Docket #: S21-166

First Report of Small Molecule inhibitors of Histone Acetyltransferase 1 (HAT1) with Anti-Tumor Activity

Using their newly developed acetyl-click screening platform, researchers at Stanford have identified riboflavin analogs as small molecule inhibitors of Histone Acetyltransferase 1 (HAT1) with anti-cancer activity. The lead compound has been shown to suppress growth of human cancer cells lines *in vitro* and impair tumor growth *in vivo*. **This is the first report of a small molecule inhibitor of the HAT1 enzyme complex and represents a step towards targeting this pathway for cancer therapy**. HAT1, an enzyme that acetylates the histone H4, is involved in a number of human disorders and conditions including cancer, aging, immune diseases, organ rejection, and viral infections. It has been shown to be overexpressed in a number of cancers and to promote tumorigenesis, as well as to promote HIV and hepatitis (especially HBV) infection and replication. To determine whether targeting HAT1 is a viable anti-cancer treatment strategy, the researchers sought to identify small molecule inhibitors of HAT1. They developed a high-throughput, click-chemistry-enabled HAT1 acetylation assay to facilitate drug discovery and enzymology. Screening of small molecules computationally predicted to bind the active site led to the discovery of multiple riboflavin analogs that inhibited HAT1 enzymatic activity by competing with acetyl-CoA binding. Hits were refined by synthesis and testing over 70 analogs, which yielded structure-activity relationships.

Stage of Development

Results from pre-clinical mouse models indicate that HAT1 can be successfully targeted *in vivo* to achieve anti-tumor efficacy.

Applications

- Development of cancer drug for tumors with high HAT1 levels, high glucose flux, EGFR mutations, KRAS mutations, PTEN mutations, Rbap46 mutations, and Rbap48 mutations.
- Other potential indications where HAT1 plays a role in viral replication, e.g., HIV, hepatitis B and C.

Advantages

- Possible first-in-class inhibitor. Currently there are no acetyltransferase inhibitors approved for any indication.
- This work is the first to suggest that HAT1 may be a therapeutic vulnerability in cancers with an acceptable toxicity profile

Publications

- Gruber, Joshua J., et al. "An acetyl-click screening platform identifies a small molecule inhibitor of Histone Acetyltransferase 1 (HAT1) with anti-tumor activity." *bioRxiv* (2021).

Patents

- Published Application: WO2022272313

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