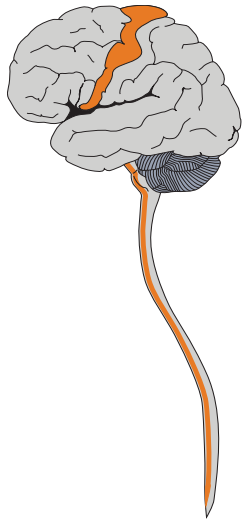
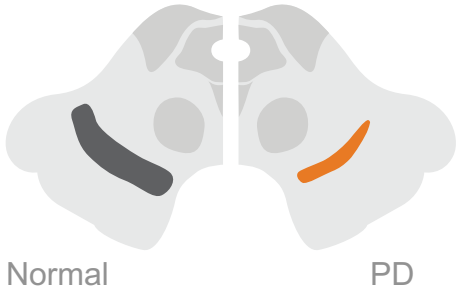
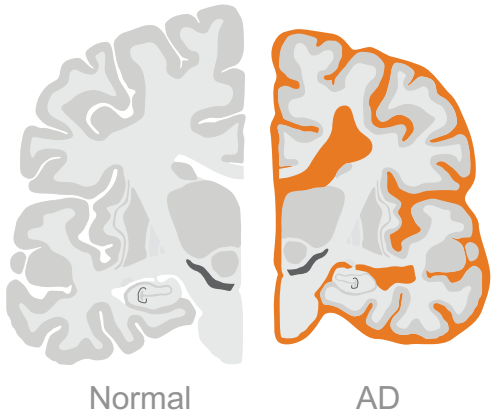

DENALI™
Defeat Degeneration
June 2020

OUR PURPOSE: DEFEAT DEGENERATION

RARE NEURODEGENERATIVE DISEASES	AMYOTROPHIC LATERAL SCLEROSIS	PARKINSON'S	ALZHEIMER'S
Orphan	20,000+ (US)	1,000,000+ (US)	5,500,000+ (US)
>30 lysosomal storage diseases	>45 known genetic associations	>95 known genetic associations	>35 known genetic associations



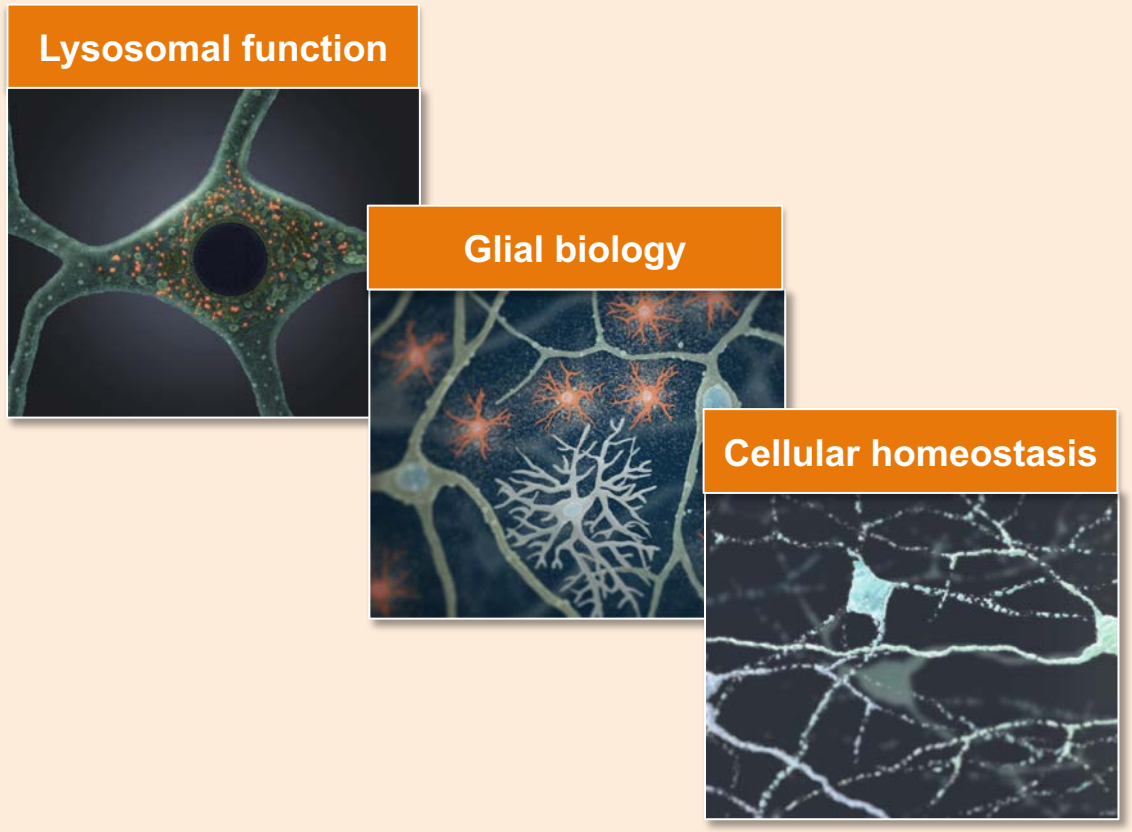




Significant unmet medical need with few disease-modifying medicines

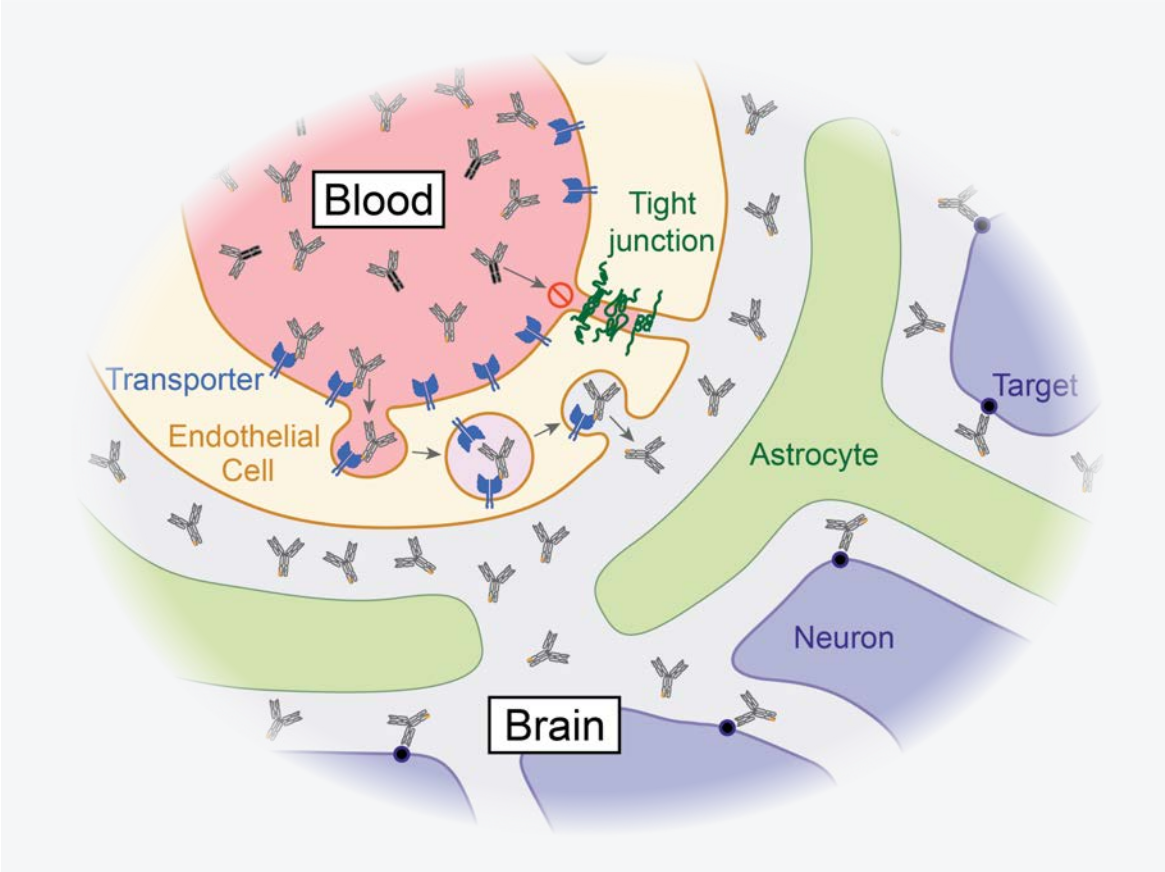
OUR APPROACH: TWO PLATFORMS

DEGENOGENE BIOLOGY



Deep biology and drug discovery expertise in three focus areas

BLOOD-BRAIN BARRIER TECHNOLOGIES



Engineering brain delivery of small molecules, biotherapeutics, and gene therapies

OUR JOURNEY: CLINICAL MILESTONES AND KEY PARTNERSHIPS

FILINGS

- RIPK1 — DNL104 P1
- LRRK2 — DNL201 P1
- LRRK2 — DNL151 P1
- RIPK1 — DNL747 P1
- LRRK2 — DNL201 P1b
- RIPK1 — DNL747 P1b (ALS+AD)
- pRIPK1 — DNL758 P1
- LRRK2 — DNL151 P1b
- ETV:IDS — DNL310 P1/2
- EIF2B — DNL343 P1

CLINICAL DATA

- DNL104 — Phase 1
- DNL747 — Phase 1
- DNL201 — Phase 1
- DNL151 — Phase 1
- DNL201 — Phase 1b

2015	2016	2017	2018	2019	2020

ENABLING

HARVARD UNIVERSITY

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Genentech — A Member of the Roche Group

F-star — BISPECIFIC. BY DESIGN.

UCSD

DZNE

VIB — science meets life

AbCellera

Lonza

CENTOGENE — THE RARE DISEASE COMPANY

SIRION BIOTECH

NDC[1]

STRATEGIC PARTNERSHIPS

Takeda

SANOFI

[1]Collaboration with Neurodegenerative Consortium (NDC) researchers based at MD Anderson

OUR PORTFOLIO

Large Molecule (TV Platform) | Small Molecule | AAV

PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT	PARTNER
			Drug Discovery / IND-Enabling / Early Clinical / Late Clinical / Approved	
LYSOSOMAL FUNCTION PATHWAY				
LRRK2	DNL201	Parkinson's	Early Clinical	
	DNL151	Parkinson's	Early Clinical	
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)	Early Clinical	
PGRN	DNL593	Frontotemporal Dementia	IND-Enabling	Takeda
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA	Drug Discovery	
Sulfamidase	ETV:SGSH	MPS IIIA (Sanfilippo Syndrome)	Drug Discovery	
Undisclosed	ETV:LF1	LSD with Neurodegeneration	Drug Discovery	
Undisclosed	AAV:LF2	Parkinson's	Drug Discovery	
GLIAL BIOLOGY PATHWAY				
RIPK1 (CNS)	DNL747	Alzheimer's, ALS, MS	Early Clinical	Sanofi
TREM2	DNL919	Alzheimer's	IND-Enabling	Takeda
Undisclosed	GB1	ALS	Drug Discovery	
CELLULAR HOMEOSTASIS				
EIF2B	DNL343	ALS, FTD	Early Clinical	
Tau	ATV:Tau	Alzheimer's	Drug Discovery	Takeda
Undisclosed	CH1	ALS, Parkinson's	Drug Discovery	
OTHER				
RIPK1 (Peripheral)	DNL758	Peripheral Inflammatory Diseases	Early Clinical	Sanofi
LRRK2 (Peripheral)	DNL975	Crohn's Disease	Drug Discovery	
Undisclosed	OT1	Other	Drug Discovery	

OUR 2020 CLINICAL PIPELINE DELIVERABLES

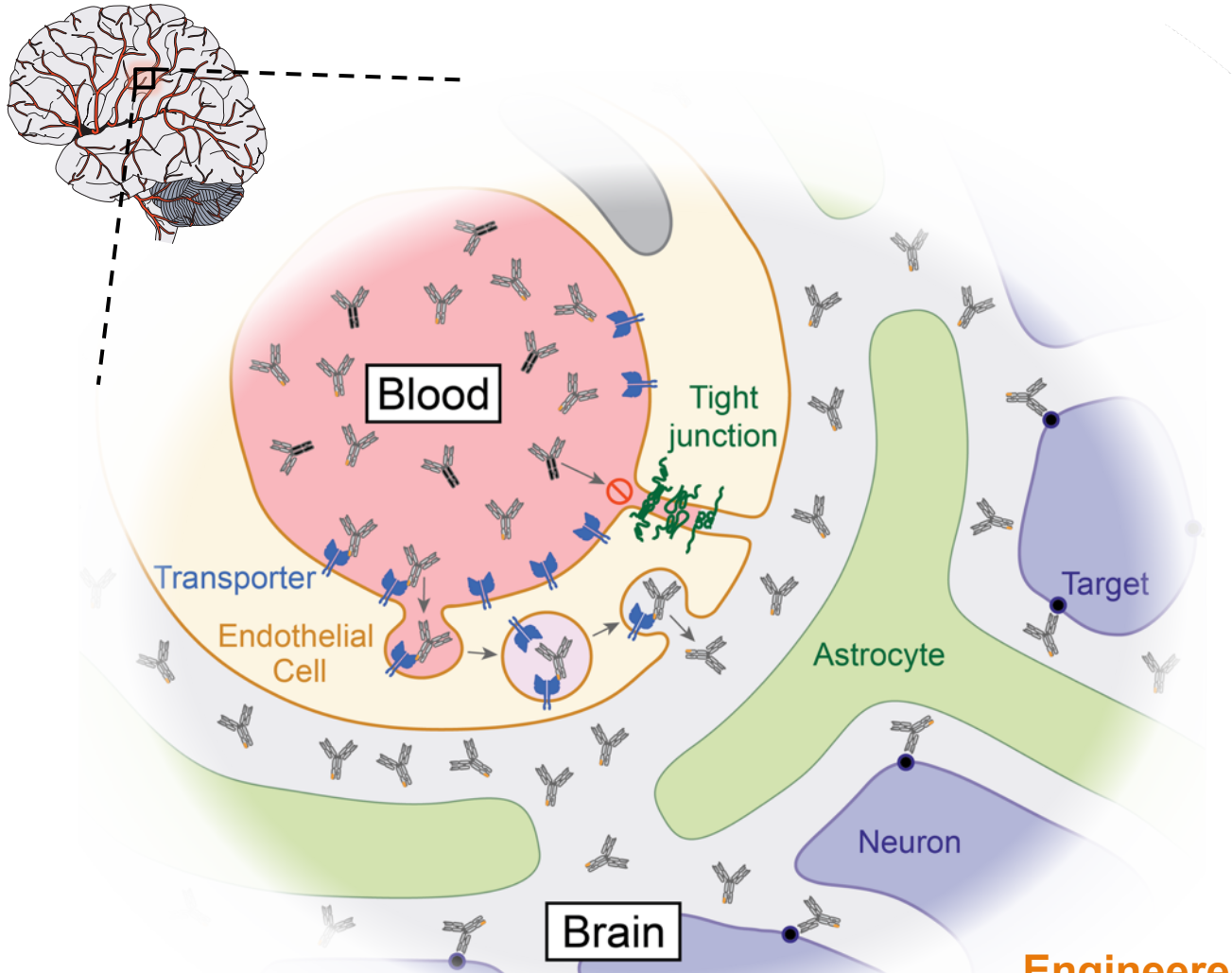
	2020 Plans	Expected Timing
LRRK2 Parkinson's	▪ Select molecule and prepare for Phase 2/3	▪ Mid 2020
ETV:IDS Hunter syndrome	▪ Establish biomarker proof-of-concept in patients	▪ Late 2020
EIF2B ALS	▪ DNL343 Phase 1 in HV results to potentially enable patient study (COVID delay)	▪ Late 2020
RIPK1 ALS, Alzheimer's	▪ Results from DNL747 ALS and Alzheimer's studies to potentially enable progression	▪ Mid 2020
BBB Platform	▪ Establish TV Platform PoC in humans (ETV:IDS) ▪ Initiate IND-enabling studies for additional programs	▪ Late 2020

