

SCAF/18/01 - Bench to bedside Parkinson's research: Finding cures through better understanding disease

Parkinson's disease (PD) is a devastating neurodegenerative condition that affects over 5 million people worldwide and 12000 here in Scotland. There is no simple test for diagnosis and no cure. What is needed most are treatments that slow down or better prevent the relentless progression of disabling symptoms and underlying neurodegeneration. However, a real challenge is the complexity of the condition in terms of clinical presentation, genetics and underlying key molecular pathways. The MRC Protein Phosphorylation and Ubiquitylation Unit (MRC-PPU) at the University of Dundee where I am based is an internationally leading research institution at the heart of the matter of dissecting cell communication mechanisms and how disruption of these processes causes PD.

Although the underlying cause for PD is largely unknown (idiopathic PD), 1% of all sporadic and 2-4% of all familial cases can be explained by genetic changes or mutations in the Leucine rich repeat kinase 2 (LRRK2), which results in hyperactivation of the LRRK2 kinase. The current concept is that LRRK2 inhibitor compounds might counteract the effect of the genetic changes in LRRK2 and have potential therapeutic benefit in LRRK2-associated PD. Excitingly, LRRK2 kinase inhibitors have recently entered clinical trials.

I have developed a blood test that allows measuring of the activity of the LRRK2 kinase. This has already led to very exciting new discoveries including the finding that genetic changes in another Parkinson's associated gene, VPS35, also result in increased LRRK2 kinase activity. During my fellowship, I will take a translational approach combining genetics, clinical and mechanistic stratification of people with sporadic and familial Parkinson's disease to understand the role of the LRRK2 kinase in more detail and unravel novel LRRK2 network components. The hope is that this work will contribute to matching people with PD with the most appropriate emerging disease modifying treatments and identify new targets for drug development. I will also focus on the physiological role of LRRK2 during infection and the recently discovered link between LRRK2 and inflammatory bowel disease.