
DENALI™
Discover, Develop, Defeat Degeneration
June 2018

Disclaimers

Forward Looking Statements

This presentation contains forward-looking statements. 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"), business strategy, business plans, product candidates, planned preclinical studies and clinical trials, expectations regarding the timing of results of such studies and trials, planned regulatory filings, 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. 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, risks related to: Denali's early stages of clinical drug development; Denali's ability to complete the development of, and if approved, commercialization of its product candidates; Denali's dependence on successful development of its BBB platform technology, product candidates currently in its core program and biomarker strategy; expectations and potential benefits of strategic collaboration agreements and Denali's ability to attract collaborators with development, regulatory and commercialization expertise; Denali's ability to conduct or complete clinical trials on expected timelines; the uncertainty that any of Denali's product candidates will receive regulatory approval necessary to be commercialized; Denali's ability to obtain and maintain regulatory approval of its product candidates, and any related restrictions, limitations and/or warnings in the label of any approved product candidate; Denali's ability to continue to create a pipeline of product candidates and develop commercially successful products; Denali's ability to obtain, maintain, or protect intellectual property rights related to its product candidates and BBB platform technology; implementation of Denali's strategic plans for its business, product candidates and BBB platform technology; Denali's ability to obtain funding for its operations, including funding necessary to develop and commercialize its product candidates; and other risks. In light of these risks, uncertainties and assumptions, the forward-looking statements and events discussed in this presentation 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 Report on Form 10-K filed with the SEC on March 19, 2018, Denali's Quarterly Report on Form 10-Q filed with the SEC on May 11, 2018 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.

SUMMARY

Neurodegeneration

ONE OF THE BIGGEST UNMET MEDICAL NEEDS OF OUR TIME

- Alzheimer's, Parkinson's, ALS and other neurodegenerative diseases affect millions
- Few effective therapeutic options currently available

Time is Right

SCIENCE IS BREAKING OPEN

- Degenogenes enhance our understanding of disease biology and pathways
- Biomarkers enable identification of patients with the relevant disease biology

Our Approach

PRINCIPLES AND PARTNERSHIPS

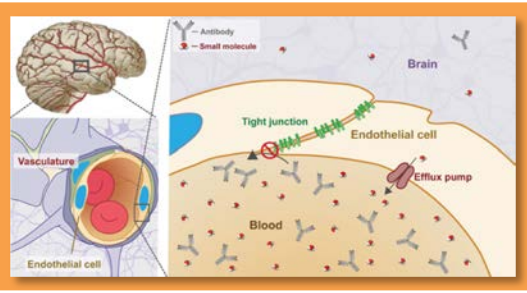
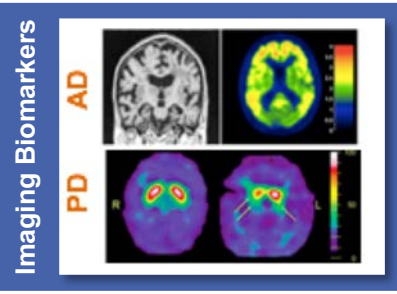
- Driven by three principles to increase probability of success
- Strategic collaborations to build, develop and commercialize broad portfolio

Our Pipeline

DIVERSIFIED AND DEEP EFFORT

- 8 core programs + 5 seed programs + discovery programs
- BBB platform technology to improve delivery of large molecules to brain
- 2018: Human target engagement for 2 programs, initiate patient studies

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

	Our Approach		Rationale
Genetic Pathway Potential	• Human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Targeted patient population • Target & pathway engagement		• The right patients • The right molecule • The right dose

Broad Portfolio | **Parallel Investment (lead and back-ups)** | **Strategic Partnering**

INCREASED PROBABILITY OF SUCCESS

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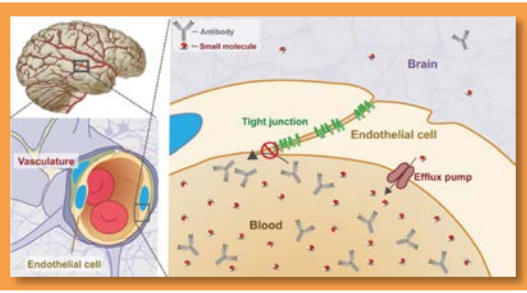
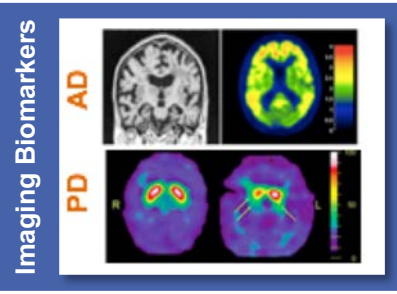
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Targeted patient population • Target & pathway engagement		• The right patients • The right molecule • The right dose

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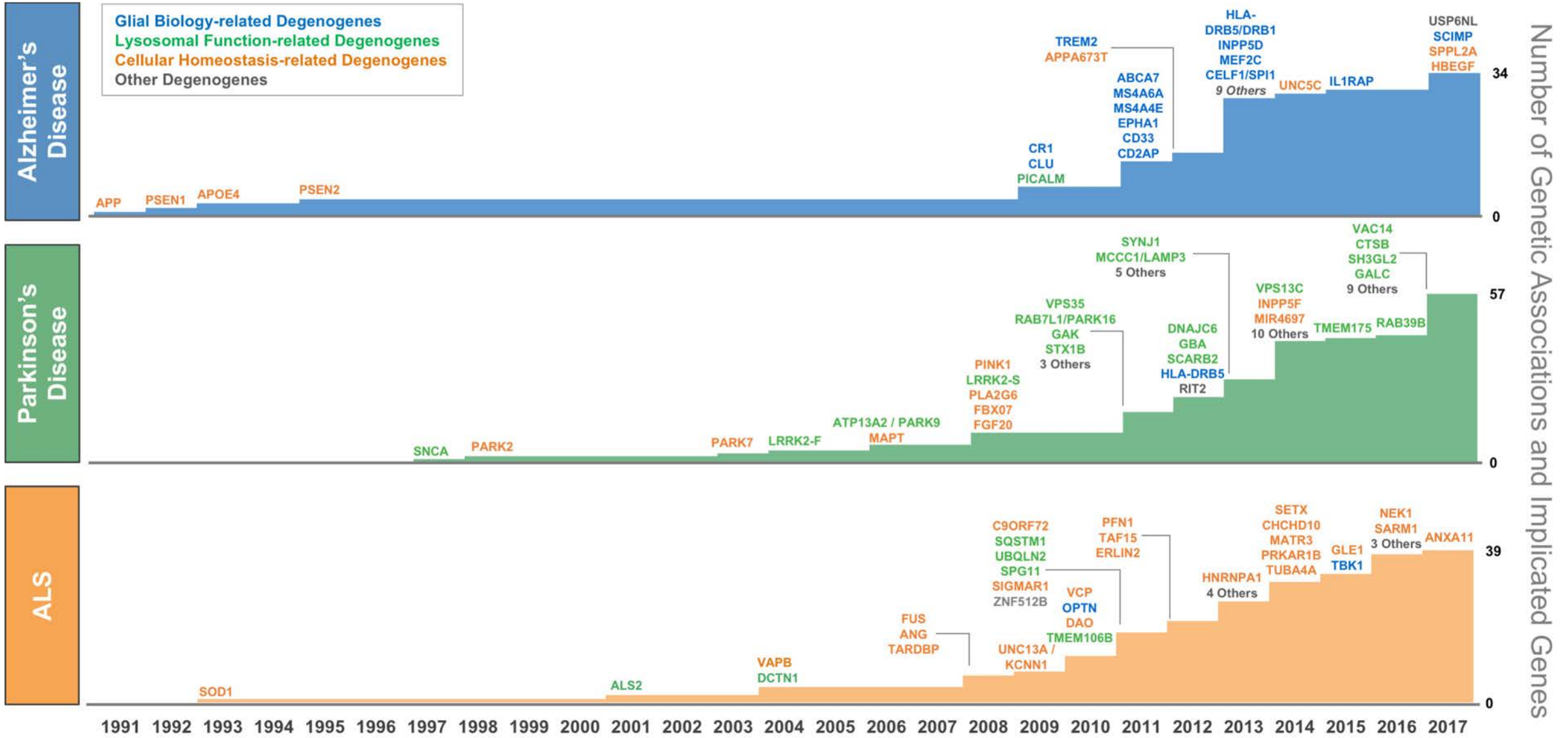
INCREASED PROBABILITY OF SUCCESS

DEGENOGENES DEFINE NEURODEGENERATION BIOLOGY

NEW GENETIC INSIGHTS IN ALZHEIMER'S, PARKINSON'S AND ALS



GENETIC PATHWAY POTENTIAL: BUILDING DEEP SCIENTIFIC INSIGHT

Indications

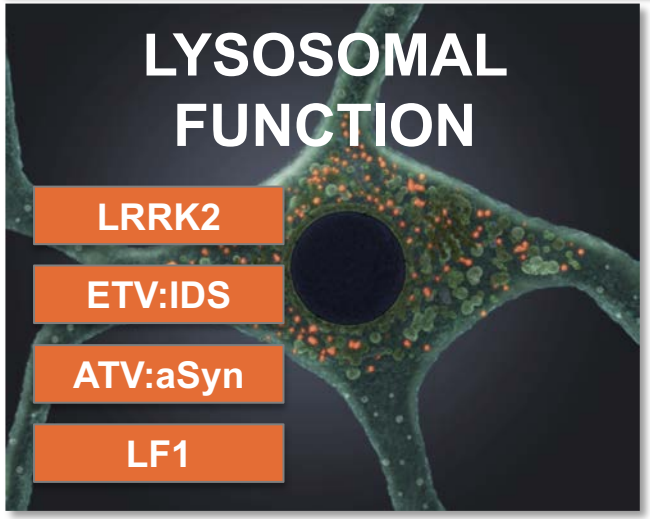
- Alzheimer's disease
- Parkinson's disease
- Amyotrophic Lateral Sclerosis
- Lysosomal Storage Diseases
- Huntington's disease
- Frontotemporal Dementia
- Multiple System Atrophy
- Other Diseases

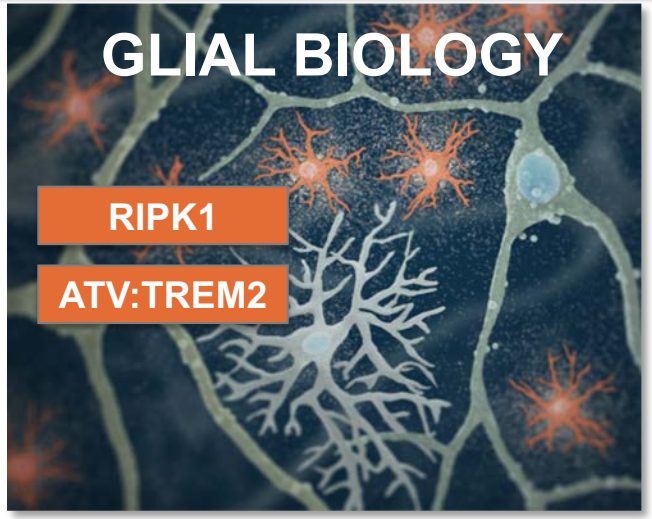
Human Genetics

CORE (8)

SEED (5)

Pathways





DENALI PORTFOLIO JUNE 2018

PROGRAM TARGET	DRUG CANDIDATE	THERAPEUTIC MODALITY	DISEASE INDICATION	DRUG DEVELOPMENT				BIOMARKER		PARTNERSHIP
				LEAD FINDING	LEAD OP	PRECLINICAL	PH 1	P	C	
LYSOSOMAL FUNCTION PATHWAY										
LRRK2	DNL201	Small Molecule	Parkinson's Disease					✓	✓	
	DNL151	Small Molecule	Parkinson's Disease					✓	✓	
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's Disease, DLB, MSA					✓		
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)					✓	✓	
LF1	LF1	Protein	Neurodegeneration					✓	✓	Takeda
GLIAL BIOLOGY PATHWAY										
RIPK1	DNL747	Small Molecule	Alzheimer's Disease, ALS					✓	✓	
	DNL788	Small Molecule	Alzheimer's Disease, ALS					✓	✓	
TREM2	ATV:TREM2	Antibody	Alzheimer's Disease					✓		Takeda
GB1	GB1	Antibody	Alzheimer's Disease							
CELLULAR HOMEOSTASIS										
BACE1/Tau	ATV:BACE1/Tau	Antibody	Alzheimer's Disease					✓	✓	Takeda
CH1	CH1	Small Molecule	Neurodegeneration					✓		
CH3	CH3	Small Molecule	Neurodegeneration					✓		
CH4	CH4	Small Molecule	ALS, Parkinson's Disease							
OTHER										
OP1	OP1	Small Molecule	Other					✓	✓	
OP2	OP2a	Antibody	Other					✓	✓	
	OP2b	Antibody	Other					✓	✓	

CORE program (8)

SEED program (5)

BIOMARKER
P = Preclinical
C = Clinical

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

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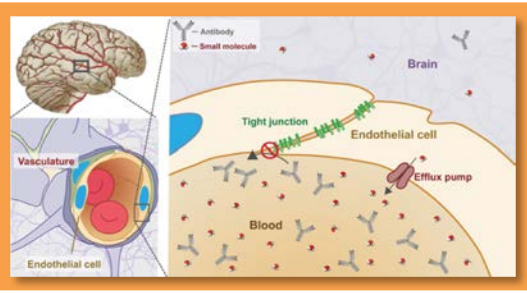
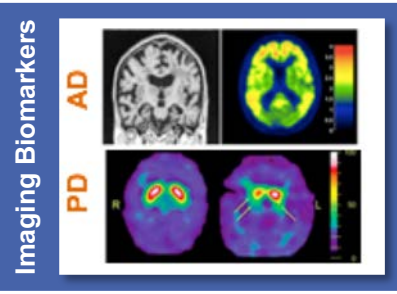
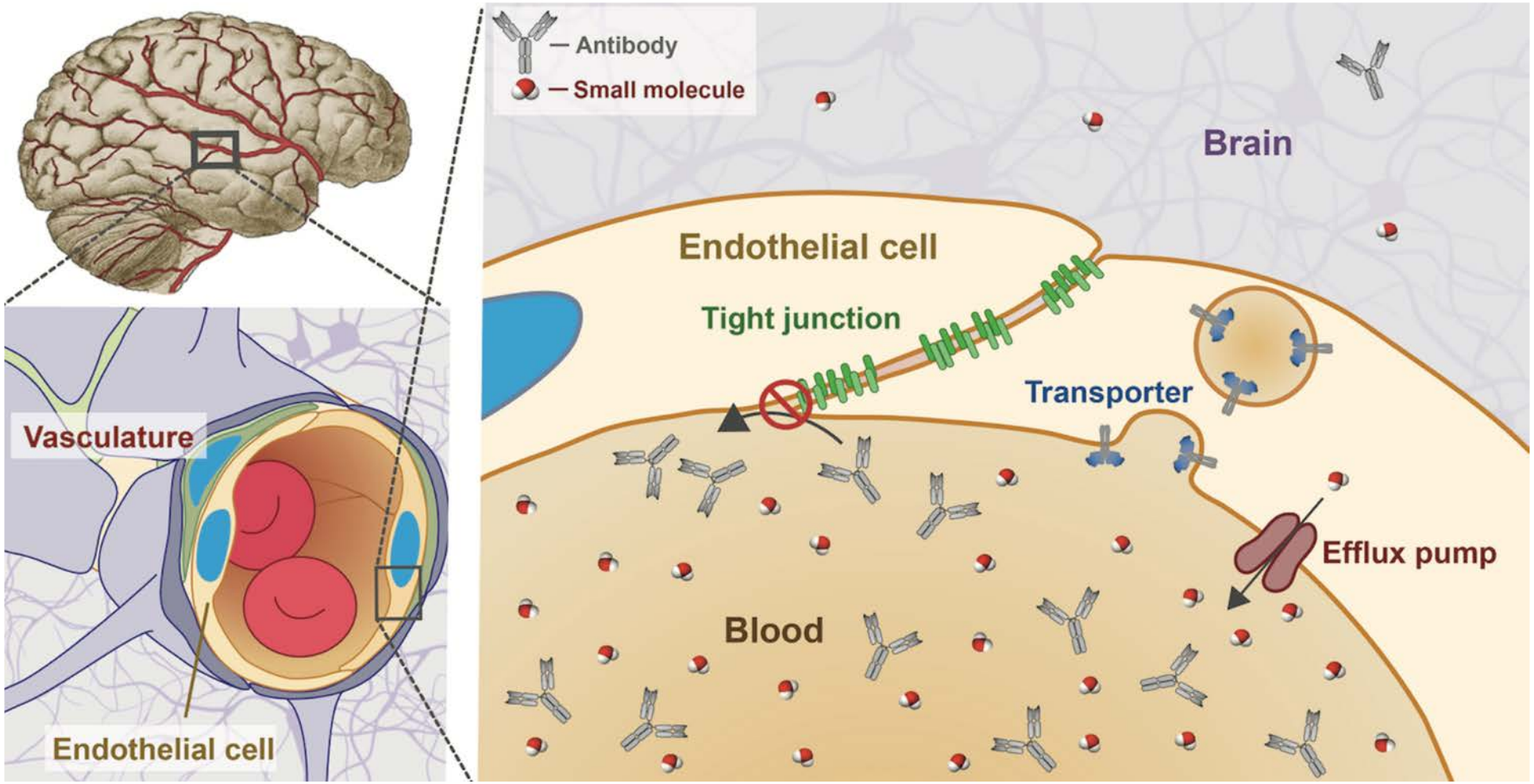
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Targeted patient population • Target & pathway engagement		• The right patients • The right molecule • The right dose

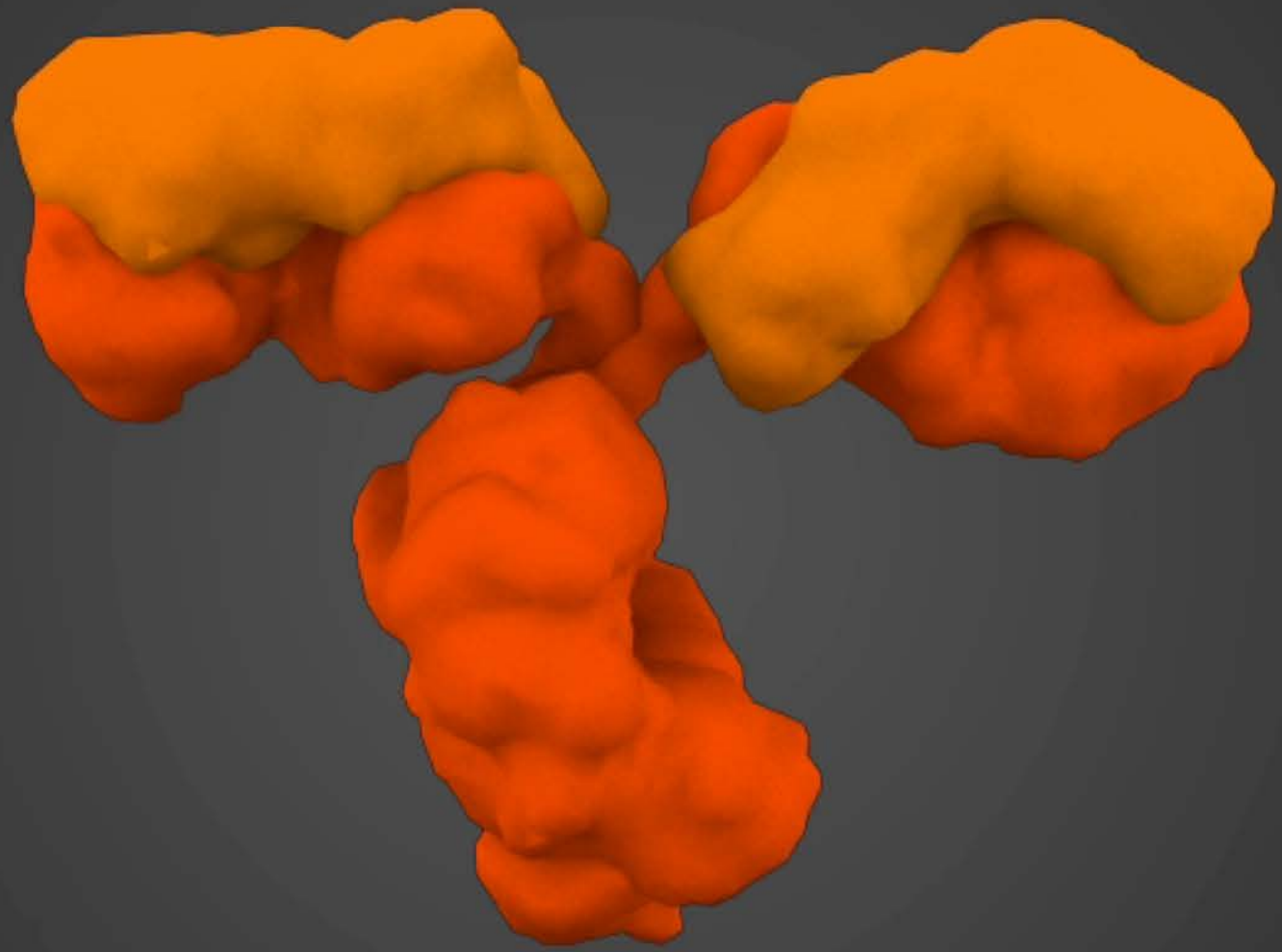
Broad Portfolio | **Parallel Investment (lead and back-ups)** | **Strategic Partnering**

