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Advancing Precision Care in IBD: From Static Biomarkers to Mechanistic Insight

Shrinivas Bishu, MD

*Associate Program Director GI Fellowship
Clinical Director of IBD
University of Michigan
Ann Arbor, Michigan*

Disclosures

- **Shrinivas Bishu, MD:** Relevant committees—AGA CPU, ACG Guidelines, CCF Litwin; research funding—CCF, NIH, Johnson & Johnson, AbbVie, Helmsley Foundation; consulting and speaking—Johnson & Johnson, AbbVie

Learning Objectives

- Identify the limitations of commonly used biomarkers (eg, CRP, FCP) in predicting personalized treatment response in IBD
- Evaluate the scientific evidence/rationale for targeting upstream inflammatory pathways, including TREM-1, given their association with inflammatory activity and mucosal damage
- Describe how emerging multiomic and mucosal biomarker approaches could support future precision-medicine strategies in IBD, including potential integration with upstream innate immunity targets

Roadmap

1 The Clinical Challenge

Unmet needs and the precision care gap in IBD.

2 Precision care and biomarkers

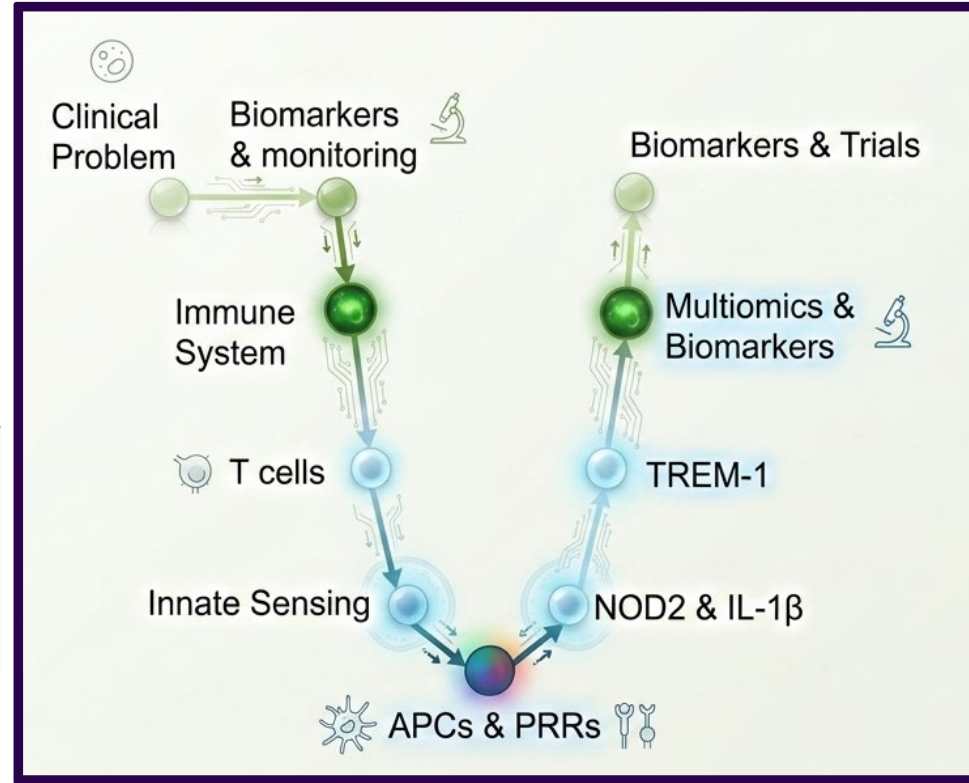
Current biomarkers & the case for better ones.

3 Innate Immunity and IBD

Microbes, innate sensing, and IBD

4 The Future

Toward precision approaches to IBD



Section 1: The Unmet Needs

The Clinical Challenge: The “Therapeutic Ceiling”

Primary Non-Response

Approximately **30-50%** of patients do not respond to initial advanced therapies (primary non-response).

Loss-of-Response

An estimated 30-50% of patients may lose response to advanced therapies over 5 years

How do we overcome the therapeutic ceiling?

Let's start with how we monitor disease

The First Core Problem: Primary Non-Response

2005

Therapeutic
Gap

2022

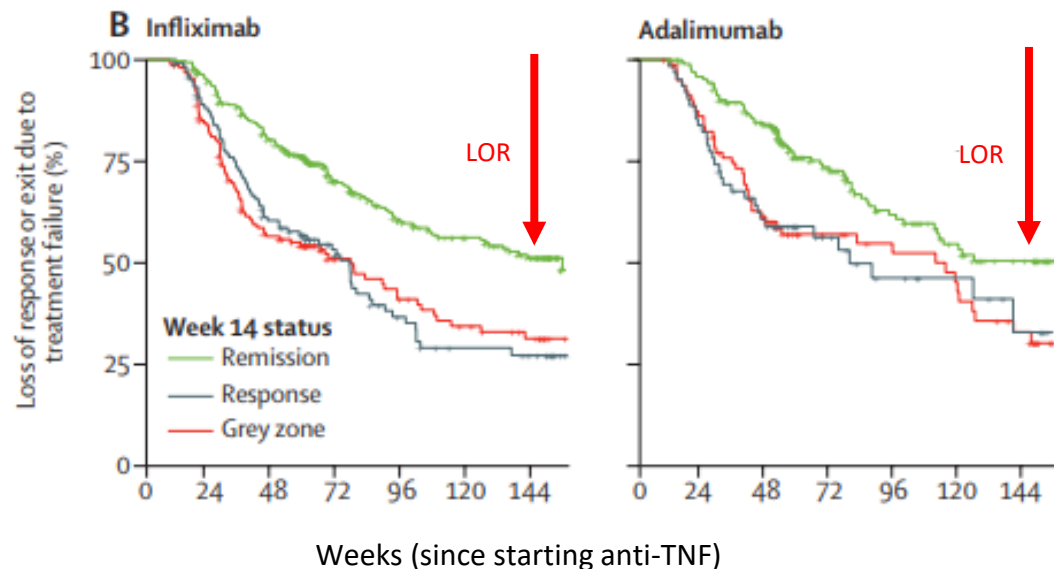
Therapeutic
Gap

- Primary non-response (PNR) = no response an advanced therapy (AT)
- ACT1 & ACT2 [IFX] vs U-Achieve [upa]
- Decades have passed and we have many new—and probably better—therapies!
- But—30-50% still do not respond to treatment!

