Australian Parkinson's Mission

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Is Dementia Inevitable in PD

Movement Disorders
Vol. 23, No. 6, 2008, pp. 837–844

The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years

Mariese A. Hely, MBBS,[1*] Wayne G.J. Reid, PhD,[1] Michael A. Adena, PhD, ASTAT,[2]
Glenda M. Halliday, PhD,[3] and John G.L. Morris, MD[1]

- Sydney "invented" dementia
  - At 20 years – 80% dementia

Prevalence of PDD

- Prevalence of PDD 28%
  - Aarsland et al *Arch Neurol 1996*
- UK community-based study 44% of PD patients met DSM IV criteria for dementia.
  - Hobson & Meara *Age Ageing 1999*

Neuropathology in PDD

- Concomitant Alzheimer's Disease
- Lewy body degeneration
  - Limbic or cortical
- Subcortical pathology
  - Loss of neurotransmitters
- Cerebral Amyloid Angiopathy
- Cerebrovascular disease

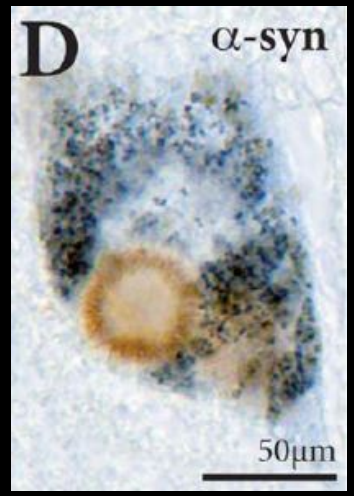
Predominant AD pathology in PDD

- 200 consecutive PD autopsy examinations
- 33% had moderate to severe dementia
- PDD correlated with AD pathology
- 94% of PDD had cortical changes of AD
- Only 3% with neuropathological changes representative of PD alone had PDD
- Lewy body pathology was not examined in this study

Jellinger et al *J Neural Transm 2002*

Lewy body related pathology in PDD

- Differential Lewy body density load
  - Harding & Halliday Acta Neuropathol 2001
- Even after correcting for AD pathology
- Temporal lobe
  - PDD>> PD
- Frontal and limbic cortical regions
  - PDD=PD



Memory Training for PD

Movement Disorders

Official Journal of the Movement Disorder Society

Improving memory in Parkinson's Disease: Evaluation of a healthy brain ageing cognitive training

Sharon L. Naismith, BA Hons, MClinNpsych, DPsych, MAPS, CCN, Loren Mowszowski, BPsych Hons, DPsych, Kerri Diamond BPsych Hons, Dpsych, and Simon J.G. Lewis, MBBCh, BSc, MRCP, FRACP, MD*

- 7 weeks
- Twice weekly
  - Education
  - Brain exercises
- All stages H&Y

Rivastigmine for PDD

- EXPRESS study
- 541 patients with mild to moderate PDD
  - Rivastigmine (up to 12 mg/day)
  - Placebo
  - 24 weeks
- Primary endpoints significantly improved
  - Alzheimer's Disease [AD] Assessment Scale–Cognitive Subscale [ADAS-cog]
  - Clinical Global Impression of Change scale

Emre et al N Engl J Med 2004

Rivastigmine for PDD

- Secondary endpoints significantly improved
  - Mini–Mental State Examination
  - Neuropsychiatric Inventory
  - Clock drawing test
  - Verbal fluency
  - Computer-based attention tests
- Activities of Daily Living (ADL) scores
  - Significantly worse decline in Placebo group

Emre et al N Engl J Med 2004

Rivastigmine for PDD

- Adverse events significantly increased in treatment arm
  - Nausea and vomiting
  - Worsening of tremor 10% rivastigmine patients
  - UPDRS part III: Non significant
- Subgroup analysis
- Hallucinators derived more cognitive benefits

Emre et al N Engl J Med 2004

Rivastigmine for PDD

- 6-month extension period
  - Beneficial effects maintained
    Poewe et al Mov Disord 2006
- No evidence of worsening motor function
  - Oertel et al Drug Saf 2008

Donepezil for PDD

- 550 patients with mild-to-moderate PDD
  - Placebo for 24 weeks
  - Donepezil 5 mg/day for 24 weeks
  - Donepezil 10 mg/day for 24 weeks
- Primary endpoints NOT significant
  - ADAS-cog
  - Global measure of change from baseline

Dubois et al Mov Disord 2012

N-Methyl-D-Aspartate Antagonists in PD

- Memantine
  - Approved for treatment of AD
- Glutamatergic dysfunction in PDD?
- 199 patients either with DLB or PDD
  - Memantine or Placebo
- PDD
  - No benefit
- DLB
  - Global outcome scale improved

Emre M et al Lancet Neurol 2010

Pharmacological Treatment: PD-MCI

- 69 non-demented PD-MCI
  - Galantamine (16-24 mg) for 16 weeks
  - Placebo for 16 weeks
- Primary endpoints
  - No significant improvements
- Adverse events significant
  - Gastrointestinal (GI) side effects
  - Self-reported worsening of PD symptoms

Grace et al JNNP 2009

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
AMERICAN ACADEMY OF NEUROLOGY®

April 09, 2019; 92 (15 Supplement) MAY 5, 2019

SYN120 (a dual 5-HT6/5-HT2A antagonist) study to evaluate safety, tolerability, and efficacy in Parkinson's disease dementia (SYNAPSE): Phase 2a study results (S4.005)

- SYN120
  - Did not improve cognition in PDD
  - May have improved cognition-based daily function
  - Generally well tolerated
  - But a worsening in motor symptoms was observed

JAMA Neurology | Original Investigation

Bilateral Deep Brain Stimulation of the Nucleus Basalis of Meynert for Parkinson Disease Dementia

A Randomized Clinical Trial

- London, UK
  - 6 PDD patients
  - Low-frequency NBM DBS
- No SAEs
- Primary cognitive outcomes
  - No improvements

A Study of LY3154207 in Participants With Dementia Due to Lewy Body Dementia (LBD) Associated With Idiopathic Parkinson's Disease (PD) or Dementia With Lewy Bodies (DLB) (PRESENCE)

Eli Lilly and Company

ClinicalTrials.gov Identifier: NCT03305809

- USA
  - Estimated Completion Date 22/06/2020
- LY3154207
  - Enhancer of dopamine receptor D1
  - Modulating Attention

ANAVEX2-73 Study in Parkinson's Disease Dementia

Anavex Life Sciences Corp ClinicalTrials.gov Identifier: NCT03774459

- Spain and Australia
  - Estimated Completion Date 31/12/2019
- Anavex2-73
  - Muscarinic receptor agonist
  - Sigma1 receptor agonist
  - Anti-apoptotic and anti-oxidant activity

To Assess the Efficacy and Safety of Ceftriaxone in Patients With Mild to Moderate Parkinson's Disease Dementia

BrainX Corporation

ClinicalTrials.gov Identifier: NCT03413384

- Taiwan
  - Estimated Completion Date 31/12/2020
- Ceftriaxone
  - Reduces glutamatergic hyperactivity and excitotoxicity
  - May exhibit neuro-protective functions

Ambroxol as a Treatment for Parkinson's Disease Dementia

Lawson Health Research Institute

ClinicalTrials.gov Identifier: NCT02914366

- Canada
  - Estimated Completion Date 31/12/2021
- Ambroxol
  - Raise levels of the enzyme beta-glucocerebrosidase
  - Lowers levels of the alpha-synuclein

What do we mean by *treating dementia*

- Parkinson's Dementia
  - Chemistry set or Circuits
  - Inexorable cell death
- Treat Dementia or Disease?
  - Cure?

What do we mean by *cure*

- Parkinson's doesn't happen over night
  - Long prodromal (non-motor) period
  - 5-20 years?
- Would a cure reincarnate dead cells?
  - Probably not…
- Does a cure need to offer reincarnation?
  - Probably not…
  - Would stopping progression = Cure

Clues to a Cure?

