

- **MTAI-1025: A First-in-Class Oral NRF2 Agonist Targeting the Pathogenic Drivers of Ulcerative Colitis**

Immunometabolism across organs 2026

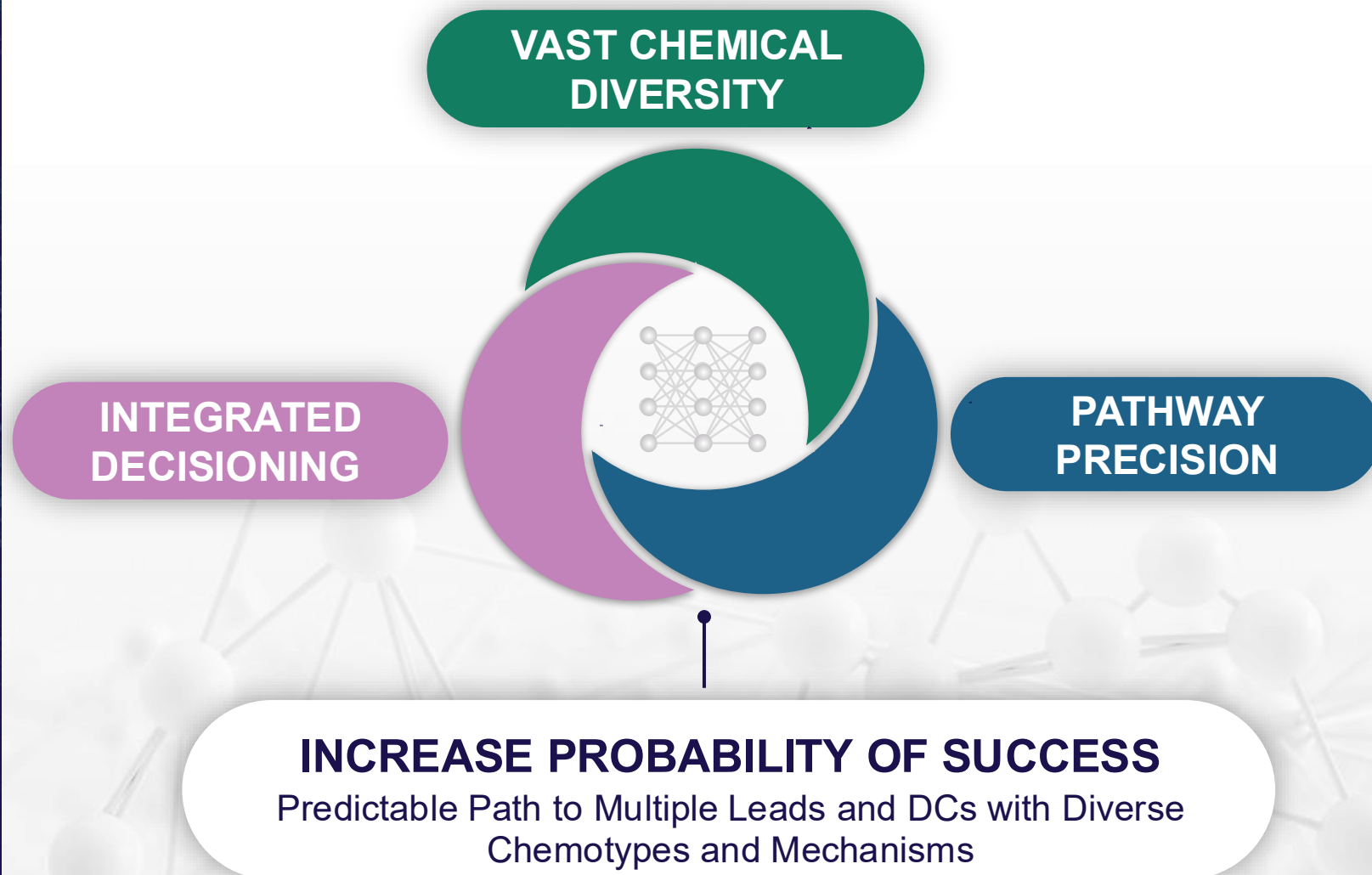
Lamya Shihabuddin

Montai's CONNECTA® AI Platform

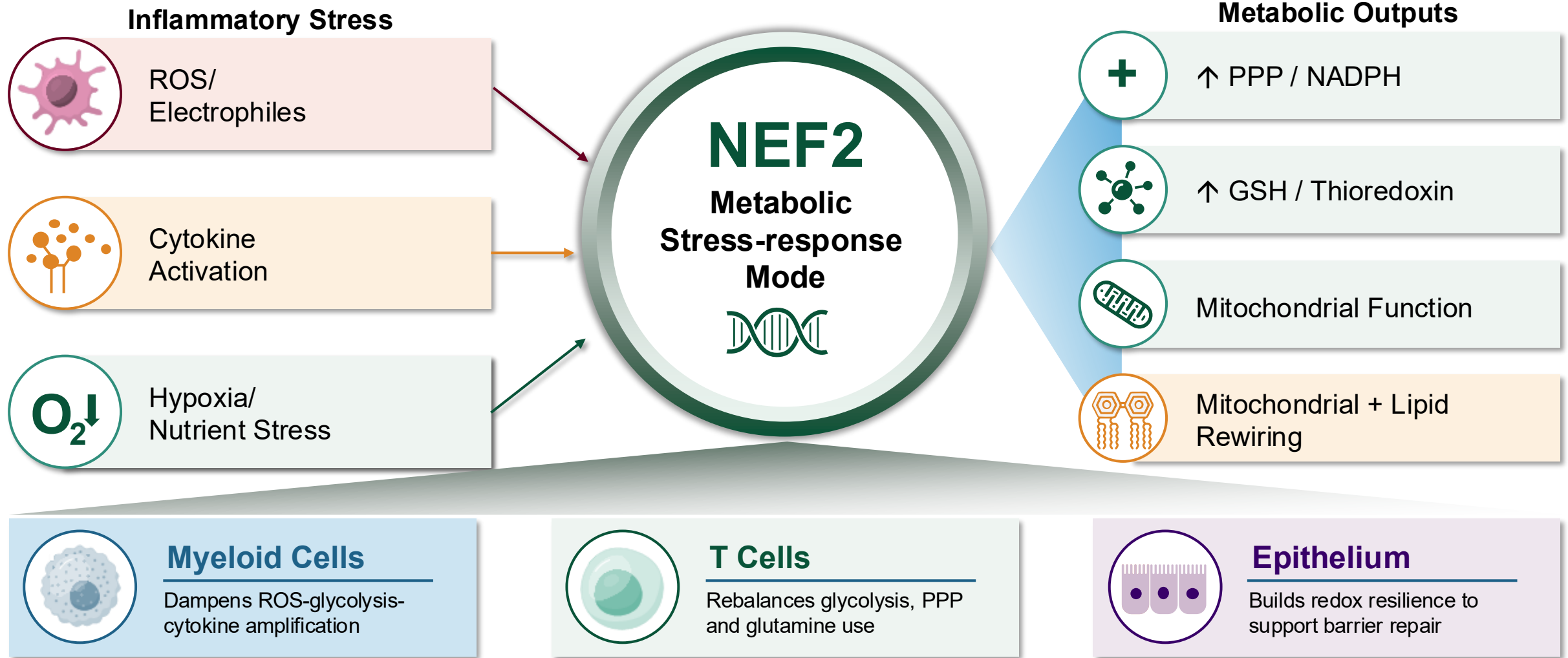


**Decodes Nature's
Diverse Chemical
Intelligence to Unlock
Once Daily Orals for
Hard-to-Drug Biology**

3 Transformational Pillars



NRF2 | NRF2 may shift inflamed tissue from self-reinforcing oxidative metabolism toward resolution and repair

