
DENALI™
Discover, Develop, Defeat Degeneration
September 2018

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Forward Looking Statements

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Accuracy of Data

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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

OUR PEOPLE

SCIENTISTS AND DRUG DEVELOPERS

165+ BASED IN SOUTH SAN FRANCISCO

BOARD OF DIRECTORS

VICKI SATO (CHAIR) | MARC TESSIER-LAVIGNE | DOUG COLE | JAY FLATLEY | PETER KLEIN | ROBERT NELSEN | DAVID SCHENKEIN | RYAN WATTS

HARVARD UNIVERSITY · FLAGSHIP PIONEERING · Microsoft · agios · Stanford University · illumina · ARCH Venture Partners · DENALI THERAPEUTICS

SENIOR LEADERSHIP

RYAN J. WATTS, PHD – CEO

- Previously built and led Genentech's neuroscience strategy, portfolio and research department
- Stanford University, PhD Biological Sciences

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; Neurology Residency, Harvard

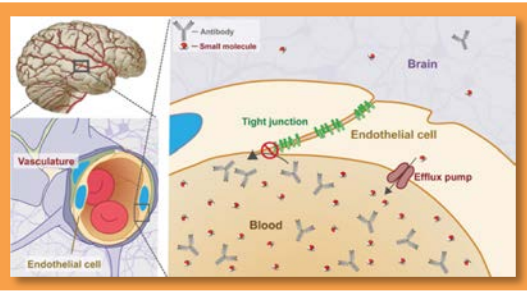
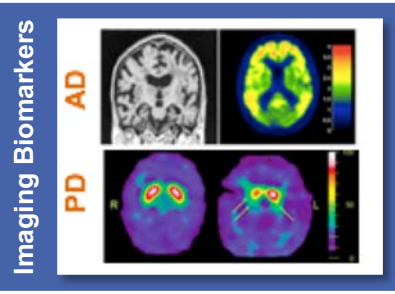
STEVE KROGNES – CFO

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

DANA ANDERSEN – CTMO

- Formerly VP and Global Head of Technical Development Project & Portfolio Management, Genentech/Roche
- Stanford University, PhD Chemical Engineering

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

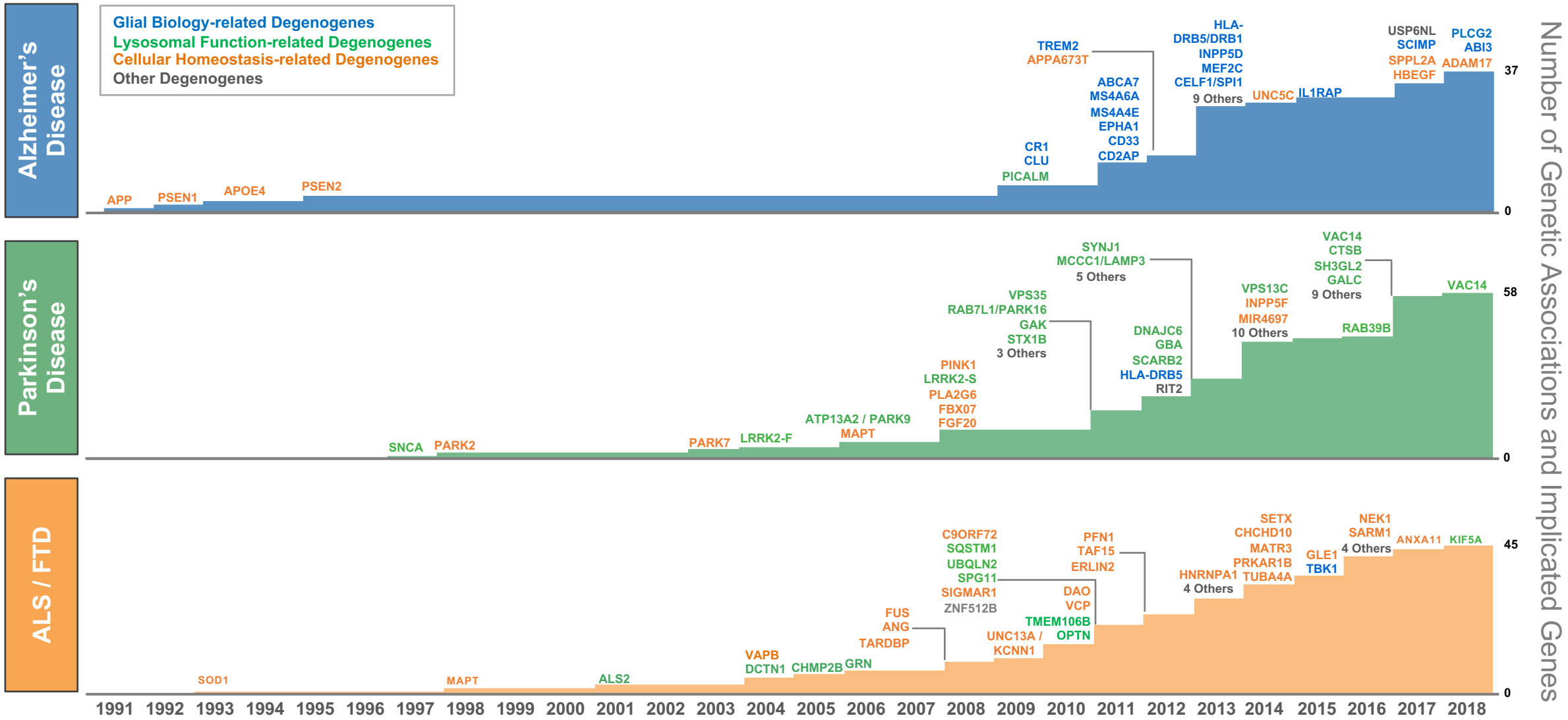
	Our Approach		Rationale
Genetic Pathway Potential	• Human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven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

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

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

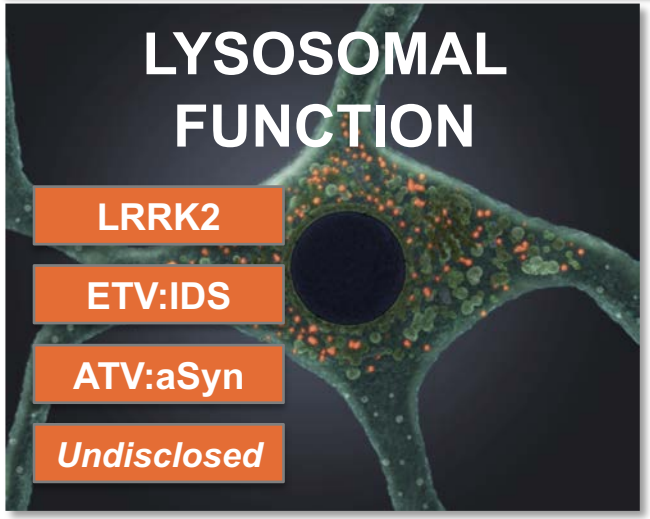
- Alzheimer's disease
- Parkinson's disease
- Amyotrophic Lateral Sclerosis
- Lysosomal Storage Diseases
- Huntington's disease
- Frontotemporal Dementia
- Multiple System Atrophy
- Other Diseases

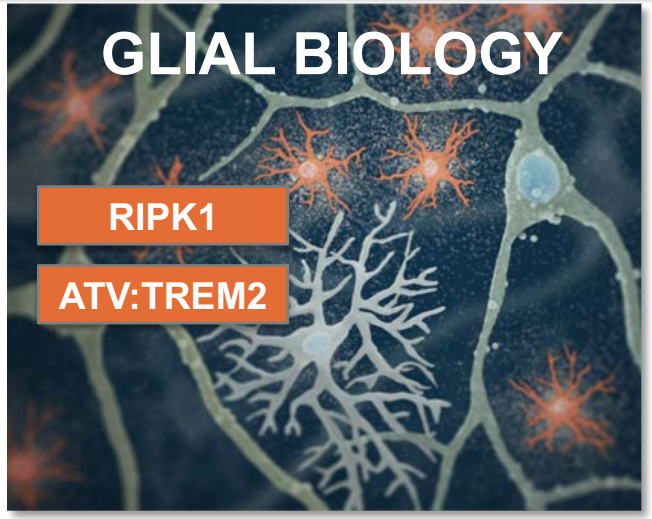
Human Genetics

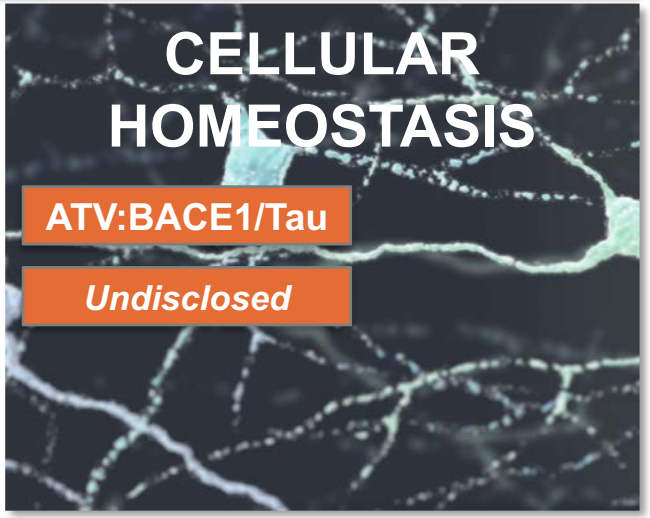
CORE (8)

SEED (5)

Pathways







DENALI CORE PORTFOLIO SEPTEMBER 2018

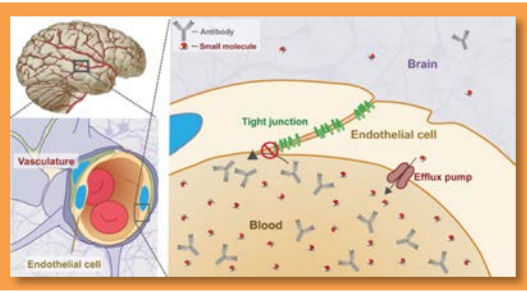
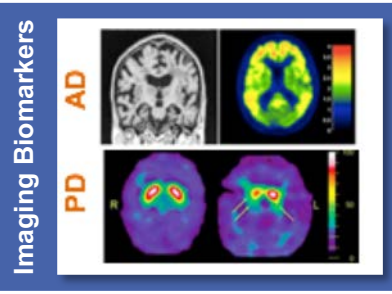
PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT					BIOMARKER ENABLED	
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	P	C
LYSOSOMAL FUNCTION PATHWAY									
LRRK2	DNL201 ●	Parkinson's						✓	✓
	DNL151 ●	Parkinson's						✓	✓
Iduronate 2-sulfatase	DNL310 ●	MPS II (Hunter Syndrome)						✓	✓
Alpha-Synuclein	ATV:aSyn ●	Parkinson's, DLB, MSA						✓	
Undisclosed	LF1 ●	Neurodegeneration						✓	✓
GLIAL BIOLOGY PATHWAY									
RIPK1	DNL747 ●	Alzheimer's, ALS						✓	✓
TREM2	ATV:TREM2 ●	Alzheimer's						✓	
CELLULAR HOMEOSTASIS									
BACE1/Tau	ATV:BACE1/Tau ●	Alzheimer's						✓	✓
Undisclosed	CH1 ●	Neurodegeneration						✓	

● **Antibody** ● **Small Molecule** ● **Protein** ● **Enzyme**

BIOMARKER ENABLED
P = Preclinical
C = Clinical

Denali's total portfolio currently consists of thirteen programs. To prioritize the allocation of our resources, we designate certain programs as CORE programs and others as SEED programs. Our current portfolio includes eight CORE programs listed above and five SEED programs in Drug Discovery and IND-enabling stages of development.

