Rescuing Toxic Drugs Using Synthetic Proteolysis

Bcl-xl is a well validated cancer target that is responsible for protecting many types of cancer cells from apoptosis and chemotherapy. We generated a highly potent and specific Bcl-xl syntholytic (DT2216) that can selectively induce Bcl-xl protein degradation in all the cells examined except platelets by targeting Bcl-xl to an E3 ligase barely expressed in platelets. DT2216-induced Bcl-xl degradation can selectively kill tumor cells but not normal cells and platelets. DT2216 has a favorable drug property and PK and safety profile, and a broad-spectrum anti-cancer activity in vitro and in xenograft mouse models of human cancers in vivo.

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