
DENALI™
Discover, Develop, Defeat Degeneration
December 2018

AGENDA

12:00 – 12:10 PM	**Welcome** – Ryan Watts, *PhD, Co-Founder and CEO, Denali Therapeutics*
12:10 – 12:40 PM	**The Time is Right to Conquer Degeneration** – Marc Tessier-Lavigne, *PhD, Co-Founder and Board Member, Denali Therapeutics*
12:40 – 12:50 PM	**Denali's Approach and Progress** – Ryan Watts
12:50 – 1:15 PM	**Engineering Brain Delivery** – Ryan Watts
1:25 – 1:40 PM	**Biomarker-Driven Development** – Carole Ho, *MD, CMO, Denali Therapeutics*
1:40 – 2:20 PM	**LRRK2 Program Overview and Clinical Development Plan** – Carole Ho
2:20 – 2:45 PM	**LRRK2 Genetic Architecture and Underlying Biology: Implications for Patient Selection** – Mark Cookson, *PhD, Senior Investigator, NIH*
2:55 – 3:30 PM	**RIPK1 Program Overview and Clinical Development Plan** – Carole Ho
3:30 – 3:45 PM	**Discovery Portfolio** – Ryan Watts
3:45 – 4:00 PM	**Q&A and Wrap-Up**

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, plans and expectations regarding patient recruitment, planned regulatory filings, long-term development plans and near-term pipeline milestones, 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; the risk that a transaction or collaboration may not close in a timely manner or at all, and the ability to obtain any requisite regulatory approvals related to such transaction or collaboration; 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 November 8, 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

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DENALI
THE TIME IS RIGHT TO
CONQUER DEGENERATION
MARC TESSIER-LAVIGNE

FOUNDERS' VISION

FOUNDERS' VISION

We have embarked on a deeply personal journey to conquer neurodegenerative diseases. Collectively, these diseases represent one of the most significant medical challenges facing us today, impacting millions of people including our own families and friends. We are passionately dedicated to understanding these diseases. Our goal is nothing short of defeating neurodegeneration by harnessing the power of modern science and technology to discover and develop medicines that meaningfully improve the lives of patients and their families.

This is a formidable challenge and opportunity. Defeating degeneration – to us – is akin to summiting the tallest mountains. Hence the name Denali. For the longest time, mankind was unable to summit the highest peaks. But when the time was right, bold mountaineers succeeded, enabled by technological progress and a better understanding of the elements. We believe that the same is possible in neurodegeneration today.

We are well aware that we are taking on a major challenge, yet we believe that success is within our reach. Recent genetic insights, better diagnostic tools and the ability to engineer medicines to cross the blood-brain barrier are crucial components in defeating degeneration. We have contributed to and experienced firsthand the advances that are made possible by following breakthrough science. We believe that the field of neurodegeneration is now at the inflection point where oncology was years ago when genetic discoveries revealed biological pathways responsible for cancer growth that resulted in powerful drug targets, and biomarkers enabled the diagnosis and selection of patients for targeted treatment approaches. Similar success is within reach in neurodegeneration.

Just like the mountaineers who set out to conquer the highest peaks, it takes a courageous team with a singular focus and unrelenting persistence to succeed. At Denali, we have assembled an outstanding team of driven and passionate scientists and drug developers, and a powerful network of collaborators in academia and industry.

The science is breaking open, and the time is right to discover and develop effective medicines for neurodegeneration. Every day matters. To patients, to their families and to society at large. We invite you to join us on our journey to the summit.

Ryan Watts, Ph.D.
CEO and Co-Founder

Alexander Schuth, M.D.
COO and Co-Founder

Marc Tessier-Lavigne, Ph.D.
Director and Co-Founder

AGENDA

- Significant Unmet Medical Need
- Challenge and Opportunity
- The Time is Right
- Denali's Approach and Focus

NEURODEGENERATION: A PATIENT PERSPECTIVE

Alzheimer's Disease

US Prevalence
~5,700,000

Parkinson's Disease

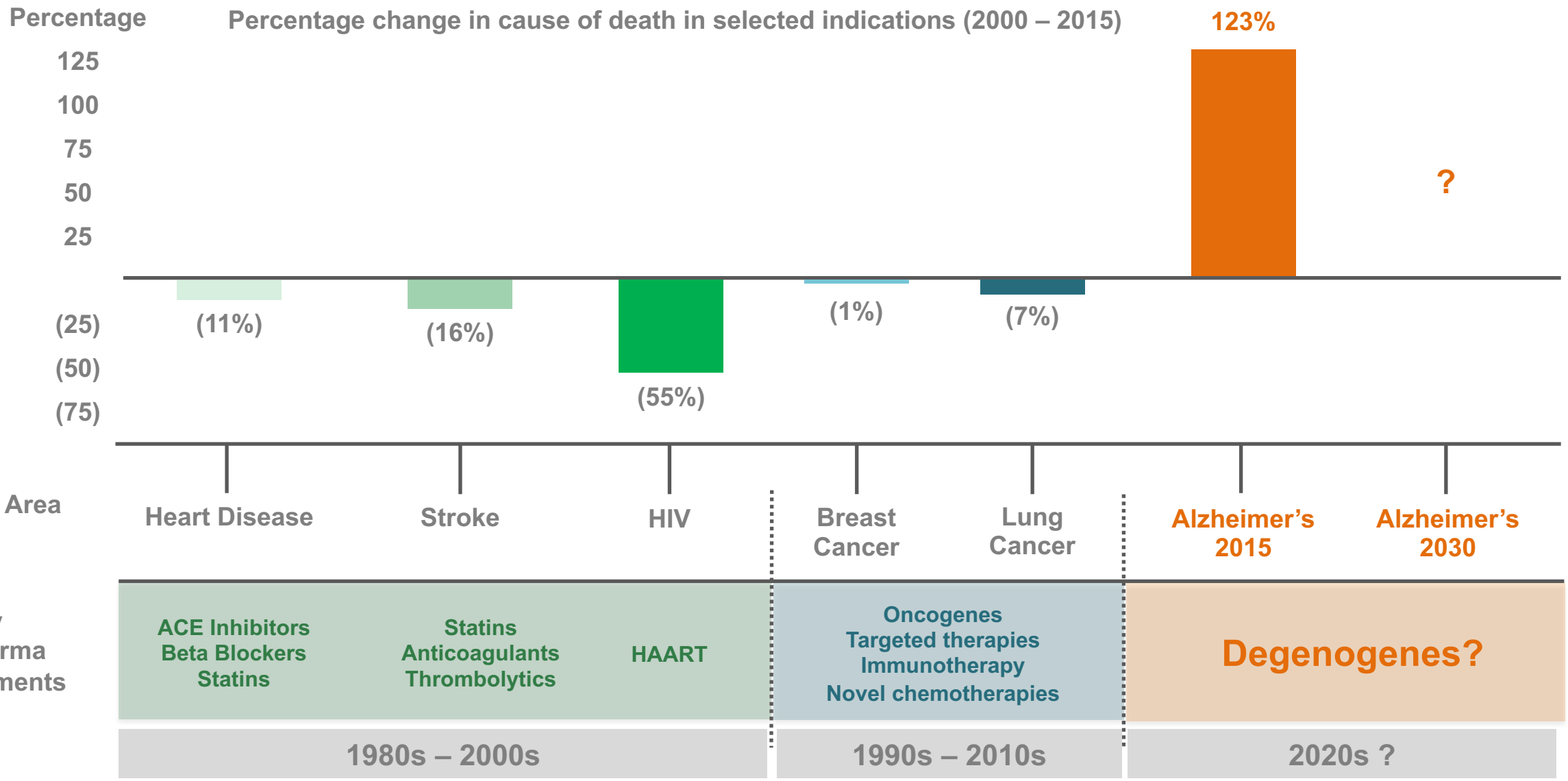
US Prevalence
~1,000,000

ALS

US Prevalence
~20,000

Sources: Alzheimer's Disease International, Parkinson's Foundation, ALS Association

NEURODEGENERATION: A SIGNIFICANT UNMET MEDICAL NEED



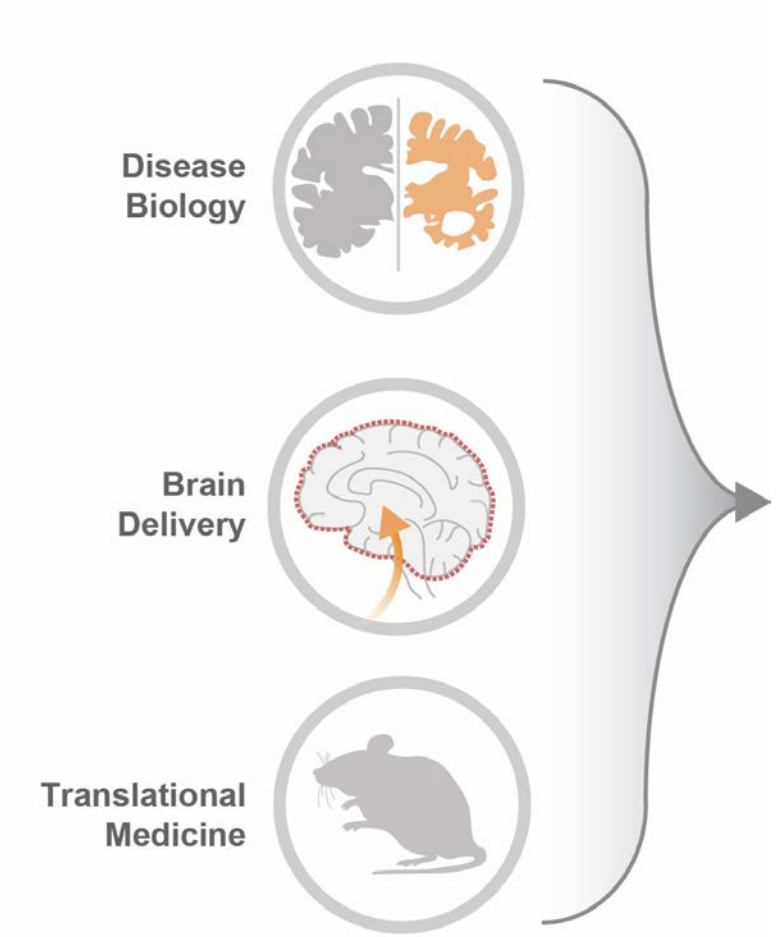
Created from data from the National Center for Health Statistics

PERSPECTIVE ON DRUG DEVELOPMENT IN NEURODEGENERATION

Poorly understood link from pathology to molecular mechanisms

Insufficient drug exposure in the brain

Failure to provide evidence of target engagement and rationale for dose selection



- High failure rates in clinical development in the past
- Low investment by industry
- Few, if any, disease-modifying therapies approved

THE TIME IS RIGHT

SCIENTIFIC DRIVERS:

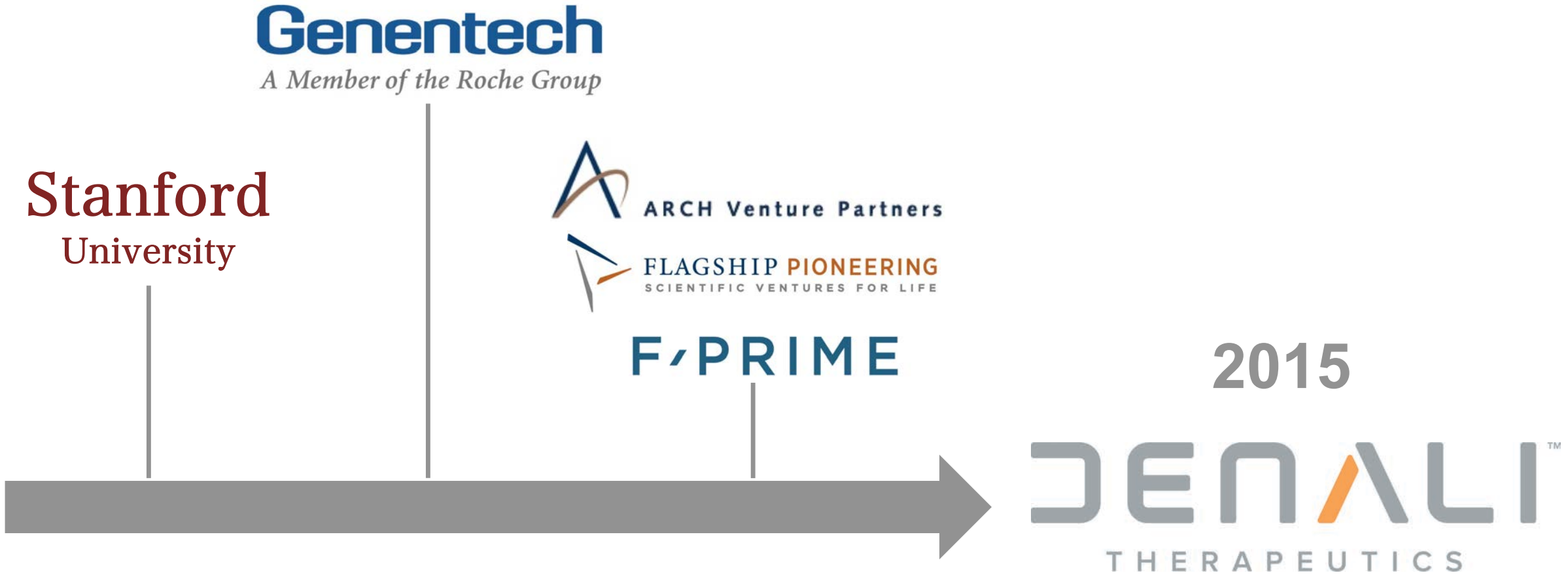
- **Science breaking open**
  - Human genetics informing Degenogenes
- **Crossing the BBB within reach**
- **Biomarkers informing drug development**

BUSINESS PRINCIPLES:

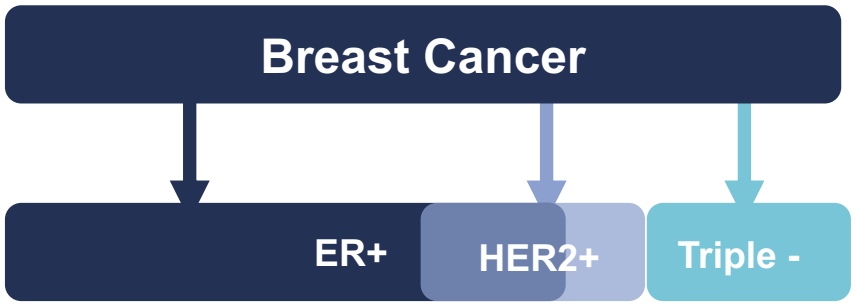
- **Learning from oncology**
- **The right team and approach**

DENALI™
THERAPEUTICS

FOUNDING DENALI: HOW WE MET



ONCOGENES: AN INFLECTION POINT IN ONCOLOGY



1980s - Monoclonal antibodies and HER2 oncogene discovered

Early 90s – Antibody humanization; HER2 as patient selection biomarker

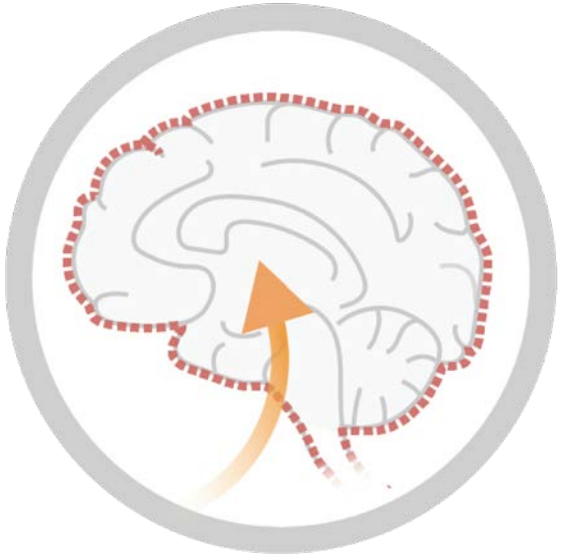
Herceptin®
trastuzumab

1998 - FDA approves Herceptin

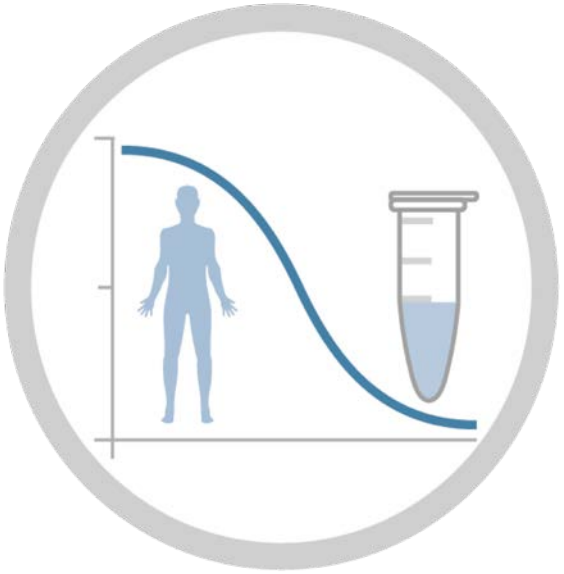
DENALI'S THREE SCIENTIFIC PRINCIPLES

Mining Genetic Pathway Potential

Engineering Brain Delivery



Biomarker-Driven Development



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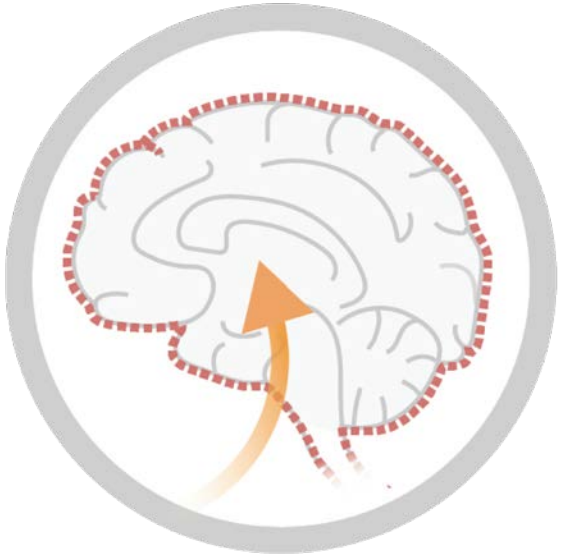

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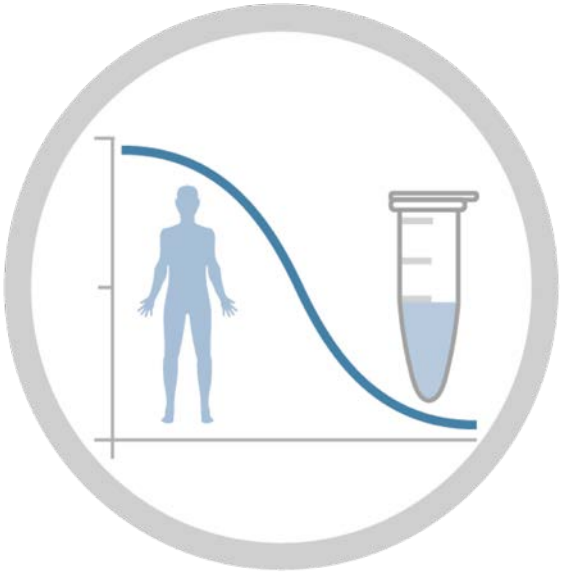
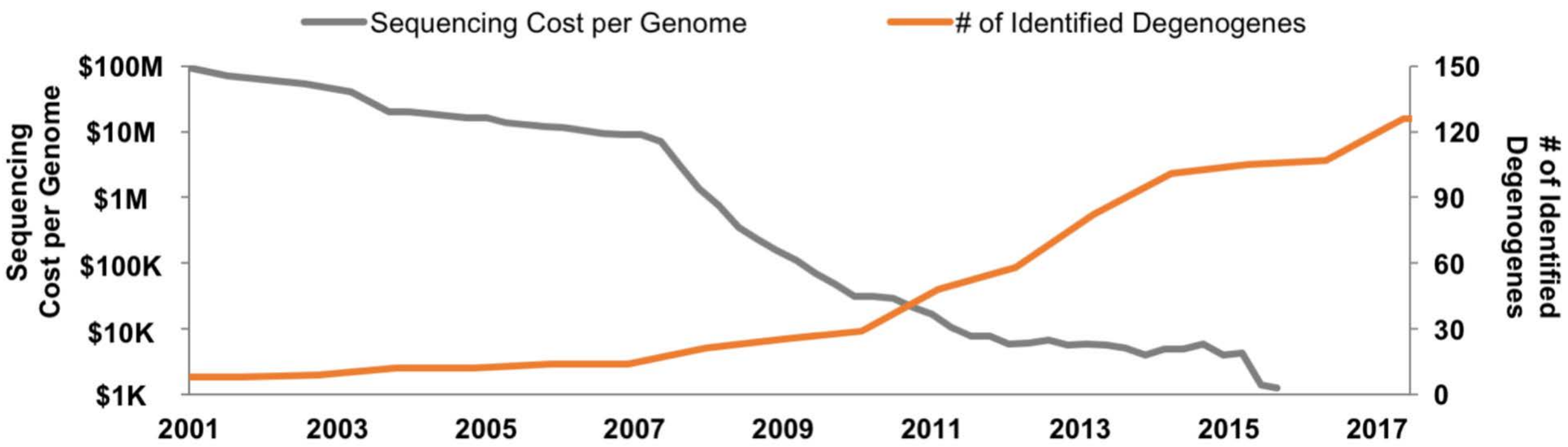
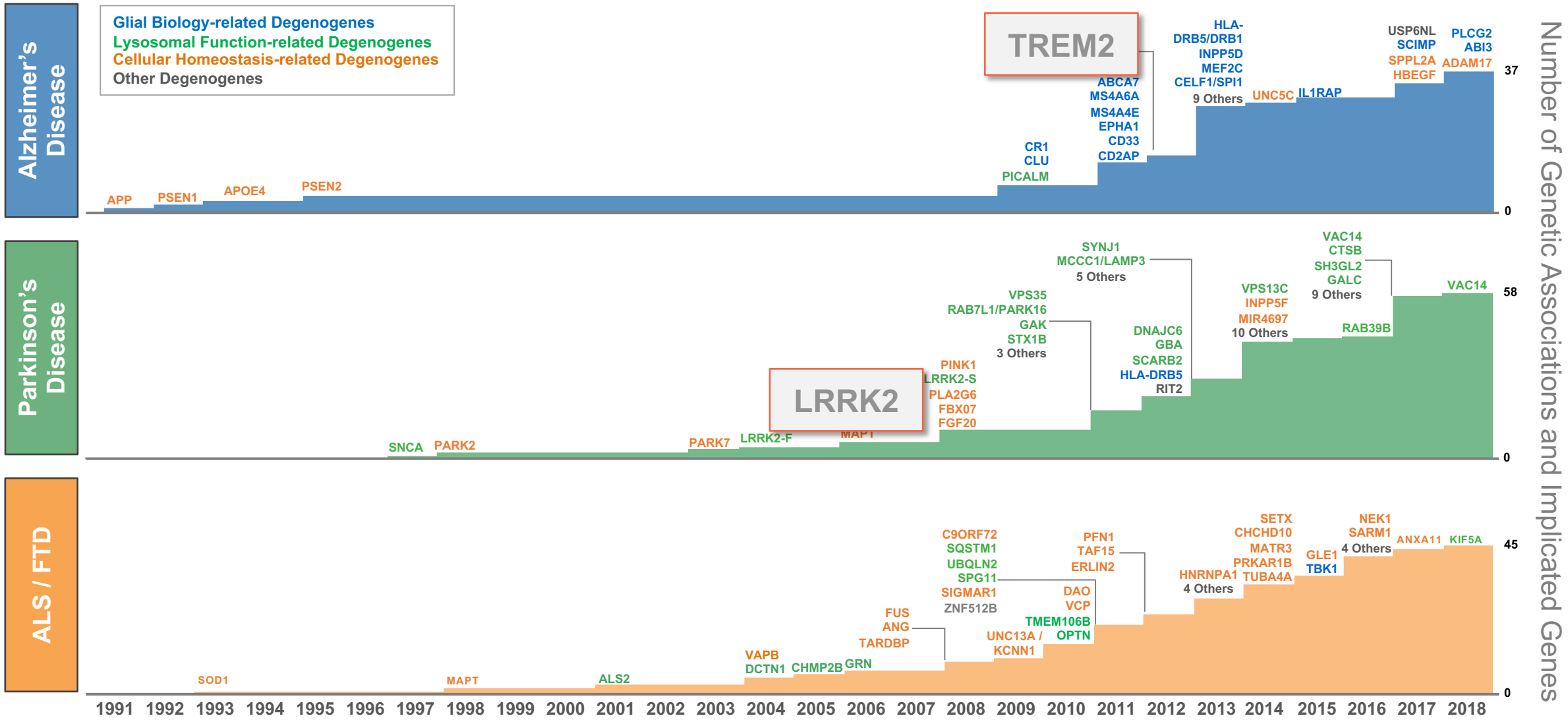


DEGENOGENES: GENES THAT CONTROL NEURODEGENERATION

DISCOVERY VS COST OF SEQUENCING



SCIENCE IS BREAKING OPEN: DEGENOGENES



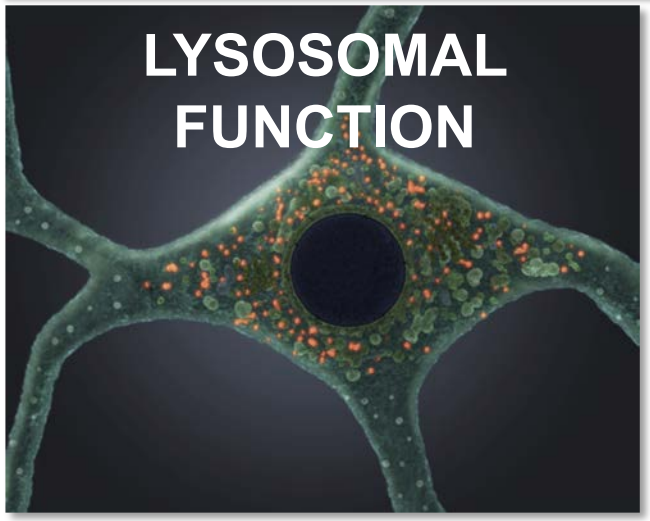
GENETIC PATHWAY POTENTIAL: BUILDING DEEP SCIENTIFIC INSIGHT

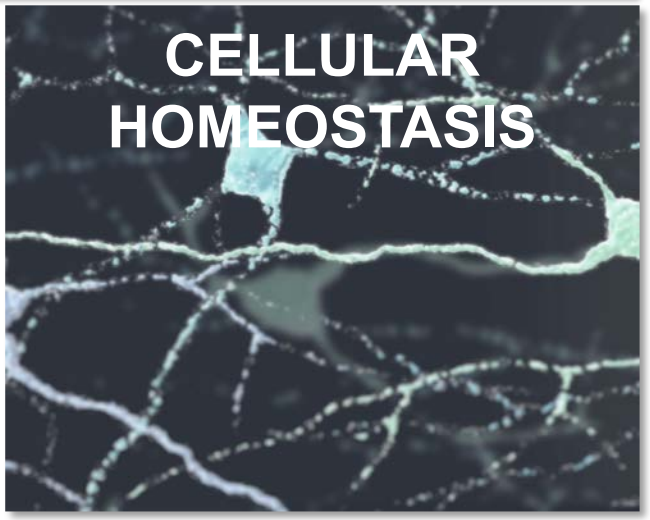
Indications

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

Human Genetics

Pathways





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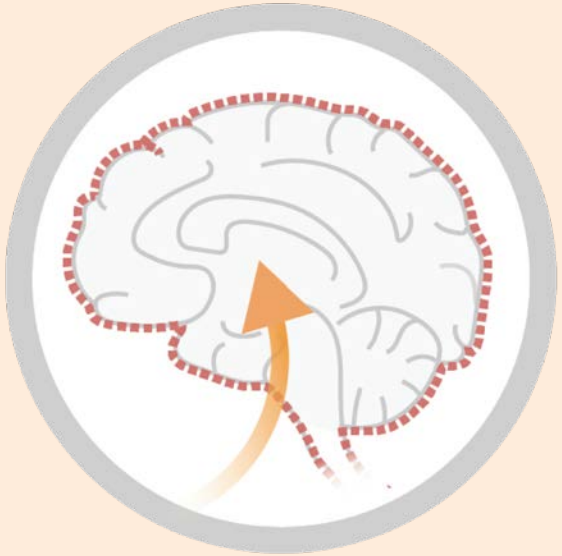
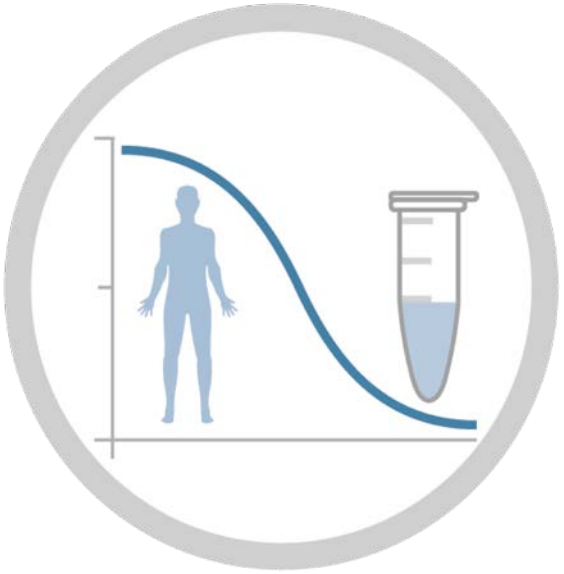
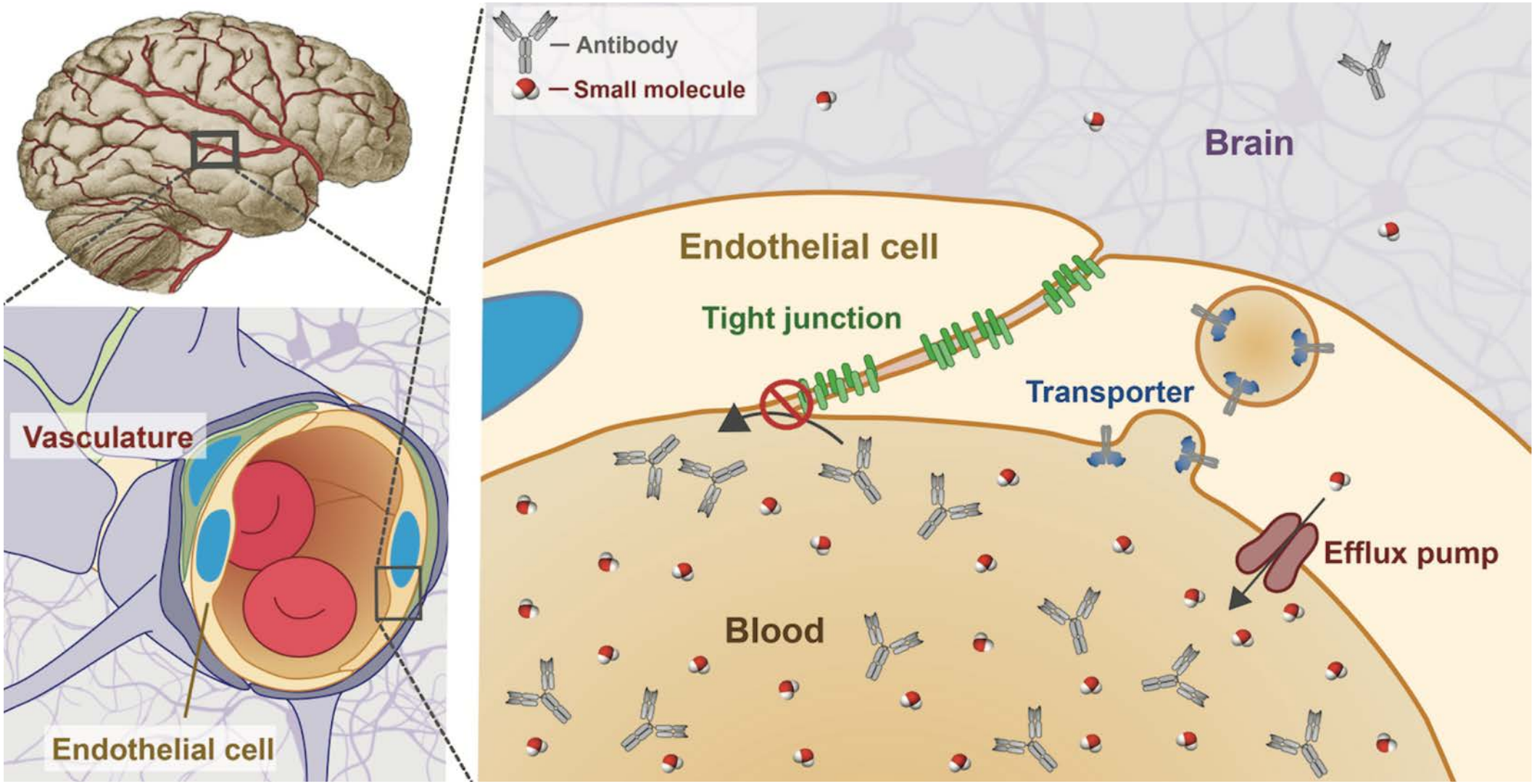


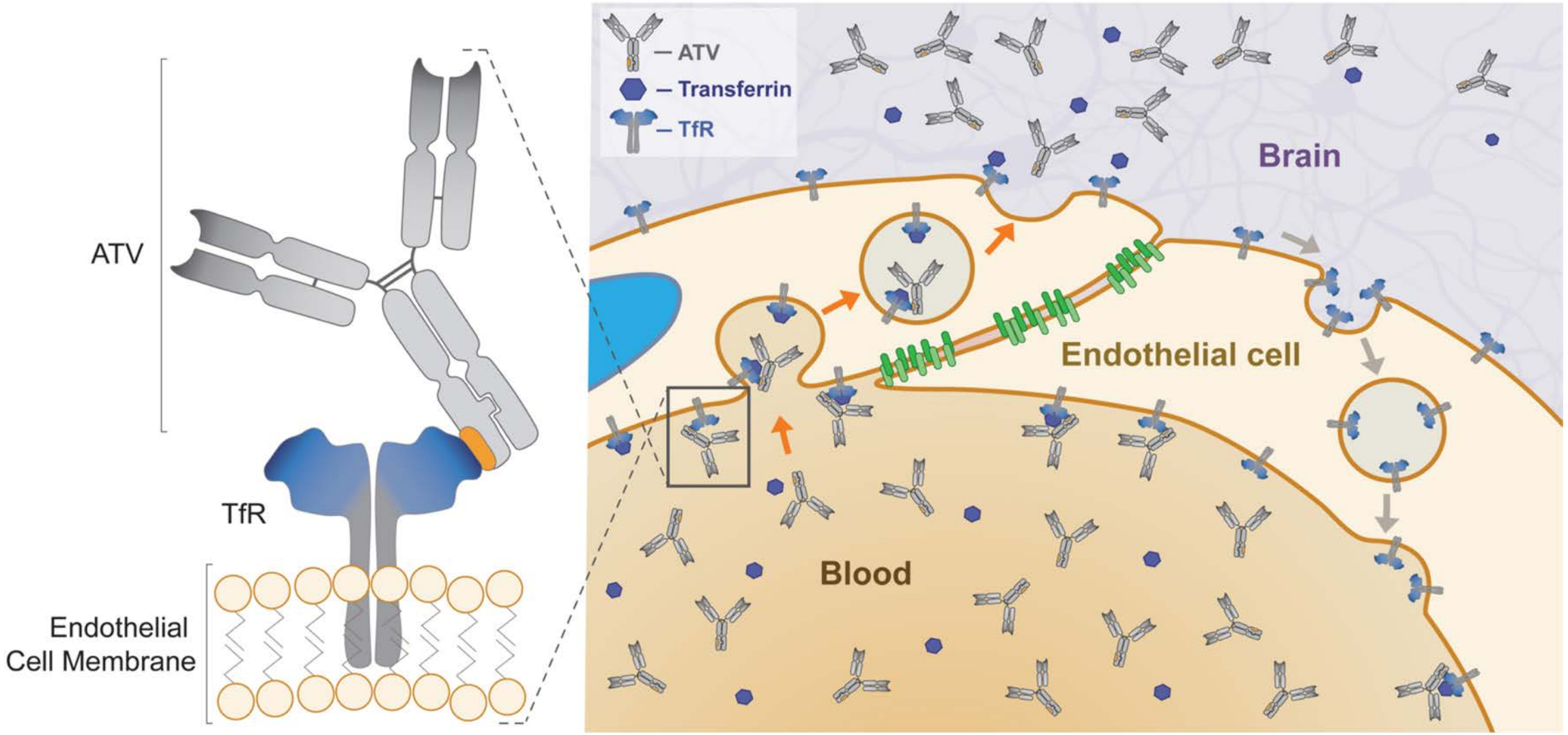
Biomarker-Driven Development



BBB CHALLENGE: WE HAVE LEARNED FROM THE PAST 20 YEARS



OVERCOMING THE BBB CHALLENGE: RECEPTOR-MEDIATED TRANSCYTOSIS (RMT)



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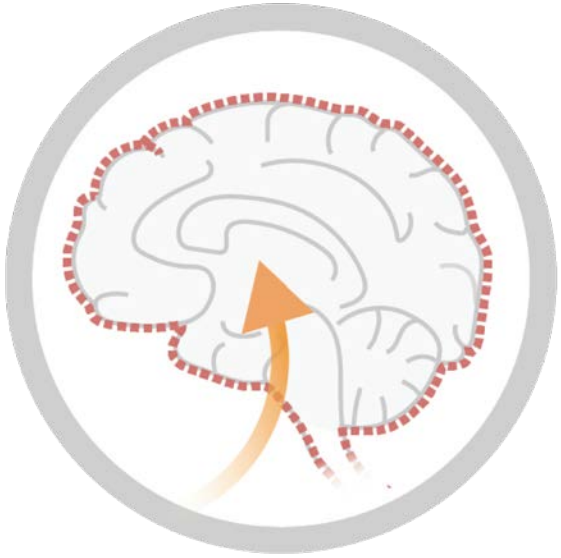

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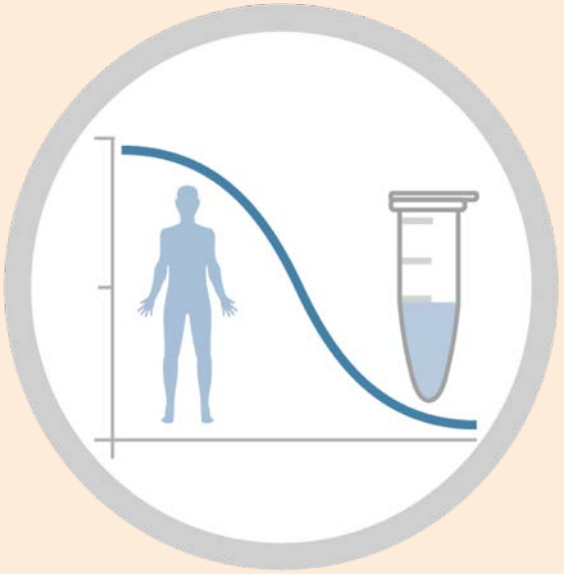
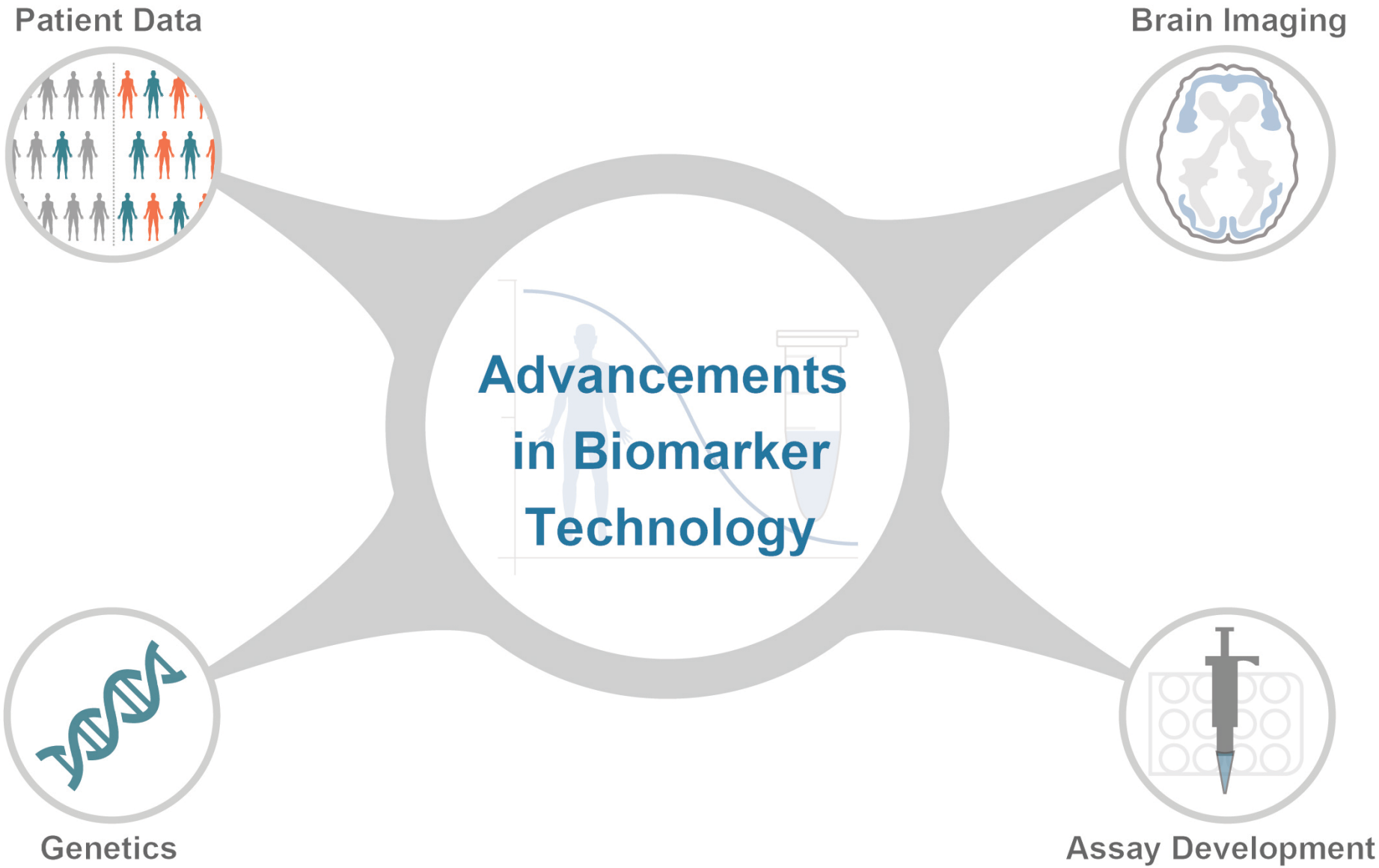


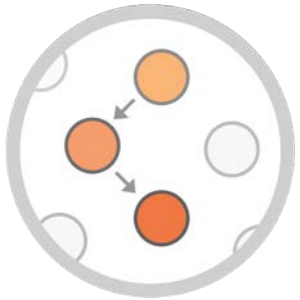
BREAKTHROUGHS IN BIOMARKER-DRIVEN DEVELOPMENT



BIOMARKER-DRIVEN DEVELOPMENT PRINCIPLES

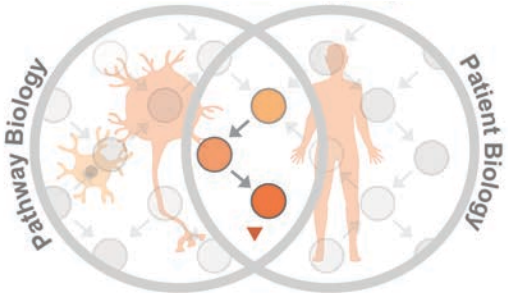
Target Engagement

Determine the relationship between dose and drug response



Pathway Engagement

Demonstrate an effect on Pathway Biology



Patient Phenotyping

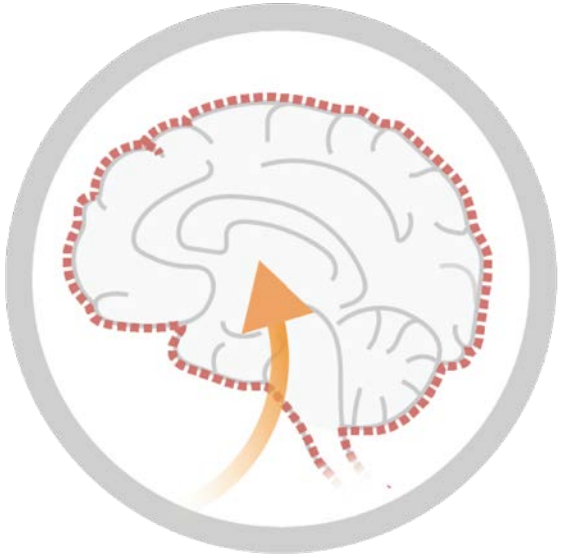
Intersection of Pathway Biology & Disease Biology

