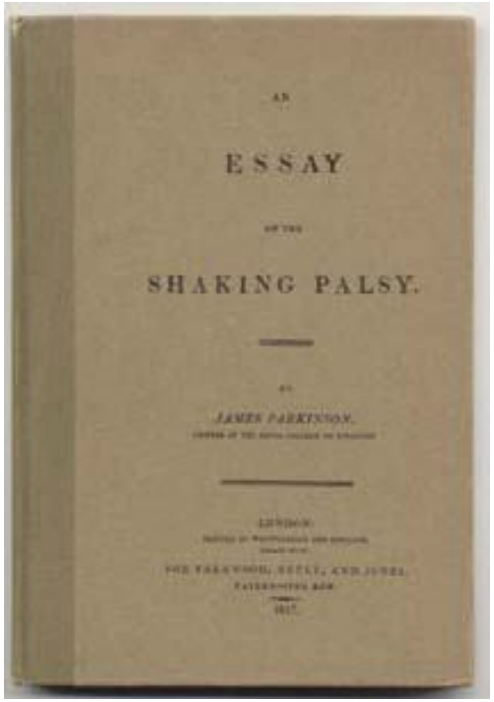
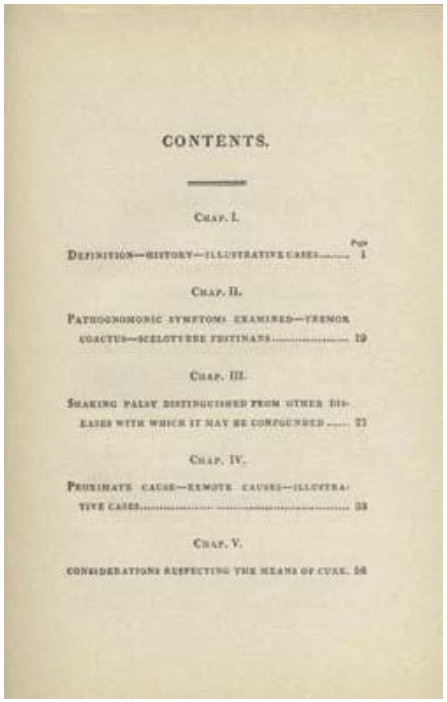
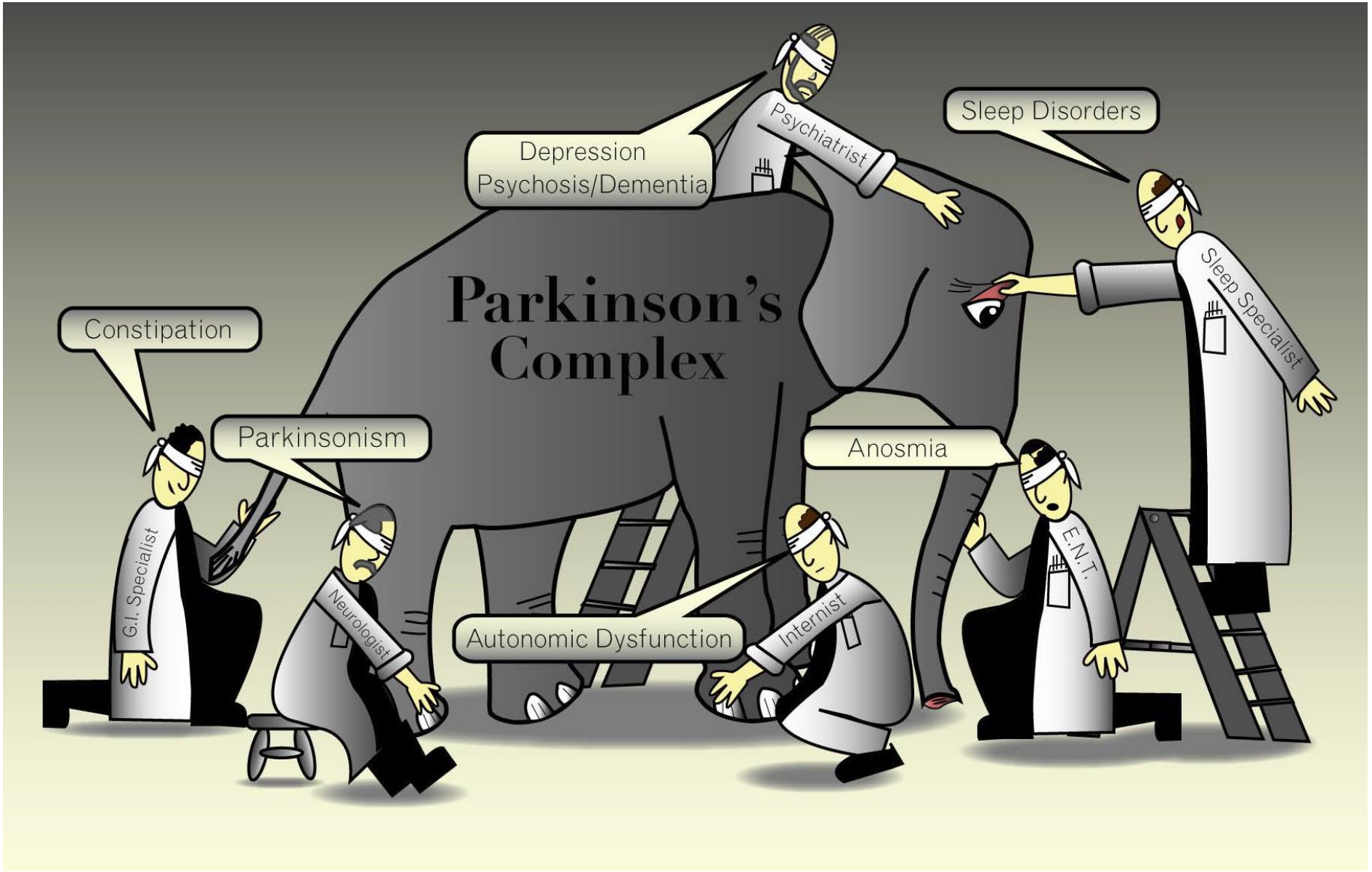
Essay on the Shaking Palsy: James Parkinson 1817



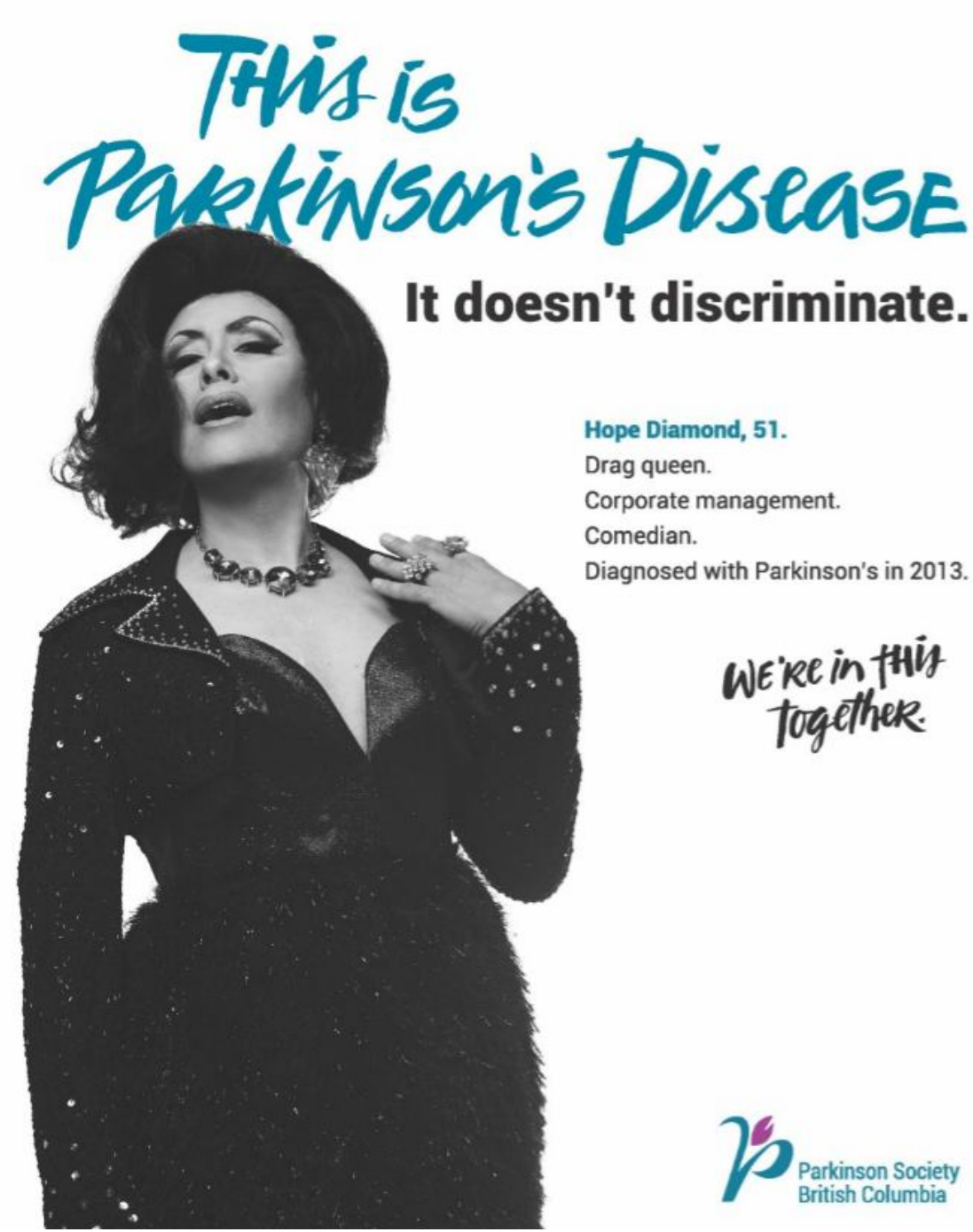


6 Cases: 3 in his clinic and 3 observed on the street
Described all of the essential features of the illness
50 years later, Charcot: “Parkinson’s Disease”



Langston 2006
Source: Anthony Lang slides

From Canada:



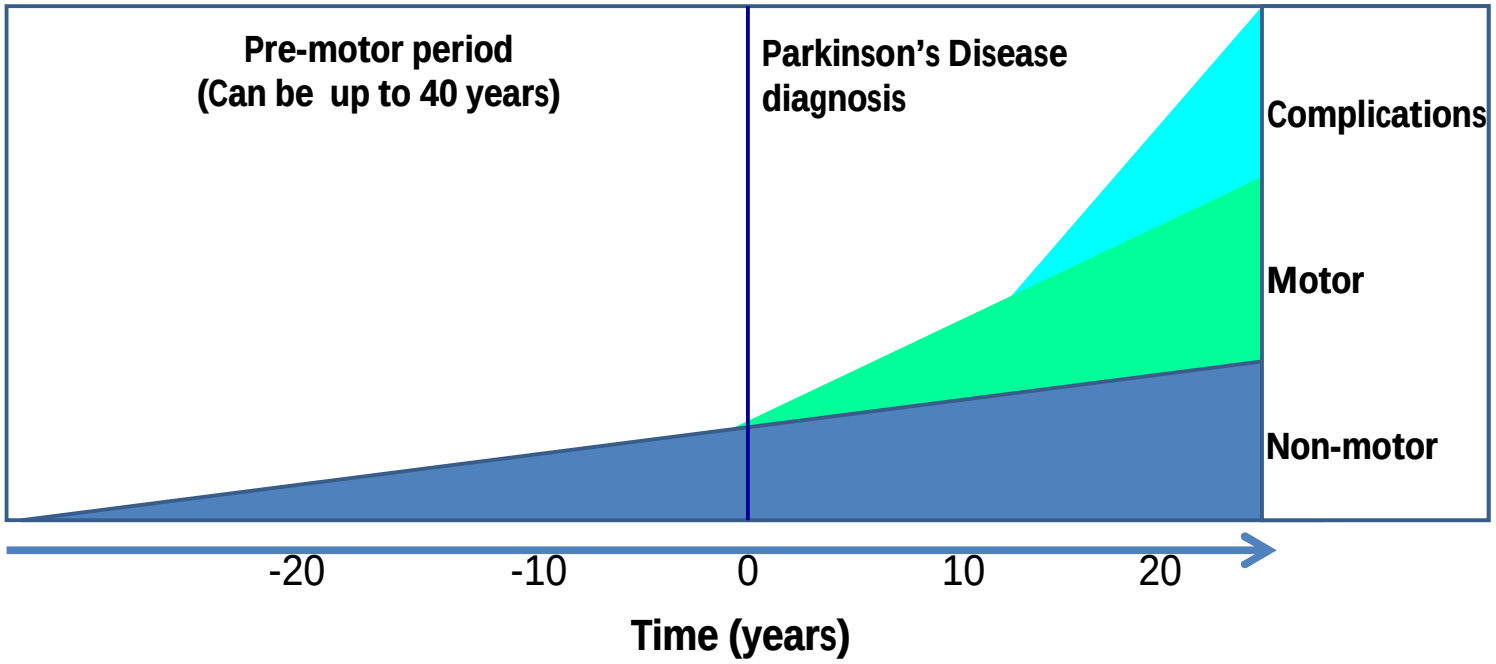
Source: Alice Lazzarini slides

Our first Perspective – Research

New-to-us information

Context:

PD as a multi-system, complex, whole-body condition



Source: Anthony Lang slides

Incidence by Age and Gender

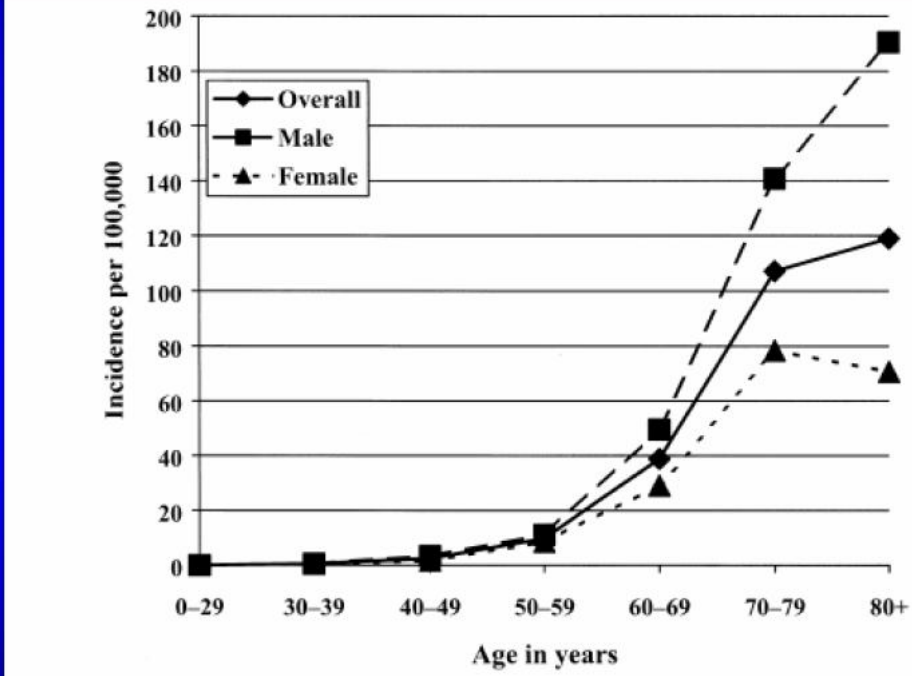
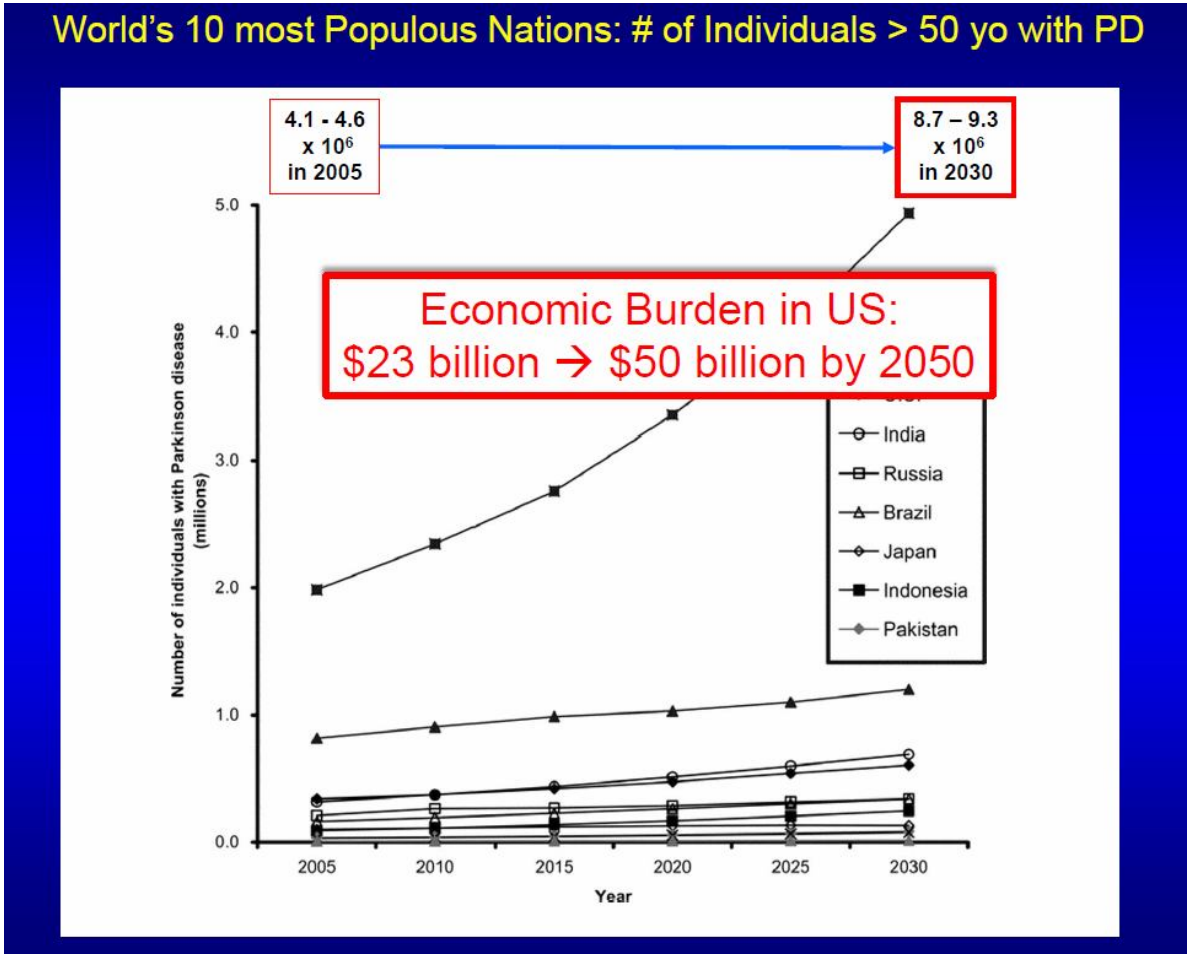


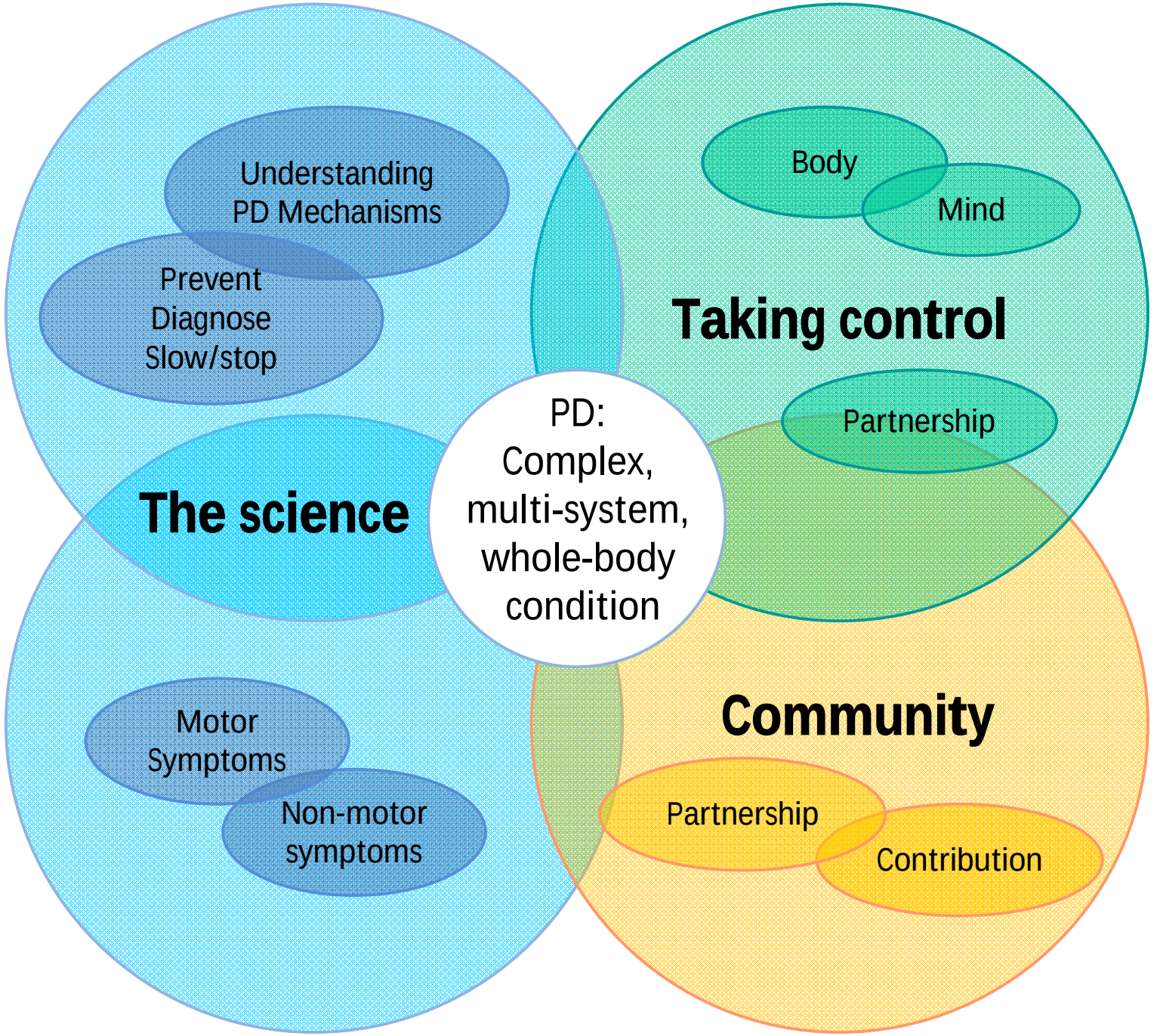
FIGURE 1. Incidence of Parkinson's disease by age and gender, Kaiser Permanente, 1994–1995.

Anthony E Lang

World incidence projected for PD



Anthony E Lang


Understanding
PD Mechanisms
Prevent
Diagnose
Slow/stop
Body
Mind
Taking control
Partnership
The science
PD:
Complex,
multi-system,
whole-body
condition
Motor
Symptoms
Non-motor
symptoms
Community
Partnership
Contribution

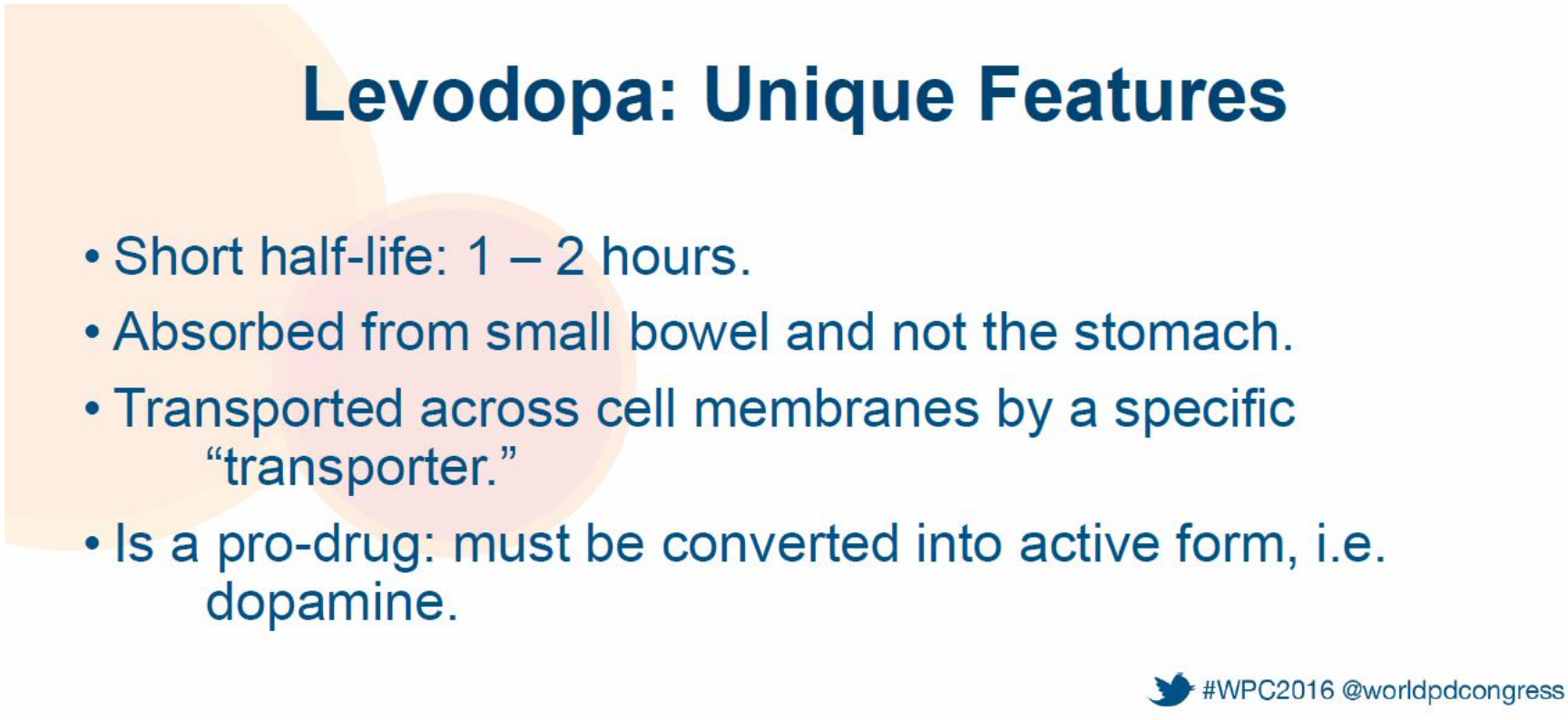
Our reviews:

1. Levodopa
2. (mention of DBS)
3. Mention of alpha-synuclein
4. Cell restoration?
5. Genetics
6. Disease modelling

1 - Prof. John Nutt

James Parkinson's Special Lecture

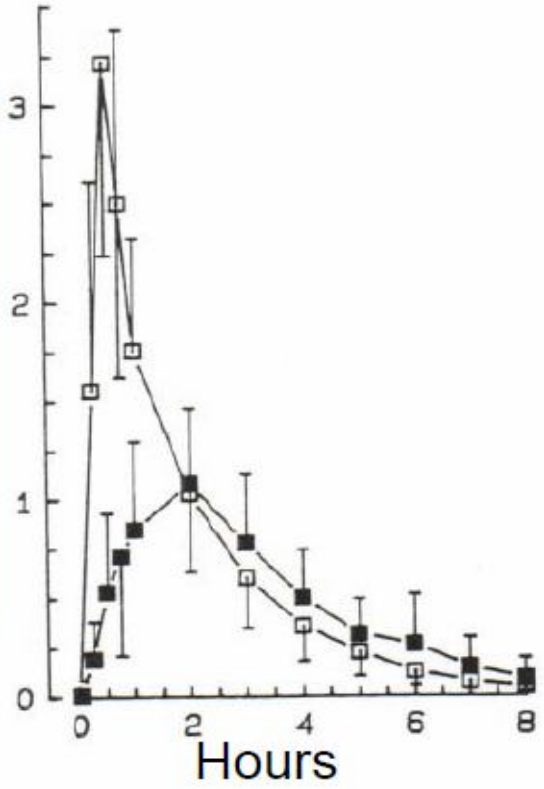
Levodopa: where we have been…and where we are going



James Parkinson's Special Lecture: Prof John Nutt slides

Blood Levels of Levodopa

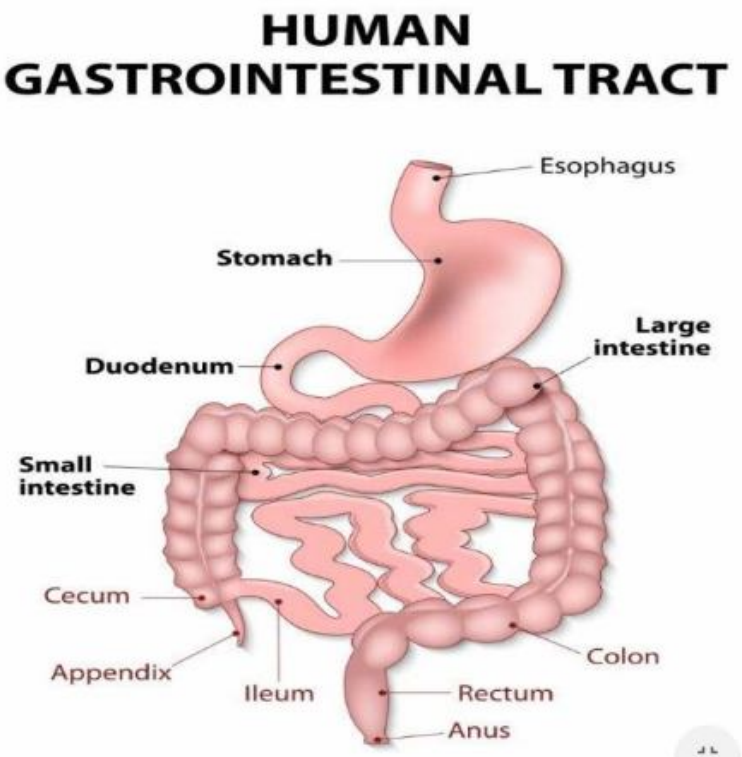
L-DOPA
Concentration



Yeh et al. 1989

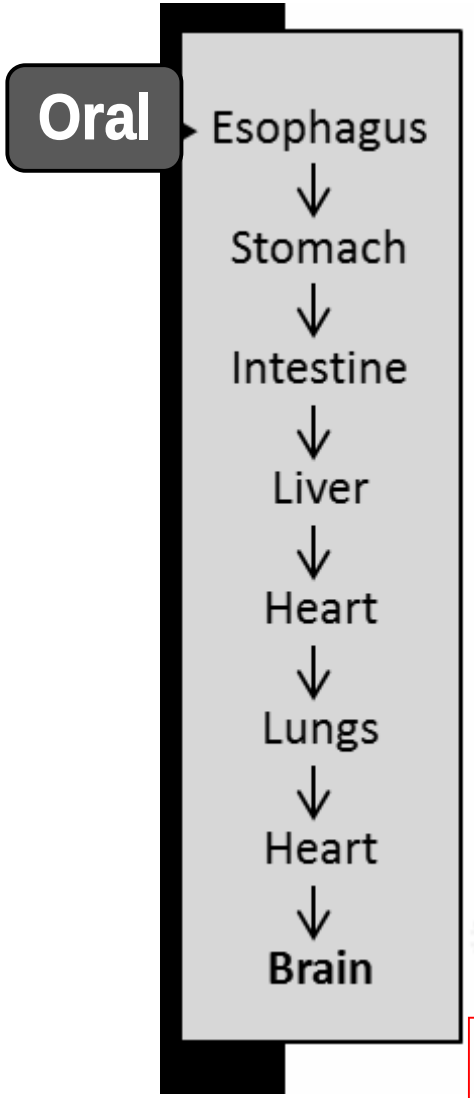
Levodopa Absorption

- **Transit Times**
- Stomach: 3 hours
- Small Intestine: ½ to 3 hours
- Large Intestine: 30-40 hours



James Parkinson's Special Lecture: Prof John Nutt slides

Improved delivery of levodopa:



- Continuous infusion into upper small intestine (liquid gel)
- Gastric-retentive formulations (accordion pill)
- Subcutaneous infusion (belt or patch pump)
- Continuous intra-oral release (behind the teeth)
- Inhalation (emergency)

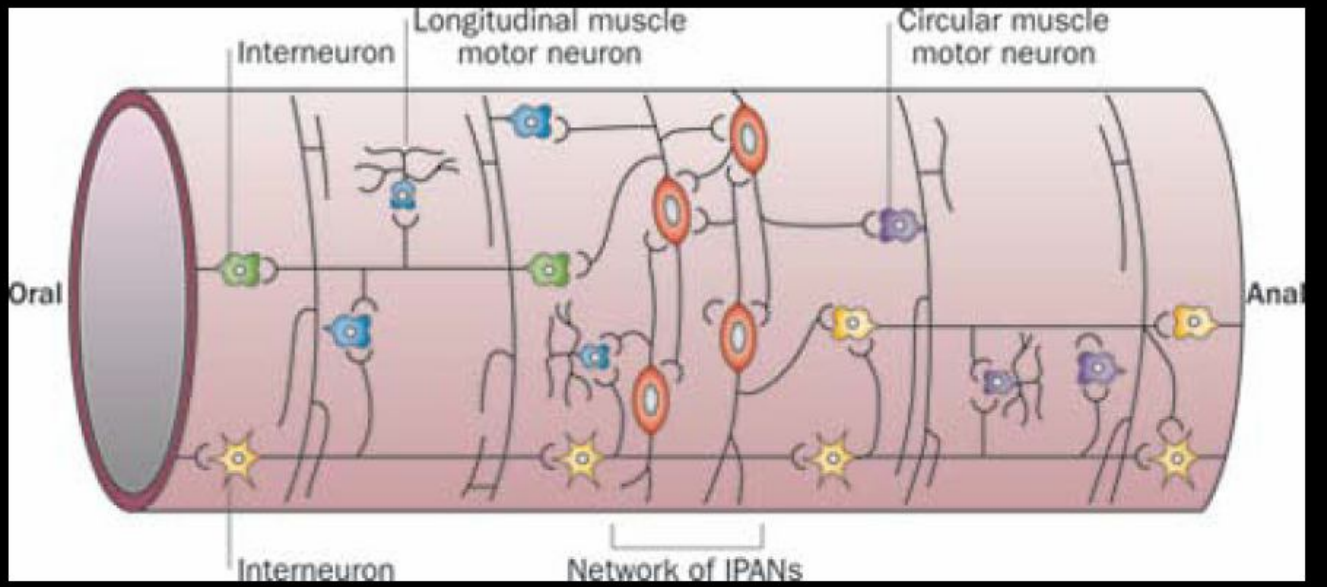
New-to-us information

Only 2 – 3% of the Levadopa reaches the brain
(Agonists are different)

Source: Peter A. LeWitt slides

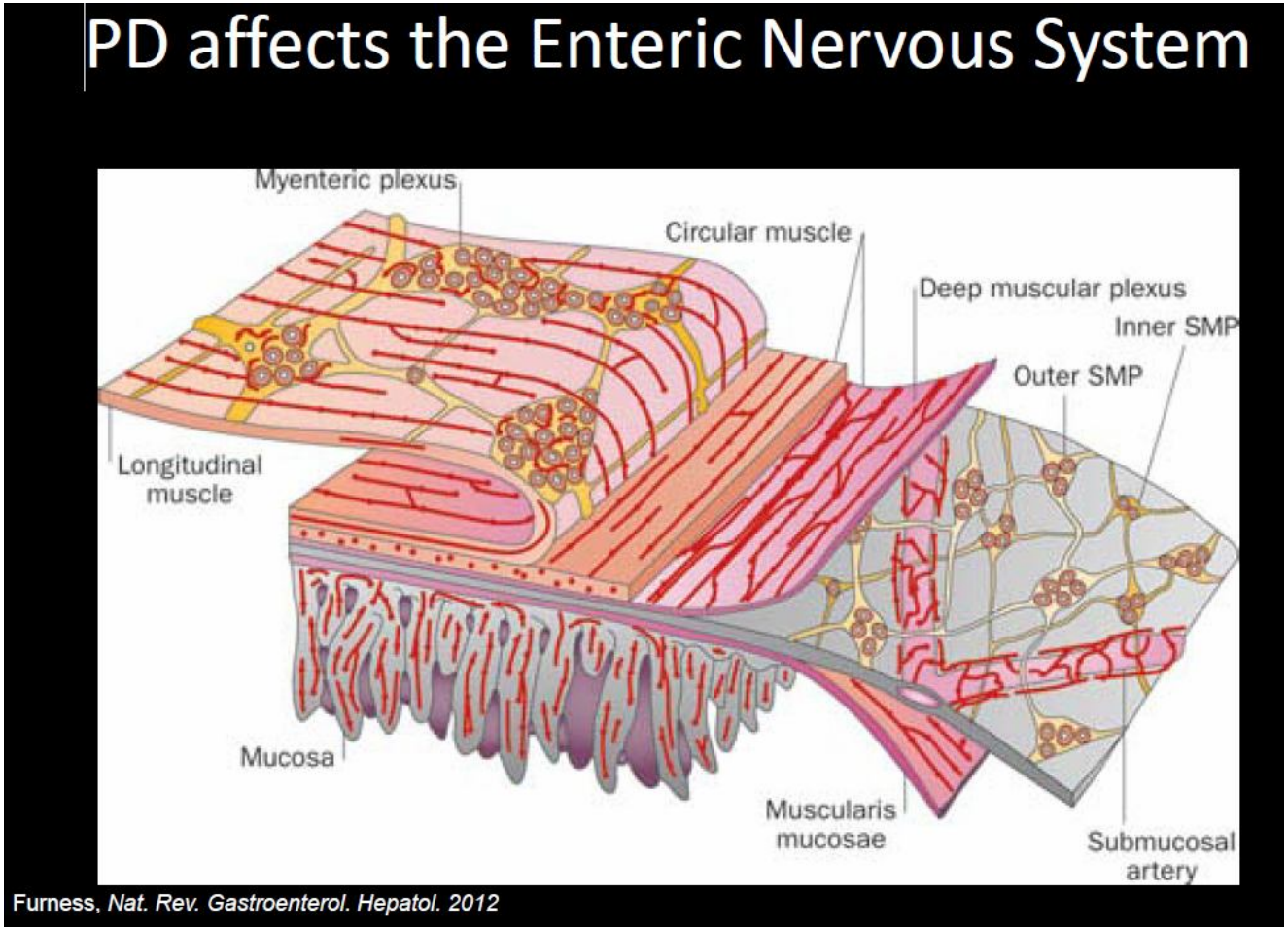
Gut intelligence?