INCREASED PROBABILITY OF SUCCESS

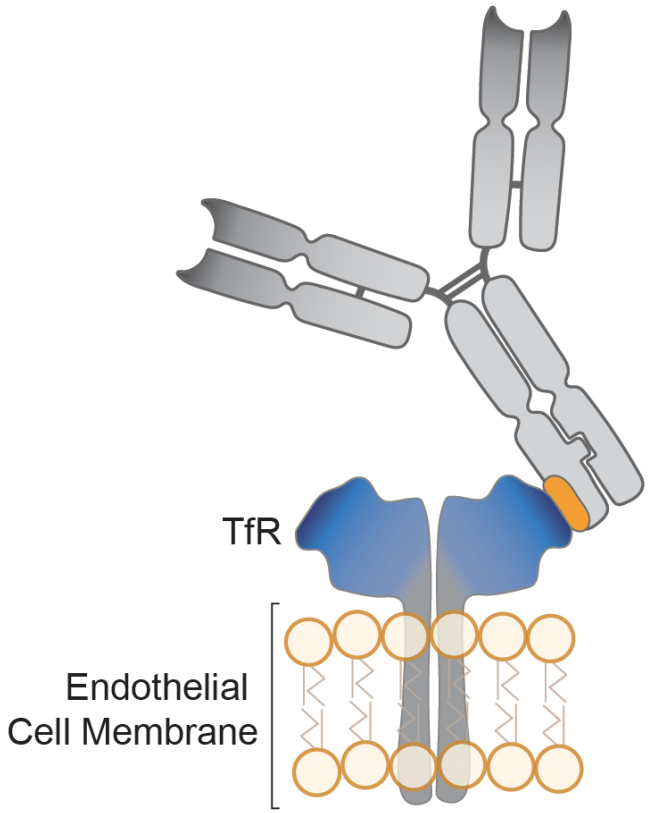
THE BLOOD-BRAIN BARRIER (BBB) CHALLENGE

- BBB evolved to protect the central nervous system from toxins via tight junctions and efflux pumps
- The molecular and cellular components of the BBB limit therapeutic uptake in brain
- Achieving therapeutically relevant drug concentrations in brain has been a major challenge in the past





ENGINEERING BRAIN DELIVERY: TRANSPORT VEHICLE

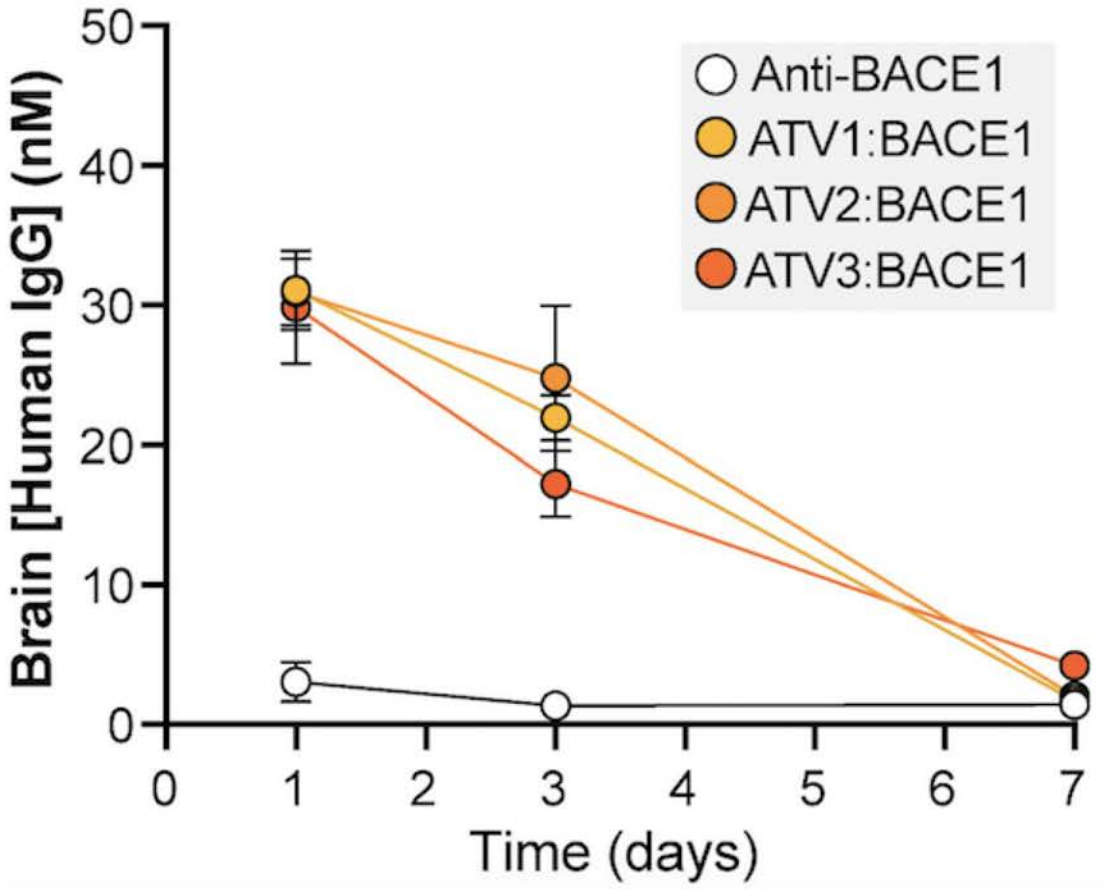


Advantages of TV

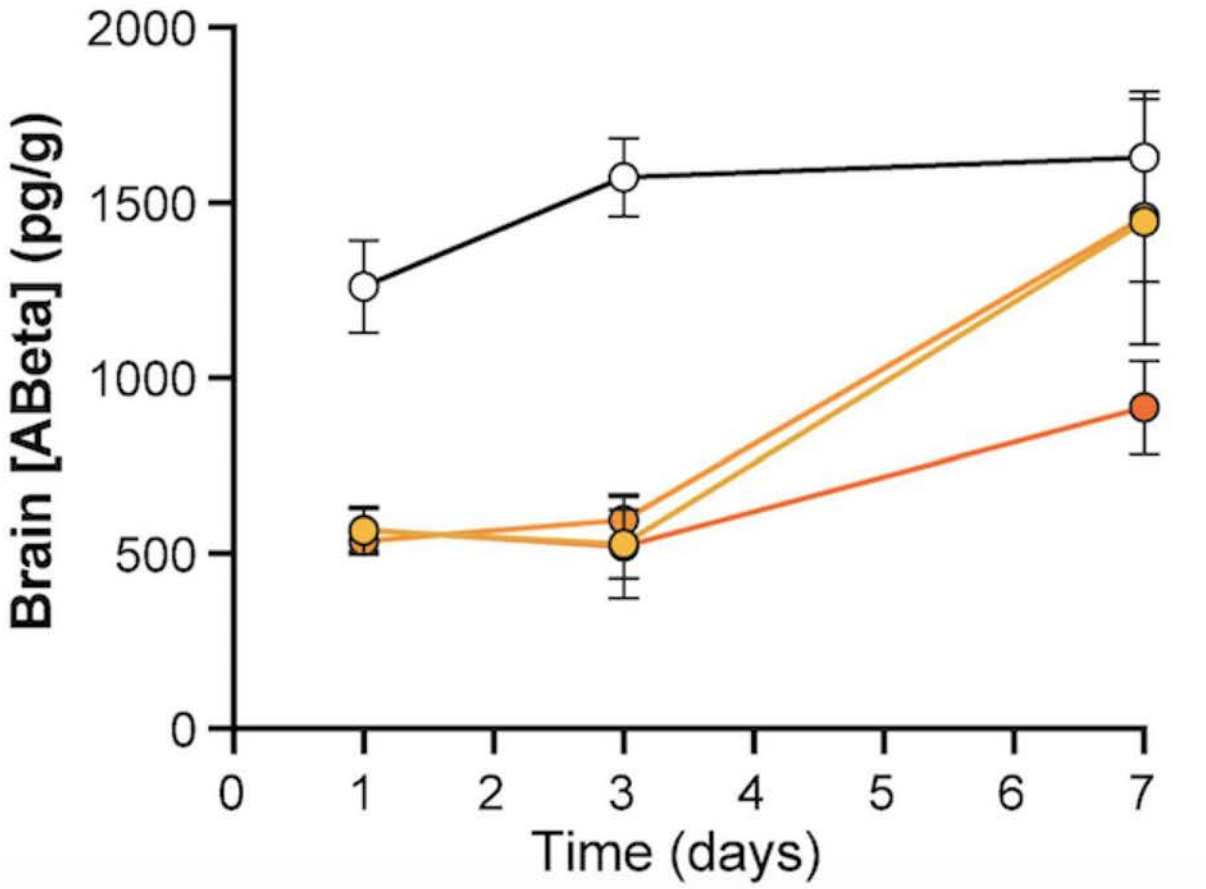
- Integrates BBB target binding into **Fc**
- No need for unnatural linkers or appended sequences
- Modularity:
  - **A**ntibody **T**ransport **V**ehicle (**ATV**)
  - **E**nzyme **T**ransport **V**ehicle (**ETV**)
  - Potential for other modalities
- ATV: retains **bivalent binding** to target or **two** different targets
- ATV: retains **stability** and **pharmacokinetics** of IgG
- TV: **well-differentiated** from existing approaches

SUSTAINED BRAIN UPTAKE AND ABETA REDUCTION IN HU/MS TfR MOUSE

PK: drug concentration in brain



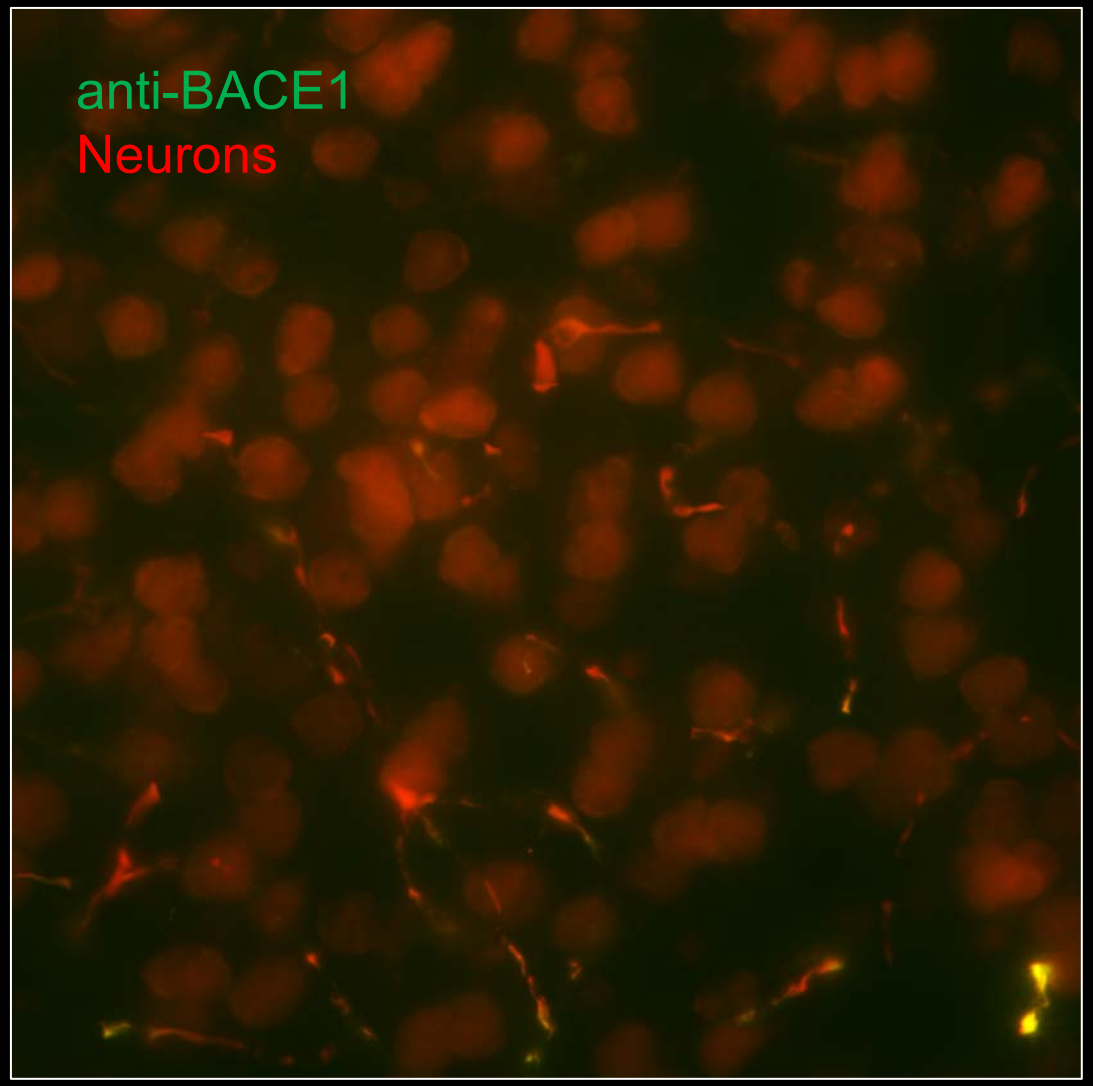
PD: Abeta reduction in brain

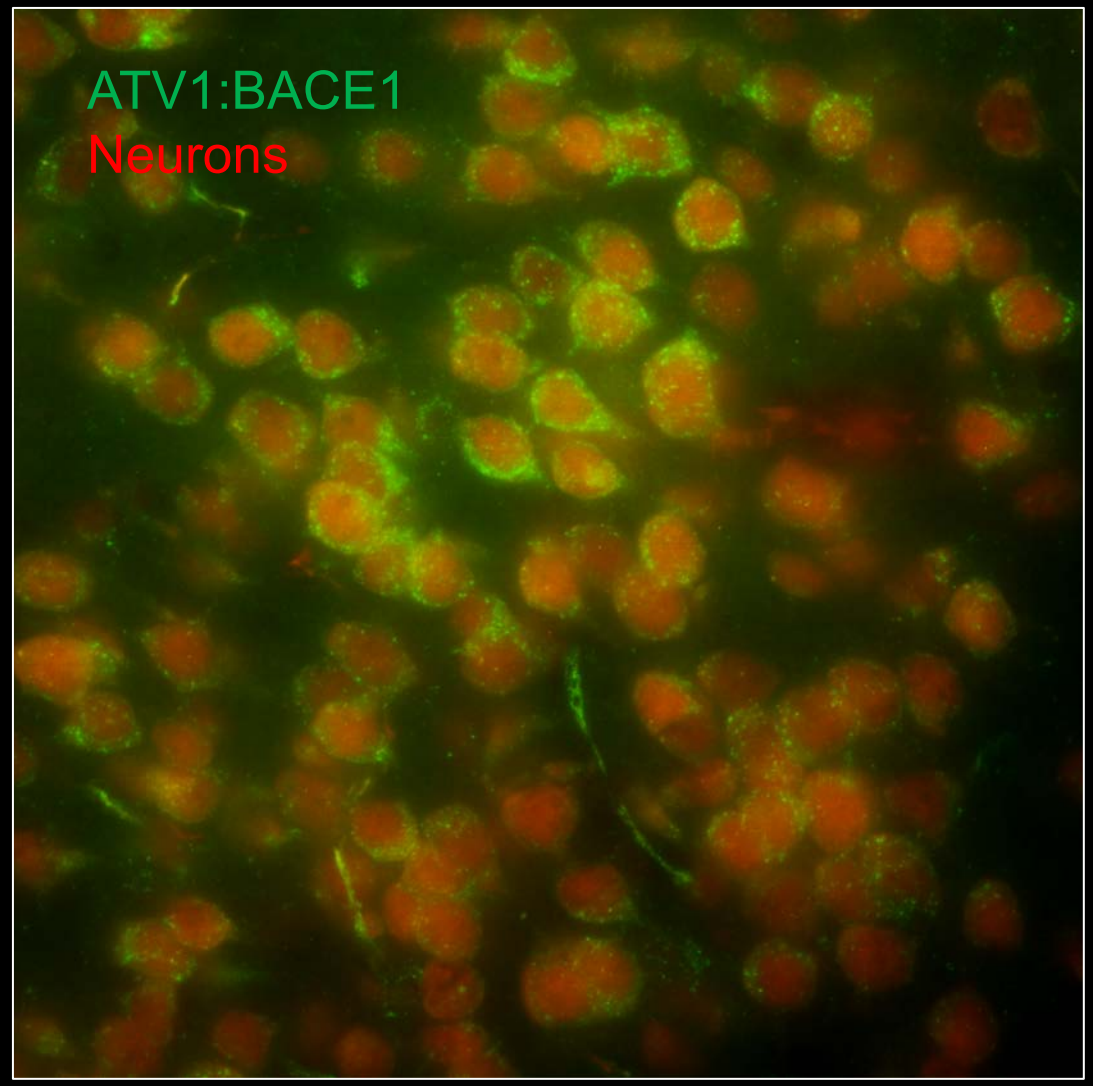


- 50 mg/kg IV dose in $TfR^{hu/ms}$ KI mice – time course

BROAD DISTRIBUTION OF ATV IN BRAIN

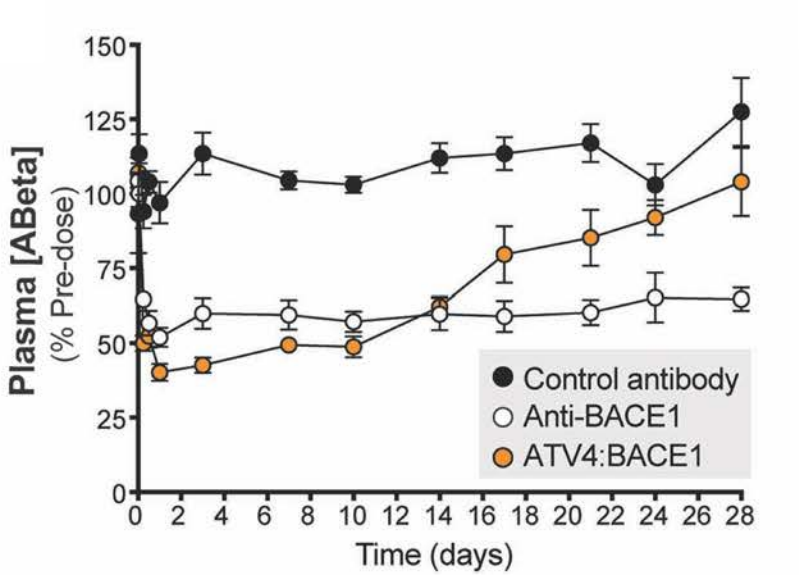
Localization of antibody in $TfR^{hu/ms}$ KI brain cortex 24hrs after 50 mg/kg IV

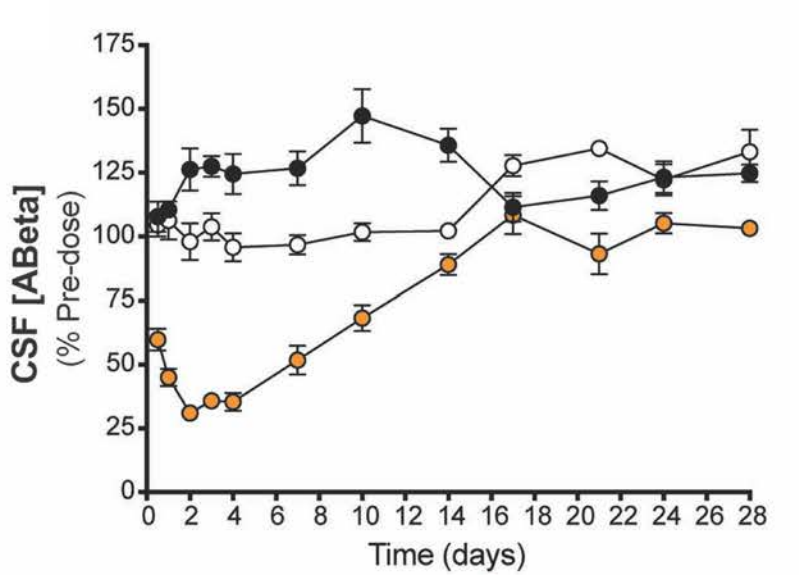


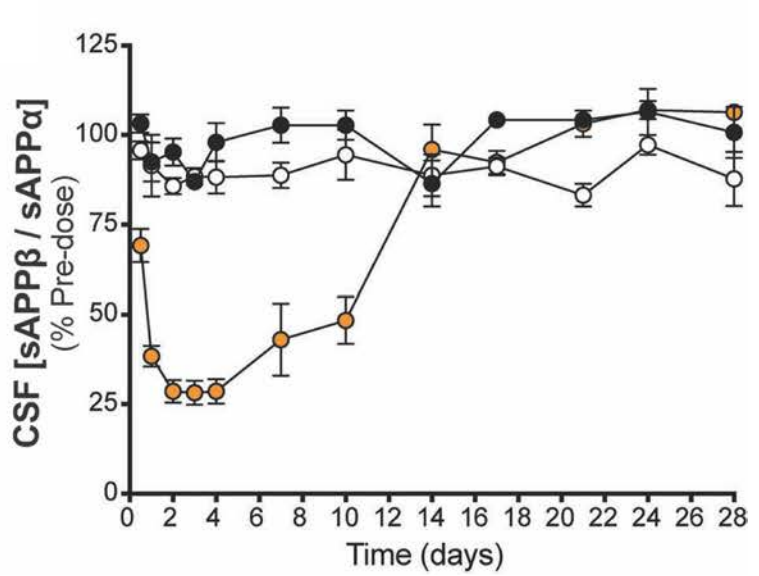


ROBUST PHARMACODYNAMIC RESPONSE IN NONHUMAN PRIMATES

PD: Abeta and sAPPbeta reduction in CSF taken from living monkeys (translatable biomarker)



