receptor binding site engineered into the **Fc for optimal properties and modularity**

Safety

Architecture

Conventional Fab Approaches



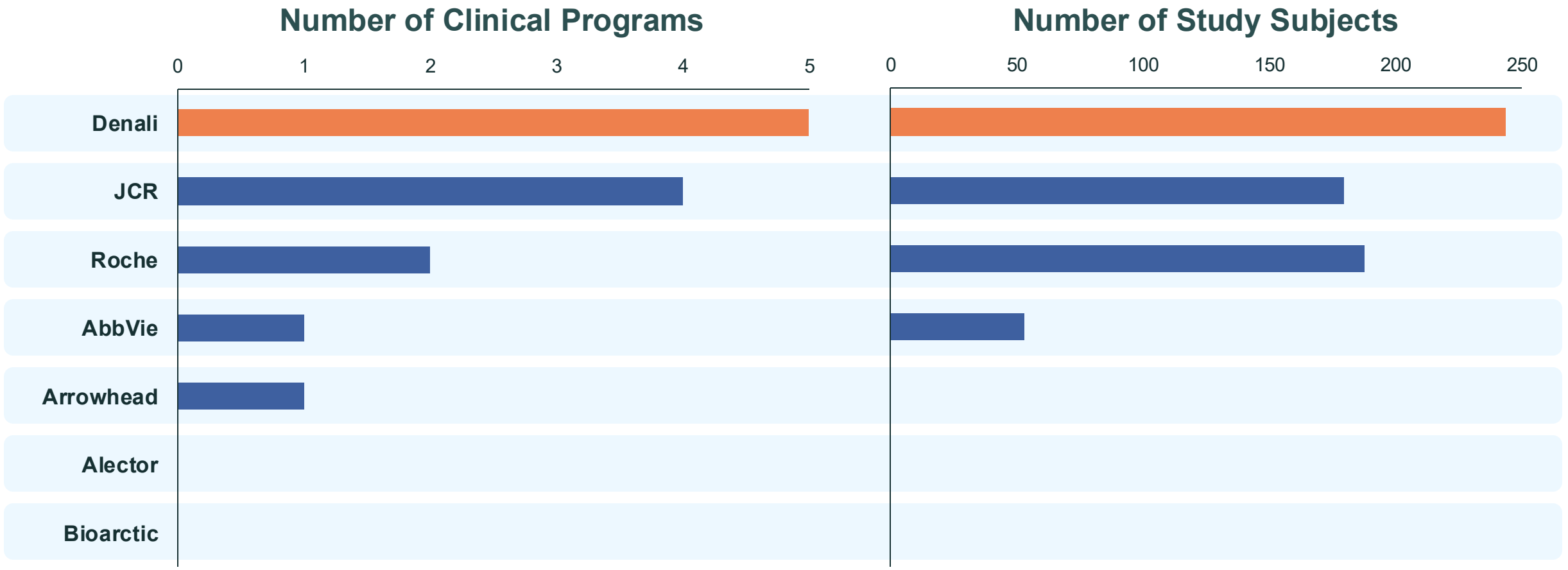
Linker chemistry adversely affects stability

Full effector function increases anemia risk

High affinity, bivalent binding leads to suboptimal brain biodistribution

Low fidelity to natural protein increases risk of immunogenicity

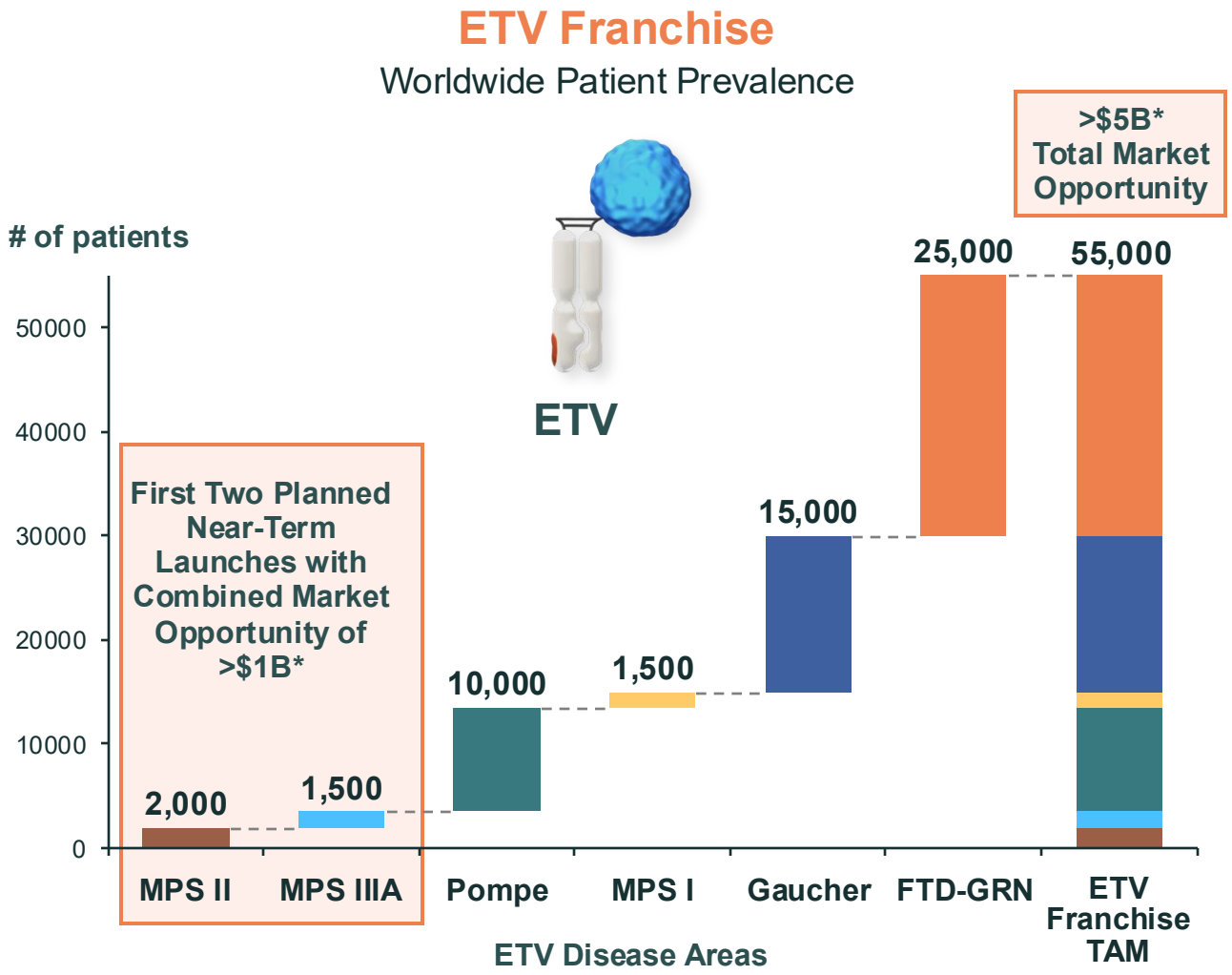
TransportVehicle™ Has Broad Clinical Experience



Denali's TV is the most clinically validated BBB technology with over 11,000 doses administered, and including patients who have been continuously dosed for more than 5 years

Includes companies with TfR-based platforms and is not a comprehensive list. Peer company estimates are based on publicly available sources, i.e., investor presentations, medical congress presentations, and actual number of participants enrolled in studies as posted on ClinicalTrials.gov as of December 3, 2025. Roche number of subjects does not include two Phase 3 studies in AD recently initiated and for which actual enrollment number is not available on ClinicalTrials.gov.

ETV: Foundational Franchise for Lysosomal Storage Disorders



Delivering Next Generation Enzyme Replacement Therapy (ERT)

- ~30,000 people with LSDs worldwide
- Single enzyme deficiencies
- 2/3 LSDs with CNS manifestations
- 23 ERTs currently marketed; ~$9B in sales
- ~90% historical ERT approval rate
- Traditional ERTs do not penetrate CNS
- ETVs address full spectrum of the disease

*Based on internal Denali estimates. **TAM** – Total Addressable Market; **ETV –** Enzyme Transport Vehicle™; **ERT –** Enzyme Replacement Therapy

OTV & ATV: Opportunity to Set the Bar in Alzheimer's Disease


Science 7 AUGUST 2025

NEUROSCIENCE

Transferrin receptor–targeted anti-amyloid antibody enhances brain delivery and mitigates ARIA

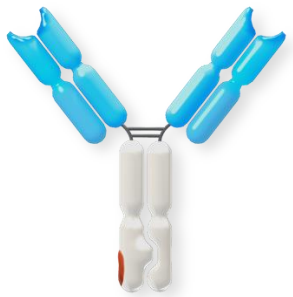
Michelle E. Pizzo[1], Edward D. Plowey[2], Nathalie Kh
Wanda Kwan[1], Jordan Abettan[2], Sarah L. DeVos[1]†,
Claire B. Discenza[1], Timothy Earr[1]‡, David Joy[1], Mi
Elysia Roche[1], Darren Chan[1], Jason C. Dugas[1], Kap
Stefan Hamann[2], René Meisner[1], Jennifer Sebalus
Ana Claudia Silva Amaral[2], Isabel Becerra[1], Roni C
Johann Chow[1], Allisa J. Clemens[1]§, Mark S. Dennis
Laura Fusaro[1], Jennifer A. Getz[1], Mihalis S. Kariolis
Kendra J. Lechtenberg[1]¶, Amy Wing-Sze Leung[1],
Arash Moshkforoush[1], Hoang N. Nguyen[1], Emmanu
Elliot R. Thomsen[1], Vanessa O. Torres[1], Pascal E. Sa
Lu Shan[1], Adam P. Silverman[1], Zachary K. Sweeney
Raymond Tong[1], Meredith E. Calvert[1], Ryan J. Watt


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

DRUG DELIVERY

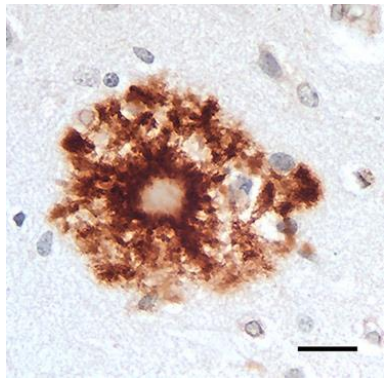
Targeting the transferrin receptor to transport antisense oligonucleotides across the mammalian blood-brain barrier

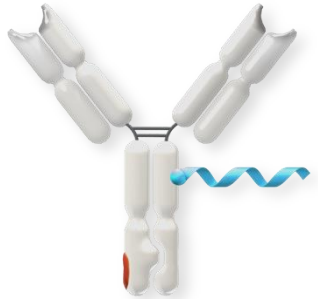
Scarlett J. Barker[1]*†, Mai B. Thayer[1]†, Chaeyoung Kim[1]‡, David Tatarakis[1]‡, Matthew J
Rebekah Dial[1], Lizanne Nilewski[1], Robert C. Wells[1], Yinhan Zhou[1], Megan Afetian[2],
Padma Akkapeddi[1], Alfred Chappell[2], Kylie S. Chew[1], Johann Chow[1], Allisa Clemens[1],
Claire B. Discenza[1], Jason C. Dugas[1], Chrissa Dwyer[2]§, Timothy Earr[1], Connie Ha[1], Yvon
David Huynh[1], Edwin I. Lozano[1], Srini Jayaraman[1], Wanda Kwan[1]¶, Cathal Mahon[1],
Michelle Pizzo[1], Yaneth Robles-Colmenares[1], Elysia Roche[1], Laura Sanders[1],
Alexander Stergioulis[1], Raymond Tong[1]#, Hai Tran[1]**, Y. Joy Yu Zuchero[1], Anthony A.



ATV

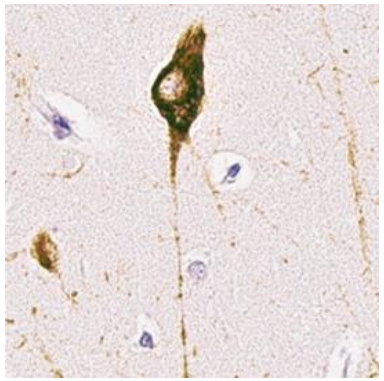
Targeting Abeta Plaques





OTV

Targeting Tau Tangles



Advancing the Next Generation of Therapeutics for AD

Reducing risk of amyloid-related imaging abnormalities (ARIA)

Clearing amyloid plaque faster via better brain biodistribution

Addressing tau pathology by suppressing MAPT expression

Unmet medical need provides opportunity for BBB-enabled AD therapeutics with $5B+ market potential

Walker L, *Free Neuropath*, 2020; Bengoa-Vergniory et al, *Acta Neurop*, 2021; **ATV –** Antibody TransportVehicle™; **OTV –** Oligonucleotide TransportVehicle™; **AD** – Alzheimer's disease

Today's Agenda

Session	Topic	Speaker	Time
Leading a New Era of BBB-Crossing Therapeutics	**Key Messages** • Opportunity, Technology, Portfolio, 3-Year Goals	**Ryan Watts, Ph.D.** Chief Executive Officer	8:30am ET
Enzyme TransportVehicle™ (ETV) Franchise for Lysosomal Storage Disorders	**Overview** • MPS II, MPS IIIA and Pompe Disease	**Barbara Burton, M.D.**	8:45am ET
	MPS Diseases • Clinical Development & Regulatory Path • Market Opportunity & Commercial Launch Plans • MPS II Community Perspectives (Moderated Panel)	**Peter Chin, M.D.,** Acting Chief Medical Officer **Katie Peng,** Chief Commercial Officer **Dr. Burton, Jason Madison** and **Kim Stephens, Ph.D.**	9:05am ET
	Building a Broader ETV Portfolio	**Peter Chin, M.D.** Acting Chief Medical Officer	10:05am ET
TransportVehicle™ Platform: Transforming Treatment for Alzheimer's Disease (AD)	**Why Now Is the Time for Breakthroughs in AD**	**Ryan Watts, Ph.D.** Chief Executive Officer	10:20am ET
	Next-Generation of TV-Enabled Therapeutics for AD	**Joe Lewcock, Ph.D.** Chief Scientific Officer	10:30am ET
Integrated Manufacturing	**Driving Speed, Flexibility and Value**	**Dana Andersen, Ph.D.** Chief Technical and Manufacturing Officer	10:50am ET
Evolving Our Business	**Delivering the Value of the TransportVehicle™**	**Alexander Schuth, M.D.** Chief Operating and Financial Officer	11:00am ET
Q&A	**Portfolio and Strategy**	**Denali's Leadership Team**	11:10am ET

Denali's Leadership Team

Ryan Watts, Ph.D.
Chief Executive Officer

Alexander Schuth, M.D.
Chief Operating and Financial Officer

Peter Chin, M.D.
Acting Chief Medical Officer and Head of Development

Katie Peng
Chief Commercial Officer

Joe Lewcock, Ph.D.
Chief Scientific Officer

Dana Andersen, Ph.D.
Chief Technical and Manufacturing Officer

Cindy Dunkle
Chief People Officer

Chris Walsh, J.D., Ph.D.
General Counsel

Analyst Day Guest Speakers

Barbara Burton, M.D.

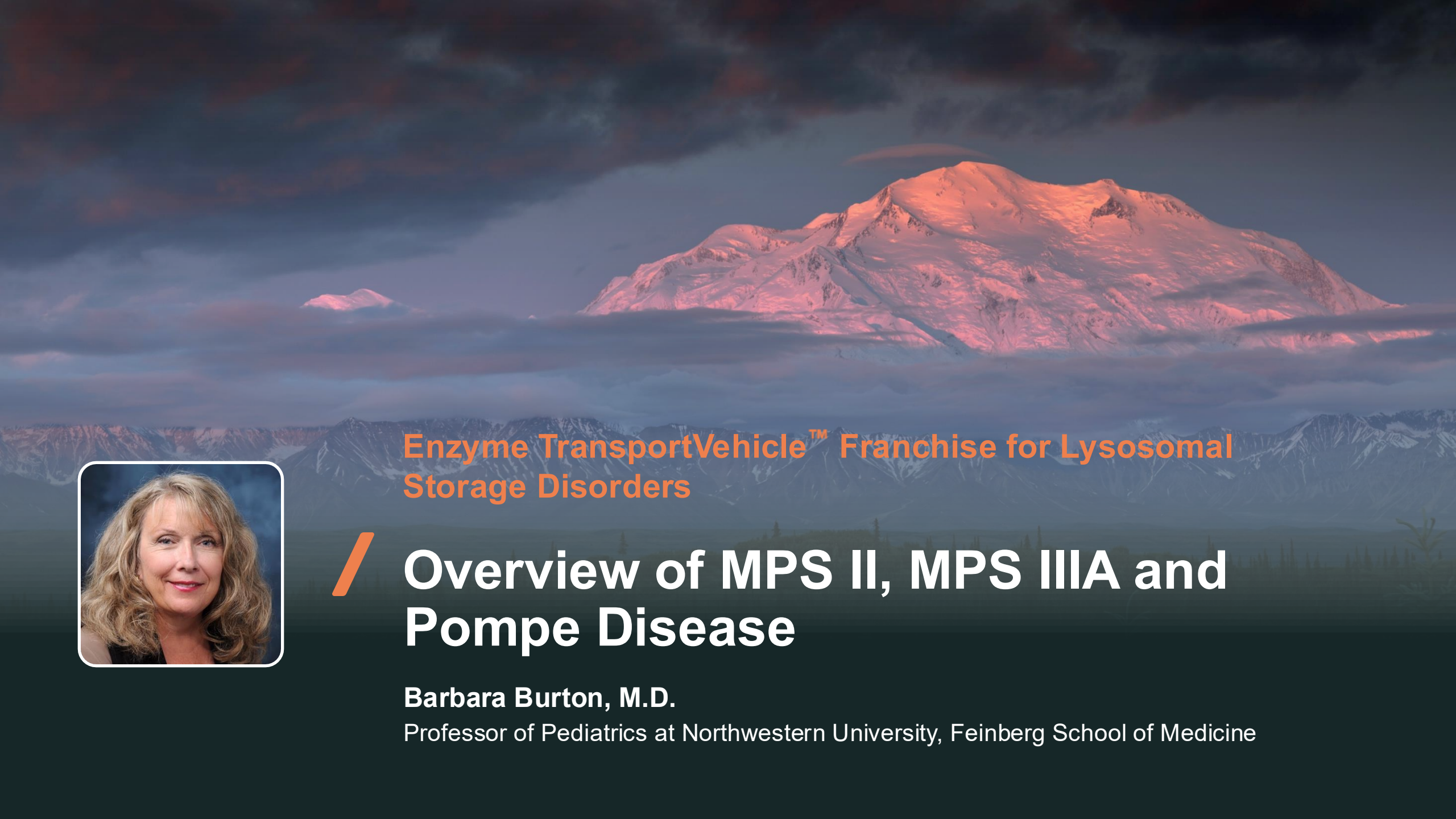
- Professor of Pediatrics at Northwestern University and Attending Physician in Genetics, Genomics, and Metabolism at Lurie Children's Hospital
- Board certified in Pediatrics, Clinical Genetics, and Clinical Biochemical Genetics with research focused on inborn errors of metabolism and newborn screening
- Leading researcher in metabolic and lysosomal disorders and author of 300+ peer-reviewed papers and co-editor of two textbooks

Kim Stephens, Ph.D.

- Executive Director of the Dr. Joseph Muenzer MPS Research and Treatment Center at UNC, Chapel Hill
- Mother to Cole, who was diagnosed with MPS II when he was 2 ½ and has been in a clinical trial at UNC for the past ten years
- Former co-chair of the Newborn Screening Committee for EveryLife Foundation
- Board Member Emeritus for Project Alive, a research and advocacy organization for MPS II

Jason Madison

- Longtime member of the MPS II (Hunter syndrome) community and active leader based in Allentown, Pennsylvania
- More than 25 years of service with the National MPS Society, including Board membership and founding the Adult Resource Committee; background in graphic design and music composition
- Dedicated patient advocate contributing to multiple research studies and a unifying voice within the adult MPS community



Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

Overview of MPS II, MPS IIIA and Pompe Disease

Barbara Burton, M.D.
Professor of Pediatrics at Northwestern University, Feinberg School of Medicine

What are LSDs?

- A group of over 50 disorders, each associated with deficiency of a different lysosomal enzyme or transport protein
- Inherited in an autosomal recessive or X-linked fashion
- Very heterogenous

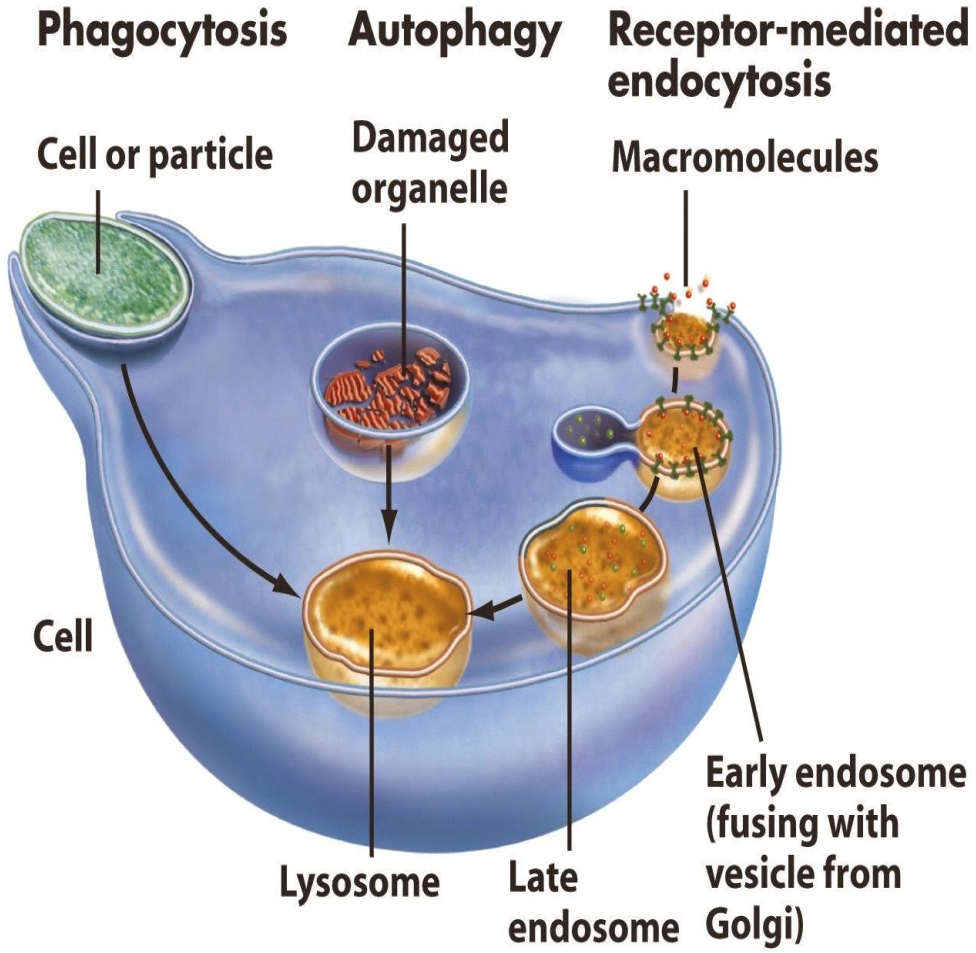
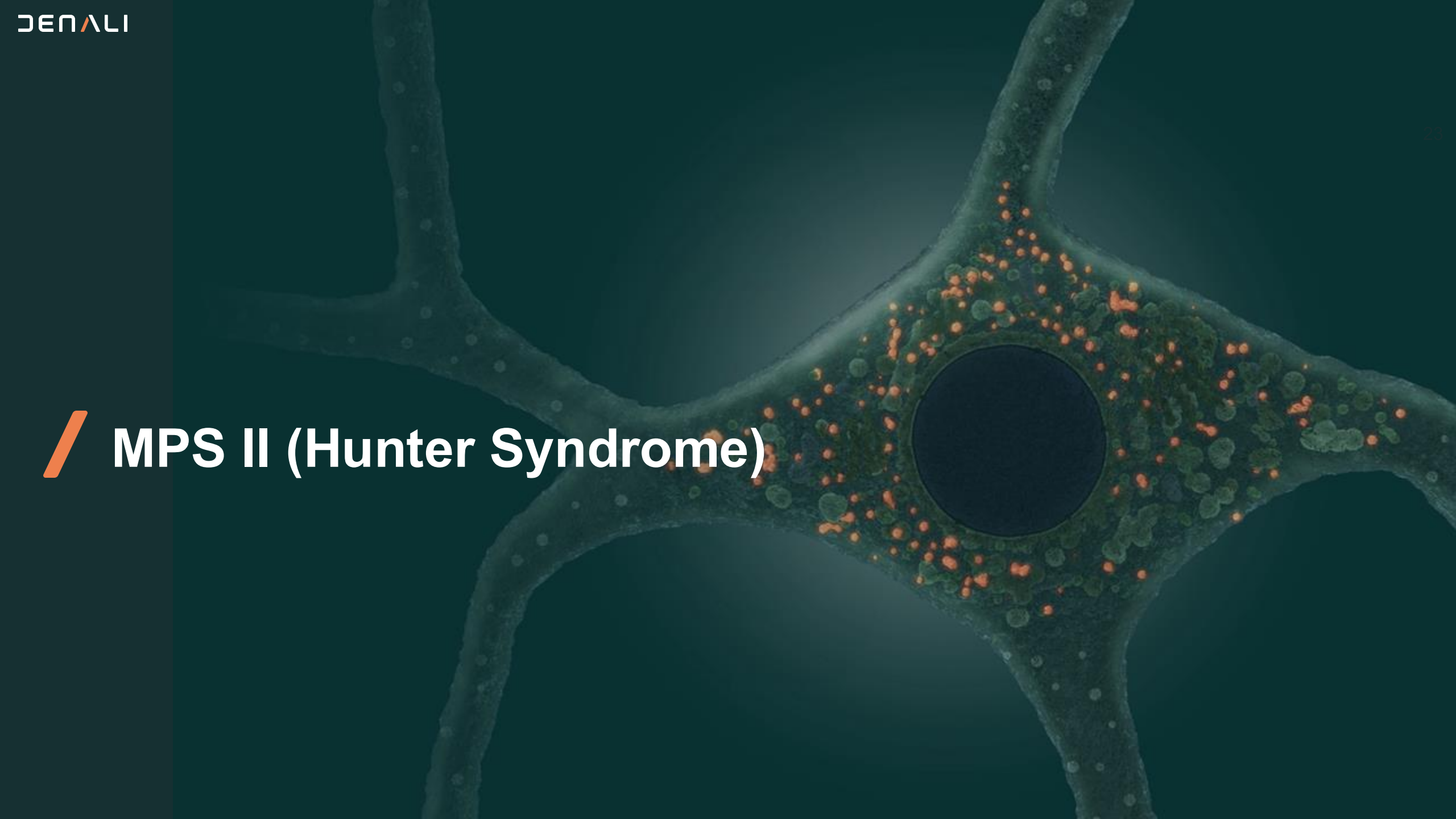


Figure 7-14, *Biological Science*, 2/e, ©2005 Pearson Prentice Hall, Inc.



MPS II (Hunter Syndrome)

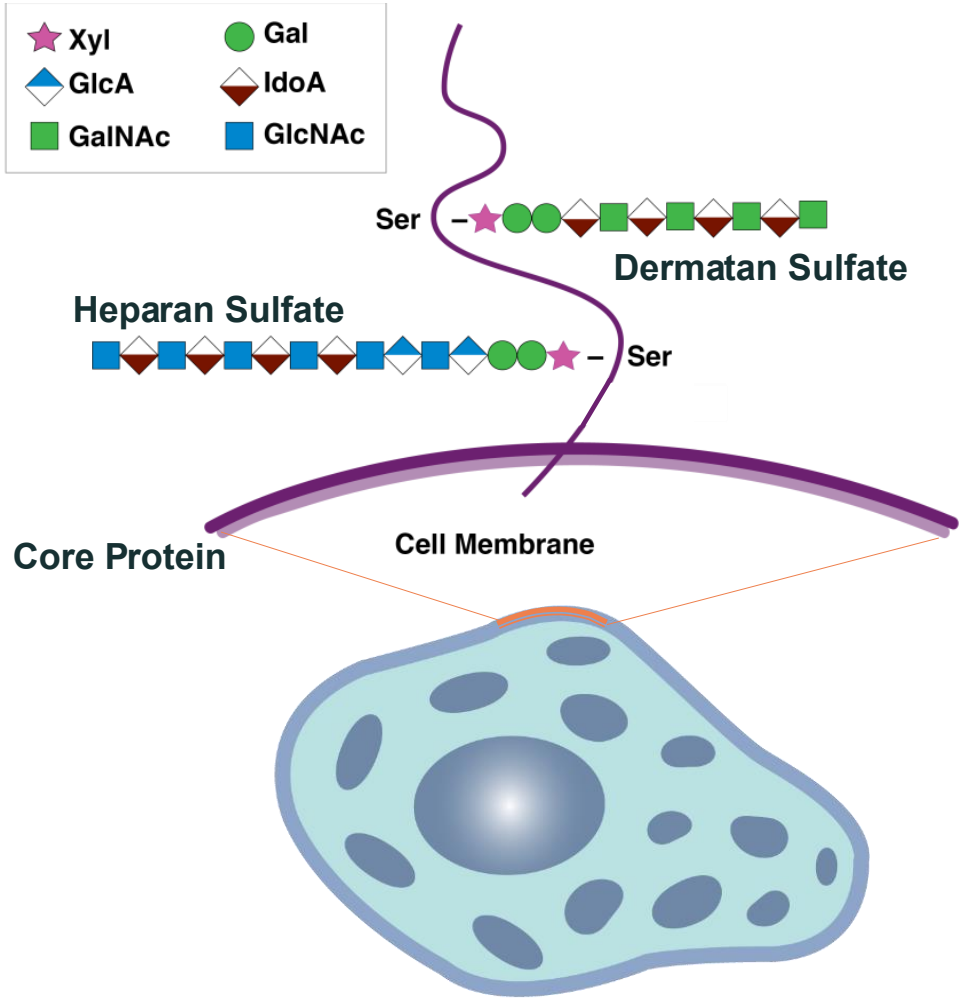
Hunter Syndrome (MPS II) is a Type of Mucopolysaccharidosis, a Subset of the Lysosomal Storage Disorders (LSDs)[1,2]

- Mucopolysaccharidosis (MPS) conditions are rare, progressive genetic disorders that can affect nearly every organ in the body[1,2]
- Hunter syndrome, or mucopolysaccharidosis type II (MPS II), is one of 8 distinct MPS disorders
  - It is estimated that 1 in every 25,000 infants born will have an MPS disorder[4]
  - Approximately 1 in every 100,000 infants will have Hunter syndrome. This is an X-linked disorder so almost all affected infants are male
- MPS diseases are caused by a deficiency of lysosomal enzymes, which are needed to degrade glycosaminoglycans (GAGs)
- The specific enzymatic deficient in MPS II is iduronate-2-sulfatase which is coded for by the IDS gene. Enzyme deficiency leads to progressive accumulation of the glycosaminoglycans heparan and dermatan sulfate.

1. Giugliani R et al. *Genet Mol Biol*. 2014;37(2):315-329; **2.** Wang RY et al; ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. *Genet Med*. 2011;13(5):457-484; **3.** Muenzer *J. Rheumatology*. 2011;50:v4-v12; **4.** NINDS, Mucopolysaccharidoses Fact Sheet, November 2019. NIH Publication No. 19-NS-5115; **5.** Meikle PJ et al. *JAMA*. 1999;281(3):249-254.