INCREASED PROBABILITY OF PHASE 2 AND 3 SUCCESS

RECAP: DENALI'S THREE SCIENTIFIC PRINCIPLES

Mining Genetic Pathway Potential

Engineering Brain Delivery



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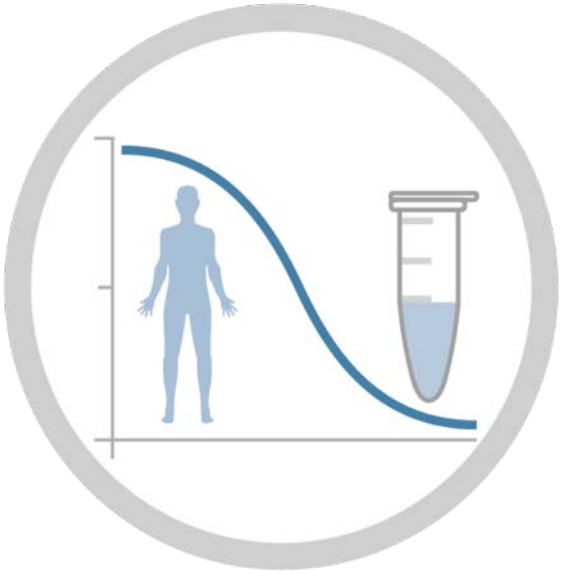
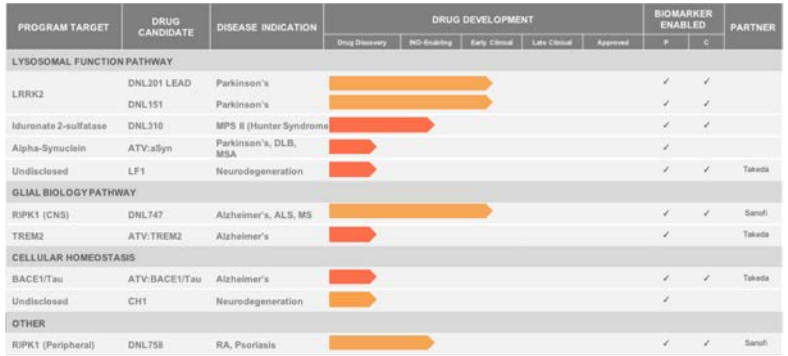


DENALI BUSINESS PRINCIPLES

Portfolio Approach



PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT	BIOMARKER ENABLED		PARTNER
			Drug Discovery / IND-Enabling / Early Clinical / Late Clinical / Approved	P	C	
LYSOSOMAL FUNCTION PATHWAY						
LRRK2	DNL201 LEAD	Parkinson's		✓	✓	
	DNL151	Parkinson's		✓	✓	
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)		✓	✓	
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA		✓		
Undisclosed	LF1	Neurodegeneration		✓	✓	Takeda
GLIAL BIOLOGY PATHWAY						
RIPK1 (CNS)	DNL747	Alzheimer's, ALS, MS		✓	✓	Sanofi
TREM2	ATV:TREM2	Alzheimer's		✓		Takeda
CELLULAR HOMEOSTASIS						
BACE1/Tau	ATV:BACE1/Tau	Alzheimer's		✓	✓	Takeda
Undisclosed	CH1	Neurodegeneration		✓		
OTHER						
RIPK1 (Peripheral)	DNL758	RA, Psoriasis		✓	✓	Sanofi

- Core and Seed (12) prioritization
- Discovery targets (6)
- Pathway-focused

Parallel Investments

Example: LRRK2 program

Molecule	Phase	Status
DNL201	Lead	Ph1b (PD)
DNL151	Backup 1	Ph1 HV
DN 1965	Backup 2	IND enabling
DNL022	Former Lead	Discontinued

- Lead molecule
- Backup molecule(s)
- 9 discontinued molecules

Strategic Partnering

Takeda SANOFI

- ~ 30 partnerships
- 4 programs partnered
- NeuroD partner of choice

THE DENALI TEAM – IT IS ALL ABOUT THE PEOPLE

SCIENTISTS AND DRUG DEVELOPERS

175+ BASED IN SOUTH SAN FRANCISCO

BOARD OF DIRECTORS

HARVARD UNIVERSITY | FLAGSHIP PIONEERING | Microsoft | agios | DENALI THERAPEUTICS

VICKI SATO (CHAIR)

DOUG COLE

PETER KLEIN

DAVID SCHENKEIN

RYAN WATTS

MARC TESSIER-LAVIGNE

Stanford University

JAY FLATLEY

illumina

ROBERT NELSEN

ARCH Venture Partners

JENNIFER COOK

GRAIL

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, PHD – CTMO

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

DENALI'S APPROACH AND PROGRESS

RYAN WATTS

OUR JOURNEY TO DATE AND NEAR-TERM OUTLOOK

2015 — **Building capabilities, pipeline and raising capital**

- 175+ including scientists & drug developers
- 700+ issued & pending patents
- 30+ partnerships
- $950 million raised

Takeda

SANOFI

2018 — **Early clinical testing and data in humans**

- Discover and develop molecules
- Submit successful IND's
- Define and execute on phase 1 clinical studies

DNL104 (discontinued)

DNL747 (P1 HV completed)

DNL201 (P1b PD ongoing)

DNL201 (P1 HV completed)

DNL151 (P1 HV ongoing)

2020 — **Pivotal clinical studies (efficacy)**

- Successfully complete early clinical studies
- Define pivotal studies and gain FDA approval
- Execute on robust pivotal studies

United States Patent and Trademark Office
An Agency of the United States Department of Commerce

Nasdaq

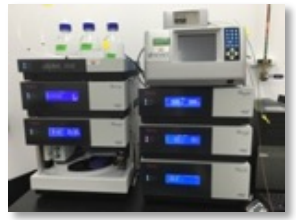
BUILDING A FULLY INTEGRATED BIOTECHNOLOGY COMPANY

INTEGRATED INFRASTRUCTURE

- 175+ full time employees (75% PhD or MD)
- Based in South San Francisco, CA
- Established capabilities
  - Biology, Therapeutic, and Biomarker Discovery, including vivarium and chemistry ~100 scientists
  - ~30 Development clinicians and scientists
- Manufacturing collaboration with Lonza

LONG-TERM FINANCIAL RESOURCES

- Raised ~$950M between equity capital and cash upfront from partnerships
- Our strategic partnerships include development cost sharing and significant milestones
  - Takeda (3 named ATV programs)
  - Sanofi (RIPK1)





DENALI LEADERSHIP

RYAN WATTS, PHD
CEO
Formerly Director of Neuroscience, Genentech
Stanford PhD, University of Utah

ALEXANDER SCHUTH, MD
COO
Formerly Head of Neuroscience Partnering, Genentech
Charite MD, Wharton MBA

CAROLE HO, MD
CMO
Formerly VP Early Clinical Development at Genentech
Cornell MD, Harvard

STEVE KROGNES
CFO
Formerly CFO Genentech and Head of M&A Roche
Harvard MBA, UPenn

DANA ANDERSEN, PHD
CTMO
Formerly VP & Global Head of Technical Dev PPM, Genentech
Stanford PhD, University of CO

MARK DRESSER, PHD
DEV SCIENCES
Formerly Head of Oncology Clinical Pharmacology, Genentech
UCSF PhD, RPI / ETH Zurich

CINDY DUNKLE
HUMAN RESOURCES
20 years Human Resources experience, Genentech
Metropolitan State University

JOE LEWCOCK, PHD
BIOLOGY DISCOVERY
Formerly Director of Department of Neuroscience, Genentech
Johns Hopkins PhD, UC San Diego

ZACH SWEENEY, PHD
THERAPEUTIC DISCOVERY
Formerly Director of Global Discovery Chemistry, Novartis Emeryville
UC Berkeley PhD, Stanford

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

	Our Approach		Our Goal
Genetic Pathway Potential	• Selection of targets based on human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Proprietary BBB platform for large molecules • Engineering approach for small molecules		• Improved brain exposure • Improved target engagement
Biomarker-Driven Development	• Target Engagement • Pathway Engagement • Patient Phenotyping		• The right molecule • The right dose • The right patients

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

INCREASED PROBABILITY OF SUCCESS

DENALI CORE PORTFOLIO

PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT					BIOMARKER ENABLED		PARTNER
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	P	C	
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GLIAL BIOLOGY PATHWAY										
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TREM2	ATV:TREM2	Alzheimer's						✓		Takeda
CELLULAR HOMEOSTASIS										
BACE1/Tau	ATV:BACE1/Tau	Alzheimer's						✓	✓	Takeda
Undisclosed	CH1	Neurodegeneration						✓		
OTHER										
RIPK1 (Peripheral)	DNL758	RA, Psoriasis						✓	✓	Sanofi

Large Molecule (Transport Vehicle)

Small Molecule

BIOMARKER ENABLED
P = Preclinical
C = Clinical

In addition to the programs listed above, Denali is also pursuing a number of SEED programs in Drug Discovery and IND-enabling stages of development

COLLABORATIONS ARE CENTRAL TO OUR STRATEGY

Select current and former collaborators in academia and industry

BUILDING A HIGH QUALITY SHAREHOLDER BASE

SERIES A		SERIES B		INITIAL PUBLIC OFFERING	
MID-2015	$ 219 MILLION	MID-2016 / Q3 2017	$ 160 MILLION	END-2017	$ 288 MILLION

ARCH VENTURE PARTNERS

ALASKA PERMANENT FUND Established 1976

FLAGSHIP PIONEERING
SCIENTIFIC VENTURES FOR LIFE

F-PRIME

Crestline

FBRI
A division of F-Prime

BAILLIE GIFFORD

TEMASEK

ALASKA PERMANENT FUND Established 1976

QIA
جهاز قطر للاستثمار
QATAR INVESTMENT AUTHORITY

Nasdaq

Fidelity INVESTMENTS

BAILLIE GIFFORD

ALASKA PERMANENT FUND Established 1976

TEMASEK

GIC

BARON CAPITAL

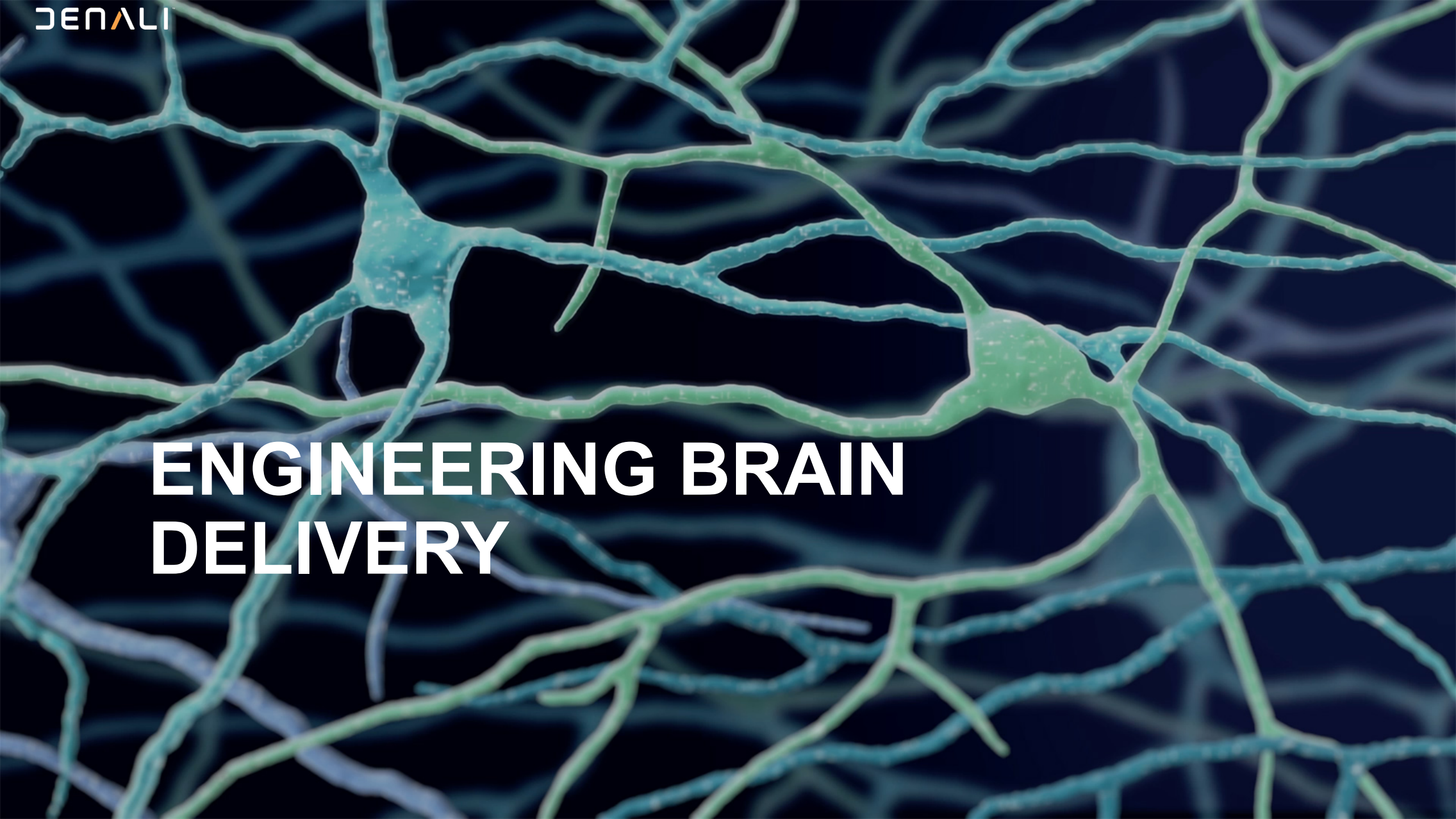
INVUS

DENALI PORTFOLIO: STATUS AND MILESTONES 2018 TO 2020

Program		IND	Ph 1 HV Data	Patient Biomarker Data	Initiate Ph 2 or Ph 3 Trial
LRRK2 (DNL201)		●	●		
(DNL151)		●	●	●	●
RIPK1 (DNL747)	ALS			●	●
	Alzheimer's	●	●	●	●
	MS				●
ETV:IDS (DNL310)		●		●	●
ATV:aSyn		●			
ATV:TREM2		●			
ATV:BACE1/Tau		●			
Undisclosed SM (CH1)		●			

DELIVERING CLINICAL DATA AND MOVING TO PIVOTAL TRIALS

● Achieved ● Planned


DENALI
ENGINEERING BRAIN
DELIVERY

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

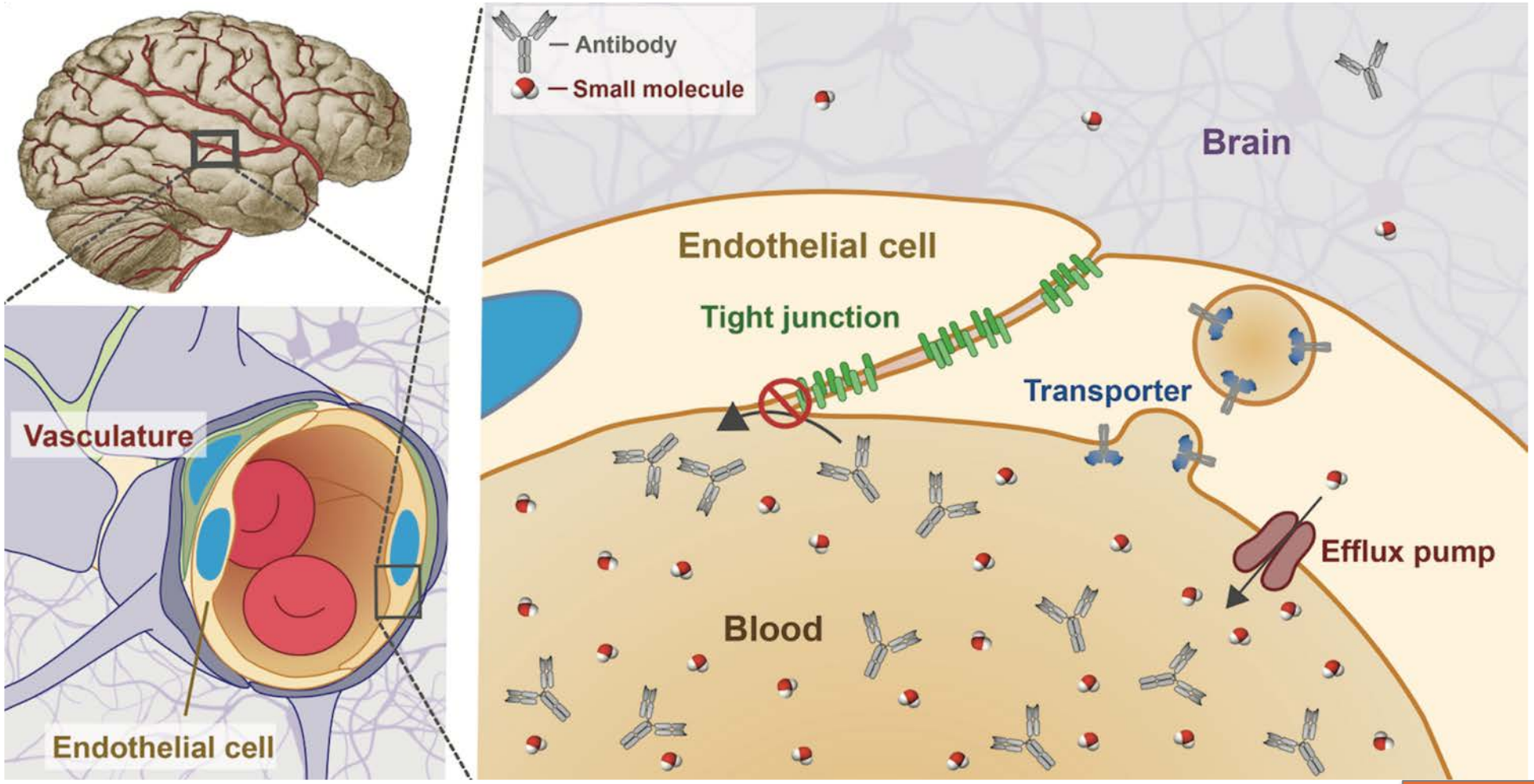
	Our Approach		Our Goal
Genetic Pathway Potential	• Selection of targets based on human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Proprietary BBB platform for large molecules • Engineering approach for small molecules		• Improved brain exposure • Improved target engagement
Biomarker-Driven Development	• Target Engagement • Pathway Engagement • Patient Phenotyping		• The right patients • The right molecule • The right dose

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

INCREASED PROBABILITY OF SUCCESS

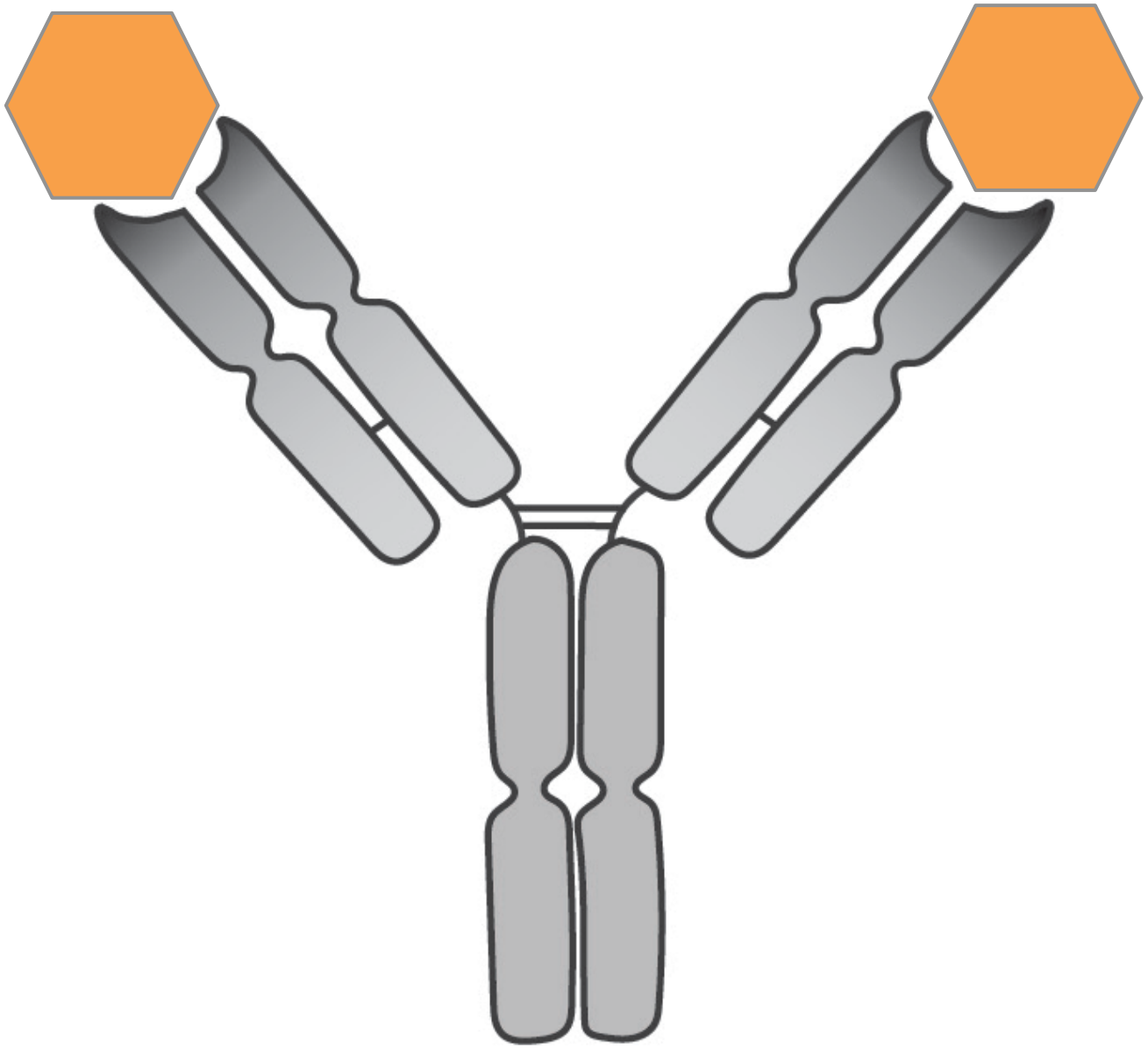
THE BLOOD-BRAIN BARRIER (BBB) CHALLENGE

- The blood-brain barrier evolved to protect the central nervous system and maintain a homeostatic environment in the brain
- Tight junctions, efflux pumps, and transporters regulate access of substances to the brain
- Achieving therapeutically relevant drug concentrations in the brain has been a major challenge



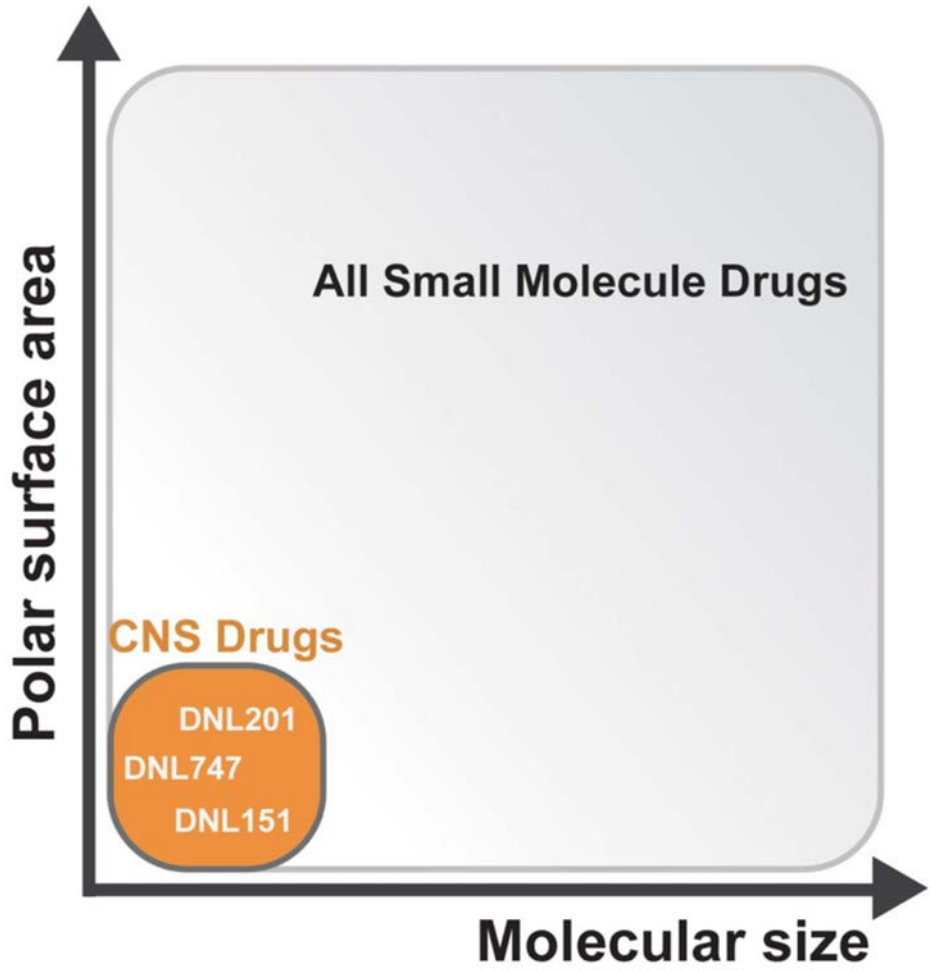
ENGINEERING LARGE AND SMALL MOLECULES TO CROSS THE BBB

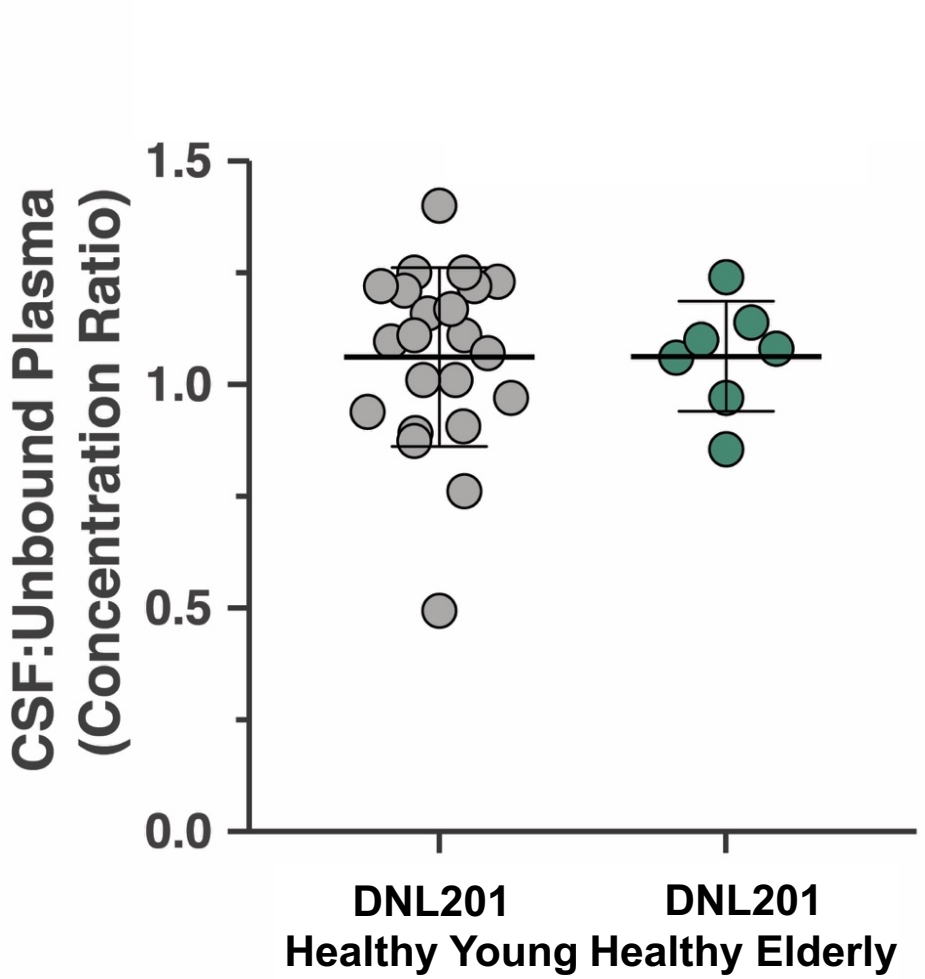
ANTIBODIES ARE ~375X LARGER THAN SMALL MOLECULES



Note: these are drawn to scale
[150 kDa vs 400 Da]

ENGINEERING SMALL MOLECULES TO CROSS THE BBB

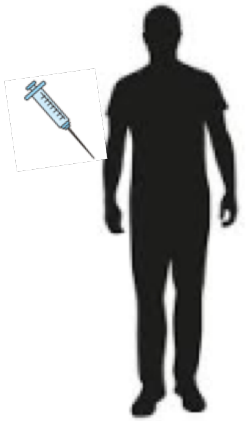




Source: Denali Therapeutics Inc.

POOR BRAIN EXPOSURE DIMINISHES LIKELIHOOD OF SUCCESS FOR BIOTHERAPEUTICS FOR NEURODEGENERATIVE DISEASES

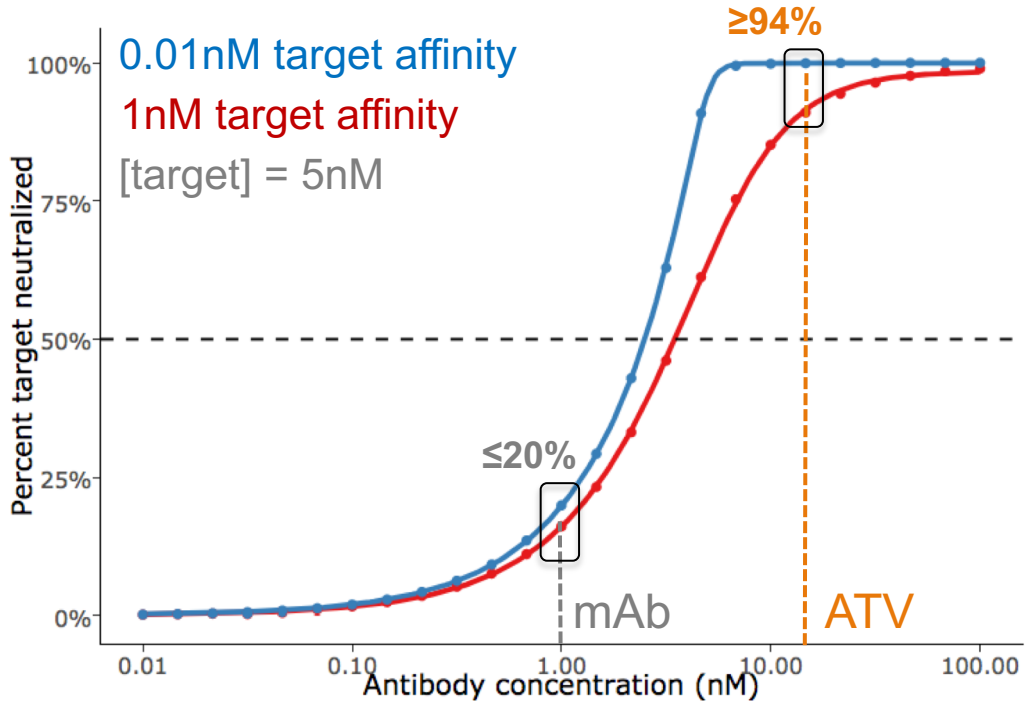
10mg/kg i.v.
antibody dose



C_{max}(serum) = 1.3μM

C_{max}(brain) mAb = ~1nM
(insufficient for therapeutic effect)

C_{max}(brain) ATV = ~20nM
(in therapeutic range for most targets)



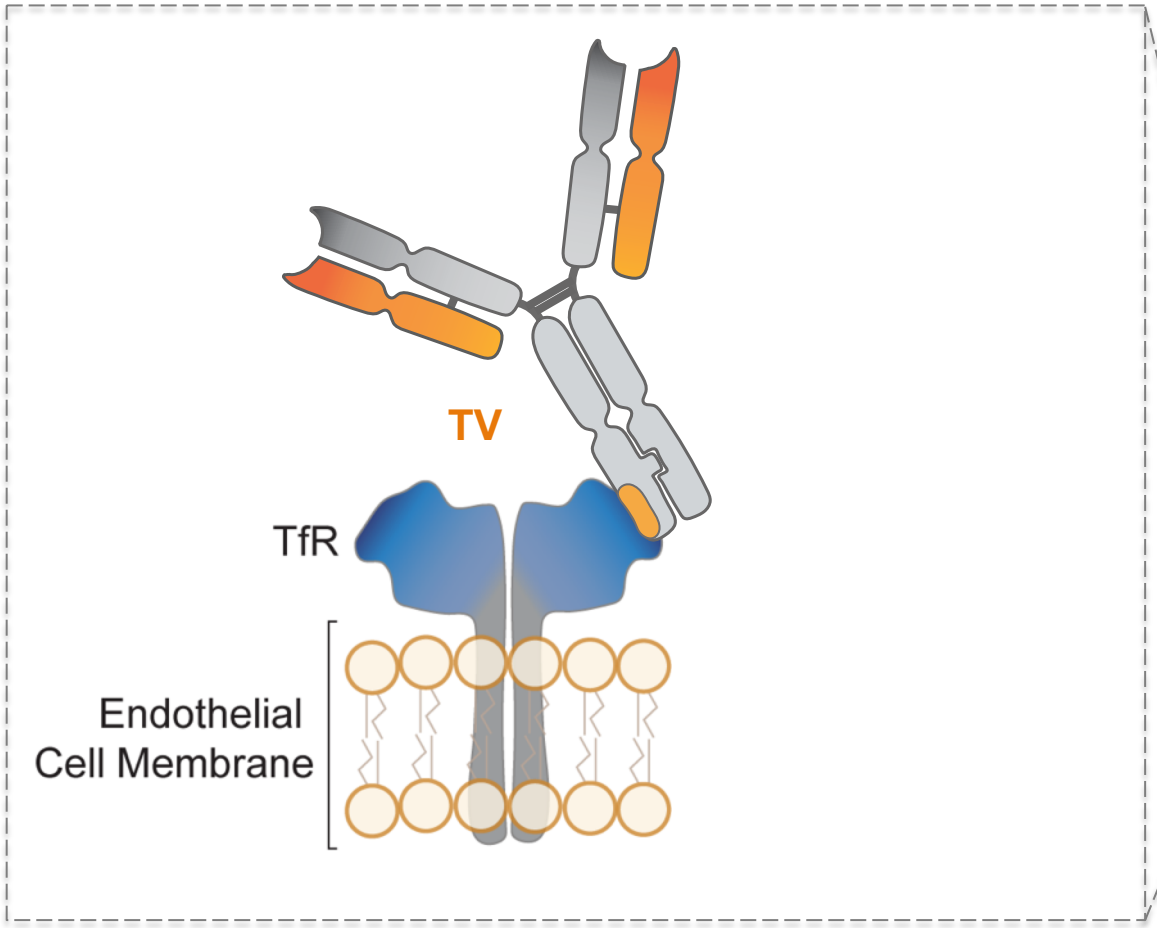
Enhanced ATV brain exposure increases extent of target engagement and improves potential for successful treatment of neurodegeneration

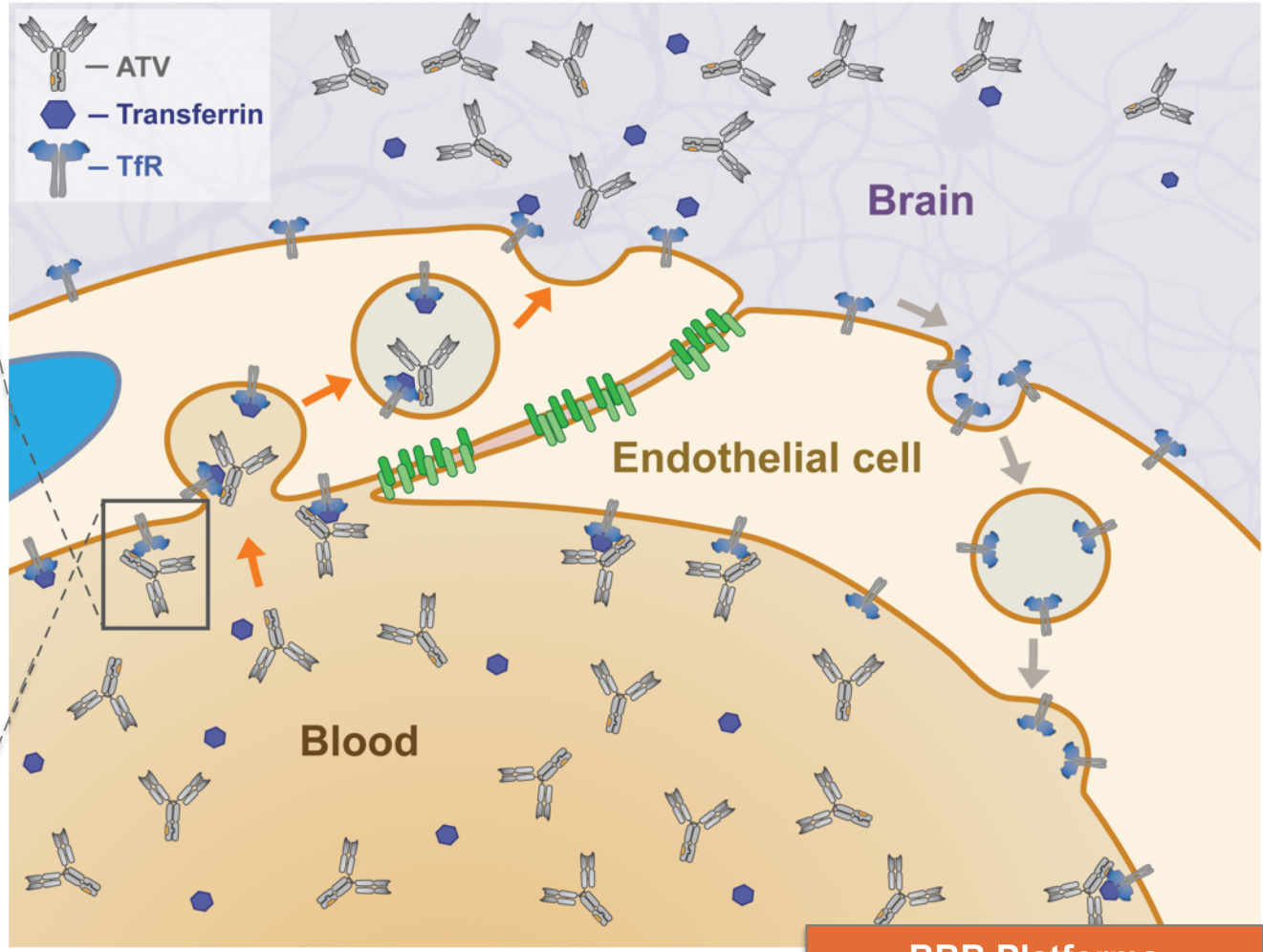
Low mAb exposure limits target engagement (≤20%)

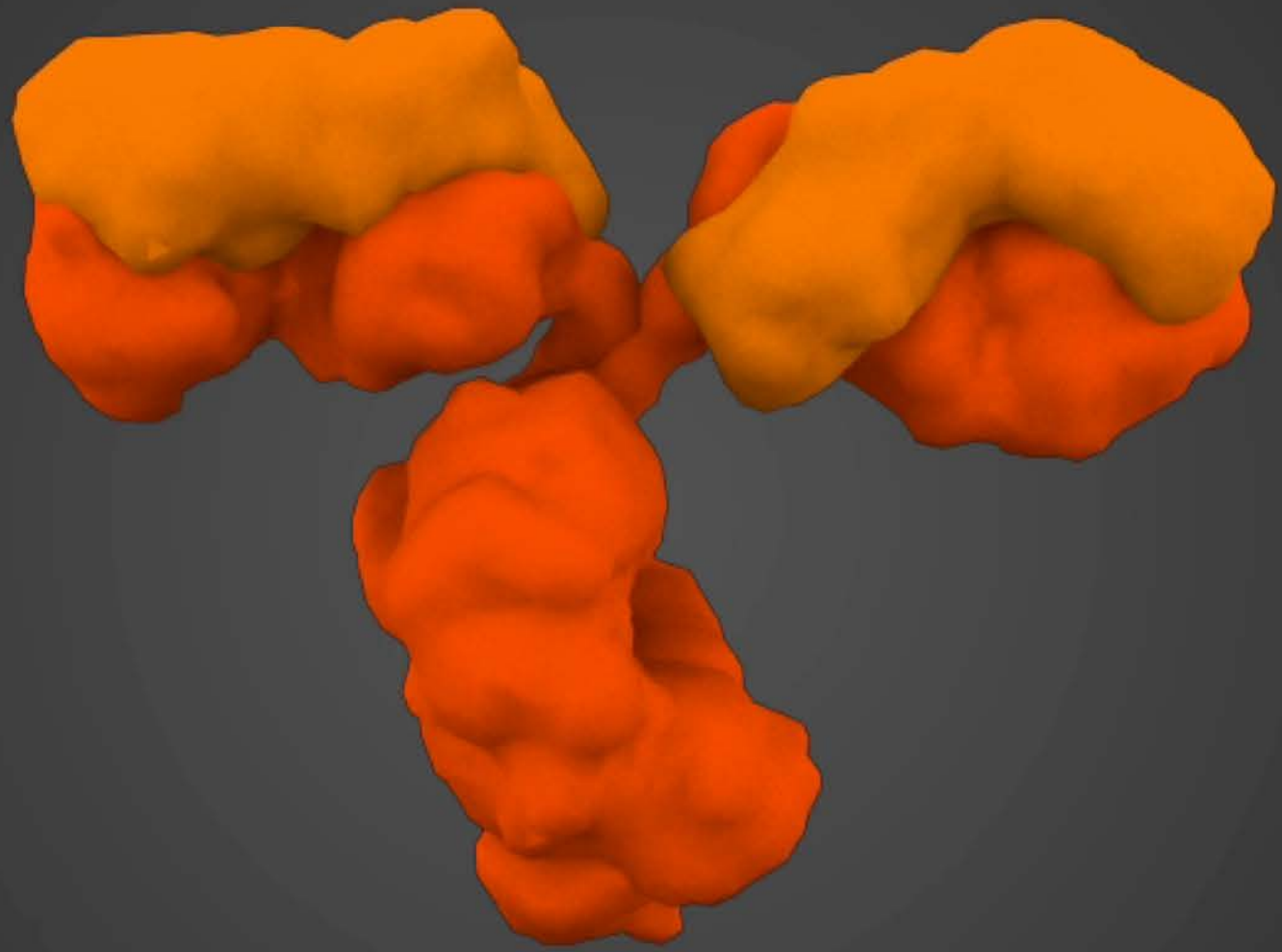
Higher ATV exposure drives full target engagement (≥94%)

ENGINEERING BRAIN DELIVERY: TRANSPORT VEHICLE

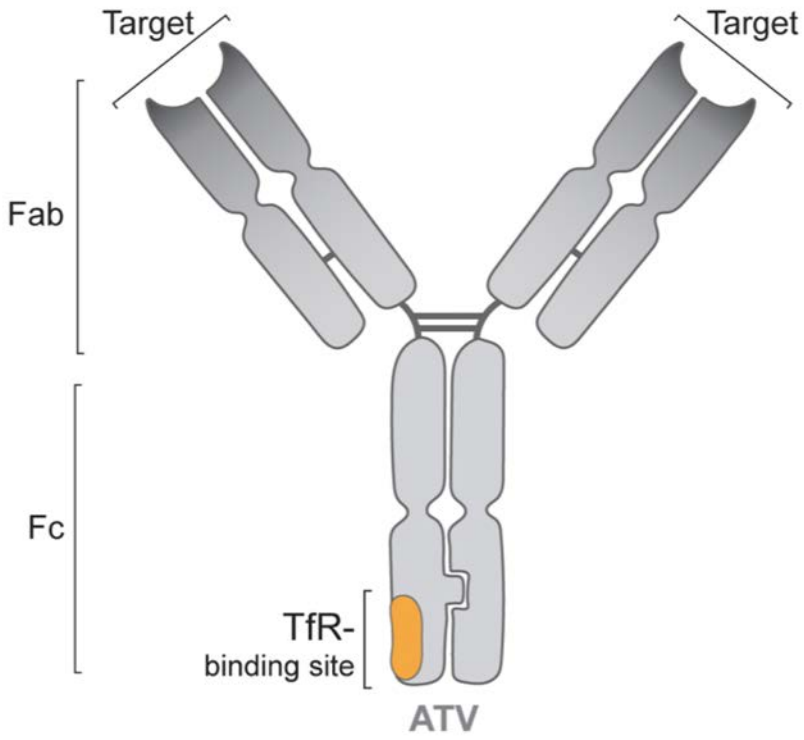
- **TV is an Fc engineered to bind to Transferrin receptor (TfR)**
- **TfR/TV complexes** are endocytosed in endothelial cells of the blood-brain barrier
- TV dissociates in the endosome and is released for **broad distribution into the brain parenchyma**







