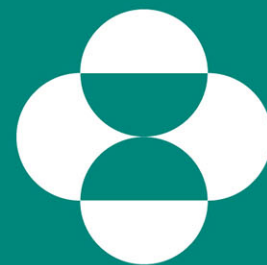


NAVIGATING THE CROSSROADS OF NEUROSCIENCE DRUG DISCOVERY

DARRYLE D. SCHOEPP, PH.D.



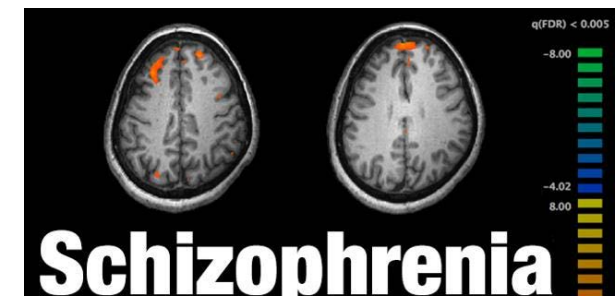
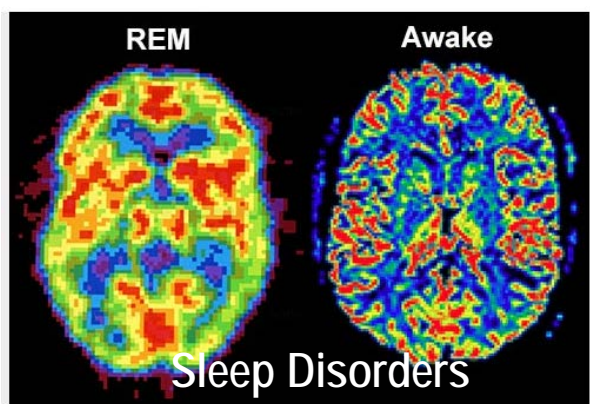
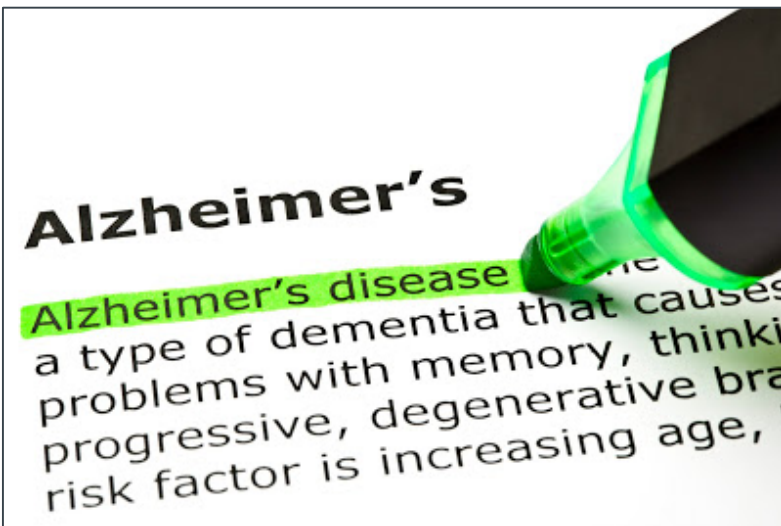
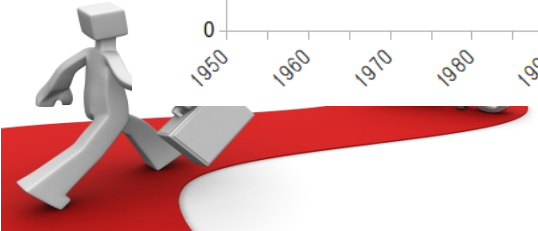
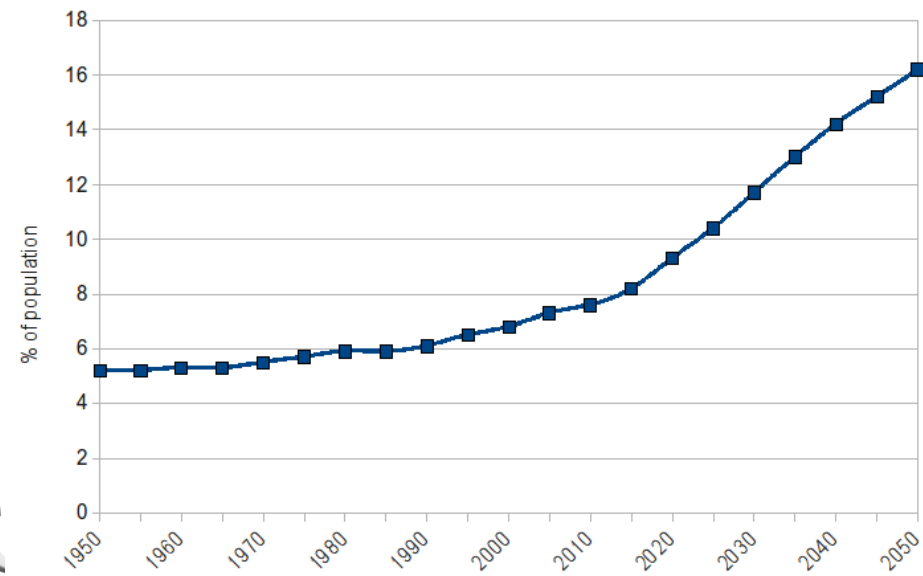
MSD

INVENTING FOR LIFE

AT THE FRONTIERS OF NEUROSCIENCE; SIGNS AND SYMPTOMS
OCTOBER 23TH, 2018

Medical Need in Neuroscience is Still High and is Growing with the Aging Population

Percentage of the World Population Over 65, 1950-2050
Source: UN World Population Prospect, 2008



Delivering Innovation in Neuroscience

Past

Product-focused

Research

- Psychi
- E
- S

- Neu

How are we doing?
What have “we” learned?

Development

- Exten
- exper

- Testing molecules in the clinic (i.e. multiple shots on goal)
- Molecules used to validate animal models

- Candidates competed internally for development

Transform

Refocus Psychiatry

Loadening focus on Neurological Diseases

Partnerships Leverage External Environment

Novel Technologies Increase Productivity

Creative Development Approaches

Future

Customer-centric

- Mono-therapy and augmentation strategies
- Novel mechanisms
- Defined symptom profiles

- Focus on key DAs: Alzheimer's/Parkinson's, Pain
- Target and pathway driven
- Disease modifying and symptomatic treatments

- Partnerships for technology, capacity, or expertise (Industry / Academics / Government)

- Hypothesis-focused testing
- Biomarkers
- Translational models

- Multiple Avenues for compound Development

Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets

What's in our toolbox?



Genetics



Pathophysiology

Pharmacology



Understanding of human disease



New ideas for drug targets

Modify/prevent disease

Restore function

Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets

What's in our toolbox?



Genetics



Pathophysiology

Pharmacology



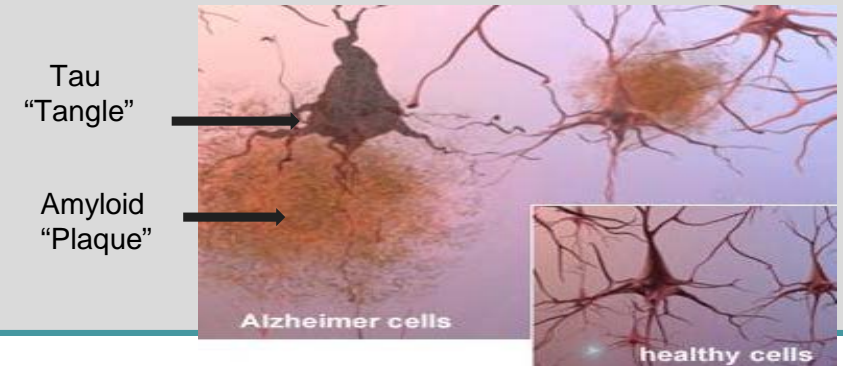
Understanding of human disease



New ideas for drug targets

1. Modify/prevent disease

Example: target pathophysiology



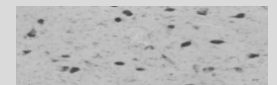
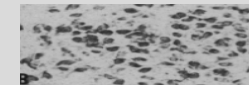
2. Restore function