Study title	Year	Design	AT-exposed
ACT 1&2	2005	Treat-through	0%
U-Achieve	2022	Re-randomized	47-54%

The Second Core Problem: Loss-of-Response

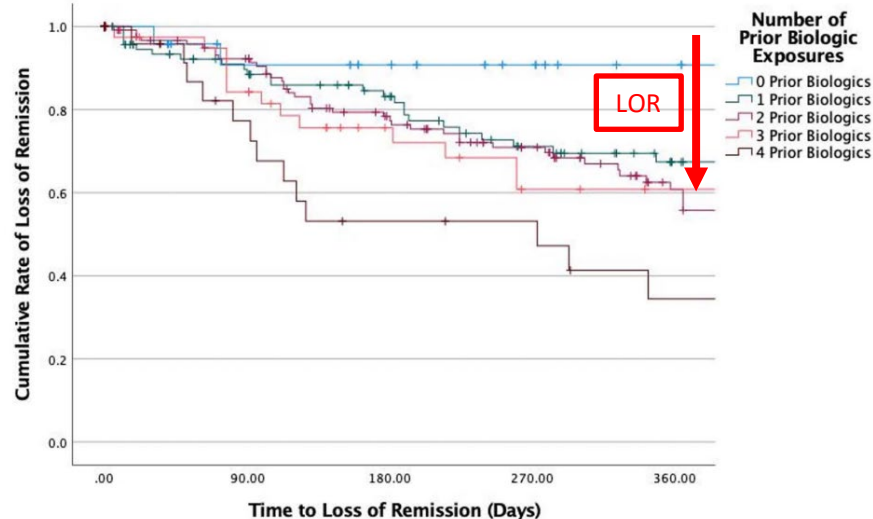
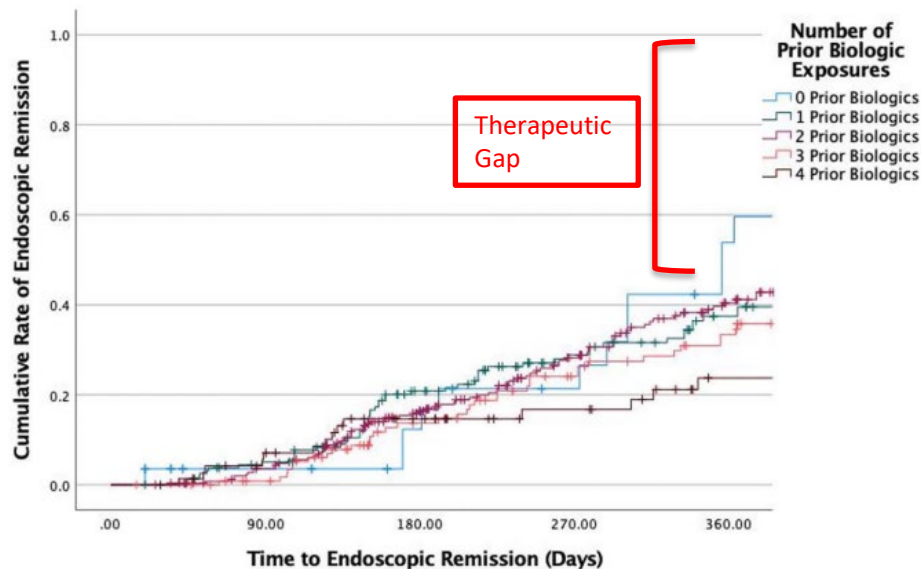
PANTS Cohort
Tracked patients who started IFX and ADL



- Loss-of-response = loss of remission status in those previously in remission
- PANTS study (personalizing anti-TNF therapy in Crohn's Disease)
- LOR = patients who lost response after induction
- Half of patients lose response over 3 years!
- “Pharmacodynamic” vs “mechanistic” LOR

Better Drugs—but Core Problems Persist

Real World Evidence: Ustekinumab
Uncontrolled retrospective cohort study



Unmet Needs: The “Therapeutic Ceiling”

Primary Non-Response

Can we reduce PNR by tailoring therapy (“precision medicine”)?

Loss-of-Response

Can we overcome LOR by intervening early if it is about to occur?

To address this, we need biomarkers that can

- Identify the best agent for any given patient (reduce PNR)
- Predict response before treatment (reduce PNR)
- Anticipate loss of response (prevent LOR)

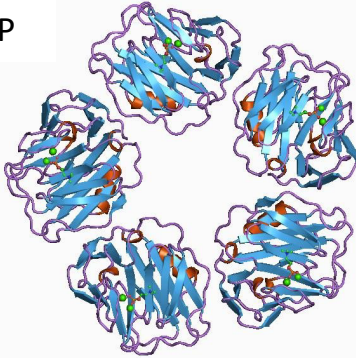
Section 2: Precision Care and Biomarkers

Biomarkers: Basic Classification

Biomarker	Definition (role)	Practical meaning
Monitoring Biomarkers	Assess the status of a disease	Tell you how things are <i>now</i>
Predictive Biomarkers	Identify those who are likely to experience an event from an exposure	Tell you which treatment suits which patient (“personalized medicine”)
Prognostic Biomarkers	Identify the likelihood of a clinical event	Tell you what may happen <i>in the future</i> .

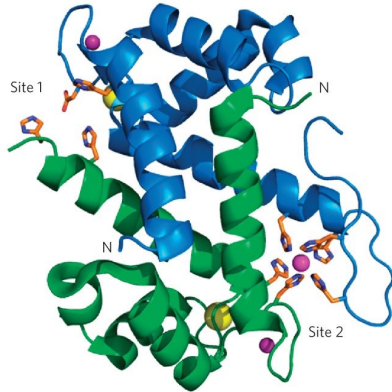
Biomarkers: CRP and FCP

CRP



1. CRP = cyclic pentameric protein
2. Made by hepatocytes in response to inflammation
3. Binds to pathogens and damaged cells and facilitates clearance

FCP



1. FCP = heterodimer (or tetramer) of S100A8 + S100A9
2. Released by neutrophils
3. An antimicrobial peptide (AMP) with antibacterial and antifungal properties

Biomarkers: CRP and FCP

Biomarker	Practical meaning
C-reactive protein (CRP)	Tells you about the now
Fecal calprotectin (FCP)	Tells you about the now > predict the <i>future</i>

1. CRP = insensitive and nonspecific
2. FCP = high specificity for gut inflammation
3. FCP = lower sensitivity in small intestinal Crohn's (and probably limited extent colitis)

Biomarkers: CRP and FCP

Diagnostic Accuracy of CRP (>5 mg/L) in UC

Clinical Scenario (Pretest Probability)	Prevalence of Active UC	False Negative	False Positive	Certainty of Evidence
Low (RBS 0, SF 0-1)	15%	5.5%	19.5%	Very Low
Intermediate (RBS 0-1, SF 2-3)	50%	18.5%	11.5%	Very Low
High (RBS 2-3, SF 2-3)	85%	31.4%	3.4%	Very Low

Diagnostic Accuracy of FCP (>150 ug/g) in UC

Clinical Scenario (Pretest probability)	Prevalence of Active UC	False Negative	False Positive	Certainty of Evidence
Intermediate (RBS 0-1, SF 2-3)	50%	14.5%	15.5%	Very Low
High (RBS 2-3, SF 2-3)	85%	24.7%	4.6%	Very Low

RBS = rectal bleeding score; UC = ulcerative colitis.
Singh S, et al. *Gastroenterology*. 2023;164(3):344-372.

