

MOLECULAR TARGETS AND CANCER THERAPEUTICS

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Preclinical efficacy landscape of the pan-CLK/DYRK inhibitor Cirtuvivint (SM08502)

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A monumental challenge facing cancer therapy is the vast mechanistic diversity of tumors among and even within cancer patients. This severely limits the number of patients that respond to any given therapy and the durability of responses that do occur. Deep phenotypic profiling of almost 9000 thousand patient samples indicates perturbation of alternative pre-mRNA splicing (AS) is often a root cause of cancer. This offers an extraordinary opportunity to restore health through normalization of AS in diseased tissue. The bottleneck to progress has been finding and drugging the right targets. The CLK/DYRK kinases modulate AS efficiency and specificity, and therefore, targeting them offers the potential to address this bottleneck. The isoquinoline cirtuvivint is a potent ATP-competitive inhibitor of the Cdc2-like kinases (CLK1-4) and the dual-specificity tyrosine phosphorylation-regulated kinases (DYRK1-4), with activity against only a minimal number of the remaining members of the CMGC-family kinases or the kinome as a whole. Cellular target engagement assays indicated biological IC_{50} s below $0.06 \mu\text{M}$ across the CLK/DYRK target class. Thus, SM08502 has utility for robust chemical evaluation of the overarching contribution of CLK/DYRK family activity to tumor biology in general and context- dependent AS in particular. To help assess the breadth and depth of CLK/DYRK dependencies in human cancers, the consequences of pan-CLK/DYRK inhibition on growth and survival of 153 cancer cell line models, 46 PDX models and 43 CDX models were tested. EC_{50} s in cell viability assays ranged from 0.014 to $0.73 \mu\text{M}$ in culture with strong effects observed in subsets of cell lines across all lineages tested. Molecular profiles associated with high sensitivity to cirtuvivint included somatic mutations in the RBM10 splicing factor. Tumor growth inhibition assays with daily dosing at exposures about 2X below the MTD resulted in significant disease control ($\geq 75\%$ TGI) in 15/46 PDX and 18/43 CDX models. Together, these results indicate broad cancer relevance, at least in the preclinical setting, and are consistent with a common reliance on CLK/DYRK-dependent alternative splicing among otherwise highly mechanistically heterogeneous disease.

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