Investigation of disease mechanisms and screening for treatments in beta-propeller protein-associated neurodegeneration (BPAN)

Dr Apostolos Papandreou, London, UK

LMCB
MRC LABORATORY FOR MOLECULAR CELL BIOLOGY

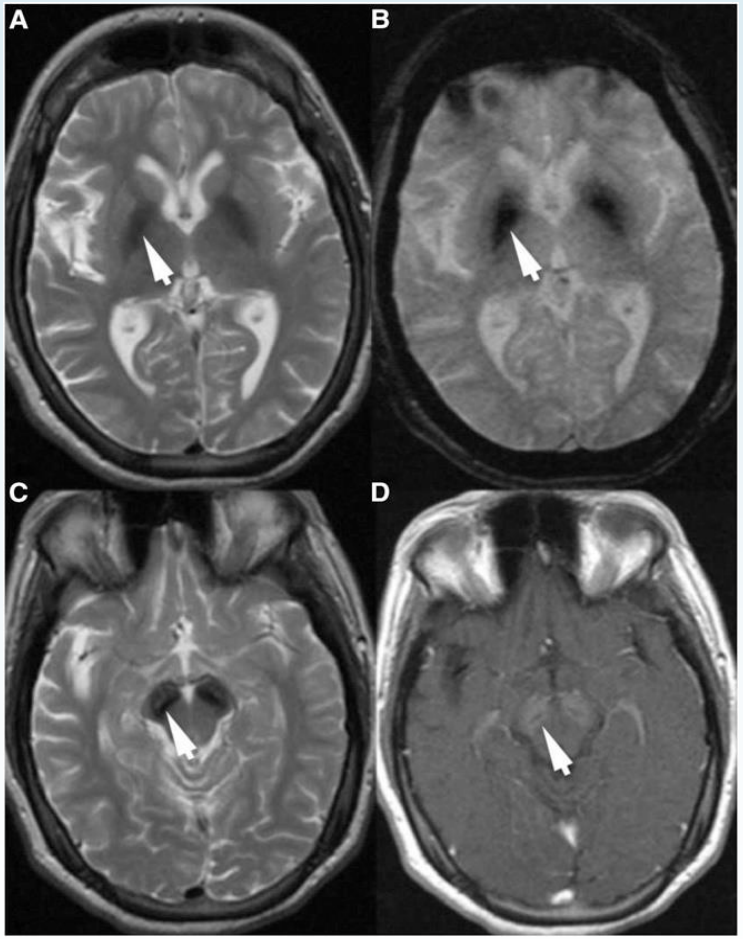
Great Ormond Street Hospital for Children NHS Trust

