Corporate Overview

January 2023

Disclaimers

Forward-Looking Statements. This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements do not relate strictly to historical or current facts and they may be accompanied by such words as “anticipate,” “believe,” “could,” “estimate,” “expected,” “forecast,” “intend,” “may,” “plan,” “potential,” “possible,” "future," “will” and other words and terms of similar meaning. All statements other than statements of historical facts contained in this presentation, including, without limitation, statements regarding future results of operations and financial position of Denali Therapeutics Inc. (“Denali” or the “Company”); Denali’s business strategy and business plans, expected progress and expansion, and expected key milestones for Denali's therapeutic portfolio in 2023 and beyond; Denali’s ability to execute on its tailored commercial strategies and accelerate commercial launch readiness in key markets, including the US and China; expectations relating to the potential for Denali's product candidates to treat various neurodegenerative diseases including MPSI, MPS II (Hunter Syndrome), MPS IIIA (Sanfilippo Syndrome), ALS, MS, PD, AD, FTD-GRN, CLE, UC, and related peripheral inflammatory diseases, as well as expectations and timelines relating to the continued progress and potential of its small molecule programs; 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, and current and future therapeutic and commercial opportunities related to Denali's Transport Vehicle (TV) platform, including its Enzyme Transport Vehicle (ETV), Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV), and Oligonucleotide (OTV) technologies, and other programs enabled by these platforms, as well as potential targets and differentiation strategies; plans, timelines, and expectations relating to DNL310, including safety profile and exploratory clinical outcomes data from the ongoing Phase 1/2 study, enrollment in the Phase 2/3 COMPASS study, and the initiation of future clinical trials; plans, timelines and expectations related to DNL126, including planned regulatory filings; Denali's and Takeda's plans and expectations regarding DNL593 and DNL919, including ongoing and future clinical trials, the availability of data, and planned regulatory filings; Denali's priorities, regulatory approvals, timing and likelihood of success and expectations regarding Takeda's option exercise to co-develop and co-commercialize DNL919; expectations relating to the ability of Denali's ATV technology to enhance the therapeutic efficacy of DNL919; expectations and potential benefits relating to ATV:Abeta for the potential treatment of AD; plans, timelines, and expectations relating to the Biogen-led development of DNL151, including a Phase 2b trial and Phase 3 trial, as well as other LRRK2 inhibitor molecules; expectations relating to LRRK2 inhibitor DNL201 for the treatment of PD; plans, timelines, and expectations related to DNL343, including the availability of data and the initiation of future clinical trials; Denali's and Sanofi's plans, timelines, and expectations related to DNL788 and DNL758, including with respect to the availability of data and the initiation of future clinical trials; the potential benefits and results of the collaborations with Denali’s partners, including Biogen, Sanofi, and Takeda, and expected milestone payments; Company priorities, regulatory approvals, timing and likelihood of success and expectations regarding collaborations; and plans and expectations regarding Denali's global organization and clinical operations, the growth of its in-house clinical manufacturing capabilities, and the expected timing and likelihood of success of its commercial growth, are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events.

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: Denali’s business and operations caused directly or indirectly by the evolving COVID-19 pandemic; risk of the occurrence of any circumstance that could give rise to the termination of Denali’s agreements with its collaborators; Denali’s early stages of clinical drug development; Denali's and its collaborators' ability to scale manufacturing capabilities; 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; whether DNL310 will impact downstream biomarkers of neurodegeneration; significant adverse events, toxicities or other undesirable side effects; the risk that preclinical profiles of Denali’s product candidate DNL919may not translate in clinical trials; 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 including DNL919 will receive regulatory approval or be commercialized; the uncertainty in the outcome of Denali’s discussions with the FDA regarding the clinical hold on the DNL919 IND; 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; 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 Annual and Quarterly Reports filed on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 28, 2022, and November 3, 2022, respectively, and 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.

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.

BUILDING DENALI TO DEFEAT DEGENERATION

Accomplishments to Date

Track Record of Invention & Execution

10 INDs across 6 indications, **7 programs in clinical development** with **3 in late-stage**

Invented and validated BBB **Transport Vehicle (TV)** technology

Discovery engine with **>14 programs** in discovery stage, **20+ publications** in top-tier journals, and **90+ patents** granted WW

Strategic partnerships with Biogen, Sanofi and Takeda totaling **$1.3B** in upfront payments and **>$3B** in milestones

Mid-Term Goals (2023-2025)

Creating Value & Delivering Medicines

Complete **3 - 4 late-stage** clinical studies and establish **commercial launch readiness**

Expand TV platform with **OTV candidates in the clinic**

Productive discovery engine to deliver at least **3 additional NMEs in the clinic**

Selectively evaluate **new partnering opportunities**

Long-Term Goals

Defeating Degeneration

Commercial **portfolio of products** in key markets

Solve BBB challenge for broad range of therapeutics and indications

Break open new science and fuel growth through **invention**

Partner of choice in neurodegeneration

OTV: Oligonucleotide Transport Vehicle
NME: New Molecular Entity
WW: Worldwide

OUR FOCUS AND STRATEGIC PRINCIPLES

OUR FOCUS

Defeat Degeneration

Lysosomal Storage Diseases

Rare Neurodegenerative Diseases (ALS, FTD)

Parkinson's Disease

Alzheimer's Disease

OUR SCIENTIFIC PRINCIPLES

Increase Likelihood of Success

Degenogene Pathways

Brain Delivery

Biomarker-Driven Development

OUR BUSINESS PRINCIPLES

Create Value

Broad Portfolio

Integrated Global Capabilities

Strategic Partnering

OUR DEVELOPMENT PORTFOLIO

MODALITY	TARGET	BIOLOGY	DRUG CANDIDATE*	DISEASE INDICATION	DEVELOPMENT STAGE	PARTNER
LARGE MOLECULE (TV-ENABLED)	Iduronate 2-Sulfatase	Lysosomal Function	**DNL310** (ETV:IDS)	MPS II (Hunter)	IND-Enabling / Early Clinical	
	PGRN	Lysosomal Function	**TAK-594/DNL593** (PTV:PGRN)	Frontotemporal Dementia-Granulin	IND-Enabling / Early Clinical	Takeda
	TREM2	Glial Biology	**TAK-920/DNL919** (ATV:TREM2)	Alzheimer's	IND-Enabling / Early Clinical	Takeda
	Sulfamidase	Lysosomal Function	**DNL126** (ETV:SGSH)	MPS IIIA (Sanfilippo)	IND-Enabling	
	Alpha-L-iduronidase	Lysosomal Function	**DNL622** (ETV:IDUA)	MPS I (Hurler)	IND-Enabling	
	Multiple	Multiple	**OTV:Multiple**	Multiple	IND-Enabling	
SMALL MOLECULE	LRRK2	Lysosomal Function	**BIIB122/DNL151** (LRRK2 inhibitor)	Idiopathic Parkinson's	Early Clinical / Mid/Late Clinical	Biogen
				LRRK2+ Parkinson's	Early Clinical / Mid/Late Clinical	Biogen
	RIPK1 (CNS)	Glial Biology	**SAR443820/DNL788** (RIPK1 inhibitor)	Neurodegeneration (ALS)	Early Clinical / Mid/Late Clinical	sanofi
	RIPK1 (Peripheral)	Other	**SAR443122/DNL758** (RIPK1 inhibitor)	Systemic Inflammation (CLE, UC)	Early Clinical / Mid/Late Clinical	sanofi
	eIF2B	Cellular Homeostasis	**DNL343** (eIF2B activator)	ALS	IND-Enabling / Early Clinical	

Biotherapeutics **Small Molecules** 50/50 US Commercial Royalty *Investigational – not approved for treatment

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

OUR STRATEGY: BROAD PORTFOLIO IN PARALLEL DEVELOPMENT

LYSOSOMAL STORAGE DISEASES

(e.g., MPS II, MPS IIIA)

DRUG CANDIDATE	PHASE IN 2023
DNL310 (MPS II)	Phase 2/3
DNL126 (MPS IIIA)	IND submission

RARE NEURODEGENERATIVE DISEASES

(e.g., ALS, FTD)

DRUG CANDIDATE	PHASE IN 2023
SAR443820 (ALS)	Phase 2
DNL343 (ALS)	Phase 2/3
DNL593 (FTD-GRN)	Phase 1/2

COMMON NEURODEGENERATIVE DISEASES

(e.g., Parkinson's, Alzheimer's)

DRUG CANDIDATE	PHASE IN 2023
BIIB122 (LRRK2+ PD)	Phase 3
BIIB122 (Idiopathic PD)	Phase 2b
DNL919 (Alzheimer's)	Phase 1

Goal is to achieve broad-reaching impact for patients across our therapeutic focus areas

* Denali estimates of world-wide aggregate prevalence

OUR VISION: COMMERCIAL ORGANIZATION TO SERVE PATIENTS

>30,000 patients WW*
$500M-1B+ per indication

LYSOSOMAL STORAGE DISEASES

(e.g., MPS II, MPS IIIA)

