82. A first in class small Molecule as a novel YB-1 inhibitor

(Oregon Health and Science University)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Ovarian cancer
Current Stage	Lead Optimization
Target	Y box binding protein 1 (YB-1)
MoA	An azopodophyllotoxin small molecule, SU056, that potently inhibits tumor growth and progression via YB-1 inhibition. This YB-1 inhibitor inhibits cell proliferation, resistance to apoptosis in ovarian cancer (OC) cells, and arrests in the G1 phase.
Brief Description	• The development of resistance to chemotherapy treatment in solid tumors is associated with up-regulation of the DNA/RNA binding protein Y box binding protein 1 (YB-1) and a worsened prognosis for cancer patients. Inventors have developed a first-in-class small molecule inhibitor of YB-1 that synergizes with chemotherapy to reduce ovarian cancer progression and potentially patient mortality. • Ovarian cancer has a high mortality rate, with frequent development of treatment resistance and disease relapse. YB-1 has a well-established role in cancer, increasing the stability of many oncogenic transcripts which are associated with disease progression and treatment resistance, and elevated YB-1 expression is associated with shorter term survival in ovarian cancer patients. • Inventors have developed a novel inhibitor of YB-1 with validated efficacy in ovarian cancer models and the potential to improve outcomes in a broad range of cancers that demonstrate treatment resistance.
Intellectual Property	WO2022120242A1
Publication	Y box binding protein 1 inhibition as a targeted therapy for ovarian cancer. Cell Chem Biol (2021)
Inventors	Sanjay V. MALHOTRA, Dhanir TAILOR, Arpit DHEERAJ

Highlights

- Potent YB-1 inhibition at low micromolar concentrations in vitro
- Mediates cell cycle arrest and significantly decreases proliferation and migration of ovarian cancer cells in vitro
- In vivo efficacy in halting ovarian cancer progression and metastasis in mouse models
- Ability to synergize with chemotherapy and radiation treatment in ovarian and head and neck cancer models
- Favorable toxicity profile, with an absence of signs of weight loss, neurotoxicity, or changes in liver enzymes

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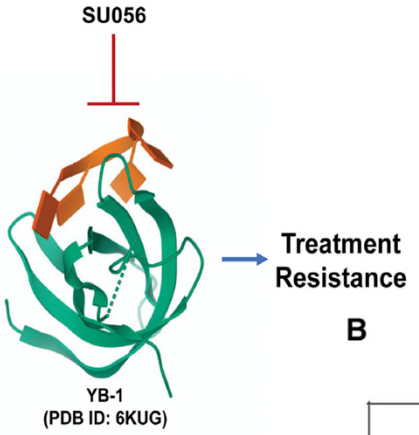
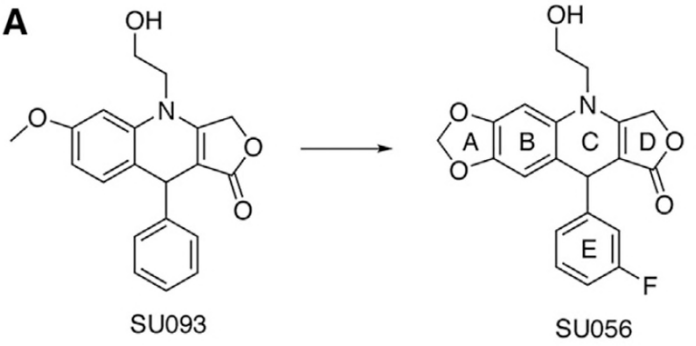
Key Data

Azopodophyllotoxin small molecule (SU093 and SU056)





Drug	IC50 values at 48 h (μM)					
	OVCAR3	OVCAR4	OVCAR5	OVCAR8	SKOV3	ID8
SU093	1.18 ± 0.03	13.69 ± 1.04	14.96 ±1.16	2.03 ± 0.43	1.9 ± 0.06	6.95 ± 0.76
SU056	1.27 ±0.14	6.8 ± 0.53	4.33 ± 0.2	3.18 ± 0.07	1.73 ± 0.16	3.75 ±0.03

SU056 treatment sensitizes the OC cell for taxane treatment