The Immune System and Parkinson’s Disease

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To be discussed

- The role of inflammation in PD
- Anti-inflammatory and PD risk
- What is alpha-synuclein and why is it bad?
- Can the gut bacteria impact PD?
- Manipulating the immune system to fight PD
- Leukemia treatment to fight PD
PD research is exploding!

- Parkinson's related research reports
  - 1865 - the naming of Parkinson's
  - Levodopa (1960)

- Parkinson's related clinical studies
  - Levodopa (1960)
Tipping the Scale

Risk factors
- Pesticides
- Dairy
- Melanoma
- TBI
- Inflammation

Inverse risk factors
- Smoking
- Caffeine
- Urate
- Physical activity
- Ibuprofen
- CCBs

Genetic causal factors
Genetic protective factors

PD
Inflammation and PD

- Microglia – the brain’s immune system and defense
- “activated microglia” are abundant in brains of PD and animal models
- Cause, effect, or both?
Ibuprofen lowers risk of PD

- 37,305 men from the Health Professionals Study
- 98,892 women from the Nurses’ Health Study
- 291 cases of PD during follow up assessed
- Ibuprofen user vs non-user – risk decrease 38 %

Use                      Risk reduction

- 1-2 tab ibuprofen/wk    –    15%
- 3-4 tab ibuprofen/wk    -    60%
- 6 or more tab/ wk       -    45%
What about other anti-inflammatory medicines?

- Relative risk of PD
What do I do with this info?

• Not quite time to take daily ibuprofen!
• Long term risks – high blood pressure, ulcers, risk of bleeding
• Prevention vs disease modification
The Alpha-Synuclein Story

Frederic Lewy – 1912

Contursi Terme, Italy 1986
Alpha-Synuclein

- Found throughout the body
- Most abundant at neuronal synapses
- Involved with neurochemical transmission
How proteins aggregate

Monomers → Dimer → Oligomers → Protofibrils → Aggregate
Alpha-synuclein & Lewy Bodies

Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

Via olfactory bulb
Via vagus nerve
Premotor symptoms
Motor symptoms

Brainstem Lewy body
Cortical Lewy body
1990s

Embryonic Stem Cells Studies

Before                         After
DOPAMINERGIC TERMINAL

T-SNAREs
V-SNAREs
DAT
SYNAPSIN-III
ACTIN FILAMENTS

DA Dopamine

α-SYNUCLEIN AGGREGATION
REDISTRIBUTION OF SYNAPTIC PROTEINS
SYNAPTIC COLLAPSE

DA RELEASE BLOCK

DA RELEASE
“All Disease Begins in The Gut!”

-Hippocrates
Gut and health

- “Leaky gut theory”
- “Intestinal dysbiosis”
- People with PD have different intestinal bacteria than the usual
- More pro-inflammatory bacteria
- Changes true with treated and untreated
- Does inflammation in the intestine promote the process of PD or GI symptoms?
Can we change PD (or risk) by changing the gut bacteria?

PD genetic Mouse

Germ-free (Antibiotics)

Typical Gut bacteria

Minimal symptoms & pathology in brain & gut

Expected symptoms & pathology in brain & gut
Can we change PD (or risk) by changing the gut bacteria?

PD Mouse → Gut microbiome of person with PD → Worsened PD motor symptoms
So now what to do?

- Don’t eat feces from people with PD!!!
- Should and how do I change my intestinal microbiome?
Harnessing the Immune System to Slow PD
Different types of immunotherapy

- Immunosuppression
- Active/ acquired / adaptive immunity (vaccination)
- Passive immunity (IV monoclonal antibodies)
Active Immunity

- Administered as an injection
- Several shots, then maintained with infrequent boosters
- No IV required

**Cons**

- Can't control the immune response
- Difficult to turn it off/down if excessive

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How to make a PD vaccination

Alpha Synuclein

Introduce the protein along with immune triggering substances

The body creates antibodies against the target

The immune system mounts an attack to eliminate the protein
How do we decide if a vaccine is a success?

1. Antibodies against the target are in the blood
2. It prevents or reduces the severity of the disease
AFFITOPE - PD Vaccine

- 2016-7
- Phase 1 (first human study)
- Open label
- 22 treated with 4 doses
- 63% developed antibodies
- Well tolerated – injection site reactions common
- Further study expansion up to 36 total
- With booster, 86% mounted antibodies
Passive Immunity

• Pros
  • Better control of dose / intensity
  • If excessive, you can stop the treatment

• Cons
  • Require IV infusion
  • Possible indefinite treatment monthly
Making Designer Antibodies

- **Mouse** injected into a mouse
- Mouse produces plasma cells
- Plasma cells fused with tumor cells to form hybridoma
- Hybridoma produces endless supply of monoclonal antibodies
Blocking α-synuclein by passive immunotherapy

First-in-Human Assessment of PRX002, an Anti–α-Synuclein Monoclonal Antibody, in Healthy Volunteers

*P < 0.05
Phase 2 - Alpha Synuclein Monoclonal Ab

PASADENA study

• Now enrolling at UVM
• Early PD with mild symptoms - not yet on levodopa or dopamine agonists
• Monthly antibody IV infusion
• 1 year double blind placebo
  – Placebo vs lower dose vs higher dose
• 1 year blinded active treatment
  – Lower dose vs higher dose
Phase 2 - Alpha Synuclein Monoclonal Ab
SPARK study

- Now enrolling at UVM
- Early PD with mild symptoms - not yet on levodopa or dopamine agonists
- Monthly antibody IV infusion
- 1 year double blind placebo
  - Placebo vs lower vs medium vs higher dose
- 1 year blinded active treatment
  - Lower dose vs higher dose
A race to the finish !!!!

• Both studies
• ~300 participants
• 1 year with placebo group / 1 year all treated
• Multi-Center studies

• Mass General Hospital – Biogen Study
• UVM – Roche study
What is Nilotinib?

- FDA approve treatment for resistant Chronic Myelogenous Leukemia (CML)
- A small-molecule tyrosine kinase inhibitor

- Drug repurposing - using a drug intended and approved for one condition for another

- Blocks the function of “c-Abl”
Turning on the garbage disposal
Nilotinib reverses loss of dopamine neurons and improves motor behavior via autophagic degradation of α-synuclein in Parkinson’s disease models
Michaeline L. Hebron†, Irina Lonskaya† and Charbel E.-H. Moussa*
Nilotinib Georgetown Study

• 12 participant open label study
• PD, PD with dementia, & Lewy Body dementia
• 10 completed – 36 week study
• Well-tolerated
• Confirmed to enter the CNS (spinal fluid)
• Appears to biologically reaching goal or “engaging the target”
Nilotinib results...

- Some inconsistent trend toward overall PD improvement (more self report than exam)
- Some with improved cognition
- Clinical interpretation limited by open-label
- Conclusion: acceptable safety, tolerability, and bioavailability – more study / development is indicated
Time to dance?
Georgetown vs MJ Fox Foundation
Agree to Disagree
Two studies will be done!

- Nilo-PD (Parkinson Study Group / MJFF)
  - 75 people moderately advanced – 6 months
    - placebo, 150 or 300 mg
  - If well tolerated, second study planned
- PD Nilotinib Study (Georgetown)
  - 75 people for 1 year blinded and 1 year open label