TTI-109 in Ulcerative Colitis

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Webinar Objectives

1. KOL review of ulcerative colitis: the evolving treatment landscape and the case for targeting STAT3
2. TTI-109: an oral prodrug of TTI-101 and the rationale for UC as its initial indication
3. Proposed TTI-109 proof-of-concept trial design
4. KOL perspective on the potential clinical role of STAT3 inhibition in UC

The Evolving Ulcerative Colitis Treatment Landscape

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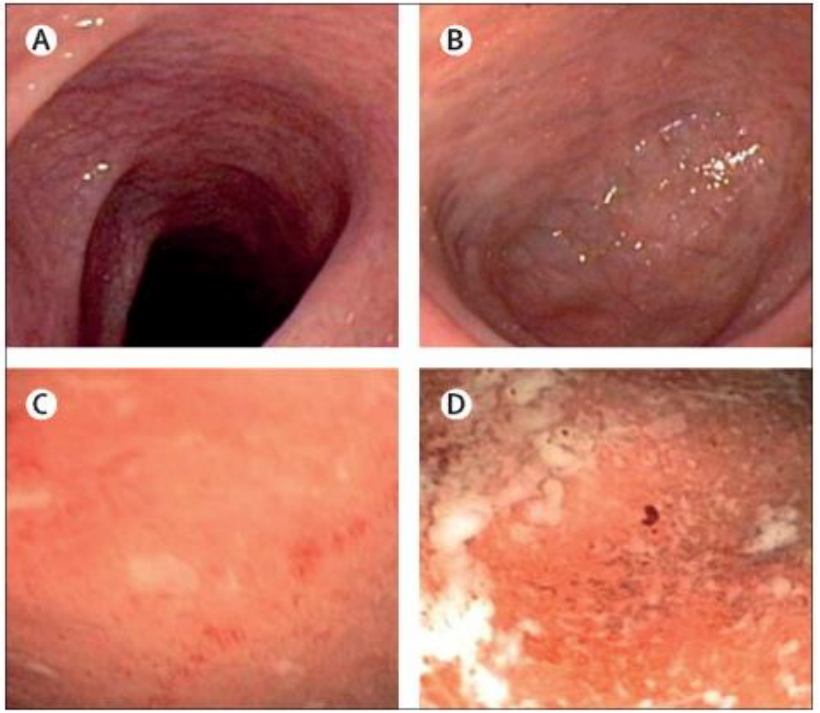
Ulcerative Colitis: Overview

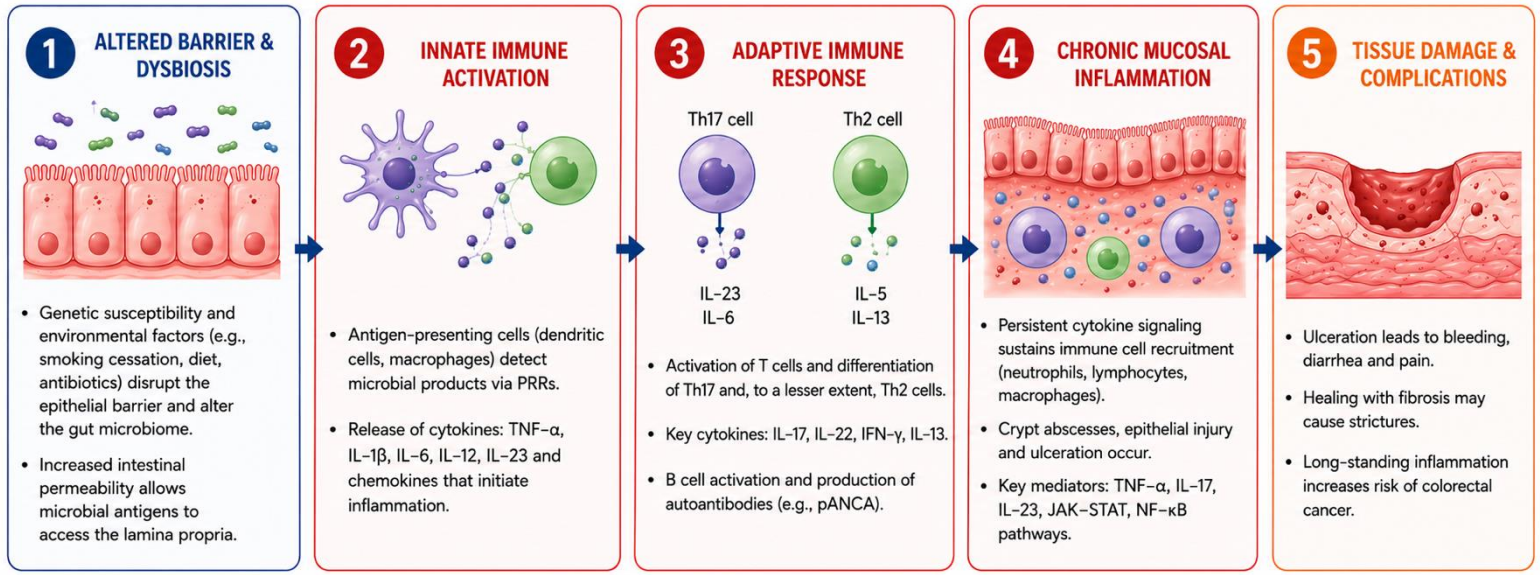
- Chronic, continuous mucosal inflammation of the large intestine
- Pathogenesis: interplay of multiple factors
- Clinical Features
  - Location: begins in rectum, extends proximally
  - Symptoms: bloody diarrhea, urgency, cramping, weight loss, fever
- Diagnosis: history, labs, endoscopy
- Treatment
  - Goal: induce and maintain remission; manage flares
  - Medical: 5-ASAs, steroids, immunomodulators, biologics, JAK inhibitors
  - Surgical: colectomy if refractory or complicated; can be curative



Endoscopic sample of A=normal; B=mild; C=moderate; D=severe UC[1]

1. Ordás I, Eckmann L, Talamini M et al. Ulcerative colitis. The Lancet, 2012; 380, 1606-1619

Ulcerative Colitis: Disease Biology and Pathogenesis



PATHOPHYSIOLOGICAL FEATURES

1 Disease phenotype

Chronic, relapsing-remitting inflammation limited to colon and rectum; mucosal and submucosal involvement

2 Immune dysregulation

Aberrant Th1, Th17, and humoral responses; dysbiosis-driven pathogenic T and B cell activation

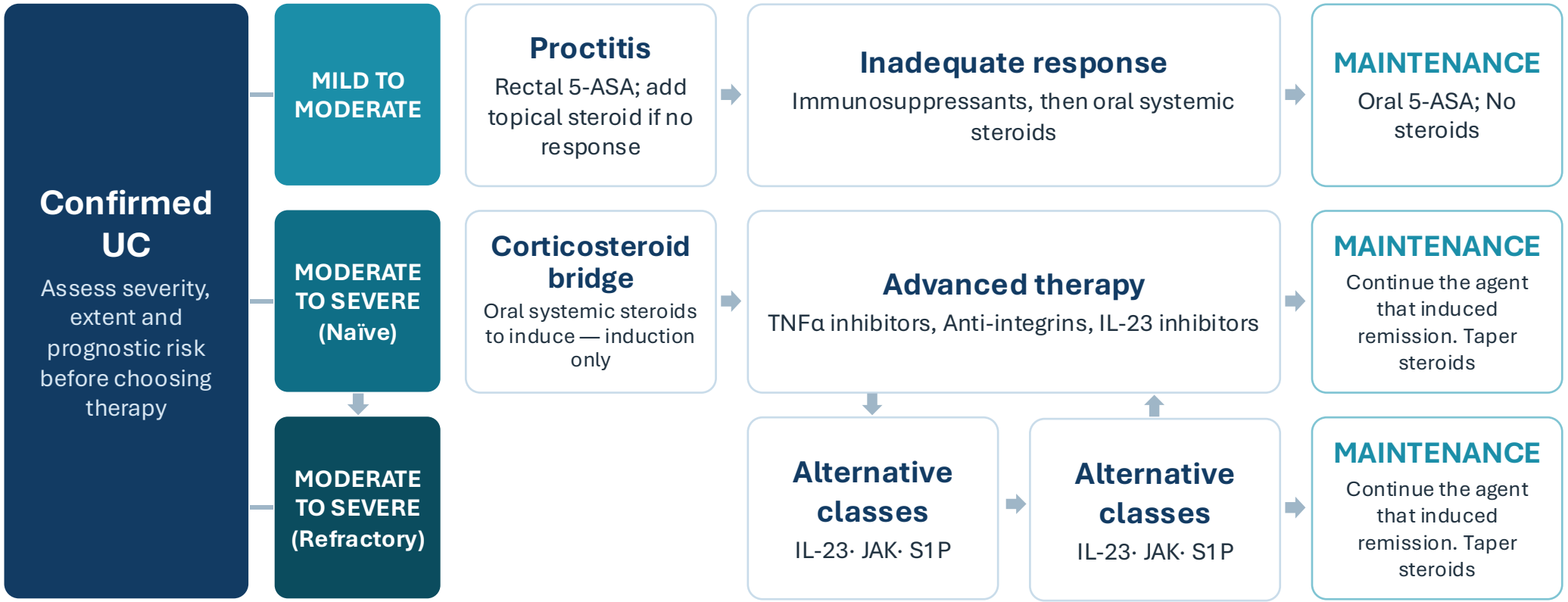
3 Genetic & environmental

Complex genetic predisposition + environmental triggers (diet, microbiota, infections)

1. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427-434.
2. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol. 2010;28:573-621.

Ulcerative Colitis Treatment Pathway

Induction and maintenance of remission by disease severity



ACG guideline recommendations; Therapy choice also reflects extent, prognostic risk, prior therapy exposure and shared decisi on-making. Reassess mild-to-moderate disease within 8 weeks; target endoscopic improvement (MES 0–1) and steroid-free remission. 5-ASA, 5-aminosalicylic acid · MMX, Multi Matrix System · TNF, tumor necrosis factor · IL, interleukin · JAK, Janus kinase · S1P, sphingosine-1-phosphate

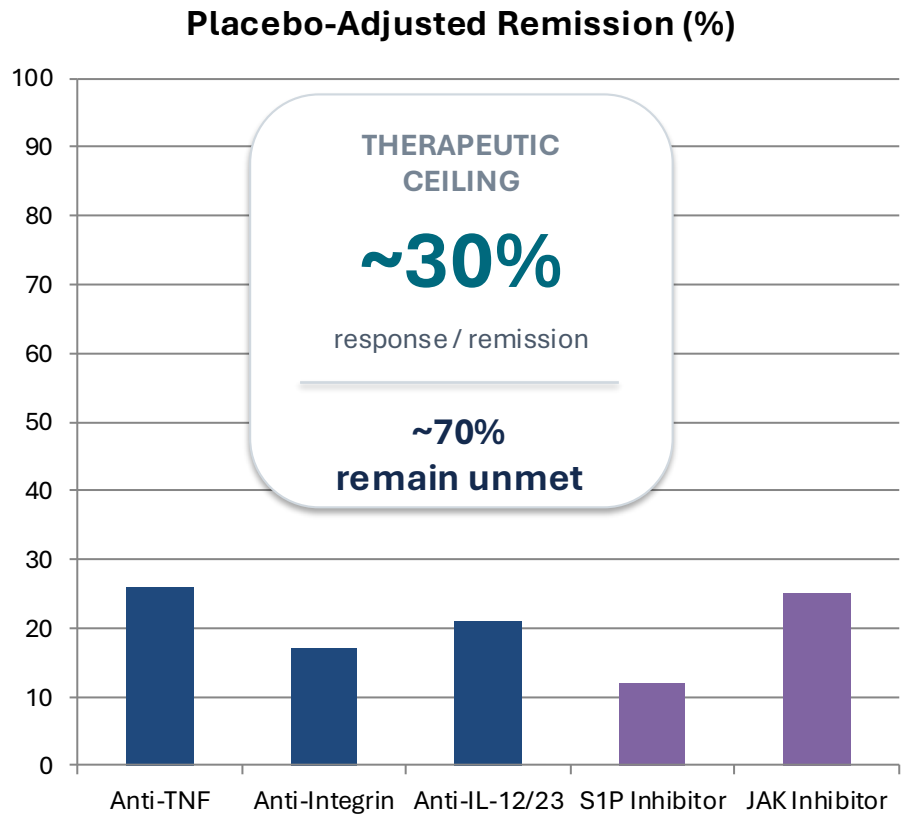
Therapeutic Classes: Mechanism and Clinical Evidence

Three broad therapeutic classes — with different mechanisms, efficacy profiles and practical tradeoffs

Therapeutic class	Mechanism and clinical considerations
CONVENTIONAL THERAPIES	
5-ASAs	Topical anti-inflammatory; uncertain mechanism in oral formulations
Immunosuppressants	Broad immune suppression; slow onset, steroid-sparing
Corticosteroids	Non-selective anti-inflammatory; effective induction but poor long-term efficacy; significant toxicity
BIOLOGIC AGENTS	
TNFα inhibitors	Moderate efficacy, variable durability
IL-23 inhibitors	IL-23p19 targeting; emerging loss-of-response concerns
Anti-integrins	Gut-selective, tolerable
ORAL SMALL MOLECULES	
JAK inhibitors	Broad JAK targeting; rapid responses observed; black-box warning and immunosuppression concerns
S1P modulators	Peripheral lymphocyte sequestration; cardiac monitoring required

1. Turner D, et al. ECCO consensus on biologics and small molecules for IBD and IIM. J Crohns Colitis. 2023;17(5):645-720.
2. Harbord M, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. J Crohns Colitis. 2017;11(6):649-670.
3. Feagan BG, et al. Risankizumab for Active Ulcerative Colitis. N Engl J Med. 2022;387(22):2025-2034.

