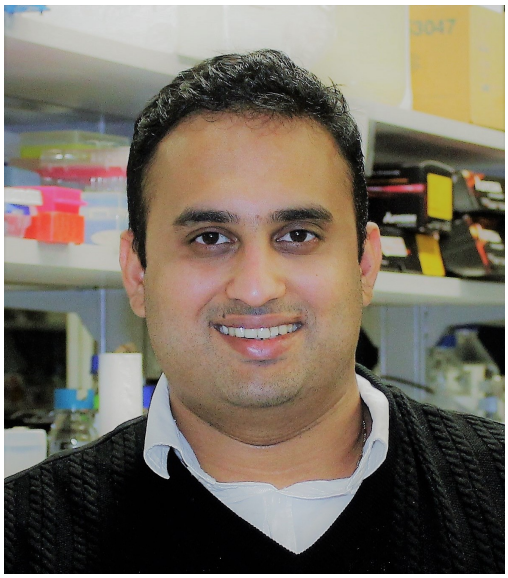
Department of Biochemistry and Molecular Biology

2017 Seminar Series – PhD Oration



Wednesday 6th of December
12-1pm
Bio21 Institute Auditorium
30 Flemington Road, Parkville

Nagaraja Moily
Hatters Laboratory,
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Defining the Htt - exon1 aggregation state induced transcriptomic changes in Huntington 's disease

The key feature of Huntington disease (HD) pathology is the accumulation of soluble mutant huntingtin (Htt) protein into micrometer - sized inclusion bodies. The expression of mutant Htt exon 1 with more than >35 glutamine repeats is enough to cause HD. There is increasing evidence that soluble mutant Htt states are most proteotoxic to the cell and trigger an enhanced risk of death prior to aggregation. Whereas inclusions confer different changes to cellular health, possibly adapting the cell to stressors with the toxicity becoming nullified as the soluble states are sequestered into visible aggregates. Yet the molecular mechanisms underpinning these changes remain unclear. This is primarily due to the difficulty in separating the cells based on their aggregation states. Using the flow cytometry method of pulse - shape analysis (PulSA) to sort neuroblastoma (Neuro2a) cells enriched with mutant or wild - type Htt into different aggregation states, we have clarified which transcriptional signatures were specifically attributable to discrete steps in the aggregation process. Soluble mutant Htt states produced maximal transcriptional dysregulation with dampened CREB signalling invoked specifically by soluble mutant Httex1 states the most striking change seen overall. We further showed CREB signalling as a viable neuroprotective target with cellular toxicity rescued by stimulation of CREB signalling. Other biological processes mapped to different steps of aggregation included transcription regulation by higher chromatin modifiers HDACs and HATs - BRD4, altered NF - kB signalling, autophagy, SUMOylation, NAD+ biosynthesis, ribosome biogenesis and altered HIF - 1 signalling. These findings could lead the way for therapeutic strategies targeting key molecular changes before and after pathological protein aggregation.

ALL WELCOME. Please join us for Pizza to celebrate this PhD Oration!
Further information: Matthew Dixon (matthew.dixon@unimelb.edu.au)