Targeted Inhibition of ADAM17 for the Treatment of Inflammatory Diseases and Cancer

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Overview

ADAM17 is a metalloprotease that regulates shedding of membrane-bound proteins, including IL-6, TNF-Î±, and others. ADAM17 is implicated in inflammatory diseases, fibrosis, cancer, and autoimmune conditions, making it a compelling target.

We developed an inhibitor based on ADAM17â€™s natural pro-domain (TPD), which selectively suppresses ADAM17 activity.

Applications

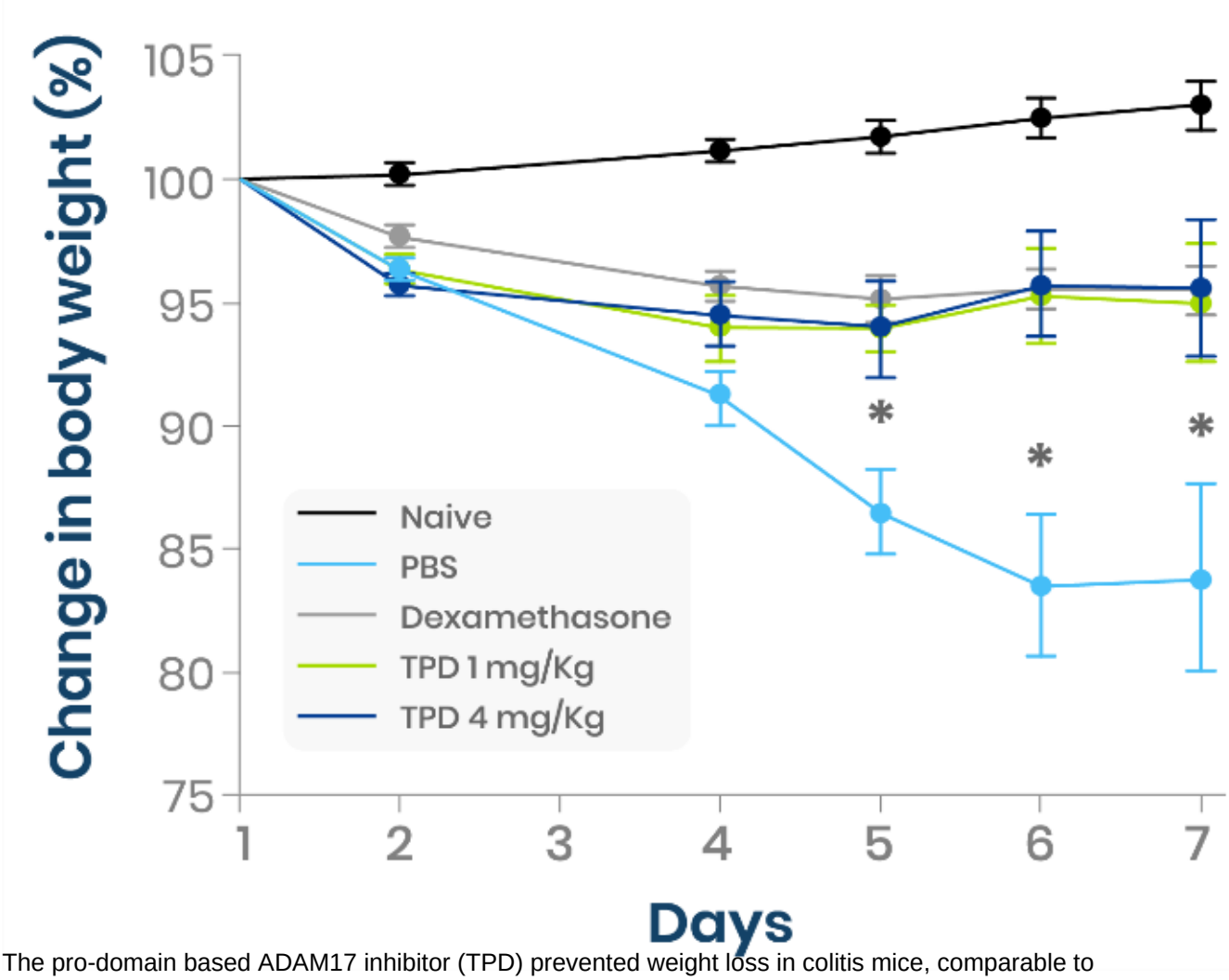
- Treatment of autoimmune, inflammatory and fibrotic diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis, multiple sclerosis (MS), systemic sclerosis, and lupus
- Cancer therapy through localized inhibition of ADAM17
- Combination with immune checkpoint inhibitors or anti-TNFs

Differentiation

- Highly selective compared to small molecules
- Smaller than an antibody, enhancing tissue penetration
- Anti-inflammatory effects in mouse models of colitis, arthritis & pancreatitis
- Anti-fibrotic in a kidney fibrosis mouse model
- Reduced tumor growth in a lung cancer mouse model

Development Stage

- Inhibitor synthesized and structurally validated
- Showed in vivo benefit in mouse models of colitis, arthritis, kidney fibrosis, pancreatitis, and lung cancer



The pro-domain based ADAM17 inhibitor (TPD) prevented weight loss in colitis mice, comparable to dexamethasone

References

Wong, E. et al. [1] *Sci Rep*., 2016

Eirini Kefaloyianni et al [2], JCI Insight. 2016

Mohamed I. Saad et al [3], PNAS, 2022