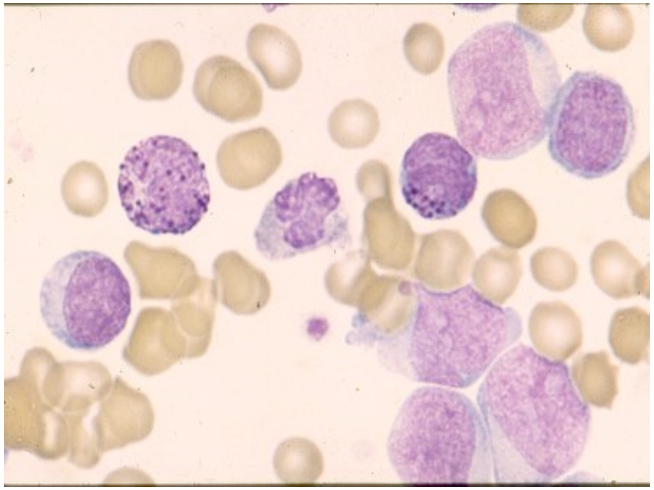
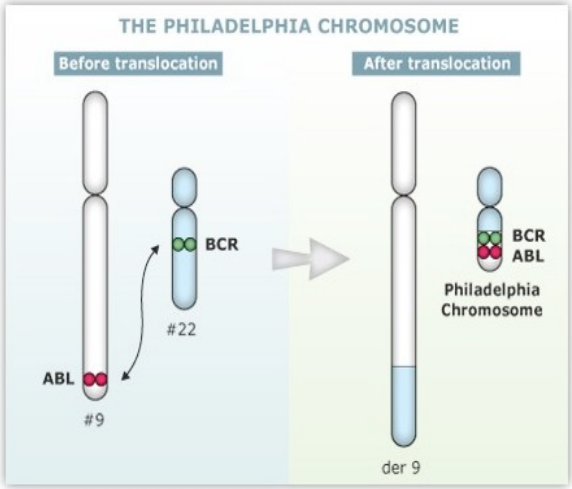
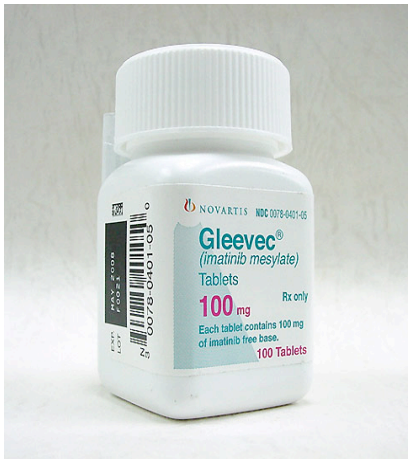
Proof of concept in CML

