Company Overview

Alexander Schuth, Chief Operating Officer

H.C. Wainwright 23rd Annual Global Investment Conference

September 13-15, 2021

Disclaimers

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. 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, business plans, product candidates, planned preclinical studies and clinical trials; expectations regarding the timing of results of such studies and trials; plans, timelines and expectations related to DNL151 and other LRRK2 inhibitor molecules; plans, timelines and expectations related to DNL310 and Denali's TV technology platform, other programs enabled by Denali's TV platform, and the ongoing Phase 1/2 study, and planned future studies, of DNL310; plans, timelines and expectations related to DNL343, including with respect to the availability of data and the initiation of future clinical trials; plans, timelines and expectations related to DNL788 and DNL758 of both Denali and Sanofi, including with respect to the availability of data and the initiation of future clinical trials; Denali's expectations regarding DNL593 and DNL919 and plans and expectations regarding planned regulatory filings and milestone payments with respect to such programs; the potential benefits and results of the collaborations with Denali's partners, including Biogen, Sanofi and Takeda, and expected milestone payments; and Company priorities, regulatory approvals, timing and likelihood of success and expectations regarding collaborations, are forward-looking statements. Denali has based these forward-looking statements largely on its current expectations and projections about future events.

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Accuracy of Data

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OUR PURPOSE: DEFEAT DEGENERATION

Degeneration creates significant unmet medical need, with few disease-modifying medicines

RARE NEURODEGENERATIVE DISEASES

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

PARKINSON'S DISEASE

ALZHEIMER'S DISEASE

OUR PRINCIPLES: DISCOVERY AND DEVELOPMENT

DEGENOGENES GENETIC PATHWAY POTENTIAL

ENGINEERING BRAIN DELIVERY

BIOMARKER-DRIVEN DEVELOPMENT

PATIENT IMPACT

Increase the likelihood of success to bring effective therapies to patients and families

OUR DEVELOPMENT PORTFOLIO

Small Molecules | Biotherapeutics

PROGRAM TARGET	DRUG CANDIDATE*	DISEASE INDICATION	DRUG DEVELOPMENT					PARTNER
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	
LYSOSOMAL FUNCTION PATHWAY								
LRRK2	DNL151	Parkinson's						Biogen 50/50 US commercial
Iduronate 2-sulfatase	DNL310	MPS II (Hunter)						
Sulfamidase	DNL126	MPS IIIA (Sanfilippo)						
PGRN	DNL593	Frontotemporal Dementia						Takeda 50/50 US commercial
GLIAL BIOLOGY PATHWAY								
RIPK1 (CNS)	DNL788	ALS, MS, Alzheimer's						SANOFI 50/50 US commercial
TREM2	DNL919	Alzheimer's						Takeda 50/50 US commercial
CELLULAR HOMEOSTASIS								
EIF2B	DNL343	ALS, FTD						
OTHER								
RIPK1 (Peripheral)	DNL758	Cutaneous Lupus Erythematosus (CLE)						SANOFI Royalty

15+ programs in Discovery stage (including 5 ETVs, 4 ATVs, 2 OTVs, and 3 small molecules)

*Investigational – not approved for treatment

OUR PROGRESS: RECENT ACHIEVEMENTS CREATE MOMENTUM

CLINICAL PORTFOLIO

- ✓ **DNL151** (Parkinson's): Positive Ph1/1b; advancing to late-stage development
- ✓ **DNL310** (Hunter syndrome): Positive six-month data; moving to late stage
- ✓ **DNL343** (ALS): Positive interim Ph1 data; Ph1b ongoing in ALS
- ✓ **DNL788** (ALS, Alzheimer's, MS): Ph1* ongoing in healthy volunteers
- ✓ **DNL758** (Inflammation): Ph2* ongoing in CLE patients

5 clinical programs

TRANSPORT VEHICLE (TV) PLATFORM

- ✓ **1st human biomarker Proof of Concept** with ETV:IDS (DNL310)
- ✓ **PTV:PGRN and ATV:TREM**: on track for IND filing
- ✓ **Expanded ETV portfolio** with ETV:SGSH (DNL126) and five other ETVs
- ✓ **TV-enabled ASOs (OTV)** validated pre-clinically

15 TV-enabled programs

CORPORATE STRATEGY

- ✓ **~$1.4 B in cash and investments** (as of 6/30/21)
- ✓ **Strong corporate partnerships** (Biogen, Sanofi, Takeda)
- ✓ **Building manufacturing and commercial capabilities**

~$1.4B Well-resourced to build fully integrated company and deliver for patients

* Sanofi study ** Cash and equity

OUR FUTURE: FULLY INTEGRATED GLOBAL ORGANIZATION TO SERVE PATIENTS

ORGANIZATIONAL GROWTH PATH

- Deep focus on science and commitment to discovery
- Comprehensive global clinical development capabilities
- Internal manufacturing capabilities
- Staged buildout of commercial infrastructure

1 **LYSOSOMAL STORAGE DISEASES**

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

>30,000 patients WW*

2 **RARE CNS DISEASES**

(e.g. ALS, FTD)

>200,000 patients WW*

3 **LARGE NEURODEGENERATIVE DISORDERS**

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

>50M patients WW*

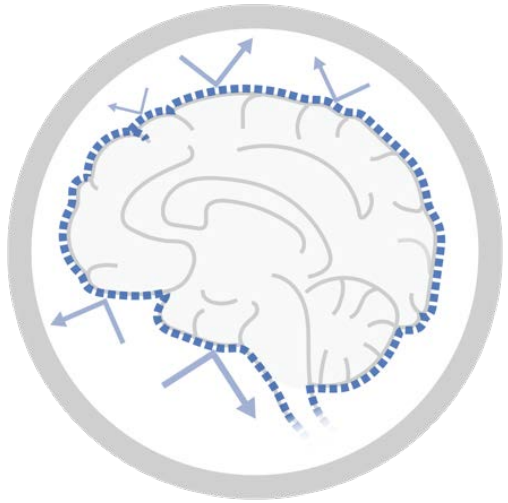
Commercial growth concurrent with development timelines of portfolio

