SELECTED OPPORTUNITIES IN INFLAMMATORY DISEASES

Targeting The Mucosal Thrombin or PAR1 for the Prevention or Treatment of Inflammatory Bowel Diseases (BIO20161)

TARGETING THE MUCOSAL THROMBIN OR PAR1 FOR THE PREVENTION OR TREATMENT OF INFLAMMATORY BOWEL DISEASES (BIO20161)

Product factsheet

Preclinical

- **Target:** Mucosal Thrombin or protease-activated receptor-1 (PAR1)
- **Product:** Thrombin inhibitor or PAR1 antagonist
- **Application:** Bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC)
- **Rationale:**
  - Active forms of thrombin are increased in Crohn's disease patient tissues
  - Elevated thrombin expression and activity are associated with intestinal epithelial cells
  - Increased thrombin activity and expression are also a feature of experimental colitis in rats
  - Colonic exposure to doses of active thrombin comparable to what is found in inflammatory bowel disease tissues caused mucosal damage and tissue dysfunctions in mice, through a mechanism involving both protease-activated receptors -1 and -4
  - Intracolonic administration of the thrombin inhibitor dabigatran, as well as inhibition of PAR1, prevents trinitrobenzene sulphonic acid-induced colitis in rodent models
- **Patent and publication:**
  - Increased Mucosal Thrombin is Associated with Crohn's Disease and Causes Inflammatory Damage through Protease-activated Receptors Activation. Motta JP et al. J Crohns Colitis. 2021 May 4;15(5):787-799
  - Active thrombin produced by the intestinal epithelium controls mucosal biofilms.Motta JP et al. Nat Commun. 2019 Jul 19;10(1):3224
  - Thrombin modifies growth, proliferation and apoptosis of human colon organoids: a protease-activated receptor 1- and protease-activated receptor 4-dependent mechanism. Sébert M et al. Br J Pharmacol. 2018 Sep;175(18):3656-3668
  - PCT/EP2021/074438: METHODS OF TREATMENT OF INFLAMMATORY BOWEL DISEASES

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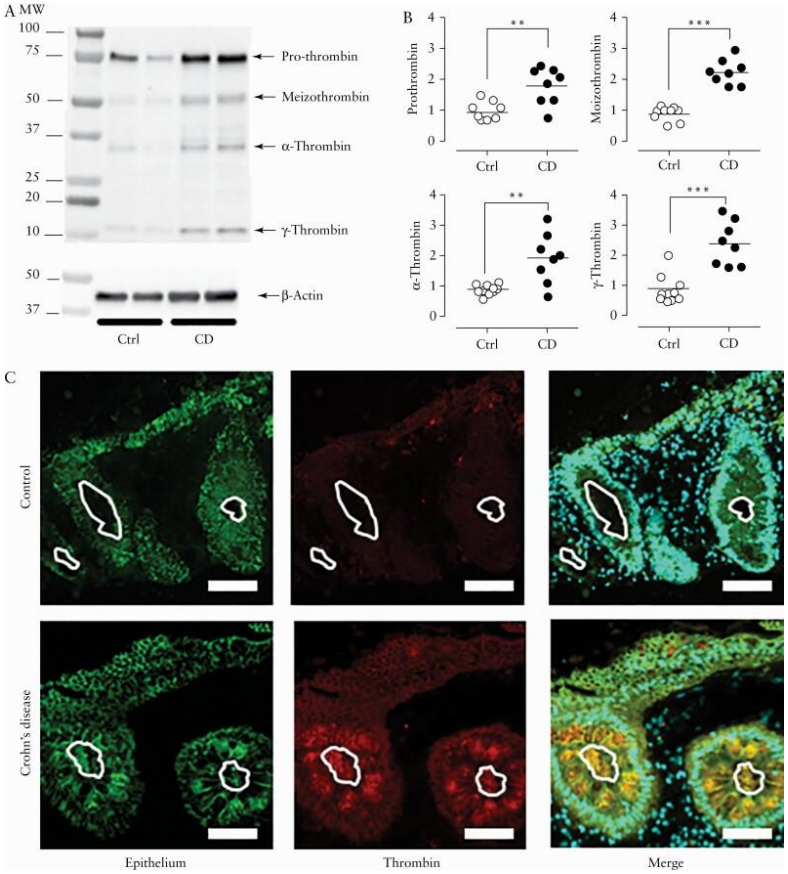
Proof of Concept

