USING PRECISION MEDICINE TO HELP PATIENTS WITH PARKINSON’S DISEASE

The Michael J. Fox Foundation for Parkinson’s Research
MJFF IS THE WORLD’S LARGEST NONPROFIT FUNDER OF PD RESEARCH

Our Mission
We are dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today

Who We Are
» Founded in **2000** by actor Michael J. Fox
» Headquarters in **New York City**
» **Public charity** supported entirely by donations: individuals, corporations, other nonprofits
» Nearly **$750M** in research programs funded to date
  – Fund **academics, biotech and pharma**
  – Fund **internationally** with more than a third of projects led by researchers outside U.S.
We work closely with the research and patient communities, industry and other key stakeholders and policy makers to identify critical challenges where MJFF can have impact.
People with Parkinson’s vary greatly in progression, symptom severity and response to treatment suggesting potential subtypes.

Cause likely multi-factorial: genetic forms vs ‘idiopathic’ forms.

Biological understanding suggests many cellular systems involved: divergent vs convergent mechanisms?

Shared biology with other neurodegenerative disorders.

“We will only get to true cures if we can move away from historical clinical disease definitions, based purely on symptoms to one more nuanced and linked to underlying biology, genetics and pathology.”

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What are the clinical, pathological and biological features of Parkinson’s disease and what can they tell us about how best to model it in the laboratory?
PARKINSON’S DISEASE: 1817 - 2017

Key Background

» First described as the “shaking palsy” in 1817 by Dr. James Parkinson

» Diagnosed by onset of motor symptoms: bradykinesia (slow movement), rigidity, resting tremor, (postural instability in some)

» Also exhibits “non-motor” features (some prior to motor symptoms): cognitive impairment, mood disorders, autonomic dysfunction, loss of smell, REM sleep behavior disorder, etc.

Parkinson’s disease is currently diagnosed by clinical (primarily motor) features despite clear heterogeneity caused likely by multiple triggers and/or pathogenic mechanisms
PARKINSON’S DISEASE PATHOLOGY: DOPAMINE AND ALPHA-SYNUCLEIN

Key Observations

» Parkinson’s motor features linked to loss of dopaminergic neurons in substantia nigra
» Pathologically confirmed by presence of Lewy bodies in brain
» Major protein component of Lewy bodies is accumulation of alpha-synuclein
» Although important criteria for confirming Parkinson’s disease, presence of other pathologies indicates other pathological forms may exist

These pathologies have been the leading drivers for development of Parkinson’s disease symptomatic and disease-modifying therapies

Obeso et al., Mov Disorders, 32:9, 2017
PROGRESSION OF PARKINSON’S DISEASE: TIME AS IMPORTANT FACTOR IN MODELING DISEASE AND TREATMENT

Kordower et al., Brain 2013

DISEASE SEVERITY

PRESYMPTOMATIC
Motor symptoms have not occurred
» Identify at risk
» Prevent

EARLY SYMPTOMATIC
Symptoms mostly motor and partially managed
» Improve diagnosis
» Slow, stop, protect

LATE SYMPTOMATIC
Motor complications, side effects, and non-motor symptoms
» Manage disease
» Restore, repair, replace

DISEASE PROGRESSION

Kordower et al., Brain 2013
Whether these clinical differences represent true disease subtypes or just “snapshots” of the same disease over time remains a major question in the field.
NON-HUMAN MODELS OF PARKINSON’S DISEASE FOCUS ON TWO MAIN TRIGGERS

“Environmental” Triggers
- Neurotoxins (MPTP, 6-OHDA, rotenone, paraquat)
- Other triggers (e.g., inflammatory)

“Genetic” Triggers
- Strategies: knockouts, knockins, transgenics, viral vectors
- Genetic forms of PD: SNCA, LRRK2, GBA1, Parkin, PINK1, DJ-1, VPS35

Many Parkinson’s research models have been generated but to date none are considered predictive of the human condition.
Imaging alpha-synuclein in the brain: tool critically needed!!!

Reduced levels of alpha-synuclein in spinal fluid suggests potential marker of disease?

Presence of alpha-synuclein in other regions

Correlating relationship of different forms of alpha-synuclein in different regions of the body critical for development of informative biomarkers

MJFF is supporting activities to measure alpha-synuclein throughout the body to better define its specific role in Parkinson’s disease
MODELING SPREAD OF ALPHA-SYNUCLEIN PATHOLOGY IS IMPORTANT NEW APPROACH

Model Details

» Model based on observed human spread of alpha-synuclein pathological ‘transfer’ in brain
» Model exhibits pathology-induced neurodegeneration suggestive of human condition
» Model meets some face and construct validity for human disease, but predictive validity still uncertain

Debate remains in field about whether this pathological ‘spread’ is a true feature in human Parkinson’s disease
MODELING OTHER FORMS OF PARKINSON’S DISEASE PATHOLOGY: GBA1 AND LRRK2

Data generated in collaboration with Pfizer

Ito et al., Biochem. J. (2016) 473, 2671–2685

Phosphoproteomics reveals that Parkinson’s disease kinase LRRK2 regulates a subset of Rab GTPases

Martin Steger1, Francesca Tonelli2, Genta Ito2, Paul Davies3, Matthias Trost4, Melanie Vetter4, Stefanie Wachter4, Esben Lorentzen5, Graham Duddy5,6, Stephen Wilson5, Marco AS Baptista5, Brian K Fiske6, Matthew J Fell7, John A Morrow8, Alastair D Reith8, Dario R Alessi8,9, Matthias Mann10

Ito et al., Biochem. J. (2016) 473, 2671–2685
Collecting data from cohorts of people with Parkinson’s over time is the best way to build a clear picture of disease and will ultimately inform best ways to model disease in the lab.
THANK YOU

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