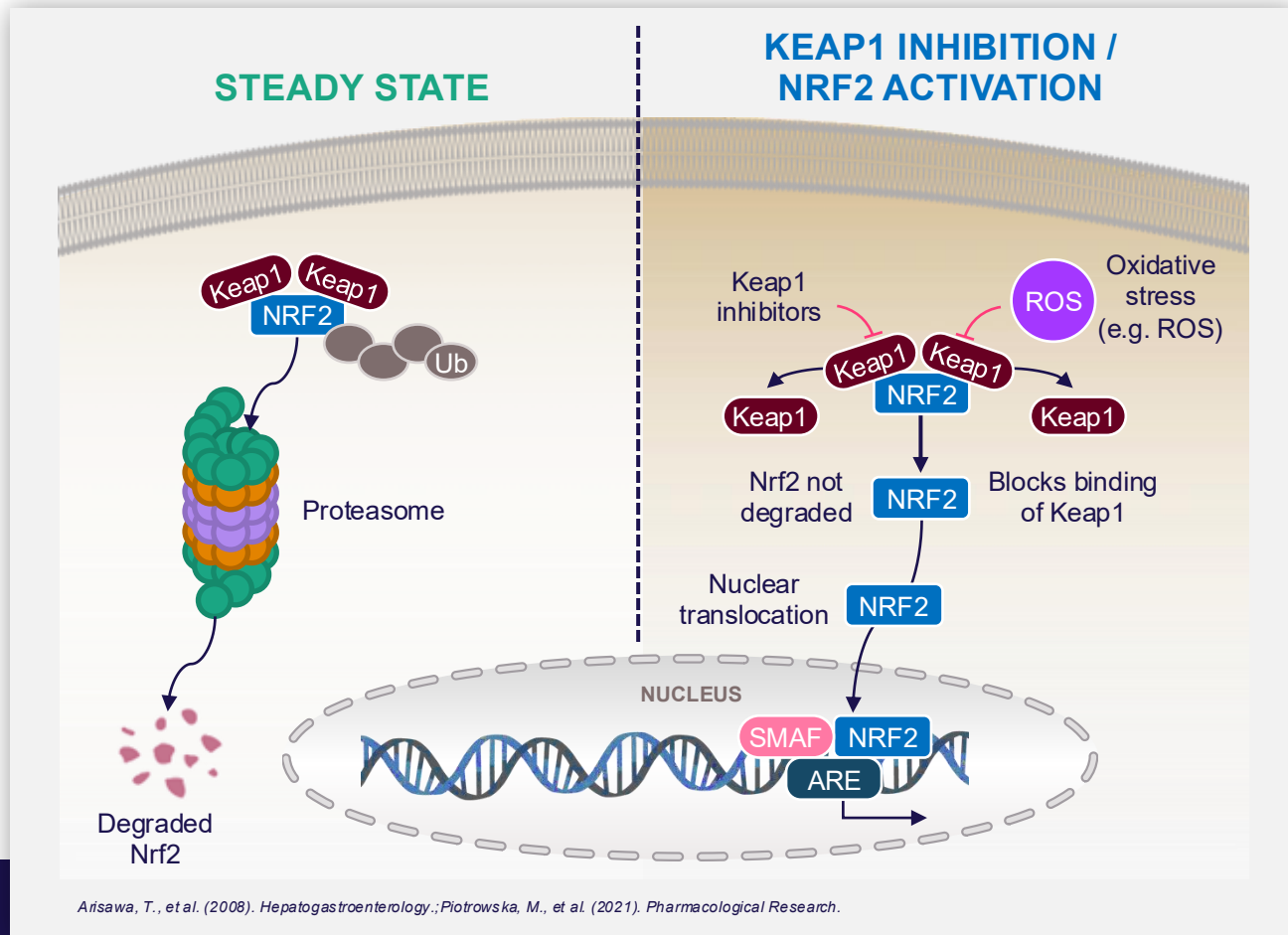


A stress response pathway that can reset inflammatory cell state than broadly suppress immunity

NRF2 | Target Biology and Rationale for UC

NRF2 is a transcription factor and master immunomodulator that dampens inflammation and oxidative stress to restore homeostasis.

MTAI-1025 inhibition of Keap1 elevates levels of NRF2 through slowing degradation



✓ Genetic Validation

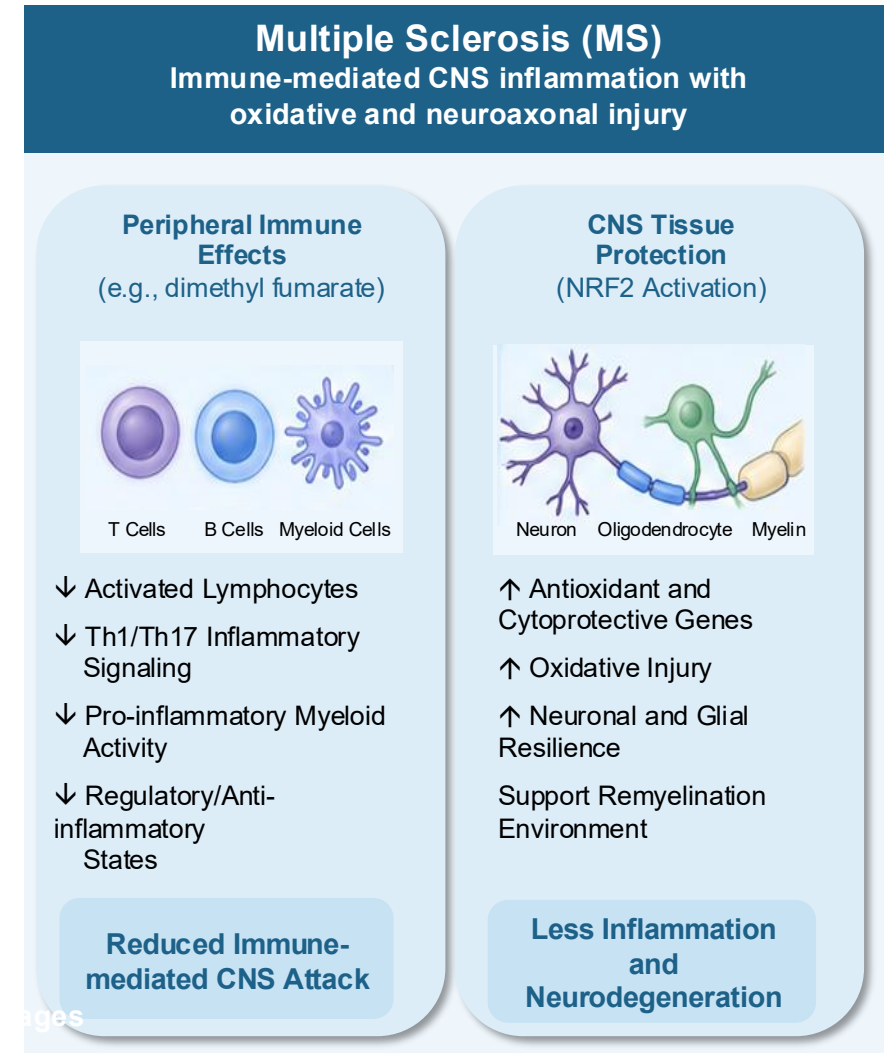
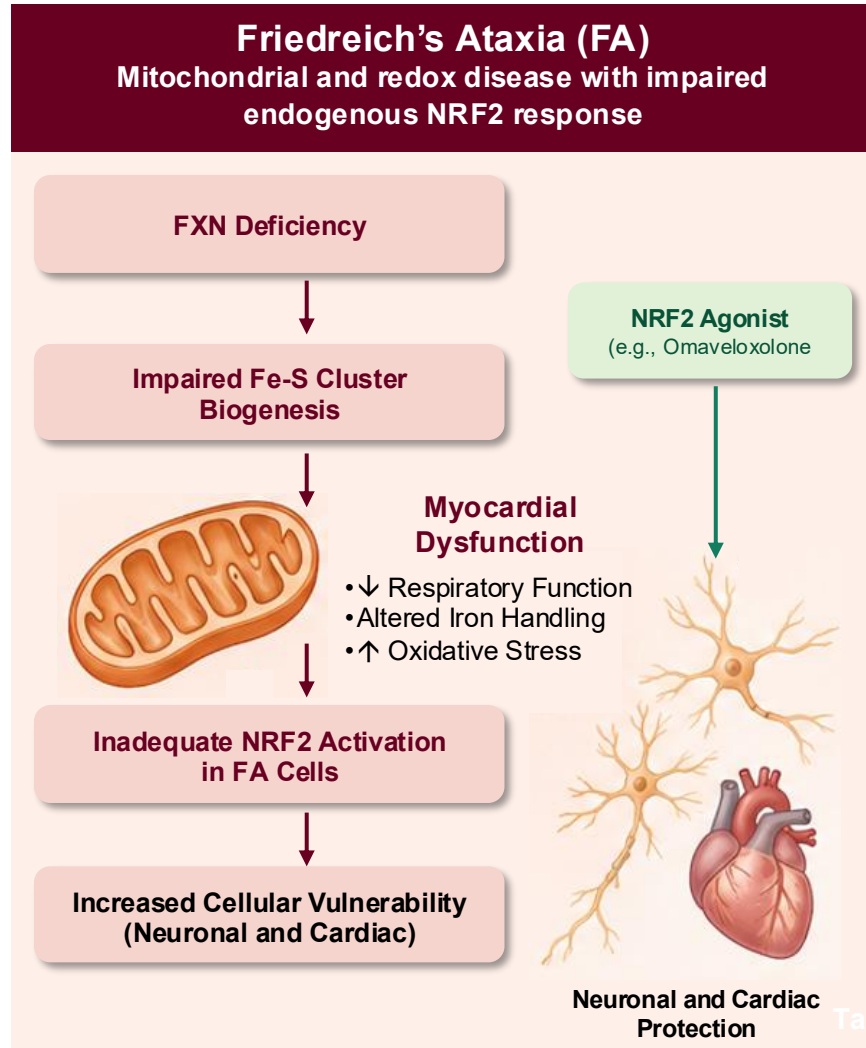
- Human polymorphisms reducing NRF2 function are associated with increased risk and severity of UC
- Nrf2 protein expression is dysregulated in UC patients, diminishing the protective response against oxidative stress and inflammation
- NRF2 KO mice more susceptible to DSS induced Colitis