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

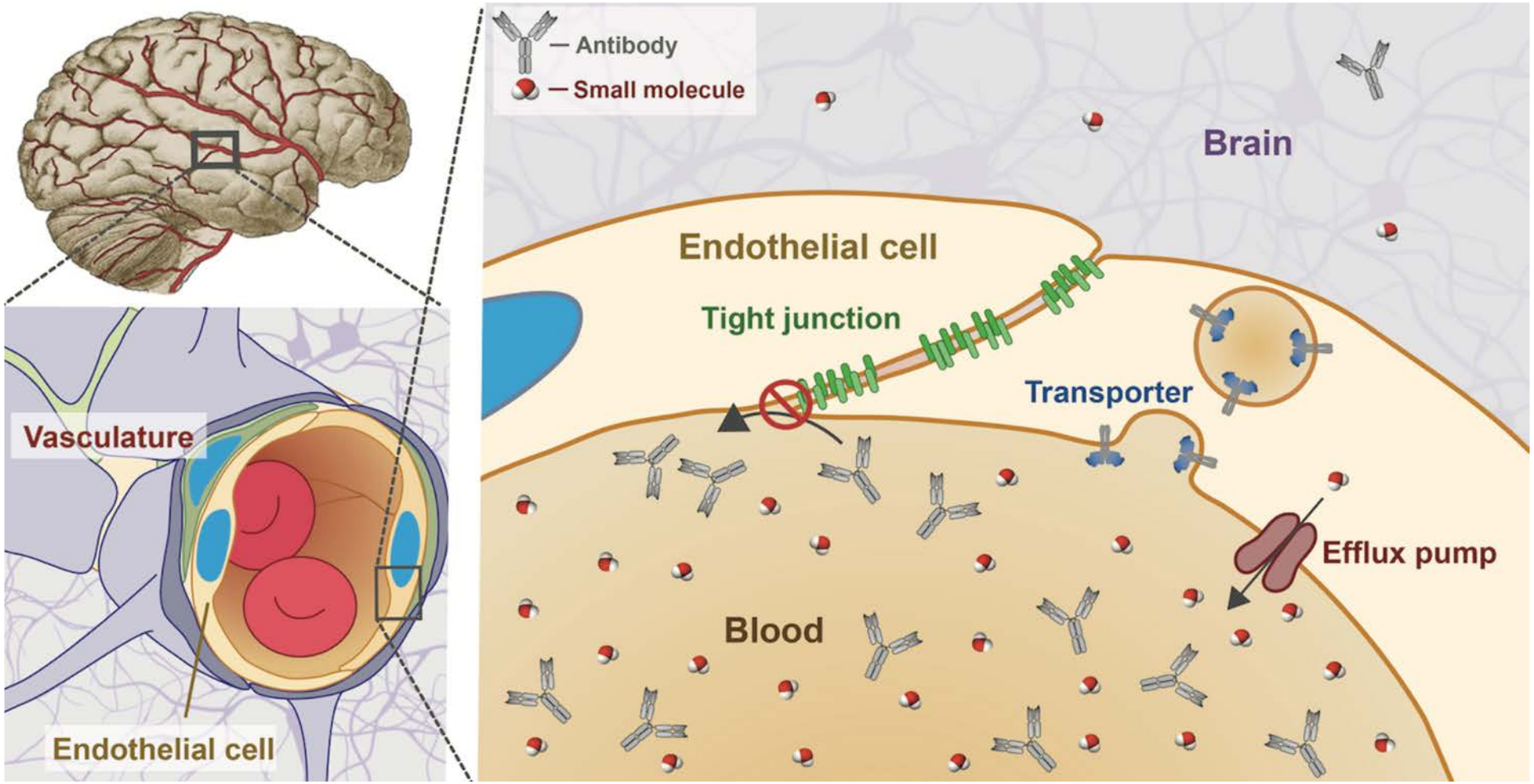
	Our Approach		Rationale
Genetic Pathway Potential	• Human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven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