UCL INSTITUTE OF CHILD HEALTH

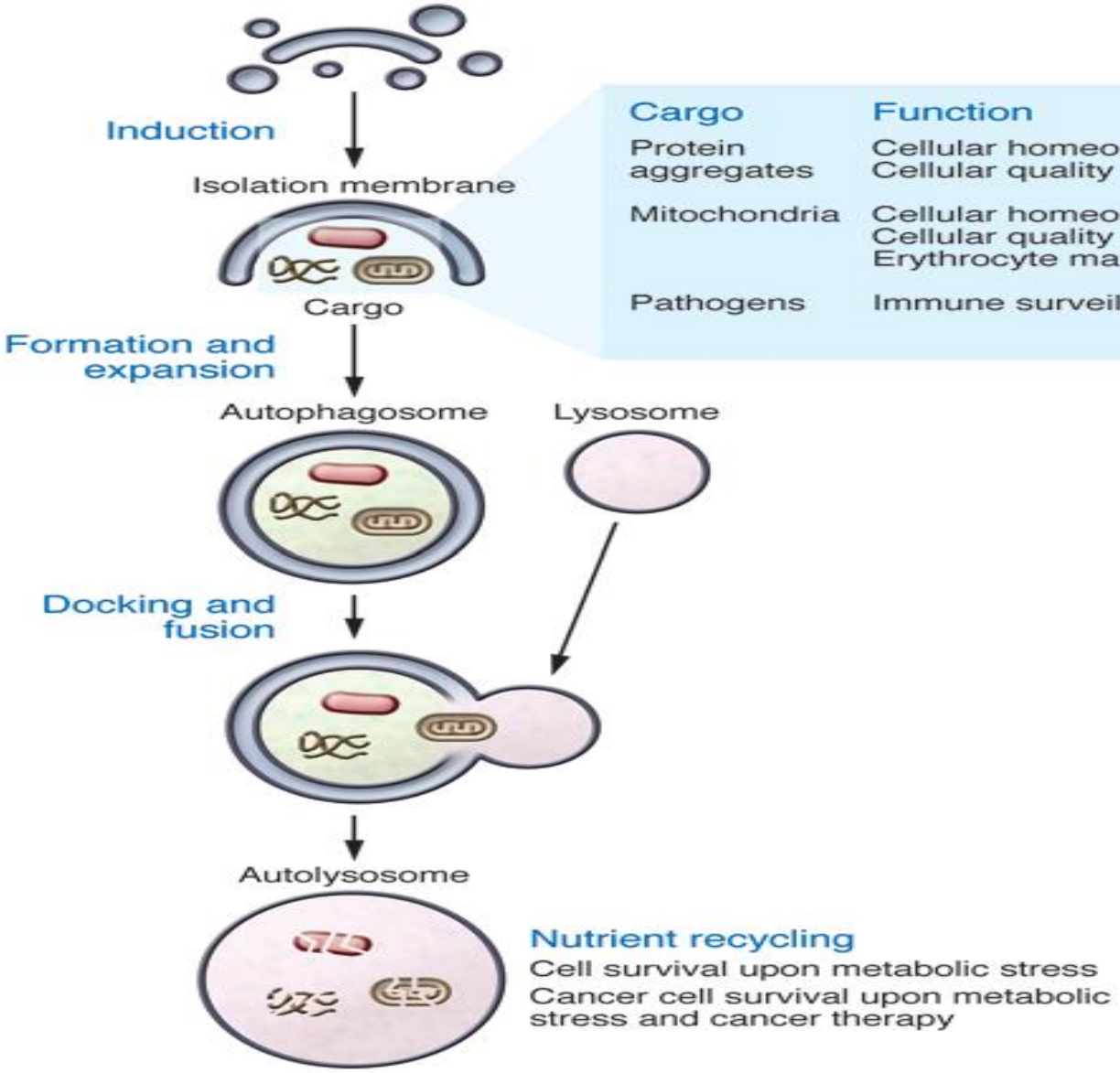
Background

- WDR45: present in all cells, but problems primarily neurological

- MRI findings: areas of the brain involved in movement control



Autophagy



Cargo	Function	Deficiency/disease
Protein aggregates	Cellular homeostasis Cellular quality control	Neurodegeneration, heart disease, etc.
Mitochondria	Cellular homeostasis Cellular quality control Erythrocyte maturation	Neurodegeneration, DNA damage, tumor initiation, etc.
Pathogens	Immune surveillance	Infectious diseases Immune disorder

