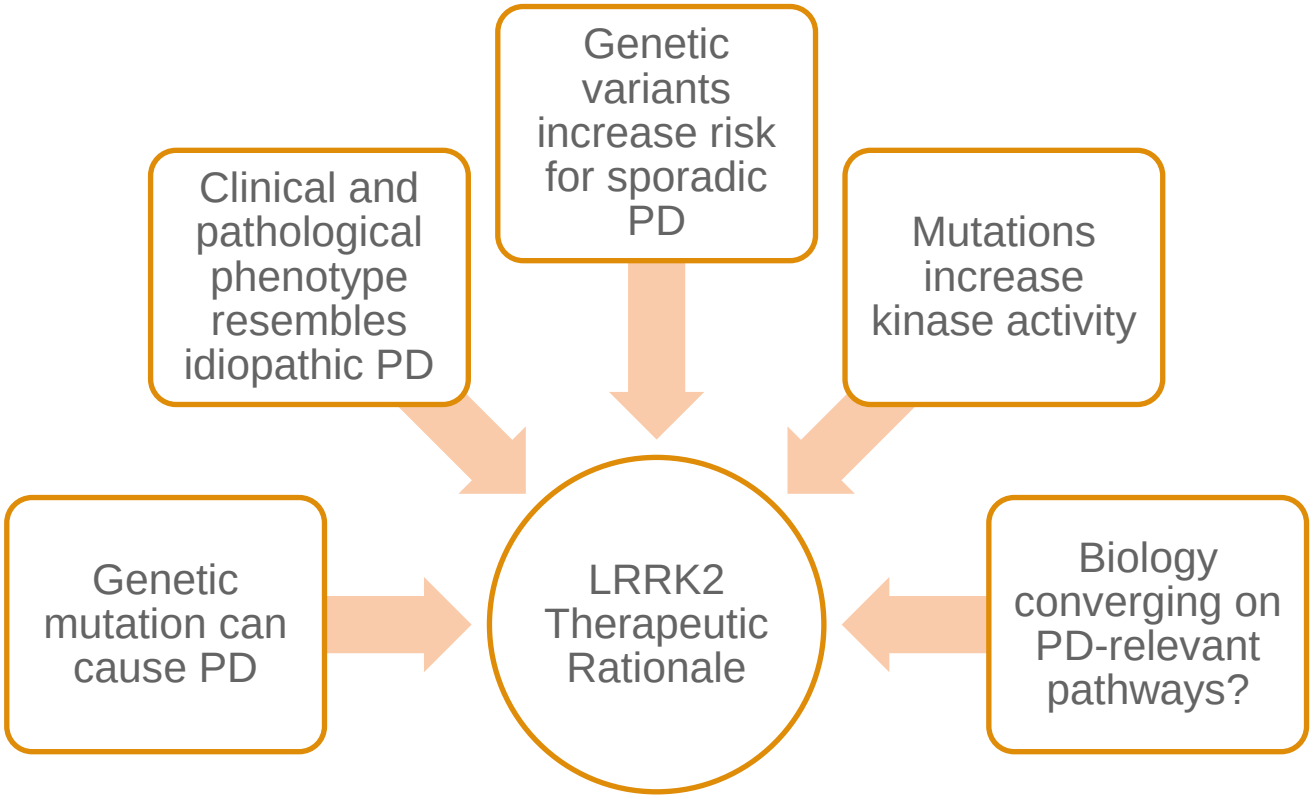
LRRK2 KINASE INHIBITORS: THE PATH TO THE CLINIC