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

INCREASED PROBABILITY OF SUCCESS

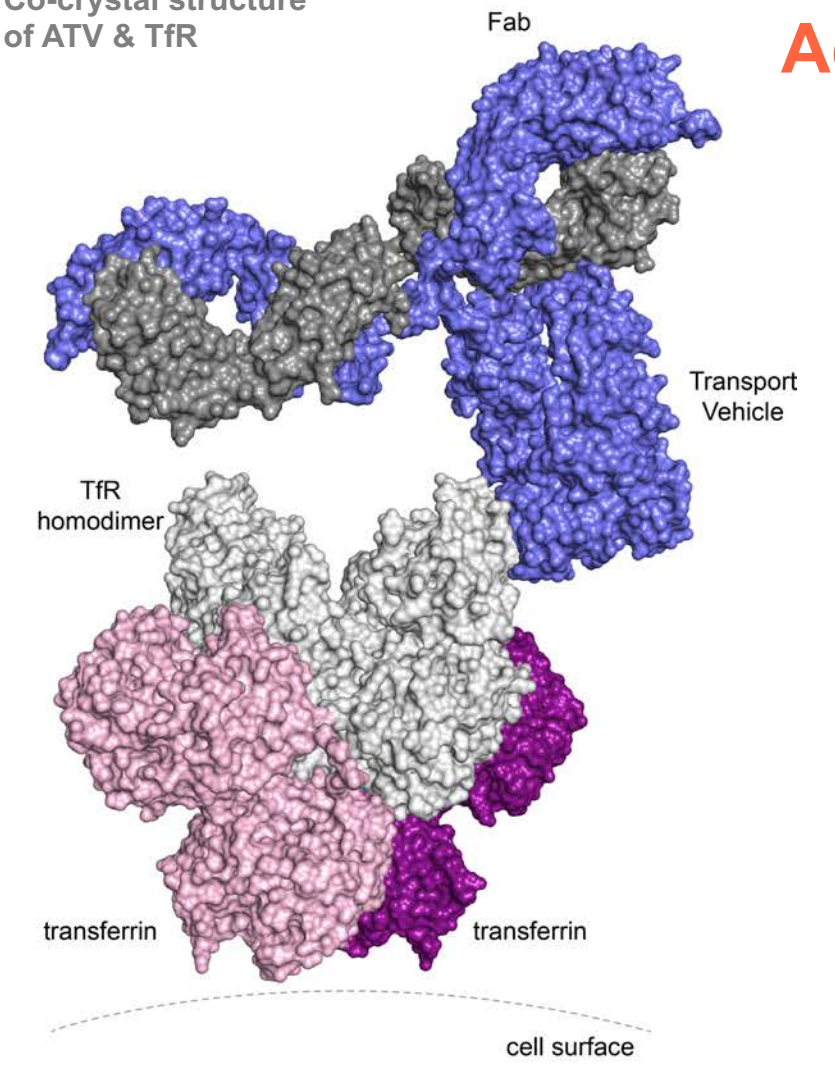
THE BLOOD-BRAIN BARRIER (BBB) CHALLENGE

- 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

Co-crystal structure of ATV & TfR

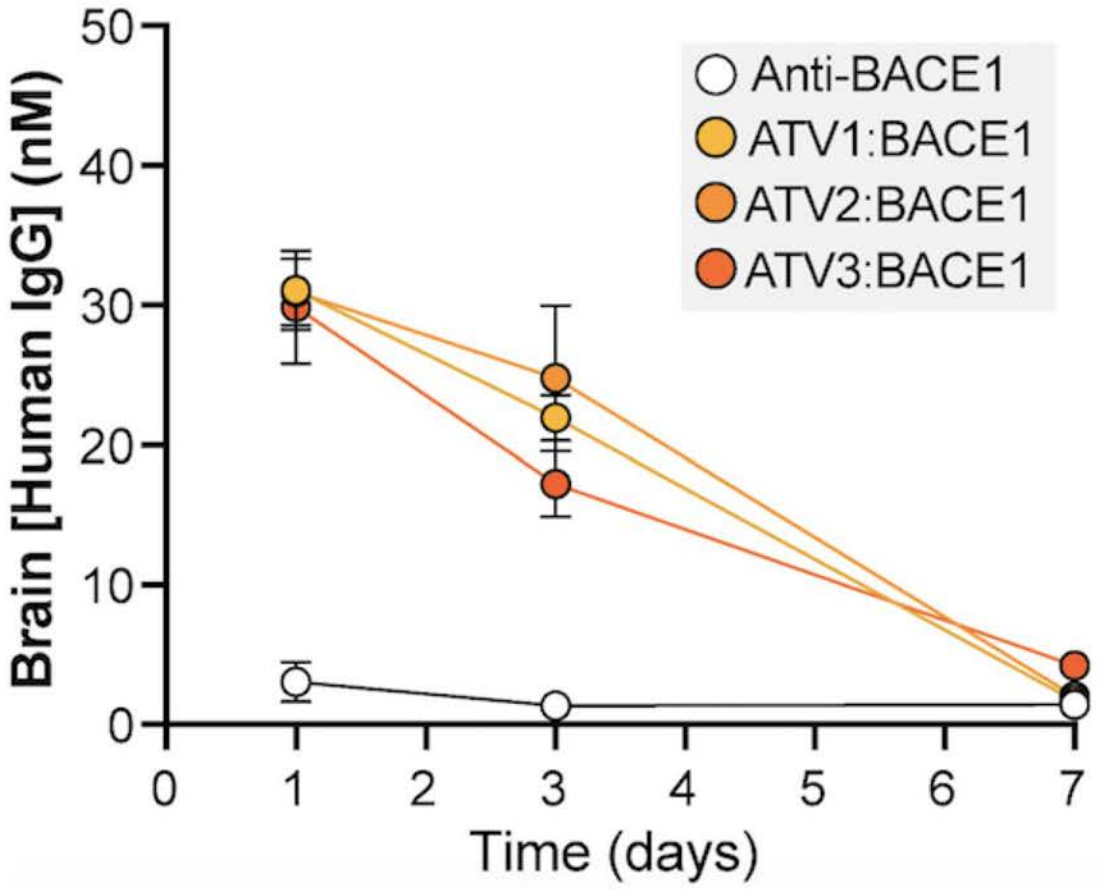


Advantages of TV

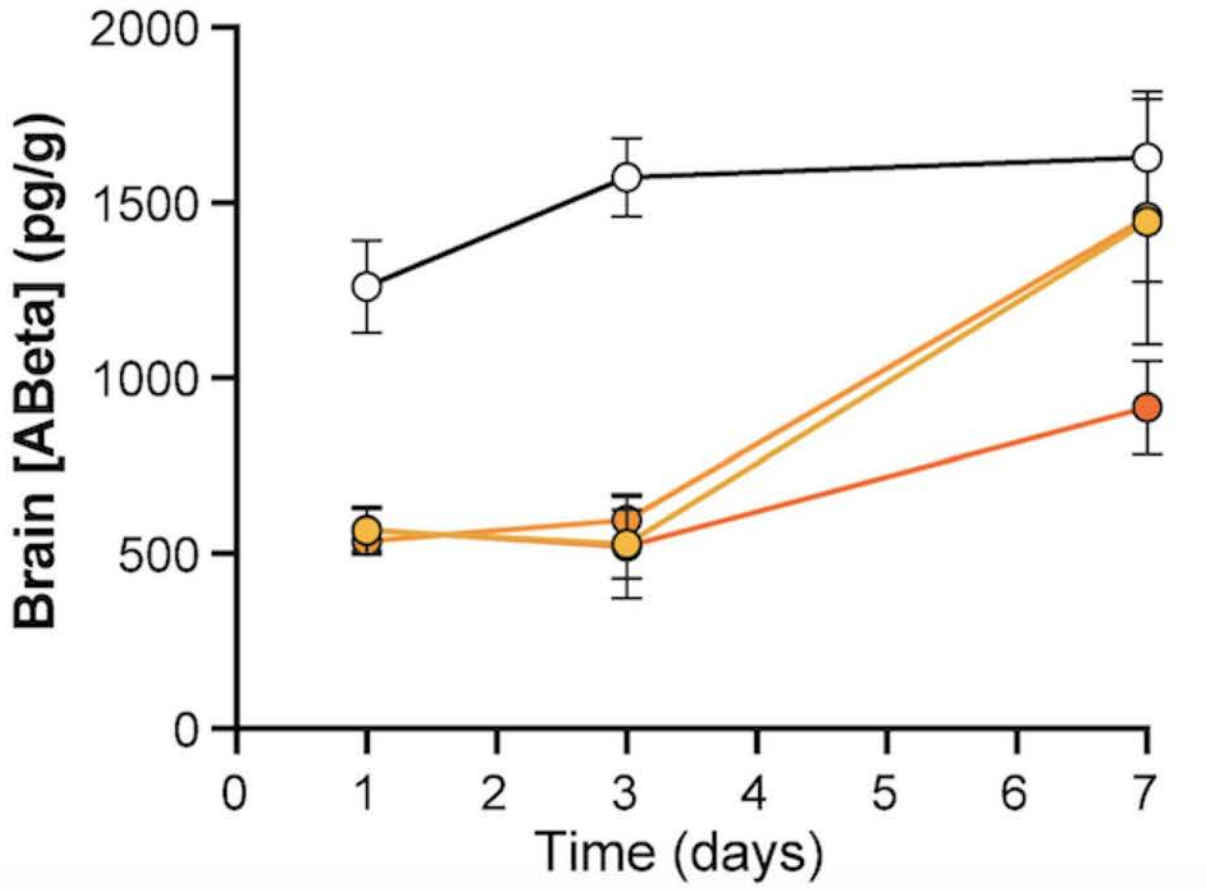
- Integrates BBB target binding into **Fc**
- No need for unnatural linkers or appended sequences
- Modularity:
  - **A**ntibody **T**ransport **V**ehicle (**ATV**)
  - **E**nzyme **T**ransport **V**ehicle (**ETV**)
  - Potential for other modalities
- ATV: retains **bivalent binding** for one or **two** 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



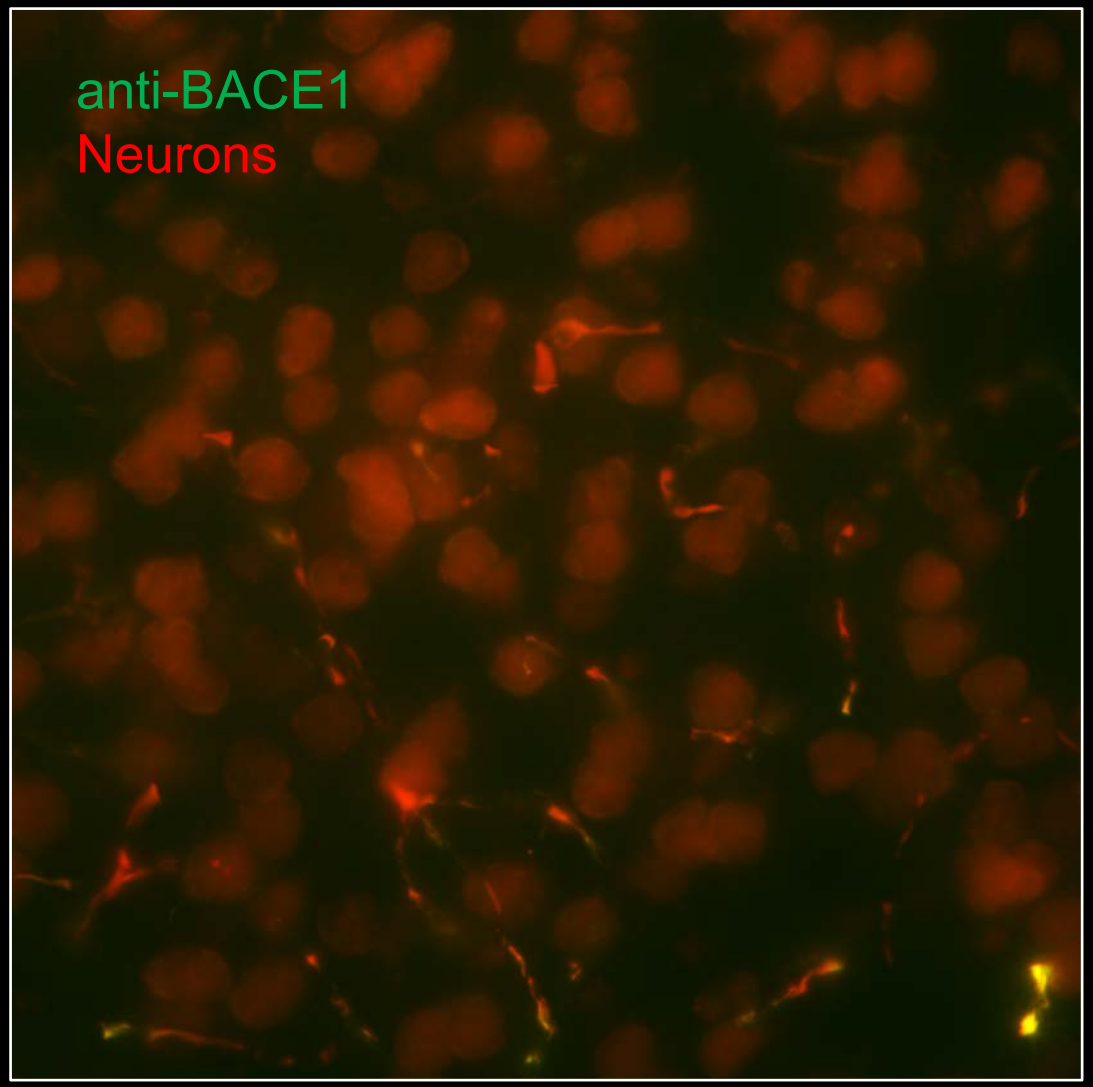
PD: Abeta reduction in brain

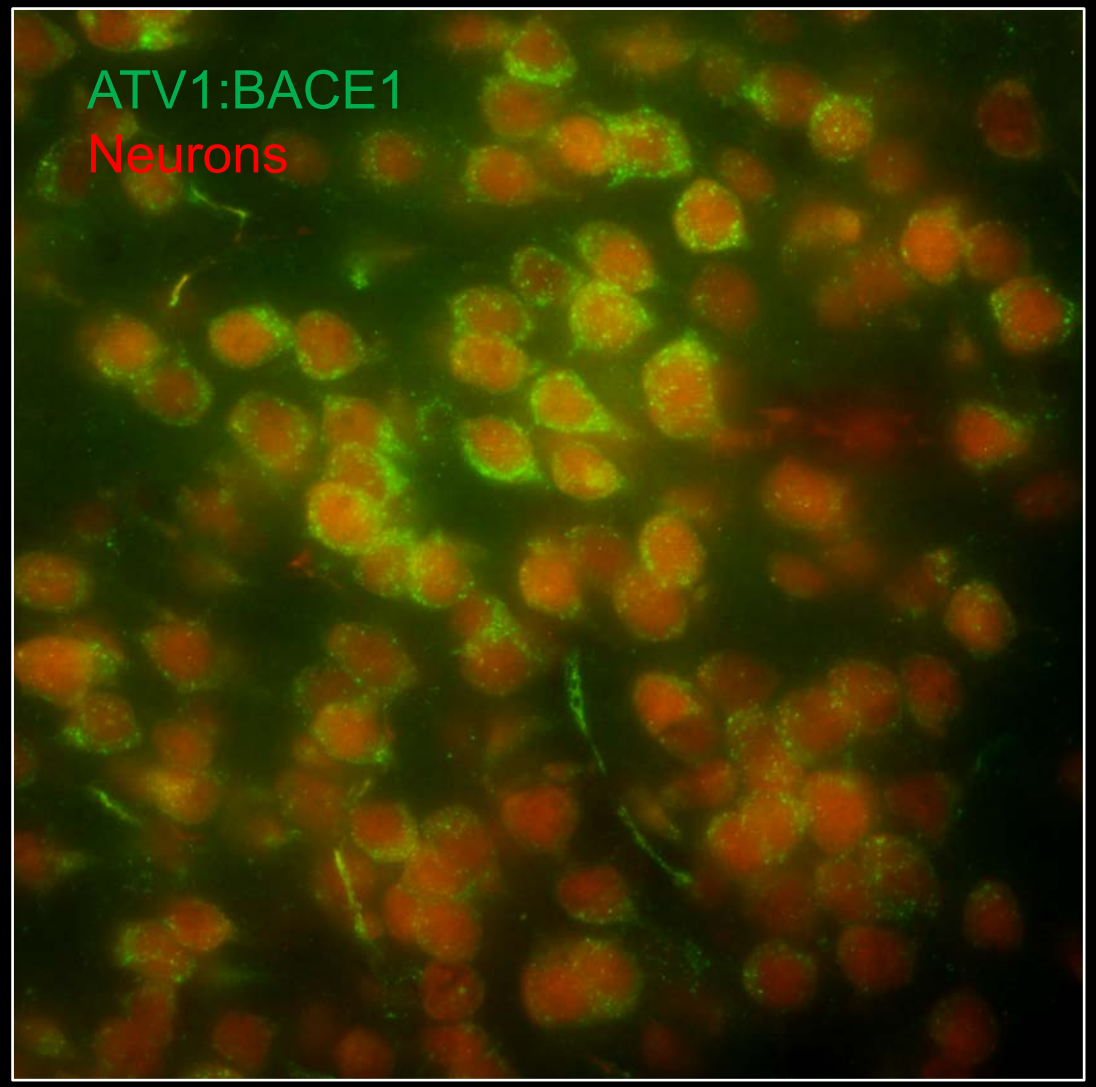


- 50 mg/kg IV dose in $TfR^{hu/ms}$ KI mice – time course

BROAD DISTRIBUTION OF ATV IN BRAIN

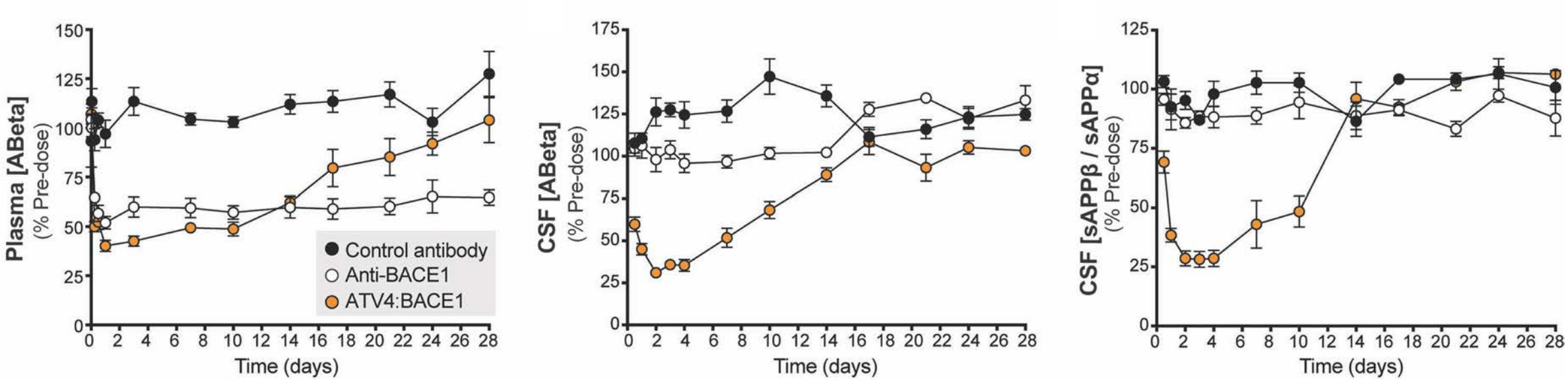
Localization of antibody in $TfR^{hu/ms}$ KI brain cortex 24hrs after 50 mg/kg IV





