

Preclinical studies of a new genetic prodrug activation system

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Minor groove binding DNA alkylating agents typified by CC-1065 and duocarmycin analogs have been studied in the past by several groups as potential potent anti-cancer drugs. However, their clinical utility has been hindered by the systemic toxicity observed at therapeutic doses. We have developed a novel approach to delivering these class of agents selectively to cancer cells '*in vivo*.' Using a novel gene directed enzyme prodrug therapy (GDEPT) approach that employs an enzyme fragment complementation strategy. Several novel enzyme activatable prodrugs of seco-CBI DNA minor groove binding alkylators have been synthesized and used in a new GDEPT approach that has been validated in human tumor xenograft models. This approach will be described and its potential for the targeted therapy of cancer discussed.

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