What are Glycosaminoglycans (GAGs)?

- GAGs consist of a core protein plus simple carbohydrates to form a type of molecule called proteoglycans
- Proteoglycans are expressed throughout the extracellular matrix and cell surface to support cell signaling and proliferation, tissue morphogenesis, and the interaction of growth factors



Gal – Galactose; **GalNAc** – N-acetylgalactosamine; **GlcA** – Glucuronic acid; **GlcNAc** – N-acetylglucosamine; **IdoA** – Iduronic acid; **Xyl** – Xylose; Mizumoto S et al. *Biomed Res Int*. 2014;2014:495764. https://doi.org/10.1155/2014/495764. Accessed April 6, 2020.

Variability of MPS II

- MPS II occurs along a spectrum of severity but there are two major subtypes – the neuronopathic form (70% of cases) characterized by progressive neurodegeneration and cognitive decline and the non-neuronopathic or attenuated form (30%) characterized by normal or near-normal cognitive development without progressive decline
- Within the neuronopathic subtype there is considerable variability in the pattern of decline
- There are a small number of “intermediate” patients with stable mild to moderate cognitive impairment- 5-10% of total patients – may be classified in either neuronopathic group or attenuated group depending on definitions used

Real Patient Symptom Progression

Abdominal Hernia[1]

Aiden's age at symptom onset:
4-10 months

Otitis Media[1]

Aiden's age at symptom onset:
4-10 months

Enlarged Tongue and Tonsils[1]

Aiden's age at symptom onset:
18 months

Aiden, Age 3 Aiden, Age 5

Developmental Delays[2]

Aiden's age at symptom onset:
18 months

Coarse Facial Features[1]

Aiden's age at symptom onset:
30 months

Stiff Joints and Claw-Like Hands[1]

Aiden's age at symptom onset:
36 months

1. Wraith JE et al. *Genet Med*. 2008;10(7):508-516; **2.** Burton K et al. *Eur J Pediatr*. 2012;17(2):631-639.

Later Signs/Symptoms of MPS II

- Progressive airway narrowing
- Cardiac valve thickening and dysfunction, cardiomyopathy
- Carpal tunnel syndrome
- Retinal degeneration with progressive visual impairment
- In neuronopathic patients, developmental slowing followed by progressive neurodegeneration
- **Death in teens for most neuropathic patients; those with attenuated disease may live into their 40’s, 50’s or beyond**

Newborn Screening

- MPS II was added to RUSP in 2017; approximately 25% of US newborns are now screened but this is expected to increase rapidly

Current Treatment of MPS II

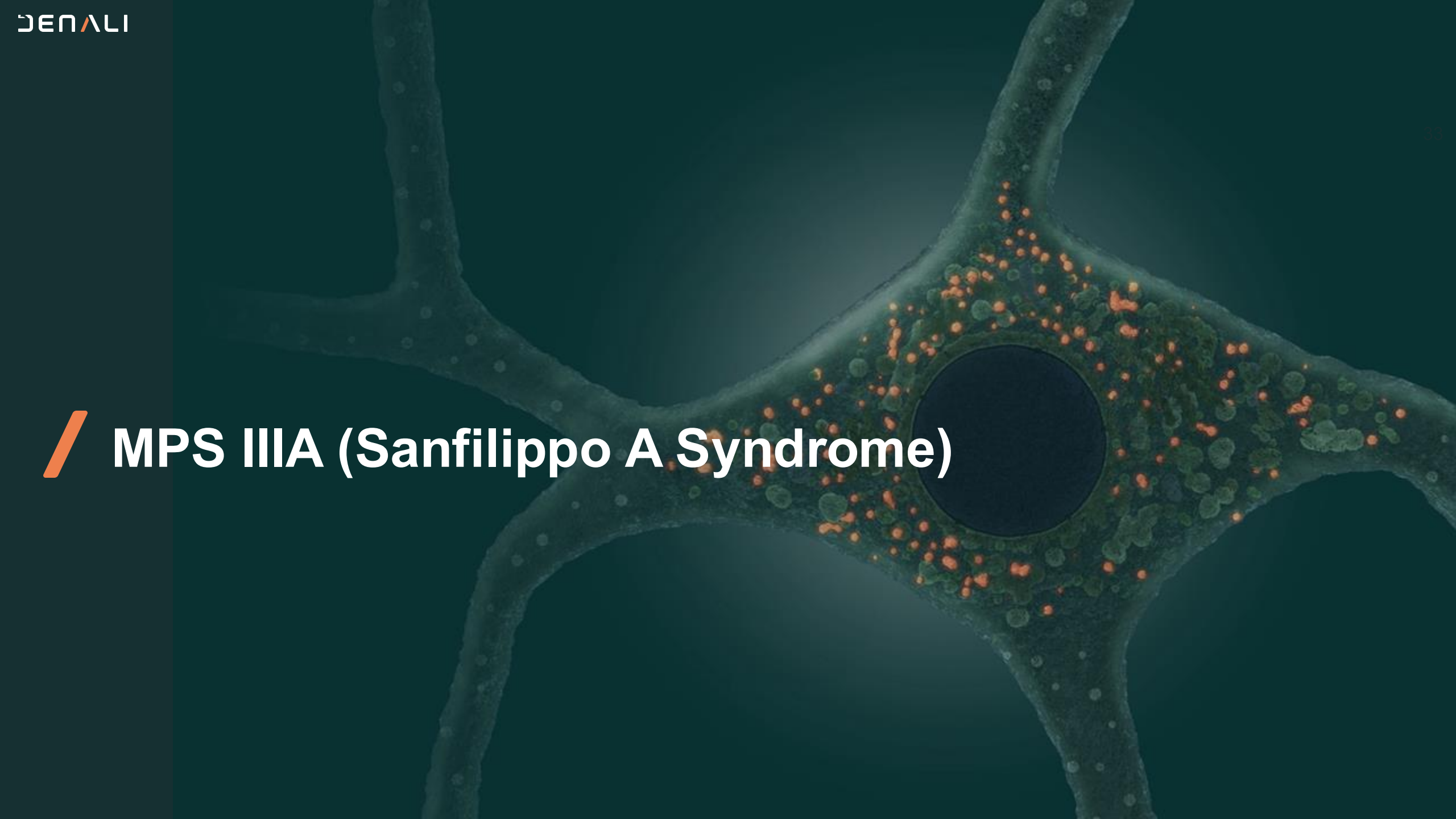
- Most affected individuals receive enzyme replacement therapy with Elaprase® from time of diagnosis
- Surveillance for complications with symptomatic treatment as needed
- Hematopoietic stem cell transplantation is used in some cases but relatively infrequently in North America. It provides somatic benefit and may provide some CNS benefit if done within first year of life but data are limited.

Limitations of Current ERT

- Does not cross the blood brain barrier in significant amounts so does not alter the course of neurodegeneration leading to death
- Cardiac valve and airway issues continue to progress and are the major cause of death in attenuated patients
- Does not prevent retinal disease
- Does not prevent progressive hearing loss so most patients require hearing aids

Unmet Need in MPS II

- A treatment is needed to address the progressive neurodegeneration and cognitive decline seen in the neuronopathic form of the disease
- Better treatment for the hard to reach peripheral tissues in which disease progression continues to occur despite current ERT



MPS IIIA (Sanfilippo A Syndrome)

MPS IIIA – Sanfilippo Syndrome, Type A

- Autosomal recessive disorder resulting from deficiency of the enzyme N-sulfoglucosamine sulfohydrolase (SGSH), also referred to as sulfamidase or heparan sulfate sulfatase. This leads to progressive accumulation of heparan sulfate.
- **Most common of the 4 types of MPS III, accounting for about 70% of cases**
- **Overall incidence estimated at 1 in 125,000 births**

MPS IIIA – Clinical Findings

- Primarily (but not exclusively) a neurologic disorder
  - Infants are normal at birth but exhibit developmental slowing at about 2 years of age with speech delay
  - Hyperactive/aggressive behavior at about age 3
  - Developmental regression becomes apparent typically by 4-5
  - Often initially misdiagnosed as ADHD, non-specific developmental delay or autism
- Average age at clinical diagnosis 4-5 years; average age of death 10-15 years. Approximately 20 % of patients have a more attenuated course with later diagnosis and longer survival.

MPS IIIA – Additional Findings

- Hepatosplenomegaly
- Recurrent otitis media and other respiratory infections
- Chronic or recurrent diarrhea
- Coarse facial features- less prominent than in other MPS disorders
- Prominent GI dysmotility late in the disease
- Cardiac valve disease
- Skeletal findings such as hip dysplasia

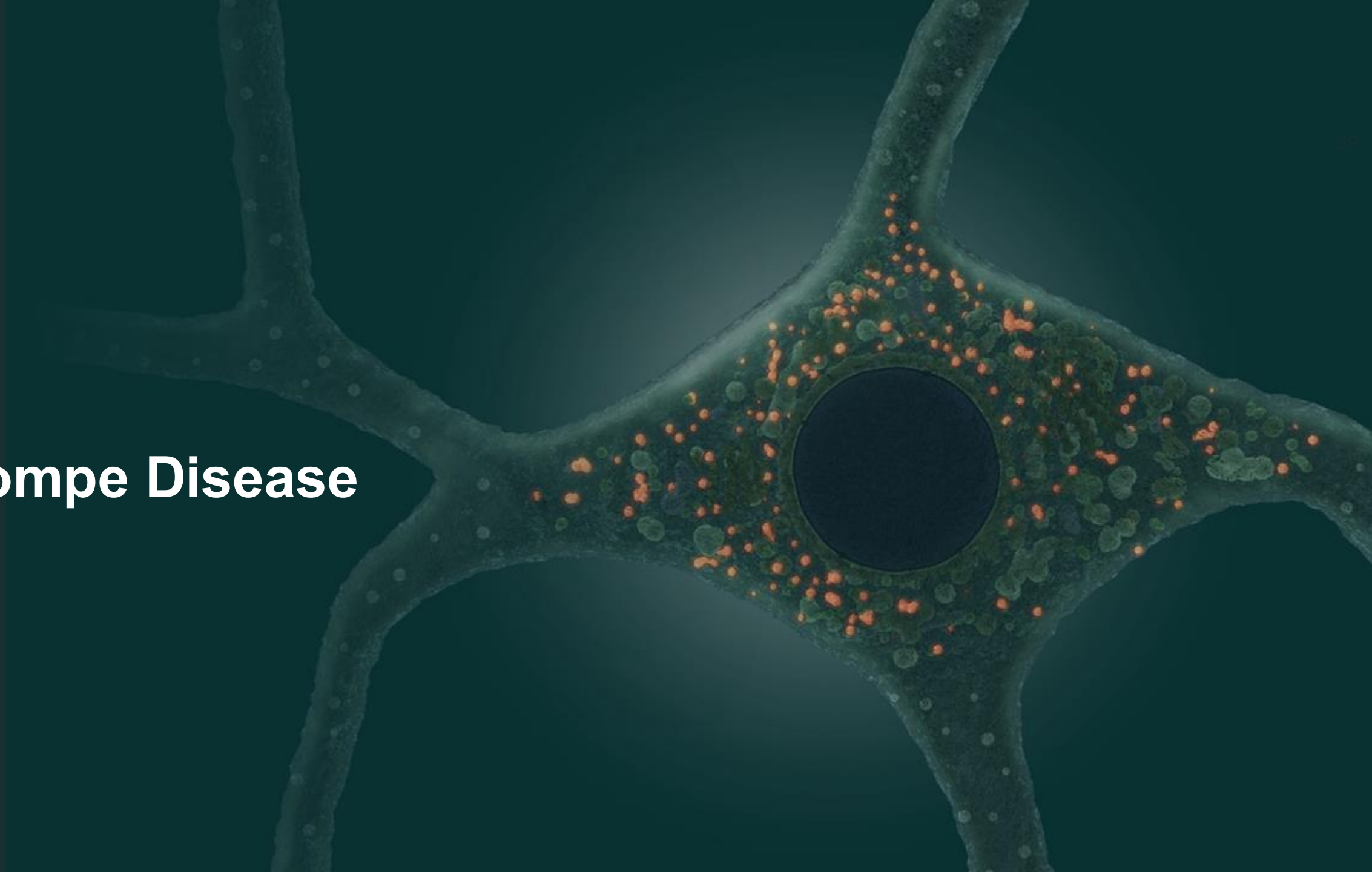
MPS IIIA – Current Treatment

- Primarily symptomatic
- No approved disease-modifying therapy; HSCT does not alter the course of the disease
- Many patients currently receive anakinra (Kineret®) approved for a different disorder but with some data showing benefit in MPS III
- **Many therapeutic trials including trials of IV or intrathecal ERT and gene therapy have failed in past. The frustration in the patient community is very high.**
- **No newborn screening underway at present but it is feasible**

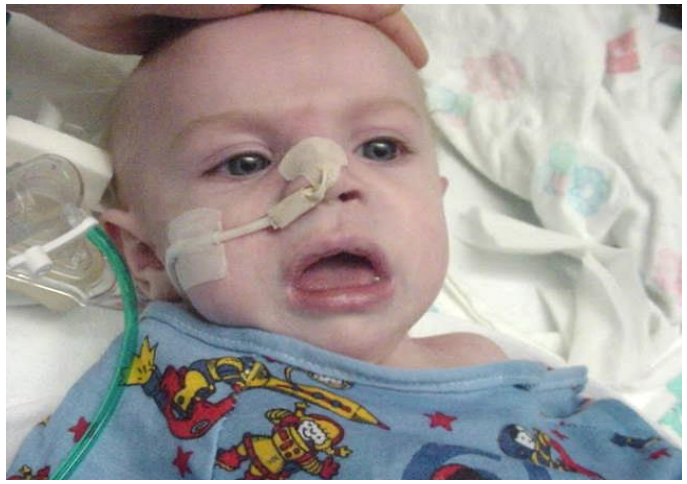
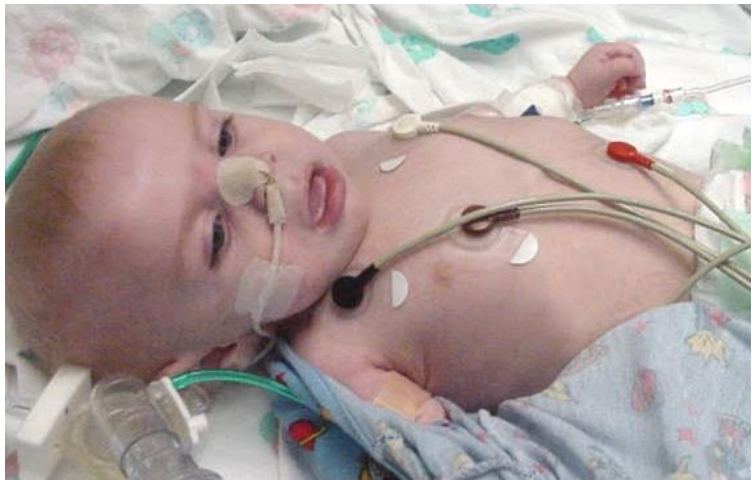
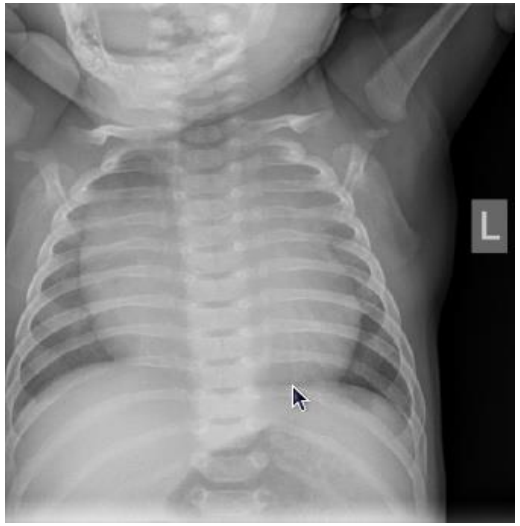
MPS IIIA – Unmet Need

- There is a pressing need for any disease-modifying therapy to health or slow down the relentless progression of the disease and prolong life
- The focus is on the brain but if treatment of the brain is successful, the need for effective treatment of peripheral tissues is likely to become more pressing

Pompe Disease



Pompe Disease


Photos courtesy of Dr. Ficicioglu and Dr Herman F.M. Busch, Erasmus MC, Rotterdam, The Netherlands.

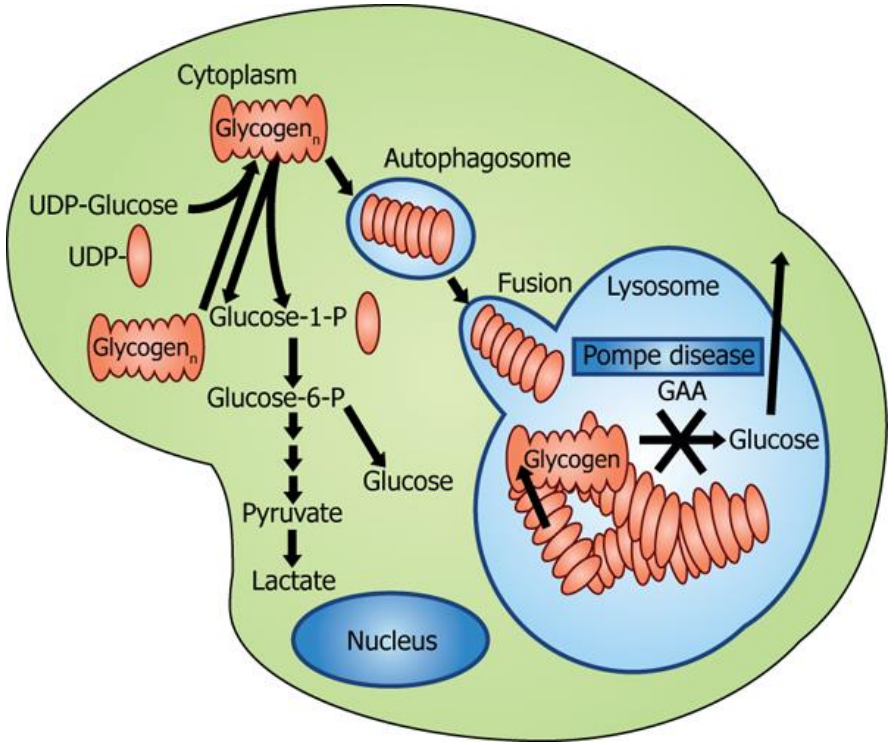
What is Pompe Disease

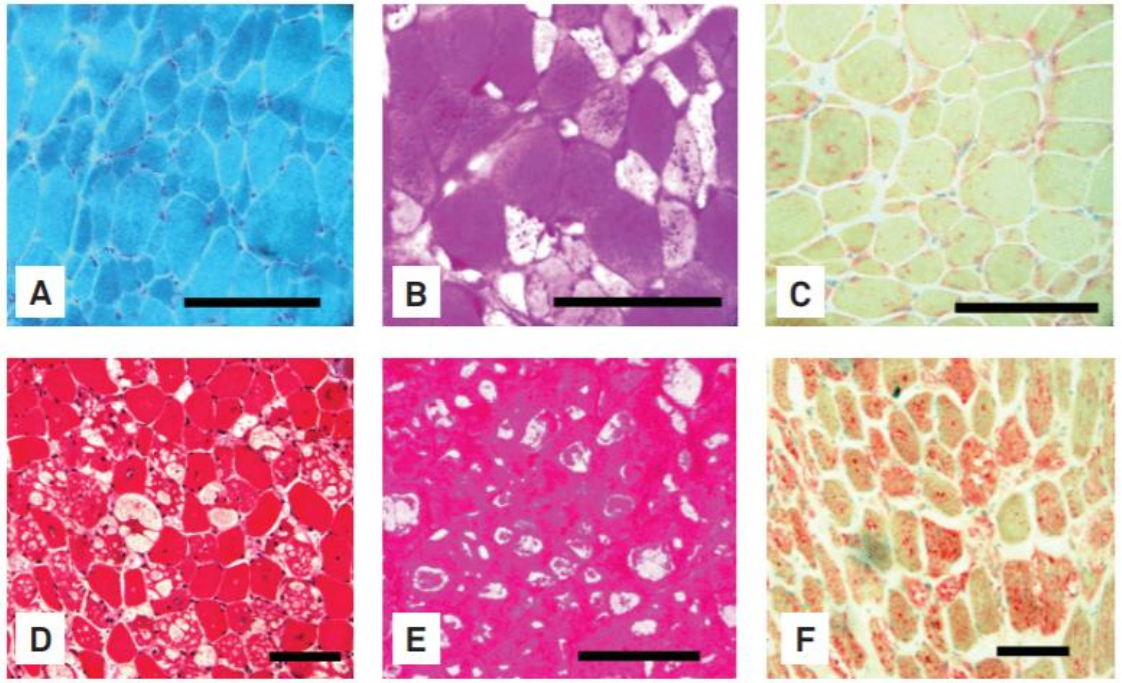
- It is a progressive, genetically determined disorder inherited in an autosomal recessive fashion
- Biallelic mutations in the GAA gene lead to deficiency of the lysosomal enzyme alpha-glucosidase and progressive accumulation of glycogen in lysosomes of cells
- Other names for Pompe disease used in past: acid maltase deficiency, glycogen storage disease type II

Leslie N, Bailey L. In: Adam MP, et al. *GeneReviews*. University of Washington, Seattle; 2007 [updated 2017], pp 1993-2019

Pompe Disease: Glycogen Storage Disorder Type II and Lysosomal Storage Disorder

Incidence: 1 in 20,000; Males and Females Affected in Equal Numbers

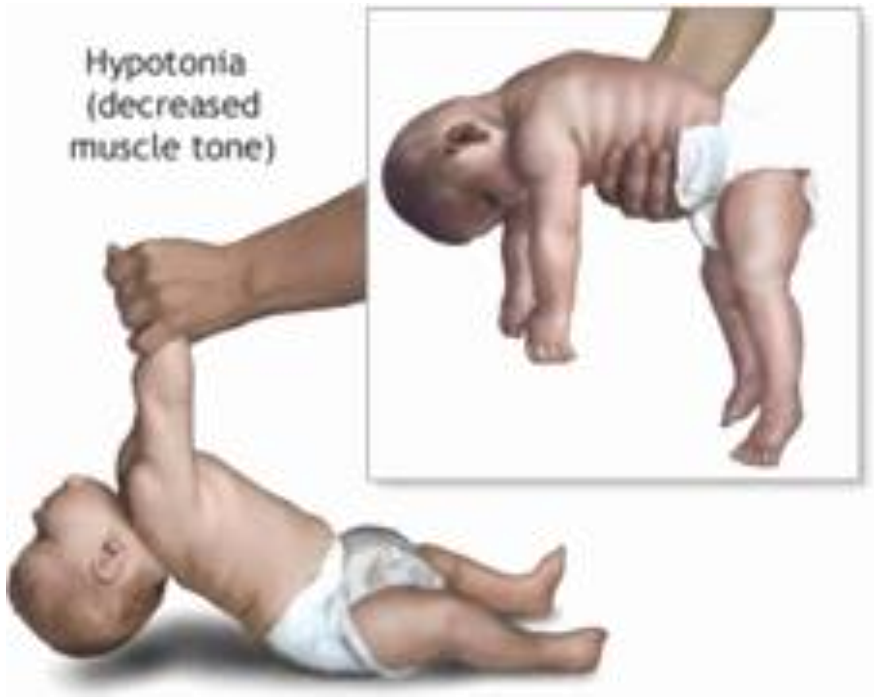




Rabin N, et al. *Am J Med Genet C Semin Med Genet*. 2012;160:13-21; Werneck LC, et al. *Arq Neuropsiquiatr*. 2013;71(5):284-289; National Institutes of Health. Genetics Home Reference. *Pompe Disease*. 2020. https://ghr.nlm.nih.gov/condition/pompe-disease#statistics

Infantile-Onset Pompe Disease (IOPD)

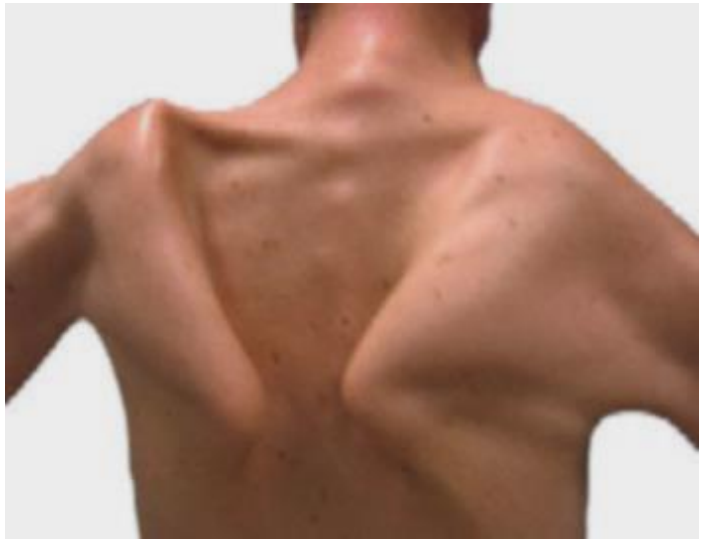
- Poor feeding/failure to thrive
- Motor delay/muscle weakness
- Hypertrophic cardiomyopathy
- Onset within 1st few months of life
- Death within 12-18 months of life without treatment
- Emerging post-treatment phenotype includes persistent and progressive muscle weakness, hearing loss and white matter changes in the brain with progressive neurologic decline reported in a few



Hirschhorn R, Reuser AJ. *In* Scriver CR, et al; eds. The Metabolic and Molecular Bases of Inherited Disease. NY: McGraw-Hill, 2001, pp 3389-3420; van den Hout HM, et al. *Pediatrics*. 2003;112(2):332-340; EBIX A.D.A.M; Images. http://www.adamimages.com/Illustration/SearchResult/1/hypotonia

Late-Onset Pompe Disease (LOPD)

- Onset across the lifespan: <12 months to 7th decade
  - Includes juvenile- and adult-onset forms
- Progressive proximal and axial muscle weakness
  - Gower's sign, winging scapula
  - Common misdiagnosis: LGMD
- Respiratory dysfunction
  - Diaphragmatic weakness
  - Intercostal muscle weakness
  - Ventilatory support may be needed at night
- No apparent cardiac involvement



Leslie N, Bailey L. *In*: Adam MP, et al. GeneReviews. University of Washington, Seattle; 2007 [updated 2017], pp 1993-2019; Heaver C, et al. *Orthoped Trauma*. 2019;33(4)239-248; Oncohema Key. https://oncohemakey.com/13-pompe-disease/.

Newborn Screening for Pompe Disease

- Added to the RUSP in 2015
- Now on the NBS panel in all 50 states

Current Treatment of Pompe Disease

- 3 approved forms of ERT available in US
  - Lumizyme – approved for both IOPD and LOPD
  - Nexviazyme – approved for LOPD in children and adults
  - Pombiliti – given with Opfolda (miglustat) approved for adults not improving on their current ERT
- Patients with IOPD are treated urgently at time of diagnosis. Patients with LOPD diagnosed clinically are offered treatment at diagnosis; those diagnosed by NBS are monitored and treated once symptoms appear

How Well Does Current Treatment Work

- If immunologic issues are addressed with appropriate immune modulation, it is very effective for treatment of cardiomyopathy in IOPD and is live-saving
- It is much less effective for skeletal muscle disease. Most patients exhibit modest improvement in muscle strength, mobility and respiratory function after onset of treatment followed by variable period of stability but ultimate disease progression.
- Long term data not available for the two newer ERT's but the improvement seen is incremental when patients are switched. Considerable unmet need still exists

Why is Treatment Less Effective for Skeletal Muscle?

