Cell Therapy-2013
OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Conference and Exhibition on
Cell & Gene Therapy
October 23-25, 2013 Holiday Inn Orlando International Airport, USA

Preclinical studies of a new genetic prodrug activation system

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Abstract

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 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.