* Denali estimates of world-wide aggregate prevalence


OUR TV PLATFORM FOR BRAIN
DELIVERY OF BIOTHERAPEUTICS

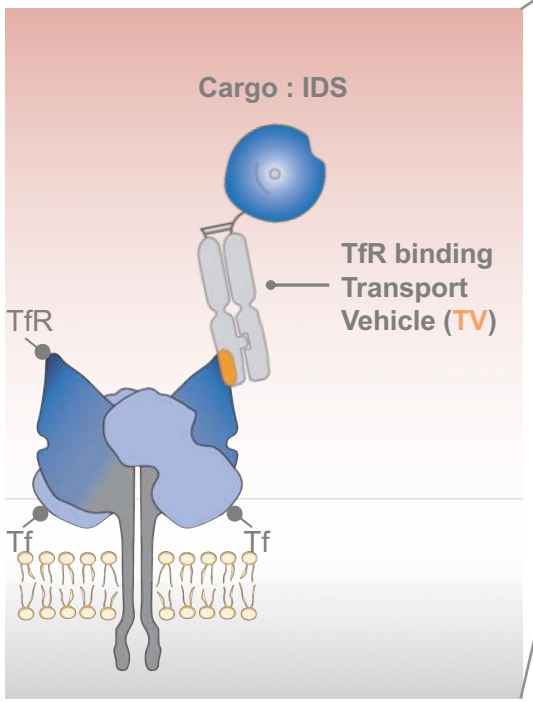
SOLVING THE BBB CHALLENGE FOR BRAIN DELIVERY OF BIOTHERAPEUTICS

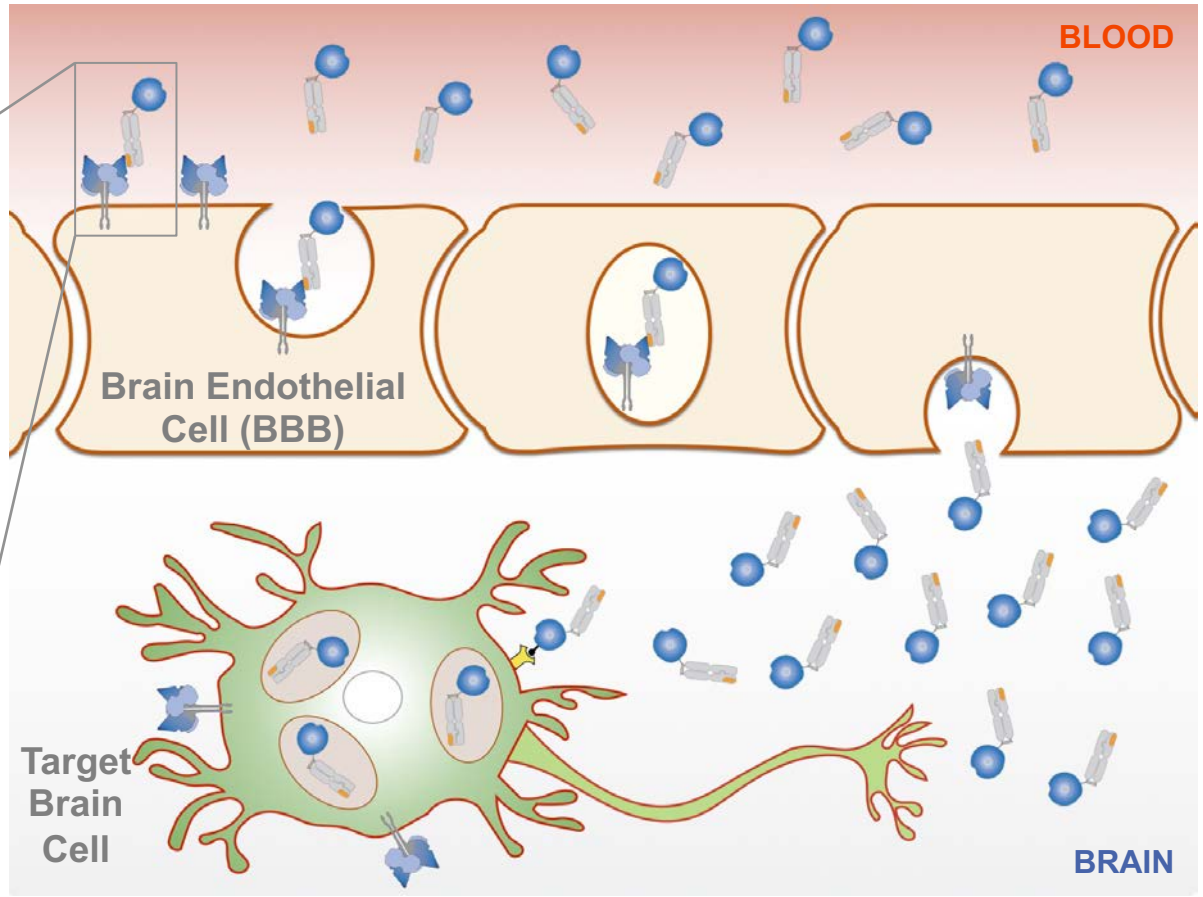
THE BBB CHALLENGE



The **blood-brain barrier (BBB)** is a major obstacle for brain delivery of biotherapeutics

OUR SOLUTION





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

TV TECHNOLOGY DELIVERS BIOTHERAPEUTICS TO THE BRAIN

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

BLOOD-BRAIN BARRIER

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

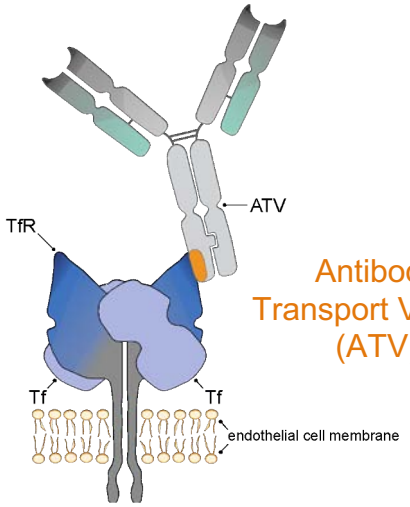
Mihalis S. Kariolis*†, Robe
Raymond Tong, Do Jin Kir
Victoria A. Assimon, Xiaoc
Pascal E. Sanchez, Lesley
Nicholas Liang, Meredith
Sejal Hall‡, Zachary K. Swe
Adam P. Silverman†, Y. Jo

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

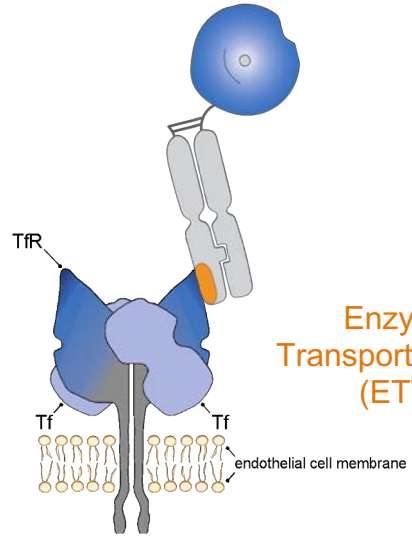
BLOOD-BRAIN BARRIER

Brain delivery and activity of a lysosomal enzyme using a blood-brain barrier transport vehicle in mice

Julie C. Ullman[1]*, Annie Arguello[1]*, Jennifer A. Getz[1]*, Akhil Bhalla[1], Cathal S. Mahon[1], Junhua Wang[1], Tina Giese[1], Catherine Bedard[1], Do Jin Kim[1], Jessica R. Blumenfeld[1], Nicholas Liang[1], Ritesh Ravi[1], Alicia A. Nugent[1], Sonnet S. Davis[1], Connie Ha[1], Joseph Duque[1], Hai L. Tran[1], Robert C. Wells[1], Steve Lianoglou[1], Vinay M. Daryani[1], Wanda Kwan[1], Hilda Solanoy[1], Hoang Nguyen[1], Timothy Earr[1], Jason C. Dugas[1], Michael D. Tuck[2], Jennifer L. Harvey[2], Michelle L. Reyzer[2], Richard M. Caprioli[2], Sejal Hall[1†], Suresh Poda[1], Pascal E. Sanchez[1], Mark S. Dennis[1], Kannan Gunasekaran[1], Ankita Srivastava[1], Thomas Sandmann[1], Kirk R. Henne[1], Robert G. Thorne[1], Gilbert Di Paolo[1], Giuseppe Astarita[1], Dolores Diaz[1], Adam P. Silverman[1], Ryan J. Watts[1], Zachary K. Sweeney[1], Mihalis S. Kariolis[1‡], Anastasia G. Henry[1‡]