- Sparse M6P receptors compared with other tissues
- Inadequate dosing
- Late diagnosis in some patients with some muscle fibers destroyed and replaced with fat
- Lysosomal rupture leads to accumulation of cytoplasmic glycogen which is not cleared by ERT targeted to the lysosome

Unmet Need in Pompe Disease

- We likely need treatment of the brain in IOPD although the natural history of the brain disease has not yet been fully charted
- Better treatment of the skeletal muscle disease is needed in both IOPD and LOPD

Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

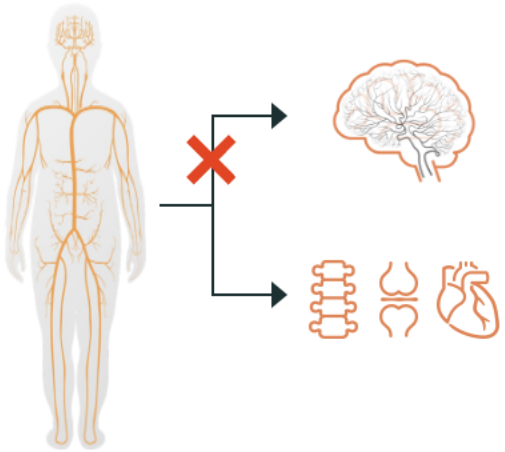
Tividenofusp alfa: Clinical Development & Regulatory Path

Peter Chin, M.D.
Acting Chief Medical Officer and Head of Development

ETV Franchise Opportunity in Lysosomal Storage Disorders

Addressing High Unmet Need

- LSDs are **single-enzyme deficiency** diseases
- **30,000** people with LSDs worldwide
- **2/3** LSDs with **CNS manifestations**

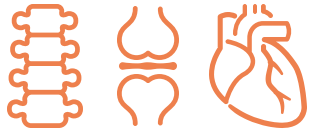


Traditional ERTs partially address somatic but not CNS symptoms

~90% historical approval rate

Targeting Brain & Body with ETV

ETVs enable brain delivery of enzymes to address cognitive and behavioral symptoms



Potential to **enhance peripheral delivery**

Goal is to treat the full disease spectrum

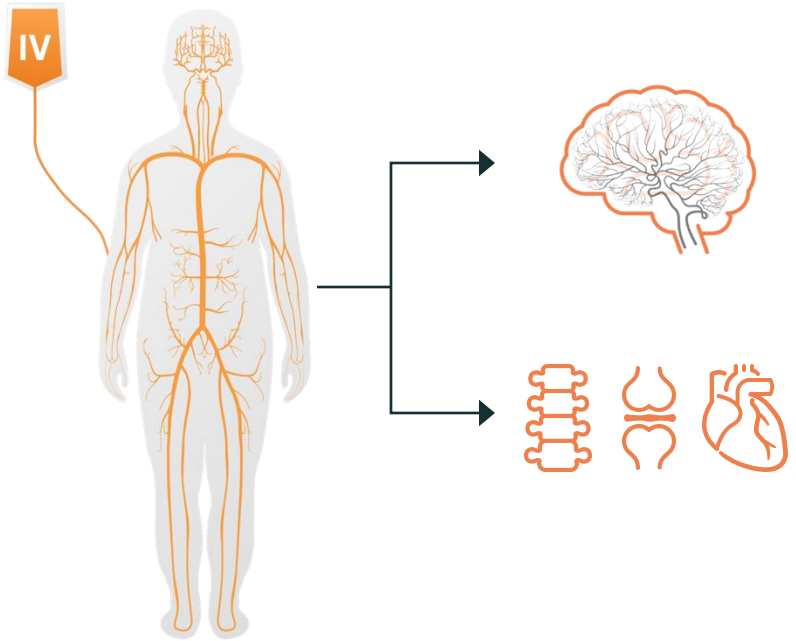
ETV – Enzyme transport vehicle; **LSDs** – Lysosomal storage disorders; **CNS** – Central nervous system; **ERTs** – Enzyme replacement therapies

Brain Delivery Is Critical Unmet Need of Hunter Syndrome Therapy

Monogenic lysosomal storage disorder caused by deficient iduronate-2-sulfatase (IDS)

tividenofusp alfa
(DNL310)

Tividenofusp alfa is a brain-penetrant ERT designed to reduce the substrate of IDS (heparan sulfate) throughout the body and treat neurocognitive and physical manifestations



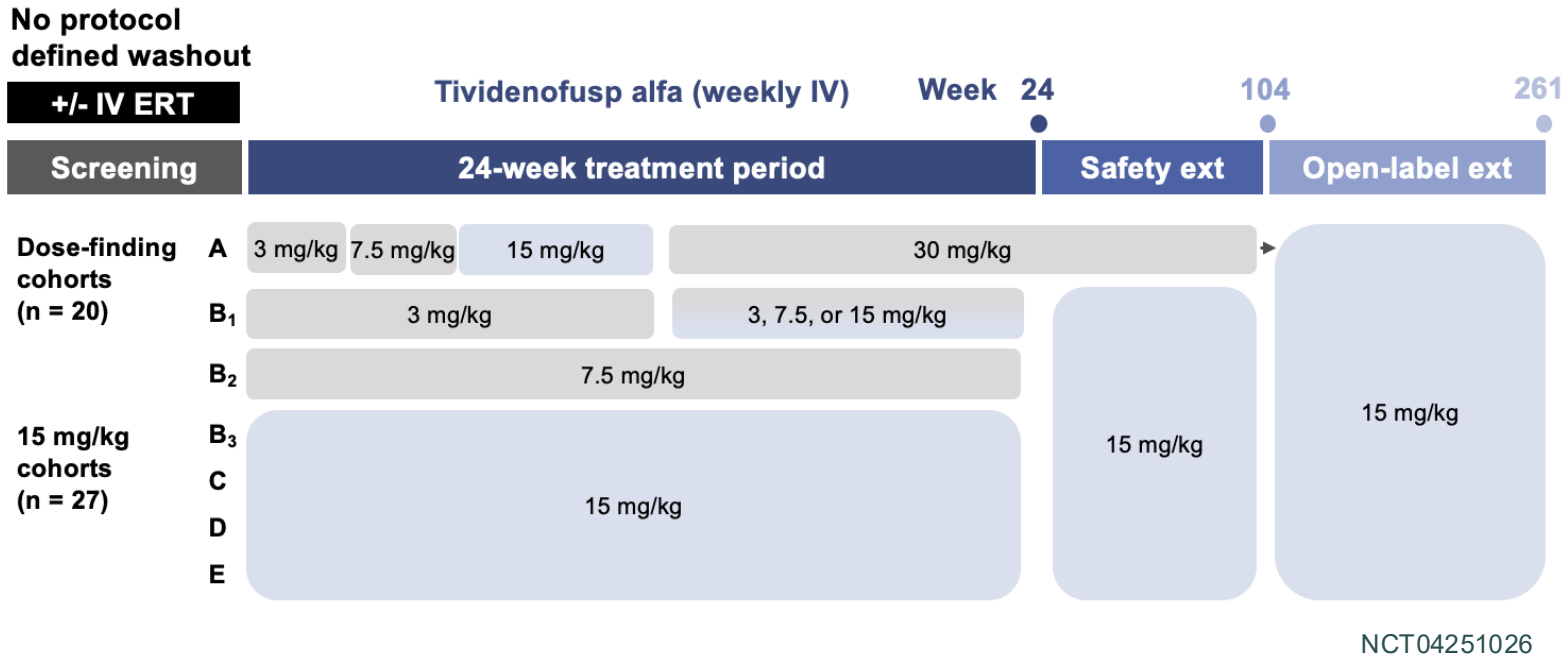
Traditional enzyme replacement therapy does not cross the blood brain barrier and only partially addresses peripheral manifestations

ERT – Enzyme replacement therapy

Tividenofusp Alfa Phase 1/2 Study Supporting US AA

Design

- **Duration:** 24-week study + 80-week safety extension + open-label extension
- **Study Design:** Open label



NCT04251026

Study Population

- Neuronopathic and non-neuronopathic MPS II, aged ≤18 years
- ERT-naïve and treatment-experienced

Key Endpoints

- **Primary:** Adverse events, Infusion-related reactions, other indicators of safety and tolerability
- **Secondary:** CSF HS, Urine HS, Adaptive behavior (Vineland), Liver volume
- **Exploratory:** Serum NfL, CSF biomarkers, hearing thresholds, cognition (BSID, KABC)

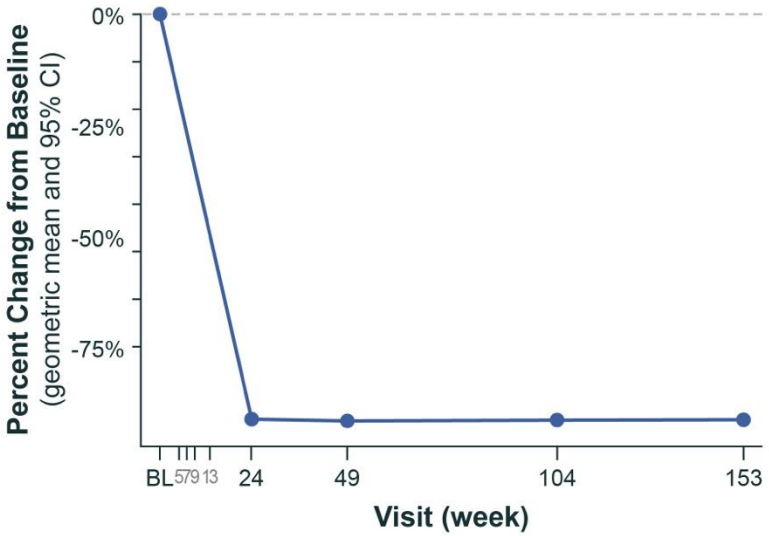
Substantial long-term safety and efficacy experience informs positive benefit-risk profile in MPS II

B_3 was part of the dose-finding cohorts; **BSID** – Bayley Scales of Infant Development; **CSF** – Cerebrospinal fluid; **ERT** – Enzyme replacement therapy; **ext** – Extension; **HS** – Heparan sulfate; **IV** – Intravenous; **KABC** – Kaufman Assessment Battery for Children; **MPS II** – Mucopolysaccharidosis type II; **NfL** – Neurofilament light chain; **SOC** – Standard of care; Source: WORLD 2025.

Tividenofusp Alfa Phase 1/2 in MPS II: Biomarker Effects

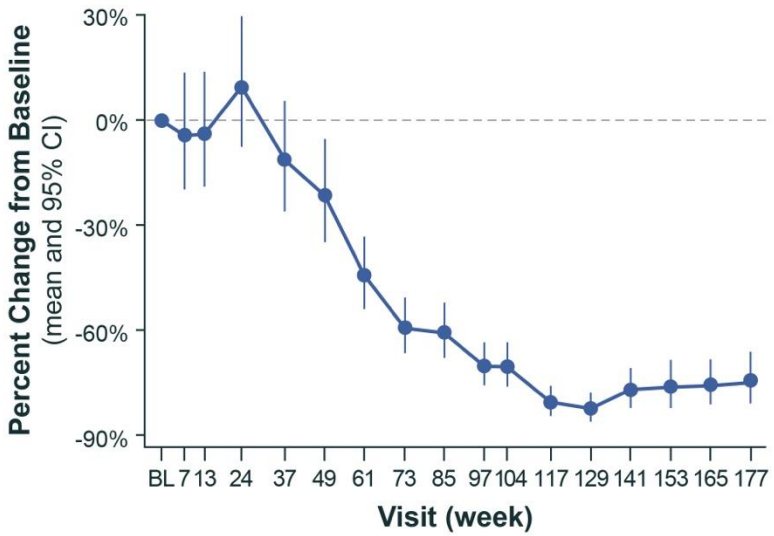
Normalization of CSF HS

Biomarker of CNS disease



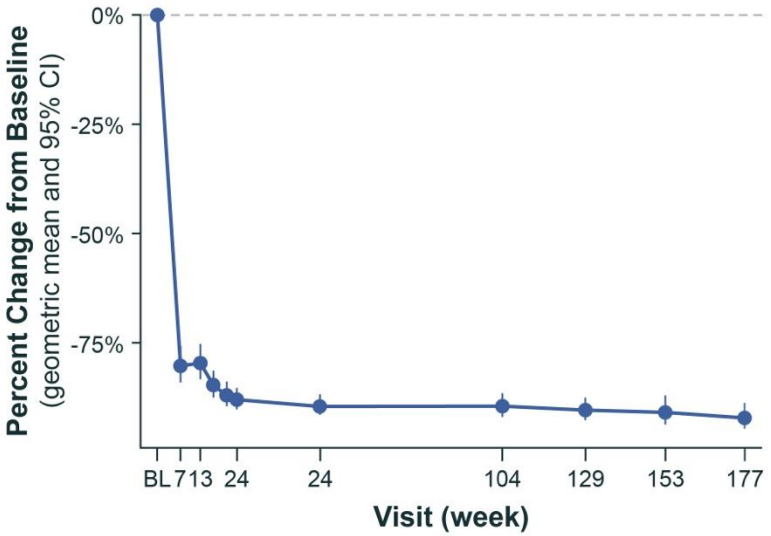
Normalization of NfL

Biomarker of neuronal damage



Normalization of Urine HS

Biomarker of peripheral disease



- Robust reductions from baseline in CSF heparan sulfate, serum neurofilament light, and urine heparan sulfate, with a majority in the normal range after treatment with tividenofusp alfa

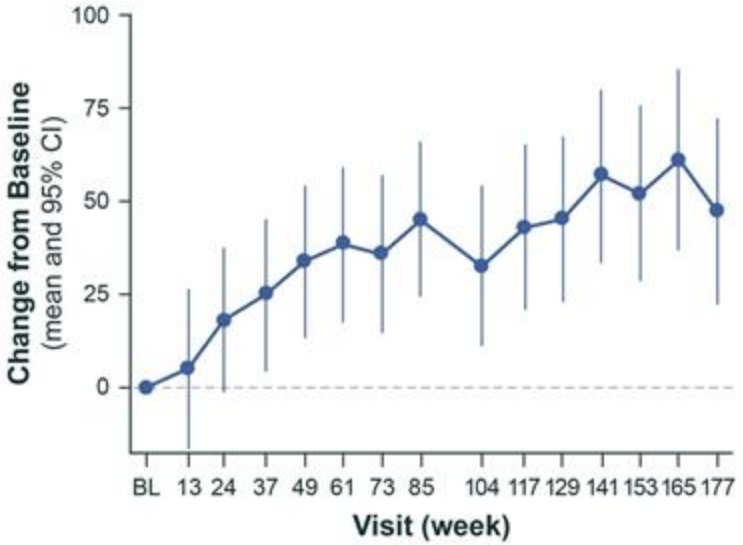
First and only therapy in development for MPS II to achieve normalization of key biomarkers

MPS II – Mucopolysaccharidoses Type II; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **NfL** – Neurofilament light; Source: WORLD 2025.

Tividenofusp Alfa Phase 1/2 in MPS II: Clinical Outcomes

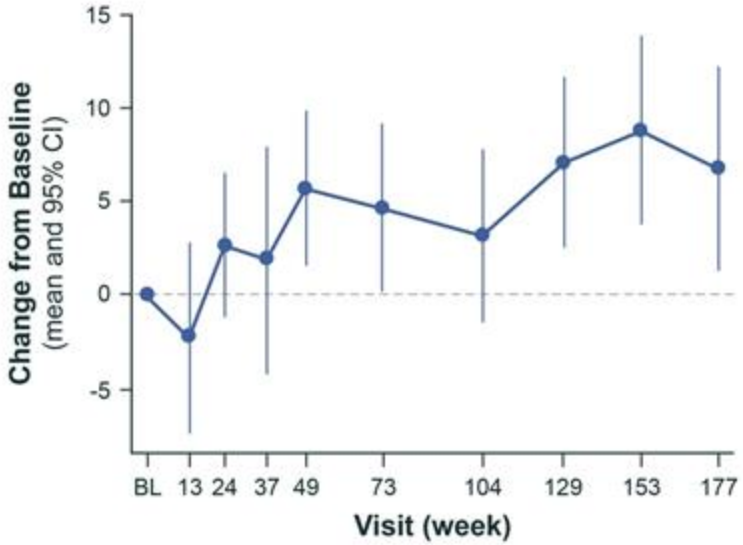
Improvement in Adaptive Behavior

Vineland-3



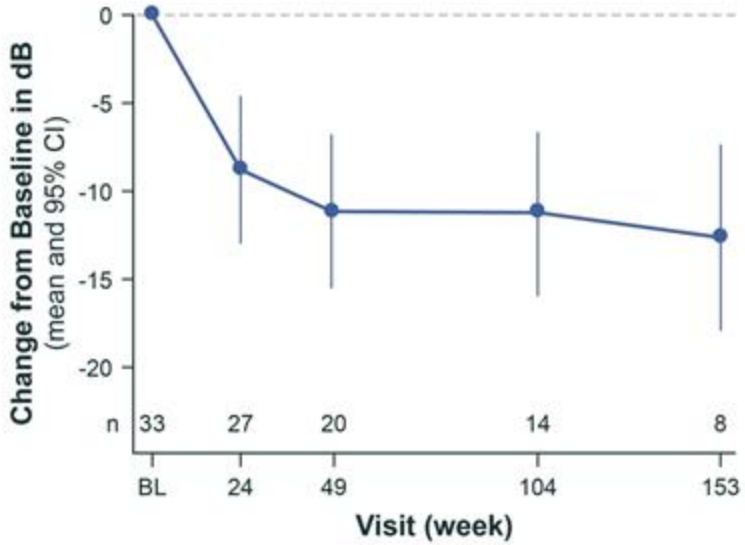
Improvement in Cognition

BSID-III



Improvement in Hearing

Auditory Brainstem Response (PTA)



- While on tividenofusp alfa, clinical outcomes showed skill gains relative to baseline in most participants on measures of adaptive behavior and cognition as well as hearing threshold improvement from baseline in all tested frequencies

Data supports impact on clinical outcomes important to individuals and families with MPS II

MPS II – Mucopolysaccharidoses Type II; **CI** – Confidence interval; **BSID-III** – Bayley Scales of Infant and Toddler Development-Third Edition; **PTA** – Pure tone average; Source: WORLD 2025.

Tividenofusp Alfa Phase 1/2 in MPS II: Safety

	24-Week Treatment Period (BL to W24) n = 47	All Periods (BL to W261) n = 47
TEAE[1], n (%)	47 (100)	47 (100)
Mild	8 (17.0)	2 (4.3)
Moderate	35 (74.5)	32 (68.1)
Severe[2]	4 (8.5)	13 (27.7)
Serious TEAE, n (%)	6 (12.8)	18 (38.3)
Treatment-Related Serious TEAE	3 (6.4)	3 (6.4)
Fatal TEAE, n (%)	0	0
TEAE Leading to Discontinuation, n (%)	1 (2.1)	1 (2.1)

- Across all periods, most participants (72%) had TEAEs that were mild or moderate in severity
  - One participant (2.1%) discontinued due to a TEAE; discontinuation was in part due to a TEAE of IRR (and other adverse events considered not related to drug)
  - Three participants (6.4%) had serious TEAEs that were considered related to treatment
    - Two participants with IRRs (one mild, one severe)[3]; both recovered and received subsequent doses
    - One participant with anemia (moderate CTCAE grade); participant remains stable with continued dosing
- In the 24-week treatment period (BL to W24), the most frequent TEAEs (>20%) were IRRs[3], anemia, vomiting, pyrexia, upper respiratory infection, and rash; the majority of these were mild to moderate in severity
  - Most IRRs were clinically manageable with standard pre-medications and/or adjustment of infusion time

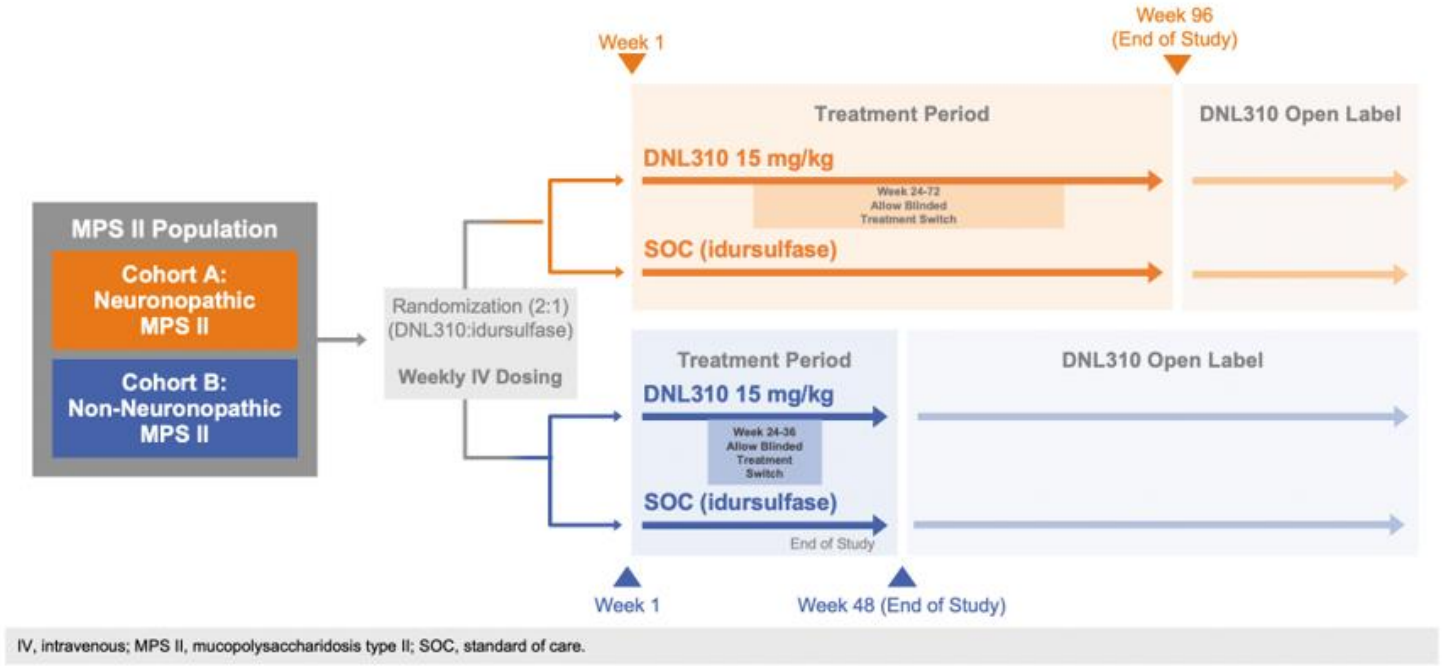
Phase 1/2 safety and clinical data supports broad indication for treatment of full spectrum of MPS II

1. TEAE by maximum severity; **2.** Missing intensity was summarized as severe; **3.** IRRs including allergic reactions and anaphylaxis; **BL** – Baseline; **CTCAE** – Common terminology criteria for adverse events; **IRR** – Infusion-related reaction; **MPS II** – Mucopolysaccharidosis type 2; **TEAE** – Treatment emergent adverse event; **W** – Week.

Tividenofusp Alfa Global Phase 2/3 Study Design

Design

- **Duration: Cohort A:** 96-week study + extension | **Cohort B:** 48-week study + extension
- **Study Design:** Randomized double-blinded active control



IV, intravenous; MPS II, mucopolysaccharidosis type II; SOC, standard of care.

NCT05371613

Study Population

- **Cohort A:** Neuronopathic MPS II, aged ≥2 to <6 years
- **Cohort B:** Non-neuronopathic MPS II, aged ≥6 to <26 years
- Receiving idursulfase for >4 months

Key Endpoints

- **Cohort A:** CSF HS, Vineland-3, BSID-II, serum NfL
- **Cohort B:** 6MWT
- **Cohorts A & B:** Urine HS and DS, Liver and Spleen MRI volume, Patient / Caregiver Impression of Change, Safety

Rigorous design to confirm efficacy and safety and support global approvals

BSID – Bayley Scales of Infant Development; **CSF** – Cerebrospinal fluid; **ERT** – Enzyme replacement therapy; **HS** – Heparan sulfate; **IV** – Intravenous; **MPS II** – Mucopolysaccharidosis type II; **NfL** – Neurofilament light chain; **SOC** – Standard of care

Tividenofusp Alfa Development and Regulatory Path

PDUFA Target Action Date: April 5, 2026

Preparing for Commercial Launch

- Filed BLA for accelerated approval; granted priority review
- BLA includes data from open-label, global Phase 1/2 study (N=47)
- Up to 18 years of age
- Treatment duration up to five years
- Measuring biomarkers, safety, and exploratory clinical outcomes

47 Phase 1/2 participants

Phase 2/3 Study Ongoing

Supporting Global Approvals

- Randomized, double blind, controlled study (N~63)
- Ages ≥2 to <6 y.o. (Cohort A, neuronopathic)
- ≥6 to <26 y.o. (Cohort B, non-neuronopathic)
- Co-primary endpoints: CSF HS and Vineland-III
- Peripheral endpoints: liver/spleen volume, 6MWT, ABR and others

63  **participants**

Robust data package supporting a target indication for the full MPS II phenotype spectrum

PDUFA – Prescription Drug User Fee Act; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **6MWT –** 6-minute walk test; **ABR –** Auditory brainstem response

MPS II siblings enrolled in the study: investigator perspe

- Pathogenic IDS variant (c.262C>T), absent I2S enzyme activity
- Diagnosed at 3 years 8 months and 5 months of age, respectively, and treated with weekly idursulfase (0.5 mg/kg)
- Both enrolled in the Phase 1/2 study and received weekly tividenofusp alfa 15 mg/kg for > 4 years:
  - Older started at 6 years 4 months
  - Younger started at 2 years 6 months

VIDEOS

Informed consents were obtained for the sibling pair with MPS II to present the information and videos on this slide.

Tividenofusp alfa (DNL310) is an investigational drug and is not approved by any Health Authority.

Tividenofusp Alfa is the Cornerstone of the ETV Franchise

	Immediate 2026	Near / Mid Term 2027 – 2028	Mid / Long Term 2028+	Clinical Value Potential
Tividenofusp alfa (MPS II) First commercial launch	✓ US AA PDUFA April 5, 2026	✓ Initial International Launches	✓ Full Global Potential	• Only therapy shown to normalize disease biomarkers in CSF and periphery
DNL126 (MPS IIIA) Path to US AA		✓ US AA	✓ Global Launch	• Ability to normalize CSF heparan sulfate
DNL952 (Pompe Disease) IND application filed[1]			✓ Global Launch	• TfR-enhanced delivery of GAA to muscle

The ETV franchise can deliver transformative treatments for the LSD community

1. Protocol amended and response to FDA submitted regarding clinical hold**; US AA** – United States Accelerated Approval; **PDUFA** – Prescription Drug User Fee Act; **CSF** – cerebrospinal fluid; **IND** – investigational new drug; **TfR** – transferrin receptor; **GAA** – acid alpha-glucosidase enzyme; **LSD –** lysosomal storage disorders

Overview of MPS IIIA (Sanfilippo Type A)

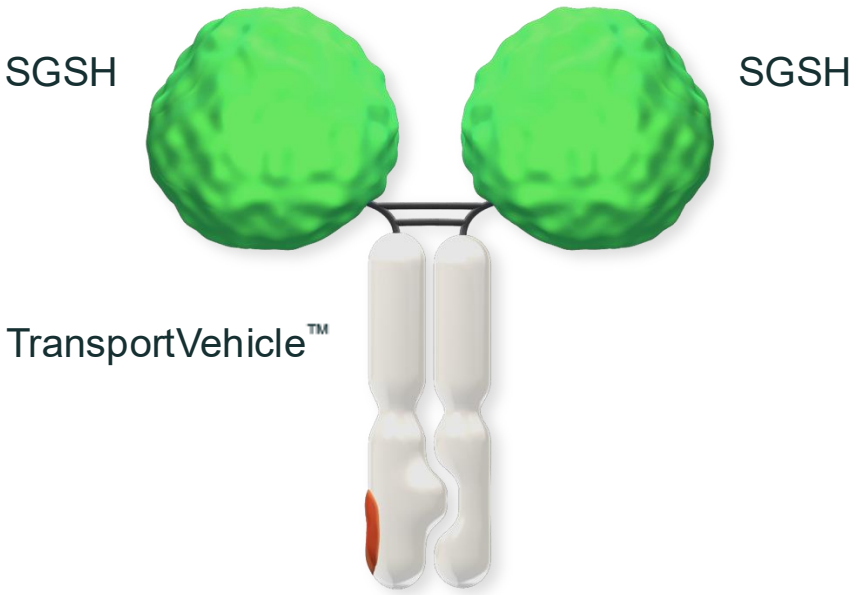
- Lysosomal storage disorder caused by deficiency in **SGSH gene encoding sulfamidase**
- Disease hallmark is accumulation of glycosaminoglycan (GAG) **heparan sulfate**, particularly in CNS
- **~1,500+** patients worldwide[1]. Life expectancy for MPS IIIA patients is 15 years[2].
- Almost **all patients have CNS symptoms**, including developmental delay, behavioral disturbances, seizures, and cognition and motor decline following onset (typically between ages of 2 and 6)
- **No current standard of care**, but gene and cell therapies in clinical development

Currently no disease-modifying therapies are available

1. Excluding China and India; **2.** Lavery et al. 2017 *Orphanet J Rare Dis*; **CNS –** Central nervous system

DNL126 (ETV:SGSH) Delivers SGSH to the Brain

ETV:SGSH



Program Status

- Achieved **biomarker proof-of-concept** in Phase 1/2
- Aligned with FDA on **accelerated approval path** in MPS IIIA
- Selected for FDA **START program**
- Phase 1/2 enrollment completed
- Phase 3 protocol under development

DNL126 aims to address the relentless neurodevelopmental disease progression in MPS IIIA

FDA – U.S. Food and Drug Administration; **START** – Support for clinical Trials Advancing Rare disease Therapeutics

DNL126 Phase 1/2 Clinical Study: MPS IIIA (Sanfilippo type A)

Study Population

- Cohorts A1 – A3: Severe and attenuated MPS IIIA aged ≥ 2 to < 18 years
- Cohort B1: Severe MPS IIIA aged < 28 months
- Cohort B2[1]: Siblings of participants in B1

Dose Finding Cohorts

Cohort A1

Cohort A2

Key Efficacy Cohorts

Cohort A3

Cohort B1

Key Endpoints

- Safety
- CSF HS
- Serum NfL
- Urine HS
- Liver Volume
- PK
- Immunogenicity

NCT06181136

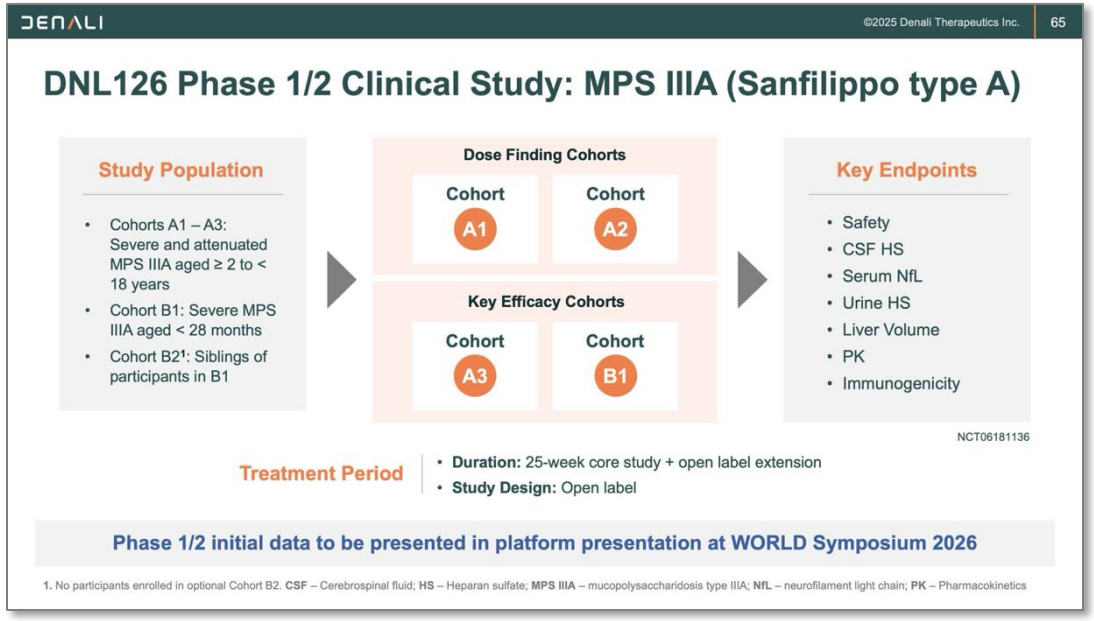
Treatment Period

- **Duration:** 25-week core study + open label extension
- **Study Design:** Open label

Phase 1/2 initial data to be presented in platform presentation at WORLD Symposium 2026

1. No participants enrolled in optional Cohort B2. **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate; **MPS IIIA** – Mucopolysaccharidosis type IIIA; **NfL** – Neurofilament light chain; **PK** – Pharmacokinetics

Study Data for the DNL126 Accelerated Approval



Data for BLA Submission

- At least 49 weeks of data for all participants (Cohorts A1-A3, B1; n=20)
- CSF HS reduction from baseline in key efficacy cohorts (n=12) – surrogate endpoint reasonably likely to predict clinical benefit
- Supportive data on central and peripheral biomarkers, clinical endpoints
- Long-term safety up to ~2.5 years

Expected BLA submission and approval in 2027

BLA – Biologics licensing application; **AA** – Accelerated approval; **CSF** – Cerebrospinal fluid; **HS** – Heparan sulfate

Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

Tividenofusp Alfa: Market Opportunity & Commercial Launch Plans

Katie Peng
Chief Commercial Officer

Living it.

We are simply amazed at his overall health and what he is capable of that we never dreamed possible when we received his diagnosis.

He has a rich vocabulary and imagination, loves listening to books, and he literally never stops talking. We are able to engage in so many family activities we enjoy together that we weren't sure we would ever be able to do as a whole family. With that said, life is not simple or easy by any means.

It is really incredible to reflect on how far he has come, while also making us wish that we could have begun treatment so much earlier … It makes us wonder (and hope) for what could be for those children who will … someday be able to initiate brain-targeted therapy at the earliest possible moment. **We are literally changing the future, truly creating a future that hasn't existed, for every family that comes ahead.**

– Message from current clinical study family to Denali

Waiting for it.

"60% of respondents emphasized the need for therapies that cross the BBB — underscoring the urgency for options that address cognition."

Recent community survey in partnership with Project Alive.

Watching it.

Change is not easy. As new treatments emerge, we know families are watching closely — seeking reassurance through others' experiences and outcomes.

Our goal is to make these early experiences with tivi both positive and inspiring, building confidence for families considering a future switch.

- ✓ Engagement with HCPs
- ✓ Payer and access strategy
- ✓ Working with advocacy to shape our plans
- ✓ Dedicated Patient Services Team

From lived experiences to hopeful anticipation — the Hunter community's voices guide our next chapter.

