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Small molecule inhibitors for treating alcoholic hepatitis

Bromodomain inhibitor, UMN627, reduces inflammation in mice models of alcoholic hepatitis.

Technology No. 2022-250

IP Status: PCT Pending; PCT/US2022/028352

Applications

- Alcoholic hepatitis treatment
- Research tool

Key Benefits & Differentiators

- **Anti-inflammatory agent:** UMN627 targets transcriptional mediators that are crucial for mediating TNFα-stimulated liver inflammation.
- **Enhanced specificity:** UMN627 preferentially binds to the BD1 domain of BRD4, minimizing interactions with other BET proteins and potential toxic side effects.

Technology Overview

Alcoholic Hepatitis (AH), a severe form of Alcohol-induced Liver Disease (ALD) resulting from excessive alcohol consumption, poses a major medical challenge due to limited treatment options and a high 30-day mortality rate exceeding 30%. Inflammation, driven by cytokines like TNFα, is at the core of AH's pathogenesis, leading to liver damage. Approximately 35% of individuals with alcohol use disorder face the risk of developing AH, marked by intense inflammation and liver failure. Recent pharmacological advancements have introduced agents targeting transcriptional mediators within super-enhancer pathways, linking TNFα with chemokine amplification in AH. Notably, (Bromodomain and Extraterminal) BET proteins, particularly Bromodomain and extraterminal domain-containing protein 4 (BRD4), have emerged as key players in controlling chromatin architecture and super-enhancer activity, making them attractive treatment targets for AH. However, the clinical application of BRD4 inhibitors is hindered by toxic side effects, highlighting the urgent need for selective BRD4 inhibitors to improve AH treatment.

Researchers at the University of Minnesota have developed BRD4-selective protein inhibitors for AH treatment in collaboration with the Mayo Clinic. One bromodomain inhibitor, UMN627, was tested in animal models of AH where it reduced liver CXCL production and neutrophil infiltration. Cleaved caspase 3 levels, a measure of liver injury and fibrogenesis, were also decreased in animals treated with UMN627. UMN627 selectively targets transcriptional mediators within super-enhancer pathways that are crucial for mediating TNFα-stimulated liver inflammation. The inhibitor preferentially binds to BRD4's bromodomain 1 (BD1), minimizing interactions with other proteins. In general, compared to pan-BET inhibitors, more-specific BET bromodomain inhibitors are anticipated to offer the advantage of causing fewer side effects while maintaining similar BRD4 inhibition, thereby demonstrating the commercial potential of these BRD4-selective inhibitors, and UMN627 in particular, as potential AH treatments.

Phase of Development

TRL: 3-4
Proof of Concept. Small molecule BRD4-selective inhibitors have been tested both in vitro and in a mouse AH model.

Desired Partnerships

This technology is now available for:

- License
- Sponsored research
- Co-development

Please contact our office to share your business' needs and learn more.

Researchers

- **William C.K. Pomerantz, PhD** Professor, Department of Chemistry

References

Gao, Jinhang; Wei, Bo; Liu, Mengfei; Hirsova, Petra; Sehrawat, Tejasav S.; Cao, Sheng; Hu, Xiao; Xue, Fei; Yaqoob, Usman; Kang, Ningling; Cui, Huarui; Pomerantz, William C.K.; Kostallari, Enis; Shah, Vijay H.(June 2021), https://doi.org/10.1002/hep.31617, https://journals.lww.com/hep/fulltext/2021/06000/endothelial_p300_promotes_portal_hypertension_ar 73(6), 2468-2483

Liu, M., Cao, S., He, L. et al.(2021), https://doi.org/10.1038/s41467-021-24843-w, https://www.nature.com/articles/s41467-021-24843-w, 12, 4560