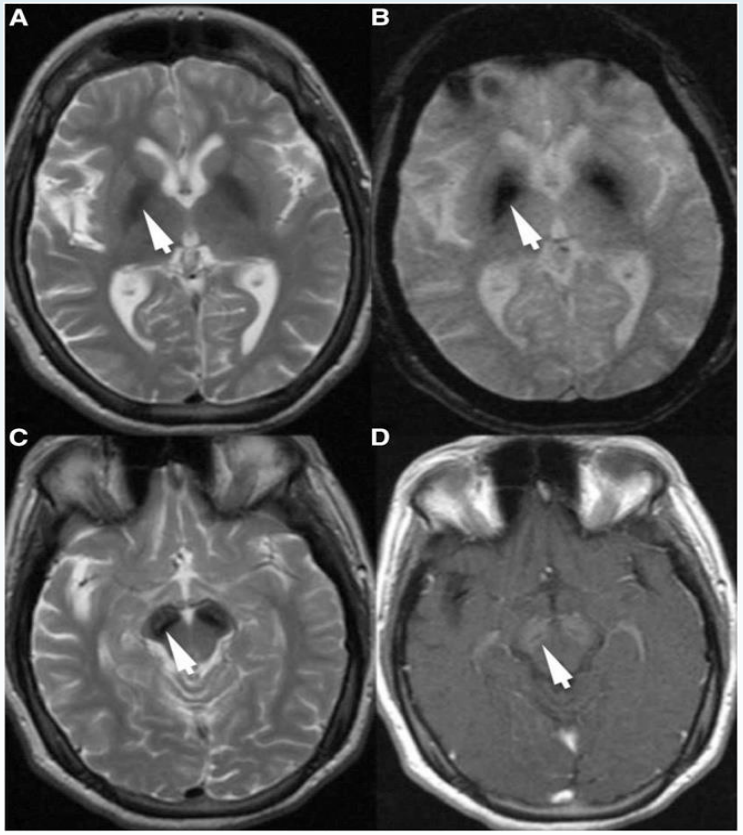
Overall Aim

- Progressive course
- No drugs currently available that can improve or cure BPAN
- Lack of understanding of disease mechanisms

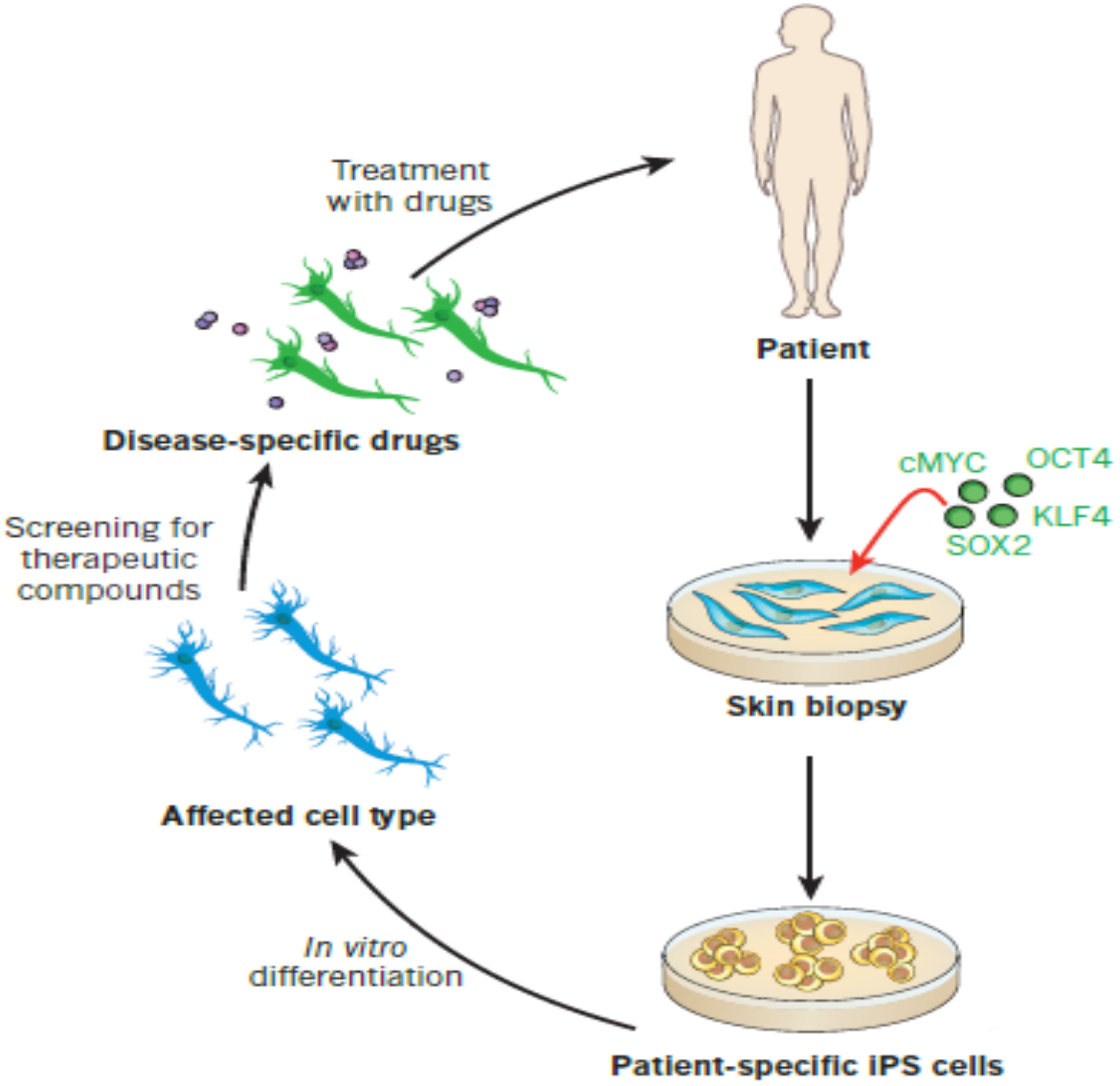
Aim: to establish a cell model for BPAN and use it to advance i) understanding of disease pathophysiology and ii) treatment development.