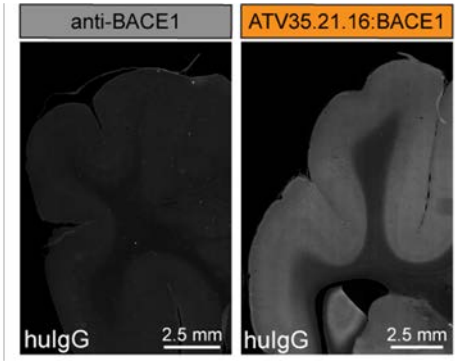


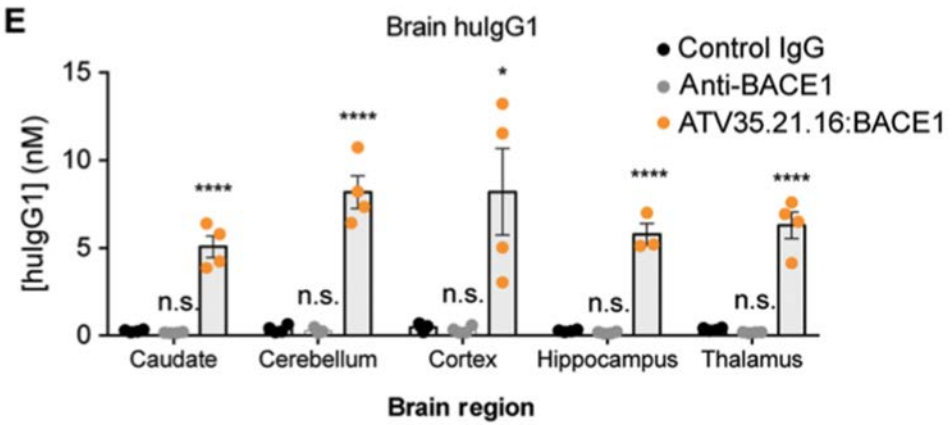
Antibody Transport Vehicle (ATV)



Enzyme Transport Vehicle (ETV)

Cortex (cynomolgus monkey)

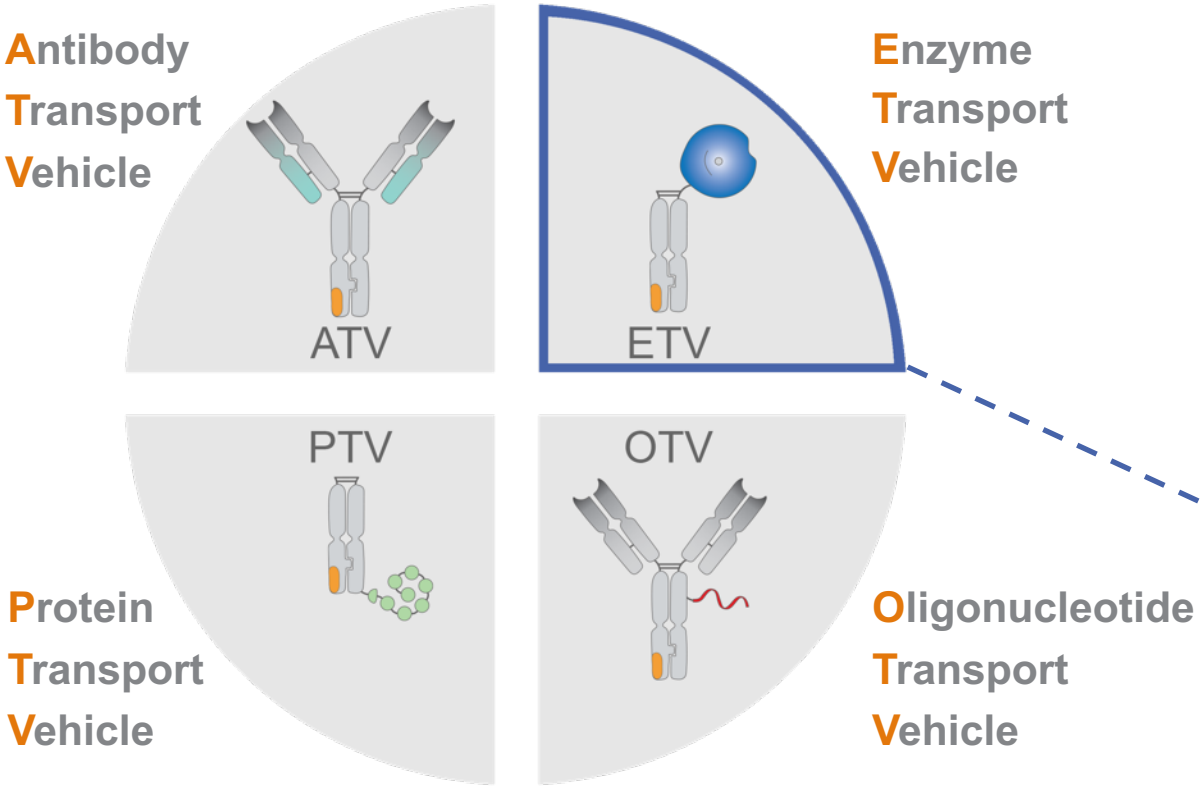




TV achieves high concentrations and broad distribution of biotherapeutic in brain

TV PLATFORM MODULARITY CREATES MULTIPLE OPPORTUNITES

MODULAR TECHNOLOGY ENABLES OPTIMAL MODALITY FOR EACH TARGET



BENEFITS OF TV PLATFORM: INCREASE BIODISTRIBUTION (~10-30X) TO BRAIN

Unlock Targets

- Brain delivery of biotherapeutics for previously intractable targets

Enhance Efficacy

- Further enhance activity through synergistic TfR and target biology

FIRST HUMAN BIOMARKER PROOF OF CONCEPT ACHIEVED WITH DNL310 (ETV:IDS) IN HUNTER SYNDROME

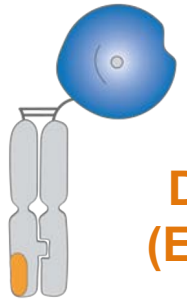
BRAIN DELIVERY IS A CRITICAL UNMET NEED OF HUNTER SYNDROME THERAPY

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

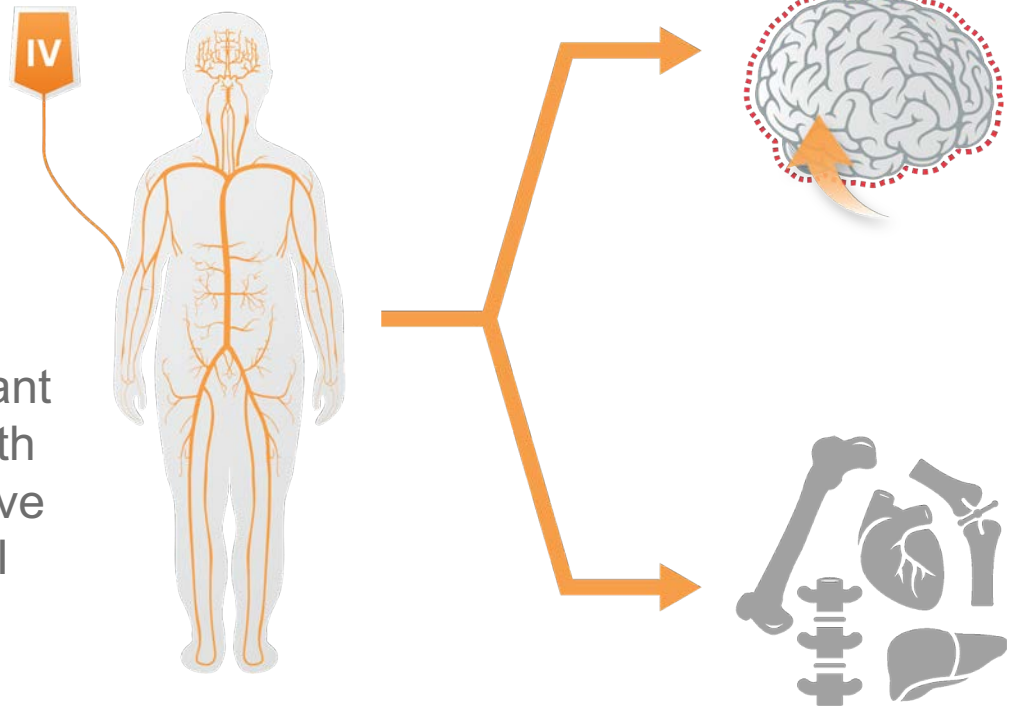
Enzyme replacement therapy (ERT)* partially addresses physical manifestations