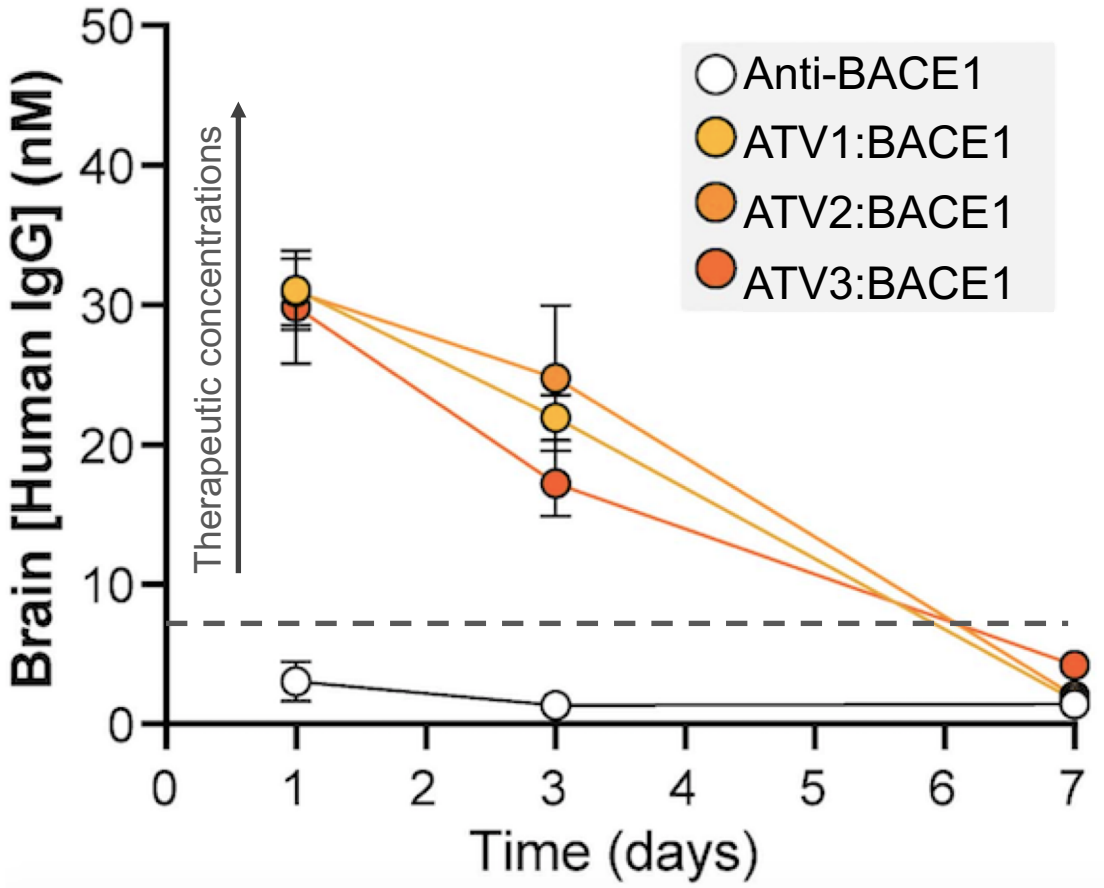
ENGINEERING BRAIN DELIVERY: TRANSPORT VEHICLE



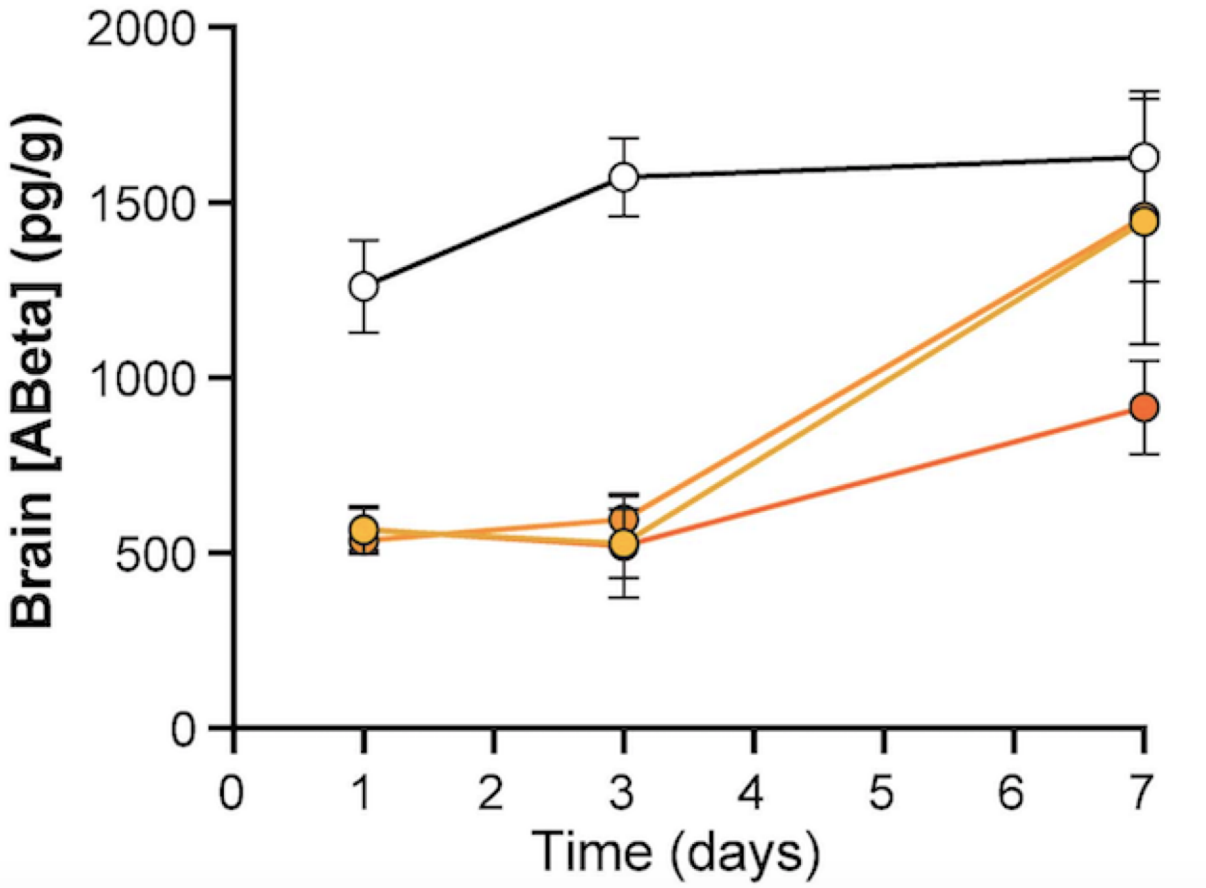
Transport Vehicle	Advantages compared to other RMT approaches
• TfR binding site integrated into the **Fc region of IgG**	• Stability and PK of human IgG • No unnatural linkers or appended sequences • Low risk of immunogenicity
• **TfR** as BBB RMT target	• Most validated BBB target with high levels of transport capacity and demonstrated safety in nonhuman primates • Solved co-crystal structure of TfR with TV
• **Bivalent** target binding	• Both Fab arms available for bivalent or bispecific target binding
• Highly **modular** platform	• Ability to deliver antibodies (ATV), enzymes (ETV) and potentially other proteins

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

PK: drug concentration in brain



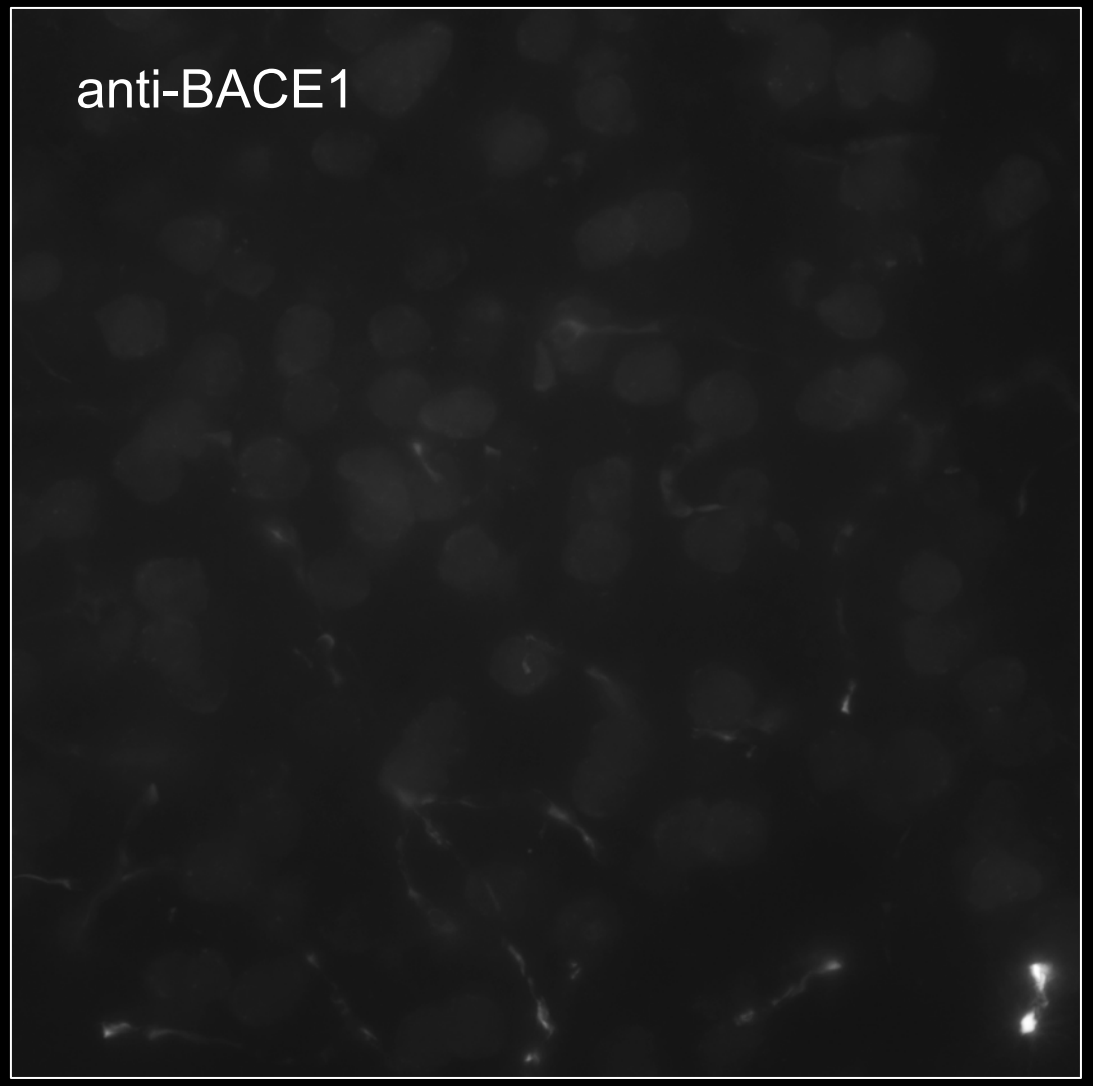
PD: Abeta reduction in brain

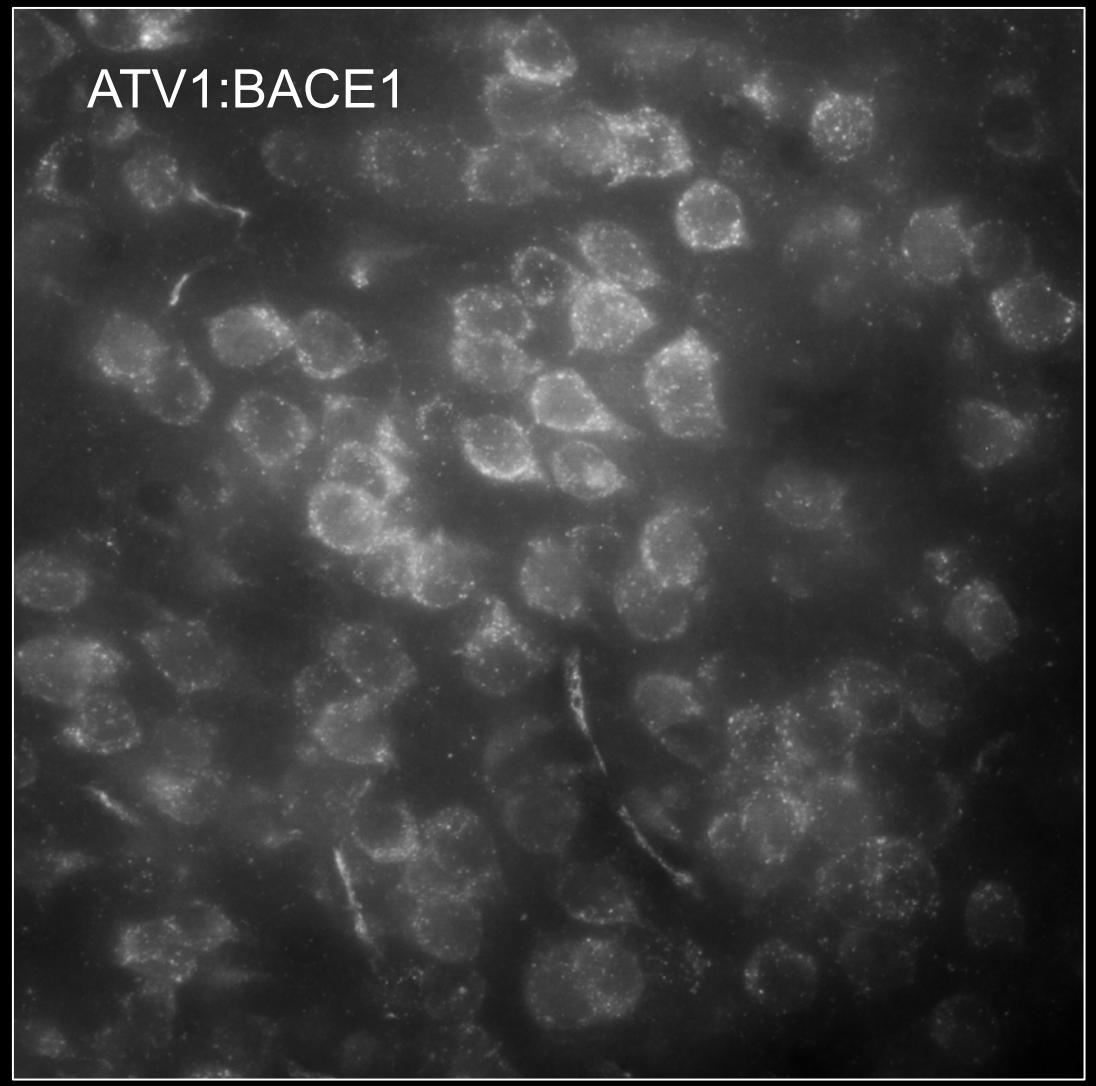


- 50 mg/kg IV dose in $TfR^{hu/ms}$ KI mice – time course

BROAD DISTRIBUTION OF ATV IN BRAIN

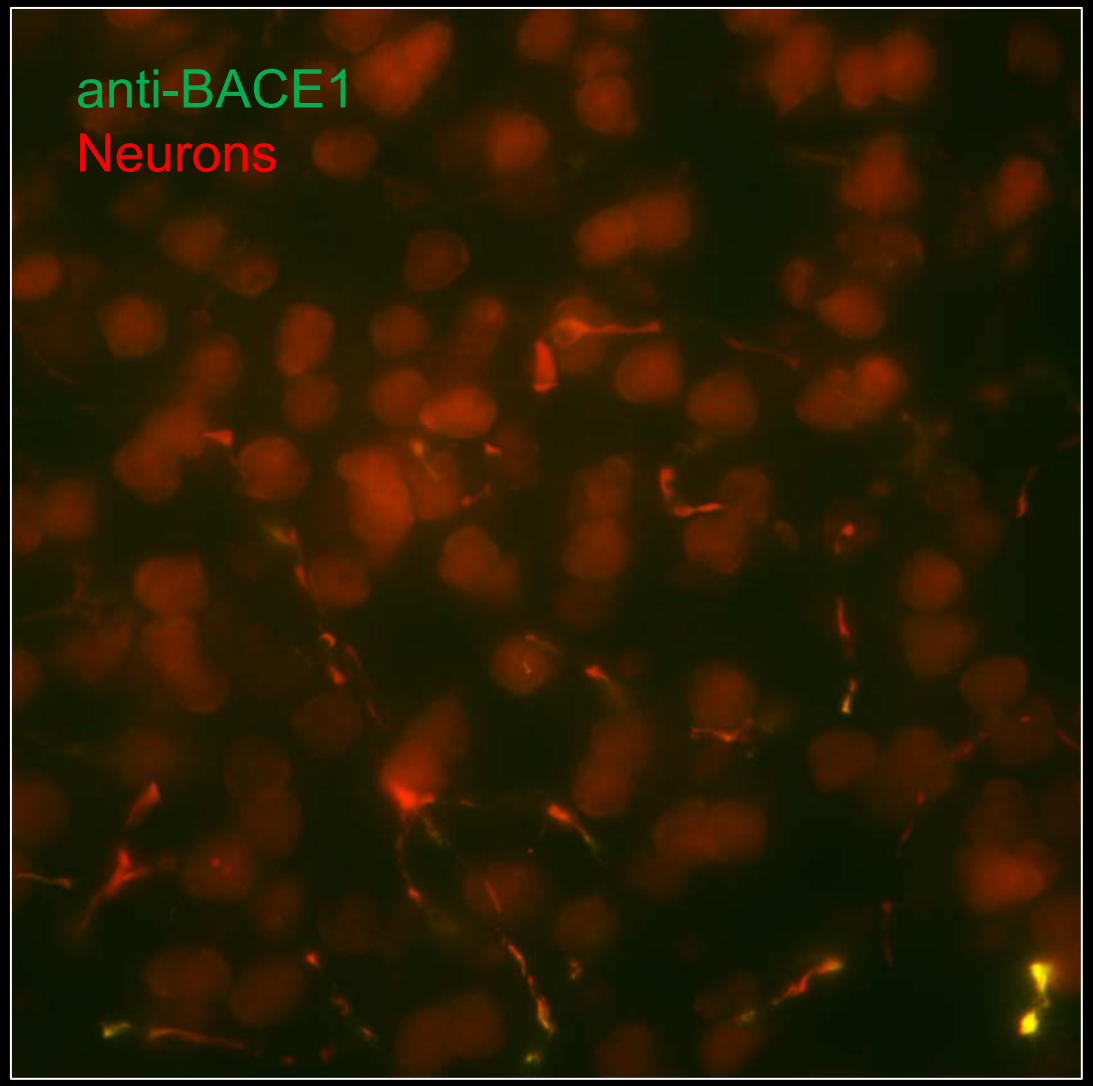
Localization of antibody in $TfR^{hu/ms}$ KI brain cortex 24hrs after 50 mg/kg IV

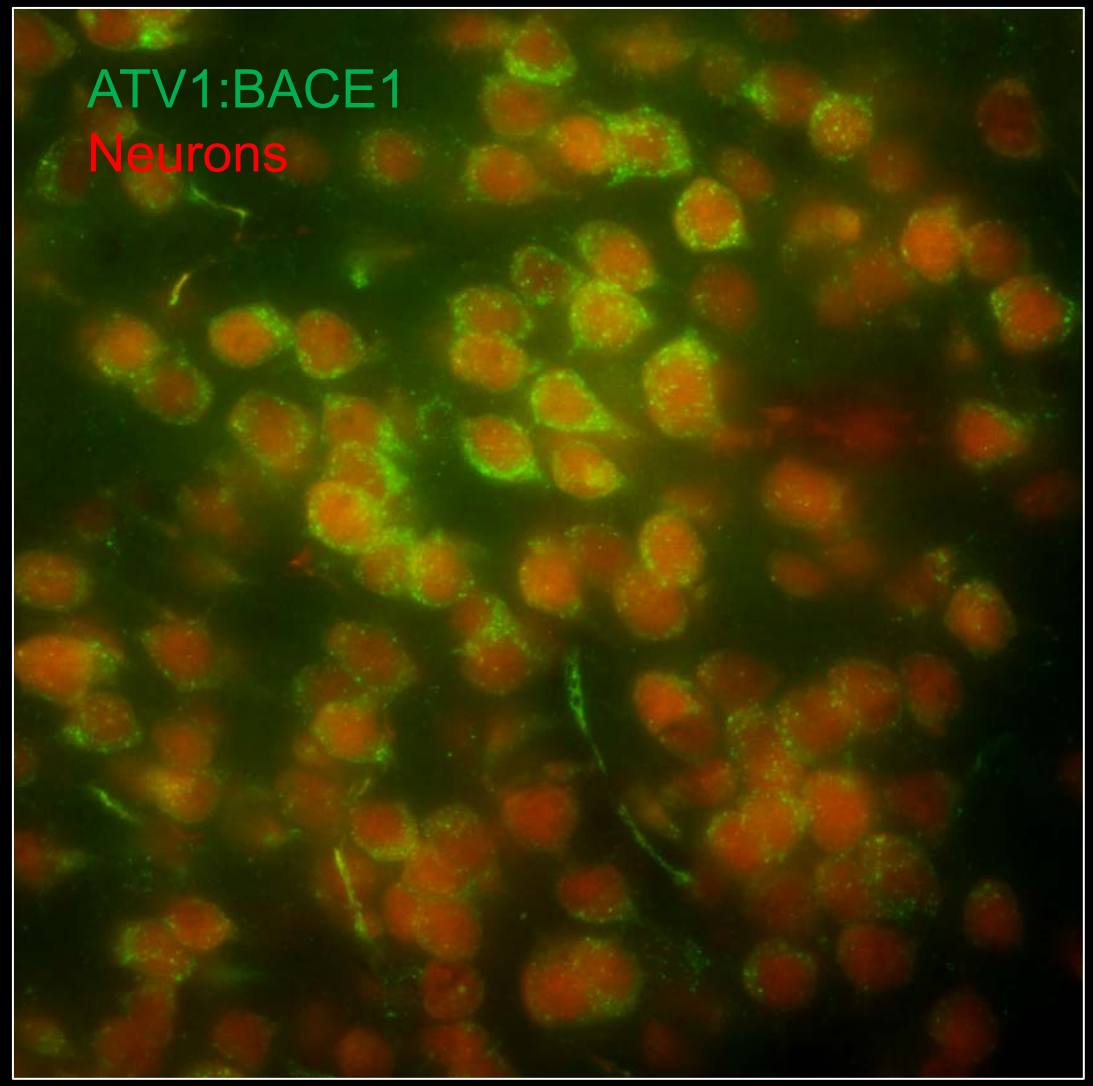




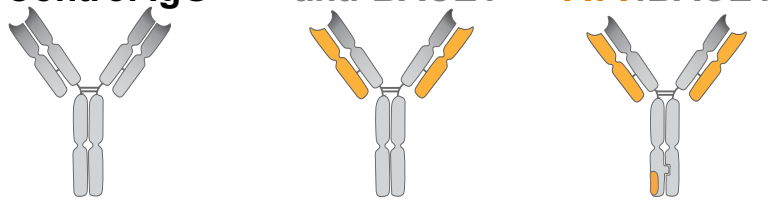
BROAD DISTRIBUTION OF ATV IN BRAIN

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





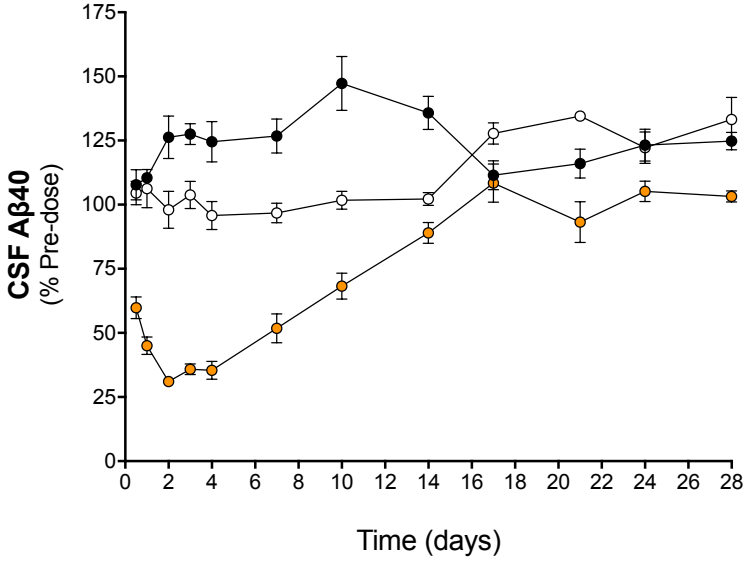
ATV:BACE1 REDUCES CSF ABETA LEVELS IN NONHUMAN PRIMATES



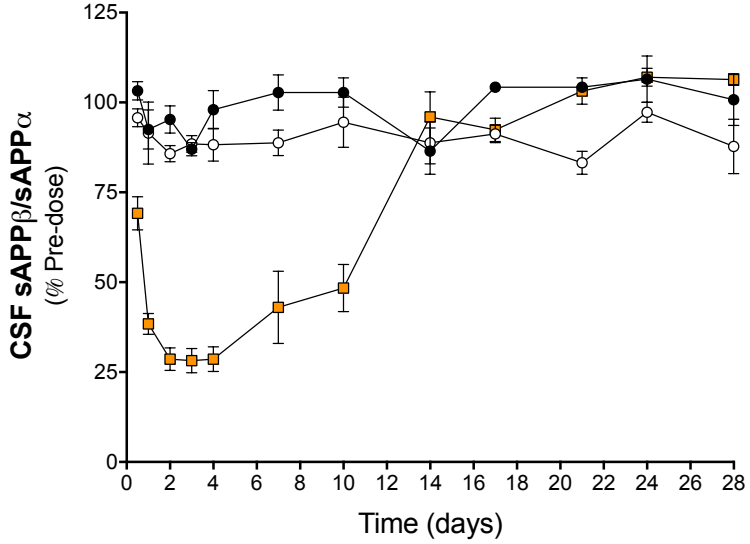
Cynomolgus monkey

30 mg/kg IV dose
28-day PKPD (serum and CSF)

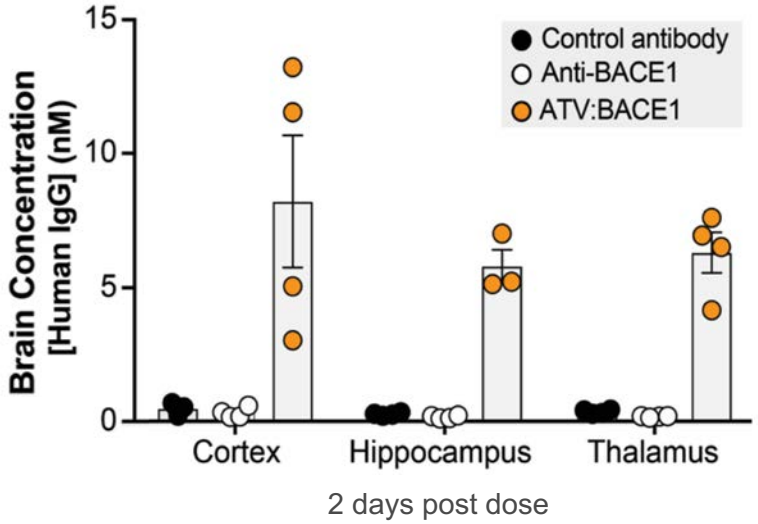
CSF Aβ



CSF sAPPα/sAPPβ



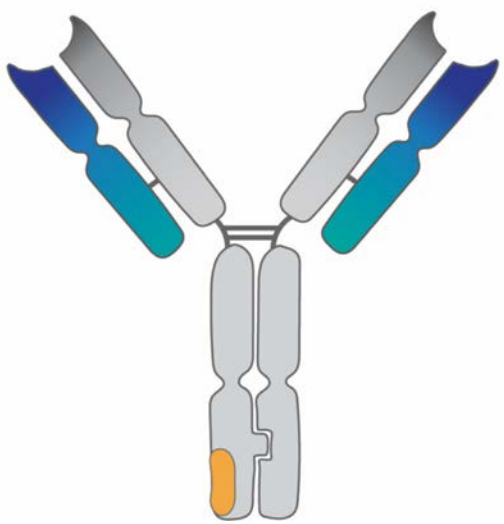
Brain Concentration



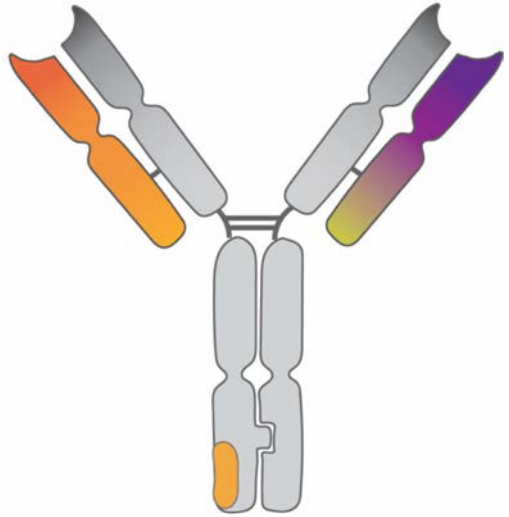
TV delivers antibodies in therapeutically effective concentrations leading to sustained PD effect

THE TRANSPORT VEHICLE (TV): A NOVEL BBB PLATFORM

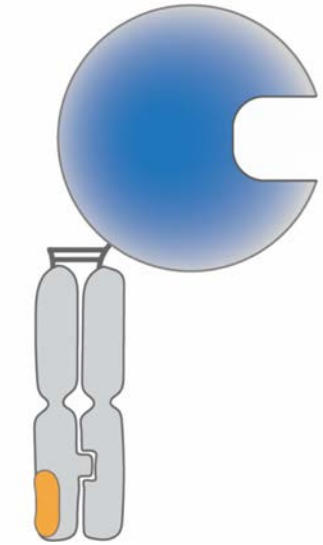
Bivalent Antibodies



Bispecific Antibodies

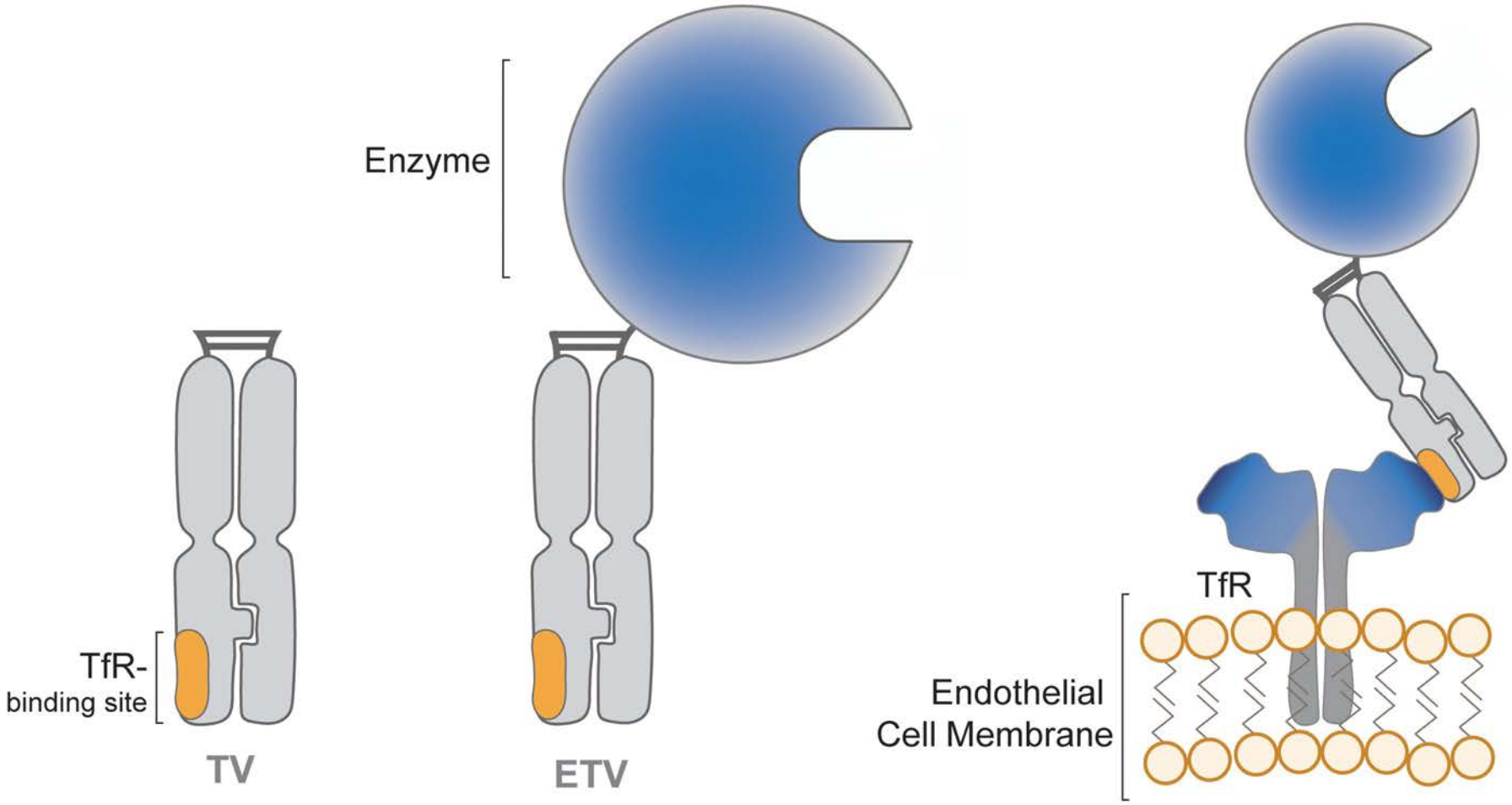


Proteins



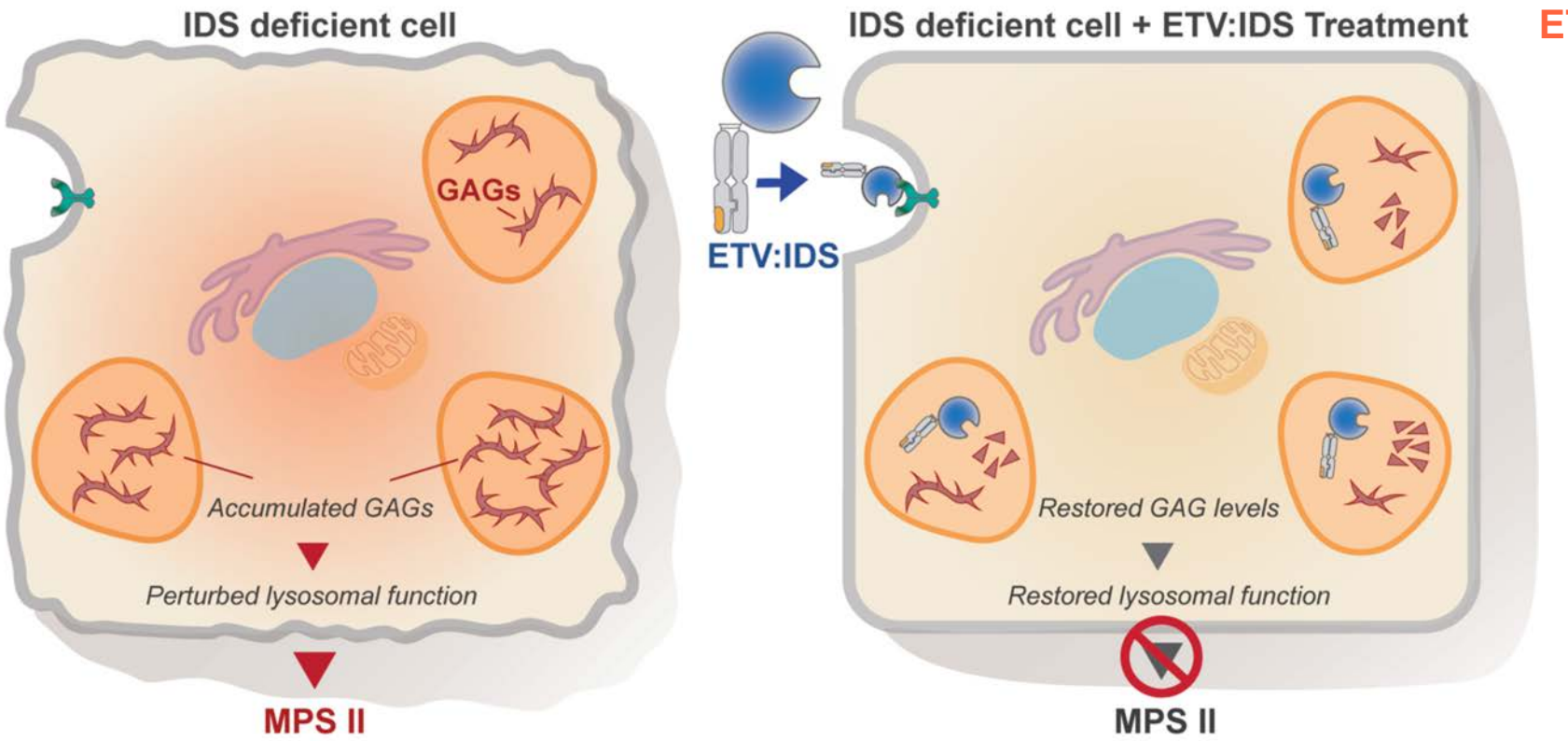
- ✓ Integrate BBB target binding site into IgG format
- ✓ No unnatural linkers or appended domains
- ✓ Retain stability and pharmacokinetics of IgG
- ✓ Modular to allow brain uptake of multiple formats

ENZYME TRANSPORT VEHICLE

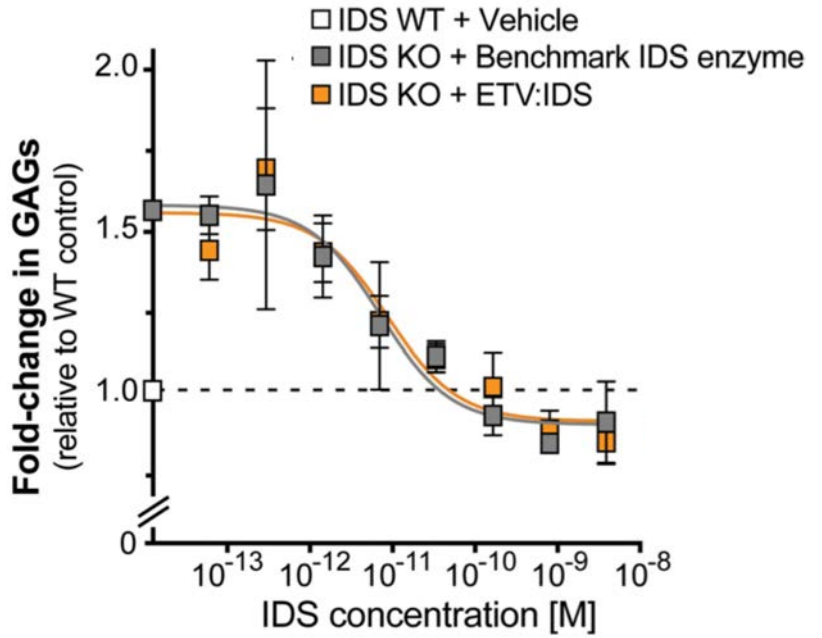


- ETV technology contains BBB receptor (TfR) binding Fc domain fused to an enzyme
- Enables transport of enzymes into the brain through TfR-mediated transcytosis

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



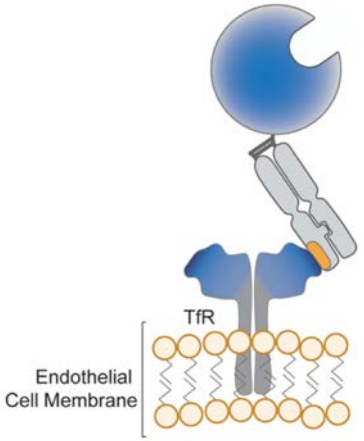
ETV:IDS reduces substrate in IDS KO cells

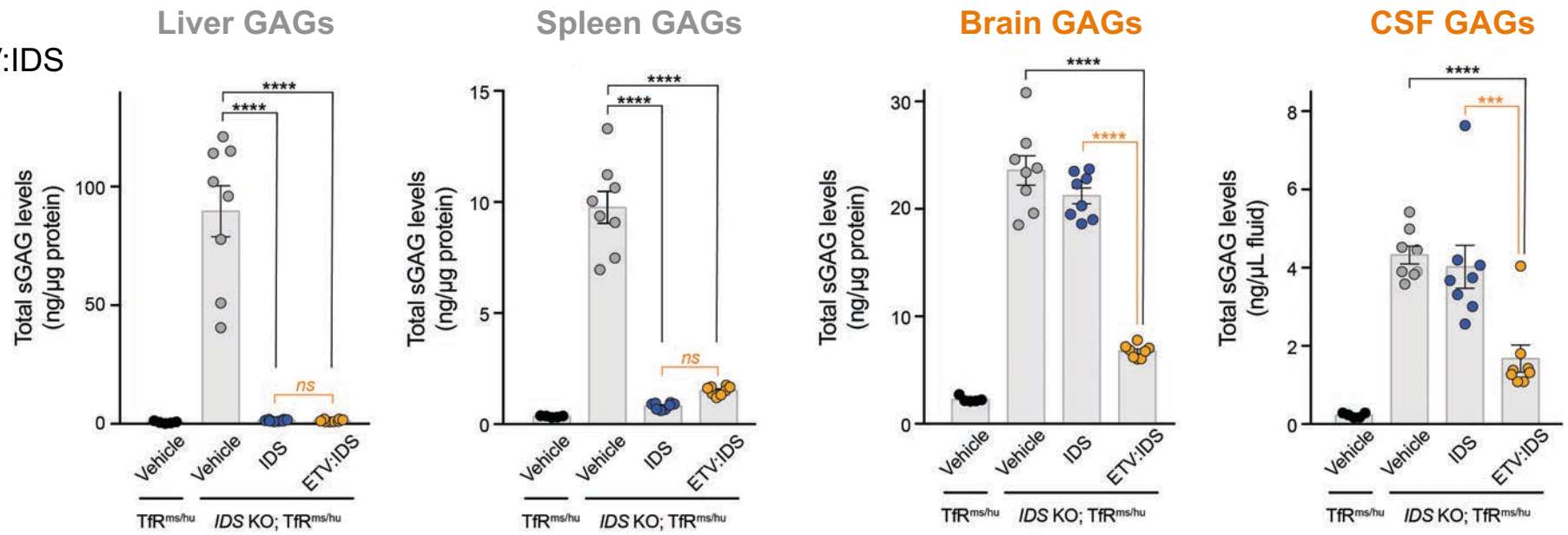


- Treatment with ETV:IDS should promote GAG processing and may rescue neurons from degeneration

ETV:IDS ROBUSTLY REDUCES GAGS IN THE PERIPHERY AND BRAIN

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



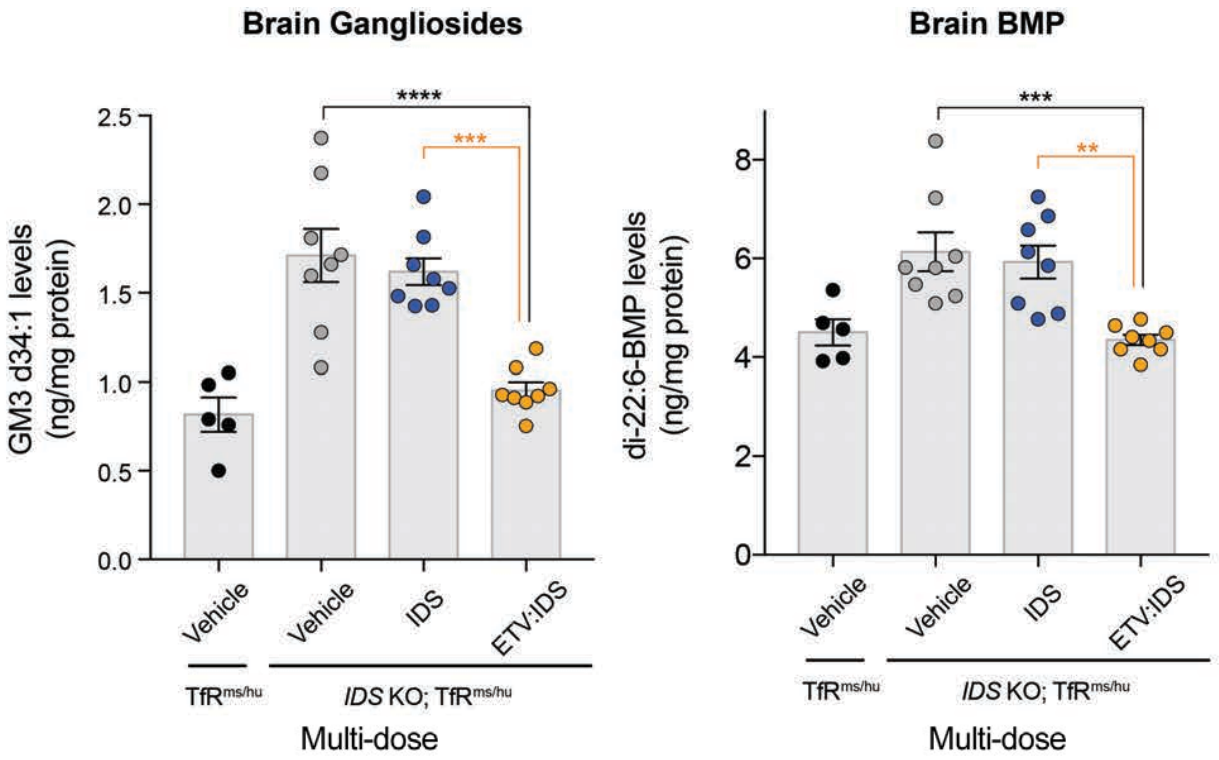


*n=8 per IDS KO; TfR$^{mu/hu}$ group or 5 per TfR$^{mu/hu}$ group, data shown as mean ± s.e.m.; *** p < 0.001, **** p < 0.0001 ; ns = not significant*

ETV:IDS reduces GAGs in liver, spleen, brain, and CSF after 4 weekly doses
Elaprase (IDS) does not effectively reduce GAG levels in the CNS

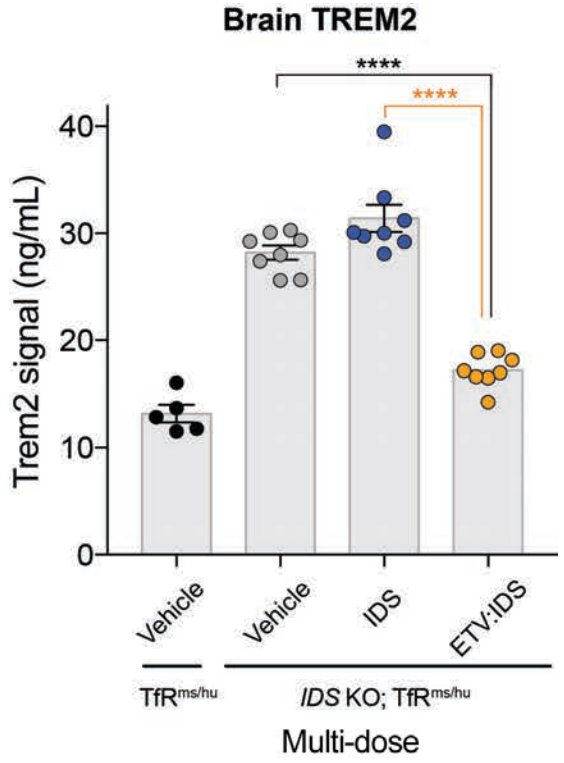
ETV:IDS CORRECTS DOWNSTREAM PATHWAY DYSFUNCTION