The gut has its own internal nervous system that can functions independently



Sarah Diamond slides

Amazing detail



Sarah Diamond slides

Levodopa: John Nutt's final thoughts

- Levodopa therapy will remain a priority in PD for many years, even if protective therapies emerge
- Research should focus on more than continuous delivery and consider variable delivery in relation to need
- New methods to measure motor function throughout the day will change our concepts about motor patterns and permit tailoring to patient's minute to minute needs

James Parkinson's Special Lecture: Prof John Nutt slides

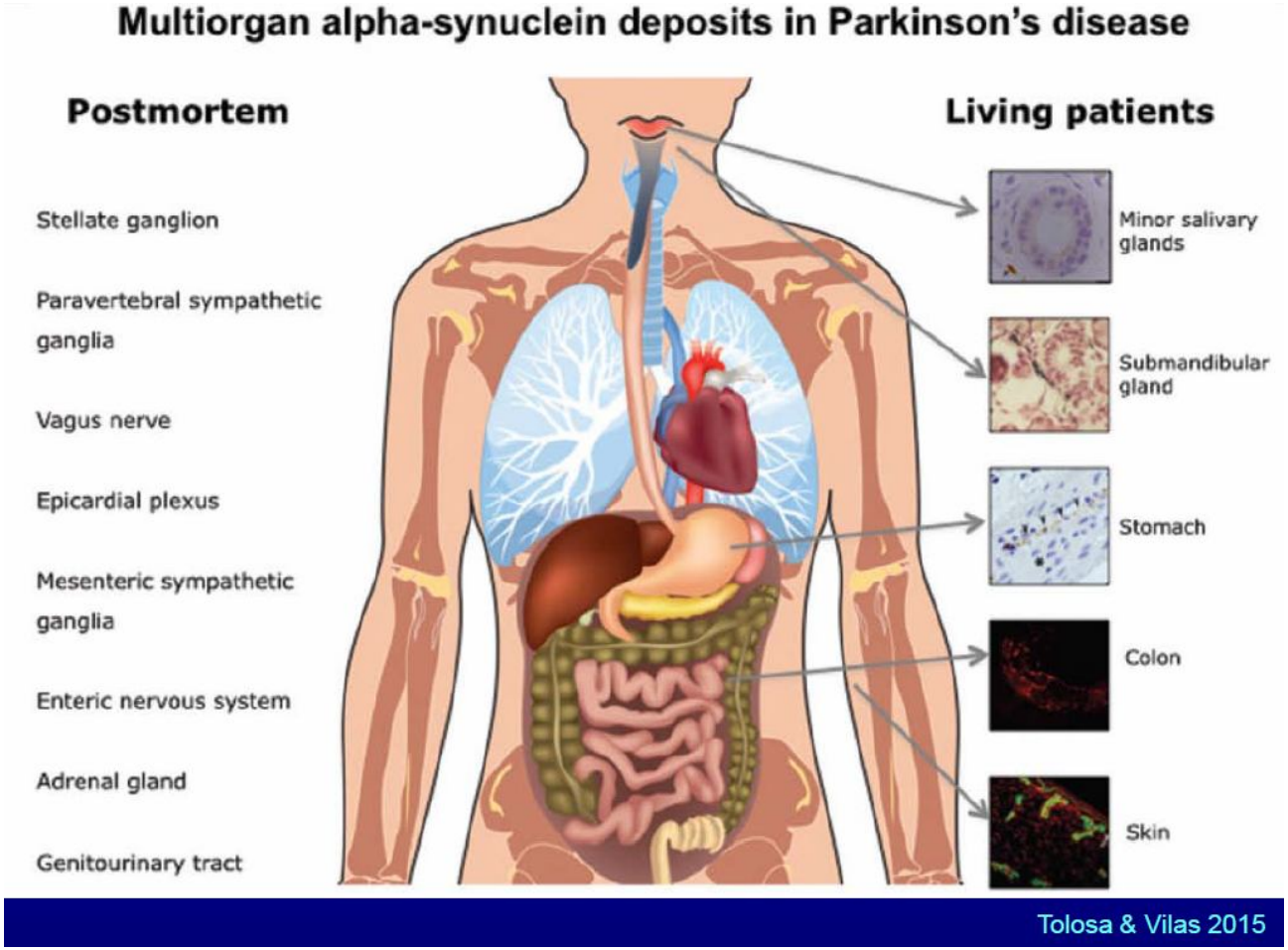
2 - Deep Brain Stimulation?

- A very big area in the Congress
- Difficult choice not to attend sessions
- Met a lady with a hula-hoop..

3 - Alpha-synuclein

- A protein that folds abnormally inside cells and spreads to other cells to cause PD
- Major studies are taking place:
  - What causes abnormal folding?
  - How does it get past cell defences?
  - How could it be stopped?

It can be in many parts of the body



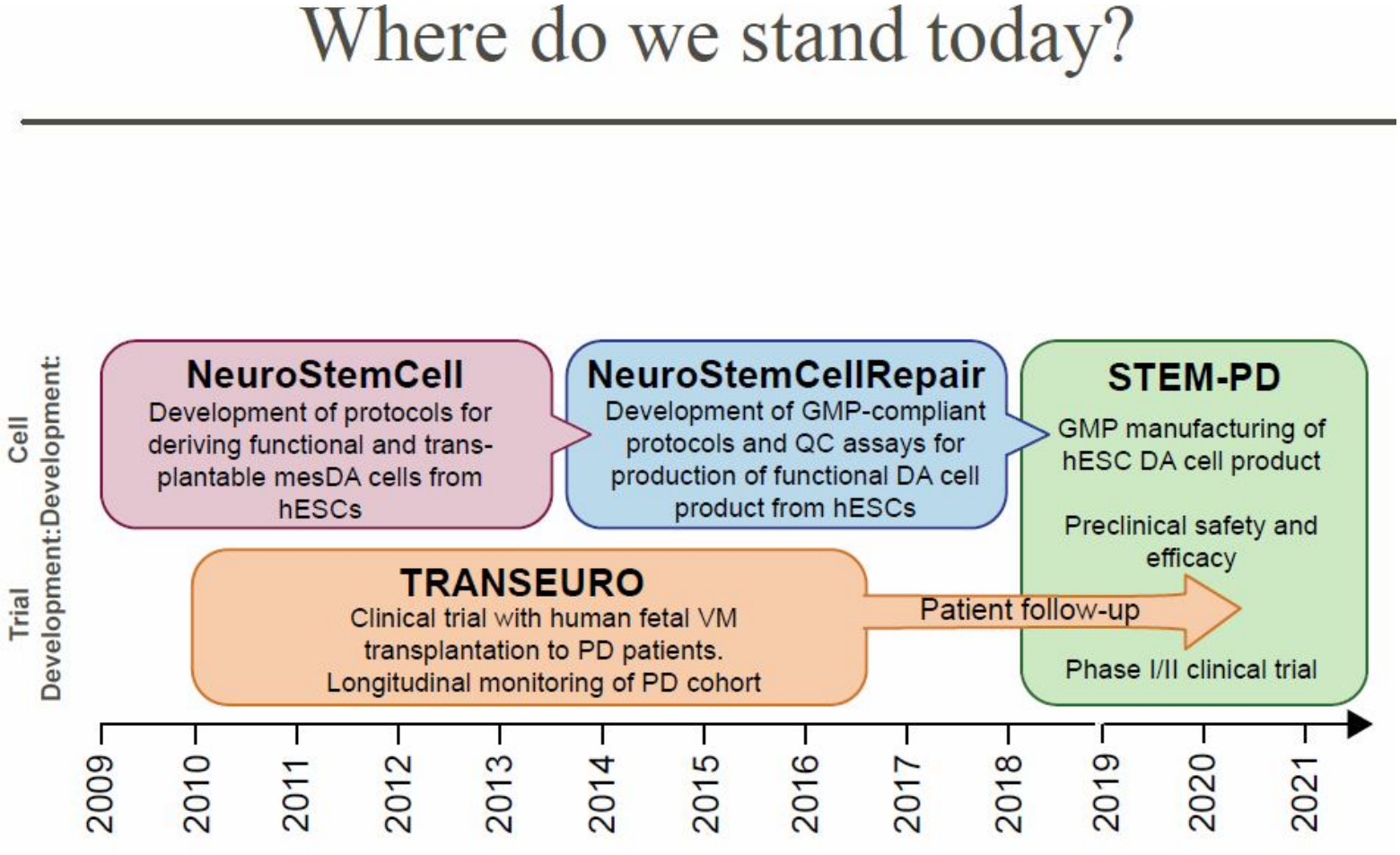
4 - Restoration?

Can defective dopamine cells be replaced with effective ones?

After many trials, the current focus is on

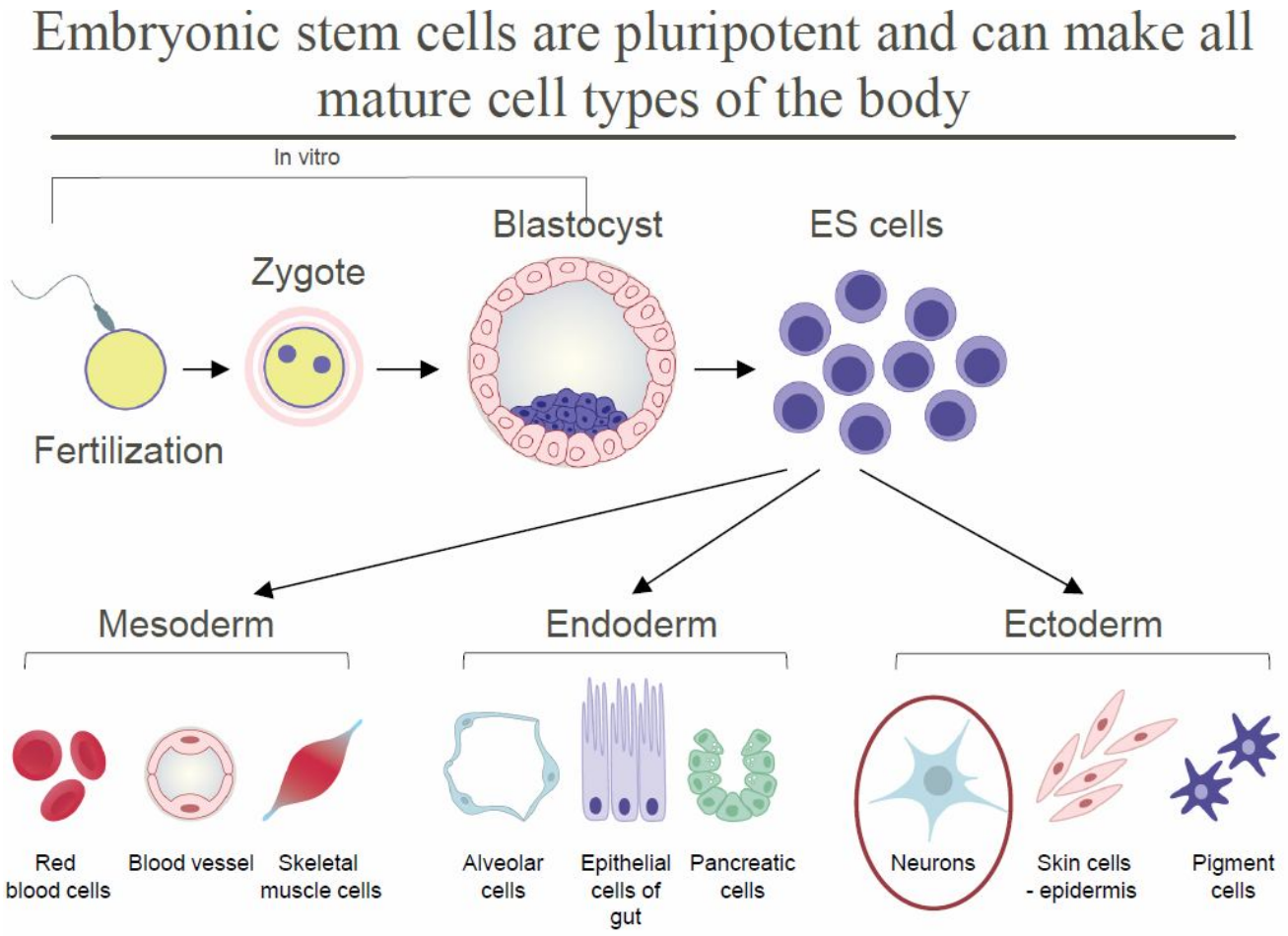
Embryonic Stemcells - ES
and
Induced Pluripotent Stemcells - iPS

