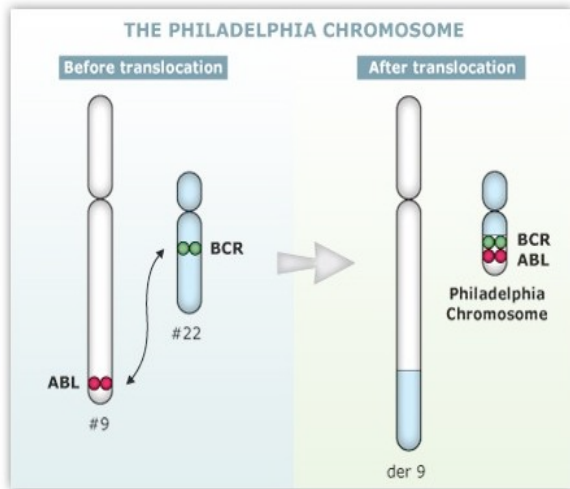
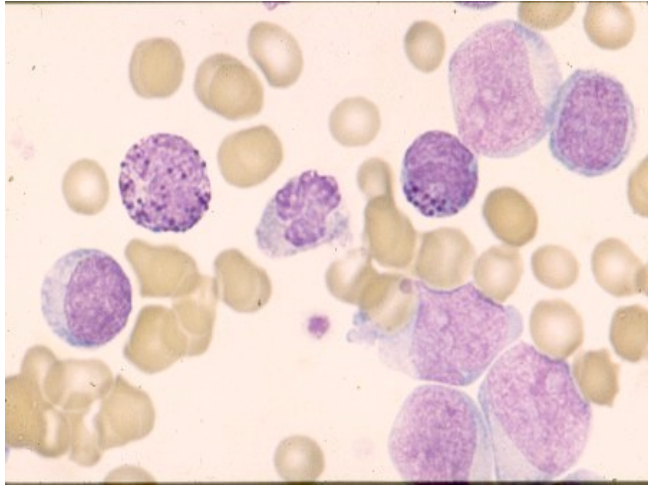


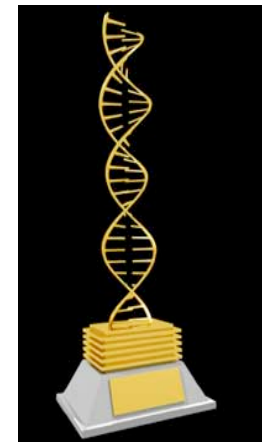
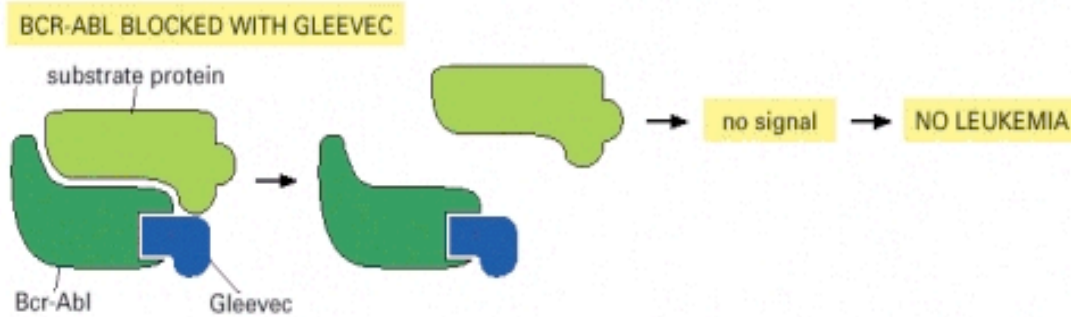
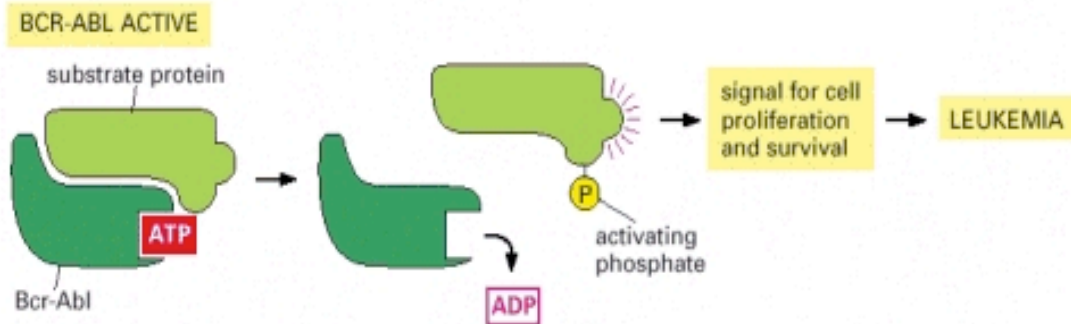
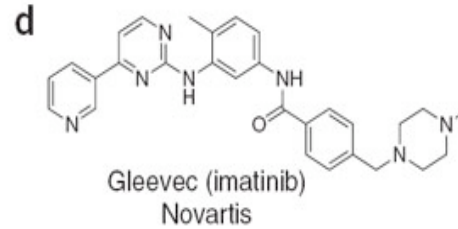
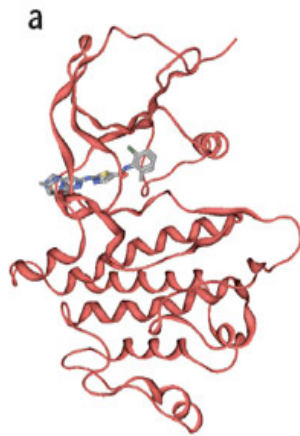
Proof of concept in CML



STI-571



Gleevec is paradigm of targeted therapy



Lasker Prize 2009

Targeted therapies against kinases in cancer

<u>Name</u>	<u>Target</u>	<u>Company</u>	<u>Class</u>
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