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

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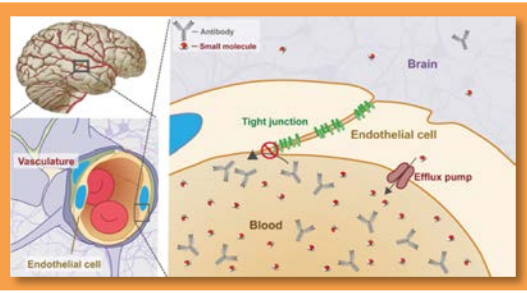
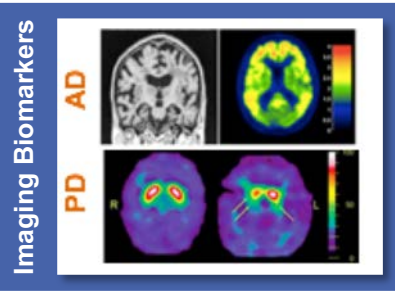
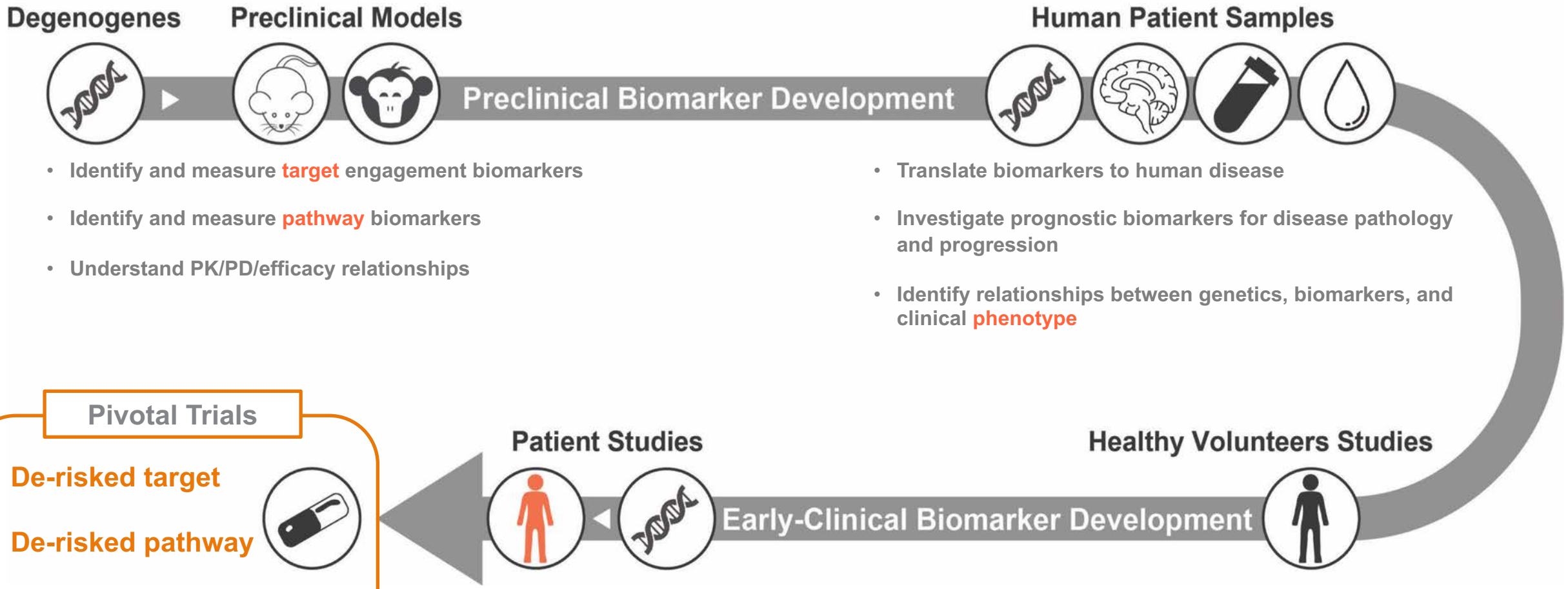
Engineering Brain Delivery	• Engineering approach for small molecules • BBB platform for large molecules		• Improved brain penetration • Improved target engagement
Biomarker-Driven Development	• Target Engagement • Pathway Engagement • Patient Profiling		• The right molecule • The right dose • The right patients

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

INCREASED PROBABILITY OF SUCCESS

BIOMARKERS GUIDE DEVELOPMENT



- Identify and measure **target** engagement biomarkers
- Identify and measure **pathway** biomarkers
- Understand PK/PD/efficacy relationships

- Translate biomarkers to human disease
- Investigate prognostic biomarkers for disease pathology and progression
- Identify relationships between genetics, biomarkers, and clinical **phenotype**

- **De-risked target**
- **De-risked pathway**
- **Rational dose selection**
- **Best patient population**

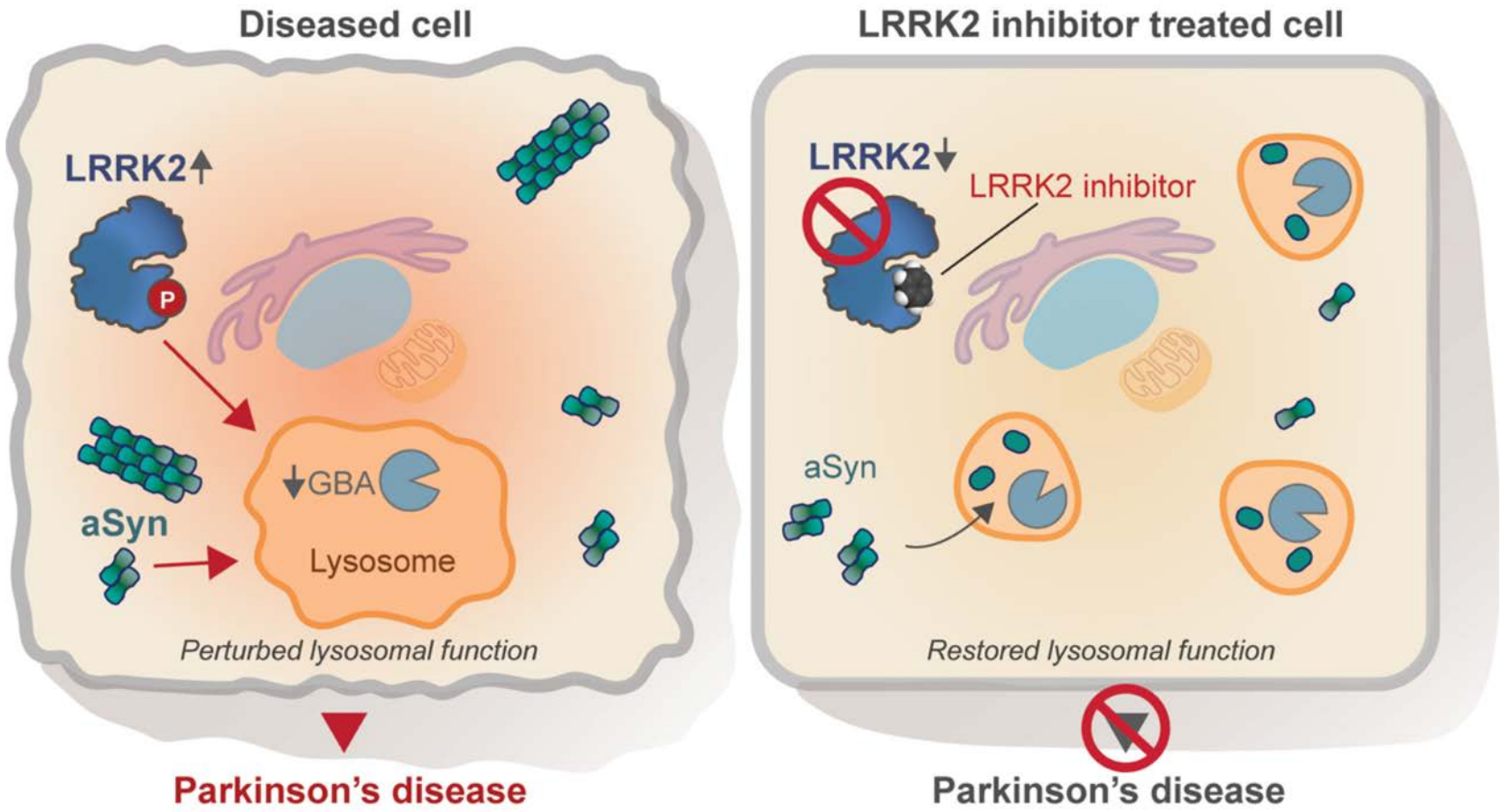
- Link pathway biomarkers to **disease pathology**
- Define patient population likely to respond
- Confirm PK/PD relationship and dose selection

- Validate target biomarkers in healthy volunteers
- Validate pathway biomarkers in healthy volunteers
- Understand PK/PD relationship and select dose