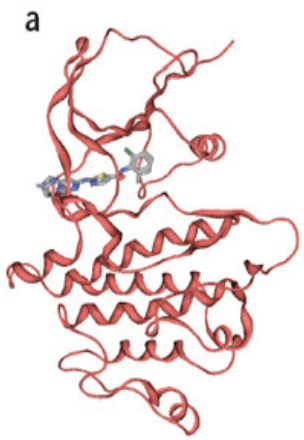


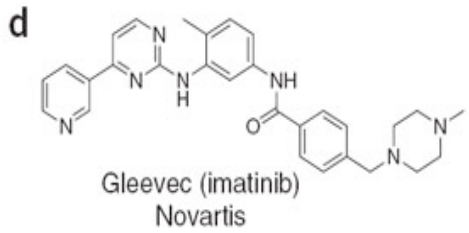


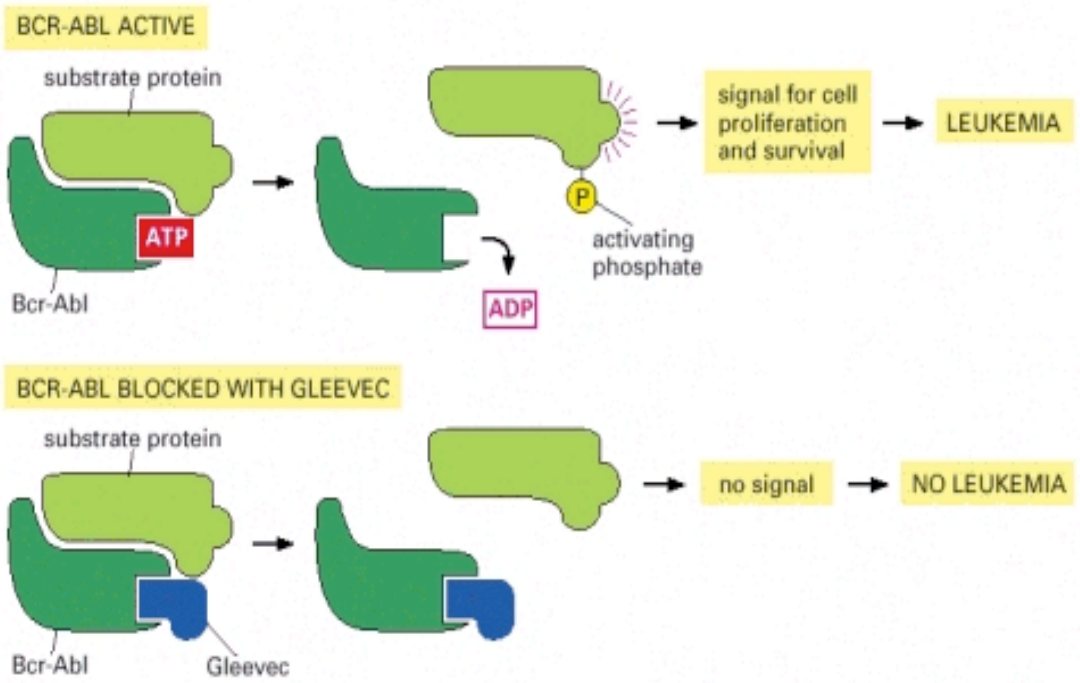
STI-571

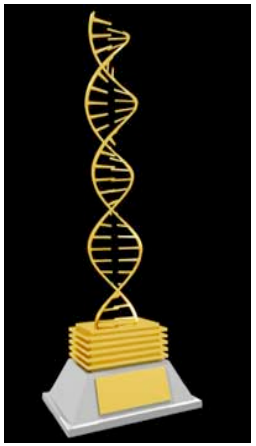
Gleevec is paradigm of targeted therapy









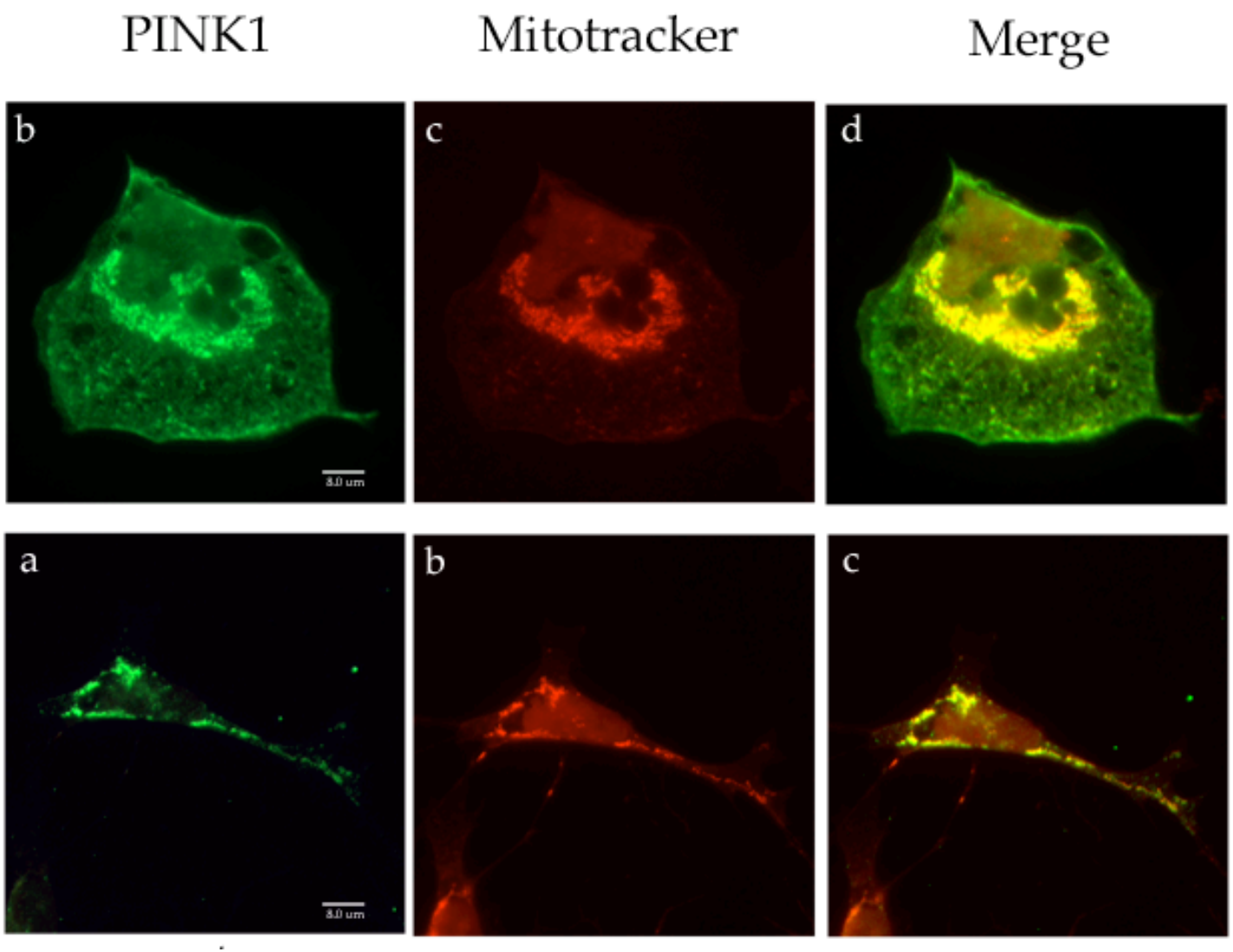


Lasker Prize 2009

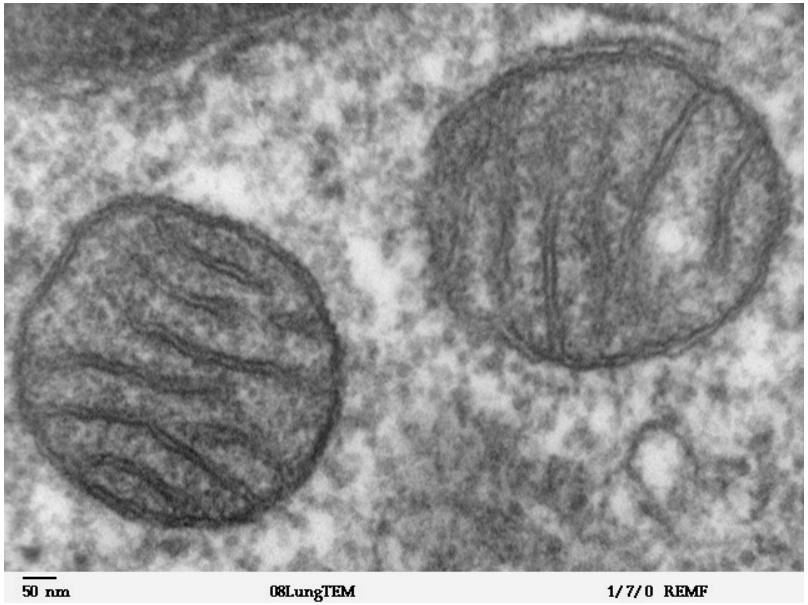
Targeted therapies against kinases in cancer

Name	Target	Company	Class
Bevacuzimab	VEGF	Genentec	Monoclonal antibody
Gefitinib	EGFR	Astra-Zeneca	Small molecule
Sunitinib	Multi	Pfizer	Small molecule
Trastuzimab (Herceptin)	Erb1/2	Genentech	Monoclonal antibody
Dabrafenib	b-Raf	GSK	Small molecule