The Michael J. Fox Foundation

PARKINSON'S IS AN INCREASINGLY COMMON BRAIN DISEASE

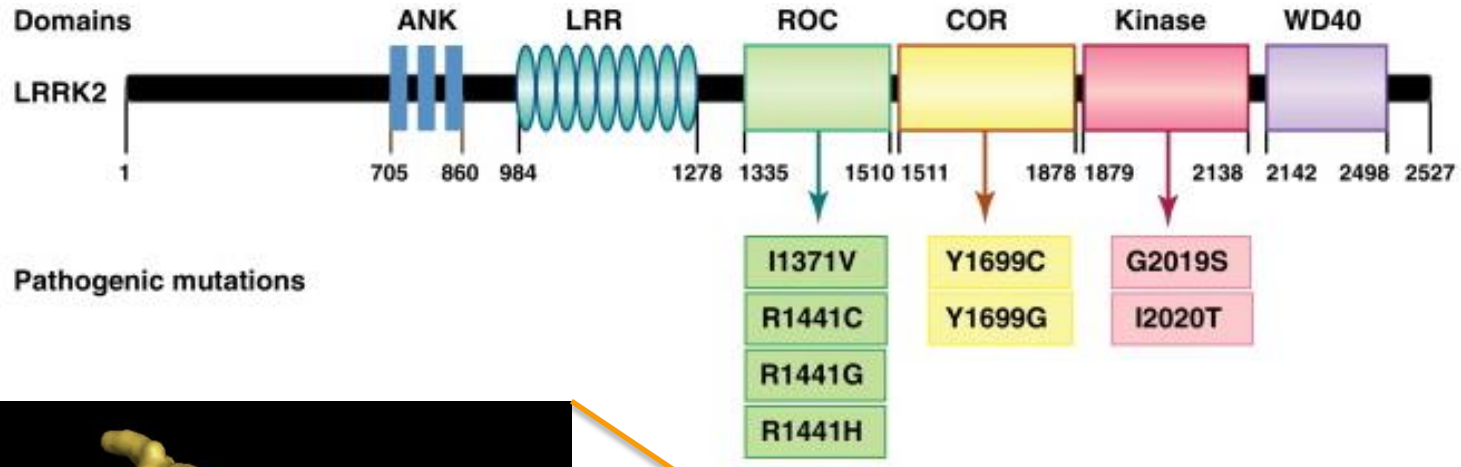
Today one million people in the United States and more than five million worldwide live with Parkinson's. Those numbers will only grow as our population ages.

RATIONALE FOR LRRK2 PARKINSON'S THERAPEUTIC DEVELOPMENT IS STRONG



LRRK2 kinase inhibitors are currently a leading strategy for Parkinson's disease modification among multiple companies and academic centers

KINASES ARE DRUGGABLE!



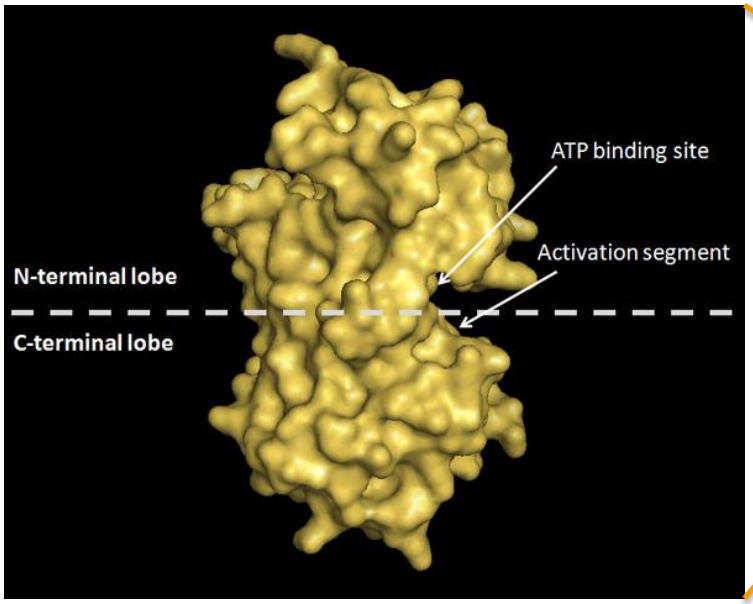
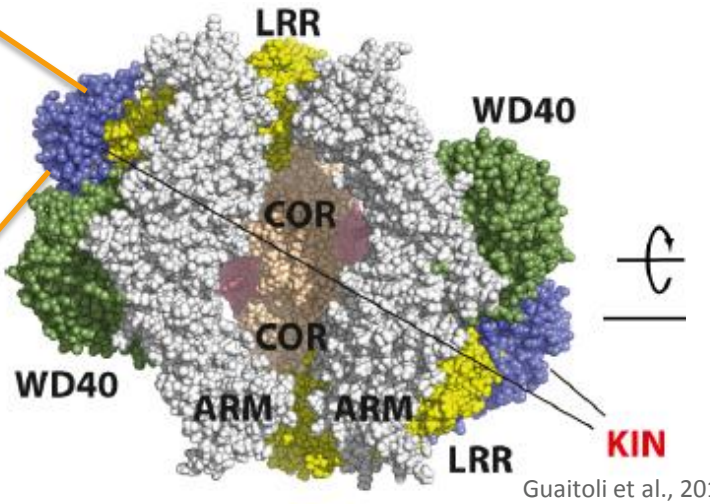