Persistent Unmet Needs Despite Therapeutic Advances



1. **Secondary loss of response**
2. **Heterogeneity of disease biology**
3. **Safety and tolerability**

Disease Complexity: Rationale for Multi-Driver Targeting

Interconnected pathogenic drivers of UC

1 **Immune dysregulation**

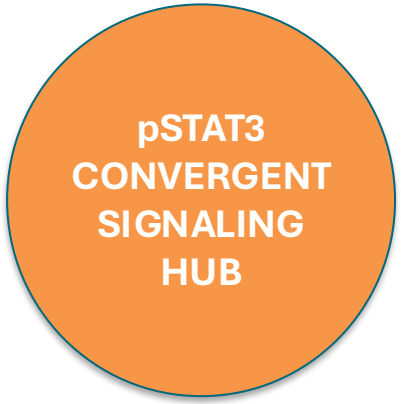
Th17, Th1, follicular helper T cells, pathogenic B cells; abnormal IL-6, IL-23, TNFα signaling

2 **Inflammation**

IL-17A, IL-23, TNFα, IL-6 drive mucosal inflammation and effector cell differentiation

3 **Tissue remodeling & fibrosis**

Chronic inflammation leads to structural changes, stricture formation, potential progression to complicated disease



Rather than targeting individual upstream pathways, therapies targeting convergent signaling hubs may offer broader efficacy

1. Neurath MF. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014;14(5):329-342.
2. Jiang W, et al. IL-22 is Increased in Patients with Primary Biliary Cirrhosis and IL-22 Primes Hepatic Cells to Produce Chemokines and IL-6. J Hepatol. 2011;54(3):489-498.
3. Zenewicz LA, et al. Homeostasis and inflammation in the intestine. Cell. 2012;140(6):859-870.

Potential Role of STAT3 in the IBD Landscape

FRONT-LINE UC (ADVANCED-THERAPY NAÏVE)	BIOLOGIC-EXPOSED / REFRACTORY UC	CROHN'S DISEASE
Current standard: **IL-23 and TNFα inhibitors**	Current standard: **Switch to alternate pathway (TL1A, JAK, S1P)**	Current standard: **TNFα, IL-23 inhibitors; JAK if refractory**
STAT3 inhibitor opportunity: Oral multi-driver alternative to single-pathway IL-23 or TNFα; potentially more durable	**STAT3 inhibitor opportunity**: STAT3 blockade addresses the escape biology rather than switching to another single target	**STAT3 inhibitor opportunity**: Shared STAT3-driven biology supports cross-indication expansion in transmural, fibrostenotic disease

TTI-109 in Ulcerative Colitis

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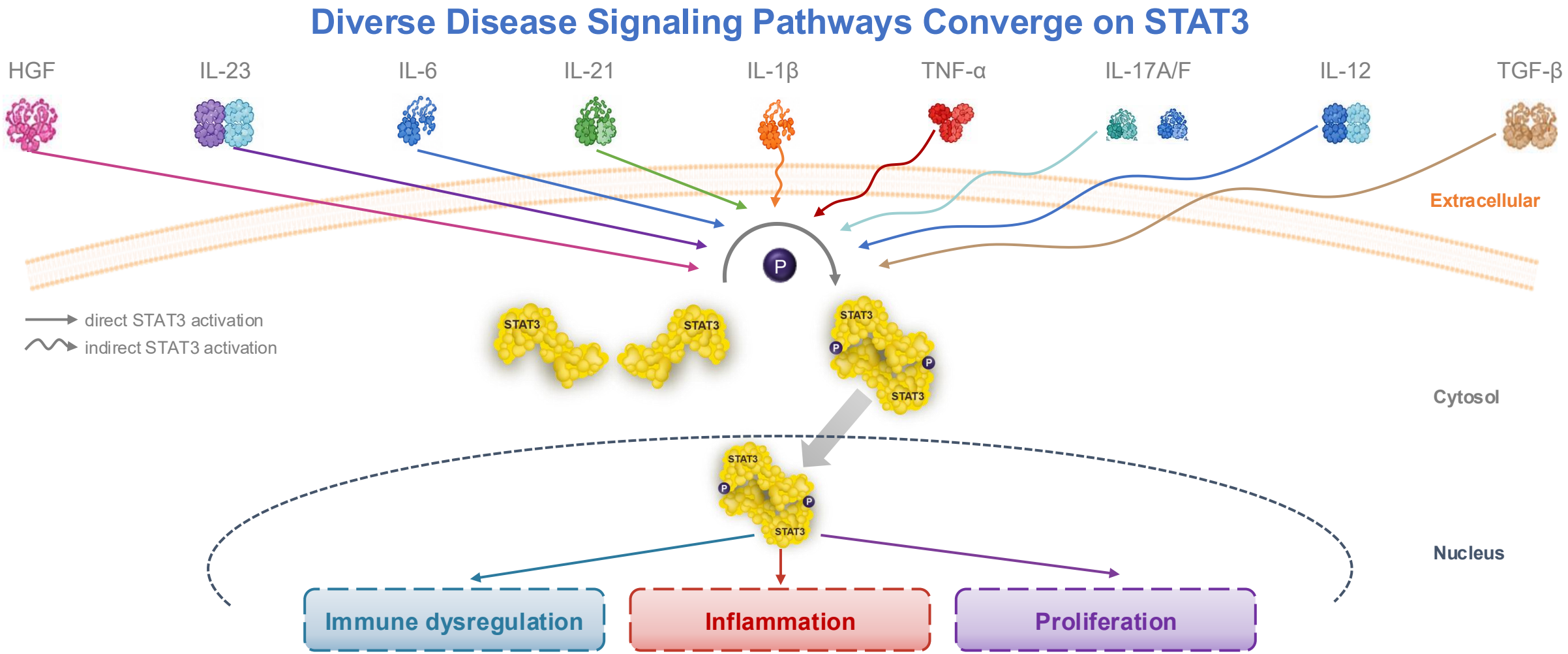
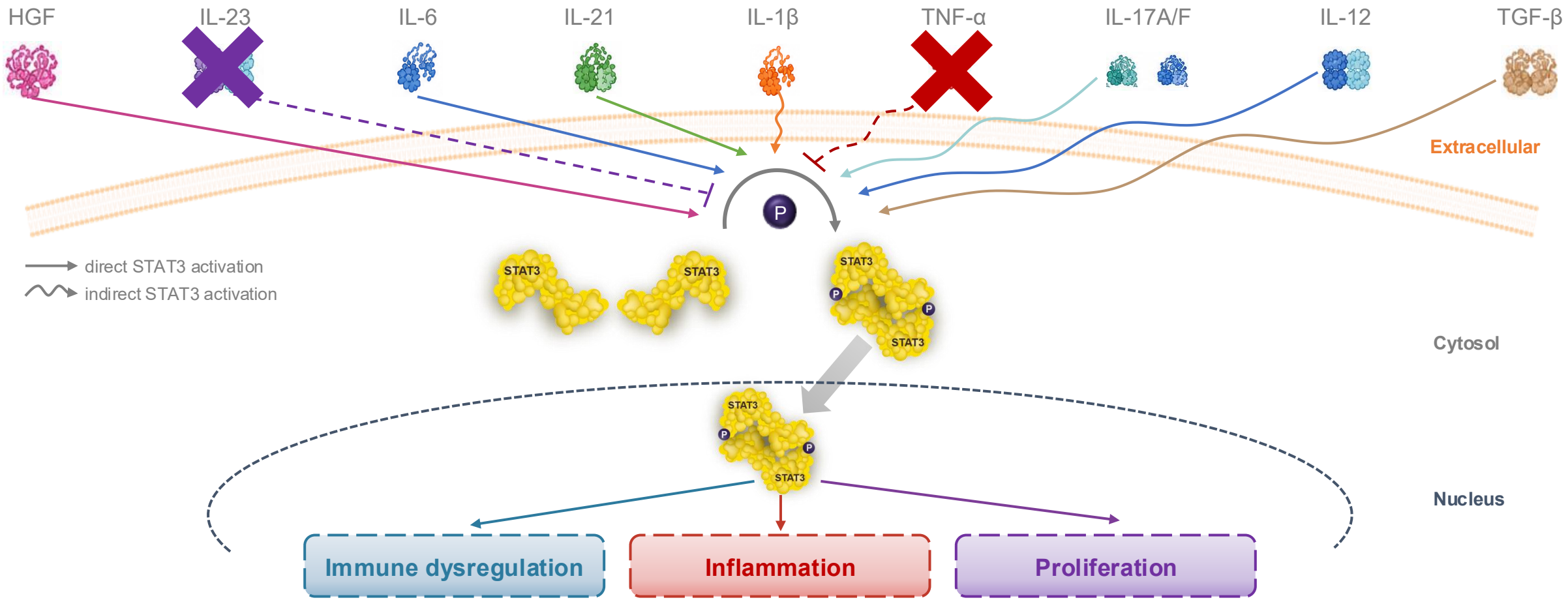
Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease



Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease

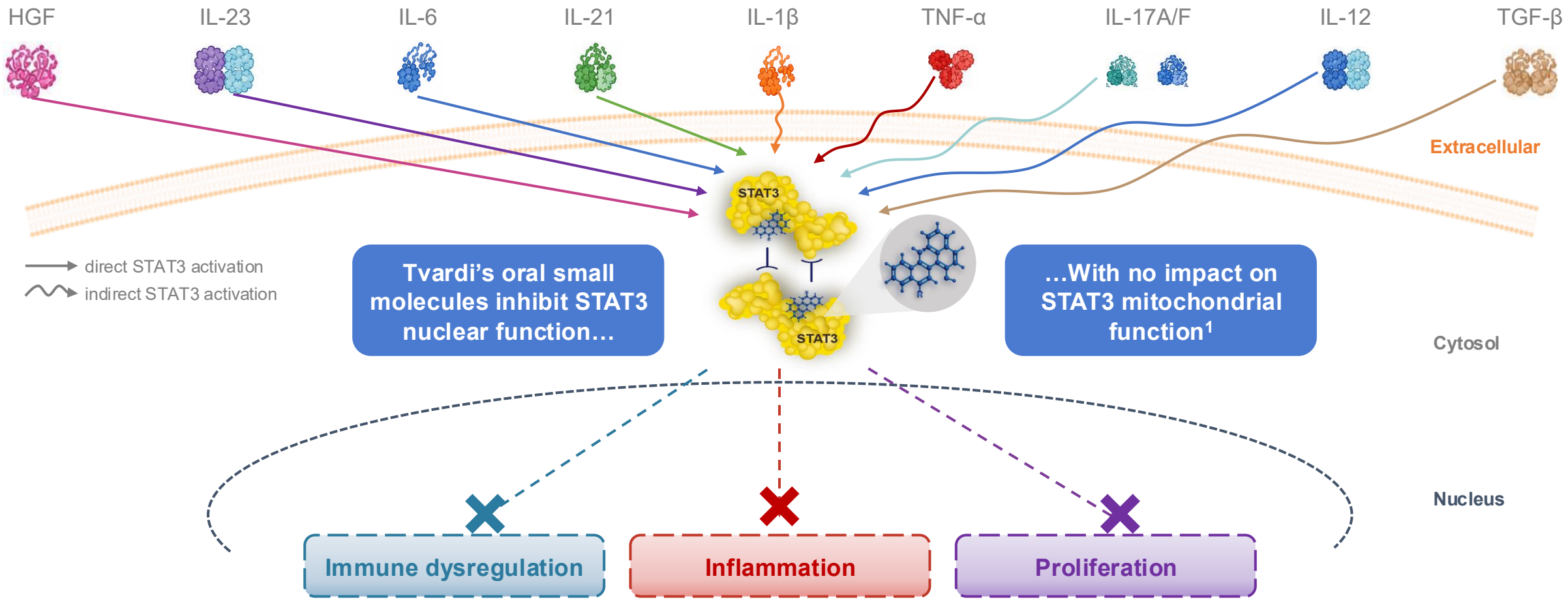
Current Therapies Target Individual Pathways