Denali Hunter Syndrome Patient Advocacy Survey Distributed 12/10/24-1/20/25; **BBB** – Blood-brain barrier; **HCPs** – Healthcare professionals

Hunter Syndrome Patients Fall on a Disease Spectrum, with CNS and Peripheral Manifestations in All

Severe Phenotype

Significant CNS Disease

e.g., reduced cognitive function, communication skills, motor skills (some require wheelchair)

Significant Peripheral Disease

e.g., facial dysmorphism, enlarged spleen/liver, joint stiffness, and eventually pulmonary and cardiac complications

Significantly Shorter Lifespan (10-20 years)

Birth | Age 10 | Age 20 | Age 30+

Attenuated Phenotype

CNS Symptoms Appear and Progress Over Time

e.g., behavioral issues, inattentiveness, retinal degeneration

Peripheral Disease Manifestations Range from Mild to Significant

Vary in severity; same symptoms may occur as in severe patients, although over longer time

Lifespan into Early Adulthood

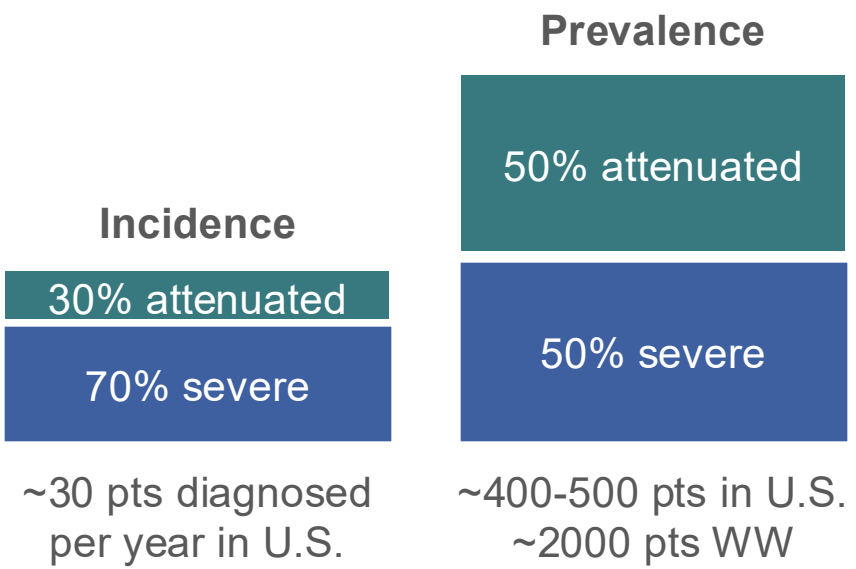
Tividenofusp alfa has the potential to address both CNS and peripheral manifestations of disease

CNS – Central nervous system

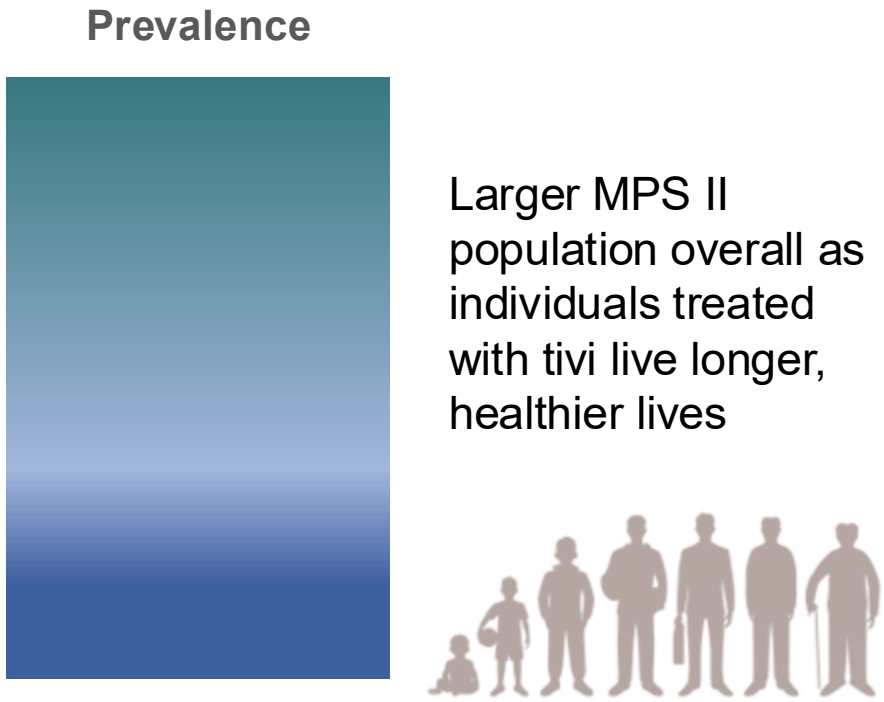
Tivi Has the Potential to Reduce the Disease Burden and Extend Survival, Leading to Growth in the MPS II Population

Current Standard Of Care Paradigm

The prevalent MPS II population reflects a higher early death rate for individuals born with severe disease



Future Tivi Treatment Paradigm



Larger MPS II population overall as individuals treated with tivi live longer, healthier lives

MPS II – Mucopolysaccharidosis type II; **WW** – worldwide

Tivi Setting a New Bar for the Treatment of MPS II

Tividenofusp alfa is an enzyme replacement therapy for **all people** with **Hunter syndrome**. It is the **first therapy to treat both the brain and body,** and the **only** therapy to **normalize GAG** levels.

Broad Indication Statement

No need to determine disease severity

(pending FDA label)

Differentiated Positioning

Only option to address all disease manifestations

Reason to Believe

GAG normalization fundamental to tivi's potential of delivering superior clinical outcomes

All strategies and tactics are subject to Legal review prior to implementation; **GAG** – Glycosaminoglycans; **FDA** – U.S. Food and Drug Administration; **MPS II** – Mucopolysaccharidosis type II

Our Stakeholders Are Ready and Waiting for Tivi

Physicians

- Recognize significant **unmet needs** across **brain** and **body**
- 90% view tivi's data as **highly motivating to prescribe**
- **No** overall **concerns** with **safety profile**

Patients & Caregivers

- Perceive significant **unmet needs**, across **brain** and **body**
- **80%+ are aware** of new treatments coming and **excited to try tivi**
- **Advocacy orgs** and **peer to peer** communications **most influential**

Payers

- **Robust** payer **engagement** underway
- **Perceive therapeutic benefit** due to ability to cross the BBB
- View tivi's **benefit/risk profile favorably**

1. HCP Insights from HCP Survey (N=68) conducted in Q1 2025 and from KOL Adboard conducted March 2025; **2.** Caregiver Insights from Caregiver Survey (N=47) Conducted Q4 2024;
3. Payer Insights from AdBoard conducted April 2025 and Payer Engagements; All strategies and tactics are subject to Legal review prior to implementation.

Strategy and Path to Establish Tivi as Standard of Care

Broad Patient Reach Through Community Centered, High-Touch Engagement Model

Community & Advocacy

Strong partnership

Disease state awareness campaign

Scientific & Clinical Engagement

Medical congresses

COE engagement

Provider & Institutional Preparation

Account profiling & in-servicing

Experienced field team ready to go

Activate and maintain switch to tividenofusp alfa

Seamless Access for All Patients

Patient Access & Support

Comprehensive patient support programs

Experienced distribution network

Payer & P&T Preparation

Payer education

Engaging P&T at COEs

Drive fast broad coverage

All strategies and tactics are subject to Legal review prior to implementation; **COE** – Centers of excellence; **P&T** – Pharmacy & Therapeutics committee

Strong Scientific Outreach and Community Engagement

Scientific Outreach

Policy Support

Advocacy Partnerships & Community Council

Continued engagement with the Hunter syndrome community and HCPs

All strategies and tactics are subject to Legal review prior to implementation; **HCPs** – Healthcare professionals

Denali Pricing Principles

Access

Enable broad, equitable, and sustainable access for patients, the healthcare system, and society

Affordability

Address affordability by providing comprehensive support to patients and families

Fuel R&D

Ensure our ability to fuel R&D in the pursuit of meaningful and impactful treatments

Value of Our Medicines

Reflect the clinical, economic, and societal value delivered by our medicines

Expect to price tivi at a premium to standard of care, balancing access with the value to patients

All strategies and tactics are subject to Legal review prior to implementation.

Broad Reimbursement Supported by Clear Clinical Value Proposition for Tividenofusp Alfa

Value Proposition: Tividenofusp alfa could become the first FDA-approved ERT to cross the BBB to target the CNS and eliminate GAG buildup in both brain and body for all MPS II patients

Significant Disease Burden

- Progressive disease with widespread organ involvement
- Significant decline across brain and body

Current SoC Leaves Many Unmet Needs

Current SoC ERT:

- Does not treat CNS symptoms
- Cannot adequately penetrate hard-to-reach peripheral tissues

Low Budget Impact

- U.S. prevalence of ~400 – 500 patients
- ~1-2 MPS II patients per 1-million-member plan

Commercial & Medicaid

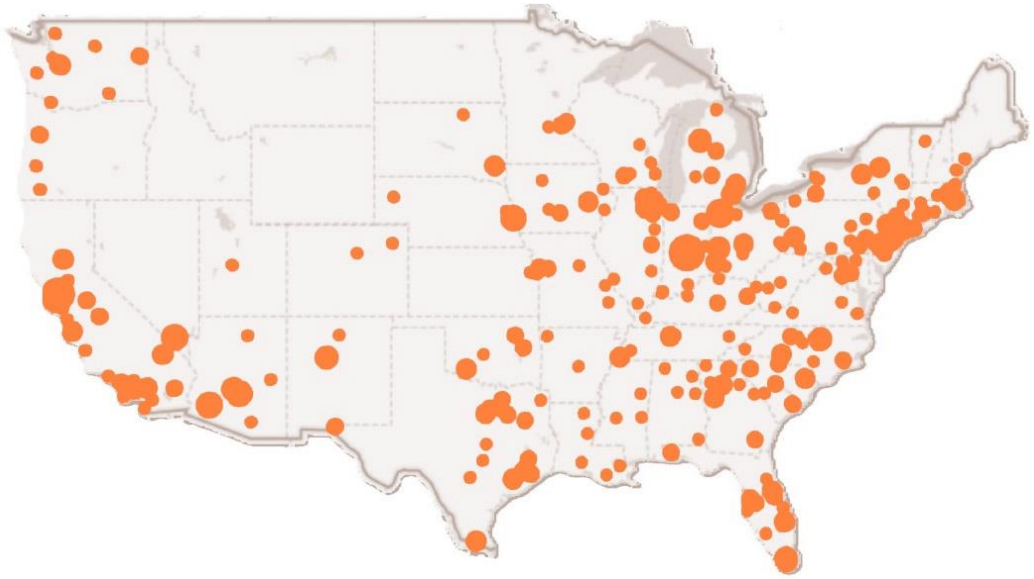
- ~50/50 across Commercial & Medicaid
- Longer time to coverage on Medicaid compared with commercial

Payer coverage will be achieved by communicating compelling tividenofusp alfa value proposition

All strategies and tactics are subject to Legal review prior to implementation; **ERT** – Enzyme replacement therapy; **SoC** – Standard of care; **MPS II** – Mucopolysaccharidosis type II; **GAG** – Glycosaminoglycans

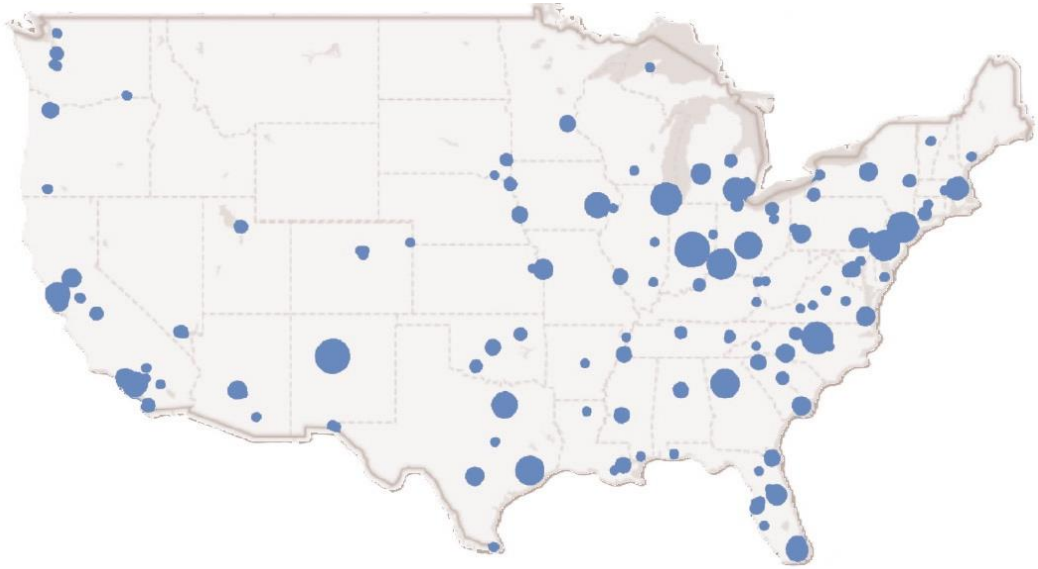
Concentrated Stakeholders Enable Us to Reach All Patients Treated Across the 80 to 100 Centers of Excellence in the U.S.

MPS II Patient Distribution



400 to 500 patients in the US on SoC ERT

MPS II Treating Physician Distribution

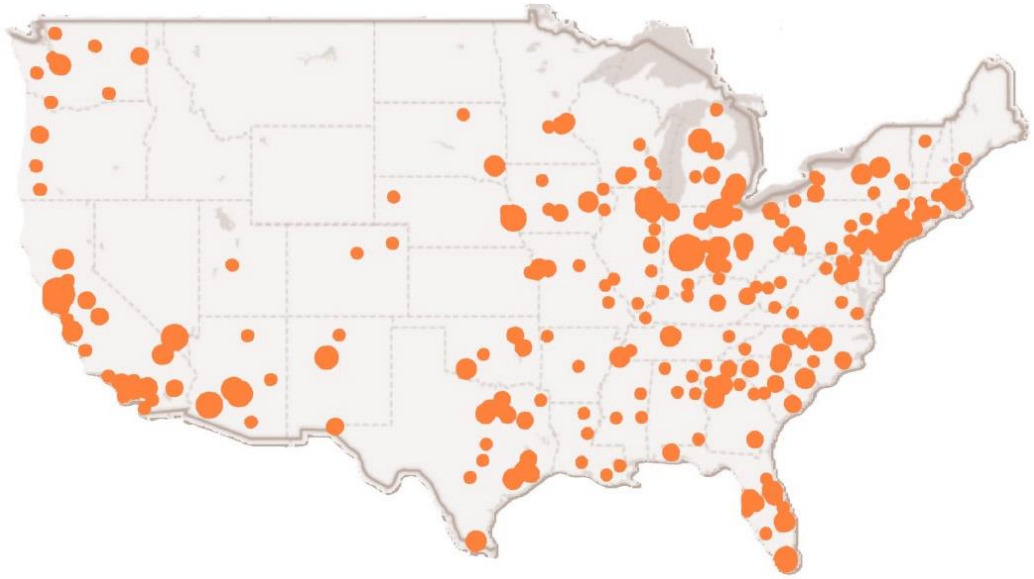


Most MPS II patients treated by **clinical geneticists at ~80-100 genetic centers**

All strategies and tactics are subject to Legal review prior to implementation; **MPS II** – Mucopolysaccharidosis type II

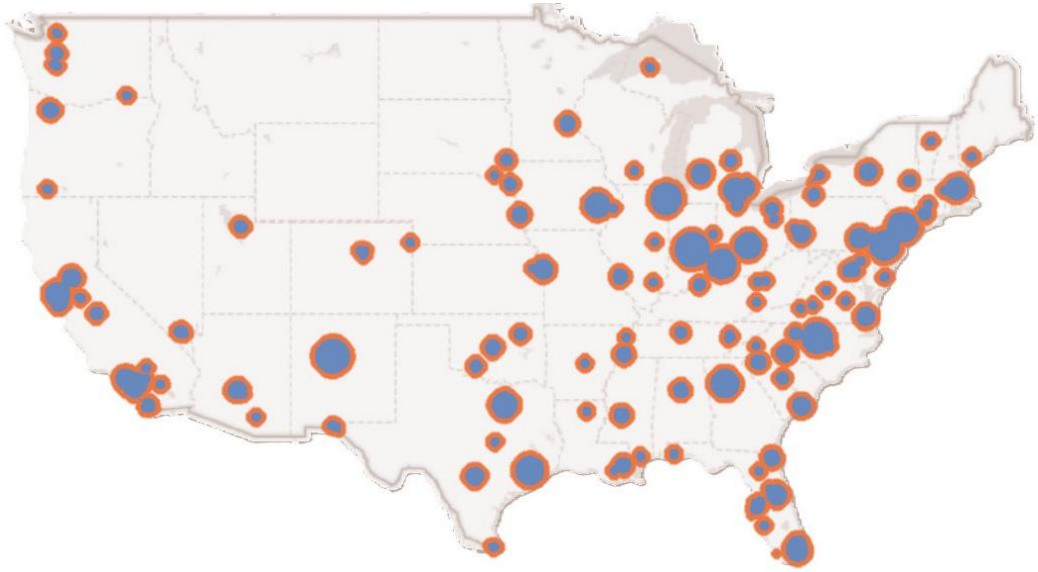
Concentrated Stakeholders Enable Us to Reach All Treaters Across the 80 to 100 Centers of Excellence in the U.S.

MPS II Patient Distribution



400 to 500 patients in the US on SoC ERT

Denali's Established Relationships



Denali has **already established relationships** with **all major** MPS II treatment centers

All strategies and tactics are subject to Legal review prior to implementation; **MPS II** – Mucopolysaccharidosis type II

Built a Winning Team Ready for Launch

Leadership Team

Significant Experience Across Functions

- ✓ Product Strategy
- ✓ US and Global Marketing
- ✓ US and Ex-US Market Access
- ✓ Market Planning and Analytics
- ✓ Medical Affairs & Med Info
- ✓ Field Sales
- ✓ Field Medical
- ✓ Patient Advocacy

25+ Successful Product/Indication Launches Worldwide

Including Rare Diseases

ACTEMRA, AUBAGIO, AVASTIN bevacizumab, BLINCYTO, CIMZIA, DOJOLVI, ENSPRYNG, Evrysdi risdiplam, FOSRENOL, Galafold migalastat, HEMLIBRA, IMLYGIC, Kyprolis, LEMTRADA, Lialda, LUCENTIS, MAVENCLAD, OCREVUS, PERJETA, plegridy, TAKHZYRO, Tarceva, Tecfidera, TEPEZZA, Valcyte, Vyvanse, xofluza, Xolair, zolgensma

US Field Team

Deep Industry and Disease Expertise

- ✓ 25 Years Average Biopharma Industry Experience
- ✓ 96% LSD / Rare Disease Experience
- ✓ Average Rare Disease Experience: 12 Years

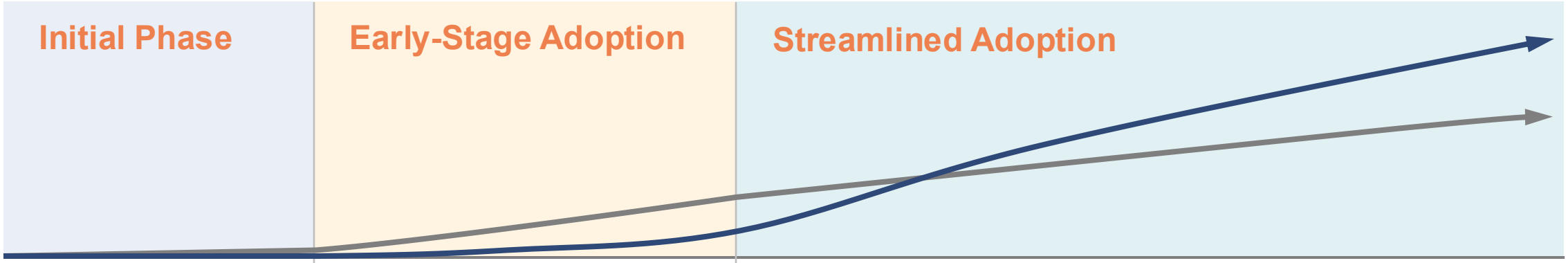
Multiple Successful Product Launches

All Rare Diseases

Arcalyst (rilonacept), elaprase (idursulfase), Evrysdi risdiplam, KRYSTEXXA pegloticase, Pombiliti + Opfolda, TEPEZZA teprotumumab-trbw, Vyjuvek beremagene geperpavec-svdt, zolgensma

All strategies and tactics are subject to Legal review prior to implementation; **LSD** – Lysosomal storage disorders

Tividenofusp Alfa Launch Expected to Follow Established Rare Disease Launch Dynamics



~First Quarter of Launch

Preparing for Patient Uptake

Initial uptake constrained by operational aspects of launch

- Hospitals need to stock tivi
- HCPs discuss with families
- Insurance approval only by medical exception
- Need to schedule initial infusion

~First Year of Launch

Patient Uptake In Full Swing

- Physicians start prescribing tivi
- Many patients wait until their scheduled visit to discuss tivi
- Commercial insurance approvals by policy; Medicaid more limited

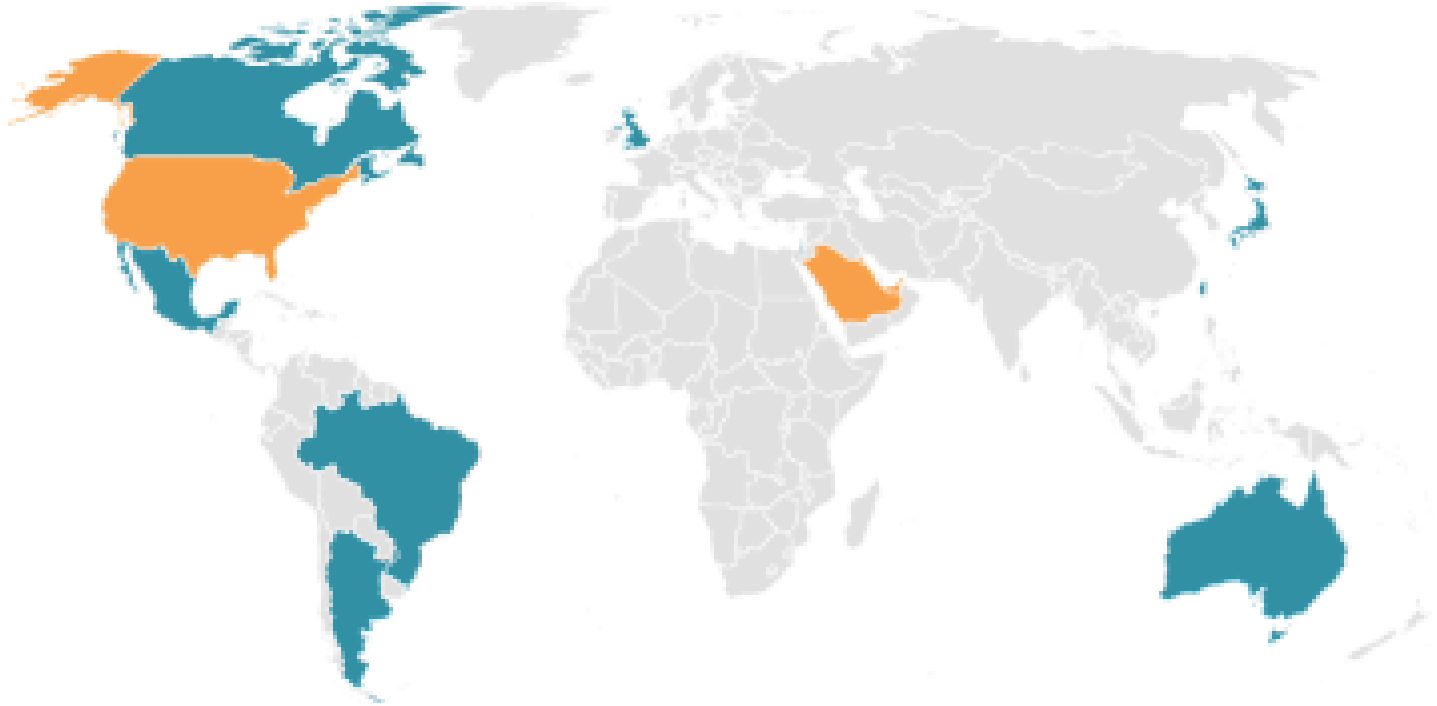
Years 2-4 of Launch

Continued Patient Uptake and Persistence Leads to Fast Revenue Growth

- HCPs see tivi as the SoC
- All patients offered tivi as an option, including those newly diagnosed
- Streamlined access for most patients (Commercial and Medicaid)
- Patient persistence and growth leads to sustained revenue growth

All strategies and tactics are subject to Legal review prior to implementation; **HCPs** – Healthcare professionals; **SoC** – Standard of care

Majority of Global Market Available Based on U.S. Accelerated Approval and/or Phase 1/2 Data



~33% of Market
Short Term[1] (2026-2027)

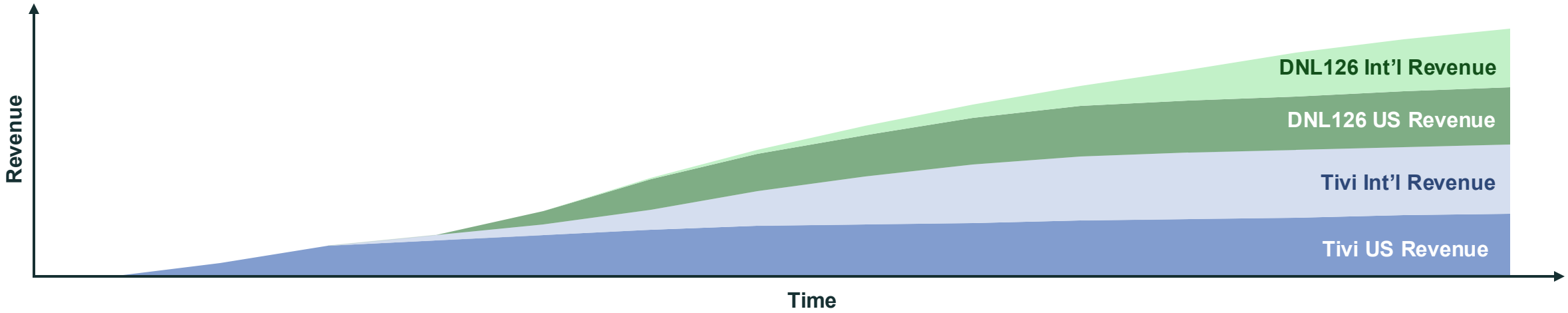
~33% of Market
Mid-Term[1] (2027-2028)

~33% of Market
Longer Term (2028+)

- We will pursue ex-U.S. approvals via the U.S. Certificate of Pharmaceutical Product (CPP) for marketing authorization or conditional pathways, as available
- We are targeting all ~2,000 patients worldwide in commercially accessible geographies

Note: Based on estimated WW split of Elaprase annual revenues of $650M to $700M, assuming we launch in ~90-95% of Elaprase geographies; 1. COMPASS Phase 2/3 data not needed for regulatory filings; All strategies and tactics are subject to Legal review prior to implementation.

Building a Rare Disease Franchise: First Two Near-Term Launches Combined Opportunity of >$1B



Successfully Launching Tividenofusp Alfa Will Be the Bedrock of a Successful Commercial Franchise

Significant Near-Term Opportunity
- Revenue starting 2026
- $1B+ Opportunity between MPS II and MPS IIIA

Infrastructure Synergies
- Plan to leverage existing Denali infrastructure across both launches
- Ability to redeploy resources to translate into favorable margins

Established LSD Leadership
- Established relationships with key LSD stakeholders
- Ability to drive increasingly fast launches and product uptake throughout franchise

All strategies and tactics are subject to Legal review prior to implementation.

Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

Moderated Panel: MPS II Community Perspectives

Barbara Burton, M.D., Kim Stephens, Ph.D., and Jason Madison

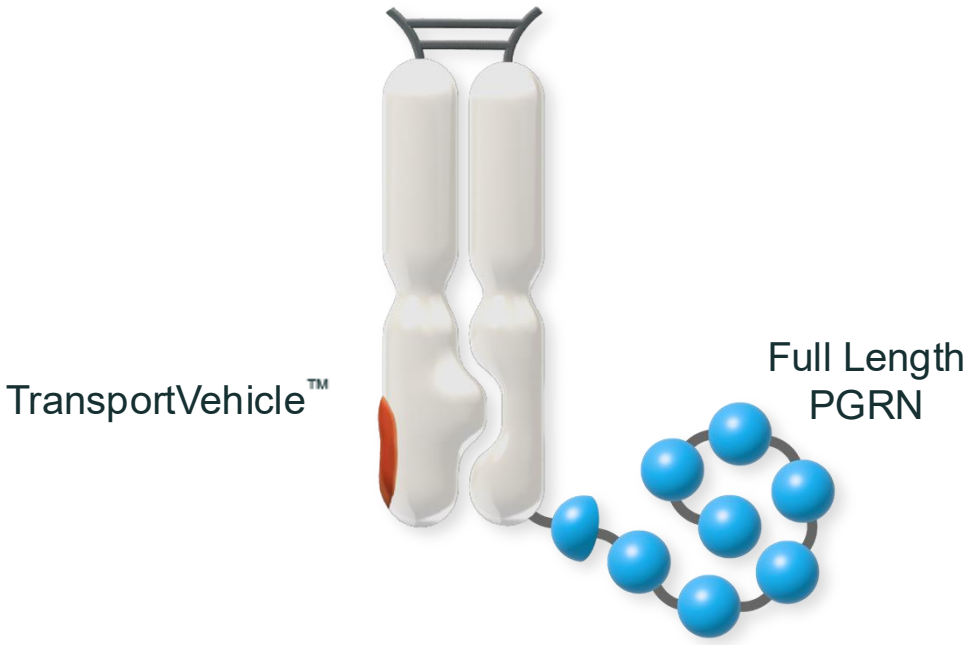
Enzyme TransportVehicle™ Franchise for Lysosomal Storage Disorders

Building a Broader ETV Portfolio

Peter Chin, M.D.
Acting Chief Medical Officer and Head of Development

DNL593 (PTV:PGRN) Delivers PGRN to Key Cell Types in the Brain

PTV:PGRN



Program status: Phase 1/2 Study Ongoing

Key Characteristics

- Molecule delivers full length PGRN that retains binding to Sortilin receptor
- TfR tuned to maximize delivery of PGRN to the CNS and uptake into lysosomes of neurons and glial cells
- Fc domain portion of TransportVehicle™ improves manufacturability and drug-like properties

DNL593/TAK-594* approach is highly differentiated from competitor PGRN approaches

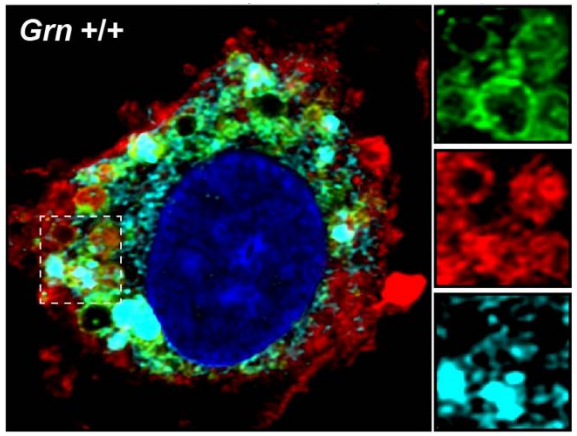
*In collaboration with Takeda

PGRN Depletion Results in Lysosomal Abnormalities Rescued by DNL593

Rescue of a lysosomal storage disorder caused by *Grn* loss of function with a brain penetrant progranulin biologic

Cell

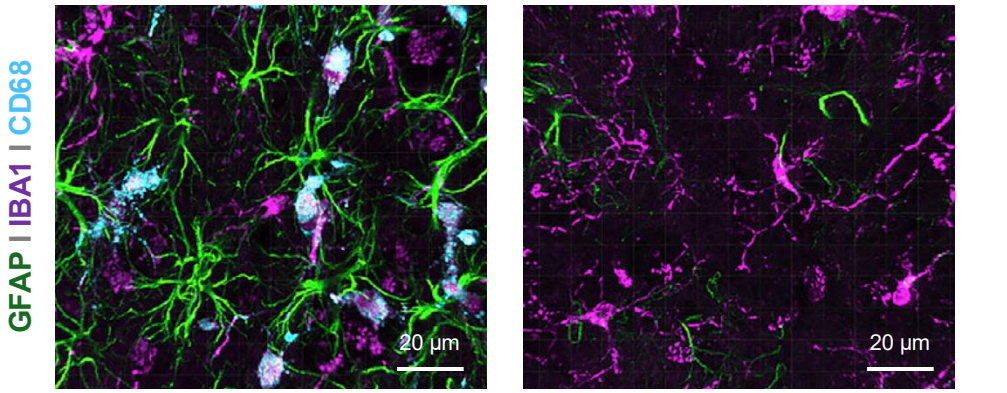
Todd Logan,[1,6] Matthew J. Simon,[1,6] Anil Rana,[1,7] Gerald M. Cherf,[1,7] Ankita Srivastava,[1,7,8] Sonnet S. Davis,[1] Ray Lieh Yoon Low,[1] Chi-Lu Chiu,[1] Meng Fang,[1] Fen Huang,[1] Akhil Bhalla,[1] Ceyda Llapashtica,[1] Rachel Prorok,[1] Michelle E. Pizzo,[1] Meredith E.K. Calvert,[1] Elizabeth W. Sun,[1] Jennifer Hsiao-Nakamoto,[1] Yashas Rajendra,[1] Katrina W. Lexa,[1] Devendra B. Srivastava,[1] Bettina van Lengerich,[1] Junhua Wang,[1] Yaneth Robles-Colmenares,[1] Do Jin Kim,[1] Joseph Duque,[1] Melina Lenser,[1] Timothy K. Earr,[1] Hoang Nguyen,[1] Roni Chau,[1] Buyankhishig Tsogtbaatar,[1] Ritesh Ravi,[1] Lukas L. Skuja,[1] Hilda Solanoy,[1] Howard J. Rosen,[2,3] Bradley F. Boeve,[3,4] Adam L. Boxer,[2,3] Hilary W. Heuer,[2,3] Mark S. Dennis,[1] Mihalis S. Kariolis,[1] Kathryn M. Monroe,[1] Laralynne Przybyla,[1,9] Pascal E. Sanchez,[1] Rene Meisner,[1] Dolores Diaz,[1] Kirk R. Henne,[1] Ryan J. Watts,[1] Anastasia G. Henry,[1] Kannan Gunasekaran,[1] Giuseppe Astarita,[1,5] Jung H. Suh,[1] Joseph W. Lewcock,[1] Sarah L. DeVos,[1,*] and Gilbert Di Paolo[1,10,*]

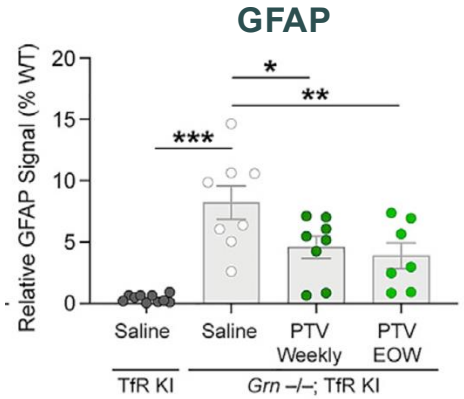


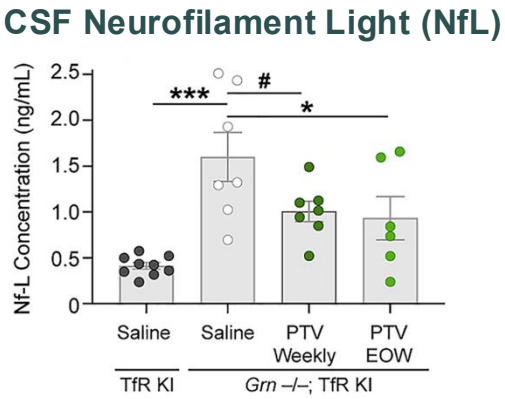
LAMP2
Lysosome Marker

BMP
Lipid critical for lysosome activity

PGRN
Localized to lysosome





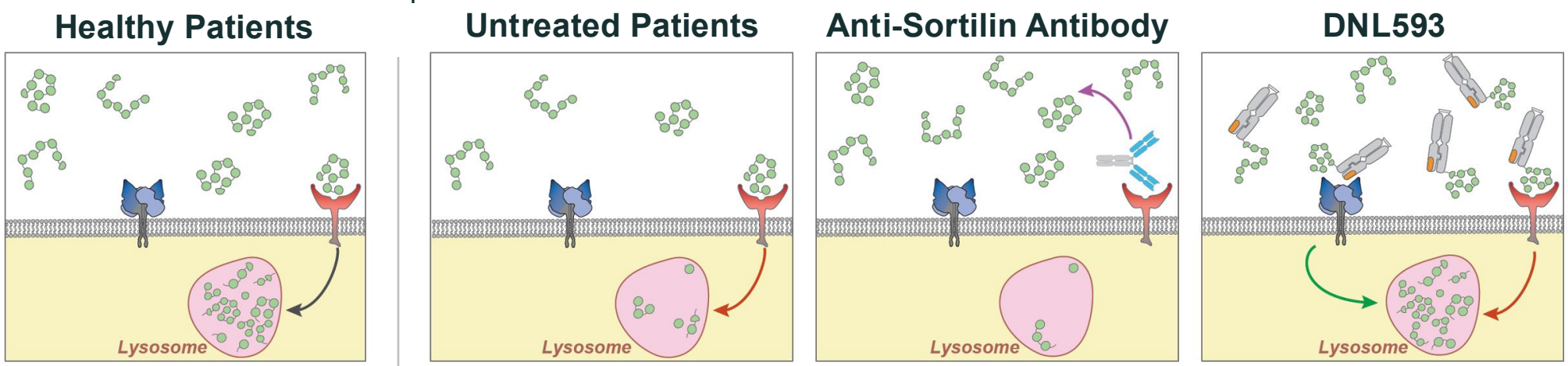


In preclinical models, DNL593 improves both glial activation and neurodegeneration biomarkers relevant in FTD-*GRN*

Logan et al. *Cell* 2021

DNL593 Mechanism Is Distinct from Other Therapeutic Approaches

FTD-*GRN*



DNL593 is a protein replacement therapy designed to restore extracellular and lysosomal PGRN while Anti-Sortilin MOA boosts extracellular PGRN but leaves lysosomal deficiency unresolved

Modified from Simon et al. *TICB* 2022

DNL593 Phase 1/2 Clinical Study

Study Population

- Part A: healthy volunteers aged ≥ 18 to ≤ 55 years
- Part B: *GRN* mutation carriers; symptomatic participants diagnosed with FTD-*GRN*; aged ≥ 18 to ≤ 80 years
- Part C: participants who complete Part B

Completed

SAD Cohort A

Enrolling (Screening Closed)

MAD Cohort B

Optional OLE Ongoing

MAD Cohort C

Goals & Objectives

- Part A: safety, PK
- Parts B & C:
  - Safety, PK, PD biomarkers
  - Clinical, neuropsychology, and imaging outcomes

NCT 05262023

Treatment Period

- **Duration:** 25-week core study + open label extension
- **Study Design:** Randomized double blinded placebo controlled

Phase 2 Part B interim data in patients with FTD-*GRN* will read out in 2026

FTD – Frontotemporal dementia; ***GRN*** – Granulin; **MAD** – Multiple ascending dose; **PD** – Pharmacodynamics; **PK** – Pharmacokinetics; **SAD** – Single ascending dose

Accumulating ETV Clinical Experience Supports Broad Platform Potential

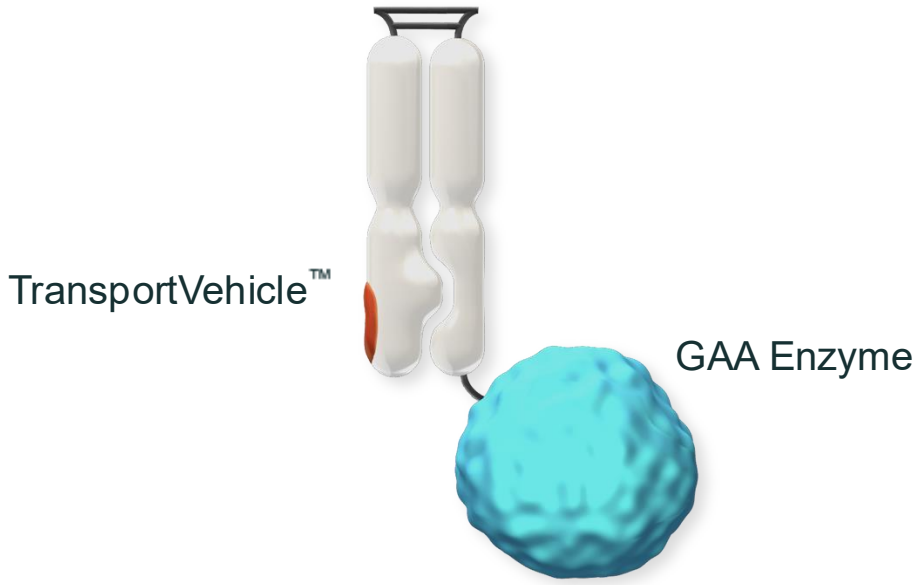
Franchise	Current Study	Efficacy to Date	Safety to Date
tividenofusp alfa DNL310 **MPS II** (Hunter syndrome)	**Phase 1/2** DNLI-E-0002 Primary analysis[1]	• >90% reduction in CSF HS • Normalization of CSF and urine HS • Reduction and normalization of serum NfL	• IRR's clinically manageable and decrease over time • Anemia: early declines in hemoglobin generally returning to baseline, clinically manageable, no discontinuations due to anemia • Anemia frequently observed at baseline in MPS II
ETV:SGSH DNL126 **MPS IIIA** (Sanfilippo syndrome)	**Phase 1/2** DNLI-I-0001 Initial data[2]	• Biomarker POC achieved	• IRR's clinically manageable and decrease over time • Anemia: mild anemia (Grade 1) in 1 participant with iron deficiency at baseline
PTV:PGRN DNL593 **FTD-*GRN*** (Frontotemporal dementia-granulin)	**Phase 1/2** DNLI-H-0001 Blinded study ongoing[3]	• Dose-dependent increase in CSF progranulin in healthy volunteers	• IRR's appear clinically manageable with standard measures including pre-medications • No anemia-related TEAEs to date

Robust CNS activity and manageable safety observed across multiple ETV programs

1. October 9, 2024 CCOD (N=47); **2.** June 4, 2025 CCOD (N=14); **3.** As of November 20, 2025; **CCOD –** clinical cut off date

DNL952 (ETV:GAA) Enhances Delivery of GAA to Muscle

ETV:GAA



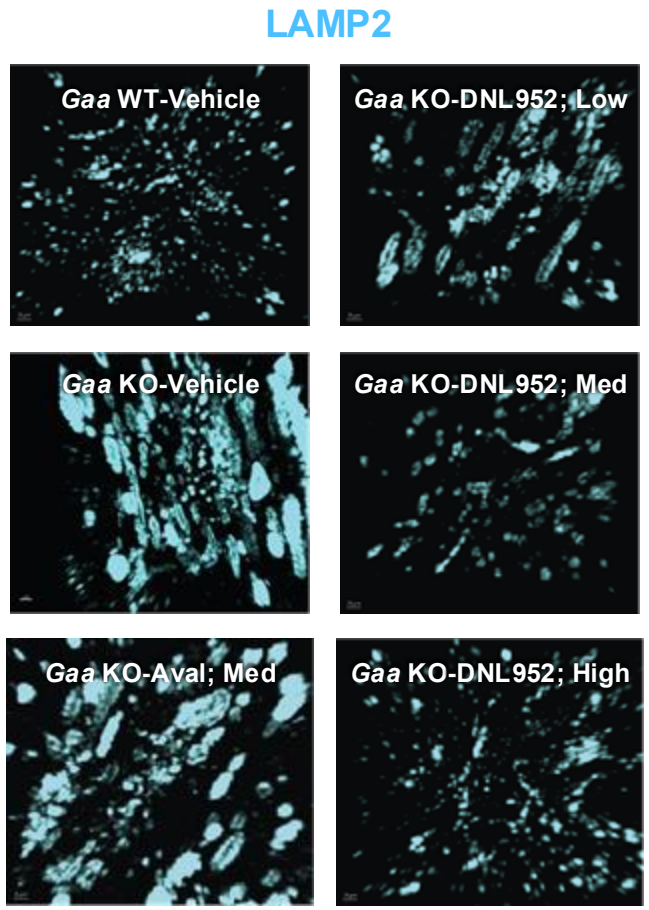
Program status: Protocol amended and response to FDA submitted regarding clinical hold

Key Characteristics

- Molecule delivers GAA to whole body, including difficult to access tissues
- TfR tuned to maximize delivery of GAA to both muscle and CNS
- Fc domain portion of TransportVehicle™ improves manufacturability and drug-like properties

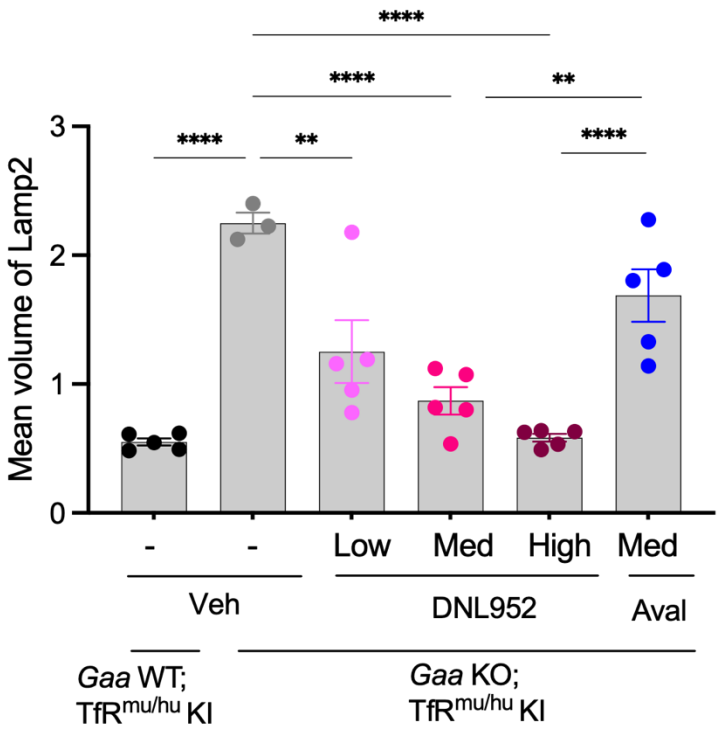
DNL952 aims to improve GAA delivery to muscle over existing therapy and deliver GAA to the brain

DNL952 (ETV:GAA) Superior to Competitor Enzyme in Both Muscle and Brain



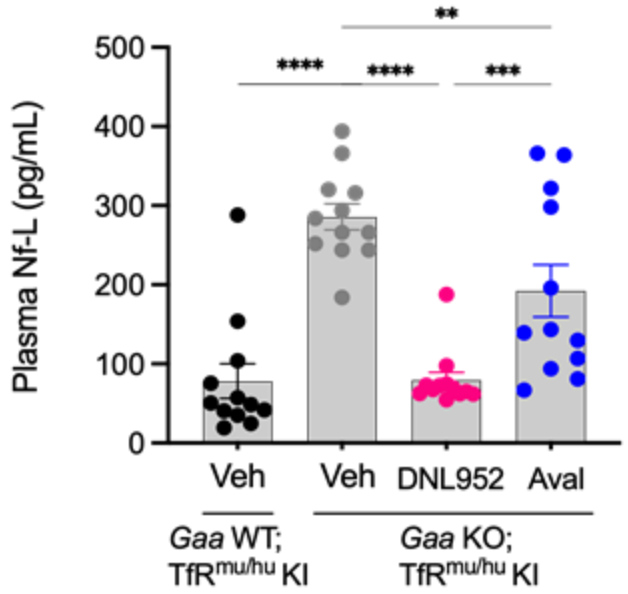
Muscle Lysosome Volume

Multiple Dose, IV (5X EOW)



Plasma Neurofilament

Multiple Dose, IV (10X EOW)



DNL952 improves muscle and CNS biomarkers relative to 2nd generation ERT in a preclinical model

Standard of care: **Aval.** – avalglucosidase alfa-ngpt

DNL952 Phase 1 Clinical Study Plan

Study Population

- Patients with Late Onset Pompe Disease (LOPD)
- 2nd Gen ERT experienced (A Cohorts) and optional naïve (B Cohorts)

2nd Gen Treatment-Experienced

- Cohort A1
- Cohort A2

Optional: Additional Cohorts

Optional: Treatment-Naïve

- Cohort B1

Goals & Objectives

- Safety
- PK
- Analysis of clinically established biomarkers
- Immunogenicity

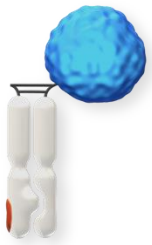
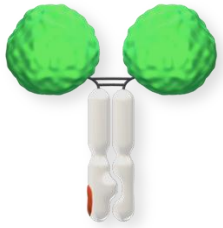
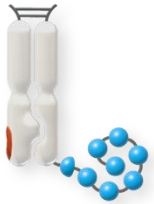
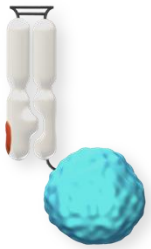
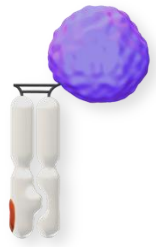
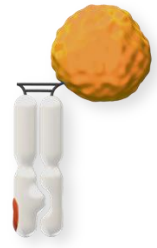
Treatment Period

- **Duration:** 24-week core study + 24-week safety extension
- **Study Design:** Open label

Phase 1 biomarker data expected in 2027[1]

1. Protocol amended and response to FDA submitted regarding clinical hold**; ERT** – Enzyme replacement therapy; **LOPD** – Late onset Pompe disease; **PK** – Pharmacokinetics

Building the ETV Franchise Portfolio

	Tividenofusp alfa (ETV:IDS; DNL310)	ETV:SGSH (DNL126)	PTV:PGRN (DNL593)	ETV:GAA (DNL952)	ETV:GCase (DNL111)	ETV:IDUA (DNL622)
						
	MPS II (Hunter syndrome)	**MPS IIIA** (Sanfilippo syndrome)	**FTD-*GRN*** (Frontotemporal dementia-granulin)	**Pompe Disease**	**Parkinson's and Gaucher**	**MPS I** (Hurler syndrome)
Patients WW[1]	**~2,000**	**~1,500+**	**~25,000+**	**~5,000 – 10,000**	**~300,000+ (GBA-PD) ~10,000 – 15,000 (GD)**	**~1,500+**
Status	Phase 2/3 BLA filing[2]	Phase 1/2	Phase 1/2	IND application submitted[3]	IND-enabling	IND-enabling

We are developing the next generation of enzyme replacement therapies designed to treat brain and body manifestations of serious genetic diseases

WW – Worldwide; **BLA** – Biologics license application; **IND** – Investigational new drug application; **GBA-PD** – Parkinson's Disease with GBA mutation; **GD** – Gaucher's Disease;
1. Excluding China and India; **2.** PDUFA target action date of 4/5/26 for accelerated approval; **3.** Protocol amended and response to FDA submitted regarding clinical hold

TransportVehicle™ Platform: Transforming Treatment for Alzheimer's Disease (AD)

Why Now Is the Time for Breakthroughs in AD

Ryan Watts, Ph.D.
Chief Executive Officer

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

55 Million People Live with AD and Other Forms of Dementia

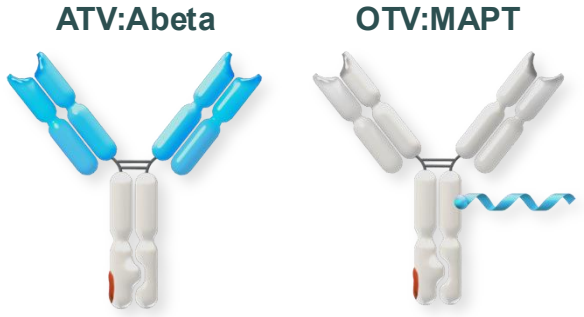
Opportunity for New Therapies to Improve Efficacy and Safety

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

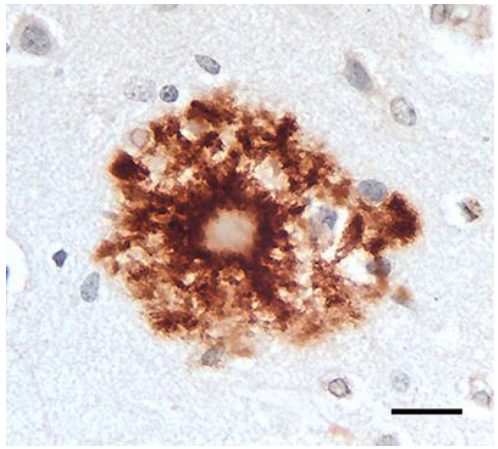
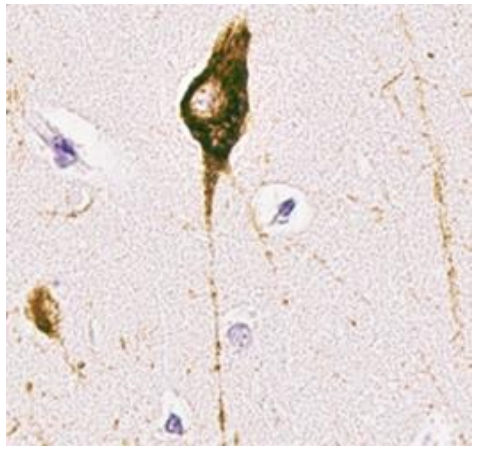
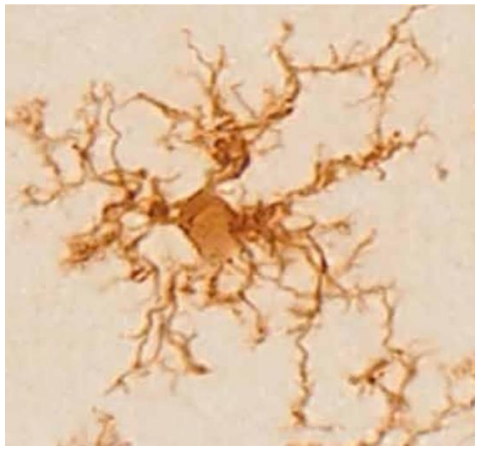
- Discovery programs for multiple AD targets
- Best in class opportunities to improve efficacy and safety



We Aim to Deliver Effective Medicines with Broad Societal Impact

TfR – Transferrin receptor; **ARIA** – Amyloid-related imaging abnormalities

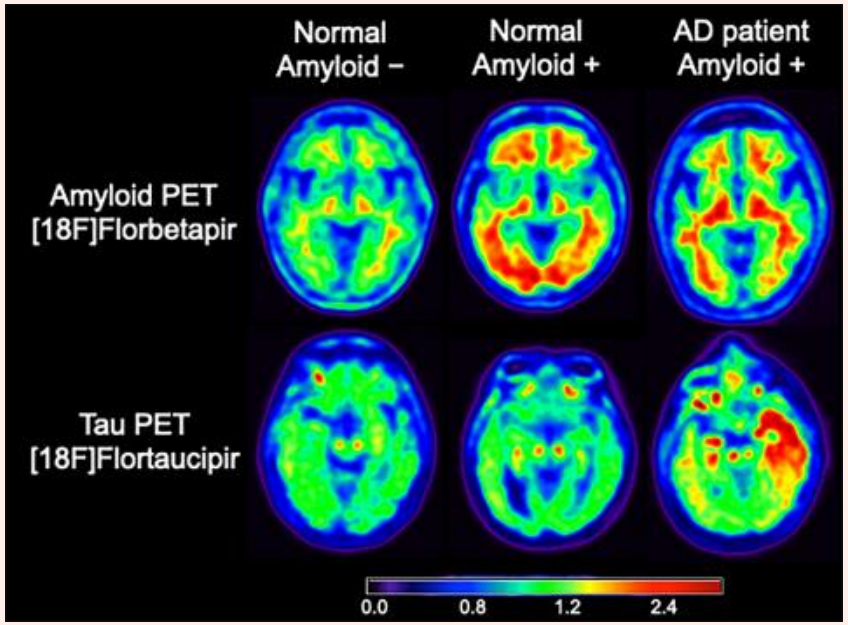
Three Pillars of Alzheimer's Disease Pathology

	1 Amyloid-Beta (Abeta) Plaques	2 Neurofibrillary (Tau) Tangles	3 Neuroinflammation & Hypometabolism
			
Disease Pathology	Often thought to be the "trigger" that kicks-off the disease	Most closely associated with cognitive decline in AD	Characterized by microglial activation
Therapeutic Strategy	Anti-Abeta clinically validated	Knockdown of Tau emerging as optimal strategy	Currently higher biology risk; ideal mechanism unclear
TV Opportunity	Clear path to differentiate with TfR	TfR delivery enables improved BioD and peripheral dosing	TfR delivery possible pending target validation

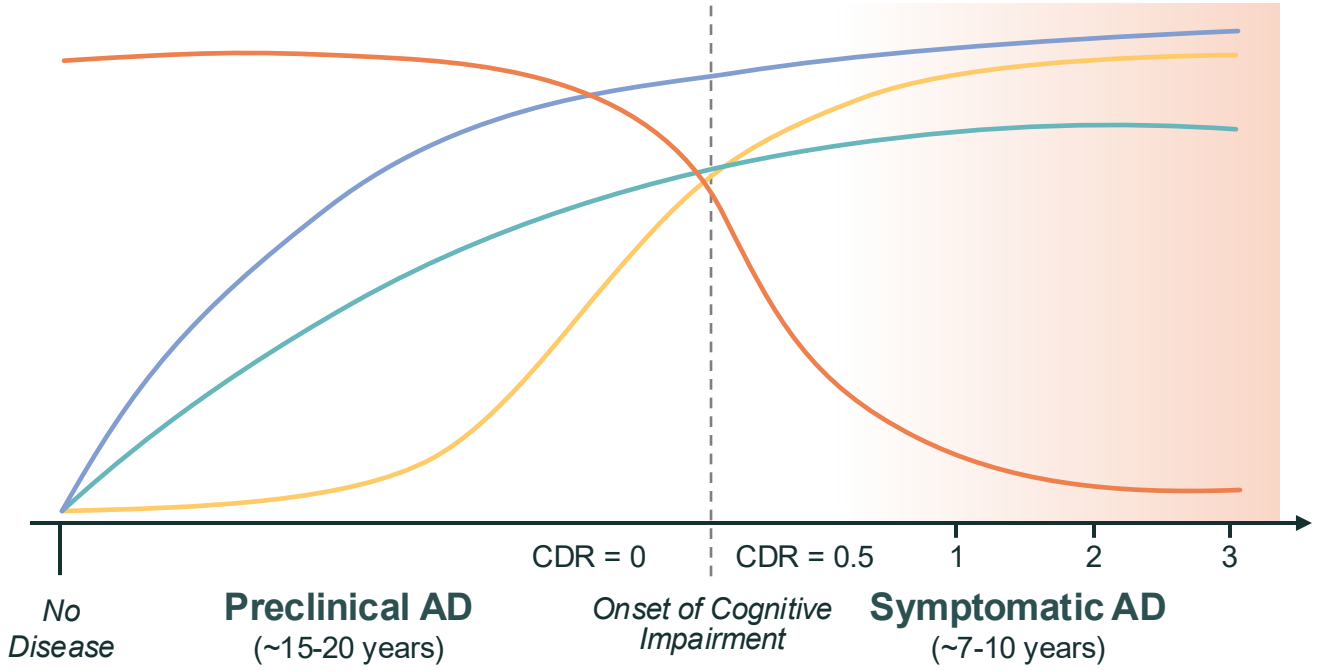
Walker L, *Free Neuropath*, 2020; Bengoa-Vergniory et al, *Acta Neurop*, 2021; Fernandez-Arjona et al, *Frontiers*, 2017

Alzheimer's Disease Progresses Over Decades

Hallmarks of AD Pathology



Major AD Pathophysiological Hallmarks in Relation to Clinical Course



Left image from Carney Institute for Brain Science / Brown University (HEAD Study); Right image adapted from Long and Holtzman (2019) *Cell* Volume 179, Issue 2p312-339

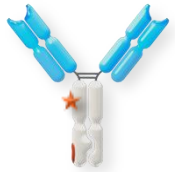
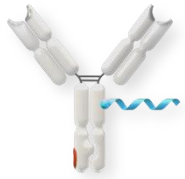
Advancements in Biomarkers Enable AD Trial Optimization

Current Biomarkers in AD Clinical Studies

	Blood	PET	CSF	Advancements
Patient ID	Abeta pTau	Abeta Tau	Abeta	• Tests less expensive and less invasive • Accurately IDs patients for study inclusion
Patient Stratification	–	Tau	–	• Stratification by tau severity predicts clinical progression rate and response magnitude
Target Engagement (TE)	pTau	Abeta Tau	Tau pTau	• Enables assessment of magnitude and duration of tau therapy • Enables TE assessment for Abeta therapy

AD trial precision, speed and efficiency improved by recent biomarker breakthroughs

AD Treatment Landscape is Rapidly Evolving

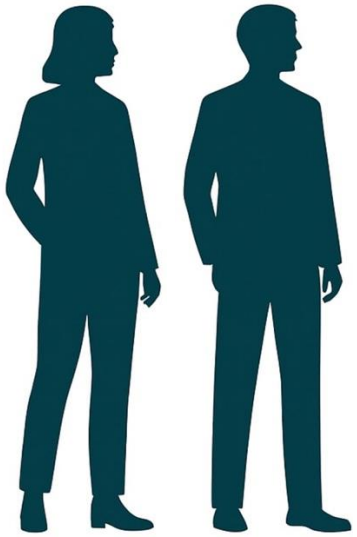
	Safety	Efficacy	Route of Administration	
 **1st Gen Abeta (Abeta mAbs)**	–	+	IV	Risk of ARIA; modest benefit
 **Next-Gen Abeta TfR-Enabled Antibody**	+	+++	IV, SC	Better brain uptake, faster plaque clearance and safer route of entry into brain
 **1st Gen Tau (ASO/siRNA)**	+	+	IT	Limited brain biodistribution
 **Next-Gen Tau TfR-Enabled ASO/siRNA**	+	++	IV	Better brain uptake and more convenient / less invasive

TransportVehicle™ is positioned to deliver best in class Next-Gen TfR-enabled therapies for AD

The Future of Alzheimer's Disease Prevention: Treating Before Cognitive Decline Begins

Preclinical Alzheimer's Disease

- Earliest stages of AD
- Brain changes begin
- **No signs of cognitive decline**
- Positive brain biomarkers (lesions)