PINK1 is localised to mitochondria in cells



Underpinnings of Parkinson's disease: Mitochondrial Dysfunction



Parkinson's disease & Mitochondria Timeline

1983: MPTP causes Parkinsonism in man
Langston et al. Science

1985: MPTP is an inhibitor of complex I
Nicklas et al. Life Sci

1989: Complex I activity is reduced in PD
Schapira et al. Lancet

2000 Rotenone causes Parkinson's in rat
Betarbet et al., Nature Neurosci

Protein Phosphorylation and Dundee

Pfizer

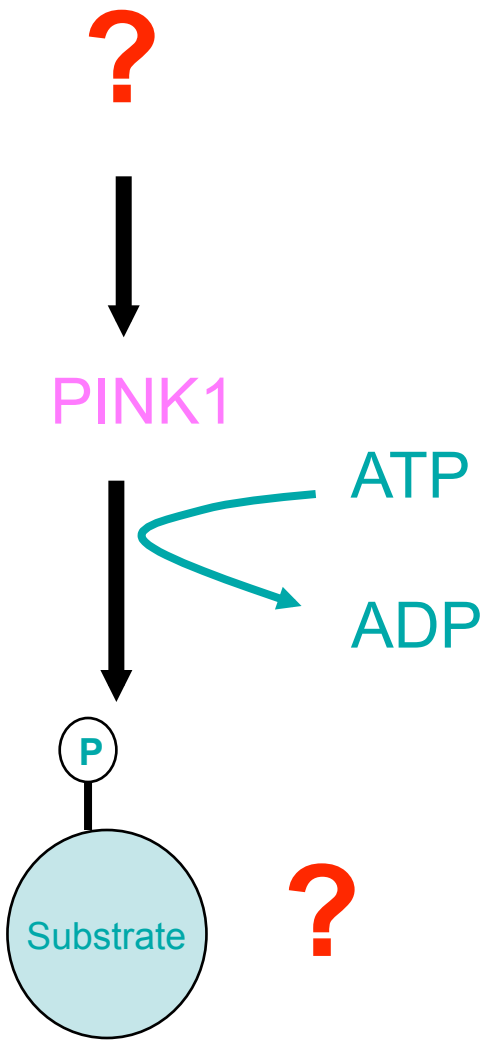
MERCK SERONO

Boehringer Ingelheim

gsk GlaxoSmithKline

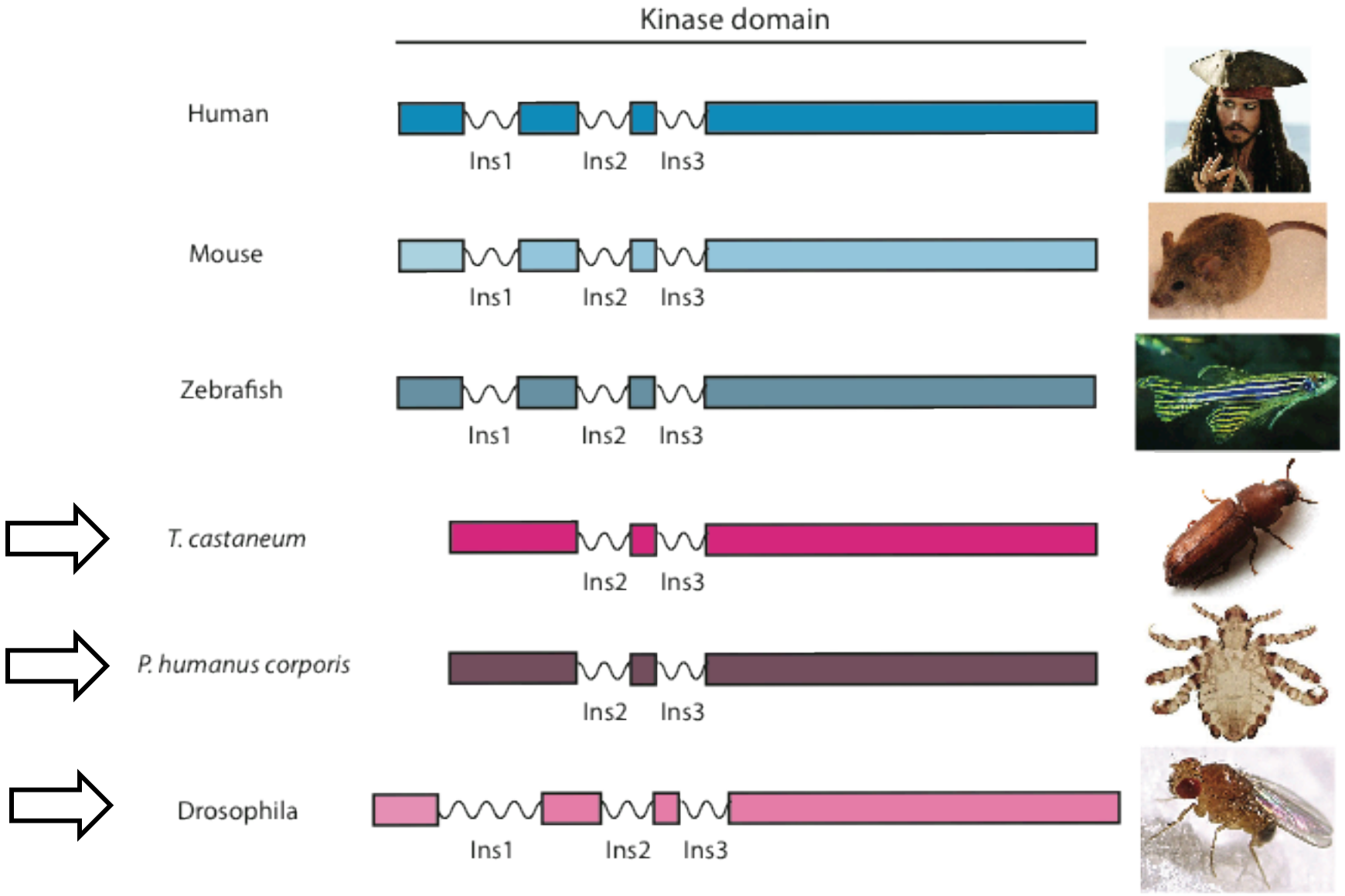
AstraZeneca UNITED KINGDOM

Understanding what PINK1 does will lead to the heart of PD mechanisms

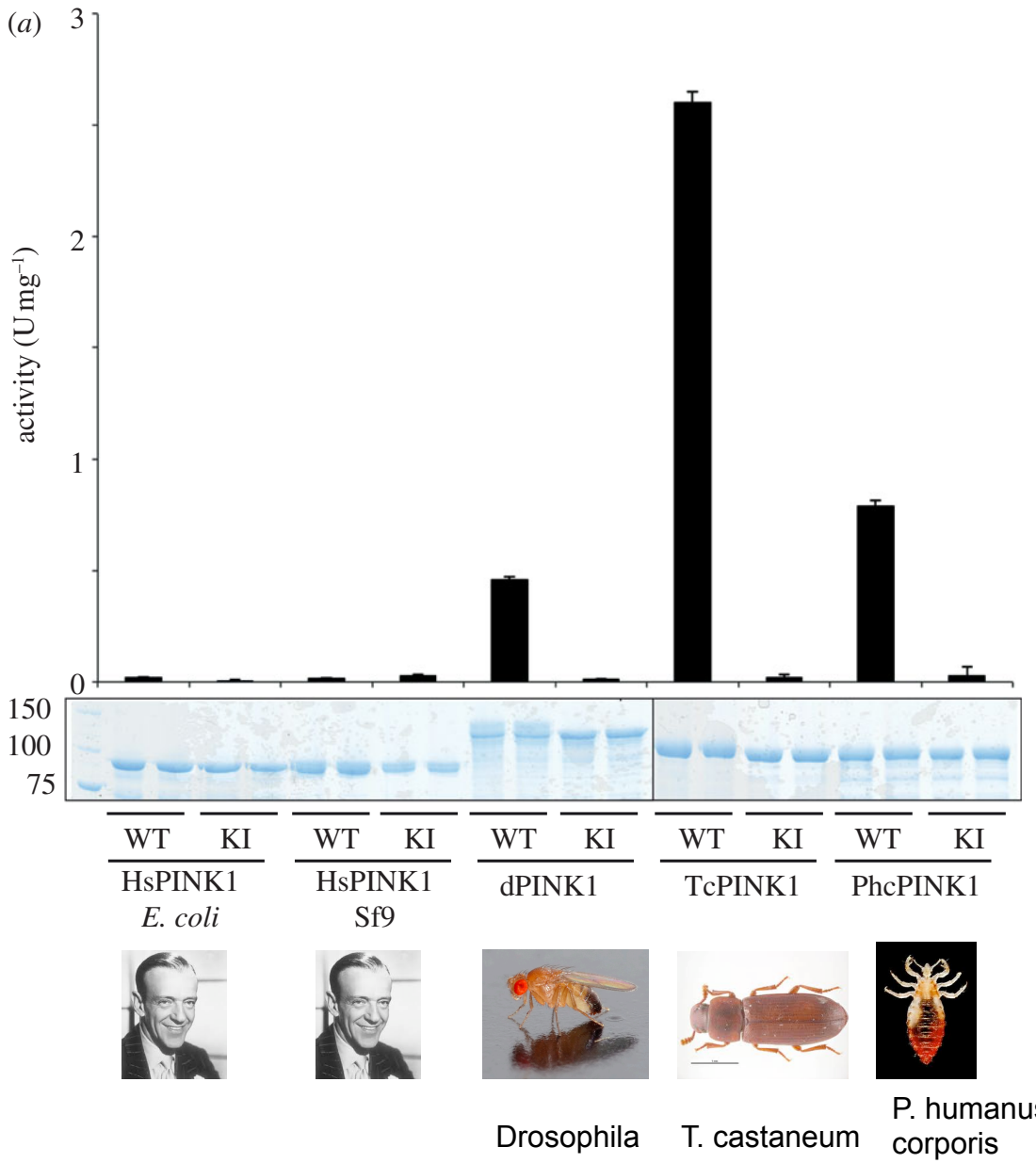