Overview



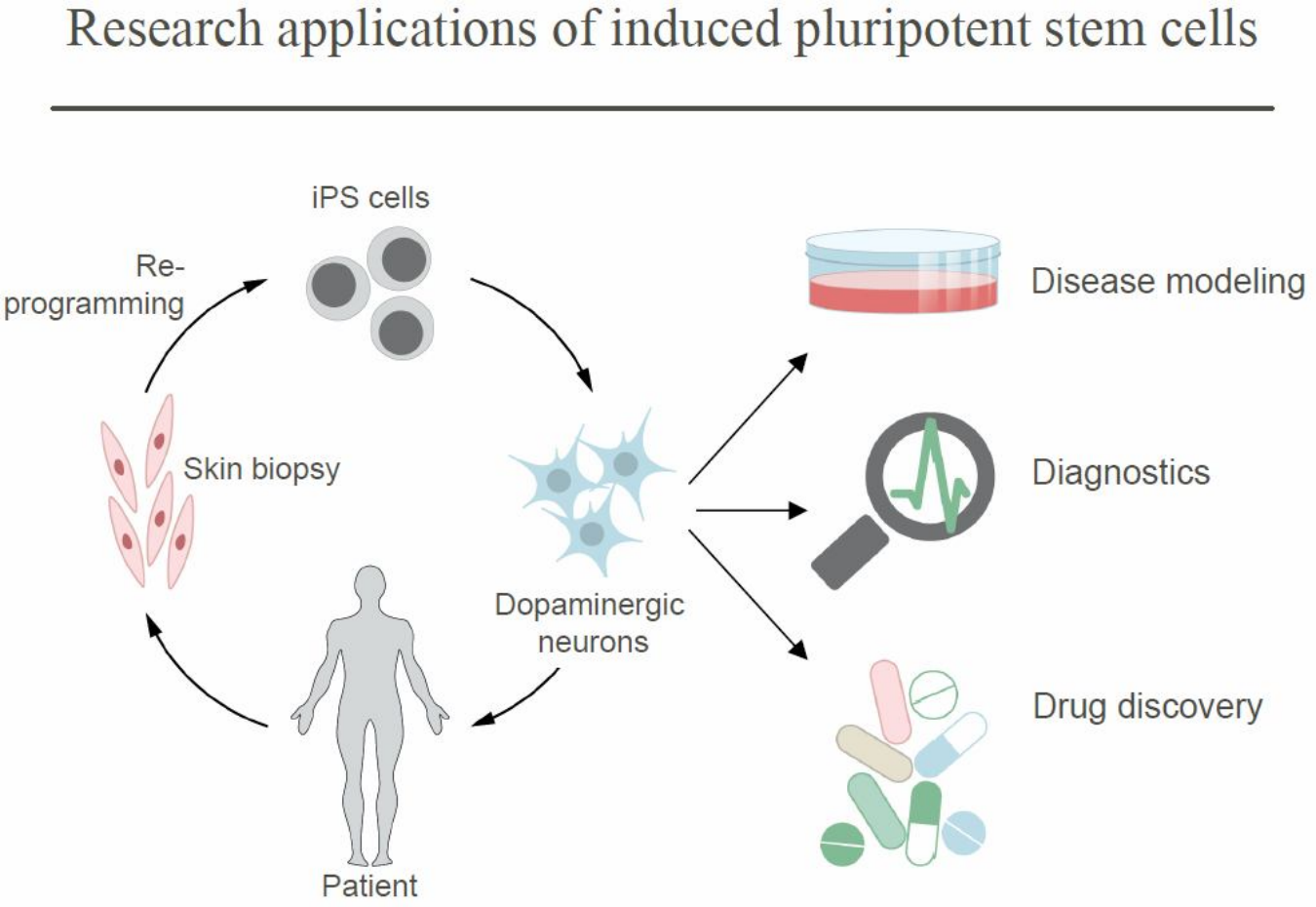
Malin Parmar slides

ES Cells



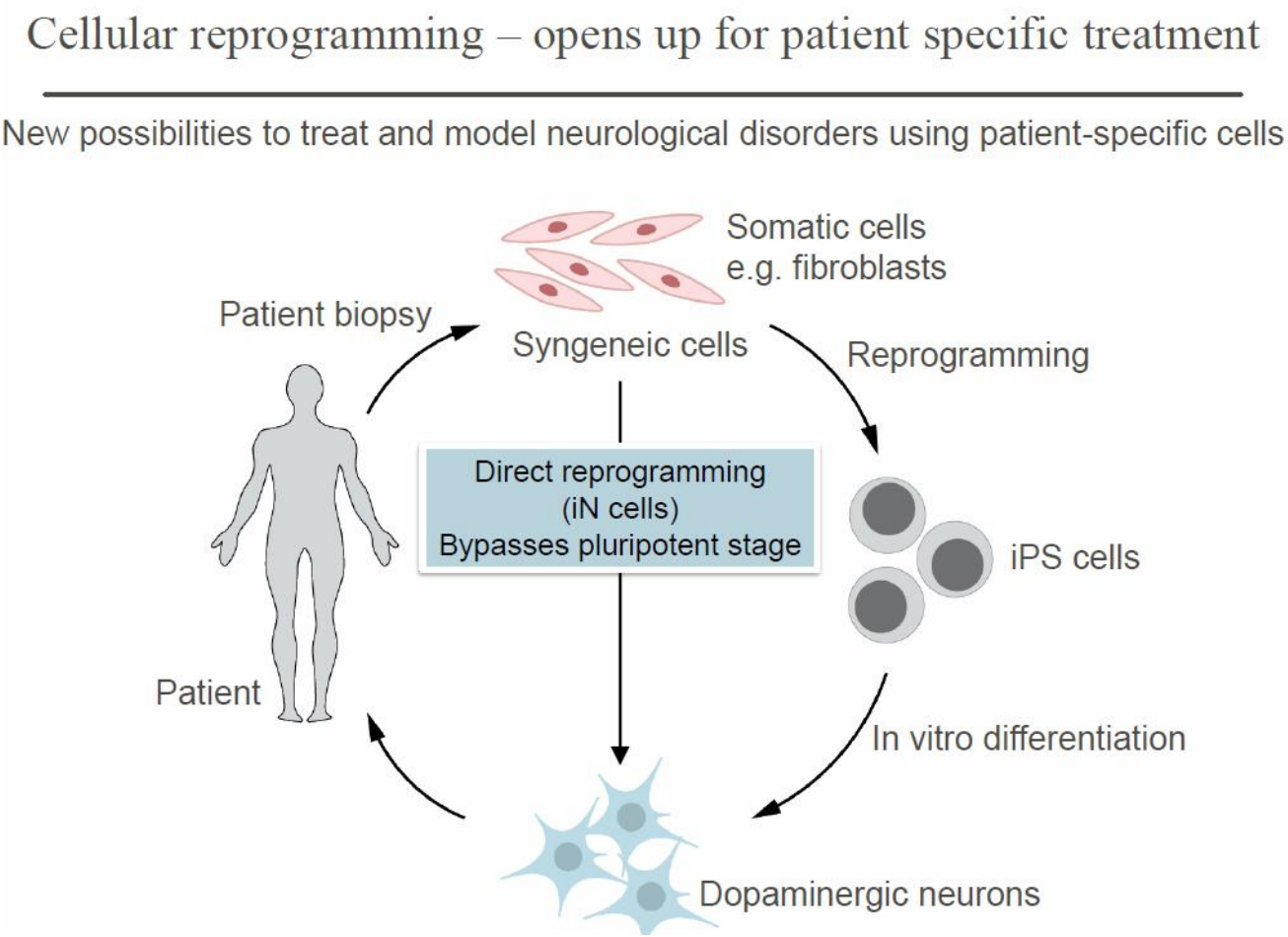
Malin Parmar slides

iPS Cells



Malin Parmar slides

Patient-specific iN cells



Malin Parmar slides

Current cell therapies

CONCLUSIONS
CELL THERAPIES FOR PARKINSON'S DISEASE

- **CELL BASED THERAPIES IN PD HAVE PRODUCED MIXED RESULTS BECAUSE OF ISSUES TO DO WITH PATIENT SELECTION; CHOICE OF CELL; TRIAL DESIGN; FOLLOW UP; IMMUNOSUPPRESSION ETC**

- **WHEN IT WORKS WELL IT WORKS VERY WELL WITH FETAL DOPAMINE CELLS, BUT IT DOES NOT ALWAYS WORK WELL**

- **ATTEMPTS ARE ONGOING TO DESIGN BETTER TRIALS THAT WILL GIVE CLEARER RESULTS FOR CELL BASED THERAPIES- STARTING WITH FETAL DOPAMINE CELLS AND THEN MOVING TO STEM CELLS**

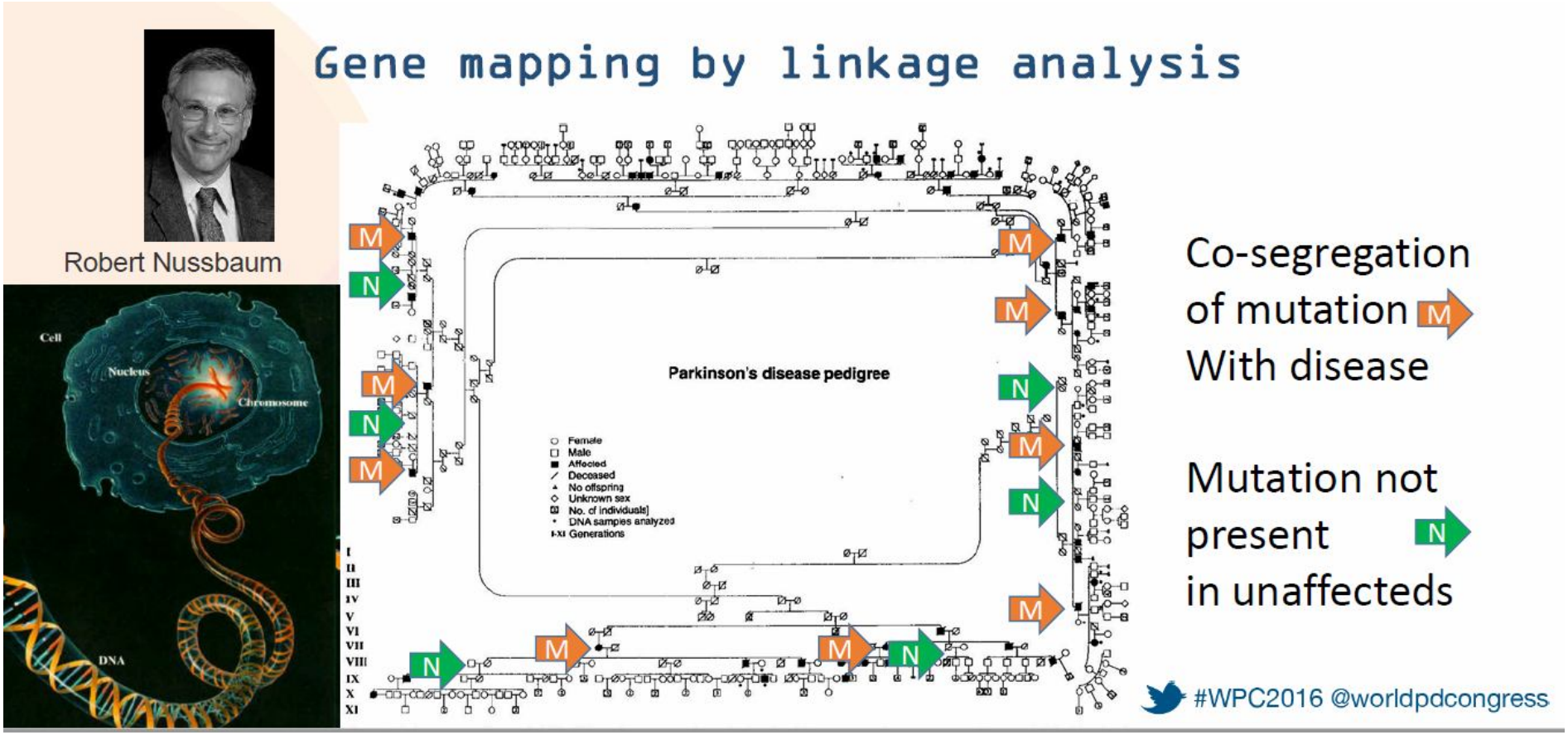
- **BUT BEWARE of any new ADVERTISED stem cell trials especially if YOU ARE BEING ASKED TO PAY TO JOIN IT- because if these go wrong the whole field goes wrong!**

Roger Barker slides

5 - Genetics and Risk?

Can we discover genetic risk factors and head off potential PD?

Genetics: subtle and complex!



Robert Nussbaum slides

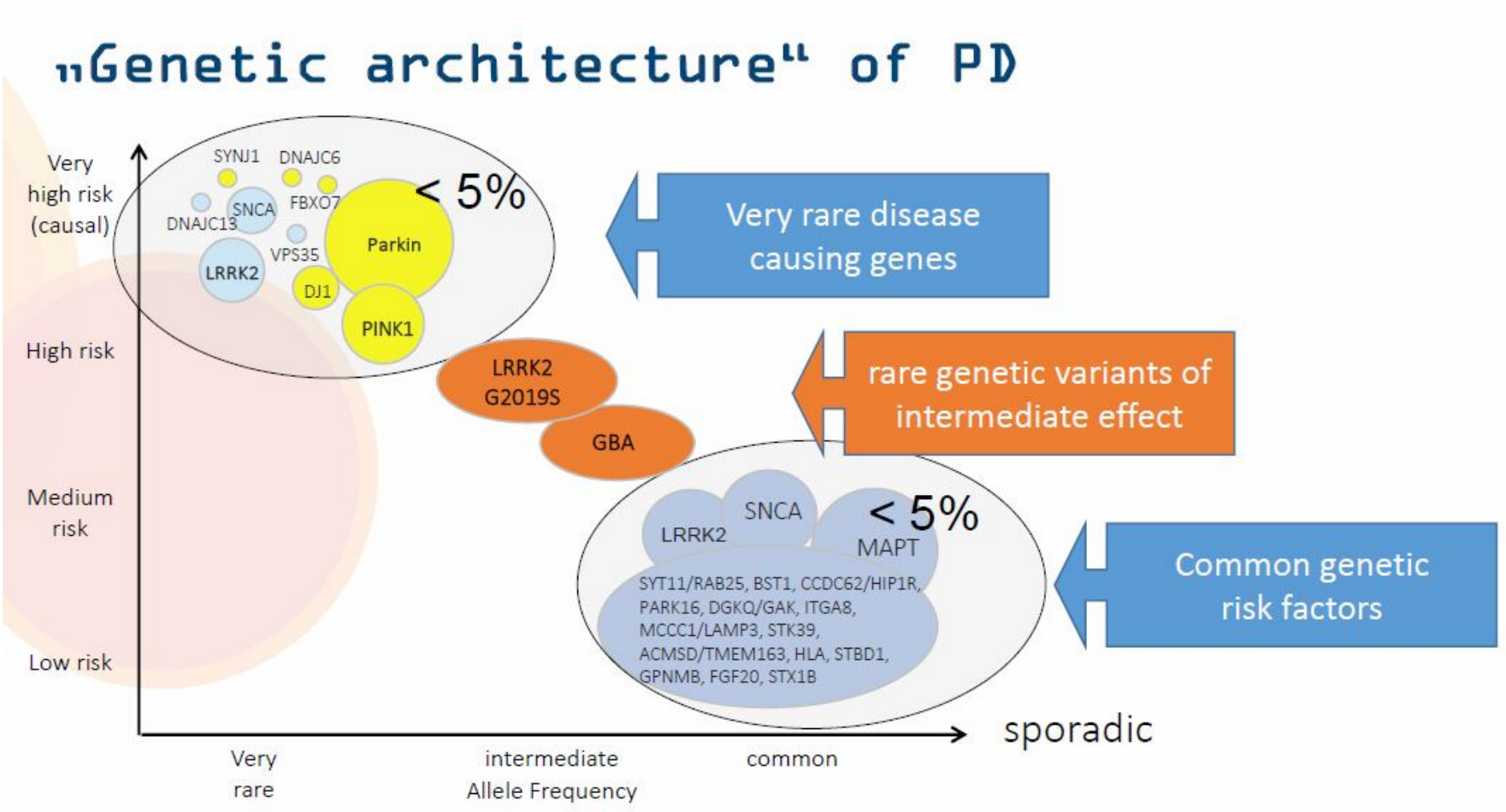
Genetic Testing
Empowerment or Risk for People with Parkinson's?

