Discovery and characterization of CX-4945, a selective orally bioavailable small molecule inhibitor of protein kinase CK2: Phase 1 initiated

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CX-4945 is a highly screened, specifically active serine/threonine protein kinase found in the cytoplasmic and nuclear compartments of multiple cell types. CX2 has been implicated in critical cellular processes such as cell cycle regulation, signal transduction, apoptosis and angiogenesis. Elevated CK2 activity has been associated with malignant transformation and aggressive tumor growth. Overexpression of CX2 has been documented in multiple cancer indications including breast tumors where CK2 protein levels and CK2 activity levels are increased 10-fold when compared to normal breast. CK2-56 is a selective CK2 kinase inhibitor that blocks cell cycle progression and inhibits angiogenesis. CX-4945 is a selective and potent CK2 kinase inhibitor that induces G2/M arrest in cancer cell lines. The IC50 for 8 most sensitive kinases was determined for CX-4945. This inhibitor does not inhibit CDK1 activity in the cell. This further demonstrates selectivity for CK2 over other kinases. CX-4945 induces cell line dependent G1 or G2 cell cycle arrest, which is consistent with CK2 activity in the cell. This further demonstrates selectivity for CK2 over other kinases. CX-4945 shows potent antitumor activity in BxPC3 and PC3 xenografts. CX-4945 is orally bioavailable and exhibits potent antitumor activity when dosed PO twice daily.

Abstract
CX-4945 Molecular Structure and Kinase Selectivity

G2/M Arrest SUM 149PT

G2/M 10μM CX-4945

The antibodies/beads-bound proteins were then eluted, and applied to 4-12% native polyacrylamide gels. The gels were subjected to Western blotting using antibodies to p-p70S6 (T389), AKT-S473 and p21-T145.

CX-4945 Blocks PI3K/AKT Signaling BxPC3 Cells

CX-4945 Shows Antiproliferative Activity in Alamar Blue Assay

CX-4945 Selectively Blocks Phosphorylation of Ser/Thr Substrates

CX-4945 Suppresses Endogenous CK2 Activity

CX-4945 Inhibits S30-Methionine Incorporation

CX-4945 Blocks PI3K/AKT Signaling MDA-MB-231 Cells

CX-4945 Does Not Inhibit S30-Methionine Incorporation