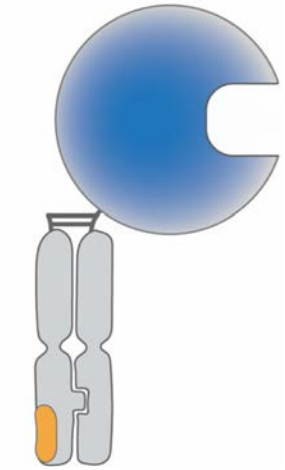




- 30 mg/kg single IV dose in cynomolgus monkey – time course

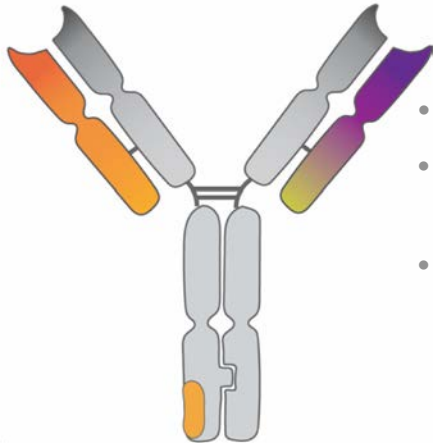
LARGE MOLECULE TARGETS: ATV AND ETV PLATFORM PORTFOLIO

ETV:IDS



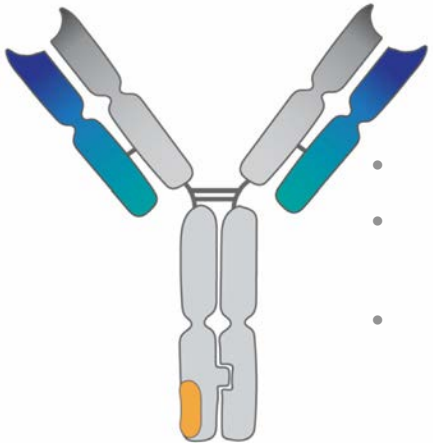
- Indication: **Hunter Syndrome**
- Status: *in vitro* and *in vivo* activity, candidate selected
- IND or CTA filing planned in 2019

ATV:BACE1/Tau



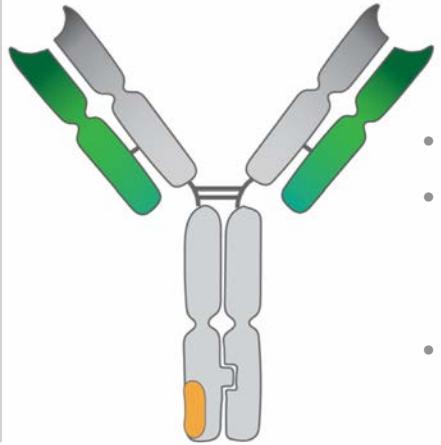
- Indication: **Alzheimer's disease**
- Status: high affinity, humanized leads for BACE1 & Tau
- IND or CTA filing planned in 2020

ATV:aSyn



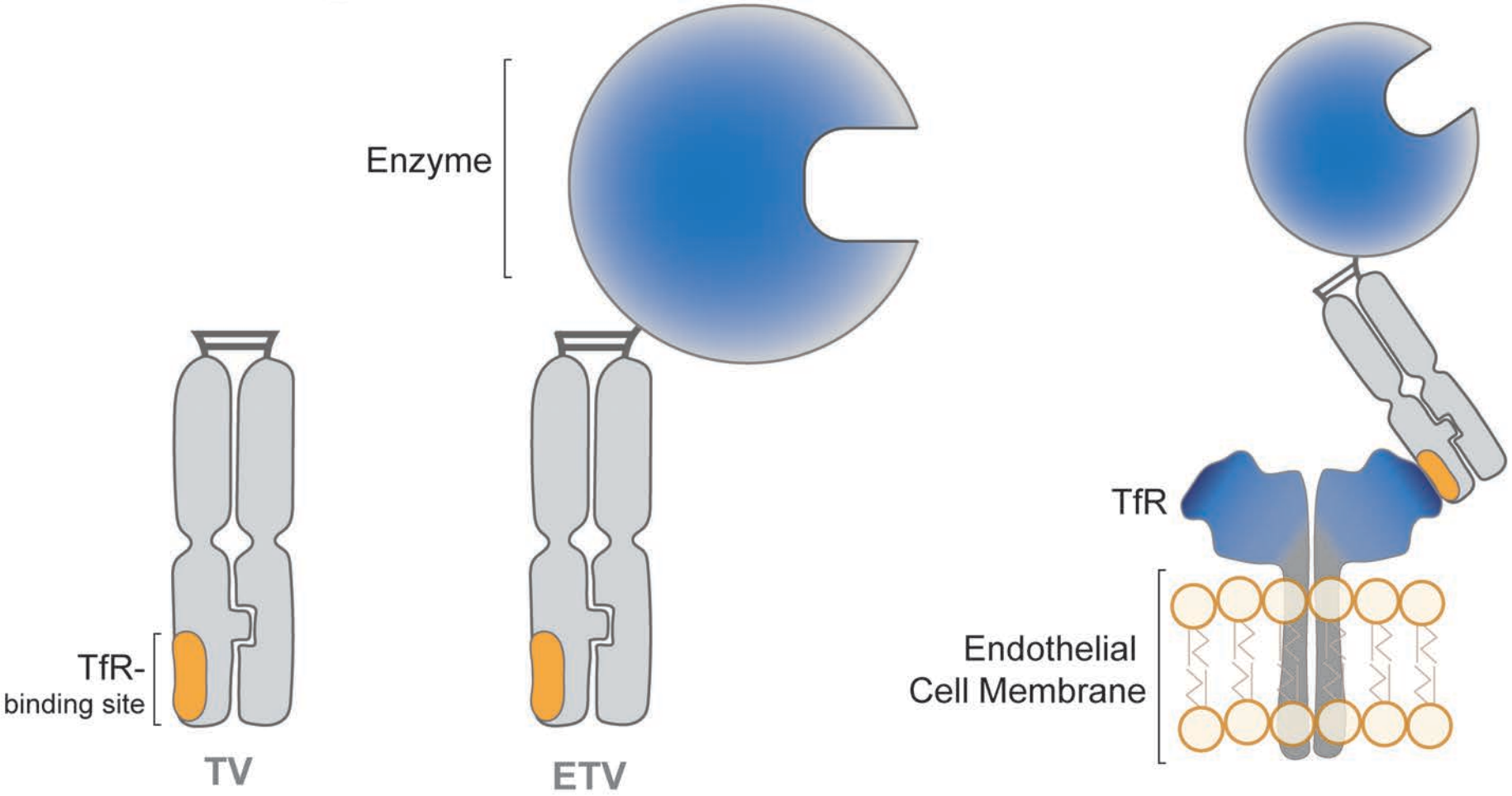
- Indication: **Parkinson's disease**
- Status: multiple lead antibodies identified with robust binding to human CSF derived aSyn
- IND or CTA filing planned in 2020

ATV:TREM2



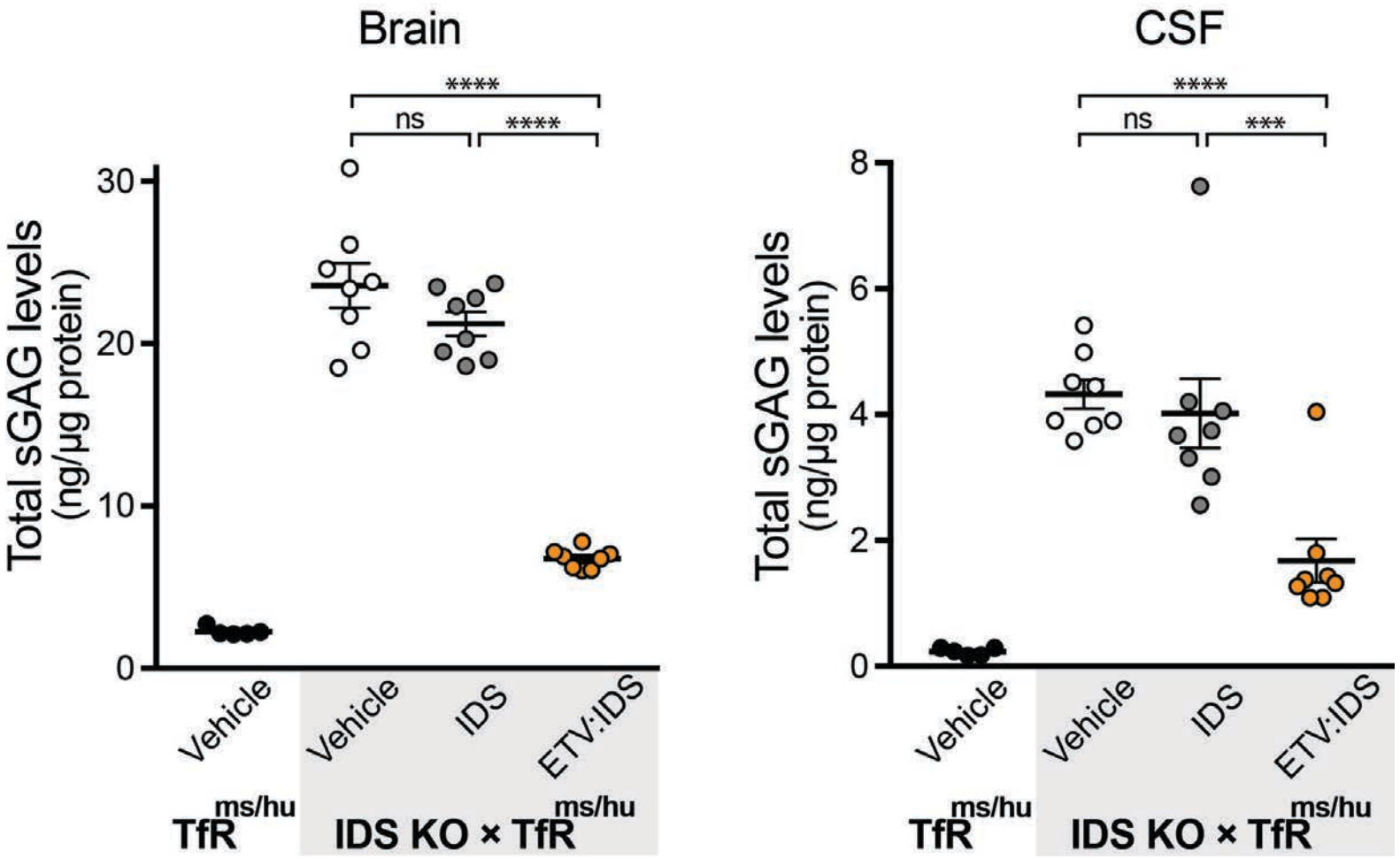
- Indication: **Alzheimer's disease**
- Status: high affinity candidate antibodies with diverse properties
  - Shedding blockers and agonist antibodies
- IND or CTA filing planned in 2020

ENZYME TRANSPORT VEHICLE



- ETV technology contains BBB receptor (TfR) binding Fc domain fused to an enzyme
- Enables transport of enzymes into the brain through TfR-mediated transcytosis

ETV:IDS REDUCES GAGs IN HUNTER SYNDROME MODEL



**** P < 0.0001
*** P < 0.001
ns = not significant
1-way ANOVA
IDS & ETV:IDS dosed at activity equivalent 746 µmol/min/kg

F-STAR GAMMA BUYOUT (MAY 30, 2018)

F-star
BISPECIFIC. BY DESIGN.

OVERVIEW

- Acquired F-star Gamma, a subsidiary of F-star Ltd
  - Pursuant to a pre-negotiated buyout option agreement from 2016
  - F-star Gamma holds IP and licenses related to our TV BBB technology
  - Expanded collaboration to include two more undisclosed BBB-TV targets
- Total consideration to F-star
  - F-star Gamma acquisition
    - $18M upfront
    - Up to $447M in development, regulatory and commercial milestones
  - New BBB-TV targets
    - $6M in total payments ($3M per target)

RATIONALE FOR ACQUISITION

- **Triggered by preclinical proof-of-concept in mice and nonhuman primates for TV**
- **Ability to use TV technology for an unlimited number of therapeutic programs**
- Favorable financials
  - No royalties on any BBB-TV enabled programs
  - 40% discount on upfront compared to late exercise of option in Phase 1

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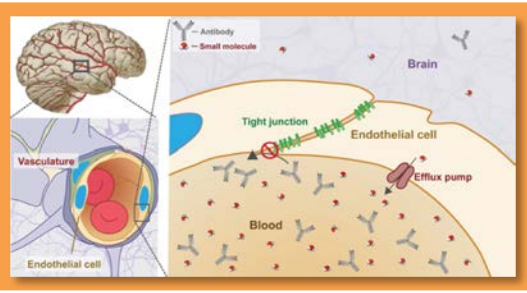
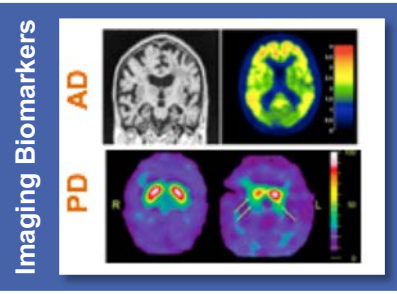
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Targeted patient population • Target & pathway engagement		• The right patients • The right molecule • The right dose

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INCREASED PROBABILITY OF SUCCESS

DENALI PORTFOLIO JUNE 2018

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LYSOSOMAL FUNCTION PATHWAY										
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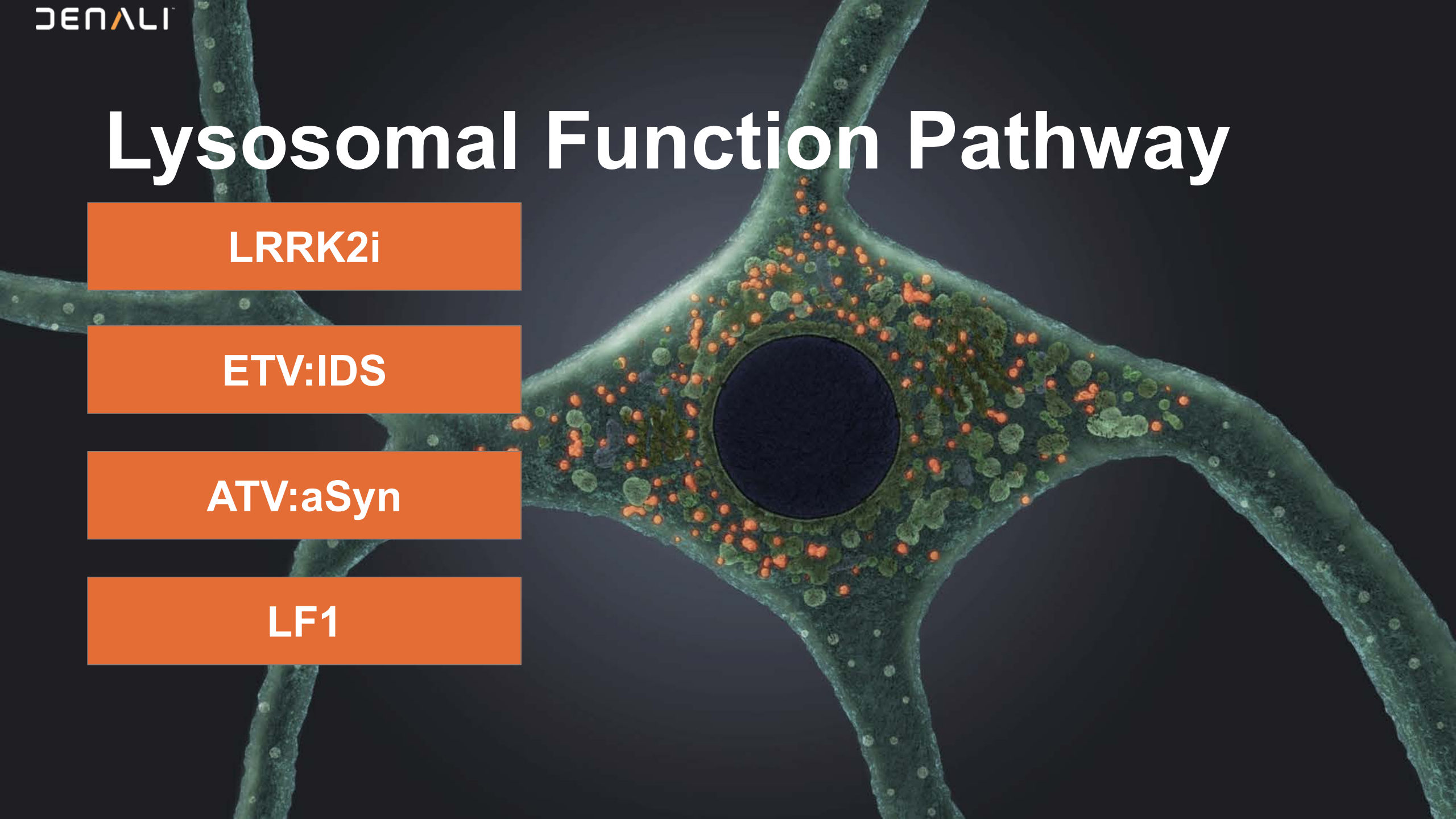
	DNL151	Small Molecule	Parkinson's Disease					✓	✓	
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's Disease, DLB, MSA					✓		
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)					✓	✓	
LF1	LF1	Protein	Neurodegeneration					✓	✓	Takeda
GLIAL BIOLOGY PATHWAY										
RIPK1	DNL747	Small Molecule	Alzheimer's Disease, ALS					✓	✓	
	DNL788	Small Molecule	Alzheimer's Disease, ALS					✓	✓	
TREM2	ATV:TREM2	Antibody	Alzheimer's Disease					✓		Takeda
GB1	GB1	Antibody	Alzheimer's Disease							
CELLULAR HOMEOSTASIS										
BACE1/Tau	ATV:BACE1/Tau	Antibody	Alzheimer's Disease					✓	✓	Takeda
CH1	CH1	Small Molecule	Neurodegeneration					✓		
CH3	CH3	Small Molecule	Neurodegeneration					✓		
CH4	CH4	Small Molecule	ALS, Parkinson's Disease							
OTHER										
OP1	OP1	Small Molecule	Other					✓	✓	
OP2	OP2a	Antibody	Other					✓	✓	
	OP2b	Antibody	Other					✓	✓	

CORE program (8)

SEED program (5)

BIOMARKER
P = Preclinical
C = Clinical

Lysosomal Function Pathway

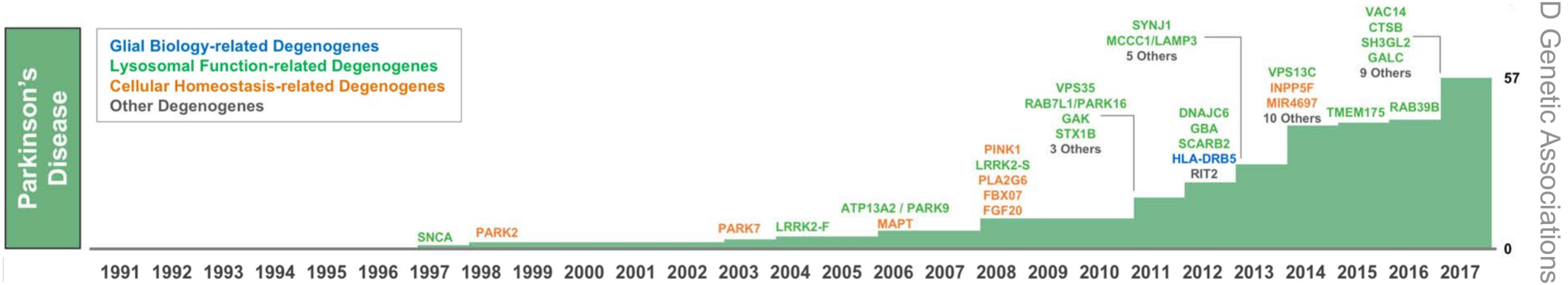


- LRRK2i
- ETV:IDS
- ATV:aSyn
- LF1

DEGENOGENES IMPLICATE LYSOSOMAL FUNCTION IN PD

NEW GENETIC INSIGHTS IN PARKINSON'S DISEASE

- Lysosomal dysfunction is a central pathophysiology of PD
- Parkinson's genetic risks highlight lysosomal impairment in PD
  - Lysosomal enzymes, GALC and GBA, are major risk factors for PD