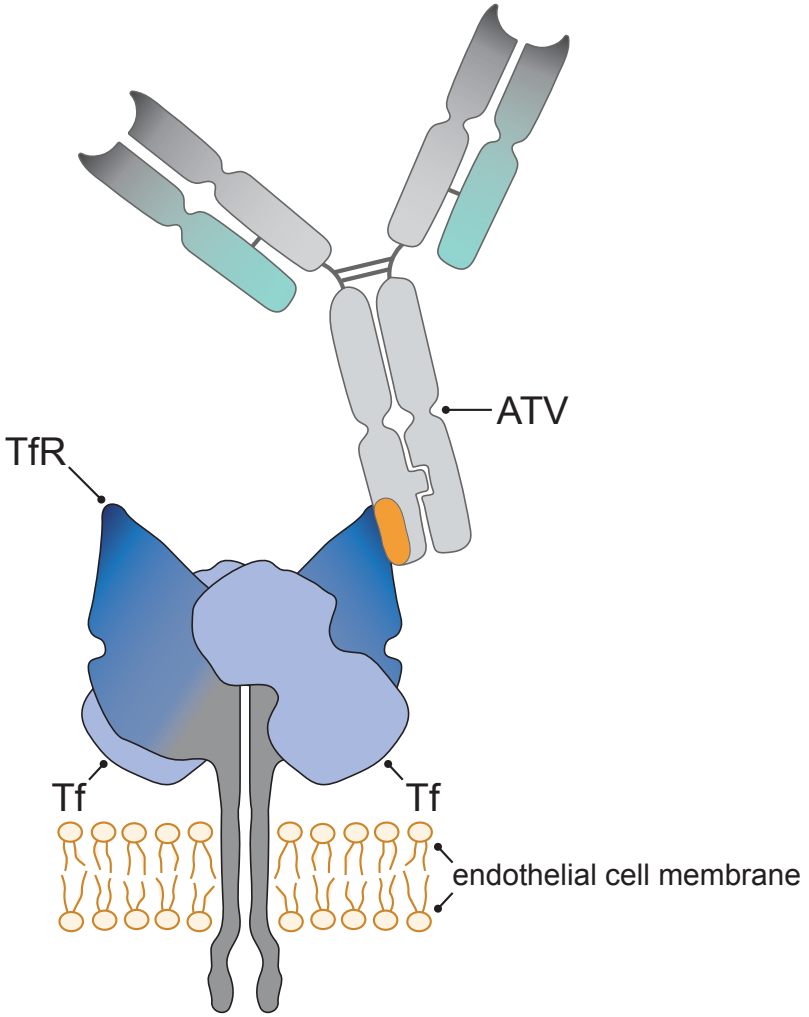
DENALI UPDATE FROM COVID-19 PANDEMIC

- Onsite and remote operations nearly at full productivity levels
- Enrollment for DNL151 (LRRK2) and DNL343 (EIF2B) clinical trials poised to restart as sites reopen
- Key 2020 clinical readouts and decisions remain on track
- Strong balance sheet with just under $600M in cash at end of Q1 2020


DENALI
TRANSPORT VEHICLE
BBB PLATFORM

THE BLOOD-BRAIN BARRIER IS AN OBSTACLE FOR TREATING NEURODEGENERATIVE DISEASES





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

TV TECHNOLOGY DELIVERS BIOTHERAPEUTICS TO THE BRAIN

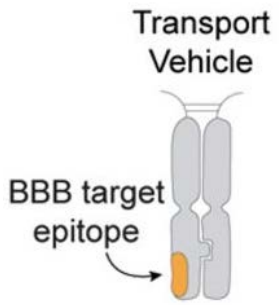
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

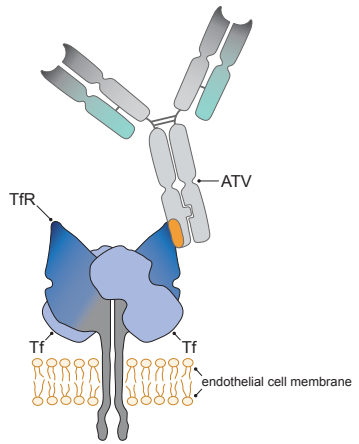
BLOOD-BRAIN BARRIER

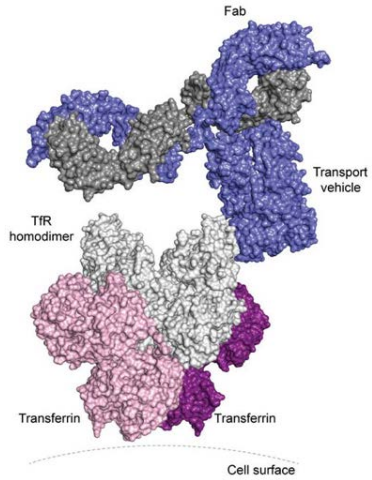
Brain delivery of therapeutic proteins using an Fc fragment blood-brain barrier transport vehicle in mice and monkeys

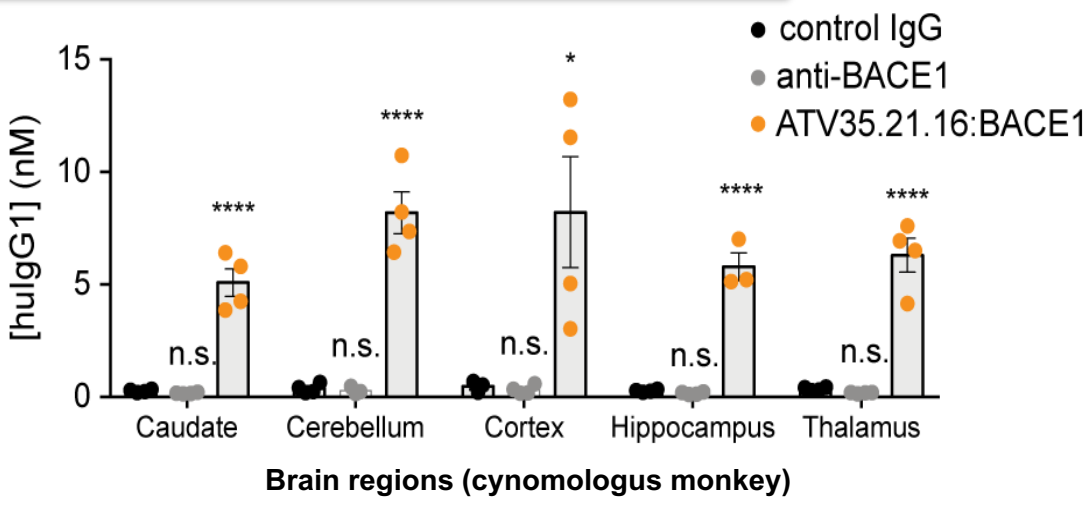
Mihalis S. Kariolis*†, Robert C. Wells†, Jennifer A. Getz, Wanda Kwan, Cathal S. Mahon, Raymond Tong, Do Jin Kim, Ankita Srivastava, Catherine Bedard, Kirk R. Henne, Tina Giese, Victoria A. Assimon, Xiaocheng Chen, Yin Zhang, Hilda Solanoy, Katherine Jenkins, Pascal E. Sanchez, Lesley Kane, Takashi Miyamoto, Kylie S. Chew, Michelle E. Pizzo, Nicholas Liang, Meredith E. K. Calvert, Sarah L. DeVos, Sulochanadevi Baskaran, Sejal Hall‡, Zachary K. Sweeney, Robert G. Thorne, Ryan J. Watts, Mark S. Dennis, Adam P. Silverman†, Y. Joy Yu Zuchero*†

Published May 27, 2020

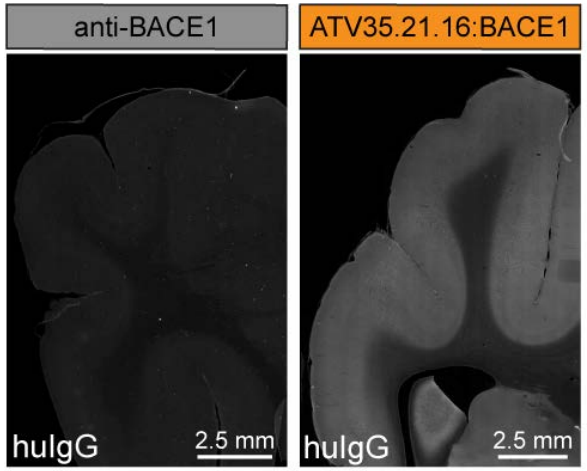








Brain regions (cynomologus monkey)



Cortex (cynomologus monkey)

ATV achieves high concentrations and broad distribution of antibodies in nonhuman primate brains

ETV TECHNOLOGY DELIVERS ENZYMES TO THE BRAIN

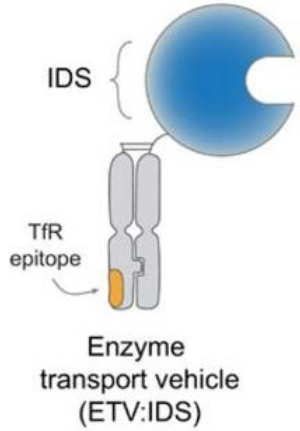
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

BLOOD-BRAIN BARRIER

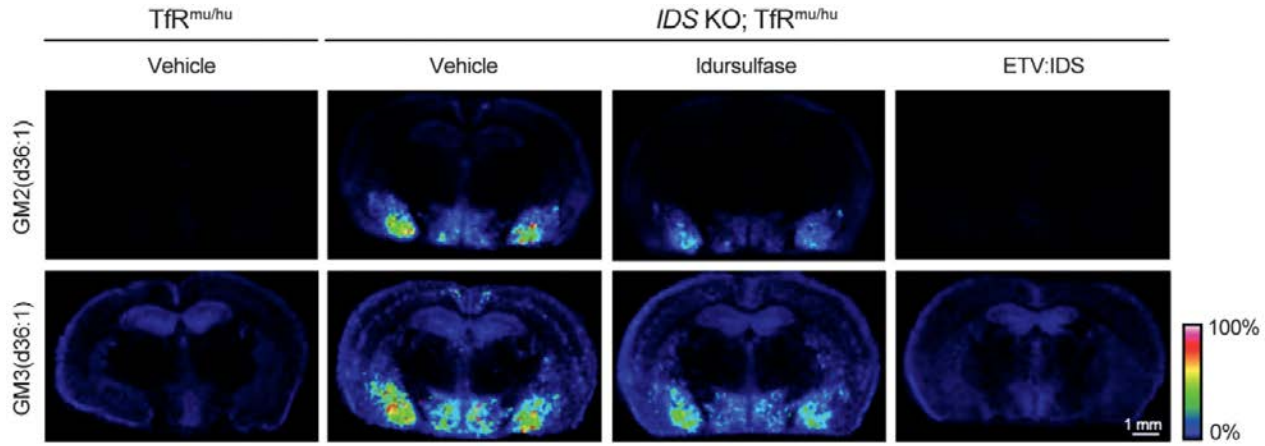
Brain delivery and activity of a lysosomal enzyme using a blood-brain barrier transport vehicle in mice

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‡]

Published May 27, 2020



ETV:IDS Reduces GAG accumulation in the brain

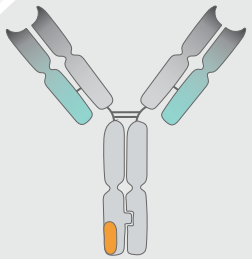


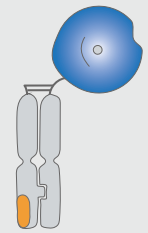
ETV achieves high concentration and broad distribution of enzymes in the brain after i.v. administration

MODALITY-BASED BRAIN DELIVERY PLATFORMS ENABLED BY TV

Antibody Transport Vehicle

- Deliver **antibodies** in bivalent or bispecific format to the brain
- Natural IgG structure and properties
- E.g.: ATV:TREM2, ATV:aSyn



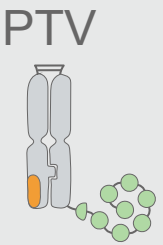


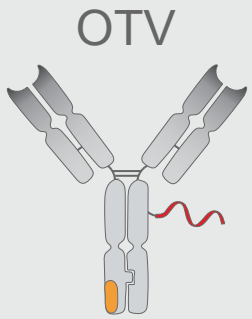
Enzyme Transport Vehicle

- Deliver **enzymes** to the brain
- Treat neuronopathic symptoms of lysosomal storage diseases
- E.g.: ETV:IDS, ETV:SGSG

Protein Transport Vehicle

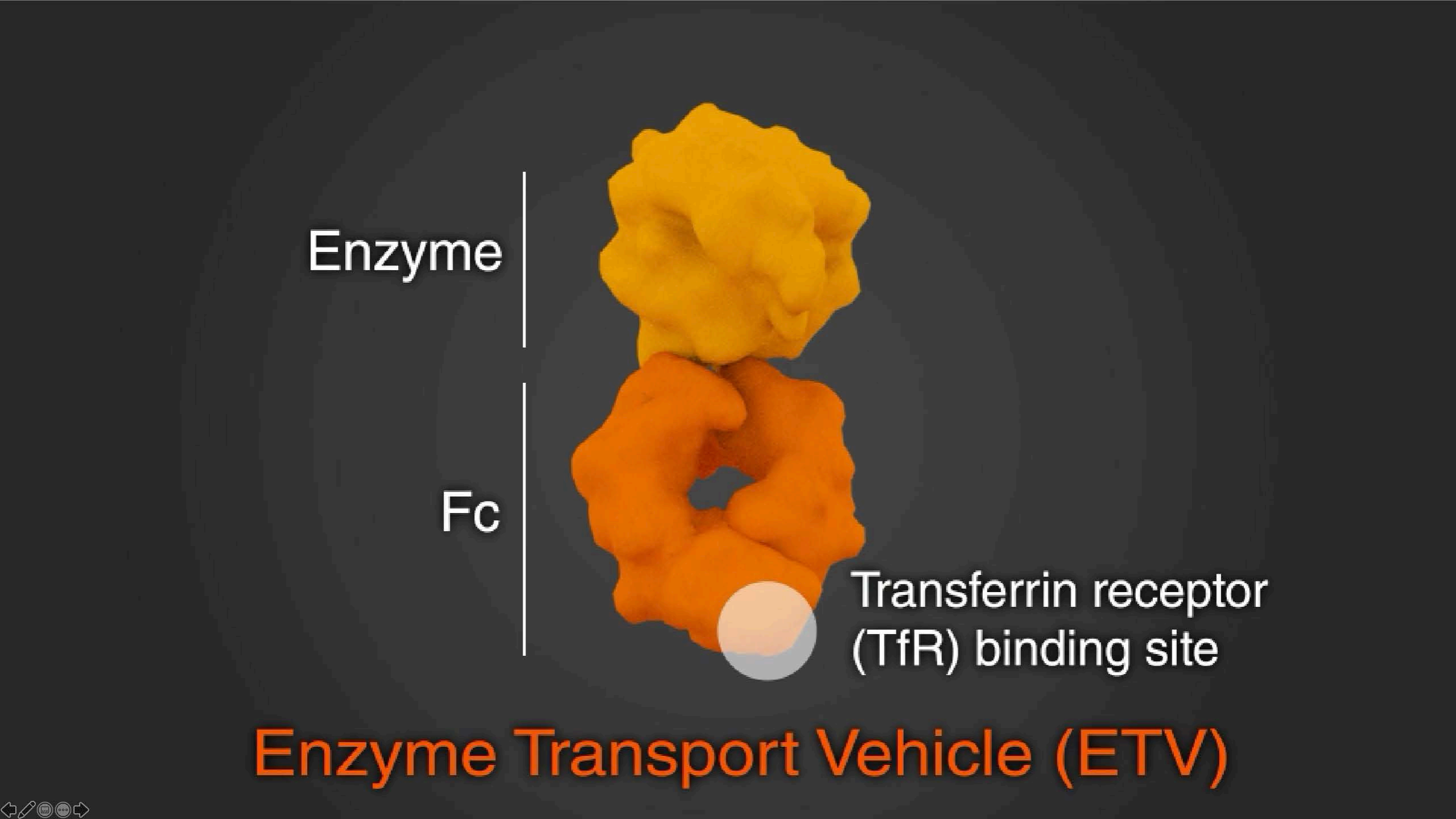
- Deliver **proteins** to the brain
- Replace or enhance function of natural proteins
- E.g.: PTV:PGRN