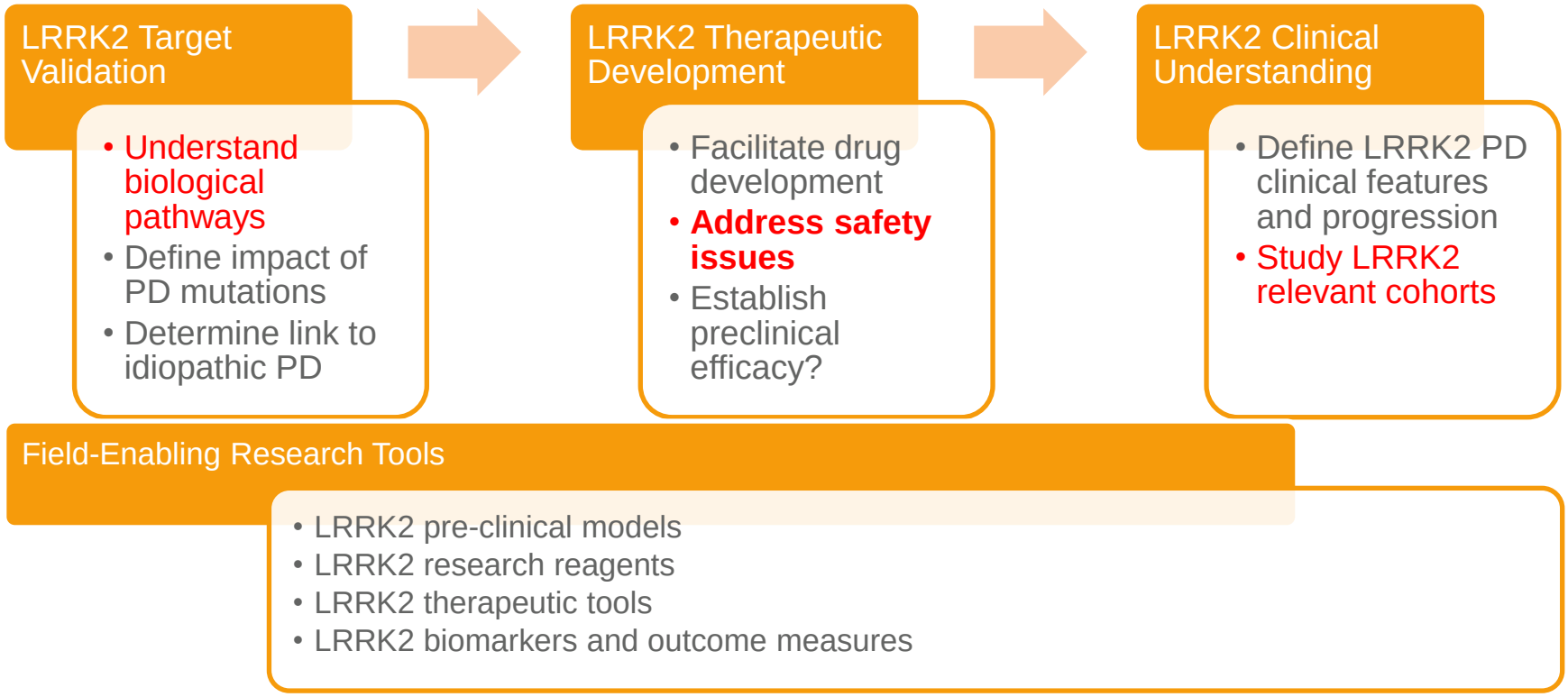
Figure 3; Jeffrey *et al*. 1995

TRENDS in Pharmacological Sciences



Guaitoli et al., 2016 PNAS

MJFF LRRK2 STRATEGY



MJFF has made significant investments in translating LRRK2 into therapies for Parkinson's patients

LRRK2 SUBSTRATE IDENTIFICATION

LRRK2 SUBSTRATE (RAB10) DISCOVERED!