Thursday, September 22nd 10:45 am

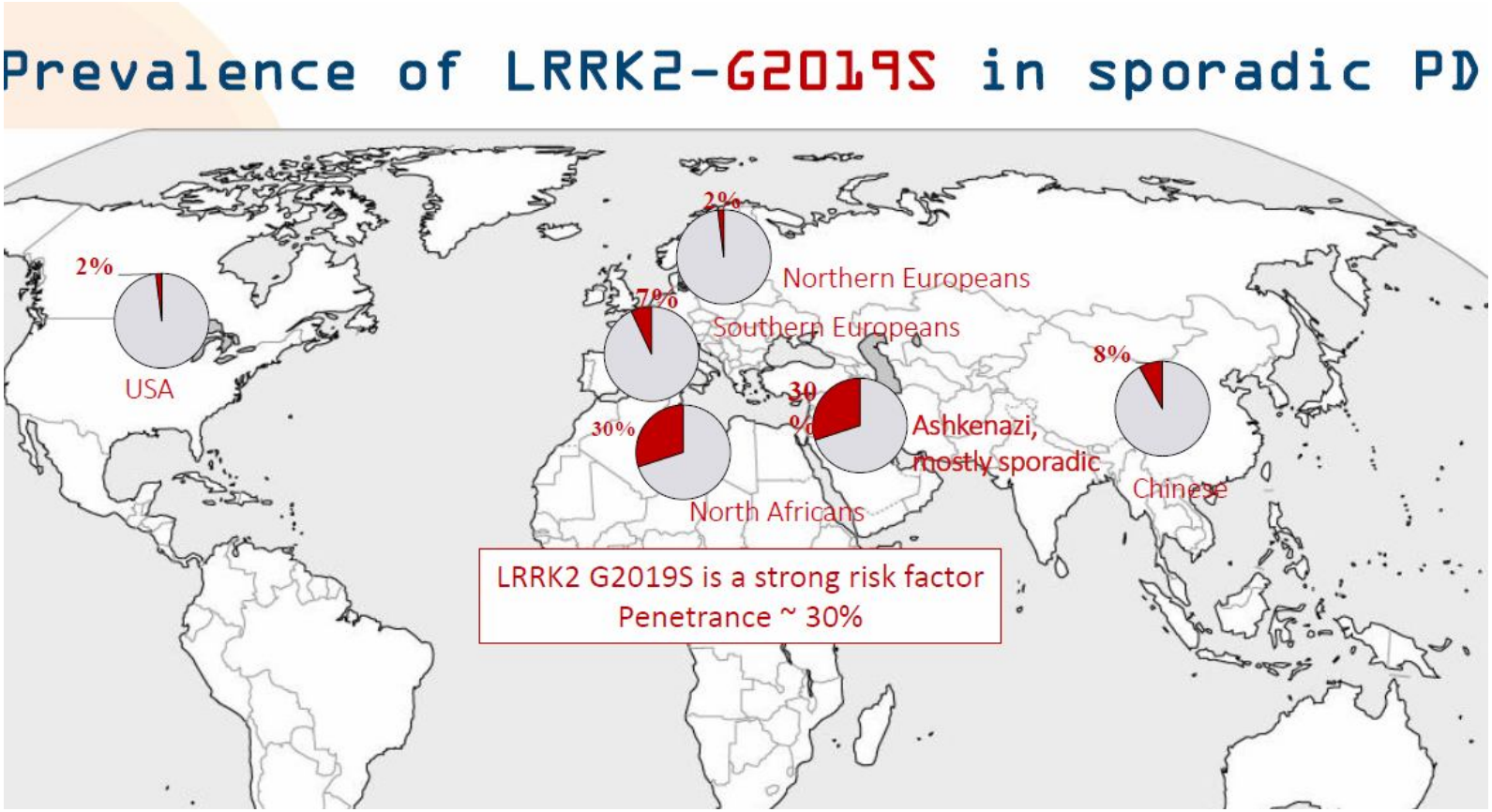
Alice Lazzarini, Ph.D.

Alice Lazzarini slides

LRRK2 & GBA - emerging opportunity?

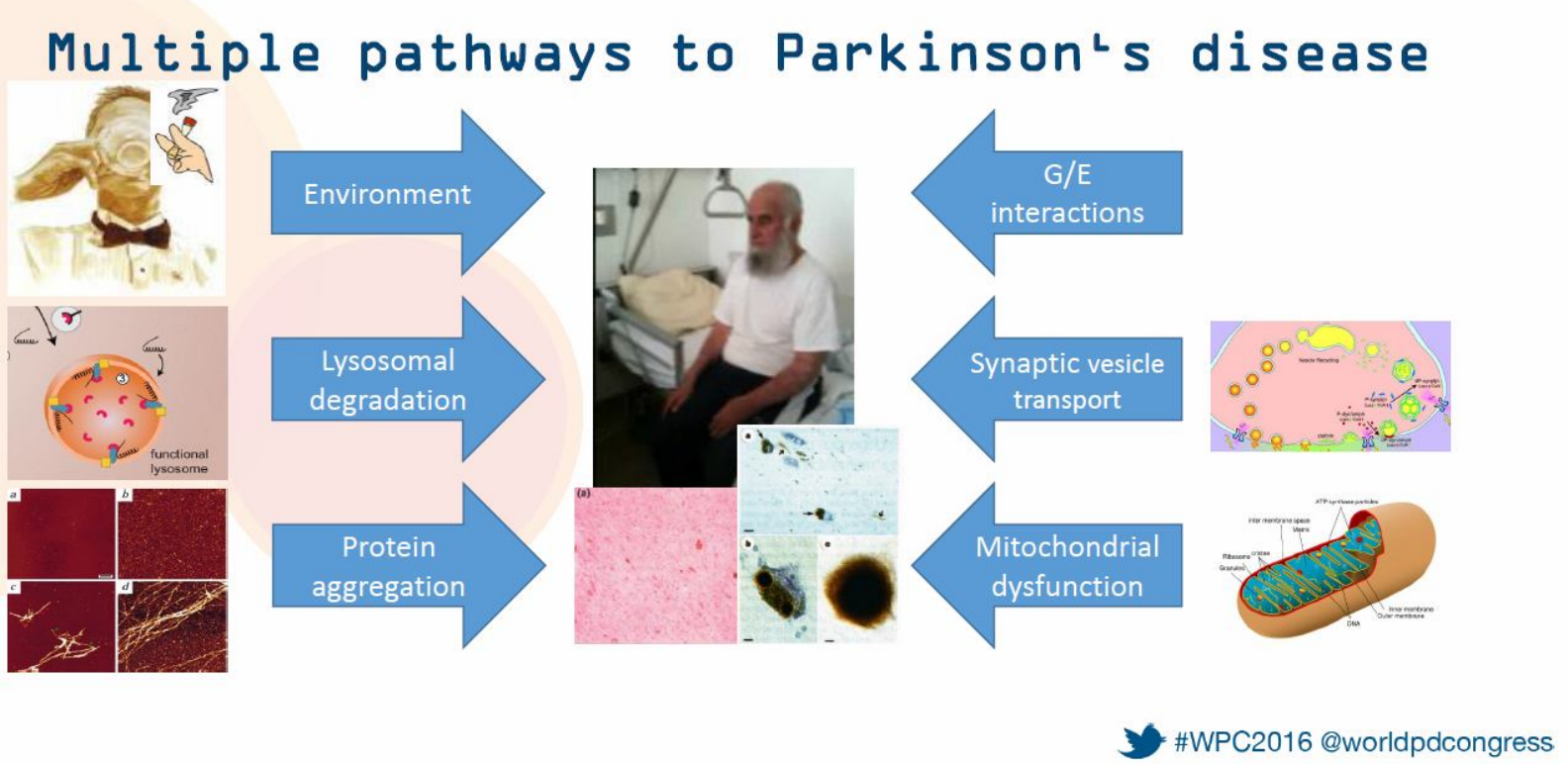


Alice Lazzarini slides



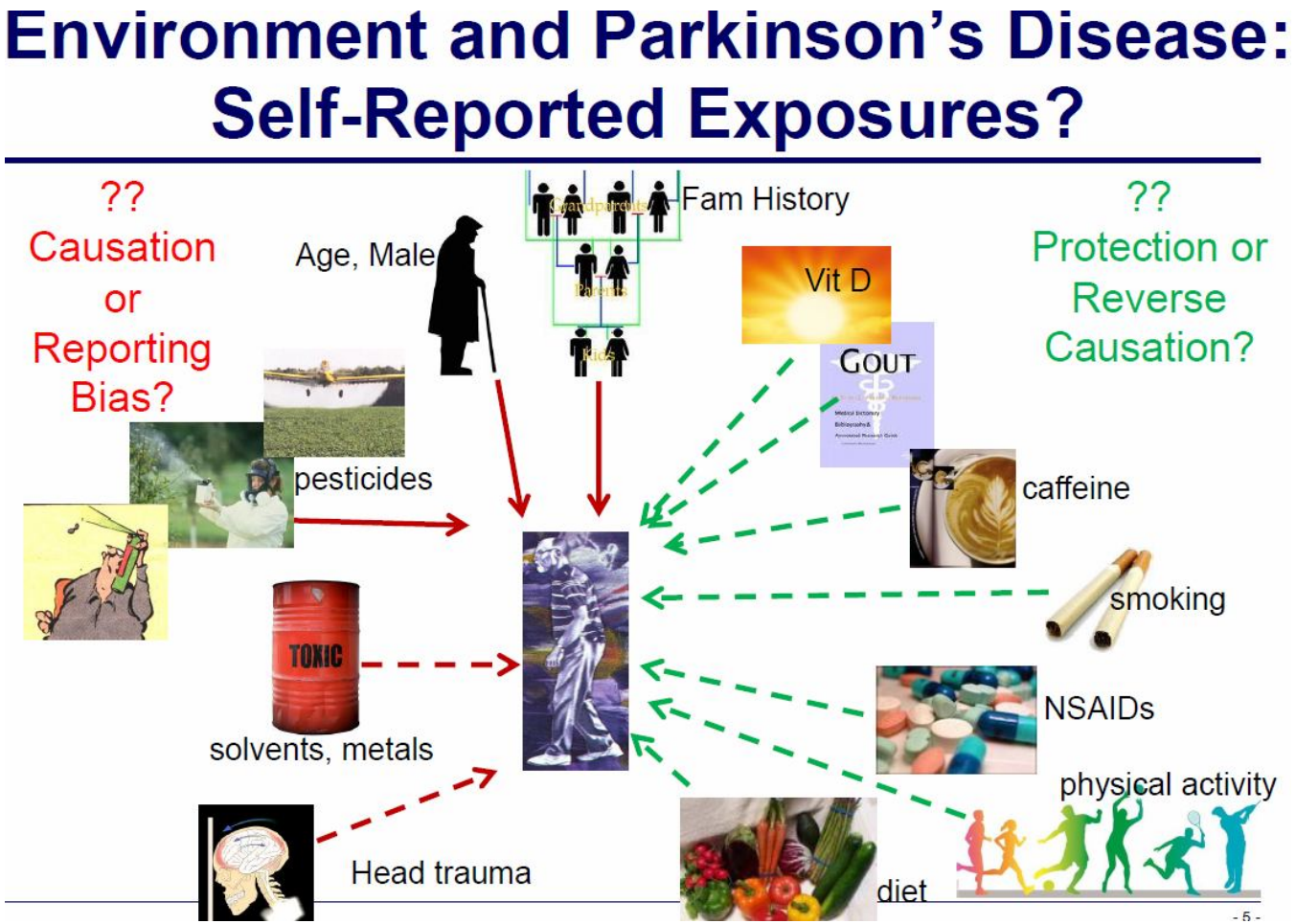
Alice Lazzarini slides

It’s tricky...



Alice Lazzarini slides

So is this..



