Synthesis and Characterization of Zinc-Selective Ionophores for Mutant p53 Protein Refolding

Meagan Hackey, Anthony Bencivenga, Stewart Loh, Darren Carpizo, David Augeri
Roger Williams University and Rutgers, The State University of New Jersey

Mutation of the TP53 gene commonly leads to p53 protein with an impaired ability to bind zinc and a loss of its native conformation. These mutants have been implicated in a large percentage of cancers, and renaturation of this protein may minimize tumor growth. By raising intracellular zinc concentrations, a class of molecules termed zinc metallochaperones (ZMC'S) can refold some p53 mutants into their native conformation. Through a reactive oxygen species-dependent mechanism, these molecules also activate the newly refolded proteins, and in turn send the cells down an apoptotic pathway. In order to further study the mechanism of these ZMC's, it is necessary to separate the two distinct activities of these molecules. To this end, a series of zinc-ionophores analogous to metal chelators BAPTA and FluoZin3 were designed to selectively buffer intracellular zinc concentrations and to induce mutant p53 refolding, while removing the reactive oxygen species-dependent activation of p53. Biological assays will be performed to analyze the zinc-binding efficiency of these ionophores and to determine future modifications to optimize buffering potential for treatment of p53 mutants.