Single-pathway inhibition fails to suppress STAT3 due to redundant signaling cascades

Targeting STAT3: a Convergence Point of Inflammatory and Proliferative Disease

Diverse Disease Signaling Pathways Converge on STAT3

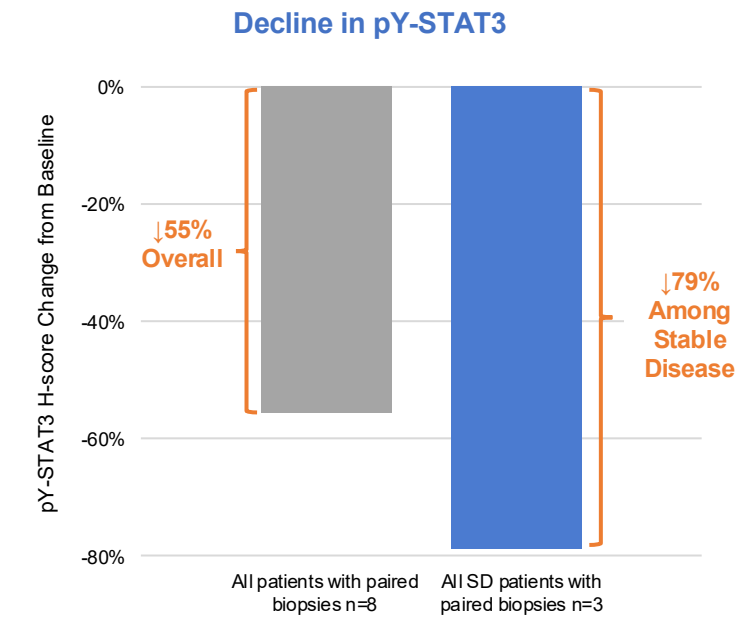


Selective inhibition of STAT3 nuclear function blocks three drivers of disease from a single target

1. Kasembeli et al. *Biochem Pharmacol.* 2021

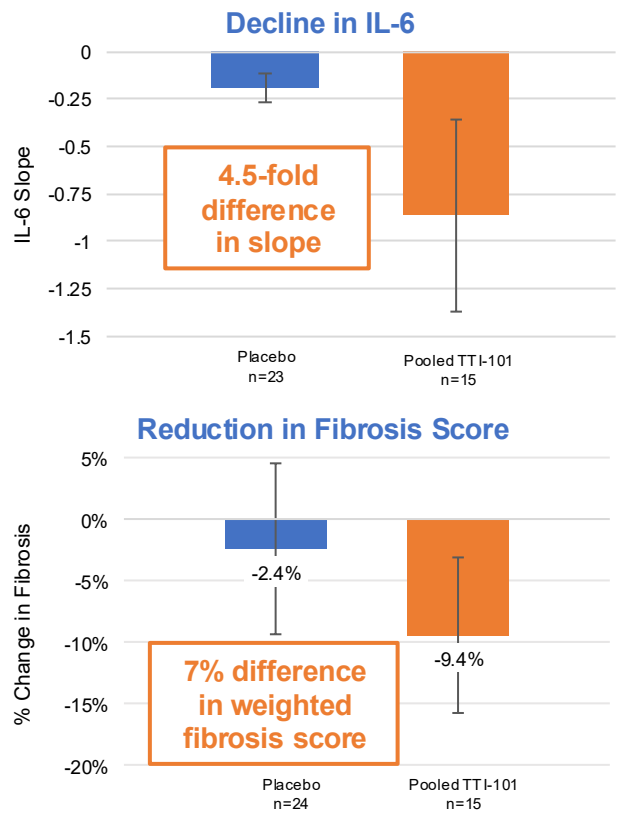
TTI-101 Clinical Foundation for Development of TTI-109

pY-STAT3 Target Engagement Oncology Phase 1[1]



100% of patients with elevated baseline pY-STAT3 demonstrated a decrease within ~6 weeks

IL-6 & Fibrosis Reduction REVERT IPF Phase 2[2]



Overall TTI-101 Safety

In over 300 subjects treated with TTI-101:

Mitochondrial toxicities observed with other STAT3 inhibitors[3] not observed with TTI-101:

- Peripheral neuropathy
- Lactic acidosis

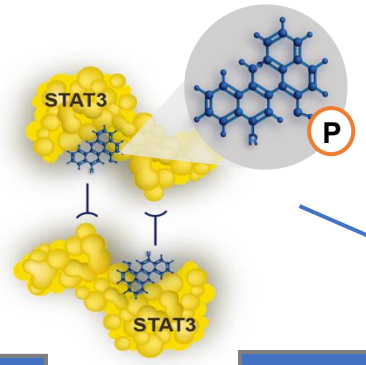
Safety signals observed with JAK inhibitors[4] not observed with TTI-101:

- Major cardiovascular events
- Malignancy
- Cytopenias

Most commonly reported adverse event with TTI-101: diarrhea[1]

1. Tsimberidou et al. *Clin Cancer Res.* 2025; 2. Tvardi Press Release: January 8, 2026; Pooled results; TTI-101 vs placebo baseline-weighted percent change in fibrosis score; 3. Kasembeli et al. *Biochem Pharmacol.* 2021; 4. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; SD: stable disease

We Believe TTI-109 Advances TTI-101's Clinical Profile Across PK, GI Tolerability and Immune Modulation



TTI-109 is designed to enhance delivery & improve tolerability while preserving mechanism of action

TTI-101 Clinical Observations[1,2]

- ✓ **Target Engagement**
  - ↓ pY-STAT3
- ✓ **Inflammation**
  - ↓ IL-6
- ✓ **Proliferation**
  - ↓ Fibrosis

+

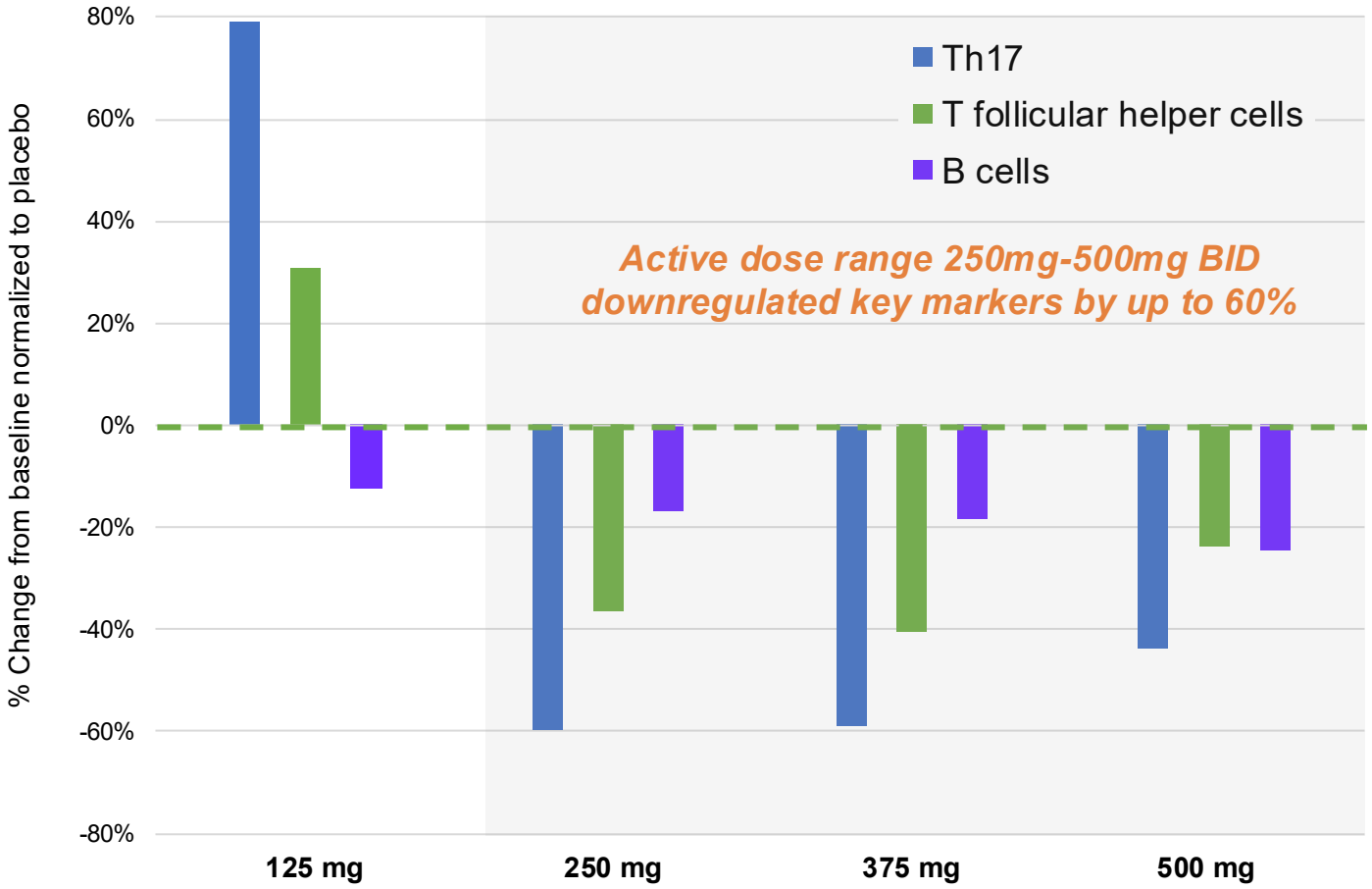
TTI-109 Clinical Observations

- ✓ **PK**
  - Rapid conversion with dose-proportional exposure >STAT3 IC_{50}
- ✓ **GI Tolerability**
  - Similar to placebo and improved over TTI-101
- ✓ **Immune Modulation**
  - ↓ Cellular and ↓ humoral disease related immune populations in UC

1. Tsimberidou et al. *Clin Cancer Res.* 2025; SD: Stable Disease; 2. Tvardi Press Release: January 8, 2026; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; STAT3 IC_{50}: in a controlled system where proliferation is driven by pY-STAT3, TTI-101 inhibits cell growth with an IC_{50} of approximately 1.5μM (707ng/mL)

TTI-109 Selectively Reduced Immune Cell Populations Driven by STAT3 in Phase 1 MAD Cohort

MAD



At active doses, downregulation of STAT3-driven immune populations observed:

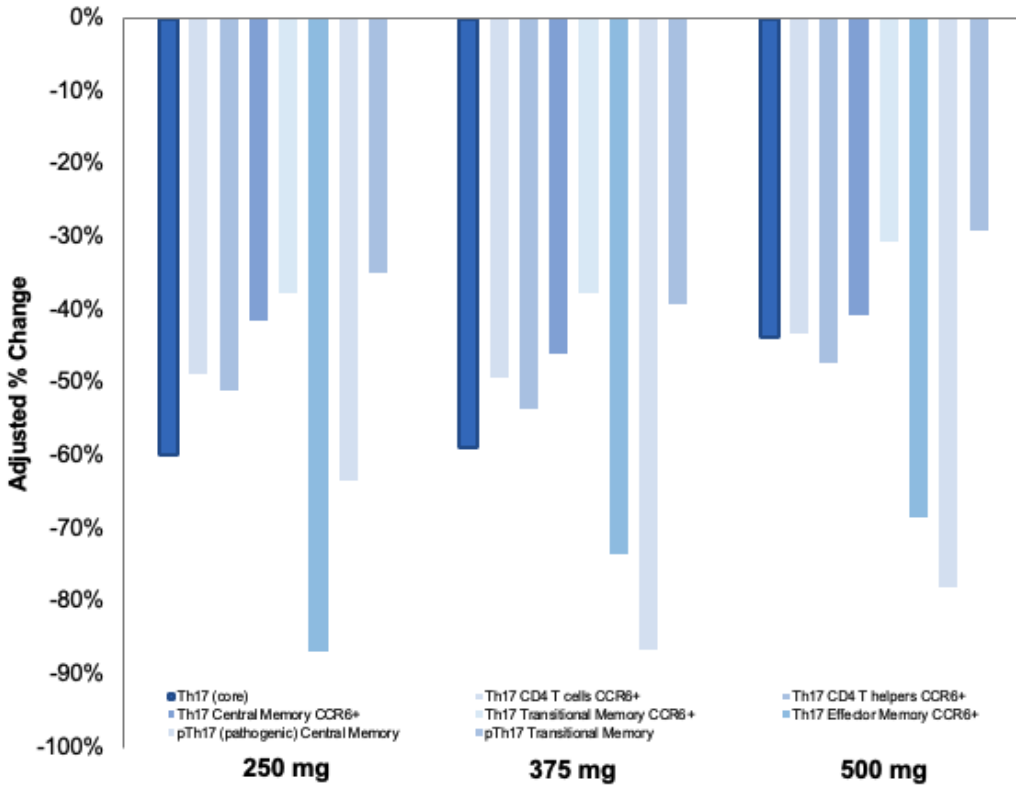
- ✓ Effects **sustained** across active dose range
- ✓ **Reduced** Th17, Tfh and B cell populations
- ✓ **Reductions** across 16 cellular and humoral immune subsets recognized as pathologic markers of inflammatory and proliferative diseases