*ERT (idursulfase ~$700M WW annual sales)

2/3 of patients with Hunter syndrome (MPS II) have neuronopathic disease



DNL310 (ETV:IDS)

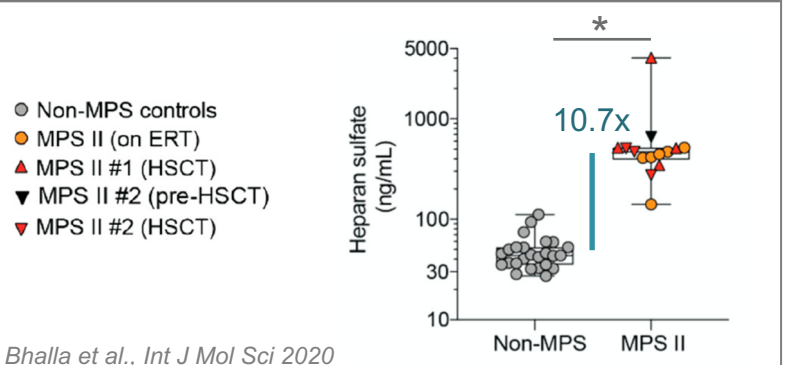


DNL310 is a brain-penetrant ERT designed to treat both physical and neurocognitive manifestations of MPS II (IV, once weekly)

CSF HEPARAN SULFATE (HS)

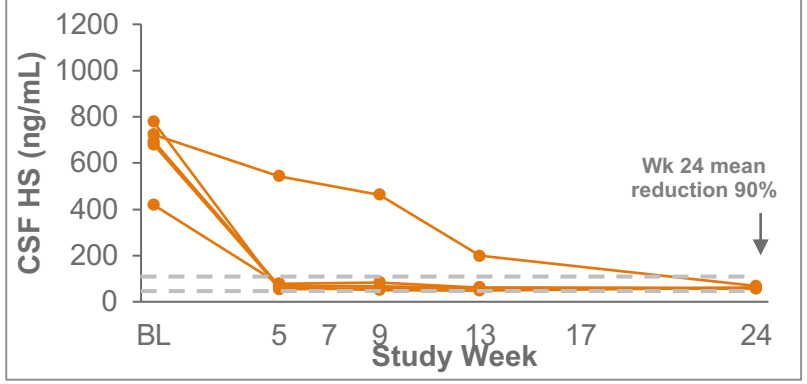
BIOMARKER POPULATION N=15 (COHORT A N=5 AND COHORT B N=10)

CSF HS is increased in MPS II patients

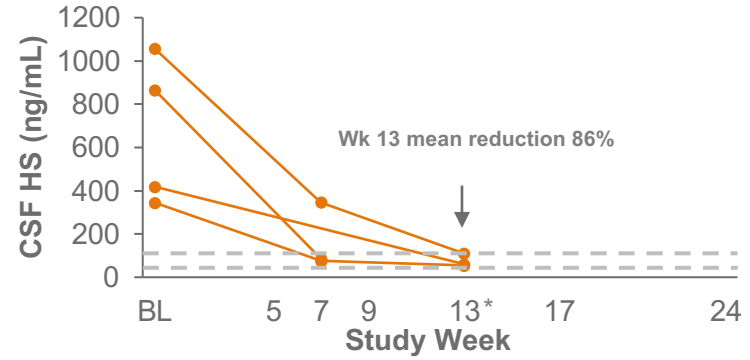


Bhalla et al., Int J Mol Sci 2020

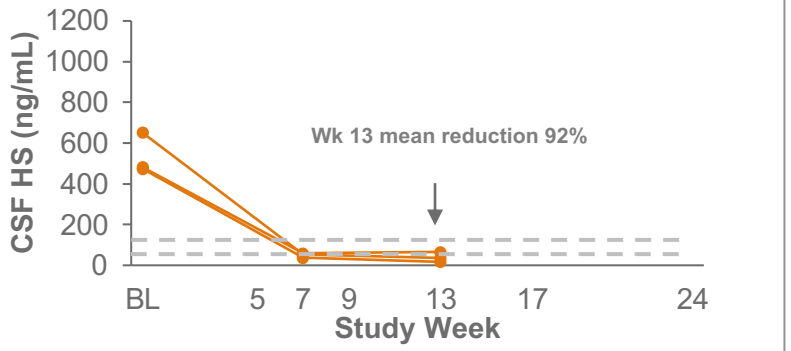
Cohort A – 3 to 30 mg/kg



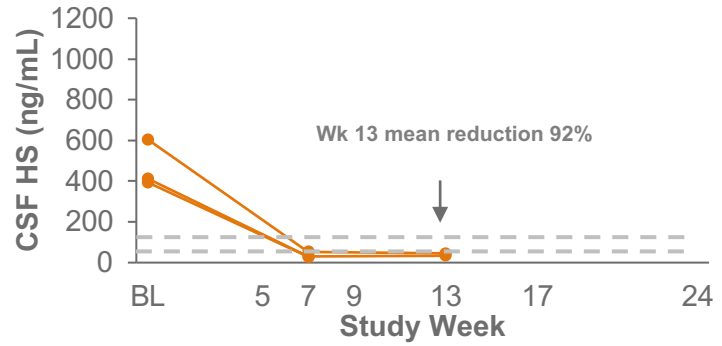
Cohort B1 – 3 mg/kg



Cohort B2 – 7.5 mg/kg



Cohort B3 – 15 mg/kg



*Preliminary normal range (10th and 90th %ile gray dashed bars) 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). *One patient in Cohort B1 escalated to higher dose one week before Week 13 CSF collection. Timepoints on x-axis represent intended collection times and may vary by ~1 week in some subjects.*

CSF Heparan Sulfate normalized in all patients after switching from idursulfase to DNL310, with rapid response in 12 patients by Week 7

DNL310 MPS II DEVELOPMENT PLAN

Cohort A
Ages 5-10 y.o.
Neuronopathic

Cohort B
Ages 2-18 y.o.
Neuronopathic &
Non-neuronopathic

- ✓ Rapid reductions in CSF heparan sulfate and sustained normalization demonstrate BBB crossing, CNS activity and durability of response of DNL310; enhanced peripheral activity also observed
- ✓ Cohort A 6-month data suggest clinical improvement based on Global Impression of Change scales in children aged 5-10
- ✓ Exploratory biomarker data is consistent with improved lysosomal function
- ✓ Safety profile with up to 43 weeks of dosing is consistent with standard of care ERT