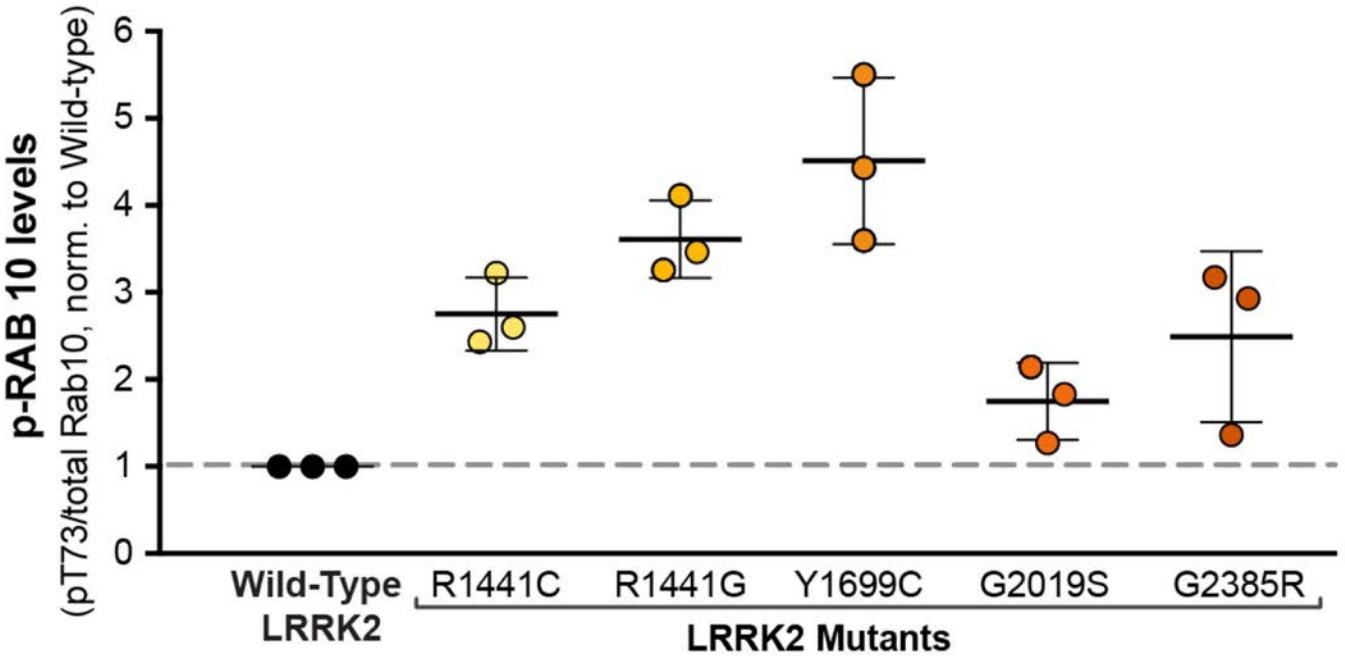


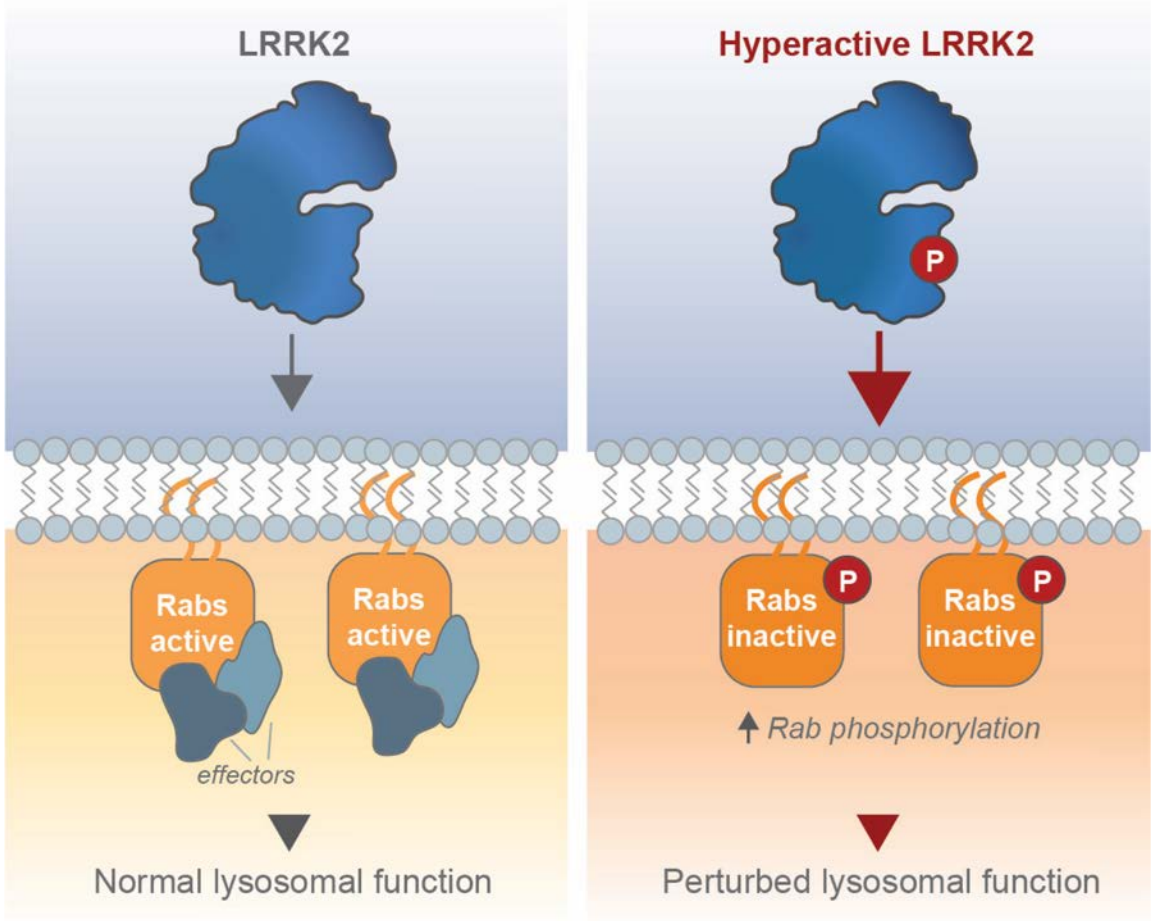
- Lysosomal dysfunction contributes to aSyn aggregation, the pathologic hallmark of PD
- LRRK2 and aSyn are linked to lysosomal function, and represent promising therapeutic targets

LRRK2 Inhibitor

LRRK2 DISEASE CAUSING MUTATIONS INCREASE KINASE ACTIVITY

LRRK2 Parkinson's mutations increase pRab

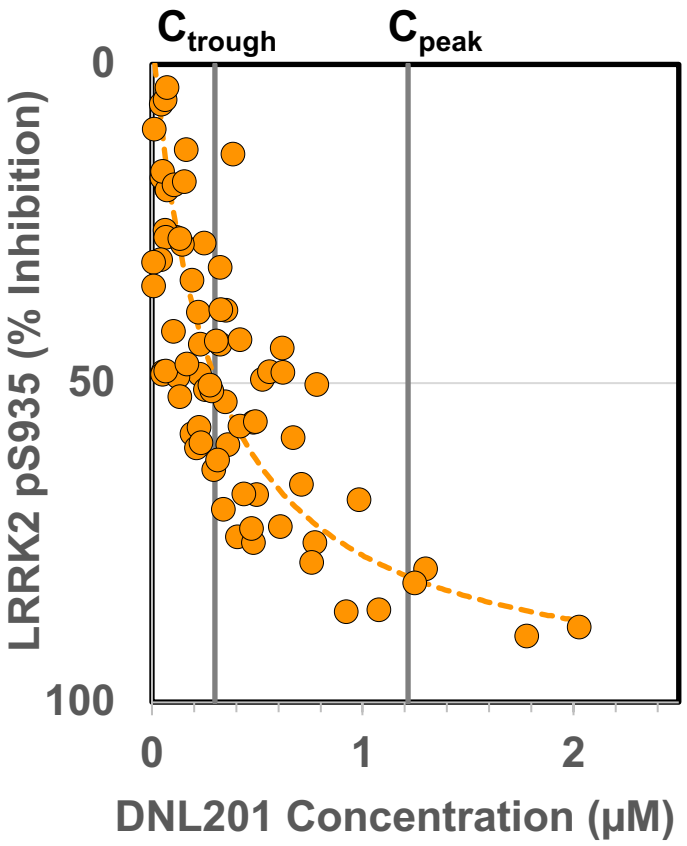




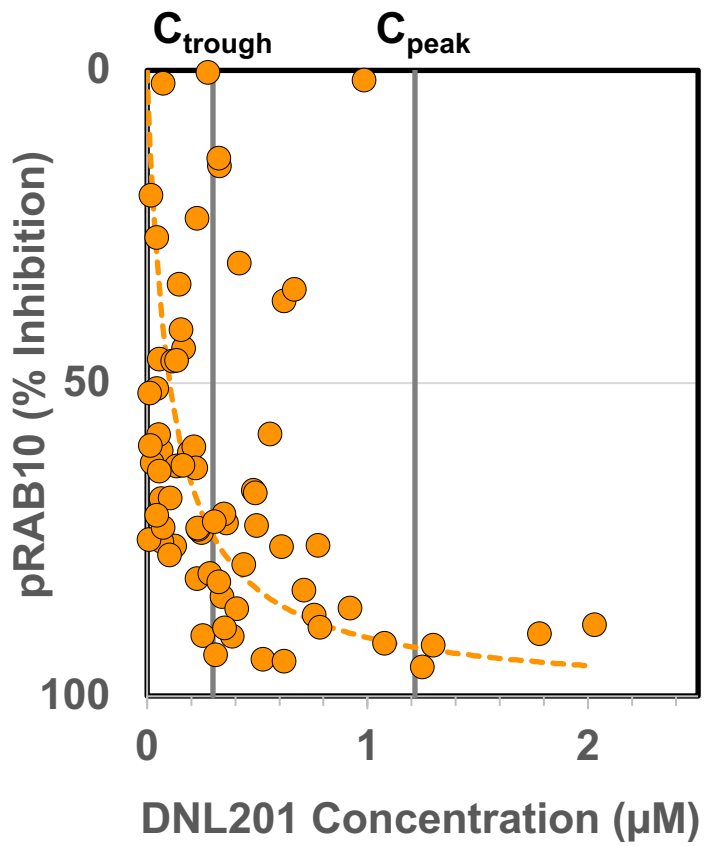
LRRK2 Inhibitor

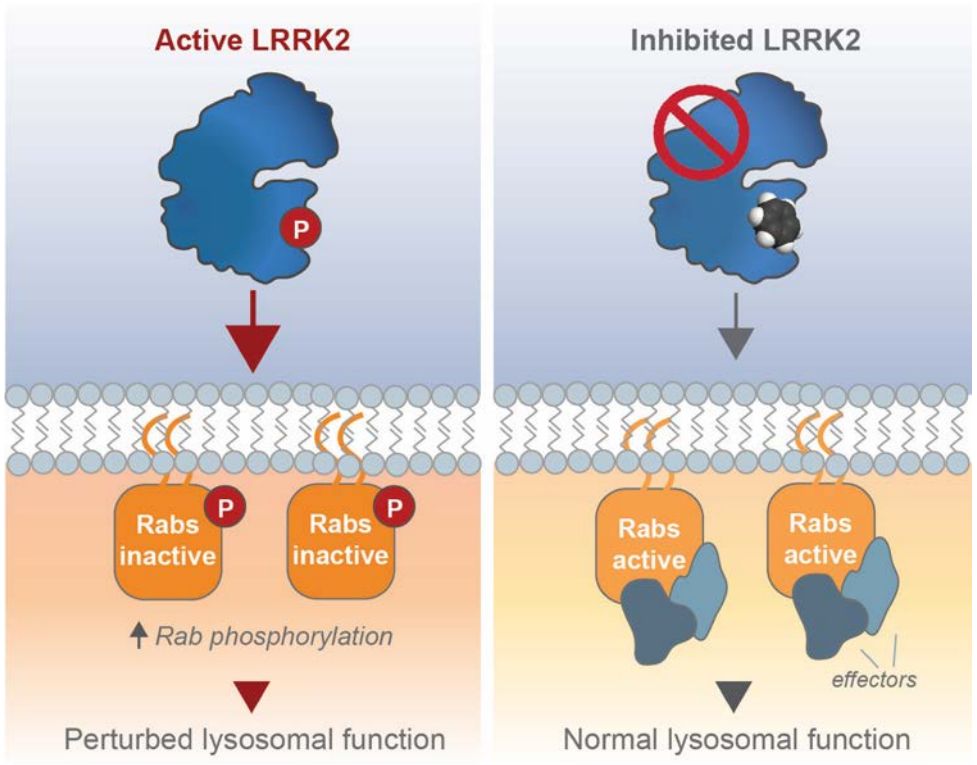
PK/PD CORRELATION IN HUMANS DOSED WITH DNL201

LRRK2 pS935



pRAB10

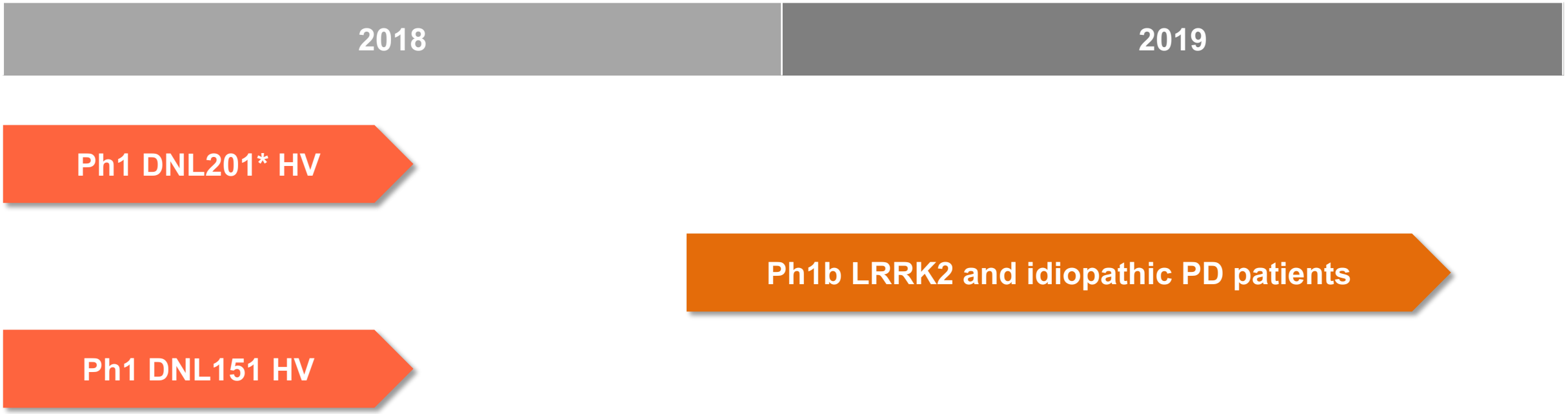




- Each point represents % target inhibition at the corresponding level of drug exposure, showing data from all active individuals at all time points at 40 mg bid dose
- Concentration dependent target engagement and inhibition
- Mean greater than 50% and 90% inhibition of LRRK2 kinase activity observed at trough and peak drug levels, respectively

LRRK2 Inhibitor

LRRK2 CLINICAL PROGRAM SUMMARY



HV = Healthy Volunteer
*Target engagement reported for DNL201 (Dec 2017)

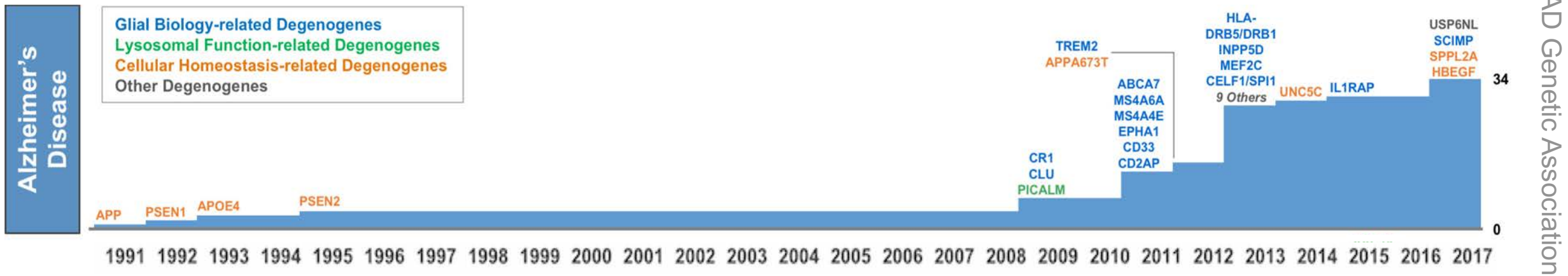
LRRK2 Inhibitor


DENALI
Glial Biology
RIPK1i
ATV:TREM2

DEGENOGENES IMPLICATE GLIAL BIOLOGY (IMMUNE FUNCTION) IN AD

NEW GENETIC INSIGHTS IN ALZHEIMER'S DISEASE

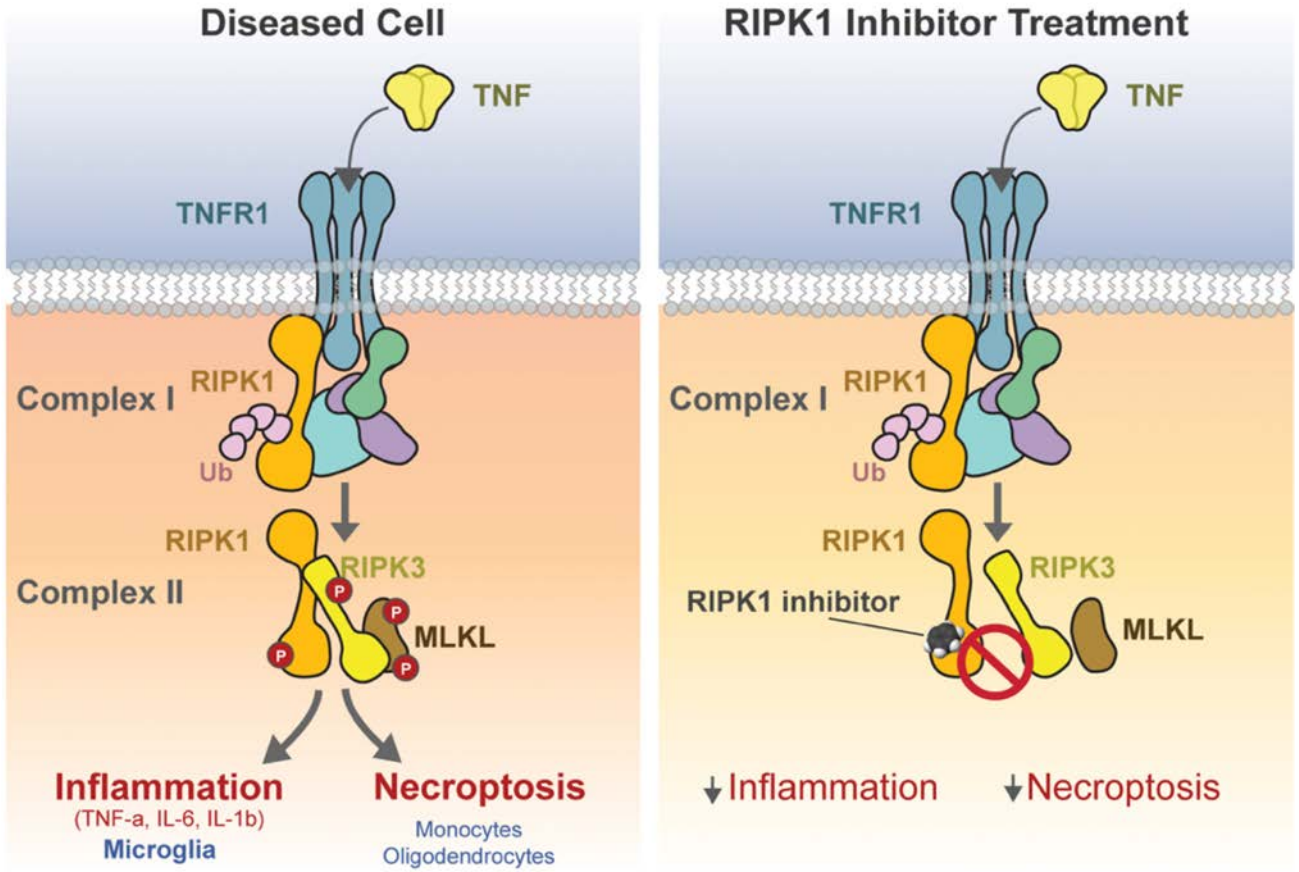
- Immune dysfunction is observed in patients with AD and other neurodegenerative diseases
- Degenogenes include TREM2 and numerous other genes that are highly expressed in inflamed microglia, the resident immune cells of the brain



- Neuro-immune modulation in neurodegeneration is a promising therapeutic approach
- RIPK1, a kinase downstream of the TNF receptor pathway, is overactive in inflamed microglia and several other cells in the brain

RIPK1 Inhibitor

RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS



- Activation of RIPK1 kinase activity generates a pro-inflammatory response in microglia and cell death via necroptosis in other cell types, including monocytes and oligodendrocytes
- Inhibition of RIPK1 is sufficient to block both the production of pro-inflammatory cytokines and necroptosis

RIPK1 Inhibitor

RIPK1 CLINICAL PROGRAM SUMMARY

HV = Healthy Volunteer

RIPK1 Inhibitor

MAJOR PIPELINE MILESTONES AND PRIORITIES

	SINCE IPO	NEXT 12-18 MONTHS
LRRK2	▪ DNL201: Target engagement HV ▪ DNL151: FIH dosing HV Ph1 study	▪ DNL201 & DNL151: Ph1 data in HV ▪ Nominate candidate for Ph1b study in LRRK2 PD patients ▪ **Initiate Ph1b safety and biomarker study in LRRK2 and idiopathic PD patients**
RIPK1	▪ DNL747: CTA and initiated HV Ph1 study	▪ Obtain safety and biomarker data in DNL747 Ph1 study in HV ▪ **Initiate Ph1b safety and biomarker studies in ALS and AD patients**
TV	▪ Robust and sustained increase in brain exposure in hTfR mice ▪ Proof of concept in nonhuman primates ▪ **IDS: Data from hTfR mouse model; *in vivo* PK/PD data**	
TV platform		▪ ETV: Progress and complete cell line / manufacturing for clinical supply ▪ Optimize existing lead antibodies and select further lead antibodies for multiple programs ▪ ATV: Commence cell line / clinical supply manufacturing ▪ Expansion of TV platform technology
Deals	▪ Collaboration with Takeda on 3 named ATV programs ▪ F-star Gamma buyout	


