Our ageing society is confronted with a dramatic increase of patients suffering from neurodegenerative diseases, for which no mechanism-based cures are available. Among these disorders Tauopathies including Alzheimer’s disease (AD) and certain Frontotemporal dementias (FTD) are most prevalent.

We generated transgenic zebrafish recapitulating hallmarks of Tauopathies based on Gal4-UAS based vectors that allow expression of very high amounts of disease related proteins in parallel with a fluorescent reporter protein for easy transgene detection. The transgenic lines express high levels of human Tau with the FTD associated mutation P301L. As early as 48 hours post fertilization pathologically phosphorylated and misfolded Tau is detectable in the Tau transgenic zebrafish. The phosphorylation phenotype of Tau could be efficiently reduced by genetically and chemically reducing endogenous kinase activity. Furthermore, they show defects in axonal outgrowth of motoneurons resulting in swimming defects 48 hours post fertilization. Ultimately, Tau transgenic zebrafish show substantial neuronal cell death at 5 days post fertilization, which can be visualized by in vivo microscopy of the living transparent zebrafish larvae.

Crossing the Tau transgenic zebrafish with a reporter line labeling the mitochondria in neurons further allowed us to study mitochondrial transport in vivo. Time-lapse microscopy revealed that transgenic Tau expression in zebrafish disrupts microtubule dependent transport of mitochondria. The transgenic Tau zebrafish represent a novel animal model for further studies of Tau induced axonal transport deficits, Tau phosphorylation, neuronal cell death, and drug evaluation.