Example: Restoring acetylcholine signaling

Normal Brain

Alzheimer's Brain

Cholinergic Neurons



Vehicle

Hippocampal Neuron

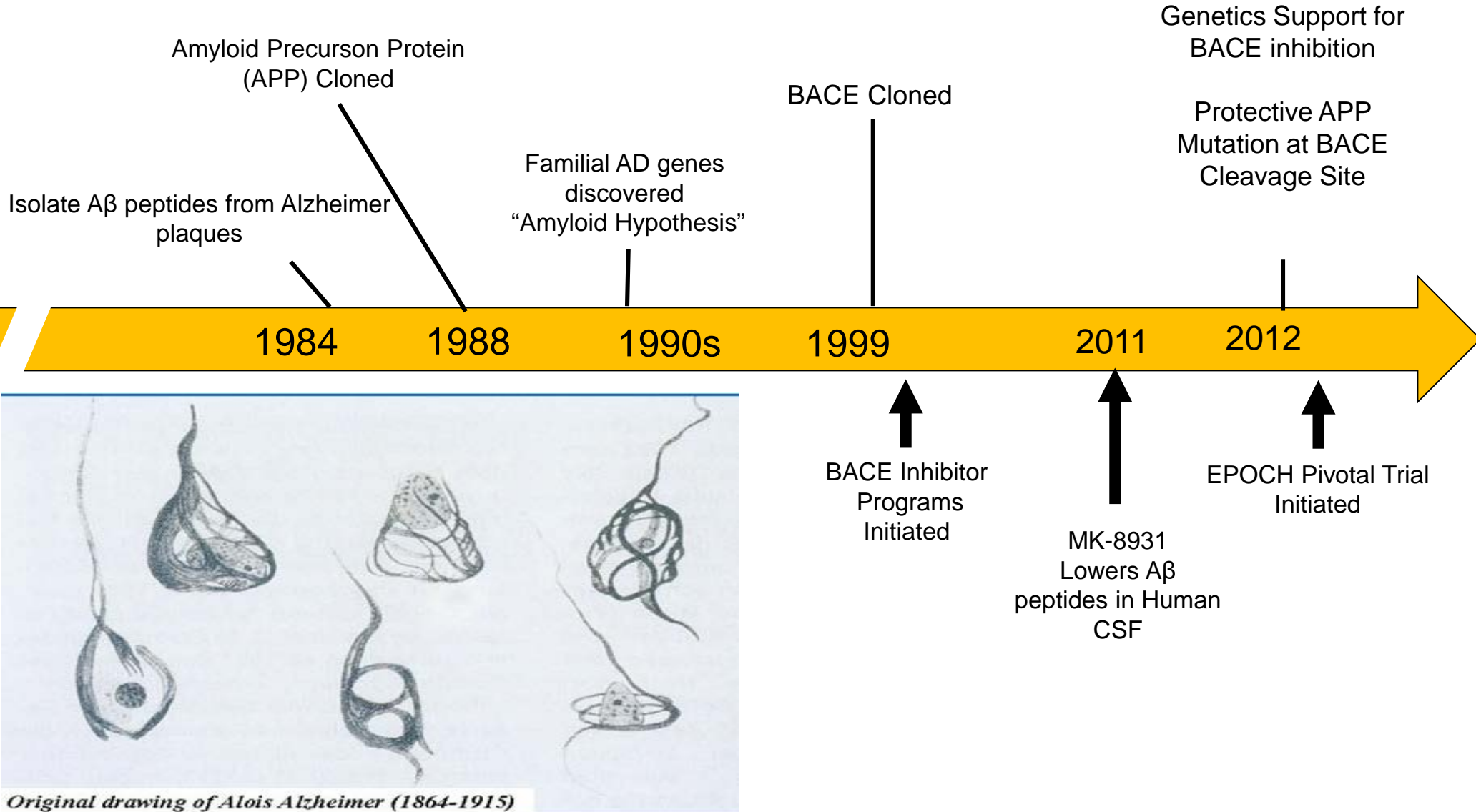
Compound

Receptor PAMs
Nicotinic
Muscarinic

The BACE Inhibitor (MK-8931) Will Test the Leading Alzheimer's Hypothesis



Figure 3: Auguste D
Photograph dated November, 1902.



Clinical Doses of MK-8931 (Verubestat) Have a Major Impact on CSF / Brain A β

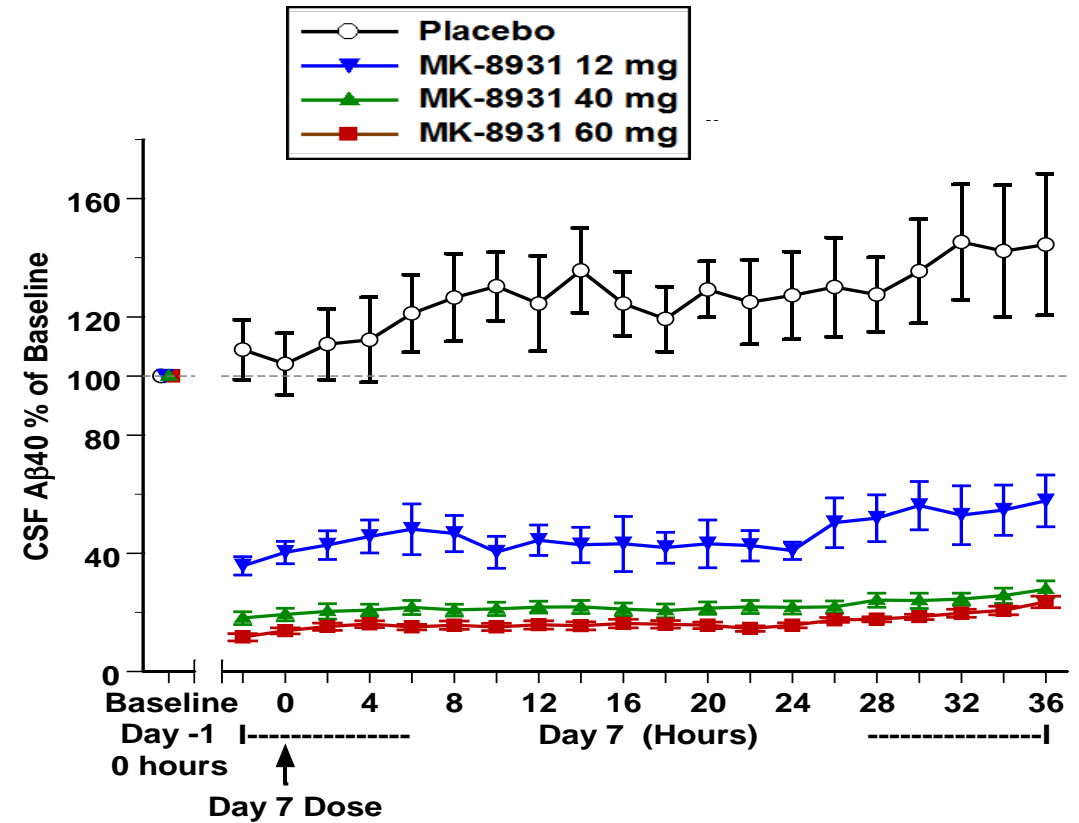
Merck Is Proud to Announce the Approved
Generic Name for Its Investigational
BACE Inhibitor MK-8931...



Verubecestat

Clinical trials for this investigational drug are underway.

MK-8931 AD Subjects



Co-primary endpoints: change from baseline (model-based mean \pm SE)

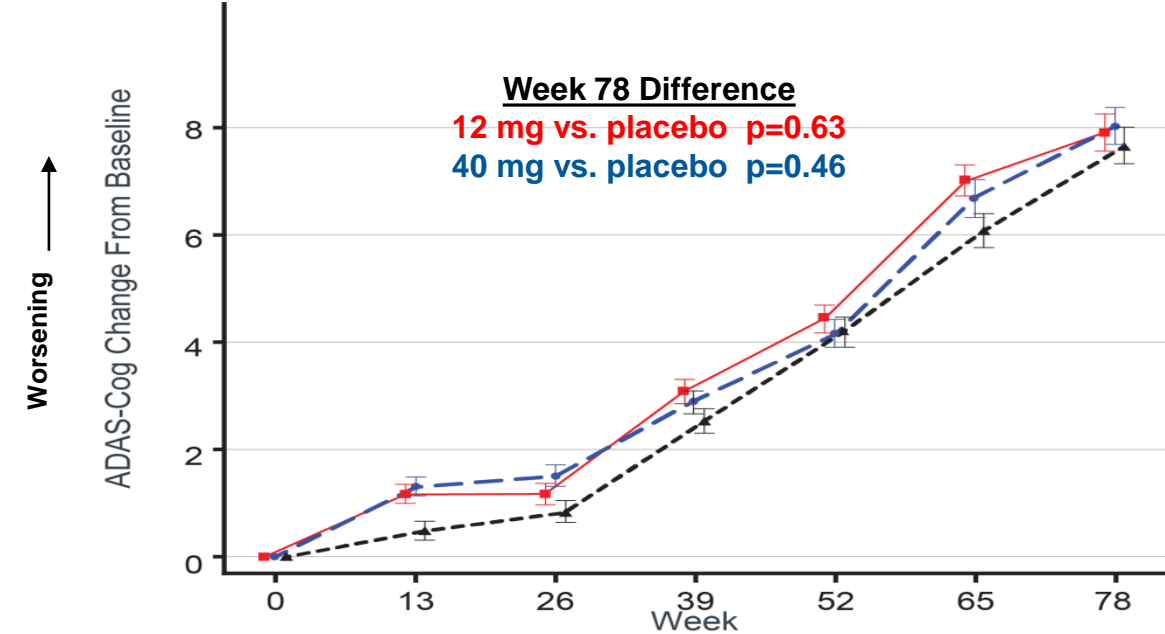
ADAS-Cog11

Treatment (observed baseline mean \pm SD)