TTI-109 modulated STAT3-driven cellular (T cell) and humoral (B cell) immune populations

TTI-109 by dose paired %Δ = (Post−Pre)/Pre; placebo-adjusted (n=8 per dose). Cell population changes assessed by flow cytometry (FACS) on peripheral blood mononuclear cells (PBMC) collected from subjects in the Phase 1 multiple ascending dose (MAD) cohort; values shown represent percentage change from baseline, normalized to placebo, for each active dose cohort. Th17, T follicular helper (Tfh), and B cell populations identified by surface marker immunophenotyping

TTI-109 Reduced Th17 Cells Implicated in UC Pathology

MAD



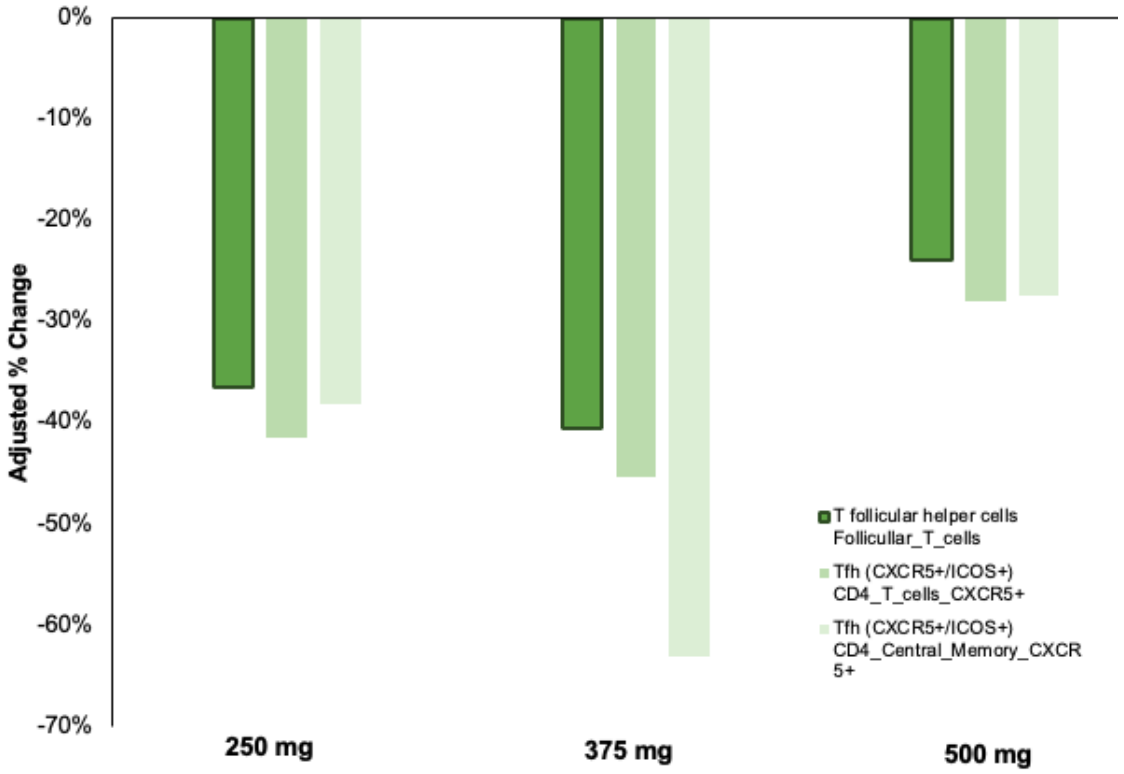
Broad suppression of pathogenic Th17-associated immune populations

Cell Type	%Δ	UC Rationale
Th17 cells (core)	**-54%**	**Central pathogenic effectors in UC and drive mucosal inflammation.**[1]
CD4 T cells CCR6+	-47%	Enriched in active UC biopsies.[2]
CD4 T helpers CCR6+	-51%	Drive IL-21-mediated B cell activation and pathogenic antibody production in UC.[2]
CD4 Central Memory CCR6+	-43%	Expanded in UC patients and drive pathogenic Th17 differentiation[2]
CD4 Transitional Memory CCR6+	-35%	Enriched in UC mucosa and contribute to the sustained Th17 cytokine milieu driving colonic inflammation.[1]
CD4 Effector Memory CCR6+	-76%	Accumulate in inflamed UC mucosa and are a major source of pathogenic IL-17 and IFN-γ.[1]
CD4 Central Memory CXCR3+CCR4−CCR6+ (pTh17)	-76%	Strongly associated with mucosal destruction and treatment-refractory UC.[1,4]
CD4 Transitional Memory CXCR3+CCR4−CCR6+ (pTh17)	-34%	Co-produce IL-17 and IFN-γ, accumulating in IBD mucosa and sustaining tissue-destructive inflammation.[1]

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Wen Y, et al. *Therap Adv Gastroenterol*. 2024; 2. Meitei HT, et al. *iScience*. 2025; 3. Sun L, et al. *Gastroenterol Res Pract*. 2021; 4. Paroni M, et al. *J Crohns Colitis*. 2026

TTI-109 Reduced T Follicular Cells Implicated in UC Pathology

MAD



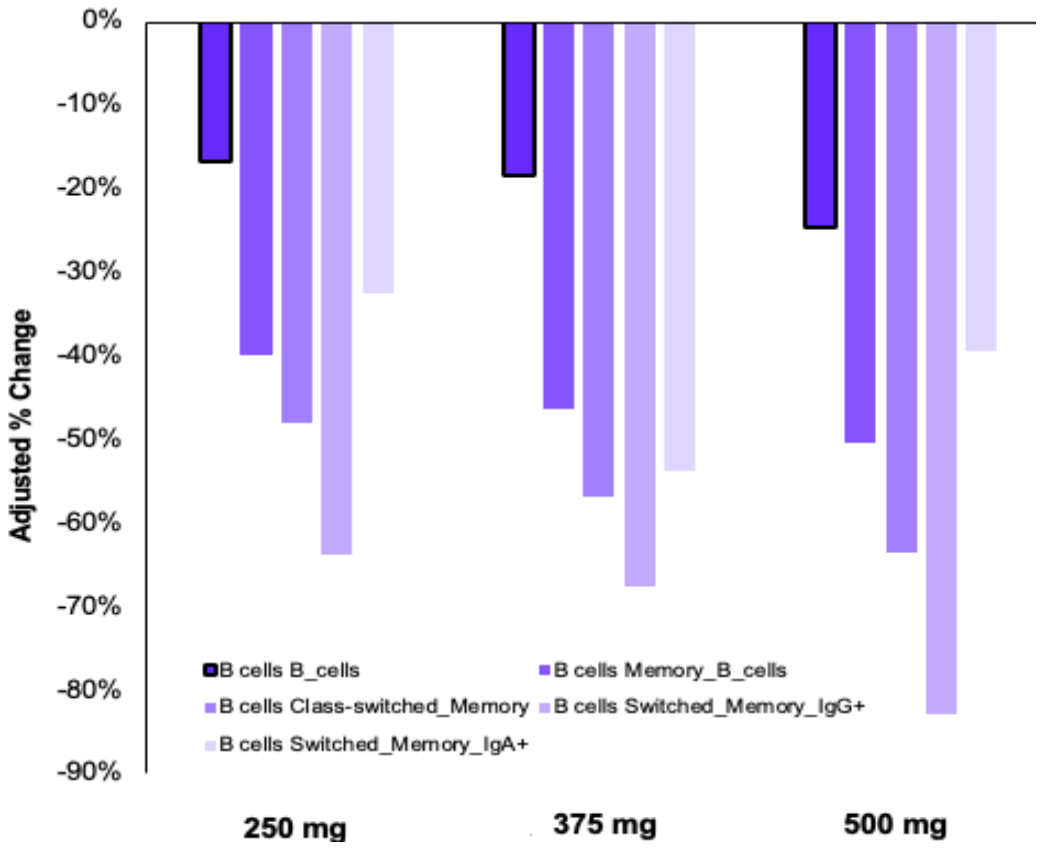
Cell Type	%Δ	UC Rationale
T follicular helper cells (Tfh)	-34%	**Drive UC through humoral autoantibody production and direct cellular Bcl6-dependent mucosal inflammation.[1,2]**
CD4 T cells CXCR5+	-38%	Track with UC disease activity and provide IL-21-driven B-cell help.[3]
CD4 Central Memory CXCR5+	-43%	Elevated in active UC, correlating with disease activity, memory B cell expansion, and plasmablast generation.[2]

Suppression extended beyond cellular immunity to the Tfh immune populations that drive mucosal B cell responses

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Sun L, et al. *Gastroenterol Res Pract*. 2021; 2. Long Y, et al. *Front Immunol*. 2020; 3. Xue G, et al. *Medicine*. 2019

TTI-109 Reduced B Cells Implicated in UC Pathology

MAD



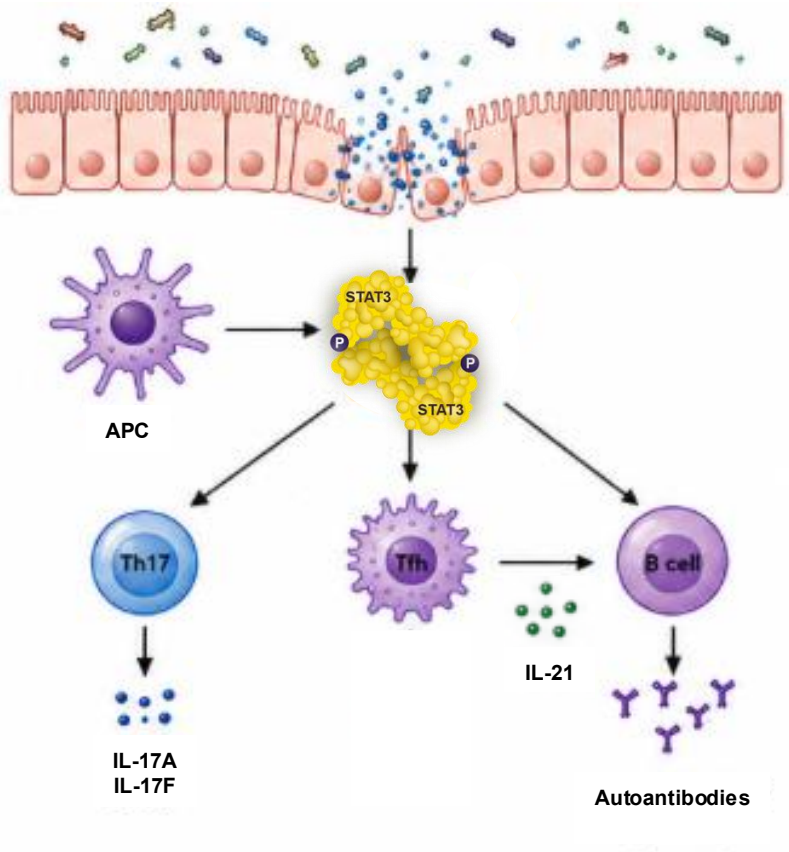
Cell Type	%Δ	UC Rationale
B cells	**-20%**	**Mucosal B-cell and plasma cell expansion is a hallmark of active UC, contributing directly to colonic inflammation and tissue injury.**[1]
Memory B cells	-46%	Track serum Ig levels and humoral activity in active UC.[2]
Class-switched Memory	-56%	Plasmablast-skewed, class-switched humoral response correlates with UC disease activity.[1]
Switched Memory IgG+	-71%	Accumulate in the inflamed colon and generate autoantibodies against the gut lining, directly linking class-switched IgG B cells to mucosal damage.[1]
Switched Memory IgA+	-42%	Aberrantly express cytotoxic granzyme B, contributing to epithelial damage.[3]

Suppression extended to B cell (humoral) immunity associated with colonic inflammation and tissue damage

*Placebo-adjusted % change (**%Δ**)= TTI-109 dose-group mean − pooled placebo mean (per-subject % change). Paired n: D2=8, D3=8, D4=8; pooled placebo n=8. 1. Uzzan M, et al. *Nat Med*. 2022; 2. Masaki Y, et al. *Clin Exp Immunol*. 2016; 3. Cupi ML, et al. J *Immunol*. 2014

