Apoptosis serves as a natural barrier to cancer development, and the resistance to apoptosis represents one of the key capabilities acquired during tumor development or progression. Impairment of the intrinsic apoptotic pathway exemplifies one of the established mechanisms of constitutive or acquired drug resistance. As most of the currently used cytotoxic drugs initiate tumor cell death by direct or indirect triggering of the intrinsic apoptotic pathway, impairment of the intrinsic pathway is associated with therapy failure. Targeting of the death receptors, however, enables induction of apoptosis even in the chemotherapy resistant cancer cells. TRAIL is a death ligand belonging to the TNFα superfamily that specifically kills tumor cells while sparing healthy tissues. Much enthusiasm has been generated for TRAIL as a highly promising targeted anti-cancer agent. However, many primary tumors have been shown to be TRAIL resistant. In attempt to overcome such an intrinsic TRAIL resistance a wide array of agents have been shown to sensitize tumor cells to TRAIL. Previous studies reported that roscovitine, a cyclin-dependent kinase inhibitor, sensitized various solid cancer cells to TRAIL.

In this study we analyzed the sensitivity of diverse hematologic malignancies to TRAIL-induced apoptosis and measured the ability of roscovitine to potentiate TRAIL-induced apoptosis or to sensitize TRAIL resistant tumor cells to TRAIL both *in vitro* and *in vivo* using a mouse xenograft model of human lymphoma. In addition, we analyzed molecular mechanisms responsible for the cytotoxic synergism between roscovitine and TRAIL.

We showed that roscovitine and TRAIL demonstrated synergistic cytotoxicity in 21 hematologic malignant cell lines and 26 primary cell samples. Pretreatment of TRAIL resistant leukemia and lymphoma cells with roscovitine induced enhanced cleavage of the death-inducing signaling complex-bound proximal caspases after exposure to TRAIL. We observed increased levels of both pro- and anti-apoptotic BCL-2 proteins at the mitochondria following exposure to roscovitine. These results suggest that roscovitine induces priming of

cancer cells for death by binding anti-apoptotic BCL-2 proteins to pro-apoptotic BH3-only proteins at the mitochondria thereby decreasing the threshold for diverse proapoptotic stimuli. We propose that the mitochondrial priming and enhanced processing of apical caspases represent major molecular mechanisms of roscovitine-induced sensitization to TRAIL in leukemia / lymphoma cells.