12 mg (21.3 \pm 7.5)

40 mg (21.4 \pm 7.6)

Placebo (21.7 \pm 7.6)



Count Table

12 mg	629	619	607	577	559	519	448
40 mg	621	616	591	565	545	519	432
Placebo	639	628	616	597	576	539	463

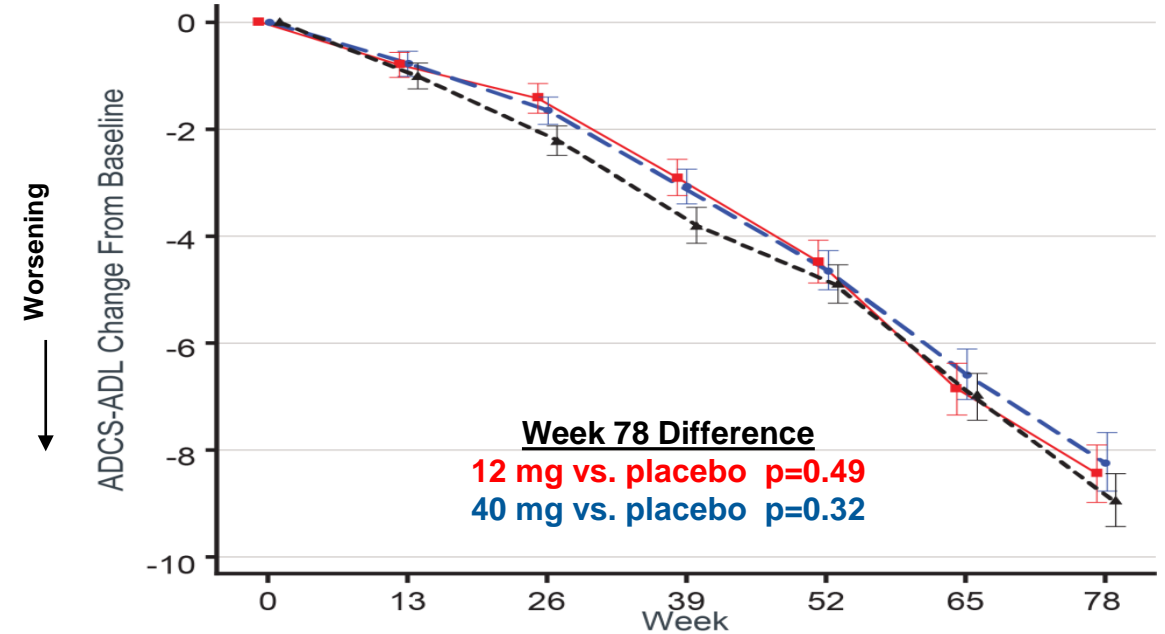
ADCS-ADL

Treatment (observed baseline mean \pm SD)

12 mg (63.1 \pm 9.4)

40 mg (62.9 \pm 9.9)

Placebo (62.1 \pm 10.5)



625	605	601	572	557	517	443
617	601	584	561	541	521	436
631	606	608	593	570	531	453

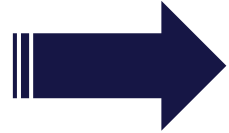
Jun 2018 - Early termination (futility) - Lanabecestat (BACE inhibitor; Prodromal/Mild AD; AMARANTH and DAYBREAK)
May 2018 – Liver tox (safety) - Atabecestat (BACE inhibitor; Subjects at risk of AD; EARLY)
Apr 2018 – Did not meet primary endpoint – Azeliragon (RAGE inhibitor; Mild AD; STEAFast)
Feb 2018 - Early termination (futility) - Verubecestat (BACE inhibitor; Prodromal AD; APECS)
Jan 2018 - Early termination (futility) – Pioglitazone (PPAR γ agonist; onset to MCI; TOMORROW)
Feb 2017 - Early termination (futility) - Verubecestat (BACE inhibitor; Mild to Moderate AD; EPOCH)
Jan 2017 - Terminated early - Solanezumab (Abeta antibody; prodromal AD; EXP-PRO)
Nov 2016 - Failed – Solanezumab (Abeta antibody; mild AD; EXP-III)

Alzheimer's Drug Trials Keep Failing -- It May Be Because We Don't Understand the Disease

The theory of what causes the disease and how it develops may be wrong.

Using Human Genetics to Shape Therapeutic Approaches?

Understanding of human disease



Alzheimer's Disease

APP (amyloid precursor protein)

PSEN1/2 (presenilin 1 & 2)

APOE4 (apolipoprotein E)

APP BACE cleavage site

TREM2 (Triggering receptor expressed on myeloid cells 2)



Genetics

Important to also understand the biology of the gene linked to the disease

Using Human Genetics to Shape Therapeutic Approaches and Select the Best Drug Targets

Understanding of human disease



How are we doing?
What have “we” learned?

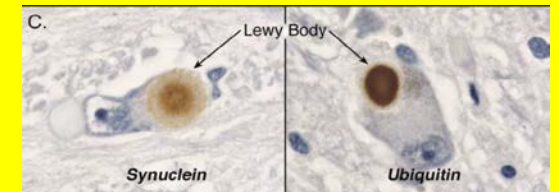


Alzheimer's Disease

APP (amyloid precursor protein)
PSEN1/2 (presenilin 1 & 2)
APOE4 (apolipoprotein E)
APP BACE cleavage site
TREM2 (Triggering receptor expressed on myeloid cells 2)

Parkinson's Disease

SNCA (alpha synuclein)
GBA (glucocerebrosidase)
LRRK2 (Leucine Rich Repeat Kinase 2)



Amyotrophic Lateral Sclerosis (ALS)

SOD1 (superoxide dismutase 1)
TDP43 Protein (TAR DNA-binding protein 43)
C9orf72 (chromosome 9 open reading frame 72)



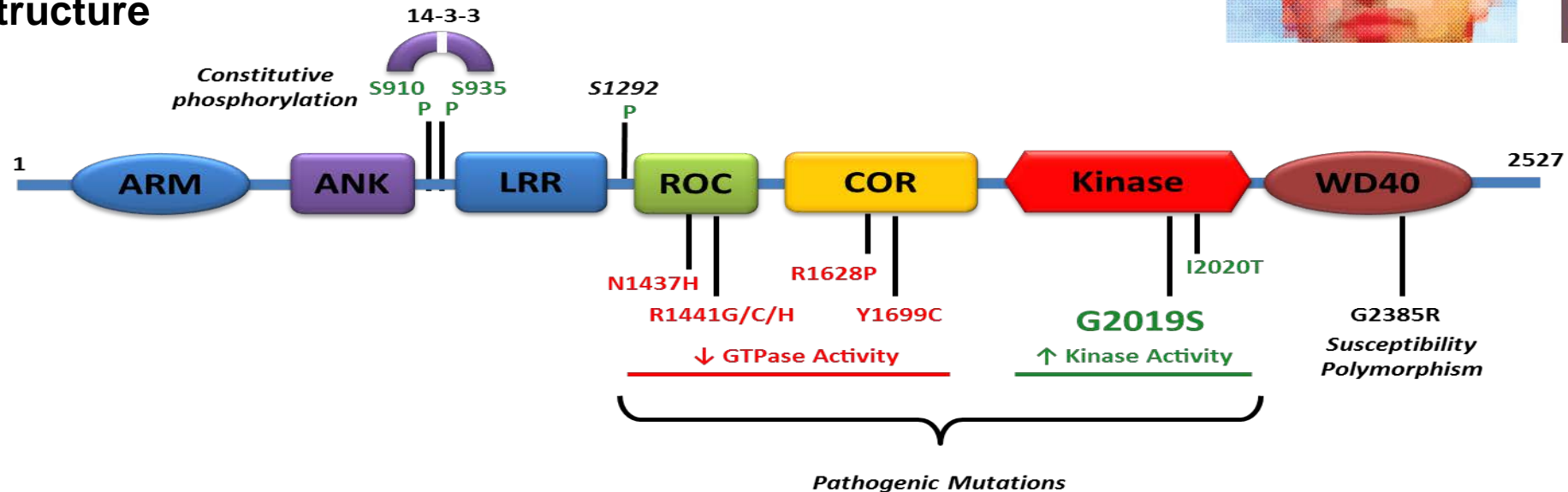
Genetics

LRRK2 kinase inhibition as a genetically supported target for disease modification in Parkinson's disease