THANK YOU

OUR PEOPLE

SCIENTISTS AND DRUG DEVELOPERS

150 BASED IN SOUTH SAN FRANCISCO

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HARVARD UNIVERSITY | FLAGSHIP PIONEERING | ARCH Venture Partners | Microsoft

Stanford University | illumina | agios | DENALI THERAPEUTICS

LEADERSHIP

RYAN J. WATTS, PHD – CEO

- Previously built and led Genentech's neuroscience strategy, portfolio and research department
- Led several clinical development programs in neurodegeneration and oncology
- Stanford PhD, University of Utah

ALEXANDER SCHUTH, MD – COO

- Formerly head of Genentech's BD groups for neuroscience and discovery technologies
- Previously Merrill Lynch ECM (London)
- Charite Medical School (Berlin) MD, Wharton MBA

CAROLE HO, MD – CMO

- Formerly VP Early Clinical Development at Genentech
- Previously Medical Director at J&J and clinical neurologist at Stanford
- Cornell Medical School MD, Harvard University

STEVE KROGNES – CFO

- Formerly CFO Genentech and Head of M&A Roche
- Previously Goldman Sachs and McKinsey
- Harvard Business School MBA, Wharton

STATEMENT OF OPERATIONS AND BALANCE SHEETS

(In thousands, except per share amounts)	Three Months Ended March 31, 2018	Three Months Ended March 31, 2017
Revenue		
Collaboration Revenue	$ 641	$ —
Operating Expenses		
R&D expenses	20,819	18,470
G&A expenses	5,570	3,274
Total operating expenses	**26,389**	**21,744**
Operating loss	**(25,748)**	**(21,744)**
Interest income, net	2,070	424
Net loss	**(23,678)**	**(21,320)**
Net loss per share	$ (0.26)	$ (2.36)

Key Balance Sheet Data (In millions)	March 31, 2018	December 31, 2017
Cash, cash equivalents and marketable securities	**$ 592.8**	**467.0**
Total assets	**614.0**	**486.7**
Total liabilities	**74.9**	**20.9**
Total stockholders' equity	$ 539.1	465.8

STRATEGIC PARTNERSHIP WITH TAKEDA

Rationale

- Share development risk and commercial returns on early stage assets for large indications
- Enables Denali's broad portfolio approach and ability to fully explore potential of BBB technology
- Leverages Takeda's strong clinical development and global commercial capabilities

Scope (3 Named Programs)

- ATV:BACE1/Tau (IND or CTA planned for 2020)
- ATV:TREM2 (IND or CTA planned for 2020)
- Additional named (but undisclosed) discovery stage program (IND or CTA planned post 2020)

Roles and Responsibilities

- Denali responsible for all pre-IND R&D activities
- Post opt-in (at IND), Denali will lead early clinical development and Takeda late stage development
- Co-commercialization in US and China; Takeda will commercialize in all other countries

Key Financial Terms (to Denali)

- $150M upfront payments between cash and equity*
- Up to $90M in pre-clinical milestones and opt-in payments, total deal value up to >$1.1B
- 50% of world wide commercial profits

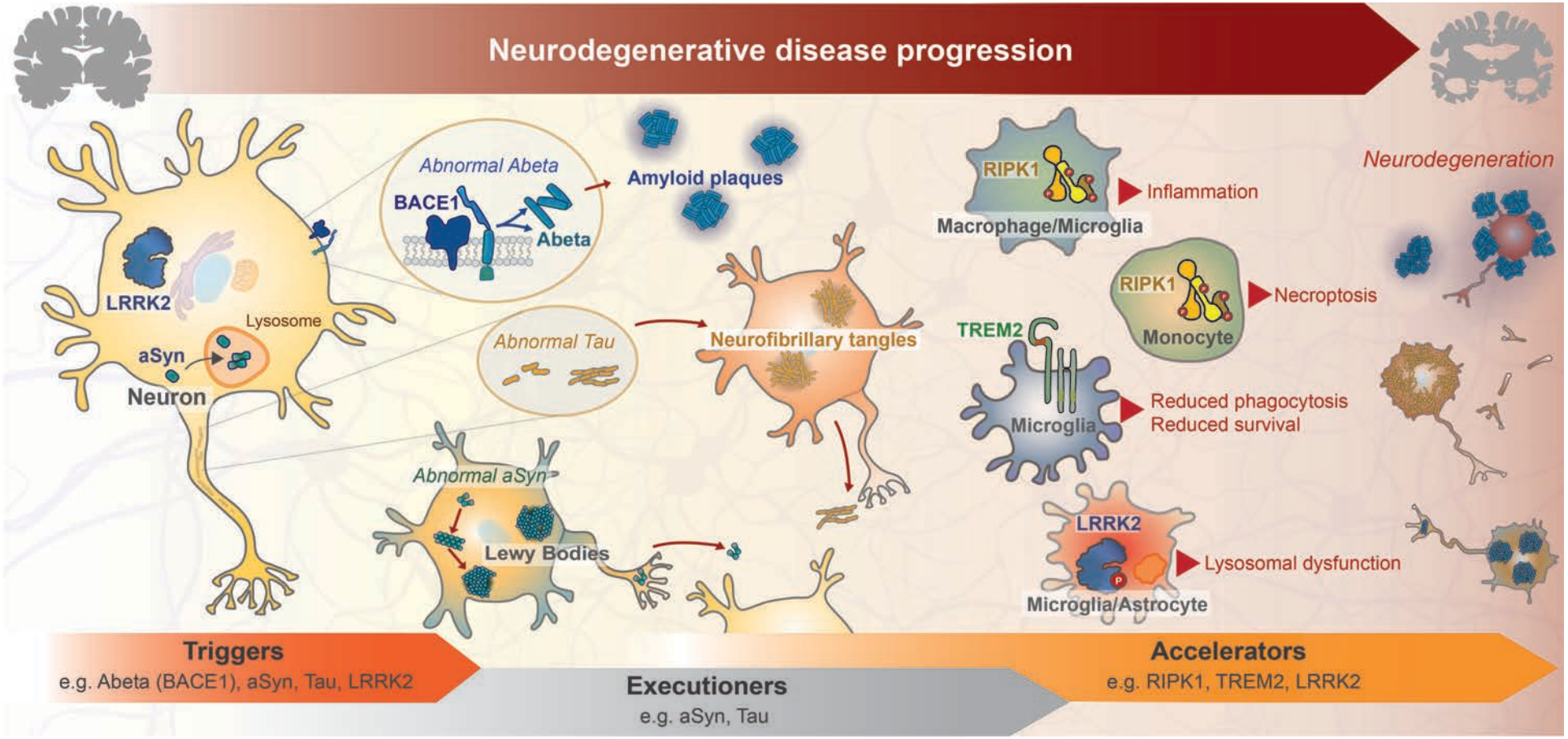
*** Upfront payment includes purchase of approx. 4.2 million shares (~4.5% of DNLI equity) at $26.10/sh, i.e. 45% premium to IPO price**

PARTNERING IS CENTRAL TO OUR STRATEGY

- Network of current and former collaborators in academia and industry to build broad portfolio and deepen scientific expertise
- Continuing to explore partnering options with global biopharma companies for co-development and co-commercialization

THERAPEUTIC OPPORTUNITIES TO HALT OR SLOW NEURODEGENERATION

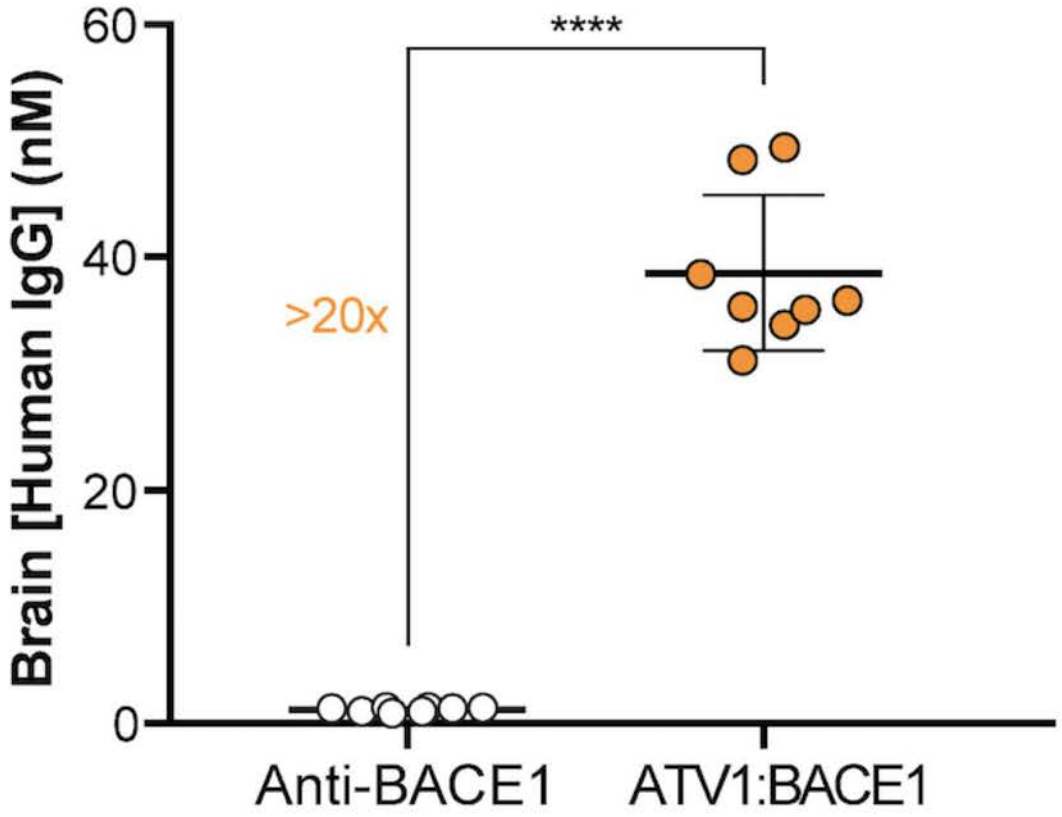
- **Triggers** of neurodegeneration initiate disease mechanisms and lie upstream of neuronal cell death
- **Executioners** impair cellular homeostasis, promote propagation of disease and ultimately execute death mechanisms
- **Accelerators** are non-cell autonomous mechanisms that speed up disease progression, such as inflammation



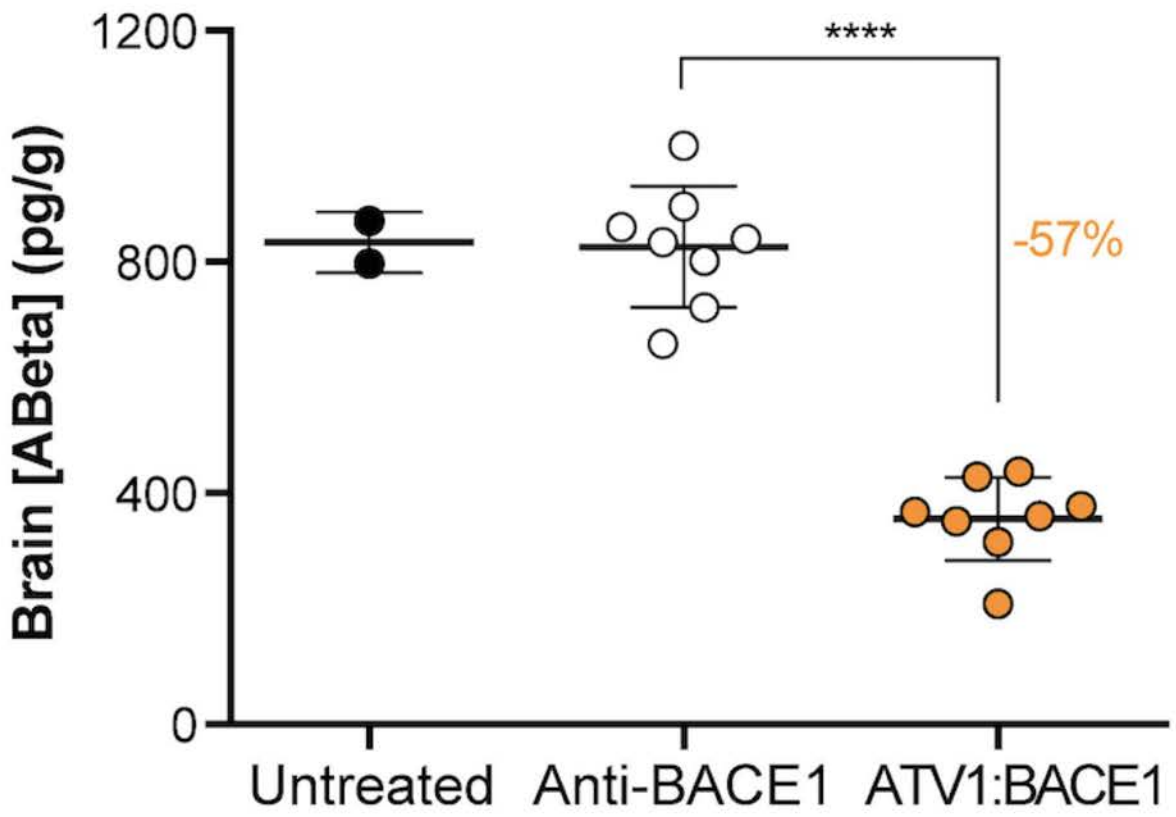
TV Platform Appendix

ROBUST BRAIN UPTAKE AND ACTIVITY IN HU/MS TfR MOUSE

PK: drug concentration in brain

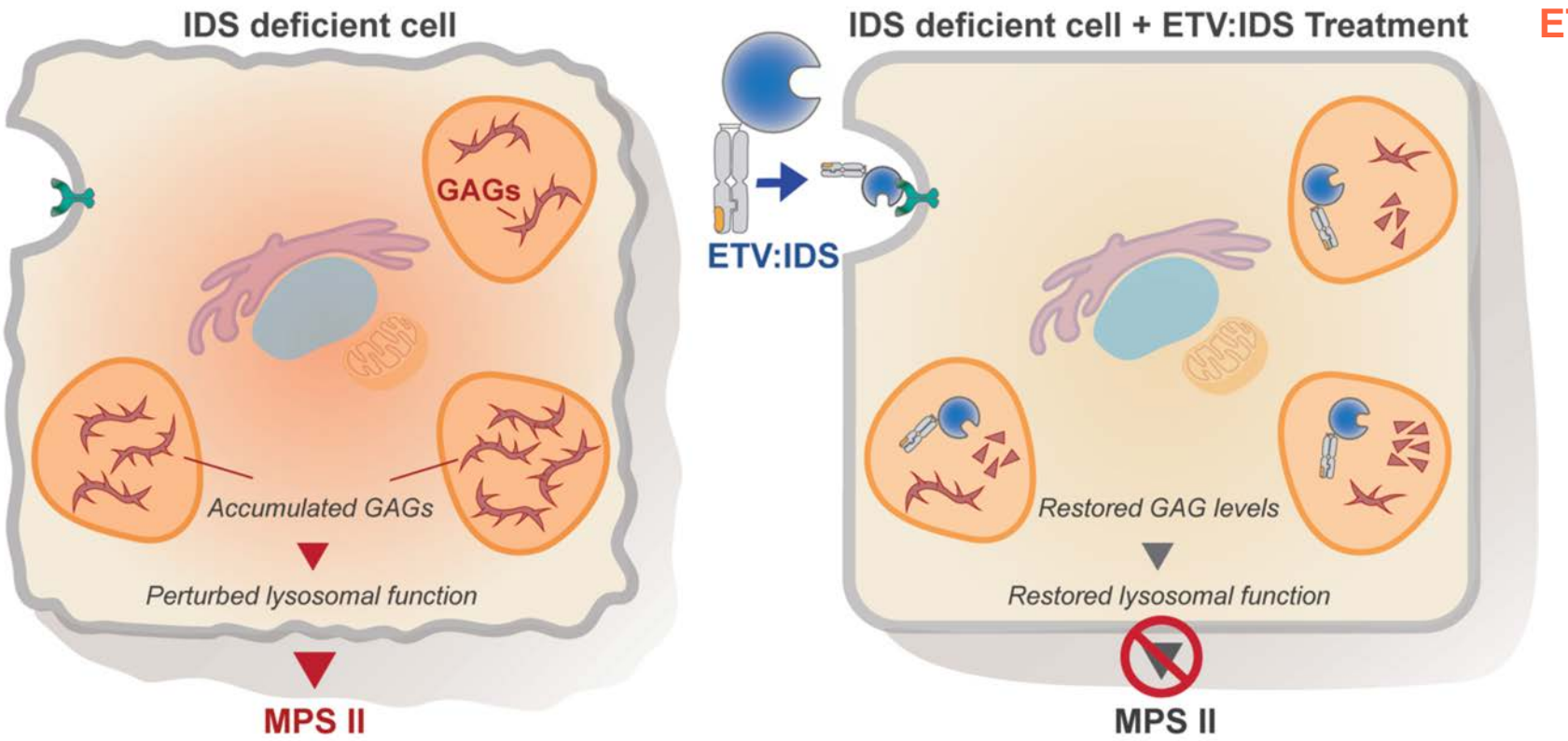


PD: Abeta reduction in brain

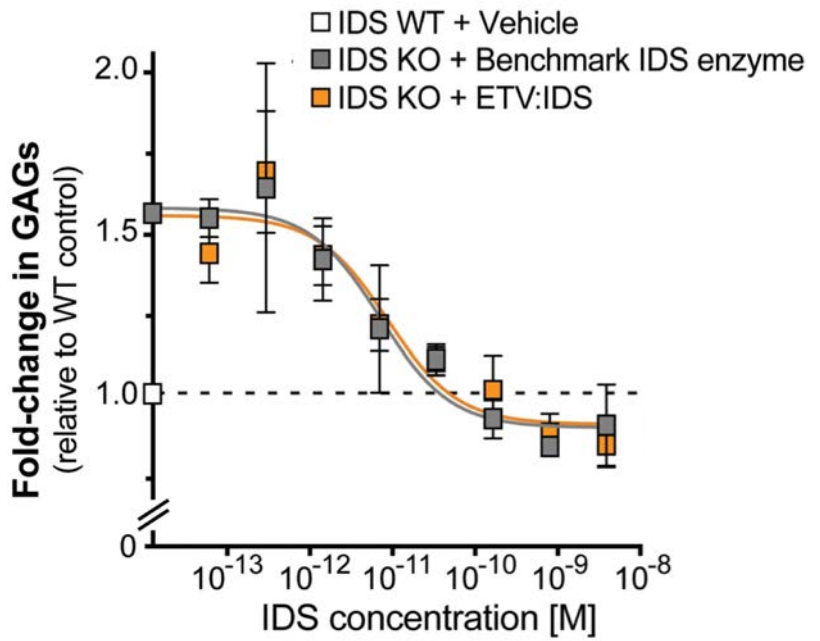


- 50 mg/kg IV dose in $TfR^{hu/ms}$ KI mice – 24 hour

LACK OF LYSOSOMAL ENZYME IDS RESULTS IN MPS II (Hunter Syndrome)



ETV:IDS reduces substrate in IDS KO cells

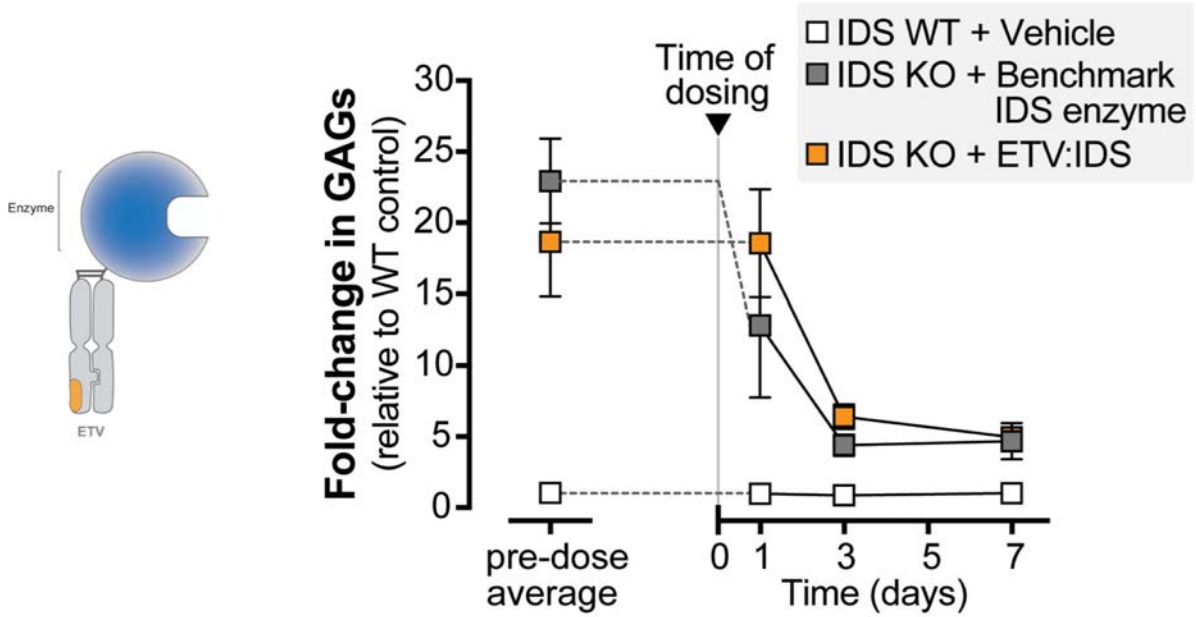


- Treatment with ETV:IDS should promote GAG processing and may rescue neurons from degeneration