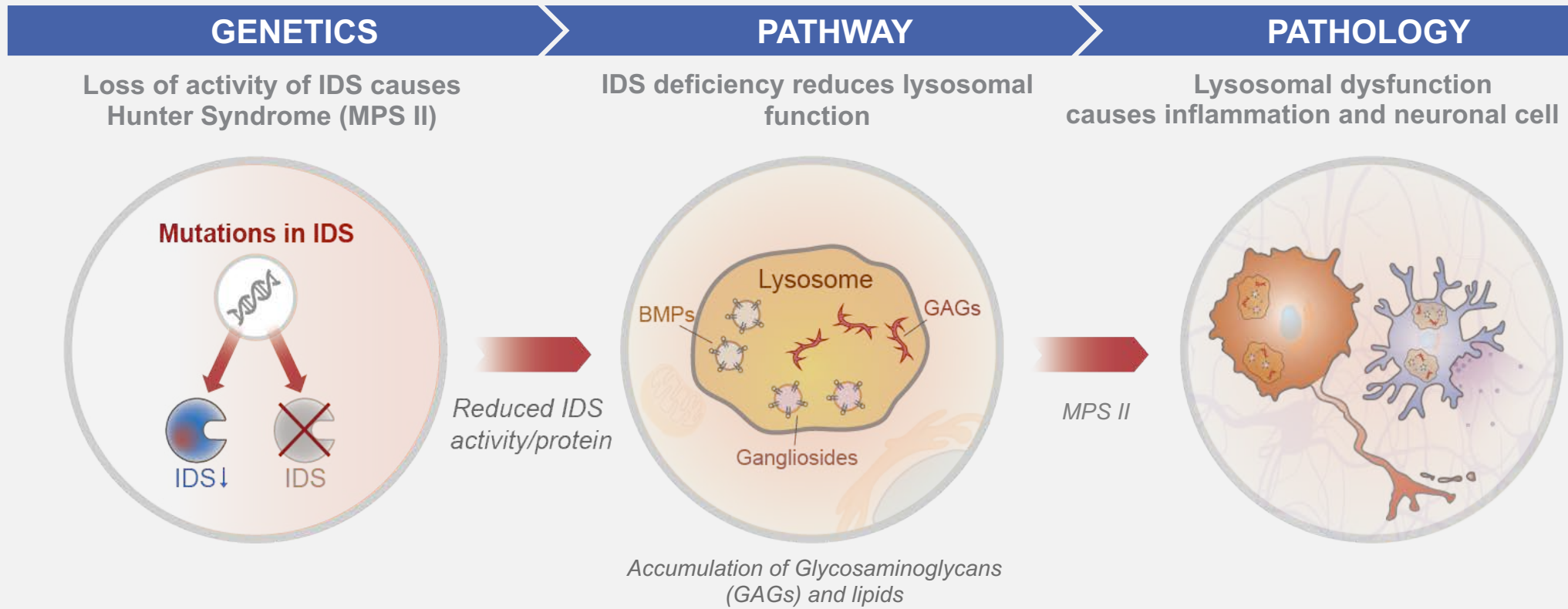
Oligonucleotide Transport Vehicle

- Deliver **oligonucleotides** to the brain
- Protein knockdown with ASO or siRNA



Enzyme Transport Vehicle (ETV)

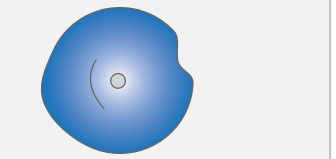
ETV:IDS (DNL310) FOR HUNTER SYNDROME



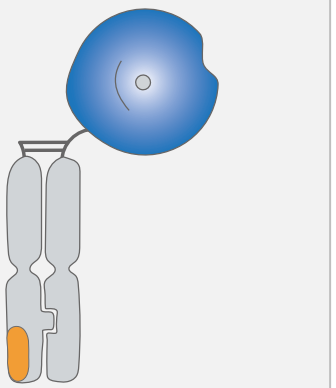
Existing enzyme replacement therapies (ERT) do not effectively cross the BBB and do not address neurodegeneration progresses

ETV:IDS CORRECTS GAGS AND LIPID STORAGE IN THE BRAIN AFTER SYSTEMIC ADMINISTRATION

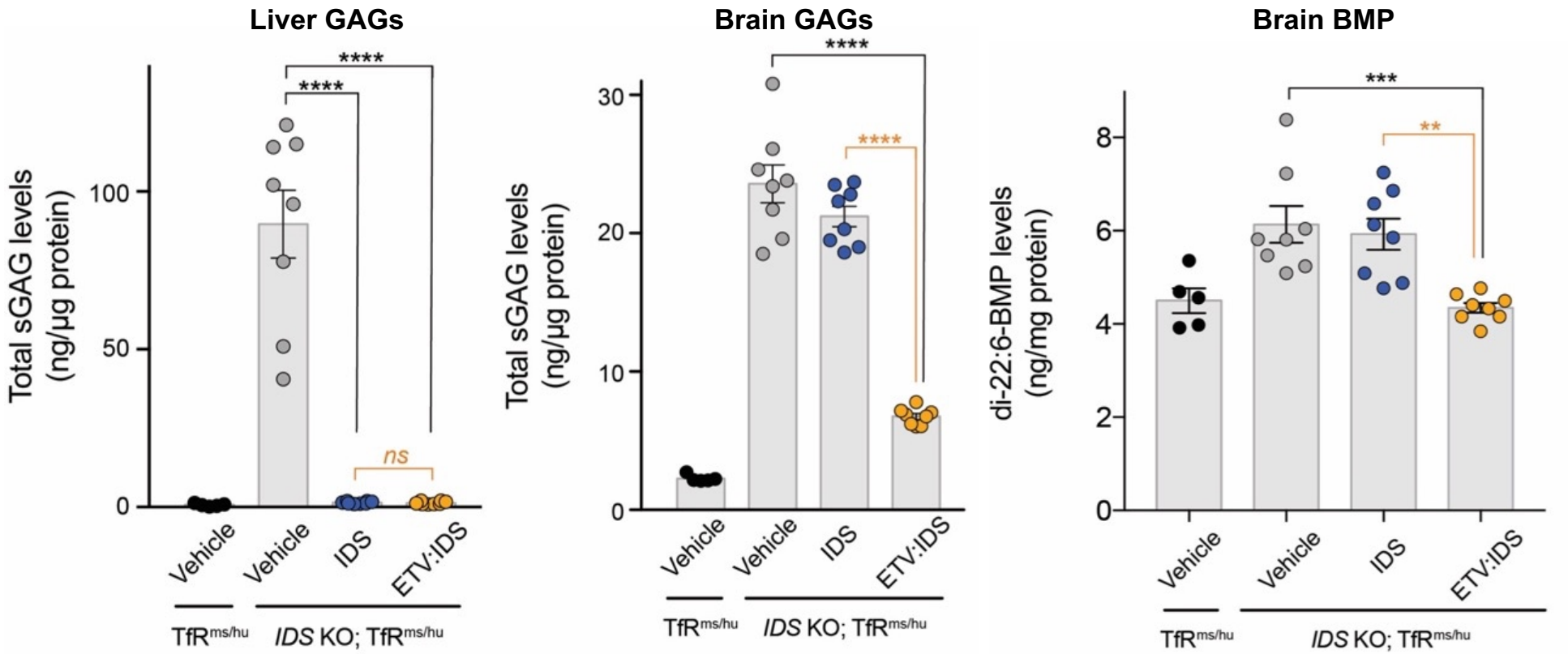
Iduronate-2-sulfatase (IDS) Architectures



Iduronate-2-sulfatase



ETV:IDS

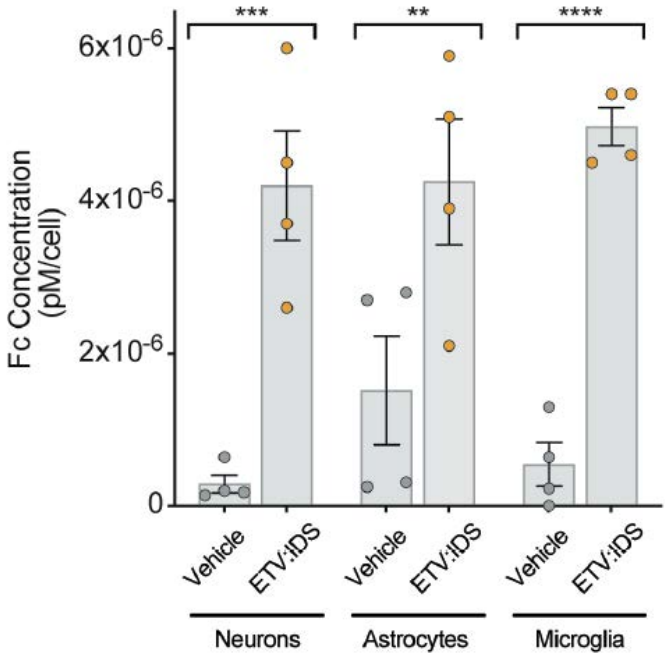


*n=8 per IDS KO; TfR$^{mu/hu}$ group or 5 per TfR$^{mu/hu}$ group, data shown as mean ± s.e.m.; *** p < 0.001, **** p < 0.0001, ns = not significant*
4 week high dose PoC study with comparable enzyme activity for IDS and ETV:IDS

ETV:IDS reduces GAGs in brain and liver and reverses brain BMP accumulation in a mouse model of Hunter syndrome

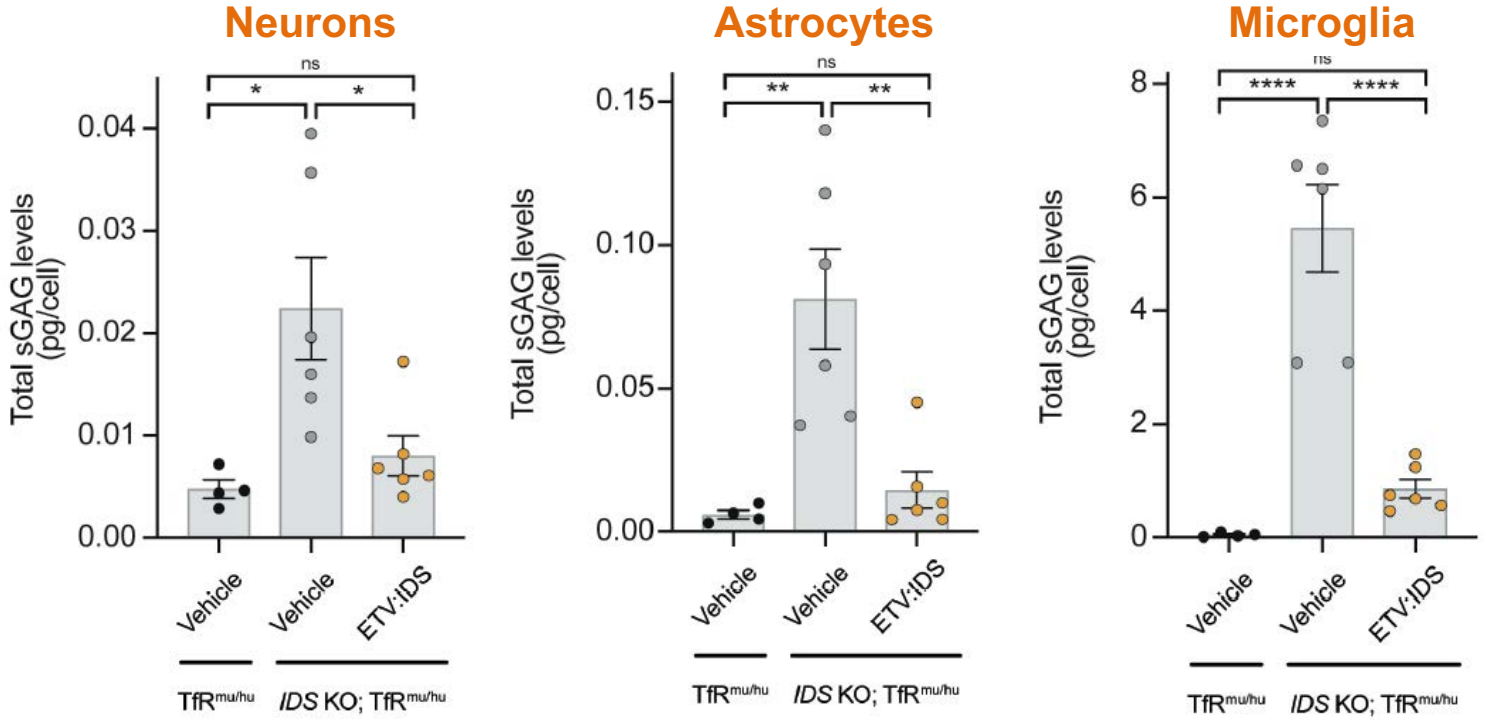
ETV:IDS DISTRIBUTES TO AND CORRECTS GAGS IN CNS CELL TYPES

ETV:IDS CONCENTRATION



2hr post-dose

EFFICACY OF ETV:IDS ACROSS CELL TYPES



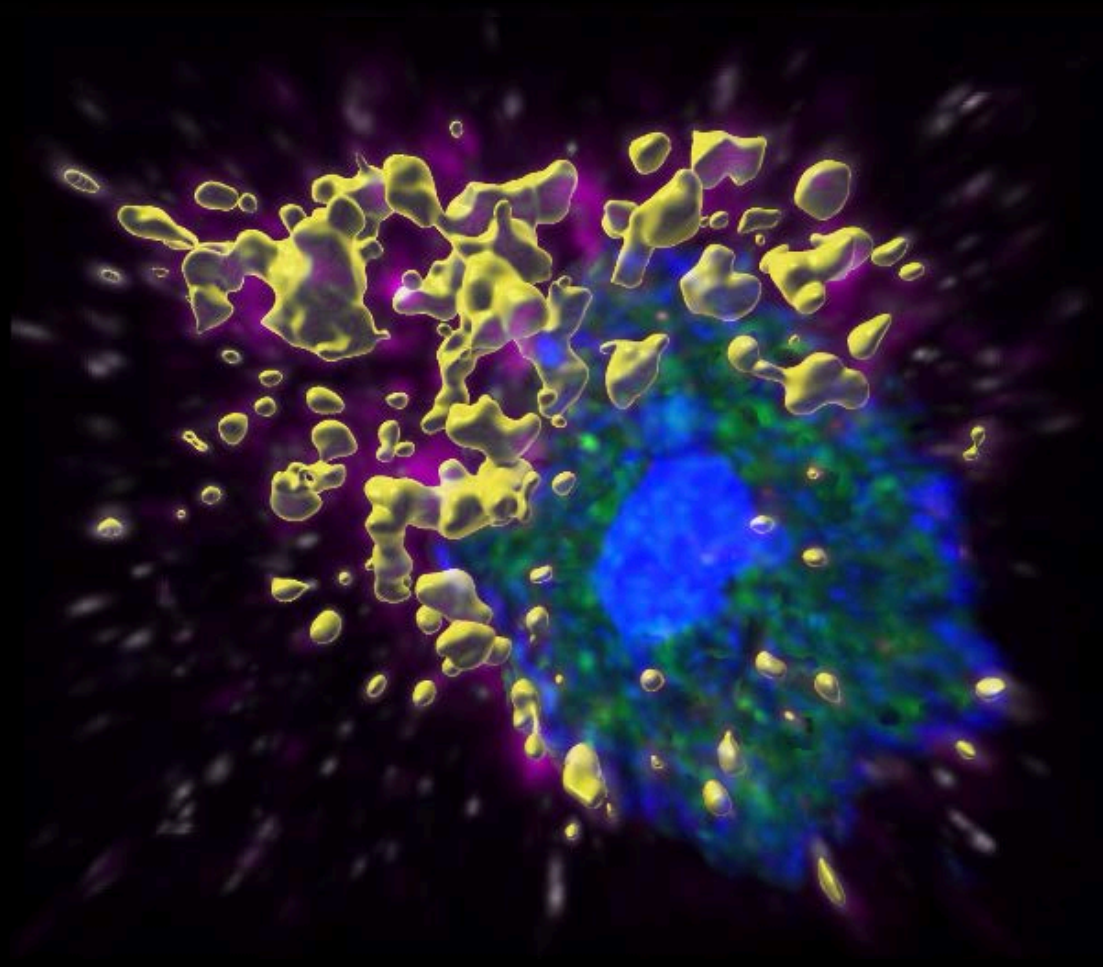
4 weeks of dosing (once a week)