Leucine Rich Repeat Kinase 2 (LRRK2)

- LRRK2 (PARK8) mutations are **the most common autosomal dominant cause** of PD
 - 5–13% of familial PD, 1–3% of idiopathic PD
 - Disease penetrance: 59 yrs (28%), 69 yrs (51%), and 79 yrs (74%)
- LRRK2 driven PD is clinically and pathologically indistinguishable from idiopathic PD
- Mutations in or near the “enzymatic core” – **pathogenic gain-of-function**

LRRK2 Structure

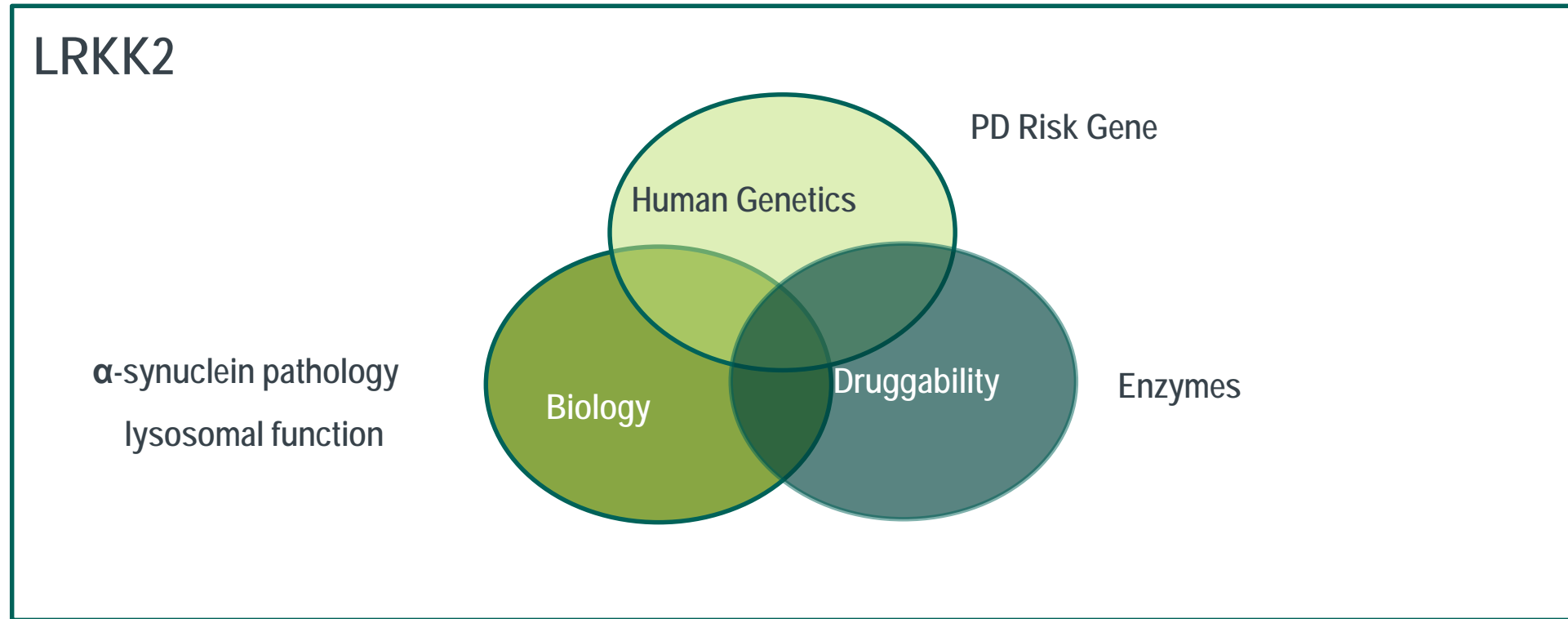


THOMAS GOETZ 06.22.10 12:00 PM
**SERGEY BRIN'S SEARCH FOR A
PARKINSON'S CURE**

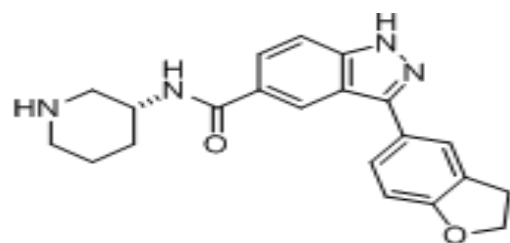


Inhibition of LRRK2 kinase activity represents a tractable and novel therapeutic target to modify the progression of Parkinson's disease

Using Human Biology to Shape Therapeutic Approaches and Select the Best Drug Targets



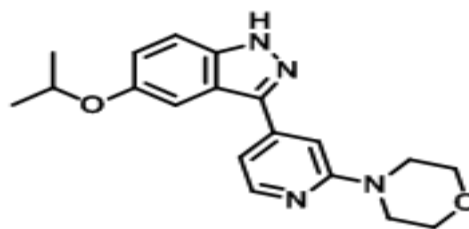
Discovery of a novel, potent and selective LRRK2 kinase inhibitor series (Indazole Core)



Exemplar HTS Hit

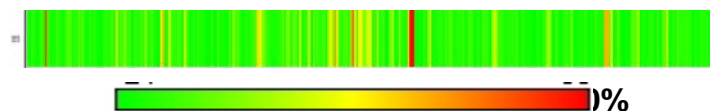
LRRK2 IC₅₀: 27 nM
Cell LRRK2 pS935 IC₅₀: N.D.

Truncation
Optimization

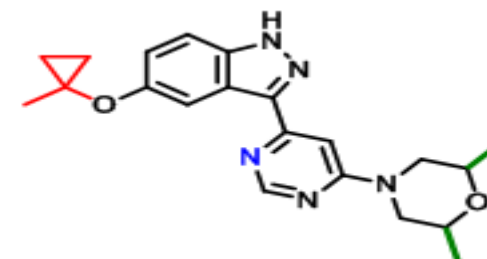


Compound A

LRRK2 IC₅₀: 2 nM
Cell LRRK2 pS935 IC₅₀: 22–64 nM

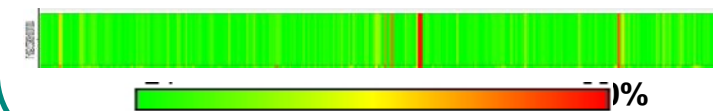


Stability
Bioavailability
Potency
Selectivity



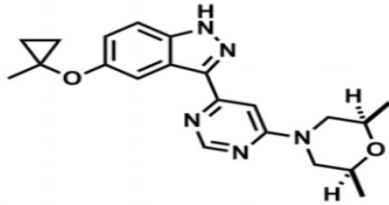
MLi-2

LRRK2 IC₅₀: 1 nM
Cell LRRK2 pS935 IC₅₀: 4 nM



Optimization of LRRK2 kinase inhibitor hit identifies MLi-2 as a highly potent and selective inhibitor of LRRK2

