Studying the effect of candidate therapeutics in rescue of cellular defects in Lowe Syndrome (LS) zebrafish models

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Lowe Syndrome (LS) is an X-linked congenital disease caused by mutations in the OCRL1 gene. Male children with LS are born with congenital cataracts, develop renal failure and mental retardation by one year of age. So far, there is no cure for the disease and affected children die of progressive renal dysfunction by end of adolescence. Our lab identified the first cellular defects in LS patient cells—namely cell spreading and migration, ciliogenesis defects. These defects have also been recapitulated in a morphant zebrafish LS model. Further, we have also identified candidate drugs that can rescue the cellular defects such as migration and ciliogenesis in patient cells (in vitro). We now possess a mutant LS zebrafish animal model in which we have characterized the previously observed cellular defects. Following a series of toxicity studies to establish working concentrations of our candidate compounds, we treated zebrafish embryos obtained from wild-type (WT) and LS mutant fish with the compounds and studied the ability of these drugs to rescue ciliogenesis defects and cell migration defects (by examining facial cartilage) in the embryos. We stained the pronephros (developing kidney) cilia or the facial cartilage of the of the embryos and employed fluorescent and brightfield microscopy respectively to image and quantitatively determine the effect of candidates on the embryos.