DNL310 CORRECTS SECONDARY LYSOSOMAL LIPID ACCUMULATION



*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*

DNL310 CORRECTS ELEVATED TREM2 LEVELS IN BRAIN



*n=8 per IDS KO; TfR$^{mu/hu}$ group or 5 per TfR$^{mu/hu}$ group, data shown as mean ± s.e.m.; **** p < 0.0001*

DNL310 corrects downstream pathology including lysosomal lipid storage and microglial activation

DENALI TRANSPORT VEHICLE PORTFOLIO

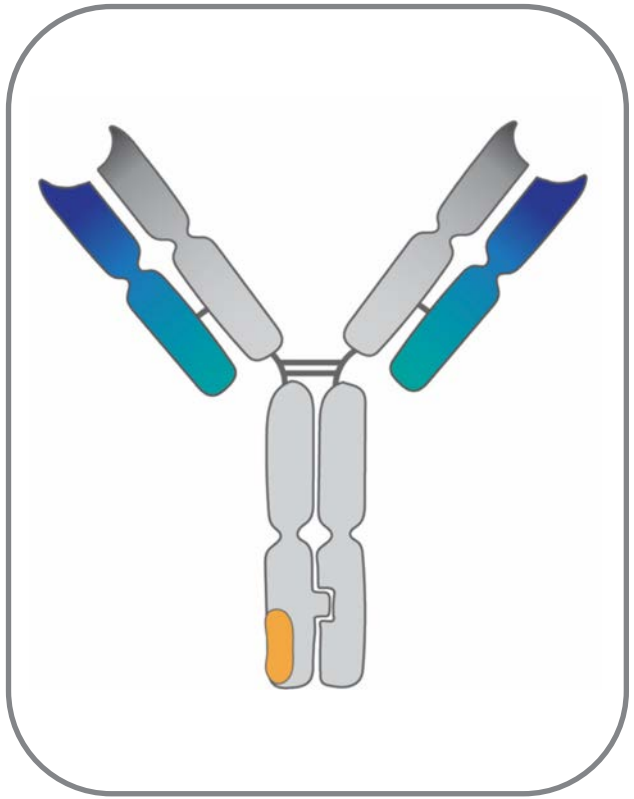
PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT					BIOMARKER ENABLED		PARTNER
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	P	C	
LYSOSOMAL FUNCTION PATHWAY										
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)						✓	✓	
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA						✓		
Undisclosed	LF1	Neurodegeneration						✓	✓	Takeda
GLIAL BIOLOGY PATHWAY										
TREM2	ATV:TREM2	Alzheimer's						✓		Takeda
Undisclosed	GB1	Alzheimer's								
CELLULAR HOMEOSTASIS										
BACE1/Tau	ATV:BACE1/Tau	Alzheimer's						✓	✓	Takeda
OTHER										
Undisclosed	OT1	Undisclosed						✓	✓	

BIOMARKER ENABLED
P = Preclinical
C = Clinical

BBB Platforms

THREE CATEGORIES OF DRUGS

SMALL MOLECULES



BIOTHERAPEUTICS

VIRAL VECTORS

Note: not drawn to scale

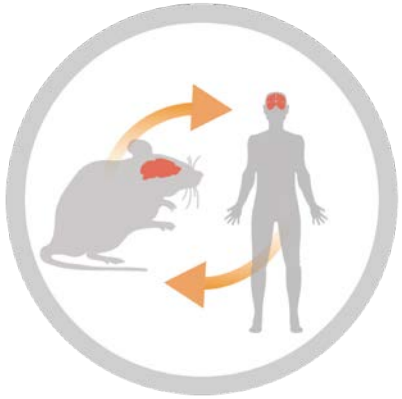
BIOMARKER-DRIVEN DEVELOPMENT

CAROLE HO

NEUROSCIENCE DRUG DEVELOPMENT

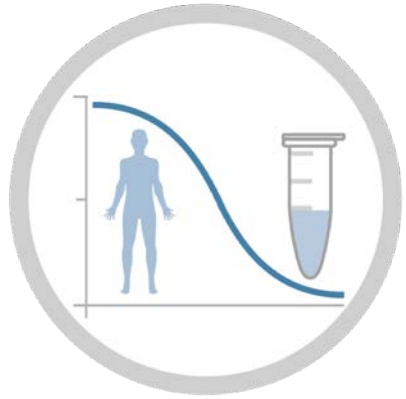
BIOMARKER APPROACHES TO OVERCOME PAST FAILURES

Target **BIOLOGY** grounded in human disease genetics



TRANSLATIONAL MEDICINE strategy focus on target and pathway engagement

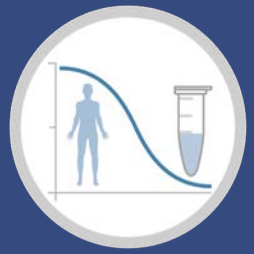
Confirmation of blood-brain barrier (**BBB**) penetration



Investment in **BIOMARKER** reagents for early evidence of drug activity and patient selection

STRONG BIOMARKER DISCOVERY EFFORT IN-HOUSE AND THROUGH COLLABORATIONS

DE-RISKING DISCOVERY & DEVELOPMENT IN NEURODEGENERATION

	Our Approach		Our Goal
Genetic Pathway Potential	• Selection of targets based on human genetics • Disease pathway focus		• Better targets • First-in-class molecules
Engineering Brain Delivery	• Proprietary BBB platform for large molecules • Engineering approach for small molecules		• Improved brain exposure • Improved target engagement
Biomarker-Driven Development	• Target Engagement • Pathway Engagement • Patient Phenotyping		• The right molecule • The right dose • The right patients

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

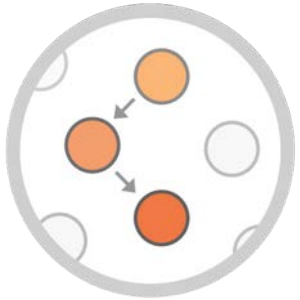
INCREASED PROBABILITY OF SUCCESS

BIOMARKER-DRIVEN DEVELOPMENT PRINCIPLES

Target Engagement

Determine the relationship between dose and drug response

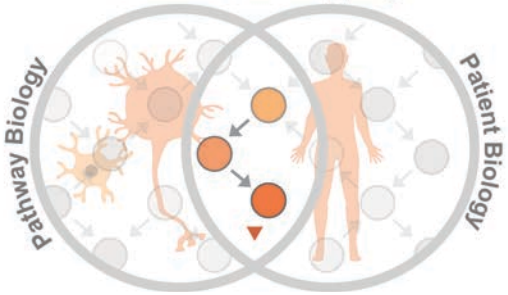
- Early dose finding
- Reduce size of clinical studies



Pathway Engagement

Demonstrate an effect on Pathway Biology

- Confirm dose finding
- Reduce size of clinical studies
- De-risk target by establishing effect on relevant biology



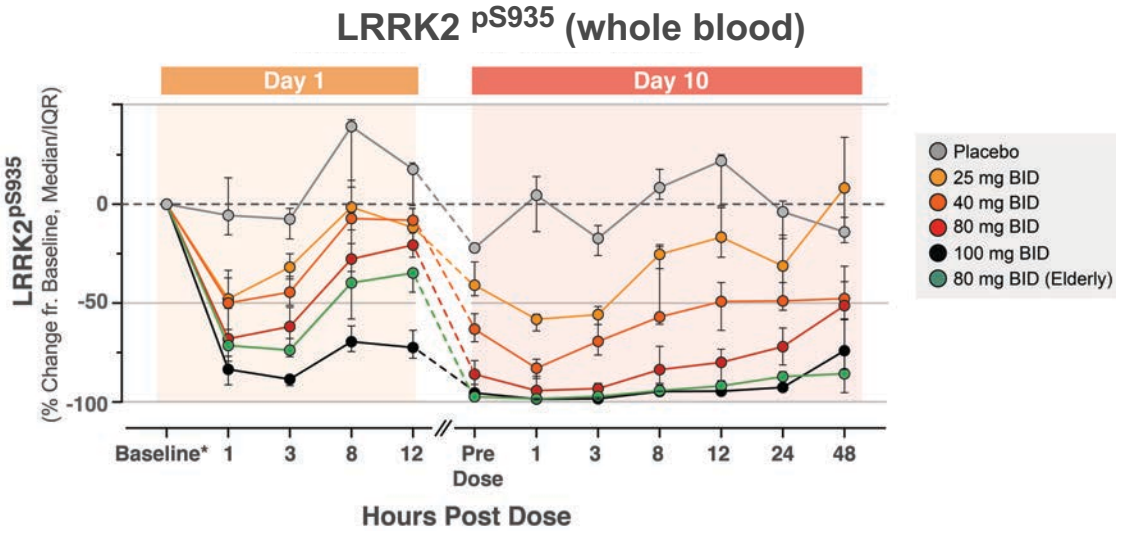
Patient Phenotyping

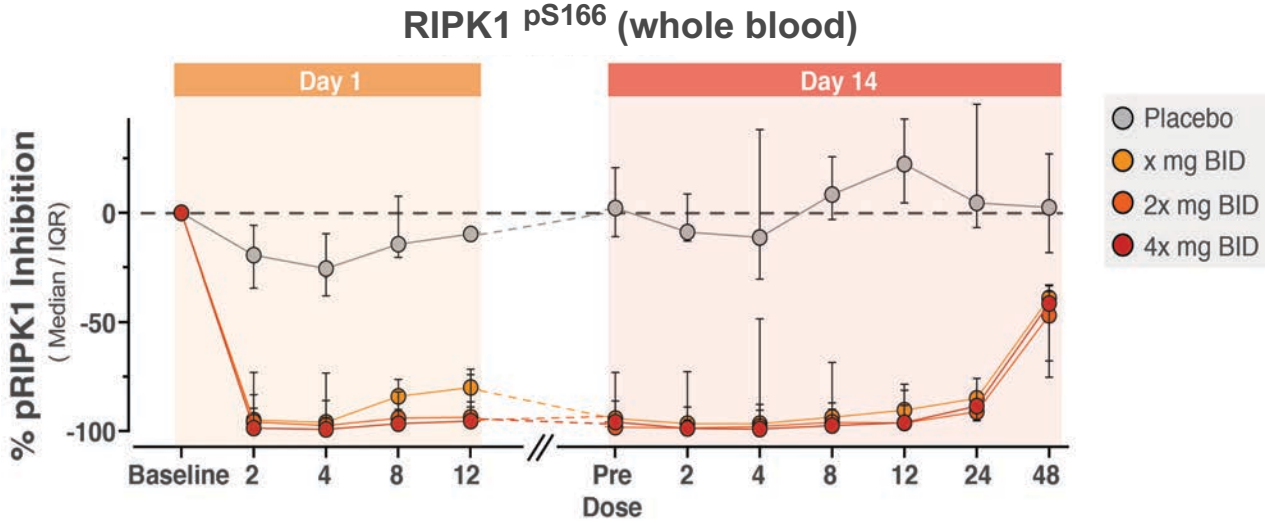
Intersection of Pathway Biology & Disease Biology

- Learn and confirm: genetic pathway biomarkers are candidate disease biomarkers
- Disease biomarkers can be used as endpoints in early studies to monitor therapeutic response
- Increase success by using biomarkers to identify patients most likely to benefit

INCREASED PROBABILITY OF PHASE 2 AND 3 SUCCESS

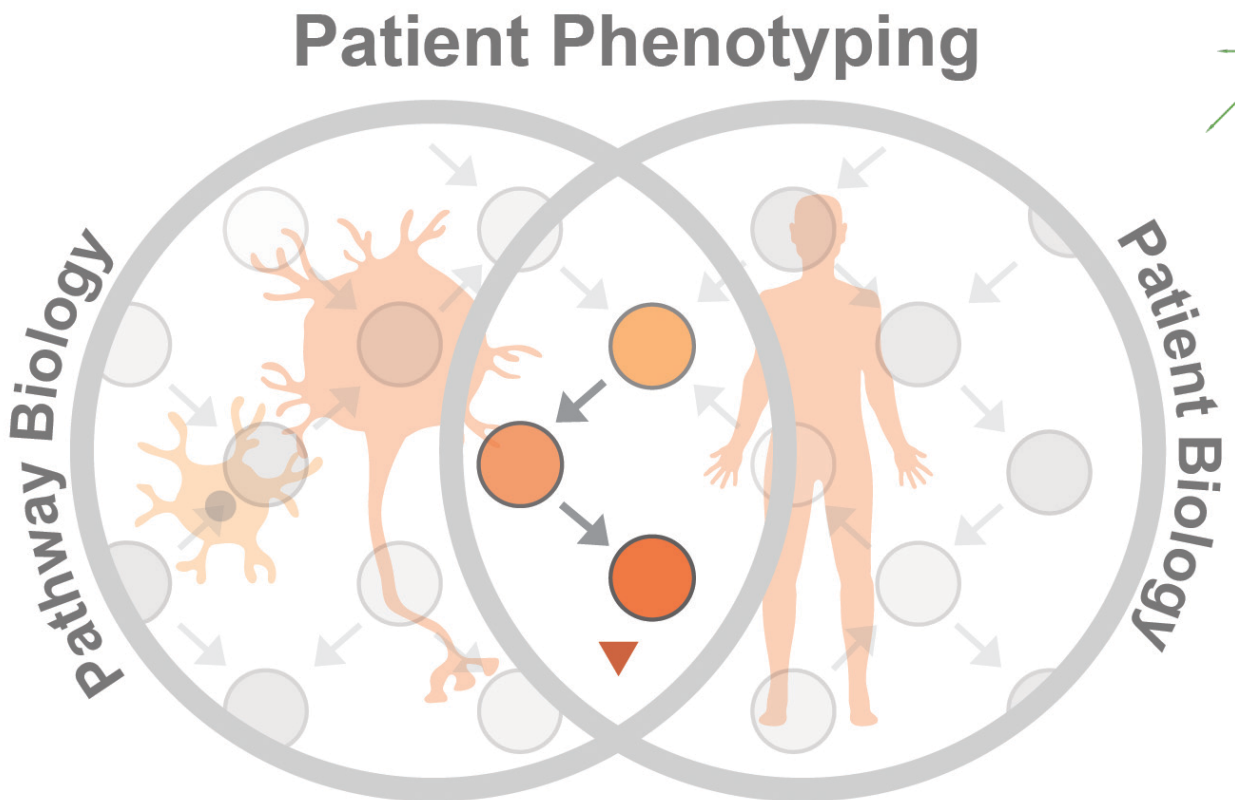
VALUE OF QUANTITATIVE BIOMARKER DATA IN EARLY CLINICAL DEVELOPMENT





- Establish dose rationale with robust target engagement
  - Objective quantitative measurement with low likelihood of false positive or negative outcomes
  - Well powered to assess endpoint measures (as compared to underpowered traditional Phase 2 neuro design)
  - Enable early dose finding in Phase 1 (as compared to traditional dose finding in Phase 2)
- Enable earlier readiness for pivotal studies and increased likelihood of successful outcomes

INTERSECTION OF PATHWAY BIOLOGY & DISEASE PATHOLOGY



simoa
Ultrasensitive Immunoassays

MSD
Meso Scale Discovery

ADNI
Alzheimer's Disease Neuroimaging Initiative

The Michael J. Fox Foundation for Parkinson's Research

Banner Health

23andMe

patientslikeme

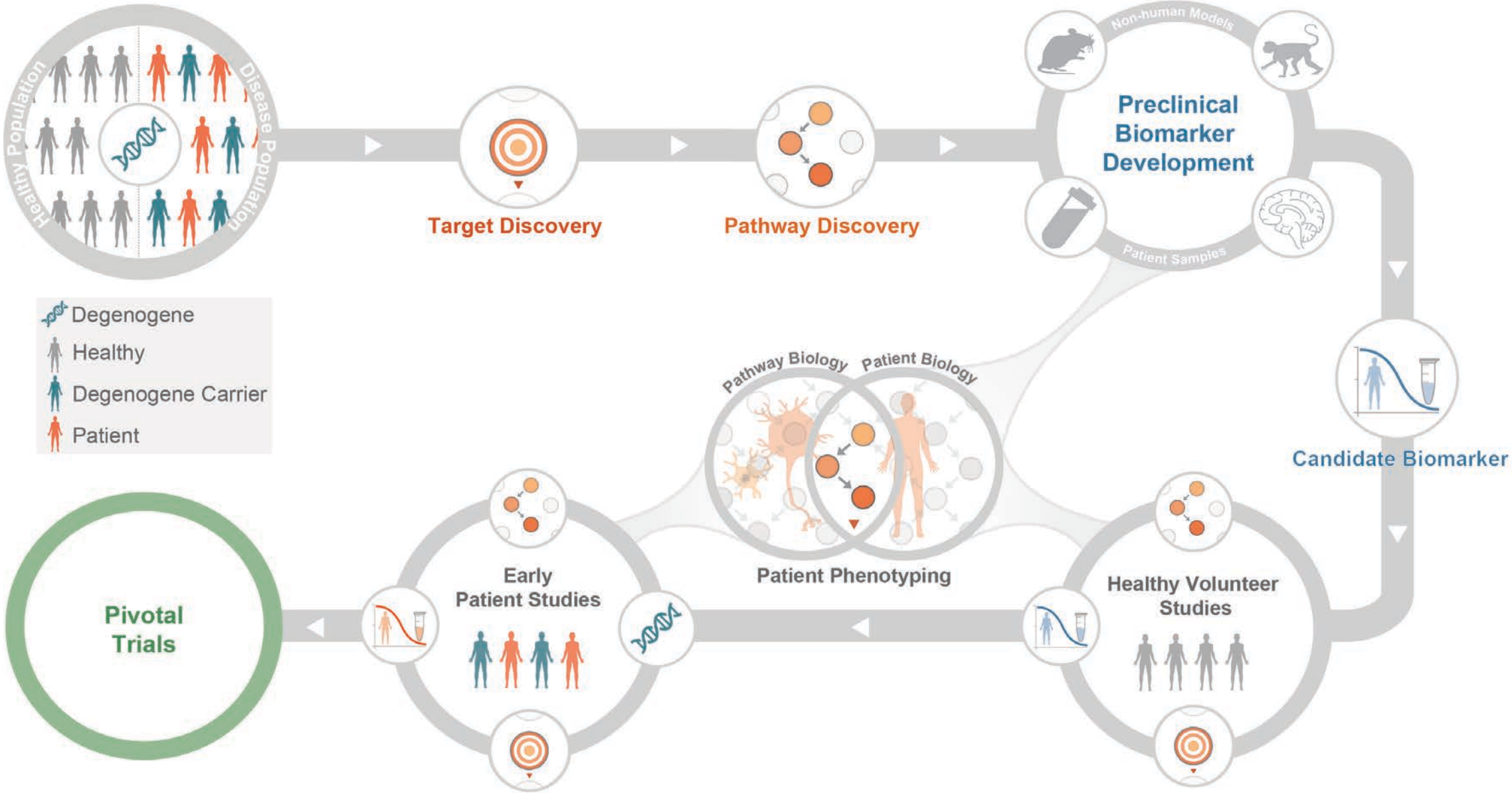
Target ALS

Parkinson's Institute and Clinical Center

NEALS

Patient phenotyping defines Phase 1b / 2a biomarker endpoints and identification of patients more likely to benefit

BIOMARKER-DRIVEN DEVELOPMENT



DENALI LRRK2 AND RIPK1 PROGRAMS

PROGRAM SUMMARY & BIOLOGY

BIOMARKER-DRIVEN DEVELOPMENT

PHASE 1 HEALTHY VOLUNTEER STUDY RESULTS

PHASE 1B STUDY DESIGN

UPCOMING MILESTONES

LRRK2 PROGRAM

LRRK2 CLINICAL PROGRAM SUMMARY

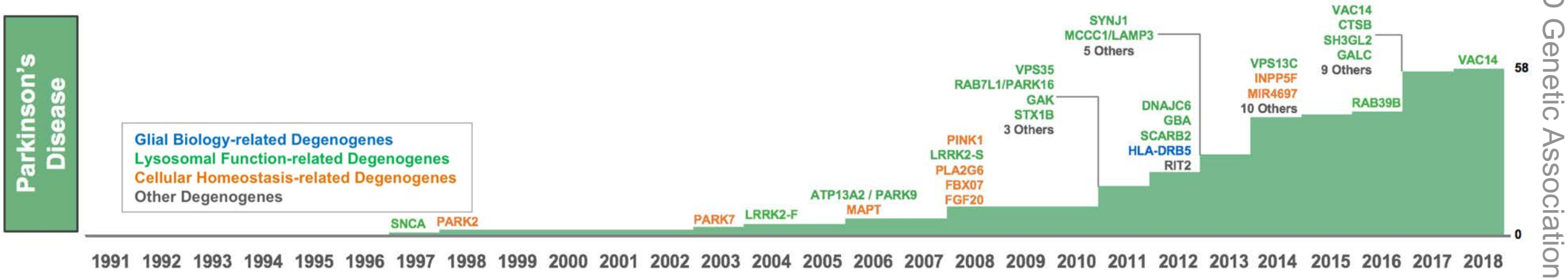
2018 Progress

- DNL201: Ph1 safety, target engagement, PD achieved
- DNL151: FIH healthy volunteer Ph1 study

LRRK2 Inhibitor

DEGENOGENES IMPLICATE LYSOSOMAL FUNCTION IN PD

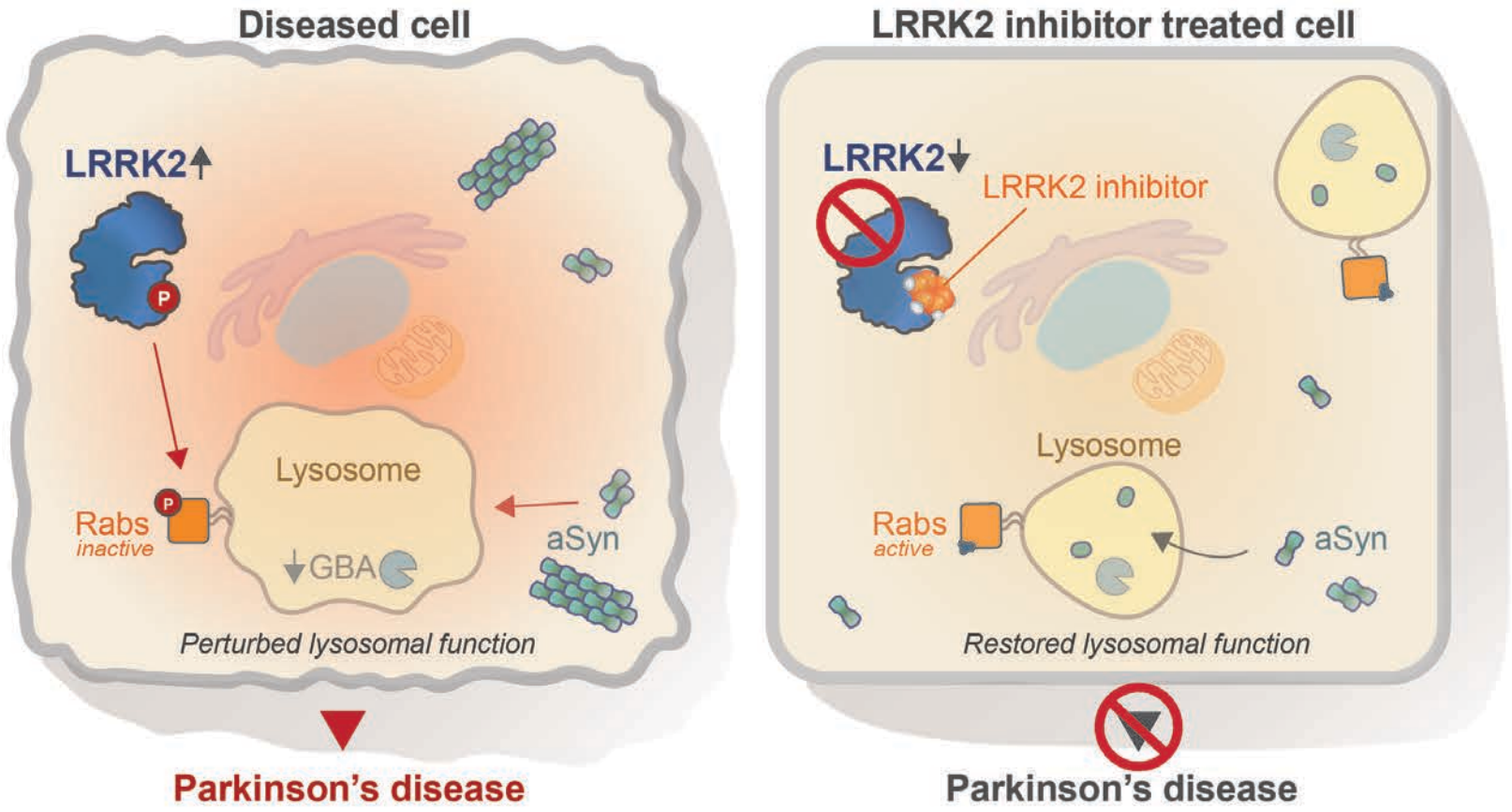
NEW GENETIC INSIGHTS IN PARKINSON'S DISEASE



- Parkinson's genetic risks highlight lysosomal impairment in PD
- Lysosomal dysfunction is a central pathophysiology of PD
- Lysosomal dysfunction contributes to αSyn aggregation, the pathologic hallmark of PD
- LRRK2 and αSyn are linked to lysosomal function, and represent promising therapeutic targets

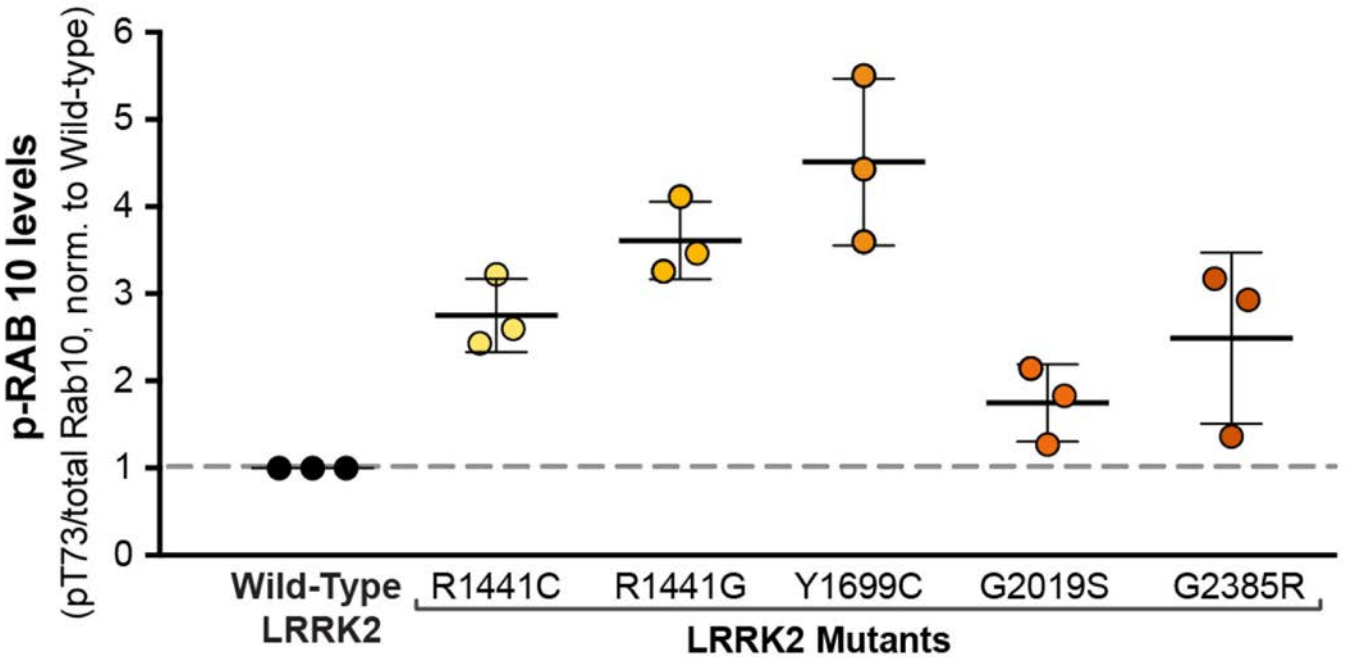
LRRK2 Inhibitor

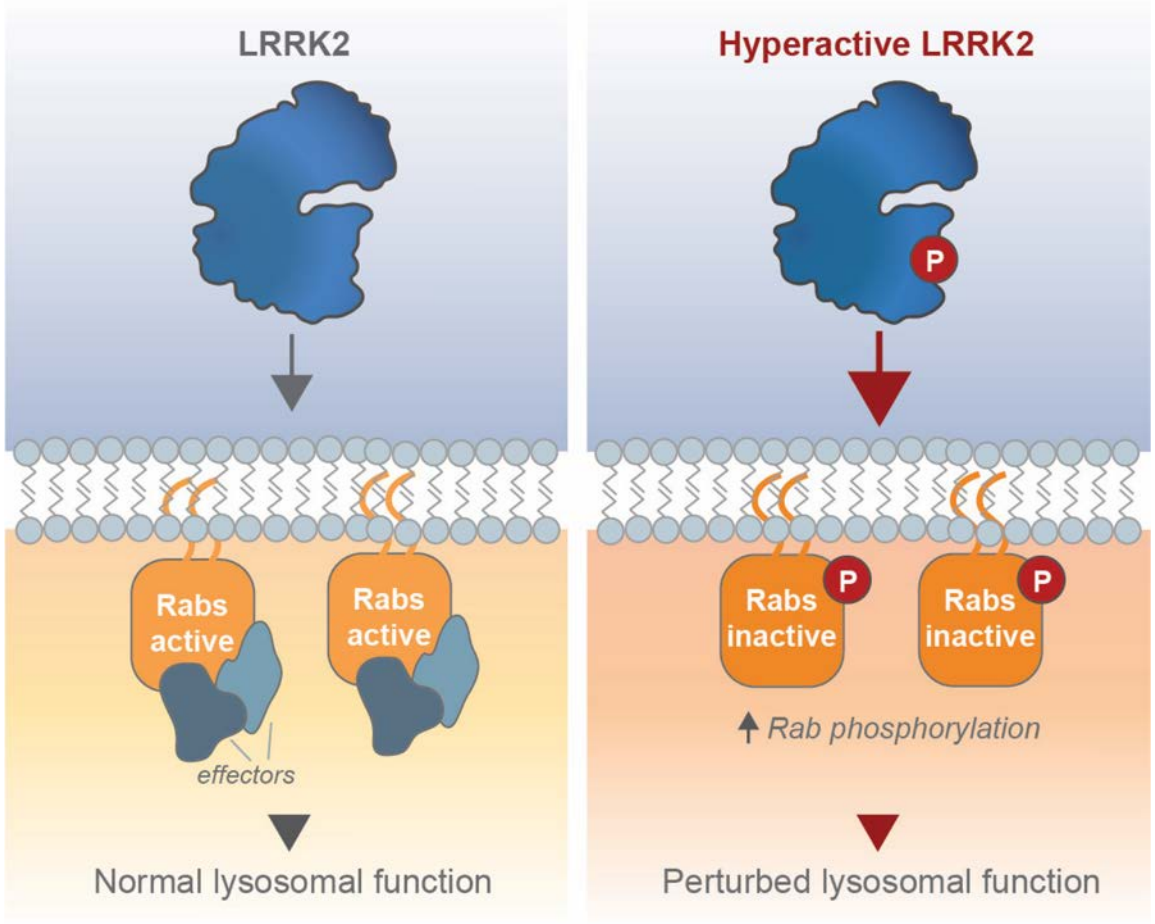
LRRK2 HYPERACTIVITY DRIVES LYSOSOMAL DYSFUNCTION AND PD



- 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 DISEASE CAUSING MUTATIONS INCREASE KINASE ACTIVITY

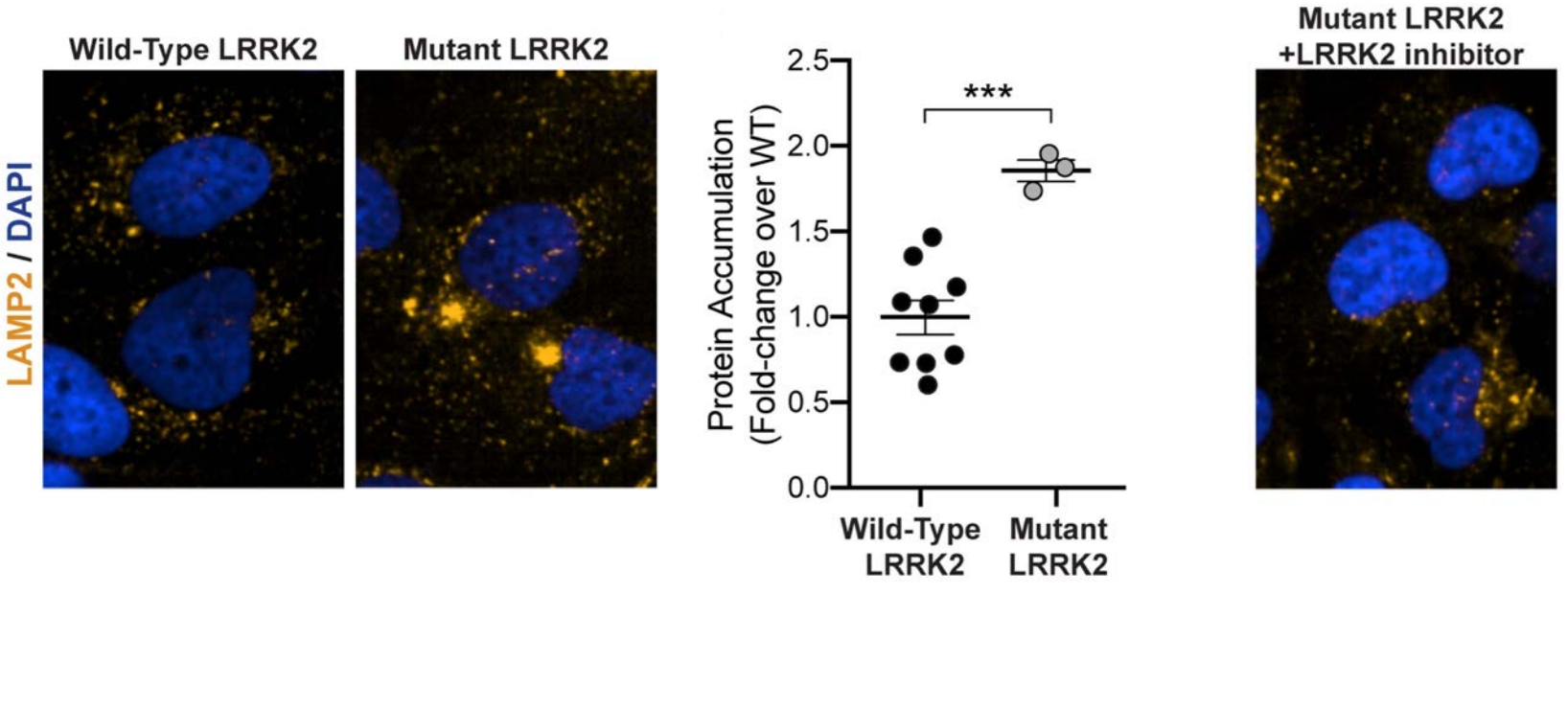




LRRK2 Inhibitor

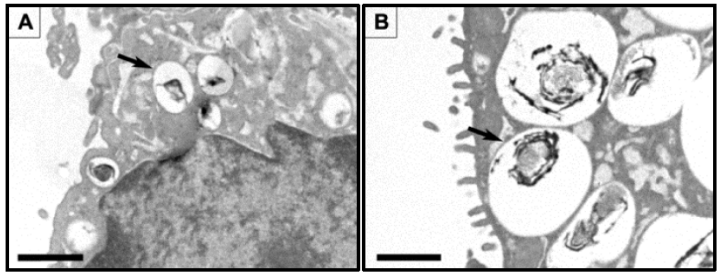
DNL201 INHIBITION OF LRRK2 RESTORES LYSOSOMAL MORPHOLOGY

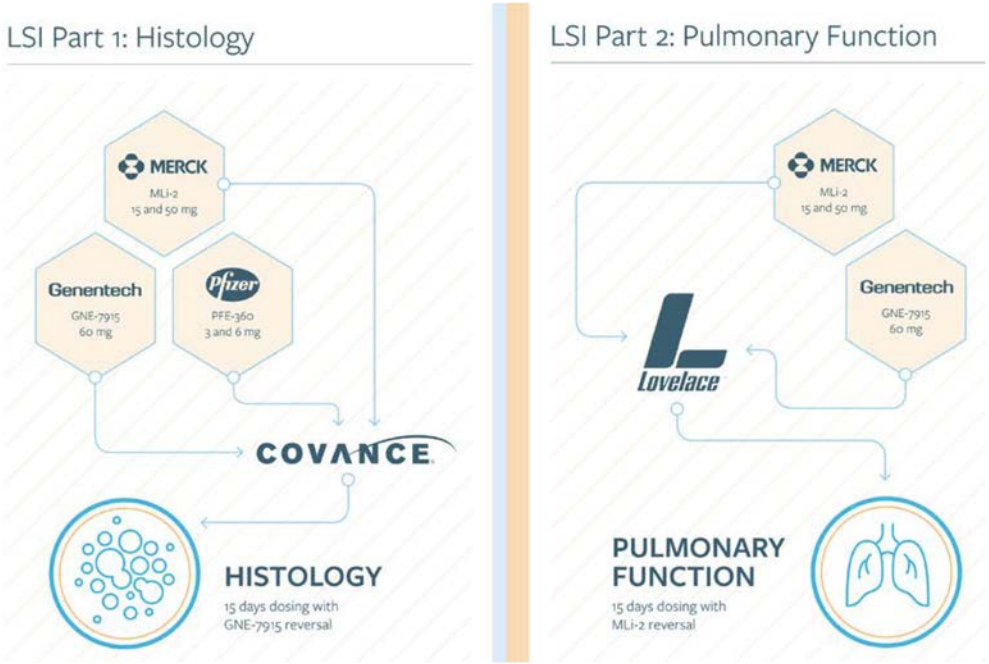
LRRK2 G2019S ALTERS LYSOSOME MORPHOLOGY AND FUNCTION IN A KINASE-DEPENDENT MANNER



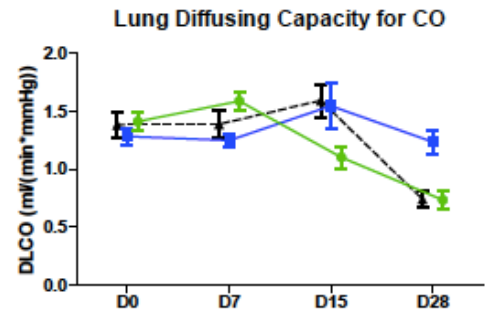
- LRRK2 inhibitor can reverse abnormal lysosomal morphology associated with overactive LRRK2 (G2019S) kinase activity

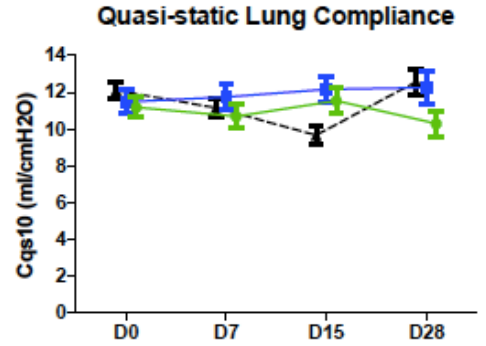
PRECLINICAL DATA SUPPORT CLINICAL STUDY OF LRRK2 INHIBITORS

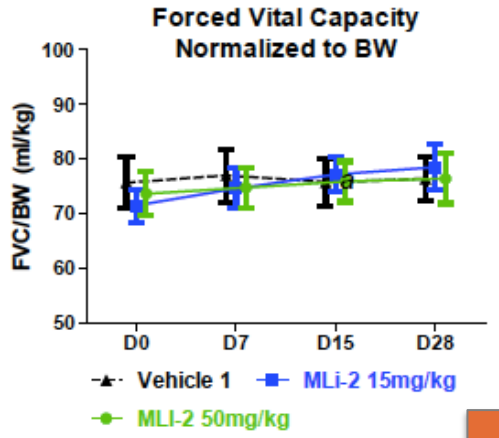




Oct 2018, *BioRxiv Preprint*, http://biorxiv.org/cgi/content/short/390815v1



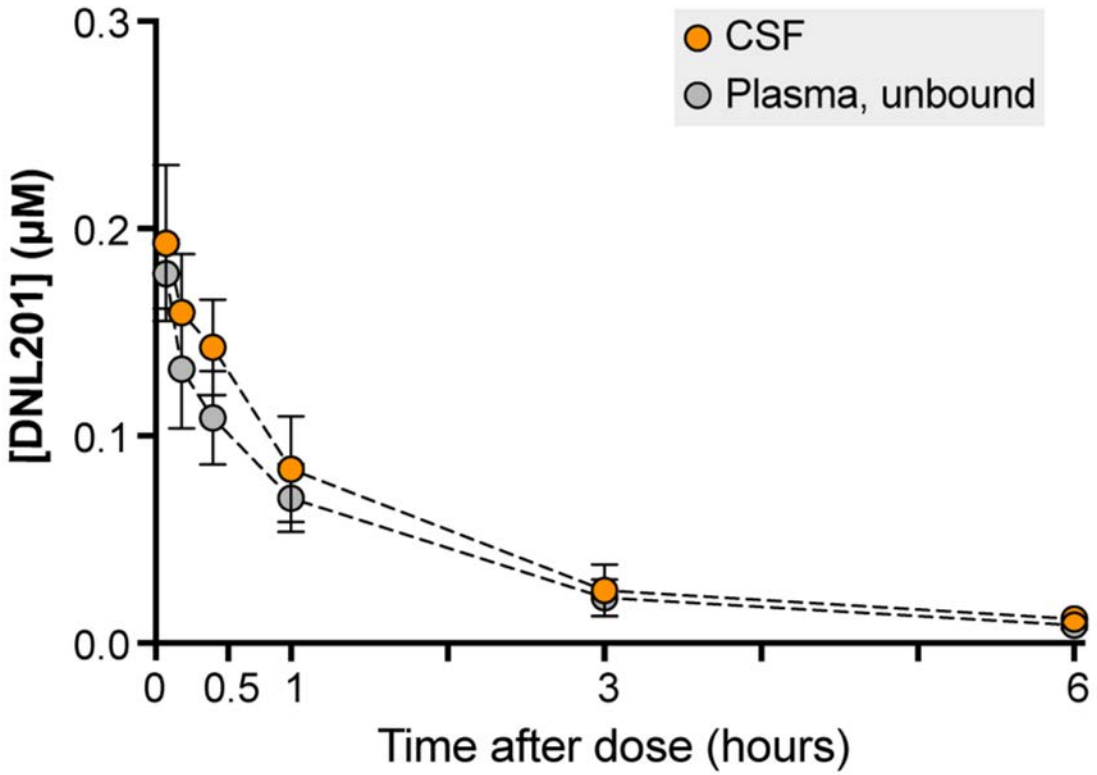


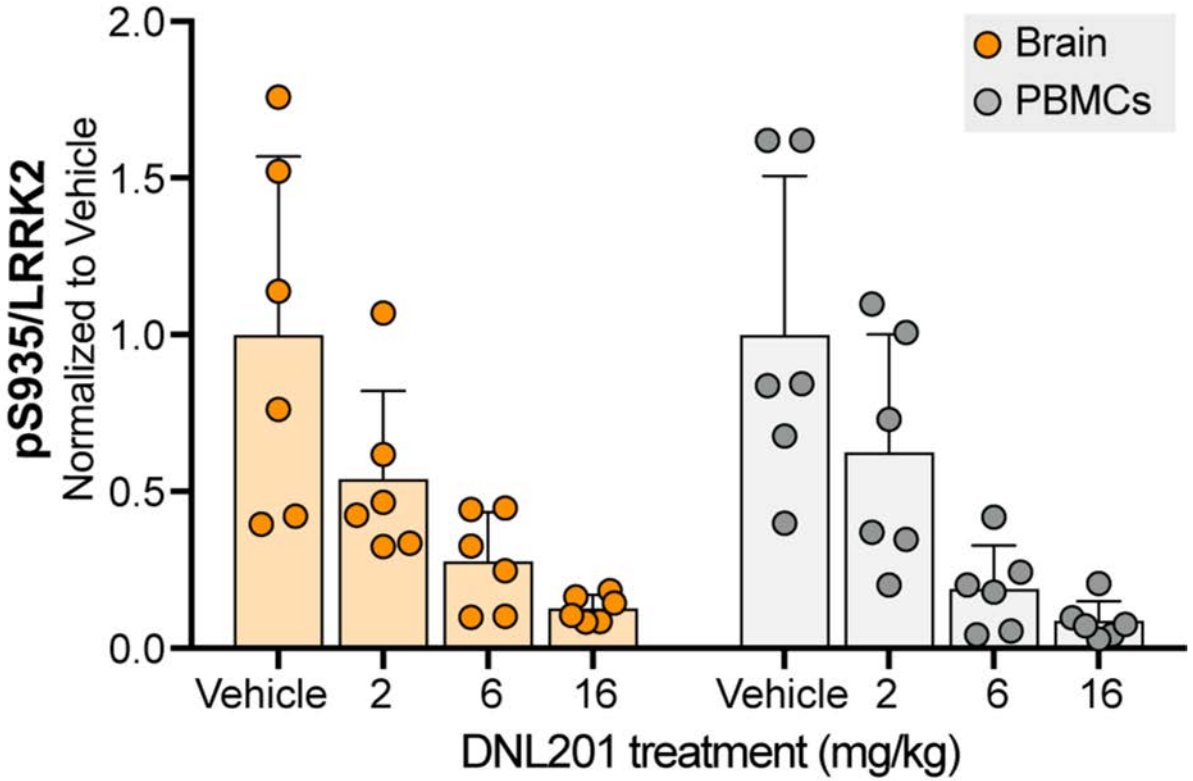


LRRK2 Inhibitor

DNL201 INHIBITS BRAIN LRRK2 ACTIVITY IN MONKEY

LRRK2 INHIBITION IN PBMCs PREDICTS BRAIN LRRK2 INHIBITION



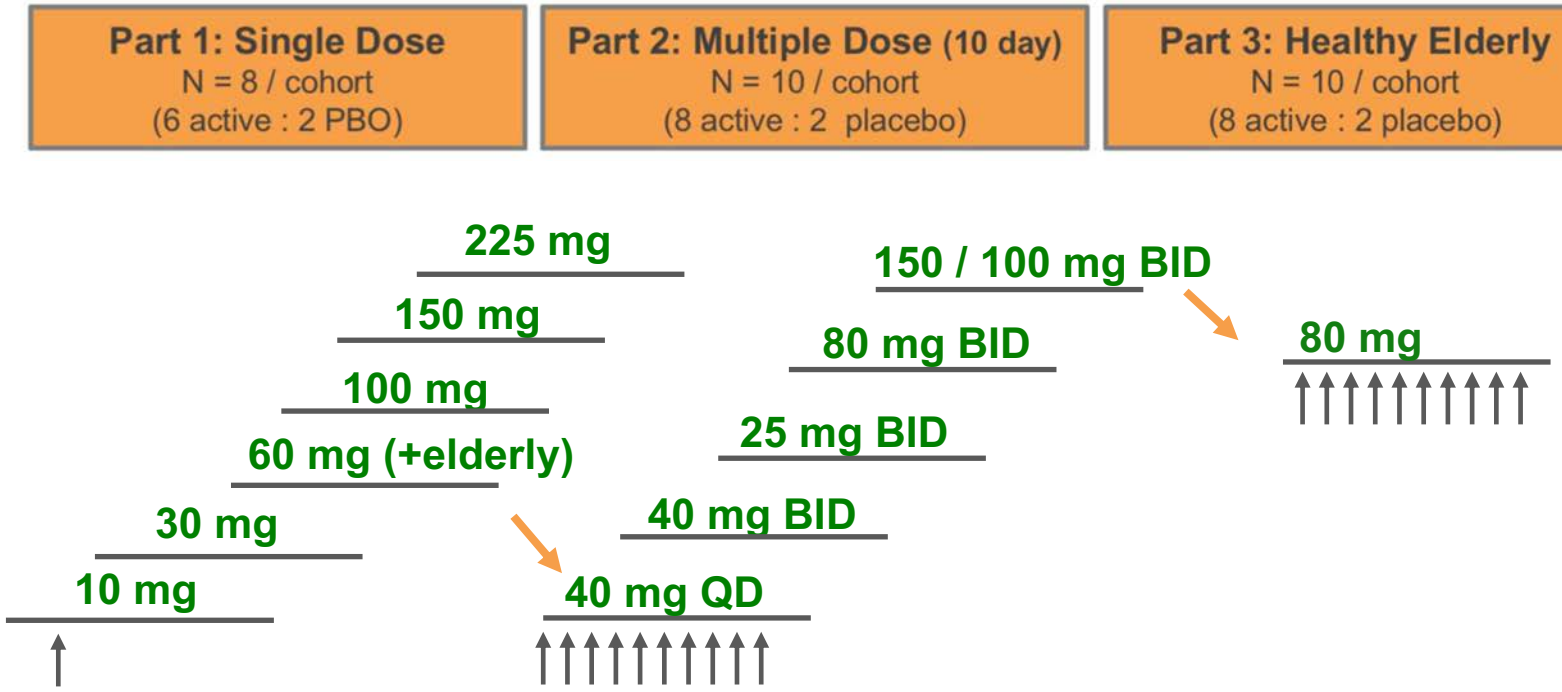


Samples collected 24 hours postdose after 28 days of dosing

- Comparable exposure of DNL201 in CSF and plasma
- Comparable inhibition of LRRK2 in brain vs. PBMCs