NORMAL NEURONAL FUNCTION

PINK1 orthologues

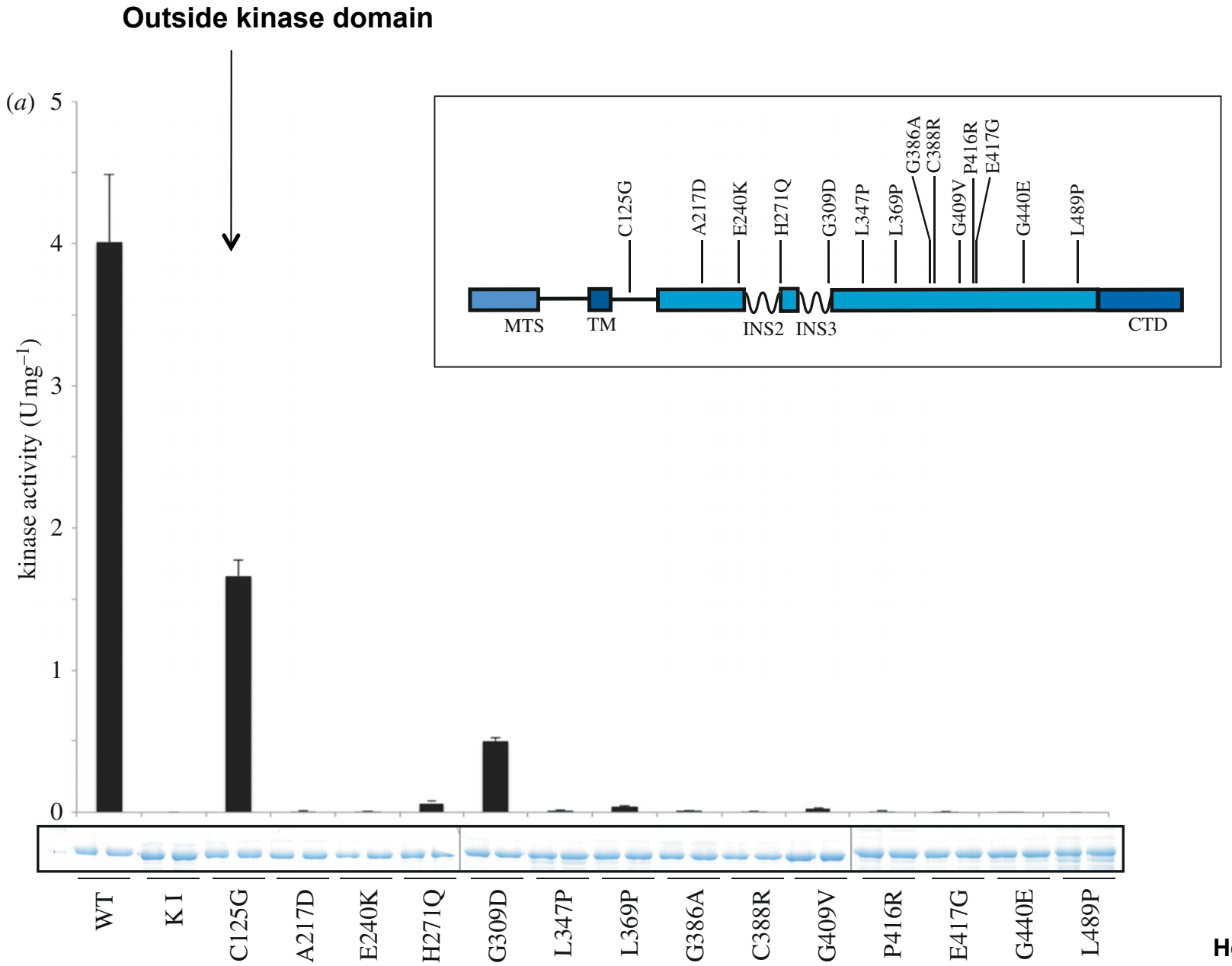


Insect PINK1 is active in vitro



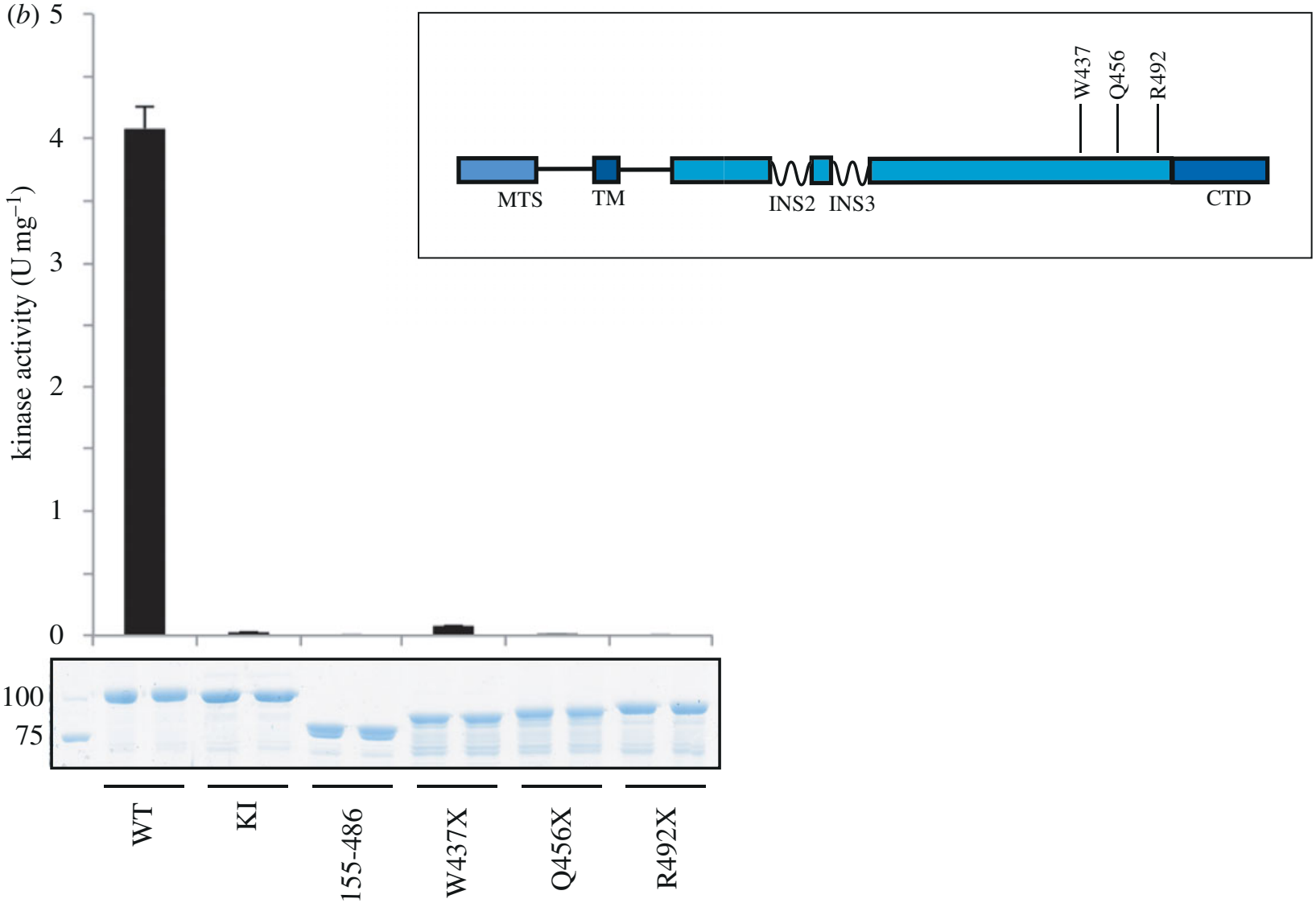
Helen Woodroof

PINK1 kinase activity is crucial to prevent Parkinsonism (1)



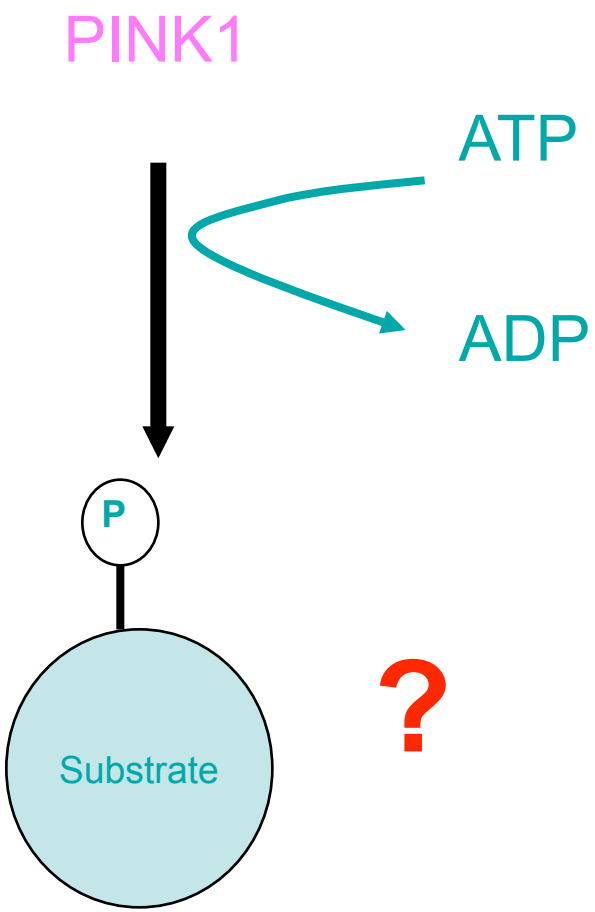
Helen Woodroof

PINK1 kinase activity is crucial to prevent Parkinsonism (2)