- Genetics
- Environment
- Pathology

Genetics and Parkinson's Disease

- A number of genes have been reported
  - *Causative* and *Risk*
- 10% of all cases
- Most *Causative* gene cases
  - Very strong family history
  - Very young onset
- However, influence of *Risk* genes
  - General population: 1 in 1000 have PD
  - PD patients: 1 in 10 have a family history

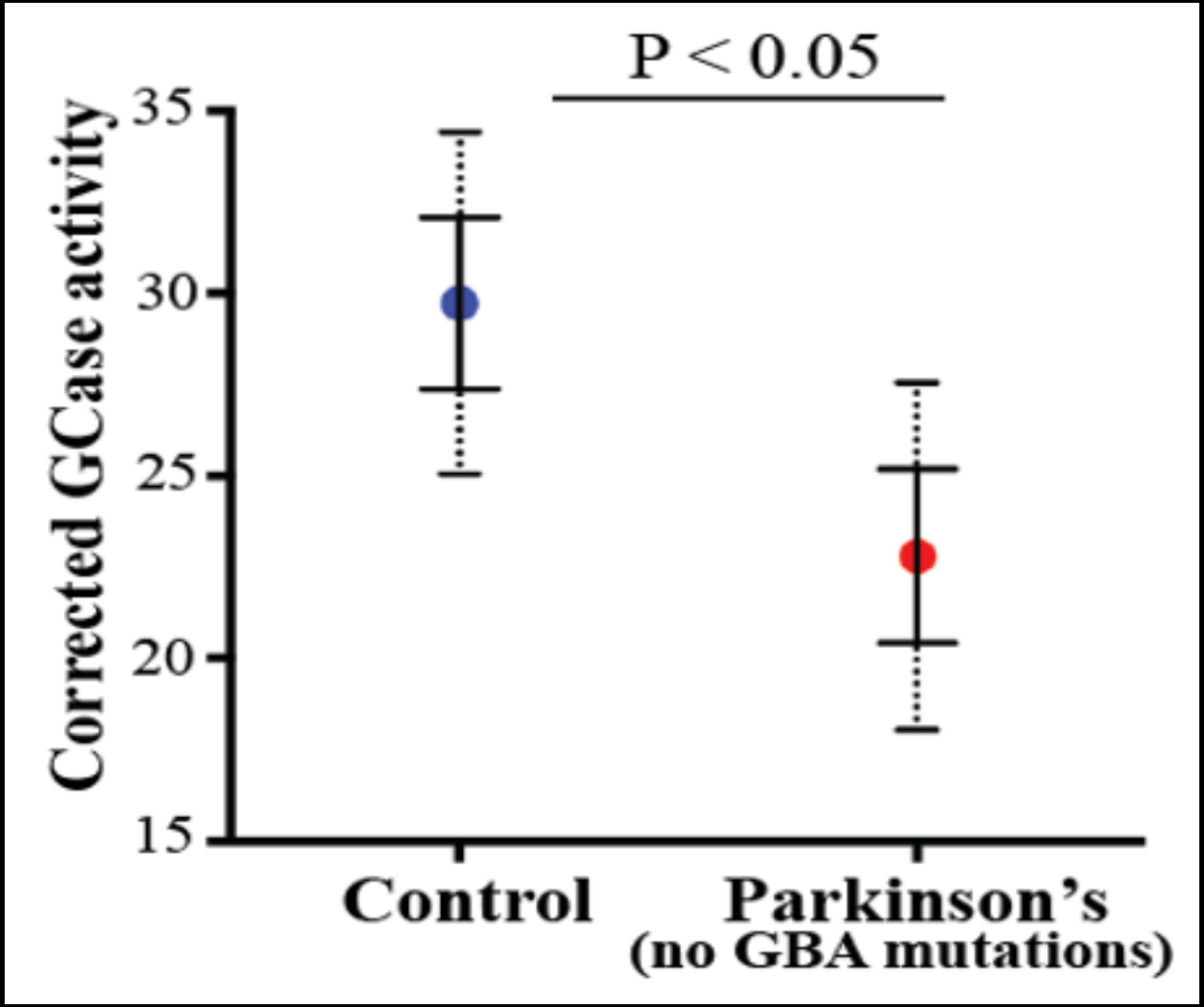
What do genes tells us about Parkinson's Disease

- Genes encode proteins
  - Building blocks
  - Enzymes that do things
- Over expression
  - Excess of protein that can then become tangled
  - Alpha-Synuclein
- Under expression
  - Not enough enzyme to clear garbage
  - Fail to regulate energy pathways, inflammation

Glucocerebrocidase Enzyme

- Glucocerebrocidase
  - Clears protein from the cell via the lysosome
- Gaucher's Disease
  - Rare storage disease (no enzyme)
  - Usually causes death in childhood
  - Ashkenazi Jewish populations
- Heterozygous – one mutated gene
  - 5-10% of PD

Glucocerebrocidase Activity



Atashrazm et al Nature Scientific Reports 2018

Environmental factors and Parkinson's Disease

- World wide risk is equal
- Increase risk of developing PD
  - 'Heavy' exposure to pesticides
  - Interaction between pesticides and risk genes
  - *Beta-Blockers (anti-hypertensives)
- Reduce risk of developing PD
  - Caffeine
  - Smoking! Not due to early death from Cancer
  - *Inhalers (Beta-Agonist)

*PLEASE DO NOT STOP ANY OF YOUR MEDICATIONS

Possible role of Beta-Agonists

- Beta2-Adrenoreceptor
  - Regulates the Alpha-Synuclein gene (*SNCA*)
- Beta-blocker
  - Up-regulated SNCA
- Beta-agonist
  - Down-regulated SNCA

Mittal et al Science 2017

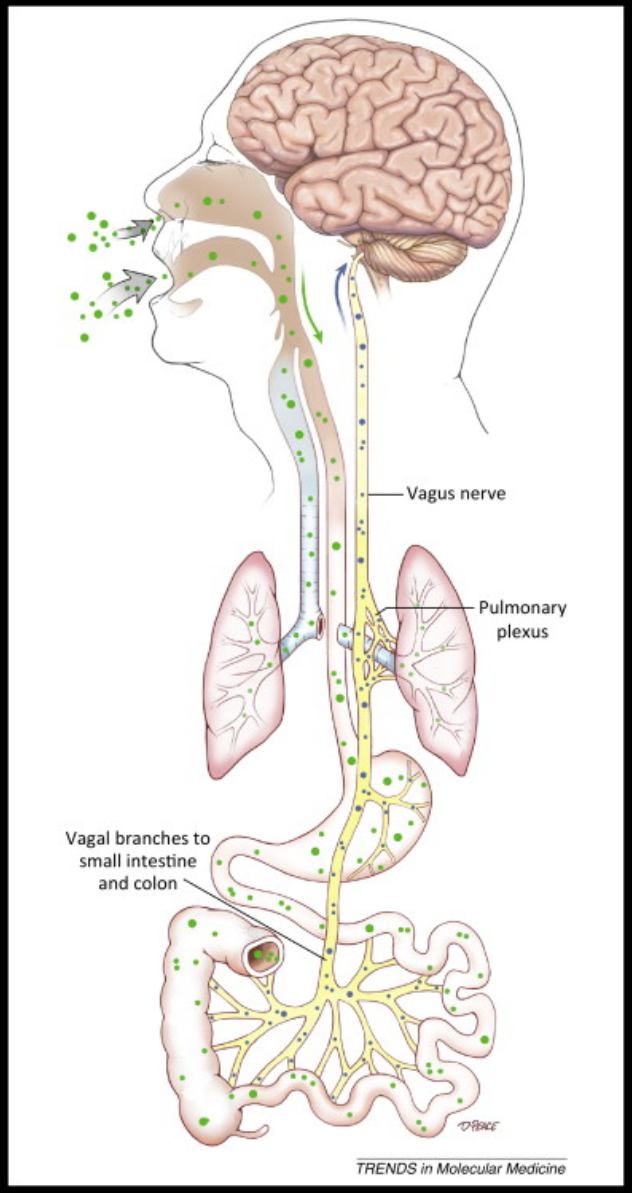
Infection and Parkinson's Disease

The *Parkinson* Connection

1. Muhammed Ali
2. Billy Connelly
3. Michael Redgrave
4. Bob Hoskins
5. Terry Thomas
6. *Robin Williams*

Prion-like Hypothesis

- Inhalation
- Ingestion

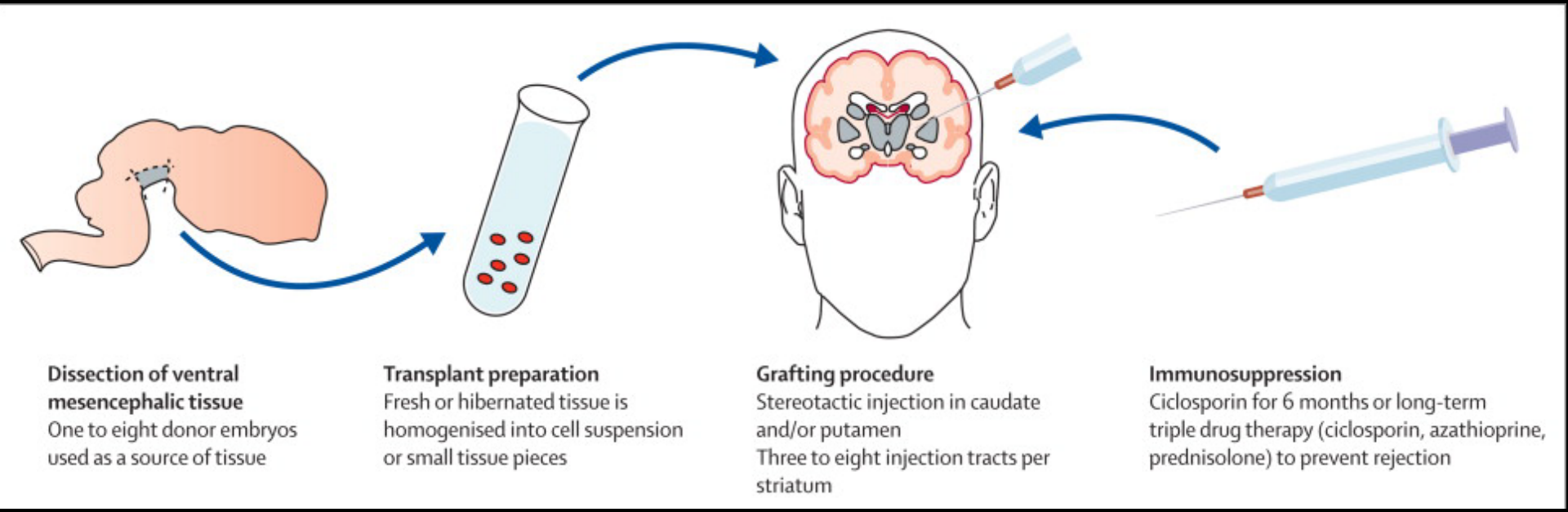


PNAS

Is Parkinson's disease a prion disorder?