1. The accuracy of CRP and FCP depend on your **clinical assessment**
2. They are **not** pure cutoff values
3. Think of it as a screening test!

Critical Limitations of CRP and FCP for Closing the Therapeutic Ceiling



Biomarker	Key Limitation
CRP	• Can't use it to pick treatment (not predictive) • Doesn't tell you about treatment response (not prognostic)
FCP	• Not predictive • Limited prognostic power—but inflammation already set in...so not much time to act

Barriers to Developing Better Biomarkers

To break the therapeutic ceiling, we need

- Predictive biomarkers
- Prognostic biomarkers

What are the barriers?

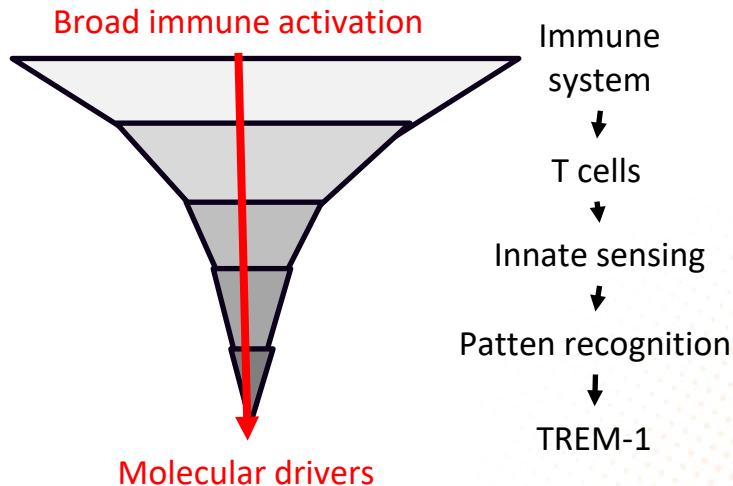
- High-quality, long-term, longitudinal data
- **Biomarkers that are linked with the biology of IBD—so let's talk about the immune system and IBD!**

Section III: Adaptive and Innate Immunity and IBD Treatments

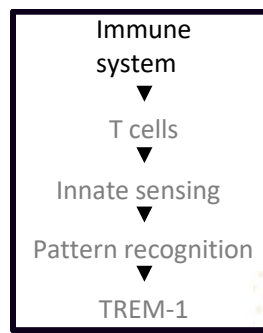
Why Precision Care Is Needed to Break the Therapeutic Ceiling

- Drug failure isn't random—it's a biological mismatch
- IBD is biologically heterogeneous → variable responses
- Immune system is multifaceted

Different immune pathways drive disease in different patients



Immune System: Simple Classification



Cells of Innate and Adaptive Immunity

INNATE IMMUNITY (Arm 1) (Fast, Non-Specific Defense)



MACROPHAGE

Engulfs Pathogens and
and Presents Antigens



NEUTROPHIL

Fast Responders
to Infection

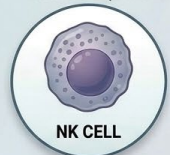
DENDRITIC CELL



DENDRITIC

Captures and Presents
Antigens to T Cells

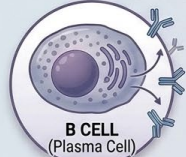
NK CELL (Natural Killer)



NK CELL

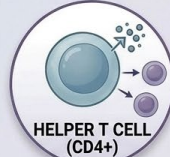
Directly Kills Infected
and Abnormal Cells

ADAPTIVE IMMUNITY (Arm 2) (Slow, Highly Specific, with Memory)



**B CELL
(Plasma Cell)**

Produces Specific
Antibodies



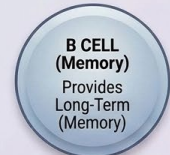
**HELPER T CELL
(CD4+)**

Activates and Coordinates
other Immune Cells



**CYTOTOXIC
T CELL (CD8+)**

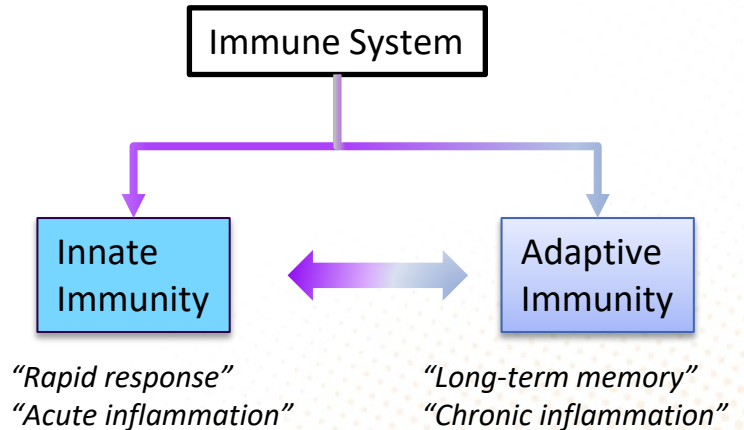
Directly Kills
Specific Infected
Host Cells



