SL-801, a novel, reversible inhibitor of Exportin-1 (XPO1) / Chromosome Region Maintenance-1 (CRM1) with broad and potent anti-cancer activity

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Abstract

XPO1/CRM1, the principal nuclear export protein in subcellular cells, is required for the nuclear-cytoplasmic transport of both proteins and RNAs. Overexpression of XPO1 is reported in many cancers, causing dysregulated protein localization, abnormal cell proliferation, and resistance to apoptosis, and is associated with aggressive characteristics and poor patient outcome.

Recent work has revealed XPO1 to be a clinically relevant target, and nuclear export inhibitors have emerged as a new class of anticancer agents with activity in multiple hematologic and solid malignancies. SL-801 is a novel small molecule that binds covalently to Cys528 of XPO1, blocking the ability of XPO1 to interact with substrate cargos (e.g., p53, FOXO3A, p21, and others), in contrast to the prototypical XPO1 inhibitor leptomycin B, which binds reversibly to XPO1 and caused significant toxicities in Phase 1 trials. SL-801 binding to XPO1 is reversible, but may be exploited to maximize its therapeutic index. Exposure to SL-801 results in potent inhibition of XPO1-dependent nuclear export, cell cycle arrest, and induction of apoptosis in a time- and dose-dependent manner. Here, the anti-tumor activity of SL-801 was investigated against a panel of 240 cell lines representing a broad range of solid and hematologic malignancies and confirmed in several SCID xenograft models.

The OncoPanelTM high content screening platform was used to evaluate the cytotoxicity of SL-801 against 205 solid tumor and 35 liquid tumor cell lines. SL-801 demonstrated potent activity, with 50% growth inhibition (GI50) values ≤ 10 nM in 51/240 (21.3%) cell lines and GI50 values ≤ 50 nM in 230/240 (95.8%) cell lines. SL-801 sensitivity was independent of cell proliferation rate or XPO1 expression levels. While SL-801 was broadly cytotoxic, cell lines of hematologic origin exhibited greater sensitivity. GI50 values in hematologic cancers ranged from 3-20 nM in leukemias, 1-10 nM in lymphomas, and 0-11 nM in multiple myelomas. SL-801 inhibited solid tumor growth, with GI50 values ≤ 10 nM in several breast, brain, cervical, ovarian, gastric, kidney, liver, lung, melanoma, prostate, and sarcoma lines. In addition, a 5-fold increase in active caspase-3 staining was observed at SL-801 concentrations ≥ 100 nM in 112/240 (46.8%) cell lines, consistent with induction of apoptosis. To understand tumor sensitivity to SL-801, results of the cell line cytotoxicity screen were analyzed against publicly available genomic datasets. This analysis revealed that only cell lines with high levels of genomic instability regardless of mutation status of key oncogenes (e.g., KRAS) and tumor suppressor genes (e.g., TP53).

The in vitro cytotoxicity of SL-801 against tumor cell lines was further validated in several xenograft models in SCID mice. In the RPMI-8226 multiple myeloma xenograft model, tumor growth was significantly inhibited at oral SL-801 doses of 31.25 mg/kg administered daily for five days. In the ARH-77 human multiple myeloma xenograft model, overall survival was increased by 50% and median survival was 39 days in the vehicle-treated group (p = 0.001). Significant tumor growth inhibition was also observed in the NCI-H226 non-small cell lung cancer and 22RV1 prostate cancer xenograft models.

These data demonstrate that SL-801 is a promising clinical candidate that inhibits a novel, clinically validated target and supports clinical development in a broad range of oncologic indications. The reversible binding of SL-801 to XPO1 may offer the potential to develop dosing schemes to enable recovery in normal tissues thus broadening the therapeutic index of this class of agents. IND-enabling work is underway to support entry into clinical trials, and a Phase I trial design will be discussed.

Anti-tumor activity of SL-801 against cancer cell lines in vitro

Anti-tumor activity of SL-801 against solid and hematologic cancers in vivo

Conclusions

• The anti-tumor effects of SL-801 were investigated in vivo against a panel of 240 cancer cell lines.
• SL-801 was broadly cytotoxic in both solid and hematologic cancers, with GI50 values ≤ 10 nM in 54/240 (22.1%) cell lines and GI50 values ≤ 50 nM in 230/240 (95.8%) cell lines.
• Sensitivity to SL-801 was independent of cell growth rate.
• At 100 µM SL-801, caspase-3 activation was induced greater than 10-fold in several cell lines.
• SL-801 was cytotoxic towards solid and hematologic cancer cell lines regardless of mutation status of key oncogenes and tumor suppressor genes.

• The anti-tumor effects of SL-801 were validated in vivo in several SCID xenograft models.
• SL-801 significantly extended overall survival in the ARH-77 and MM.1S multiple myeloma and MOLT-4 acute lymphoblastic leukemia xenograft models.
• SL-801 significantly decreased tumor volume in the RPMI-8226 multiple myeloma, NCI-H226 non-small cell lung cancer, and 22RV1 prostate cancer xenograft models.

• The in vivo and in vitro anti-tumor effects observed with SL-801 suggest that XPO1 activity in multiple malignancies contributes to neoplastic pathogenesis.

• Novel clinical trials will be needed to support initial clinical trials in both solid and hematologic cancers in early 2016.