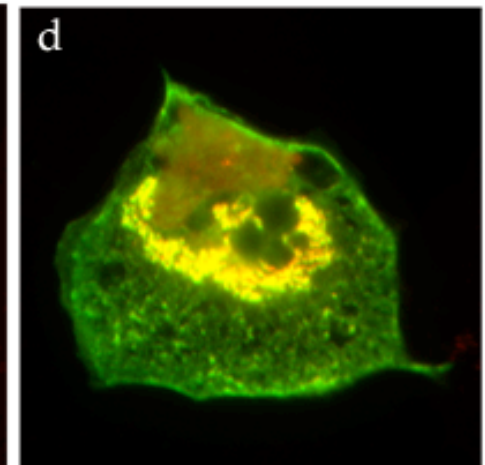
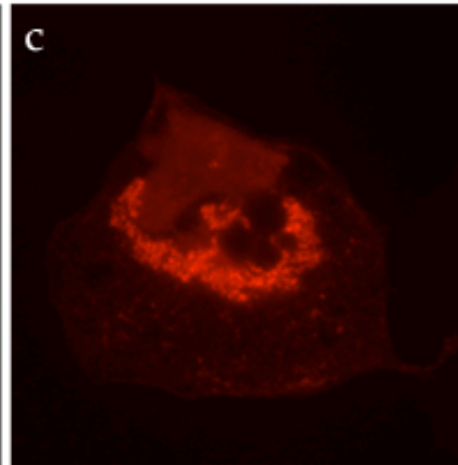
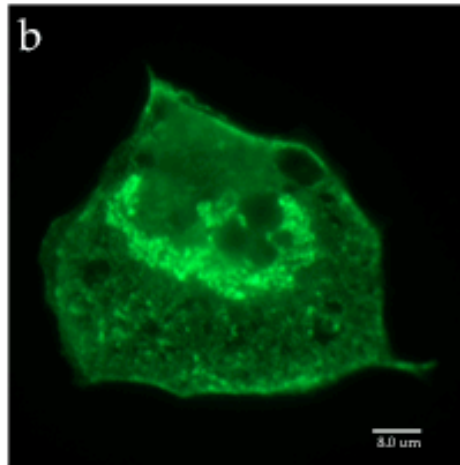
PINK1 is localised to mitochondria in cells

PINK1

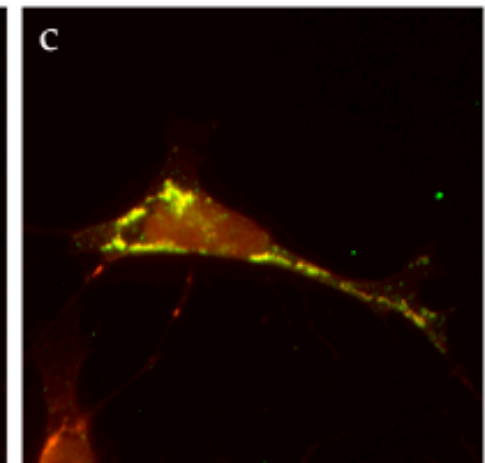
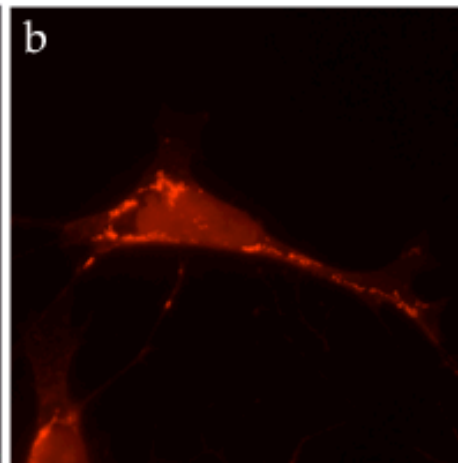
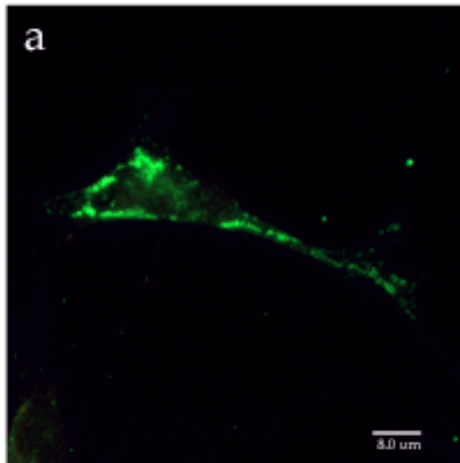
Mitotracker

Merge

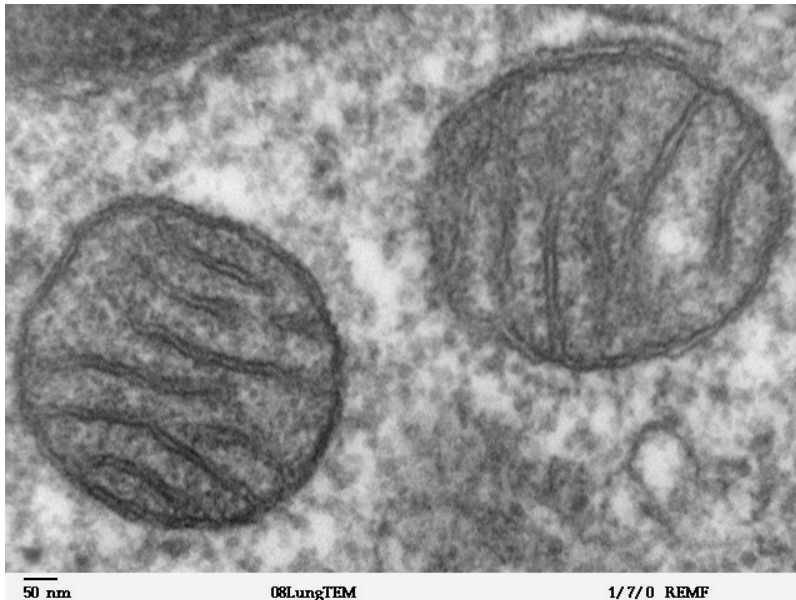
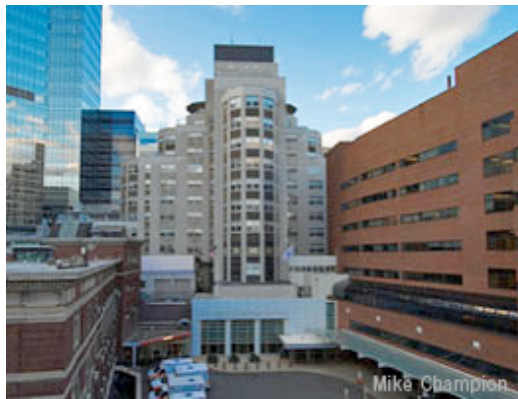
COS-7



SH-SY5Y



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

Welcome to the MRC Protein Phosphorylation Unit site

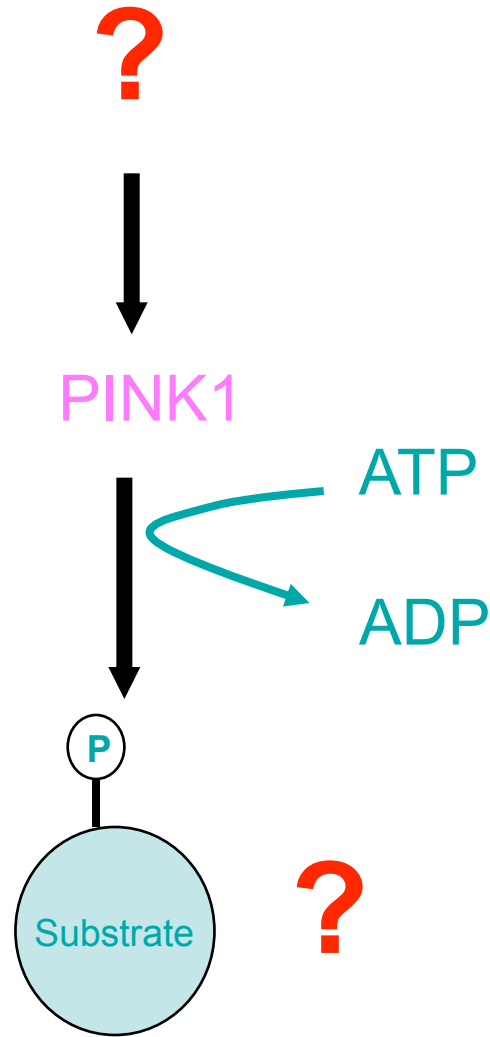
The MRC Protein Phosphorylation Unit (Director: Sir Philip Cohen FRS, FRSE, FMedSci) is one of the world's leading centres studying the role of protein phosphorylation in cell regulation and human disease.