LRRK2 UPDATE

LRRK2 HYPERACTIVITY DRIVES LYSOSOMAL DYSFUNCTION AND PD

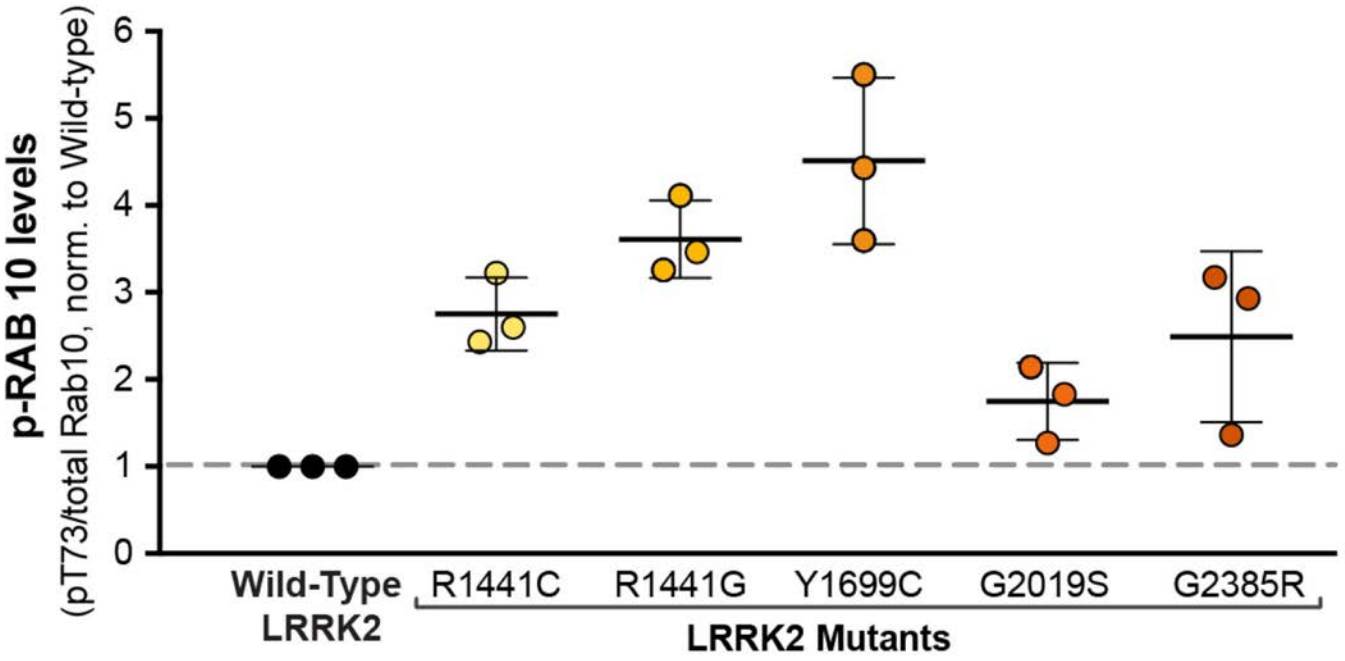
- Increased LRRK2 kinase activity impairs lysosomal function and drives familial PD
- LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in PD models

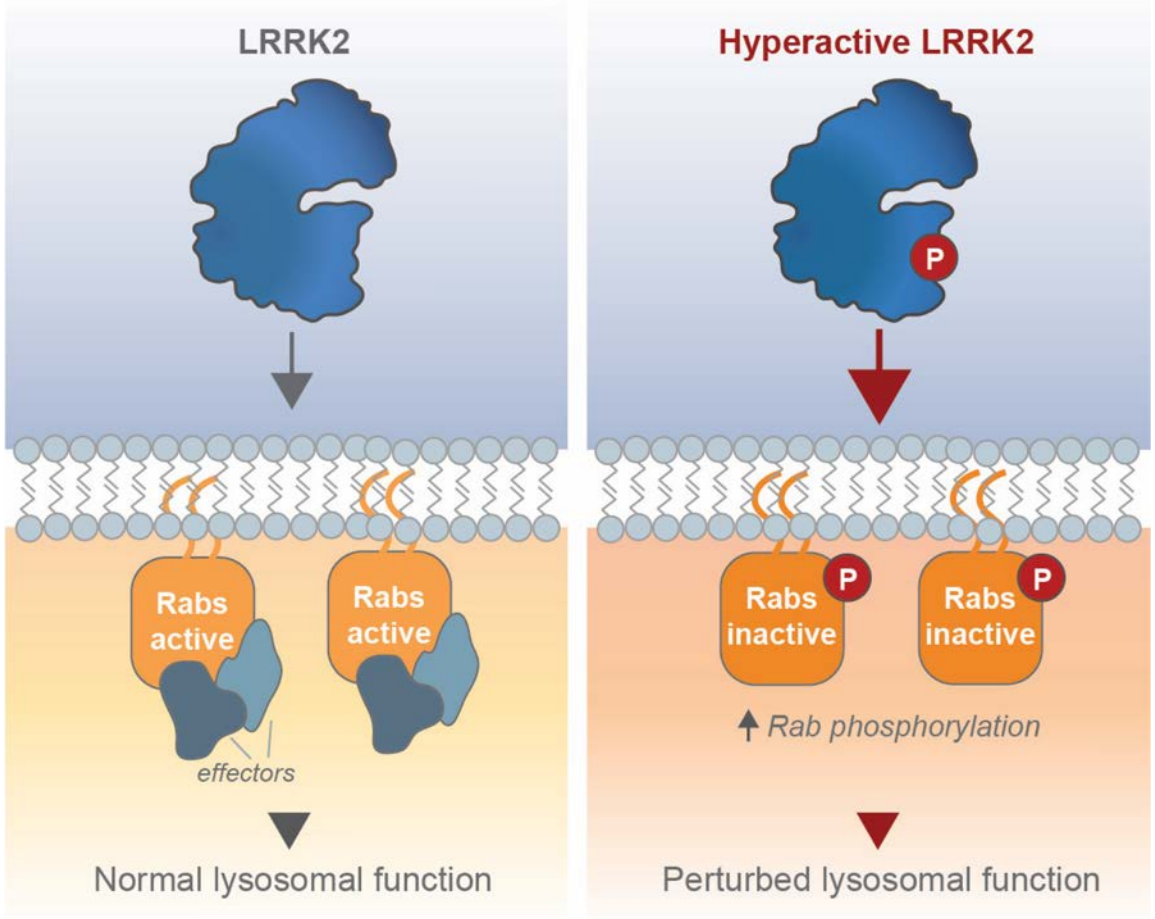


LRRK2 Inhibitor

LRRK2 DISEASE CAUSING MUTATIONS INCREASE KINASE ACTIVITY

LRRK2 Parkinson's mutations increase pRab

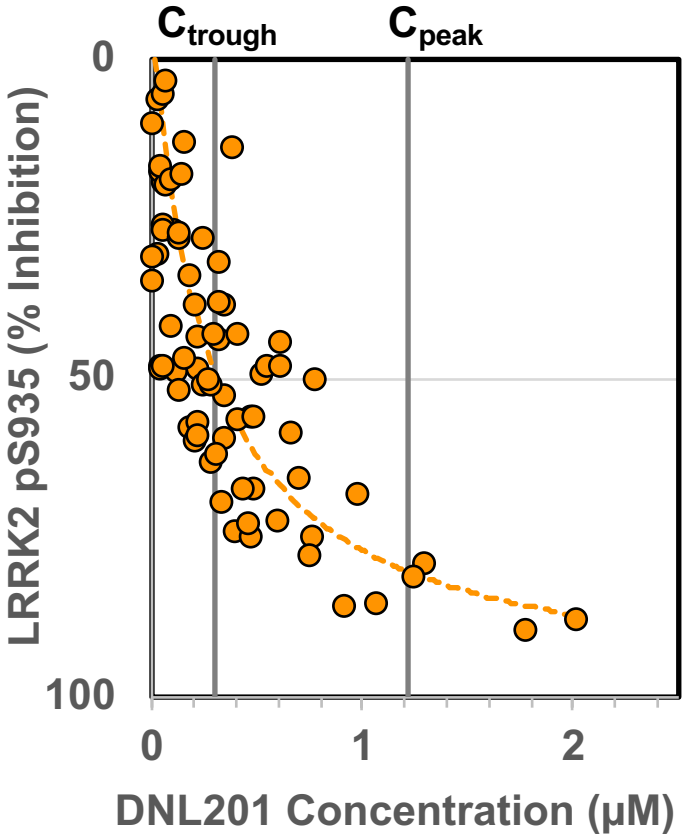




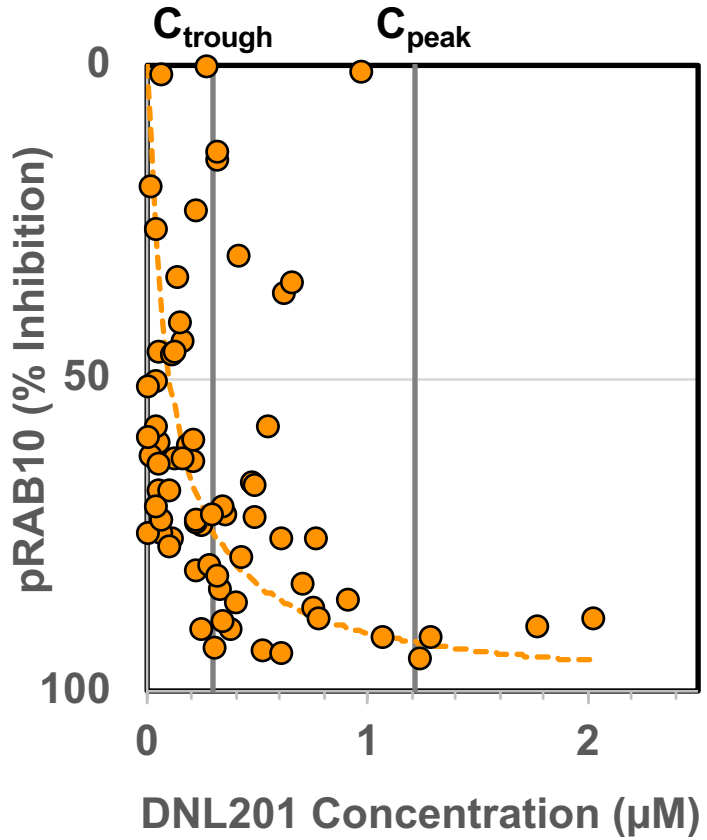
LRRK2 Inhibitor

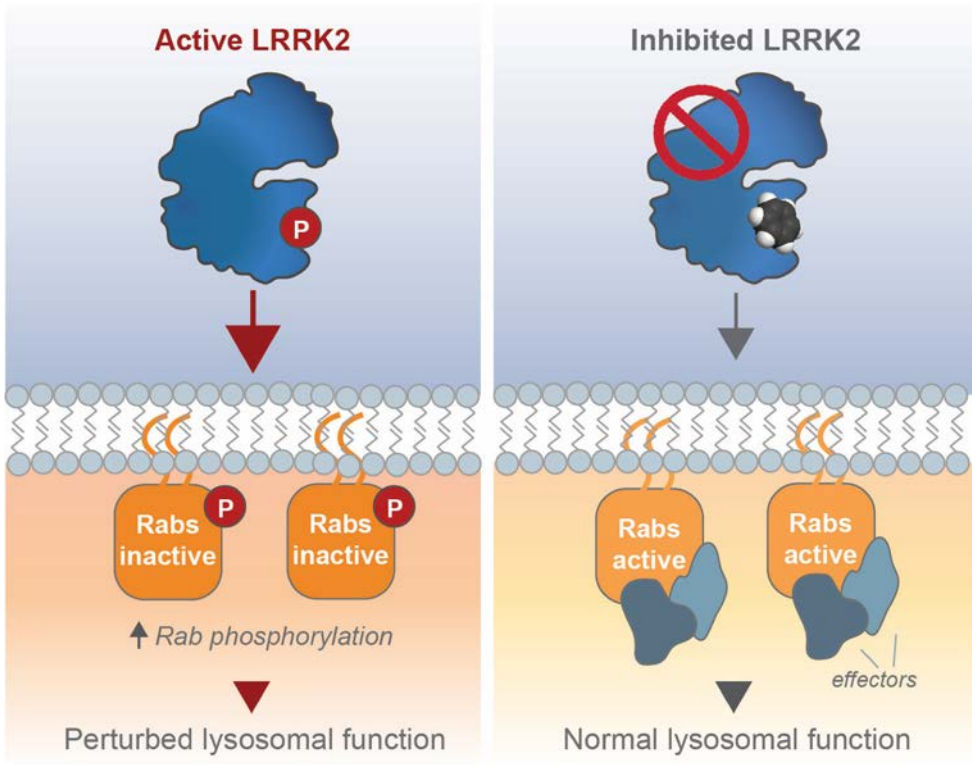
PK/PD CORRELATION IN HUMANS DOSED WITH DNL201