>500,000 patients WW*
$1-5B per indication

RARE NEURODEGENERATIVE DISEASES

(e.g., ALS, FTD)

>50M patients WW*
>$5B per indication

COMMON NEURODEGENERATIVE DISEASES

(e.g., Parkinson's, Alzheimer's)

Build in-house infrastructure

Strategically partner

- Market-based strategic plans for DNL310 & DNL343
- Patients & community engagement in MPS II and ALS
- Expand medical affairs & commercial teams
- Co-commercialize partnered assets (PD, FTD and AD) in US and China
- Execute to deliver on our patient promise

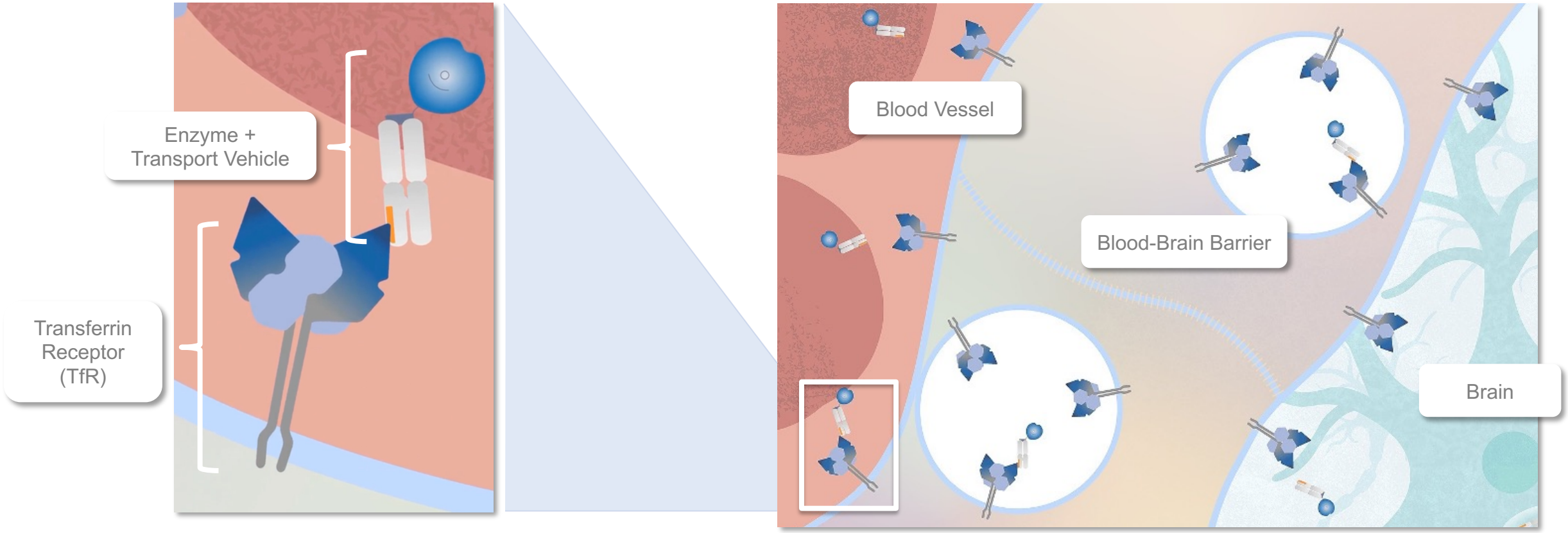
Accelerate commercial launch readiness in key markets

* Denali estimates of world-wide aggregate prevalence


OUR TV PLATFORM FOR BRAIN
DELIVERY OF BIOTHERAPEUTICS

ADDRESSING THE CHALLENGE OF DELIVERING THERAPY TO THE BRAIN

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

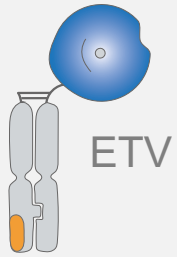


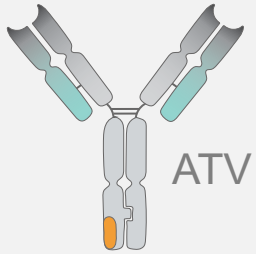
https://www.denalitherapeutics.com/patients