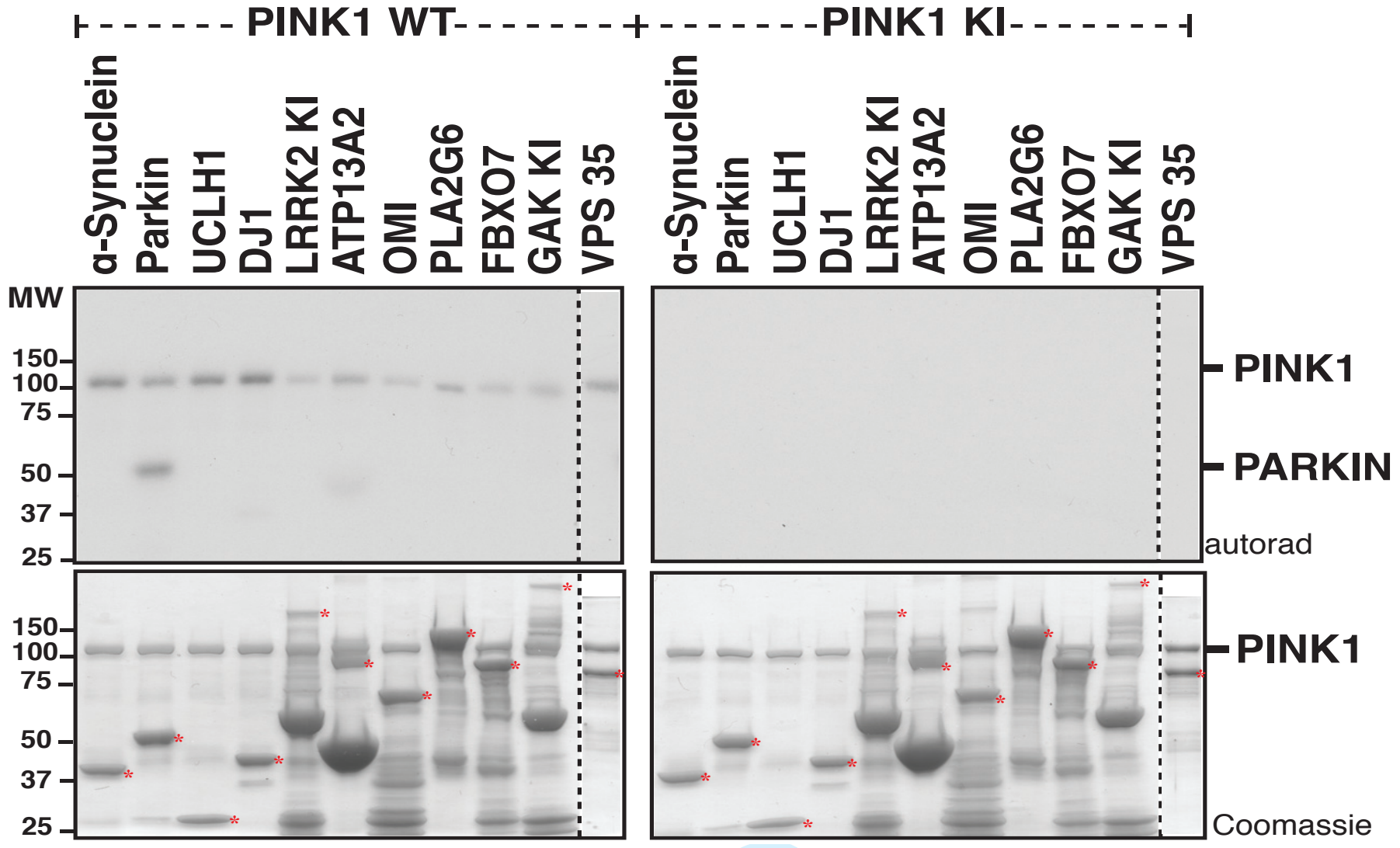


Helen Woodroof

What is the substrate of PINK1 ?



Screen of all known Parkinson's disease-linked proteins



Chandana Kondapalli

Parkin

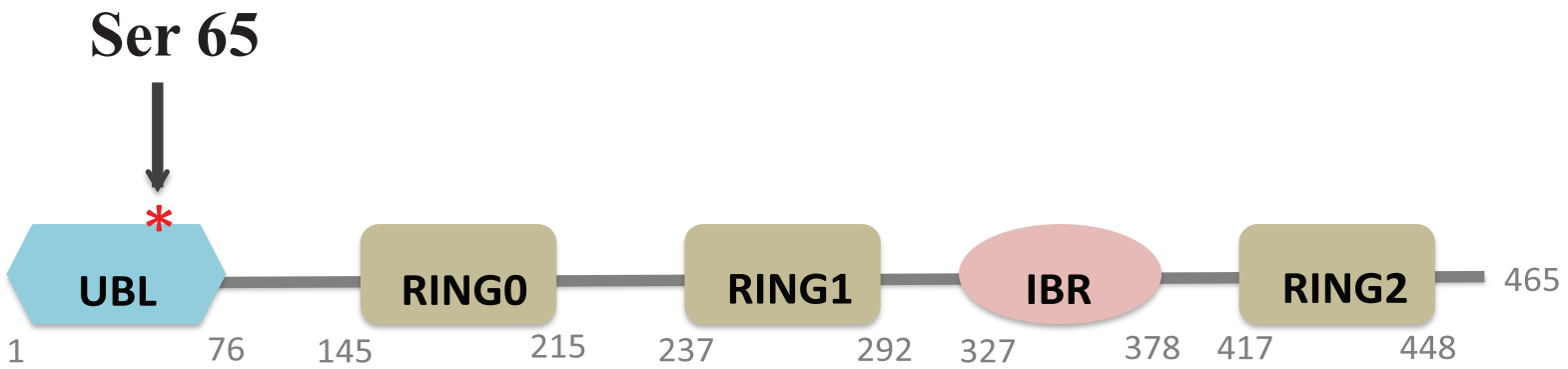
Mutations in Parkin discovered in PD patients in 1998