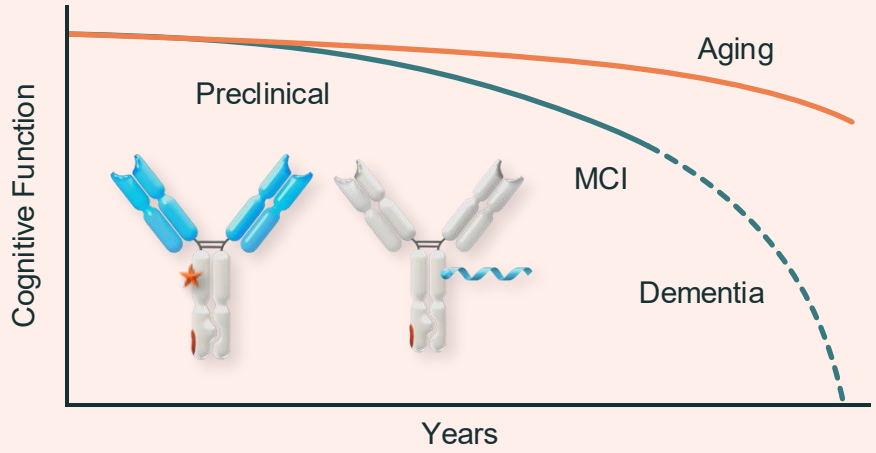
PET Amyloid / Tau

Cognitive Decline

Future State: Early Diagnosis & Safe Treatments

- Accessible screening, simple blood tests
- Safe treatments, i.e., minimize ARIA risk
- Prevent cognitive decline

Goal: Treat Early to Prevent Decline



We See a Promising Future for AD with the TransportVehicle™

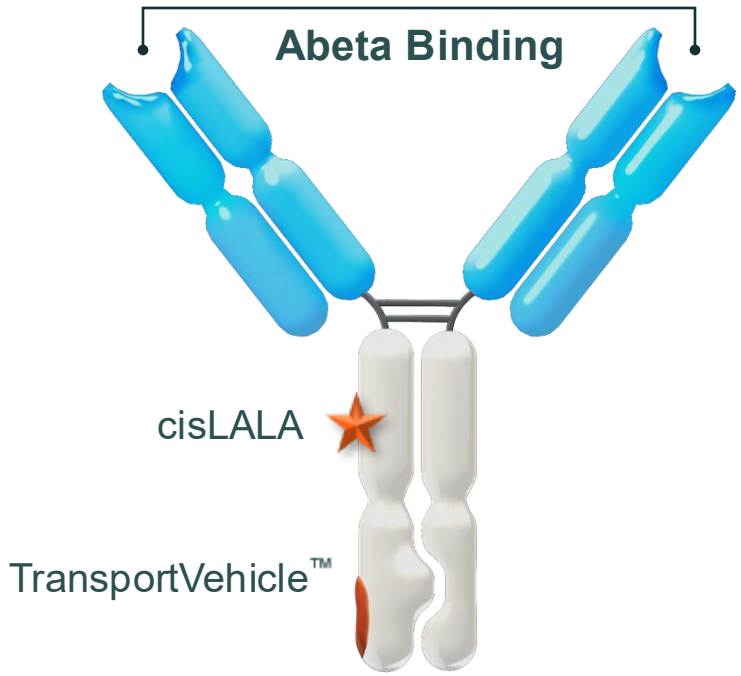
TransportVehicle™ Platform: Transforming Treatment for Alzheimer's Disease (AD)

Next-Generation of TV-Enabled Therapeutics for AD

Joe Lewcock, Ph.D.
Chief Scientific Officer

DNL921(ATV:Abeta) Designed to Maximize Efficacy and Improve Safety

ATV:Abeta



Program status: IND/CTA filing in 1H 2026

Key Characteristics

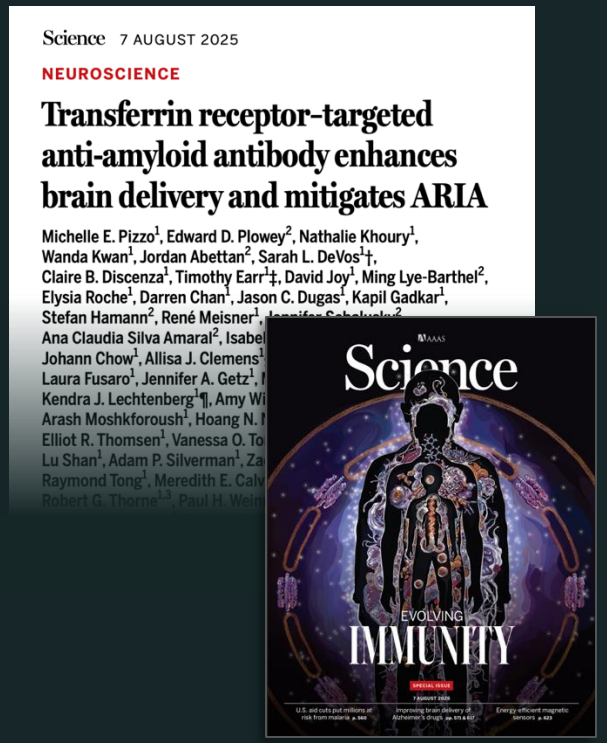
- TfR engagement tuned to maximize CNS biodistribution and target engagement while minimizing ARIA
- cisLALA architecture that is unique to TV allows molecule to safely retain effector function
- Designed to preferentially bind oligomeric Abeta and minimize monomer binding

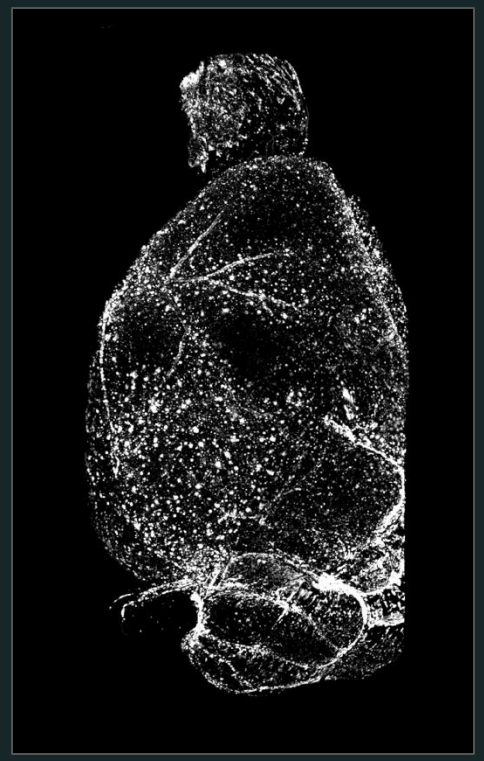
DNL921 is highly differentiated and has potential for best-in-class BBB-enabled Abeta mAb

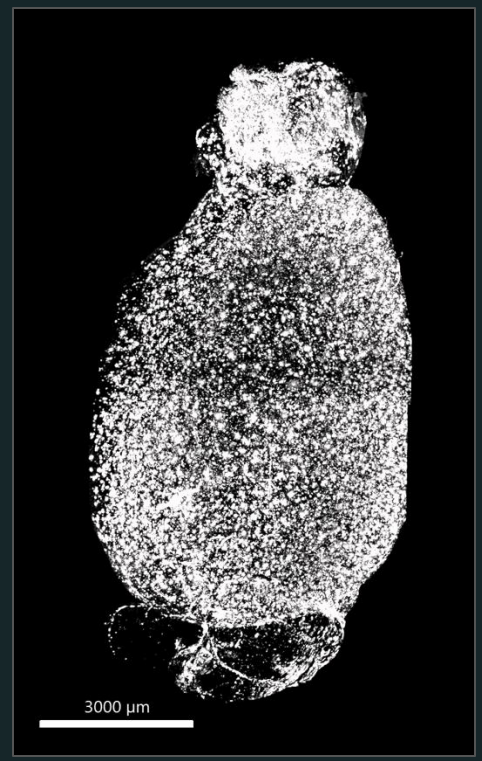
DNL921 Exhibits Superior Target Engagement and Deeper Brain Penetration Compared to First Gen Anti-Abeta

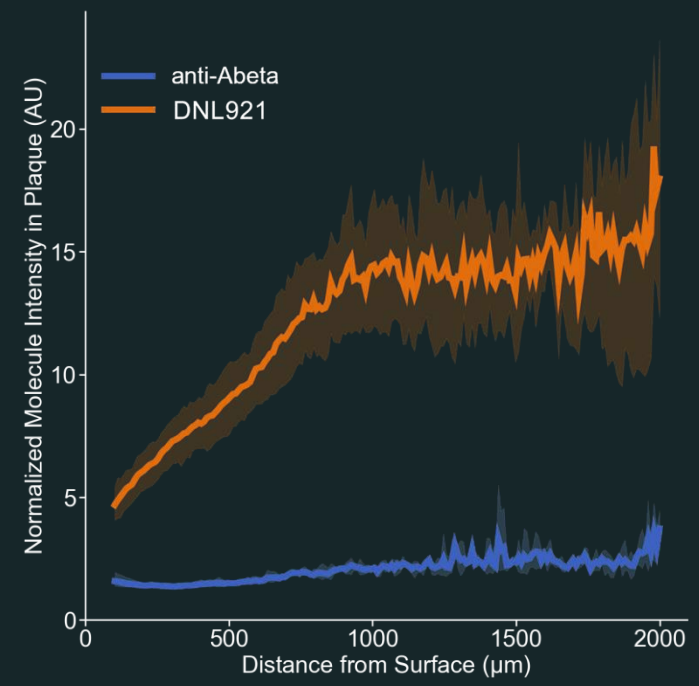
1st Generation Anti-Abeta

DNL921







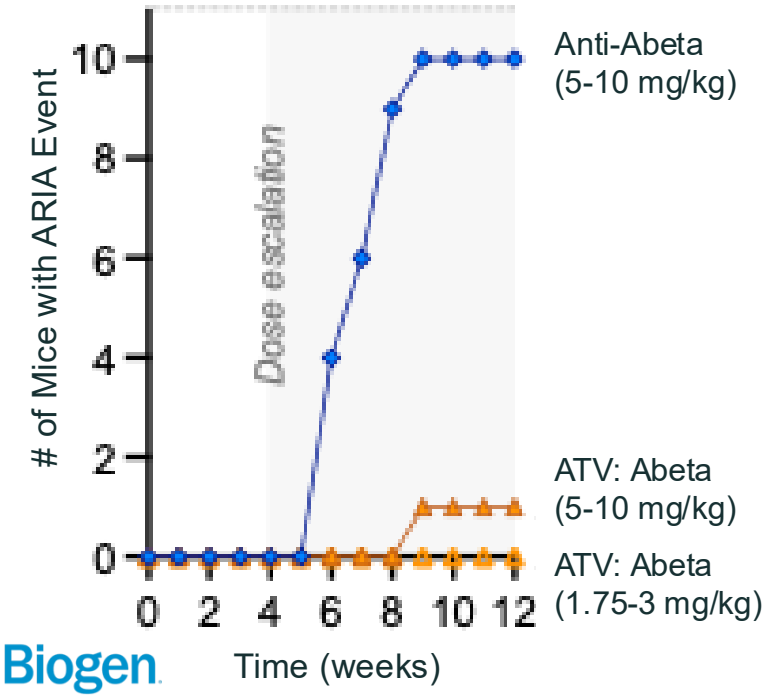


10 mg/kg, 24 hrs post-dose, iDISCO-cleared hemibrain; signal represents amyloid plaque engagement

ATV:Abeta Displays Reduced ARIA Due to TfR-Mediated Brain Uptake

Incidence of MRI Lesions

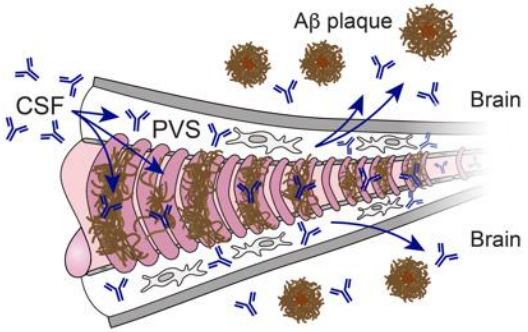
5xFAD; TfR$^{mu/hu}$ KI; QW IP



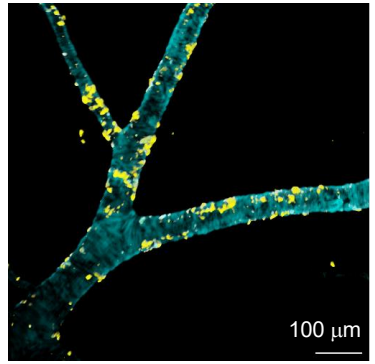
Biogen

Route of Entry into Brain

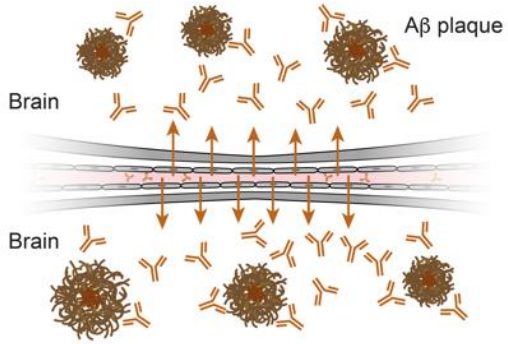
Conventional Anti-Abeta



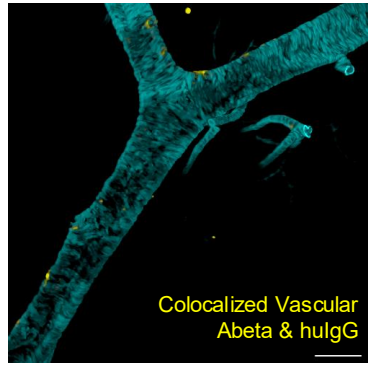
Artery / Arteriole Zone



ATV-Enabled Anti-Abeta



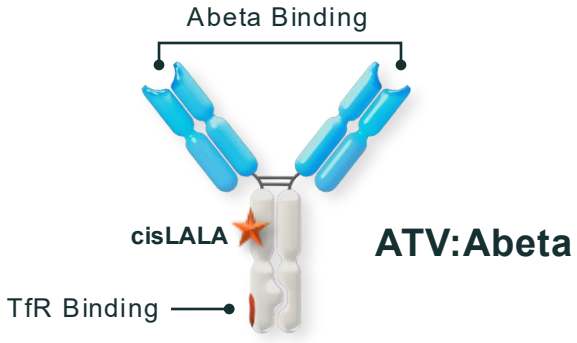
Microvessel (capillary) Zone



Bypassing vascular plaque via TfR-mediated entry into the brain through capillaries and venules improves ARIA safety

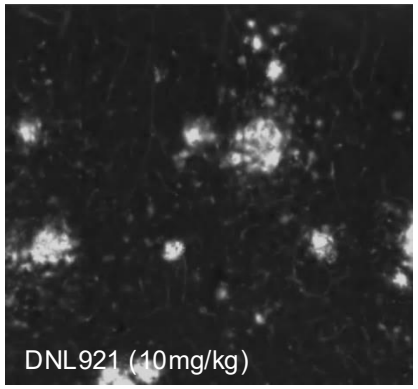
Pizzo et al., *Science*, 2025

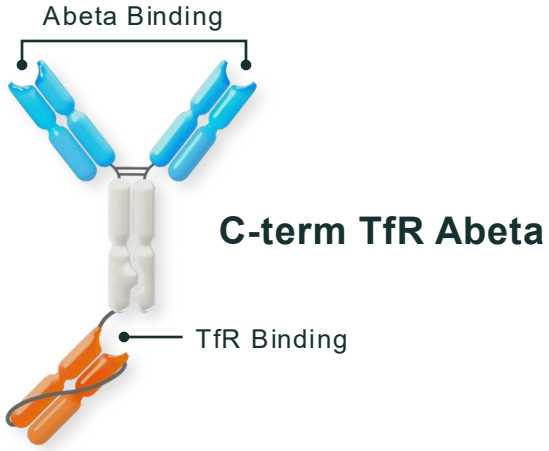
DNL921 Displays Greater Amyloid Plaque Engagement than Competitor TfR Architectures



ATV:Abeta

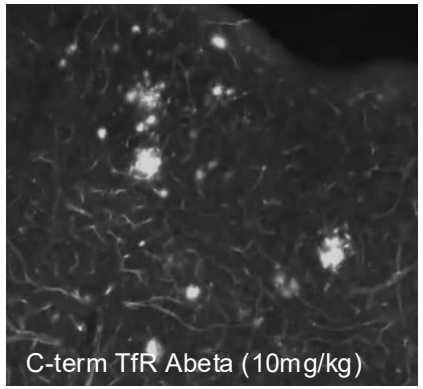
Day 1 Post-Dose



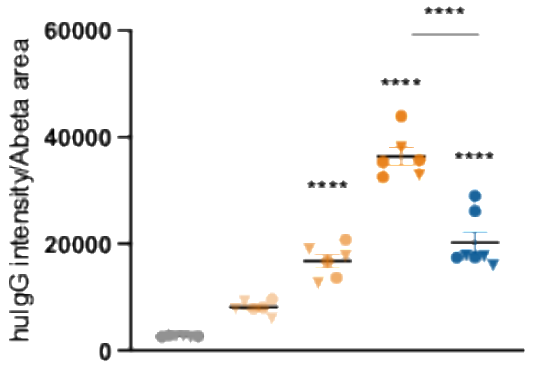


C-term TfR Abeta

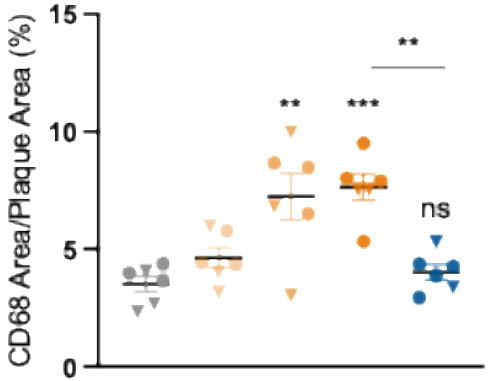
Day 1 Post-Dose

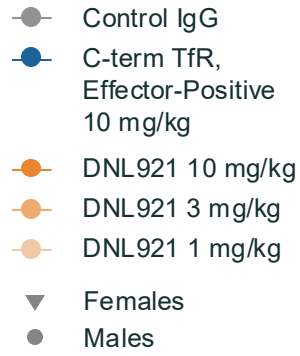


Plaque Associated Antibody



Plaque Associated Microglia





ATV:Abeta is highly differentiated and has potential for best-in-class BBB-enabled Abeta mAb

Engineering a Better Amyloid Beta Targeting Therapeutic

Approved Amyloid Beta Immunotherapies

Modest clinical benefit with significant risk of ARIA and slow plaque reduction

Opportunity for next-generation therapies to improve safety and efficacy

All TfR-Based Anti-Amyloid Beta Therapeutics are Not Engineered Equal

Desired Feature	ABBV-1758	Trontinemab	DNL921[2]
Properties			
Optimized TfR Binding	+	+	++
Effector Function	None	Full	Conditional
Efficacy			
Better Brain Uptake	++	++	+++
Improved Plaque Clearance	–[1]	++	+++
Safety			
Avoid ARIA	++	+	+++
Avoid Anemia	+++	+	+++
Avoid Immunogenicity	–	–	++

DNL921 (ATV:Abeta) has the potential to be the best-in-class anti-amyloid immunotherapy

1. Denali internal results and published data demonstrates effector function is required for maximal plaque clearance. **2.** Assessment based on Denali's preclinical data

DNL921 Clinical Study Design Enables Rapid Proof of Concept

Ph 1/1b → **Ph 3**

Study Population

SAD: Healthy Volunteers

MAD: Patients with biomarker confirmed Alzheimer's disease

Study Design

SAD

- **MAD Cohort A**
- **MAD Cohort B**
- **MAD Cohort C**

Duration: 28 weeks

Endpoints: Safety, Amyloid PET, Additional Biomarkers

Ph1b Objectives

- Safety
- Impact on Amyloid Plaque Load
- Dose Selection
- Additional biomarkers/imaging

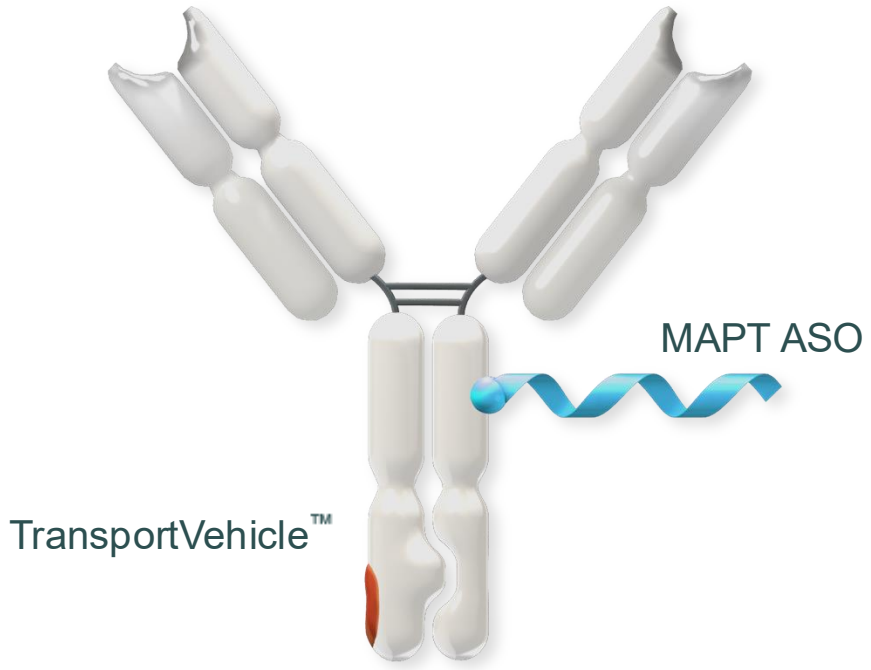
IND/CTA submission planned for 1H 2026

Potential for safety and clinical proof of concept in 2027

SAD – Single Ascending Dose; **MAD** – Multiple Ascending Dose

DNL628 (OTV:MAPT) Enables Tau Knockdown Throughout CNS Following Peripheral Administration

OTV:MAPT



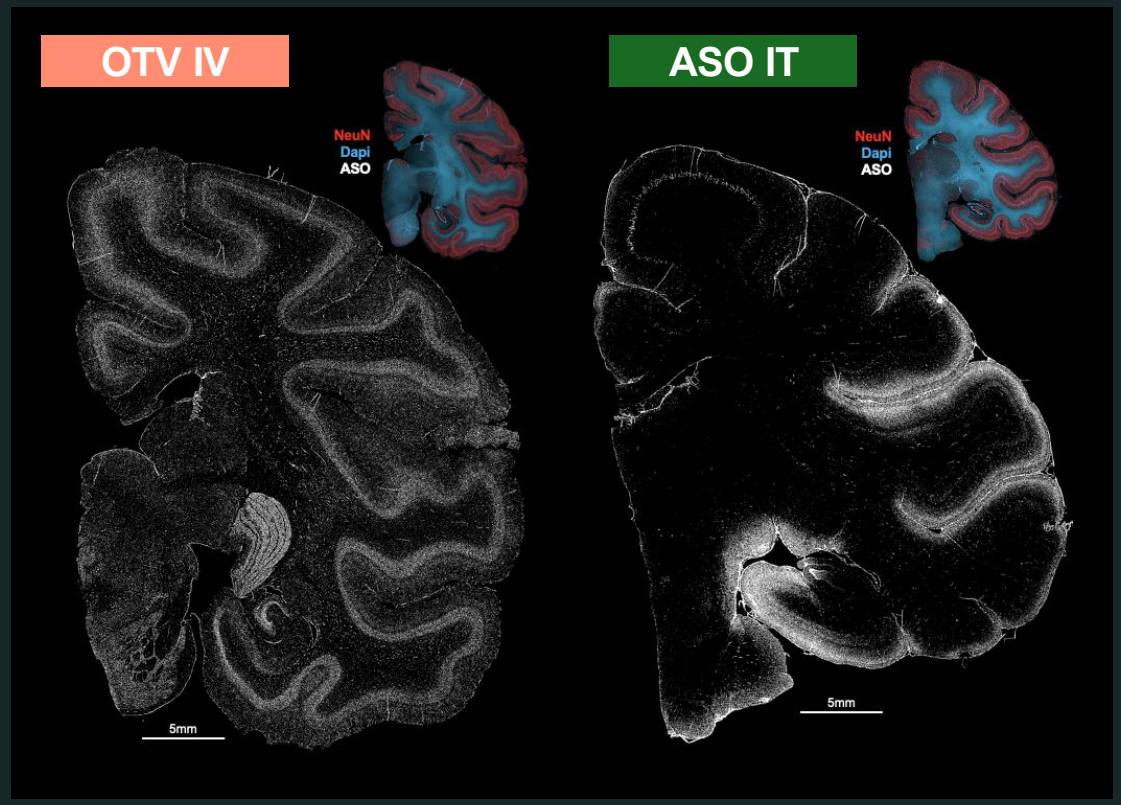
Program status: CTA Filed October 2025

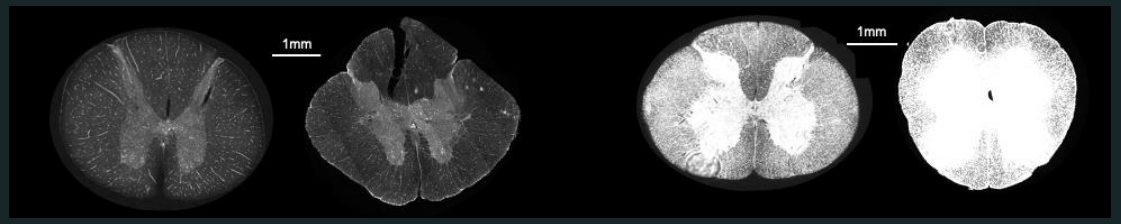
Key Characteristics

- TfR engagement optimized to maximize CNS uptake & biodistribution of oligo
- Biologic and oligo portion of molecule are engineered to improve exposure and safety
- Design principles can be readily applied to additional OTV programs

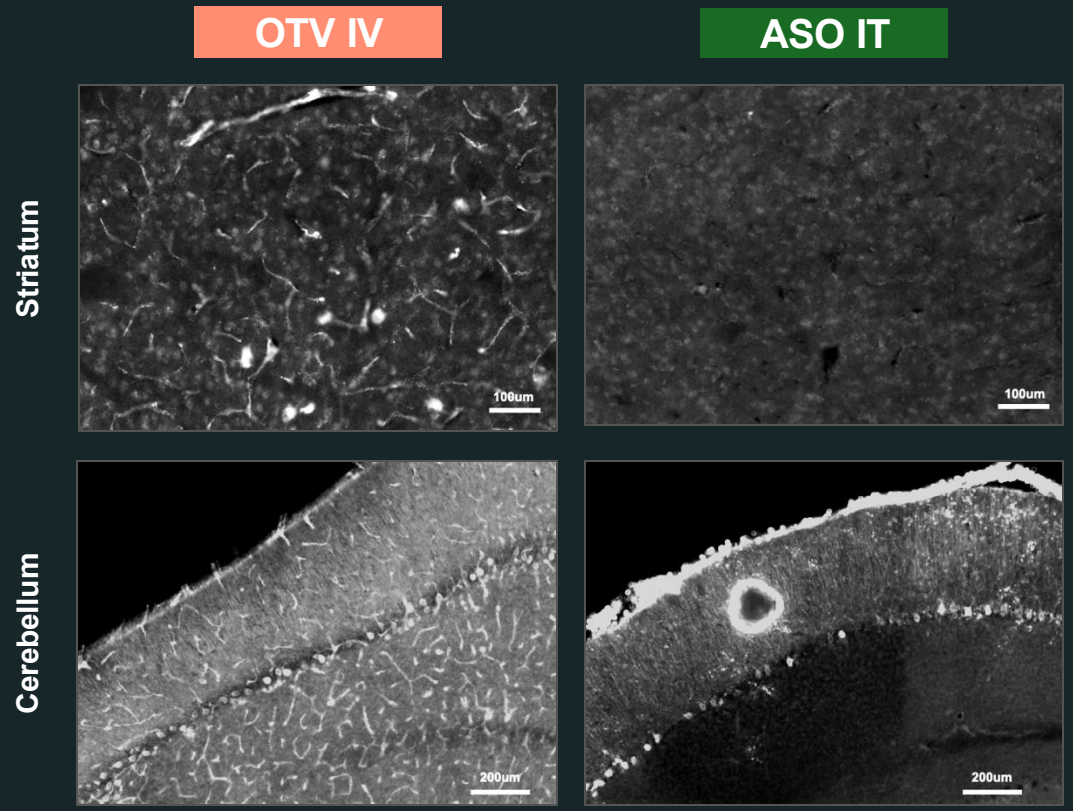
DNL628 has best in class potential based on improved brain biodistribution via peripheral administration

OTV Eliminates Sharp ASO Gradient that Results from IT Dosing





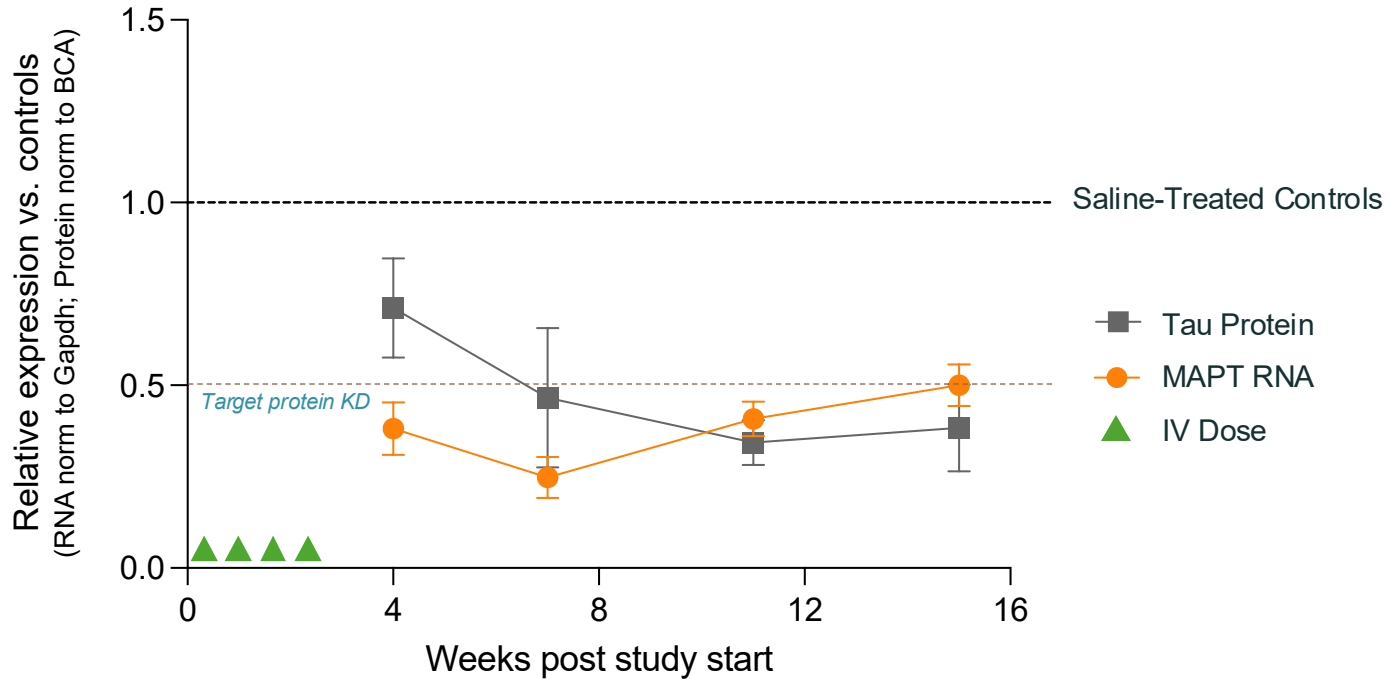
Enhanced ASO Deposition in Brain Regions that are Challenging to Target