**B CELL
(Memory)**

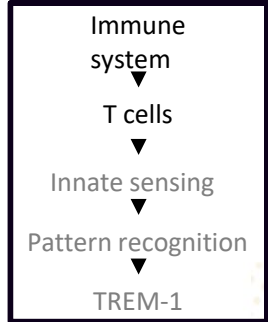
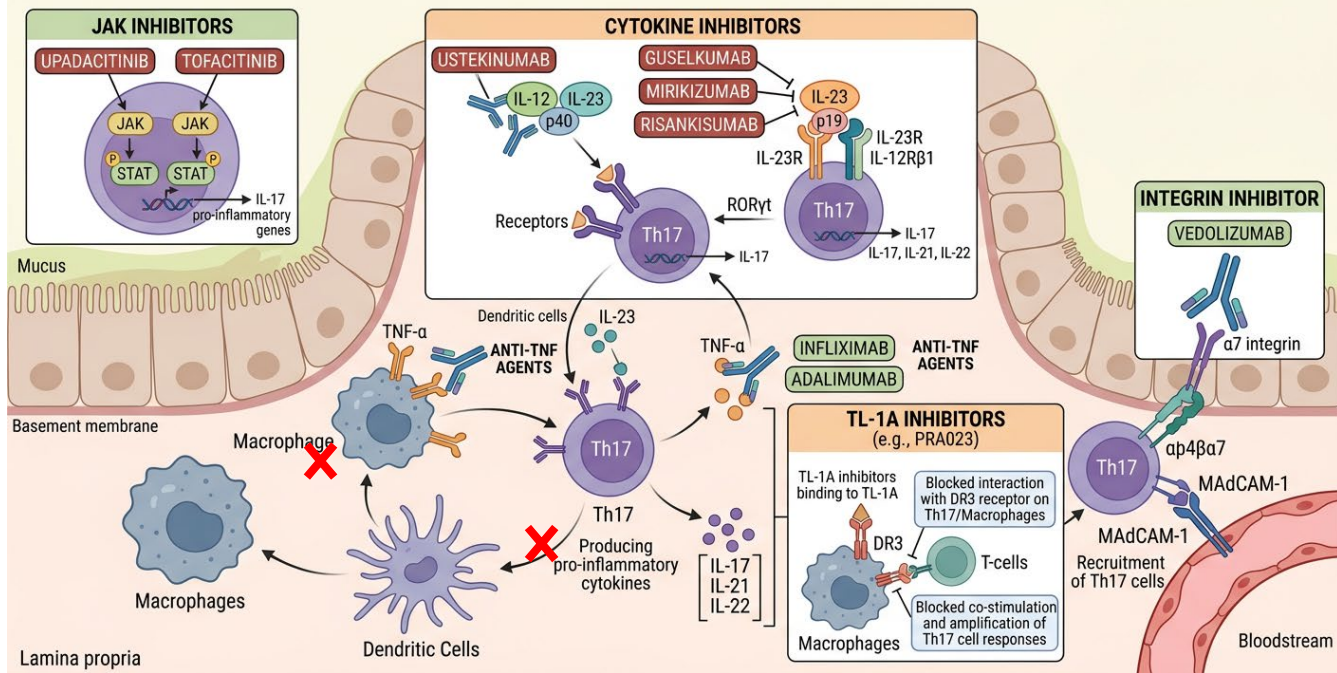
Provides
Long-Term
(Memory)

Provides Long-Term
Immunity (Memory)



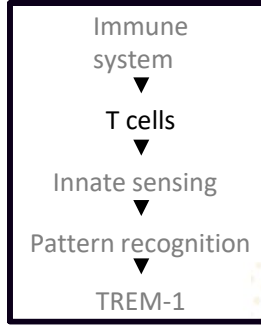
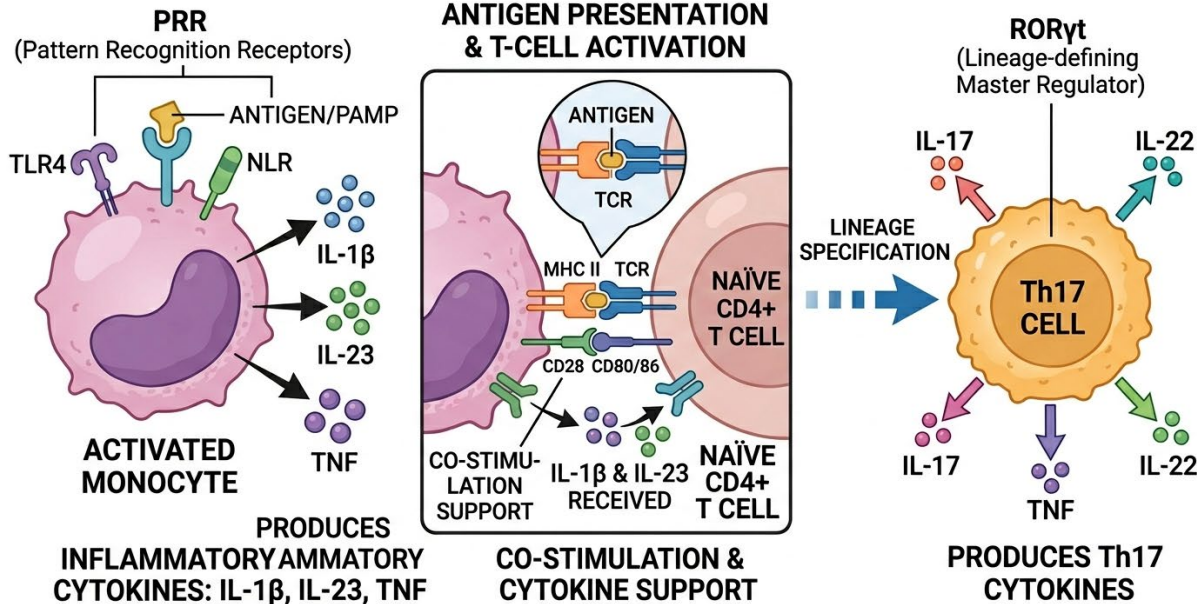
Biologic Targets of IBD Therapies

MUCOSAL IMMUNE SYSTEM: TARGETED THERAPEUTIC PATHWAYS IN INFLAMMATION



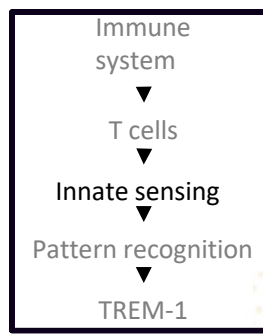
1. T cells—especially Th17 cells—are major target of treatment
2. APCs are major targets of treatment (anti-TNFs)
3. Current therapies target cytokines, cell activation (JAKi), or cell trafficking
4. Can we target more upstream pathways?