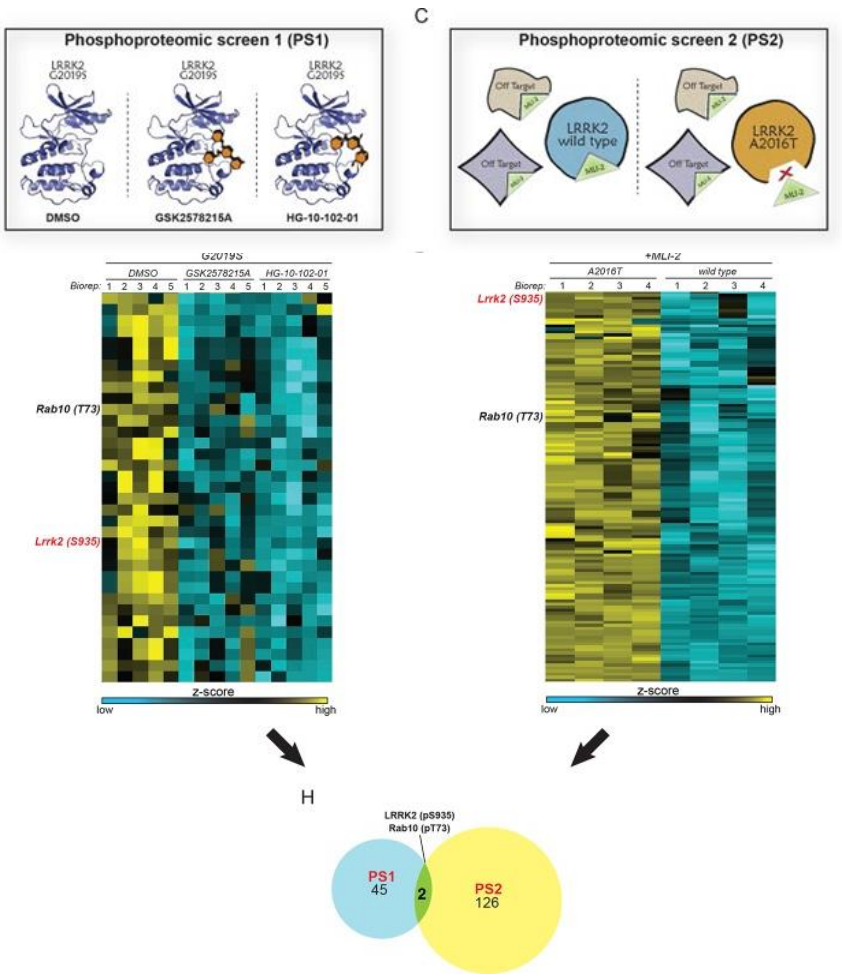
GlaxoSmithKline

MERCK

UNIVERSITY OF DUNDEE

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

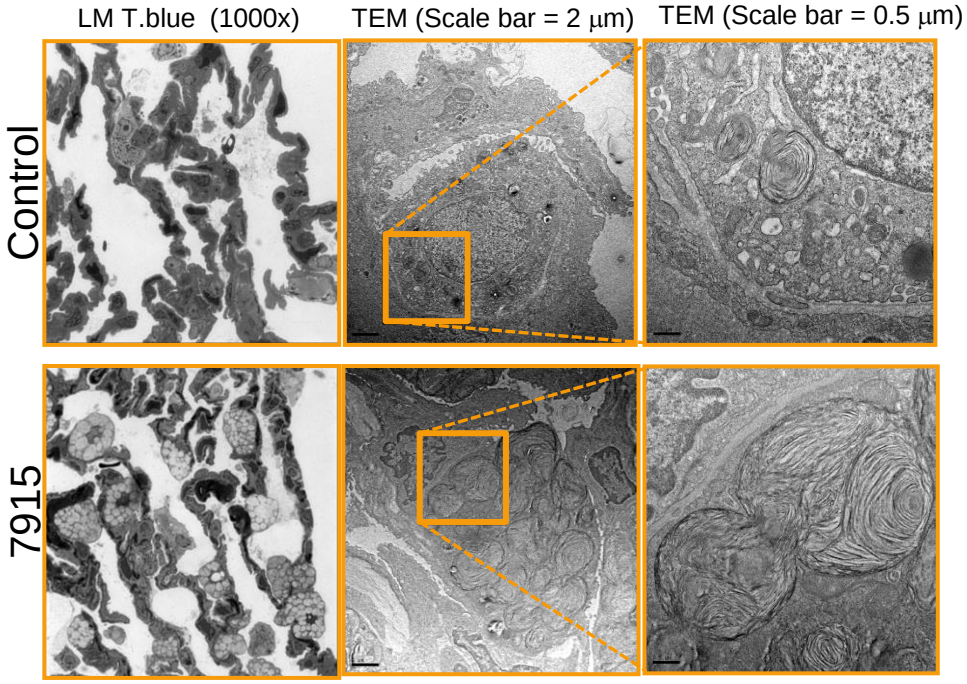
MAX-PLANCK-GESELLSCHAFT