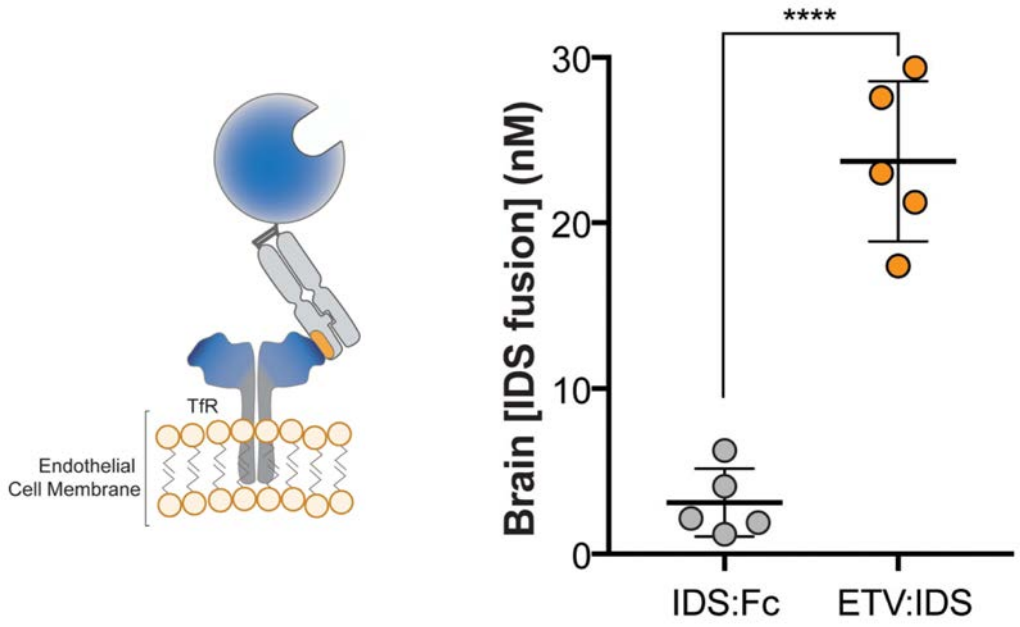
ETV:IDS

ETV:IDS REDUCES SUBSTRATE IN IDS KO MOUSE
ETV:IDS SHOWS ROBUST BRAIN UPTAKE IN HU/MS TFR KI MICE

ETV:IDS reduces substrate in IDS KO mice



ETV:IDS is taken up in TfR$^{hu/ms}$ mouse brain



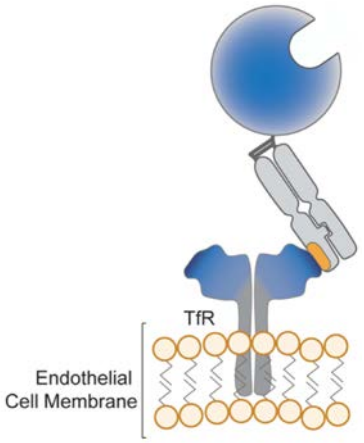
- IND or CTA filing planned for 2019

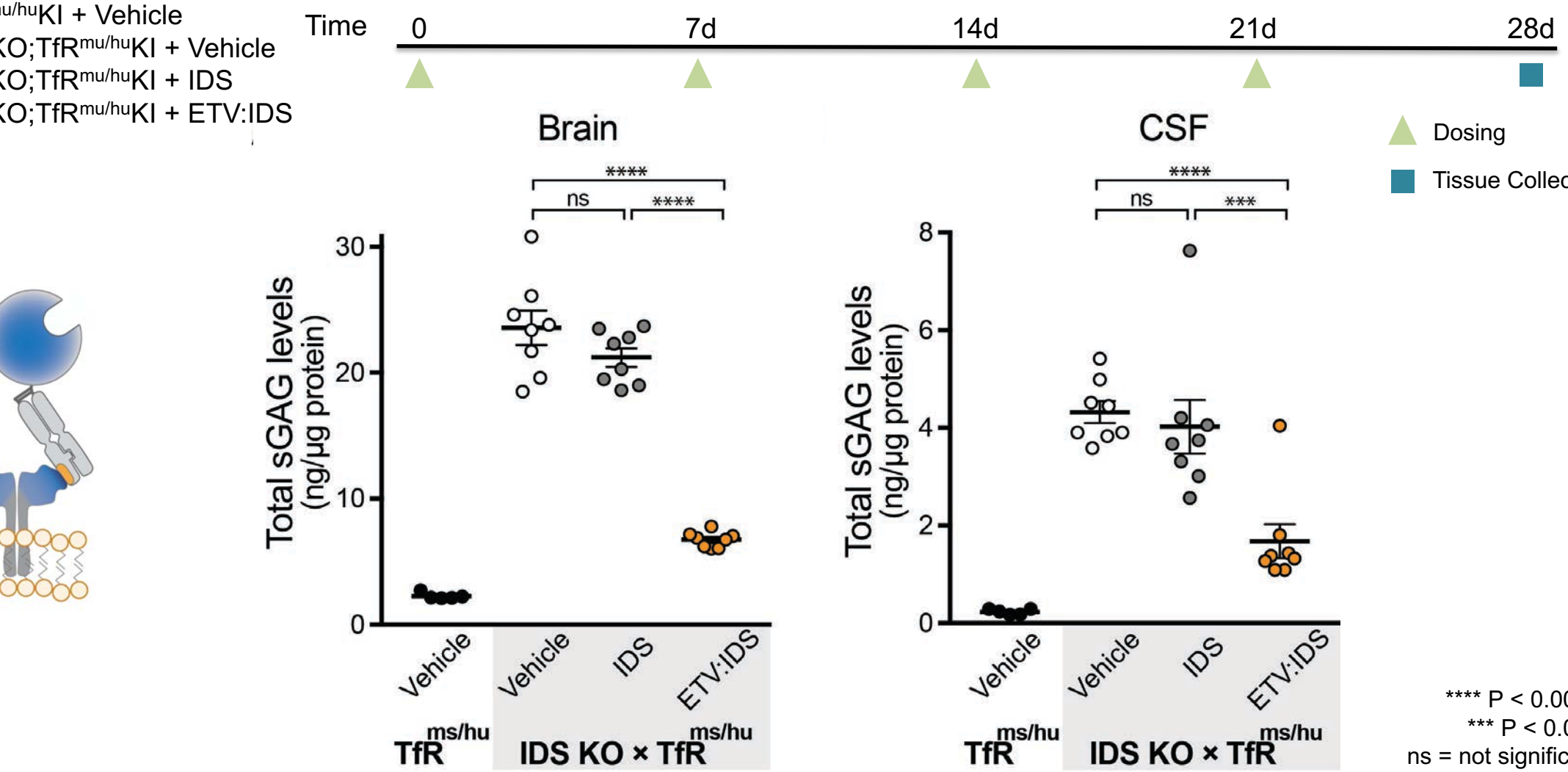
ETV:IDS

ETV:IDS REDUCES SUBSTRATE IN IDS KO; HU/MS TFR KI MOUSE BRAIN

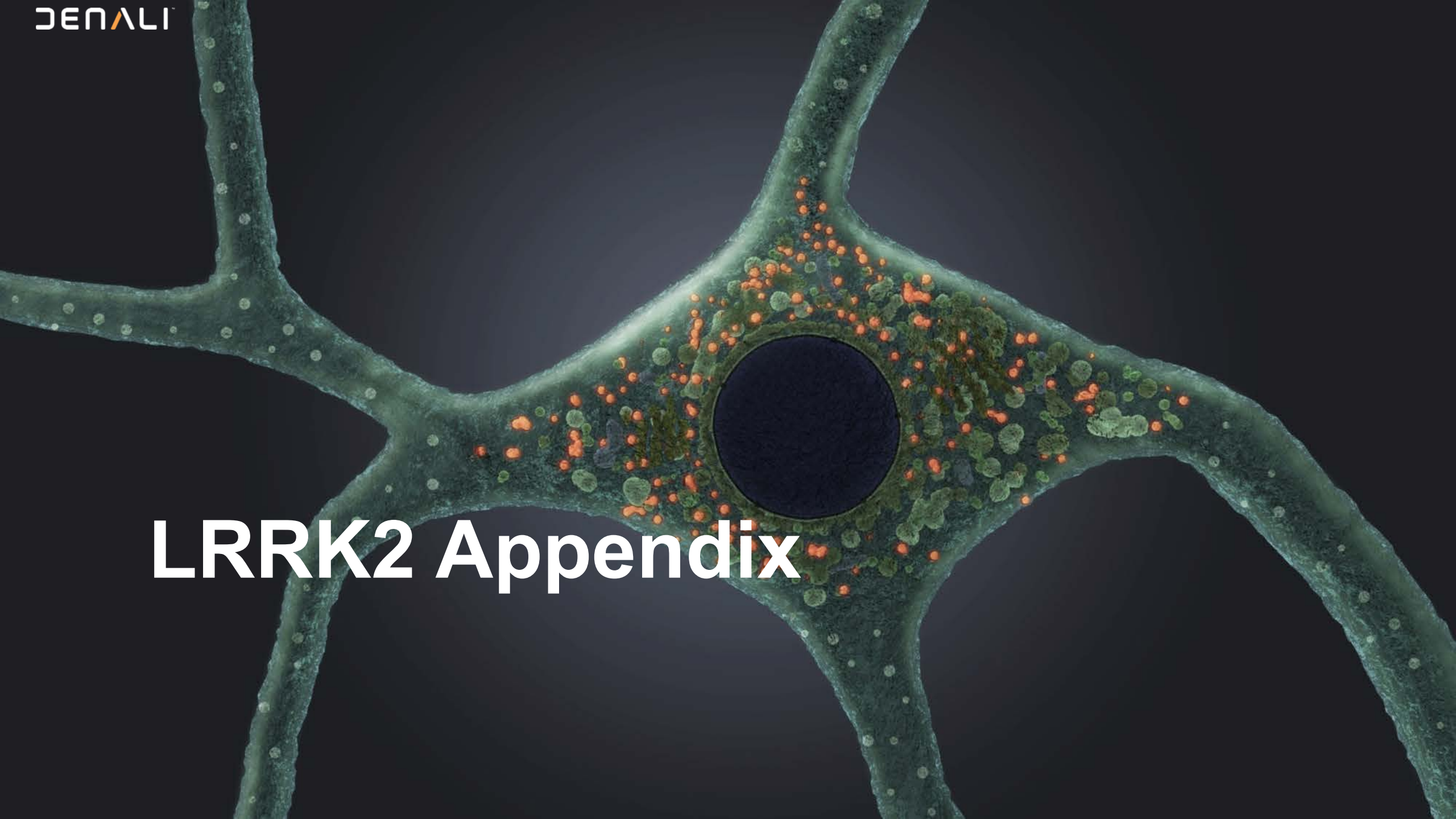
4 week cohort

TfR$^{mu/hu}$KI + Vehicle
IDSKO;TfR$^{mu/hu}$KI + Vehicle
IDSKO;TfR$^{mu/hu}$KI + IDS
IDSKO;TfR$^{mu/hu}$KI + ETV:IDS





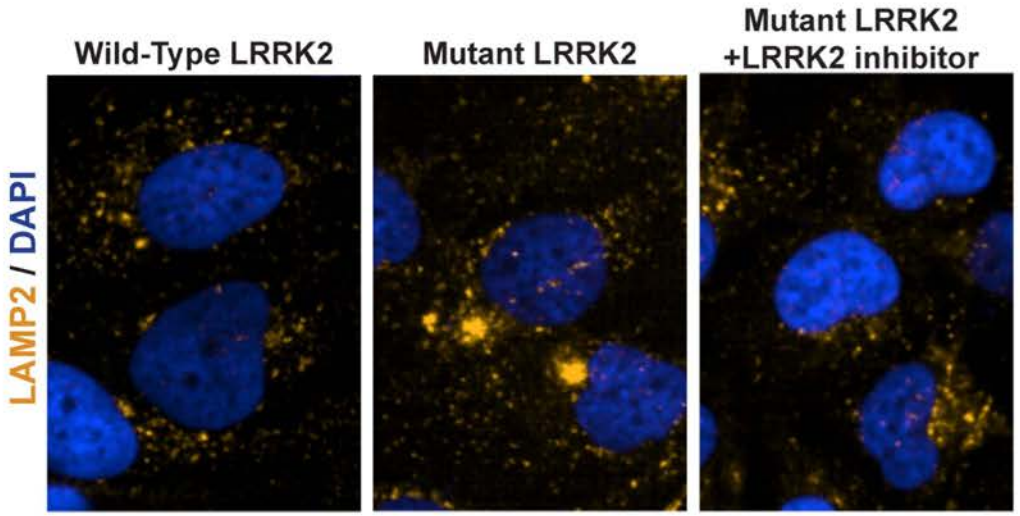
**** P < 0.0001
*** P < 0.001
ns = not significant
1-way ANOVA
IDS & ETV:IDS dosed at activity equivalent 746 µmol/min/kg

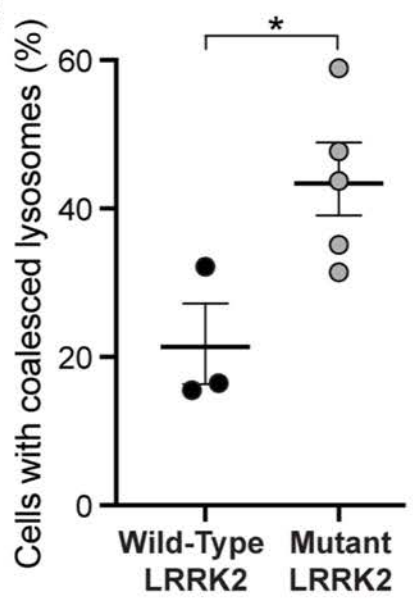


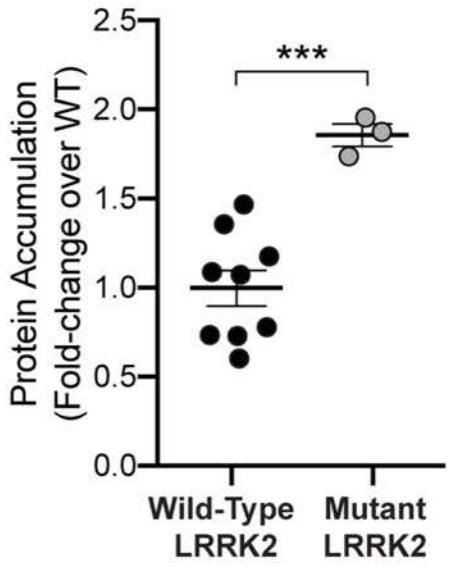
LRRK2 Appendix

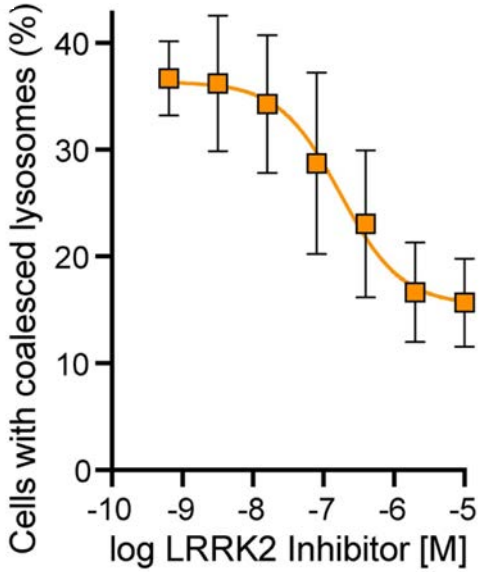
INHIBITION OF LRRK2 BLOCKS LYSOSOMAL DYSFUNCTION

Expression of mutant LRRK2 G2019S results in abnormal lysosomal biology







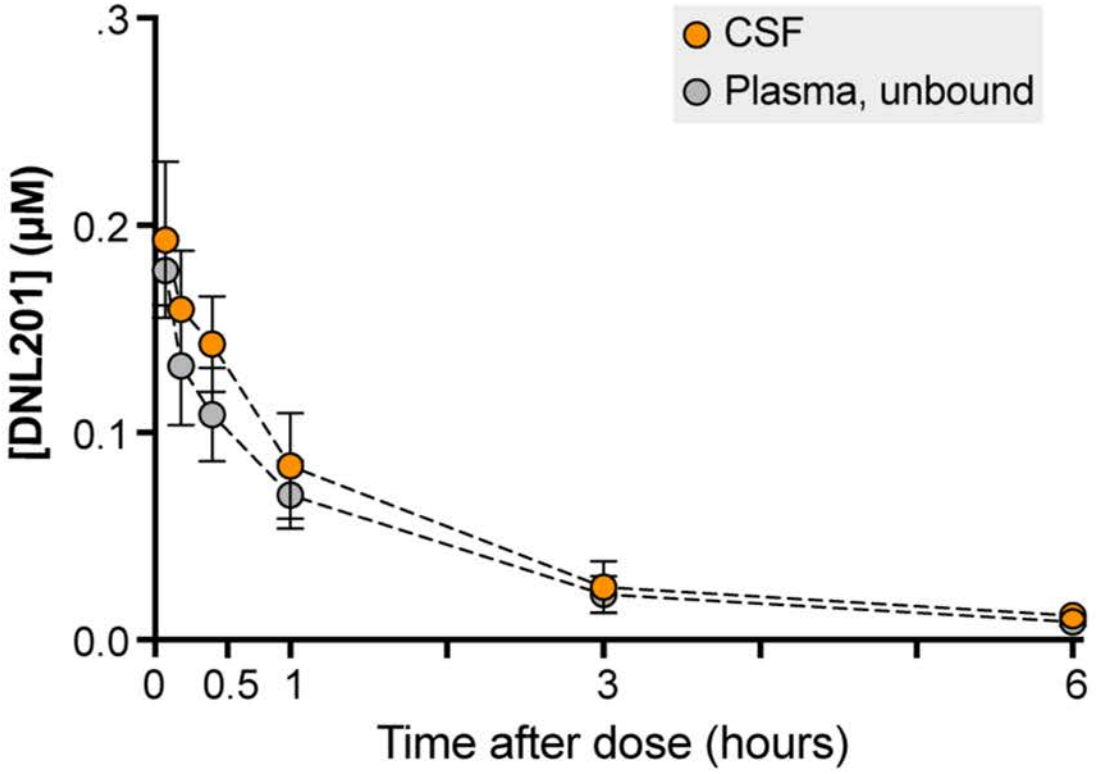


- Mutated LRRK2 (G2019S) results in coalesced, dysfunctional lysosomes (yellow; protein accumulation)
- LRRK2 inhibition with DNL201 can block abnormal lysosomal phenotype