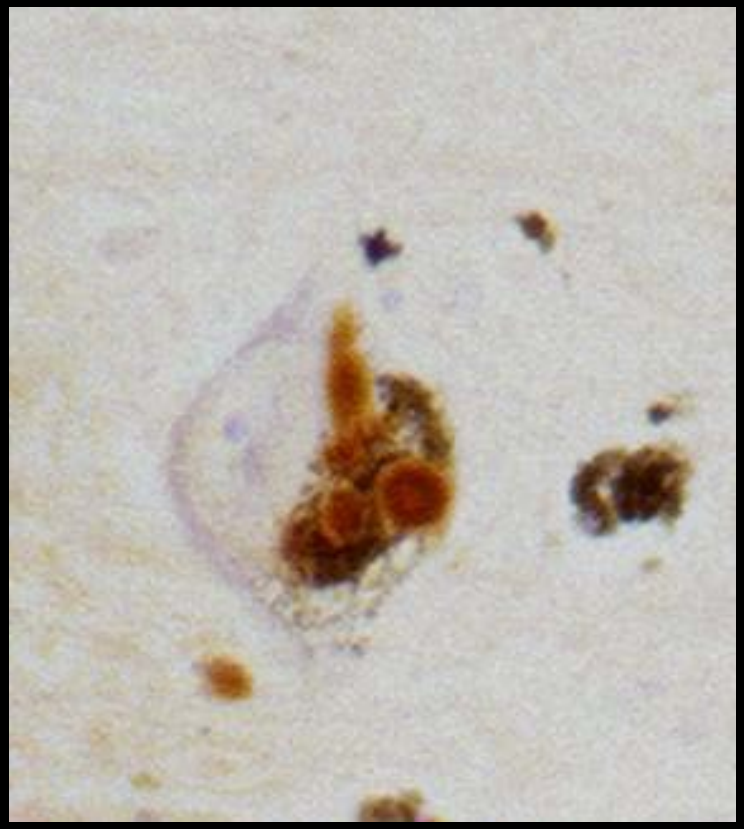
C. Warren Olanow[a,1] and Stanley B. Prusiner[b]

- Foetal graft trials
  - Freed et al
  - Green et al

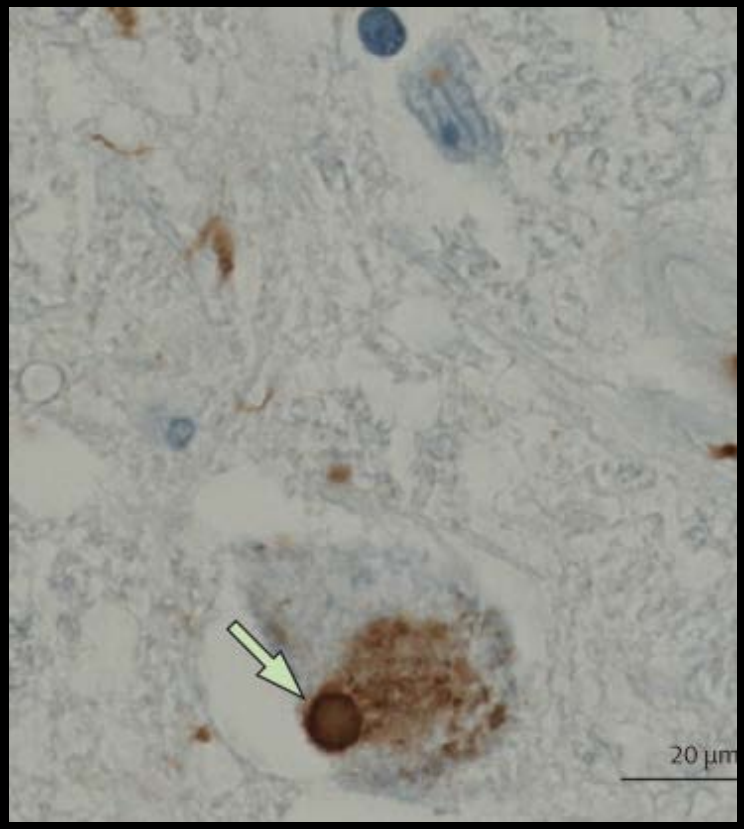


Prion-like Hypothesis

Parkinson's



Foetal Transplant



Is PD a prion-like disease?

- Caveats
  - Lewy Bodies not usually found in the Striatum
  - PD grafts only very few cells “transfected”
  - Toxicity of α-synuclein not proven (bystander?)
- Animal Models
  - Progression of α-synuclein much quicker
  - Allows testing but… different?

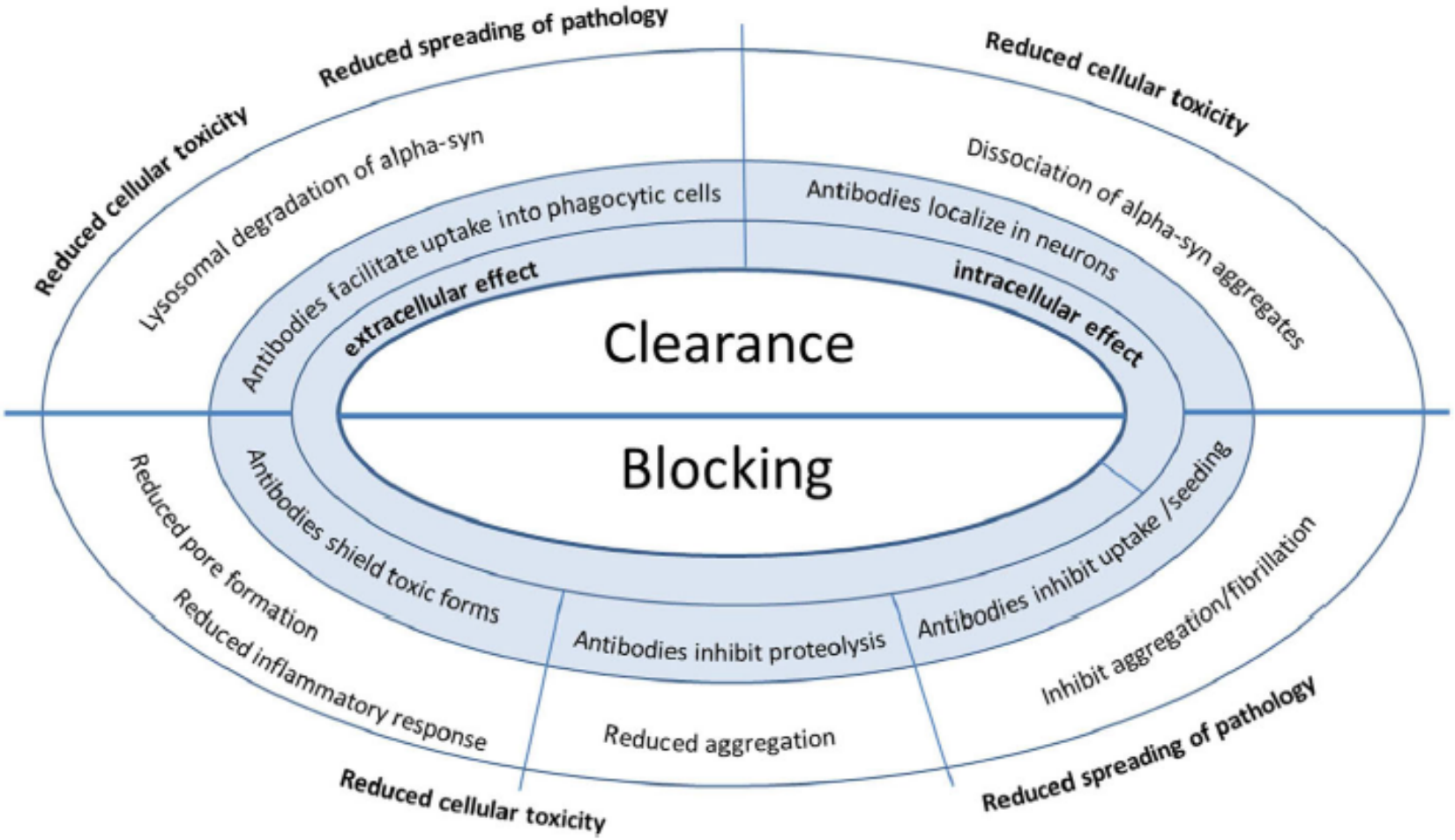
Parkinson’s Vaccine?

- Active immunisation
  - Vaccination program?
  - Generate immunity following exposure to pathogen
  - Easier to upscale and provide herd immunity

Targeted Immunotherapy

- Passive immunisation
  - Provide specific antibodies targeted to pathogen
- Already in use
  - Rheumatoid, Inflammatory Bowel Disease…
- Timing
  - Would it work in Advanced cases
- Costs and repeat dosing?