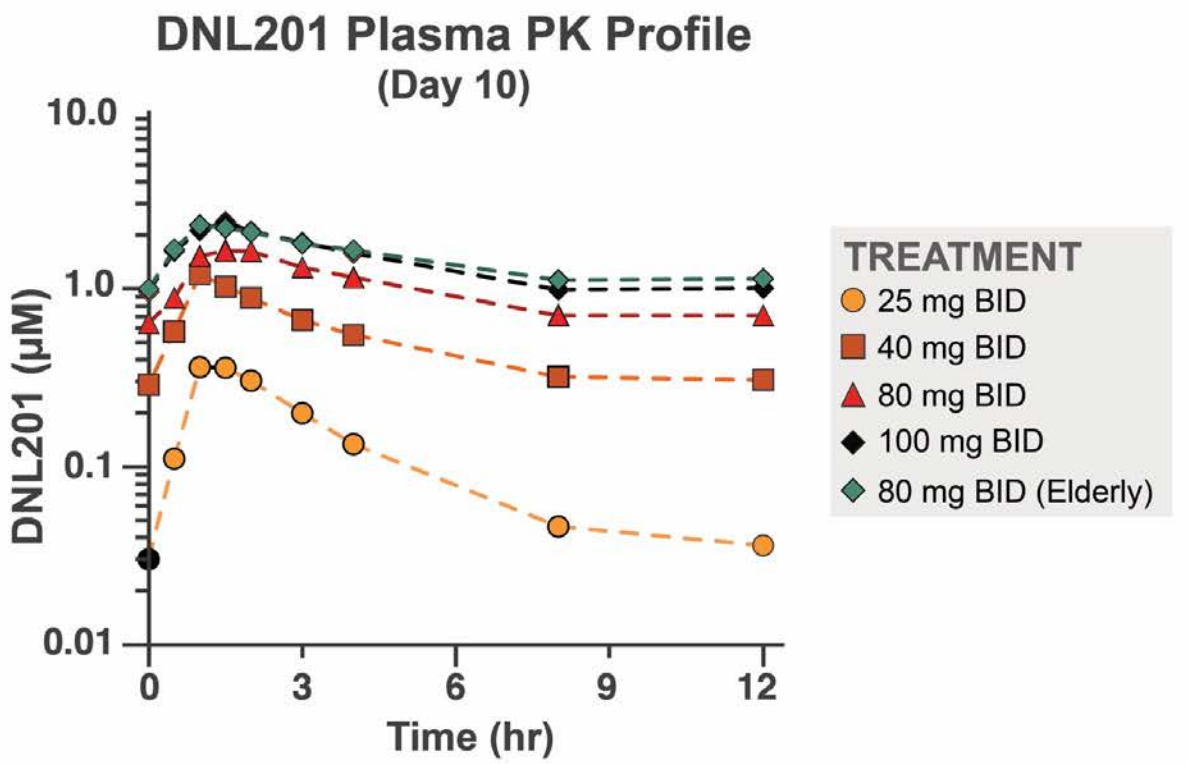
DNL201 LRRK2 PHASE 1 HEALTHY VOLUNTEER CLINICAL TRIAL

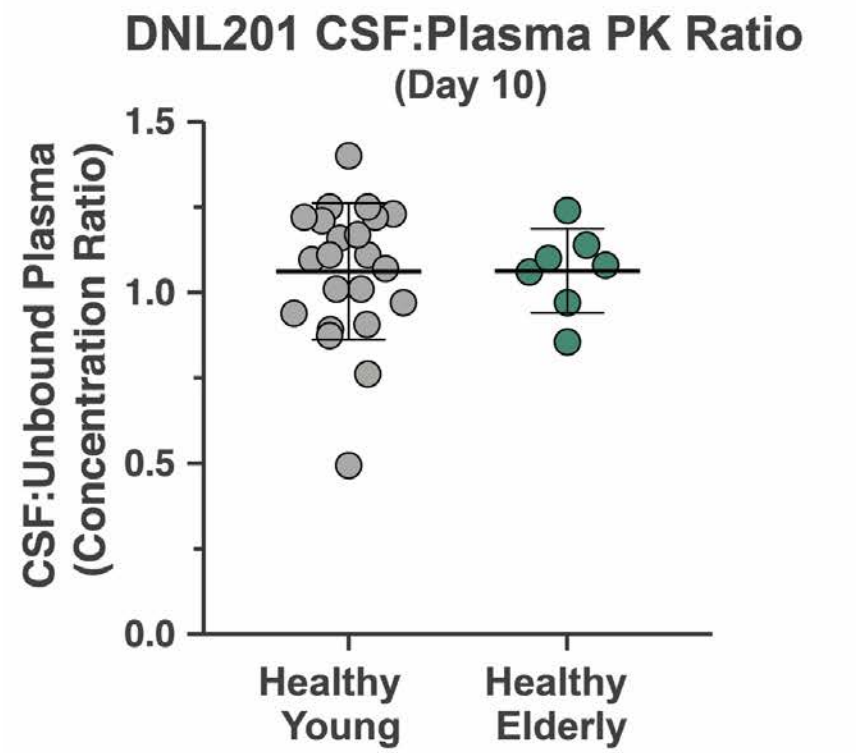
Design	Phase 1 study in healthy volunteers	
Study Size	**N=122** completed	
Key Endpoints	**Safety:** • Pulmonary function tests • Routine safety	**PK:** • Plasma • CSF • Urine
	Target engagement: • pS935 and pRab10 in whole blood / PBMCs • Exploratory endpoints • Lysosomal biomarker in CSF and urine	



- 122 healthy subjects dosed
- Overall well tolerated up to 100 mg BID in healthy young and up to 80 mg BID in healthy elderly subjects
- Safety parameters included pulmonary function and renal safety parameters

DNL201 PHARMACOKINETIC PROPERTIES AND BRAIN EXPOSURE





- PK profile supports twice daily dosing
- Terminal half life of 14-26 hours
- Low to moderate variability in Cmax and AUC
- Steady state reached by Day 10

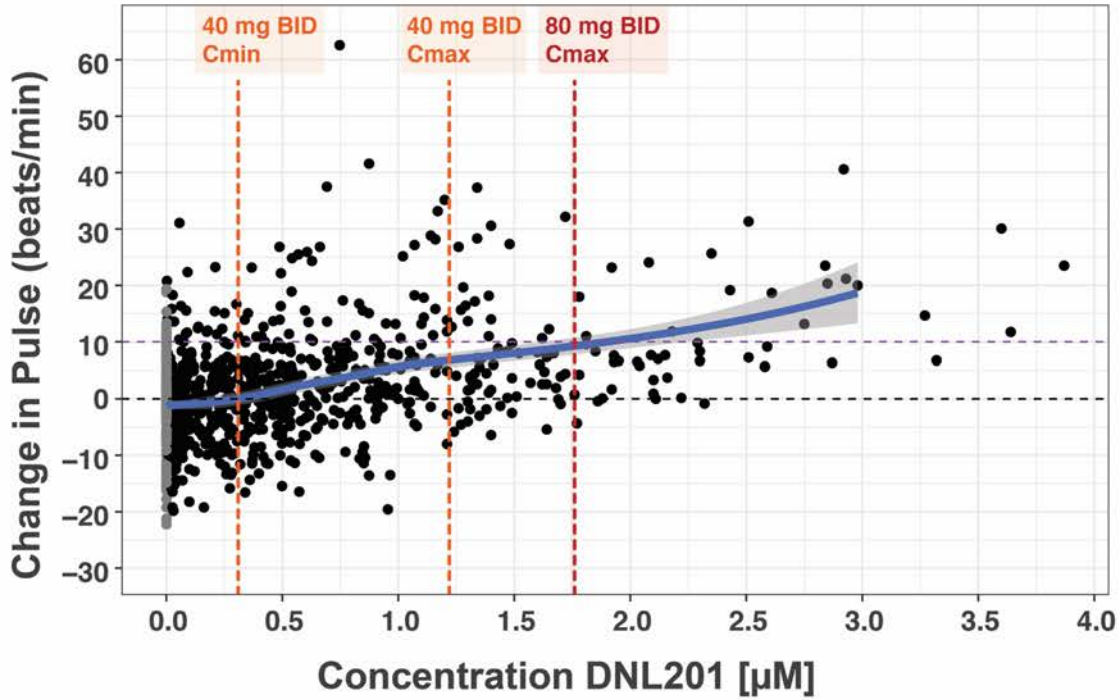
- Mean CSF to unbound plasma ratio of ~1.0
- Data from 25, 80 and 100 mg BID multiple dose cohorts

DNL201 PHASE 1 SAFETY RESULTS

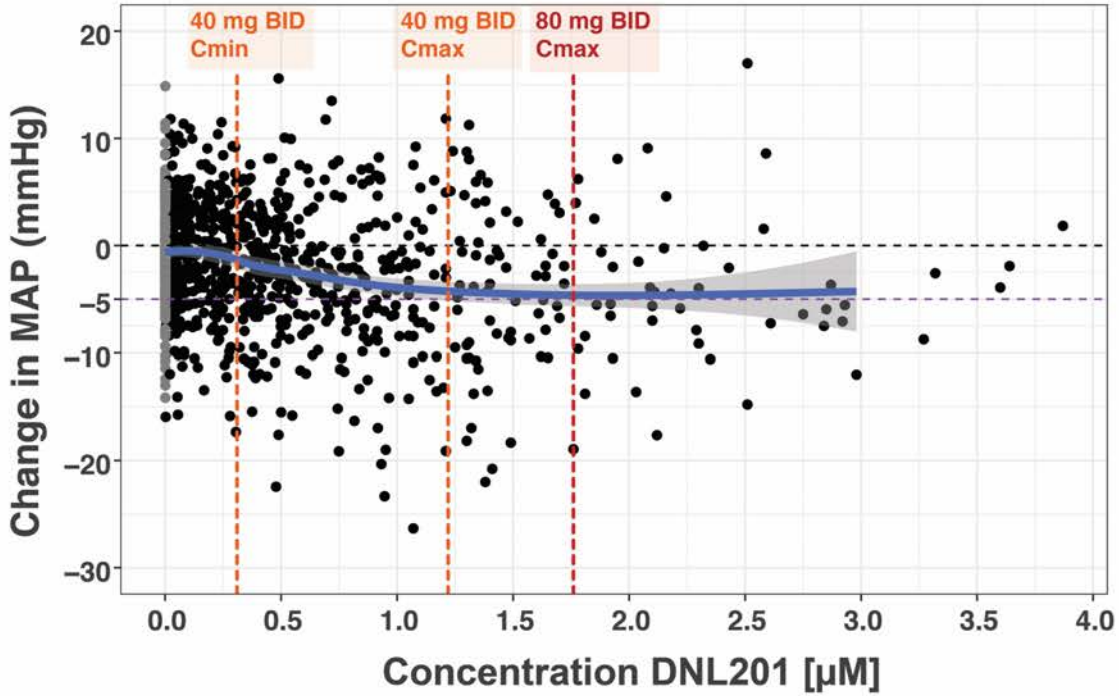
ACROSS PHASE 1 STUDY	• **No SAEs** • The most common Treatment Emergent Adverse Events (TEAEs), more frequent in active vs placebo subjects, were headache, dizziness, and nausea in both Parts 1 and 2 • C_{max} related changes in pulse rate and blood pressure were observed, generally well tolerated • No clinically meaningful changes on ECGs, physical / neurological exams, and safety laboratories, including renal parameters and pulmonary function • DL_{CO} stopping criteria not met by any subject
PART 1: SINGLE ASCENDING DOSE	• **Maximum tolerated single dose (MTD) was 150 mg** • All TEAEs were mild
PARTS 2 and 3: MULTIPLE ASCENDING DOSE	• **MTD was 100 mg BID in young HV with similar tolerability in elderly subjects at highest dose tested (80 mg BID)** • All TEAEs were mild except 2 subjects had moderate TEAEs ➢ 1 headache (Elderly 80 mg BID); 1 atrial fibrillation (40 mg BID; unrelated to study drug based on cardiac workup) • 3 early discontinuations related to TEAEs (2 headache, 1 atrial fibrillation-unrelated as described above)

DNL201 CONCENTRATION VS. PULSE, MEAN ARTERIAL PRESSURE (MAP)

DNL201 PLASMA CONC. VS. SUPINE PULSE CHANGE FROM BASELINE



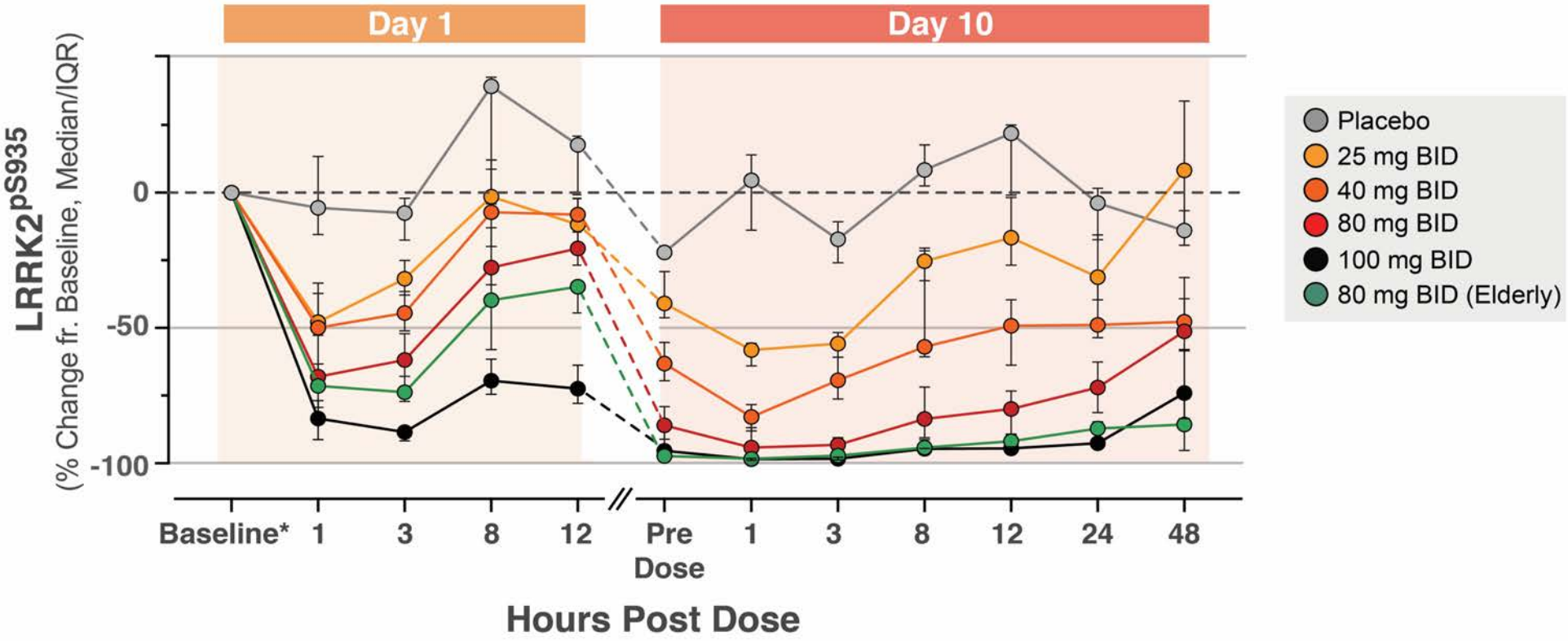
DNL201 PLASMA CONC. VS. SUPINE MAP CHANGE FROM BASELINE



- Exposure response for pulse and MAP, pooled data from all single doses and multiple doses on days 1, 8 and 10
- Mild C_{max} related changes in pulse rate and blood pressure were observed, generally asymptomatic
- C_{max} at 80 mg BID doses associated with <10 bpm mean increases in HR and <5 mm Hg mean decreases in MAP compared to baseline

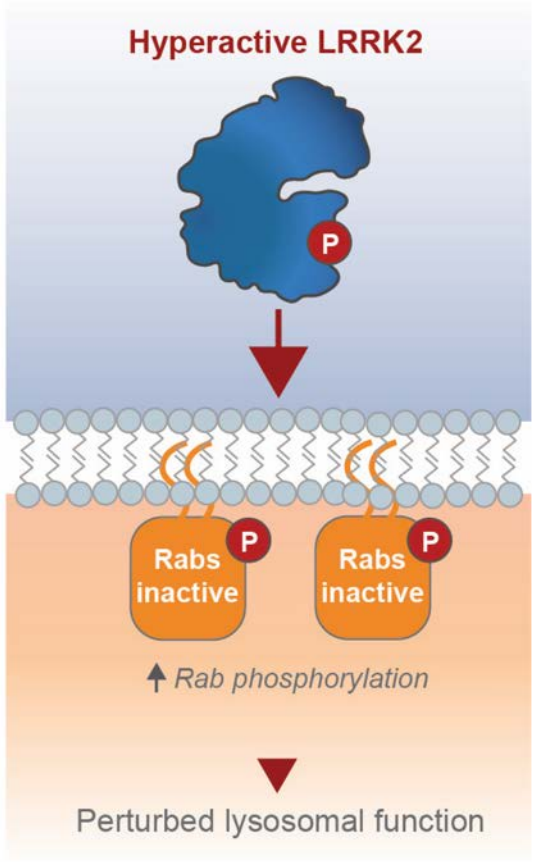
DNL201 DOSE-DEPENDENT INHIBITION OF LRRK2 IN HEALTHY SUBJECTS

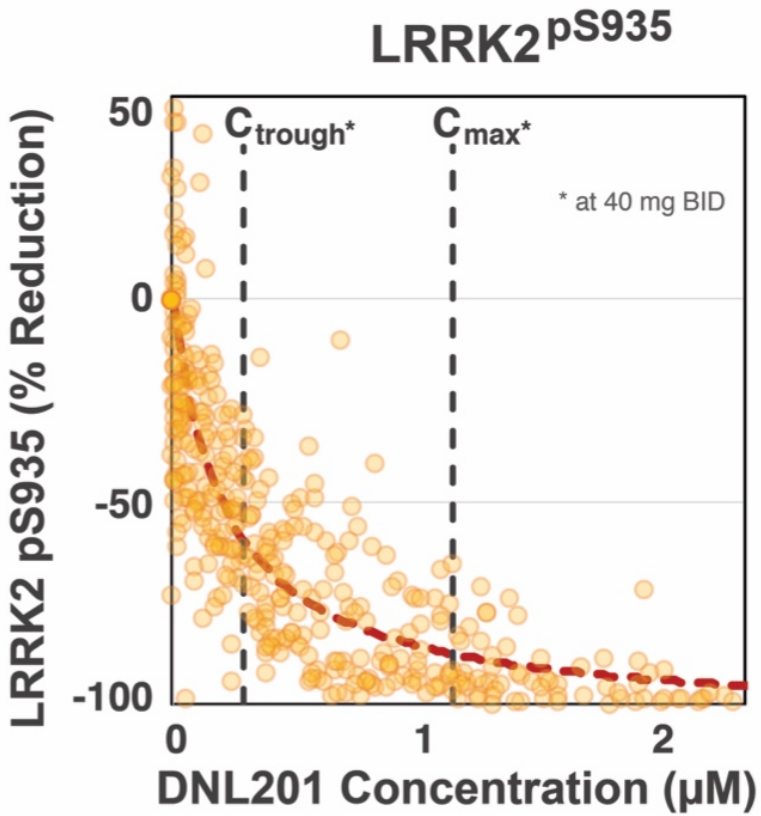
Whole Blood LRRK2^{pS935}

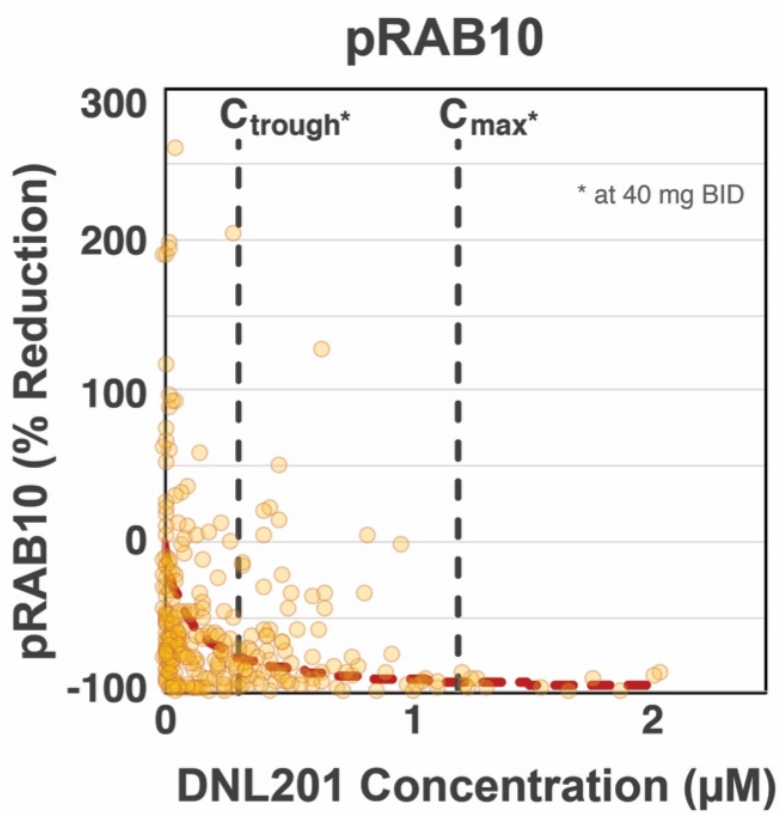


- Time course of LRRK2 pS935 inhibition after DNL201 administration every 12 hours until day 10

DNL201 EXPOSURE-RESPONSE IN HEALTHY SUBJECTS

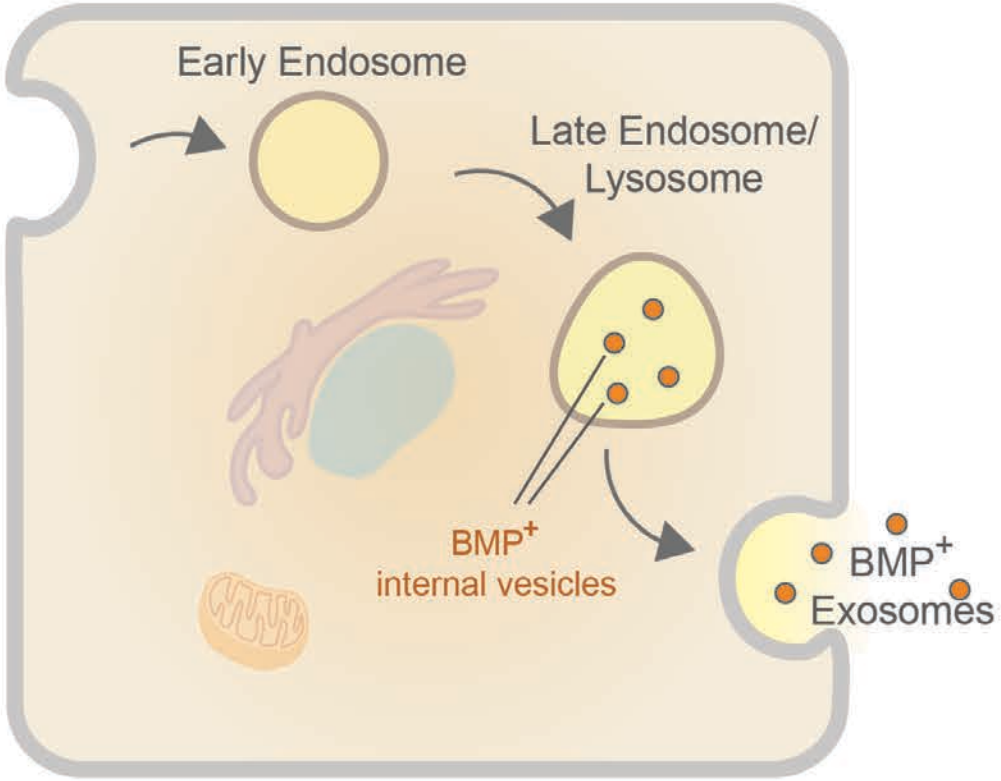






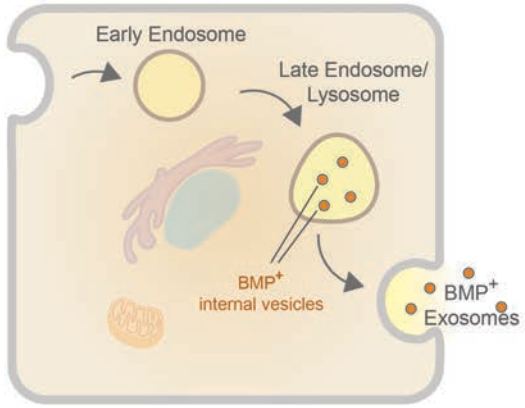
- Dose and concentration dependent LRRK2 inhibition (pS935) and pathway engagement (pRab10)
- At well-tolerated doses, >50 to 70% median inhibition observed at C_{trough} and >90% inhibition at C_{max}

LYSOSOMAL FUNCTION BIOMARKERS

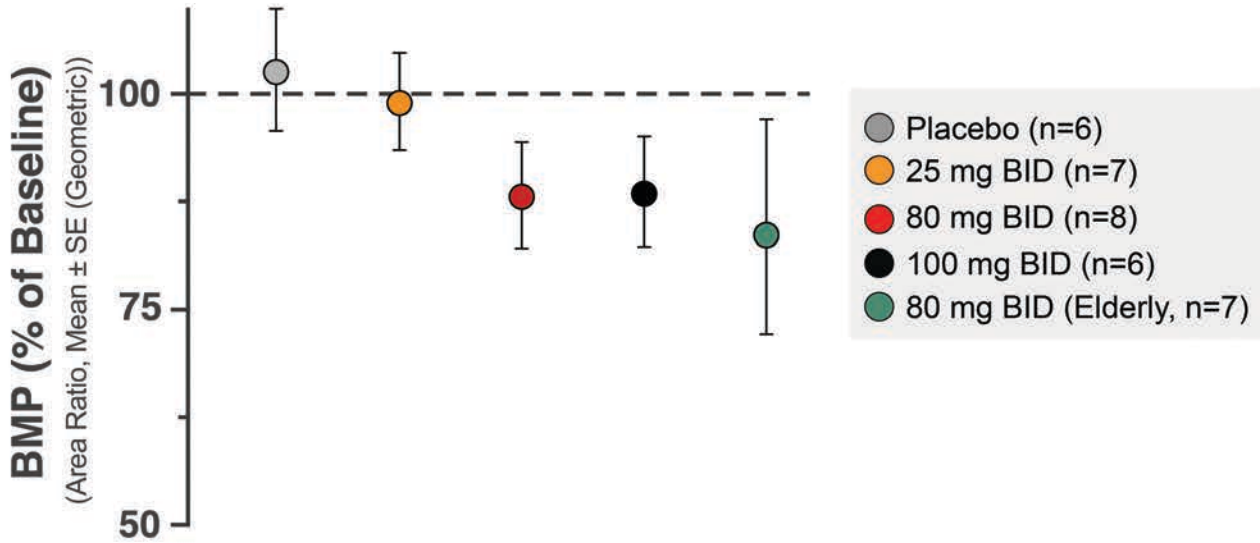


- BMP di22:6 is a lysosomal lipid enriched in lysosomal membranes
- Increases in BMP reflect lysosomal dysfunction in lysosomal storage diseases
- Reductions in urine BMP in animal studies is a well-established effect of LRRK2 inhibition

LYSOSOMAL BIOMARKER BMP DECREASES IN HEALTHY SUBJECT CSF



CHANGE IN BMP Di22:6 AFTER 10 DAYS OF DNL201 DOSING

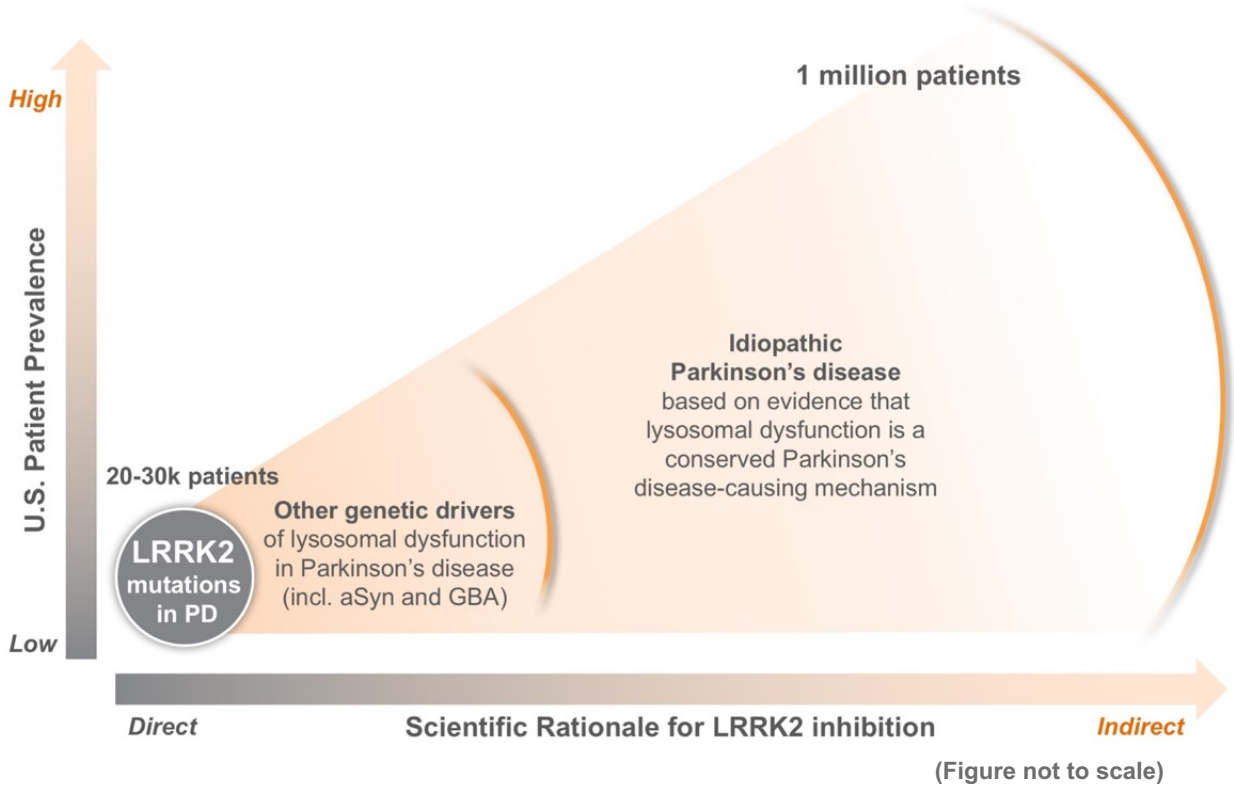


- BMP di22:6 is a lysosomal lipid; changes in BMP reflect functional change in lysosomal pathway
- Reductions in urine BMP are well-established in animals treated with structurally diverse LRRK2 inhibitors
- **DNL201** reduced urine BMP in healthy human subjects in a dose-dependent fashion
- First evidence of CSF BMP change in humans treated with a LRRK2 inhibitor

DNL201 MET ALL OBJECTIVES IN PH1 STUDY

Safety	Overall well tolerated in 95 subjects (including 13 elderly) who received DNL201 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 peripheral LRRK2 inhibition and demonstrated evidence of peripheral and CNS pathway engagement

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
- Common variants in LRRK2 modify PD risk
- LRRK2 activity is increased is PD-relevant rodent models and in idiopathic PD

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PARKINSON'S DISEASE

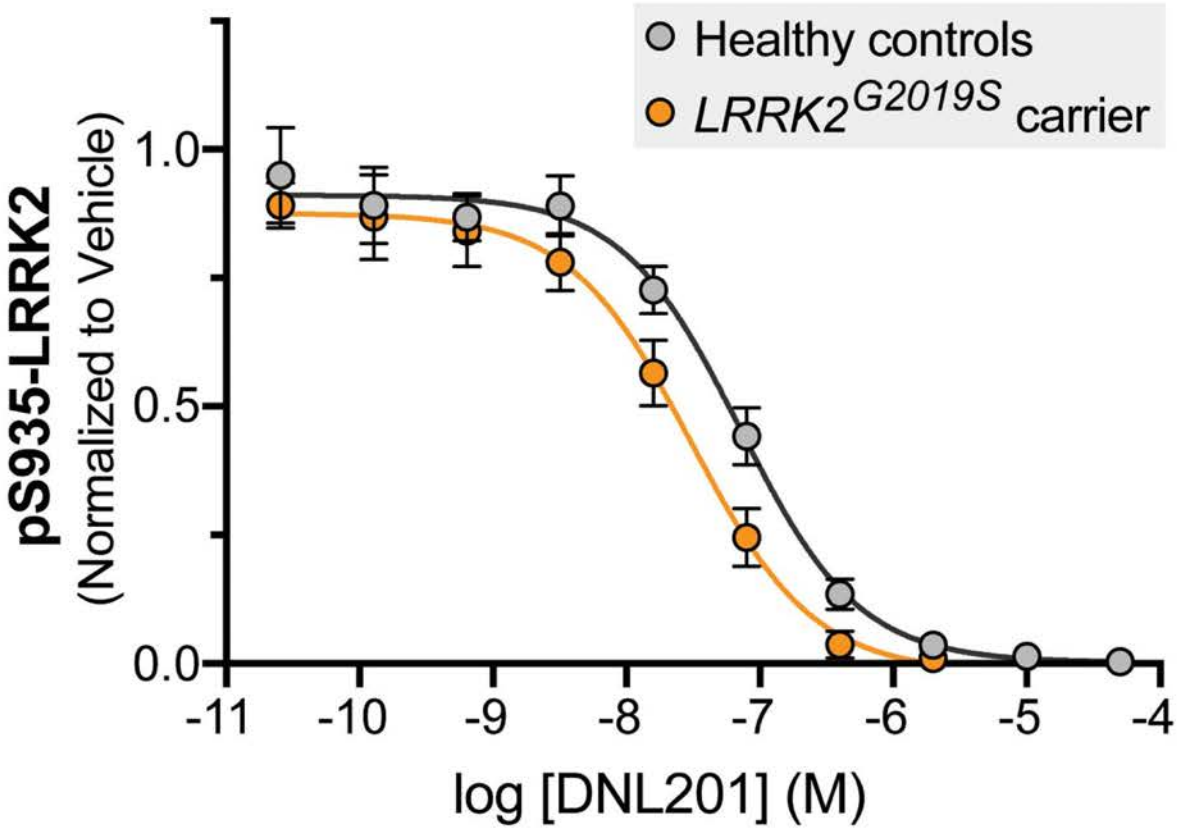
LRRK2 activation in idiopathic Parkinson's disease

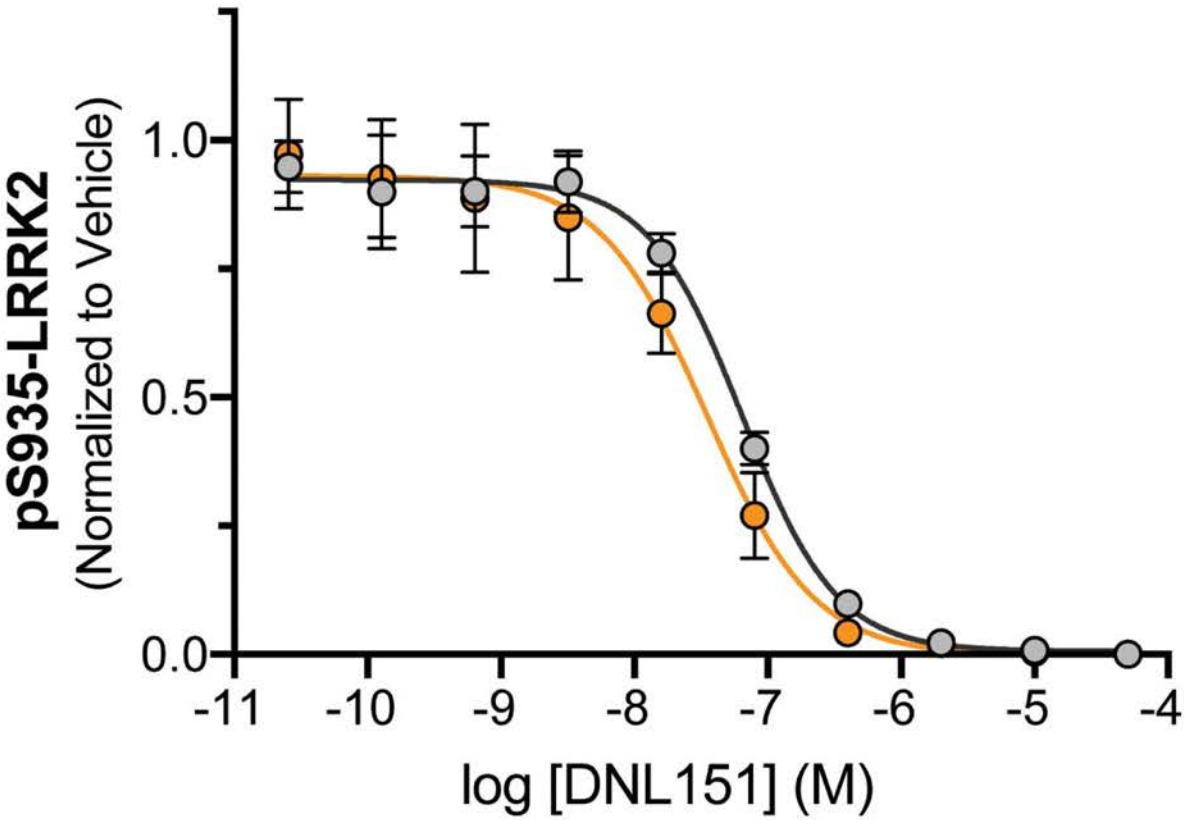
Roberto Di Maio[1,2,3], Eric K. Hoffman[1,2], Emily M. Rocha[1,2], Matthew T. Keeney[1,2], Laurie H. Sanders[1,2,4], Briana R. De Miranda[1,2], Alevtina Zharikov[1,2], Amber Van Laar[1,2], Antonia F. Stepan[5], Thomas A. Lanz[5], Julia K. Kofler[6], Edward A. Burton[1,2,7], Dario R. Alessi[8], Teresa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

LRRK2 Inhibitor

INHIBITION OF LRRK2 IN MUTATION CARRIERS

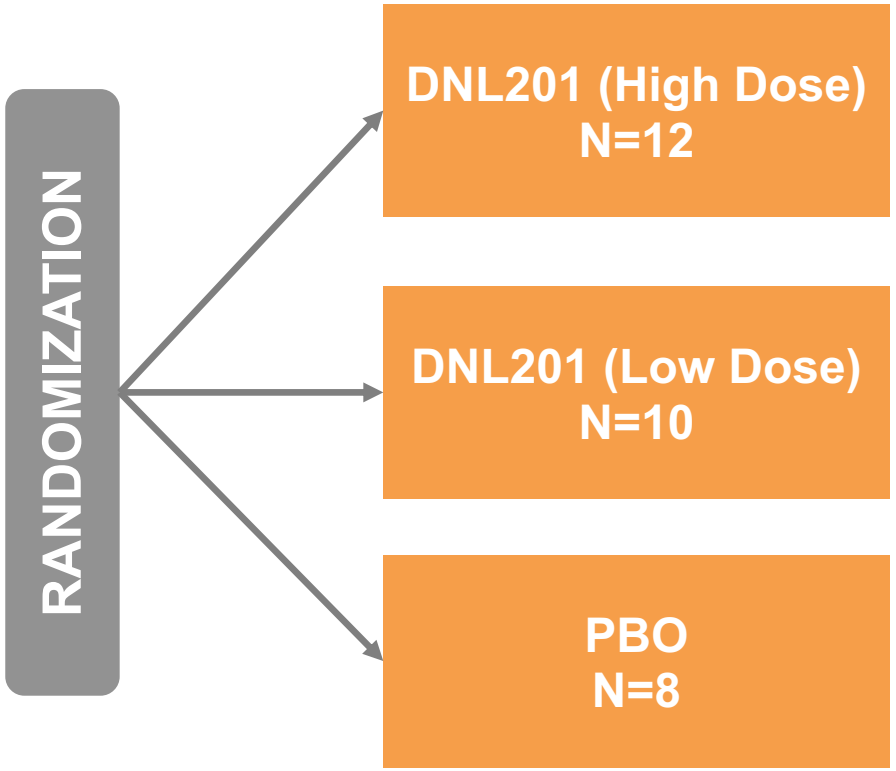




- Both DNL201 and DNL151 robustly inhibit LRRK2 in human mutation carrier blood (*ex vivo*)

DNL201 LRRK2 PHASE 1B CLINICAL TRIAL DESIGN

Design	Randomized Phase 1b study **(28 day dosing)** • Mild to Mod (H&Y Stage I-III) • 30 - 75 years of age • Screening DAT confirmation of PD • SOC therapy or Tx Naïve	
Study Size	**N=30 (15 sporadic, 15 LRRK2 PD)**	
Key Endpoints	**Safety:** • Pulmonary function tests • Routine safety	**PK:** • Plasma • CSF
	Target engagement: • Blood/PBMC pS935, pRab10 • Lysosomal biomarkers in CSF and urine **Exploratory:** • DaTscan substudy • Clinical Endpoints: MDS_UPDRS Part III, non-motor symptoms scale, quantitative gait assessment	



