Novel Targets of disease modifying therapy for Parkinson disease

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Disclosures

• Dr. Standaert has served as a paid consultant to these companies within the last 12 months:
  • Abbott/Abbvie
  • Serina Therapeutics
  • Sanofi (DSMB member)

• No off-label use of medications will be presented.
Novel Targets for disease modifying therapy in PD

- Targets emerging from genetic studies of PD
  - Alpha-synuclein
  - LRRK2
  - GBA
  - Inflammation

- How does target selection influence study cohort design?
Genetics of PD

• Most cases of PD are sporadic (>90%)
• Family studies have identified both autosomal dominant as well as autosomal recessive genes for PD
• More than 40 risk loci identified through Genome Wide Association
A meta-analysis of genome-wide association studies identifies 17 new Parkinson’s disease risk loci

Diana Chang¹, Mike A Nalls²,³, Ingileif B Hallgrimsdóttir⁴,⁶, Julie Hunkapiller¹, Marcel van der Brug¹,⁶, Fang Cai¹, International Parkinson’s Disease Genomics Consortium⁵, 23andMe Research Team⁵, Geoffrey A Kerchner¹, Gai Ayalon¹, Baris Bingol¹, Morgan Sheng¹, David Hinds⁴, Timothy W Behrens¹, Andrew B Singleton², Tushar R Bhangale¹,⁷ & Robert R Graham¹,⁷

PD Genetics and Genomics

Family studies

Mendelian
- Alpha-Syn
- LRRK2
- PINK1
- Parkin
- DJ-1

Genomic Sequencing

Intermediate
- GBA
- Others mostly unknown

GWAS

Common Variants
- Alpha-syn
- Tau
- HLA-DR
- Many others

Effect Size

Allele Frequency
Alpha-synuclein and PD

- Linked to PD through the Contursi kindred, a family with A30P mutation
- Gene multiplication also causes PD
- A principal component of Lewy bodies and Lewy neurites in sporadic PD

Spillantini et al., Nature, 1997
Synuclein: a spreading disease?

Neuron with α-Synuclein inclusions
Prion-like behavior of synuclein in mouse models

- Injection of alpha-synuclein aggregates causes a spreading process of aggregation
- Produces pathology in dopamine neurons and a motor deficit

Science, 338:949, 2013
Targeting alpha-synuclein in PD therapy

• Reducing synuclein synthesis
  • Antisense strategies
  • Transcriptional Inhibitors

• Enhancing synuclein clearance
  • Enhances of autophagy and lysosomal function
  • Antibody mediated clearance

• Targeting abnormal forms
  • Anti-aggregation strategies
  • Antibodies specific for misfolded forms
• Leucine-rich repeat kinase 2 (LRRK2) mutations are a common cause of PD
  • Most common mutation is G2019S
  • Up to 4% of sporadic PD in North American clinic populations
  • 25% of sporadic PD in Ashkenazi Jews
• Mutations increase kinase activity
• Rab family proteins are a primary substrate

LRRK2 Expression and Immune Signaling

- LRRK2 expression is abundant in Antigen Presenting Cells
- CNS inflammation leads to enhanced LRRK2 expression in brain monocytes
- Knockout or knockdown of LRRK2 attenuates inflammatory responses of microglia
- LRRK2 is linked to autoimmune diseases, including Crohn’s disease and leprosy
- Does G2019S cause PD by increasing the inflammatory “set point”?*
Inhibition of LRRK2 protects from α-synuclein–induced dopaminergic neurodegeneration

- LRRK2 KO Rats
- AAV-SYN
- Blocks nigral TH cell loss and inflammation
- Similar results with LRRK2 inhibitor drugs

Daher J P L et al. PNAS 2014;111:9289-9294
Targeting LRRK2

• G2019S mutant LRRK2 has enhanced kinase activity
• Several small molecule inhibitors of LRRK2 kinase are in preclinical and clinical development
• Literature on off-target effects (lung and renal) is mixed, not clear yet whether any of these are limiting.
Glucocerebrosidase and PD

• Homozygous mutations of *GBA1* (coding for β-glucocerebrosidase) cause Gaucher disease, a sphingolipid storage disorder.
• 1996: Neudorfer et al. described parkinsonism in 6 Gaucher patients.
• Heterozygous mutations in *GBA1* can be found in 4% to 7% of PD cases.
• GBA1 mutations are associated with more severe cognitive impairment.
• Reduced activity of β-glucocerebrosidase appears to be a common feature of many cases of PD, even without a mutation.
Lysosomal trafficking defects link Parkinson's disease with Gaucher's disease
Targeting GBA in PD

• Can we adapt enzyme replacement, an approved therapy for Gaucher?

• What about substrate reduction therapy (inhibitors of glucosylceramide synthase), blocking glycosphingolipid synthesis.
Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease

Taye H Hamza¹, Cyrus P Zabetian²³, Albert Tenesa⁴, Alain Laederach¹, Jennifer Montimurro¹, Dora Yearout¹⁻³, Denise M Kay¹, Kimberly F Doheny⁵, Justin Paschall⁶, Elizabeth Pugh⁵, Victoria I Kusel¹, Randall Collura¹, John Roberts⁷, Alida Griffith⁸, Ali Samii²³, William K Scott⁹, John Nutt¹⁰, Stewart A Factor¹¹ & Haydeh Payami¹

Hamza et al. Nature Genetics 2010
Inflammation in human PD

• Microglial activation is a constant feature of PD

• Correlated with the degree of aSYN accumulation

McGeer and McGeer, Mov Disorders, 2008

[1C](R)-PK11195 PET

In the PD patient (A and B), binding is increased in the basal ganglia, pons and frontal regions, while the healthy control person (C and D) only shows constitutive [1C](R)-PK11195 binding in the thalamus and pons.

Gerhard et al., 2006
• Discovery of functional lymphatic vessels lining the dural sinuses.
• Carry both fluid and immune cells from the cerebrospinal fluid, and are connected to the deep cervical lymph nodes.
T Cells in Human PD

• CD4+ and CD8+ T cells are found in postmortem PD brain
• Present near vessels and melanized neurons

Specific epitopes synuclein epitopes drive both cytotoxic and helper T cells from PD patients

Y39 region is displayed by DRB5*01:01 and DRB1*15:01, linked to PD
Anti-inflammatory Drugs and Risk of Parkinson Disease: A Meta-analysis

- Relative risks (95% confidence intervals) from studies of nonaspirin nonsteroidals
- Overall reduction in risk of about 15%
- No effect for aspirin or acetaminophen
Targeting inflammation in PD

- There is clear evidence for activation of both innate (microglial) and adaptive (T- and B-cell) immunity in human PD
- NSAID’s are associated with a small reduction of risk
- Experimental work suggests that targeting either microglial mechanisms or T-cell pathways can reduce the toxicity of alpha-synuclein
How does target selection influence trial design?

- **Alpha-syn**: overabundant in many cases of PD, but underlying mechanisms differ
- **LRRK2, GBA mutants** – both rare in the population
- **Inflammation** – nearly universal in PD