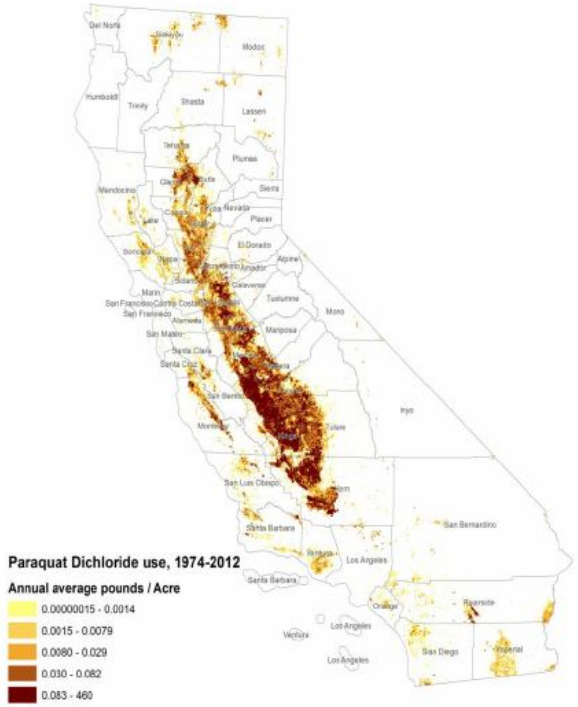
Beate Ritz slides

Pesticides

California is the ideal place to study pesticide health effects : California Agricultural Pesticide Use Reporting (PUR) exists since 1974

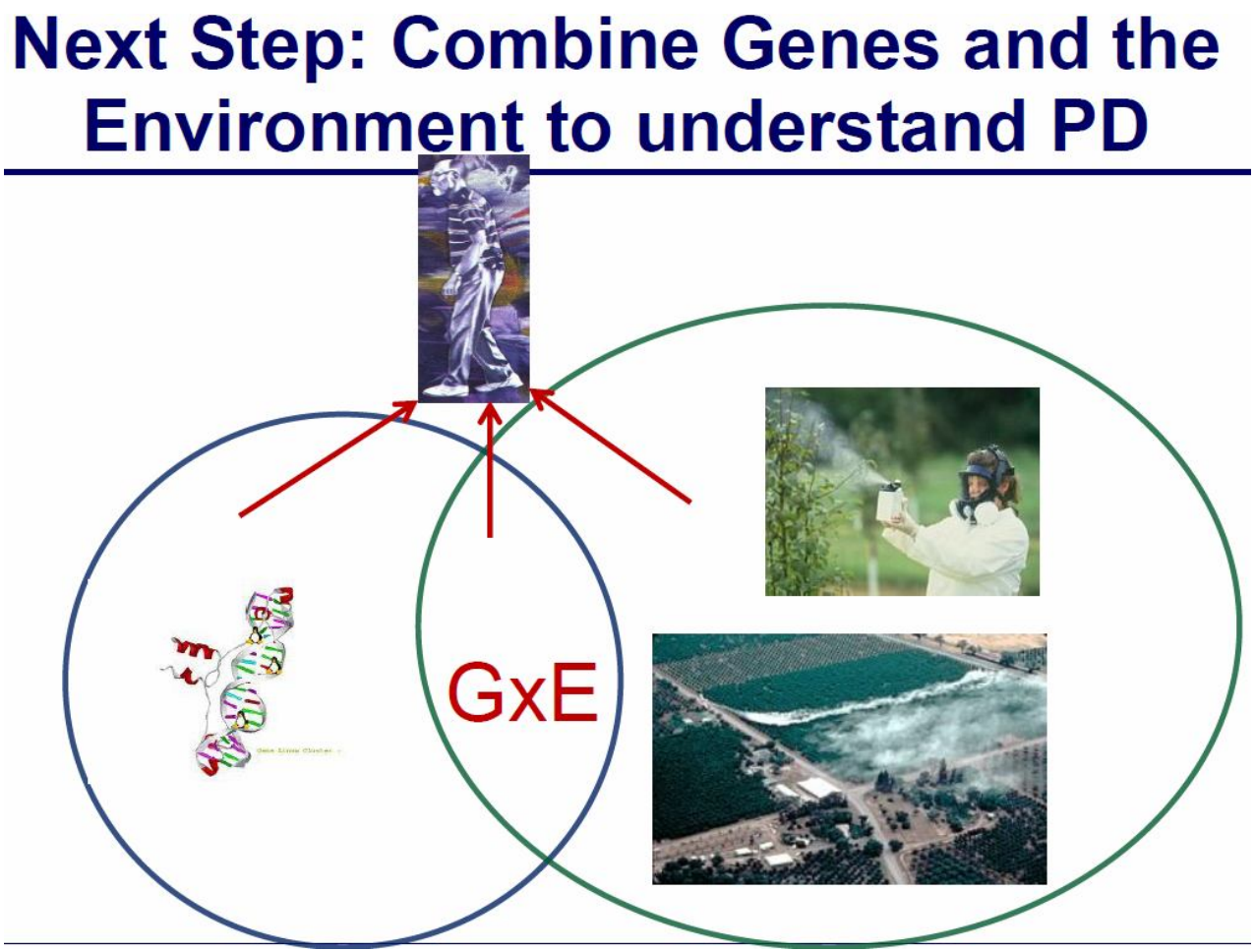
Data provided per 1 square mile land section

- County: Kern
- Location: 15M28S27E19
- Application date: 2/23/1989
- Commodity: 2503 (Grapes)
- Method: Ground
- Treated: 424 acres
- Product applied: 155 gallons
- Chemical: 00459 (Parathion)
- Percentage: 80%
- Active Ingredient Pounds: 1,241



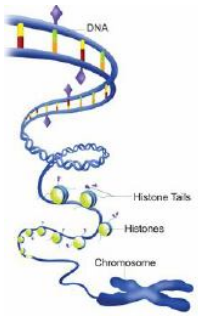
Beate Ritz slides

Putting things together



Beate Ritz slides

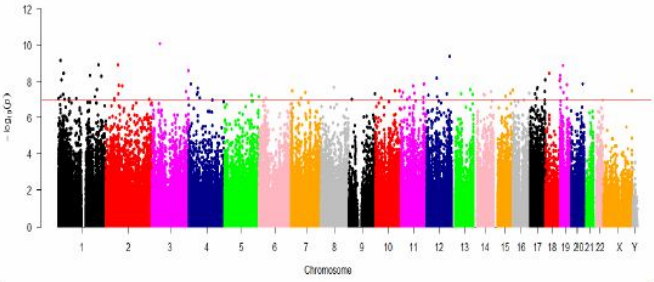
More potential

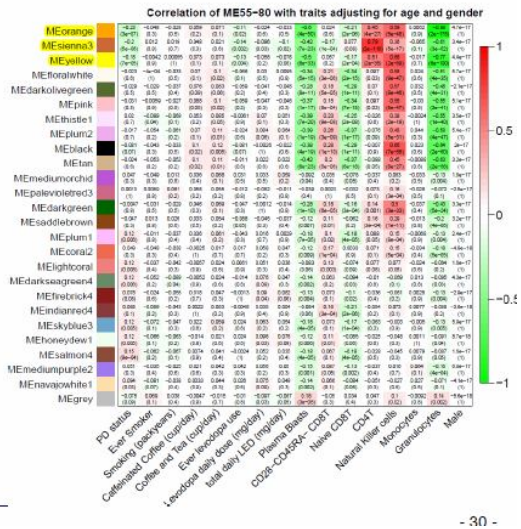


Epigenetics: New Frontier
DNA Methyl Marks in Parkinson's Patients

Epigenetic (methylation) differences in PD patient compared with community control in whole blood and saliva derived tissues related to

1) mitochondrial function
2) systemic immune response
3) cytoskeleton function
4) Wnt signaling pathways
5) iron handling (ferritin)



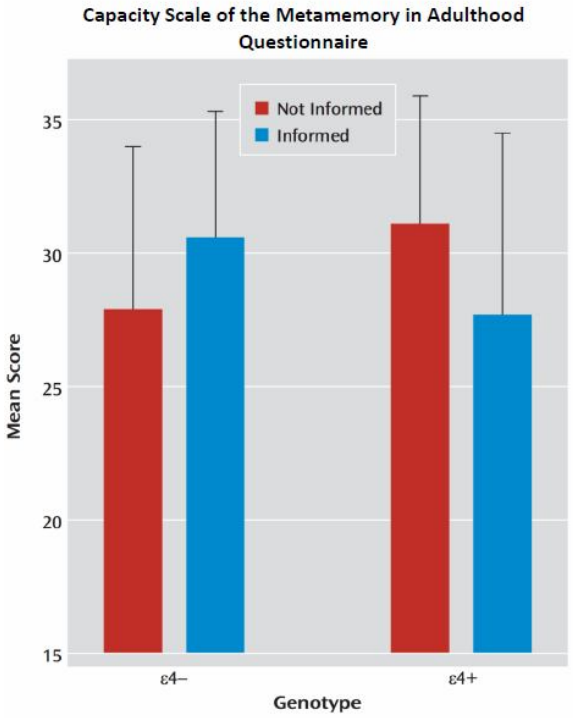


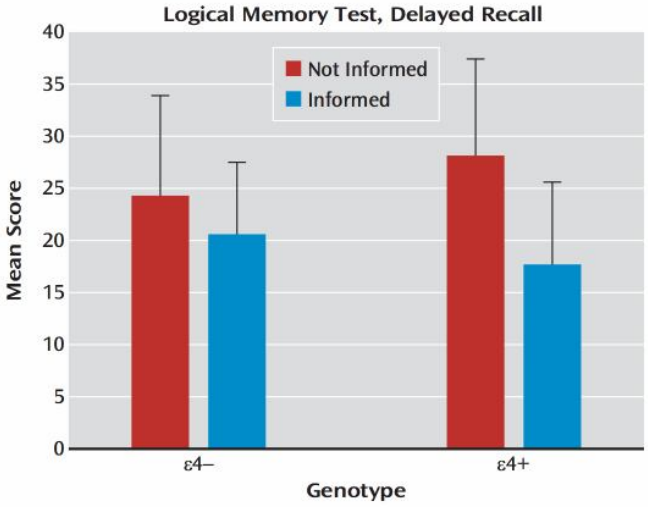
Beate Ritz slides

Adverse effects of information?

People informed about their test result do worse in tests than people not informed

Impact of Knowing APOE result





Lineweaver et al. Am J Psychiatry 2014

Jason Karlawish slides

Taking genetics personally..the conundrum
What can you do & what it'll do to you

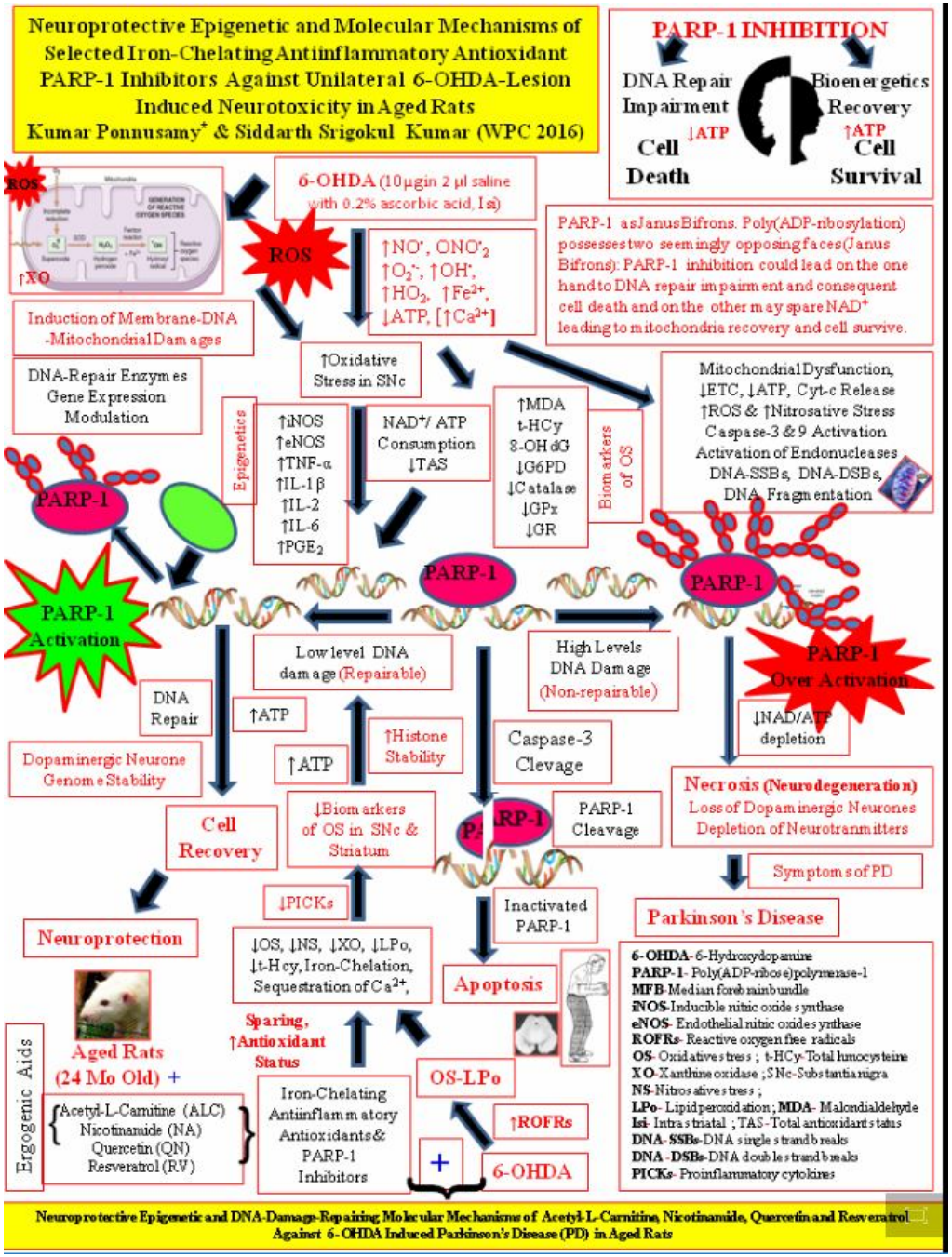
The study of the impact of learning about having PD genes and biomarkers should examine:

- Psychological well-being such as anxiety and depression
- Sense of self
  - Who do you tell: family, friends, employers?
  - What do you tell them? How do they treat you?
- Perceptions of cognitive & physical health
- Perceptions of time

5a – Preventing PD?