*n=4-6 mice per treatment group, data shown as mean ± s.e.m.; * p < 0.05, ** p < 0.01 *** p < 0.001, **** p < 0.0001; ns = not significant*

ETV:IDS reduces GAG accumulation in specific cell types in brain

ETV:IDS LOCALIZES TO LYSOSOMES IN MOUSE BRAIN

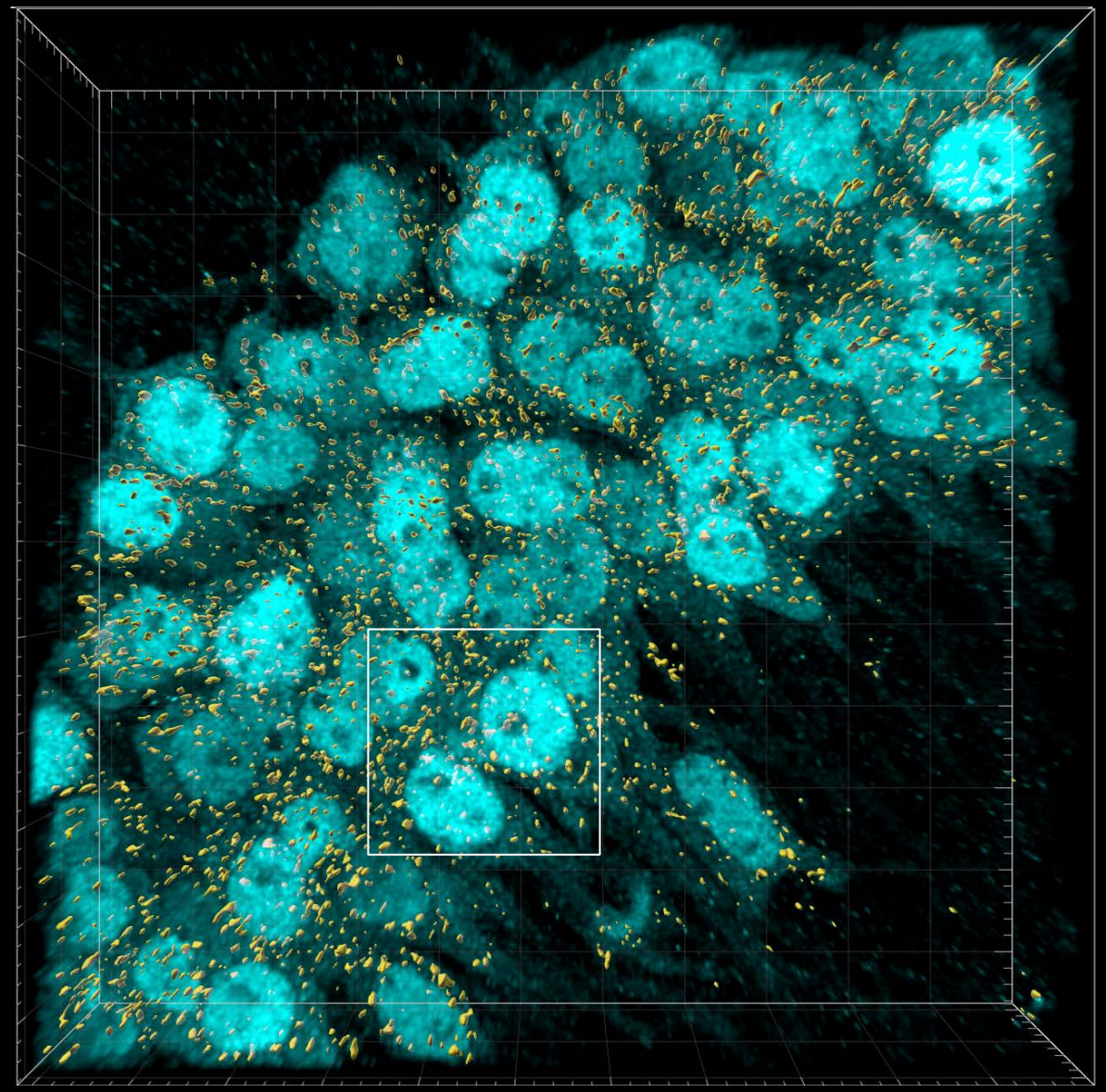
DAPI
NeuN
LAMP2
huIgG
Colocalization

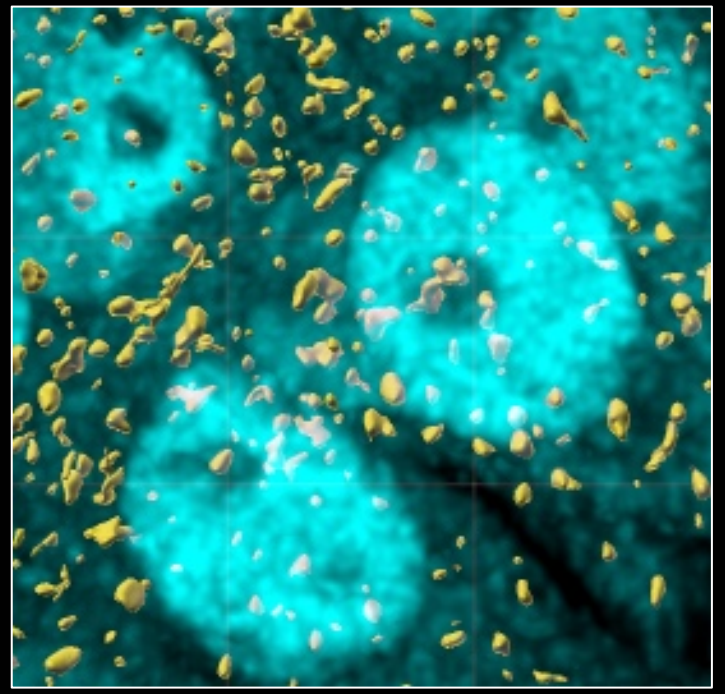


ETV:IDS distributes into the brain and co-localizes with lysosomal markers in neurons

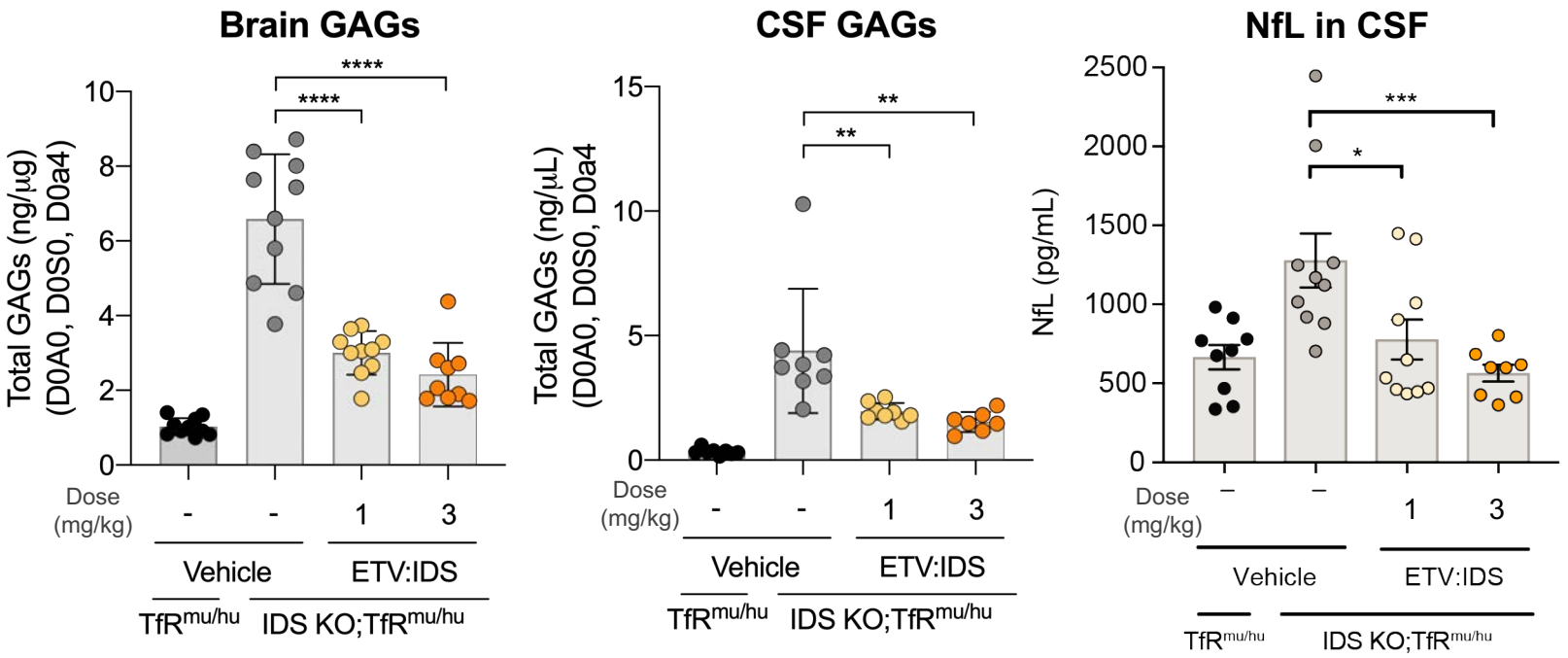
ETV:IDS DISTRIBUTES TO THE LYSOSOME IN NEURONS

Neurons
Colocalization of ETV:IDS and Lysosomes

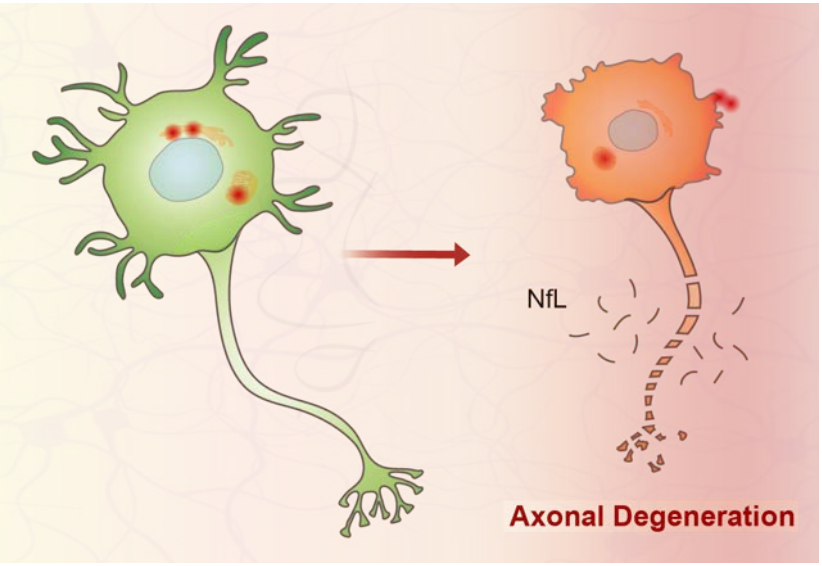




ETV:IDS RESCUES NEURODEGENERATION AS MEASURED BY NfL



NfL IS AN ESTABLISHED MARKER OF NEUROAXONAL INJURY



*n=9-10 per IDS KO; TfR$^{mu/hu}$ group or 10 per TfR$^{mu/hu}$ group, data shown as mean ± s.e.m.; * p <0.05, *** p < 0.001, **** p < 0.0001*
13 week dose range study

ETV:IDS reduces GAGs in brain and CSF and prevents neuroaxonal injury with chronic dosing at therapeutically relevant doses

DNL310 PHASE 1/2 PATIENT STUDY DESIGN AND OBJECTIVES

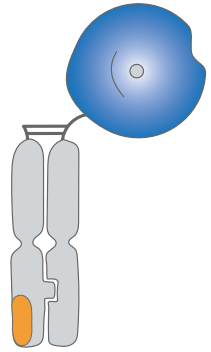
OBJECTIVE: BIOMARKER PROOF OF CONCEPT IN HUNTER SYNDROME AND ENABLE TV PLATFORM

- Phase 1/2 multicenter, open-label study in pediatric patients with Hunter syndrome
- 6 month study to evaluate safety, PK, and pharmacodynamic effect to select optimal clinical dose
- Interim PoC readout expected late 2020

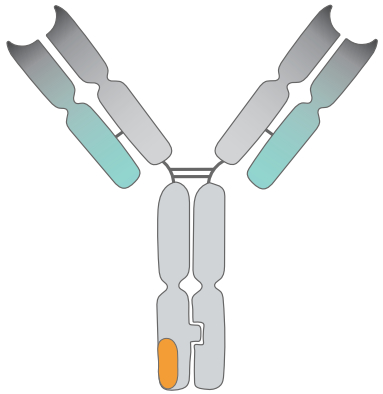
SUCCESS CRITERIA

- Safety: Well tolerated and safe at doses tested
- Biomarker: >50% reduction in CSF GAGs from baseline

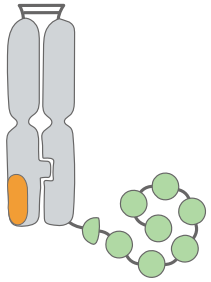
TV TECHNOLOGY: BROAD OPPORTUNITIES FOR PLATFORM EXPANSION



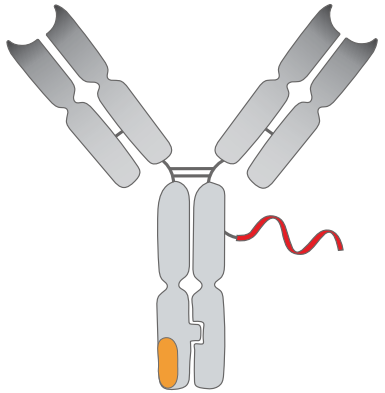
Enzyme Transport Vehicle (ETV)



Antibody Transport Vehicle (ATV)



Protein Transport Vehicle (PTV)



Oligonucleotide Transport Vehicle (OTV)

	Enzyme Transport Vehicle (ETV)	Antibody Transport Vehicle (ATV)	Protein Transport Vehicle (PTV)	Oligonucleotide Transport Vehicle (OTV)
CURRENT DENALI PROGRAMS	▪ **ETV:IDS** ▪ **ETV:SGSH** ▪ **ETV:LF1***	▪ **ATV:TREM2** ▪ **ATV:aSyn** ▪ **ATV:Tau** ▪ **ATV:CH1*** ▪ **ATV:OT1***	▪ **PTV:PGRN**	▪ **Platform validation**
POTENTIAL FUTURE APPLICATIONS	▪ Two-thirds of all lysosomal storage diseases have neuronopathic component	▪ Novel CNS targets ▪ Oncology targets ▪ Improved versions of existing antibodies (e.g. anti-Abeta, anti-HER2)	▪ Other protein targets	▪ IV delivered ASOs for CNS targets

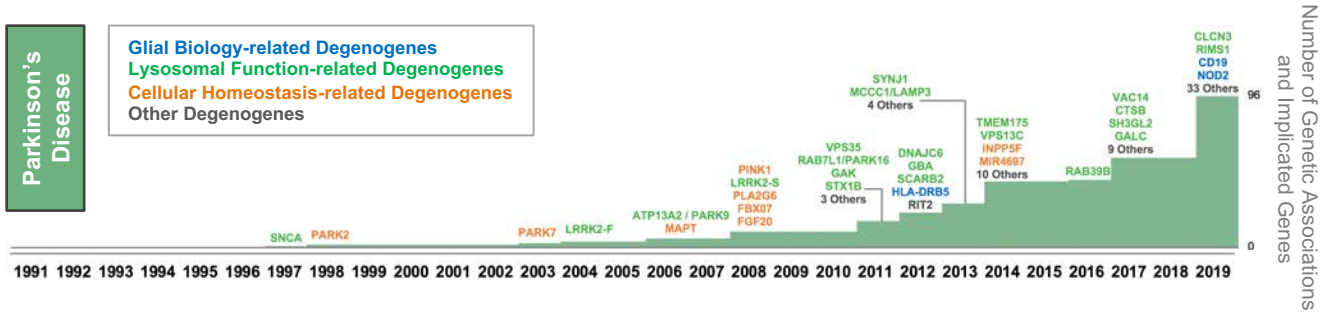
*Undisclosed program

LRRK2 PROGRAM

LRRK2 AS A THERAPEUTIC TARGET FOR PARKINSON'S DISEASE

BROAD THERAPEUTIC POTENTIAL

- Genetics indicate that lysosomal dysfunction is a central to PD



- Inhibition of LRRK2 may be a therapeutically beneficial approach for both genetic and idiopathic PD