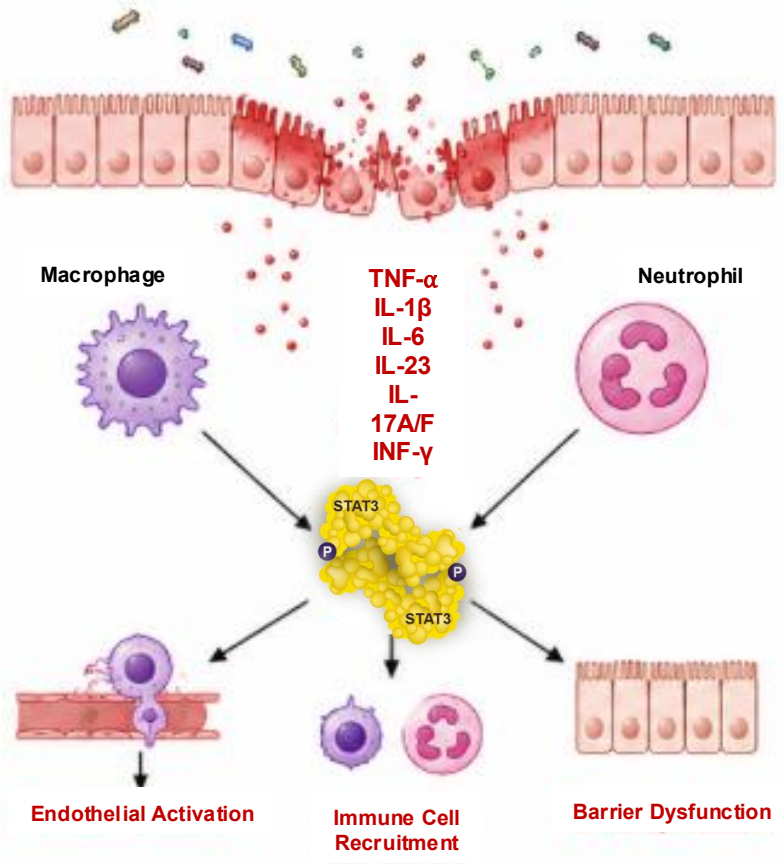
One Target, Three Mechanisms: pY-STAT3 Drives the Shared Biology of UC

Chronic immune activation and perpetuation of intestinal inflammation



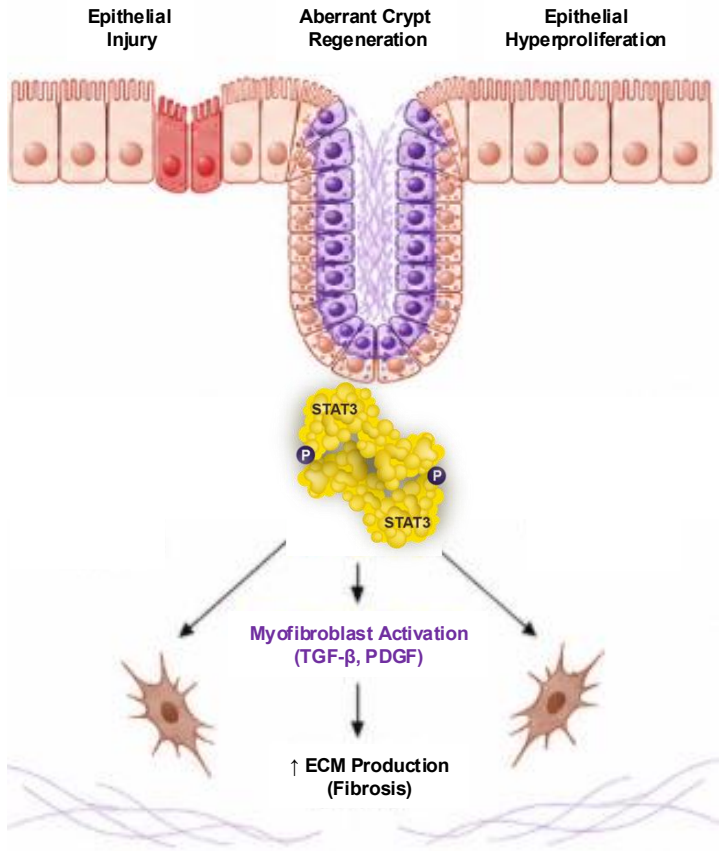
Immune Dysregulation

Persistent inflammation, tissue injury and ulceration



Inflammation

Chronic remodeling, fibrosis and increased dysplasia risk



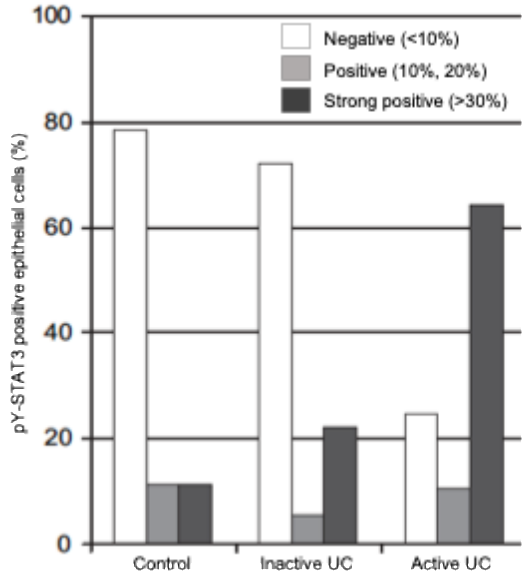
Proliferation

pY-STAT3 Reduction Demonstrated in Preclinical Models and Clinical Biopsies

Activated STAT3

pY-STAT3 is associated with UC clinical activity

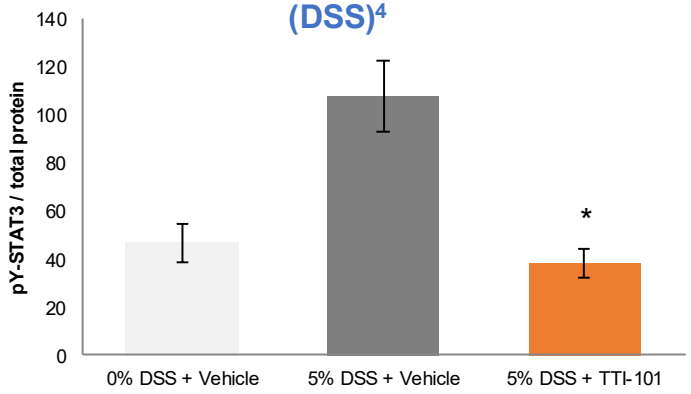
Tissue pY-STAT3 increases with UC activity[1]



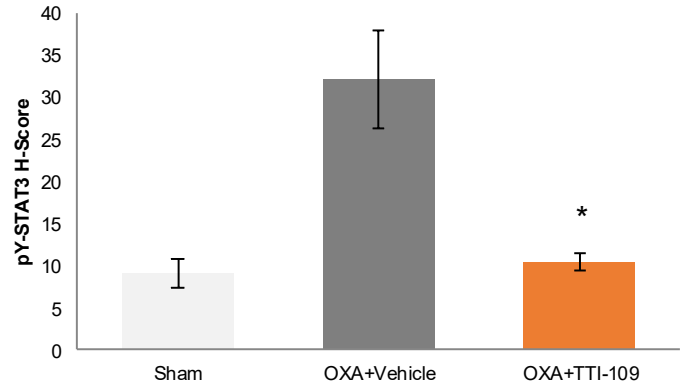
Reduction of tissue pY-STAT3 correlated with response to treatment[2,3]

pY-STAT3 levels restored to baseline after TVRD STAT3 inhibitor treatment

GI model driven by innate immune axis (DSS)[4]

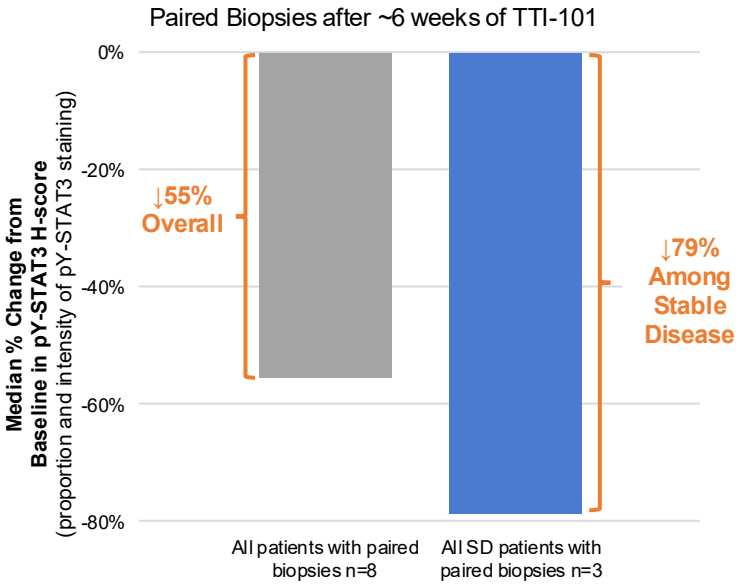


GI model driven by adaptive immune axis (OXA)[5]



Clinical PoC: Reduced pY-STAT3

Oncology Phase 1[6]



8/10 patients had elevated pY-STAT3 at baseline; elevated pY-STAT3 defined as H-score >30 on a 0-300 scale

100% of patients with elevated baseline pY-STAT3 demonstrated a decrease within ~6 weeks

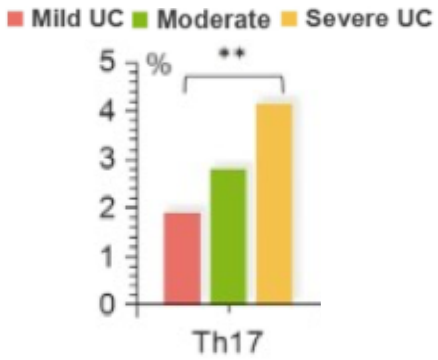
1. Li et al. *Gut* 2010; 2. Schreiber et al *Gastroenterology* 2021; 3. Verstockt et al *J. Crohn's and Colitis* 2025; 4. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 5. Tvardi data generated with CRO: WuXi oxazolone (OXA) model; n=8 per group statistical comparison using exact Mann-Whitney + Kruskal-Wallis; 6. Tsimberidou et al. *Clin Cancer Res.* 2025; SD: Stable Disease; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; *p⩽0.05

STAT3 Inhibition Normalized Preclinical and Clinical Pathogenic Immune Cell Populations

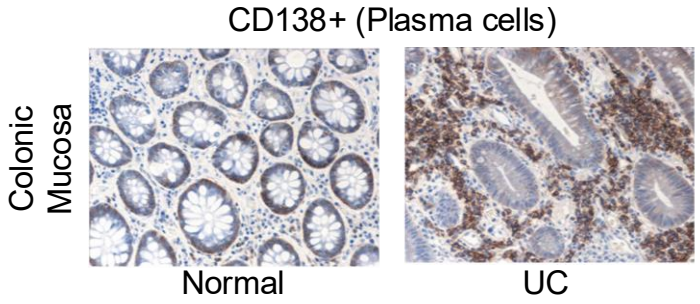
Immune dysregulation

Cellular (Th17) and Humoral (B cell) dysregulation in UC patients

Th17 cell frequency increases with UC disease severity (p<0.01). Th17 positively correlated with Mayo score (p < 0.001)[1]

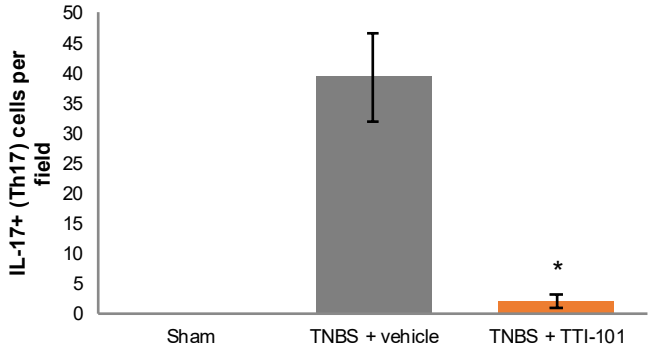


B cells/plasma cells heavily infiltrate the inflamed mucosa of UC patients[2]

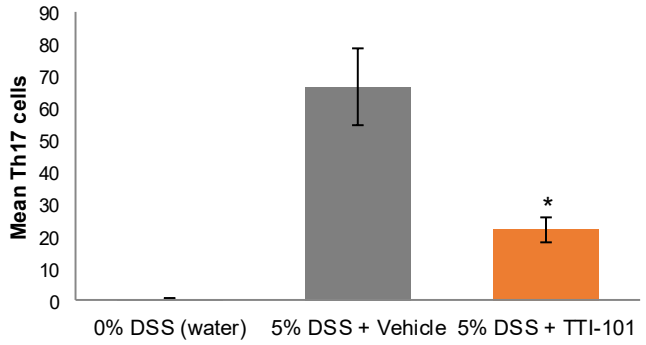


Th17 restored to homeostatic levels after TVRD STAT3 inhibitor

GI model driven by adaptive immune axis (TNBS)[3]