Cohort C
Ages <4 y.o.
Neuronopathic

Designed to further explore clinical endpoints – including behavior and cognition – in an age range for which treatment effects on developmental milestones may have the highest likelihood to be observed

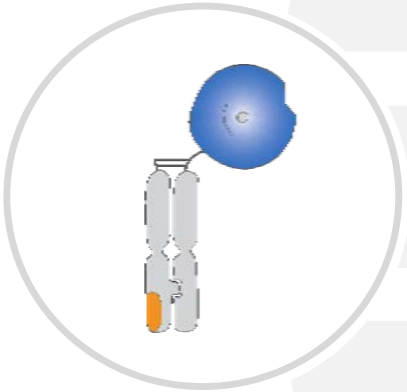
Ph2/3
Neuronopathic
Non-neuronpathic

Registrational study designed to demonstrate patient benefit in neuronopathic and non-neuronopathic MPS II

EXPANDED ETV PLATFORM DRIVING NEAR-TERM GROWTH

ETV STRATEGY

Substantial unmet need and opportunity
- CNS manifestations in 2/3 of LSDs
- ETV can treat body and brain with IV administration



Clinical Proof of Concept Achieved
- Moving DNL310 to late-stage development

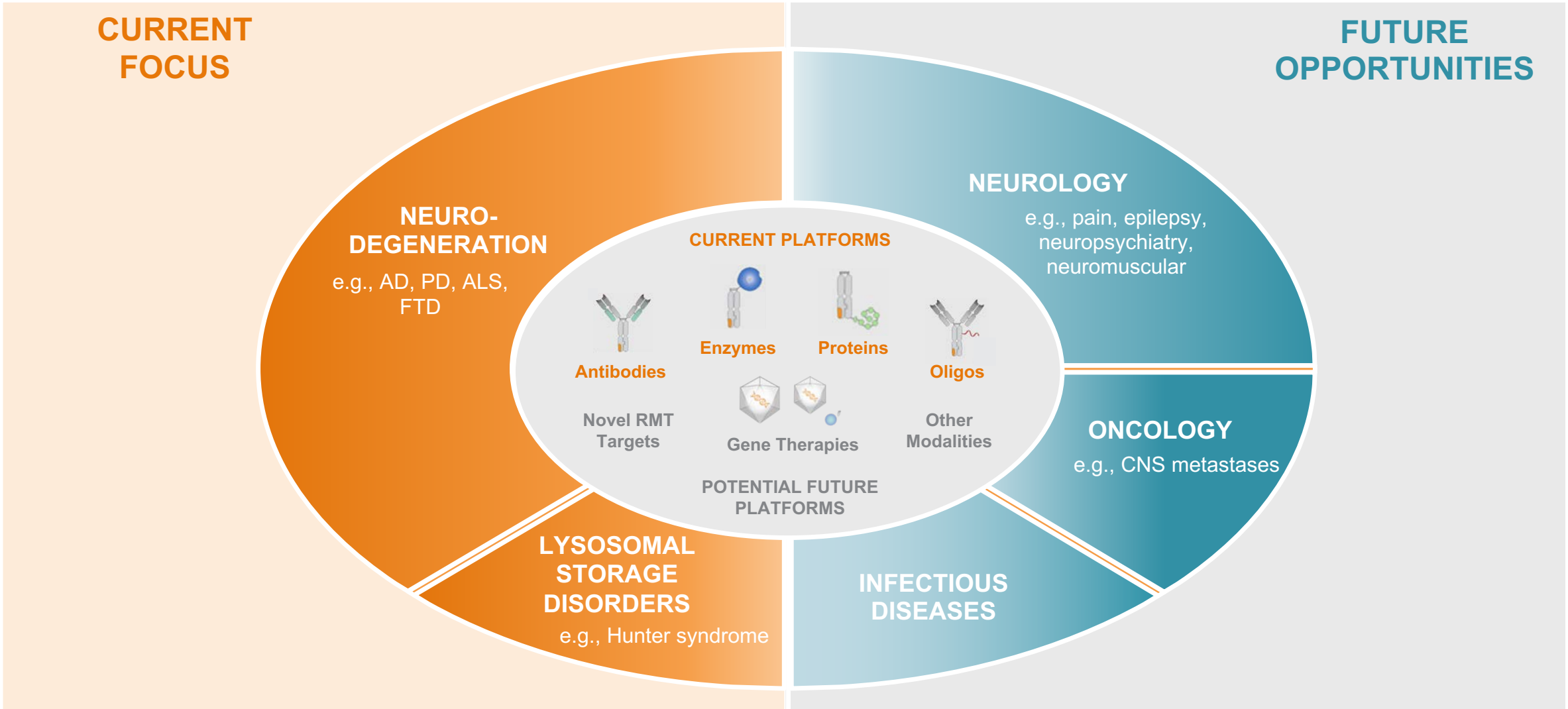
Path forward
- Expanded portfolio of ETV programs
- Build and grow internal manufacturing and commercial capabilities

ETV PORTFOLIO

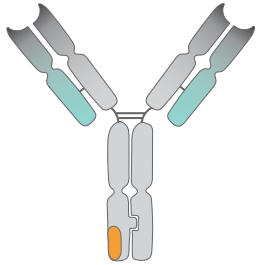
PROGRAM	INDICATION	STAGE			
		Discovery	IND-enabling	Early clinical	Late clinical
DNL310 (ETV:IDS)	MPS II				
ETV:SGSH	MPS IIIA				
ETV:GBA	Parkinson's; Gaucher				
ETV:ARSA	MLD				
ETV:NAGLU	MPS IIIB				
ETV:IDUA	MPS I				
ETV:GAA	Pompe				

Execute internally with fast-to-market strategy to serve patients and capture full potential of ETV platform

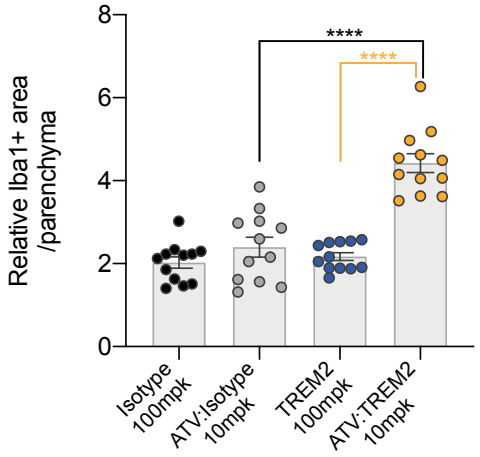
TV POTENTIAL: WIDE RANGE OF INDICATIONS AND TARGETS



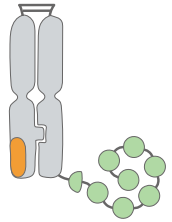
DIVERSE TV PORTFOLIO IN CNS AND BEYOND



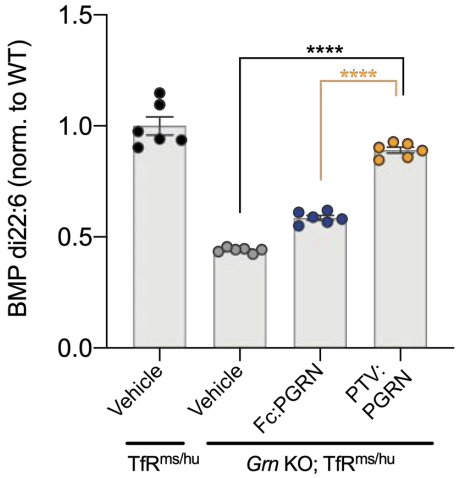
ATV:TREM2



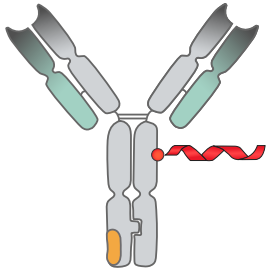
ATV:TREM2 robustly increases microglia in mice