Passive Immunisation for Synucleinopathy



Berstrom *et al* Mov Disord 2015

Passive Immunisation Clinical Trials

- Prothena Biosciences and Hoffmann-La Roche (NCT02095171)*
  - Targets epitope around amino acid 122
  - 40 Healthy Controls
  - IV increasing PRX002 antibody dosing
  - Highest doses used dropped peripheral α-synuclein to undetectable levels
- PD trial (NCT02157714) April 2016
  - 60 Patient H&Y I-III
  - Safety/Tolerability study

*LBA at MDS San Diego 2015

Safety Data

JAMA Neurology | Original Investigation

Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti–α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease

A Randomized Clinical Trial

Joseph Jankovic, MD; Ira Goodman, MD; Beth Safirstein, MD; Tonya K. Marmon, DrPH; Dale B. Schenk, PhD; Martin Koller, MD, MPH; Wagner Zago, PhD; Daniel K. Ness, DVM, PhD; Sue G. Griffith, MD, PhD, MRCP; Michael Grundman, MD, MPH; Jay Soto, BS; Susanne Ostrowitzki, MD, PhD; Frank G. Boess, PhD; Meret Martin-Facklam, PhD; Joseph F. Quinn, MD; Stuart H. Isaacson, MD; Omid Omidvar, MD; Aaron Ellenbogen, DO; Gene G. Kinney, PhD

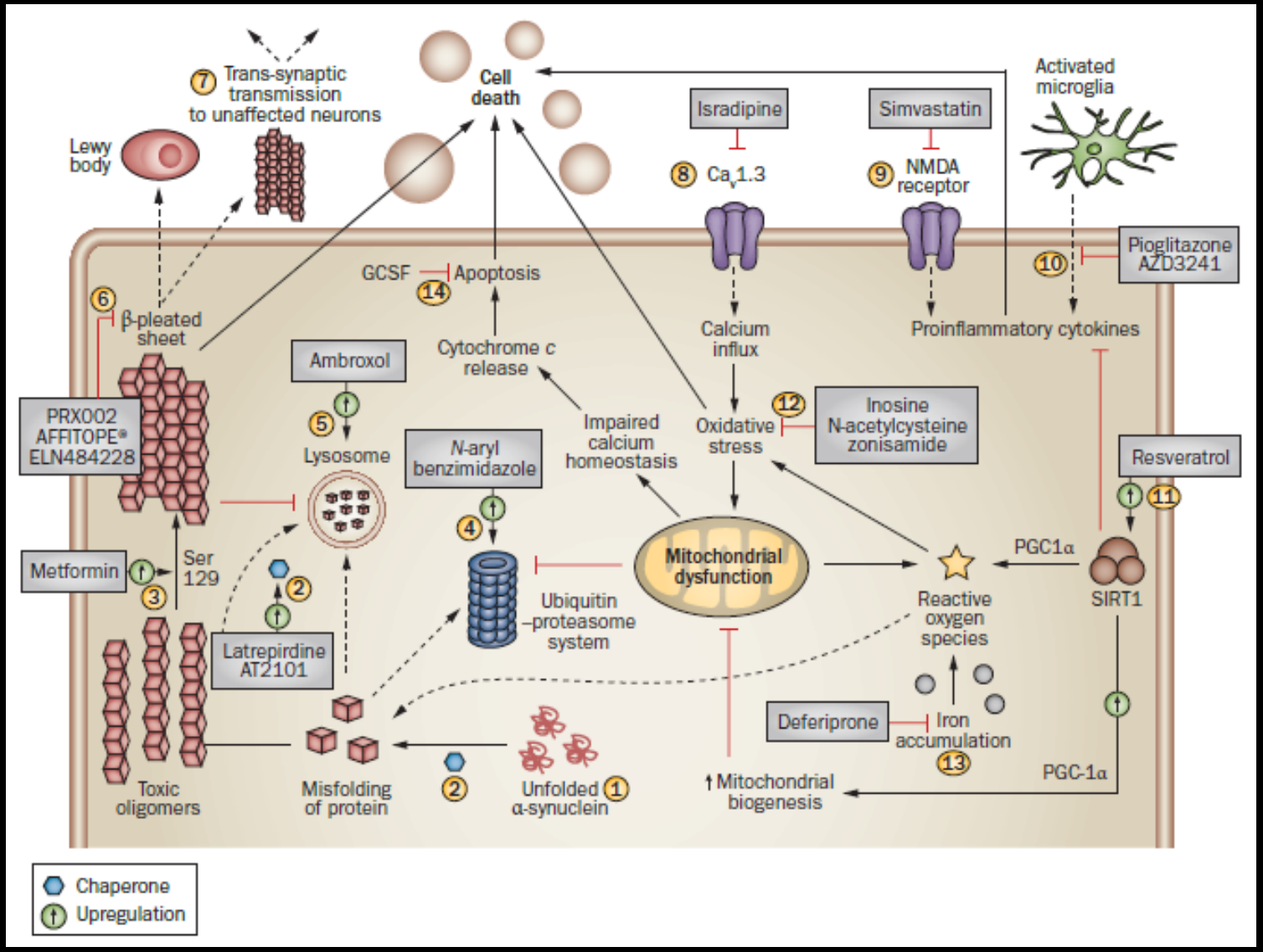
TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02157714

JAMA Neurol. 2018;75(10):1206-1214. doi:10.1001/jamaneurol.2018.1487
Published online June 18, 2018.

- 24 week exposure
  - Safety/Tolerability study
  - Phase II study recommended

Jankovic et al Neurology 2018

Neuroprotective Targets



Athauda & Foltynie Nature Reviews Neurology 2015

Neuroprotective Targets

MJA 208 (9) • 21 May 2018
Perspective

Disease-modifying approaches for Parkinson disease

While a cure might be far off, concerted efforts targeting disease modification are ramping up

- Iron chelation
- Calcium Homeostasis
- Neuroinflammation
- Oxidative Stress

doi: 10.5694/mja17.01135

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Podcast with Simon Lewis available at https://www.mja.com.au/podcasts

Australian Parkinson’s Mission

- Shake it Up Foundation
- Garvan Institute
- University of Sydney
- Cure Parkinson’s UK
- Michael J Fox Foundation
- Parkinson’s Australia

Path to a Cure

- Advances in our understanding
  - Genetics
  - Clinical epidemiology
  - Basic science
- Novel Targets
  - Cellular pathways
- Linked Clinical Trials Initiative
  - Shake it Up (AUS)
  - Cure Parkinson's Trust (UK)
  - Michael J Fox Foundation (USA)
  - Van Andel Instititute (USA)

Australia's Role

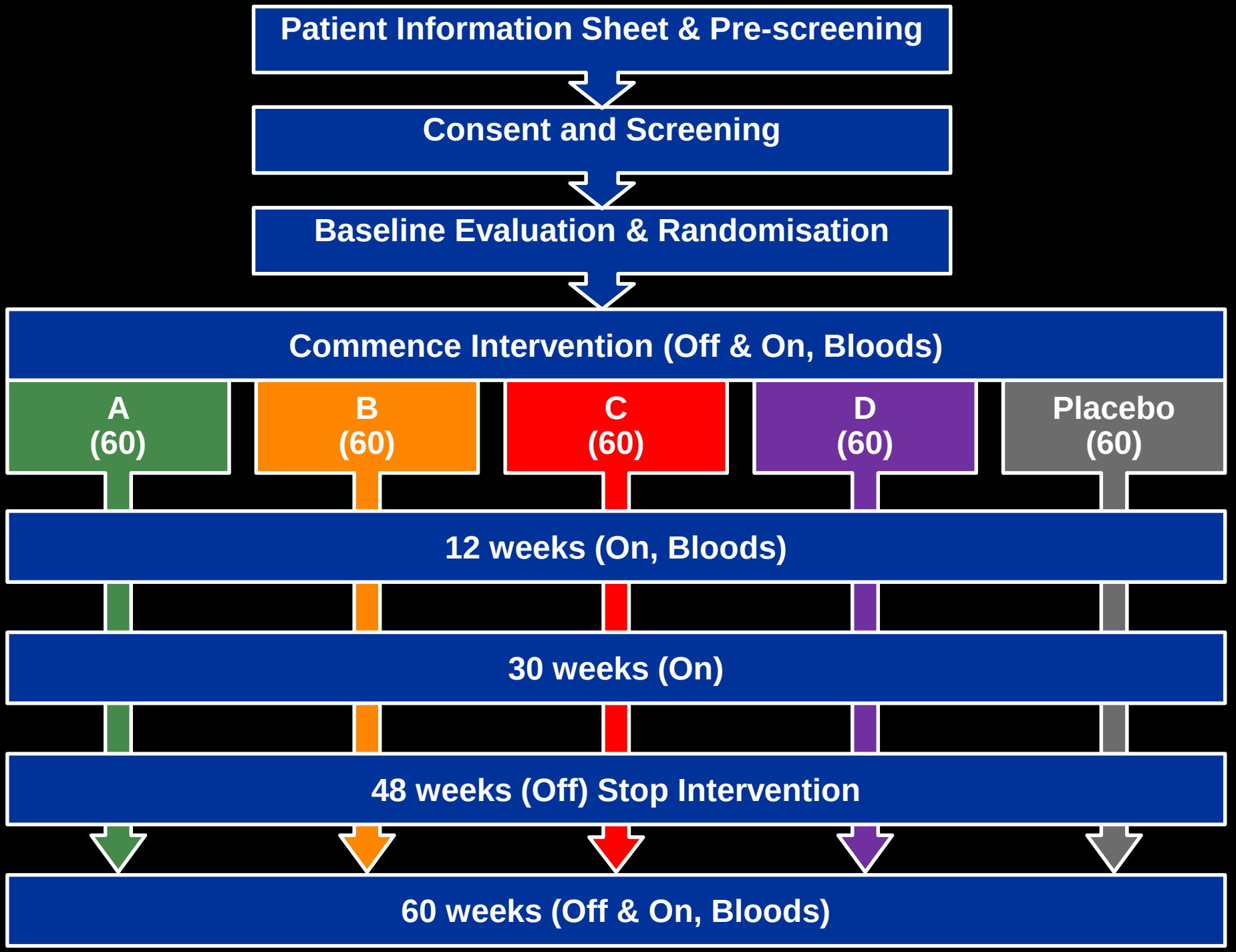
- Patients
  - Large population
  - Very willing
  - Previously 'excluded'
- Clinical workforce
  - Highly trained healthcare professionals
  - Clinical trials expertise
- Leading scientists
  - Biomarkers
  - Genomics