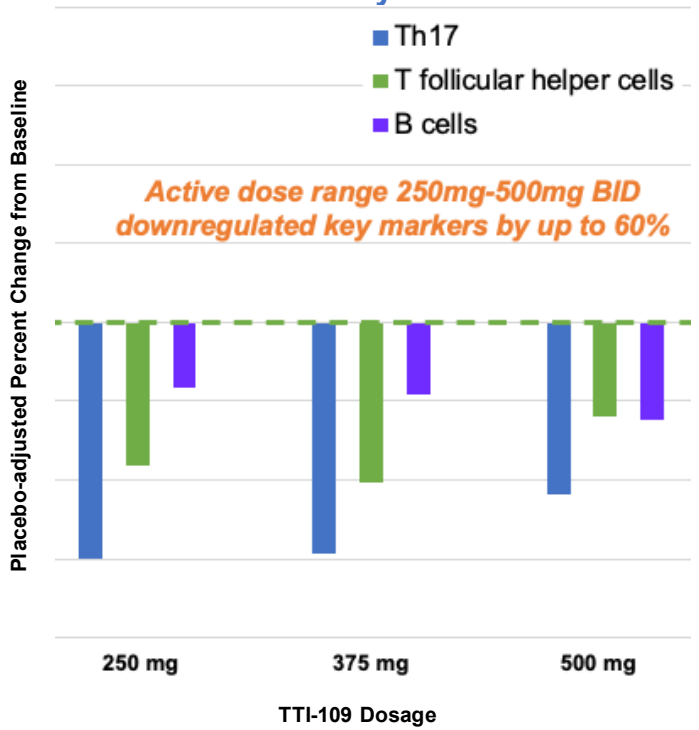


GI model driven by innate immune axis (DSS)[4]



Clinical PoC: Reduced key immune cell populations

Phase 1 Healthy Volunteers



Downregulation of STAT3-driven immune populations observed with TTI-109

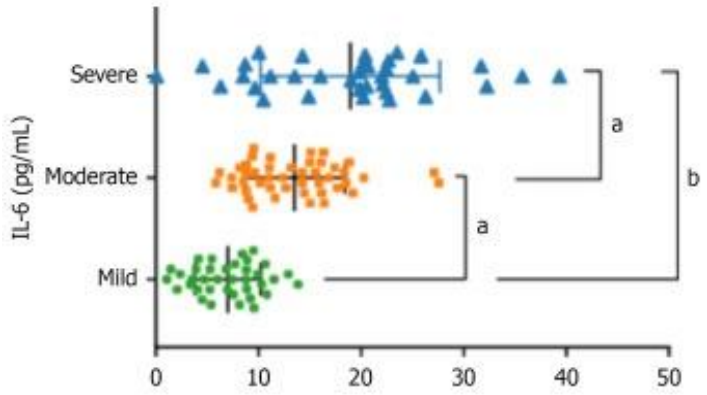
1. Zhang el al. *European Journal of Inflammation*. 2023; 2. Uo et al. *Gut* 2013; 3. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model; 4. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; *p⩽0.05 TTI-101 vs vehicle

STAT3 Inhibition Reduced IL-6 and Inflammation Preclinically and in Patients

Inflammation

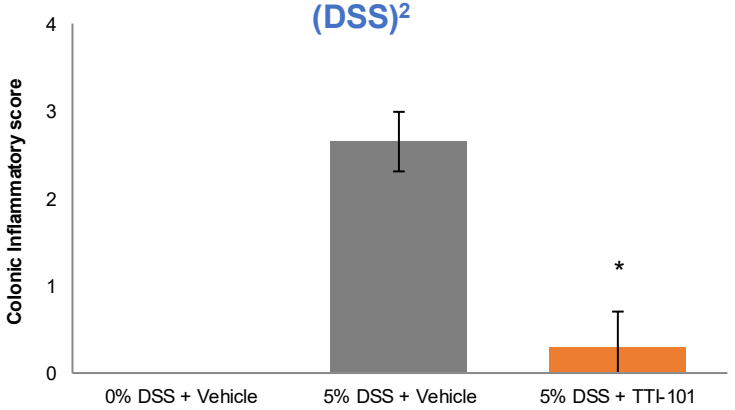
Inflammatory cytokine IL-6 correlates with UC severity

Increases in serum levels of inflammatory marker IL-6 significantly associated with worsening disease activity[1]

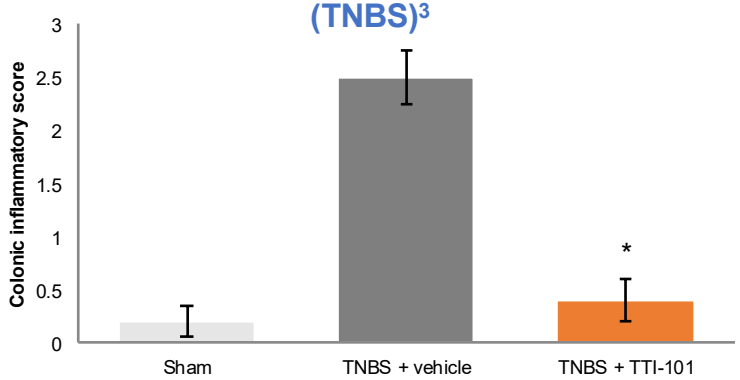


Colonic inflammation significantly attenuated with TVRD STAT3 inhibitor

GI model driven by innate immune axis (DSS)[2]



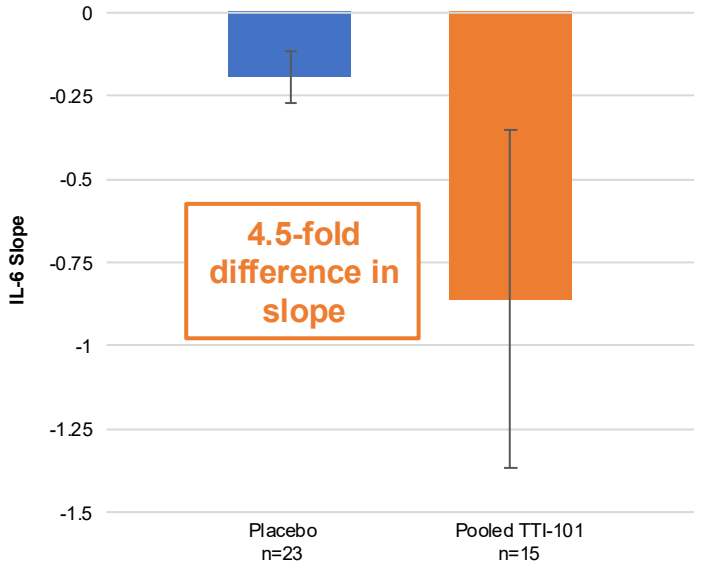
GI model driven by adaptive immune axis (TNBS)[3]



Clinical PoC: Reduced IL-6

IPF Phase 2[4]

TTI-101 vs Placebo Decline in IL-6



IL-6: a key pro-inflammatory cytokine that signals via STAT3

Greater decrease in IL-6 slope among pooled patients treated with TTI-101 vs placebo

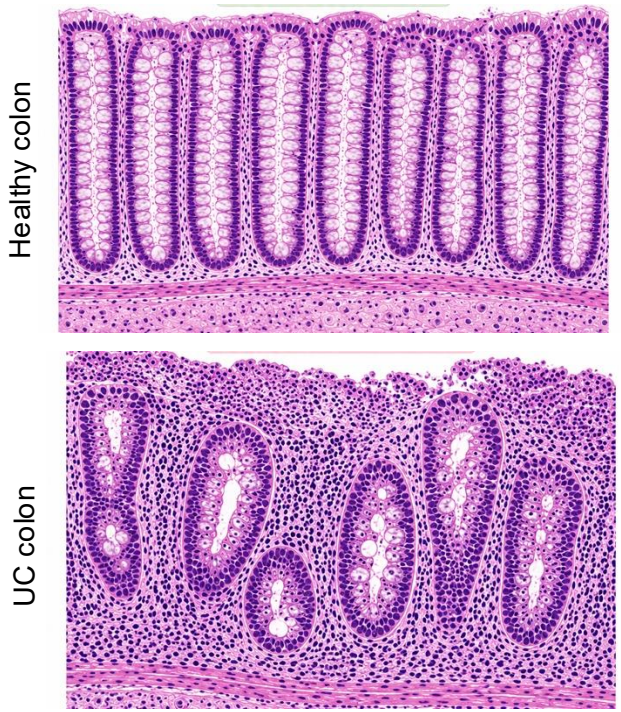
1. Fu et al. *World J Gastrointest Surg.* 2025; [a]*P* < 0.01; [b]*P* < 0.001; 2. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 3. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model; 4. Tvardi Press Release: January 8, 2026; *p⩽0.05 TTI-101 vs vehicle

STAT3 Inhibition Reduced Proliferative Signaling and Fibrosis Preclinically and in Patients

Proliferation

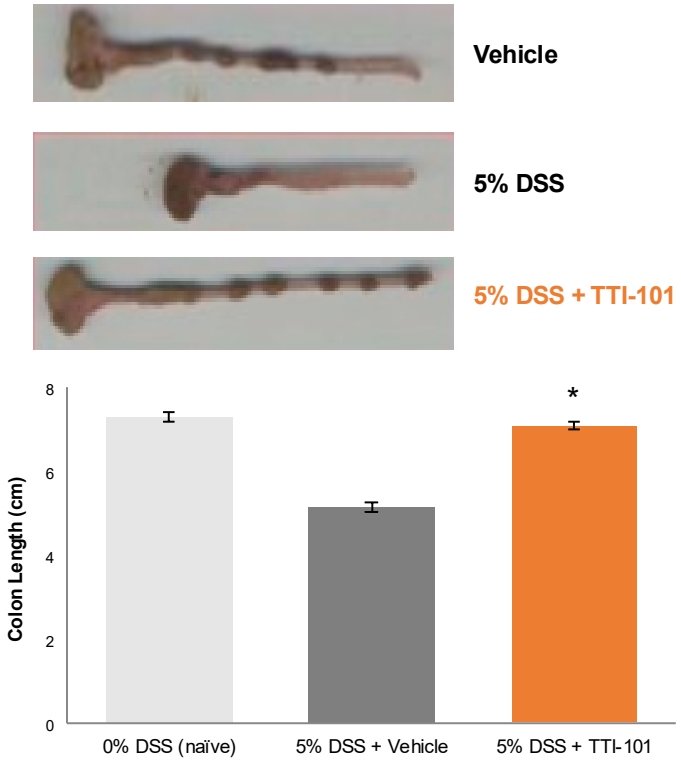
Proliferation and fibrosis correlate with UC severity

Disease severity indices integrate histologic architecture[1]



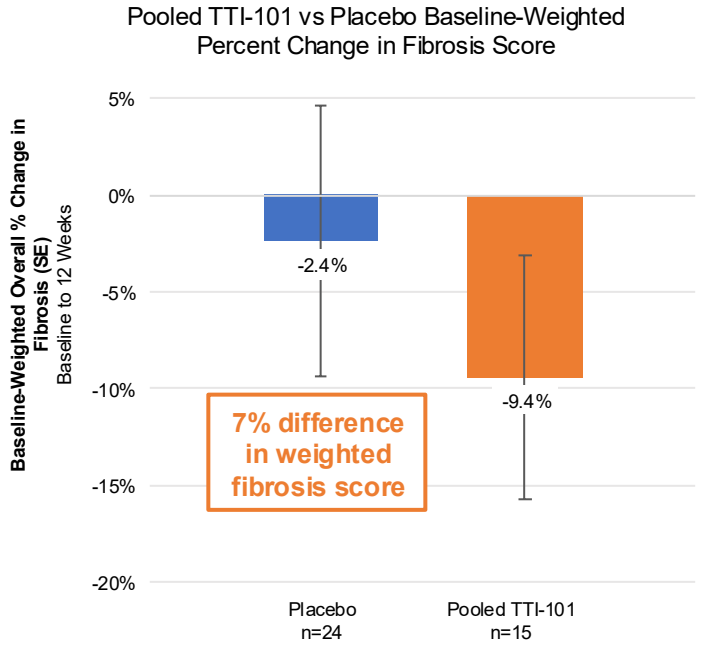
Preserved tissue integrity and colon length with TVRD STAT3 inhibitor

GI model driven by innate immune axis (DSS)[2]



Clinical PoC: Reduced fibrosis

IPF Phase 2[3]



Greater decrease in fibrosis score (improvement in fibrosis) among pooled patients treated with TTI-101 vs placebo