Generating Pathogenic T Cells

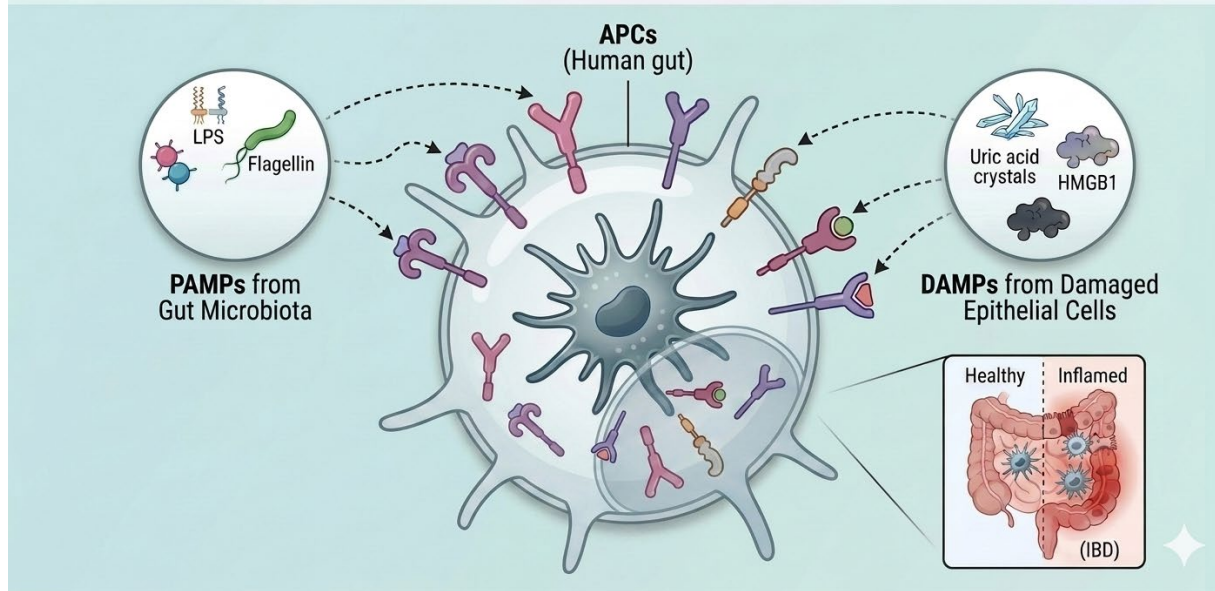


1. APCs “present” antigen to T cells
2. This generates specialized T cells
3. Some specialized T cells are major drivers of IBD (“pathogenic” T cells)
4. Can we block inflammatory cascades at even earlier stages?

Antigen Presenting Cells (APCs) and Innate Sensing



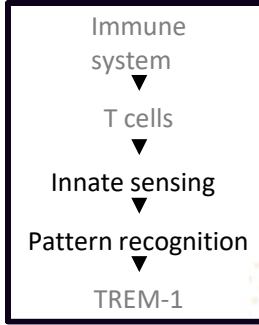
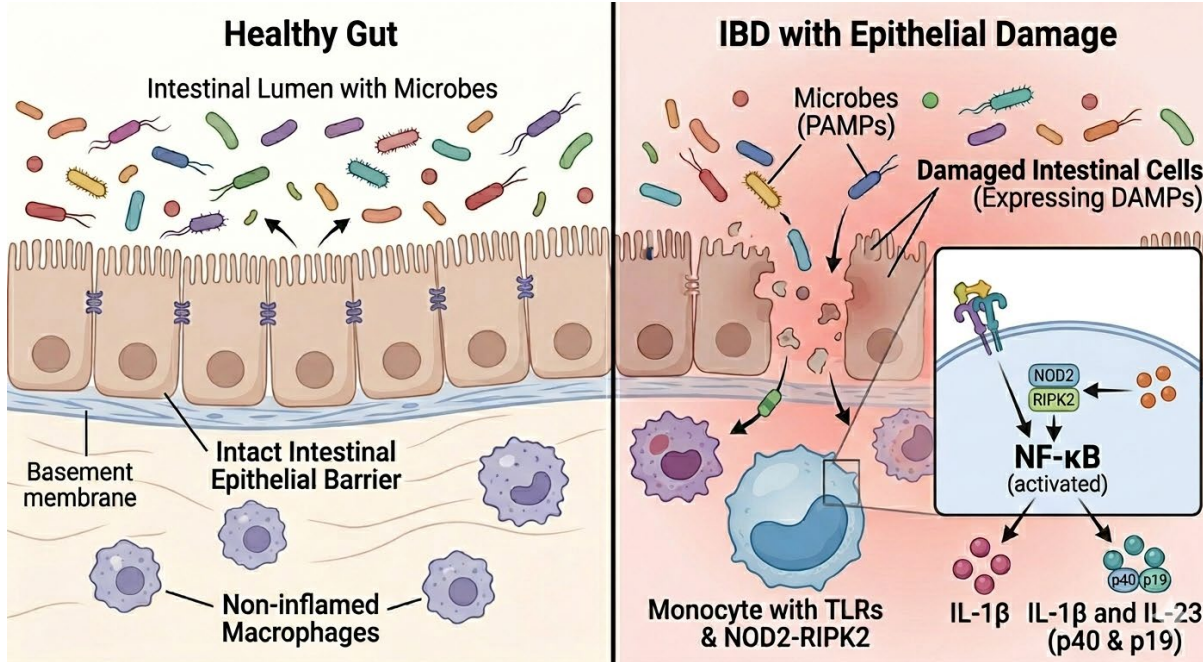
APCs: Recognizing PAMPs & DAMPs in IBD



1. APCs sense bacteria (PAMPs) and tissue damage (DAMPs)
2. The “sensing” is performed by receptors on the cell surface and cytosol
3. These receptors are termed PRRs
4. These pathways are protective—but can also cause inflammation