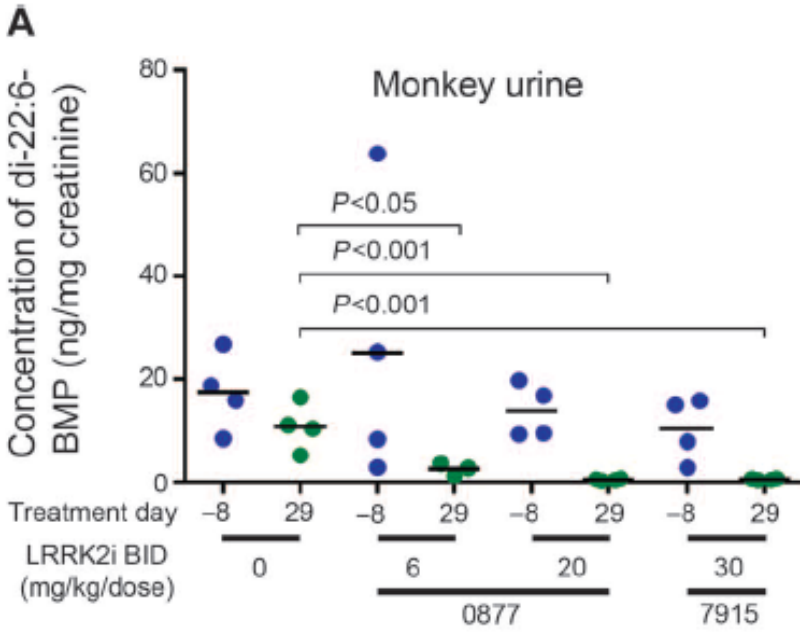


Steger et al, Elife, 2016

LRRK2 SAFETY INITIATIVE

GNE7915 Induces Abnormal Accumulation of Lamellar Bodies in NHP Type II Pneumocytes and Reduces Urine di-22:6-BMP



