

### The NLRP3 Inflammasome: A key neuroinflammatory target for neurodegenerative diseases

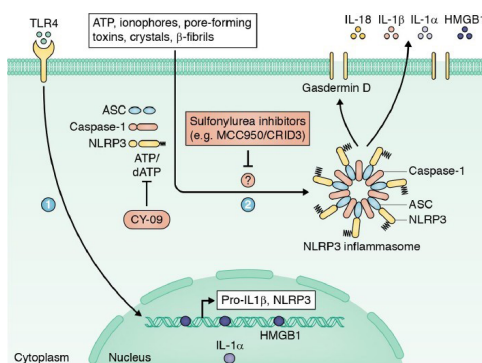
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**Statement of the Problem:** The overactivation of the innate immune system, and the subsequent downstream inflammatory responses this induces, is an important contributing factor to the pathogenesis and progression of CNS disorders. The role of the NLRP3 inflammasome in neurodegeneration is becoming apparent, since the discovery of a NLRP3 specific inhibitor (MCC950). At Inflazome, we asked the question, can inhibitory therapeutic targeting of the NLRP3 inflammasome help to treat neurodegenerative disorders such as Parkinson’s disease (PD)?

**Methodology & Theoretical Orientation:** Using human tissue and well validated in vivo models of Parkinson’s disease, we looked to explore the role of NLRP3 in this disease. We then utilized MCC950 and our CNS penetrant clinical candidate, Inzomelid, to establish the effect therapeutic intervention has in these models.

**Findings:** Our findings show that NLRP3 is upregulated in humans with PD and also in animal models of PD. Fibrillar  $\alpha$ -synuclein, activated microglial NLRP3 in the absence of aggregates, which was ameliorated in the presence of NLRP3 inhibitors. Furthermore, our clinical candidate Inzomelid, mitigated motor deficits and nigrostriatal dopaminergic degeneration in the in vivo models.

**Conclusion & Significance:** This data shows microglial NLRP3 perpetuates inflammation in PD and thus propagates dopaminergic neuropathology. NLRP3 would therefore be a valid target for disease- modifying treatments for PD. Our clinical candidate is currently in Phase I studies and we aim to enter Parkinson’s clinical trials in 2020



Lamkanfi and Dixit, J. Exp Med, 2017

### Biography

Reena Halai completed her PhD at The University of Queensland in neuropathic pain before continuing onto a post doc for six years in the GPCR biology space. She then moved to the Wellcome Trust Sanger Institute in Cambridgeshire where she was the project manager for the Human induced pluripotent stem cell initiative. Prior to her PhD, Reena had also spent time at Glaxo Smith Kline and UCB biopharma, so has experience in both the academic and industry sector. Reena joined the Cambridge site of Inflazome, an Irish biotech company developing small molecule NLRP3 inhibitors, in 2017, where she has been managing the pre-clinical biology and mechanistic studies at Inflazome

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