Australian Parkinson's Mission

- Federal Government
  - $30M MRFF
- Large scale Phase II Clinical Trials
  - Rapid screening of candidate medications
  - Umbrella Multi-arm v Single Placebo protocol
  - Novel and Repurposed treatments
- Precision Medicine
  - Embedded Biomarker and Genomic data
  - 'Target' and 'Disease' engagement
  - Genomic signatures for 'success'

Current Initiative

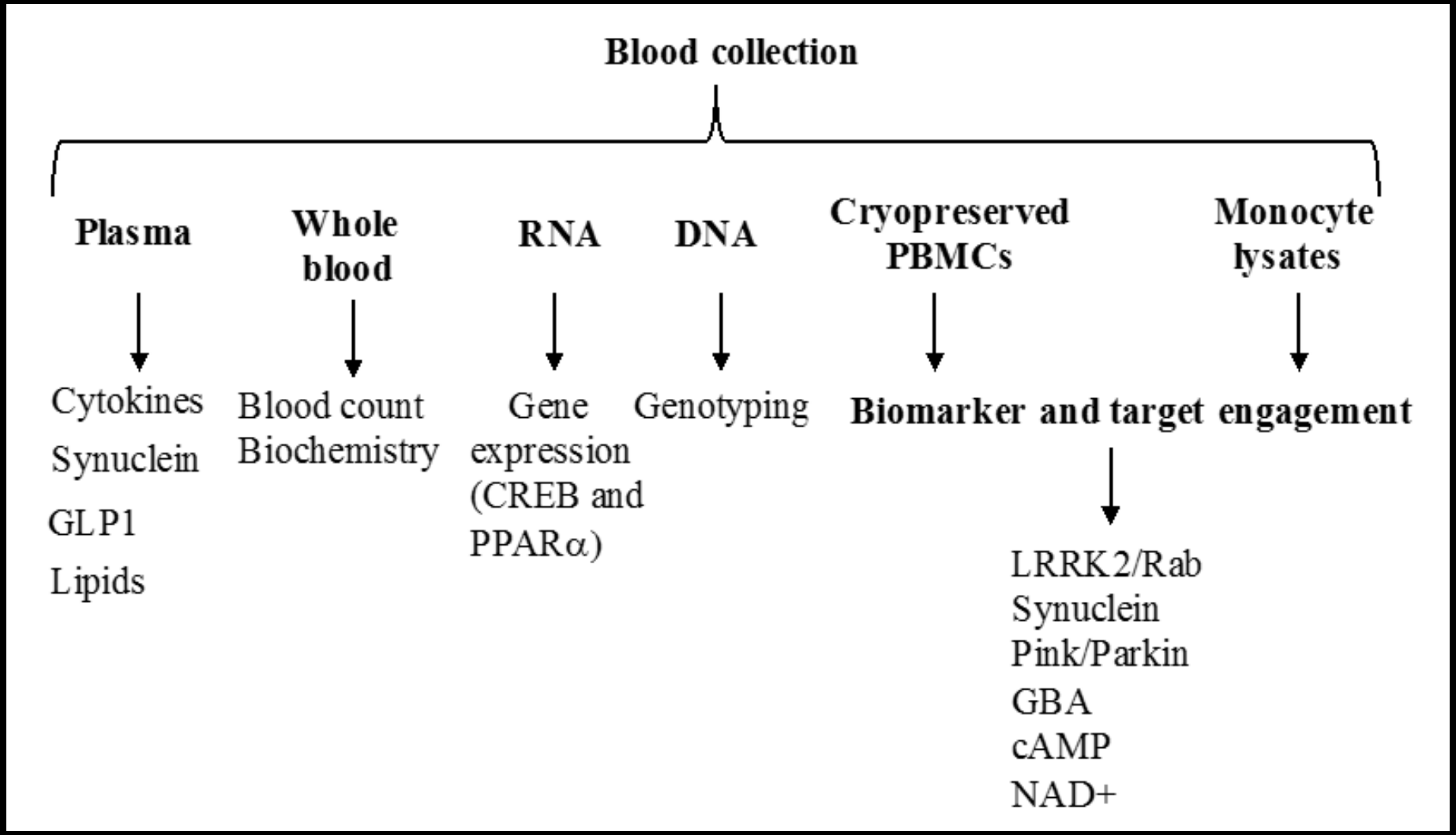
- NSW, QLD & Victoria
  - Simon Lewis, Dom Rowe, John O'Sullivan & Kelly Bertram
  - Glenda Halliday, Nic Dzamko. Richard Gordon & Antony Cooper
- Expandable model
  - Additional sites WA, SA and ACT


Patient Information Sheet & Pre-screening
Consent and Screening
Baseline Evaluation & Randomisation
Commence Intervention (Off & On, Bloods)
A (60)
B (60)
C (60)
D (60)
Placebo (60)
12 weeks (On, Bloods)
30 weeks (On)
48 weeks (Off) Stop Intervention
60 weeks (Off & On, Bloods)

Strategy

- Mixed targets
  - A, B, C and D all different proposed mechanisms of action
- No imaging
- No CSF
- Biomarkers and Genomics

Overview


Blood collection
Plasma
Whole blood
RNA
DNA
Cryopreserved PBMCs
Monocyte lysates
Cytokines
Synuclein
GLP1
Lipids
Blood count
Biochemistry
Gene expression (CREB and PPARα)
Genotyping
Biomarker and target engagement
LRRK2/Rab
Synuclein
Pink/Parkin
GBA
cAMP
NAD+

Target Engagement

- Inflammatory pathways
- Oxidative stress
- Mitochondrial function
- Calcium homeostasis
- Insulin signalling pathways
- Etc… Etc…

Disease Engagement

- Glucocerebrocidase (GCase)
- Leucine-rich repeat kinase 2 (LRRK2)
- P-Ten induced putative kinase 1 (PINK1)
- Alpha-synuclein

Genomics

- Probe genotyping and gene expression
- RNA and DNA dataset
  - Machine learning
  - Artificial intelligence
  - Pattern recognition

Current Status

- CRO engaged
- Protocol writing and database build
  - Commenced
- Investigational Products
  - Sourced and blinding with over encapsulation
- Sites identified
- Time line
  - Q1 2020

Summary

- Problem
  - Parkinson's is a growing socio-economic challenge
- Solution
  - Willing patients, clinicians and scientists
  - Rapid identification of potential cures
  - Precision medicine
- Next steps
  - Patients, Clinicians and Scientists **YES**
  - International partners **YES**
  - Your support ***HOPEFULLY***