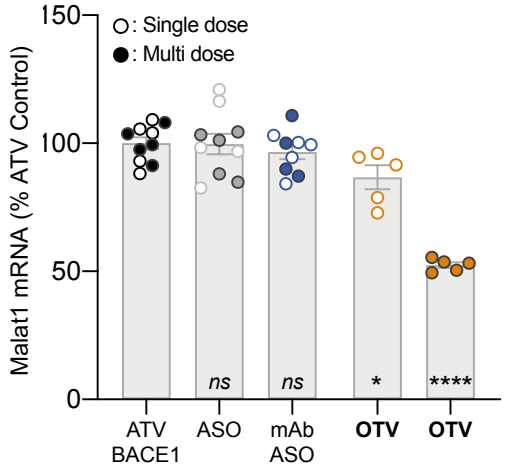
PTV:PGRN



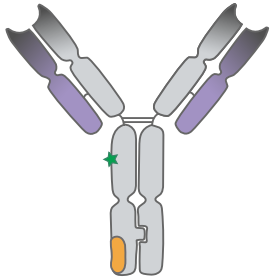
PTV:PGRN rescues lysosomal function in *GRN* KO brain



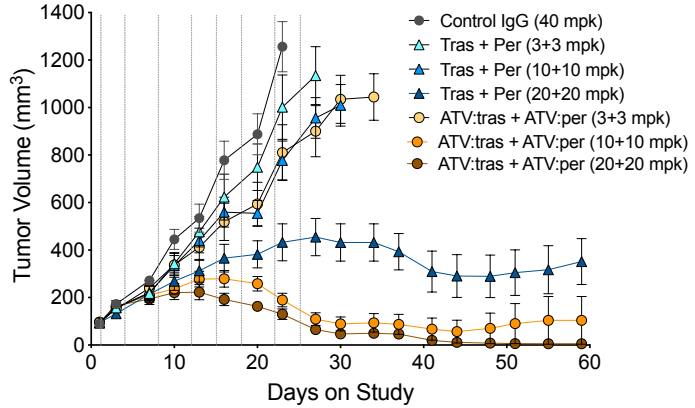
OTV



OTV knocks down gene expression in mouse brain



ATV:HER2



ATV:HER2 enhances anti-tumor activity in xenograft model

OUR TV PORTFOLIO

Undisclosed targets: LF - Lysosomal Function target; CH - Cellular Homeostasis target

PROGRAM TARGET	DRUG CANDIDATE*	DISEASE INDICATION	DRUG DEVELOPMENT					PARTNER
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	
ETV – Enzyme Transport Vehicle								
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)						
Sulfamidase	ETV:SGSH	MPS IIIA (Sanfilippo Syndrome)						
GBA	ETV:GBA	Parkinson's, Gaucher						
ARSA	ETV:ARSA	MLD						
NAGLU	ETV:NAGLU	MPS IIIB						
IDUA	ETV:IDUA	MPS I						
GAA	ETV:GAA	Pompe						
ATV – Antibody Transport Vehicle								
TREM2	DNL919	Alzheimer's						Takeda
Abeta	ATV:Abeta	Alzheimer's						Biogen
Tau	ATV:Tau	Alzheimer's						Takeda
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA						
HER2	ATV:HER2	Oncology						
PTV – Protein Transport Vehicle								
PGRN	DNL593	Frontotemporal Dementia						Takeda
OTV – Oligonucleotide Transport Vehicle								
Undisclosed	OTV:CH2	Alzheimer's						
Undisclosed	OTV:LF3	Parkinson's						

 Biogen has option rights to 1 additional undisclosed TV enabled program

*Investigational – not approved for treatment


OUR SMALL MOLECULE PROGRAMS

BIIB122/DNL151 ADVANCING INTO LATE-STAGE DEVELOPMENT IN 2021

ROBUST TARGET ENGAGEMENT AND PATHWAY ENGAGMENT CLINICAL DATA

- Over 300 individuals dosed in total with a LRRK2 inhibitor in extensive Phase 1/1b testing
- Safety and tolerability profile support further development in Parkinson's patients
- Achieved target engagement and pathway engagement goals in healthy volunteers and Parkinson's patients for both DNL201 and DNL151

MOVING DNL151 INTO LATE-STAGE STUDIES WITH A GLOBAL STRATEGIC PARTNER

- Late-stage development in both LRRK2 mutation carriers and idiopathic Parkinson's patients
- Co-development and co-commercialization agreement with Biogen in August 2020
- $1.025B upfront payment; up to $1.125B milestones plus profit sharing and royalties

DENALI THERAPEUTICS Biogen

LRRK2 INHIBITOR EARLY-STAGE DEVELOPMENT

DNL201 Phase 1
n=122 (Completed)

DNL201 Phase 1b
(n=28) (Completed)

DNL151 Phase 1
n=184

DNL151 Phase 1b
n=36

DNL151 Selected
favorable profile, including potential for once daily dosing

LRRK2 INHIBITOR LATE-STAGE DEVELOPMENT

DNL151 late-stage study
LRRK2 Mutation Carriers

DNL151 late-stage study
Idiopathic PD

Initiate late-stage development by end 2021

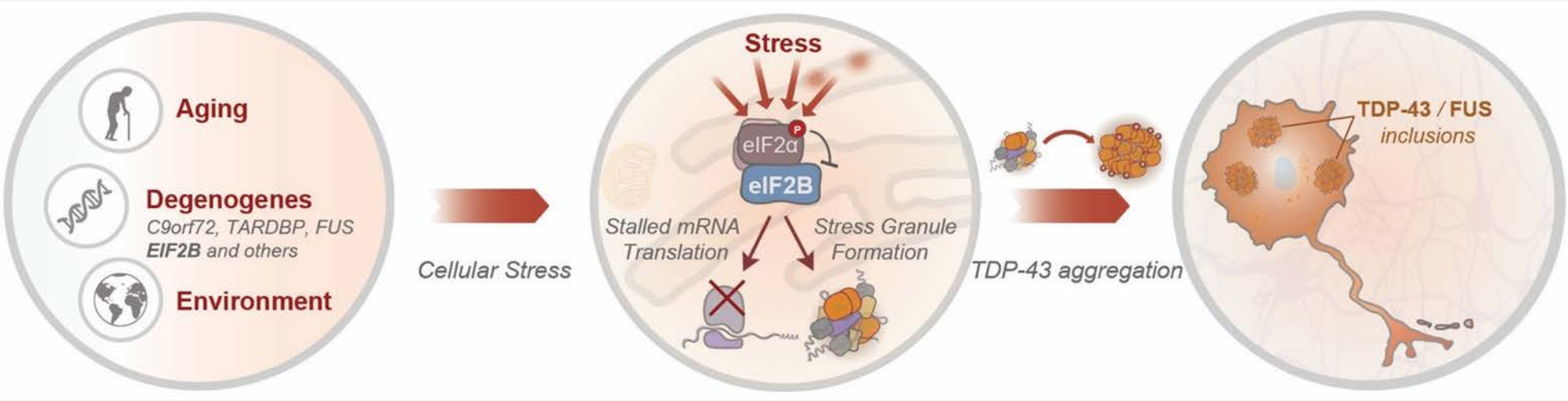
EIF2B AS A THERAPEUTIC TARGET FOR ALS/FTD