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

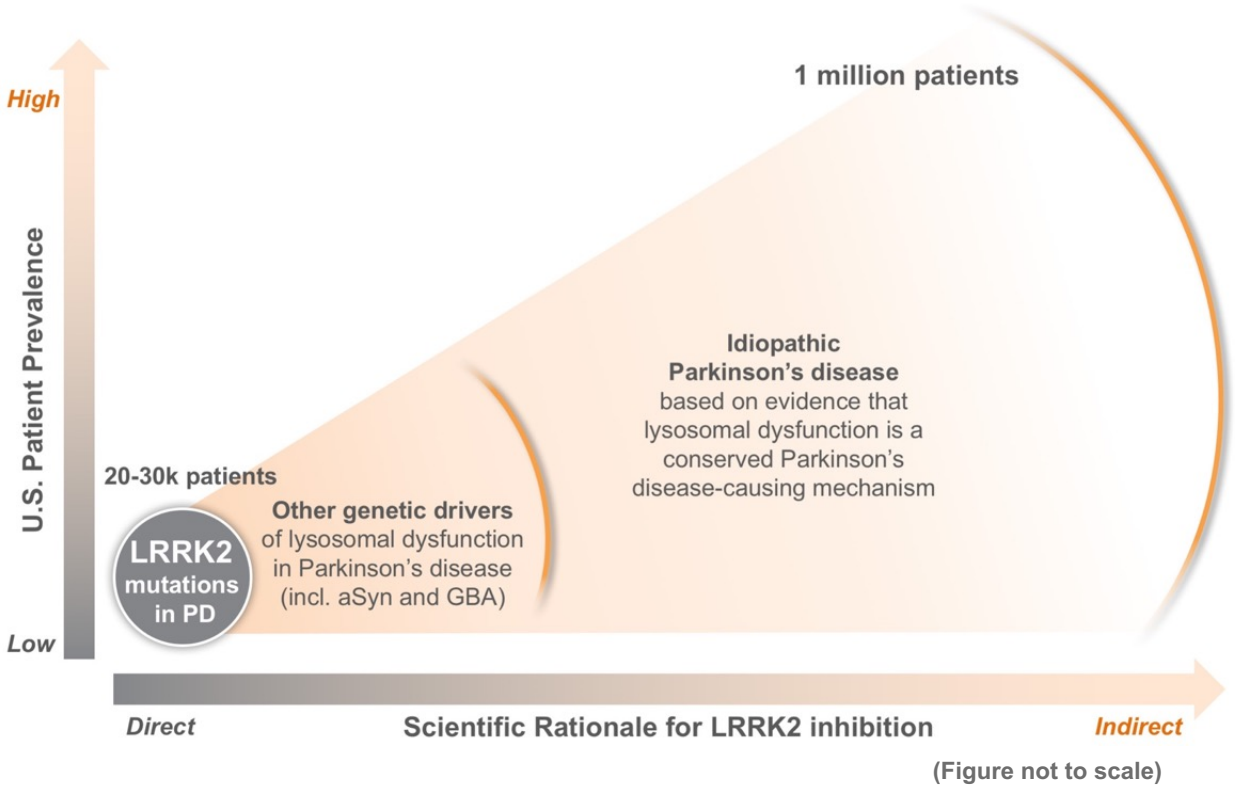
DNL201 MET ALL OBJECTIVES IN PH1 STUDY

Safety	Overall well tolerated and supports advancement to Phase 1b in Parkinson's disease patients
PK	Excellent CSF penetration and PK supports BID dosing
Target Engagement	Exceeded targeted levels of LRRK2 inhibition

Randomized, double blind, placebo-controlled, oral dose study in healthy subjects

LRRK2 Inhibitor

LRRK2 INHIBITION MAY HAVE BROAD THERAPEUTIC POTENTIAL FOR PD



(Figure not to scale)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

LRRK2 activation in idiopathic Parkinson's disease

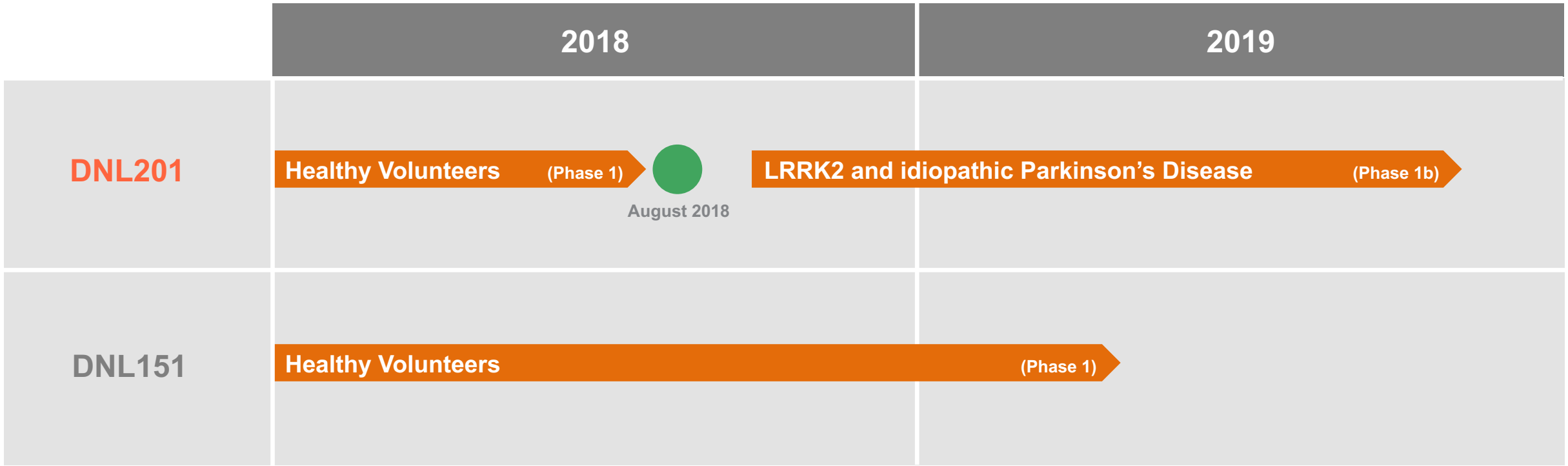
Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa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

Missense mutations in leucine-rich repeat kinase 2 (LRRK2) cause familial Parkinson's disease (PD). However, a potential role of wild-type LRRK2 in idiopathic PD (iPD) remains unclear. Here, we developed proximity ligation assays to assess Ser1292 phosphorylation of LRRK2 and, separately, the dissociation of 14-3-3 proteins from LRRK2. Using these proximity ligation assays, we show that wild-type LRRK2 kinase activity was selectively enhanced in substantia nigra dopamine neurons in postmortem brain tissue from patients with iPD and in two different rat models of the disease. We show that this occurred through an oxidative mechanism, resulting in phosphorylation of the LRRK2 substrate Rab10 and other downstream consequences including abnormalities in mitochondrial protein import and lysosomal function. Our study suggests that, independent of mutations, wild-type LRRK2 plays a role in iPD. LRRK2 kinase inhibitors may therefore be useful for treating patients with iPD who do not carry LRRK2 mutations.

- 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

LRRK2 Inhibitor

LRRK2 CLINICAL PROGRAM SUMMARY



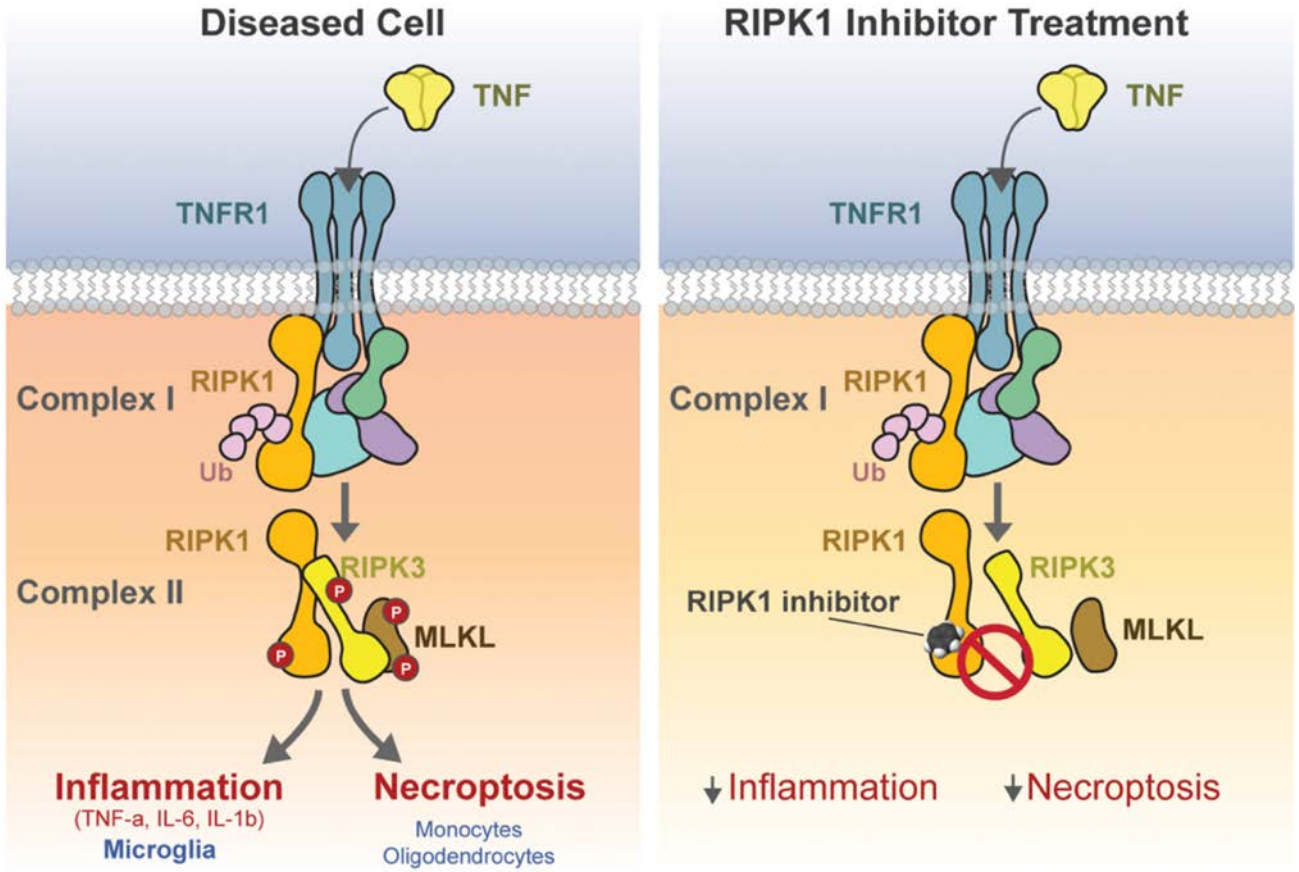
2018 Progress

- DNL201: Ph1 safety, target engagement, PD achieved
- DNL151: FIH dosing HV Ph1 study