Resources

Website: http://www.theapm.org.au

Slides: http://bit.ly/CuringPD

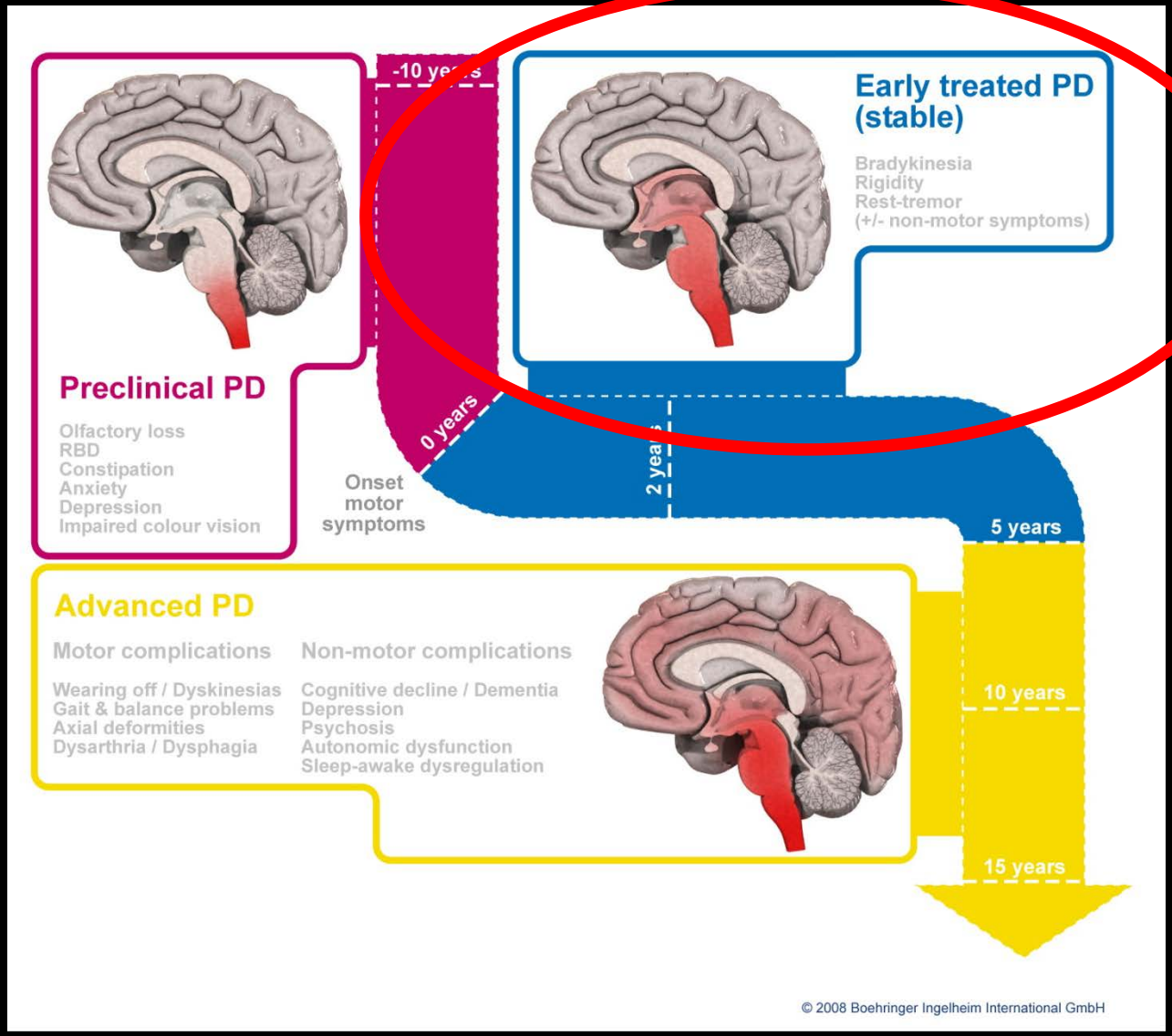
Website: http://www.profsimonlewis.com

Email: profsimonlewis@gmail.com

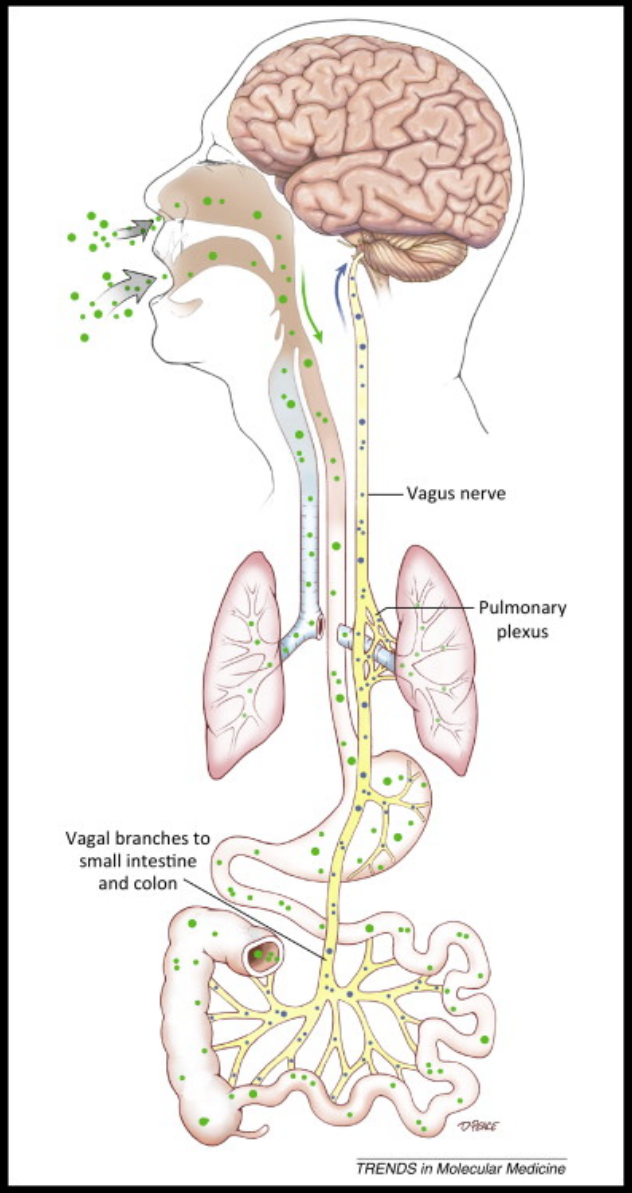
@profsimonlewis


MASTER CLASS
DISEASES OF THE
AGEING BRAIN
UNIVERSITY OF SYDNEY – OCTOBER 12TH & 13TH 2019
http://bit.ly/MasterClassBrain2019

Evolution of Pathology



Prion-like Hypothesis



- Inhalation
- Ingestion

Window on a Cure

	LR^+
Risk markers	
Male sex	1.2 (male)
Regular pesticide exposure	1.5
Occupational solvent exposure	1.5
Nonuse of caffeine	1.35
Smoking	
Current	n/a
Never	1.25
Former	n/a
Sibling had PD with age onset <50	7.5
or	
Any other first-degree relative with PD	2.5
Known gene mutation	see Supporting Table II
SN hyperechogenicity	4.7
Prodromal markers	
PSG-proven RBD	130
or	
Positive RBD screen questionnaire with >80% specificity	2.3
Dopaminergic PET/SPECT clearly abnormal (e.g., <65% normal, 2 SDs below mean)	40
Possible subthreshold parkinsonism (UPDRS >3 excluding action tremor)	10
or	
abnormal quantitative motor testing	3.5
Olfactory loss	4.0
Constipation	2.2
Excessive daytime somnolence	2.2
Symptomatic hypotension	2.1
Severe erectile dysfunction	2.0
Urinary dysfunction	1.9
Depression (± anxiety)	1.8

Berg et al Mov Disord 2015

Dream Enactment (RBD)

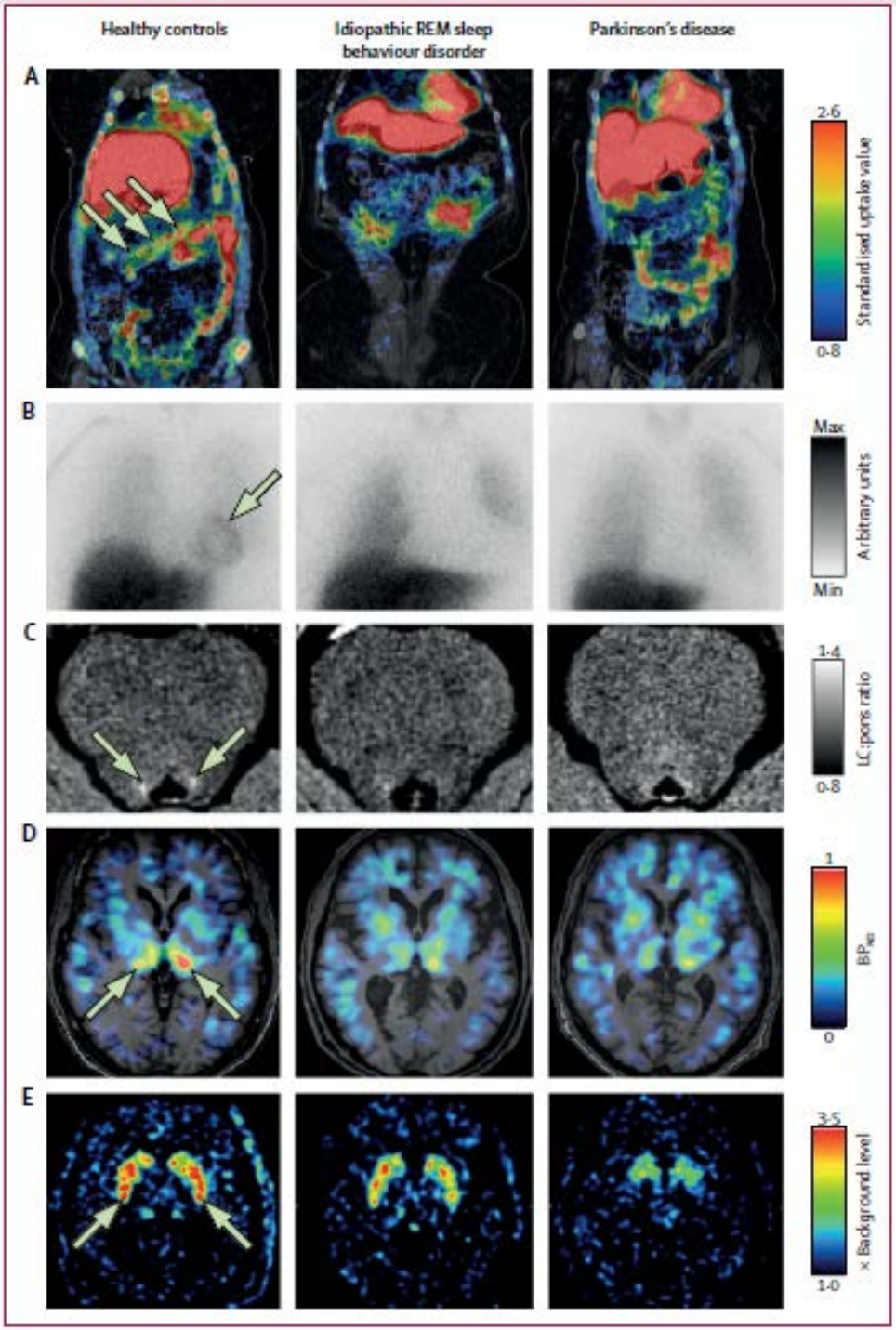
Evidence of Prodromal Disease

Lancet Neurol 2018; 17: 618–28

In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study

Karoline Knudsen, Tatyana D Fedorova*, Allan K Hansen, Michael Sommerauer, Marit Otto, Kristina B Svendsen, Adjmal Nahimi, Morten G Stokholm, Nicola Pavese, Christoph P Beier, David J Brooks, Per Borghammer*