- First Patient In (FPI) achieved Dec 2018
- Estimated data readout by Q4 2019

LRRK2 Inhibitor

LRRK2 CLINICAL PROGRAM SUMMARY

2018 Progress

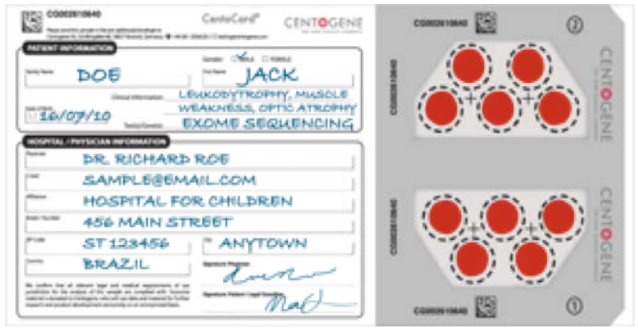
- DNL201: Ph1 safety, target engagement, PD achieved
- DNL151: FIH healthy volunteer Ph1 study

2019 Plans

- DNL201: Ph1b study in Parkinson's Disease
- LRRK2 patient recruitment

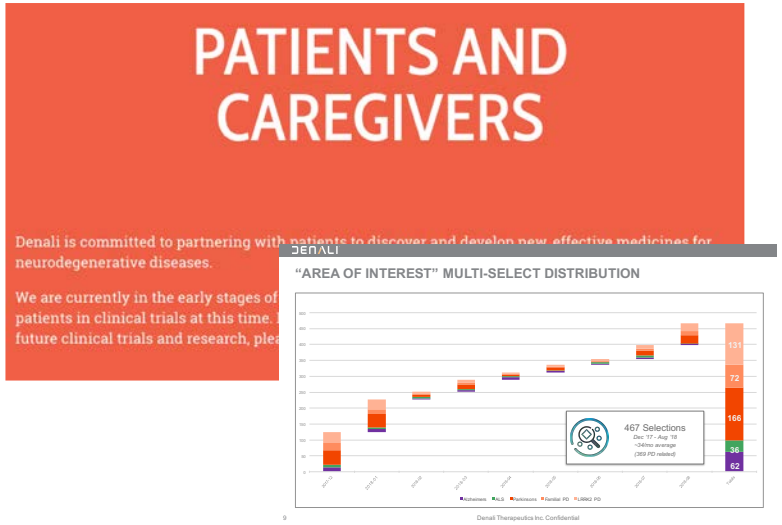
GLOBAL RECRUITMENT STRATEGY TO ENABLE PATIENT STUDIES

Centogene Collaboration



CentoCard® // CentoPortal®

Denali Patient Portal



Patient Networks

FOX INSIGHT

FOX TRIAL FINDER
THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Parkinson's Institute and Clini

UPenn Launches Large-Scale Sequencing Initiative to Improve Neurological Disease Detection
Oct 17, 2018 | John Gilmore

NATIONAL PARKINSON® FOUNDATION
A division of the Parkinson's Foundation

- Centogene / Denali collaboration: exclusive collaboration to identify and test treatment naïve Parkinson patients for LRRK2 mutations
- Leverage opportunities to engage already genotyped patients through Denali Web Portal
- Outreach to patients, physicians, advocacy groups, academic consortia
- Raise awareness of genotyping to impact patient management

LRRK2 Inhibitor

LRRK2 DNL201 LONG-TERM DEVELOPMENT PLAN

Ph 1 (HV) → **August 2018**

- Safety / Tolerability ✓
- Target Engagement ✓
- Pathway Engagement ✓
- Candidate Patient Phenotyping Biomarkers ✓

Ph 1b (PD +/- LRRK2) → **Q4 2019**

- Safety / Tolerability in Patients
- Target and Pathway Engagement
- Biomarker Driven Dose Selection in Patients
- Relevant changes in CSF Patient Phenotyping Biomarkers

Ph 2/3: LRRK2 PD Tx Naïve
(1º EP: MDS-UPDRS)

Ph 2/3: iPD Tx Naïve
(1º EP: MDS-UPDRS)

Ph 2: LRRK2 PD Standard Tx
(1º EP: DAT / VMAT imaging)

Phase 1b data intended to support progression to registrational Phase 2/3 study

LRRK2 genetic architecture and underlying biology: implications for patient selection

Mark R Cookson, PhD

National Institute on Aging, National Institutes of Health

cookson@mail.nih.gov

Neurobiology of Disease

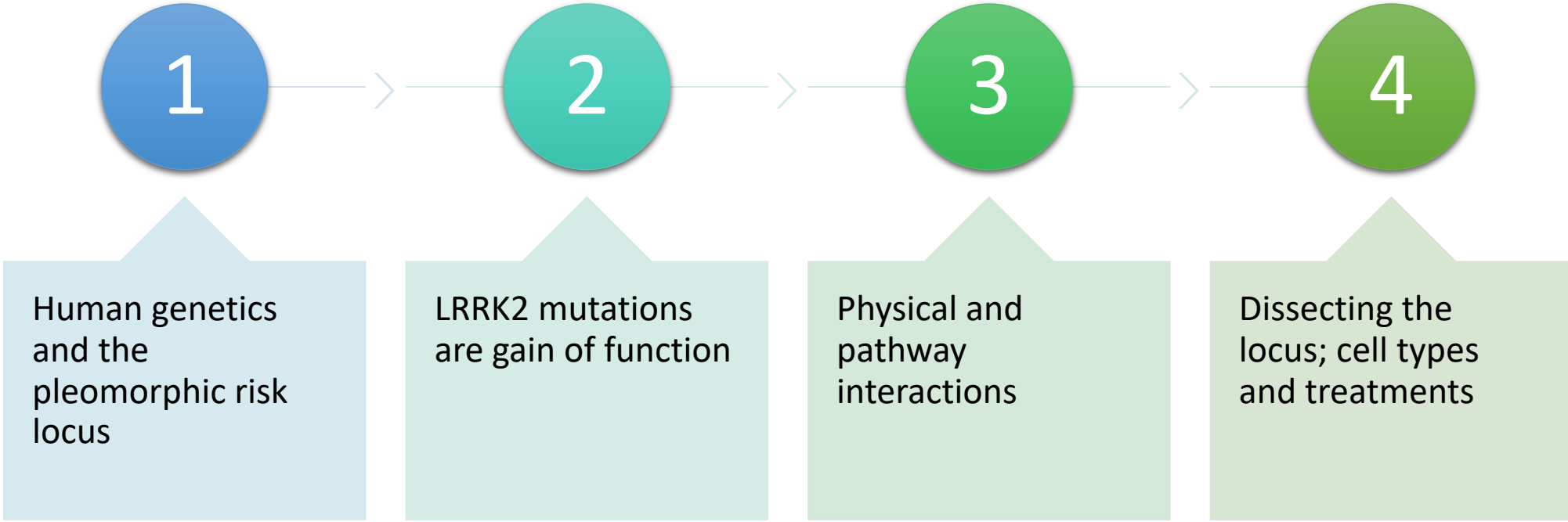
www.elsevier.com/locate/ynbdi
Neurobiology of Disease 23 (2006) 329 – 341

Kinase activity is required for the toxic effects of mutant *LRRK2*/dardarin

Elisa Greggio,[a,1] Shushant Jain,[b,1] Ann Kingsbury,[c] Rina Bandopadhyay,[c] Patrick Lewis,[a] Alice Kaganovich,[a] Marcel P. van der Brug,[a] Alexandra Beilina,[a] Jeff Blackinton,[a] Kelly Jean Thomas,[a] Rili Ahmad,[a] David W. Miller,[a] Sashi Kesavapany,[d] Andrew Singleton,[b] Andrew Lees,[c] Robert J. Harvey,[e] Kirsten Harvey,[e,*] and Mark R. Cookson[a,*]

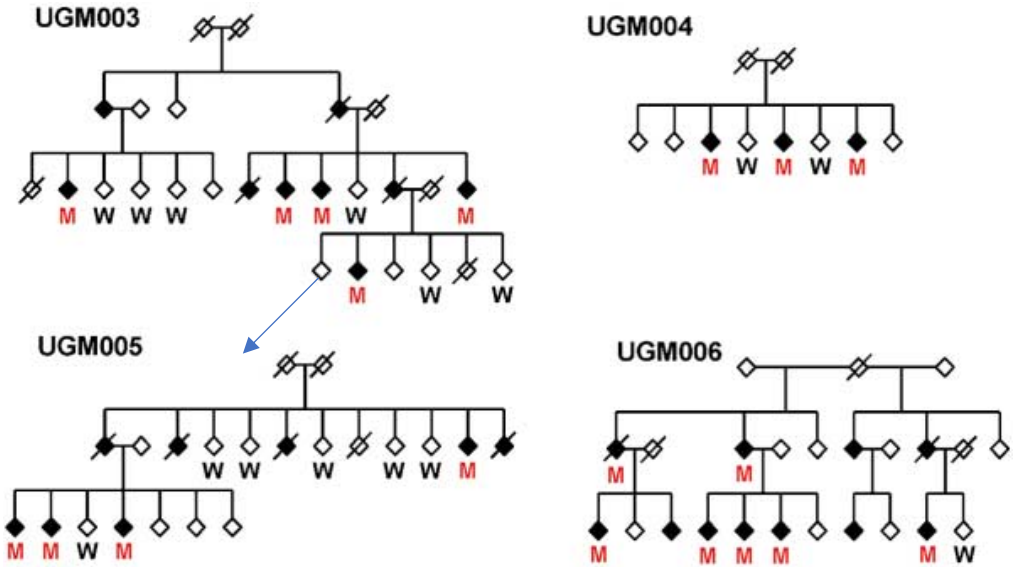
Given that both phenotypes are dependent on kinase activity, development of kinase inhibitors should be pursued as a therapeutic avenue for patients with *LRRK2* mutations and, by extension, sporadic PD. This is true of mutations outside of the

Outline

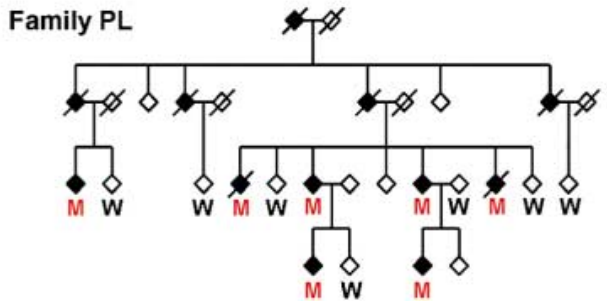

1
2
3
4
Human genetics and the pleomorphic risk locus
LRRK2 mutations are gain of function
Physical and pathway interactions
Dissecting the locus; cell types and treatments

Mutations in LRRK2 cause PD

R1441G



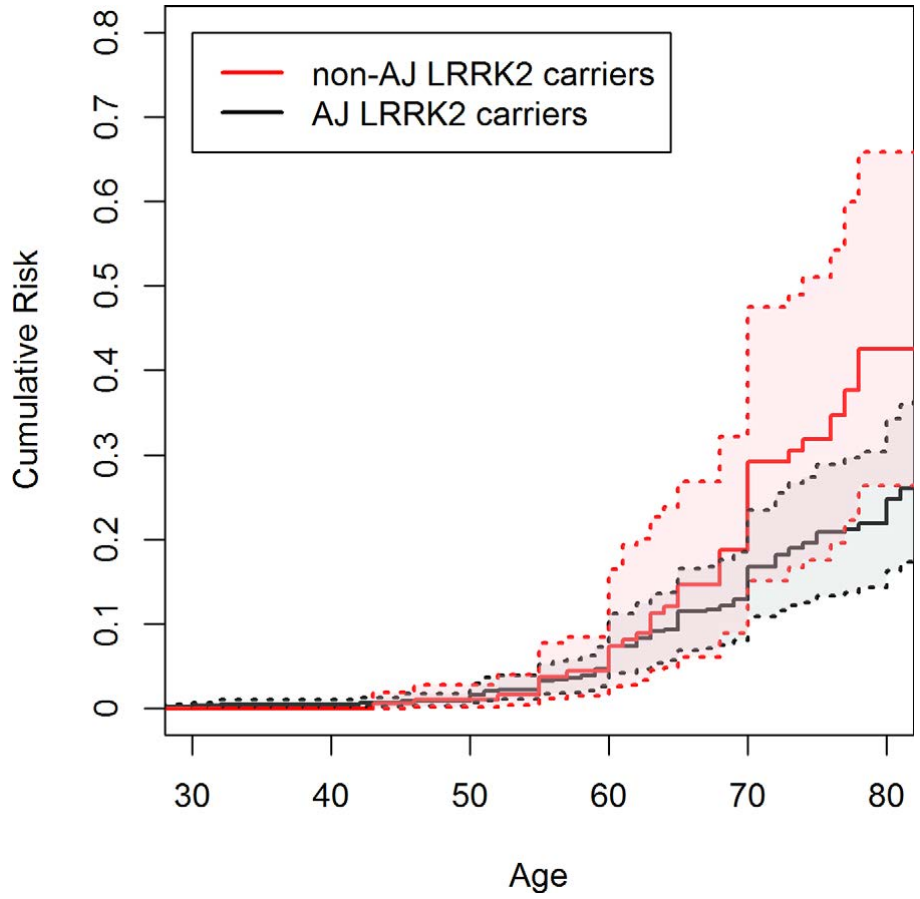
Y1699C



Paisan–Ruiz et al., Neuron 2004

Not all people with mutations get PD

G2019S



Lee et al., Movement Disorders 2017

Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia

Matthew J. Farrer[a], Jeremy T. Stone[a], Chin-Hsien Lin[b], Justus C. Dächsel[a], Mary M. Hulihan[a], Kristoffer Haugarvoll[a], Owen A. Ross[a], Ruey-Meei Wu[b,*]

The G2385R risk factor for Parkinson's disease enhances CHIP-dependent intracellular degradation of LRRK2

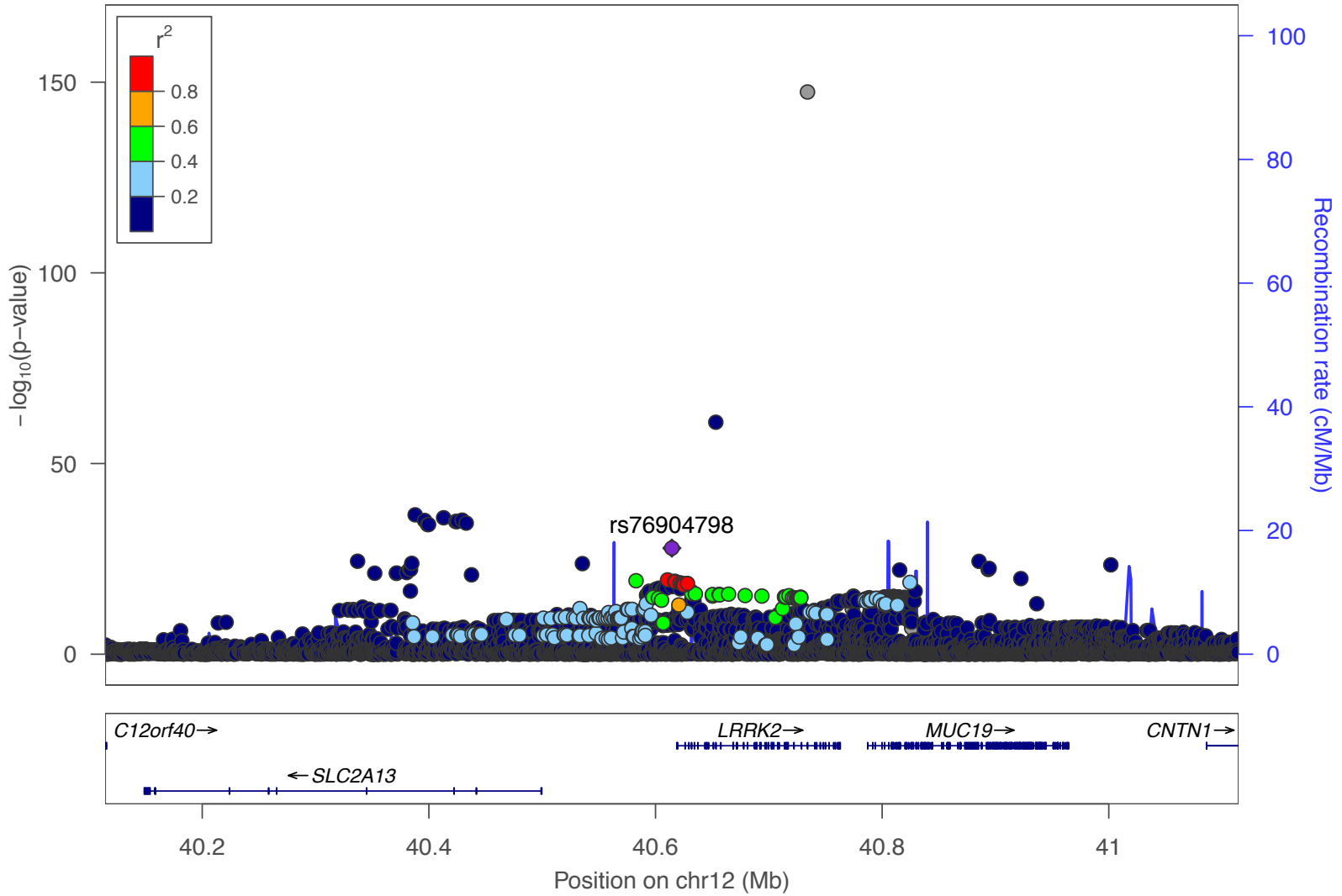
Iakov N. Rudenko*, Alice Kaganovich, Rebekah G. Langston, Aleksandra Beilina, Kelechi Ndukwe†, Ravindran Kumaran, Allissa A. Dillman‡, Ruth Chia and Mark R. Cookson

Association of *LRRK2* exonic variants with susceptibility to Parkinson's disease: a case–control study

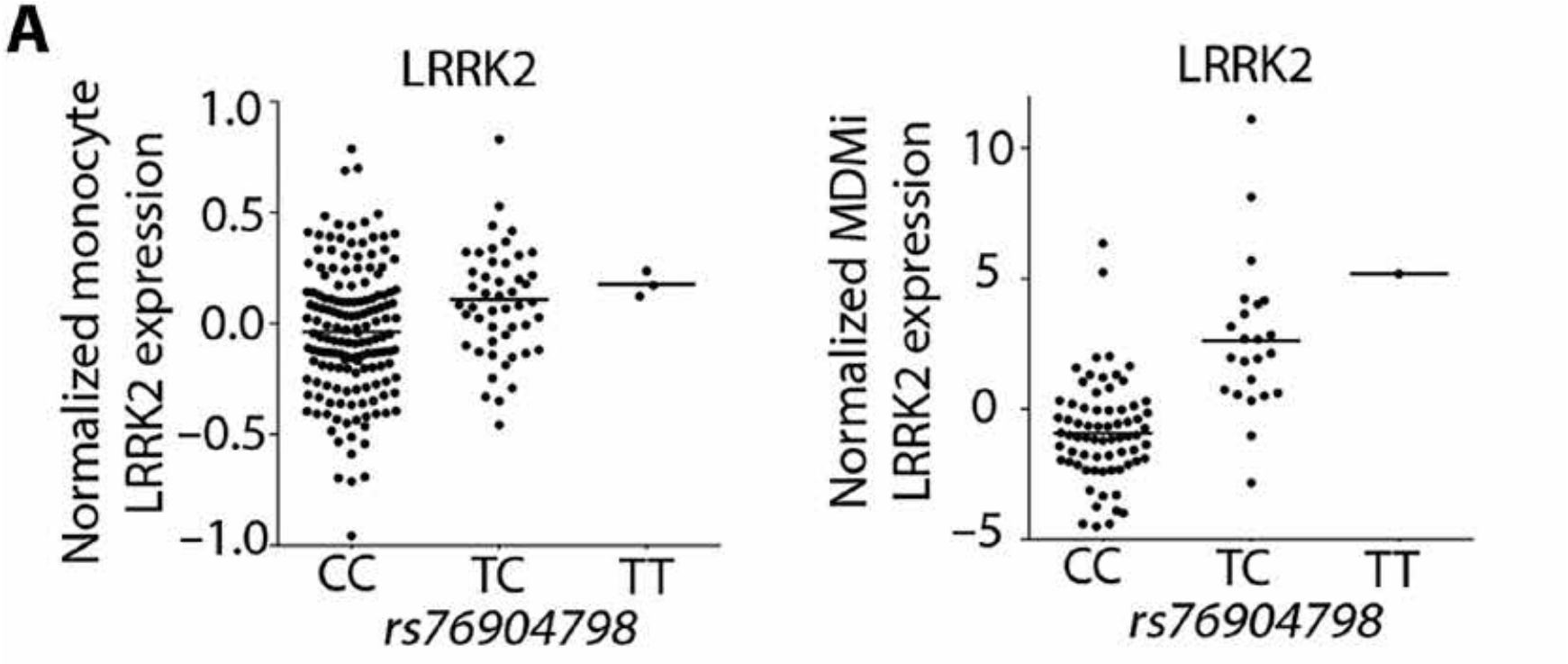
Owen A Ross, Alexandra I Soto-Ortolaza, Michael G Heckman, Jan O Aasly, Nadine Abahuni, Grazia Annesi, Justin A Bacon, Soraya Bardien, Maria Bozi, Alexis Brice, Laura Brighina, Christine Van Broeckhoven, Jonathan Carr, Marie-Christine Chartier-Harlin, Efthimios Dardiotis, Dennis W Dickson, Nancy N Diehl, Alexis Elbaz, Carlo Ferrarese, Alessandro Ferraris, Brian Fiske, J Mark Gibson, Rachel Gibson, Georgios M Hadjigeorgiou, Nobutaka Hattori, John P A Ioannidis, Barbara Jasinska-Myga, Beom S Jeon, Yun Joong Kim, Christine Klein, Rejko Kruger, Elli Kyratzi, Suzanne Lesage, Chin-Hsien Lin, Timothy Lynch, Demetrius M Maraganore, George D Mellick, Eugénie Mutez, Christer Nilsson, Grzegorz Opala, Sung Sup Park, Andreas Puschmann, Aldo Quattrone, Manu Sharma, Peter A Silburn, Young Ho Sohn, Leonidas Stefanis, Vera Tadic, Jessie Theuns, Hiroyuki Tomiyama, Ryan J Uitti, Enza Maria Valente, Simone van de Loo, Demetrios K Vassilatis, Carles Vilariño-Güell, Linda R White, Karin Wirdefeldt, Zbigniew K Wszolek, Ruey-Meei Wu, Matthew J Farrer, on behalf of the Genetic Epidemiology Of Parkinson's Disease (GEO-PD) Consortium*

Coding variants in sporadic PD include protective alleles

Non-coding variants sporadic PD

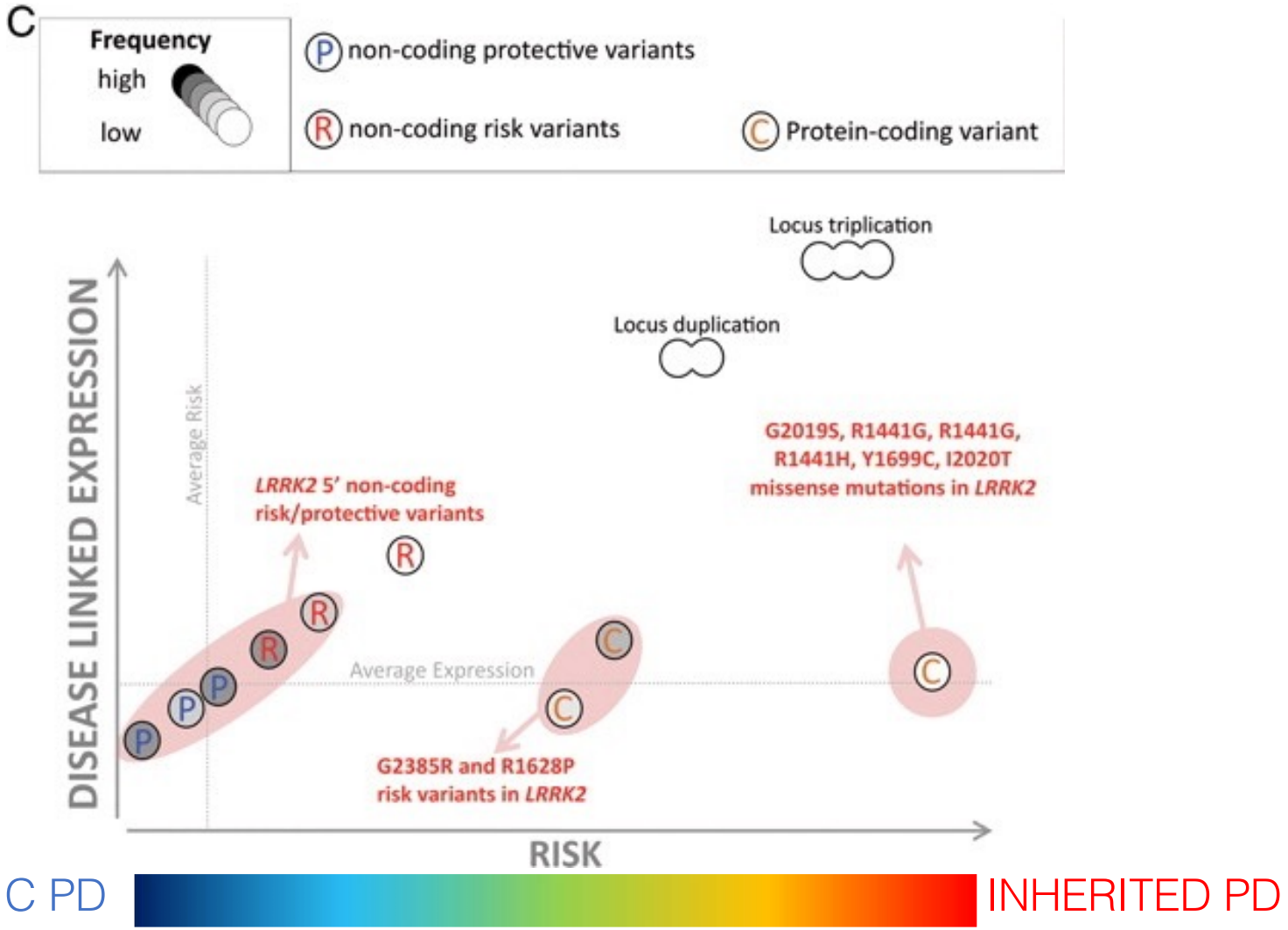


Expression quantitative trait



Ryan et al Sci. Transl. Med. eaai7635 (2017)

Pleomorphic risk locus



SPORADIC PD — INHERITED PD

Adapted from: Singleton A , and Hardy J Hum. Mol. Genet. 2011;20:R158-R162

The direction of effect is important for predicting therapeutic intervention

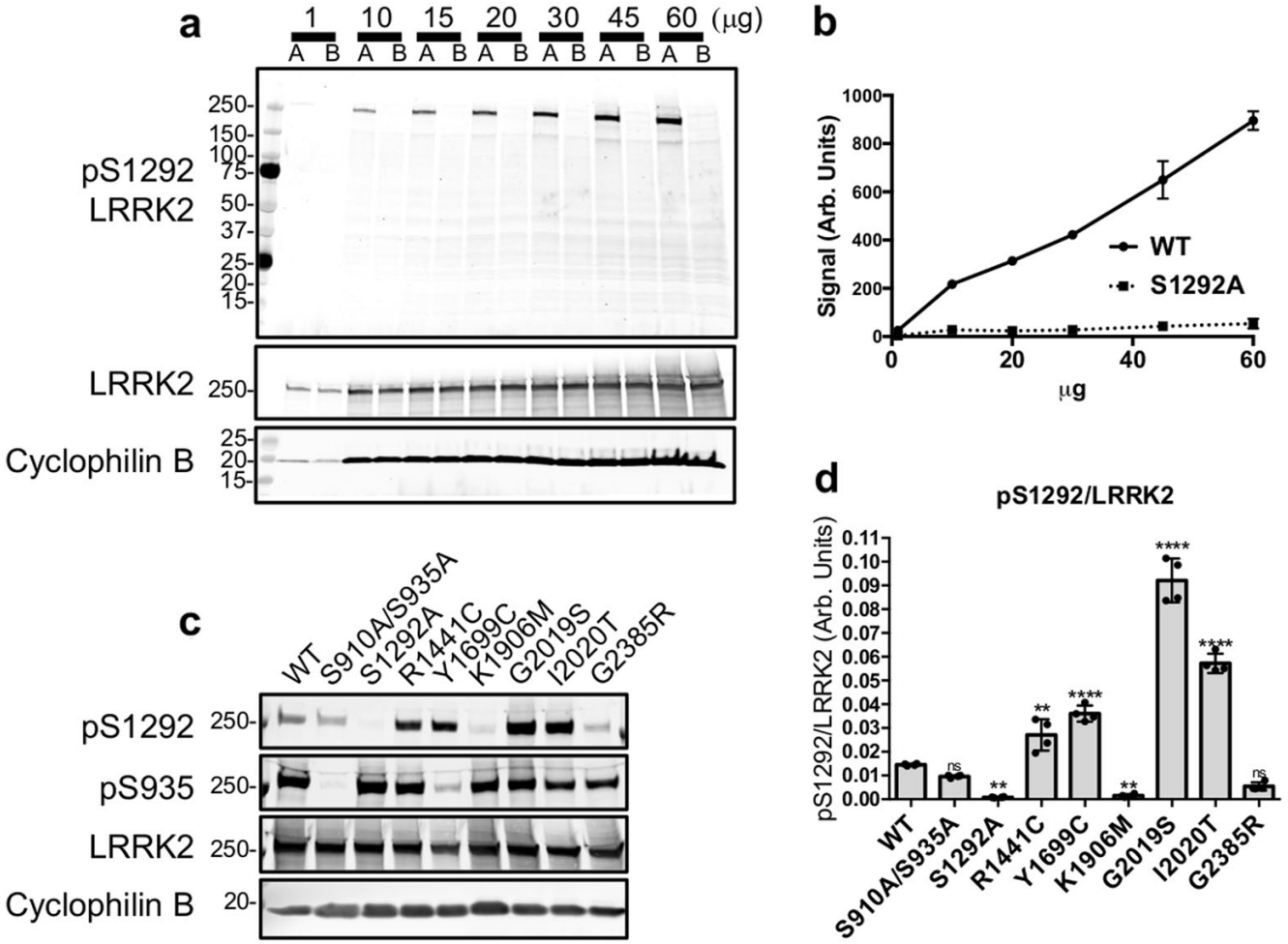
Gain of function (GOF) vs Loss of function (LOF)

Human genetics does not support LOF

Blauwendraat, Reed et al., JAMA Neurology In Press

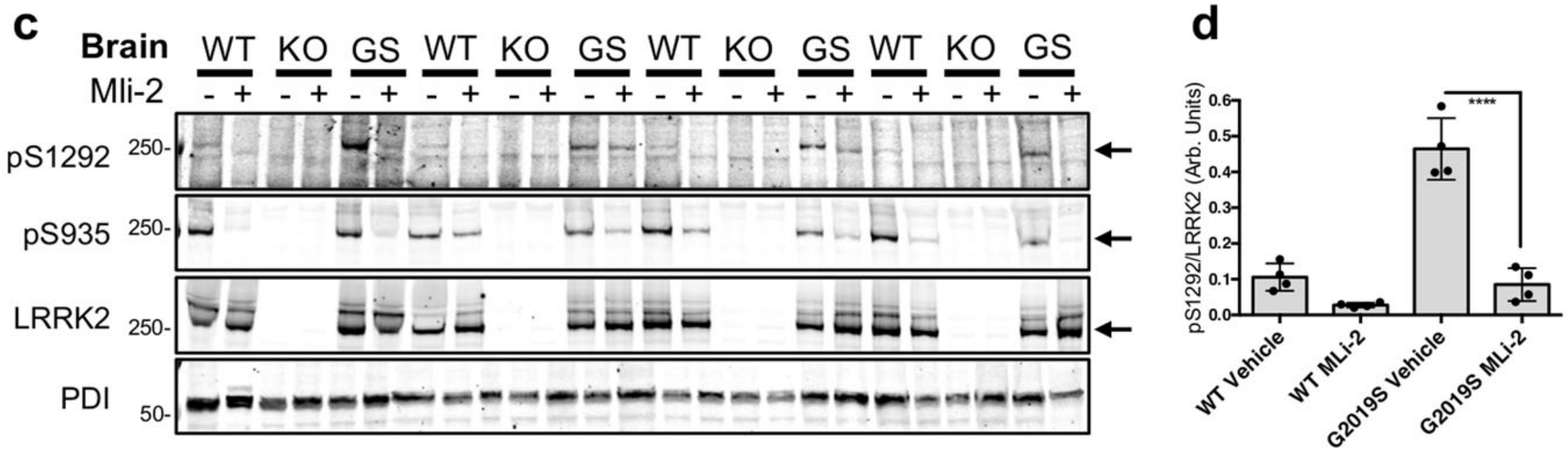
See Presentation by Xylena Reed, Tuesday 12:45

Direct assays of activity support GOF in cells



Kluss et al., NPJ Parkinsons Dis. 2018 Apr 19;4:13.

Direct assays of activity support GOF *in vivo*



Kluss et al., NPJ Parkinsons Dis. 2018 Apr 19;4:13.

Human genetic data on LRRK2 tells us:

- Coding variants variably affect risk from inherited to sporadic PD
- Non-coding variants have smaller effects on PD risk
- LOF variants are not associated with PD risk

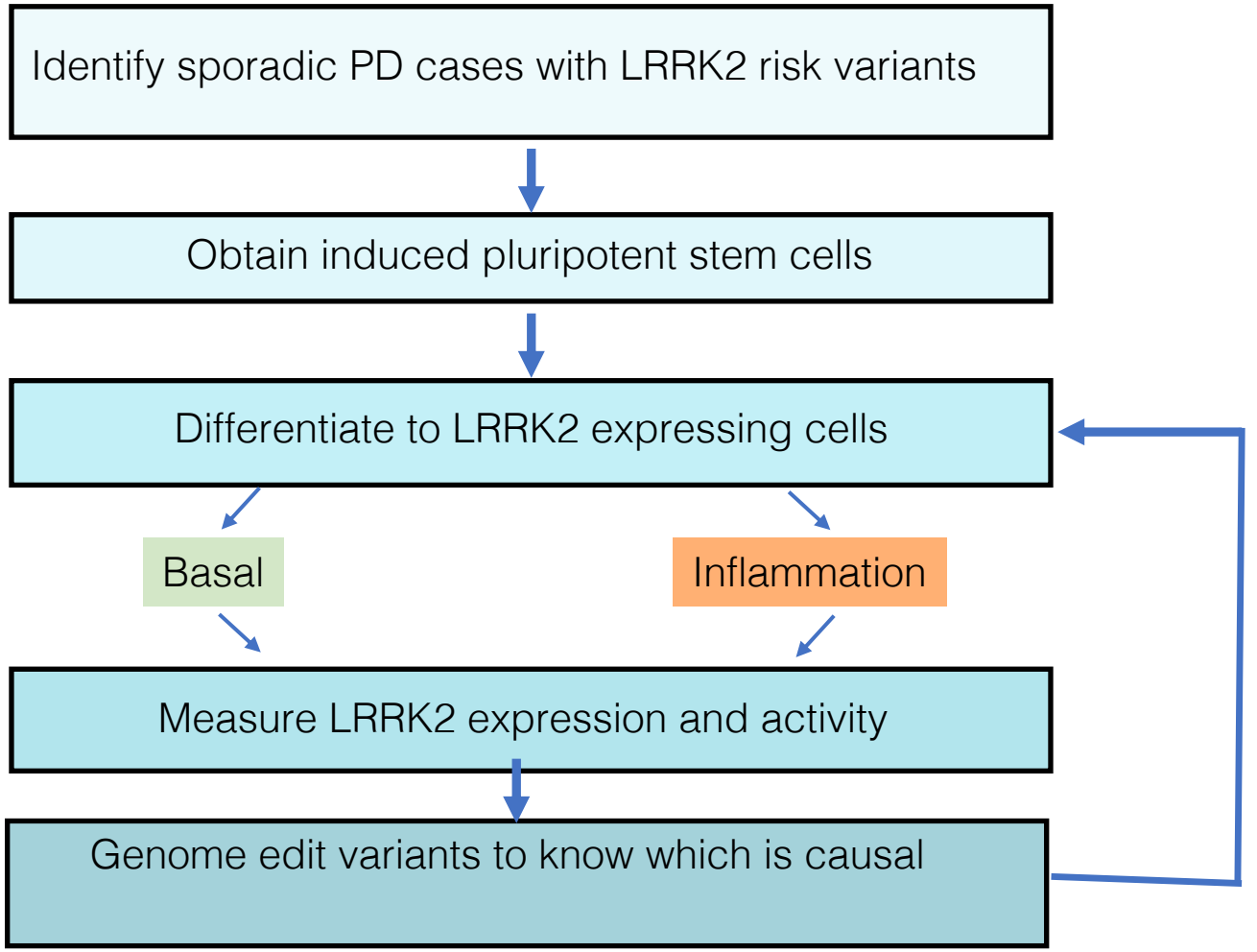
Data from model systems show:

- Mutant alleles are active, often increased activity

A reasonable inference is:

- Inherited and sporadic PD share mechanisms, via LRRK2 gain of function but due to slightly different mechanisms

Testing the Hypothesis of Sporadic PD in *In Vitro* Studies



Rebekah Langston
Supported by MJFF

Summary: LRRK2

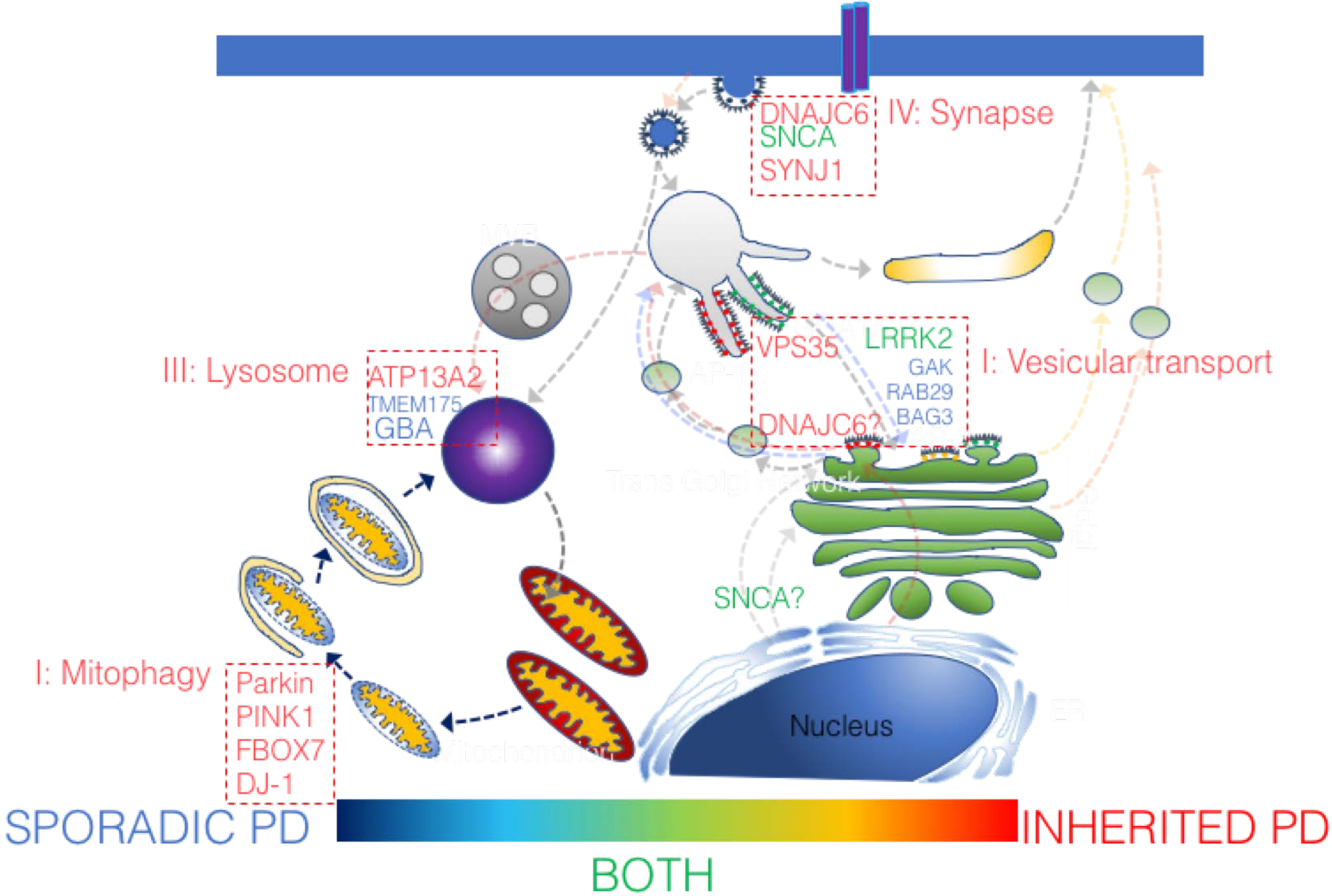
The preponderance of data suggests that mutant LRRK2 causes disease by a gain of function, related to kinase activity

LRRK2 can be linked to sporadic PD risk genes by physical and pathway interactions

The precise genetic mechanism by much non-coding variation contributes to disease is uncertain, but likely through eQTL

LRRK2 is expressed in multiple cell types, raising the possibility of non-cell autonomous mechanisms in disease

Our ongoing work aims to test these hypotheses in IPSC and mouse models


DNAJC6
SNCA
SYNJ1
IV: Synapse
VPS35
LRRK2
GAK
RAB29
BAG3
DNAJC6?
I: Vesicular transport
III: Lysosome
ATP13A2
TMEM175
GBA
SNCA?
Nucleus
ER
I: Mitophagy
Parkin
PINK1
FBOX7
DJ-1
SPORADIC PD
INHERITED PD
BOTH

Who to target?

Penetrant carriers of p.G2019S

Penetrant carriers of other *LRRK2* mutations

LRRK2 risk allele carriers with PD

All sporadic PD

Other PD genes?