LRRK2 Inhibitor


DENALI
RIPK1 UPDATE

RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS

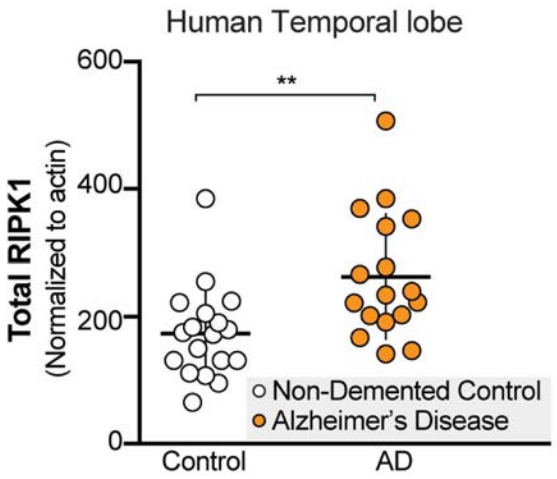


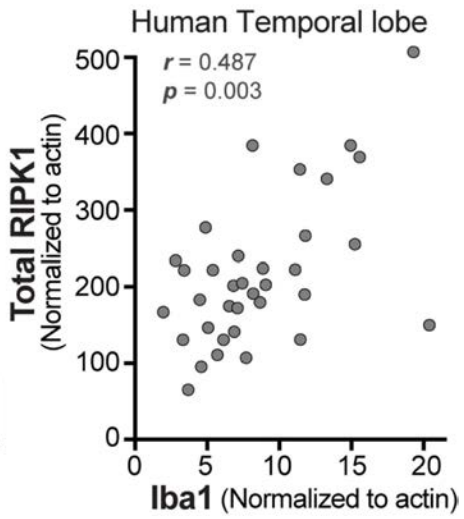
- Activation of RIPK1 kinase activity generates a pro-inflammatory response in microglia and cell death via necroptosis in other cell types, including monocytes and oligodendrocytes
- Inhibition of RIPK1 is sufficient to block both the production of pro-inflammatory cytokines and necroptosis

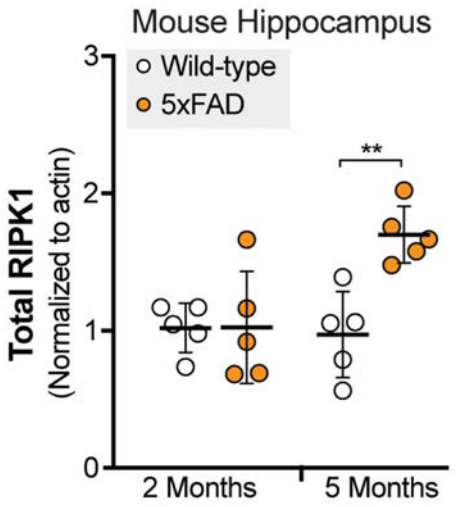
RIPK1 Inhibitor

RIPK1 IN ALZHEIMER'S DISEASE

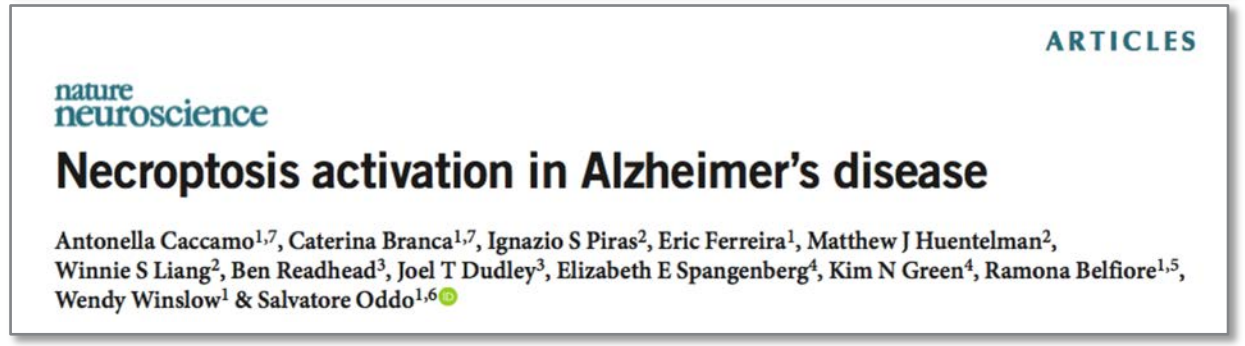
RIPK1 increased in brains of human AD patients and in an Alzheimer's mouse model







Denali Data

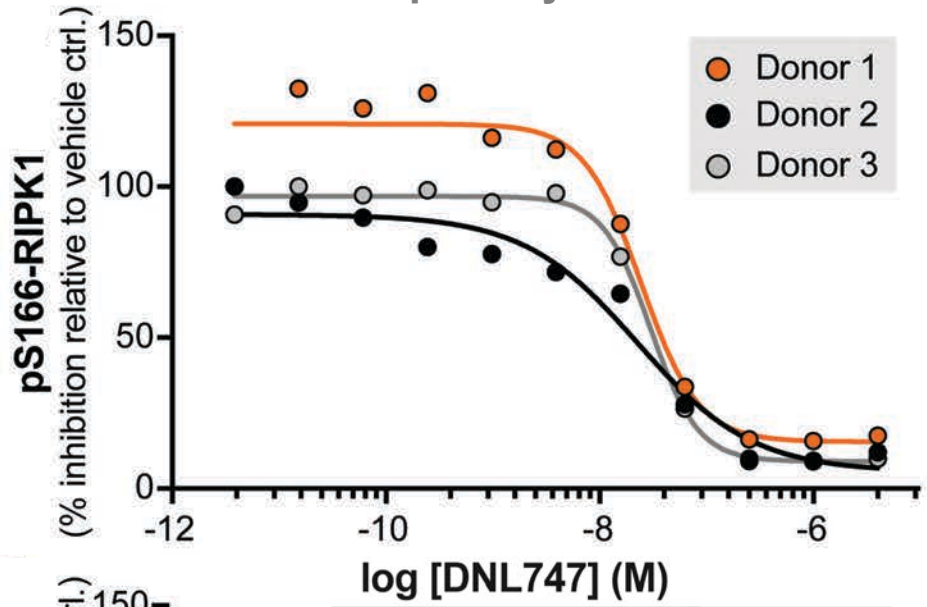


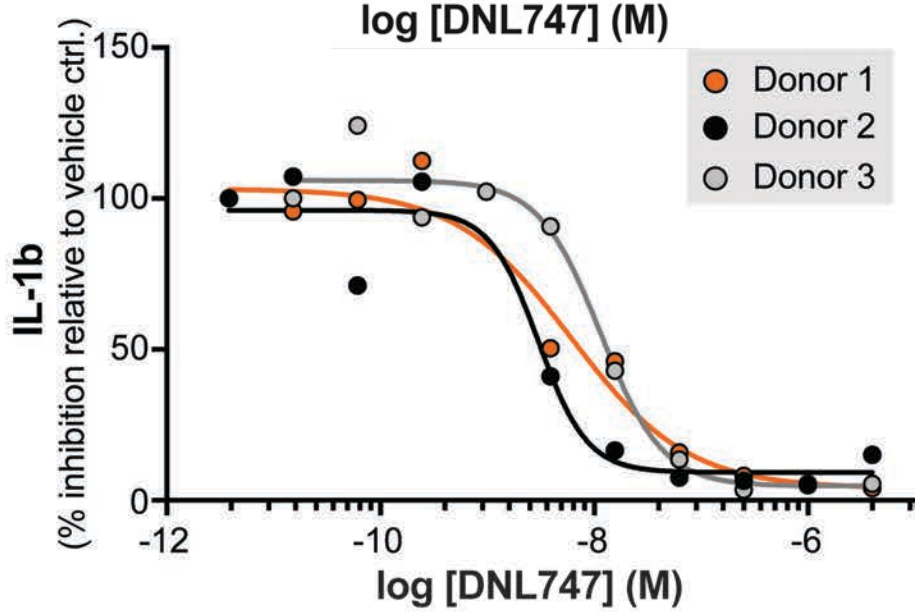
- RIPK1 pathway is activated in human AD patient brain and AD mouse models – *Denali data*
- Published literature shows protection in AD models with RIPK1 loss-of-function
- Clinical strategy: demonstrate peripheral target engagement in Ph1 healthy volunteer study; demonstrate central target engagement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

