Novel Pharmaceutical Compounds Based on Tumor-Selective KDM Inhibitors

Can inhibit cell growth with dramatically enhanced cytotoxic potency for triple negative breast cancer

Novel pharmaceutical compounds have been identified by researchers at Georgia Tech that are capable of inhibiting histone lysine demethylase (KDM) enzymes, globally changing histone modification profiles, and targeting specific tumors.

This research provides new insights into the mechanism of the antiproliferative activities of deferiprone (DFP), a hydroxypyridinone-derived iron chelator currently in clinical use for iron chelation therapy. The data show that DFP derives its antiproliferative activity primarily by inhibiting a subset of KDMs. Its docked orientations at KDM-active sites permit modifications that have enabled identification of a cohort of new DFP-based antiproliferative agents. These agents display selective cytotoxicity against specific cell lines, with one DFP-based KDM inhibitor compound displaying a tumor-selective cytotoxicity potency enhancement as high as 65-fold relative to DFP against the triple negative breast cancer (TNBC) cell lines tested.

The novel DFP-based KDM inhibitors, with composition-of-matter patent protection, have the potential to be effective tumor-selective cancer therapeutics, particularly for TNBC.

Summary Bullets

- **Selective**: Can be used to target specific types of tumors
- **Proven efficacy *in vitro***: Can be used to inhibit proliferation of cells (e.g., cancer or tumor cells), reducing tumor burden, inhibiting tumor growth, or both
- **Enhanced potency**: Displayed a 65-fold increase in cytotoxic potency against tested triple negative breast cancer cell lines

Solution Advantages

- **Selective**: Can be used to target specific types of tumors
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Potential Commercial Applications

- Primary application:
  - Breast cancer, especially TNBC
- Other applications:
  - Liver cancer
  - Lung cancer
  - Prostate cancer

Background and More Information

KDMs play a broad and significant role in the proliferation of cancer cells. In fact, specific members have been identified as essential in supporting the growth of several types of cancers. This research identifies several new DFP-based KDM inhibitors that alter the velocity of HP1-mediated heterochromatin gene repression to slow the progression and growth of many types of cancer cells.

Because high levels of iron are essential for tumor cell growth, the antiproliferative effect of DFP has been largely attributed to its iron chelation activity. Using molecular docking, it was determined that DFP adopts docked orientations in which it strongly chelates Fe2+ at the active site of KDM6A and is oriented in a way that may permit modifications to enhance binding affinity for a subset of KDMs. The docked poses adopted by DFP at KDM-active sites also permitted modifications that enabled identification of a cohort of new DFP-based antiproliferative agents, which displayed selective cytotoxicity against a TNBC cell line.

DFP was found to gain access to and form a bidentate chelate with the Fe2+ at the active site of a subset of KDMs. The DFP-KDM interaction was further stabilized by H-bonding between the oxygen moieties of DFP and key residues within the enzymes active sites. This *in silico* observation implicates DFP as a potential inhibitor of the demethylase activity of six KDMs (2A, 2B, 5C, 6A, 7A, and 7B).

This new class of molecules caused a delay in heterochromatin gene repression that was not seen in the parent DFP, and a representative compound (2j) potently suppressed the growth of T47D and MDA-MBMB-231 in murine xenograft models.

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IP Status

Patent application has been filed<o:p></o:p> : WO2019183197A1

Publications

Deferiprone: Pan-selective Histone Lysine Demethylase Inhibition Activity and Structure Activity Relationship Study, Nature - 3/18/2019

Images

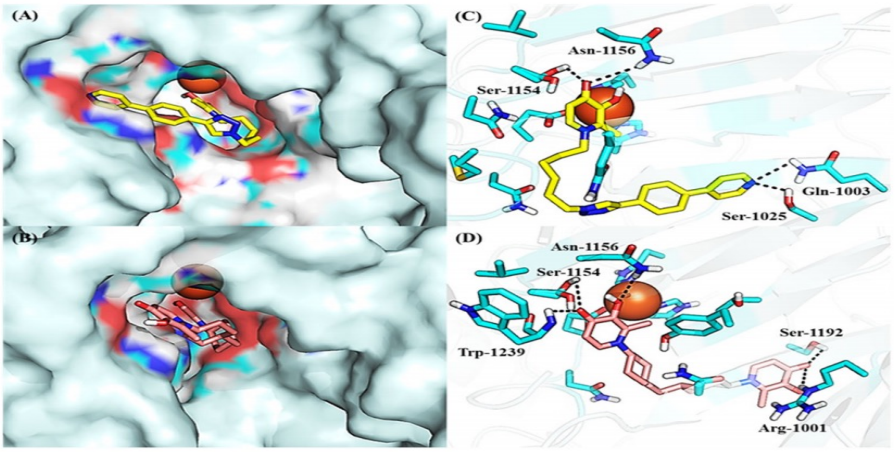

Figure 5. Docked poses of representative DFP-derivatives at active site of KDM6A. (**A**) **2 u** (yellow), and (**B**) **3g** (peach) adopt orientation at the active site of KDM6A (PDB: 3AVR, light blue)[18], that are similar to that of DFP with their N-1 moiety oriented toward the exit channel of the active site. In addition to the interaction with the active site Fe^{2+} (orange), (**C**) **2u** could form additional H-bonding interactions with Asn 1156, Ser 1154, Gln 1003 and Ser 1025 (**D**) while **3g** could form additional H-bonding interactions with Asn 1156, Ser 1154, and Trp 1239 near active site Fe^{2+}, and guanidine of Arg 1001 and Ser 1192 near the exit tunnel (**D**).

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