What type of research model?

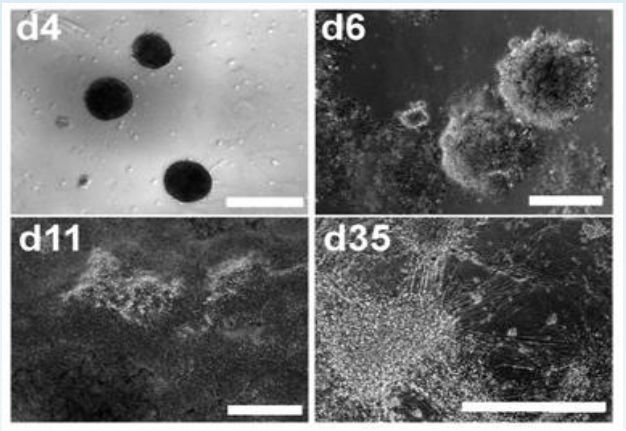
- We want to study nerve cells, as symptoms primarily neurological
- Dopaminergic neurons
- A model that 1) allows us to study patient-derived cells with known mutations; 2) has capacity for regeneration and differentiation

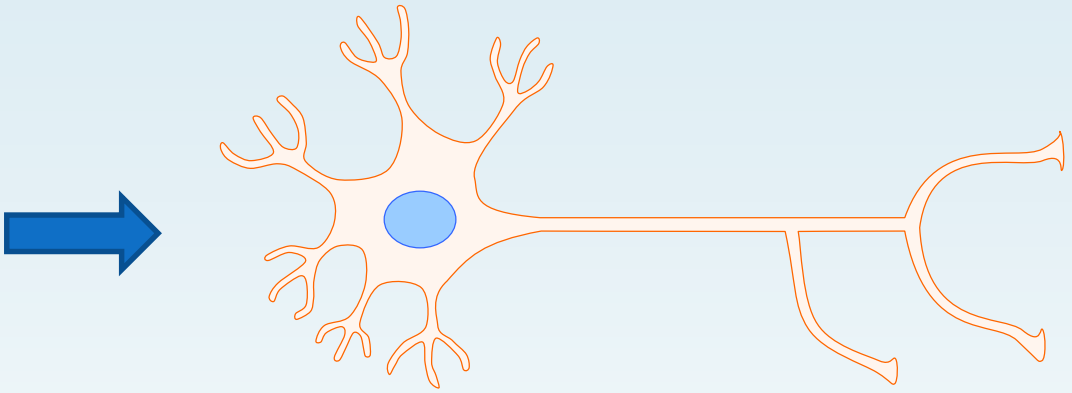


Induced Pluripotent Stem Cells (iPSc)