✓ Clinical Pathway Validation

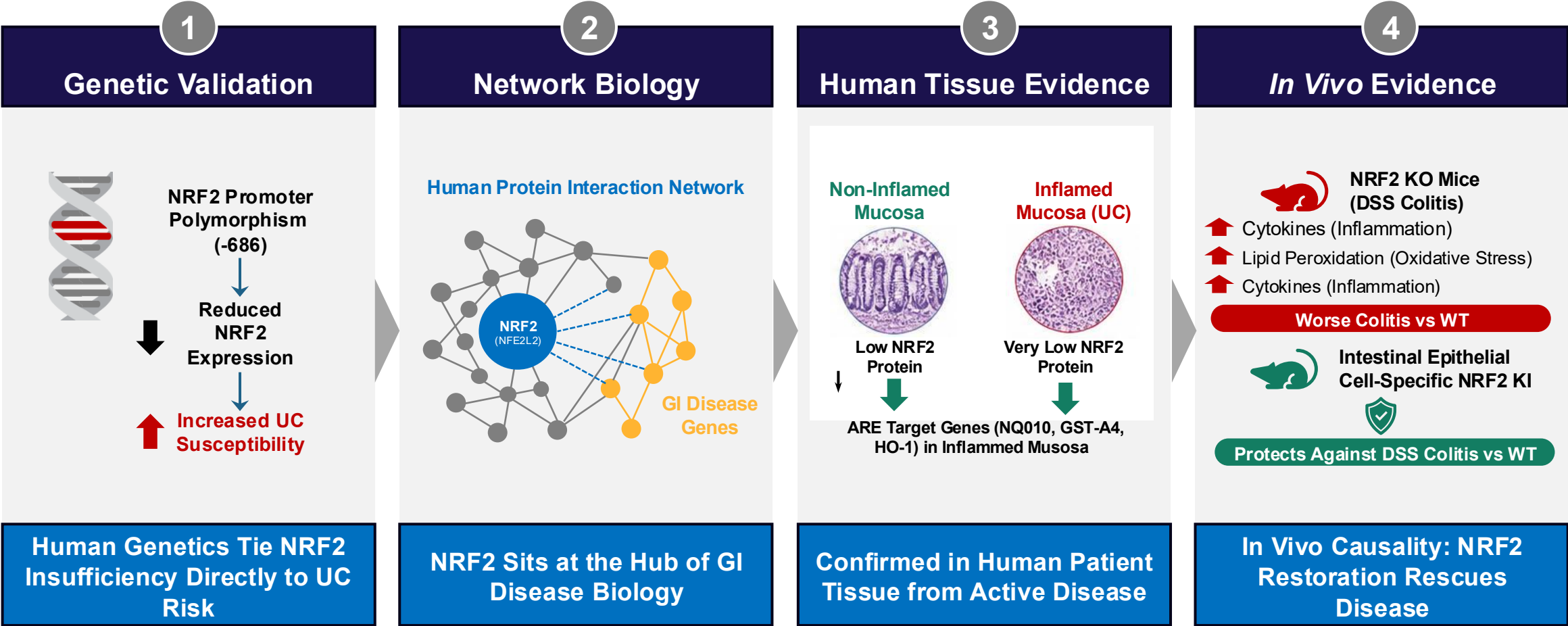
- NRF2 agonists operating via Keap1 inhibition are approved for multiple indications including Psoriasis, MS and Friedrich's Ataxia. A preceded and approved MoA

NRF2 | Clinically Validated in Friedreich's Ataxia and Multiple Sclerosis

Distinct disease biology, a shared cytoprotective mechanism, and complementary therapeutic opportunities



NRF2 | Four Independent Lines of Evidence De-Risk NRF2 as a Validated UC Target



4

In Vivo Evidence



NRF2 KO Mice (DSS Colitis)

- ↑ Cytokines (Inflammation)
- ↑ Lipid Peroxidation (Oxidative Stress)
- ↑ Cytokines (Inflammation)

Worse Colitis vs WT



Intestinal Epithelial Cell-Specific NRF2 KI

Protects Against DSS Colitis vs WT

In Vivo Causality: NRF2 Restoration Rescues Disease

Ulcerative Colitis: A Large Unmet Need for a Safe, Efficacious and Convenient Oral Therapy

A Chronic, Debilitating Disease with Significant Limitations in Current Treatment Options

Ulcerative Colitis



Chronic autoimmune disease that causes inflammation and ulcers in the colon.



Symptoms include frequent bloody diarrhea, pain, fatigue, weight loss, and loss of appetite.



Long-term complications can lead to colectomy and increased risk of colorectal cancer.

75% of UC Patients are Underserved with Current Treatments



Broad Immunosuppressants
(e.g., JAK, S1P)

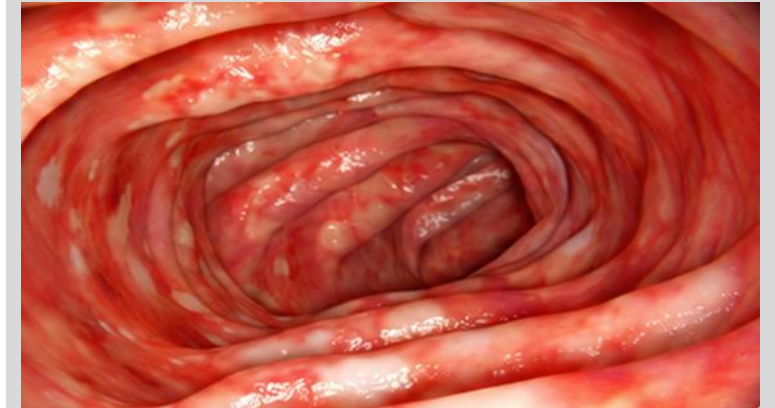
- Serious safety risks
- Limit long-term use



Single Pathway Biologics
(e.g., $\text{TNF}\alpha$, IL23)

- Limited response rates
- Accessibility challenges (injections, limited durability)

Inflammatory Bowel Disease (Ulcerative Colitis)



3.1M
in the US

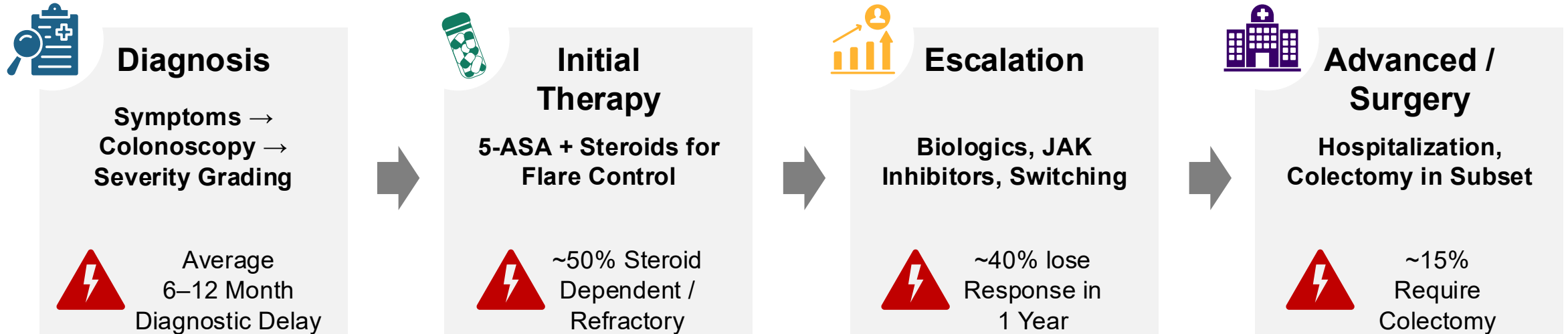


~10M
worldwide

Significant unmet need for better, safer, more convenient therapies

NRF2 | UC Patient Journey is Broken with Large Unmet Needs

Trial-and-Error Across Four Stages Drives Loss of Response, Hospitalization, and Surgery — A Persistent Commercial White Space



NRF2 Opportunity — Positioned as a First-Line Oral Therapy for Repair and Remission

~3M

UC Patients Globally; ~1M in U.S.