GENETICS → **PATHWAY** → **PATHOLOGY**

Degenogenes and neuronal insults result in reduced EIF2B function

EIF2B inhibition leads to stress granules and harmful TDP-43 aggregates

These harmful aggregates trigger neurodegeneration



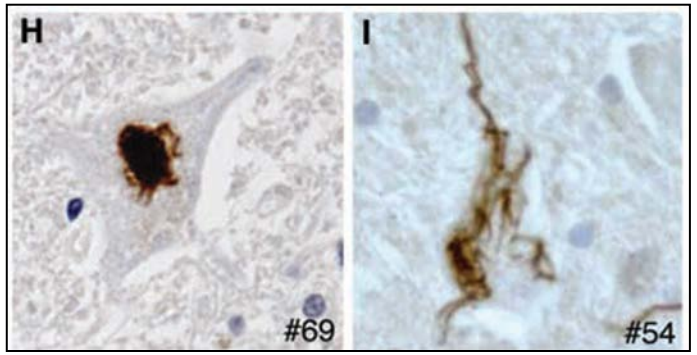
Integrated Stress Response (ISR)

Neuronal Loss (ALS / FTD)

Activating EIF2B can prevent or reverse the formation of TDP-43 aggregates and improve neuronal survival

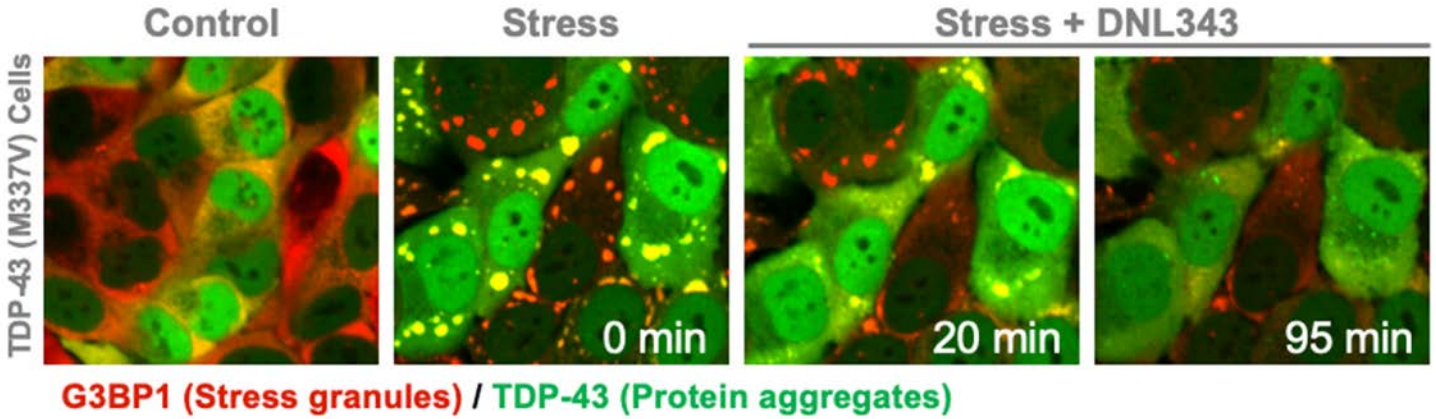
EIF2B ACTIVATOR DNL343 DISSOLVES STRESS GRANULES *IN VITRO*

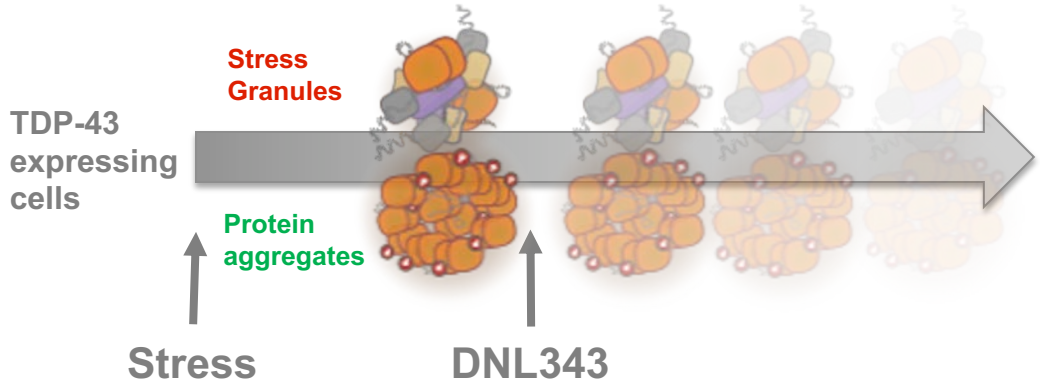
ALS patient neurons with TDP-43 pathology



Neuman et al. *Science* 2006

TDP-43 aggregates are found in >95% of ALS patients & ~50% of FTD patients[1]





EIF2B activator DNL343 reverses pre-formed stress granules and TDP-43 aggregates

[1]Goedert et al. *Cold Spring Harbor Perspectives in Medicine*, 2012.

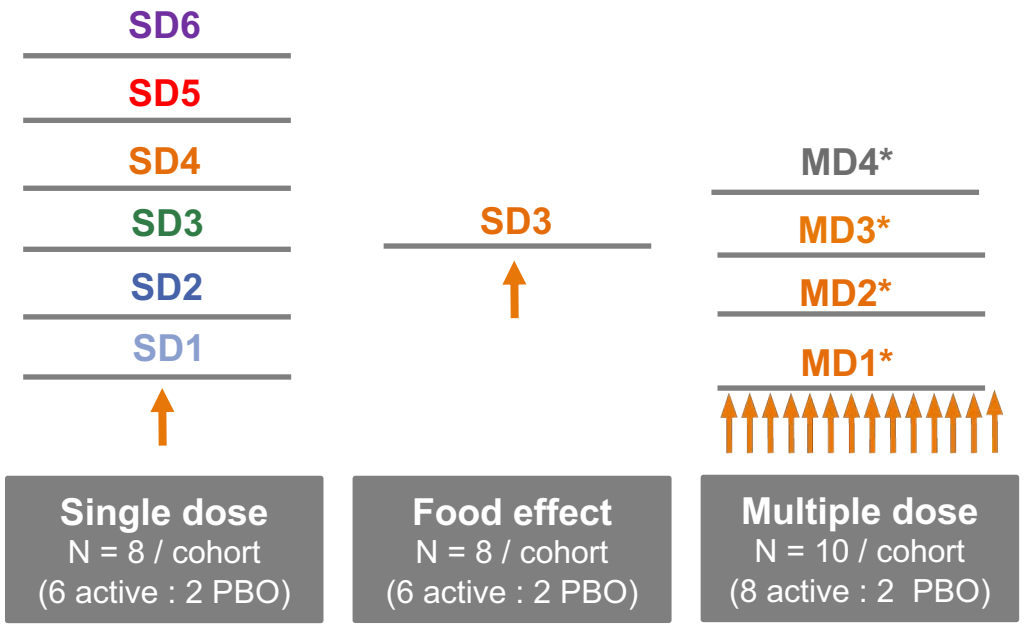
DNL343 PHASE 1 STUDY

STUDY OVERVIEW

Type	Phase 1 study in healthy volunteers	
Population	Planned: 88 healthy volunteers, 18-50 years (SAD=48; MAD=40)	
Key endpoints	**Safety** • AEs • Safety labs • ECGs • Vital Signs • C-SSRS (MAD)	**PK (+/- food)** • Plasma • CSF
	Pathway engagement in PBMCs: ATF4 protein, *CHAC1* gene expression	
	Exploratory • CSF and plasma metabolomics, lipidomics, and cytokines	