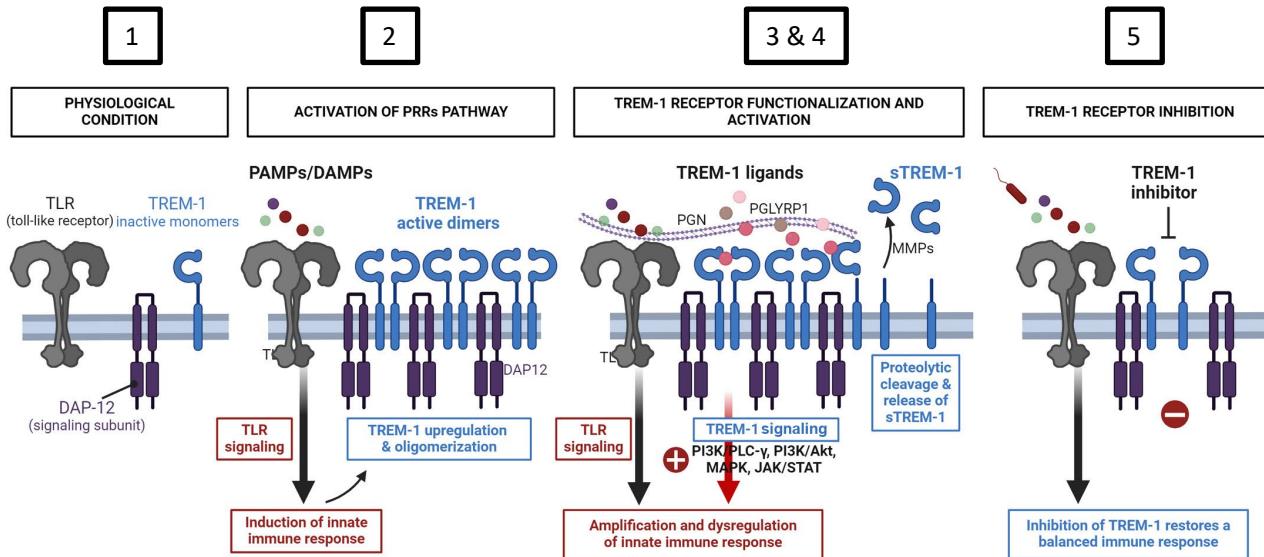
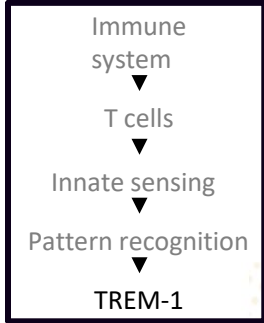
PAMP = pathogen-associated molecular pattern; DAMP = damage-associated molecular pattern.
Image generated by Bishu S using Google Gemini.

The Bigger Picture in IBD



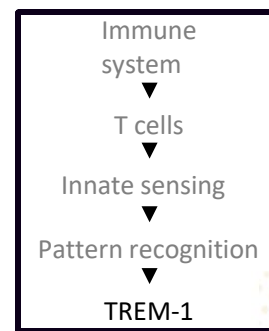
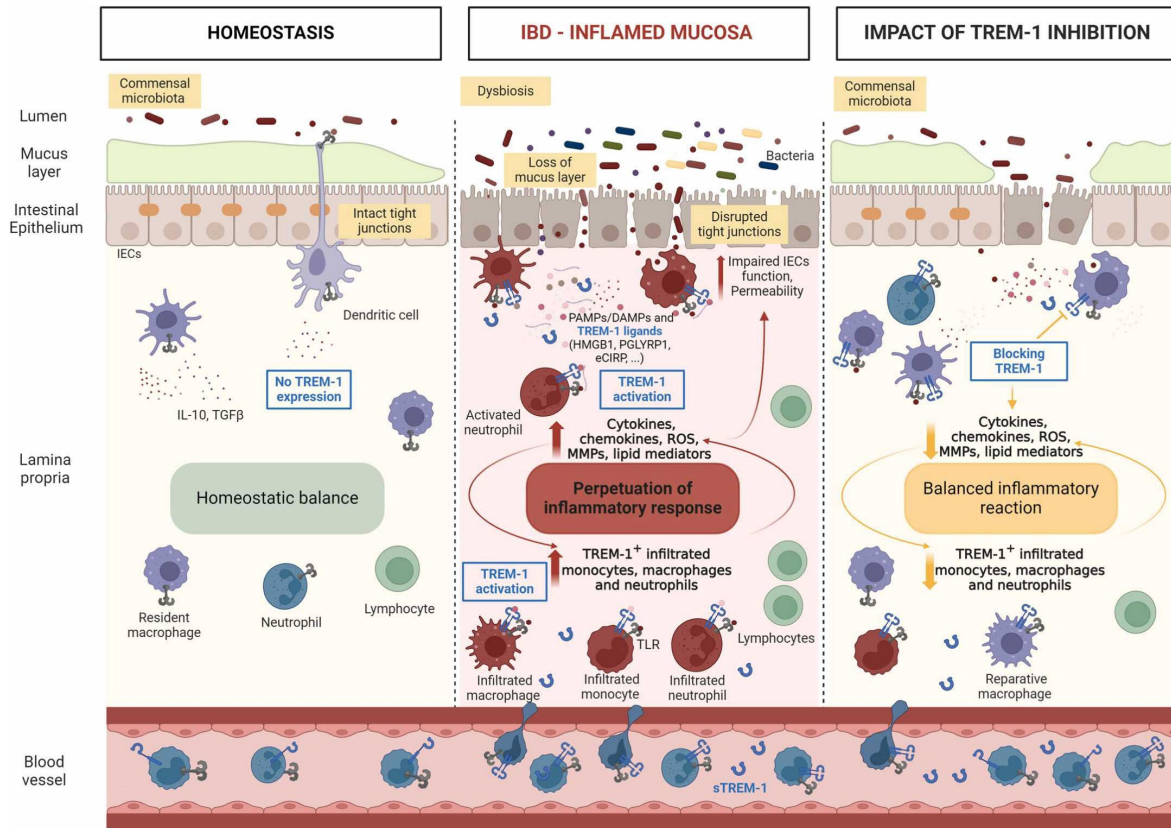
1. With IBD—tissue damage and microbes—detected by PRRs
2. PRRs activate inflammatory cytokines (IL-1 β and IL-23)
3. NOD2 = key intracellular PRR; predicts severe Crohn's
4. Can we regulate inflammation at the level of PRRs?

Limiting PRR-Driven Inflammation by Blocking TREM-1



1. In health—all good
2. With IBD—PAMPs/DAMPs → PRRs → inflammatory cytokines (IL-1b and IL-23)
3. TREM-1 membrane-associated protein with PRRs
4. TREM -1 amplifies PRR inflammatory cascades → feed-forward cycle
5. Blocking TREM-1 stops the feed-forward cycle

Limiting PRR Driven Inflammation by Blocking TREM-1



1. With IBD—PAMPs/DAMPs → trigger PRRs + TREM-1 → $\uparrow$ $\uparrow$ IL-1β and IL-23
2. Block TREM-1 = stops the inflammatory cascade at an EARLY point

Why Does This Matter Clinically?

