Insights into adhesion GPCR biological functions from zebrafish

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Zebrafish are a premier vertebrate species to study nervous system development and function. A previous forward genetic screen in zebrafish identified the then orphan adhesion G protein-coupled receptor (aGPCR) Gpr126/Adgrg6 as essential for myelination. The function of Gpr126/Adgrg6 is conserved in humans, highlighting the utility of the zebrafish model for studying Gpr126/Adgrg6 in myelination. At the time of our discovery of Gpr126/Adgrg6, very little was known about the signaling or biology of aGPCRs. I will present an overview of our work in the lab and through key collaborations in which zebrafish have been instrumental in elucidating *in vivo* functions and signaling mechanisms of aGPCRs.

In the second half of the presentation, I will discuss our ongoing work to define small molecule modulators of Gpr126/Adgrg6 via *in vivo* chemical screens in zebrafish. We have screened a library of known GPCR ligands against *gpr126/adgrg6* mutant zebrafish to identify compounds that modulate Gpr126 function in myelination. Using a *gpr126/adgrg6* hypomorphic mutant allele in which myelin is reduced in the nervous system, we have identified several compound classes that suppress the *gpr126/adgrg6* mutant phenotype and increase peripheral myelination. We are currently counter-screening hit compounds against other *gpr126/adgrg6* mutant alleles to determine their mechanism of action and identify compounds that may be directly acting on Gpr126/Adgrg6 and other possible mechanisms. In total, the compounds identified in this screen can help to define mechanisms by which Gpr126/Adgrg6 controls myelination in addition to other Gpr126-regulated biological pathways, and importantly, have the potential to advance therapies to treat peripheral neuropathies and other nervous system disorders.