Commonest cause of familial early-onset PD

Functions as RING-HECT hybrid E3 ligase

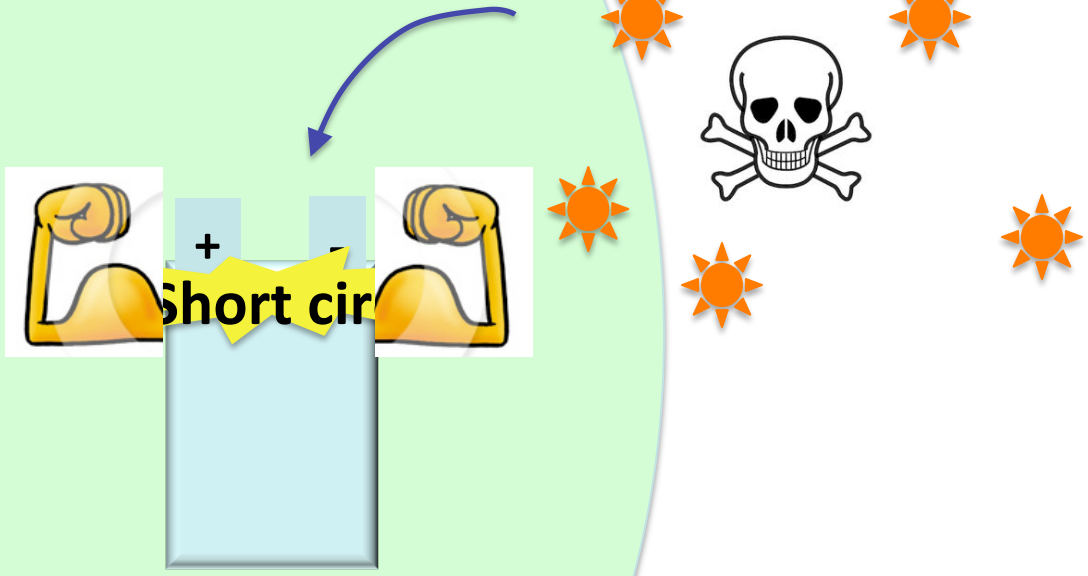
Physiological substrate unknown

Ser^{65} is highly conserved residue in the Ubl domain of parkin



Cell

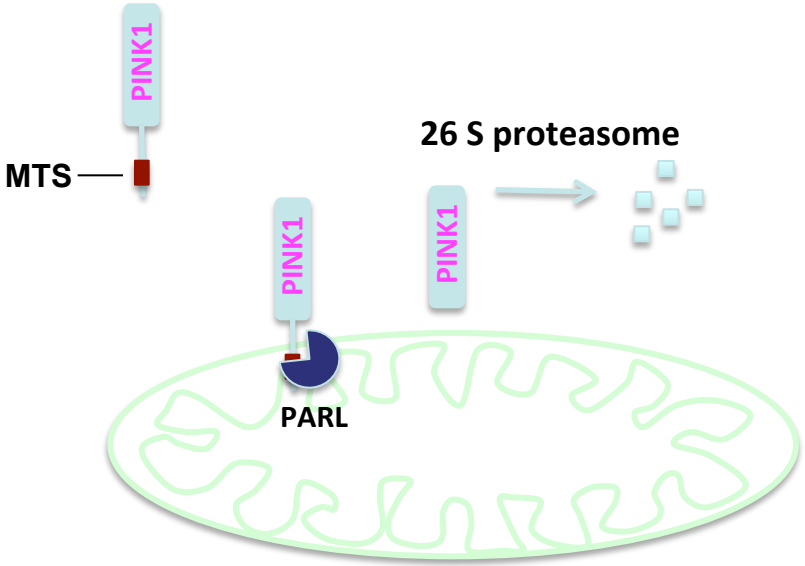
Cells treated with a chemical called CCCP