Barker et al., *STM*, 2024

DNL628 Displays Robust and Sustained Knockdown in Mice Expressing Human Tau

Brain MAPT RNA and Tau Protein Knockdown (KD) Persists for >12 Weeks After Dosing



Robust and sustained reduction in tau protein with DNL628

Triangles indicate individual doses over two week time period

DNL628 Clinical Plan Designed to Quickly Determine Tau Knockdown in Brain

Study Population

Patients with biomarker confirmed early Alzheimer's disease (CDR 0.5 to 1, MMSE 20-30)

Study Design

- MAD Cohort A
- MAD Cohort B
- MAD Cohort C

Duration: 24 weeks

Endpoints: Safety, CSF Tau, Additional Biomarkers

Ph1b Objectives

- Safety
- Impact on Tau levels
- Dose Selection
- Additional biomarkers/imaging

CTA submitted October 2025

Clinical biomarker data expected by 1H 2027

Our TransportVehicle™ Platform Sets the Bar for BBB Delivery

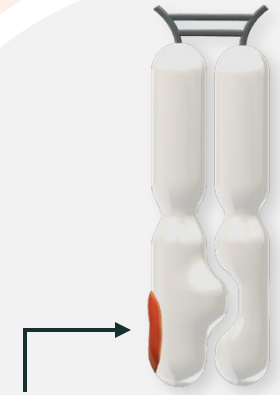
Our Fc-based TransportVehicle™ (TV) Is Designed & Engineered to Optimize Brain Delivery

1 Modularity

Enables broad ability to transport range of therapeutics, such as enzymes, oligos and antibodies

2 Brain Uptake

Optimized affinity and epitope enhance brain delivery while limiting receptor degradation



BBB receptor binding site engineered into the **Fc for optimal properties and modularity**

3 Safety

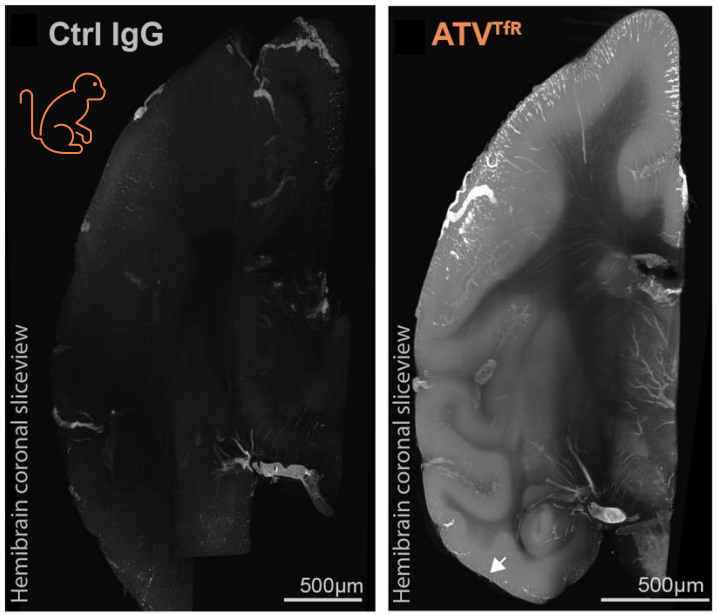
Conditional effector function avoids reticulocyte loss and minimizes anemia liability potential

4 Architecture

High fidelity to natural protein (e.g., no appended sequences) improves stability, limits immunogenicity and improves ease of manufacturing

1 Modularity: TransportVehicle™ Can Deliver Diverse Therapeutic Modalities

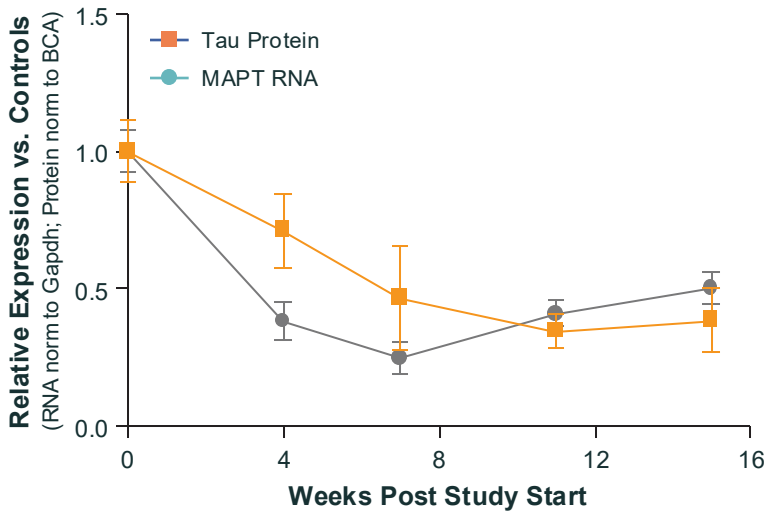
ATV



TV provides high and uniform deposition of ATV across the brain with systemic delivery

OTV

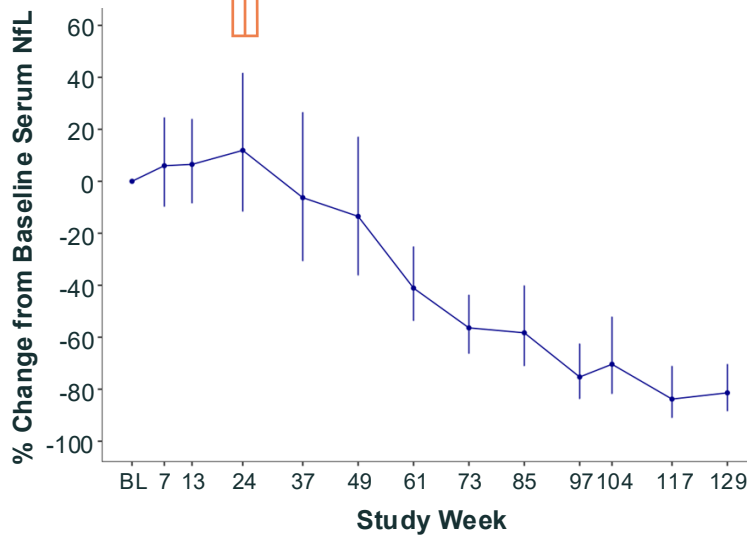
Tau Knockdown



TV enables sustained brain tau knockdown with OTV:MAPT systemic delivery

ETV

NfL Correction



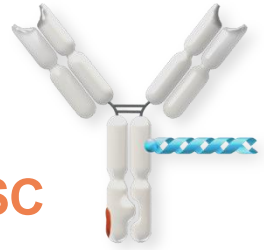
TV enables ETV:IDS to reduce serum NfL by >80%, achieving normal levels

TransportVehicle™ enables broader brain biodistribution, enhanced target engagement, and normalization of key disease biomarkers

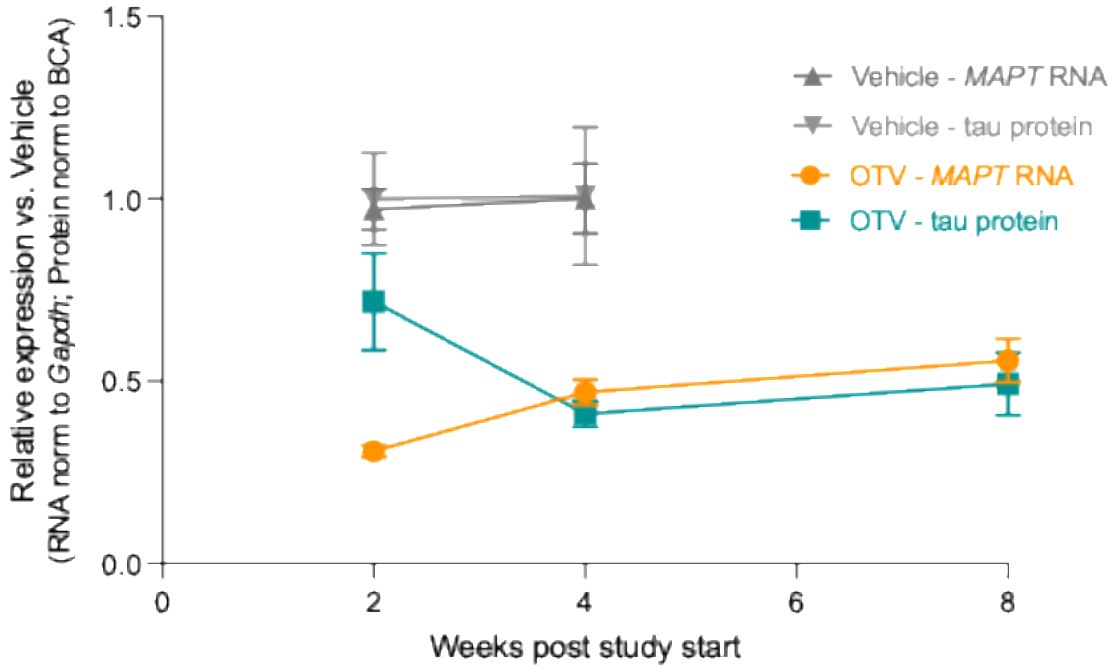
Khoury et al. *Nature Communications* (in press); **NfL** – Neurofilament light, a marker of neurodegeneration; Source: tau – Denali data on file, NfL – Adapted from SSIEM 2024

1 Modularity: TransportVehicle™ Is Compatible with Multiple Oligonucleotide-based Therapeutics

OTV:siRNA[1] Achieves Target Knockdown via RISC

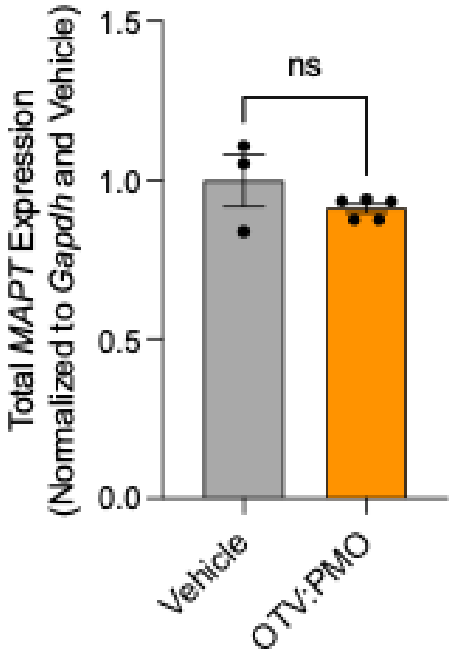


Brain *MAPT* RNA and Tau Protein

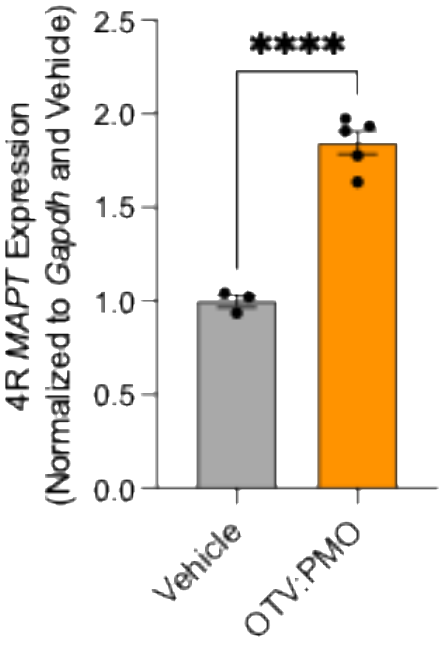


OTV:PMO[1] Achieves Isoform Modulation via Splicing Interference

Brain *MAPT* RNA



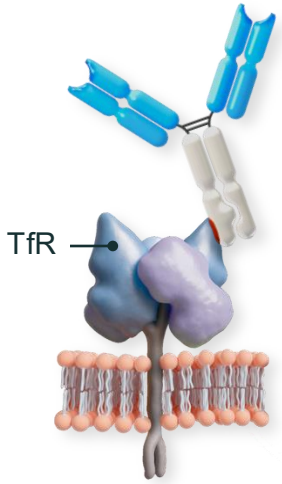
Brain 4R *MAPT* RNA



1. OTV:siRNA and OTV:PMO generated using publicly available oligo sequences as tools for platform proof of concept

1 Modularity: TransportVehicle™ Is Capable of Leveraging Additional BBB Transporters

TfR TV Platform



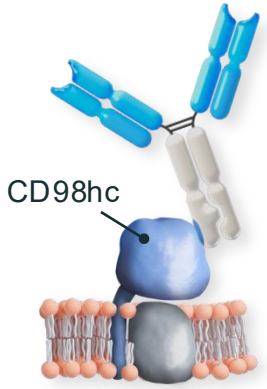
- **Highly expressed** on brain endothelium
- Undergoes constitutive endocytosis and recycling = **high transport capacity**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE May 2020

BLOOD-BRAIN BARRIER

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

CD98hc TV Platform



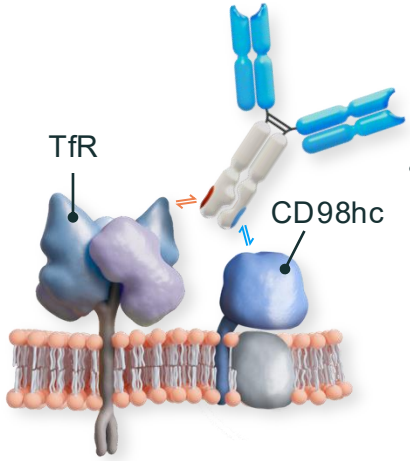
- **Highly expressed** on brain endothelial cells
- Capacity and kinetics **distinct from TfR;** opportunity for distinct target classes

nature communications

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

CD98hc is a target for brain delivery of biotherapeutics

Dual TV Platform Binds Both TfR and CD98hc



- Leveraging capacity of **two transporters** enables maximal brain uptake

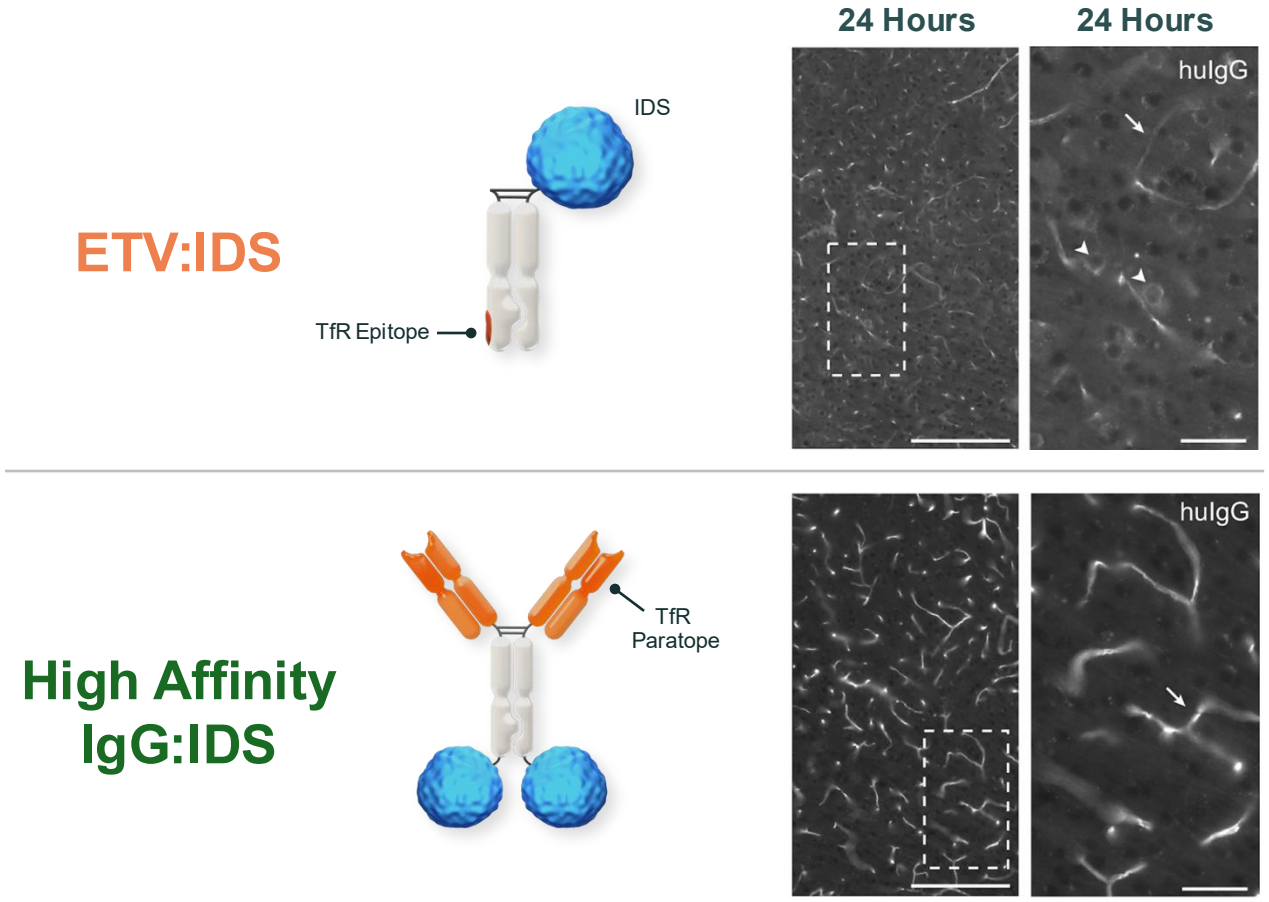
Cell Reports Article

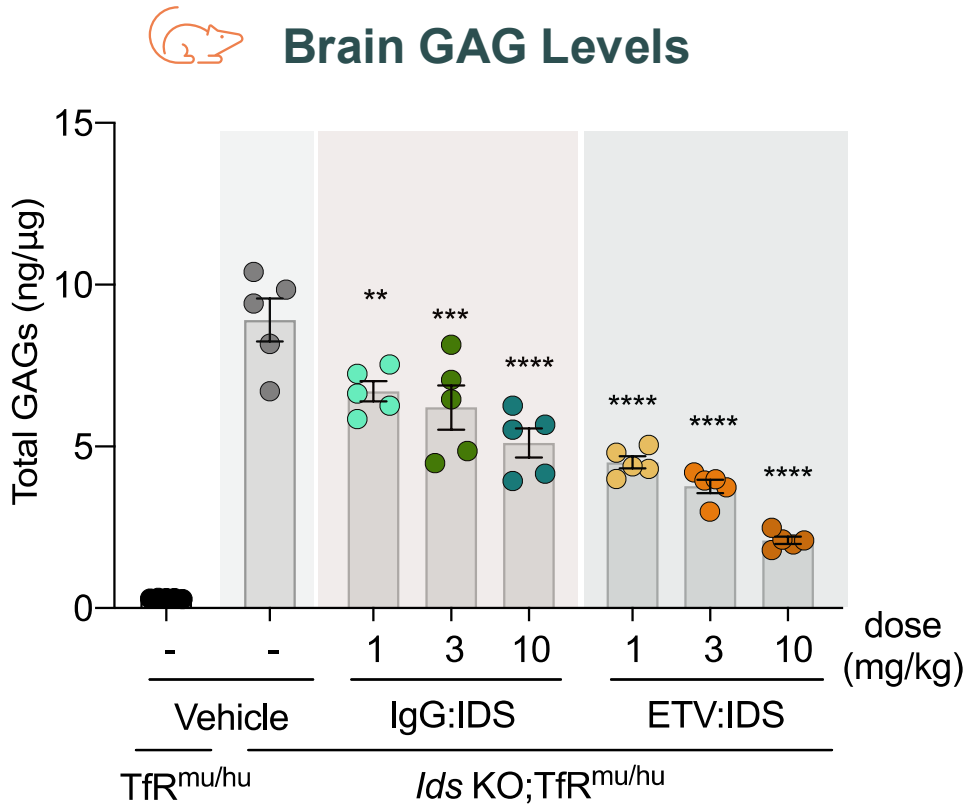
Dual targeting of transferrin receptor and CD98hc enhances brain exposure of large molecules

We continue to invent and lead the BBB field

TfR remains most validated transporter with demonstrated high capacity in humans

2 Brain Uptake: Optimized Affinity of TransportVehicle™ Drives Brain Biodistribution and Efficacy

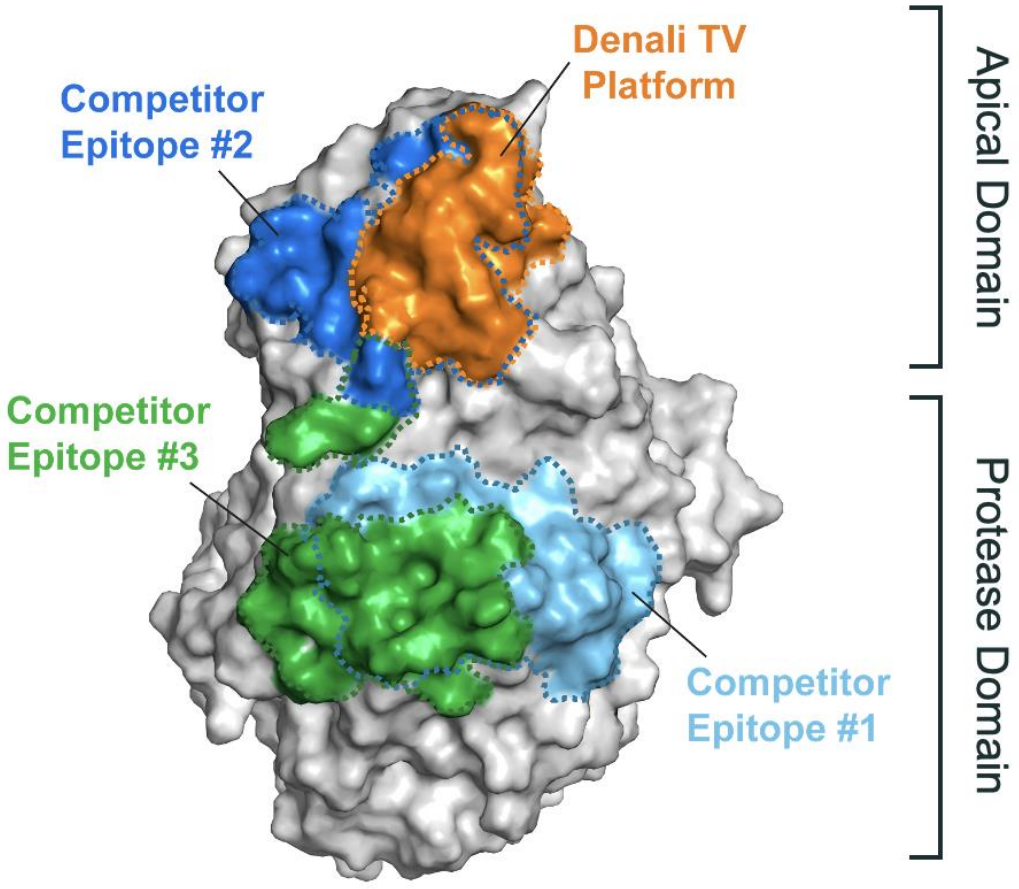




ETV:IDS shows broader biodistribution and greater GAG reduction than high affinity TfR in MPS II mouse model; results are consistent with clinical data from both architectures

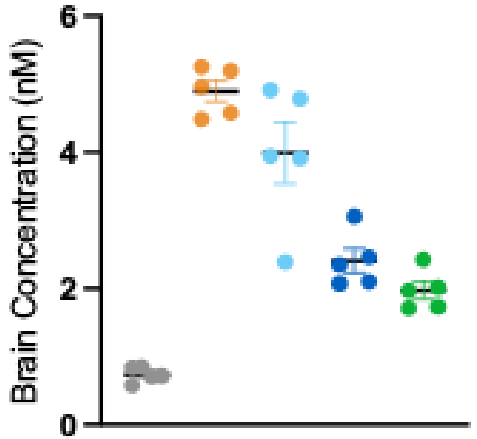
Arguello et al., *JEM*, 2022

3 Safety: TransportVehicle™ Engineering Enables Robust Brain Delivery Without Impacting Reticulocytes



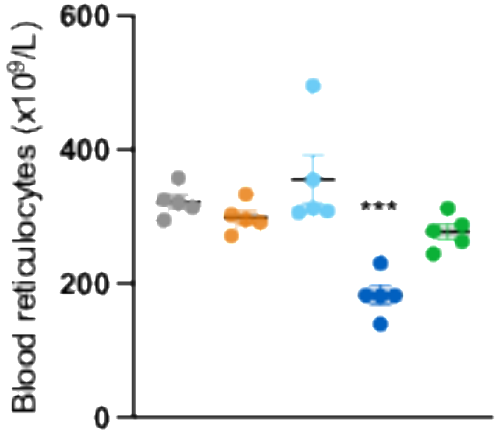
Brain Concentration

Single Dose, IV 10 mg/kg (molar-matched)



Immature Reticulocytes

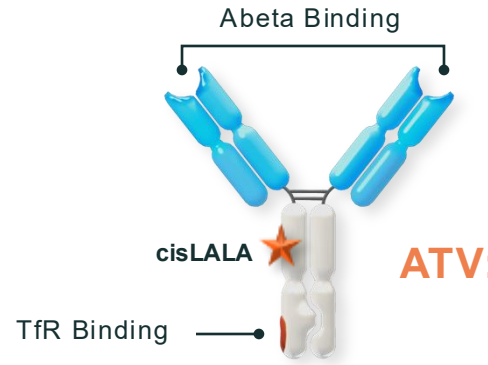
Single Dose, IV 10 mg/kg (molar-matched)



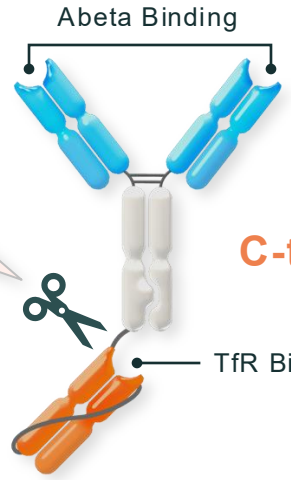
Molecule	Architecture	Epitope	Effector Function
Control	Control IgG	N/A	Full
DNL921	TV- TfR in Fc	Apical	Conditional
Competitor #1	C-term TfR	Protease	Full
Competitor #2	C-term TfR	Apical	Full
Competitor #3	C-term TfR	Apical	None

Competitor Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development

4 Architecture: Engineering of TfR Binding into Fc Domain in TransportVehicle™ Improves Stability



ATV:Abeta

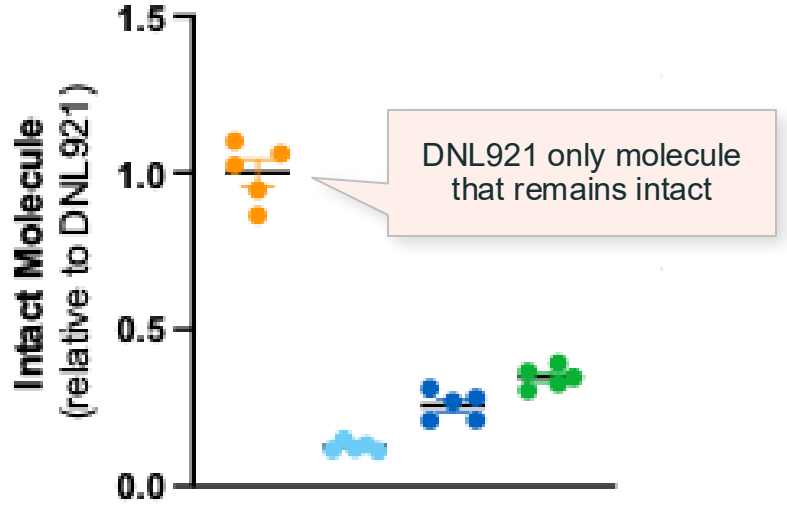


Potential clipping of TfR binding region

C-term TfR Abeta

Intact Molecule

hIgG Capture vs. TfR Capture ELISA, Single Dose IV 10 mg/kg

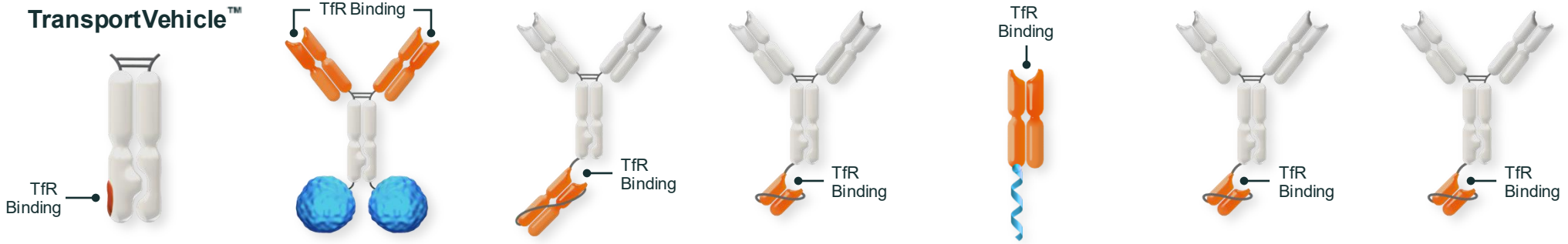


Molecule	Architecture	Epitope	Effector Function
DNL921	TV- TfR in Fc	Apical	Conditional
Competitor #1	C-term TfR	Protease	Full
Competitor #2	C-term TfR	Apical	Full
Competitor #3	C-term TfR	Apical	None

Appended TfR binding regions on competitor molecules are clipped *in vivo*; may limit brain uptake

Competitor Molecules generated at Denali based on publicly available information on TfR-binding anti-Abeta antibodies currently under development