Its innovative collaboration with a number of major pharmaceutical companies has become a model for how Academic scientists should interact with industry, for which it won the Queen's anniversary prize in 2006.

The Sir James Black Centre where the MRC Unit is based

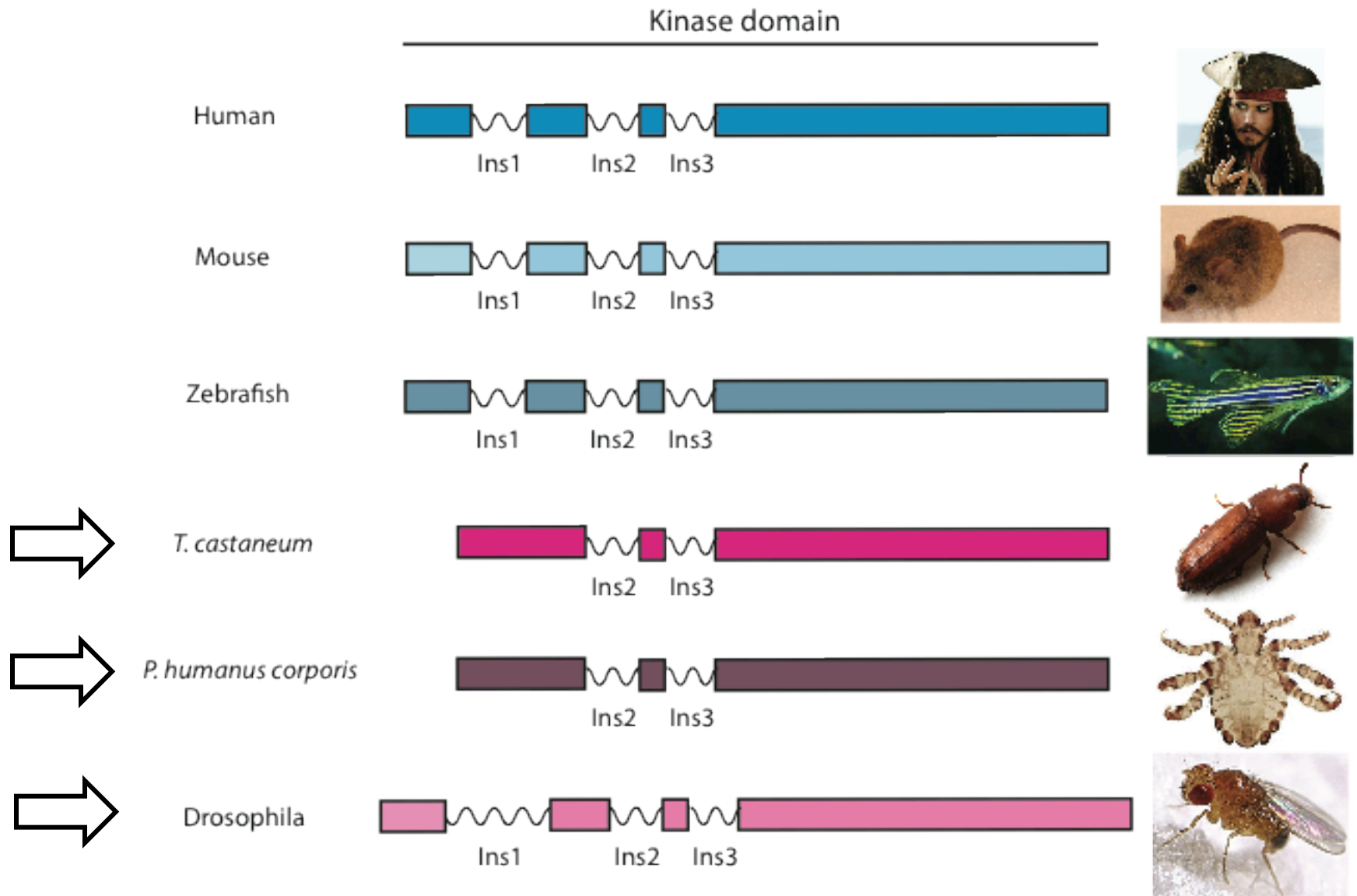


Understanding what PINK1 does will lead to the heart of PD mechanisms