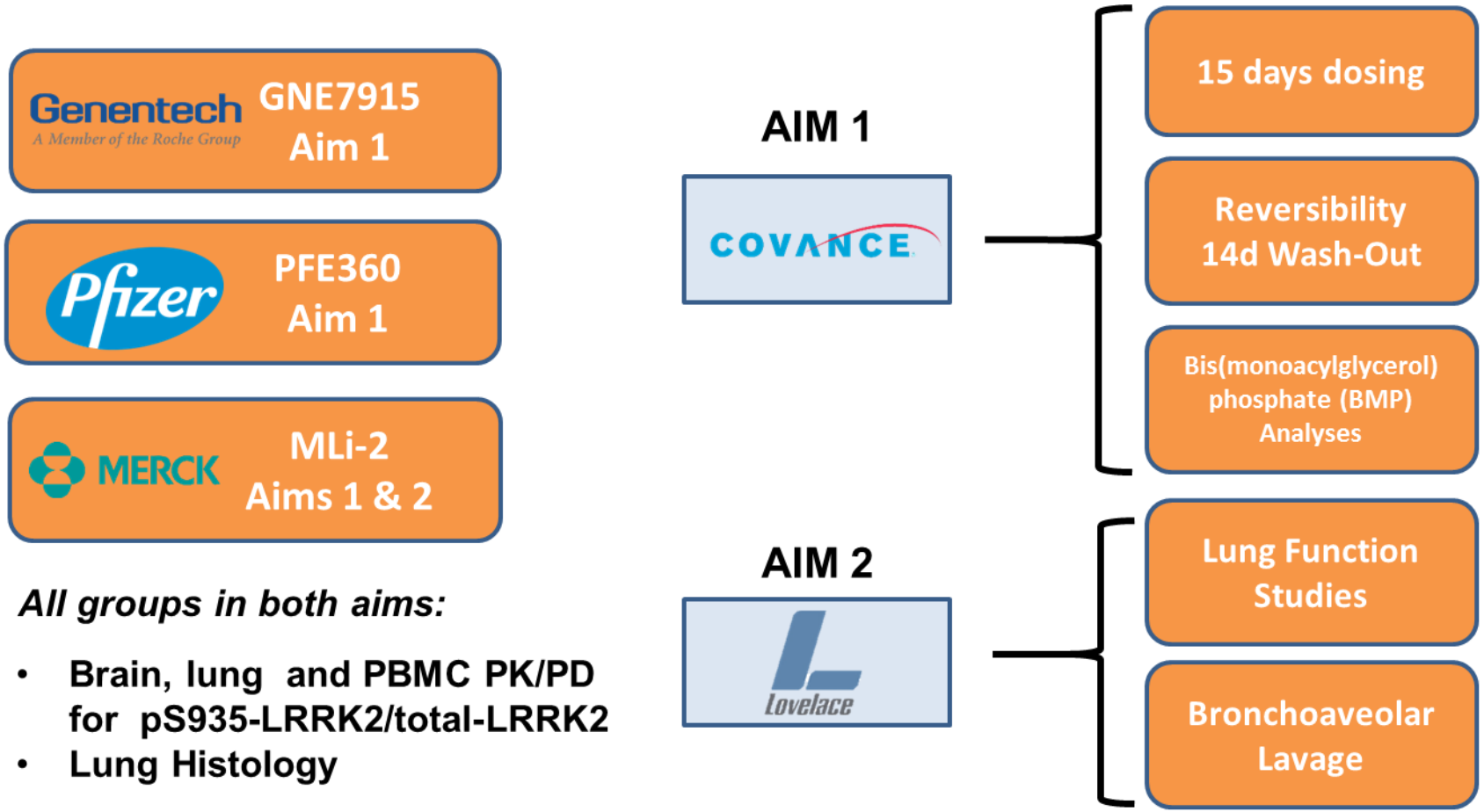


Science Translational Medicine AAAS

Fuji et al., 2015

Pulmonary abnormality resembles the phenotype of LRRK2 KO rodents, suggesting this is LRRK2-mediated rather than an off-target effect.

LRRK2 SAFETY INITIATIVE WORK FLOW



All groups in both aims:

- **Brain, lung and PBMC PK/PD for pS935-LRRK2/total-LRRK2**
- **Lung Histology**

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

AIM2: PULMONARY FUNCTIONAL STUDY WITH MLI-2 LRRK2 KINASE INHIBITOR

Baseline
- Baseline PFT
- Initiate drug dosing and blood collection
- Functional Observational Battery (FOB) in home cage and chair restraint

Week 1
- Day 7 PFT
- Continue drug dosing and blood collection
- FOB in home cage and chair restraint

Week 2
- Day 15 PFT
- Euthanize animals (4/group) for postmortem analyses
- FOB in home cage and chair restraint

Week 4
- Day 28 PFT
- Euthanize animals (4/group) for postmortem analyses
- Remaining animals available for additional studies