RIPK1 Inhibitor

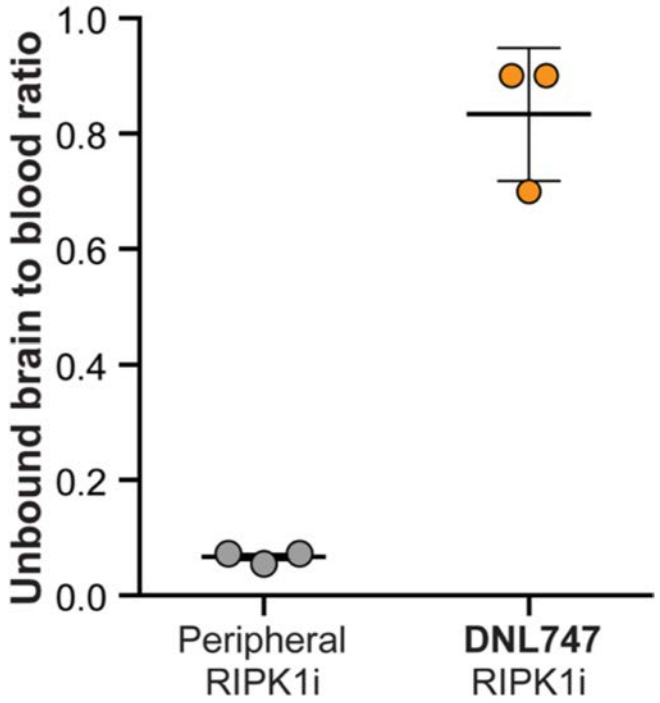
DNL747 PHARMACOLOGICAL PROPERTIES & BRAIN EXPOSURE

Treatment of primary human cells





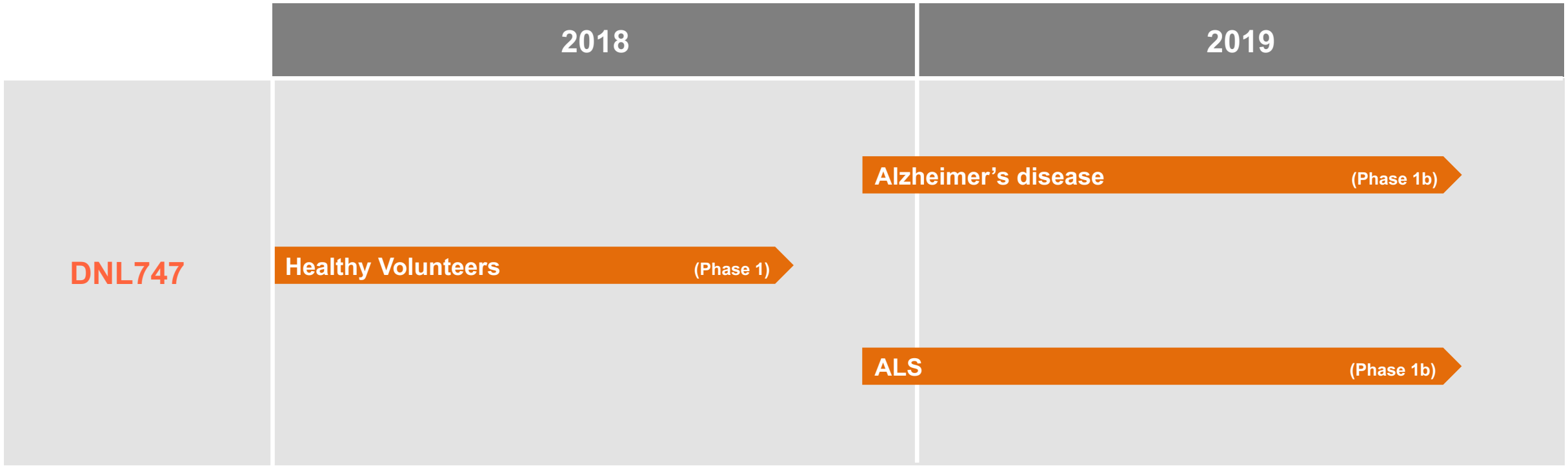
Robust brain uptake with DNL747



- 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

RIPK1 CLINICAL PROGRAM SUMMARY



2018 Progress

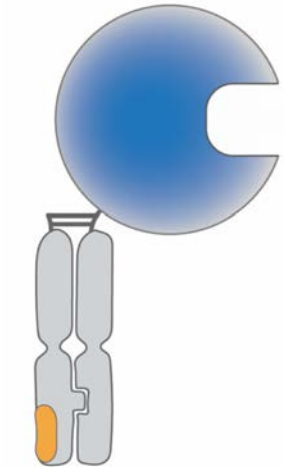
- CTA filed in February
- Phase 1 HV study ongoing

RIPK1 Inhibitor


DENALI
ETV:IDS

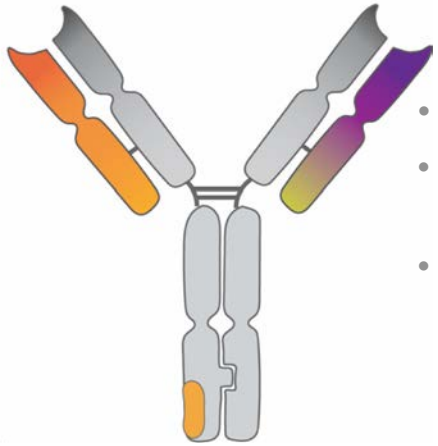
LARGE MOLECULE TARGETS: ATV AND ETV PLATFORM PORTFOLIO

ETV:IDS



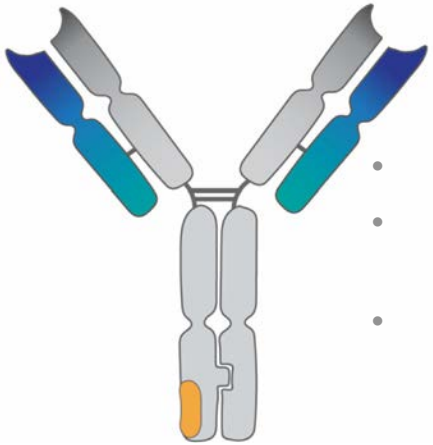
- Indication: **Hunter Syndrome**
- Status: *in vitro* and *in vivo* activity, candidate selected
- IND or CTA filing planned in 2019

ATV:BACE1/Tau



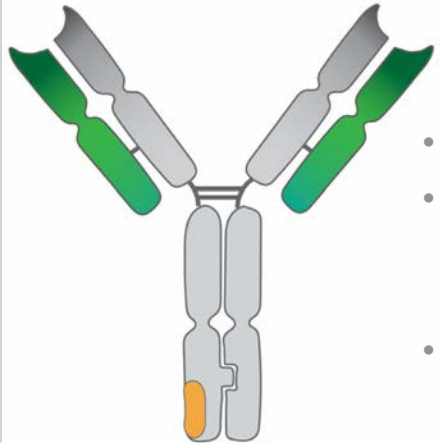
- Indication: **Alzheimer's disease**
- Status: high affinity, humanized leads for BACE1 & Tau
- IND or CTA filing planned in 2020

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

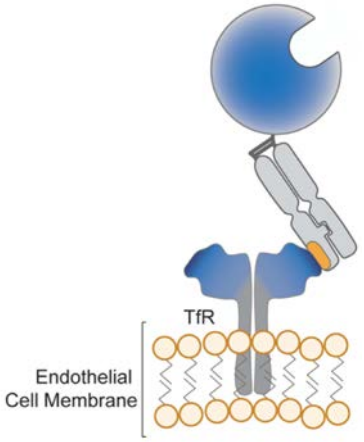
ATV:TREM2

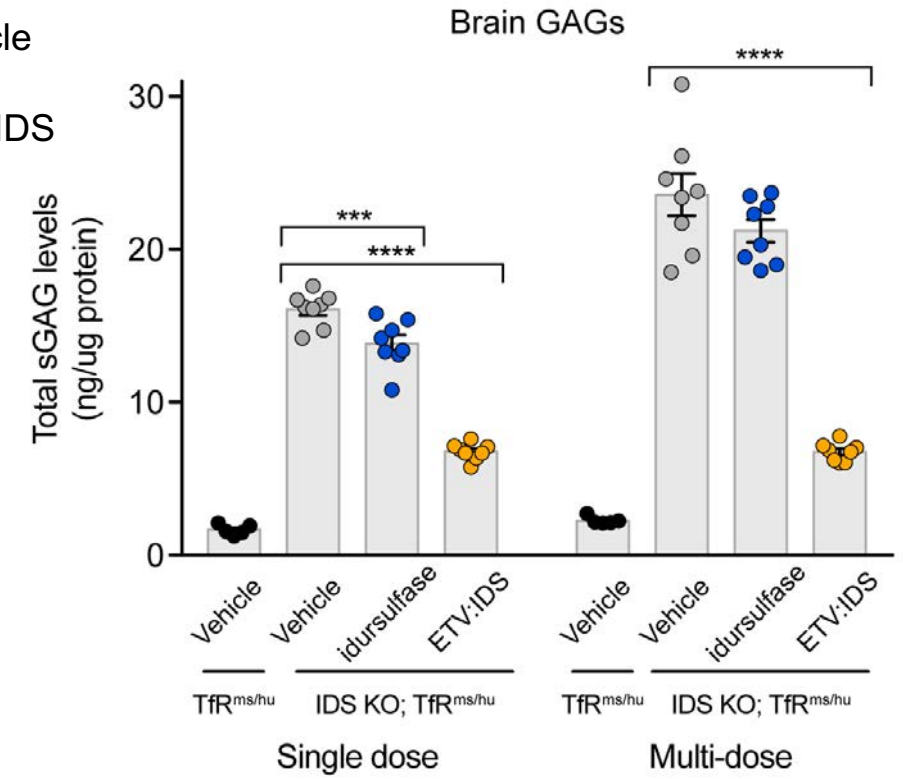


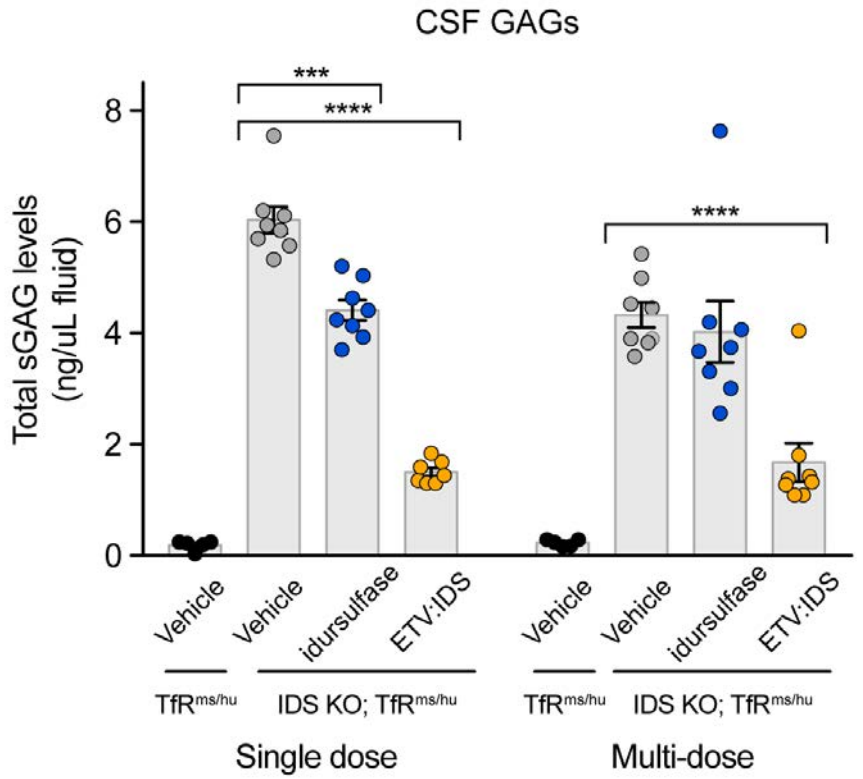
- Indication: **Alzheimer's disease**
- Status: high affinity candidate antibodies with diverse properties
  - Shedding blockers and agonist antibodies
- IND or CTA filing planned in 2020

ETV:IDS ROBUSTLY REDUCES CNS GAGS IN VIVO

TfR$^{mu/hu}$KI + Vehicle
IDSKO;TfR$^{mu/hu}$KI + Vehicle
IDSKO;TfR$^{mu/hu}$KI + IDS
IDSKO;TfR$^{mu/hu}$KI + 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, and **** p < 0.0001*

ETV:IDS reduces GAGs by 71% in brain and 75% in CSF after 4 weekly doses

Elaprase does not effectively reduce CNS GAG levels

DENALI MAJOR PIPELINE MILESTONES AND PRIORITIES

NEXT 12-18 MONTHS

LRRK2

- DNL151: Ph1 safety and PK/PD biomarker readout
- DNL201: Ph1 data to be presented October 25, 2018 (MJFF Parkinson's Disease Therapeutics Conference)
- **DNL201: Initiate Ph1b safety and biomarker study in LRRK2 and idiopathic PD patients (Q4 2018)**

RIPK1

- DNL747: Ph1 safety and PK/PD biomarker readout
- **DNL747: Initiate Ph1b safety and biomarker studies in ALS and AD patients (Q4 2018)**

TV Platform Technology

- **ETV:IDS: complete cell line development and GLP Tox - file IND / CTA (2019)**
- ATV: commence cell line / clinical supply manufacturing (ATV:aSyn, ATV:BACE1/Tau, ATV:TREM2)
- Expansion of TV platform technology


THANK YOU