38. Small Molecule Inhibitors of Mcl-1 as Anti-Cancer Agent

(Emory University)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Cancer
Current Stage	Lead Optimization
Target	Myeloid Cell Leukemia sequence 1 (Mcl-1)
MoA	MI-223 directly bound to BH1 and blocked Mcl-1–stimulated HR DNA repair, leading to sensitization of cancer cells to hydroxyurea- or olaparib-induced DNA replication stress.
Brief Description	• Chemoresistance occurs when cancer cells develop resistance to chemotherapy drugs, and appearance of chemoresistance greatly worsens the prognosis of cancer patients. Some chemotherapy drugs function by causing DNA breakages, including double strand breaks (DSBs). DSBs are repaired using either non-homologous end joining or homologous recombination (HR). These repair mechanisms allow cancer cells to resist DNA damage caused by chemotherapy drugs and develop resistance to the drugs. There is a need for improved therapies for cancer that can prevent or reverse chemoresistance. • Inventors have screened and identified small molecule inhibitors of myeloid cell leukemia 1 (Mcl-1). Mcl-1 is an anti-apoptotic protein associated with DSB repair. Mcl-1 is overexpressed in cancer cells and correlated with resistance to chemotherapy and radiation. These small molecules inhibit HR activity and strongly synergize with DNA replication stress agents against lung cancer in vitro and in vivo. The identified compounds may have applications as a combination therapy to inhibit Mcl-1-stimulated HR DNA repair in a variety of cancers.
Intellectual Property	US20200316011A1
Publication	Targeting Mcl-1 enhances DNA replication stress sensitivity to cancer therapy. J Clin Invest. (2018)
Inventors	Xingming Deng, Guo ChenAbu, Syed Md Anisuzzaman

Highlights

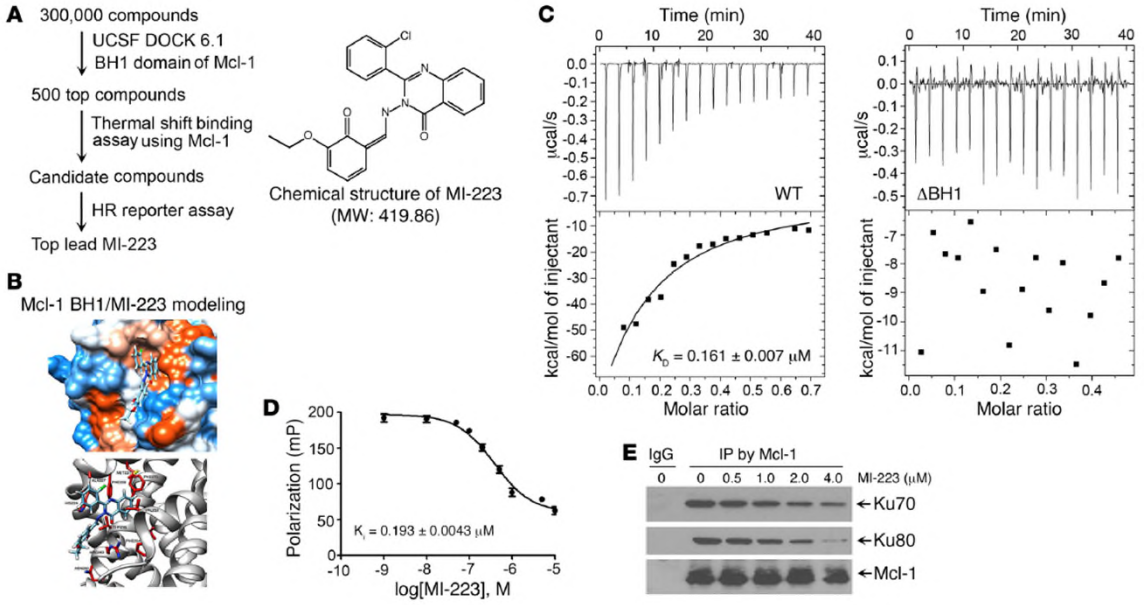
- Myeloid cell leukemia sequence 1 (Mcl-1) acts as a functional switch in selecting between HR and NHEJ pathways. Mcl-1 was cell cycle–regulated during HR, with its expression peaking in S/G2 phase. While endogenous Mcl-1 depletion reduced HR and enhanced NHEJ, Mcl-1 overexpression resulted in a net increase in HR over NHEJ. Mcl-1 directly interacted with the dimeric Ku protein complex via its Bcl-2 homology 1 and 3 (BH1 and BH3) domains, which are required for Mcl-1 to inhibit Ku-mediated NHEJ.
- Mcl-1 also promoted DNA resection mediated by the Mre11 complex and HR-dependent DSB repair. Using the Mcl-1 BH1 domain as a docking site, Inventors identified a small molecule, MI-223, that directly bound to BH1 and blocked Mcl-1–stimulated HR DNA repair, leading to sensitization of cancer cells to hydroxyurea- or olaparib-induced DNA replication stress.
- Combined treatment with MI-223 and hydroxyurea or olaparib exhibited a strong synergy against lung cancer in vivo. This mechanism-driven combination of agents provides a highly attractive therapeutic strategy to improve lung cancer outcomes.

38. Small Molecule Inhibitors of Mcl-1 as Anti-Cancer Agent

(Emory University)

Key Data

Discovery of small molecule MI-223



MI-223 synergizes with DNA replication stress agents against lung cancer in vivo