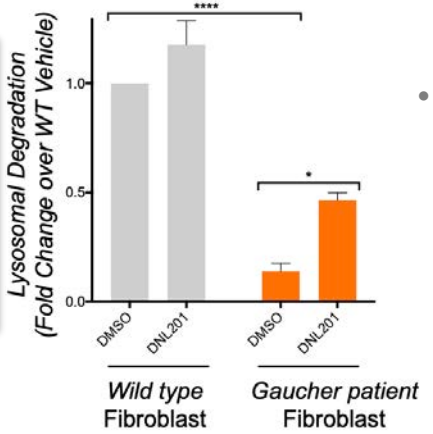
- **DNL201** and **DNL151** are clinical-stage LRRK2 inhibitors that target both wild-type and mutant forms of LRRK2 with therapeutic potential to treat LRRK2 and other drivers of lysosomal dysfunction


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

LRRK2 activation in idiopathic Parkinson's disease

Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa G. Hastings[1,2], J. Timothy Greenamyre[1,2,7]*



DE-RISKED TARGET

- Human LRRK2 LOF mutants do not have functional consequences (Whiffin et al, *Nature Med* 2020)


nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0893-5

Check for updates

OPEN

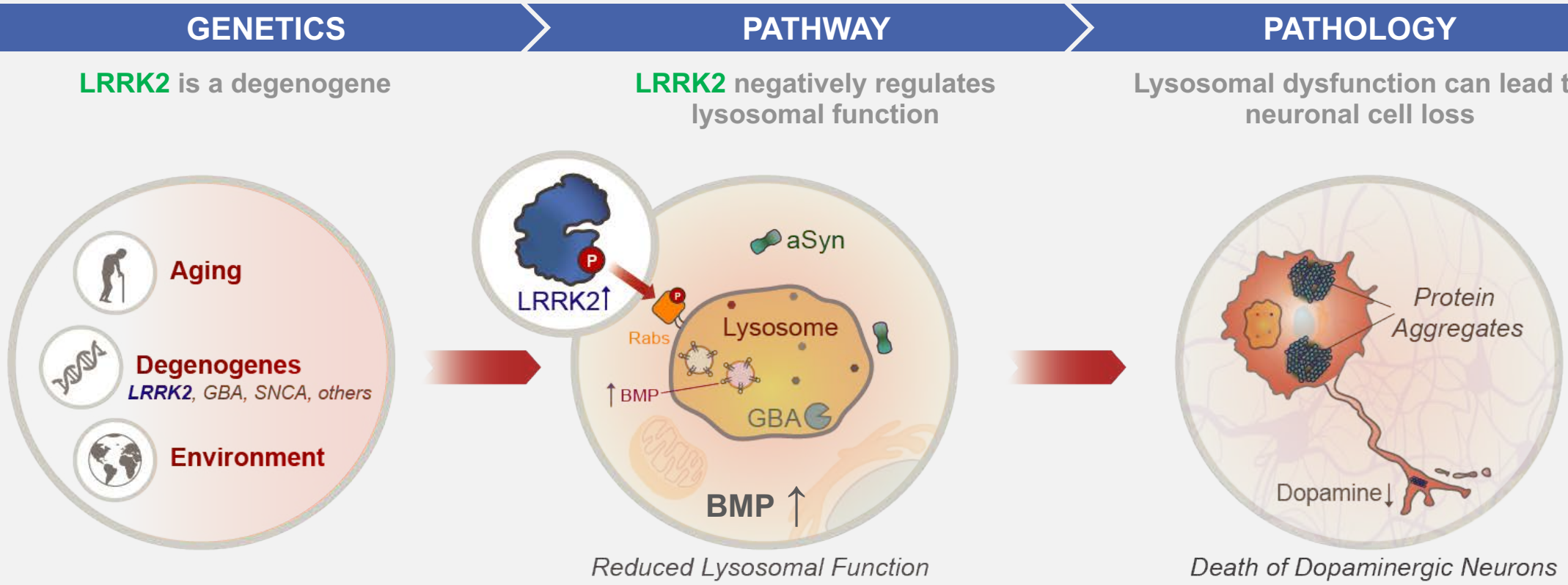
The effect of LRRK2 loss-of-function variants in humans

- Nine month chronic dosing in nonhuman primates with **DNL201** did not demonstrate effects on pulmonary function

- Pulmonary function is unaffected in nonhuman primates following following LRRK2 inhibition (Baptista et al, *STM* 2020)

- Denali clinical data with **DNL201** and **DNL151** supports tolerability of >70% inhibition at trough for 28 days in healthy volunteers and patients

INHIBITING LRRK2 RESCUES LYSOSOMAL DYSFUNCTION AND DOWNSTREAM NEURONAL DEGENERATION



Human genetic variants link **LRRK2** to familial Parkinson's and **sporadic Parkinson's disease risk**

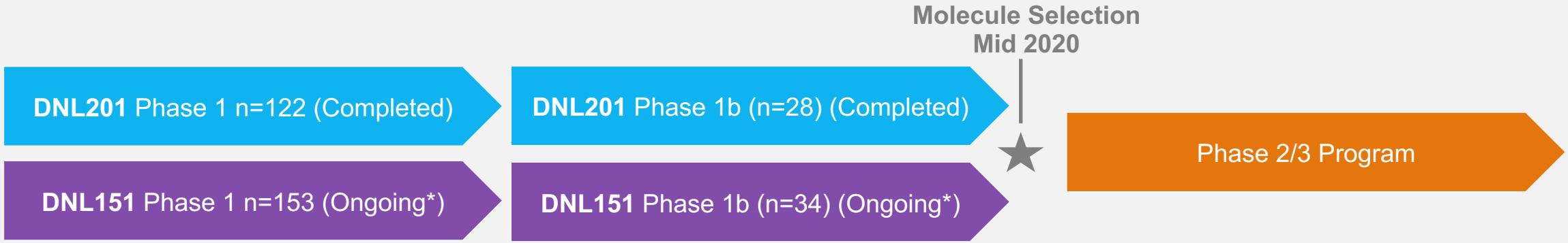
Region-specific **LRRK2** activation corresponds to lysosomal dysfunction in **sporadic Parkinson's disease**

LRRK2 inhibition is a potential therapeutic approach in both LRRK2-mutant and sporadic PD

DENALI LRRK2 PROGRAM AND DEVELOPMENT STRATEGY

PARALLEL EARLY CLINICAL DEVELOPMENT WITH TWO LRRK2 INHIBITORS (DNL201 AND DNL151)

- Most advanced LRRK2 program in clinical development
- Advanced two chemically distinct molecules through extensive Phase 1 and Phase 1b program (n >300)
  - DNL201 completed Phase 1 and Phase 1b
  - DNL151 has interim Phase 1 data; Phase 1b data expected in mid 2020
- Goal is to select the best molecule for Phase 2/3 program based on all clinical data
  - Safety, PK properties, target engagement, improvement in lysosomal biomarkers



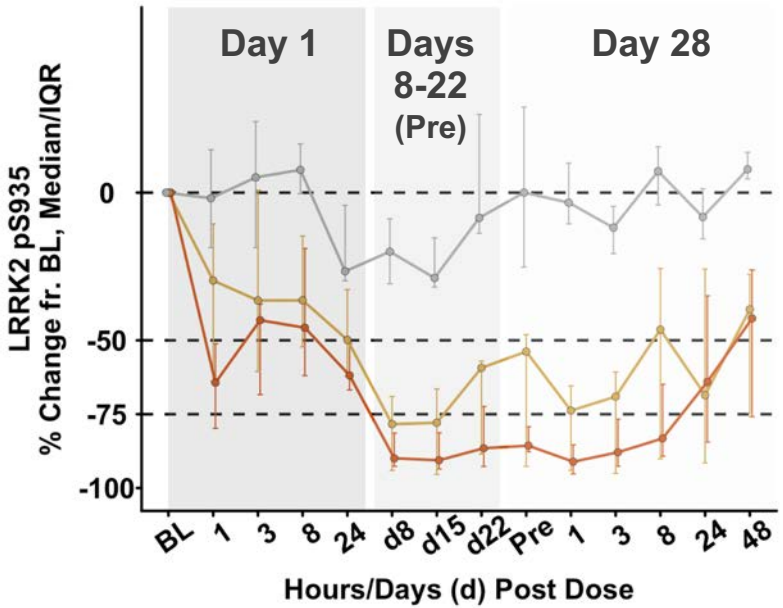
* Protocol amended to add higher dose cohorts for both DNL151 Ph 1 and Ph 1b studies

Expect to select DNL201 or DNL151 for Phase 2/3 program in mid 2020

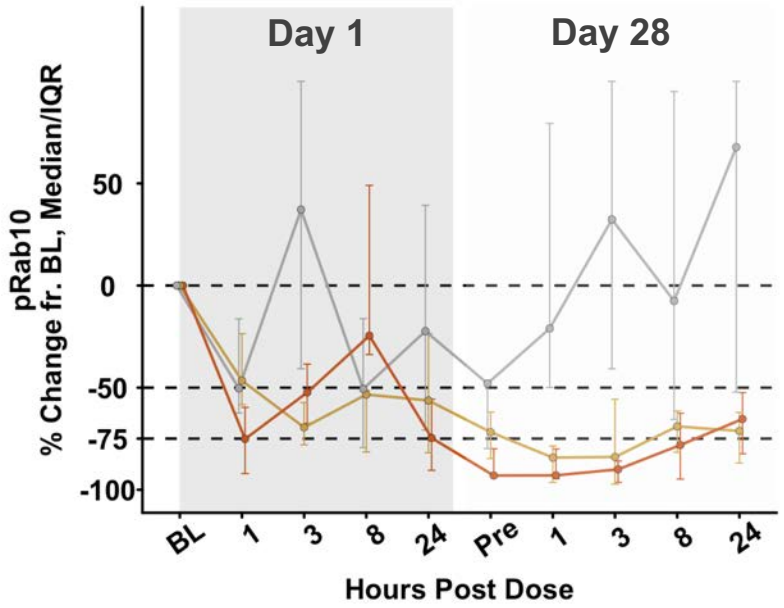
DNL201 PHASE 1B IN PATIENTS MET ALL BIOMARKER GOALS

DNL201 TID
Placebo (PBO) Low Dose High Dose **BL** = Baseline **Pre** = Pre-dose

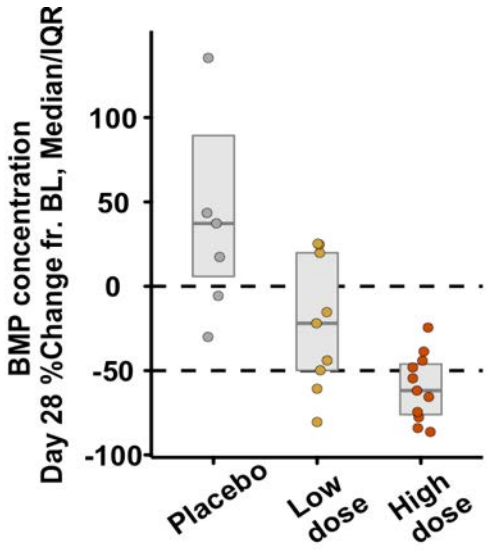
Target Engagement
Reduction of pS935 LRRK2 (Whole blood)



Pathway Engagement
Reduction of pRAB10 (PBMCs)



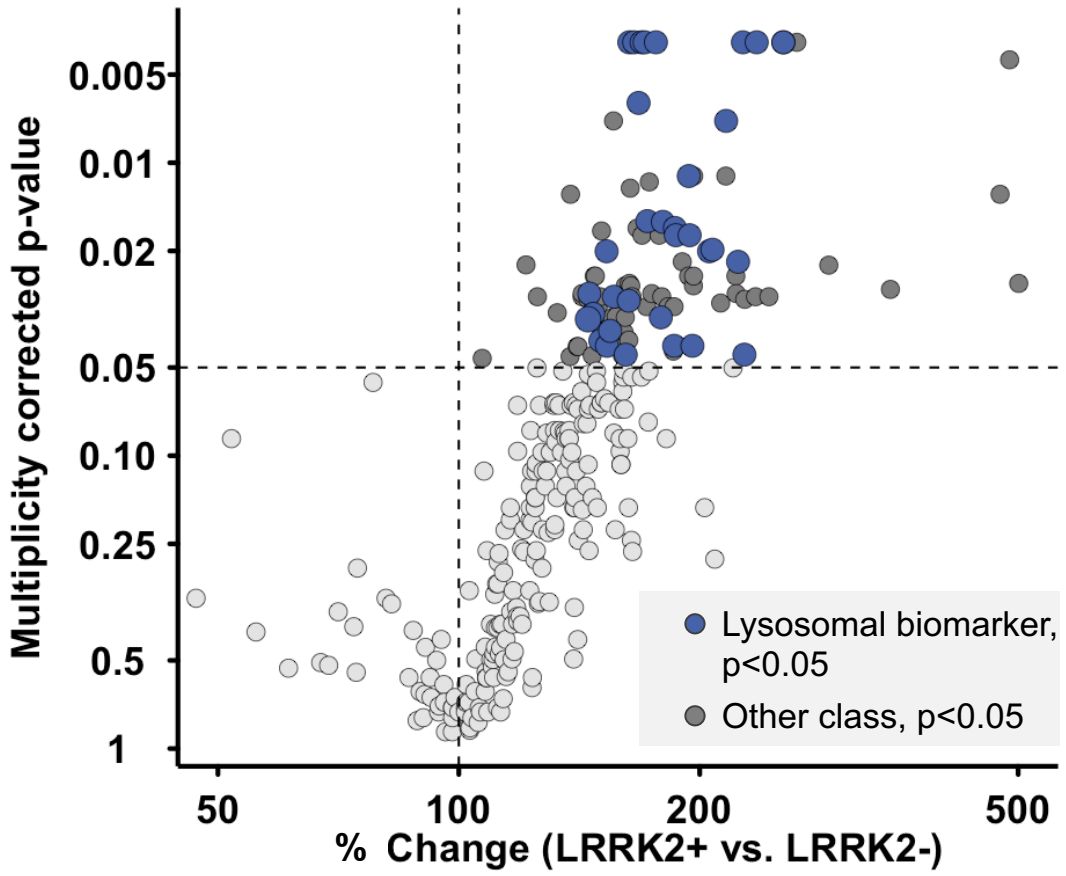
Lysosomal Function
Reduction of BMP (Urine)