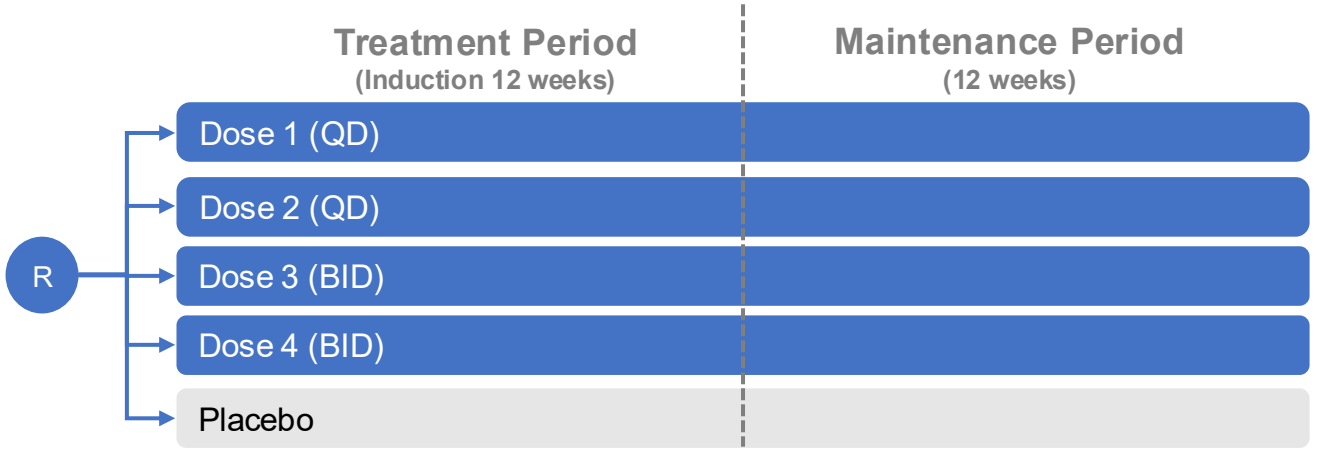
1. Vespa et al. *J. Clin Med.* 2022; 2. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model; 3. Tvardi Press Release: January 8, 2026; *p⩽0.05 TTI-101 vs vehicle

Proposed Clinical Trial Designed to Address Key Challenges in UC

Study Design

Key inclusion criteria:

- Moderate to severe UC
- Inadequate response to prior advanced therapies



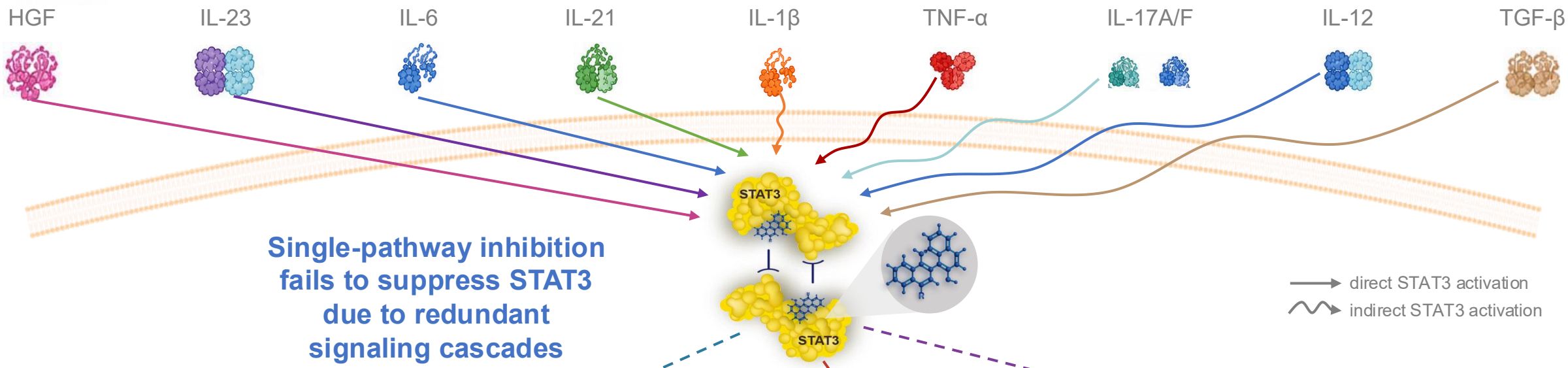
Endpoints

- Primary: Safety
- Secondary: Efficacy
  - Clinical remission at 12 weeks
- Exploratory: Pharmacodynamics
  - Serum biomarkers
  - Tissue analysis
  - Genetic SNPs

Key Challenges in UC	Why Target STAT3 with TTI-109?
Overcoming persistent disease biology	**STAT3 integrates multiple mechanisms of disease modification**
A differentiated oral therapy with targeted exposure	**Favorable safety profile, target-specific design with rapid biologic effect**
Enabling precision medicine	**Targeting STAT3 offers a distinct opportunity to develop a STAT3-mediated response signature**

QD: once daily dosing; BID: twice daily dosing; SNP: single nucleotide polymorphisms; Subject to IND submission and the availability of additional funding

Overcoming Persistent Disease Biology



Single-pathway inhibition fails to suppress STAT3 due to redundant signaling cascades

	Immune dysregulation	Inflammation	Proliferation
UC Murine Models with TTI-101/109	↓ Pathogenic Th17[1,2]	↓ Colonic inflammatory score[1,2,3]	Preserved colon integrity[1,2,3]
Human Data with TTI-101/109	↓ Key immune cell populations	↓ Inflammatory cytokine IL-6[4]	↓ Fibrosis score[4]

Targeting STAT3 integrates multiple mechanisms of UC

tvardi THERAPEUTICS

1. Robinson et al. *J Clin Med* 2022; 2. Robinson et al. *Cancers* 2023; 3. Tvardi data generated with CRO; 4. Tvardi Press Release: January 8, 2026

A Differentiated Oral Therapy with Targeted Exposure

Safety concerns

- Class-related safety risks with JAK inhibitors[1] and S1P[2,3] modulators:
  - MACE, venous thromboembolism, malignancy, immunosuppression

Exposure & durability limits

- Often require loading or extended induction periods
- Loss of response

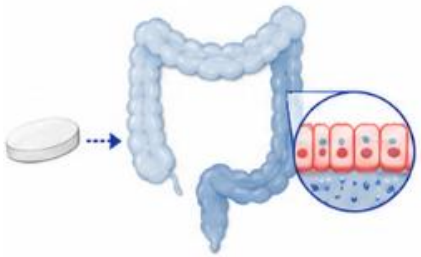
Differentiated safety profile

~400

subjects with up to **2-year exposure**

- Established clinical safety database
- Differentiated from JAK inhibitors and S1P modulators

Tissue-targeted exposure



>8x

colon tissue vs plasma

- Target-dependent accumulation in colon tissue (vs plasma) in UC models[4]

Rapid and durable biologic effect

83%

objective responses observed by **wk 8**; **durable responses** in refractory population[5,6]

- ↓ key immune subsets by day 21 (Ph 1 HV)
- ↓ fibrosis by week 12 (Ph 2 IPF)[7]

Favorable safety profile, target-specific design with rapid and durable biologic effect

1. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions; 2. Ozanimod Prescribing Information; 3. Etrasimod Prescribing Information; 4. Robinson et al. *Int. J. Mol. Sci* 2025; 5. Tsimberidou et al. *Clin Cancer Res.* 2025; 6. Based on confirmed partial response rates and median time to treatment failure for patients with hepatocellular carcinoma; 7. Tvardi Press Release: January 8, 2026; MACE: major adverse cardiovascular event

Enabling Precision Medicine

Limited Molecular Insight

- Broad, unselected patient populations
- Unpredictable response
- Molecular profiling remains an unmet need

pY-STAT3 associated with clinical activity[1,2]

Reduced pY-STAT3

Clinical response

- Reduction of pY-STAT3 correlated with clinical response
- Non-responders demonstrated little or no reduction of pY-STAT3

STAT3-associated genetic & immune signatures

Elevated UC risk[3,4]

STAT3 polymorphisms

rs744166 | rs2293152

Immune signatures

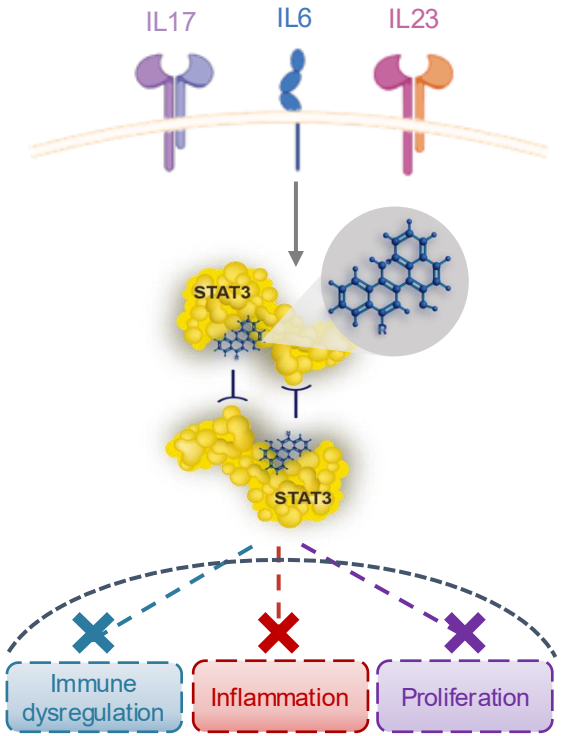
Pathogenic Th17 | Inflammatory macrophages | CD4+ Tfh

We believe targeting STAT3 offers a distinct opportunity to develop a STAT3-mediated response signature and may inform future patient enrichment strategy

1. Schreiber et al *Gastroenterology* 2021; 2. Verstockt et al *J. Crohn's and Colitis* 2025; 3. Zhang et al *Plos One* 2014; 4. Wang et al *Genet Mol Res.* 2014; pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705

Our STAT3 Inhibitors are Designed to Address the Unmet Need in Inflammatory and Proliferative Diseases

STAT3: Highly Validated Convergent Node



STAT3: central mediator in inflammatory and proliferative disease

Translational Proof-of-Concept

Preclinical

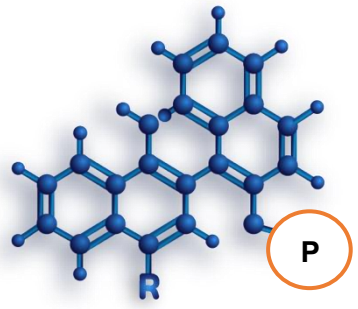
- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

Confirmed in patients

Clinical

- ↓ pY-STAT3
- ↓ immune dysregulation
- ↓ inflammation
- ↓ proliferation

TTI-109 Validation in P1 Healthy Volunteers



TTI-109

- ✓ **PK**
- ✓ **GI tolerability**
- ✓ **Immune modulation**

TTI-109 Lead Indication

Ulcerative Colitis (UC)

- Targeting a single convergent node
- Oral therapy with targeted tissue exposure
- Assessment of STAT3-mediated inflammatory response signature

tvardi THERAPEUTICS

pY-STAT3: activated STAT3 induced by phosphorylation of tyrosine residue 705; PK: pharmacokinetics

Our Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Milestones
TTI-109	Ulcerative Colitis (UC)	IND submission expected 2027*				• Study initiation expected 2027*
TTI-101	Hepatocellular Carcinoma (HCC)	Phase 1b/2				• Phase 1b/2 topline data 4Q:2026

*Tvardi's ability to initiate these programs is subject to clearance of Investigational New Drug (IND) application and the availability of additional funding

Perspective: The Potential Clinical Role of STAT3 Inhibition

Randy Longman, MD, PhD
Director, Jill Roberts Center for IBD
Jill Roberts Institute for Research in IBD
Associate Director, Tri-Institutional MD-PhD program
Program Director, GI T32 training program
Associate Professor of Medicine
Division of Gastroenterology and Hepatology
Weill Cornell Medicine

Appendix A.
Preclinical Support

TVRD STAT3 Inhibition Demonstrated Activity Across Multiple Validated IBD Immune Axes

Model Systems and Select Therapies Approved or Developed for IBD		TVRD STAT3i	Anti-TNFα	Anti-IL12/23	Anti-TL1A	Anti-IL-6	JAK1i	JAK2/3i	TyK2i	S1P1m
Model	**Immune Axis / Key Cytokines**									
DSS (UC)	• Innate → Th1/Th17 • IL-6, IL-1ß, IL-17	✅		✓	✓	✓				✓
TNBS (CD)	• Adaptive (Th1) • IFN-ɣ, TNF-α, IL-12	✅	✓	✓	✓	✓	✓		✓	✓
OXA (UC)	• Adaptive (Th2/NKT) • IL-13, IL-4	✅					✓	✓		

Unlike single-axis competitor mechanisms, TVRD STAT3-inhibitors demonstrated biologic activity across multiple, validated immune axes underlying IBD disease