- iRBD patients
  - Peripheral and Central markers of disease
  - Does the disease spread up?
  - Are different nerve cells differentially affected?
  - Does it matter if we can be confident!

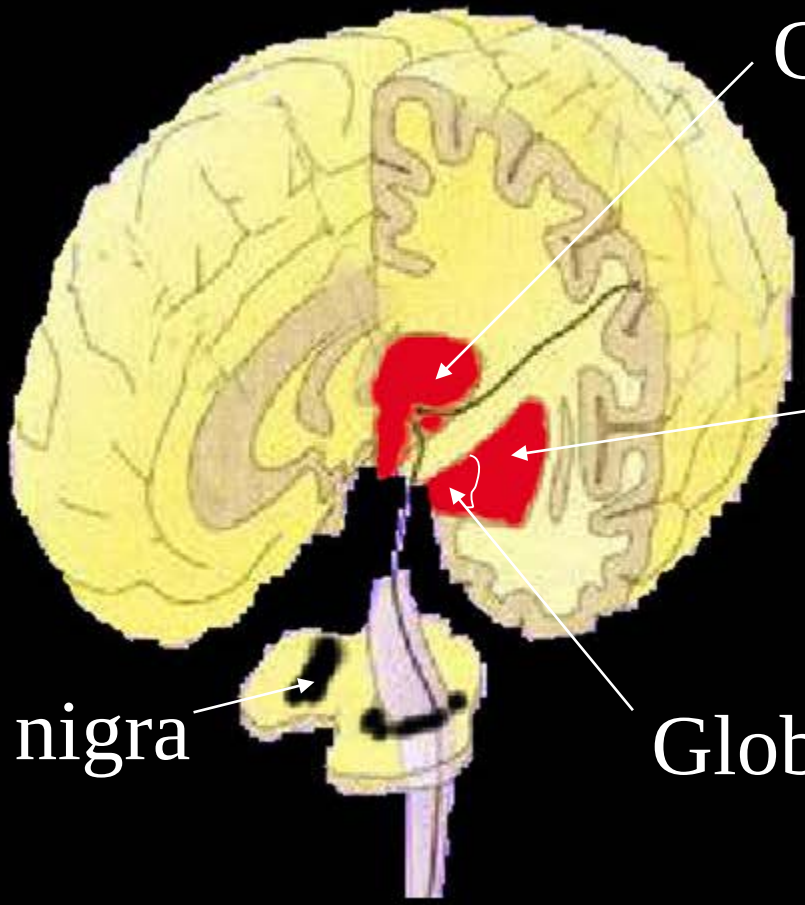


Knudsen et al Lancet Neurology 2018

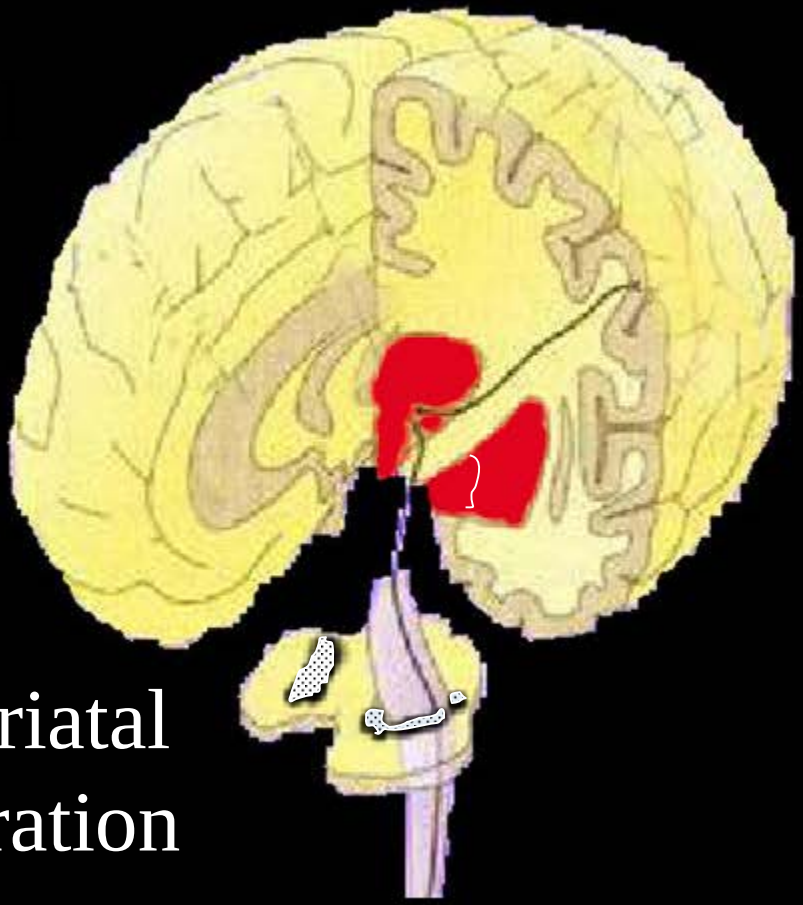
Curing Parkinson's Disease

- Might be possible for some
  - Identify at risk cohorts

Dopamine pathology

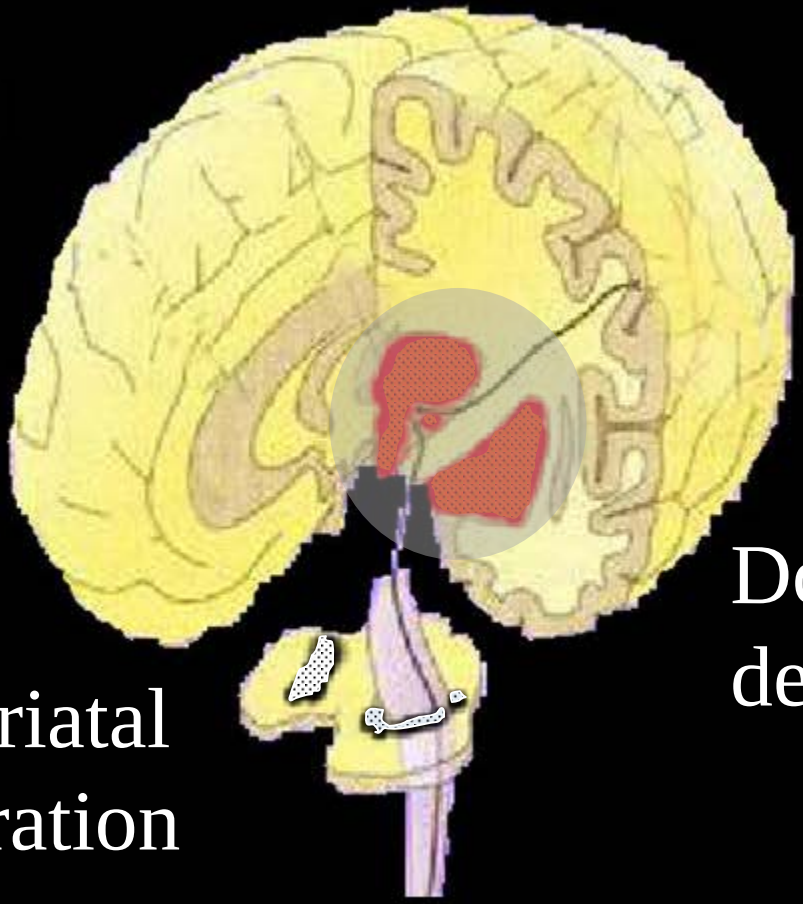


Dopamine pathology



Nigrostriatal degeneration

Dopamine pathology



Dopaminergic depletion

Nigrostriatal degeneration

Substantia Nigra

Normal

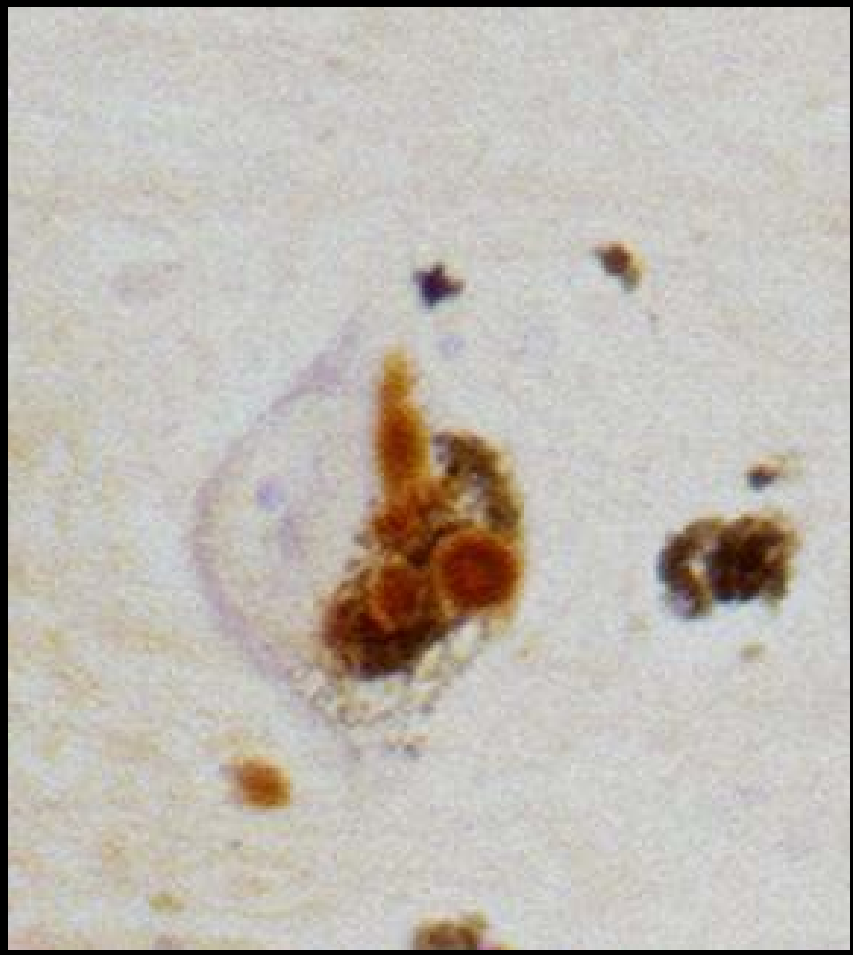
Parkinson’s Disease

Non-Dopaminergic Pathology

- Serotonergic (*Mood/Sleep*)
  - Dorsal raphe
- Noradrenergic (*Mood/Sleep*)
  - Locus coeruleus
- Cholinergic (*Memory/Sleep*)
  - Nucleus basalis
- Structural (*Memory/Hallucinations*)
  - Cortical Lewy bodies

Lewy Bodies

- Tangles of Alpha-Synuclein protein
- Inside dying neurones
- Villain or Hero?



Neuron, Vol. 46, 857–868, June 16, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.05.010

Effects of α-Synuclein Immunization in a Mouse Model of Parkinson's Disease

Eliezer Masliah,[1,2,*] Edward Rockenstein,[1] Anthony Adame,[1] Michael Alford,[1] Leslie Crews,[1] Makoto Hashimoto,[1] Peter Seubert,[3] Michael Lee,[3] Jason Goldstein,[3] Tamie Chilcote,[3] Dora Games,[3] and Dale Schenk[3]

- Mouse model
  - Transgenic overexpressing human α-synuclein
  - Exposed to human α-synuclein
- Mice producing antibodies
  - ↓Accumulation of α-synuclein
  - ↓ Neurodegeneration
  - Antibodies bind membrane associated α-synuclein and promote lysosomal degradation

Something old, something new, something borrowed…

- Golden bullet
  - Target tangled alpha synuclein protein