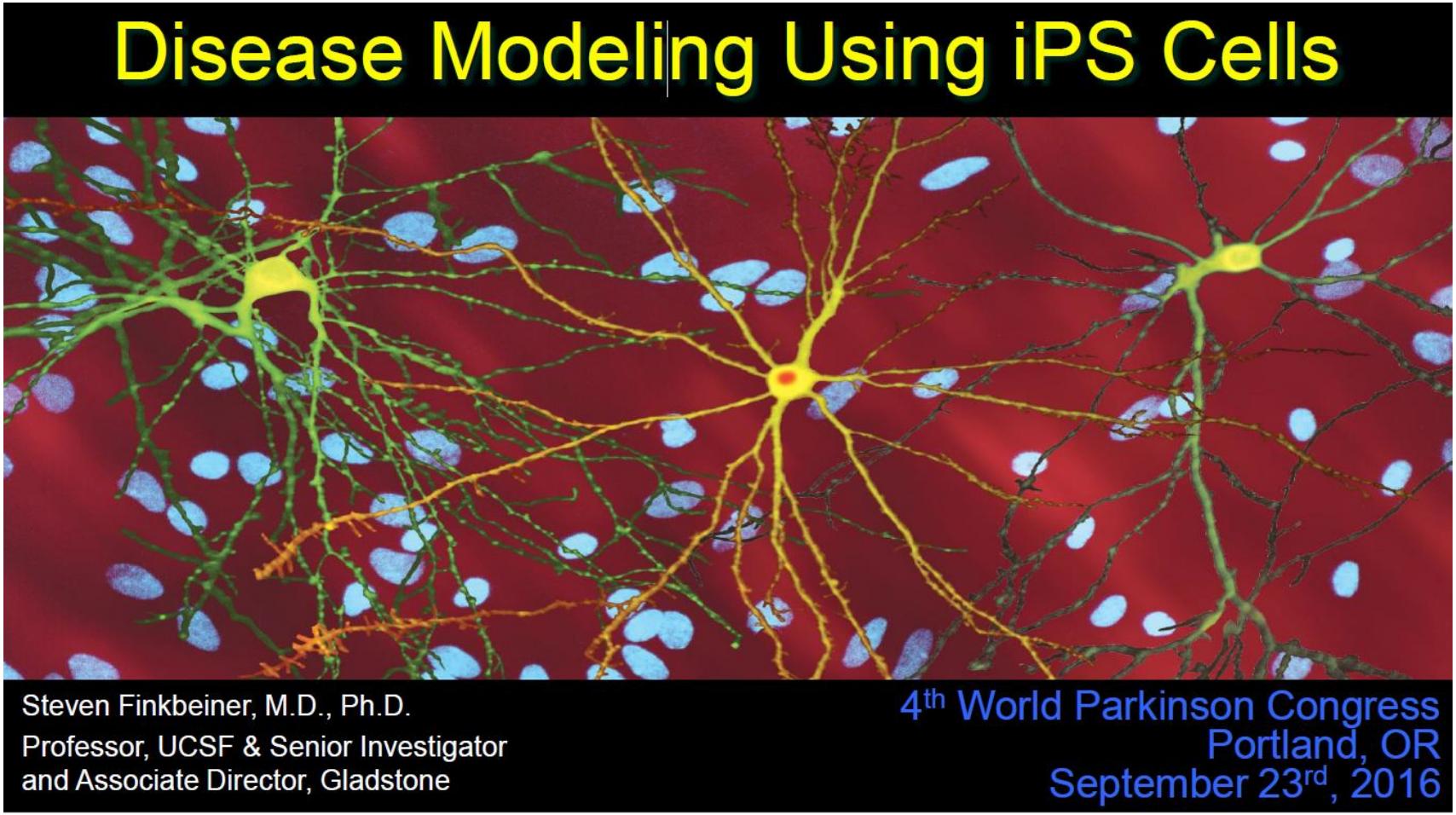
Vaccines?
Can there be protection?

It's *very* complicated…



Helene Doucet-Beaupre slides

6 - Accelerating research into PD



Steven Finkbeiner slides

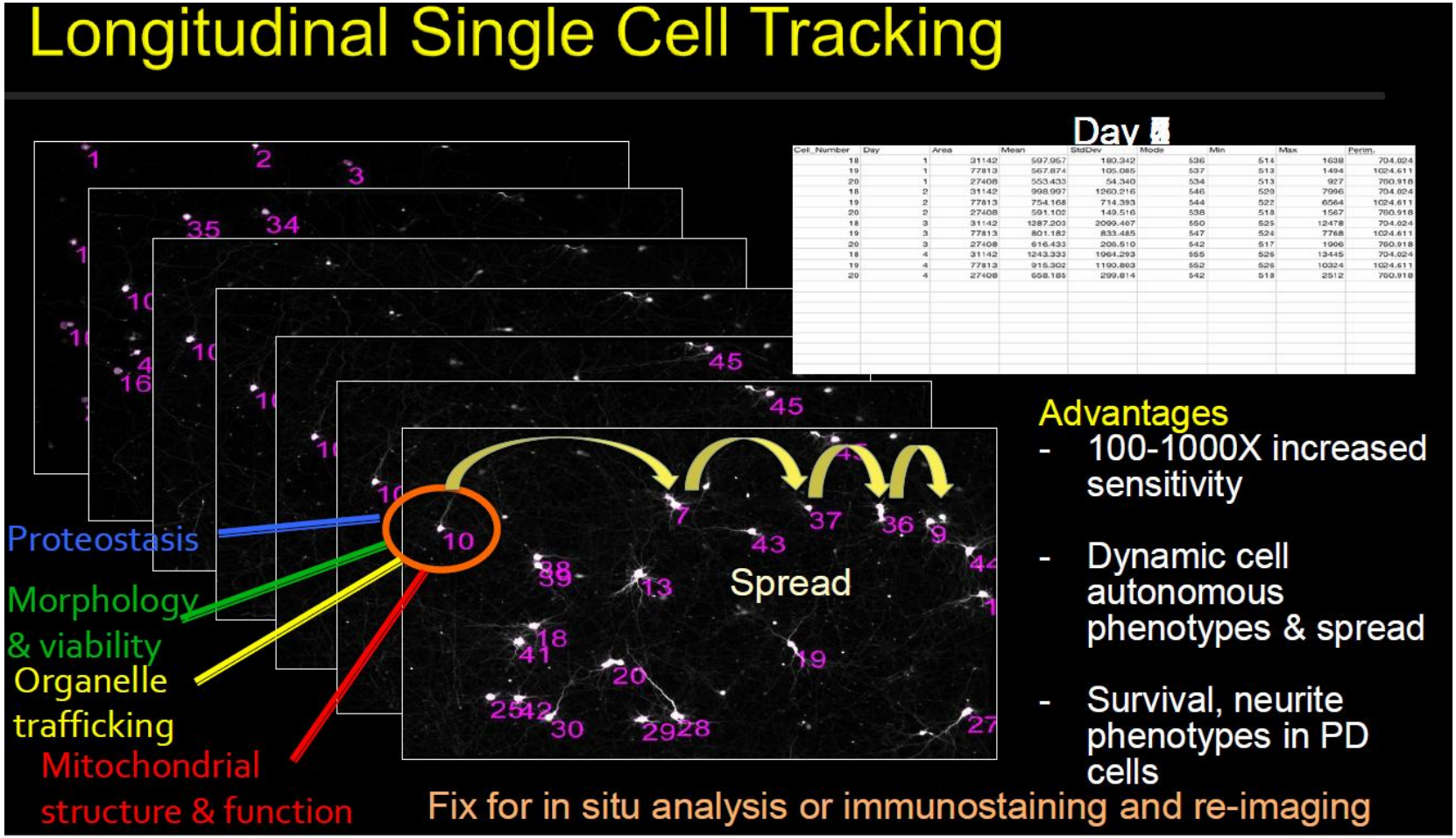
Induced Pluripotent Cell Generation (iPS)

Overview

- The unmet need for more predictive PD models
- Challenges and opportunities of patient-derived iPSCs as an experimental model system
- Applications of PD patient-derived iPSCs
  - To model PD pathobiology
  - To explore mechanisms of PD pathophysiology
  - To substantiate potential targets from PD genetics
  - To develop potentialsmall molecule therapeutics
- Future directions

Steven Finkbeiner slides

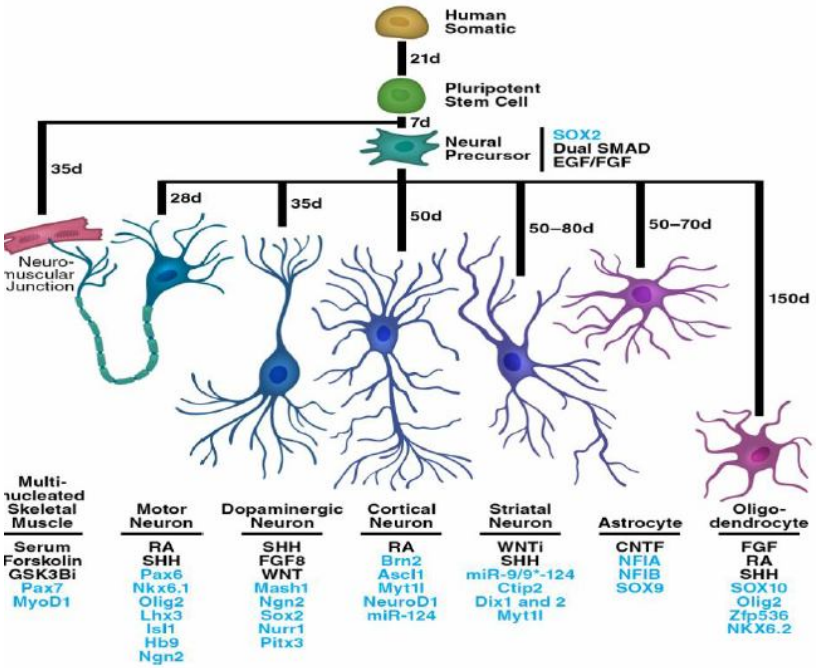
Automated Cell Tracking



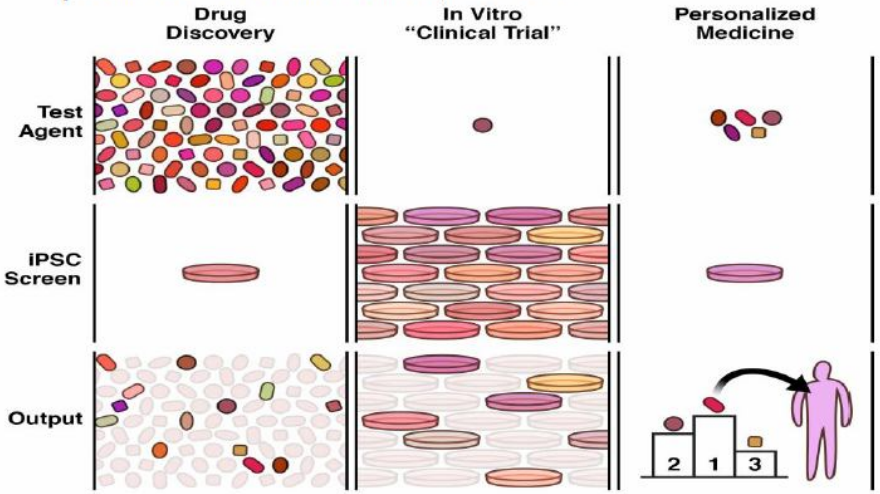
Steven Finkbeiner slides

Potential from PD Modelling

Can iPSC-based Disease Models Make Translation More Reliable and Help Deliver on the Promise of Precision Medicine?



- Human brain cells from patients with clinically defined disease
- iPSCs can be differentiated toward a variety of brain cell types
- Potential applications in drug discovery, patient stratification, etc…



Haston and Finkbeiner, Ann. Rev. Pharm. Tox, (2016)

Steven Finkbeiner slides

A pathway to prediction?

Takeaway Messages

- Patient-derived iPSCs offer exciting new opportunities to create models of PD that may be more predictive
- Human brain cells from PD patients exhibit significant changes in survival and other endpoints that are reminiscent of disease
- Using iPSCs now to understand PD, to find therapeutic targets and therapies
- Success depends on teamwork between patients, donors, funding agencies and companies

Steven Finkbeiner slides

The End!
(of this bit...)

- S-t-r-e-t-c-h exercises!

1. Levodopa
2. (mention of DBS)
3. Mention of alpha-synuclein
4. Cell restoration?
5. Genetics
6. Disease modelling