

Understanding the role of FZD receptor activation in G-protein pathway & Wnt-dependent β -catenin pathway

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FZDs (Frizzled) are GPCRs that act as the primary receptors in the Wnt signalling pathway. The Fzd receptors along with their co-receptors bind to Wnt which in turn activates the intracellular signalling pathways such as the Wnt-dependent β -catenin pathway, G-protein signalling, and Ca^{2+} pathway.

My PhD project aims to understand the conformational change occurring at FZD receptors upon Wnt binding that leads to downstream signal transduction through the assembly of signalling complexes.

The first part of my project intends to understand the role of the FZD extracellular domain (cysteine-rich domain, CRD) and FZD linker region in Wnt binding and receptor activation. To understand this, we sever the linker region between CRD and TM and examine if CRD-Wnt complexes can activate FZD-dependent signalling pathways.

The second part of my project focuses on the large FZD-associated signalling complexes at the membrane. I am using Crosslinking mass spectrometry and structural biology to understand the interactions within these complexes in purified systems and within the cells. Currently, I am optimising crosslinking protocols in purified FZD7-miniGs-G $\beta\gamma$ protein complexes. The crosslinking mass spectrometry results would also help us understand the role of CRD in the FZD-G protein complex.

Together, my project will provide information on how FZD conducts the signals across the membrane which could inform drug discovery pipelines in the future.