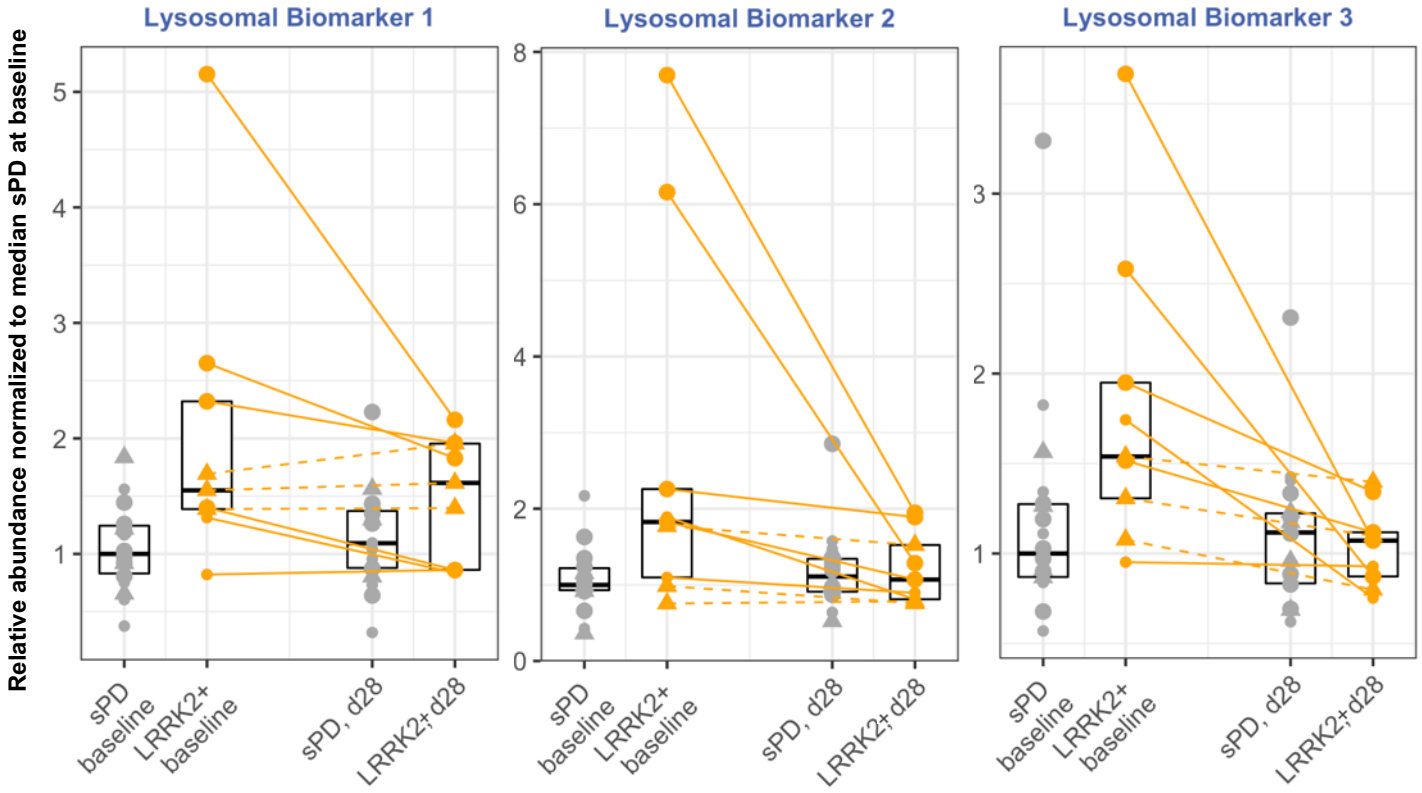
DNL201 demonstrates strong LRRK2 inhibition and improvement in lysosomal biomarkers

DNL201 PHASE 1B: POTENTIAL CORRECTION OF ELEVATED LYSOSOMAL BIOMARKERS DRIVEN BY LRRK2 MUTATION

Metabolic Profiling Accumulation of CSF Lysosomal Biomarkers in LRRK2 Carrier



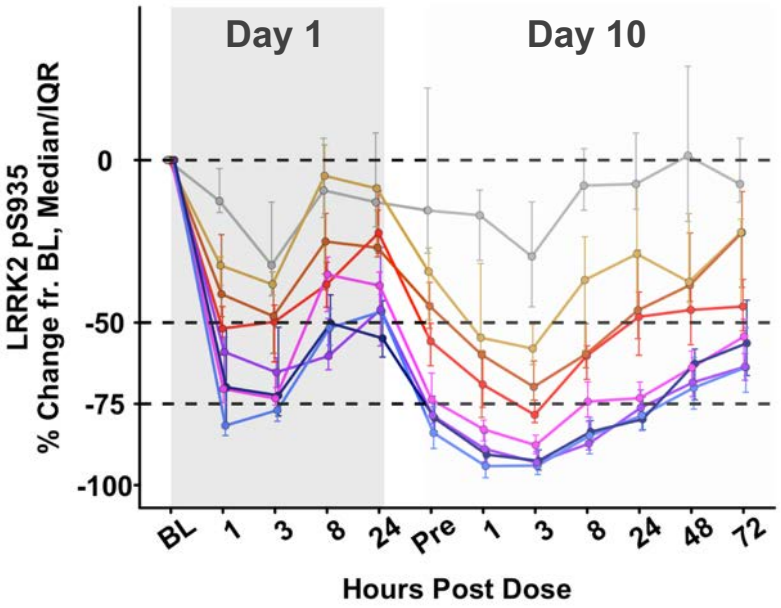
LRRK2 Inhibition Reduces Elevated Lysosomal Biomarkers in CSF of LRRK2 G2019S Carriers



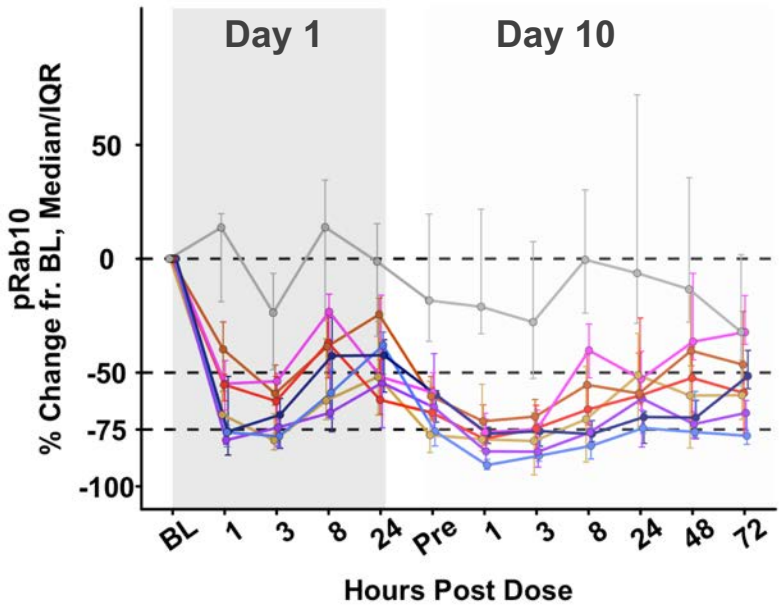
DNL151 PHASE 1 IN HV MET ALL BIOMARKER GOALS

DNL151 QD
Placebo (PBO) · Dose A · Dose B · Dose C · Dose D · Dose E · Dose F · Dose G
BL = Baseline **Pre** = Pre-dose

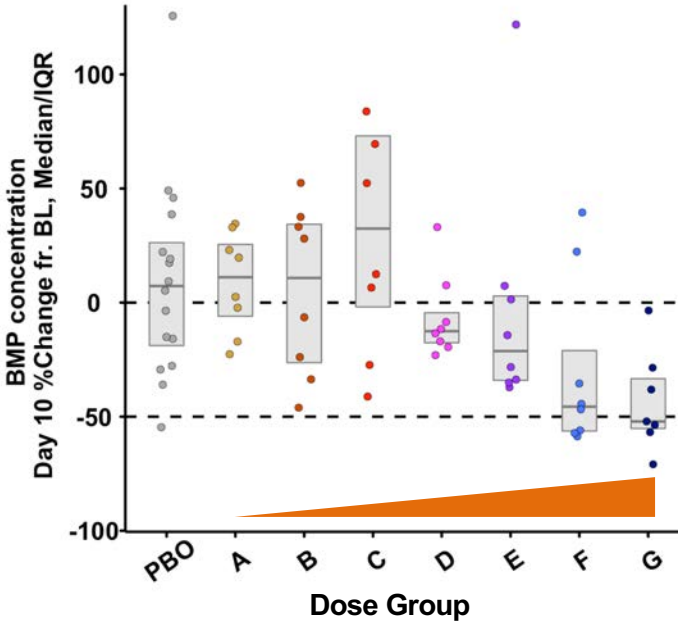
Target Engagement
Reduction of pS935 LRRK2 (Whole blood)



Pathway Engagement
Reduction of pRAB10 (PBMCs)



Lysosomal Function
Reduction of BMP (Urine)



DNL151 demonstrates strong LRRK2 inhibition and modulation of lysosomal biomarkers

% inhibition measured for the 28 Day safety cohort (Group H, not shown) was similar to the equivalent 10-day dose group (group F)

SAFETY SUMMARY TO DATE

DNL201

Phase 1

- Generally well tolerated, data presented (MJFF Oct 2018)

Phase 1b

- **Low dose** generally well tolerated
  - Most common AEs (all mild except one) were headache and nausea
  - One SAE, Legionella pneumonia, considered unrelated to study drug
- **High dose** had a higher incidence of moderate adverse events
  - One severe headache leading to dose reduction
  - One early withdrawal preceded by nausea and headache
- Across study, all treatment-related AEs were manageable and reversible
- No dose dependent effects on pulmonary function
- No dose dependent effects on supine or standing vital signs, except for increase in standing HR in 2 subject in HD
- Trend toward mild increase in creatinine (within normal range)

DNL151

Phase 1 (Ongoing)

- Generally well tolerated
- Majority of AEs were mild, no SAEs, no discontinuations related to active drug, no severe AEs
- Protocol amended to explore safety profile in higher dose cohorts

Phase 1b (Ongoing)

- No SAEs to date
- Protocol amended to add higher dose cohort

Both molecules show acceptable safety profiles to advance to Phase 2/3

LRRK2 CLINICAL PROGRAM: SUMMARY AND NEXT STEPS

SUMMARY

- Achieved **target engagement and biomarker goals** supporting the hypothesis that LRRK2 inhibition modulates and improves lysosomal function in Parkinson's disease
- Both molecules to date show acceptable safety profiles to **advance to Phase 2/3**

NEXT STEPS

- Make **selection between DNL151 or DNL201** for next stage of clinical development based on full data sets from both molecules (safety, target engagement, improvement of lysosomal biomarkers)

DNL201: Complete biomarker analysis of Ph 1b;
Develop slow release formulation to support BID dosing

DNL151: Evaluate DNL151 at higher doses in the Ph 1 HV study and Ph 1b Parkinson's disease studies

- Actively establishing a global network for **patient enrollment**:

CENTOGENE · ENGAGE PARKINSON'S · NATIONAL PARKINSON FOUNDATION® A division of the Parkinson's Foundation · FOX TRIAL FINDER THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH · PARKINSON'S UK CHANGE ATTITUDES. FIND A CURE. JOIN US.

OUR 2020 CLINICAL PIPELINE DELIVERABLES

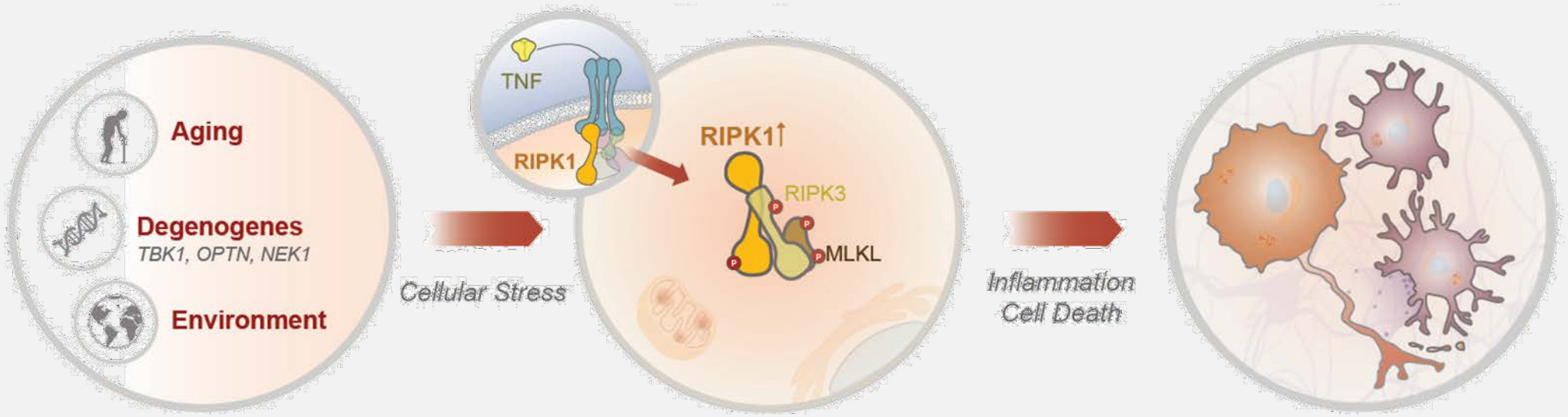
	2020 Plans	Expected Timing
LRRK2 Parkinson's	▪ Select molecule and prepare for Phase 2/3	▪ Mid 2020
ETV:IDS Hunter syndrome	▪ Establish biomarker proof-of-concept in patients	▪ Late 2020
EIF2B ALS	▪ DNL343 Phase 1 in HV results to potentially enable patient study (COVID delay)	▪ Late 2020
RIPK1 ALS, Alzheimer's	▪ Results from DNL747 ALS and Alzheimer's studies to potentially enable progression	▪ Mid 2020
BBB Platform	▪ Establish TV Platform PoC in humans (ETV:IDS) ▪ Initiate IND-enabling studies for additional programs	▪ Late 2020


THANK YOU

RIPK1 PROGRAM

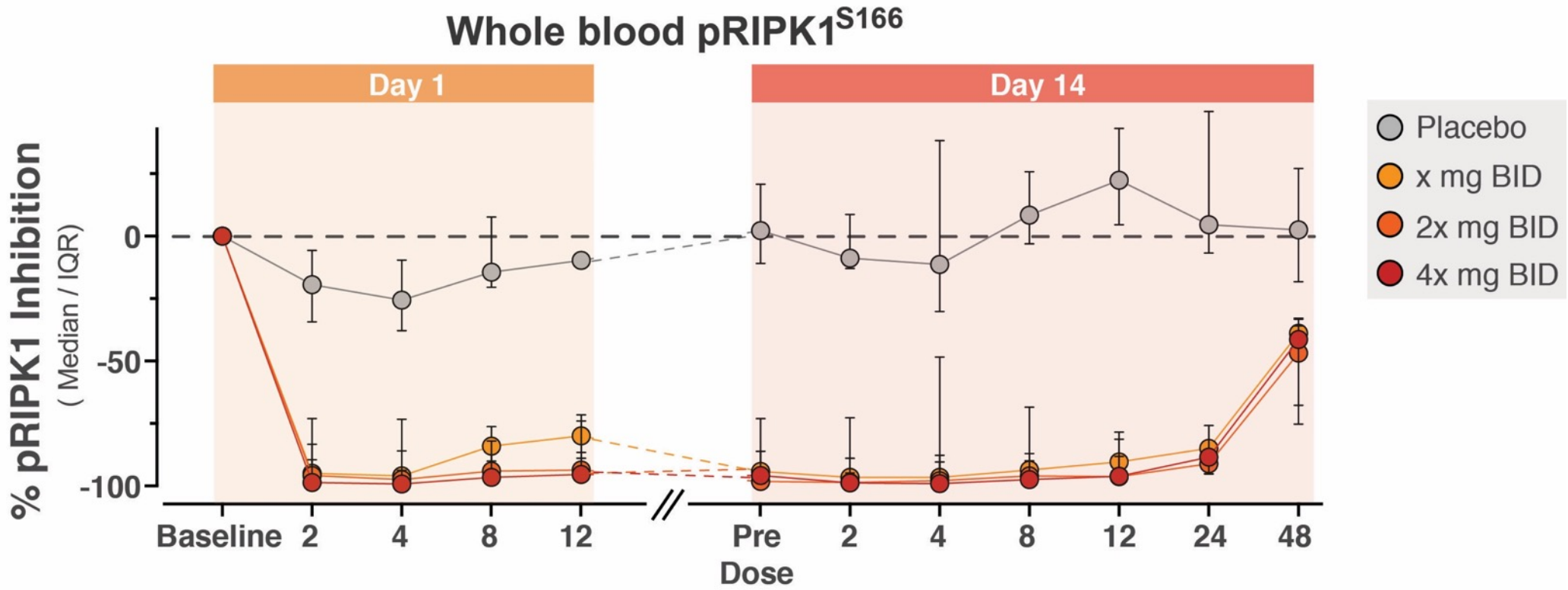
RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS

GENETICS	PATHWAY	PATHOLOGY
ALS and Alzheimer's degenogenes point to microglial dysfunction as a driver of disease	RIPK1 activation can lead to microglial dysfunction	Microglial dysfunction can lead to Inflammation and necroptosis brain cells



RIPK1 inhibition enables selective modulation of the TNFR1 pathway, reducing inflammation and necroptosis in the brain