  - Big pharma, expensive, long pipeline
- Repurposing
  - Existing drugs with a biological rationale
  - Cheaper and quicker

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Parkinson's disease, insulin resistance and novel agents of neuroprotection

Iciar Aviles-Olmos,[1] Patricia Limousin,[1] Andrew Lees[2] and Thomas Foltynie[1]

- Epidemiological links between PD & DM
  - Abnormal mitochondrial function and glucose metabolism
- Peroxisome proliferator activated receptor gamma coactivator 1-α
  - Regulator of mitochondrial respiration

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie

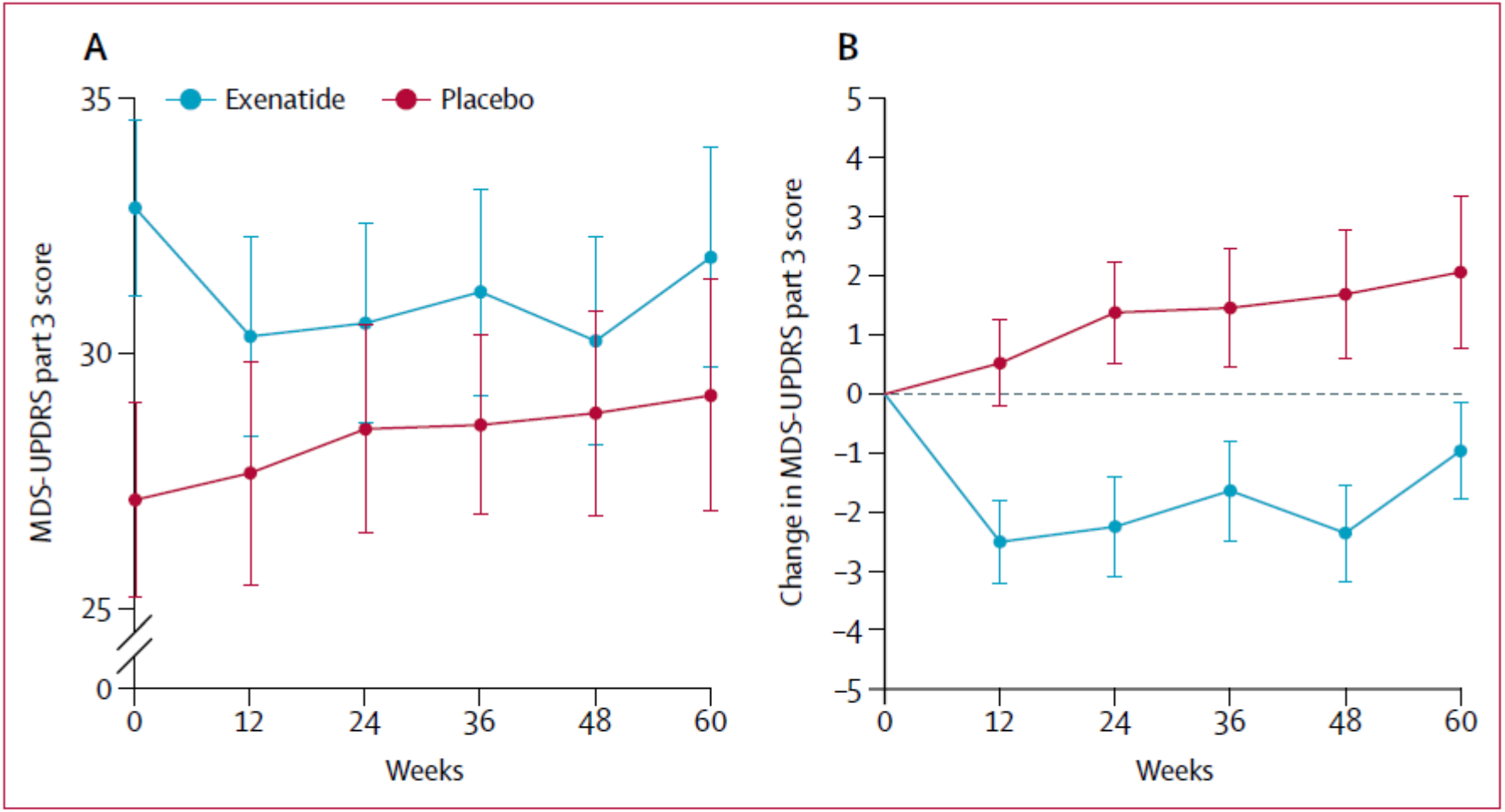


Figure 2: MDS-UPDRS part 3 scores (A) and changes in MDS-UPDRS part 3 scores (B), by study visit
Data are means for the off-medication state. Error bars represent standard error of the mean
MDS-UPDRS=Movement Disorders Society Unified Parkinson's Disease Rating Scale.

So what does Tom say?

CuATSM

- Dying regions in PD brain have LOW copper
- Copper involved in helping enzymes to reduce oxidative stress
- Montreal data
  - OPEN LABEL
  - NO PLACEBO
- Phase II being planned (Australia)

Inflamazome

- ‘Queensland drug’
- Reduce inflammation
- Animal data
  - Promising
- No human data
  - MICE DON’T GET PD
- Phase II being planned (Australia)

Still on the *whiteboard*

- Antisense therapy
  - Might be useful for genetic cases
  - ‘Knock out’ the product of a mutated gene
  - Produce a specific strand of genetic material (DNA, RNA, chemical analogue) that binds (blocks) the signaling from a mutated gene
  - Switch mutated gene off

Still on the *whiteboard*

- Nanoparticles
  - *Magic Bullet*
- Graphene quantum dots (GQDs)
- Block formation of alpha synuclein preformed fibrils
- Promote disaggregation of tangled proteins