TRANSPORT VEHICLE ENABLES MODALITY-OPTIMIZED BRAIN DELIVERY

Enzyme Transport Vehicle

Deliver **enzymes** to the brain to replace deficient or missing enzyme activity



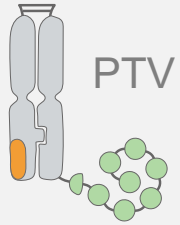


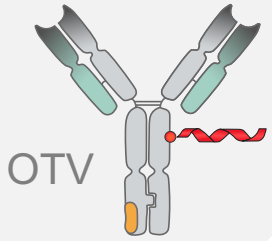
Antibody Transport Vehicle

Deliver **antibodies** in bivalent or bispecific format to the brain

Protein Transport Vehicle

Deliver **proteins** to the brain to replace deficient or missing protein





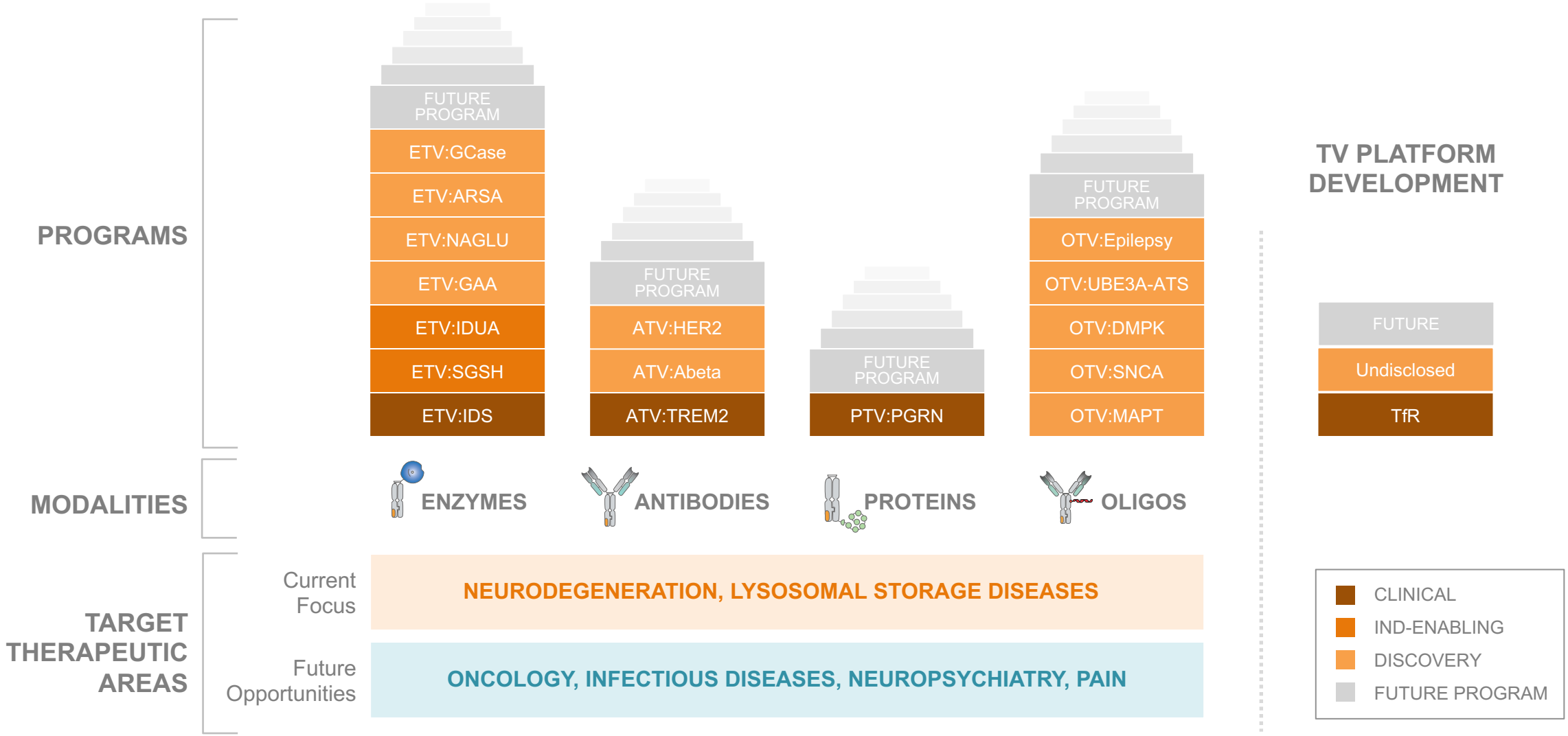
Oligonucleotide Transport Vehicle

Deliver **oligonucleotides** to the brain and modify gene expression

Each TV modality is a platform opportunity

TV PLATFORM OPPORTUNITIES DRIVE SUSTAINABLE VALUE CREATION

Each TV modality is a platform opportunity

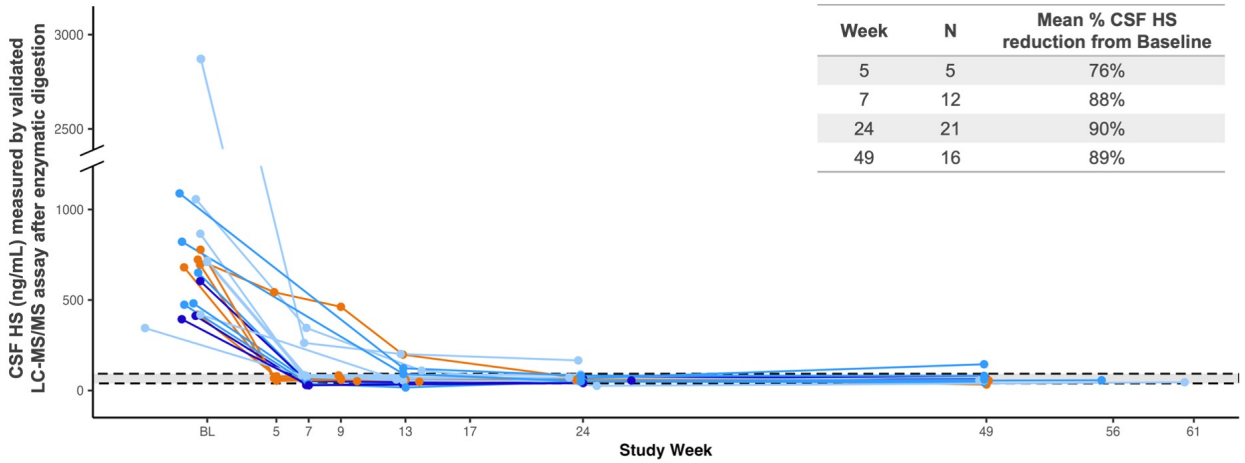


DNL310 (ETV:IDS): LEAD ETV PROGRAM TARGETING MPS II

Addressing cognitive, behavioral & physical manifestations of MPS II (Hunter syndrome)

- ~2,000 MPS II patients, mainly boys, worldwide
- Delivery of IDS enzyme to the brain is a critical unmet need of MPS II therapy
- Elevated heparan sulfate (HS) in CSF is a key biomarker of neurocognitive involvement
- DNL310 normalized CSF HS and further reduced urine HS after patients switched from ERT
- Open label data suggest improvement or stabilization of clinical symptoms in majority of Phase 1/2 participants
- Safety profile consistent with standard of care ERT

Rapid and durable normalization of heparan sulfate in CSF ongoing Phase 1/2 study



Week	N	Mean % CSF HS reduction from Baseline
5	5	76%
7	12	88%
24	21	90%
49	16	89%

Preliminary normal range (10th and 90th %ile) determined using 30 healthy adult CSF samples (age range 18-81 years, median 52 years). Total CSF GAG levels are similar in adults and children (Hendriksz et al., 2015). Normal range for CSF Heparan Sulfate (ng/mL): (39.1 - 92.51).

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestone
DNL310	ETV:IDS	MPS II (Hunter)	Phase 2/3 (COMPASS)	Additional interim Ph 1/2 data Early/Mid 2023

ETV:IDS=Enzyme Transport Vehicle Iduronate-2-Sulfatase; MPS=mucopolysaccharidoses; CSF=cerebrospinal fluid; ERT=enzyme replacement therapy; TV=Transport Vehicle

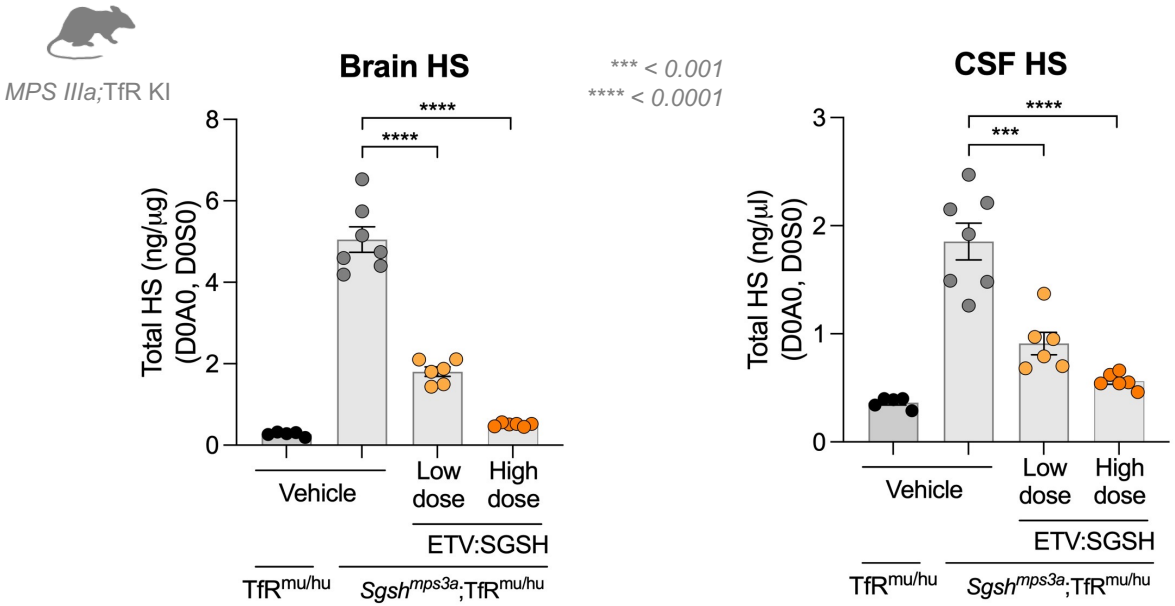
DNL126 (ETV:SGSH): EXPANDS ETV PLATFORM FOR MPS IIIA

Addressing cognitive, behavioral & physical manifestations of Sanfilippo syndrome Type A

- Rare lysosomal storage disease (LSD) that causes neurodegeneration; no treatments
- Caused by genetic mutations that result in a reduction in the activity of SGSH
- SGSH is an enzyme responsible for degrading heparan sulfates (HS) in the lysosome
- HS accumulation leads to lysosomal dysfunction
- DNL126 is designed to replace SGSH in the brain and throughout the body

ETV:SGSH=Enzyme Transport Vehicle N-Sulfoglucosamine Sulfohydrolase; MPS=mucopolysaccharidoses; CSF=cerebrospinal fluid; IND=investigational new drug

IV DNL126 treatment reduces HS in a dose-dependent manner in brain and CSF

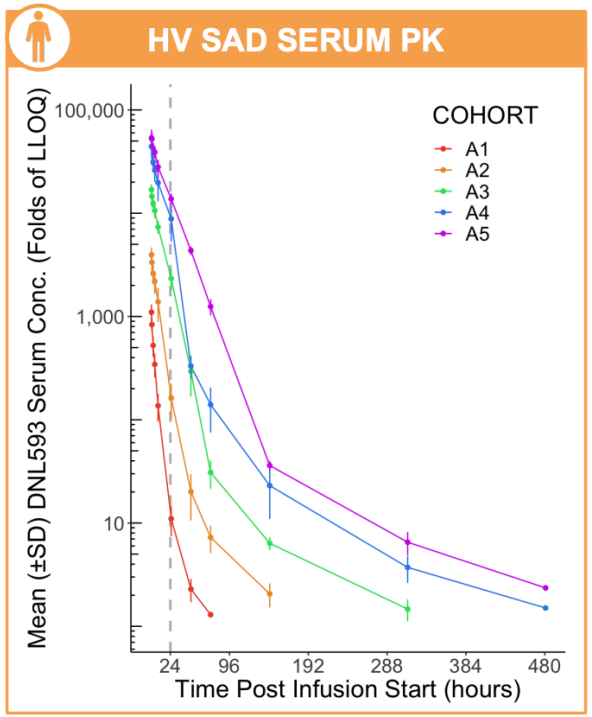


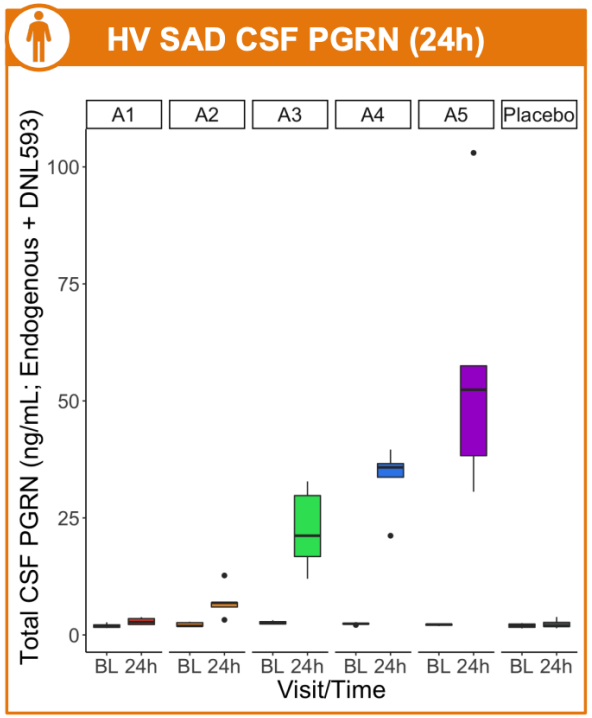
Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestones
DNL126	ETV:SGSH	MPS IIIA (Sanfilippo)	IND-enabling	Submit IND application 1H:23 and recruitment activities 2H:23
				Preclinical data at WORLD*Symposium*