A ‘noble’ longer term vision

I hope that LRRK2 kinase inhibitors are safe and efficacious for inherited PD

Because LRRK2 is embedded within networks of gene products relevant for sporadic PD, there may be utility outside of specific mutations

We should continue with basic biology efforts that support target identification with the long-term aim of having precision disease modifying PD therapies

Acknowledgements

Cell biology, LNG, NIA
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Ravindran Kumaran, PhD
Natalie Landeck, PhD
Rebekah Langston
Adam Mamais, PhD
Xylena Reed, PhD
Dorien Roosen
Nate Smith, PhD

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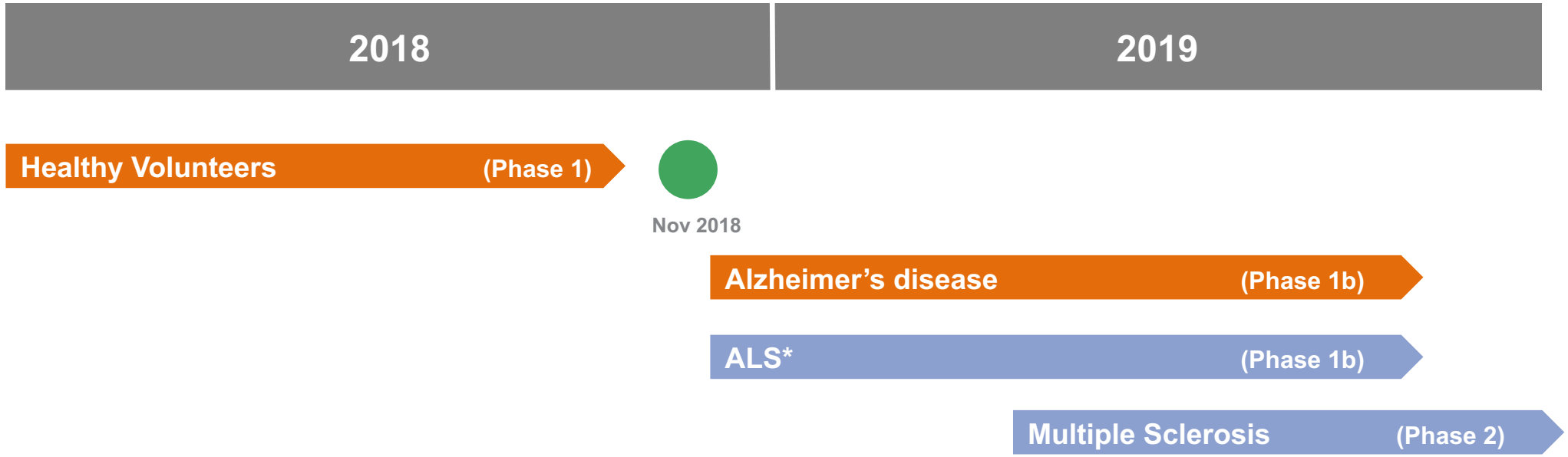
NIA IRP
MJFF

Collaborations
LNG: MGS (Singleton), NDRU (Traynor), CBC (Gibbs), GTG (Hernandez), DSG (Nalls)
International Parkinson's Disease Genetics Consortium
Elisa Greggio, Padova
Patrick Lewis, Reading
Jean-Marc Taymans, Lille
Kirsten Harvey, UCL
Yan Li, NINDS
Heather Melrose, Mayo
Darren Moore, VAI
Andy West, Duke
LEAPS: Jeremy Nichols (TPI), Mark Wilson (UNL), Quyen Hoang (IU)


DENALI
RIPK1 PROGRAM
CAROLE HO

RIPK1 CLINICAL PROGRAM SUMMARY



2018 Milestones

- DNL747: Completed Phase 1 (safety, PK, target engagement)
- DNL758: Completed IND enabling studies, ready for IND filing
- Entered into partnership with Sanofi for global development and commercialization of RIPK1 inhibitors

Led by Denali

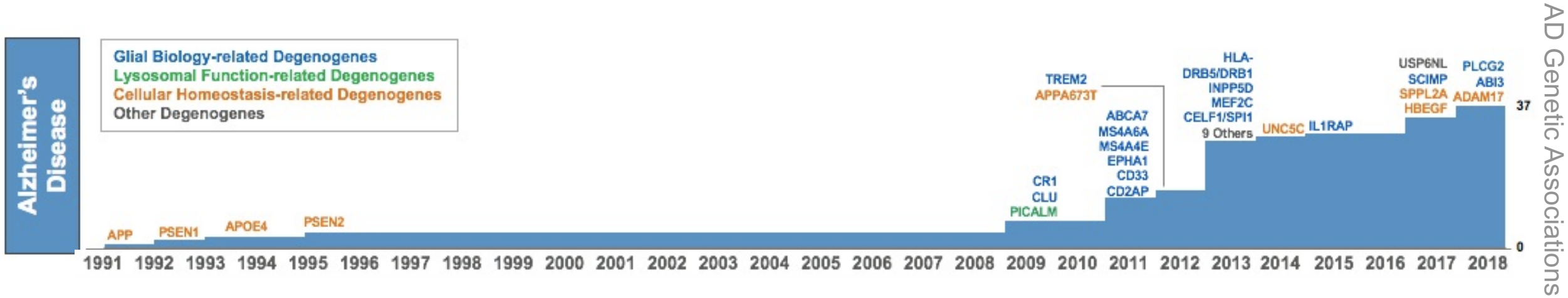
Led by Sanofi

*study design and execution by Denali

RIPK1 Inhibitor

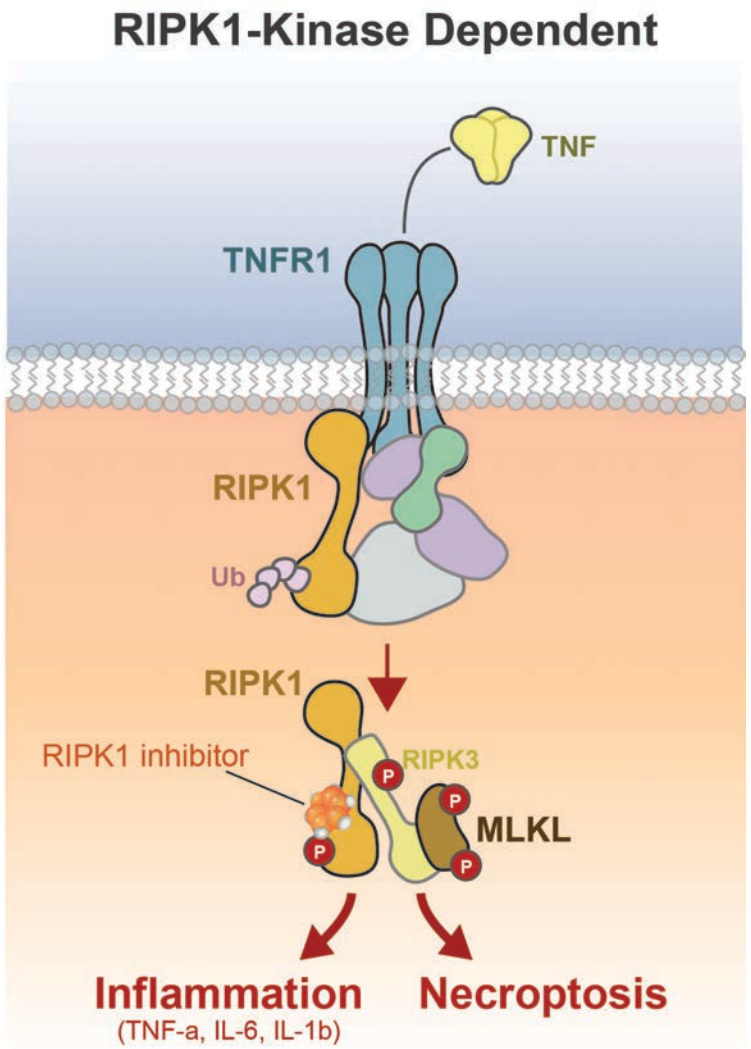
DEGENOGENES PROVIDE NEW INSIGHTS IN ALZHEIMER'S DISEASE

- Immune dysfunction is observed in patients with AD and other neurodegenerative diseases
- Neuro-immune modulation in neurodegeneration is a promising therapeutic approach



- Degenogenes including TREM2 and numerous other genes are highly expressed in inflamed microglia, the resident immune cells of the brain
- RIPK1 is a kinase downstream of the TNF receptor pathway, a major overactive inflammatory pathway in inflamed microglia and several other cells in the brain

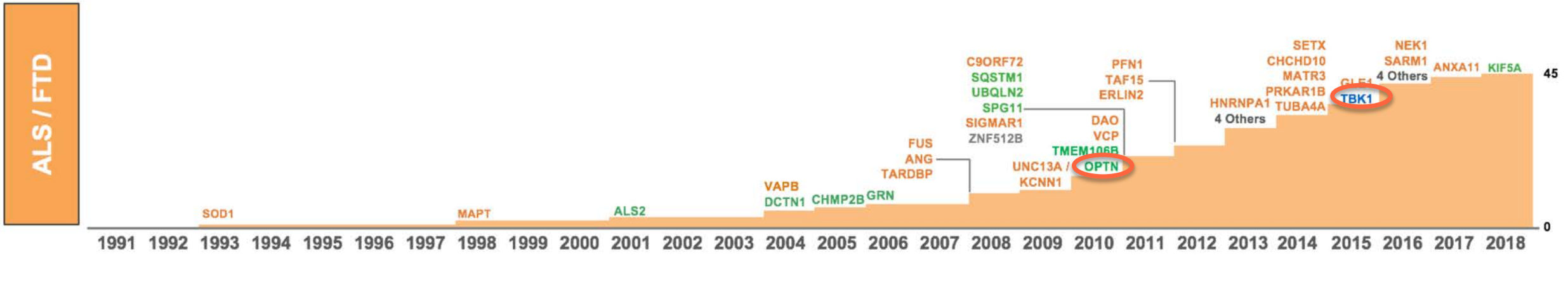
RIPK1 REGULATES INFLAMMATION AND NECROPTOSIS



- TNF pathway is one of the best validated pathways in human disease that has not been adequately tested in the brain
- 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
- RIPK1 inhibition enables selective inhibition of TNFR1 pathway
- Inhibition of RIPK1 is sufficient to block both the production of pro-inflammatory cytokines and necroptosis

DEGENOGENES PROVIDE NEW INSIGHTS IN ALS

- Loss of function of Optineurin, a multifunctional protein involved in protein trafficking by vesicles, autophagy, and signal transduction, is a familial cause of ALS
- Loss of function of TBK1, a kinase involved in autophagy, is a familial cause of ALS



- OPTN KO sensitizes cells for TNFa induced RIPK dependent cell death and cytokine releases

(Ito et al. 2016)

- RIPK1 kinase dead rescues the embryonic lethality of TBK1 KO mice and reduces cytokine release

(Xu et al. 2018)

RIPK1 Inhibitor

EFFECT OF RIPK1 SIGNALING IN NEURODEGENERATIVE DISEASE AND PERIPHERAL INFLAMMATION IS WELL-DOCUMENTED

SCIENCE sciencemag.org RESEARCH | REPORTS

AXONAL DEGENERATION

RIPK1 mediates axonal degeneration by promoting inflammation and necroptosis in ALS

Yasushi Ito,[1] Dimitry Ofengeim,[1] Ayaz Najafov,[1] Sudeshna Das,[2] Shahram Saberi,[3,4] Ying Li,[1,5] Junichi Hitomi,[1] Hong Zhu,[1] Hongbo Chen,[1] Lior Mayo,[6] Jiefei Geng,[1]

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)

CellPress Immunity Article

RIPK1 and RIPK3 Kinases Promote Cell-Death-Independent Inflammation by Toll-like Receptor 4

Malek Najjar,[1,10] Danish Saleh,[2,10] Matija Zelic,[3] Shoko Nogusa,[4] Saumil Shah,[5] Albert Tai,[6] Joshua N. Finger,[7] Apostolos Polykratis,[8] Peter J. Gough,[7] John Bertin,[7] Michael J. Whalen,[9] Manolis Pasparakis,[8] Siddharth Balachandran,[4] Michelle Kelliher,[3] Alexander Poltorak,[6] and Alexei Degterev[1,5,*]

[1]Program in Pharmacology and Experimental Therapeutics, Sackler Graduate School, Tufts University, Boston, MA 02111, USA

OPEN

Cell Death and Differentiation (2016), 1–12

www.nature.com/cdd

RIPK3 deficiency or catalytically inactive RIPK1 provides greater benefit than MLKL deficiency in mouse models of inflammation and tissue injury

K Newton*[,1], DL Dugger[1], A Maltzman[1], JM Greve[2], M Hedehus[2], B Martin-McNulty[2], RAD Carano[2], TC Cao[2], N van Bruggen[2], L Bernstein[3], WP Lee[4], X Wu[4], J DeVoss[4], J Zhang[4], S Jeet[4], I Peng[4], BS McKenzie[4], M Roose-Girma[5], P Caplazi[6], L Diehl[6], JD Webster[6] and D Vucic*[,7]

Activation of Necroptosis in Multiple Sclerosis

Dimitry Ofengeim,[1] Yasushi Ito,[1] Ayaz Najafov,[1] Yaoyang Zhang,[2] Bing Shan,[2] Judy Park DeWitt,[1] Juanying Ye,[5] Xumin Zhang,[5] Ansi Chang,[2] Helin Vakifahmetoglu-Norberg,[1,6] Jiefei Geng,[1] Benedicte Py,[1] Wen Zhou,[1] Palak Amin,[1] Jonilson Berlink Lima,[1] Chunting Qi,[3] Qiang Yu,[3] Bruce Trapp,[4] and Junying Yuan[1,2,*]

[1]Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA
[2]Interdisciplinary Research Center on Biology and Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Linglin Road, Shanghai 200032, China
[3]Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203,China
[4]Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA
[5]The State Key Laboratory of Genetics Engineering, School of Life Sciences, Fudan University, Shanghai 200433, P.R. China
[6]Present address: Division of Toxicology, Institute of Environmental Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden
*Correspondence: jyuan@hms.harvard.edu
http://dx.doi.org/10.1016/j.celrep.2015.02.051

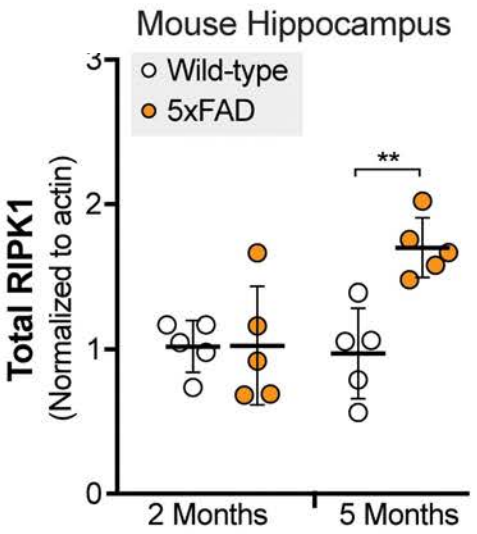
TBK1 Suppresses RIPK1-Driven Apoptosis and Inflammation during Development and in Aging

Daichao Xu,[1,7] Taijie Jin,[2,3,7] Hong Zhu,[1] Hongbo Chen,[1] Dimitry Ofengeim,[1] Chengyu Zou,[1] Lauren Mifflin,[1] Lifeng Pan,[4] Palak Amin,[1] Wanjin Li,[1] Bing Shan,[2] Masanori Gomi Naito,[1] Huyan Meng,[2,3] Ying Li,[2] Heling Pan,[2] Liviu Aron,[5] Xian Adiconis,[6] Joshua Z. Levin,[6] Bruce A. Yankner,[5] and Junying Yuan[1,2,8,*]

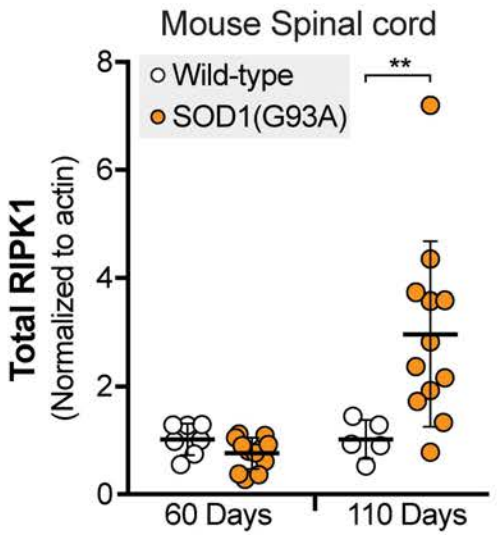
RIPK1 Inhibitor

RIPK1 PATHWAY MEDIATES MICROGLIAL RESPONSE IN DISEASE MODELS

AD mouse model



ALS mouse model



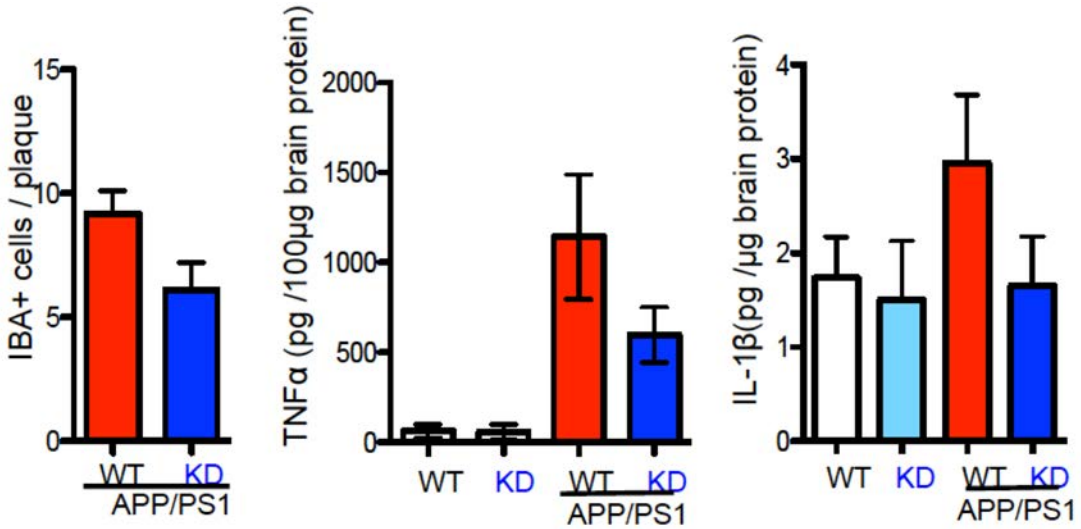
PNAS

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 Kelliher[e], Joshua Z. Levin[d], and Junying Yuan[a,2]

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

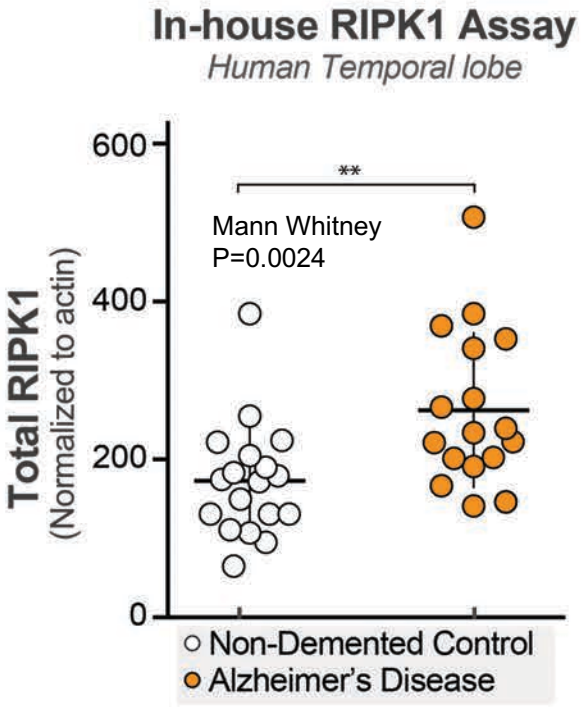
Contributed by Junying Yuan, August 15, 2017 (sent for review August 11, 2017; reviewed by J. Marie Hardwick and David Rubinsztein)

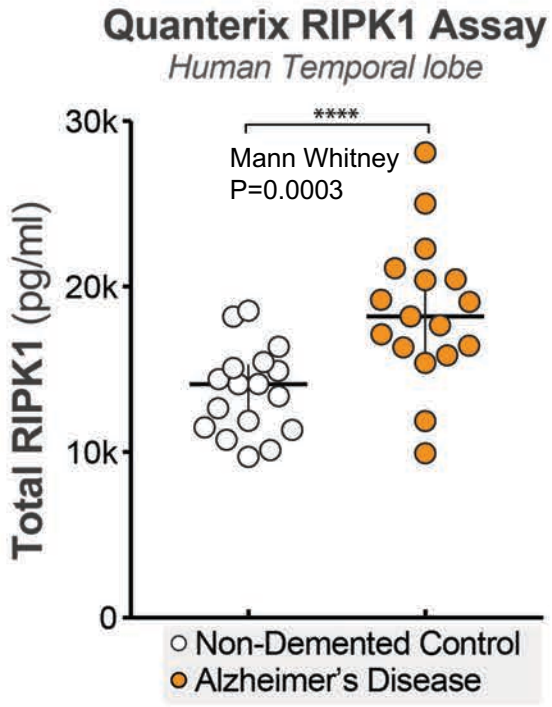


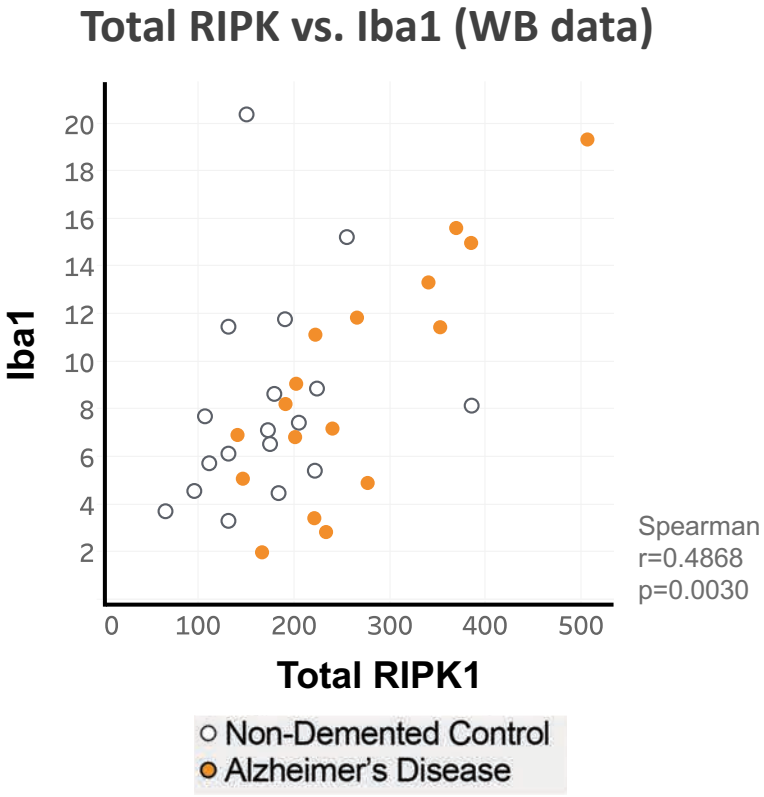
- Total RIPK1 increased in AD and ALS mouse models of disease
- Reduced microglial activation and pro-inflammatory cytokines in APP / PS1 transgenic with RIPK1 kinase dead background

RIPK1 Inhibitor

RIPK1 ELEVATED IN TEMPORAL LOBE OF ALZHEIMER'S DISEASE PATIENTS



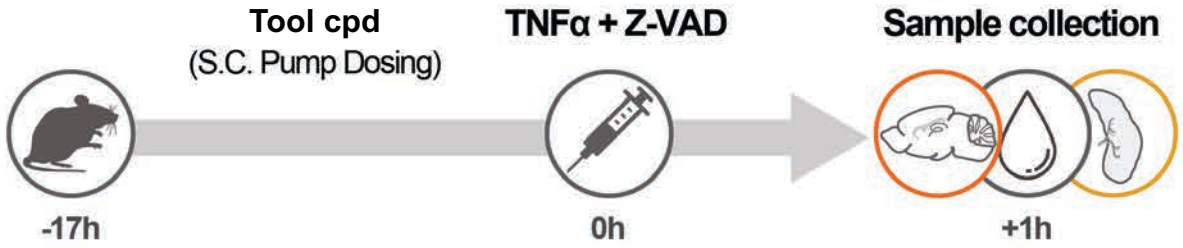




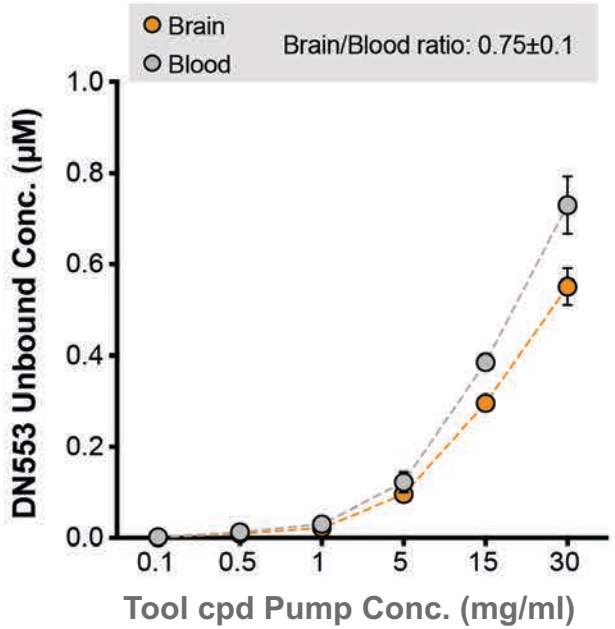
- Total RIPK1 levels increased in AD patients as measured by two distinct assays

- Total RIPK1 protein highly correlated with microglial biomarker Iba1 in AD patients

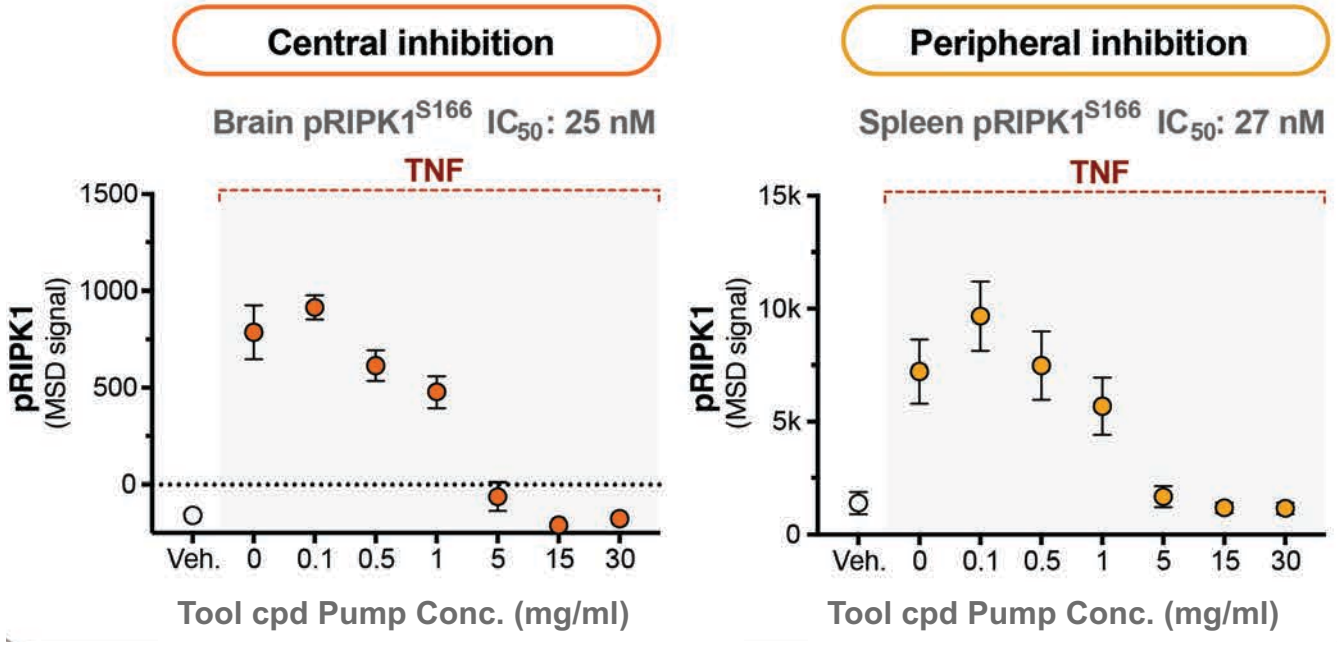
PERIPHERAL PHARMACOLOGIC PROPERTIES CORRELATE WITH BRAIN PROPERTIES (RIPK1 TOOL COMPOUND)



COMPARABLE EXPOSURE OF DN553 IN BRAIN AND BLOOD



COMPARABLE INHIBITION OF pRIPK1 IN BRAIN AND SPLEEN



- IC_{50} for cytokine inhibition similar to pRIPK1 inhibition observed in Brain and Spleen

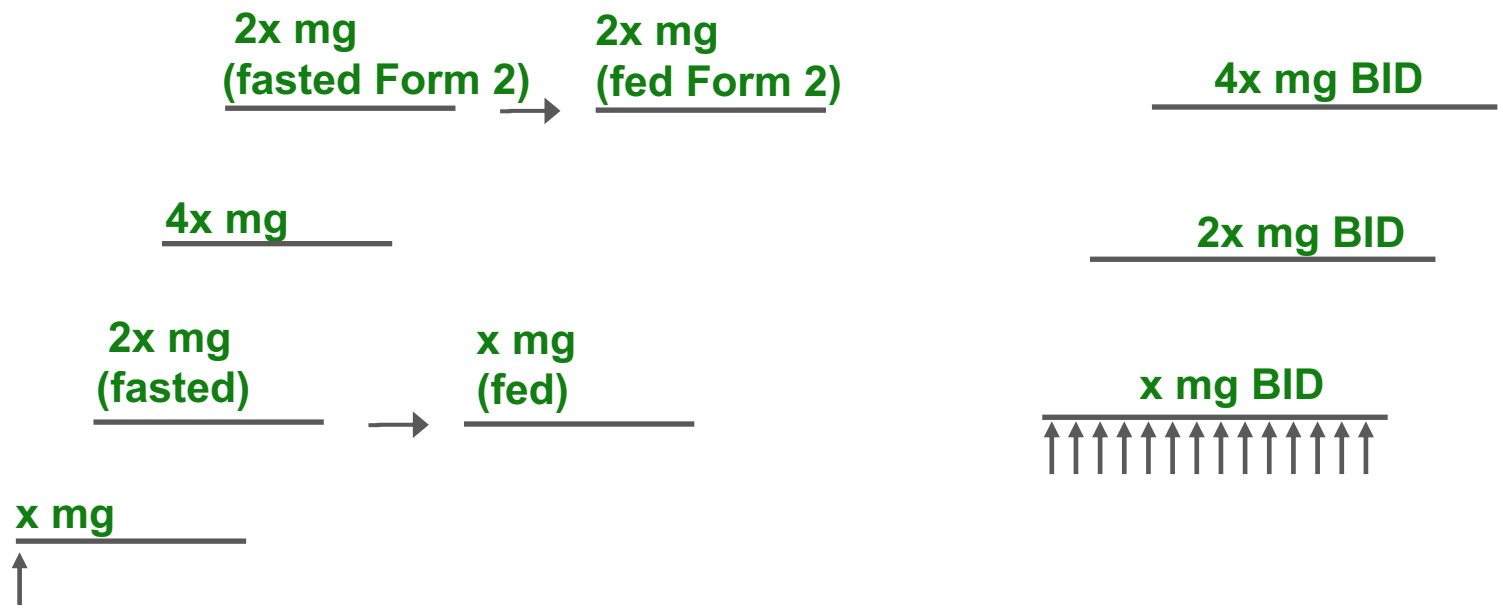
DNL747 RIPK1 PHASE I HEALTHY VOLUNTEER STUDY DESIGN

Design	Phase 1 study in healthy volunteers • Randomized, placebo-controlled, double blind	
Study Size	**N=56** (PtA=29, PtB=27)	
Key Endpoints	**Safety** • Routine safety • Skin examination	**PK:** • Plasma • CSF • Formulation and Food Effect
	Target engagement: • pS166 in PBMCs • Exploratory endpoints • CSF Cytokines, chemokines	

Part A: Single Dose
N = 8 / cohort
(6 active : 2 placebo)

Part B: Multiple Dose (14 day)
N = 10 / cohort
(8 active : 2 placebo)

Formulation 1 used for all cohorts except where noted as Formulation 2 (Form 2)



- 56 healthy subjects dosed with DNL747 or placebo
- Pre and post dose lumbar puncture in all multiple dose subjects

DNL747 PHASE 1 SAFETY RESULTS

These results are preliminary as of Dec 5th and are subject to change as the final CSR has not been completed

ACROSS PHASE 1 STUDY	• **No SAEs, no discontinuations due to study drug** • Well tolerated by 42 healthy volunteers who received at least one dose of active DNL747 • Majority of Treatment Emergent Adverse Events (TEAEs) were mild (92%) with the rest moderate • No clinically meaningful changes on ECGs, clinical exams, and safety laboratories except as noted in Part 2 • No clear dose relationship observed in TEAEs that were more frequent in active than placebo subjects • No immune-mediated toxicities observed
PART 1: SINGLE ASCENDING DOSE	• **Well tolerated to highest single dose tested** • All TEAEs were mild • 1 discontinuation, not related to a TEAE, occurred after completing the first single dose administration period in a food effect cohort; the subject did not return for the second single dose
PART 2: MULTIPLE ASCENDING DOSE	• **Well tolerated to highest multiple dose tested for 14 days** • Of 5 moderate TEAEs in subjects receiving active therapy, three were associated with the LP procedure, and two were due to cystitis and intermittent headache in different subjects

DNL747 PHASE 1 SINGLE DOSE STUDY: MOST COMMON TEAEs

These results are preliminary as of Dec 5th and are subject to change as the final CSR has not been completed

	PBO N=8	All Active N=21	x mg N=6	2x mg / x mg N=5	2x/ 2x mg (Form 2) N=5	4x mg N=5
Number of subjects (%) in each dose group with > 1 TEAE across all cohorts						
Skin irritation | Medical device site irritation (ECG and Holter Electrode skin irritation)	-	**4 (19%)**	-	1 (20%)	2 (40%)	1 (20%)
Catheter site related reaction		**2 (10%)**	1 (20%)	1 (20%)	-	-
Diarrhea	-	**2 (10%)**	-	1 (20%)	1 (20%)	-
Headache	-	**2 (10%)**	-	1 (20%)	1 (20%)	-
Nasopharyngitis	1 (13%)	1 (5%)	-	-	-	1 (20%)

- 29 healthy volunteers completed single dose study
- All doses were well tolerated
- All AEs were reported as mild intensity with no pattern of AEs by organ system or by dose cohort

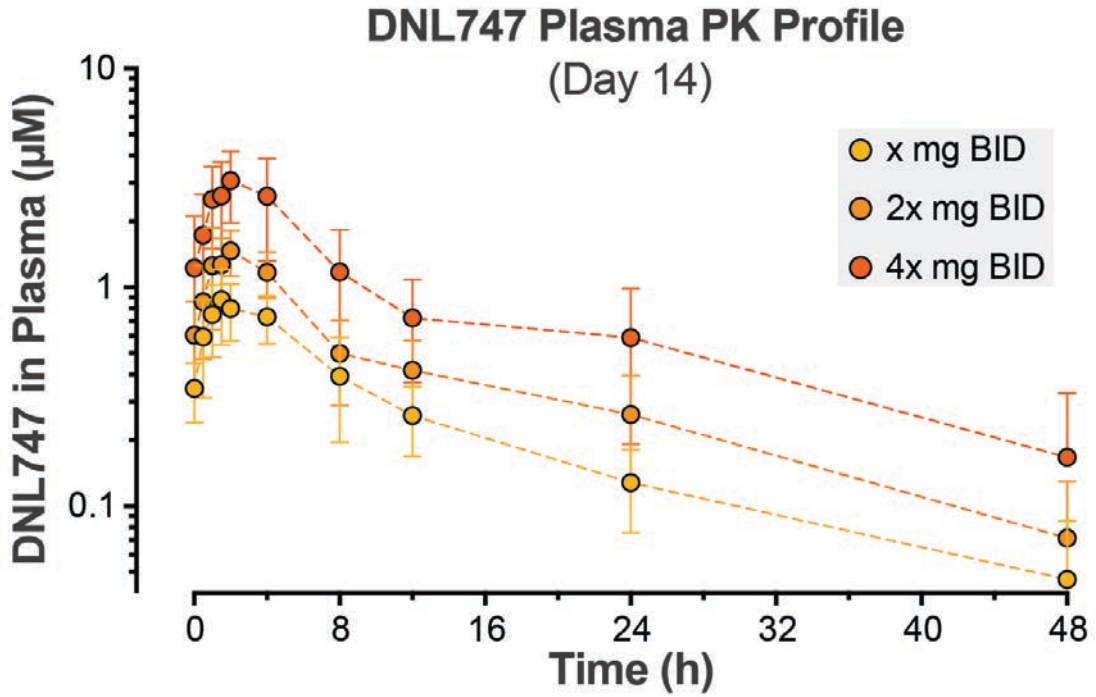
DNL747 PHASE 1 MULTIPLE DOSE STUDY: MOST COMMON TEAEs

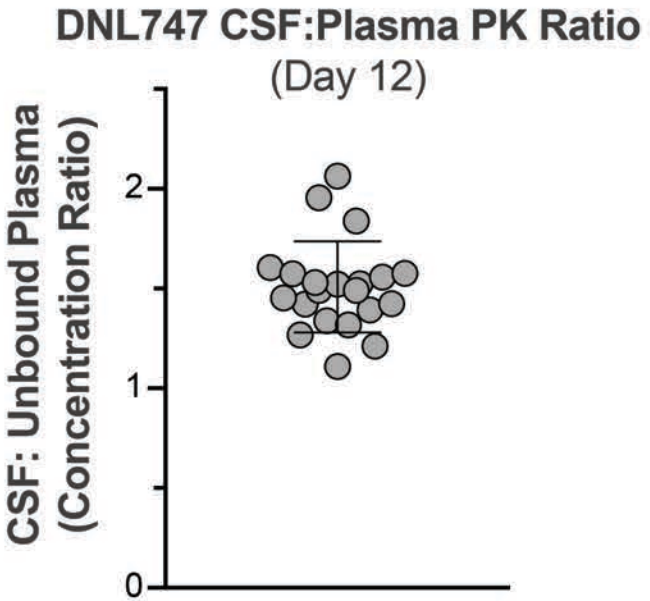
These results are preliminary as of Dec 5th and are subject to change as the final CSR has not been completed

	Placebo N=6	All Active N=21	x mg BID N=8	2x mg BID N=8	4x mg BID N=5
Number of subjects (%) in each dose group with > 1 TEAE across all cohorts					
Post lumbar puncture syndrome | Procedural pain | Post procedural discomfort (LP related adverse events)	5 (83%)	13 (62%)	7 (88%)	4 (50%)	2 (40%)
Skin irritation | Medical device site irritation (Skin irritation ECG and Holter electrodes, wristband alarm irritation)	-	**6 (29%)**	2 (25%)	3 (38%)	1 (20%)
Catheter site related reaction | Catheter site pruritis	2 (33%)	3 (14%)	1 (13%)	-	2 (40%)
Nausea	-	**3 (14%)**	-	2 (25%)	1 (20%)
Fatigue	-	**2 (10%)**	1 (13%)	-	1 (20%)
Dry skin	1 (17%)	1 (5%)	1 (13%)	-	-
Headache	1 (17%)	1 (5%)	-	1 (13%)	-

- Five moderate TEAEs were reported after DNL747 treatment in the MAD (required a treatment intervention); three were associated with the LP procedure with the other two due to intermittent headache and cystitis
- No clinically significant abnormalities except for 1) single subject mild (~2x ULN) AST/ALT elevation (concurrent with cystitis treated with Bactrim and modest alcohol consumption; no increase in bilirubin) and 2) single subject with CPK changes (~3x ULN) in setting of increased physical activity

DNL747 PHARMACOKINETIC PROPERTIES AND BRAIN EXPOSURE

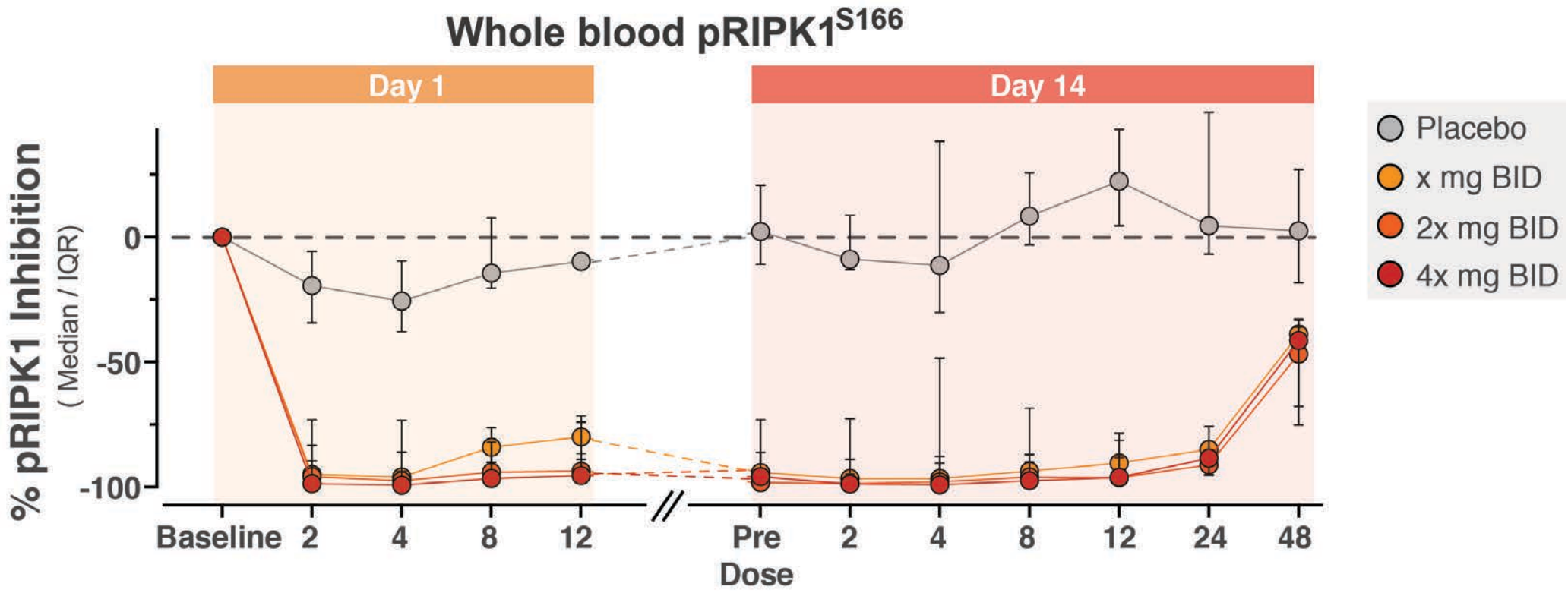




- Well behaved PK profile
- Terminal half life of 12 hours across dose levels
- Low to moderate variability in Cmax and AUC

- Mean CSF to unbound plasma ratio of 1.51 ± 0.23
- Data from all multiple dose cohorts

DNL747 DOSE-DEPENDENT INHIBITION OF RIPK1 IN HEALTHY SUBJECTS



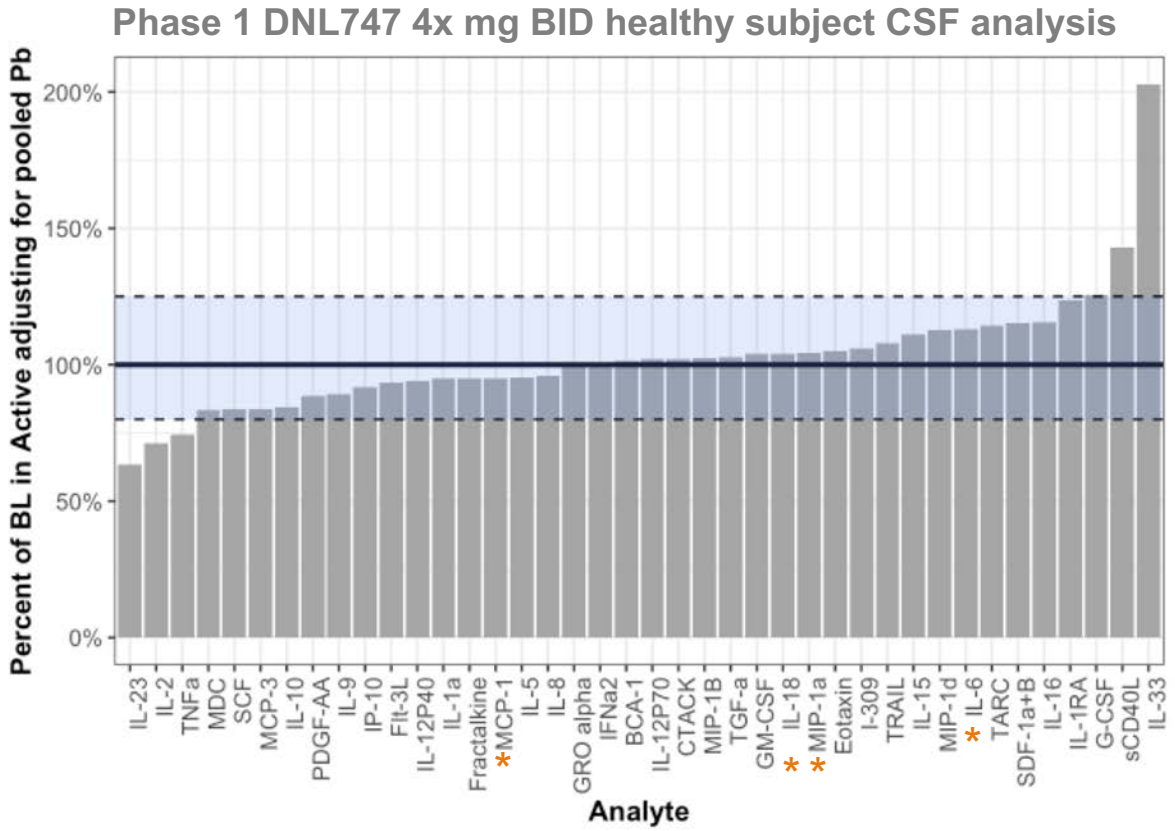
- Time course of RIPK1 pS166 inhibition after DNL747 administration every 12 hours until day 14

DNL747 MET ALL OBJECTIVES IN PH1 STUDY

Safety	Overall well tolerated in 42 subjects who received DNL747 and supports advancement to Phase 1b in ALS and Alzheimer's disease
PK	Excellent CSF penetration and PK
Target Engagement	Robust target engagement with >90% pRIPK1 inhibition at steady state

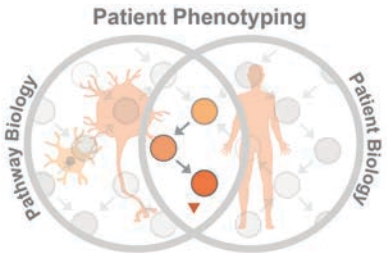
DNL747 PH 1 CSF SAMPLES IDENTIFY CANDIDATE CNS PATHWAY BIOMARKERS

	Cytokine percentage reduction with RIPK1 inhibition	
	In vitro TZ stimulated human macrophage	*In vivo* TZ stimulated mouse model (brain)
IL1beta	97%	N/A
IL-18	94%	Not measured
MIP-1a	87%	N/A
IL6	78%	90%
MCP1	34%	36%

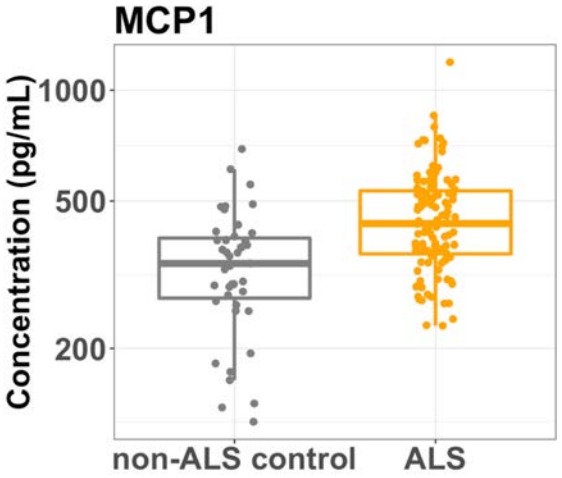


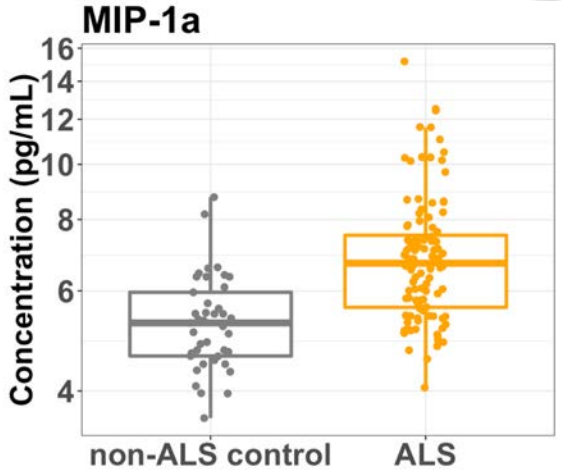
- Induced RIPK1 pathway preclinical models identify RIPK1 dependent pathway cytokines of interest
- Analysis of cytokines / chemokines in Phase 1 identifies candidate RIPK1 dependent CNS biomarkers and assay methodology
- Further assessment in patients with active inflammatory pathways is required due to minimal pathway activation in healthy CSF

