Washington University in St. Louis
Office of Technology Management

INFLAMMATORY BOWEL DISEASE BIOMARKERS AND THERAPEUTIC TARGET

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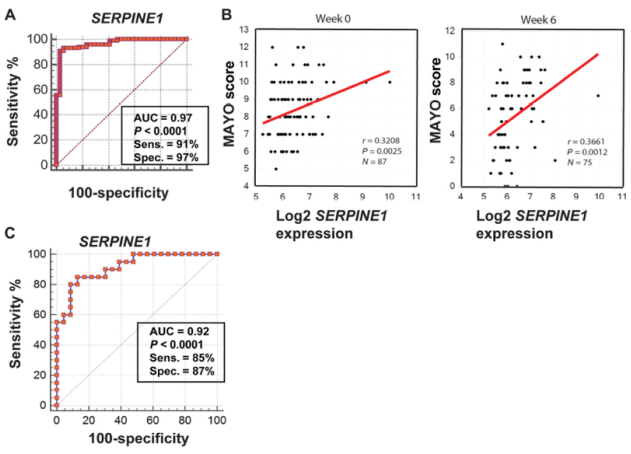
Plasminogen activator inhibitor-1 (PAI-1) has been identified as a specific biomarker that is significantly elevated in patients with inflammatory bowel disease (IBD) and is correlated with disease severity. It could be used to both diagnose the disease (including ulcerative colitis and colonic Crohn's disease) and predict the outcome of treatment with anti-TNF therapy. PAI-1 has also been validated as a first-in-class therapeutic target that offers an alternative drug development strategy for hard-to-treat patients who are unresponsive to anti-TNF therapy.

IBD is heterogeneous disease that is difficult to diagnose because current biomarkers are not specific for the disease. Furthermore, conventional therapies that suppress inflammation (such as anti-TNF drugs) are ineffective for about half of patients with IBD. PAI-1 offers an alternative approach by targeting a previously untapped, non-inflammatory pathway that appears to be a key link between the gut epithelium and inflammatory cascade. Notably, PAI-1 is especially active in patients with severe IBD who do not respond to TNF blockers. In addition, PAI-1 inhibitors have demonstrated effects in reducing signs of IBD in a mouse model. PAI-1 could be used as a precision medicine biomarker to diagnose IBD, monitor disease severity and predict response to treatment.

Stage of Research:

- **Biomarker discovery:** Using transcriptome analysis of colon biopsies, the inventors discovered that PAI-1 expression was highly enriched in active disease and in patients with IBD who did not respond to anti-TNF therapy.
- **Target validation:** The inventors characterized the mechanism of action and further validated PAI-1 by demonstrating the effects of a PAI-1 inhibitor compound in a mouse model of IBD.



SERPINE1 (the gene that encodes PAI-1) is elevated in active disease and in patients that don't respond to anti-TNF therapy

Publications: PAI-1 augments mucosal damage in colitis. Kaiko GE, Chen F, Lai CW, Chiang IL, Perrigoue J, Stojmirović A, Li K, Muegge BD, Jain U, VanDussen KL, Goggins BJ, Keely S, Weaver J, Foster PS, Lawrence DA, Liu TC, Stappenbeck TS. *Sci*

Transl Med. 2019 Mar 6;11(482). pii: eaat0852. (Potential new therapy for Crohn's, colitis identified, *theSource*, March 6, 2019.)

Applications

- **Diagnostics/prognostics/precision medicine for IBD**:
  - identify patients with IBD, classify level of disease activity and monitor progression
  - stratify patients that will benefit from targeted therapy
- **Drug target for IBD** – novel epithelial/coagulation pathway to treat IBD without directly suppressing inflammation

Key Advantages

- **Specific, predictive biomarker**: PAI-1 levels have the potential to indicate level of disease activity and predict patient response to anti-TNF therapy
- **Detectable in blood:** PAI-1 is readily detectable in plasma and has been used as a biomarker of other conditions (e.g., cardiovascular disease) where plasma levels correlate to tissue levels
- **First-in-class target**:
  - downstream of key pro-inflammatory pathways linked to ulcerative colitis and Crohn's disease
  - alternative for hard-to-treat patients who are unresponsive to anti-TNF therapy

Patents: Methods and uses of inflammatory bowel disease biomarkers (PCT Application, Publication No. WO2019018571)