The novel oral Cdc7 inhibitor, SRA141, demonstrates robust efficacy in preclinical cancer models

Ryan J. Hansen, Snezana Milutinovic, Bryan Strouse, Gregg Smith, Christian Hassig
Sierra Oncology, Vancouver, BC, Canada.

Abstract

SRA141 is a potent, highly-selective, orally bioavailable Cdc7 inhibitor that selectively inhibits Cdc7 in the S phase of the cell cycle. In preclinical models, SRA141 inhibits Cdc7 in biochemical kinase assays and demonstrates differential sensitivity of various tumor cells relative to normal cells. Although the in vitro Cdc7 enzyme potency of SRA141 is comparable to TAK-931, a Cdc7 inhibitor currently in Phase 1/2 testing, using the DiscoverX kinase profiling platform, SRA141 demonstrated more potent inhibition of Cdc7 in human cancer cells in vitro compared to TAK-931. Despite this intriguing observation, the poor pharmacokinetics of SRA141 limited even modest therapeutic activity in long-term treatment of cancer cells in vitro. Further mechanistic studies demonstrated increased phosphorylation status of the downstream targets for Cdc7 (pMCM2, S40 and S53), and several novel Cdc7 substrates including YAP1 and MCL-1 was observed at higher concentrations of SRA141. These findings support a potential role for SRA141 in blocking DNA replication through inhibition of Cdc7 in tumor cells and tumor xenografts.

Results

The relative sensitivities of cell lines within each assay format were generally concordant. A consistent and robust reduction of total protein levels (MCM2, STAT1 and YAP1) was observed at 1 and 3.3 μM SRA141. Minimal inhibition of STAT1, YAP1 and MCL-1 was observed at 3.3 μM, although a dose-dependent increased pMCM2 (S40) levels was observed at 10 μM. The relative phosphorylation of the downstream targets for Cdc7 (pMCM2, S40 and S53), and several novel Cdc7 substrates including YAP1 and MCL-1 was observed as expected. These findings demonstrated that SRA141 inhibits Cdc7 in both human cancer cell lines and tumor xenografts.

Conclusions

SRA141 is a potent, highly-selective, orally bioavailable Cdc7 inhibitor that selectively inhibits Cdc7 in the S phase of the cell cycle. In preclinical models, SRA141 inhibits Cdc7 in biochemical kinase assays and demonstrates differential sensitivity of various tumor cells relative to normal cells. Although the in vitro Cdc7 enzyme potency of SRA141 is comparable to TAK-931, a Cdc7 inhibitor currently in Phase 1/2 testing, using the DiscoverX kinase profiling platform, SRA141 demonstrated more potent inhibition of Cdc7 in human cancer cells in vitro compared to TAK-931. Despite this intriguing observation, the poor pharmacokinetics of SRA141 limited even modest therapeutic activity in long-term treatment of cancer cells in vitro. Further mechanistic studies demonstrated increased phosphorylation status of the downstream targets for Cdc7 (pMCM2, S40 and S53), and several novel Cdc7 substrates including YAP1 and MCL-1 was observed at higher concentrations of SRA141. These findings support a potential role for SRA141 in blocking DNA replication through inhibition of Cdc7 in tumor cells and tumor xenografts.

Known Functions of Cdc7/Dbf4

- Initiation of DNA Replication
- Control of Cell Cycle Progression
- Regulation of Cell Growth and Differentiation

Functions of Cdc7/Dbf4 in S phase

- Inhibits tumor growth
- Increases apoptosis
- Reduces cell proliferation

Background

- Cdc7 is a serine-threonine kinase involved in the initiation of DNA replication. It is a component of the CDC-Elk-Elk complex (CEN-Elk-Elk) that is responsible for the completion of the replication fork and the maintenance of genomic stability.

References