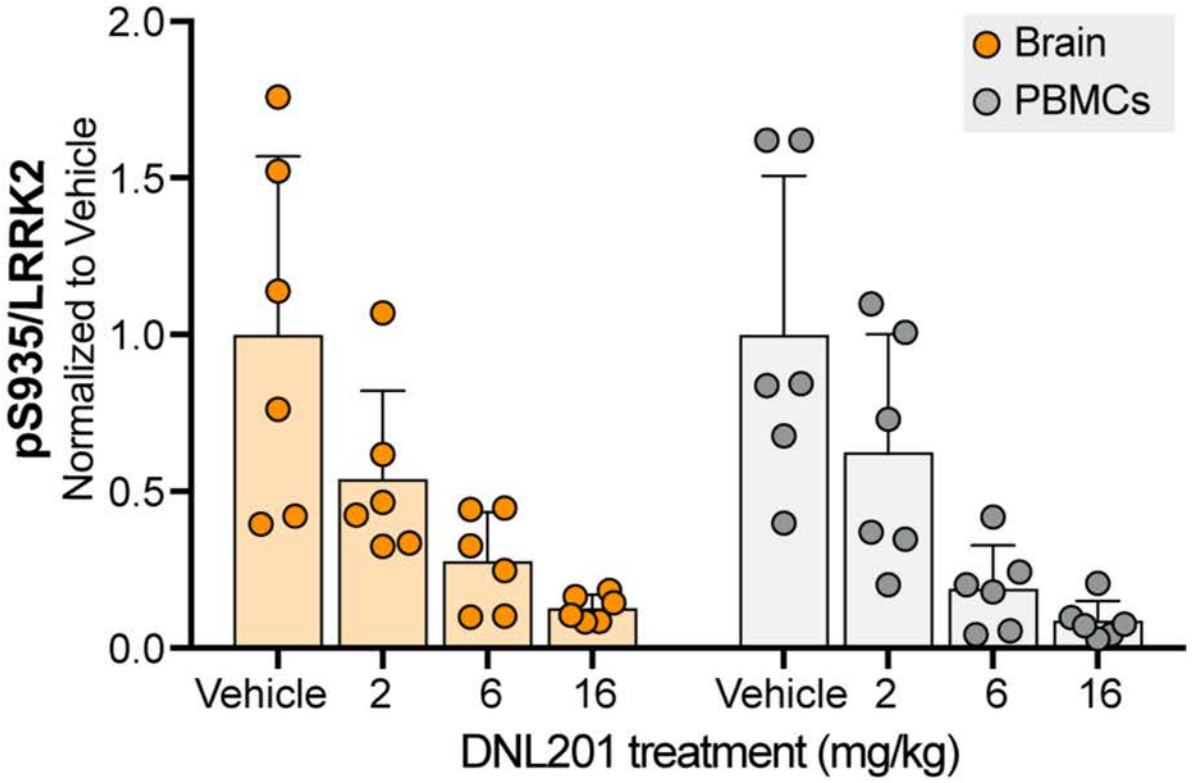
LRRK2 Inhibitor

DNL201 PHARMACOLOGICAL PROPERTIES AND BRAIN EXPOSURE

PK: drug concentration brain (CSF) and blood



PD: equal LRRK2 inhibition in brain and blood

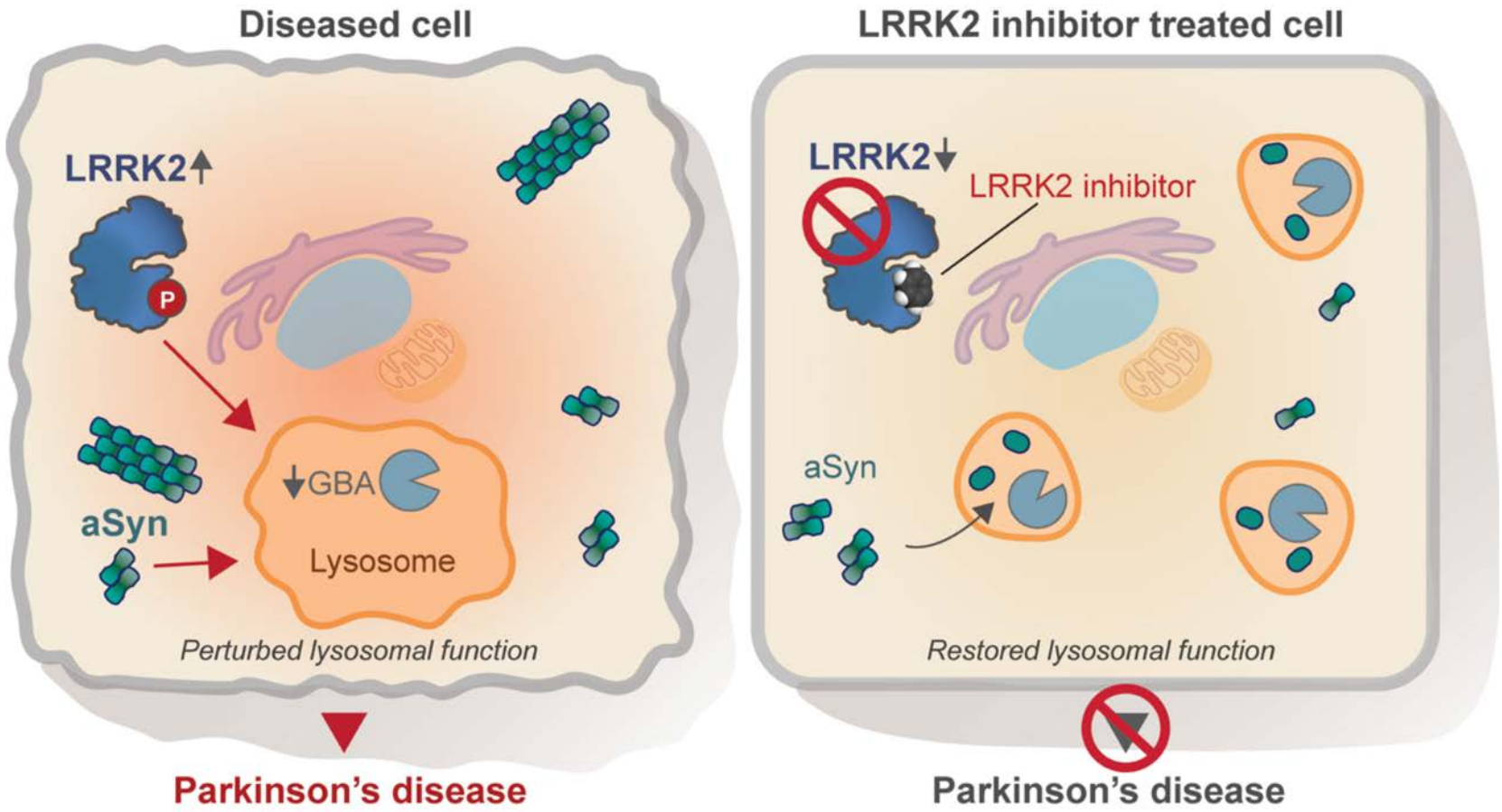


- DNL201 concentrations in monkey plasma (unbound) and CSF demonstrate comparable plasma unbound and CSF exposures
- Comparable pS935 inhibition in PBMCs and brain is observed in monkey 24 hours after the last dose is given

LRRK2 Inhibitor

LRRK2 HYPERACTIVITY DRIVES LYSOSOMAL DYSFUNCTION AND PD

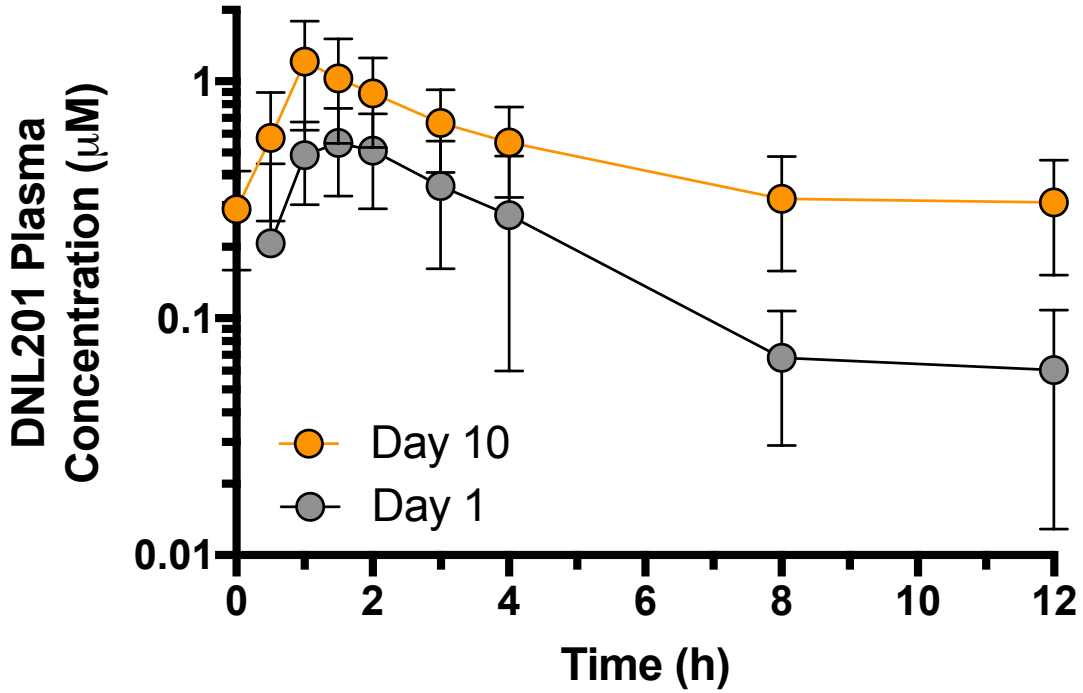
- Increased LRRK2 kinase activity impairs lysosomal function and drives familial PD
- LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in PD models



LRRK2 Inhibitor

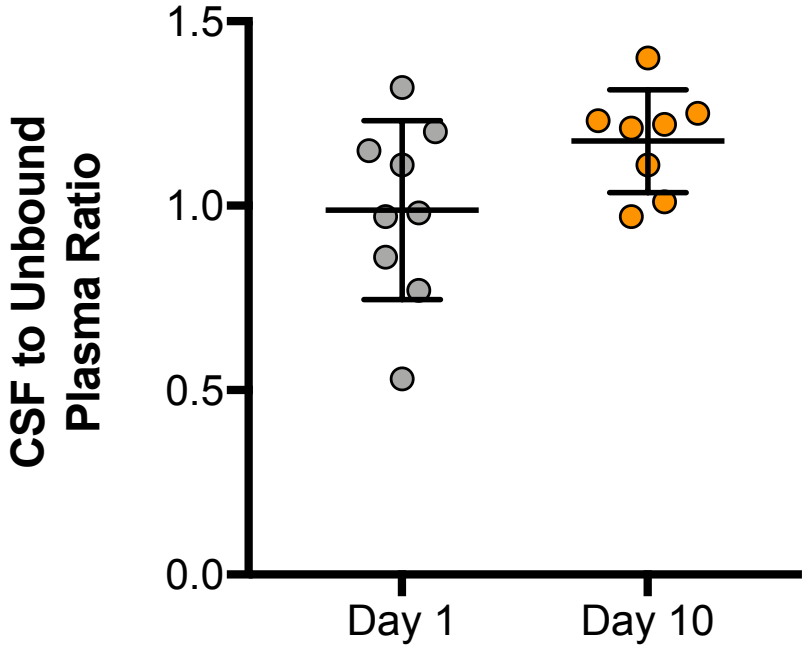
DNL201 PHARMACOKINETIC PROPERTIES AND BRAIN EXPOSURE

PK: drug concentration in blood



- PK profile supports twice daily dosing
- Terminal half life of 14-22 hours
- Low to moderate variability
- Steady state reached by Day 10

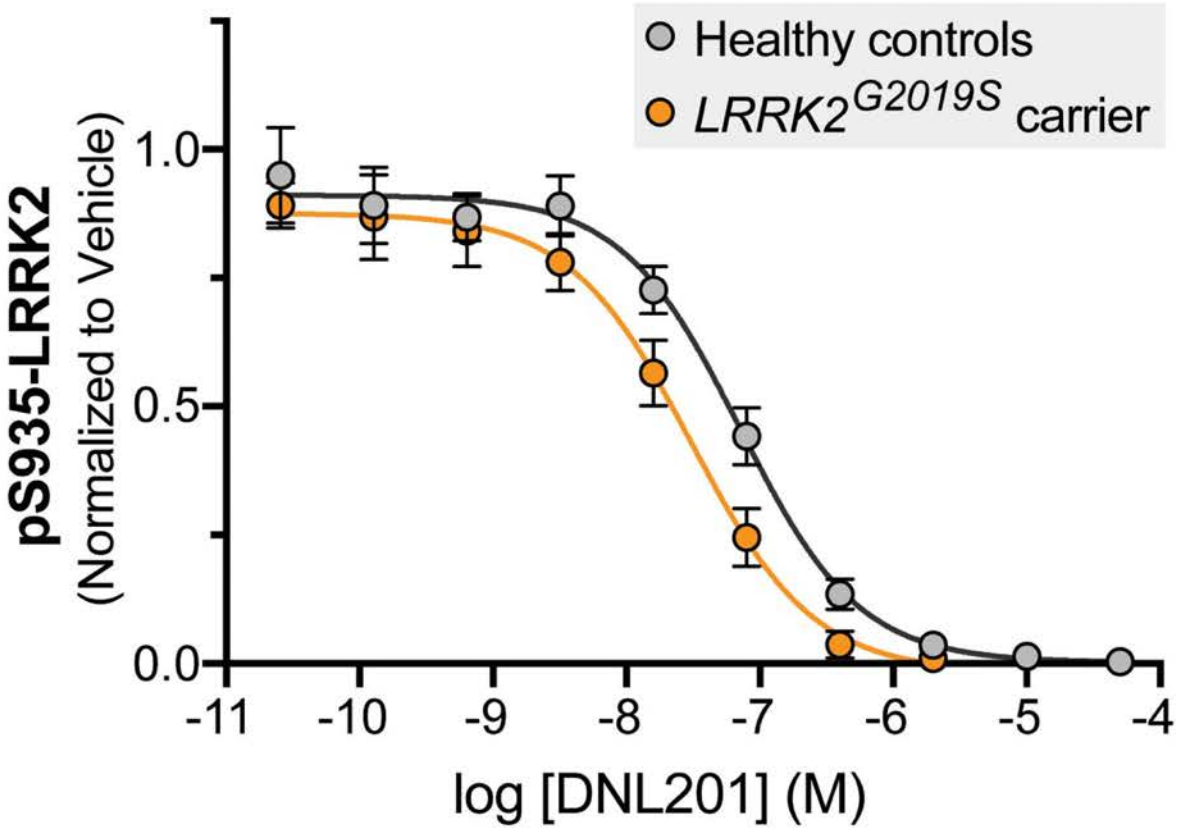
PK: drug concentration in CSF

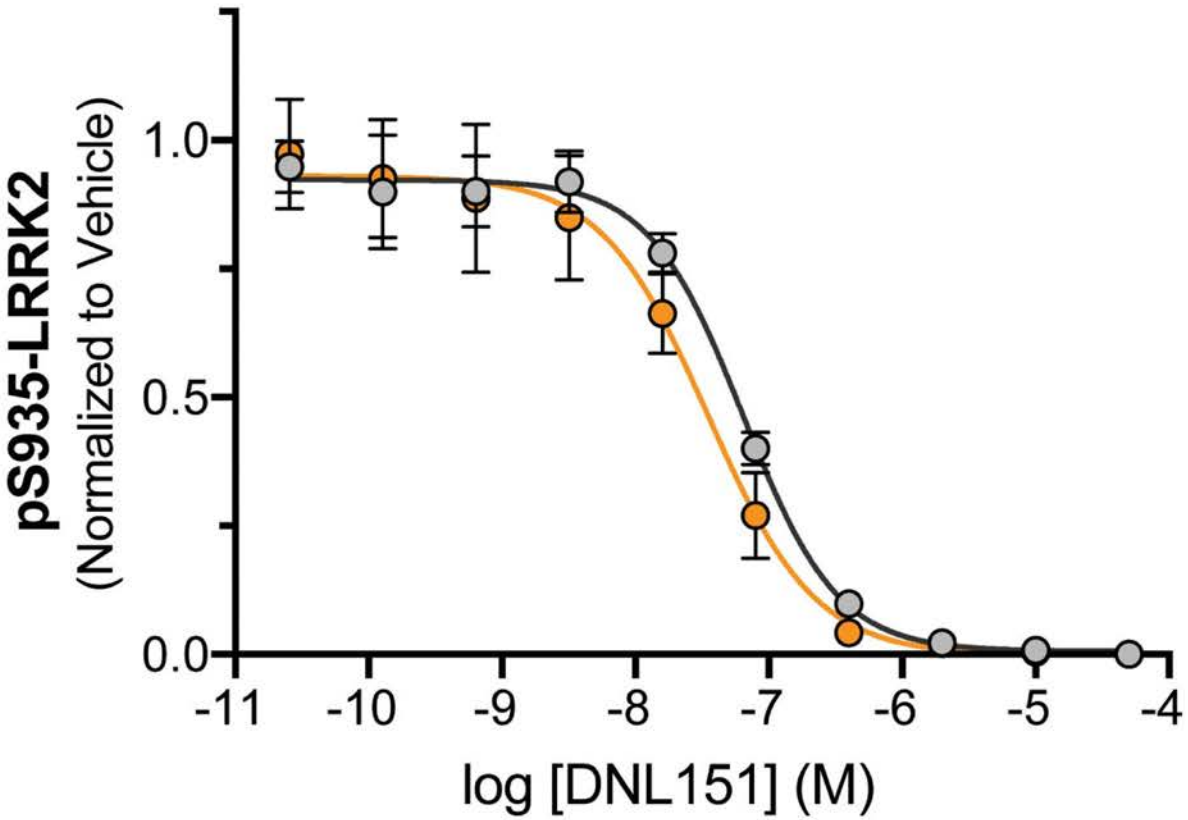


- DNL201 shows a mean CSF to unbound plasma ratio of ~1.0

LRRK2 Inhibitor

INHIBITION OF LRRK2 IN MUTATION CARRIERS

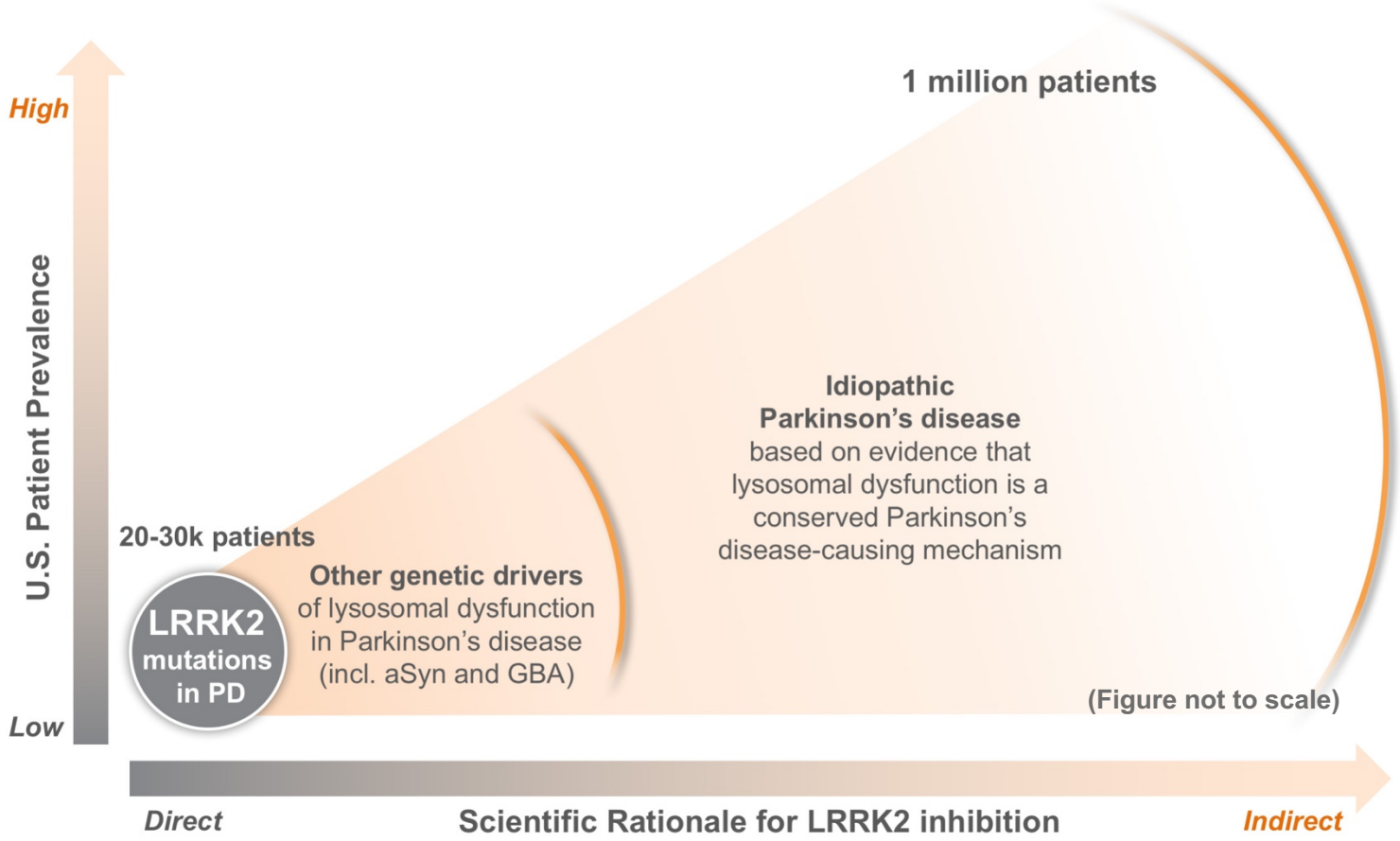




- Both DNL201 and DNL151 robustly inhibit LRRK2 in human mutation carrier blood (*ex vivo*)

