

Fishin' for Solutions to Hearing Loss: Finding Genetic and Chemical Modulators of Inner Ear Hair Cell Death

I will present studies aimed at the discovery of genes and drugs that will help us understand how and why inner ear hair cells die as a result of a variety of intrinsic and extrinsic challenges, and that will ultimately provide tools to prevent hearing cell loss and balance disorders. We have been using the lateral line system of larval zebrafish, *Danio rerio*, to study modifiers of aminoglycoside and cisplatin hair cell toxicity. This model is particularly advantageous for genetic screening and for screening large drug libraries to find protective or toxic compounds. Large numbers of animals can be processed readily, and a variety of fluorescent markers have been identified that can be used to examine the viability of hair cells in living animals. I will provide two examples of how we have used this model to find molecules that alter hair cell susceptibility to aminoglycoside ototoxicity. From a genetic screen we have identified a several mutations that confer dramatic resistance to drug-induced hair cell degeneration. By further analysis of the mutant phenotypes we can determine the physiological and structural targets of the mutations. By a combination of classical and modern genetic analyses we determine the chromosomal location and identity of the genes. The second example will be from screening small molecule libraries of drug-like compounds and libraries of drugs already approved for clinical use by the US Federal Drug Administration. Several protective compounds have been discovered and found and further analyzed. One example is a novel compound has shown robust protection against hearing loss in the mammals subjected to ototoxic aminoglycoside treatment.