RIPK1 INHIBITOR DNL747 DEMONSTRATES DOSE-DEPENDENT INHIBITION IN HEALTHY SUBJECTS



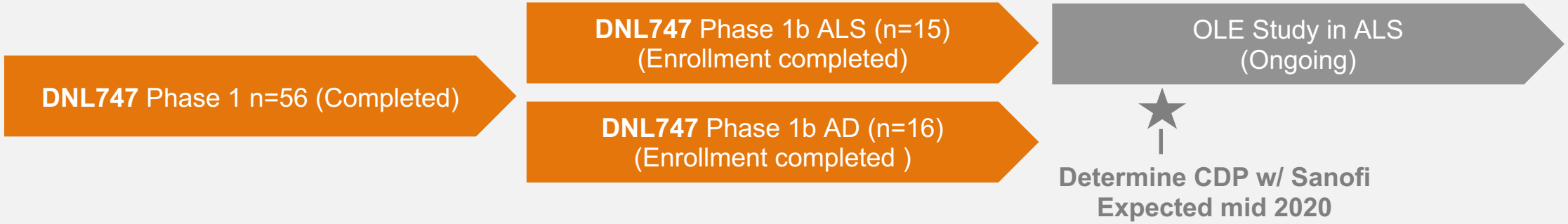
Time course of RIPK1 pS166 inhibition after DNL747 administration every 12 hours until day 14

Data from DNL747 Phase 1 in HV met all biomarker goals

DENALI RIPK1 PROGRAM AND DEVELOPMENT STRATEGY

BROAD EARLY CLINICAL DEVELOPMENT PROGRAM

- Partnered with Sanofi for development of RIPK1 inhibitors in CNS indications and peripheral inflammatory indications
  - Denali and Sanofi jointly develop CNS program (DNL747), Sanofi leads peripheral program (DNL758)
- DNL747 completed enrollment of Phase 1b programs in ALS and AD and initiated OLE study for ALS in 2019
  - Decision on future studies based on data from Phase 1 HV study, Phase 1b studies, OLE in ALS and ongoing chronic toxicology studies in mid 2020
- DNL758 is in Phase 1 study led by Sanofi



Determine clinical development plan for RIPK1 program with Sanofi expected in mid 2020


DENALI
EIF2B PROGRAM

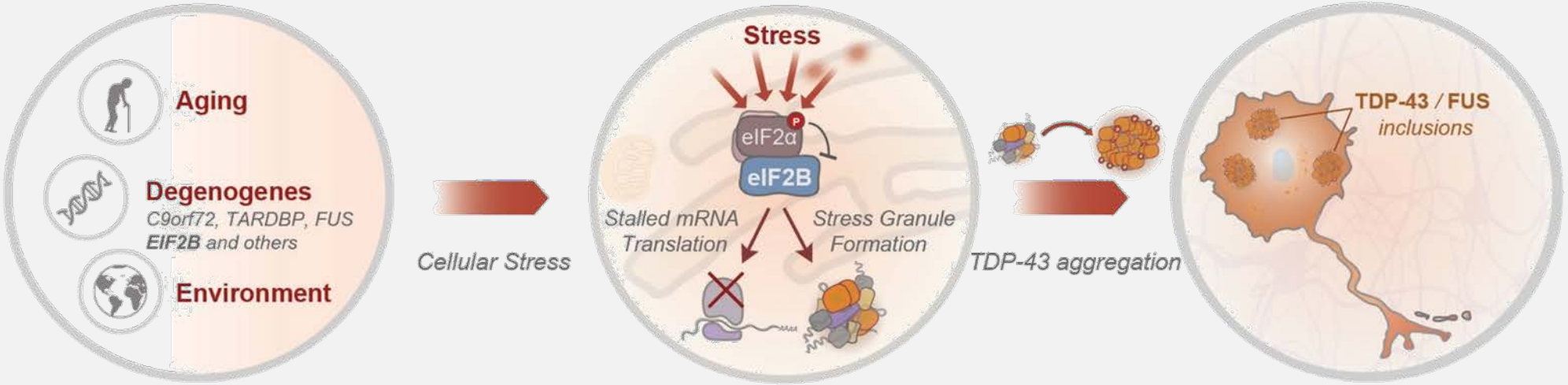
ACTIVATING EIF2B CAN DISSOLVE CELLULAR STRESS GRANULES WHICH ARE CAUSED BY THE INTEGRATED STRESS RESPONSE

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

Degenogenes, including EIF2B, cause an integrated stress response (ISR)

ISR leads to aggregation of RNA-binding proteins (e.g. TDP-43) into stress granules and harmful aggregates

These harmful aggregates trigger neurodegeneration



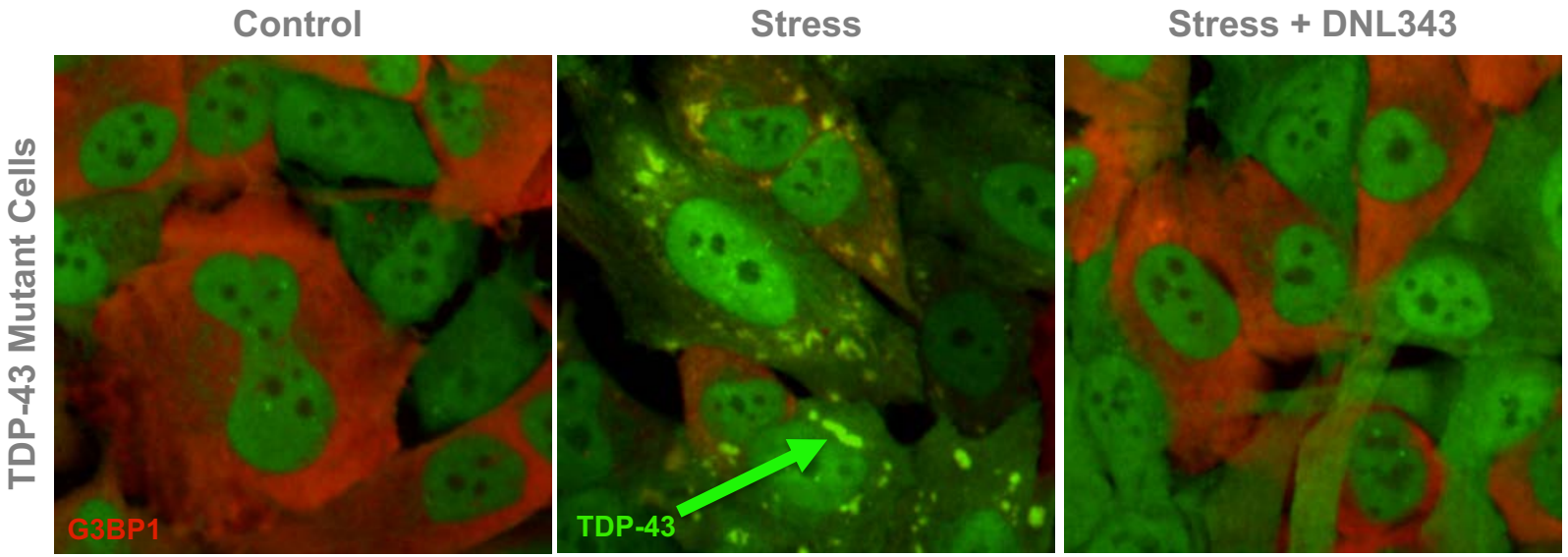
Integrated Stress Response (ISR)

Neuronal Loss (ALS / FTD)

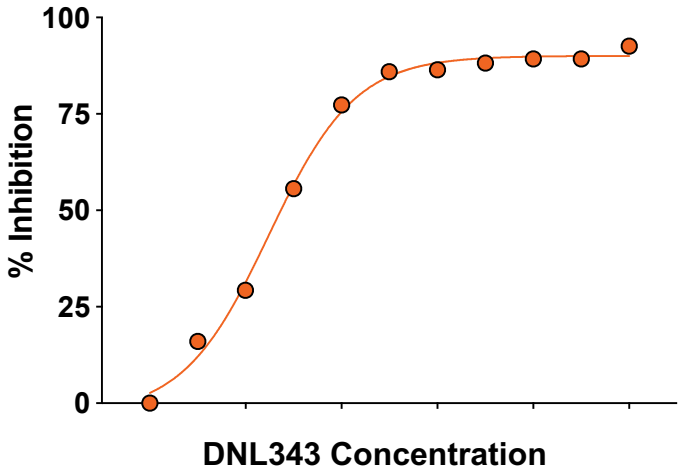
Activating EIF2B can inhibit the ISR pathway and prevent and reverse the formation of stress granules associated with disease

DNL343 TREATMENT CAN REVERSE TDP-43 AGGREGATION

EIF2B activator DNL343 reverses TDP-43 inclusions



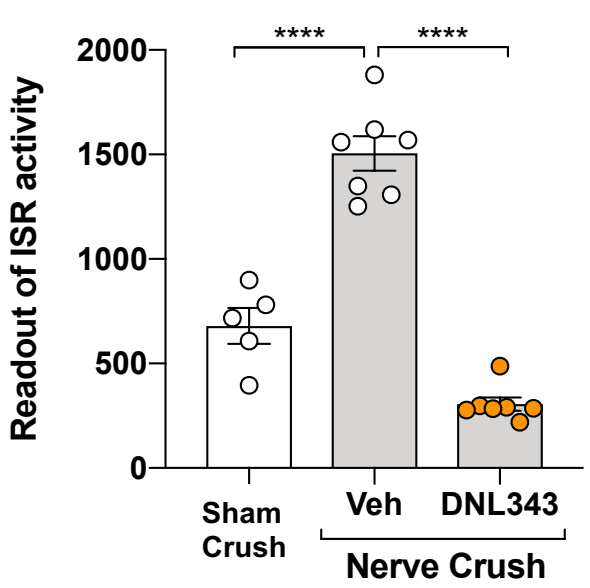
DNL343 Inhibition Curve

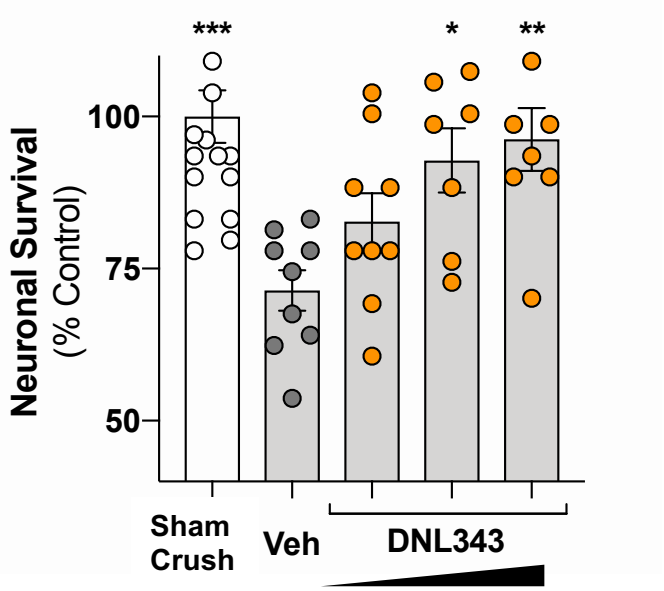


- DNL343 potently blocks the ISR through activation of EIF2B
- DNL343 dissolves stress-induced RNA binding protein aggregates, including TDP-43 mutant proteins
- DNL343 demonstrates increased inhibition of biomarker linked to stress granule formation

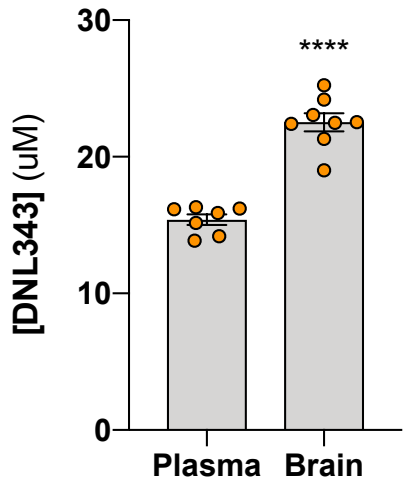
DNL343 REDUCES ISR IN MULTIPLE PRECLINICAL NEURODEGENERATION MODELS

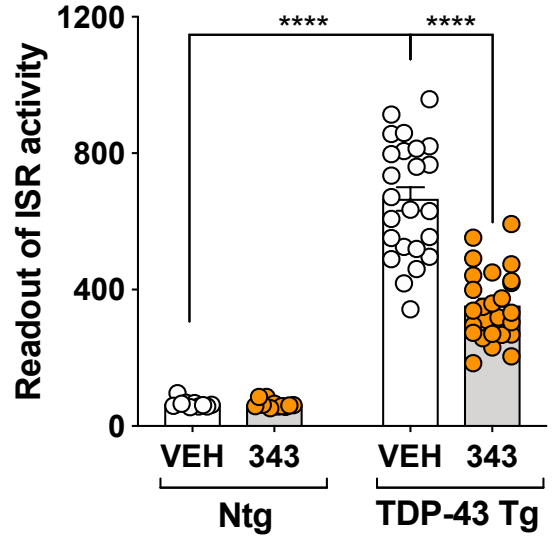
DNL343 reduces ISR activation & prevents neuronal degeneration after nerve crush injury





DNL343 is brain penetrant & reduces ISR activation in a TDP-43 mouse model





DNL343 is brain penetrant and displays robust target engagement and neuroprotection *in vivo*

EIF2B ACTIVATOR DNL343 HAS A PROMISING PRECLINICAL PROFILE

SAFETY

Non-GLP tox studies completed with DNL343
- Well tolerated at expected therapeutic doses
- Pancreatic toxicities associated with other ISR pathway inhibitors (i.e. PERK) not observed

PK

Excellent CNS penetration and PK profile in animal models

TARGET ENGAGEMENT

Robust pathway engagement and neuroprotection observed *in vivo*

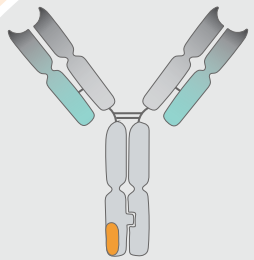
Phase 1 initiated in February 2020

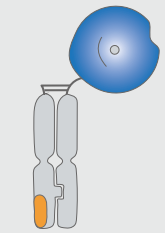
TV PLATFORM Appendix

MODALITY-BASED BRAIN DELIVERY PLATFORMS ENABLED BY TV

Antibody Transport Vehicle

- Deliver **antibodies** in bivalent or bispecific format to the brain
- Monovalent, optimized binding to the transferrin receptor (TfR)
- Natural IgG Fc structure
- Extensive target potential



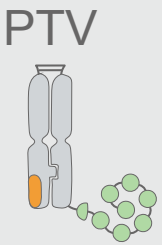


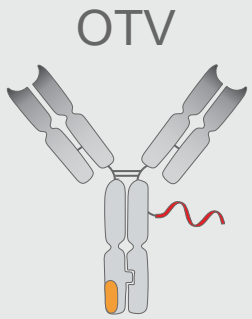
Enzyme Transport Vehicle

- Deliver **enzymes** to the brain
- Monovalent, optimized binding to the TfR
- Wide range of neuronopathic lysosomal storage diseases

Protein Transport Vehicle

- Deliver **proteins** to the brain
- Potential to replace or augment function of extensive target proteins





Oligonucleotide Transport Vehicle

- Deliver **oligonucleotides** to the brain
- Protein knockdown with ASO or siRNA
- Extensive target potential