\$8B+

Global UC Market, Growing at High Single Digits

>70%

of Moderate-to-Severe UC Patients Remain Underserved

40+%

Fail or Lose Response to Current Biologics

NRF2 | Opportunity: First-Line Oral for Repair and Remission

Break the UC Efficacy Ceiling in a Once Daily Pill



Directly Address All 3 Drivers of UC

Differentiated mechanism to drive active barrier repair



Oral, Once Daily

Expands addressable patient population



Safety & Selectivity

Non-immunosuppressive, improved selectivity from 1st generation NRF2s

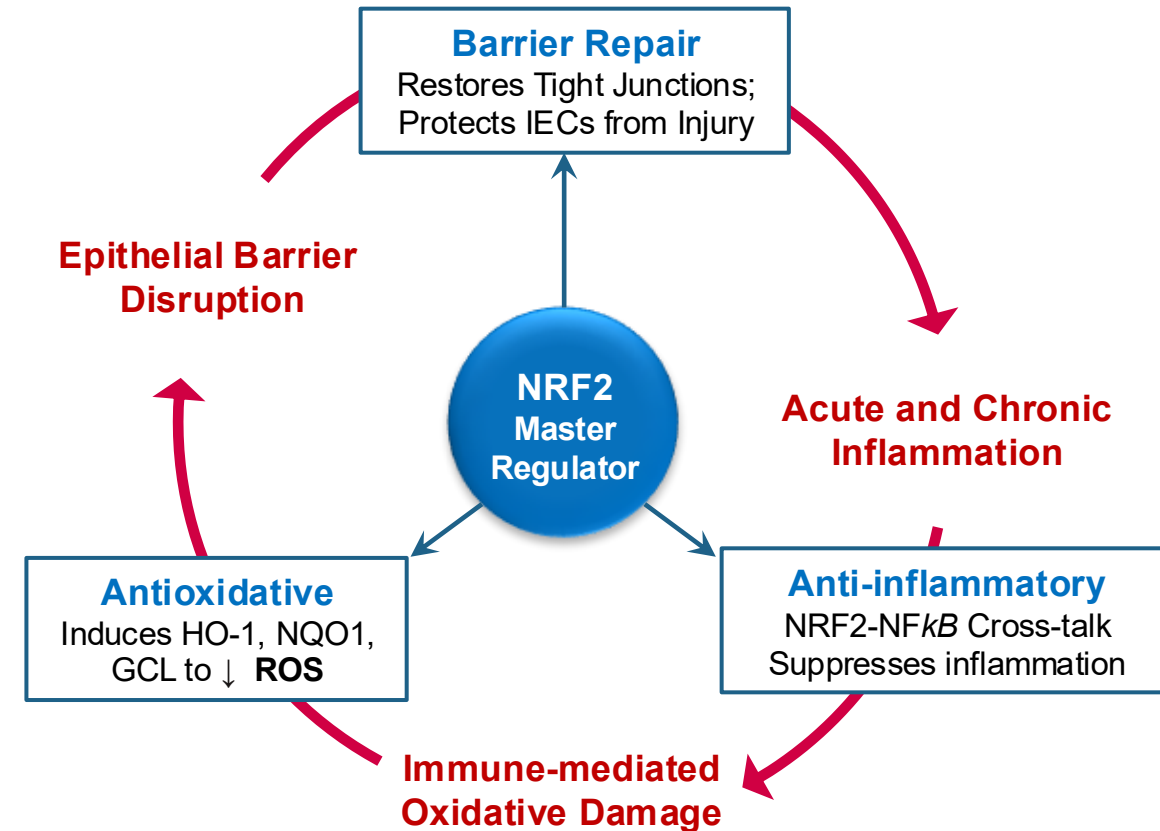
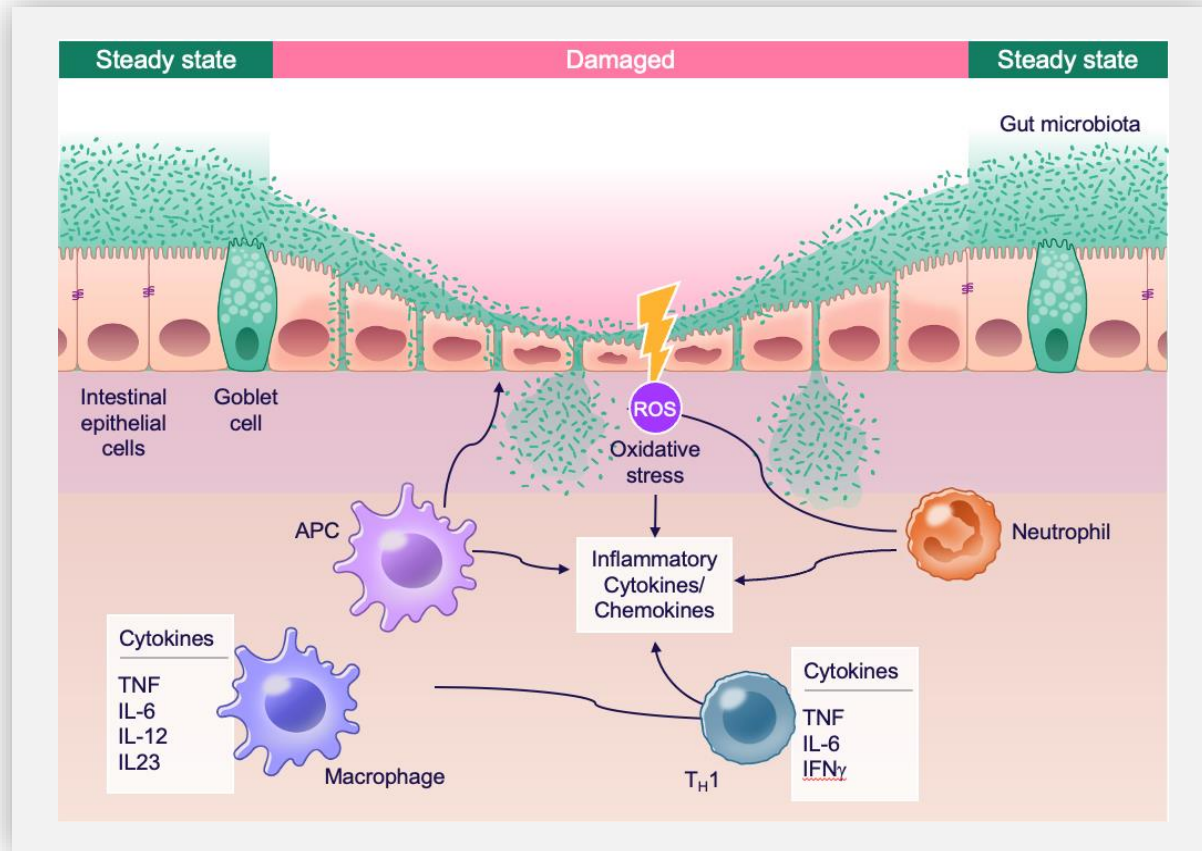


Combinable

Complementary mechanism to approved and emerging UC therapies

NRF2 | One Molecule, Three Drivers of UC - A Differentiated Path to Durable Remission

Single Oral Agent Directly Addresses Inflammation, Oxidative Stress, and Barrier Repair



NRF2 | MTAI-1025: Differentiated, De-Risked, and Ready for Clinic

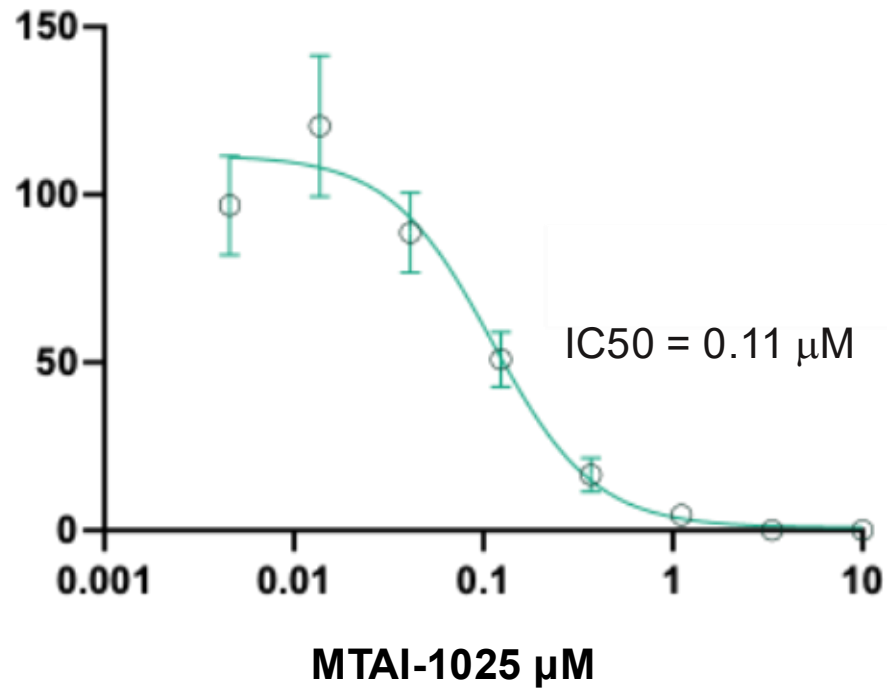
Precise NRF2 Targeting	Robust Activity Across Human Cellular assays	Oral Therapy to Break the Efficacy Ceiling	Derisked for Clinic
• Reversible covalent KEAP1 binding (C151) confirmed by X-ray • Site specific targeting: >40× potency loss in C151S mutant • >20–100× selectivity vs off-targets	• Fully inhibits production of key inflammatory cytokines • Fully inhibits T cell activation and differentiation • Protects colonic epithelium and restores barrier integrity	• Efficacy in mouse DSS colitis model outperforms biologic (anti-IL12/23) • PK supports once-daily dosing • PD biomarker of target engagement established - NQO1	• Highly selective with clean in vitro safety profile - SafetyScan47® and proteome scan • GLP tox studies support clinical dosing at predicted efficacious dose levels with strong safety margins • Tablets selected for FIH

Differentiated Efficacy × Small-Molecule Convenience × Safe and Selective for Once-Daily Oral dosing

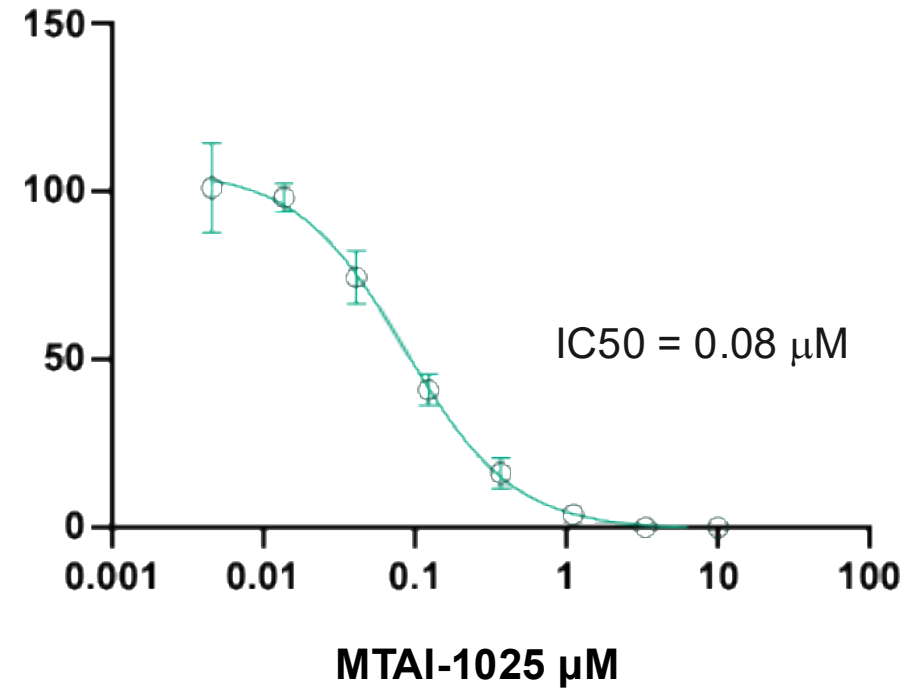
NRF2 | MTAI-1025 Is Highly Potent and Fully Reduces IL-12 and IL-23 Cytokines in Human Derived Dendritic Cells