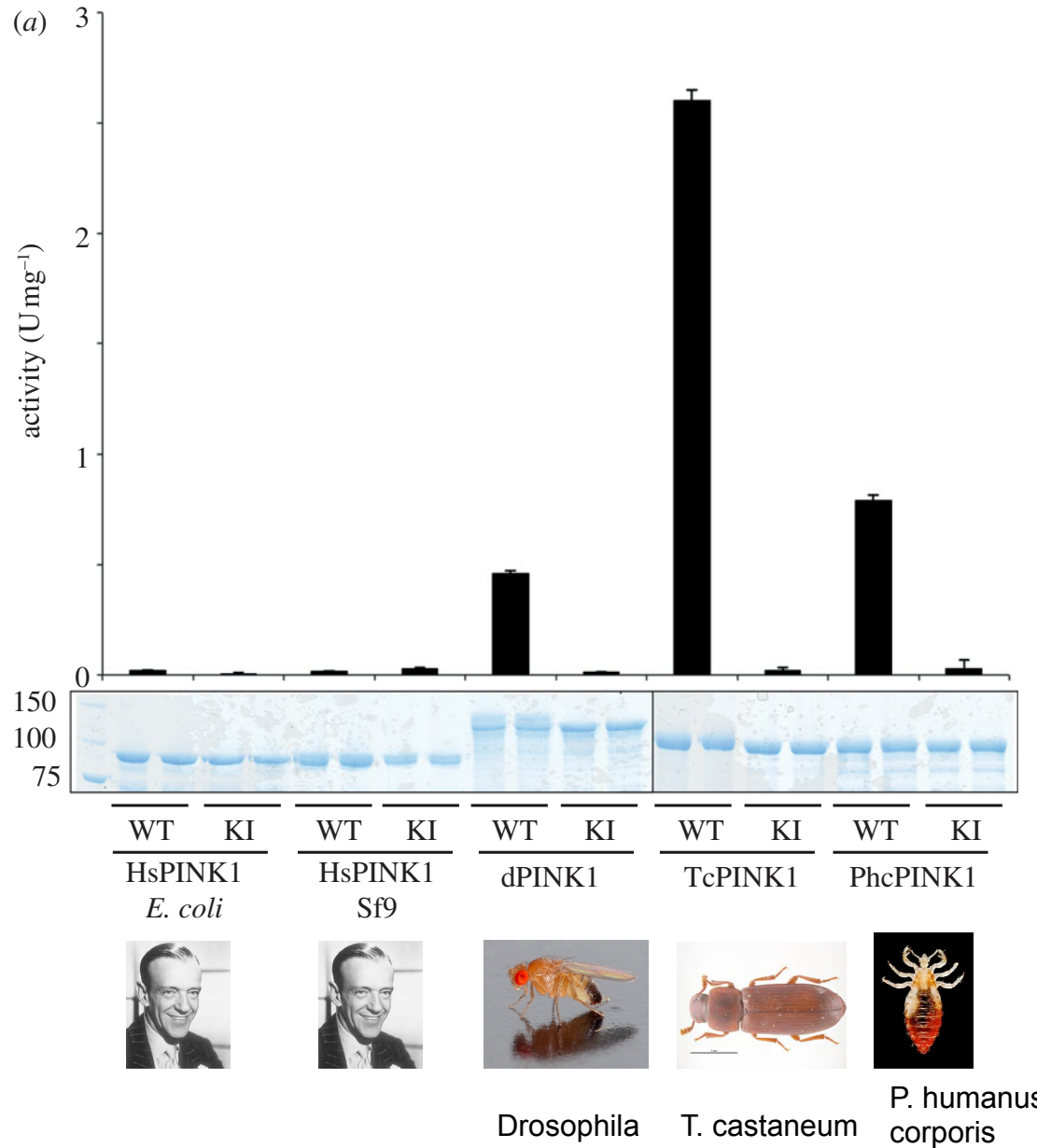


NORMAL NEURONAL FUNCTION

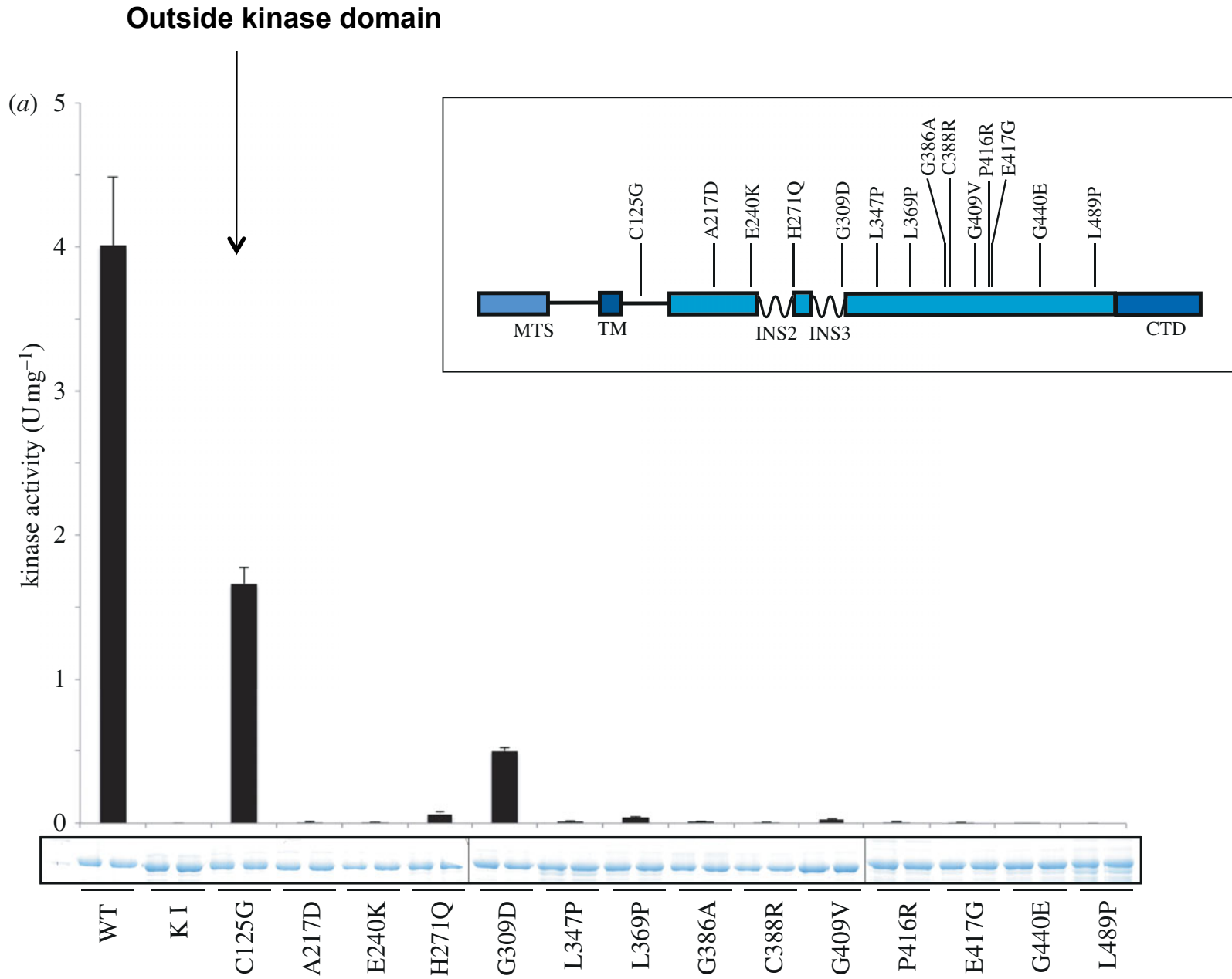
PINK1 orthologues



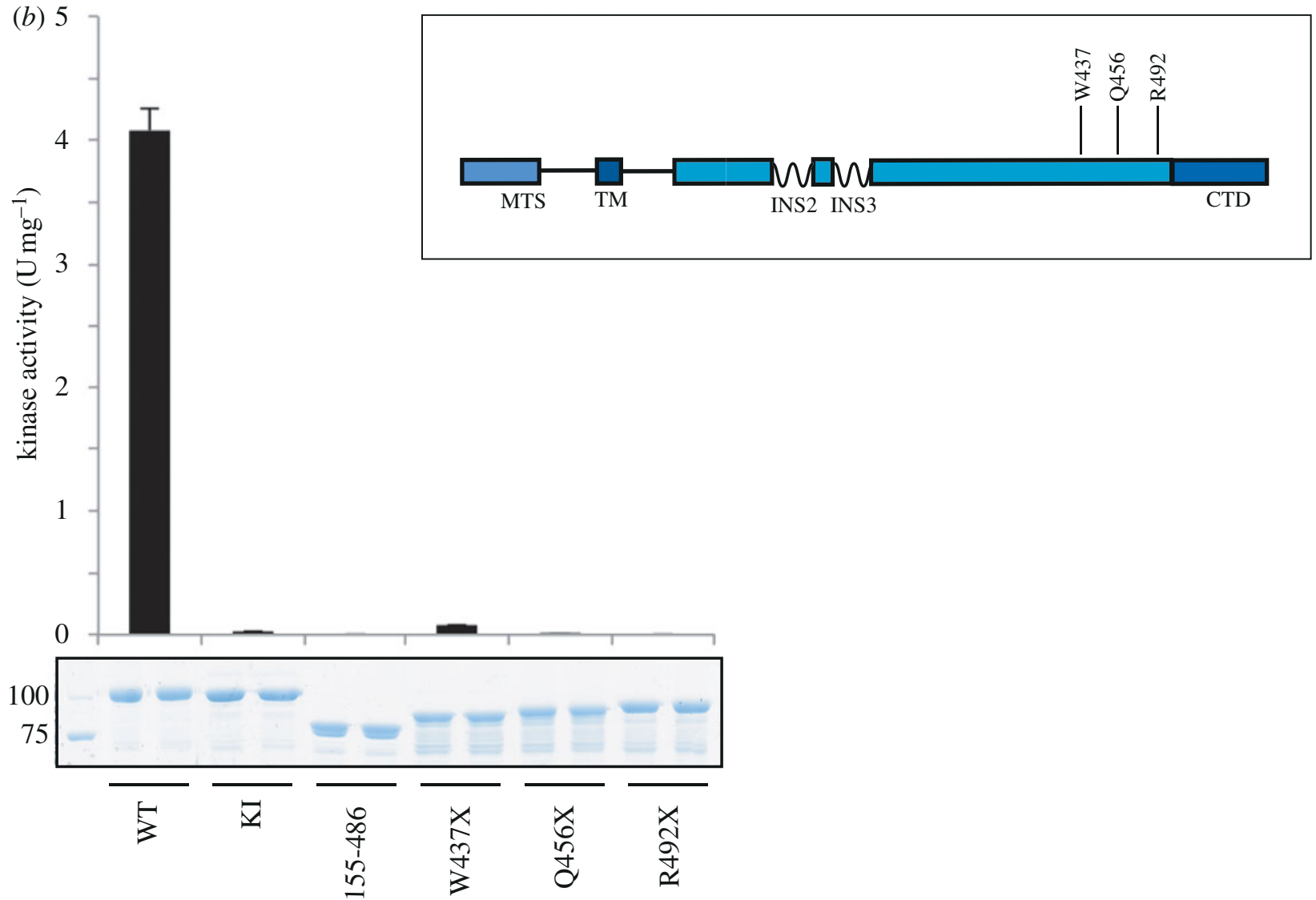
Insect PINK1 is active in vitro



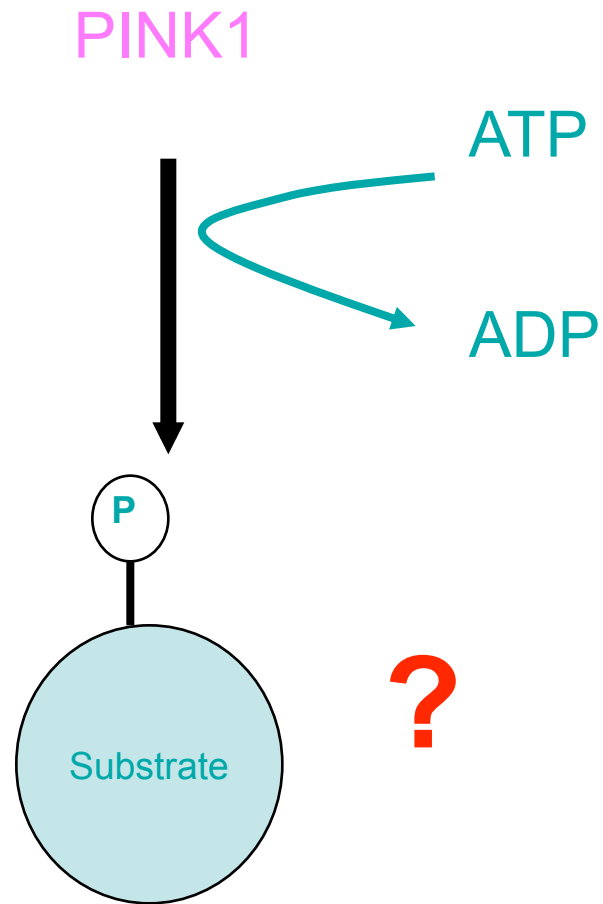
PINK1 kinase activity is crucial to prevent Parkinsonism (1)