Active Forms of Thrombin are Increased in Crohn's Disease Patient Tissues

Representative western blot analysis [A] and relative abundance quantification [B] of thrombin protein expression in protein extracts from human colonic biopsies harvested from healthy control or Crohn's disease [CD] patients and incubated for 1 h in PBS buffer. Bands with different molecular weights and corresponding to different forms of thrombin [prothrombin, meizothrombin, α-thrombin, β-thrombin, γ-thrombin] were detected [A] and quantified [B]. Significant difference compared with controls were noted by ** for p <0.01 and *** for p <0.005, Student's t test. [C] Immunohistochemistry for nuclei [DAPI staining in Cyan], epithelial cell marker [EpCAM, epithelial cell adhesion molecule, green], and thrombin [red] expression in human colonic biopsies harvested from healthy controls or CD patients. Lines indicate the limit between intestinal epithelium and lumen. Scale bar is 50 µm.



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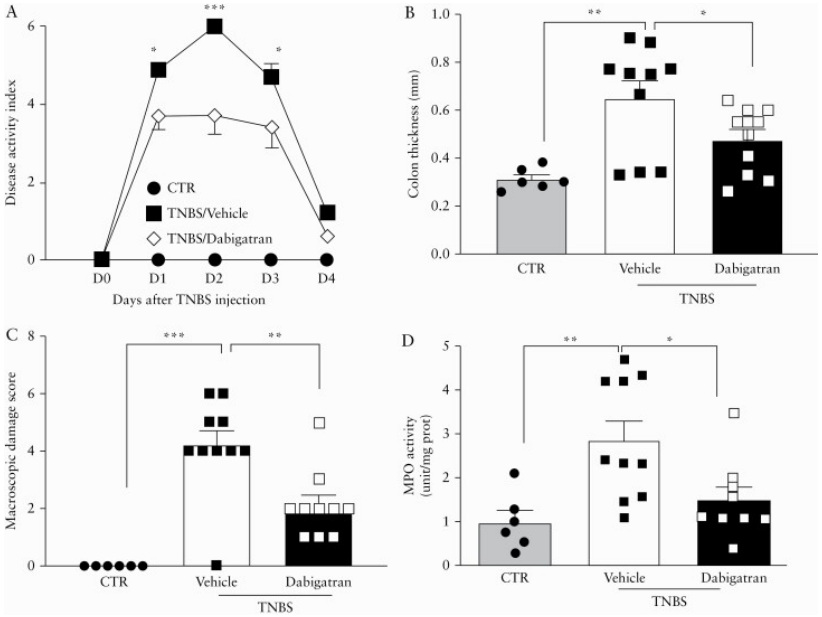
Proof of Concept

Intracolonic Administration of the Thrombin Inhibitor Dabigatran Prevents Trinitrobenzene Sulphonic Acid-induced Colitis in Rat Model



Effect of daily intracolonic administration of dabigatran on TNBS-induced colitis in rats [*n* = 10], compared with uninflamed controls [CTR, that have received intracolonic PBS administration, *n* = 6]. A group of colitis rats [*n* = 10] was treated daily with intracolonic administration of vehicle [saline]. Disease activity index was recorded daily [A], and at sacrifice, colon thickness [B], macroscopic damage score [C], and myeloperoxidase [MPO] activity [D] were measured. Significant differences compared with CTR and vehicle-treated rats were noted * for $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$, two-way ANOVA with Bonferroni post hoc test in [A] and ANOVA with Newman-Keuls post hoc test for [B-D]

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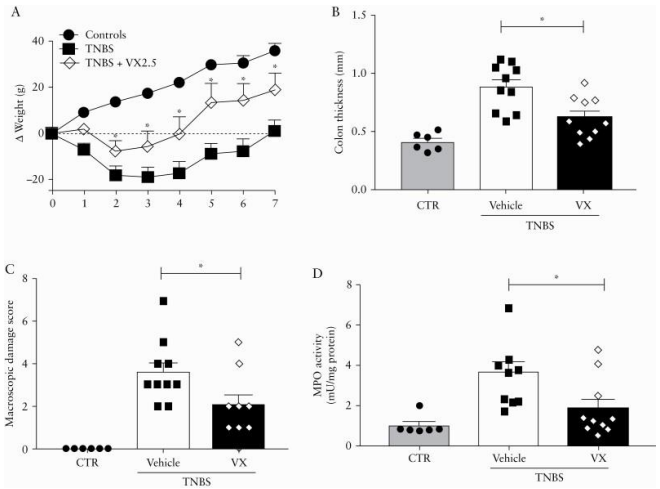
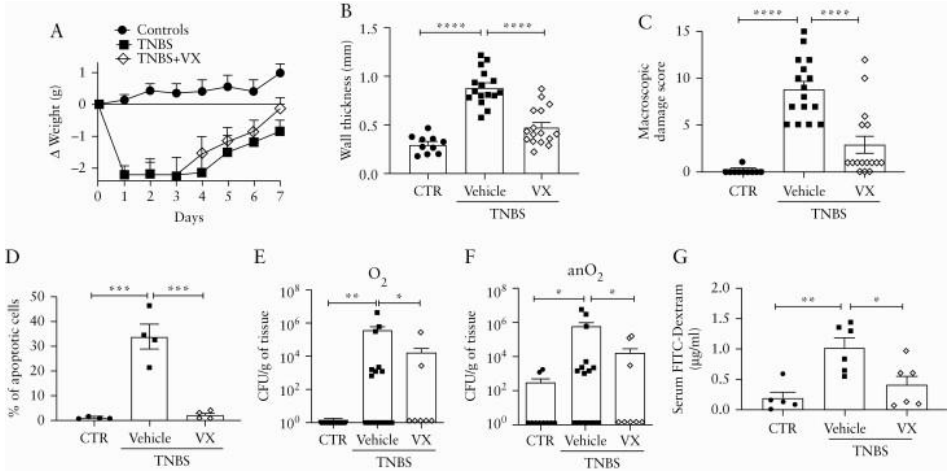
Proof of Concept

Inhibition of Protease-activated Receptor-1, Prevents Trinitrobenzene Sulphonic Acid-induced Colitis in Rodent Models



Effects of daily vorapaxar oral treatments [2.5 mg/kg] on TNBS-induced colitis in rats, compared with uninflamed controls [receiving intracolonic PBS instead of TNBS in 50% ethanol]. Animal weight was recorded daily [A], and at sacrifice, colon thickness [B], macroscopic damage score [C], and myeloperoxidase [MPO] activity [D] were measured. Significant differences compared with vehicle-treated rats were noted by * for p <0.05, two-way ANOVA with Bonferroni post hoc test in [A] and ANOVA with Newman-Keuls post hoc test for [B-D].



Effects of daily vorapaxar oral treatments [2.5 mg/kg] on TNBS-induced colitis in mice, compared with uninflamed controls [receiving intracolonic PBS instead of TNBS in 40% ethanol]. Animal weight was recorded daily [A], and at sacrifice, colon thickness [B], macroscopic damage score [C], percentage of apoptotic cells [D], aerobic [E] and anaerobic [F] bacteria translocated to mesenteric lymph nodes, and FITC-dextran passage to blood [G] were measured. Significant differences compared with vehicle-treated mice were noted by * for p <0.05, ** for p <0.01, *** for p <0.005, **** for p <0.001, two-way ANOVA with Bonferroni post hoc test in [A] and ANOVA with Newman-Keuls post hoc test for [B-G].