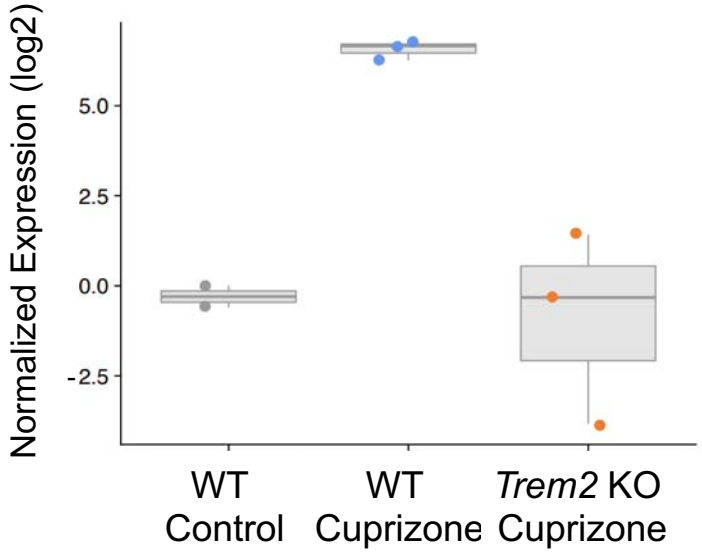
ATV:TREM2 IMPROVES MICROGLIAL FUNCTION

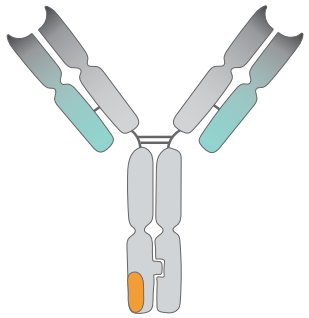
Neuron
Article
CellPress

TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge

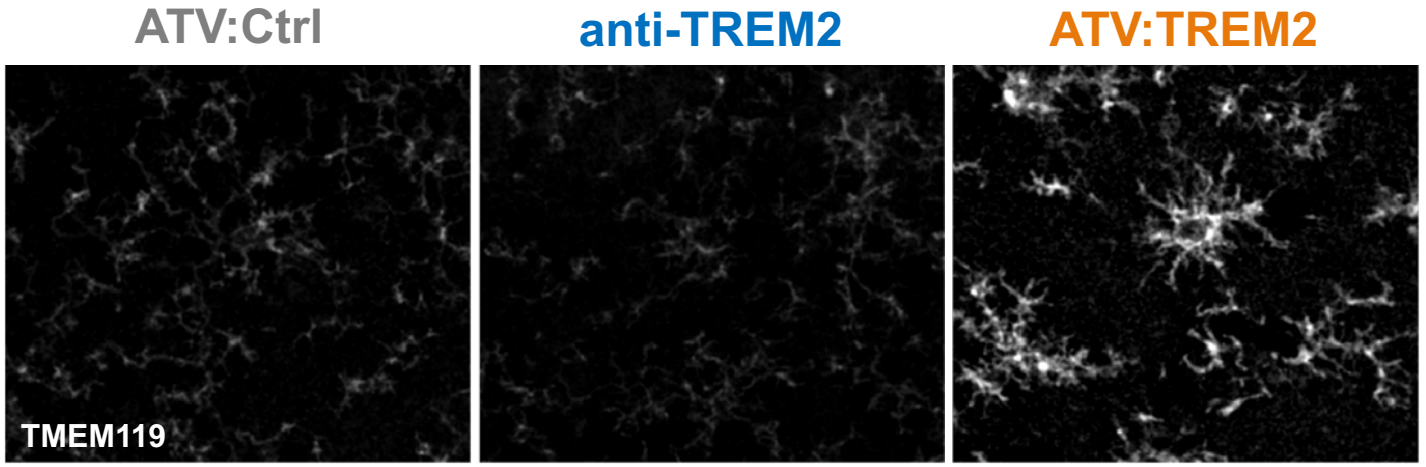
Alicia A. Nugent,[1,2] Karin Lin,[1,2] Bettina van Lengerich,[1] Steve Lianoglou,[1] Laralynne Przybyla,[1] Sonnet S. Davis,[1] Ceyda Llapashtica,[1] Junhua Wang,[1] Do Jin Kim,[1] Dan Xia,[1] Anthony Lucas,[1] Sulochanadevi Baskaran,[1,3] Patrick C.G. Haddick,[1] Melina Lenser,[1] Timothy K. Earr,[1] Ju Shi,[1,4] Jason C. Dugas,[1] Benjamin J. Andreone,[1] Todd Logan,[1] Hilda O. Solanoy,[1] Hang Chen,[1,5] Ankita Srivastava,[1] Suresh B. Poda,[1] Pascal E. Sanchez,[1] Ryan J. Watts,[1] Thomas Sandmann,[1] Giuseppe Astarita,[1] Joseph W. Lewcock,[1] Kathryn M. Monroe,[1,*] and Gilbert Di Paolo[1,6,*]
[1]Denali Therapeutics, South San Francisco, CA 94080, USA

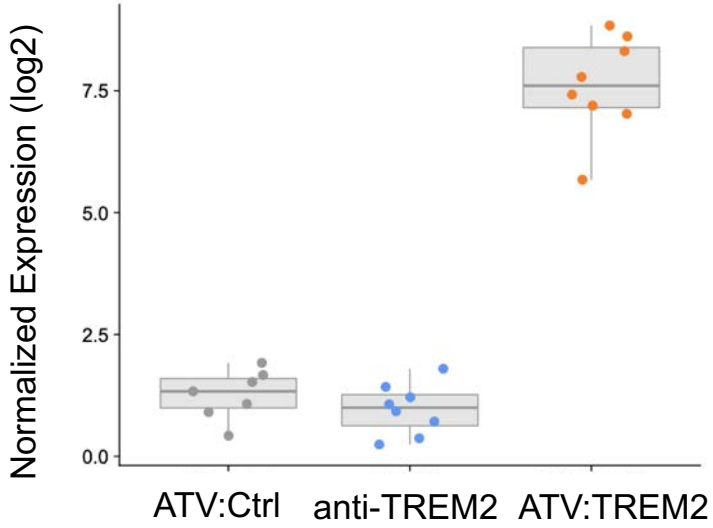
Microglial Gene Expression
Cholesterol Metabolism Enzyme





ATV:TREM2





TV technology can be applied to antibodies to enhance brain uptake and function

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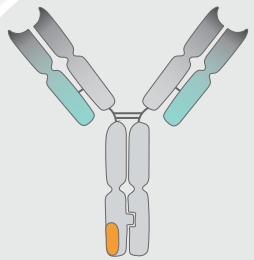

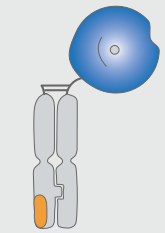

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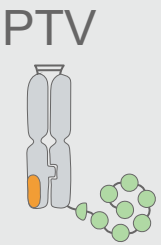

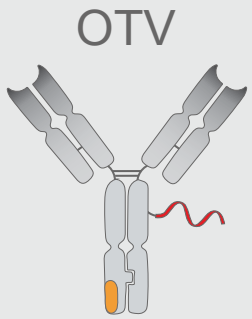

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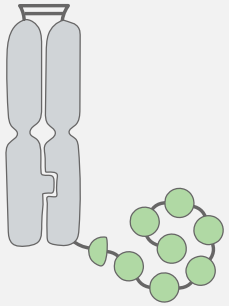
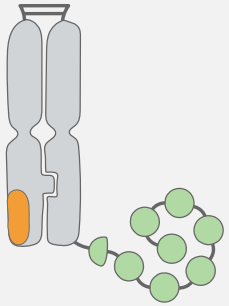
PTV:PGRN IMPROVES LYSOSOMAL FUNCTION IN BRAIN

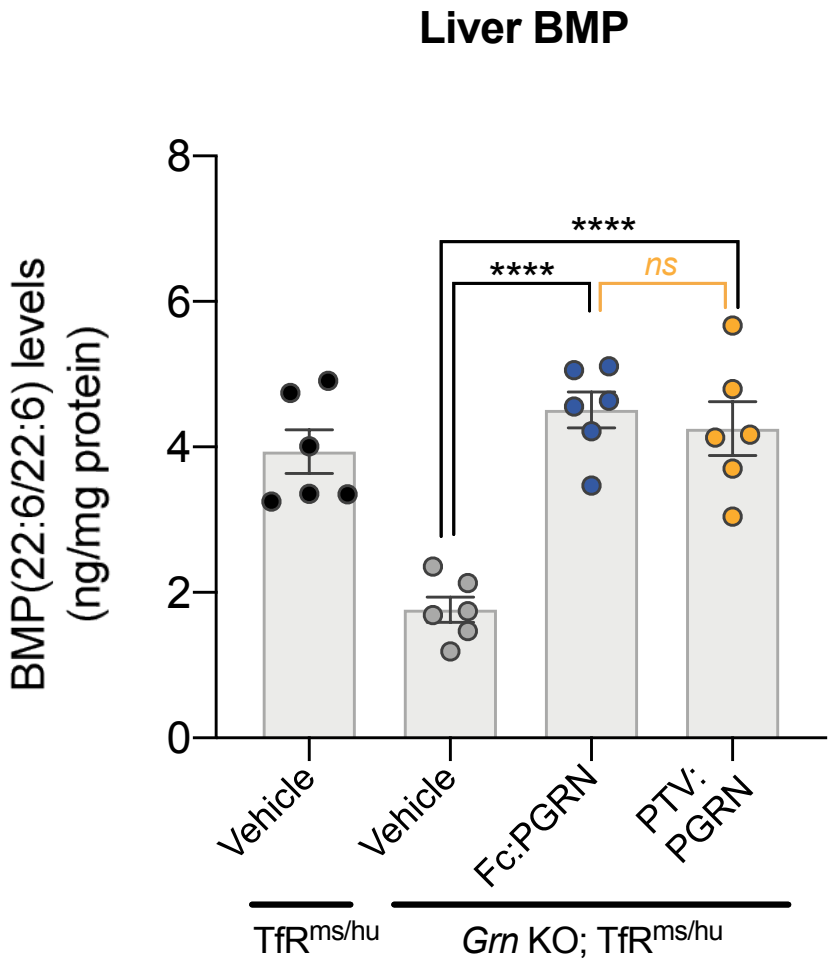
Progranulin (PGRN) Architectures

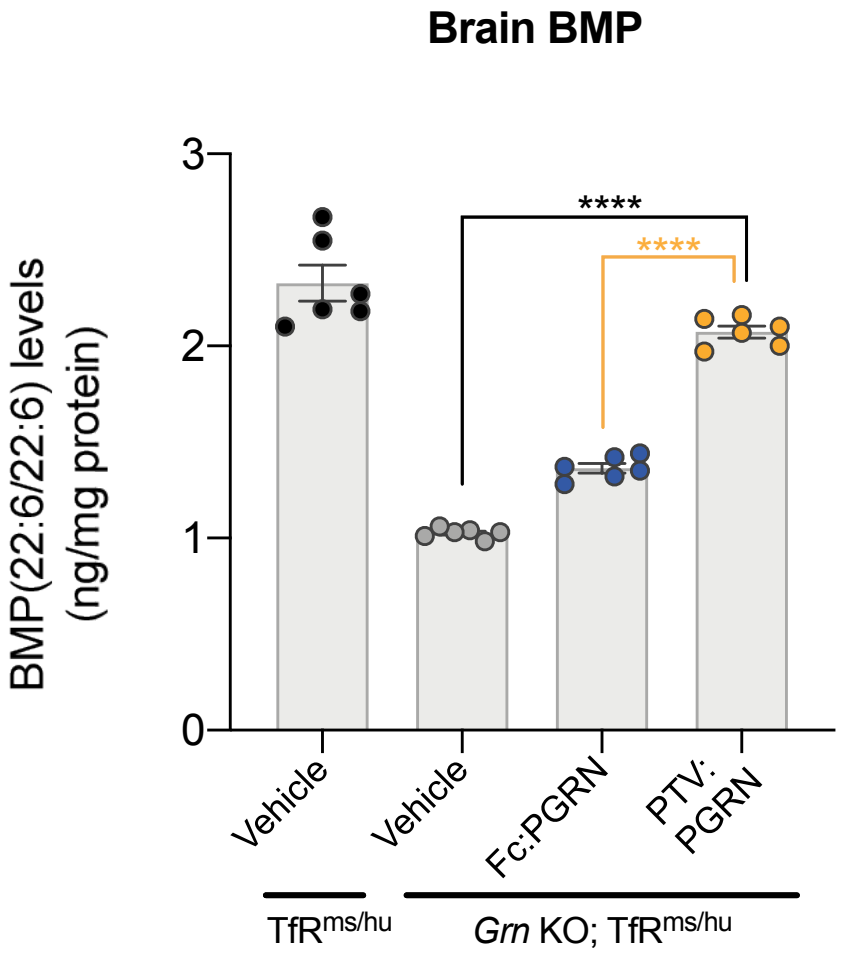


Fc:PGRN



PTV:PGRN



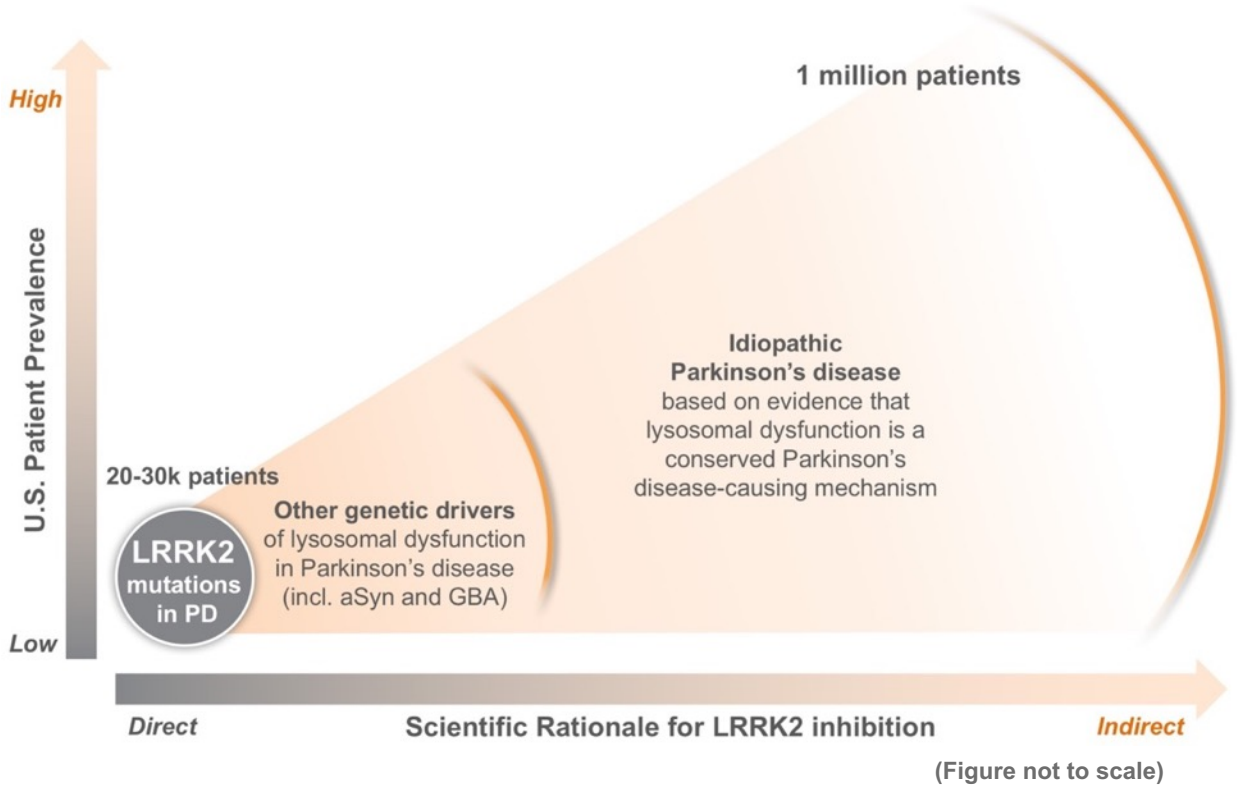


TV technology can effectively deliver other proteins to brain

*data shown as mean ± s.e.m.; **** p < 0.0001*
One-way ANOVA, Sidak's multiple comparison correction

LRRK2 Appendix

LRRK2 INHIBITION MAY HAVE BROAD THERAPEUTIC POTENTIAL FOR PD



(Figure not to scale)

EMERGING EVIDENCE LINKS LRRK2 BROADLY TO PD

- Variants in lysosomal genes are associated with PD risk
- Variant in LRRK2 identified that reduces PD risk
- LRRK2 activity is increased in sporadic PD

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

LRRK2 activation in idiopathic Parkinson's disease

Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa G. Hastings[1,2], J. Timothy Greenamyre[1,2,7]*

- Lysosomal dysfunction is a central pathophysiology of PD in patients with and without known genetic drivers of PD
- Inhibition of LRRK2 may be a therapeutically beneficial approach for many forms of PD, including idiopathic PD