IL-12 and IL-23: Two Primary Inflammatory Drivers of UC

IL-12 Cytokine Reduction

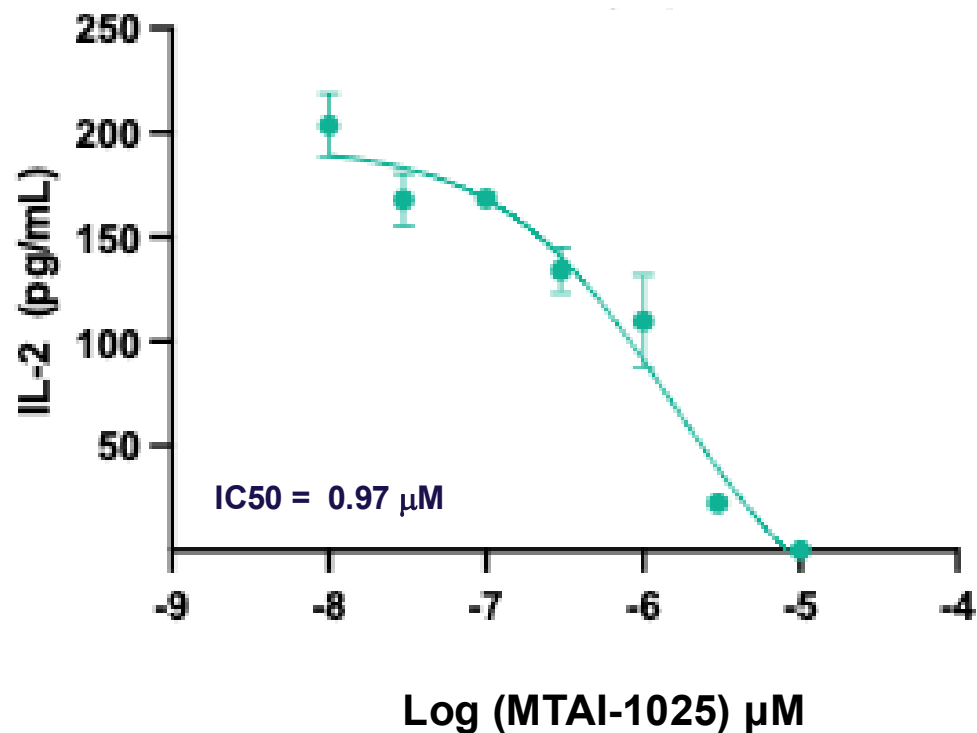


IL-23 Cytokine Reduction

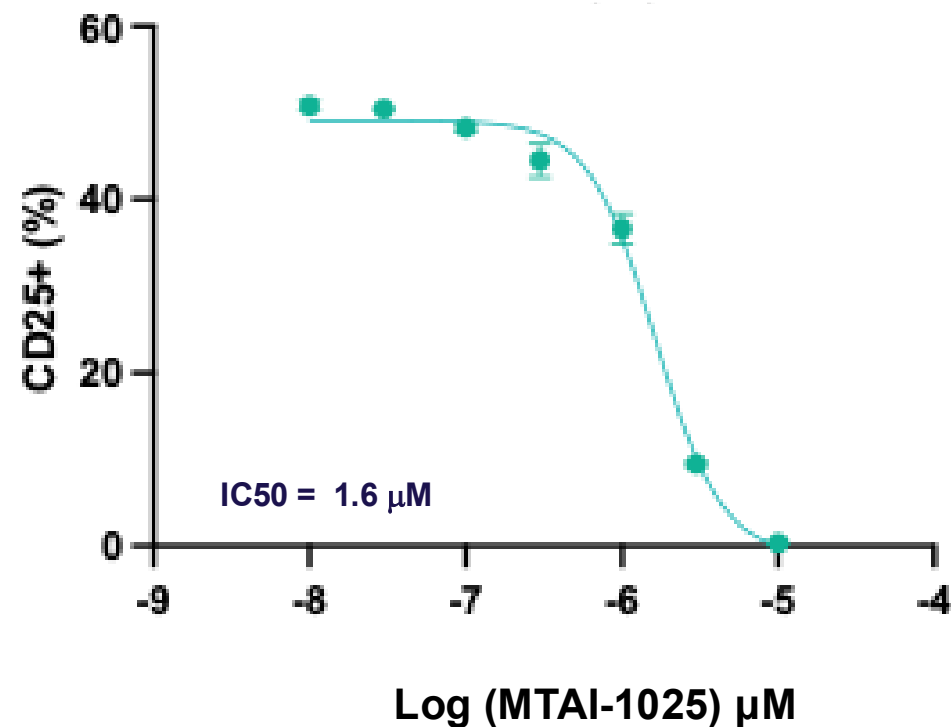


NRF2 | MTAI-1025 Delivers Full Inhibition of Biomarkers of T-Cell Activation in Purified Human T-Cells

IL-2 Secretion Cytokine Secreted During T-cell Activation



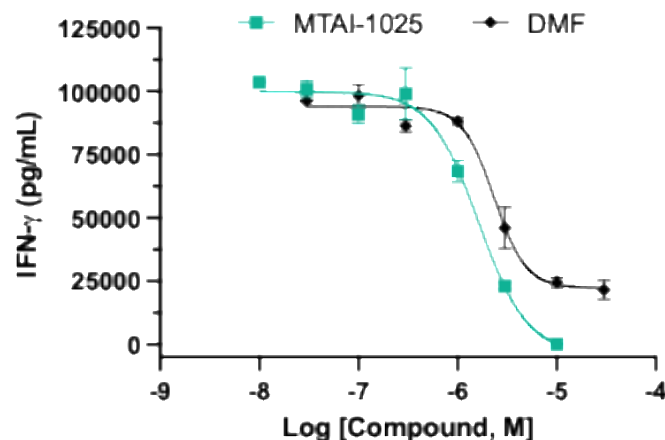
CD25 Expression Cell surface marker of T-cell activation



Purified human T-cells; 24h preincubation; 24h CD3/CD28 activation

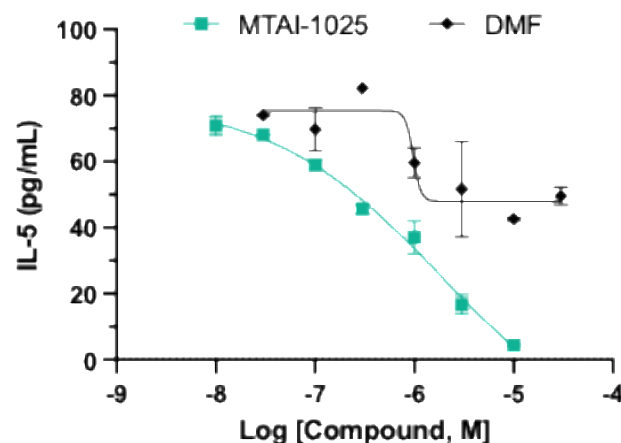
NRF2 | MTAI-1025 Fully Inhibits Differentiation of Naïve T-cells to Effector T-cells in Purified Human T-Cells

Th1 Differentiation



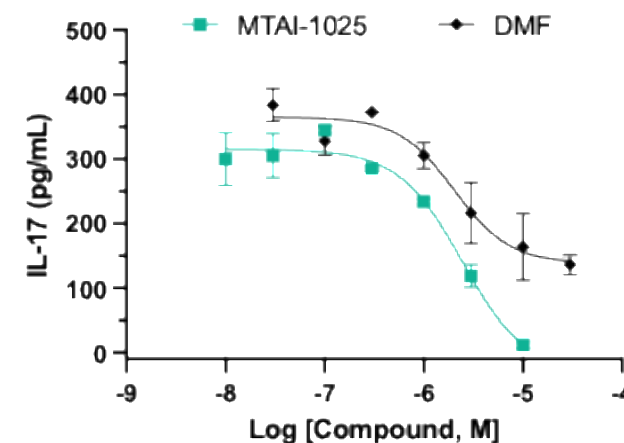
MTAI-1025 IC₅₀ = 1.6 μ M
DMF IC₅₀ = 2.3 μ M (Partial)

Th2 Differentiation



MTAI-1025 IC₅₀ = 1.2 μ M
DMF IC₅₀ = 1.0 μ M (Partial)