TV Is Differentiated Relative to Other BBB Approaches

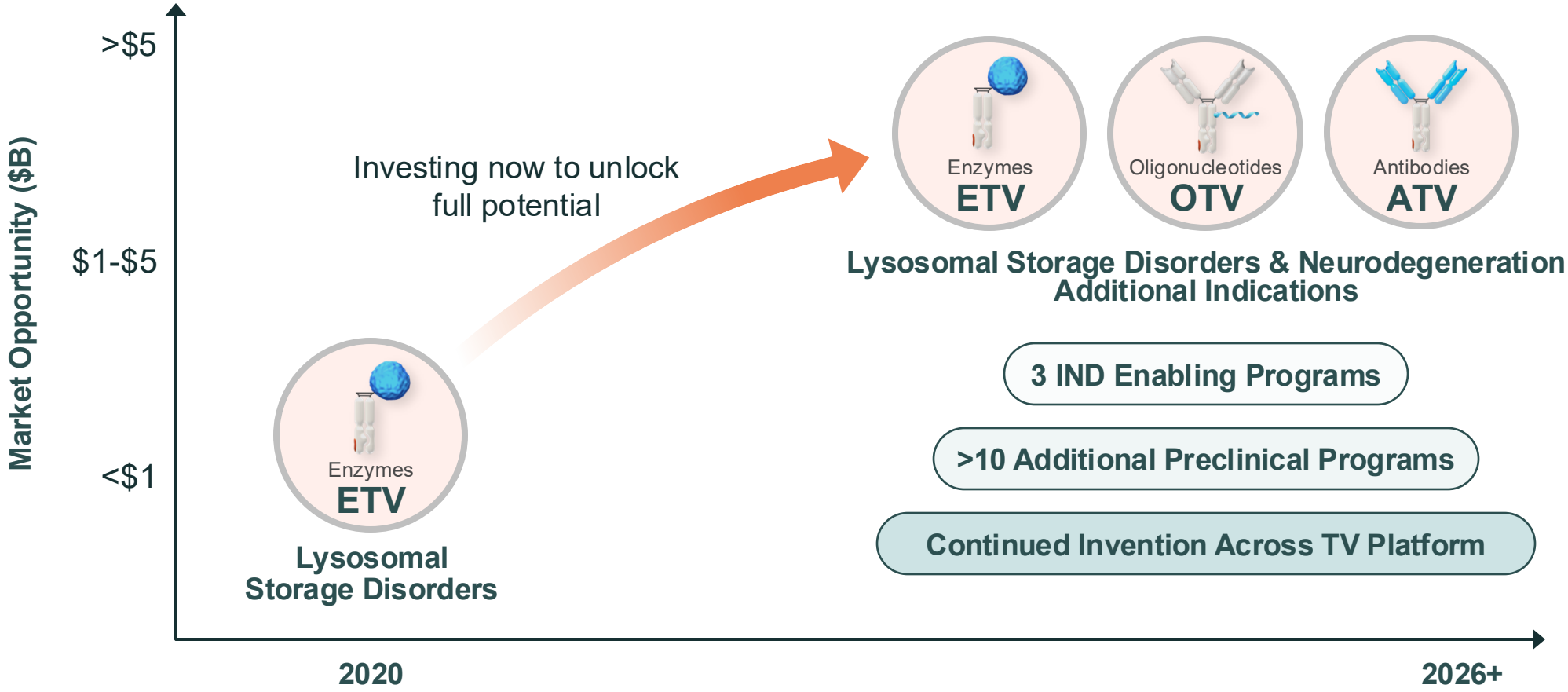


	DENALI	JCR Pharma	Roche	Aliada/Abbvie	Arrowhead	BioArctic	Alector
TfR Binding Format	Engineered into Fc	High affinity antibody fusion	Fab fusion	Single-chain variable fragment fusion	High affinity single-chain Fab	Single-chain variable fragment fusion	Single-chain variable fragment fusion
TfR Binding Domain	Apical	Apical	Apical	Protease-like	Apical	Protease-like	Apical
1 **Modularity**	Enzymes, Abs, oligos, proteins	Enzymes, gene therapy	Abs	Abs	Oligos	Abs	Claimed but limited data
2 **Brain Uptake**	Optimized for each program	High affinity limits uptake	Inferior compared H2H with TV	Inferior compared H2H with TV	No H2H data vs TV platform	Inferior compared H2H with TV	No H2H data vs TV platform
3 **Safety**	Conditional effector function	Safety caps at low doses	Some anemia	Safety strategy may limit efficacy	No data reported	Preclinical data only	Retic loss in monkey reported
4 **Architecture**	No appended sequences	Dose limited	Immunogenicity/ stability concern	Immunogenicity/ stability concern	Rapid clearance predicted	Immunogenicity/ stability concern	Immunogenicity/ stability concern

Clinical data reported | Clinical stage; No data reported | Preclinical

Heatmap based on publicly disclosures and head to head (H2H) data generated at Denali in preclinical models for any direct comparisons

Expanding the TV Franchise



We aim to recognize the full value of the TransportVehicle™ platform
Each TV Franchise has a market potential of $5B+

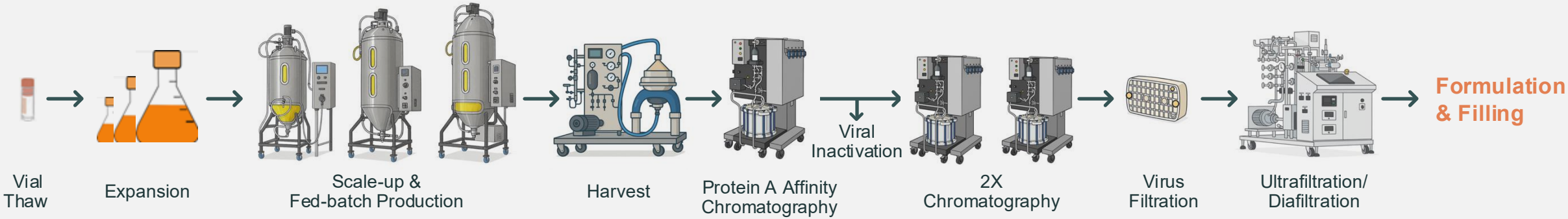
Integrated Manufacturing

Driving Speed, Flexibility and Value

Dana Andersen, Ph.D.
Chief Technical and Manufacturing Officer

Denali Platform Enables Efficient Manufacturing

TransportVehicle™ (TV) architecture uses antibody-like manufacturing processes



Platform Efficiency

- Architecture enables 3-column antibody-like purification process
- Fits seamlessly within global antibody manufacturing capacity
- Royalty-free cell line and vector

Cost Impact

- Efficient processes enable projected COGS <20% of revenue
- Reduces cost and time to IND
- High productivity TV processes will support large markets

Strategic Use of Partners

- Leverage CDMOs for large-scale manufacturing to manage capacity and efficiency
- Drug product and oligonucleotide manufacturing outsourced until internalization is beneficial

Denali Has Built Internal Manufacturing Capability

GMP Manufacturing Facility Completed and Operational

(Q1 2025)

- Purpose-built to support clinical production across the TransportVehicle™ platform

Strategic Benefits

Speed & Flexibility

- Enables rapid scale-up and response to evolving program needs
- Can nimbly reprioritize schedule when data supports moving quickly

Cost Efficiency

- Integrated development & manufacturing has reduced cost to IND
- Eliminates reservation fees at CDMOs

Risk Reduction

- Increases control over supply chain and product quality
- Mitigates tariff exposure

Integrated Platform Advantage

- Supports broad application of TransportVehicle™ technology
- Learnings leveraged across portfolio to increase efficiency

State-of-the-art Salt Lake City facility built for efficiency, flexibility, and speed to clinic

Manufacturing Highlights

Denali's Manufacturing Facility

- ~70,000 sq. ft. GMP facility constructed for < $80M in Salt Lake City, UT
- 2 × 2000-L fermenters with purification train
- Designed for single-use technology and modular expansion

Flexible, Efficient Operations

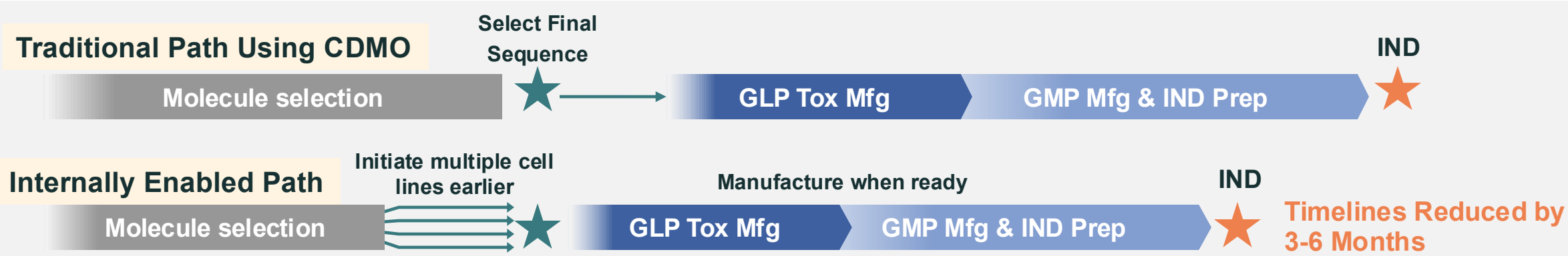
- Up to 40 batches per year with staff expansion
- Single-use design enables rapid changeover between programs
- Supports both early clinical and commercial manufacturing

2025

- ☑ 8 GMP & GLP batches
- ☑ Successful GMP audit enabling EU clinical supply

All future early clinical products and commercial launch of DNL126 planned from this facility

Integrated Manufacturing Drives Speed, Flexibility & Value



Acceleration Through Integration

- Enables parallel risk-taking and quickly responding to data
- Avoids restrictions from CDMO capacity constraints
- Accelerating IND timelines by ~1 quarter for first 2 programs

Strategic Control & Risk Reduction

- Reshored DNL126 manufacturing for BLA filing and commercial launch
- Reduces at-risk manufacturing by enabling rapid response to demand signals

Economic & Strategic Advantages

- Optimized DNL126 production scale reduced COGS by ~50%
- Increased process understanding and proprietary manufacturing IP

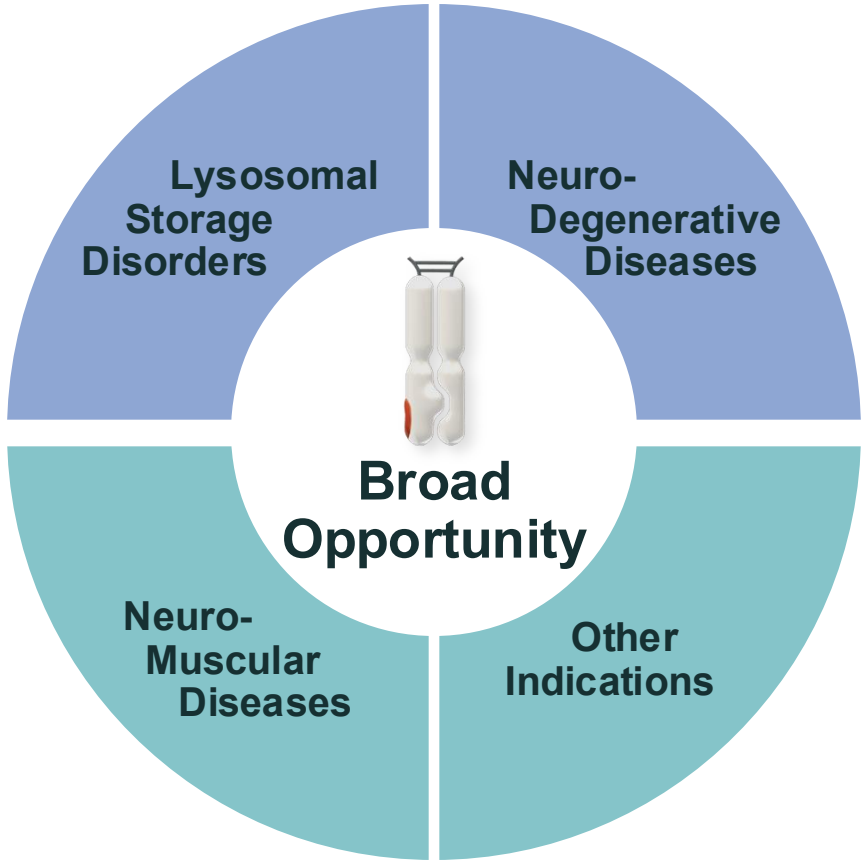
End-to-end capabilities accelerate development, reduce risk, and strengthen long-term economics

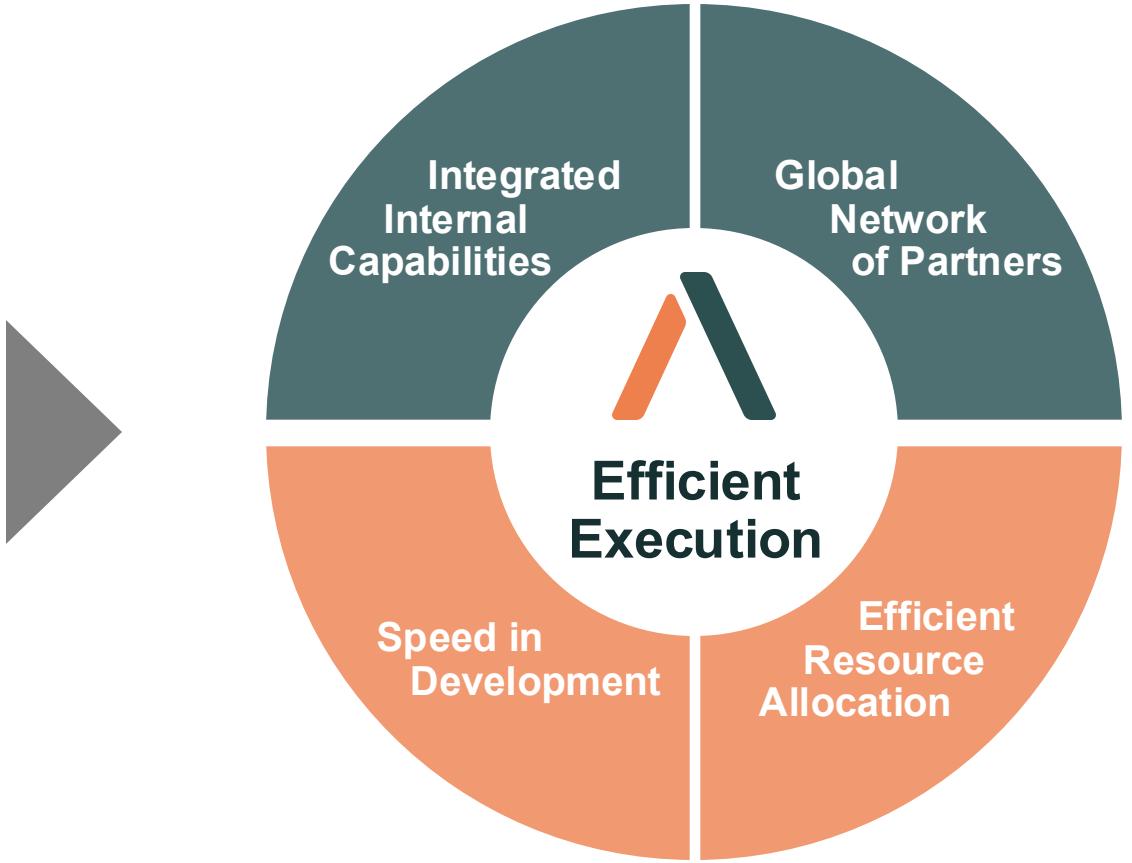
Evolving Our Business

Delivering the Value of the TransportVehicle™

Alexander Schuth, M.D.
Chief Operating and Financial Officer

Growing and Executing the Leading Portfolio of BBB-Enabled Programs





Leading a new class of biologic therapeutics that can reach the whole body, including the brain

Broad Portfolio to Create Near-Term and Long-Term Value

Molecule	Indication	IND-Enabling	Phase 1	Phase 2	Phase 3	Reg. Filing	Partner
Tividenofusp Alfa (DNL310) ETV:IDS	MPS II (Hunter)						
DNL126 ETV:SGSH	MPS IIIA (Sanfilippo type A)						
DNL593 PTV:PGRN	FTD-*GRN*						Takeda
DNL952[1] ETV:GAA	Pompe						
DNL111 ETV:GCase	Gaucher/ Parkinson's disease						
DNL622 ETV:IDUA	MPS I (Hurler)						
DNL628 OTV:MAPT (tau)	Alzheimer's disease						
DNL921 ATV:Abeta	Alzheimer's disease						
DNL422 OTV:SNCA	Parkinson's disease						
BIIB122 LRRK2 Inhibitor	Parkinson's disease						Biogen
Eclitasertib (SAR443122) RIPK1 inhibitor	Ulcerative colitis						Sanofi

$500M - $1B per indication

$5B+ per indication

ATV OTV ETV Small Molecule

1. Protocol amended and response to FDA submitted regarding clinical hold

Integrated Capabilities to Execute for Long Term Value

Scale and Infrastructure

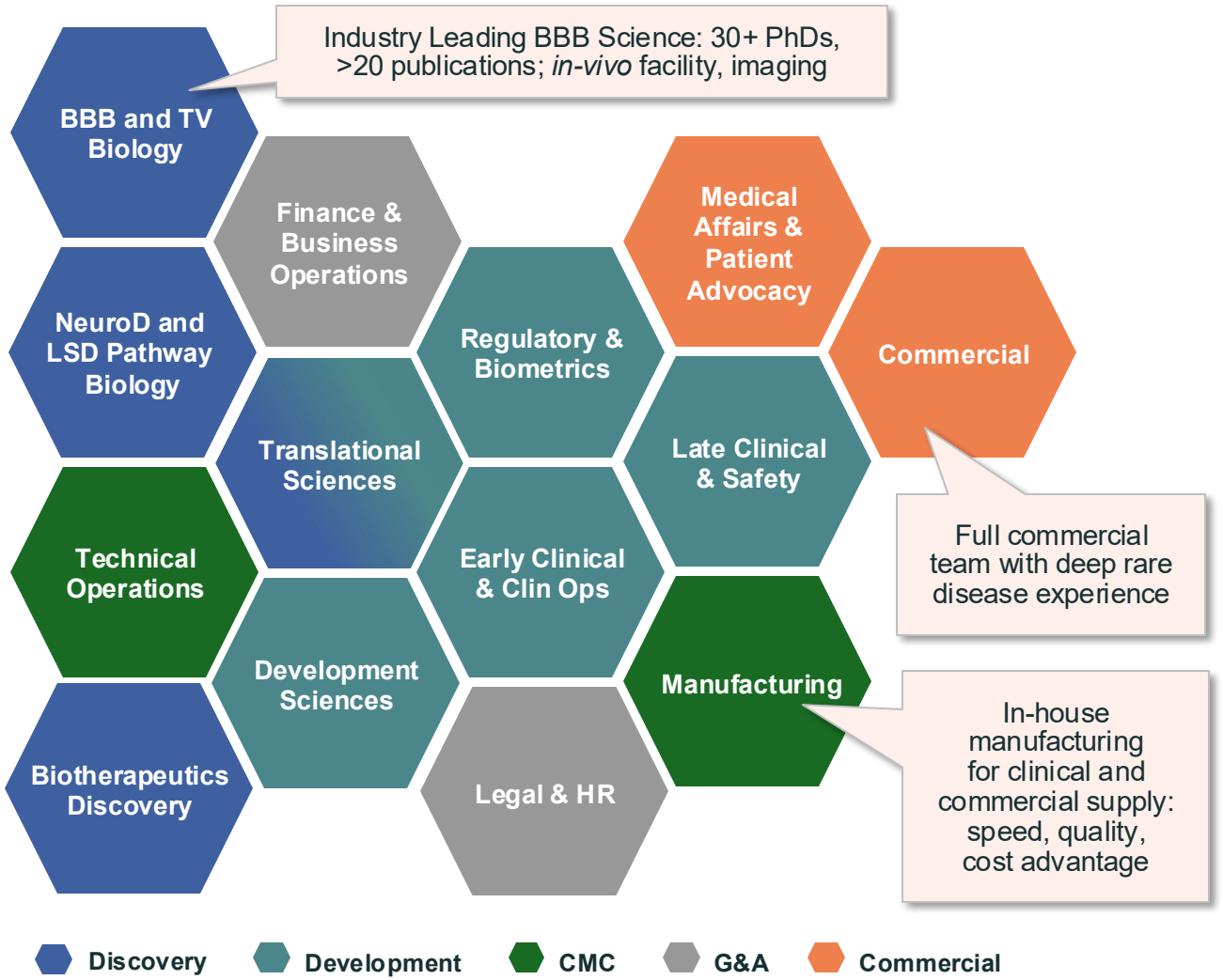
- **Scale** to successfully discover, develop, manufacture and commercialize
- **Integrated infrastructure** with ~520 full time employees in South San Francisco, Salt Lake City and Zürich

South San Francisco, California

Salt Lake City, Utah

Zurich, Switzerland

Established Capabilities



Capital to Execute

Key Capital Allocation Priorities

Invest Strategically

- Successful launches of tividenofusp alfa and DNL126
- Focused R&D investments to accelerate and expand pipeline

Drive Capital Efficiency

- Apply learnings from tividenofusp alfa to develop next programs faster and at lower cost

Maintain Capital Optionality

- Partnerships remain core to strategy
- Diversifying sources of capital

Strong Financial Foundation

$873M + $275M

Cash and investments as of Q3 2025 plus new royalty financing[1]

2 Commercial Launches

Potential revenues from tivi and DNL126

3 Partnerships

Cost share and potential milestone income

1. Royalty financing will contribute $200M upon approval of DNL310 by June 30, 2026 and an additional $75M upon EMA approval by December 31, 2029

Royalty Financing Agreement with Royalty Pharma (12/4/25)

DENALI ROYALTY PHARMA

Denali Therapeutics and Royalty Pharma Announce $275 Million Royalty Funding Agreement

SOUTH SAN FRANCISCO, Calif. and NEW YORK, N.Y. — December 4, 2025 — Denali Therapeutics Inc. (Nasdaq: DNLI) and Royalty Pharma plc (Nasdaq: RPRX) today announced a $275 million synthetic royalty funding agreement based on future net sales of tividenofusp alfa.

Tividenofusp alfa is Denali's lead investigational TransportVehicle™-enabled enzyme replacement therapy for the treatment of mucopolysaccharidosis type II (MPS II, or Hunter syndrome). A Biologics License Application (BLA) for accelerated approval of tividenofusp alfa is under review by the U.S. Food and Drug Administration (FDA) with a Prescription Drug User Fee Act (PDUFA) target date of April 5, 2026.

"We are pleased to partner with Royalty Pharma, whose investment recognizes the value and potential of tividenofusp alfa for the Hunter community and supports our ability more broadly to realize the promise of the TransportVehicle platform," said Ryan Watts, Ph.D., Chief Executive Officer of Denali Therapeutics. "With these additional funds, we are well positioned to advance our development programs as we prepare for the launch of tividenofusp alfa, unlocking broad opportunities across serious diseases."

"We are delighted to partner with Denali and acquire a royalty on tividenofusp alfa, an innovative therapy that addresses a significant unmet need in the cognitive and physical manifestations of Hunter syndrome," said Pablo Legorreta, Chief Executive Officer and Chairman of the Board of Royalty Pharma. "Denali's technology platform delivers therapeutics across the blood-brain barrier and is a promising new approach to brain diseases. We are thrilled to establish a relationship with Denali and believe tividenofusp alfa is a potential practice-changing therapy that could transform the lives of patients with Hunter syndrome."

$275M potential total funding[1]:

$200M at US approval and

$75M at EMA approval

9.25% royalty payable on worldwide net sales of tividenofusp alfa

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Royalty payments capped at 2.5x by Q1 2039 and 3x thereafter

Investment to support successful commercial launch and portfolio execution

1. $200M funded upon U.S. approval by June 30, 3026, and $75M upon EMA approval by Dec 31, 2029

Efficient Capital Allocation and Acceleration in Execution

Applying Learnings, Leveraging Networks and Capturing Operational Synergies

- Streamlined clinical studies and validated biomarkers
- Established relationships with stakeholders (health authorities, KOLs, patient groups, policy makers)
- Preferred partnerships with clinical sites and CROs
- In-house manufacturing for all future TV programs
- Commercial infrastructure to support future launches

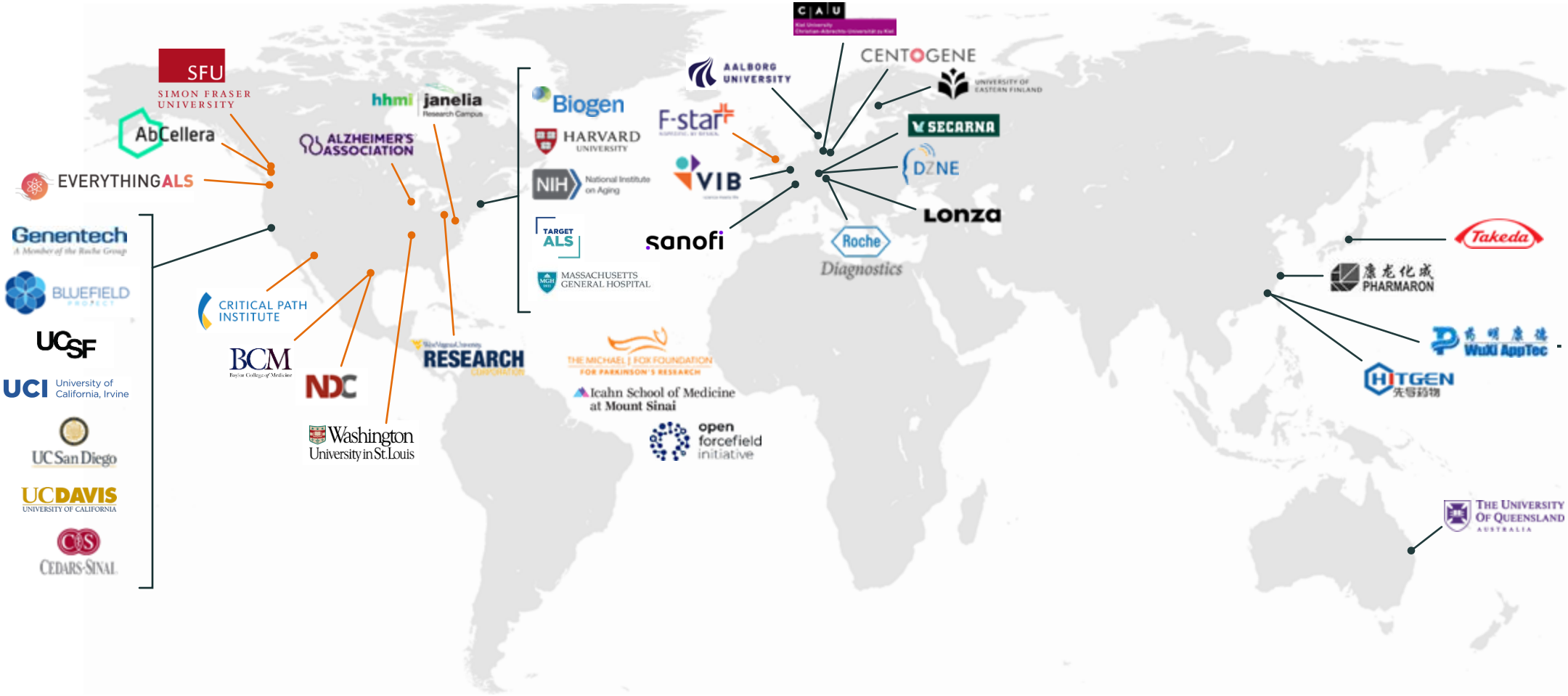
Case Study: DNL126 vs. DNL310

	Potential 1st Launch DNL310[1]	Potential 2nd Launch DNL126[2]	Acceleration / Cost Saving
Number of Patients to Enable Accelerated Approval	47	20	55%
Total Manufacturing Costs	$280M	$100M	65%
Time from FIH to Potential US Approval	5 yrs 8 months	4 yrs	30%
Total Expected Development Costs to Approval	**$700M**	**$340M**	**50%**

Develop next programs with significantly increased speed and cost efficiency

1) PDUFA date April 5, 2026 for DNL310; 2) Potential AA in Q4 2027

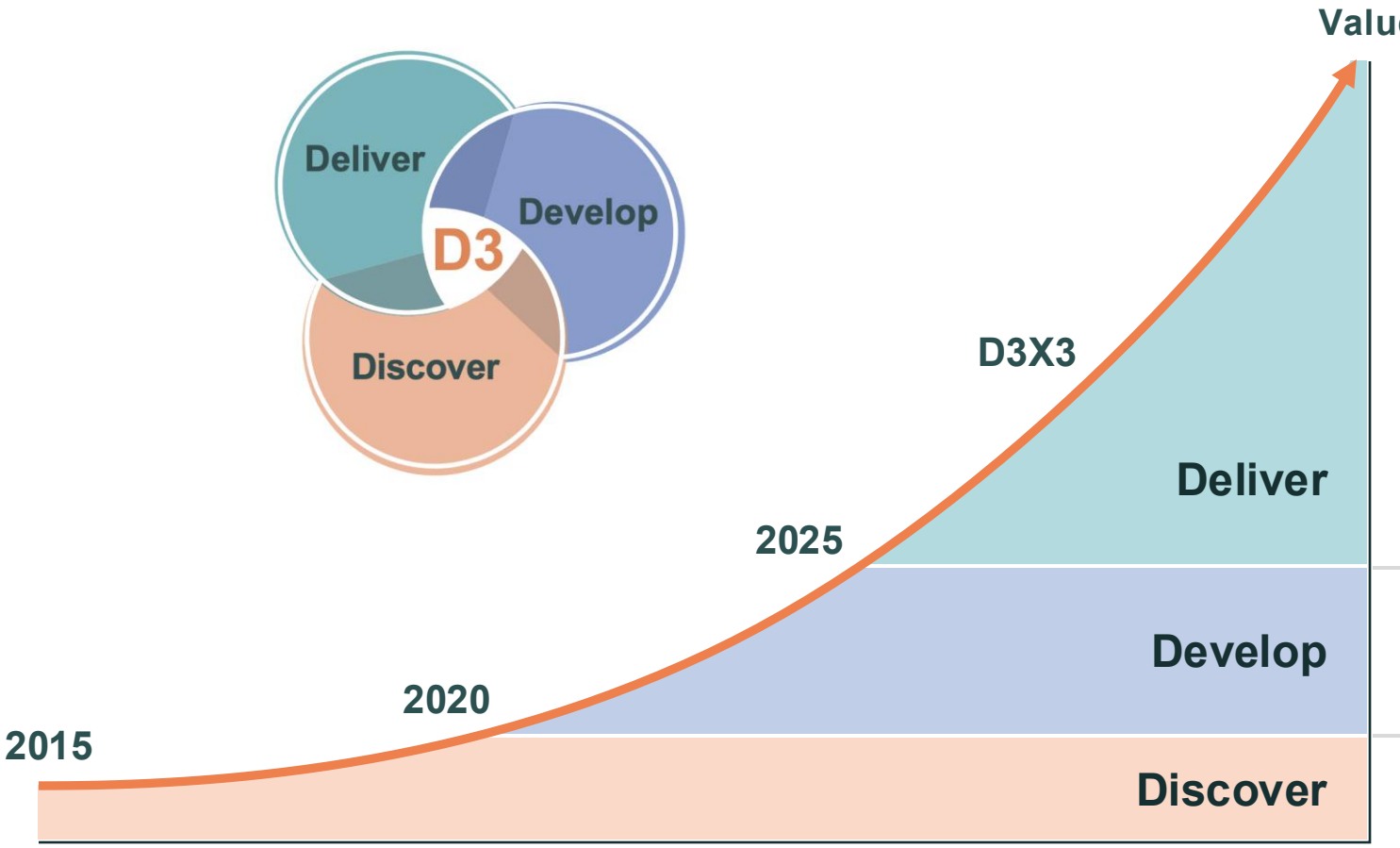
Collaborations Are Central to Our Execution Strategy



Network in academia and industry strengthens depth in science and global reach in execution

Note: Includes current and former partners

Entering a New Phase on the Path to the Summit



3-Year Goals (D3X3)

2 Growing Brands

5 Clinical Proof of Concepts

4-6 New Clinical Programs

Pioneering a new class of biotherapeutics and capturing the full potential of the TransportVehicle™

2026-2027 Expected Milestones

1. Protocol amended and response to FDA submitted regarding clinical hold

Our Purpose

Deliver the power of biotherapeutics to the whole body, including the brain, transforming life for people living with serious diseases

Q&A

Denali’s Leadership Team

DENALI

Thank You