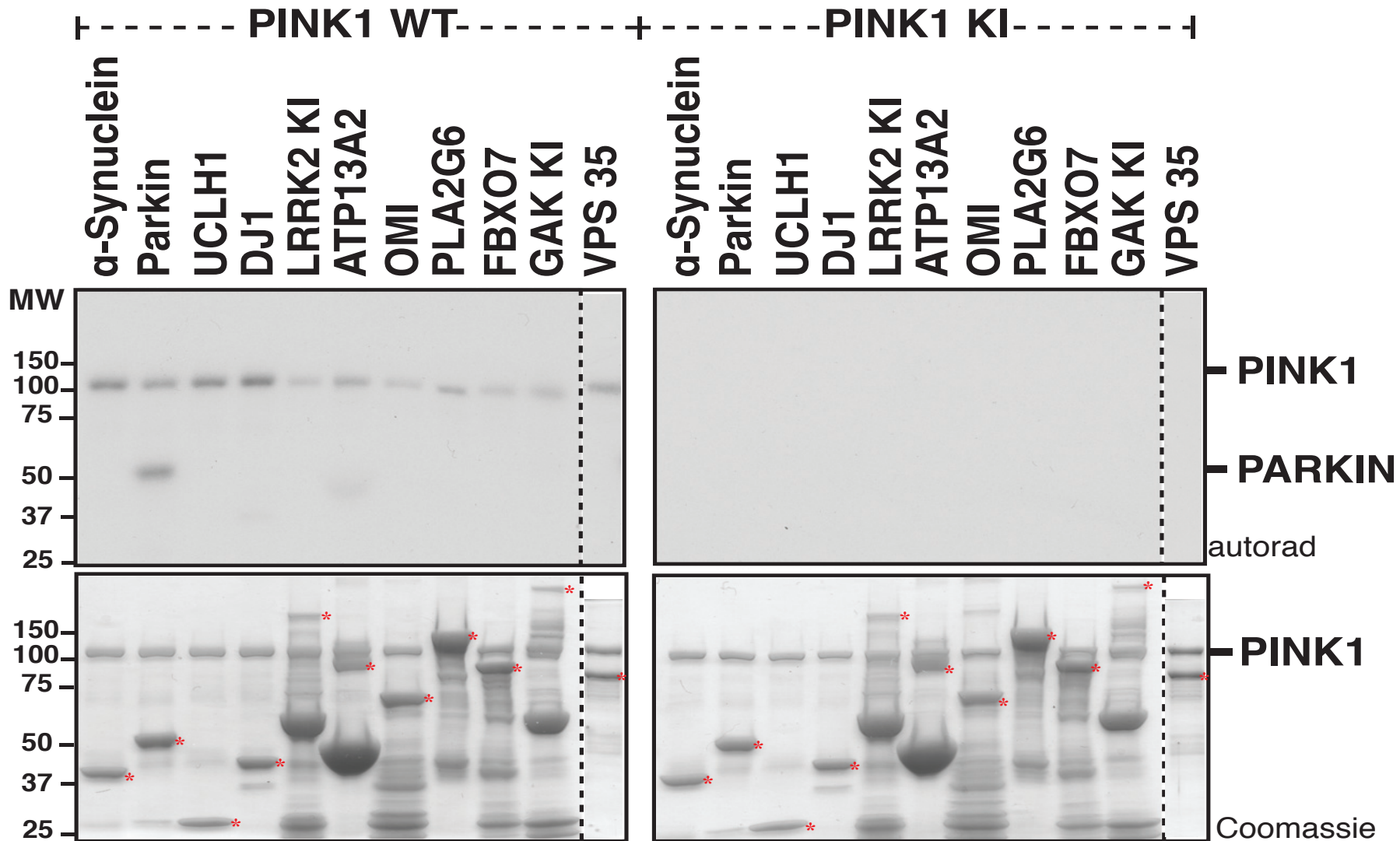
PINK1 kinase activity is crucial to prevent Parkinsonism (2)



What is the substrate of PINK1 ?



Screen of all known Parkinson's disease-linked proteins



Parkin



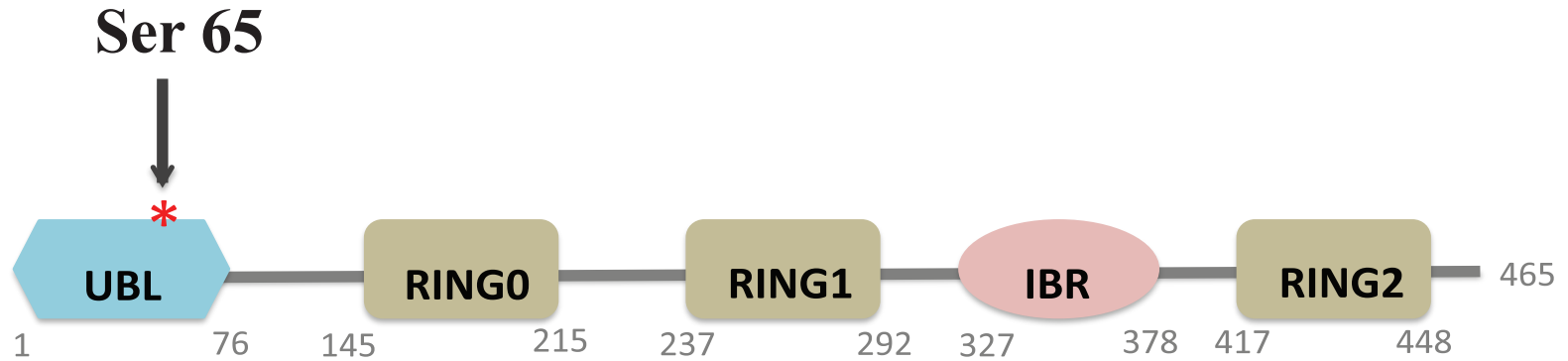
Mutations in Parkin discovered in PD patients in 1998

Commonest cause of familial early-onset PD

Functions as RING-HECT hybrid E3 ligase

Physiological substrate unknown

Ser⁶⁵ is highly conserved residue in the Ubl domain of parkin

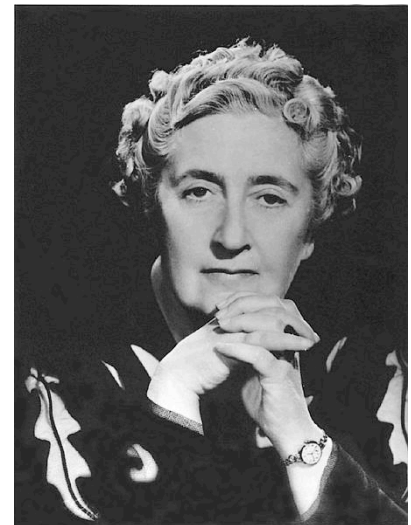
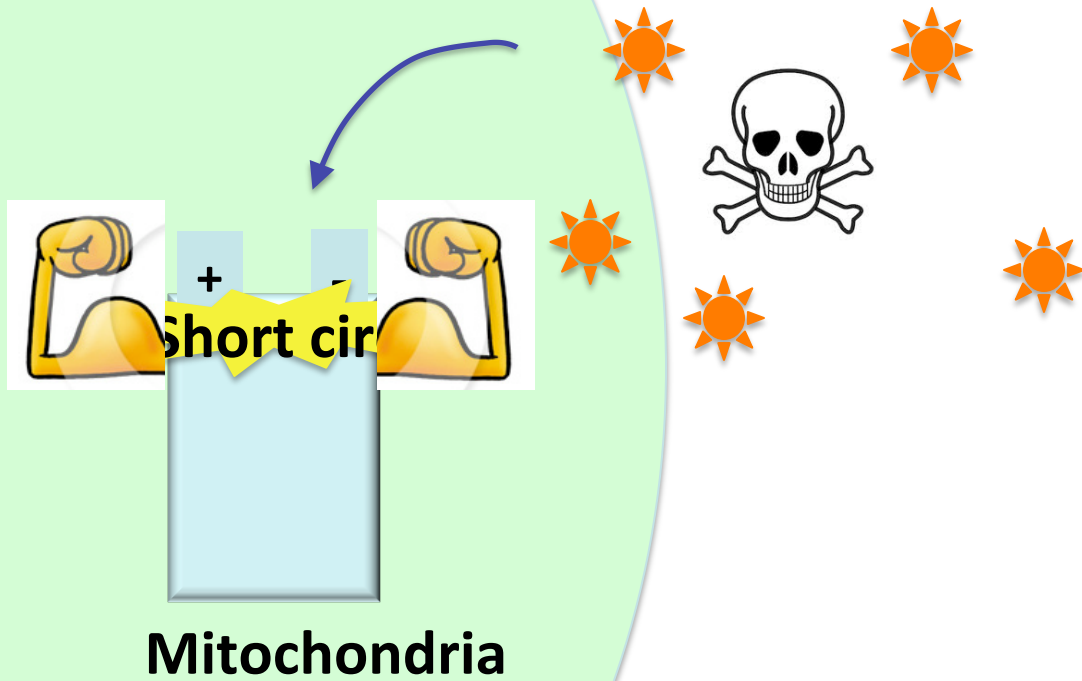