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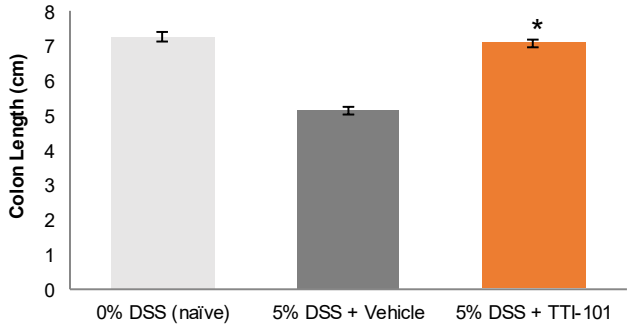
Tvardi data generated with CRO: WuXi; Comparative targets in the IBD space and select therapies approved or developed for IBD used for demonstrative purposes; DSS: dextran sodium sulfate ulcerative colitis (UC) model; TNBS: 2,4,6-trinitrobenzene sulfonic acid Crohn's disease (CD) model; OXA: oxazolone ulcerative colitis (UC) model

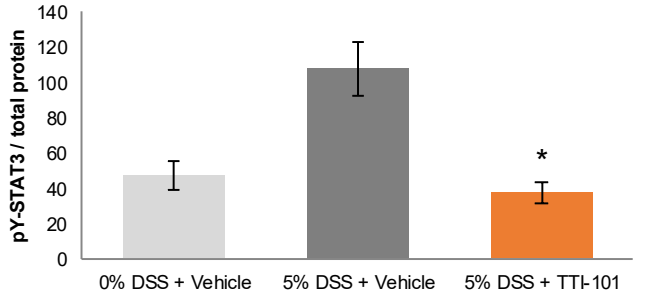
TVRD STAT3 Inhibitors in the DSS-UC Model

5% DSS UC Model with TTI-101[1]

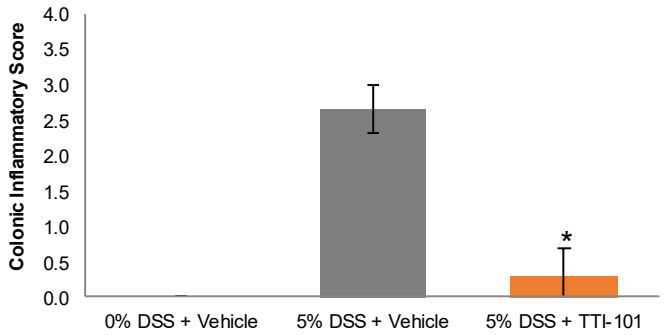
Colon Morphology and Length



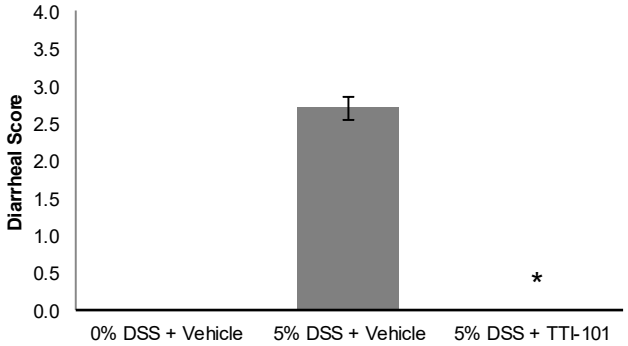
pY-STAT3



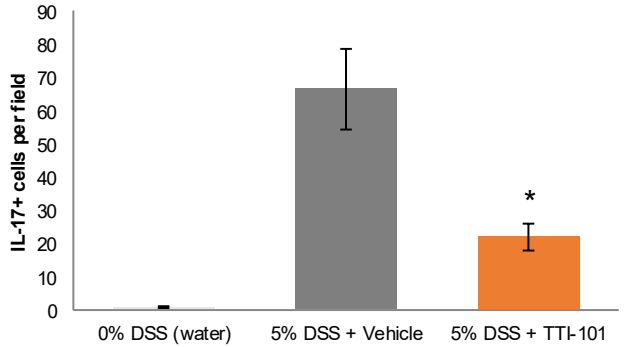
Colonic inflammation



Diarrhea



Colonic IL-17⁺ Cells



*p ⩽0.05 for all TTI-101 arms relative to DSS + vehicle

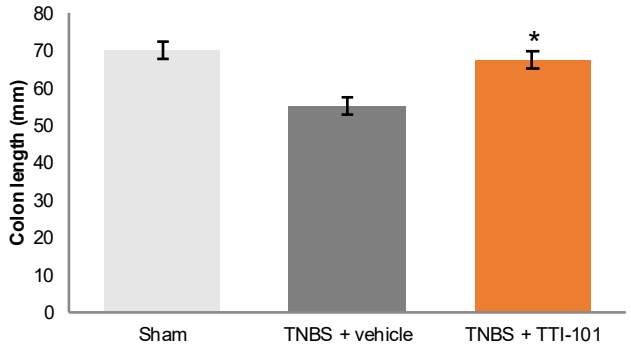
TTI-101 treatment in DSS model normalized all hallmarks of UC

1. Figures digitized from Robinson et al. *Cancers* 2023: dextran sodium sulfate (DSS) model

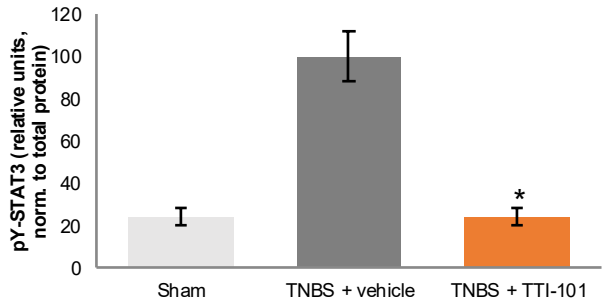
TVRD STAT3 Inhibitors in the TNBS-CD Model

TNBS CD Model with TTI-101[1]

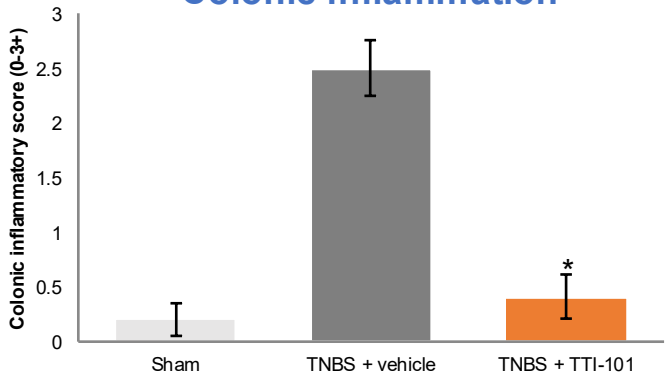
Colon Morphology and Length



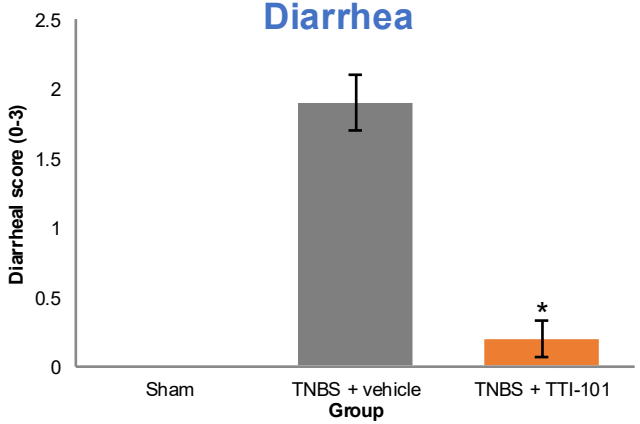
pY-STAT3



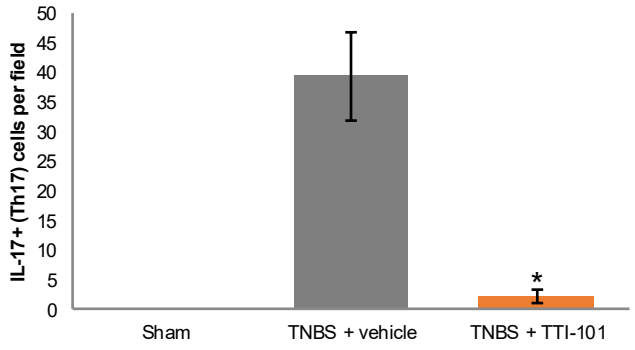
Colonic inflammation



Diarrhea



Colonic IL-17⁺ Cells



*p ⩽0.05 for all TTI-101 arms relative to TNBS + vehicle

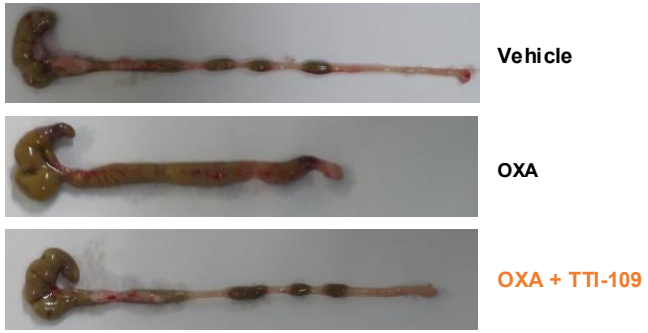
TTI-101 treatment in TNBS model normalized all hallmarks of CD

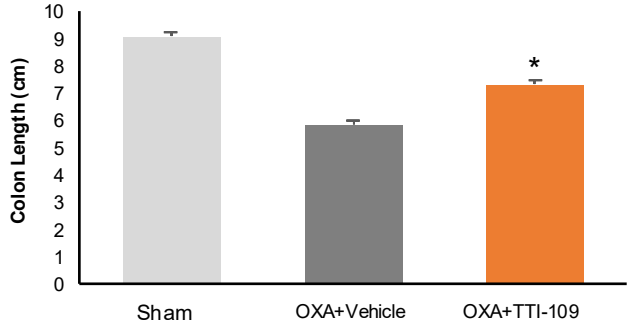
1. Figures digitized from Robinson et al. *J Clin Med* 2022: 2,4,6-trinitrobenzene sulfonic acid (TNBS) model

TVRD STAT3 Inhibitors in the OXA-UC Model

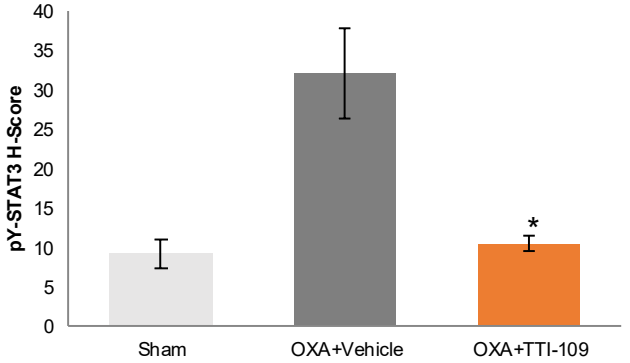
OXA UC Model with TTI-109[1]

Colon Morphology and Length

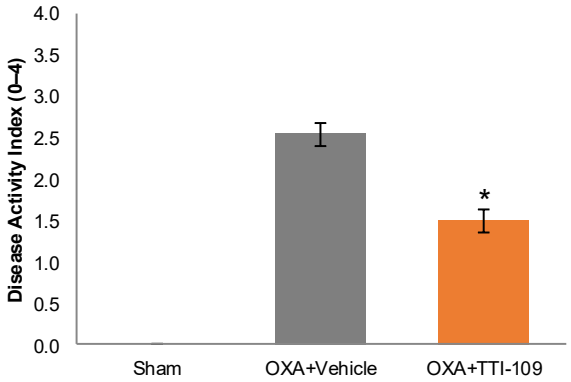




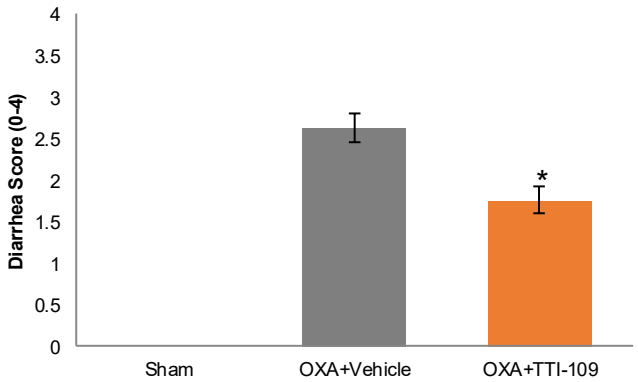
pY-STAT3



Colonic inflammation



Diarrhea



** p ⩽0.05 for all TTI-101 arms relative to OXA + vehicle

TTI-109 treatment in OXA model normalized all hallmarks of UC

1. Tvardi data generated with CRO: WuXi; n=8 per group statistical comparison using exact Mann-Whitney + Kruskal-Wallis