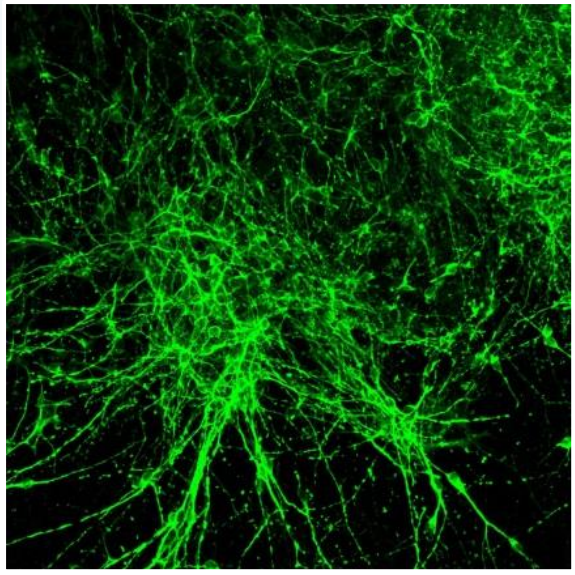


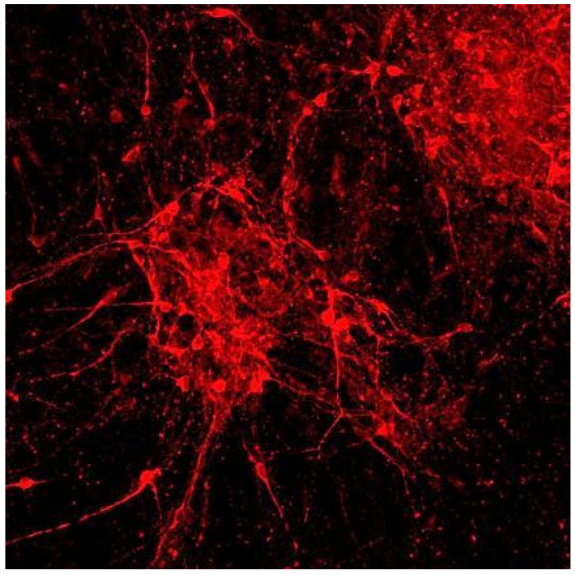
Neuronal Cell Differentiation

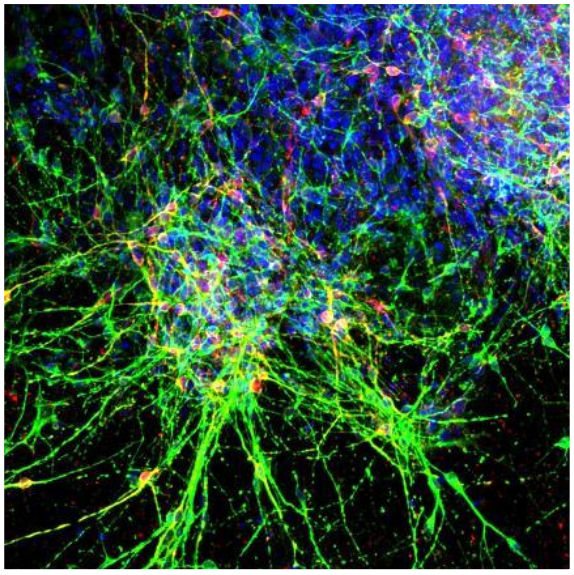




MAP2	TH	merge

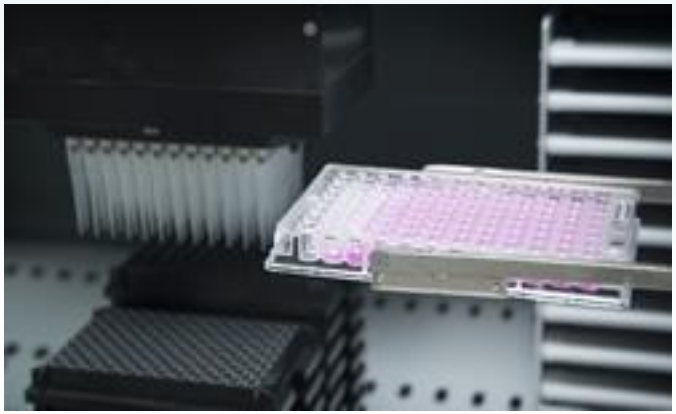


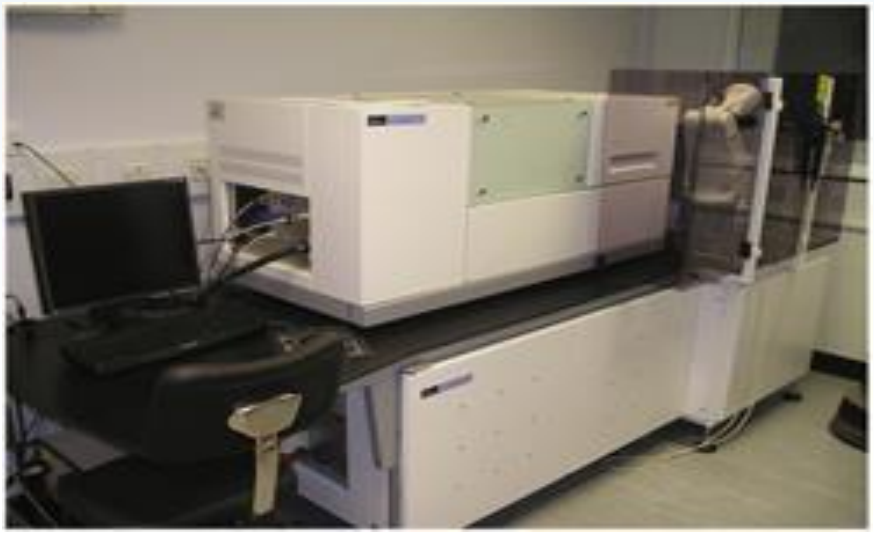




Further Experiments

- Eventually: brain cells that
  - carry disease-causing mutations
  - do not have mutations and are expected to be functioning normally





- **Identify** defective cell functions and processes

- **Test** thousands of chemicals for the ability to ‘cure’ the cells

Potentially effective chemicals: further testing, aiming to take the best compound forward for a future clinical trial.

Progress so far

- Early stages

- 2 patients recruited so far
- iPSc ready from one patient, being generated from the 2nd

- Aiming to perform experiments on cells deriving from at least 5-6 patients in total (ideally with different mutation types)

Benefits of our approach

- Regeneration and differentiation capacity
- Studies on human nerve cells
- Large number of drug screening experiments in a short time period
- Potential for drug repurposing

Timelines and Laboratory Realities

Time Consuming experiments

Genetic make-up of our nerve cells?

Studies on cells vs networks of nerve cells/ the whole brain

Acknowledgements

UCL- Institute of Child Health, Developmental Neurosciences Programme, London

MA Kurian
E Meyer
S Barral
J Ng
A McTague
A Ngoh
K Kramer
R Privolizzi

UCL-Laboratory of Molecular Cell Biology

R Ketteler lab
D Little

ICH-Genetics and Genomic Medicine Unit

P Gissen
PB Mills
PC Clayton
K Mills
F Mazzacuva
E Sirka
C Pollard

Child Brain Research

Great Ormond Street Hospital for Children NHS Foundation Trust

action medical research for children

BPNA British Paediatric Neurology Association