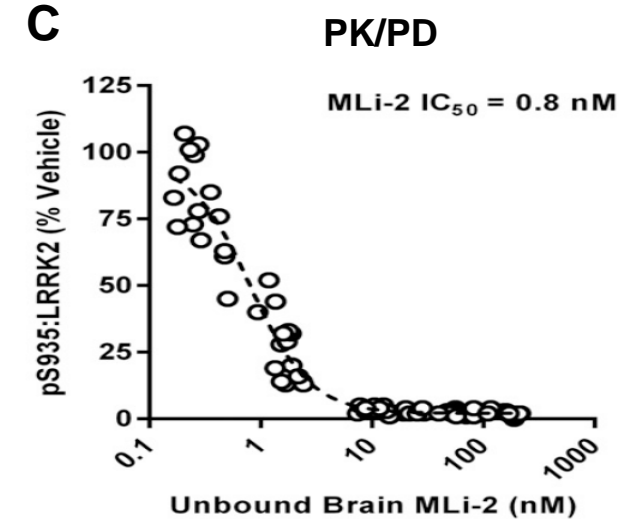
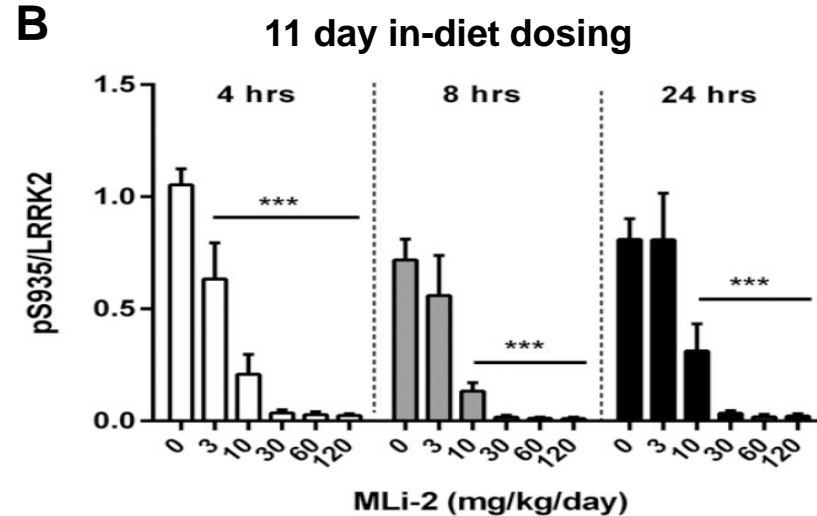
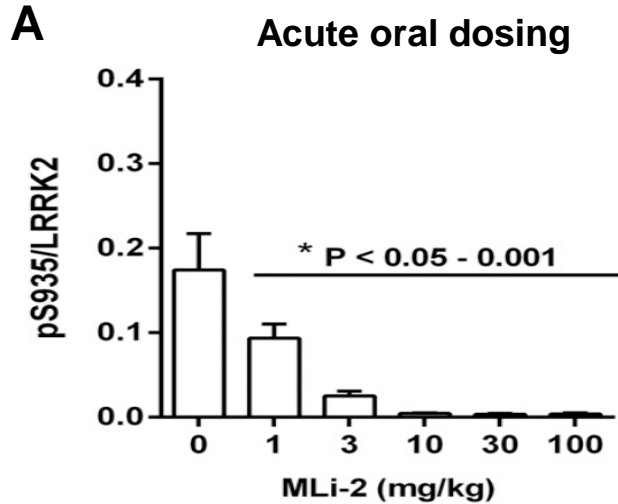
Pharmacological characterization of the novel, potent and selective LRRK2 kinase inhibitor MLi-2



Fell et al., (2015)
J. Pharmacol. Exp. Ther. 355,
397– 409

MLi-2

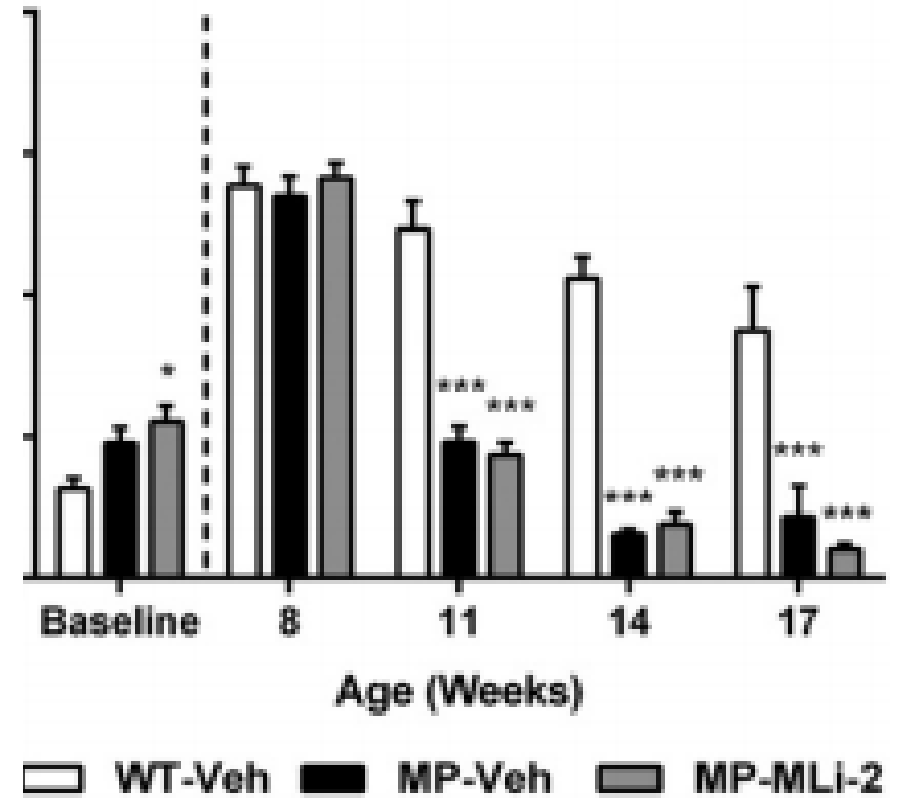
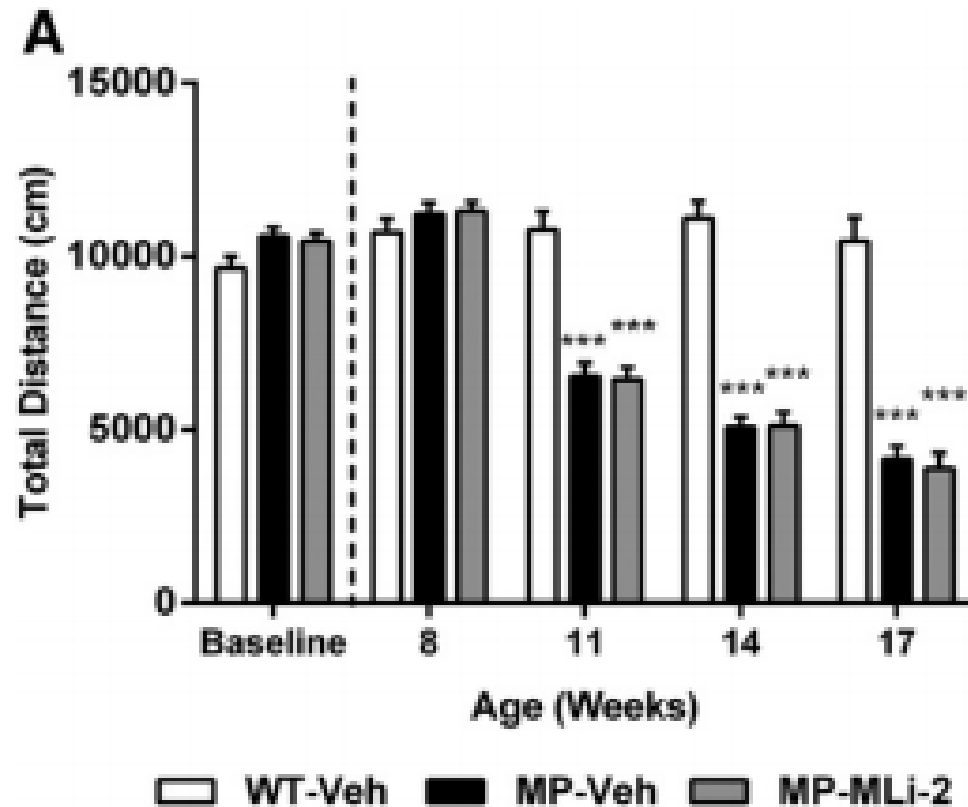
- Potent inhibitor of LRRK2 kinase activity in vivo
- In vivo brain (mouse) pSer935 IC₅₀ = **0.8 nM**
- Well tolerated in mice after chronic dosing with >95% CNS target engagement