Th17 Differentiation

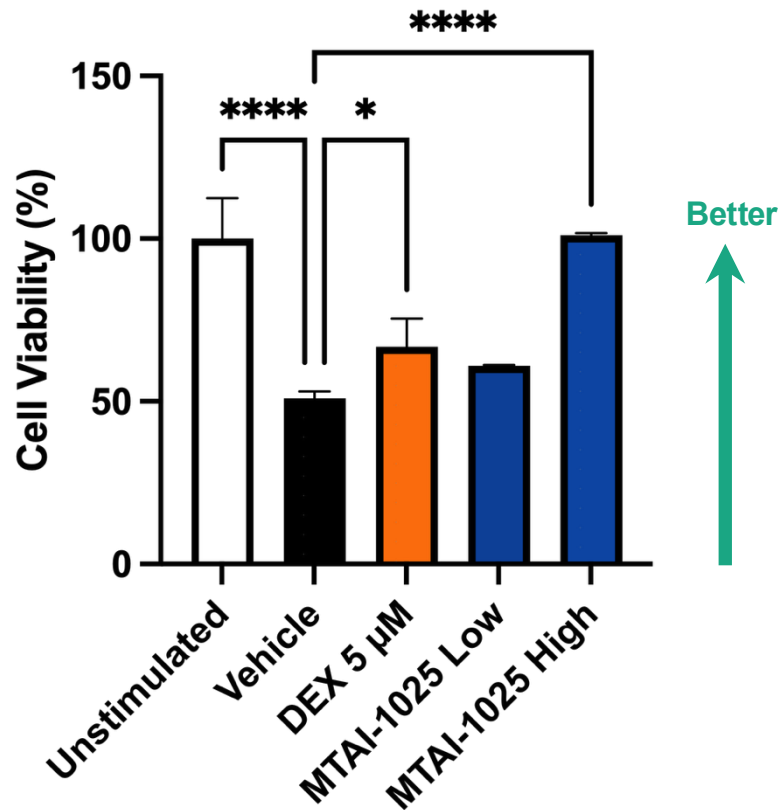


MTAI-1025 IC₅₀ = 3.0 μ M
DMF IC₅₀ = 2.0 μ M (Partial)

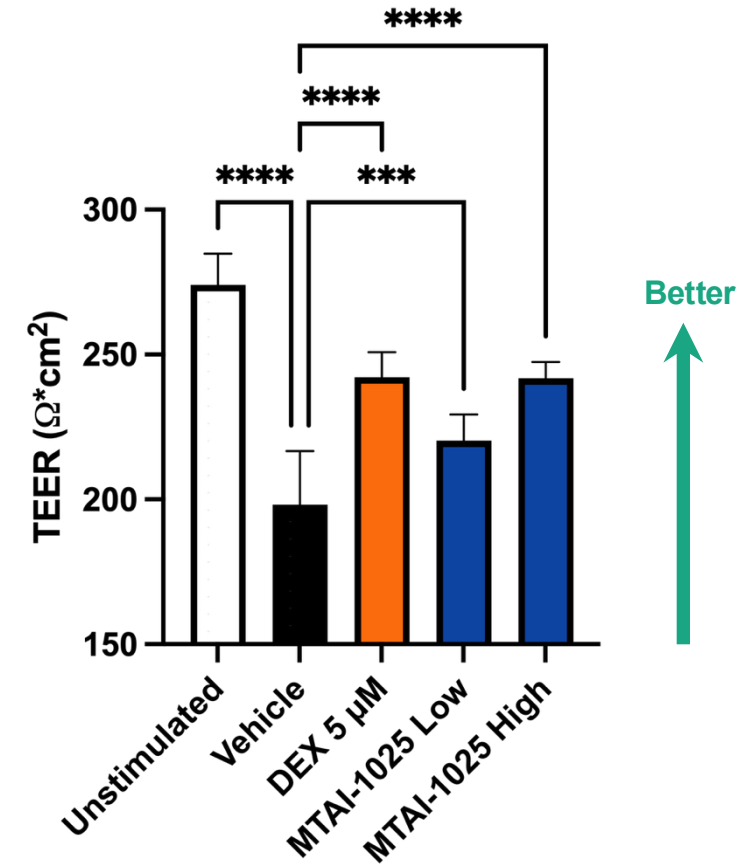
Purified naïve human T-cells activated with CD3/CD28 Dynabeads and cultured for 3d in the presence of cytokines for Th1/Th2/Th17 differentiation. Compounds added 24h prior to activation.

NRF2 | MTAI-1025 Protects Colonic Epithelial Barrier Integrity

Epithelial Cell Viability



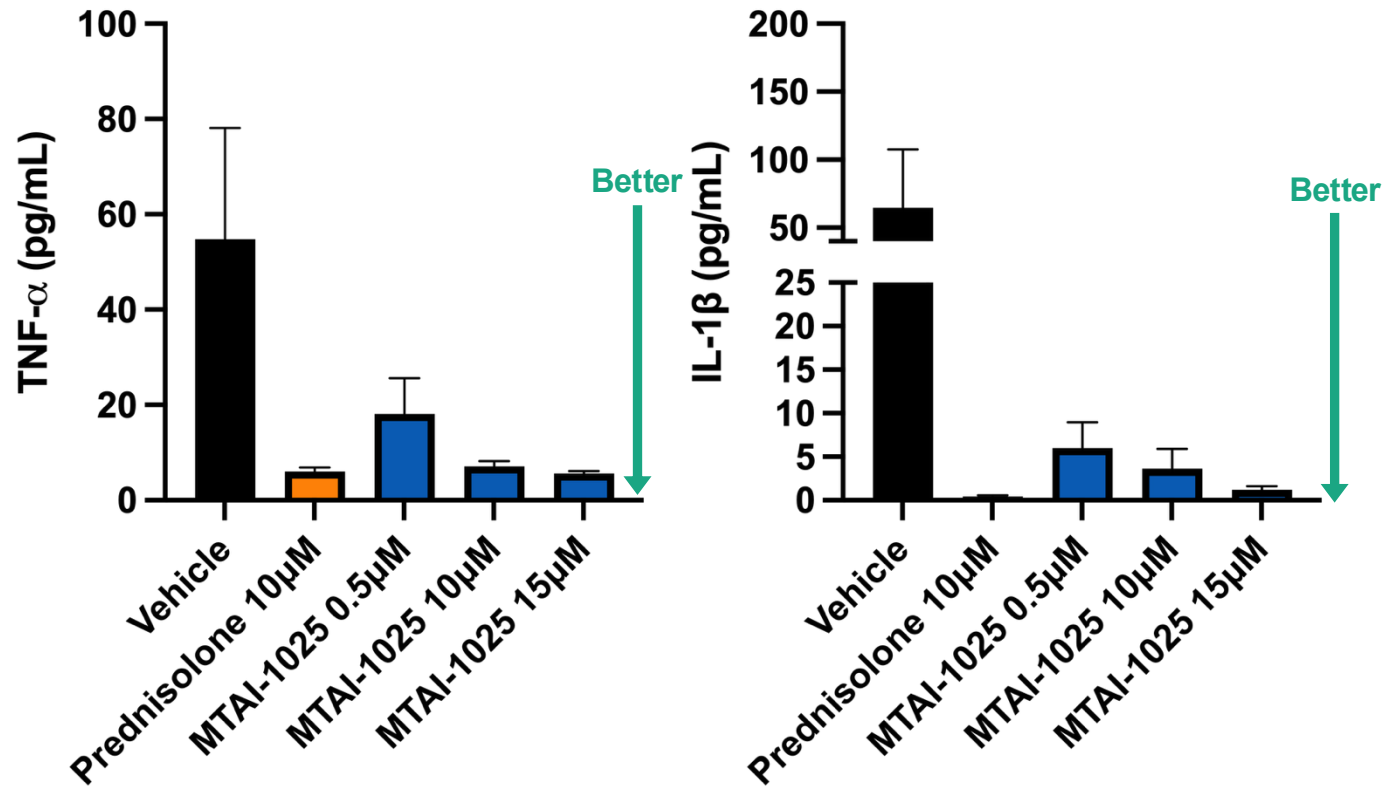
Barrier Integrity TEER (Ion Flow)



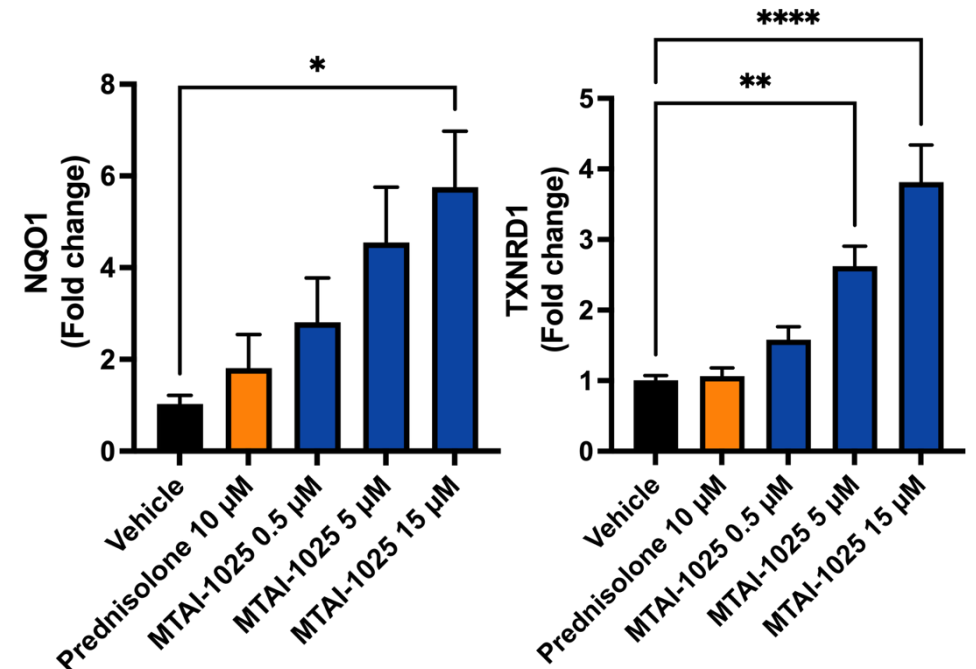
Colonic epithelium co-cultured with differentiated THP-1; viability and TEER measured at 24h.
MTAI-1025 matches high-dose dexamethasone at EC₅₀.