- Different biology → different responses to treatment
- Current tools don't identify underlying biology
- To better treat patients we need—***new pathways + better ways to match each patient to the right drug***

Roadmap

1 The Clinical Challenge

Unmet needs and the precision care gap in IBD

2 Precision care and biomarkers

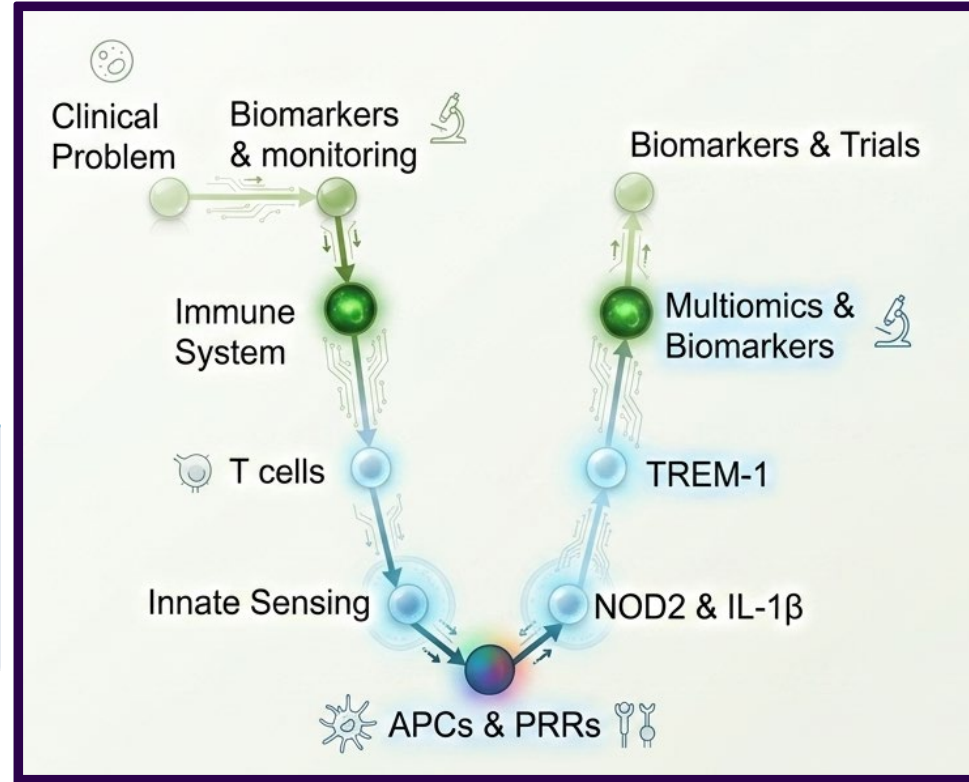
Current biomarkers and the case for better ones

3 Innate Immunity and IBD

Microbes, innate sensing, and IBD

4 The Future

Toward precision approaches to IBD



Section IV: Multiomics, Precision Biomarkers, and the Future

What Is Multiomics, and Why Is It Promising for Developing Precision Biomarkers?

The core problem = therapeutic ceiling

To address this, we need biomarkers that can

- Identify the best agent for any given patient (reduce PNR)
- Predict response before treatment (reduce PNR)
- Anticipate loss of response (prevent LOR)

We have good monitoring biomarkers, but we need good predictive and prognostic biomarkers.

What is “multiomics,” and can it help bridge this gap?

What Is Multiomics?

Bulk sequencing

Molecule	Term	Tissues
Proteins	Proteomics	Blood
RNA	Transcriptomics	Tissue or blood
Metabolites	Metabolomics	Blood or stool
Microbiome	Microbial taxonomy	Stool

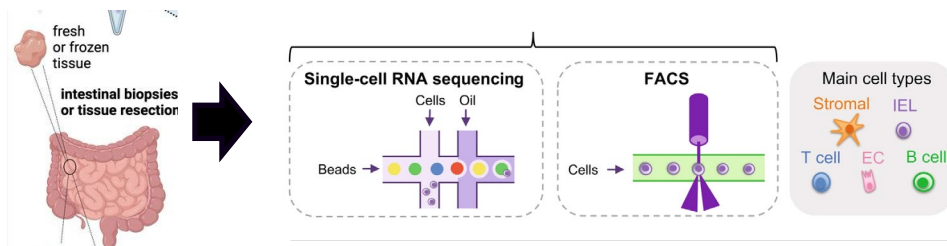
Single-cell sequencing

Molecule	Term
RNA	Single-cell sequencing
RNA on tissue	Spatial transcriptomics (ST)

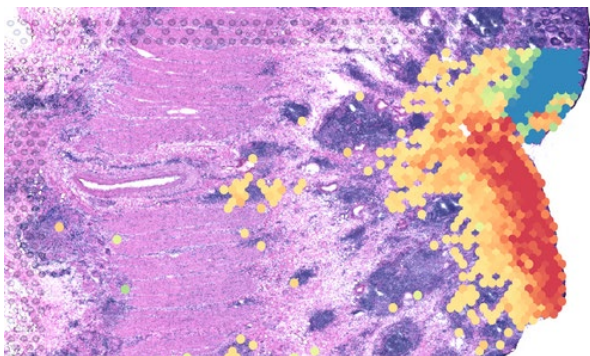
1. “Omics” = complete dataset of biological molecules (RNA, DNA, etc.)
2. “Bulk” = all molecules in a body fluid or tissue
3. “Single-cell” = all molecules expressed by cells individually, in a body fluid or tissue

What Is Multiomics?

Single-cell transcriptomics (scRNA-seq)



Spatial transcriptomics (ST)



1. sc-RNA-seq generates data at the single-cell level
2. Tells you which genes are active in each cell
3. ST allows you to overlay that data on anatomic specimens (H&E slides)
4. Tells you which genes are active in each cell and where they are in tissue

FACS = fluorescence-activated cell sorting.

Venema WTCU, et al. *Sci Rep.* 2022;12:9897. Kong L, et al. *Nat Genet.* 2025;57(7):1742-1753.

Why Does Multiomics Show Promise for Precision Biomarkers?



THE PROMISE OF MULTIOMICS IN PRECISION MEDICINE

CURRENT BIOMARKERS (e.g., CRP, Fecal Calprotectin)

WEAKLY LINKED TO BIOLOGY: Primary markers are general, systemic inflammation responses, not root cause drivers.

PRIMARILY ASSOCIATIVE: They provide an inflammation status signal, without identifying the primary defect.



UPGRADE TO PRECISION

MULTIOMICS BIOMARKERS

DEEP MOLECULAR PROFILING: Reveals the specific, deep-seated pathogenic causal factors in disease drivers.

EXPLORES THE “WHY” AND “HOW” OF IBD
Pinpoints distinct mechanistic pathway alterations and targetable nodes.