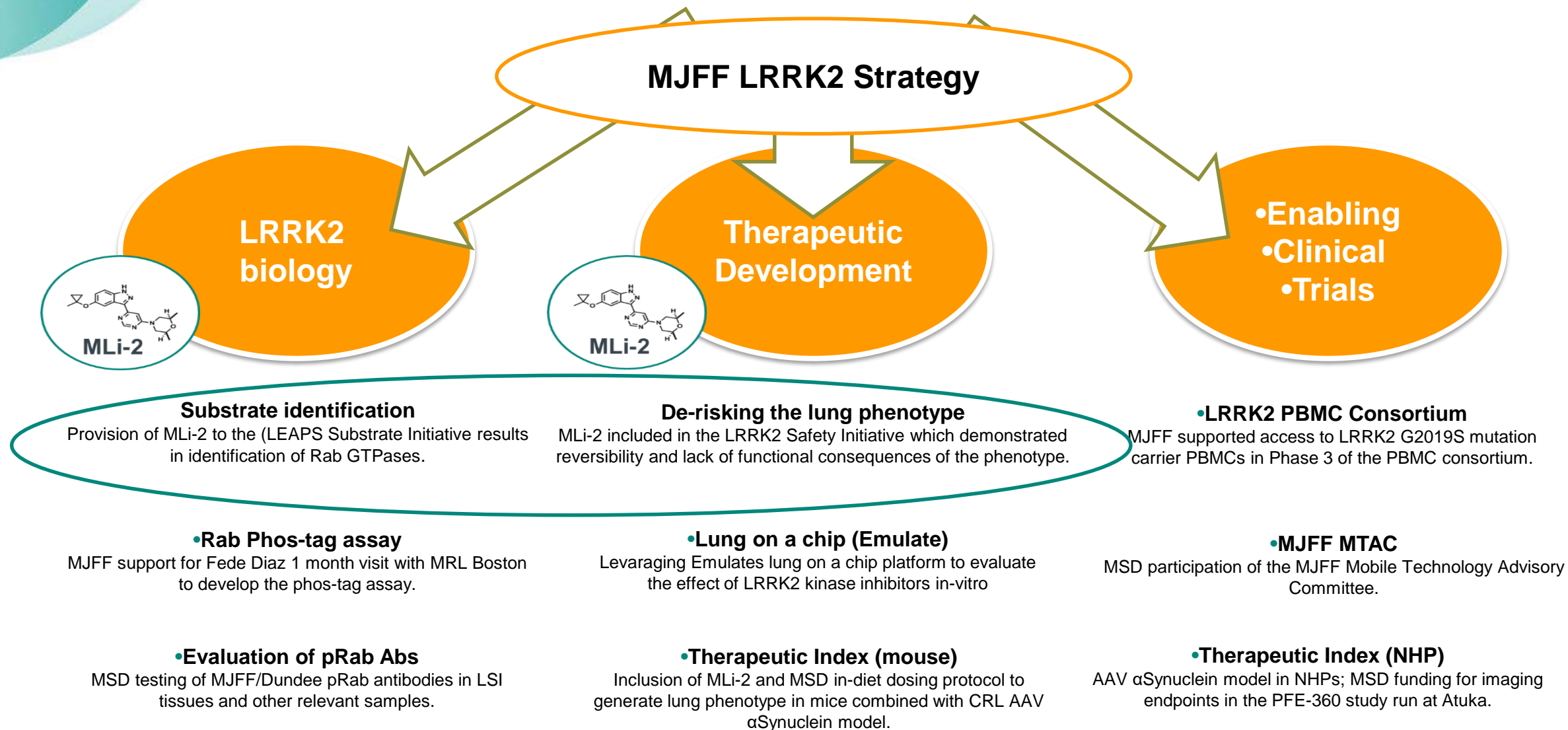
MLi-2 is an excellent molecule to probe the biology of LRRK2 kinase inhibition in vivo

Chronic in-diet dosing of Mli-2 does not attenuate the behavioral phenotype of the MitoPark mouse

Fell et al (2015) JPET 355: 397 – 409.

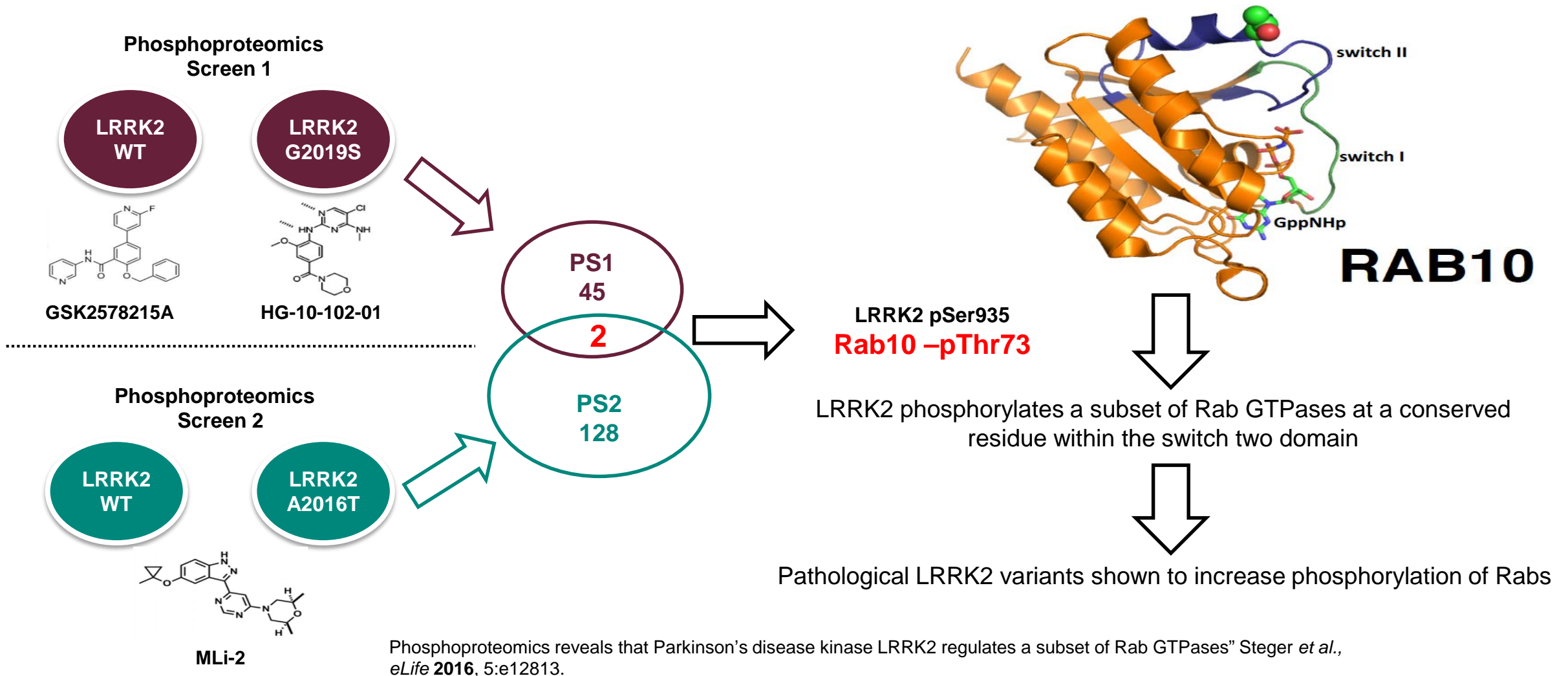


Collaboration with the Michael J. Fox Foundation to advance LRRK2 kinase inhibitors for PD: Areas of focus



Sharing of MLI-2 with MJFF LEAPS initiative enables identification of bona fide LRRK2 substrates

MJFF Linked Efforts to Accelerate Parkinson's Solutions (LEAPS)



Functional interplay between Rab GTPases and several Parkinson's factors

Neuron
Article

Neuron. 2013 Feb 6;77(3):425-39



***RAB7L1* Interacts with *LRRK2* to Modify Intraneuronal Protein Sorting and Parkinson's Disease Risk**

Am J Hum Genet. 2014 Dec 4;95(6):729-35

REPORT

Mutations in *RAB39B* Cause X-Linked Intellectual Disability and Early-Onset Parkinson Disease with α -Synuclein Pathology

Science 2006 July 21; 313 (5785):324-8

α -Synuclein Blocks ER-Golgi Traffic and Rab1 Rescues Neuron Loss in Parkinson's Models

