

MONAI : Mechanisms of NFIL3' action in immune cell development

The mechanisms underlying immune cell development are not well-understood. Transcription factors that activate lineage-specific transcriptional programs are well-established to play important functions in this process. However, roles for repressor transcription factors in driving lineage decisions remain unexplored. This proposal investigates the mechanism by which a single transcription factor drives development of several immune lineages through distinct gene repression mechanisms.

The transcription factor NFIL3 play key function in the development of type 1 conventional dendritic cells (cDC1), and we recently discovered that it is also sufficient to drive development of innate lymphoid cells (ILC), a recently discovered immune cell type with immunotherapeutic potential. Our preliminary data indicates that NFIL3 specify the two lineages using distinct mechanisms of gene repression, and that it acts by recruiting co-factors that mediate gene regulation.

We propose to start investigating NFIL3 mechanisms of action by allying the expertise of two teams: an experimental expertise in immune cell development and an expertise in molecular modelling of proteinprotein interactions. Together, we will identify NFIL3 co-factors and investigate their relative contributions in mediating NFIL3 functions in cDC1 and ILC development. We will explore whether NFIL3 post translational modifications modulate its ability to recruit distinct co-factors and subsequently drive distinct cell fates.

The results of this project will impact our understanding of immune cell development, and enlighten NFIL3's role into other biological processes. Our work on NFIL3 post translational modifications should additionally unravel a novel link between environmental cues and cell fate. In the long run, the results obtained in this proposal and subsequent work shall enable us to manipulate NFIL3 mechanisms of action, so as to produce either ILCs or cDC1 in vitro, for therapeutic purpose.