- Pulmonary Function Testing (PFT)
  - Lung diffusion capacity for carbon monoxide (DLCO)
  - Quasi-static lung compliance (Cqs10)
  - Forced vital capacity (FVC)
- Bronchoaveolar Lavage
  - Surfactant

LRRK2 SAFETY SUMMARY

- Three distinct LRRK2 kinase inhibitors produced the previously reported lung histopathology (mild accumulation of lamellar bodies in type II pneumocytes) in NHPs - confirming an on-target lung effect.
    - No morphologic effects were seen with any LRRK2 inhibitor in brain or kidney.
    - GNE7915 effects on lung were **reversed** after 14d washout.
- Other LRRK2 kinase inhibitors induced lung histologic effects **only at high doses**, despite both low and high dose groups substantially decreasing LRRK2 activity by an pS935 PK/PD readout.
- MLi-2 effects on lung histology were **not** associated with functionally significant alterations in **any pulmonary functional endpoint** examined.
- Overall, these data suggest that the on target morphological changes observed in the lungs of LRRK2 kinase inhibitor treated NHPs may not prevent the clinical evaluation of the therapeutic potential of LRRK2 kinase inhibitors in PD.

LRRK2 COHORT IDENTIFICATION

OBSERVATIONAL STUDIES OF LRRK2 COHORTS

Cohorts cover a spectrum of characterization

Registry – minimal characterization

- Both virtual and clinic-based registries
  - Limited clinic visits (1-2 years)
  - Virtual self-reported data
- Centrally verified genotype
- Recruitment ongoing

Moderate characterization – biomarker resource

- Leveraging researcher with existing cohorts
- Cross-sectional dataset
- Clinician confirmed diagnosis
- Biospecimen and data available as open resource

Robust characterization

- Intensive longitudinal follow-up
- Biospecimen, imaging, neuropsych assessments, etc.
- Centrally verified genotype
- Recruitment ongoing

MJFF LRRK2 DATA AND SPECIMEN RESOURCES

Cohort	iPD	LRRK2+ PD	LRRK2+ Carriers	Controls
Parkinson's Progression Markers Initiative (PPMI) Genetic Cohort		92	96	
PPMI Genetic Registry		112	95	
LRRK2 Cohort Consortium (LCC) Cross-Sectional Study (clinical data and samples)	70	170	160	200
LCC Cross-Sectional Study (clinical data only)	720	750	660	300
LCC Ashkenazi Jewish (AJ) Longitudinal Study	105	110	115	120
LCC 23andMe Blood Collection Study (Limited clinical data)	20	52	152	18
LRRK2 Biobanking Initiative	11	2	2	6

Please note: The only clinical data available from 23andMe subjects are demographics (year of birth, gender, education, race, PD status, age at diagnosis, age at onset), LRRK2 status, limited family history, UPDRS Part II (excluding question 13), UPDRS Part IV (questions 5, 6, 8, and 11 only), UPSIT, and limited information on anti-inflammatory medications and head injury or concussion.

MJFF LRRK2 DATA AND SPECIMEN AVAILABILITY

Number of LRRK2 Carriers with Biospecimen Available at Baseline

Cohort	DNA	RNA	CSF	Whole blood	Plasma	Serum	Urine	Cell Lines	PBMCs
PPMI Genetic Cohort	74	169	151	167	166	168	166	5	0
PPMI Genetic Registry	155	204		204	204	204	196	3	
LCC (Cross-Sectional, AJ Longitudinal, and 23andMe Blood Collection Studies)		296	69	336	322	256	259		
LRRK2 Biobanking Initiative							4		4

AS MORE DRUGS MAKE IT TO TRIALS, NEED FOR PD BIOMARKERS GROWS

Parkinson's Progression Markers Initiative

- Three study arms with different cohorts:
  - Recently diagnosed PD and controls: Completed enrollment in 2014
  - Risk factors of smell loss and RBD: Completed enrollment in 2015
  - People with genetic mutations, with or without PD: Recruiting
- CSF, blood, urine, DNA, RNA, iPSCs
- Learning more about how biology correlates to clinical experience

All data is made available at www.ppmi-info.org

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*Currently at Denali
#Currently at Biogen