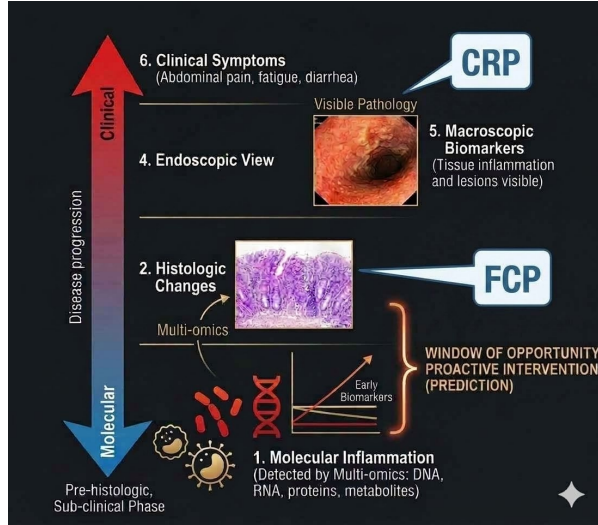
PREDICTIVE BIOMARKERS: Pair the patient with the *best* specific agent (e.g., matching a patient profile to a drug with a high efficacy prediction value).



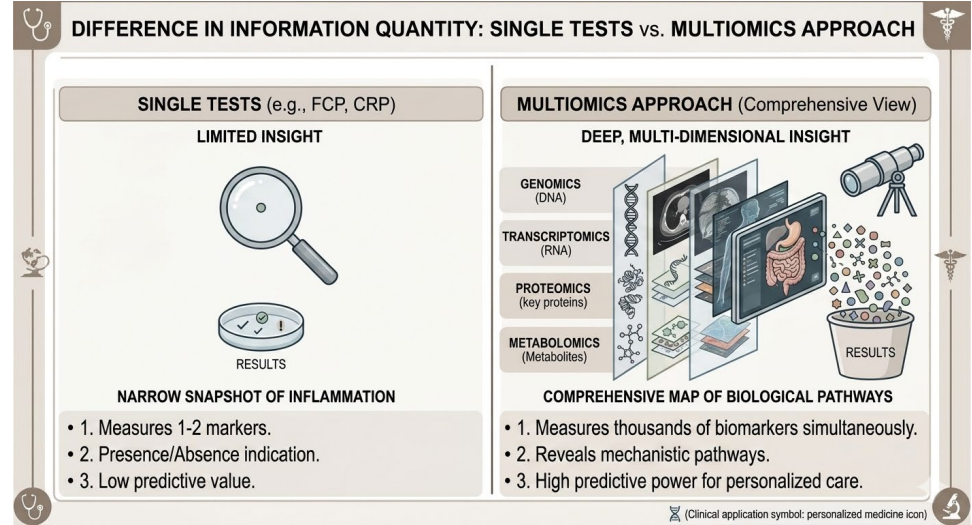
PROGNOSTIC BIOMARKERS: Predict patient outcomes accurately (e.g., a patient icon on a path to 'REMISSION' with a high probability value).

1. CRP and FCP are weakly linked to the biology of IBD
2. Multiomics outputs are strongly linked to the underlying biology—the “why” and “how” of IBD
3. This could tell us **which drug upfront and detect LOR early**

Multiomic Signatures, Early Warning, and High Volume of Signals



- Inflammation starts at a molecular level → symptoms
- Detecting it could give you much time to act!

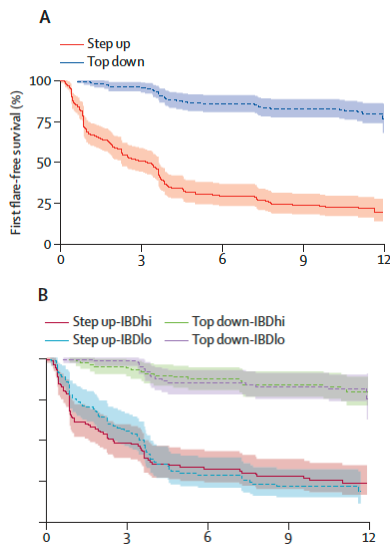


- Standard labs measure few data points or single values
- Multiomics measures thousands
- Uniquely suited to identify new treatment pathways

Back to The Clinic—What Is the Future of Biomarkers?

A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial

Nurulamin M Noor*, James C Lee*, Simon Bond, Francis Dowling, Brijana Brezina, Kamal V Patel, Tariq Ahmad, Paul J Barim, James W Barril, Rachel Cooney, Juan De La Revilla Negro, Shanika de Silva, Shahida Din, Dharmaraj Durai, John N Gordon, Peter M Irving, Matthew Johnson, Alexander J Kent, Klaartje B Kok, Gordon W Moran, Craig Mowat, Pritash Patel, Chris S Probert, Tim Raine, Rebecca Saich, Abigail Seward, Dan Sharpstone, Melissa A Smith, Sreedhar Subramanian, Sara S Upponi, Alan Wiles, Horace RT Williams, Gijis R van den Brink, Séverine Vermeire, Vipul Jairath, Goert R D'Haens, Eoin F McKinney, Paul A Lyons, James O Lindsay, Nicholas A Kennedy, Kenneth G C Smith, Miles Parkes, on behalf of the PROFILE Study Group†



ORIGINAL ARTICLE

Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulusokibart for Ulcerative Colitis

Bruce E. Sands, M.D., Brian G. Feagan, M.D.,
Laurent Peyrin-Biroulet, M.D., Ph.D., Silvio Danese, M.D., David T. Rubin, M.D.,
Olivier Laurent, Ph.D., Allison Luo, M.D., Deanna D. Nguyen, M.D.,
Jiandong Lu, Ph.D., Mark Yen, M.D., Jaroslaw Leszczyszyn, M.D., Ph.D.,
Radosław Kempirski, M.D., Ph.D., Dermot P.B. McGovern, M.D., Ph.D.,
Christopher Ma, M.D., Timothy E. Ritter, M.D., and Stephan Targan, M.D.,
for the ARTEMIS-UC Study Group*

1. PROFILE is a great study—early vs late treatment. It's a biomarker-stratified study.
2. Phase 2 TLA1—tuli—also a biomarker study
3. These are closer than you think!!!

Key Learning Points

- Primary non-response and loss of response remain issues even in the modern era
- CRP and FCP are good monitoring markers but are not effective predictive markers and have weaknesses as prognostic markers
- APCs and T cells are key targets of IBD medications—and targeting upstream pathways at the microbe-damage-APC interface is promising (TREM-1)
- Multiomics holds promise for predictive and prognostic biomarkers because it detects changes early and is linked to the biology of IBD

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