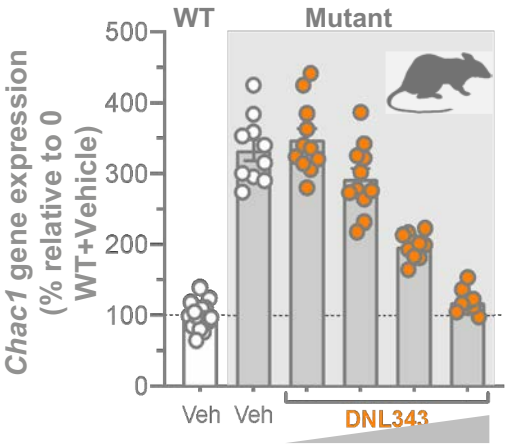
DOSING AND DETAILED DESIGN

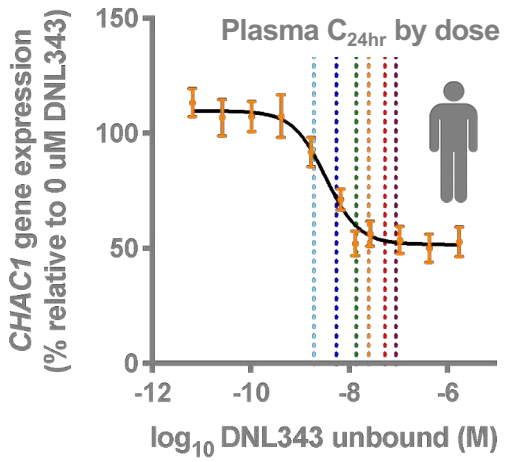
Complete cohorts (colored)
Planned cohorts
* Cohorts with CSF collection



Single dose	Food effect	Multiple dose
N = 8 / cohort (6 active : 2 PBO)	N = 8 / cohort (6 active : 2 PBO)	N = 10 / cohort (8 active : 2 PBO)

TRANSLATIONAL PHARMACODYNAMICS





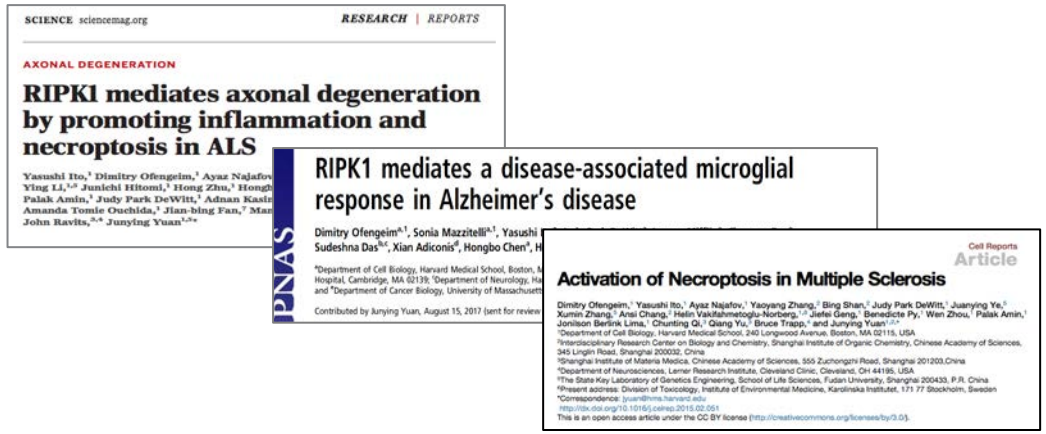
Dosing of all SAD cohorts completed; Safety, tolerability, PK and PD support further development of DNL343

Phase 1b study ongoing in patients with ALS

DEVELOPING RIPK1 INHIBITORS FOR CNS & INFLAMMATORY DISEASE

Rationale and Mechanism of Action

- RIPK1 mediates cell death and inflammatory signaling in microglia and other cells
- RIPK1 activation can lead to microglial dysfunction, which is genetically linked to ALS and AD (degenogenes)
- Microglial dysfunction can lead to inflammation and necroptosis of brain cells
- RIPK1 inhibition enables selective modulation of the TNFR1 pathway, reducing inflammation and necroptosis in the brain



DNL788 (CNS-penetrant)

- Phase 1 healthy volunteer study ongoing (led by Sanofi)
- Future potential development for ALS, MS, and Alzheimer's disease

DNL758 (peripherally-restricted)

- Phase 2 study in cutaneous lupus erythematosus (CLE) ongoing patients (led by Sanofi)
- Phase 1b study in Covid-19 completed; while the primary endpoint was not met, DNL758 was found to be generally well tolerated and did generate positive signals of relevant biological effect

Sanofi Collaboration

- Co-development and co-commercialization agreement
- 50/50 profit share in US and China; royalty ROW
- 70/30 (Sanofi/Denali) cost share in Phase 3

SANOFI


DENALI
LOOKING AHEAD

OUR PLANS: 2021 KEY MILESTONES

		EXPECTED TIMING
ETV:IDS Hunter Syndrome	✓ **DNL310:** 24-week data from Cohort A of Phase 1/2 study	▪ Mid 2021
	• **DNL310:** 24-week data from Cohort A+B of Phase 1/2 study	▪ Early 2022
LRRK2 Parkinson's	• **DNL151:** Initiate late-stage clinical development in collaboration with Biogen	▪ Late 2021
EIF2B ALS, FTD	✓ **DNL343:** Phase 1 data in healthy volunteers enabled go decision for Phase 1b	▪ 1H 2021
	✓ **DNL343:** Initiate Phase 1b study in ALS patients	▪ 2H 2021
RIPK1 CNS and Peripheral	✓ **DNL758** (inflammatory diseases): Initiated Phase 2 study in cutaneous lupus erythematosus patients (Sanofi); Phase 1b data in COVID-19 (Sanofi)	▪ 1H 2021
	• **DNL788** (ALS, Alzheimer's, MS): Phase 1 data in healthy volunteers (Sanofi)	▪ 2H 2021
ATV:TREM2 Alzheimer's	✓ **DNL919:** Milestone payment from Takeda for initiation of IND-enabling studies	▪ Q1 2021
	• **DNL919:** File IND application or CTA	▪ Late 2021/ Early 2022
PTV:PGRN FTD	✓ **DNL593:** Milestone payment from Takeda for initiation of IND-enabling studies	▪ Q1 2021
	• **DNL593:** File IND application or CTA	▪ Late 2021
TV Platform	✓ Expand ETV portfolio	▪ Ongoing
	✓ Expand manufacturing capabilities and continue to build out commercial capabilities	

DRIVING TO DEFEAT DEGENERATION

DEVELOPING DISEASE-MODIFYING THERAPEUTICS FOR PATIENTS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