Ser 65

<i>H.sapiens</i>	39	DQ	LR	VI	FAG	KE	LR	ND	WT	VQ	NC	DL	DQC	S	IV	HIV
<i>M.musculus</i>	39	DQ	LR	VI	FAG	KE	LP	NH	LT	VQ	NC	DL	EQC	S	IV	HIV
<i>R.norvegicus</i>	39	DQ	LR	VI	FAG	KE	LQ	NH	LT	VQ	NC	DL	EQC	S	IV	HIV
<i>M.fascicularis</i>	39	DQ	LR	VI	FAG	KE	LR	ND	WT	VQ	NC	DL	DQC	S	IV	HIV
<i>B.taurus</i>	39	DQ	LC	VI	FAG	KE	LR	ND	WT	VQ	SC	DL	DQC	S	IV	HIV
<i>G.gallus</i>	45	DQ	LR	VI	FAG	RE	LS	ND	LT	LQ	NC	DL	VQC	S	IV	HIV
<i>D.rerio</i>	39	DQ	LR	VI	FAG	RE	LC	NE	ST	LQ	GC	DL	PE	S	TV	HVV
<i>D.melanogaster</i>	68	DDL	KI	IF	AG	KE	LS	DA	TT	IE	QC	DL	GQC	S	VL	HAI
<i>T.castaneum</i>	54	GE	VK	II	FA	GE	LG	DN	IS	ISE	CD	LG	QC	S	TL	HAI
<i>A.aegypti</i>	68	GE	LK	II	FA	GE	LS	DT	IT	ISE	CD	LG	QC	S	II	HAV

