DEVELOPMENT OF AN INHIBITOR OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) FOR THE TREATMENT OF INFLAMMATORY AND FIBROTIC DISORDERS

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INTRODUCTION

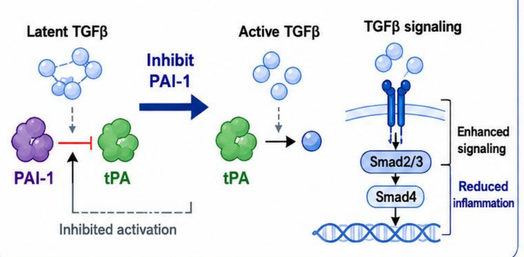
Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic relapsing inflammatory disorder that affects millions of people worldwide and often requires lifelong treatment.[1] **Persistent inflammation** can drive **intestinal fibrosis**, resulting in **excessive fibroblast activation** and **extracellular matrix deposition.**[2] **Plasminogene activator inhibitor (PAI-1) is a key mediator** that links chronic inflammation to intestinal fibrosis by decreasing the concentration of TGF-β from the latent complex and promoting extracellular matrix accumulation.[3]

AIMS

PAI-1 – tissue-type plasminogen activator (tPA) inhibition represents a promising strategy for the treatment of IBD and IBD-associated fibrosis.

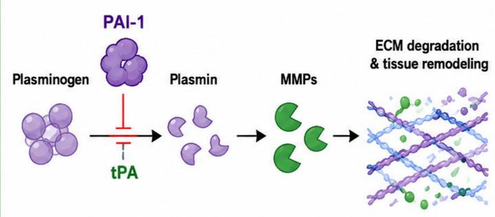
TGFβ signaling is impaired in IBD

- **Inhibition of PAI-1** increases the local concentration of mature TGFβ,
- enhances TGFβ signaling and **suppresses inflammation**.



Regulation of tissue fibrosis

- The inhibition of PAI-1 is promising strategy to **inhibit the tissue fibrosis**
- Inhibiting the activity of PAI-1 and therefore allows tPA to convert plasminogen into active plasmin, which **activates MMPs**.

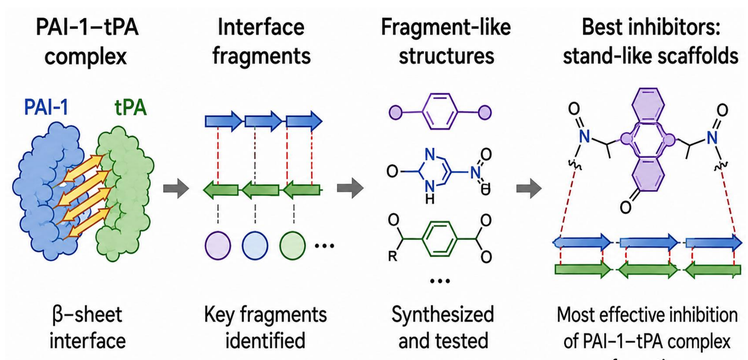


Develop a synthetic peptide-based inhibitor for PAI-1, which

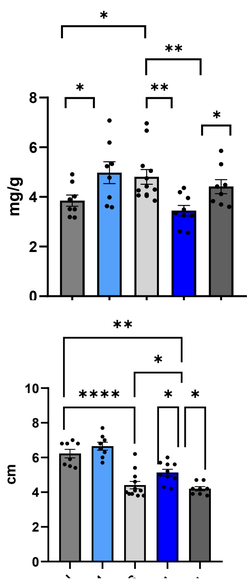
- can increase the local active concentration of TGFβ
- can promote the degradation of the extracellular matrix and tissue remodeling

CHEMICAL BACKGROUND

The PAI-1 – tPA complex is stabilized by a **ß-sheet interface**. Fragment-based screening identified **stand-like scaffolds** as the most effective inhibitors of complex formation.