Proc Natl Acad Sci. 2008 Jan 8;105(1):145-50

The Parkinson's disease protein α -synuclein disrupts cellular Rab homeostasis

Publ EMBO J. 2015 Nov 12;34(22):2840-61

Resource

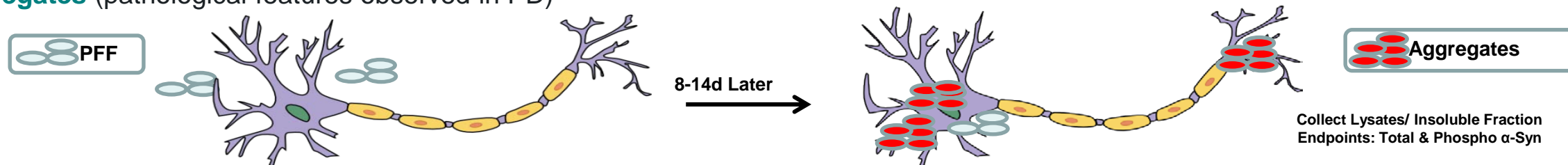


THE
EMBO
JOURNAL

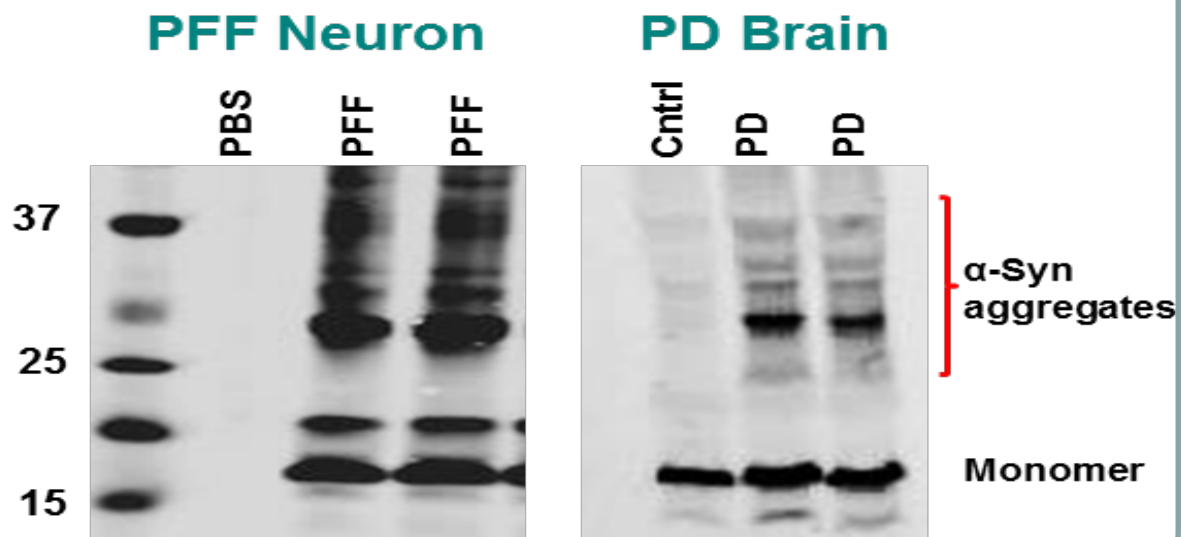
Phosphoproteomic screening identifies Rab GTPases as novel downstream targets of PINK1

Using an In Vitro α -Synuclein Preformed Fibrils (PFF) Model

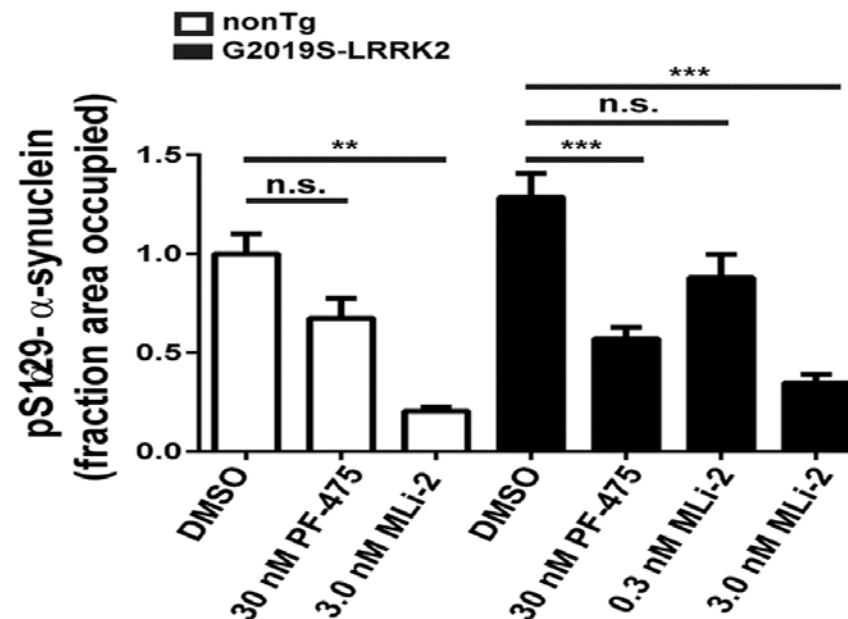
Model: Recombinant α -Syn preformed fibrils (PFFs) seed recruitment of endogenous α -Syn into **insoluble, phosphorylated α -Syn aggregates** (pathological features observed in PD)



α -Syn in Neurons vs. PD Brain



LRRK2 Inhibitors Reduce PFF Formation



Volpicelli-Daley et al. Neuron 2011

Business

Parkinson's Study Dims Ambitions for Gene Flaw Carried by Brin

by Caroline Chen

February 4, 2015, 2:00 PM EST

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Organs

Two of Roche Holding AG's experimental drugs for Parkinson's disease caused lung toxicity in monkeys, researchers said, delivering a setback to one of the most promising pathways to a new type of treatment.

Marco A. S. Baptista¹*, Kuldip D. Dave¹, Mark A. Frasier¹, Todd B. Sherer¹, Melanie Greeley², Melissa J. Beck², Julie S. Varsho², George A. Parker², Cindy Moore², Madeline J. Churchill³, Charles K. Meshul³, Brian K. Fiske¹

Herzig et al., 2011

! KO



Pharmacological inhibition of LRRK2 induces a lung phenotype in NHPs

RESEARCH ARTICLE

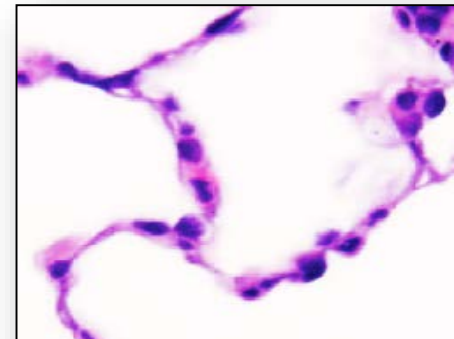
DRUG DISCOVERY

Effect of selective LRRK2 kinase inhibition on nonhuman primate lung

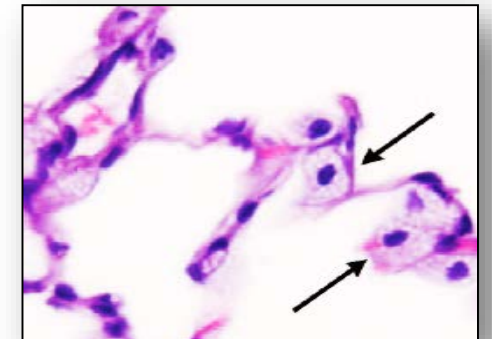
Reina N. Fuji,^{1*} Michael Flagella,¹ Miriam Baca,² Marco A. S. Baptista,³ Jens Brodbeck,¹ Bryan K. Chan,⁴ Brian K. Fiske,² Lee Honigberg,⁵ Adrian M. Jubb,² Paula Katavolos,¹ Donna W. Lee,¹ Sock-Cheng Lewin-Koh,⁶ Tori Lin,¹ Xingrong Liu,⁷ Shannon Liu,¹ Joseph P. Lyssikatos,⁴ Jennifer O'Mahony,¹ Mike Reichelt,² Merone Roose-Girma,⁸ Zejuan Sheng,⁹ Todd Sherer,³ Ashley Smith,⁵ Margaret Solon,² Zachary K. Sweeney,⁴ Jacqueline Tarrant,¹ Alison Urkowitz,³ Soren Warming,⁸ Murat Yaylaoglu,² Shuo Zhang,⁹ Haitao Zhu,⁹ Anthony A. Estrada,⁴ Ryan J. Watts^{9*}



Vehicle



GNE-7915



Fuji et al., 2015

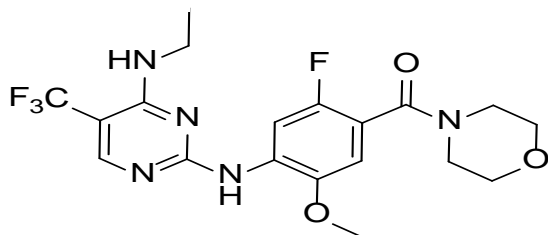
MJFF LRRK2 Safety Initiative (LSI)

Pre-competitive risk sharing to interrogate lung effects of LRRK2 kinase inhibitors