NRF2 | MTAI-1025 Reduces Cytokine Release and Induces Expression of NRF2-Driven Genes in Human UC Patient Tissue

Cytokine secretion from UC patient tissue



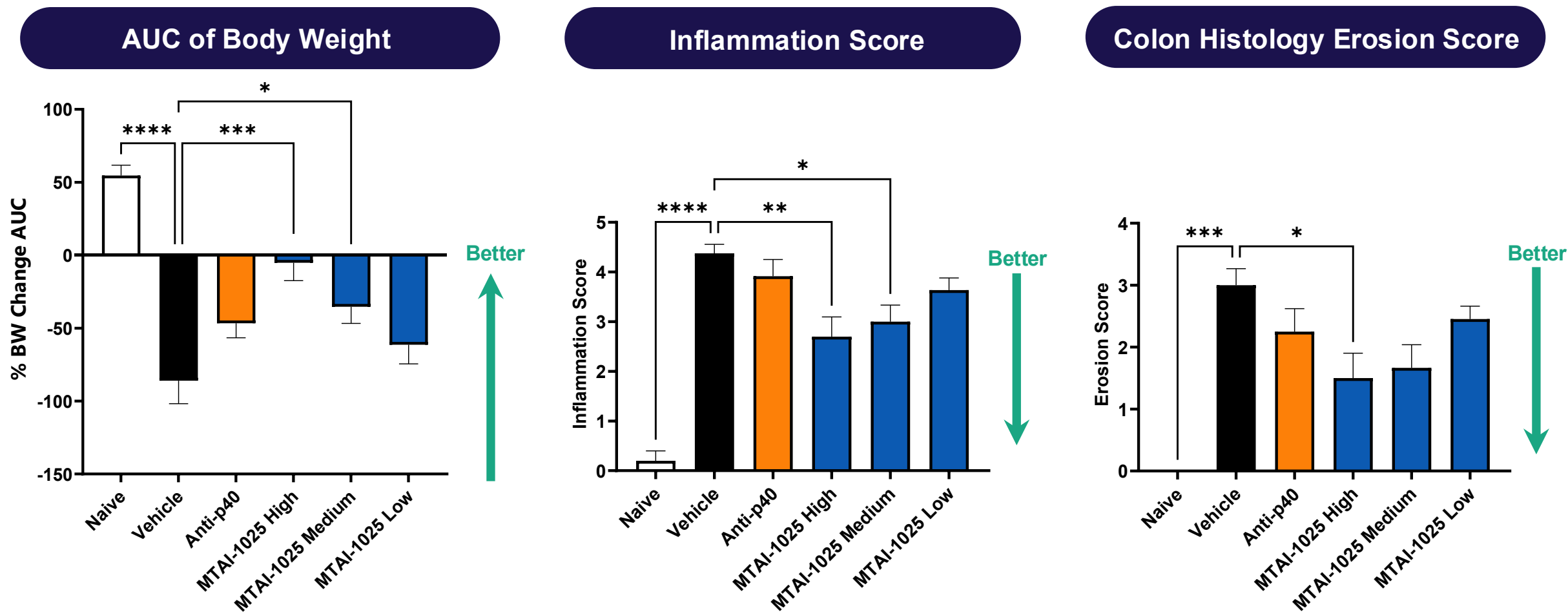
Gene Expression in UC patient tissue



3 Human UC tissue explants obtained from surgical residual. Biopsies are cultured for 18h with the indicated treatments. N=3 sample replicates per patient; one representative patient shown (2/3 were responder) Data are mean +/- SEM

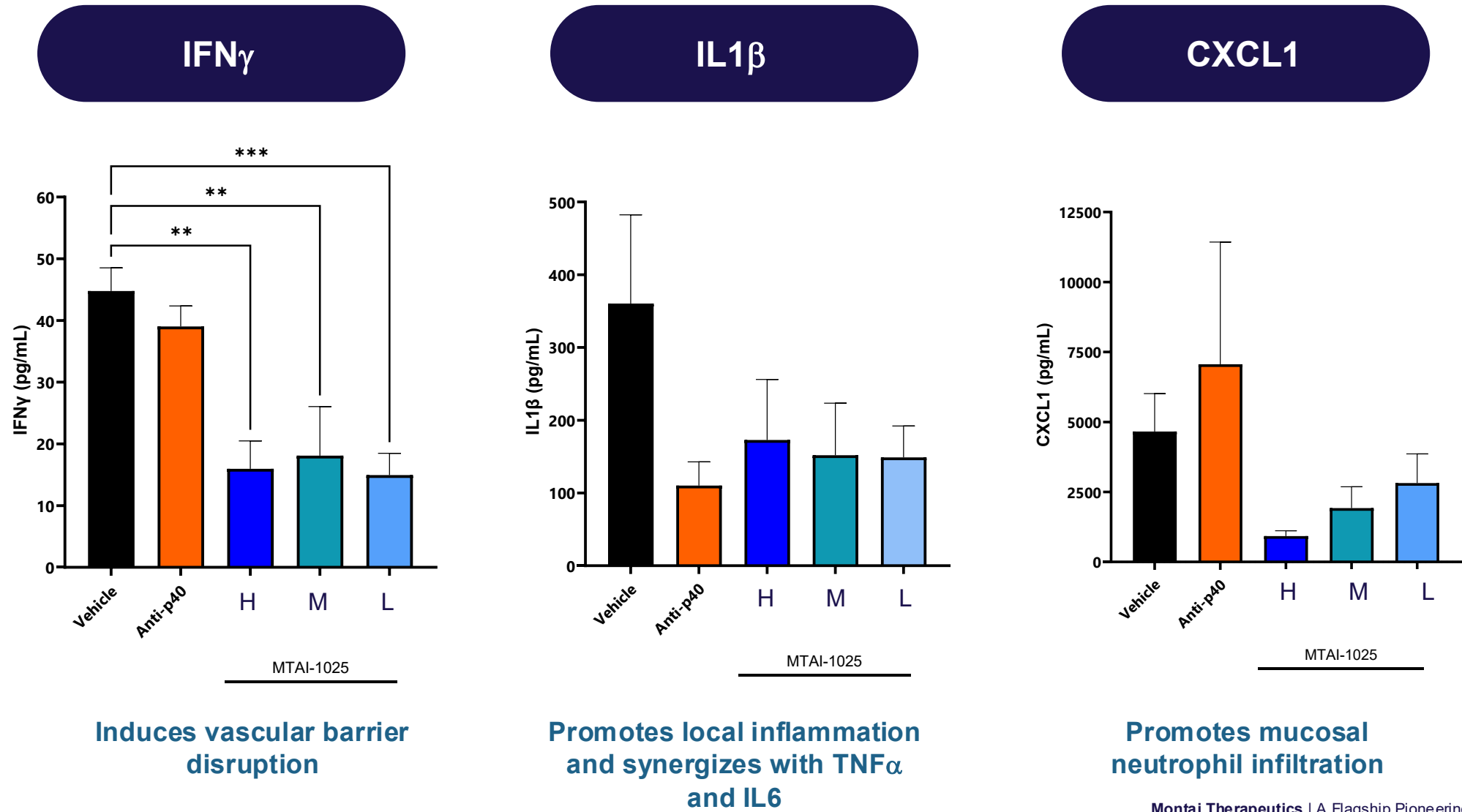
NRF2 | Oral MTAI-1025 Outperforms Biologic in Mice

14 Day Murine DSS Colitis Mechanistic Model



Anti-p40 positive control is mouse equivalent of anti-IL12/IL23 biologic Ustekinumab (Stelara®)
14 day PO treatment, N=12/treatment arm, mean ± SEM; *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

NRF2 | MTAI-1025 Outperforms Biologic (anti-p40) in Reducing IFN γ , IL1 β and CXCL1 Cytokines in Colon of the Mouse Colitis (DSS) model



NRF2 | MTAI-1025 is Highly Selective Versus Approved NRF2 Therapeutics

Safety Profile

CRITERIA	THRESHOLD	MTAI-1025
hERG (IC50)	> 30 µM	> 15 µM
AMES (DEREK)	Negative	Negative
CYP Inhibition (IC50)	≥10 µM	≥10 µM
BSEP/BCRP/ OATP/PGP Inhibition (IC50)	>10uM	>10 µM

Selectivity vs Approved NRF2 Agonists

Family (Gene)	MTAI-1025		SKYCLARYS	
	Agonist (EC50)	Antagonist (IC50)	Omaveloxolone (µM)	
			Agonist (EC50)	Antagonist (IC50)
α1A-adrenergic receptor	>50	>50	>50	1.92
α2A-adrenergic receptor	>50	>50	2.19	>50
β1-adrenergic receptor	>50	>50	>50	0.80
β2-adrenergic receptor	>50	>50	>50	1.36
Cannabinoid receptor CB2	>50	>50	0.240	>50
Dopamine receptor D1	>50	>50	>50	0.92
Dopamine receptor D2	>50	>50	2.20	>50
Endothelin receptor A	>50	>50	>50	4.71
Histamine H1 receptor	>50	>50	>50	1.62
Histamine H2 receptor	>50	>50	>50	1.32
Muscarinic acetylcholine receptor M1	>50	>50	>50	2.86
Muscarinic acetylcholine receptor M2	>50	>50	1.90	>50
δ-type opioid receptor	>50	>50	1.32	>50
κ-type opioid receptor	>50	>50	5.30	>50
μ-type opioid receptor	>50	>50	4.18	>50
5-HT1A	>50	>50	3.94	>50
5-HT2A	40.62	>50	>50	5.04
Vasopressin V1A receptor	>50	>50	>50	2.18
Androgen receptor	>50	9.55	>50	0.18
Glucocorticoid receptor	>50	8.21	>50	0.31

