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 many human disorders and conditions including cancer, aging, immune diseases, organ rejection, and viral infections. It has been shown to be overexpressed in various 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. Lead compound results from pre-clinical mouse models indicate that HAT1 can be successfully targeted in vivo to achieve anti-tumor efficacy.

Stage of Development
Pre-clinical

Applications

- Anti-cancer drugs targeting tumors with high HAT1 levels, high glucose flux, EGFR mutations, KRAS mutations, PTEN mutations, Rbap46 mutations, and Rbap48 mutations.
- Antiviral drugs for diseases such as, HIV, hepatitis B and C, where HAT1 plays a role in viral replication.

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

- Rajkumar S, Dixon D, Lipchik AM, Gruber JJ **(2024)**. An Acetyl-Click Chemistry Assay to Measure Histone Acetyltransferase 1 Acetylation. J Vis Exp. 2024 Jan 26;(203):10.3791/66054. PMID: 38345235; PMCID: PMC11103210.
- Gaddameedi, J. D., Chou, T., Geller, B. S., Rangarajan, A., Swaminathan, T. A., Dixon, D., Long, K., Golder, C.J., Vuong, V.A., Banuelos, S., Greenhouse, R., Snyder, M.P., Lipchik, A.M., & Gruber, J. J. **(2023)**. Acetyl-click screening platform identifies small-molecule inhibitors of histone acetyltransferase 1 (HAT1). *Journal of medicinal chemistry, 66*(8), 5774-5801.
- Joshua J. Gruber, Benjamin Geller, Andrew M. Lipchik, Justin Chen, Ameen A. Salahudeen, Ashwin N. Ram, James M. Ford, Calvin J. Kuo, Michael P. Snyder **(2019)**. HAT1 Coordinates Histone Production and Acetylation via H4 Promoter Binding. *Molecular Cell*, Volume 75, Issue 4, 2019, Pages 711-724.e5, ISSN 1097-2765.

Patents

- Published Application: WO2022272313

- Published Application: 20250188083

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