EXPERIMENTAL RESULTS - IBD



Spleen weight

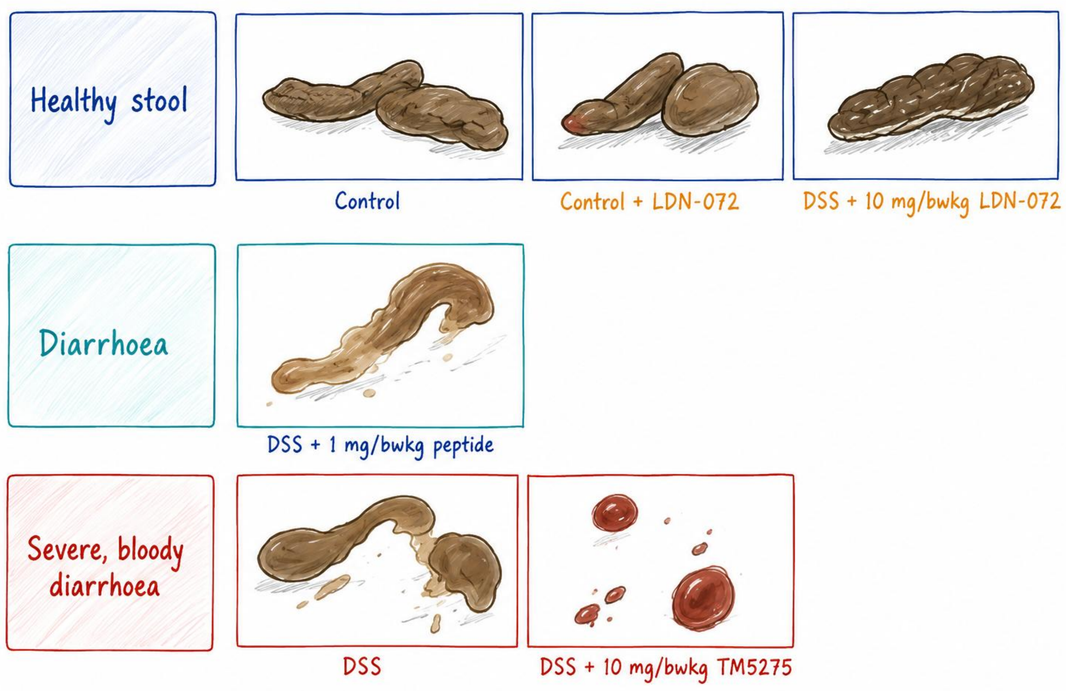
In dextran sulfate sodium (DSS) induced colitis, increased spleen weight reflects inflammation, while **peptide** (LDN-072) **treatment reduces spleen weight.**

Colon length

DSS-induced inflammation causes colon shortening, while **peptide treatment increases colon length.**

Grey: control, light blue: control + peptide , light grey: DSS , dark blue: DSS + petide , dark grey: DSS + TM5275 (PAI-1 inhibitor)

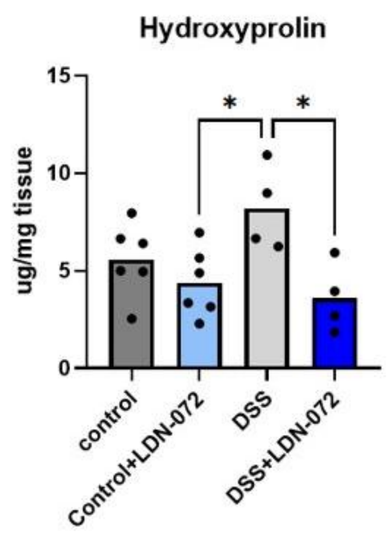
EXPERIMENTAL RESULTS - IBD



The peptide treatment **ameliorates DSS-induced colitis** and **prevents bloody diarrhoea.** In contrast to untreated DSS mice, peptide-treated mice exhibit **improved stool consistency** and **reduced signs of intestinal bleeding.**

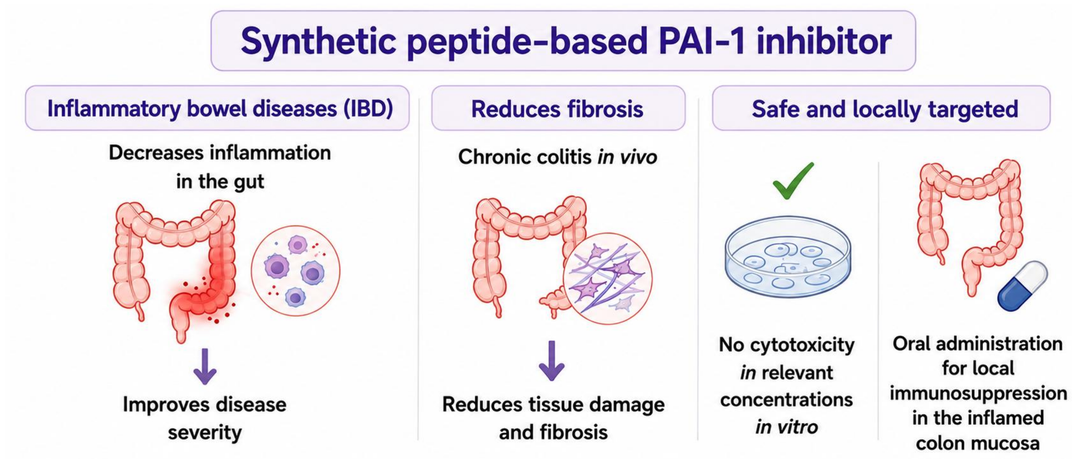
CHRONIC FIBROSIS

Chronic DSS administration induces **severe transmural inflammation, epithelial damage, loss of crypt architecture**, and **extensive fibrosis** in the colon. Treatment with **10 mg/kg peptide significantly reduces inflammation, epithelial erosion**, and **fibrosis**, indicating a protective effect against chronic DSS-induced colonic damage.



CONCLUSION

The developed synthetic peptide-based PAI-1 inhibitor **effectively ameliorates disease-associated inflammation and fibrosis**, improving key outcomes in experimental colitis and chronic pancreatitis. **Oral peptide treatment** reduces tissue damage and fibrosis without cytotoxicity at relevant concentrations, supporting its potential as a **local therapeutic strategy for inflammatory and fibrotic diseases.**



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