LRRK2 Inhibitor

LRRK2 INHIBITION HAS BROAD THERAPEUTIC POTENTIAL FOR PD

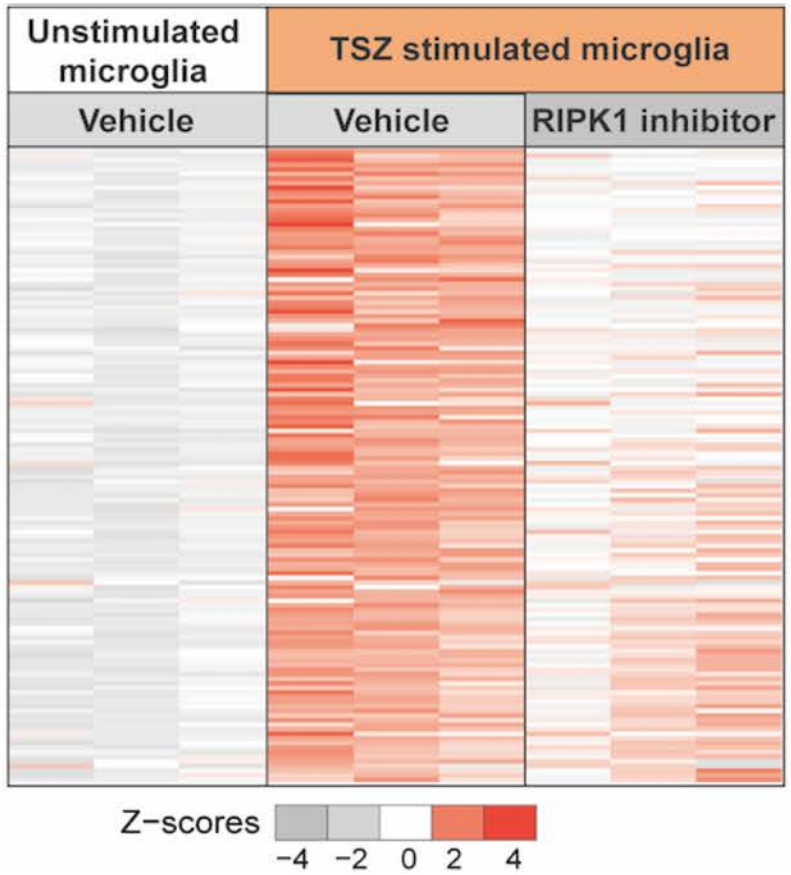


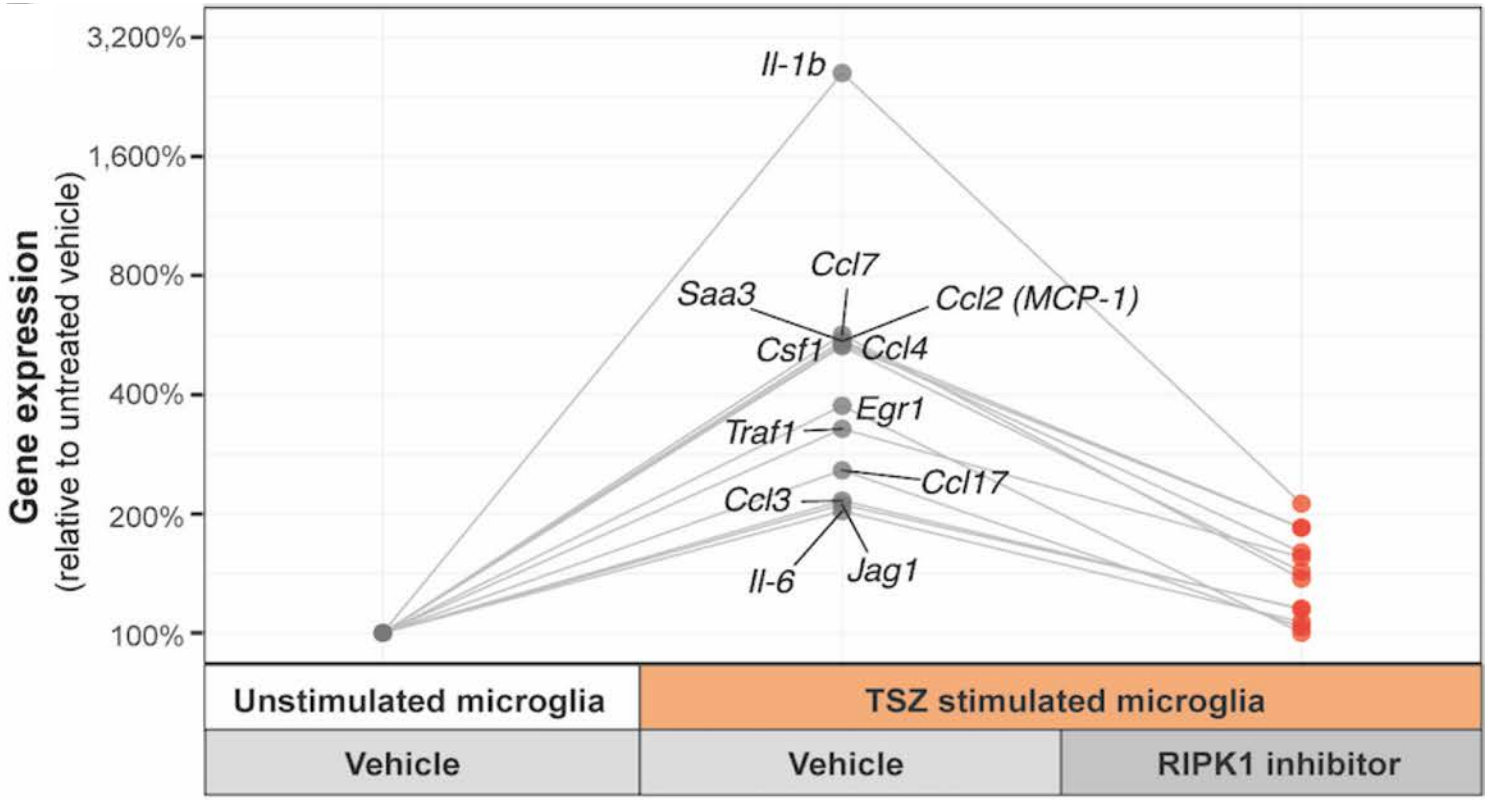
- Lysosomal dysfunction is a central pathophysiology of PD in patients with and without known genetic drivers of PD
- Inhibition of LRRK2 may be a therapeutically beneficial approach for many forms of PD

LRRK2 Inhibitor

RIPK1 Appendix

RIPK1 INHIBITION BLOCKS INFLAMMATION IN HUMAN MICROGLIA



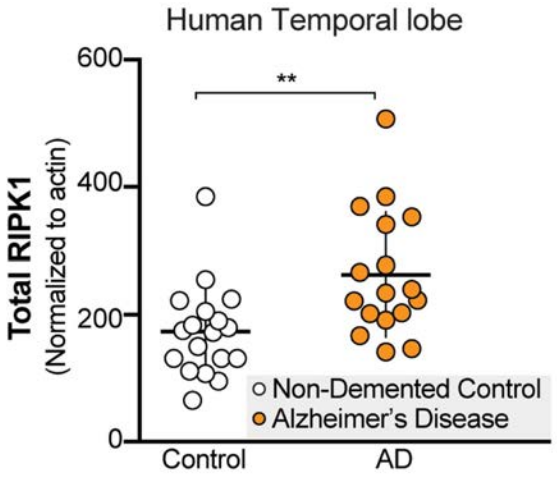


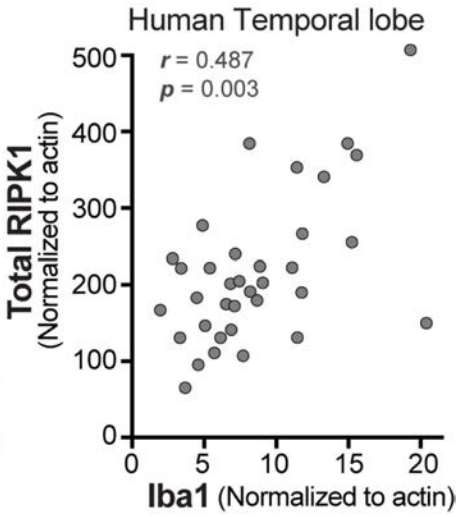
- Stimulation of microglia with a TNF cocktail (TSZ) results in induction of many genes, and the majority of these changes are reversed after treatment with a RIPK1 inhibitor
- Many of the top upregulated genes are pro-inflammatory cytokines and chemokines such as IL-1b, IL-6 and Ccl2 (MCP-1)
- Results suggest that production of pro-inflammatory cytokines in microglia is RIPK1 dependent

RIPK1 Inhibitor

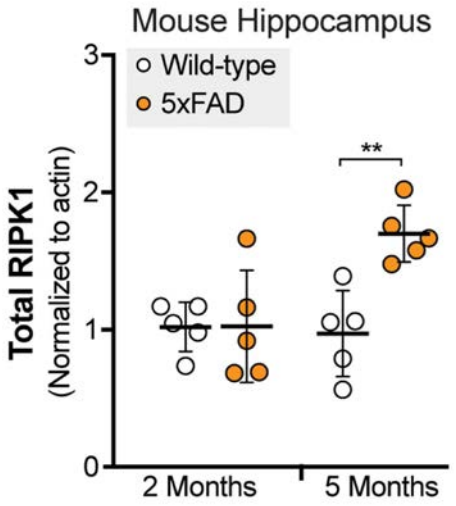
RIPK1 IN ALZHEIMER'S DISEASE

RIPK1 increased in brains of human AD patients and in an Alzheimer's mouse model





Denali Data



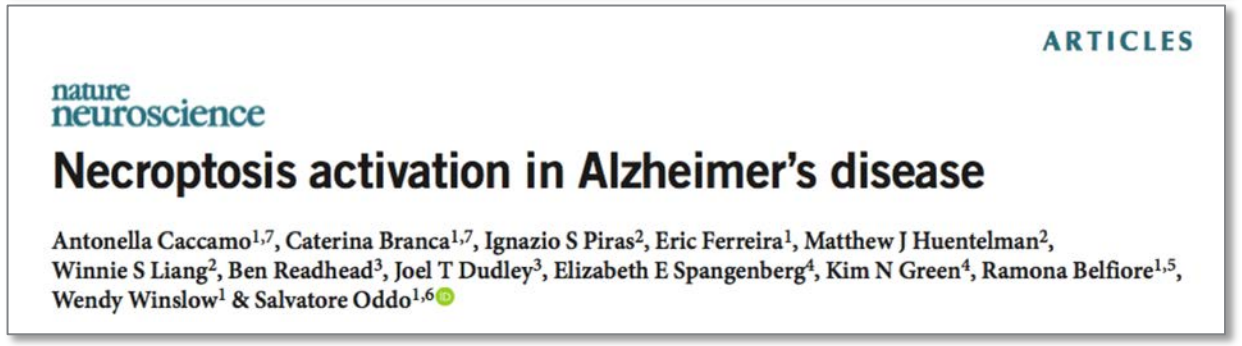
PNAS

RIPK1 mediates a disease-associated microglial response in Alzheimer's disease

Dimitry Ofengeim[a,1], Sonia Mazzitelli[a,1], Yasushi Ito[a], Judy Park DeWitt[a], Lauren Mifflin[a], Chengyu Zou[a], Sudeshna Das[b,c], Xian Adiconis[d], Hongbo Chen[a], Hong Zhu[a], Michelle A. Kelliher[e], Joshua Z. Levin[d], and Junying Yuan[a,2]

[a]Department of Cell Biology, Harvard Medical School, Boston, MA 02115; [b]MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Cambridge, MA 02139; [c]Department of Neurology, Harvard Medical School, Boston, MA 02115; [d]Broad Institute, Cambridge, MA 02142; and [e]Department of Cancer Biology, University of Massachusetts Medical School, Worcester, MA 01605

Contributed by Junying Yuan, August 15, 2017 (sent for review August 11, 2017; reviewed by J. Marie Hardwick and David Rubinsztein)



ARTICLES

nature neuroscience

Necroptosis activation in Alzheimer's disease

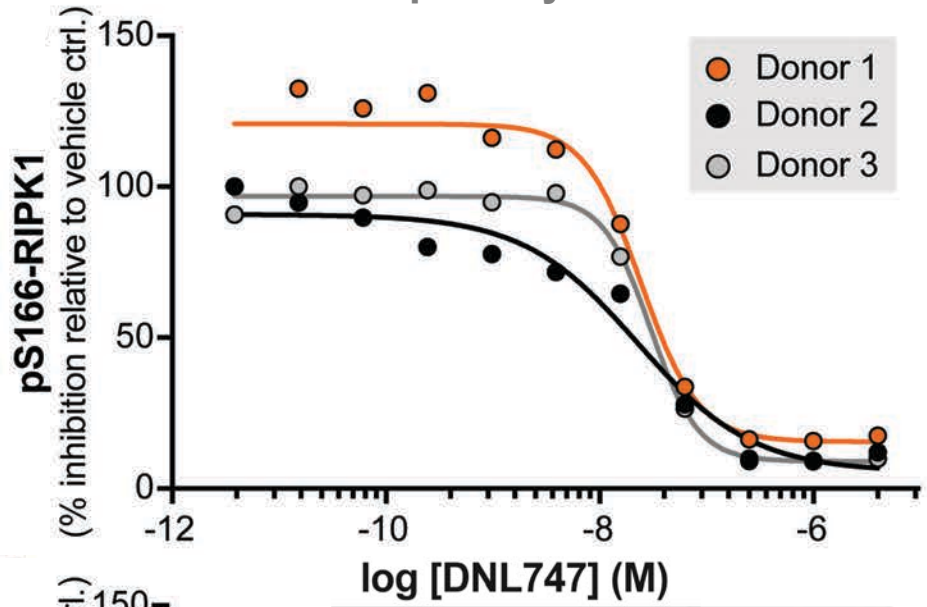
Antonella Caccamo[1,7], Caterina Branca[1,7], Ignazio S Piras[2], Eric Ferreira[1], Matthew J Huentelman[2], Winnie S Liang[2], Ben Readhead[3], Joel T Dudley[3], Elizabeth E Spangenberg[4], Kim N Green[4], Ramona Belfiore[1,5], Wendy Winslow[1] & Salvatore Oddo[1,6]

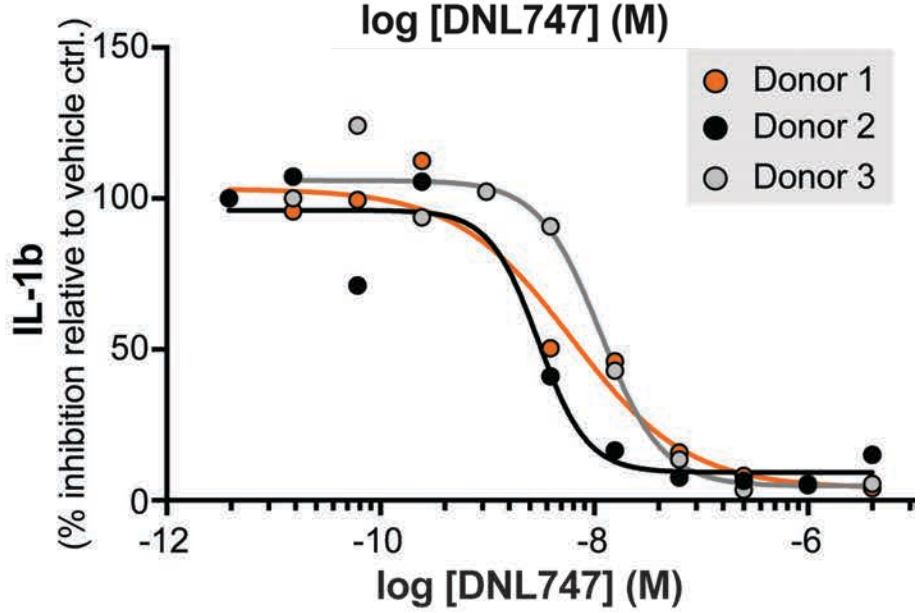
- RIPK1 pathway is activated in human AD patient brain and AD mouse models – *Denali data*
- Published literature shows protection in AD models with RIPK1 loss-of-function
- Clinical strategy: demonstrate peripheral target engagement in Ph1 healthy volunteer study; demonstrate central target engagement in a Ph2a biomarker study in AD patients

RIPK1 Inhibitor

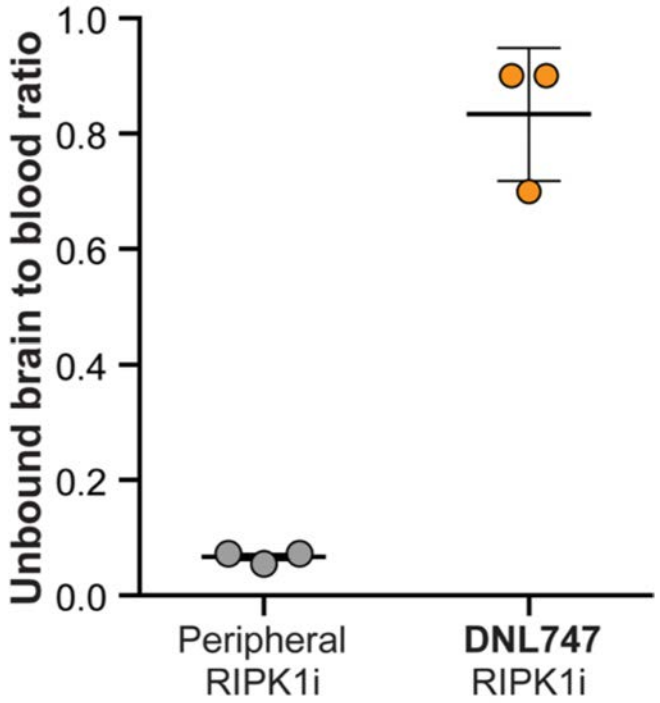
DNL747 PHARMACOLOGICAL PROPERTIES & BRAIN EXPOSURE

Treatment of primary human cells





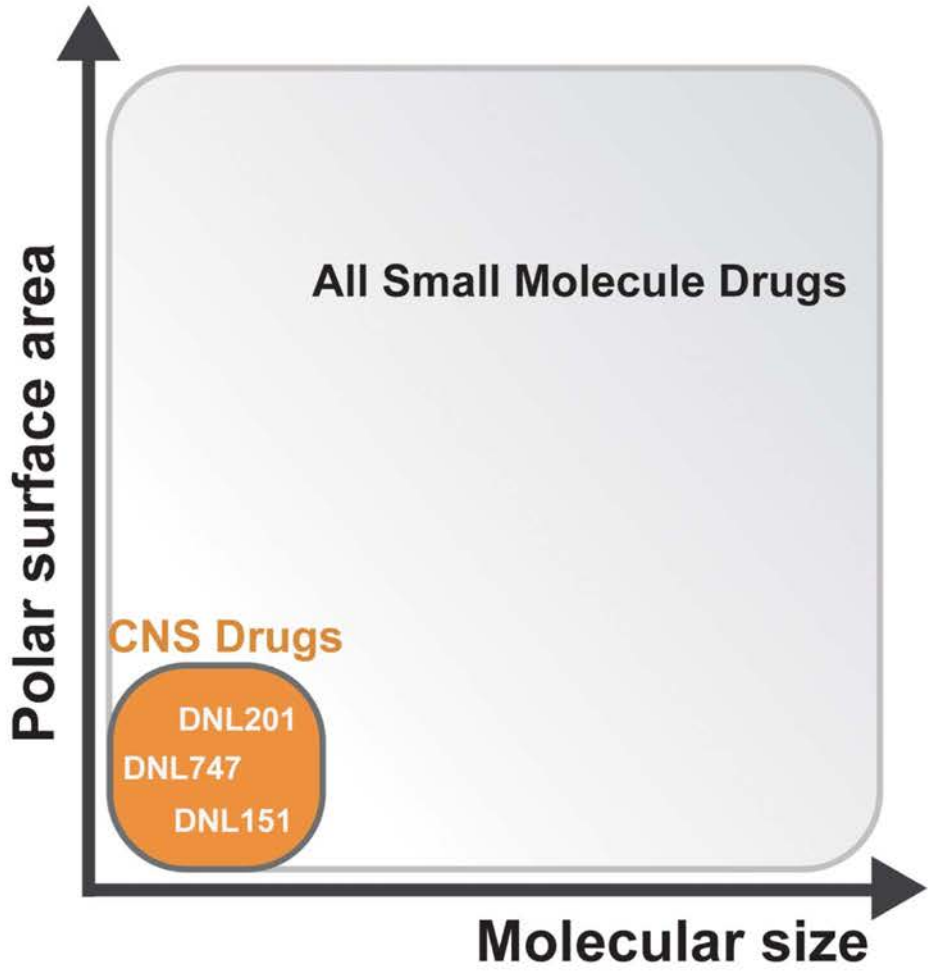
Robust brain uptake with DNL747

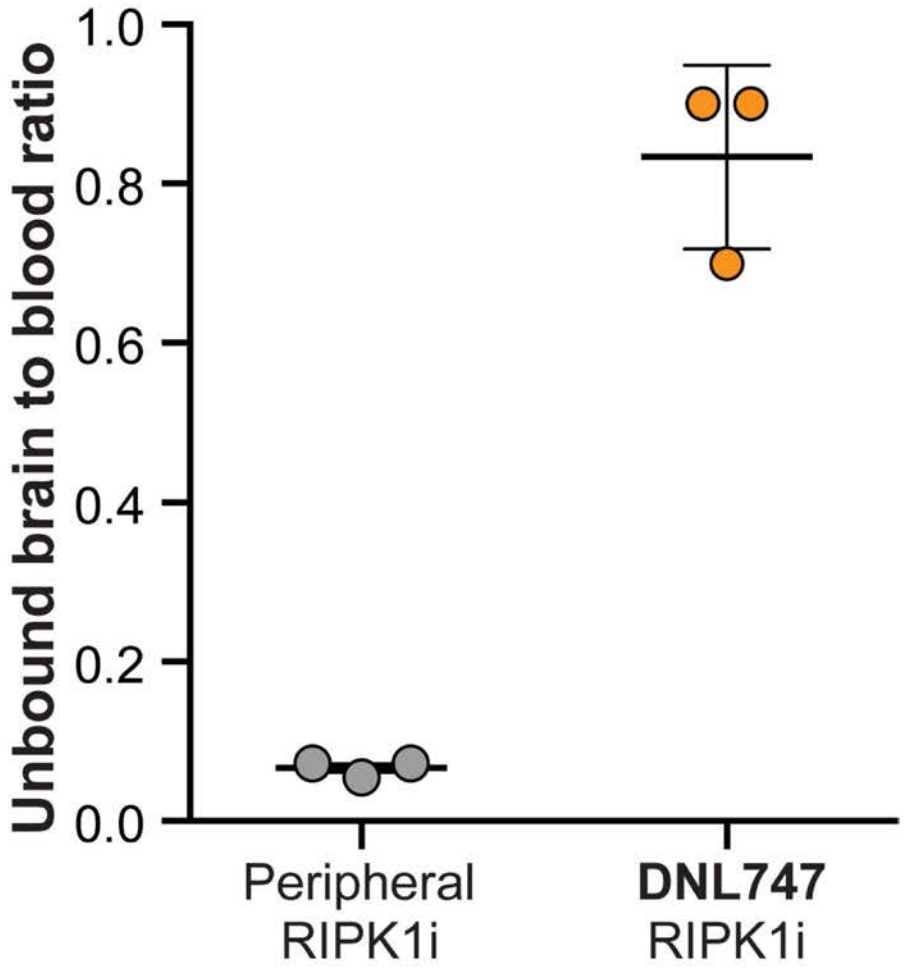


- Treatment of primary human cells with DNL747 results in a dose dependent reduction in p-RIPK1 and IL-1b
- DNL747 show a brain to blood ratio of ~0.8 while a benchmark periphery-restricted RIPK1 inhibitor displays a ratio of ~0.05
- **CTA Filing for DNL747 in February 2018 – FIH dosing in March 2018**

RIPK1 Inhibitor

ENGINEERING SMALL MOLECULES TO CROSS THE BBB





Source: Denali Therapeutics Inc.