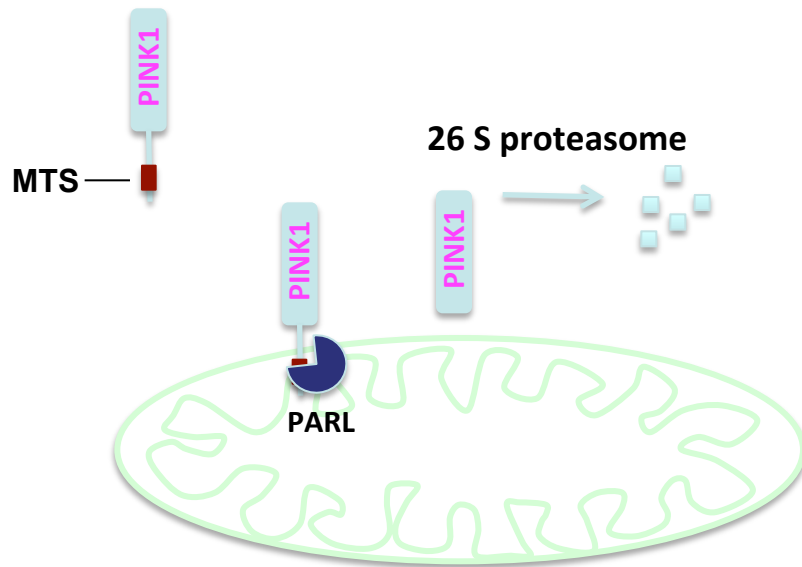
Cell

Cells treated with a chemical called **CCCP**

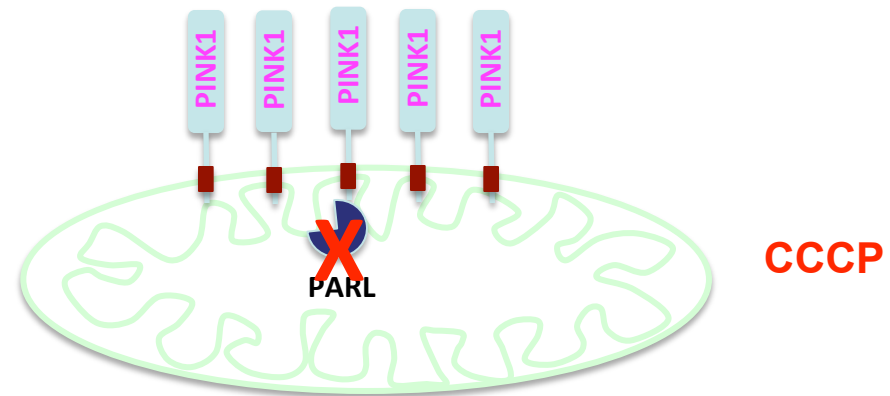


Mammalian PINK1 becomes stabilised at the mitochondria following CCCP

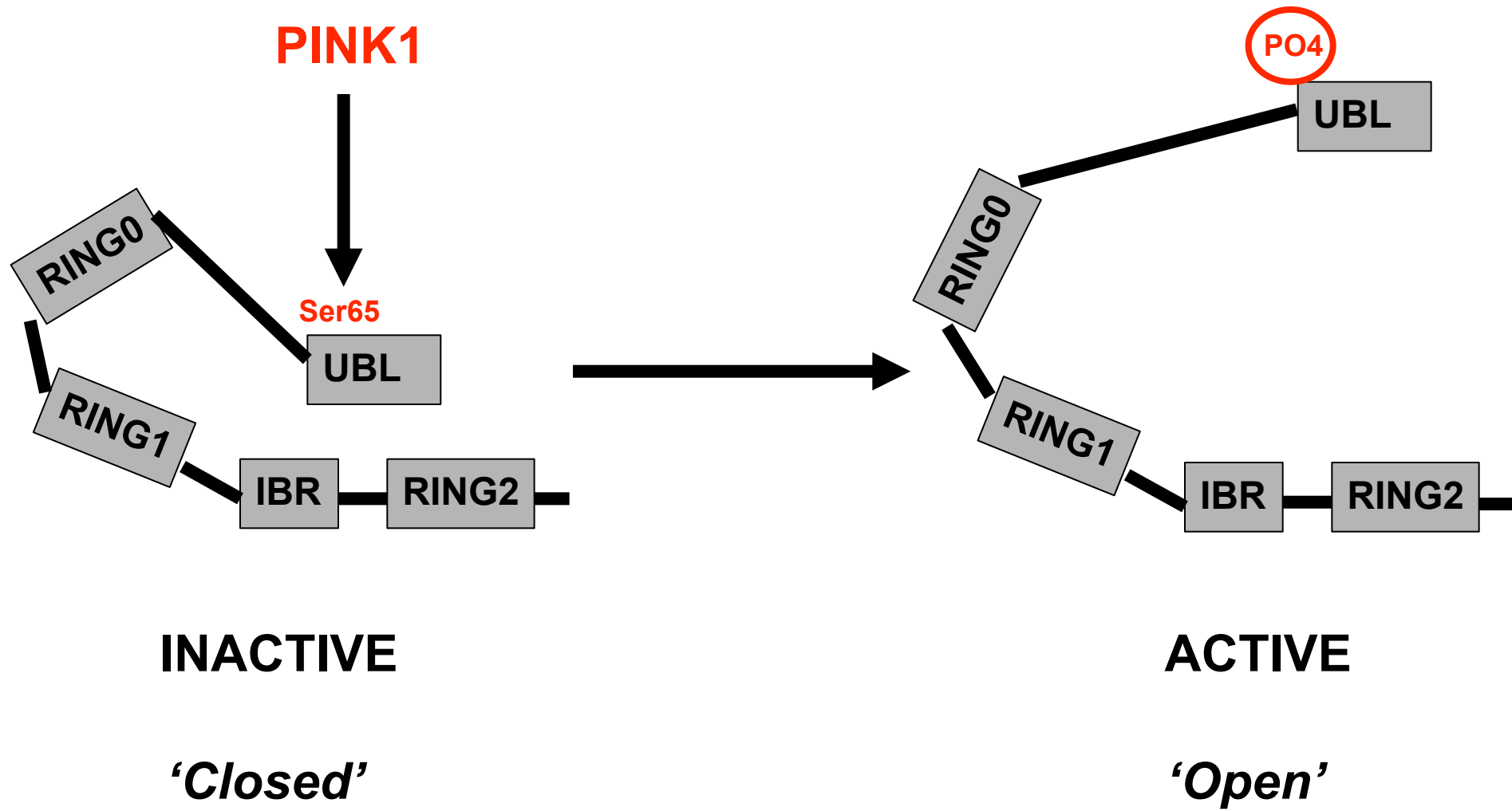
Healthy mitochondria



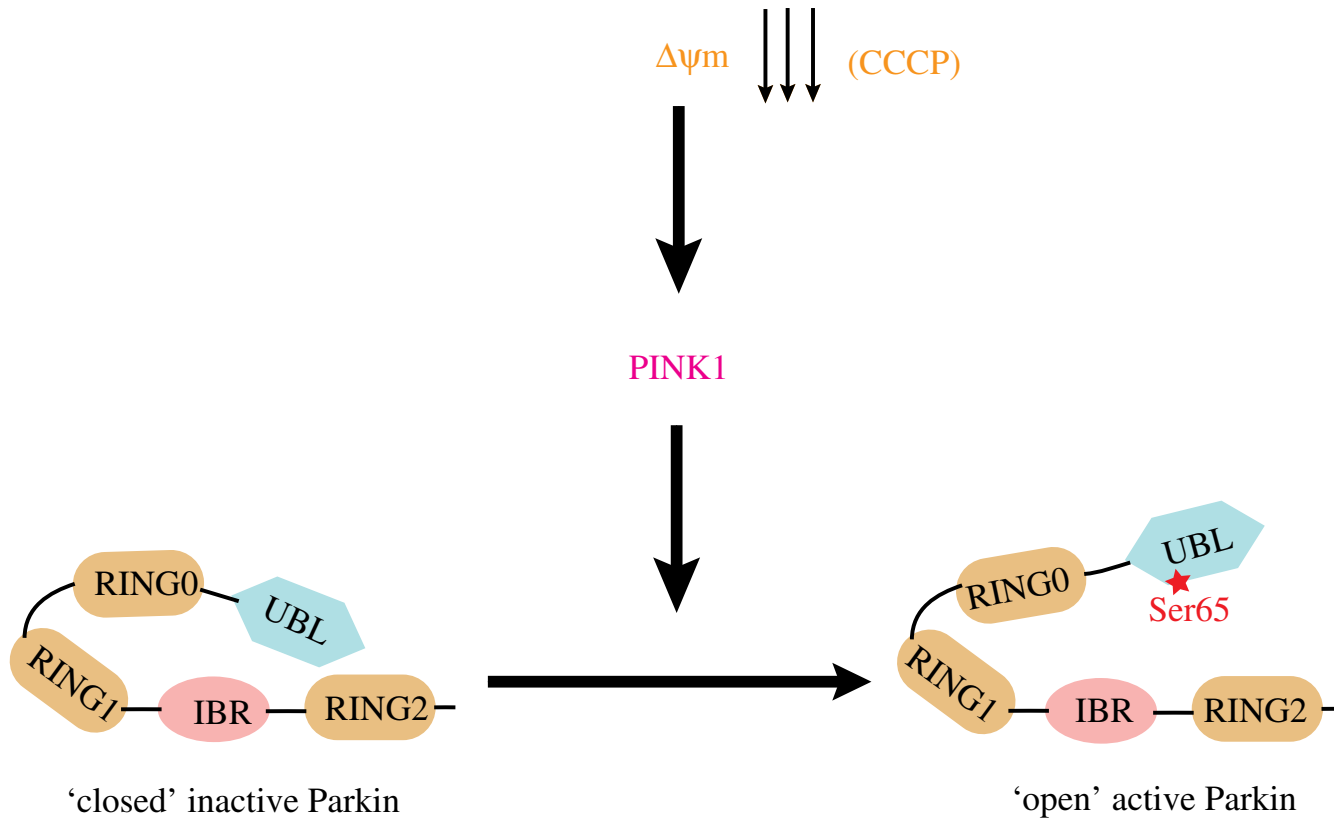
Depolarized mitochondria



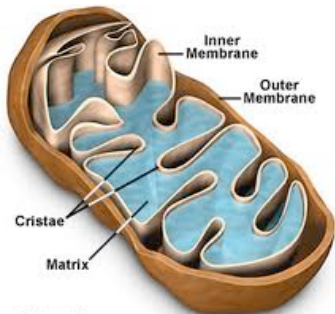
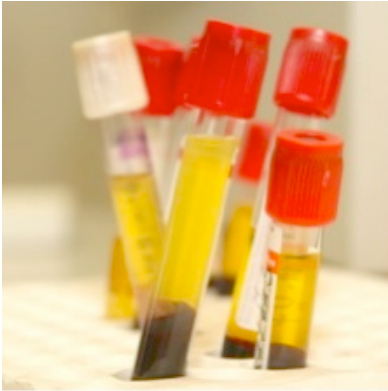
PINK1 phosphorylation of Ser65 leads to active parkin



PINK1 signaling pathway



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



STRESS



Parkinson's disease
p-Ser⁶⁵ Parkin
p-Thr²⁵⁷ PINK1

Monoclonal antibodies under development