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

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

- FTD is the most common dementia in people under 60; no approved therapies
- FTD-GRN is associated with progranulin (PGRN) deficiency; accounts for 5-10% of FTD
- Single doses of DNL593 in healthy volunteers led to dose-dependent increases in CSF PGRN and were generally well tolerated
- Data support enrolling participants with FTD-GRN in Part B of the Phase 1/2 study
- Co-development and co-commercialization with Takeda





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

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestones & Activities
DNL593 (TAK-594)	PTV:PGRN	FTD-GRN	Ph 1/2	Final Ph 1/2 Part A (HV) data Mid 2023
				Recruit Part B of Ph 1/2 ongoing

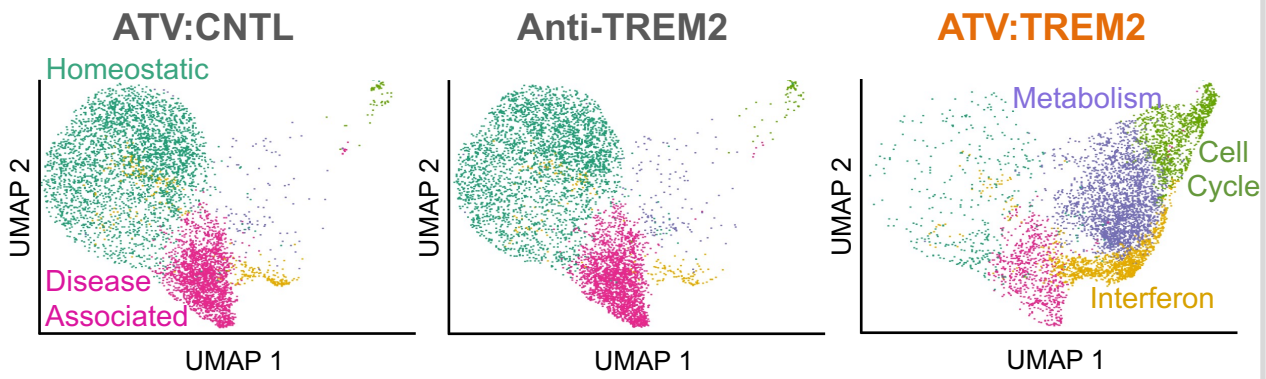
PTV:PGRN=Protein Transport Vehicle:Progranulin; CSF=cerebrospinal fluid; HV=healthy volunteer

ATV: TARGETING TREM2 AND ABETA FOR ALZHEIMER'S DISEASE (AD)

ATV enables significantly improved target engagement in mice, which may improve the therapeutic window

ATV:TREM2 shifts most microglia to responsive states compared to standard anti-TREM2 in mice

APP KI;TfR KI



Single cell RNAseq UMAP plots of brain microglia 24h post 10 mg/kg dose

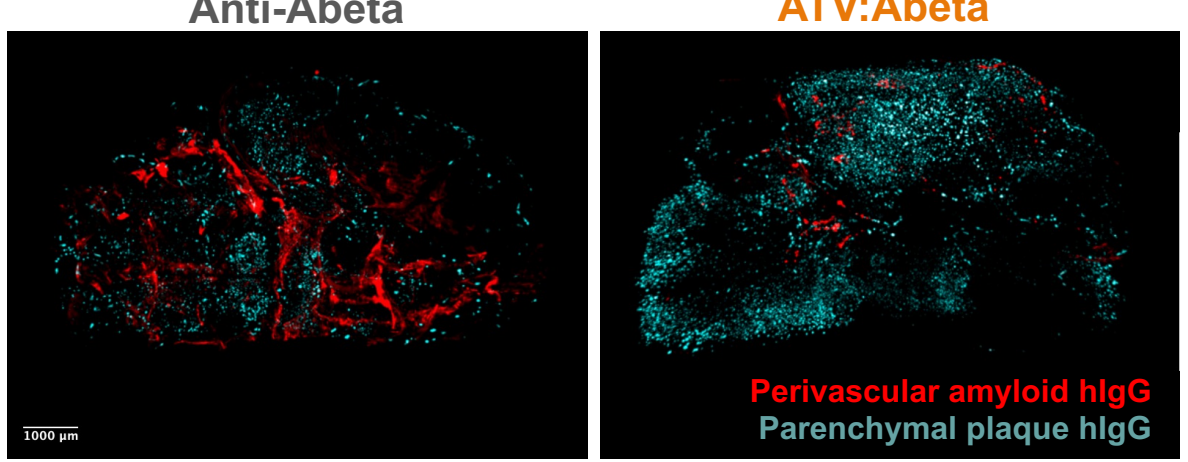
DENALI THERAPEUTICS Takeda

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestone
DNL919* (TAK-920)	ATV:TREM2	AD	Ph 1	Report Phase 1 HV data YE 2023

*The Investigational New Drug (IND) application of DNL919 is on clinical hold in the U.S; Denali initiated a Phase 1 single ascending dose study in healthy volunteers in the Netherlands

ATV:Abeta shows broad parenchymal plaque binding with minimal perivascular distribution

5xFAD;TfR KI



iDISCO whole brain image 24h post 10mg/kg single dose in AD mouse model

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Activities
ATV:Abeta	ATV:Abeta**	AD	Preclinical	Continue preclinical studies

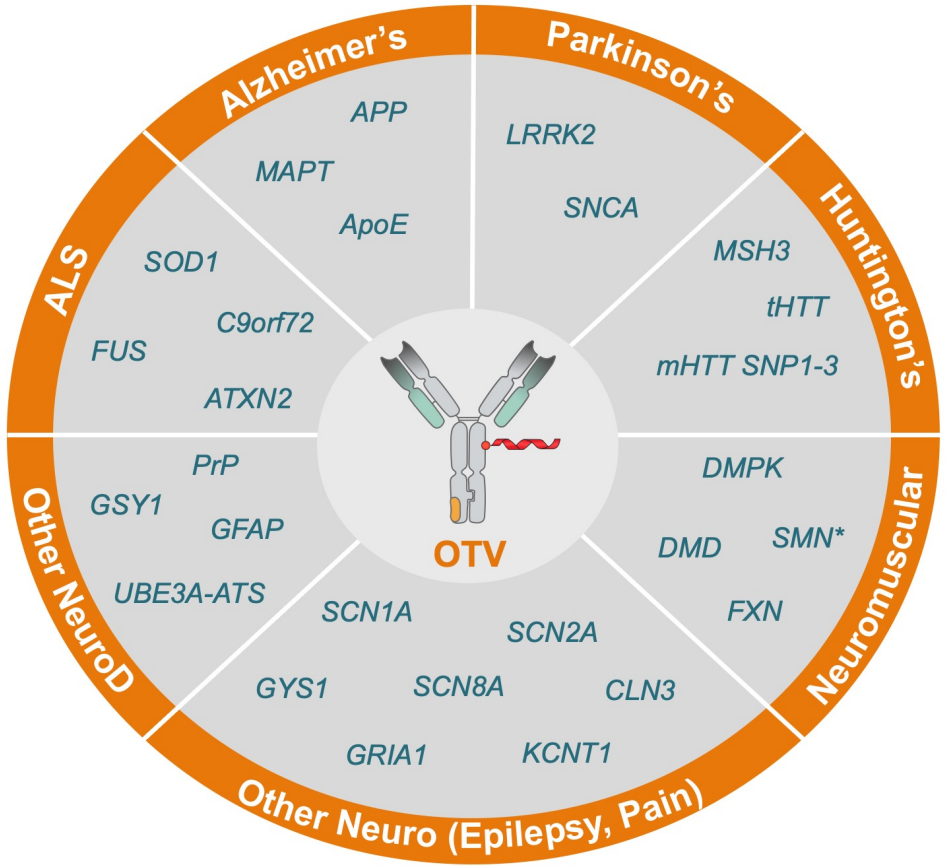
**Biogen has certain rights to license ATV:Abeta

OTV IS DESIGNED TO ENHANCE CNS DELIVERY OF OLIGONUCLEOTIDES

Therapeutic oligonucleotides have the potential to address challenging targets

- Oligonucleotide Transport Vehicle (OTV) is designed to:
  - Enable superior biodistribution of ASOs across brain regions
  - Provide superior knockdown of target gene expression across all cell types
  - Enable IV dosing
- OTV opens a large potential indication space in neurodegeneration and beyond
- Multiple OTV programs progressing toward IND-enabling studies

OTV has potential to revolutionize ASOs/oligos for treating CNS disease

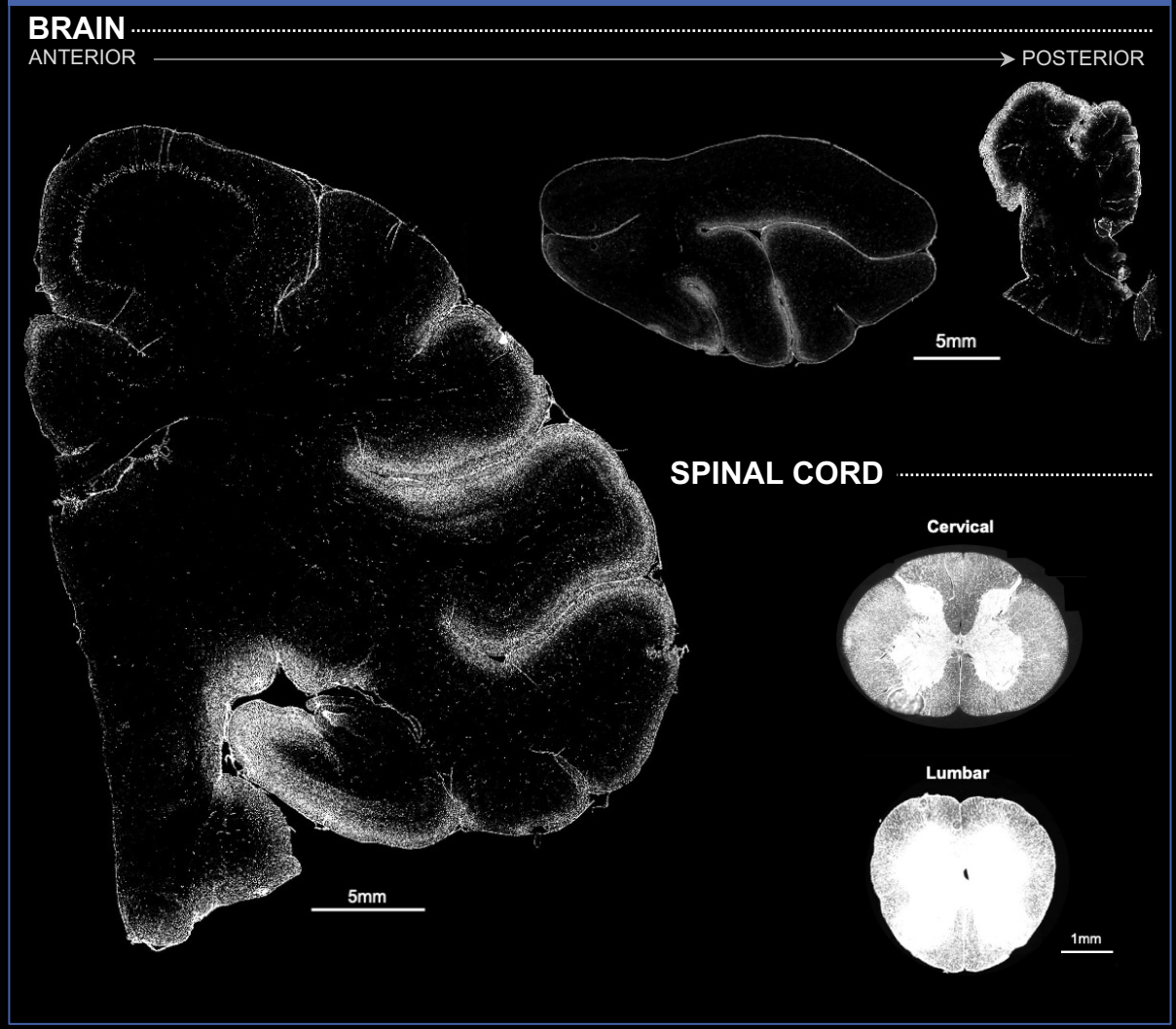


Not exhaustive

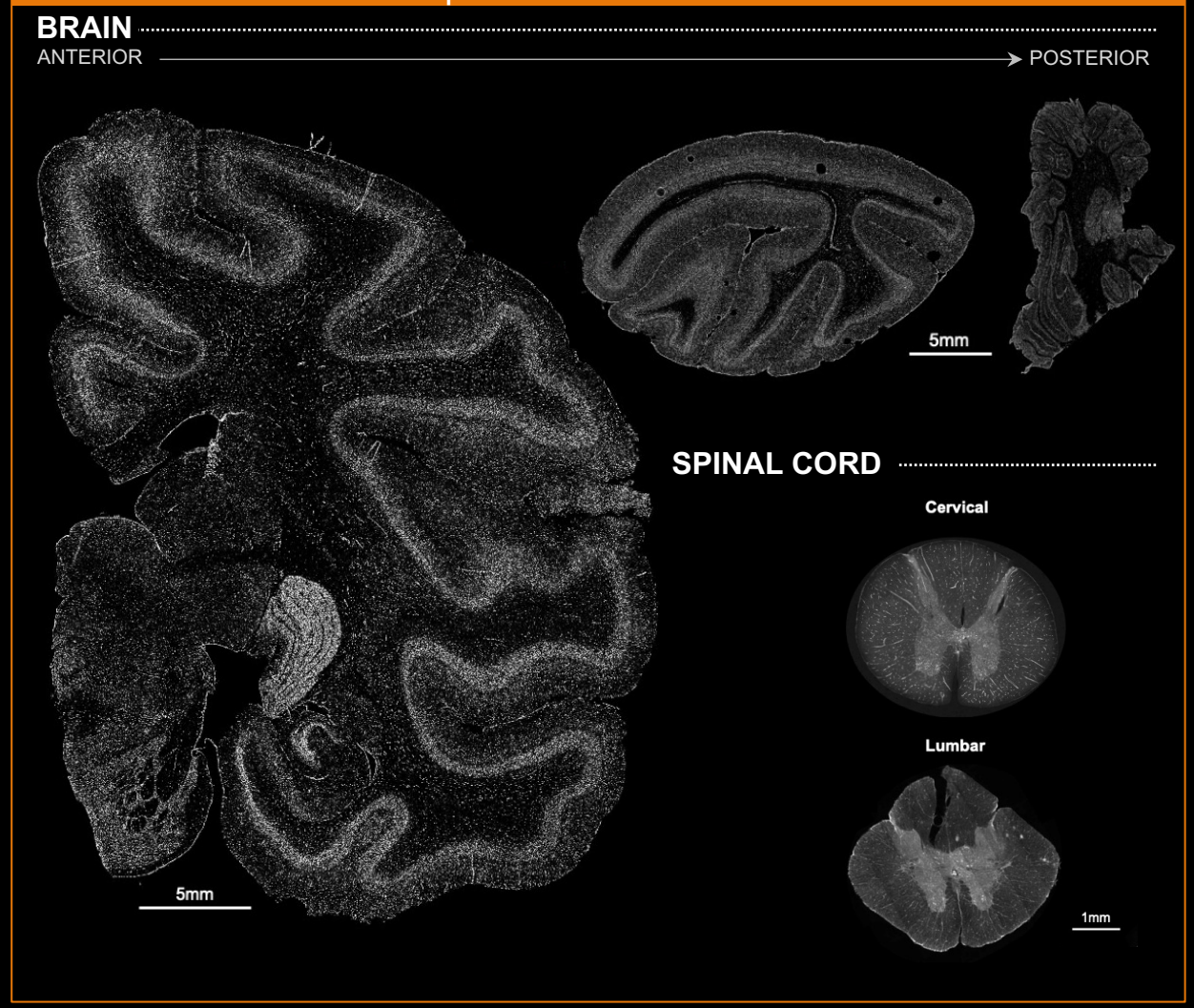
*3 approved therapies - ASO, AAV, & Small Molecule

OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

NAKED ASO INTRATHECAL (IT) DELIVERY
Limited ASO Biodistribution



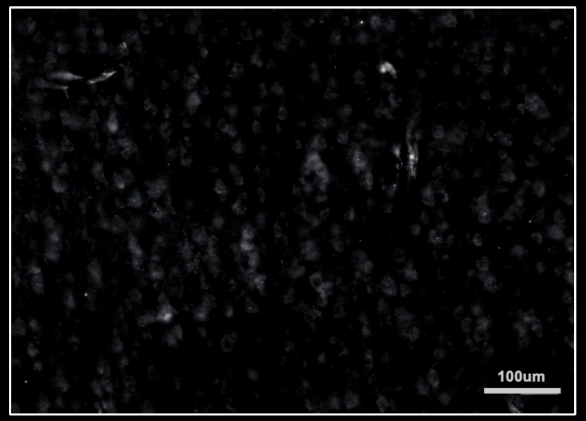
OTV INTRAVENOUS (IV) DELIVERY
Widespread ASO Biodistribution



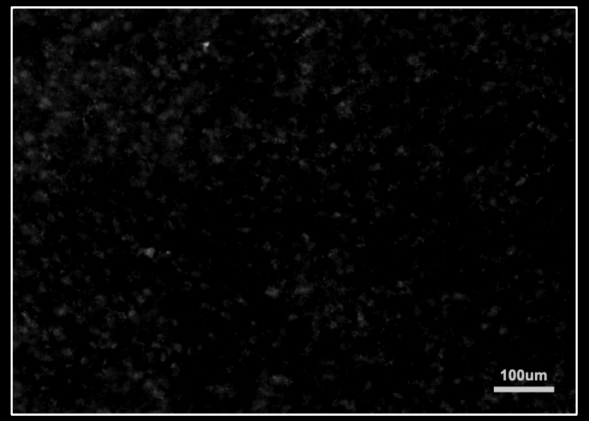
OTV PROVIDES UNIFORM ASO DEPOSITION ACROSS THE CNS WITH IV DELIVERY

NAKED ASO INTRATHECAL (IT) DELIVERY
Limited ASO Biodistribution

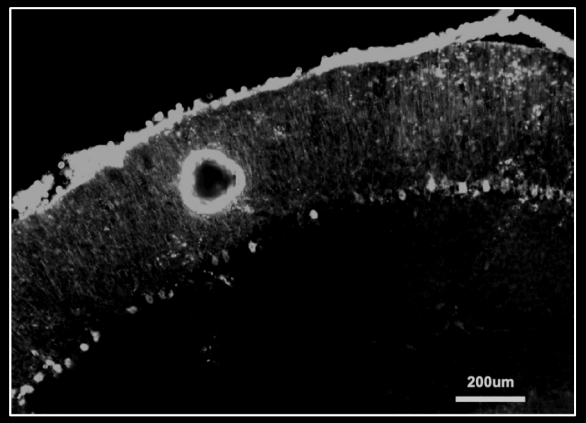
CORTEX



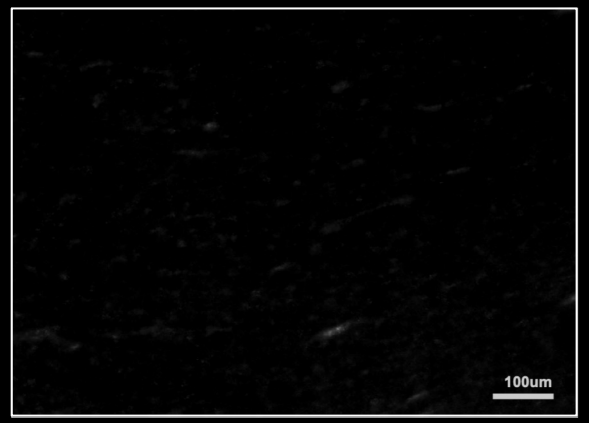
STRIATUM



CEREBELLUM

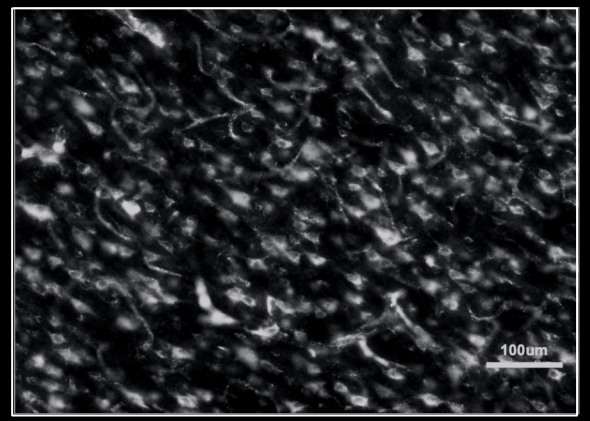


WHITE MATTER



OTV INTRAVENOUS (IV) DELIVERY
Widespread ASO Biodistribution

CORTEX



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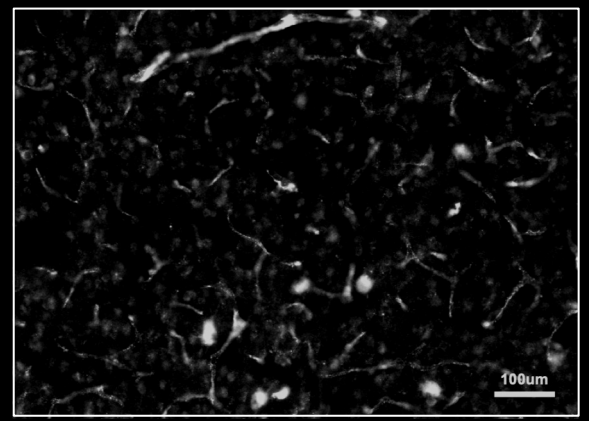

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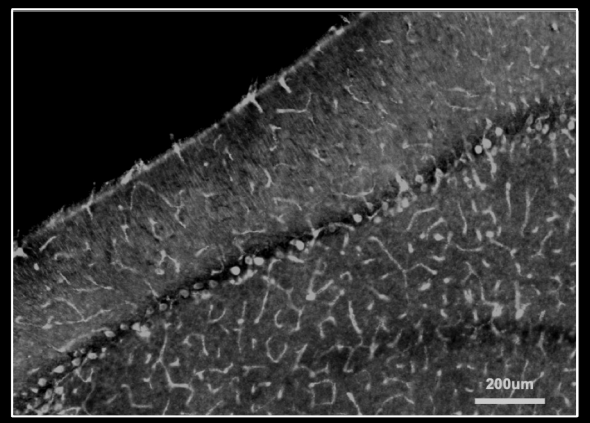

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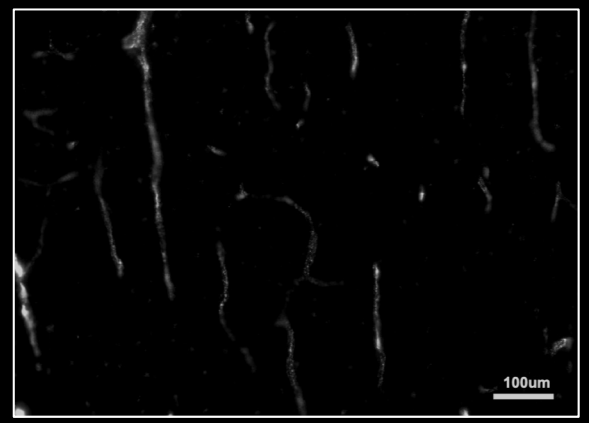
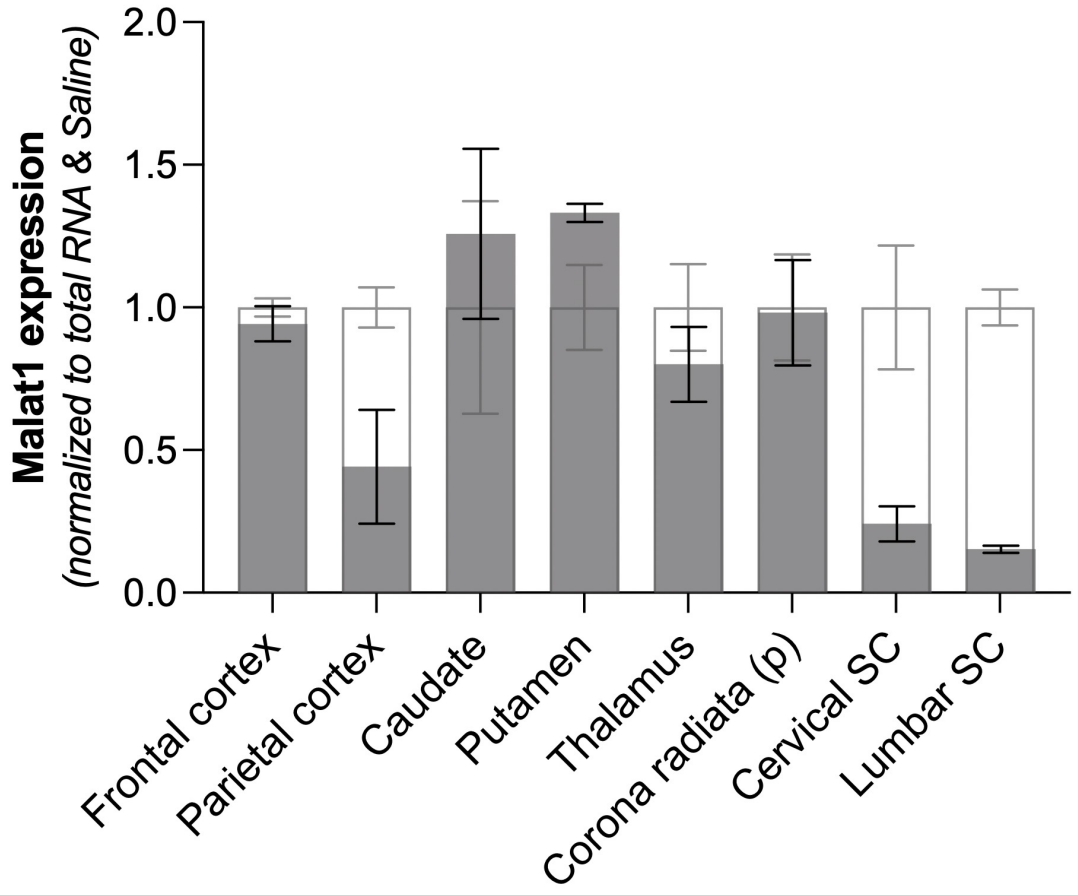


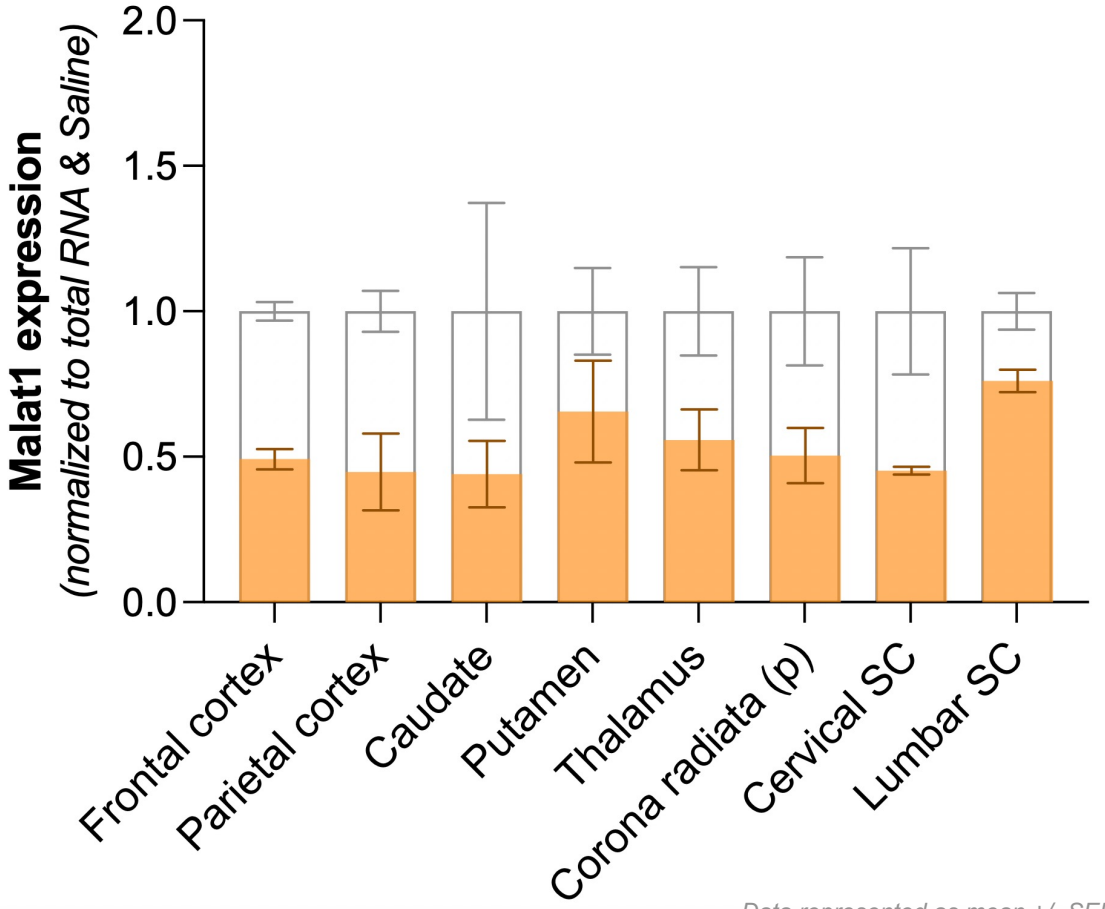
anti-ASO

OTV ENABLES MORE UNIFORM KNOCKDOWN OF TARGET GENE EXPRESSION

NAKED ASO INTRATHECAL (IT) DELIVERY



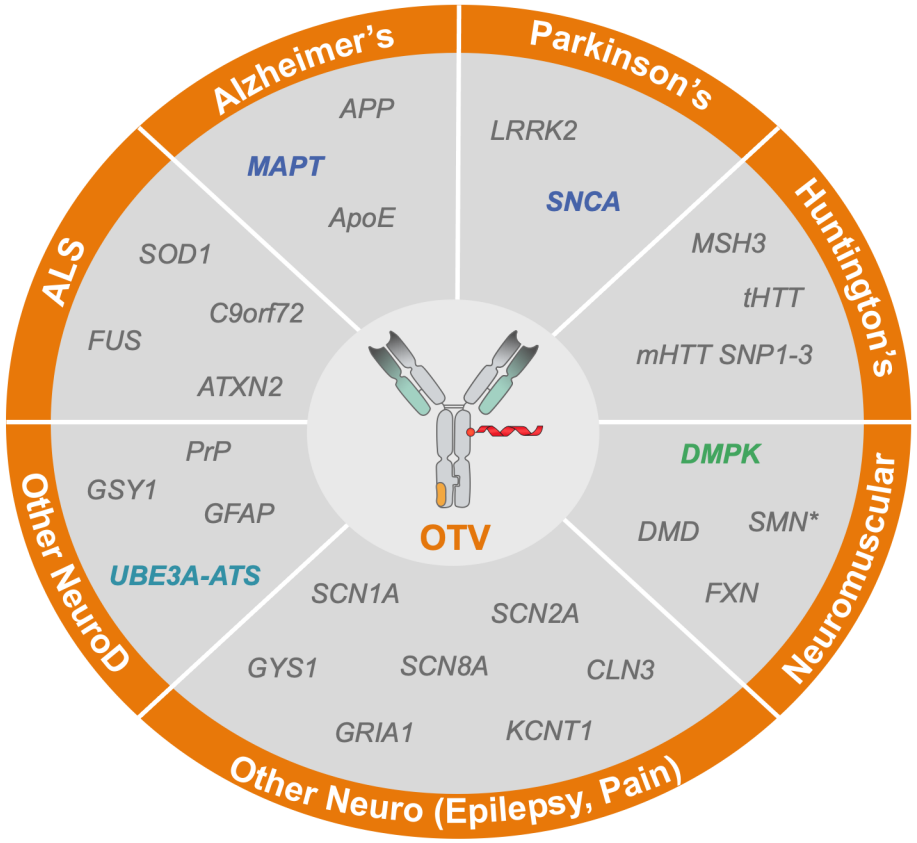
OTV INTRAVENOUS (IV) DELIVERY



Data represented as mean +/- SEM; n=3

IV OTV shows uniform knockdown across the CNS compared to IT ASO

OTV TARGET SELECTION



Not exhaustive

*3 approved therapies - ASO, AAV, & Small Molecule

OTV in IND-Enabling stage with near-term focus on acceleration of two targets to clinical testing

TARGET	INDICATION	PREVALENCE	DIFFERENTIATION STRATEGY
COMMON NEURODEGENERATIVE DISEASES			
MAPT	Alzheimer's Disease	6-10M cases US	Uniform knockdown of MAPT across the CNS to effectively reduce all forms of Tau protein & decrease aggregates
SNCA	Parkinson's Disease	1M cases US	Uniform knockdown of SNCA across the CNS to effectively reduce all forms of α-Syn protein & decrease aggregates
RARE CNS DISEASES			
UBE3A-ATS	Angelman's Syndrome	1.5-3K cases US (<8yo)	Uniform knockdown of UBE3A-ATS via systemic route to increase normal UBE3A protein levels throughout the CNS
Epilepsy Target 1	Epilepsy	1-15K cases US	Undisclosed
NEUROMUSCULAR DISEASES			
DMPK	Myotonic Dystrophy Type 1	*Adult* 40K cases US *Congenital* ~600 cases US	Knockdown of DMPK in periphery and CNS to reduce toxic RNA foci & allow MBNL proteins to resume normal splicing


DENALI
OUR BRAIN-PENETRANT SMALL MOLECULE PROGRAMS

BIIB122 (LRRK2 INHIBITOR): TARGETING THE LYSOSOME IN PD

Targeting LRRK2 may impact the underlying biology and slow the progression of PD

- 10M+ people with Parkinson's disease (PD) WW
- Mutations in LRRK2 are one of the most common genetic risk factors for PD
- Increased LRRK2 kinase activity is thought to impair lysosomal function and contribute to PD
- Denali conducted extensive Phase 1/1b testing with LRRK2 inhibitors in 300+ individuals*
- BIIB122 achieved ≥80% pS935 inhibition (target engagement biomarker) at doses of ≥ 225 mg
- Biogen is leading operational execution of the LUMA and LIGHTHOUSE studies

Rigorous development program to evaluate BIIB122 in patients with and without LRRK2 mutations

	Phase 2b LUMA Study	Phase 3 LIGHTHOUSE Study
PD patient pop.	No pathogenic LRRK2 variant	Confirmed pathogenic LRRK2 variant
Dosing	225 mg oral once daily BIIB122 vs. placebo	
Primary endpoint	Assessed using MDS-UPDRS	
No. participants	640 (320 per arm)	400 (200 per arm)
Treatment period	48 weeks (min)	96 weeks (min)
Study initiation	May 2022	September 2022

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Activities
BIIB122 (DNL151)	LRRK2 inhibition	Idiopathic PD	Ph 2b (LUMA)	Recruit Ph 2b ongoing
		LRRK2 positive PD	Ph 3 (LIGHTHOUSE)	Recruit Ph 3 ongoing

*Phase 1/1b program for BIIB122 and DNL201

LRRK2=leucine-rich repeat kinase 2; WW=worldwide; MDS-UPDRS=Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale

DENALI THERAPEUTICS

Biogen

DNL343 (eIF2B ACTIVATOR): INHIBITING THE ISR PATHWAY IN ALS

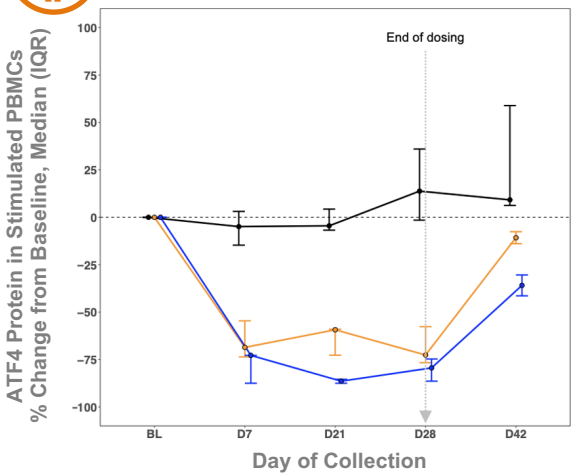
By inhibiting the ISR pathway, DNL343 is intended to prevent or slow ALS progression

- ~250,000 people with ALS WW
- eIF2B regulates protein synthesis and is required for neuronal health and function
- When neurons experience stress, activation of the ISR pathway leads to suppression of eIF2B
- Suppression of eIF2B leads to impaired protein synthesis and formation of stress granules
- Stress granules are thought to be a precursor of TDP-43 aggregation, a hallmark pathology of ALS
- DNL343 is designed to activate eIF2B and avert the deleterious effects of chronic ISR activation

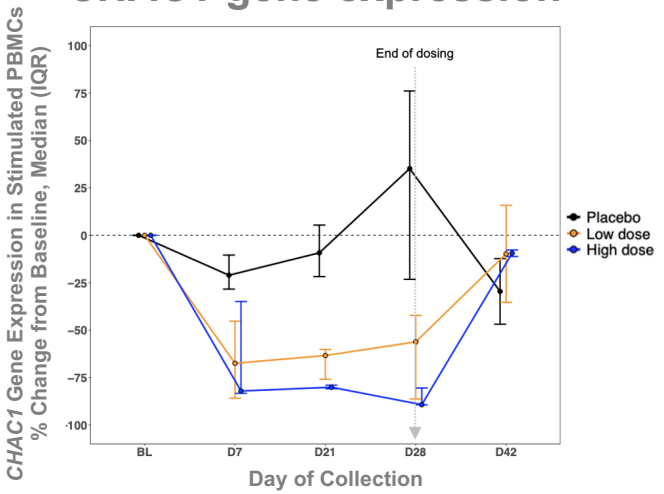
28-day dosing with DNL343 reduced ISR biomarkers in blood samples* from ALS patients

(interim Phase 1b data)

ATF4 protein levels



CHAC1 gene expression



*Fresh PBMCs were collected and stimulated ex vivo for each time point indicated for a subset of patients (per dose group: n=4-5 through day 28 and n=2-3 for day 42)

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestone
DNL343	eIF2B agonist	ALS	Ph 1b	Final 28-day Ph 1b data Mid 2023
				Initiate Ph 2/3 HEALEY study Mid 2023

eIF2B=eukaryotic initiation factor 2B; ISR=integrated stress response; ALS=amyotrophic lateral sclerosis; WW=worldwide; TDP-43=TAR DNA-binding protein 43

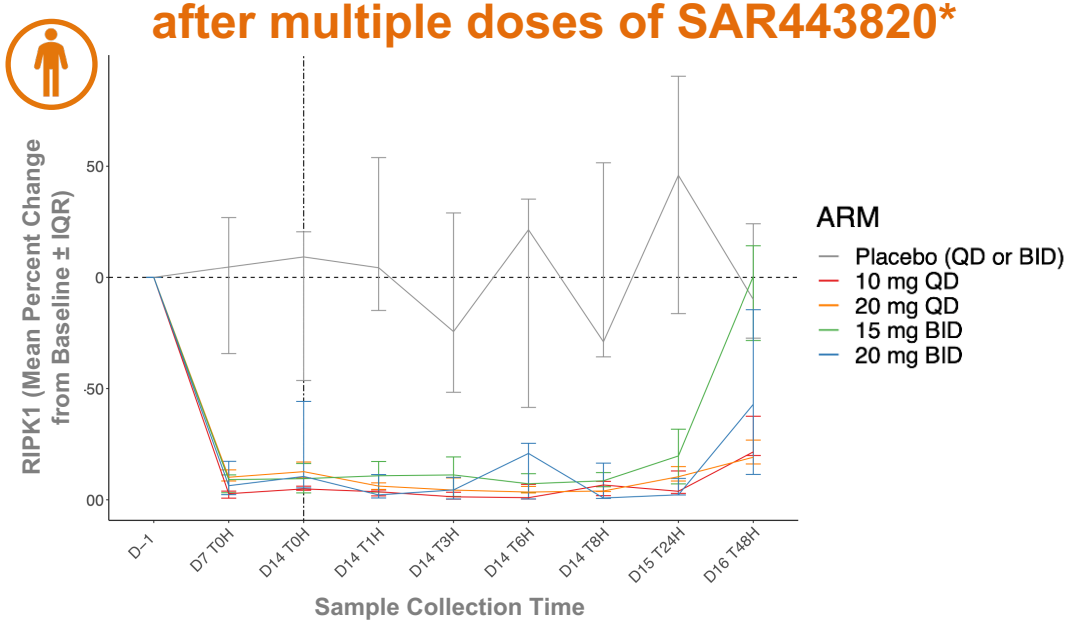
RIPK1 INHIBITORS: TARGETING INFLAMMATION AND CELL DEATH

RIPK1 is a critical signaling protein in a canonical inflammatory and cell death pathway

- Increased RIPK1 activity drives neuroinflammation and cell necroptosis and contributes to neurodegeneration
- RIPK1 inhibition achieved beneficial effects in preclinical models of ALS, multiple sclerosis and other diseases
- Denali and Sanofi have a strategic collaboration to develop and commercialize RIPK1 inhibitors
- Robust target engagement goals and safety goals were achieved in Phase 1 studies for SAR443820 and SAR443122 (eclitasertib)

RIPK1= receptor-interacting serine/threonine-protein kinase 1; ALS=amyotrophic lateral sclerosis; MS=multiple sclerosis; CLE=cutaneous lupus erythematosus; UC=ulcerative colitis

93% to 99% RIPK1 inhibition achieved in Phase 1 after multiple doses of SAR443820*



DENALI THERAPEUTICS

*Maximum median inhibition of pS66-RIPK1 levels in blood cells from healthy volunteers in the Phase 1 study ranged from 93% to 99%

sanofi

Drug Candidate	Mechanism of Action	Therapeutic Area	Stage	Expected Milestones & Activities
SAR443820	CNS penetrant RIPK1 inhibitor	ALS	Ph 2	Complete recruitment in 2023
		MS	Ph 2	Initiate Ph 2 Early 2023
SAR443122 (eclitasertib)	Peripherally restricted RIPK1 inhibitor	CLE	Ph 2	Primary completion June 2023*
		UC	Ph 2	Recruit Ph 2 ongoing

*According to current posting on ClinicalTrials.gov

OUR PRIORITIES

1 Clinical Execution

- 4 late-stage programs enrolling studies in MPS II, ALS, and PD
- Multiple earlier-stage trials designed for biomarker PoC
- Expansion of clinical operations and medical affairs in Europe
- Building out clinical manufacturing capabilities

2 TV Expansion

- Clinical data expected from 3 TV-platform enabled programs
- Fourth TV-enabled program advancing towards clinical testing
- Selected OTV targets provides broad range of opportunities
- Expand TV platform potential with additional BBB transporter

3 Commercial Readiness

- Define go-to-market strategies in the US and key global markets
- Outreach to patients and communities in MPS II and ALS to understand unmet needs
- Establish critical medical affairs and commercial capabilities to prepare for early filing scenarios

TV=Transport Vehicle; OTV=Oligonucleotide Transport Vehicle; MPS= mucopolysaccharidoses; ALS=amyotrophic lateral sclerosis; PD=Parkinson's disease; PoC=proof of concept

$1.11B in cash and investments (as of 9/30/22) plus capital raise $316M in October 2022

OUR PURPOSE: DEFEAT DEGENERATION

Thank you to all those who are part of Denali's purpose, especially our patients and their families

LYSOSOMAL STORAGE DISEASE

RARE NEURODEGENERATIVE DISEASES (ALS, FTD)

PARKINSON'S DISEASE

ALZHEIMER'S DISEASE

Denali

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


THANK YOU