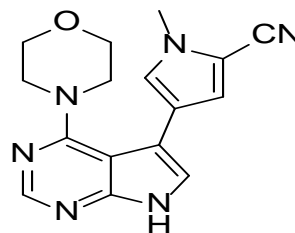


MJFF established an unprecedented collaboration of major drug makers willing to collaborate to address key questions about the safety of LRRK2 kinase inhibitors

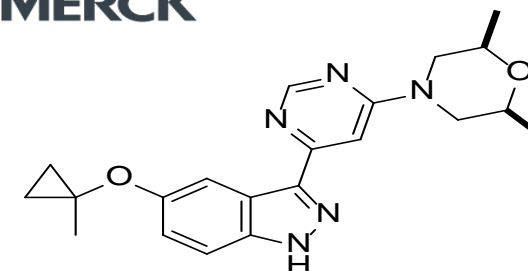
Genentech
A Member of the Roche Group



GNE-7915
pS935 *in vivo* IC₅₀
unbound brain = 97 nM



PFE-360
pS935 *in vivo* IC₅₀
unbound brain = 3 nM

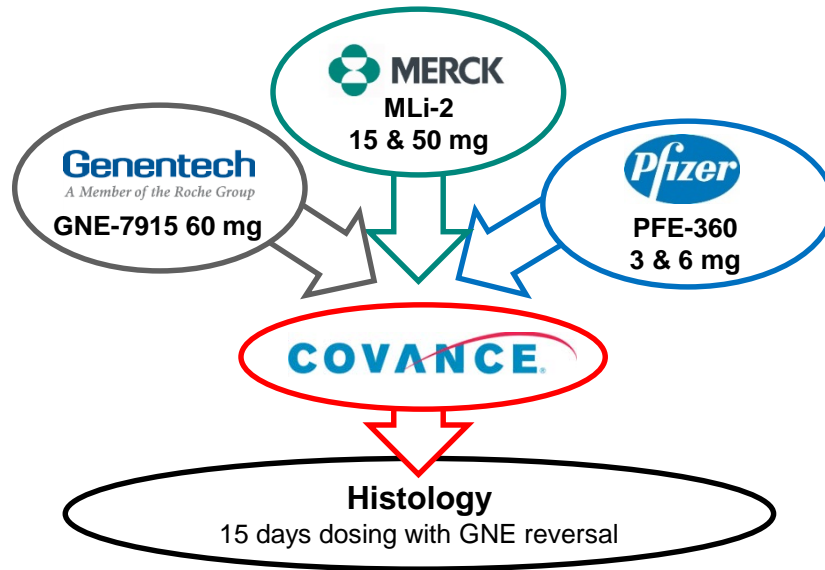


MLi-2
pS935 *in vivo* IC₅₀
unbound brain = 0.8 nM

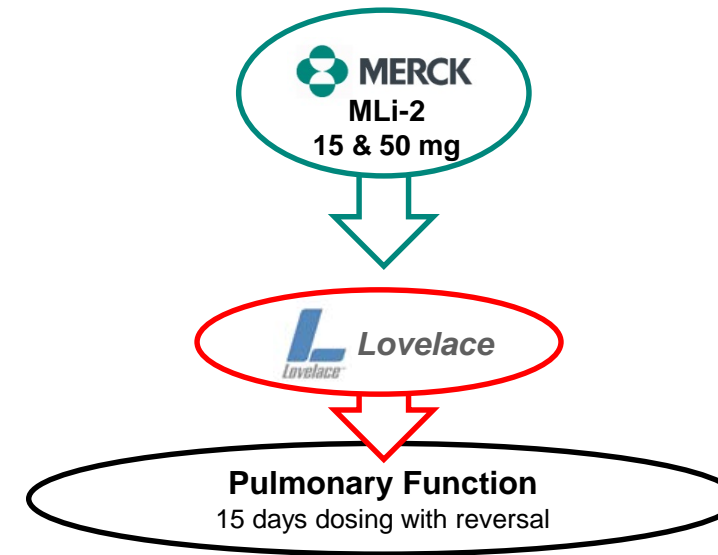
Different structural classes of inhibitors with different off-target kinase profiles

MJFF LRRK2 Safety Initiative (LSI)

LSI Study 1 – Histology



LSI Study 2 – Pulmonary Function

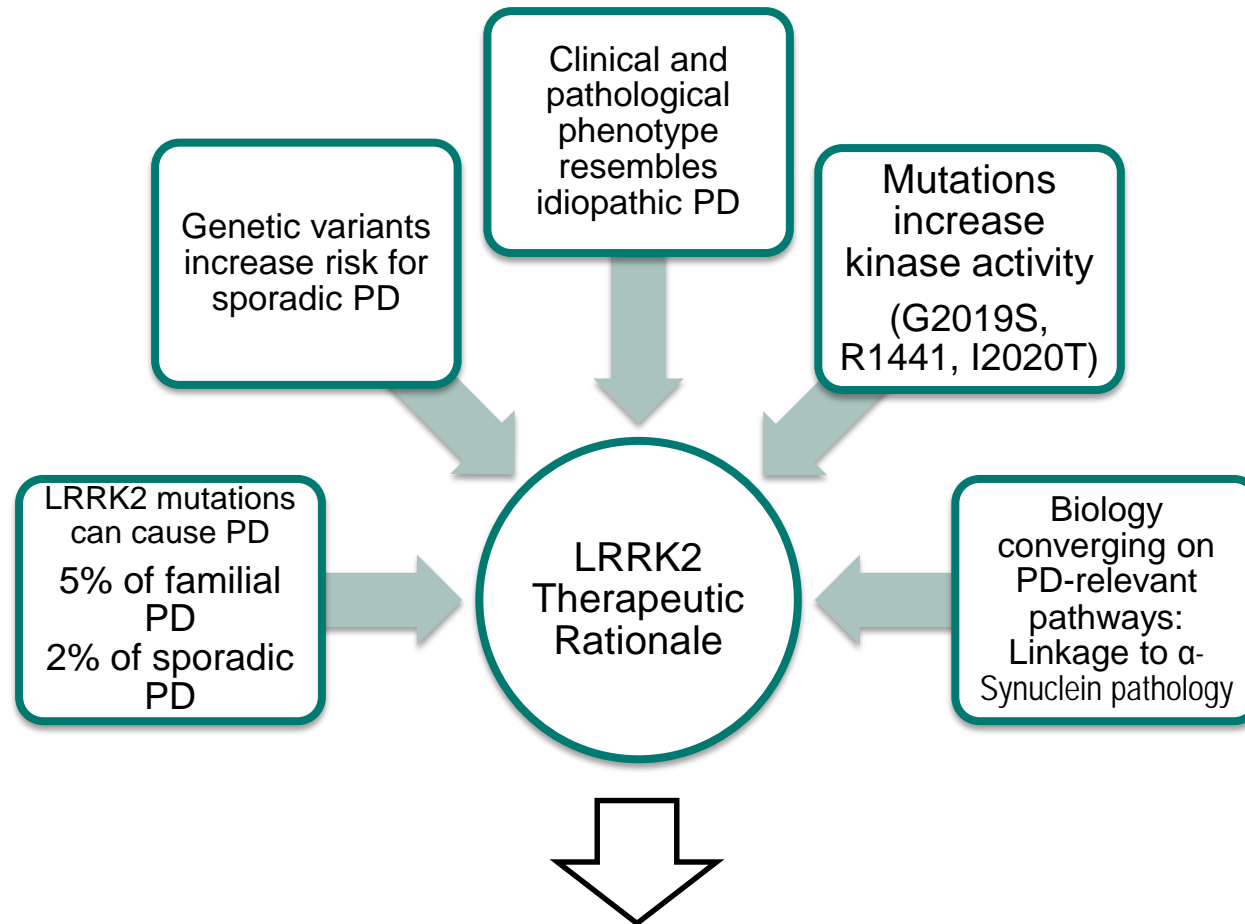


LSI Study highlights

- Mild accumulation of lamellar bodies observed in type II pneumocytes in NHPs; PFE-360 and MLi-2 induced lung histologic effects only at high doses; GNE findings reversible on washout.
- No functionally significant alterations in any pulmonary functional endpoint examined with MLi-2; histology findings were reversible after washout.

Posted online August 15, 2018: doi: <http://dx.doi.org/10.1101/390815>

LRRK2 kinase inhibition as a genetically supported target for disease modification in Parkinson's disease



Inhibition of LRRK2 kinase activity represents a tractable and novel therapeutic target to modify the progression of Parkinson's disease

Acknowledgments

THANK YOU



Special Thanks

- Michael Egan
- Matthew Kennedy
- Matthew Fell
- Sean Smith
- Samer Eid
- BACE TEAM
- LRRK2 TEAM