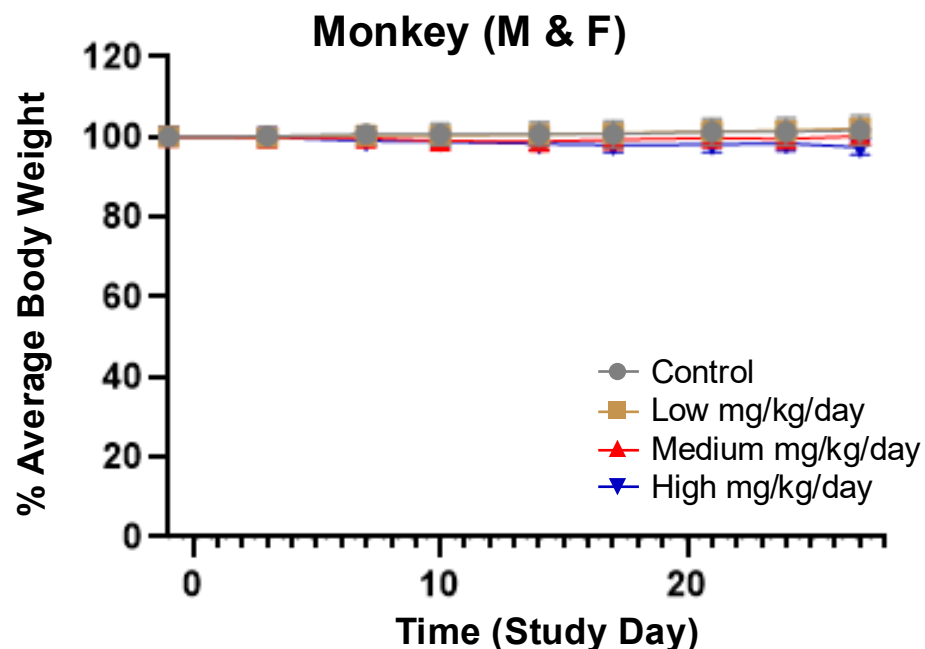
Good Moderate Poor

Internal data, Eurofins SafetyScan47

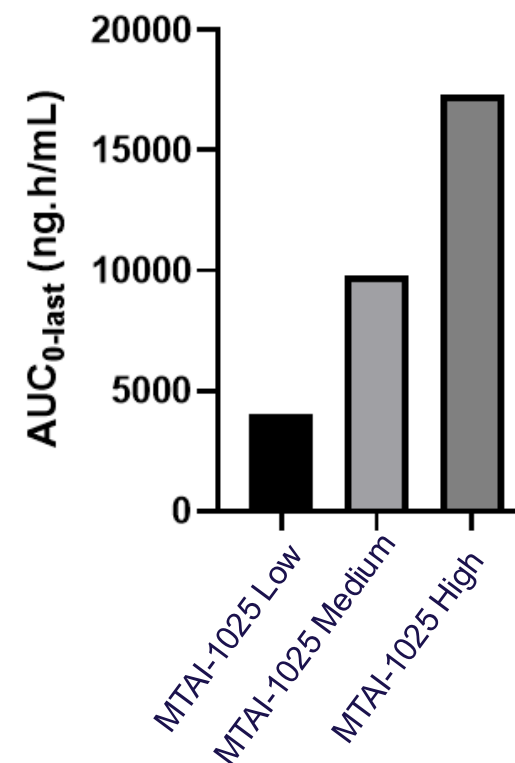
Montai Therapeutics | A Flagship Pioneering Company

NRF2 | MTAI-1025 is Safe and Well Tolerated

NHP Body Weights Normalized to Pre-dose



Monkey AUC Measured on Day 28

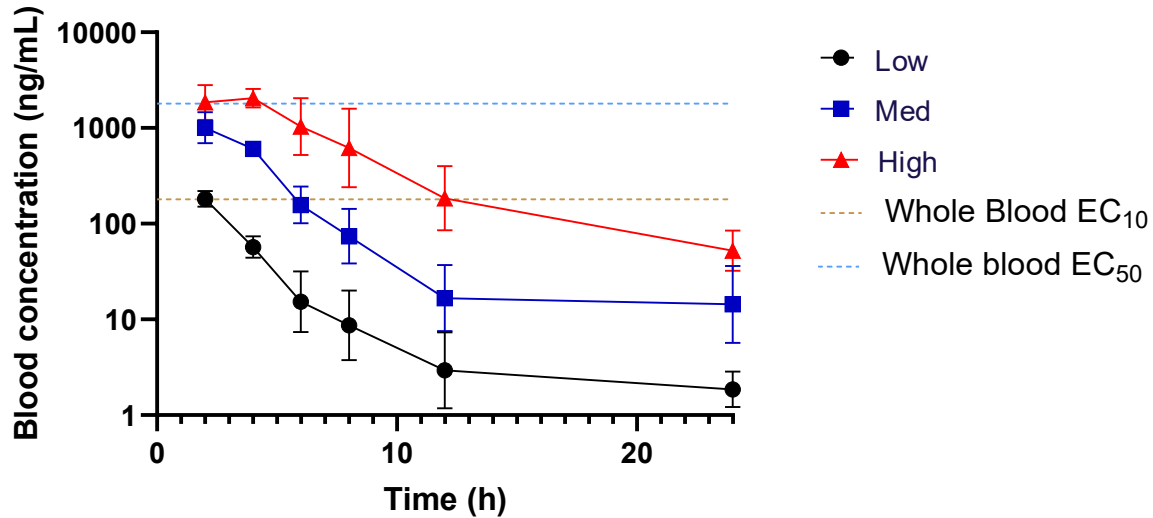


Data support advancement to the clinic with 20X safety margin from FIH starting dose

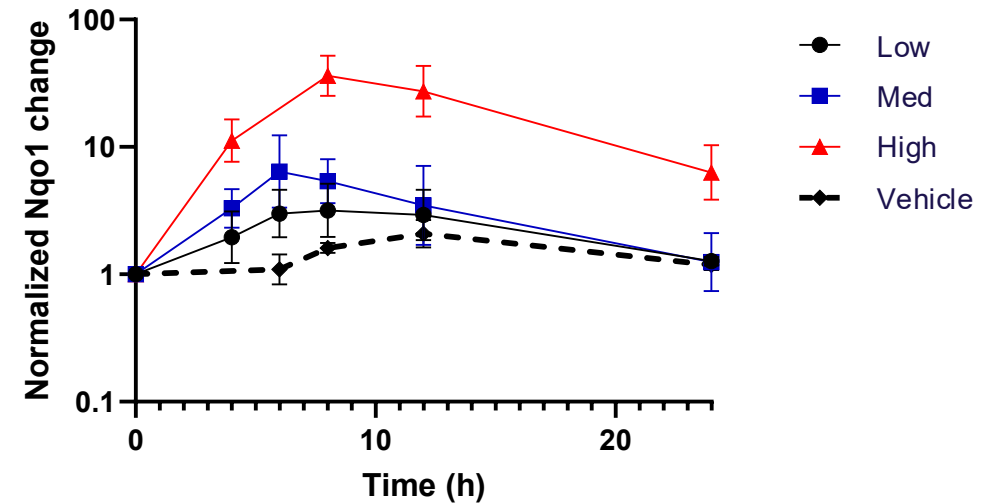
- No clinical observations in NHP and mouse 28-day GLP tox studies
- No significant findings in GLP safety pharmacology (e.g. CNS, CVS, Respiratory, micronucleus)

NRF2 | Oxidative Stress Response is a Translational PD Biomarker

NHP Dose Dependent Increase In Exposure

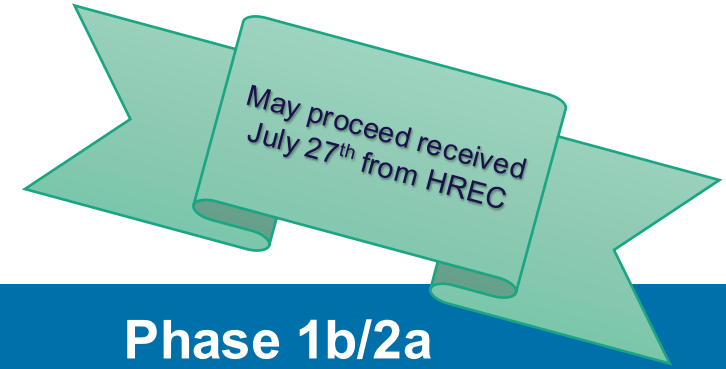


NHP Dose Response Increase in NQO1



Blood translational biomarker response and target coverage aligns with efficacious doses in DSS colitis model

NRF2 | MTAI-1025 heading to the Clinic



Phase 1 SAD-MAD Healthy Volunteers

Initiated Q3 2026

- Dose escalation (3-5 dose s, n=8/cohort, 3:1), 14-day study
- Confirm safety and tolerability
- Measure target engagement to confirm PK/PD relationship
- Define efficacious dose for Ph1b/2a study
- Tablet selected for FIH



Phase 1b/2a Ulcerative Colitis Patients

Start Q2 2027

- 60–90 patient, 12-week PoC trial
- Safety, tolerability, and early efficacy
- Endpoints: clinical remission and endoscopic improvement
- Disease biomarkers in blood, stool, and colon

Thank You