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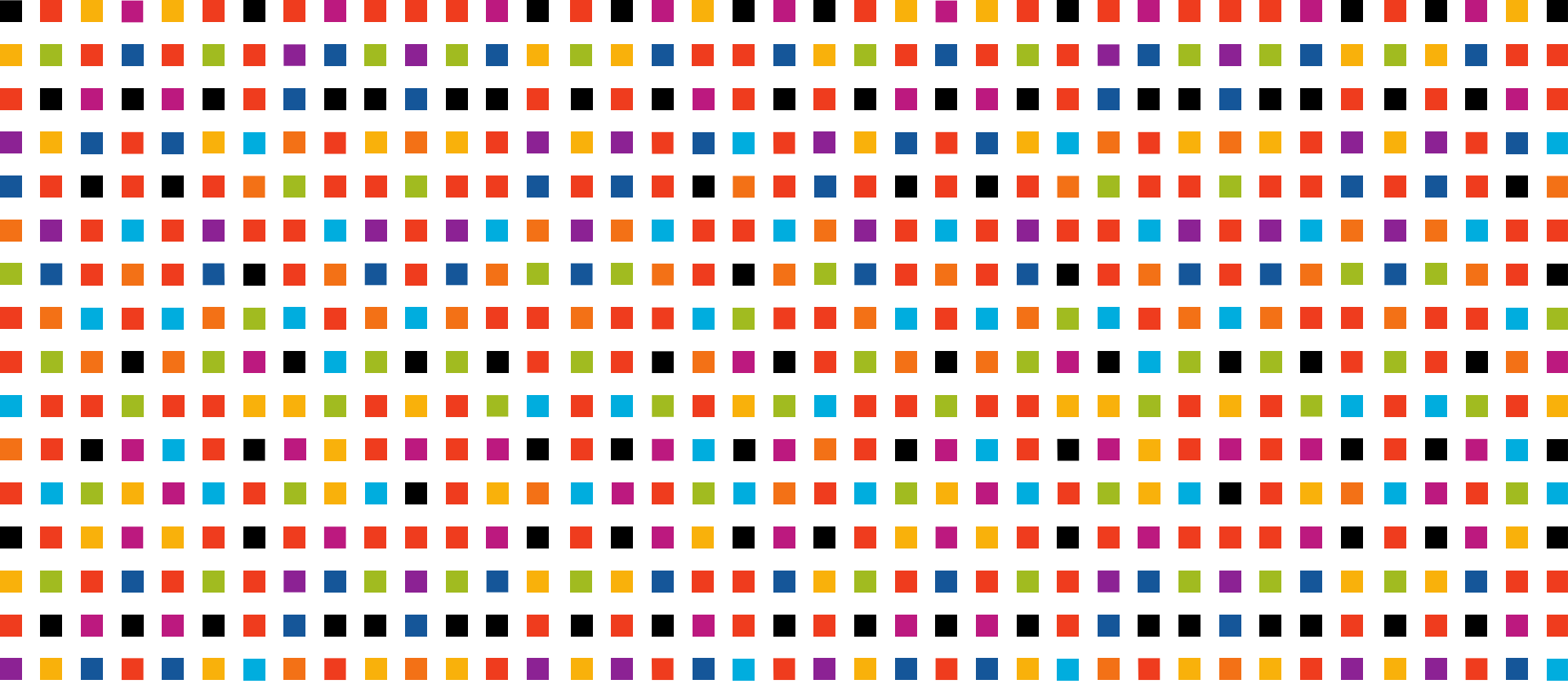

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