OS03-4 Development of GGTase-I inhibitors at UCLA

◯Fuyuhiko TAMANOI[1]
[1]University of California

At UCLA, we have developed a novel class of small molecule inhibitors of protein geranylgeranyltransferase-I (GGTase-I). GGTase-I catalyzes geranylgeranylation of proteins such as Rho and Ral that are critical for signal transduction and cancer. Studies on GGTase-I knockout mice validated this enzyme as a target of anticancer drug development. In collaboration with Prof. Ohyun Kwon, we have synthesized and screened chemical compound libraries based on allenoic acid derivatives. The compounds identified exhibit specific inhibition of GGTase-I by competing with substrate proteins. They inhibit growth of a variety of human cancer cell lines and induce G1 cell cycle arrest. Use of xenograft mice established that they inhibit growth of human pancreatic cancer. Characterization of the tumor after the treatment showed that geranylgeranyltransferase-I activity is inhibited and the amount of RhoA and Ral proteins in the membrane is decreased.