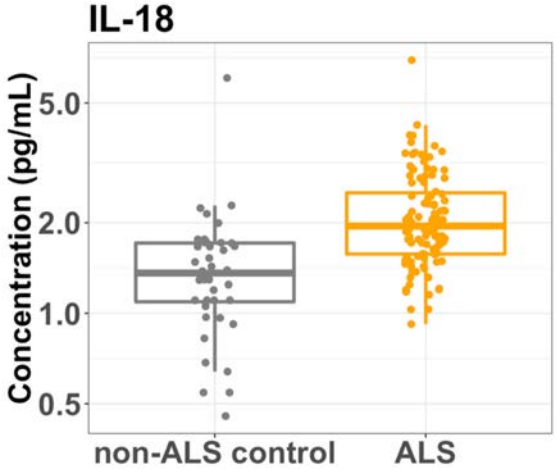
PATIENT PHENOTYPING: ANALYSIS OF CSF FROM ALS PATIENTS

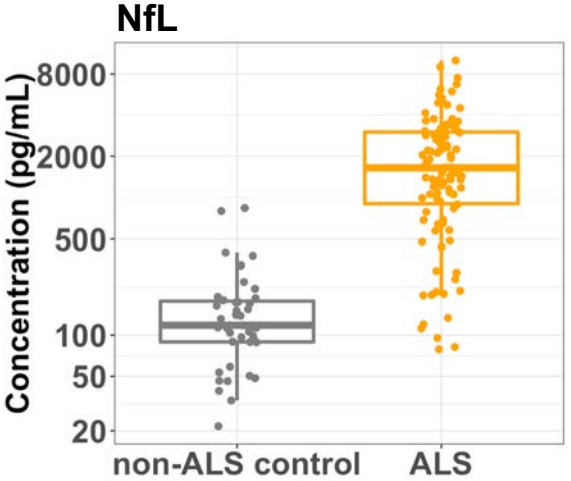


NEALS









RIPK1 dependent cytokines

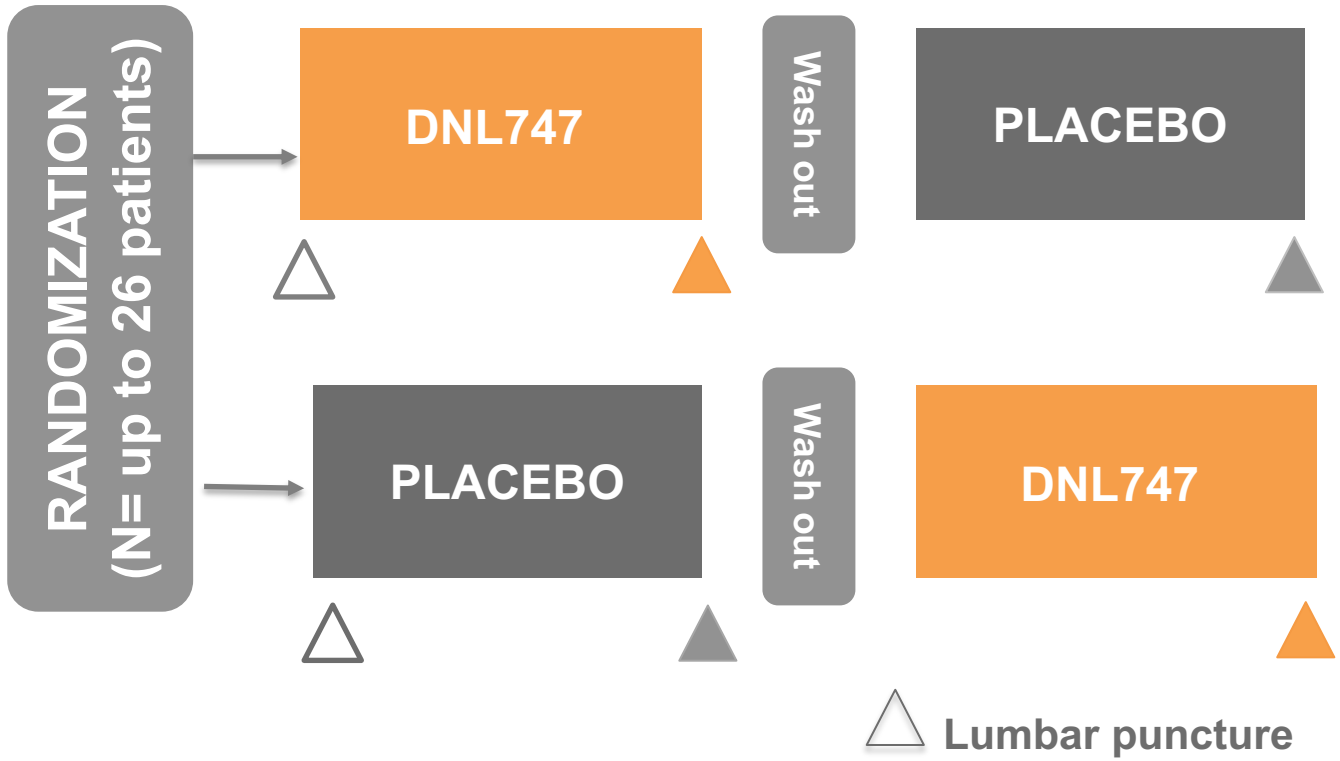
Biomarker of Neuronal Health

- Disease biomarker ALS patient phenotyping in collaborations with NEALS consortium assessed >150 longitudinal samples
- RIPK1 dependent cytokines identified in preclinical studies are increased in disease
- Phase 1b study in patients designed to assess effects on RIPK1 inhibition on candidate biomarkers of disease

RIPK1 Inhibitor

DNL747 RIPK1 PHASE 1B CROSSOVER CLINICAL TRIAL DESIGN ALS

Design	Randomized, double blind, placebo controlled, cross-over design **(28-day dosing)** • ALS diagnosis (lab-supported probable /probable / definite sporadic / familial) • <3y since symptom onset • Forced Vital Capacity > 50% • Stable meds (riluzole, edaravone)	
Study Size	**N=16 (up to 26) patients**	
Key Endpoints	**Safety:** • Routine safety	**PK:** • Plasma • CSF
	Target engagement: • PBMC pRIPK1 pS166 **Exploratory:** • CSF / blood disease biology biomarkers (cytokines / chemokines), NfL • Clinical endpoint: ALSFRS-R	



- Phase 1b crossover design enables investigation of candidate exploratory biomarkers with reduced sample size
- First Patient In (FPI) anticipated Q4 2018; data readout by Q4 2019
- Final sample size dependent on inter-subject variability

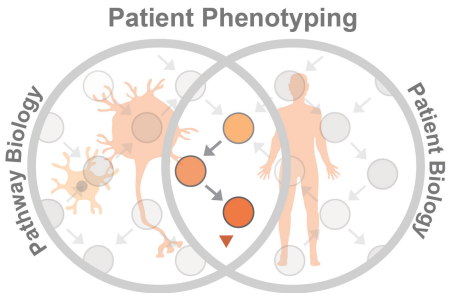
RIPK1 Inhibitor

PATIENT PHENOTYPING: ANALYSIS OF CSF FROM AD PATIENTS

UNBIASED MASS SPEC APPROACH FOR IDENTIFICATION OF NOVEL BIOMARKERS

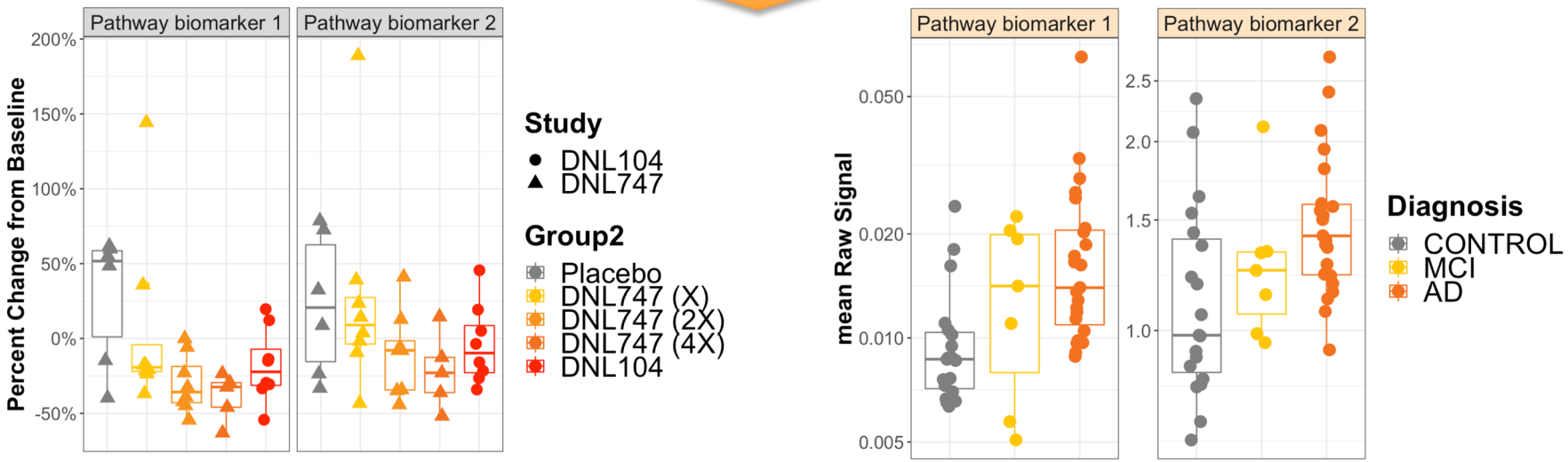
Healthy volunteer CSF from Phase 1 RIPK1 inhibitor studies:

Discovery and validation approach to identify candidate RIPK1 dependent biomarkers



Alzheimer Disease CSF:

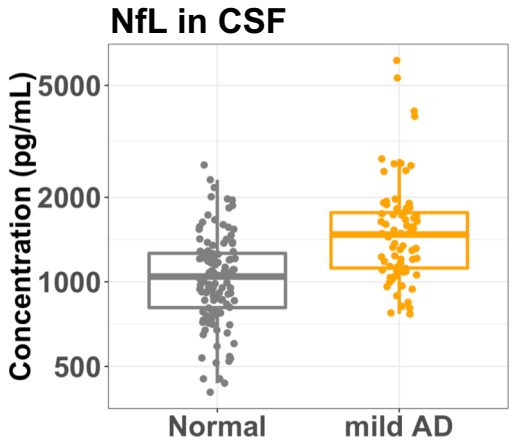
Identify biomarkers altered in disease



- 4 novel biomarkers are validated as RIPK1 dependent *and* elevated in Alzheimer Disease CSF
- Biomarkers are in same cellular pathway

CANDIDATE APPROACH

- NfL increased in mild AD
- Additional in-house analyses on acquired CSF samples in progress

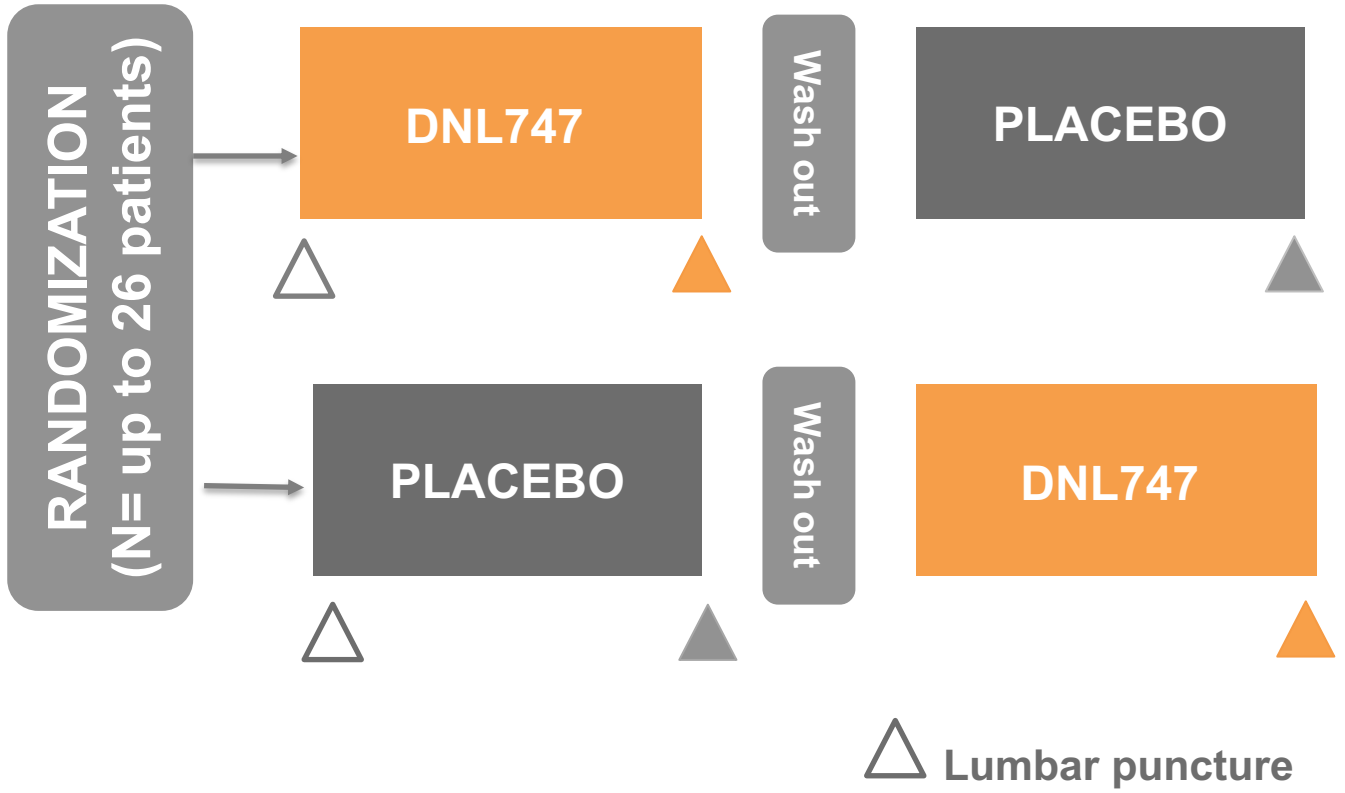


Biomarker of Neuronal Health

RIPK1 Inhibitor

DNL747 RIPK1 PHASE 1B CROSSOVER CLINICAL TRIAL DESIGN AD

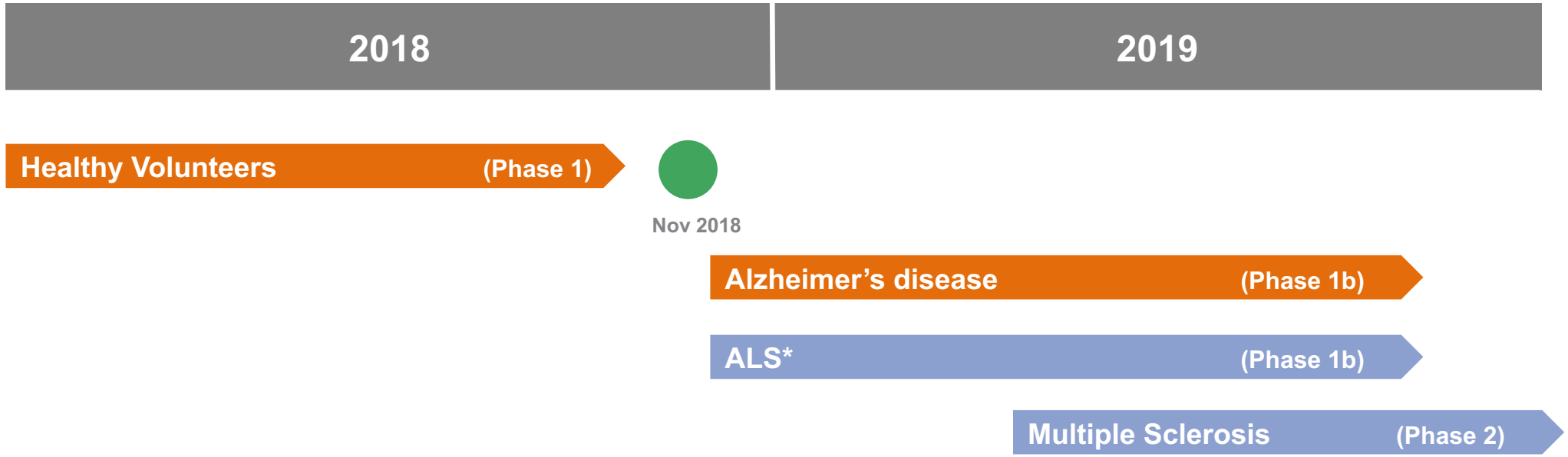
Design	Randomized, double blind, placebo controlled, cross-over design **(28-day dosing)** • AD per NIA-AA Dx Criteria • CSF Abeta42 c/w AD Dx • MMSE score >=18 AND <=26 • CDR scale 0.5 – 1.0	
Study Size	**N=16 (up to 26) patients**	
Key Endpoints	**Safety:** • Routine safety	**PK:** • Plasma • CSF
	Target engagement: • PBMC pRIPK1 pS166 **Exploratory:** • CSF / blood disease biology biomarkers (metabolomics, NfL, tau:Abeta42 ratio, cytokines) • Clinical endpoint: DCT Clock Neurocognitive Test	



- FPI anticipated Q4 2018
- Estimated data readout by Q4 2019

RIPK1 Inhibitor

RIPK1 CLINICAL PROGRAM SUMMARY



2018 Milestones

- DNL747: Completed Phase 1 (safety, PK, target engagement)
- DNL758: Completed IND enabling studies, ready for IND filing
- Entered into partnership with Sanofi for global development and commercialization of RIPK1 inhibitors

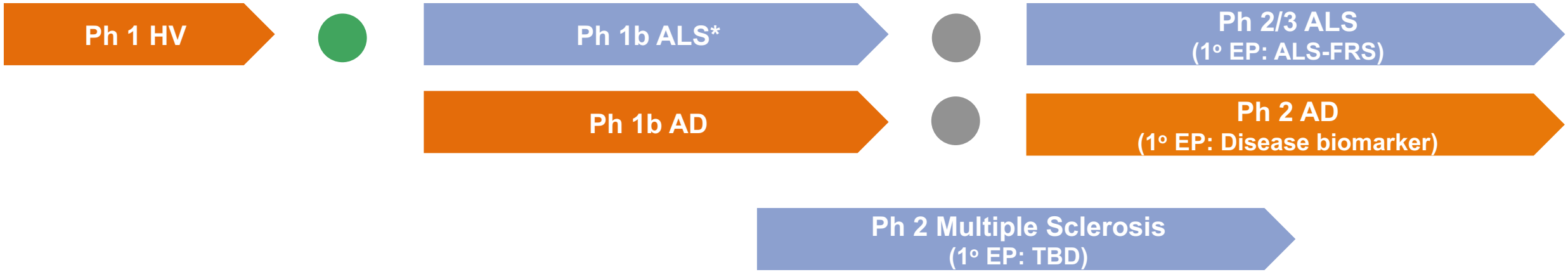
Led by Denali

Led by Sanofi

*study design and execution by Denali

RIPK1 Inhibitor

RIPK1 DNL747 LONG-TERM DEVELOPMENT PLAN



- Safety / Tolerability ✓
- Target Engagement ✓
- Dose Selection ✓
- Candidate Pathway Biomarkers ✓
- Candidate Patient Phenotyping Biomarkers ✓

- Safety / Tolerability in Patients
- Target and Pathway Engagement
- Biomarker Driven Dose Selection in Patients
- Relevant Changes in Patient Phenotyping Biomarkers

Led by Denali
Led by Sanofi

*study design and execution by Denali

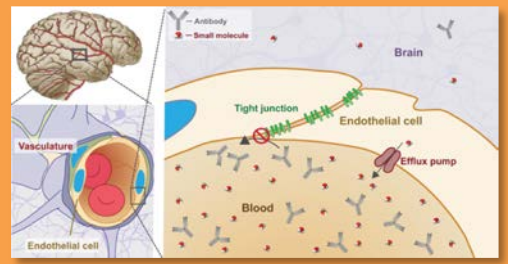
Phase 1b data intended to support progression to Ph 2/3 study in ALS and Ph 2 study in AD


DENALI
DISCOVERY PORTFOLIO
RYAN WATTS

GENETIC PATHWAY POTENTIAL: BROAD PORTFOLIO

Genetic Pathway Potential

Engineering Brain Delivery

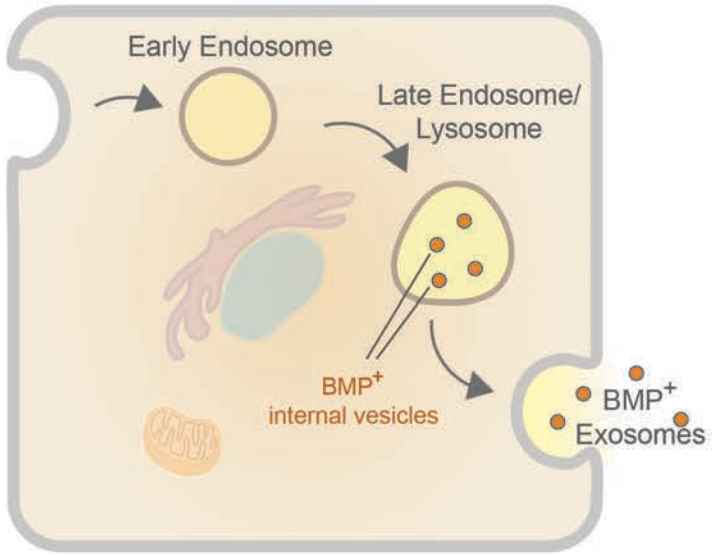


Biology Focus Areas	LYSOSOMAL FUNCTION	GLIAL BIOLOGY	CELLULAR HOMEOSTASIS	OTHER TV-ENABLED APPROACHES
Denali Programs	LRRK2, ETV:IDS, ATV:aSyn, *Undisclosed*	RIPK1, ATV:TREM2, *Undisclosed*	ATV:BACE1/Tau, *Undisclosed*, *Undisclosed*, *Undisclosed*	*Undisclosed*

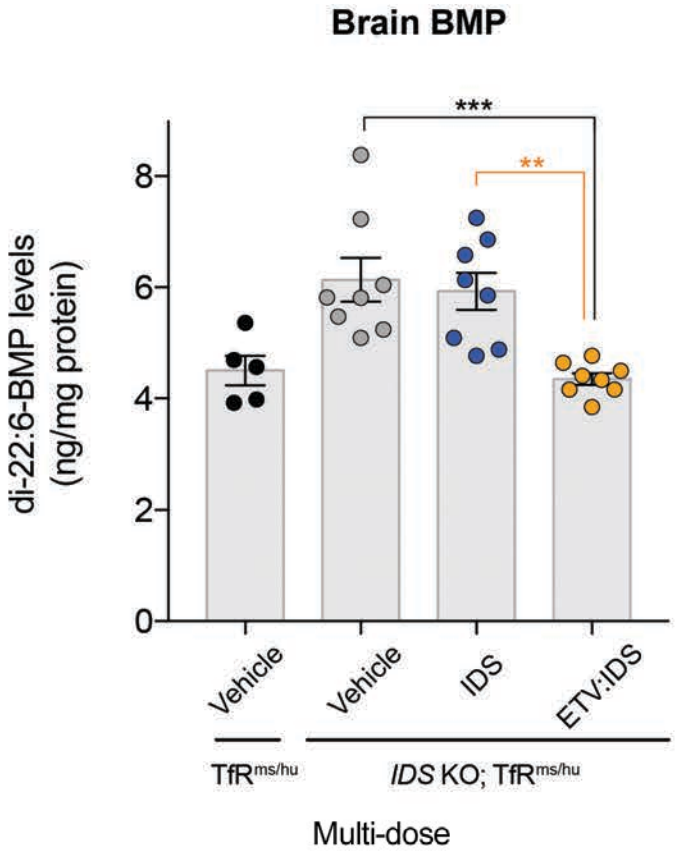
In addition to the above, Denali is pursuing six programs within Target Validation

Discovery

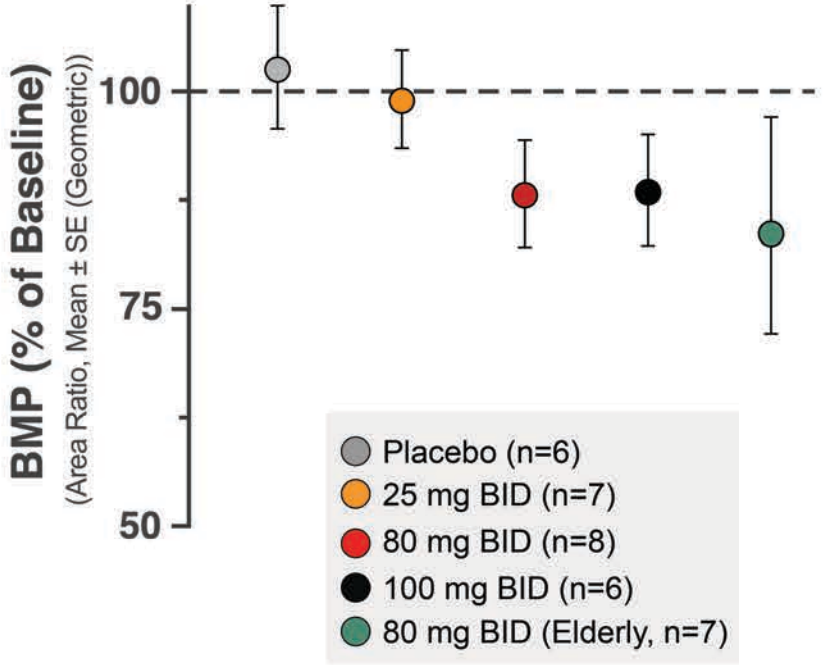
LYSOSOMAL FUNCTION EXPERTISE IN LIPIDOMICS



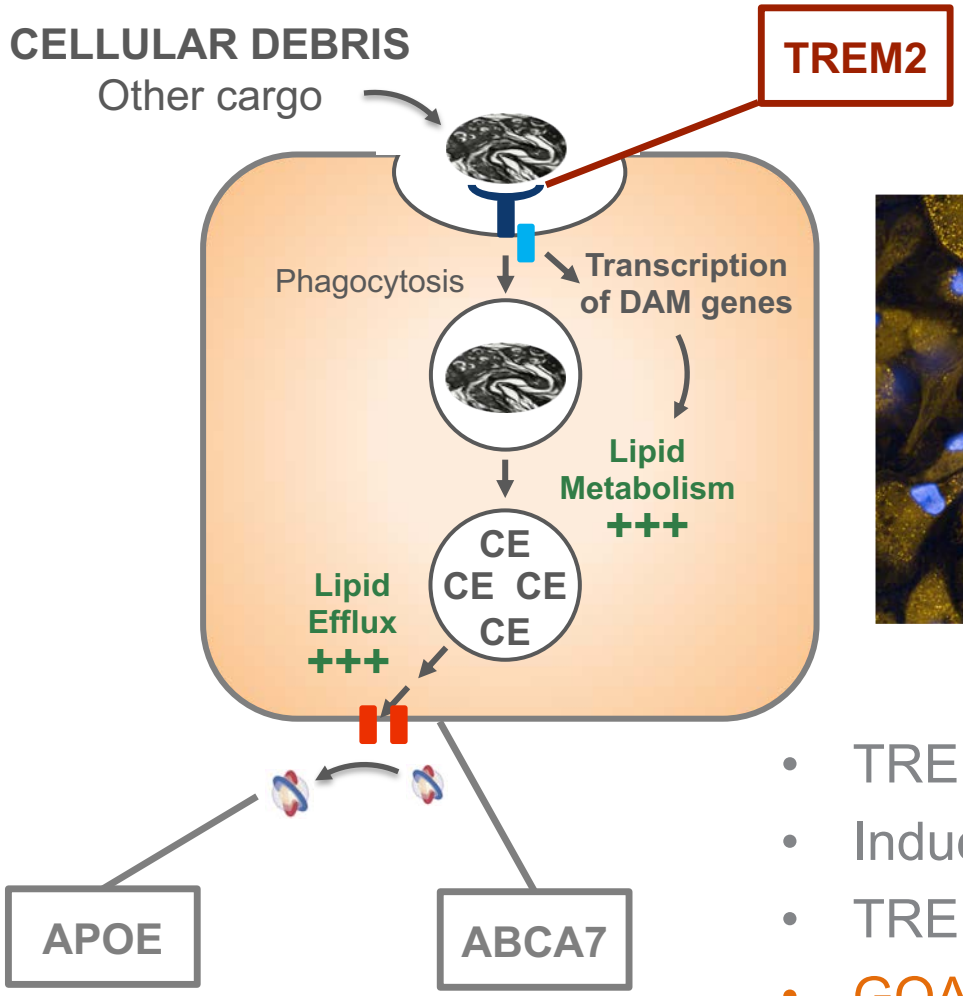
ETV:IDS (DNL310) RESCUES BRAIN BMP LEVELS



CHANGE IN BMP Di22:6 AFTER 10 DAYS OF DNL201 (LRRK2i) DOSING



GLIAL BIOLOGY TREM2 KNOCKOUT MICROGLIA DEFECTS



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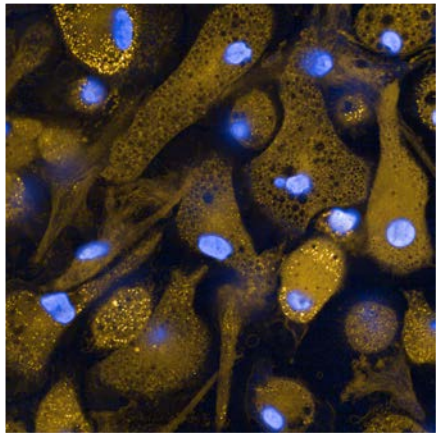
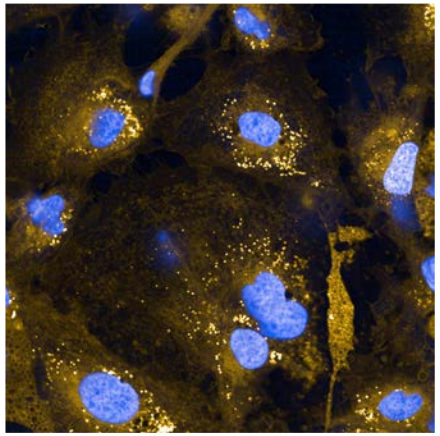
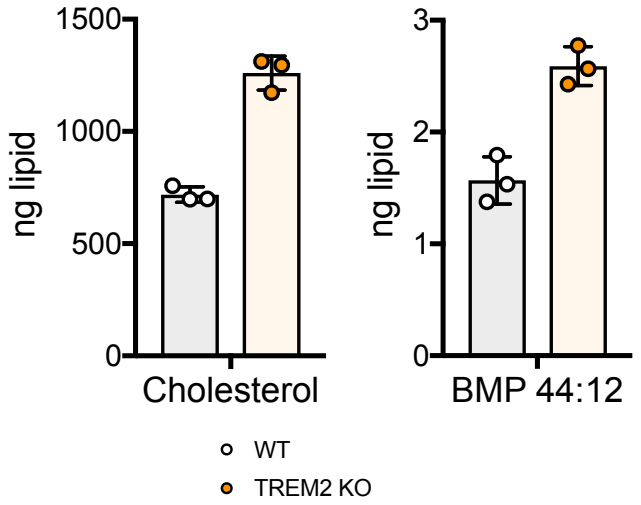


TREM2 KO



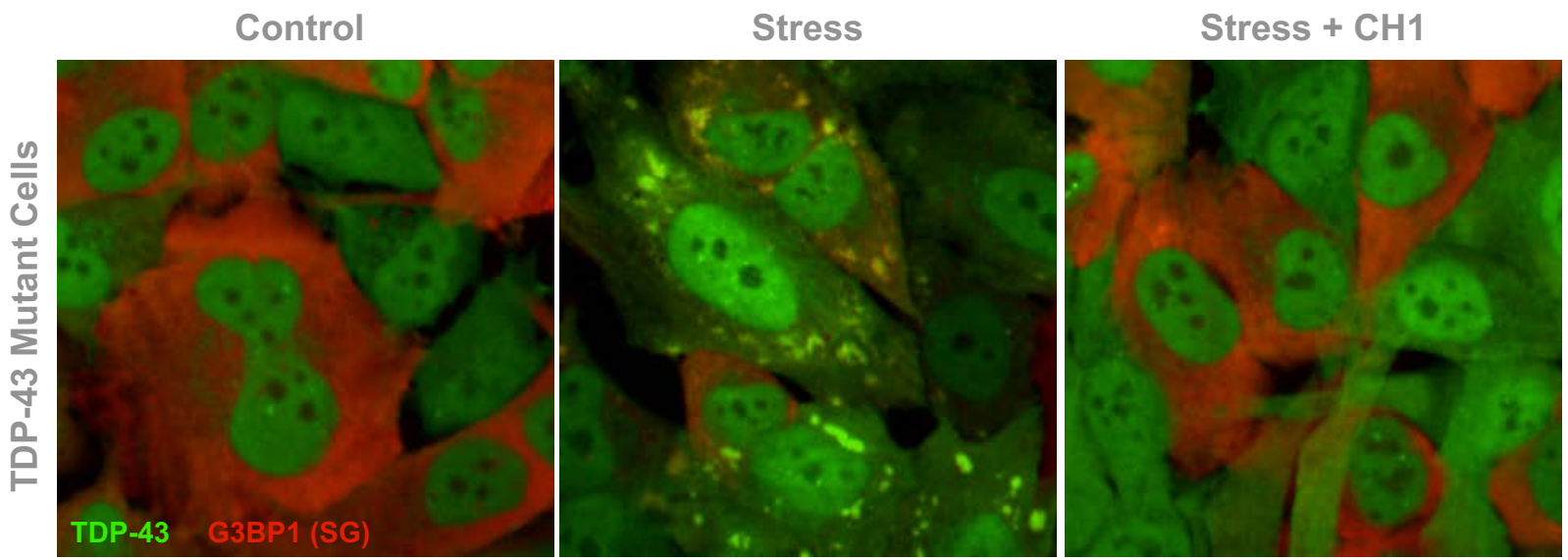
Lipid levels of myelin-treated iPSC microglia

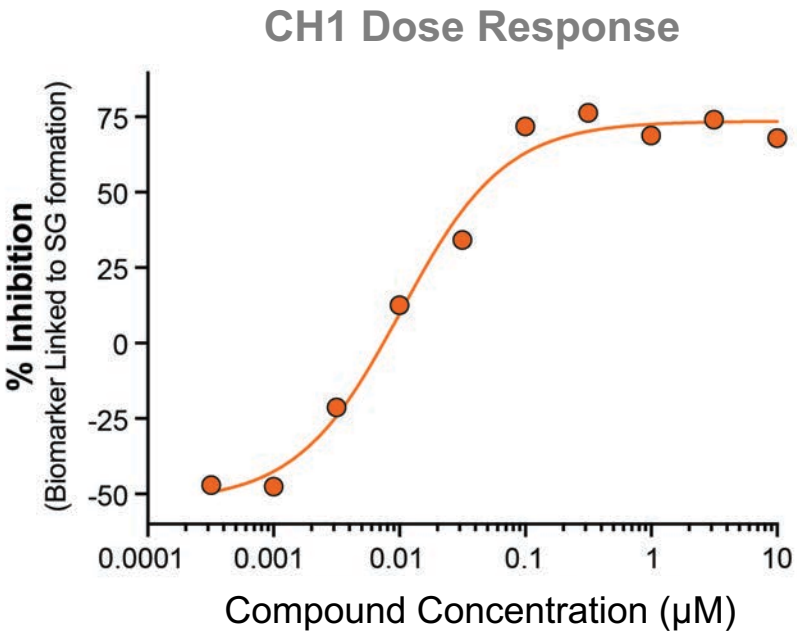


- TREM2 loss-of-function mutations linked to Alzheimer's disease
- Induction of lysosomal genes in microglia is TREM2 dependent
- TREM2 KO microglia have lipid storage defects
- GOAL: ATV:TREM2 agonist antibodies to improve brain uptake (ATV), activate TREM2, and reverse defects to treat disease

CELLULAR HOMEOSTASIS REVERSAL OF TDP-43 INCLUSIONS

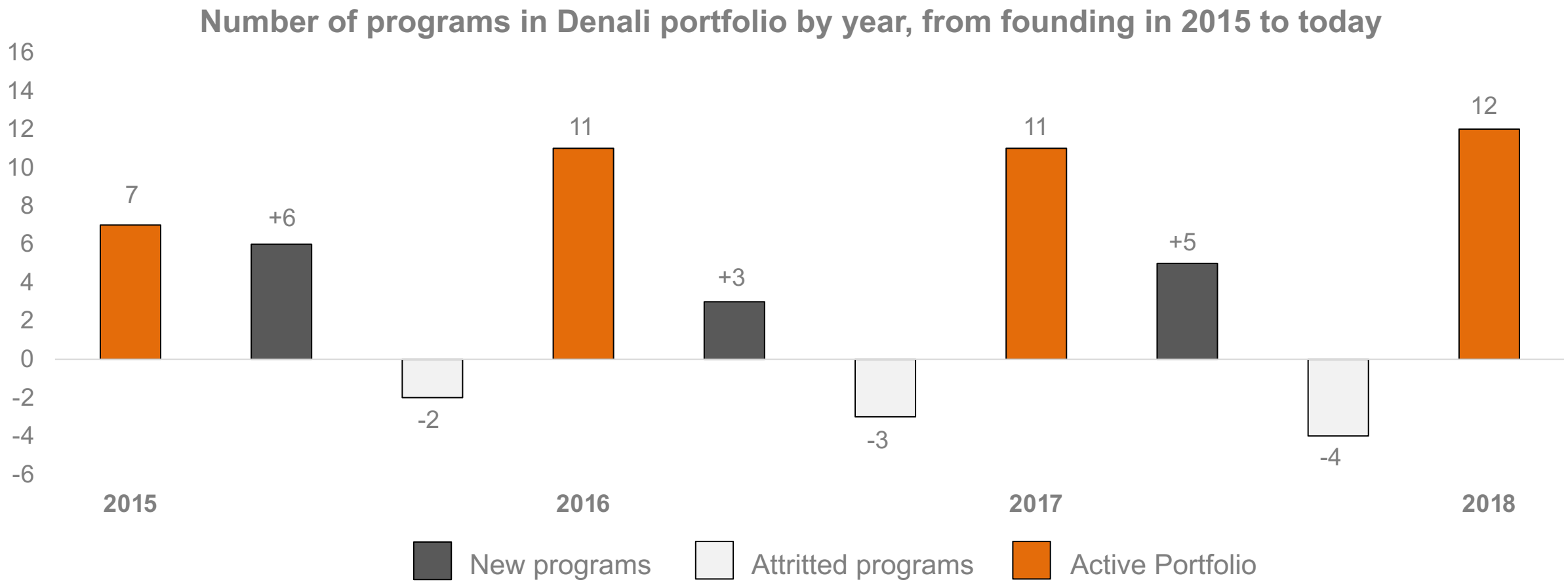
Denali small molecule stress granule modulator CH1 reverses TDP-43 inclusions





- TDP-43 pathology is present in ~97% of ALS patients
- Mutations in TDP-43 and other RNA-binding proteins can cause ALS
- TDP-43 inclusions are also found in 50% of FTD and 30% of Alzheimer's disease
- **Small molecule on track to file IND in next 12-18 months**

BUILDING AND DELIVERING ON A BROAD AND DYNAMIC PORTFOLIO



BROAD TARGET DISCOVERY AND VALIDATION EFFORT AND RIGOROUS EARLY ATTRITION

DENALI PORTFOLIO

BIOMARKER ENABLED
P = Preclinical
C = Clinical

Large Molecule (Transport Vehicle) → Small Molecule

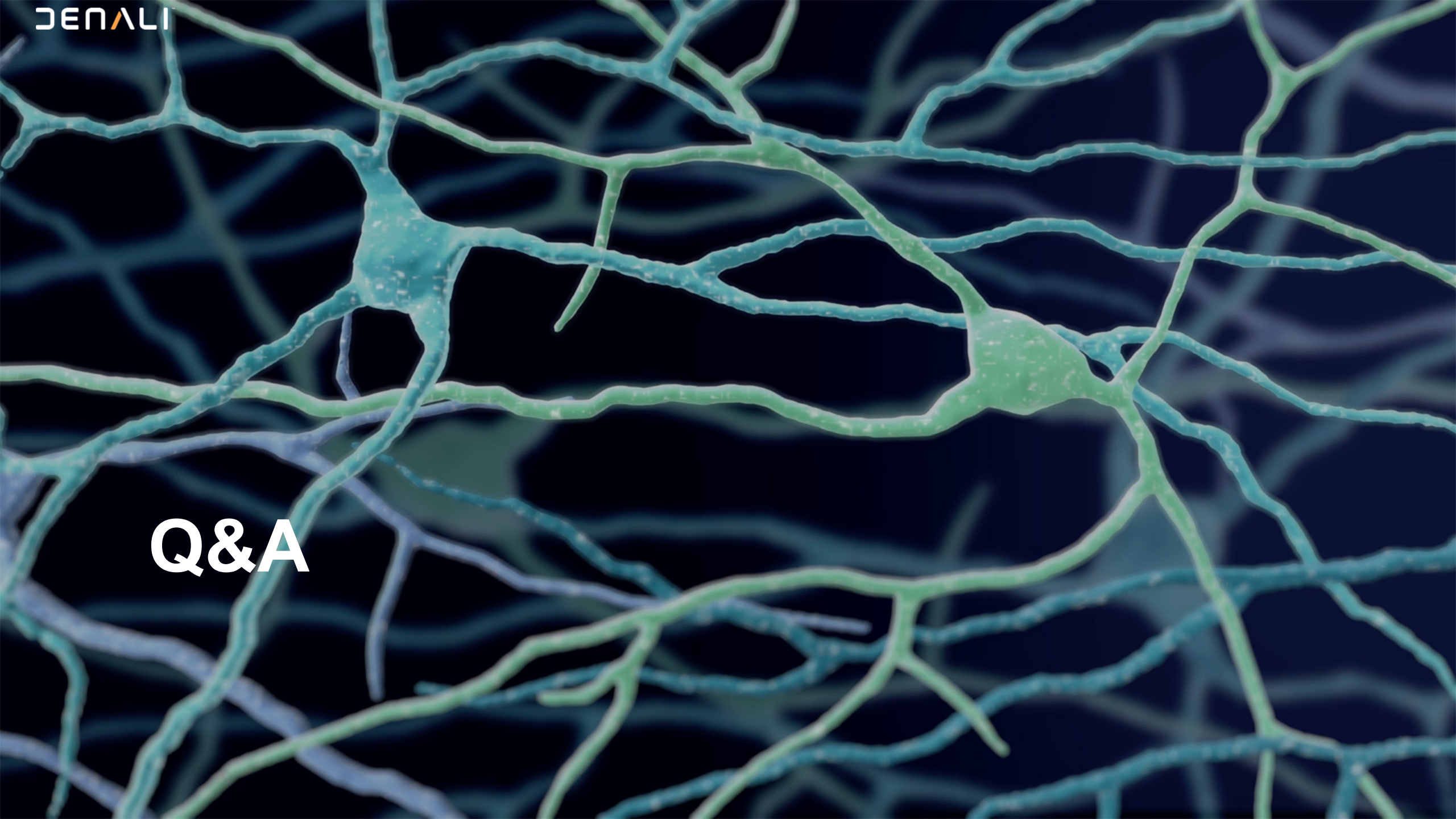
PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT					BIOMARKER ENABLED		PARTNER
			Drug Discovery	IND-Enabling	Early Clinical	Late Clinical	Approved	P	C	
LYSOSOMAL FUNCTION PATHWAY										
LRRK2	DNL201 LEAD	Parkinson's						✓	✓	
	DNL151	Parkinson's						✓	✓	
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)						✓	✓	
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA						✓		
Undisclosed	LF1	Neurodegeneration						✓	✓	Takeda
GLIAL BIOLOGY PATHWAY										
RIPK1 (CNS)	DNL747	Alzheimer's, ALS, MS						✓	✓	Sanofi
TREM2	ATV:TREM2	Alzheimer's						✓		Takeda
Undisclosed	GB1	Alzheimer's								
CELLULAR HOMEOSTASIS										
BACE1/Tau	ATV:BACE1/Tau	Alzheimer's						✓	✓	Takeda
Undisclosed	CH1	Neurodegeneration						✓		
Undisclosed	CH2	Alzheimer's, ALS						✓		
Undisclosed	CH3	ALS, Parkinson's								
OTHER										
RIPK1 (Peripheral)	DNL758	RA, Psoriasis						✓	✓	Sanofi
Undisclosed	OT1	Undisclosed						✓	✓	

MAJOR NEAR-TERM PIPELINE MILESTONES

	NEXT 12-18 MONTHS
LRRK2	• **DNL201** Complete Phase 1b biomarker study in LRRK2 and idiopathic PD patients • **DNL151** Complete Phase 1 study in healthy volunteers
RIPK1	• **DNL747** Complete Phase 1b biomarker studies in ALS and AD patients • **DNL747** Initiate Phase 2 study for MS patients
BBB PLATFORM	• **ETV:IDS** Initiate Phase 1 study for Hunter Syndrome • Advance preclinical BBB TV programs towards IND enabling studies

ADVANCE PORTFOLIO AND MAKE RIGOROUS DATA-DRIVEN DECISIONS


THANK YOU


DENALI
Q&A