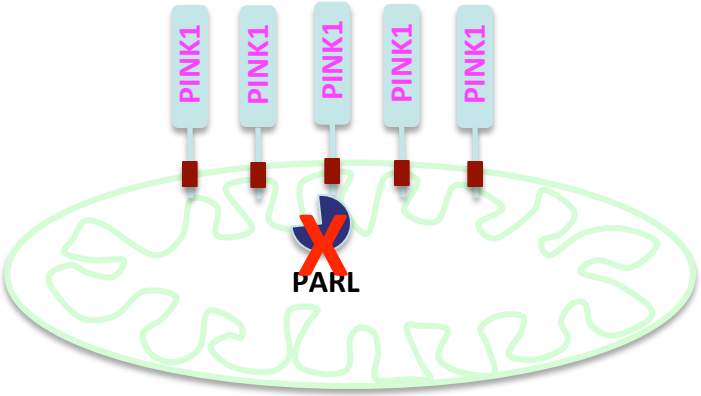
Mitochondria

Mammalian PINK1 becomes stabilised at the mitochondria following CCCP

Healthy mitochondria

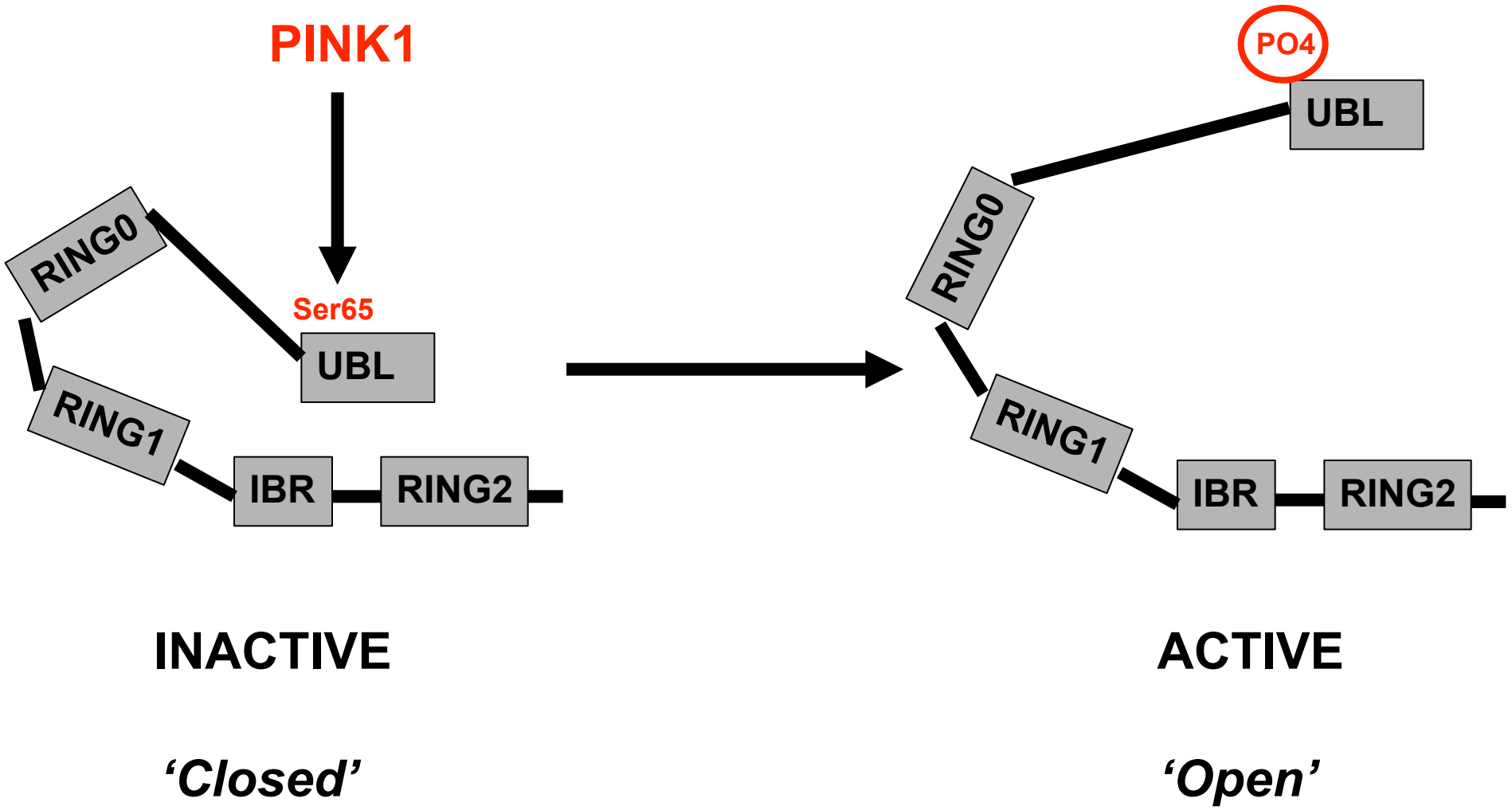


Depolarized mitochondria

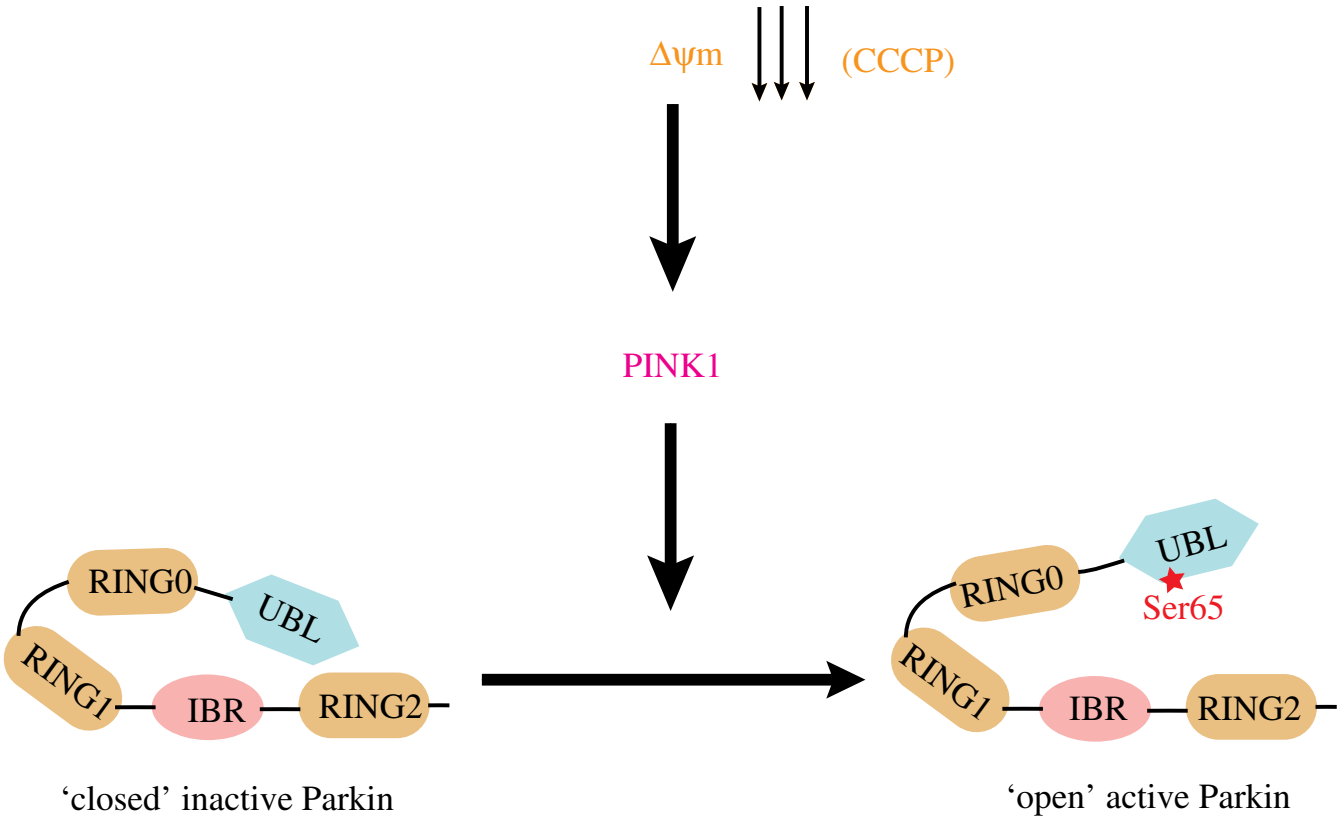


CCCP

PINK1 phosphorylation of Ser65 leads to active parkin

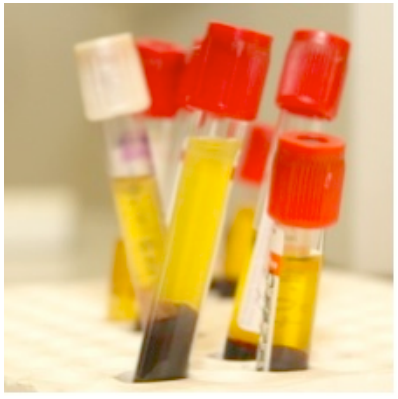


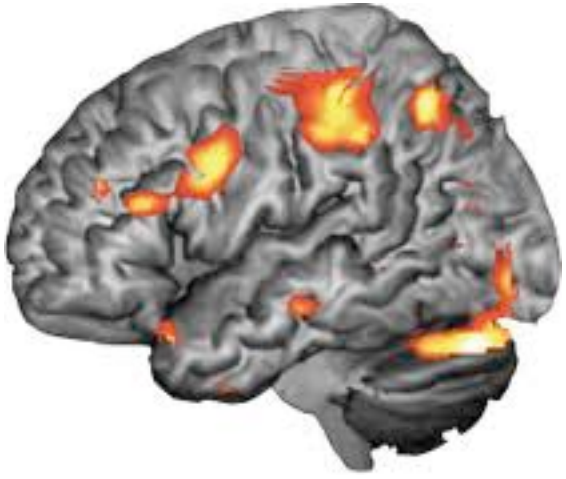
PINK1 signaling pathway

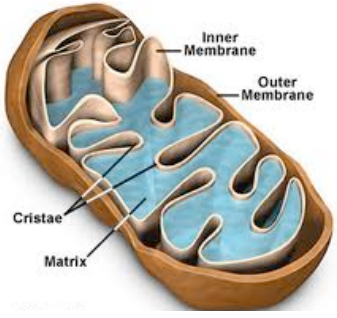


Kondapalli et al. Open Biology 2012

Investigating the potential of p-Ser65-Parkin and p-Thr257-PINK1 as biomarkers







STRESS

Parkinson's disease

p-Ser^{65} Parkin

p-Thr^{257} PINK1

Monoclonal antibodies under development

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH