

Inflammatory Pathways in Immune-Mediated Diseases: What is downstream?

Canada Future Directions in IBD
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“Inflammatory Pathways in Immune-Mediated Diseases: What is downstream?”

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Disclosures of potential conflicts of interest:

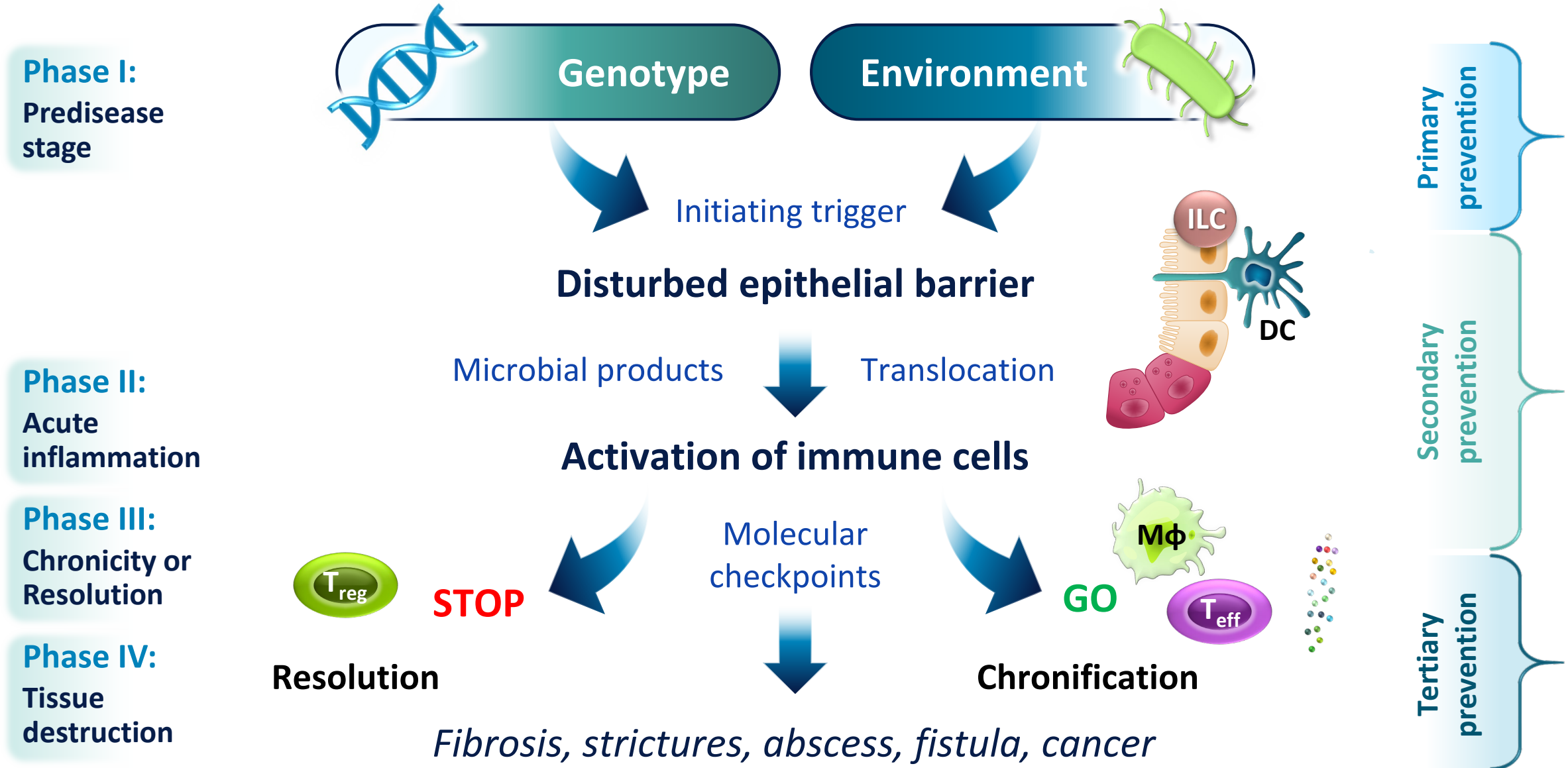
Grant:

Abbvie

Honoraria:

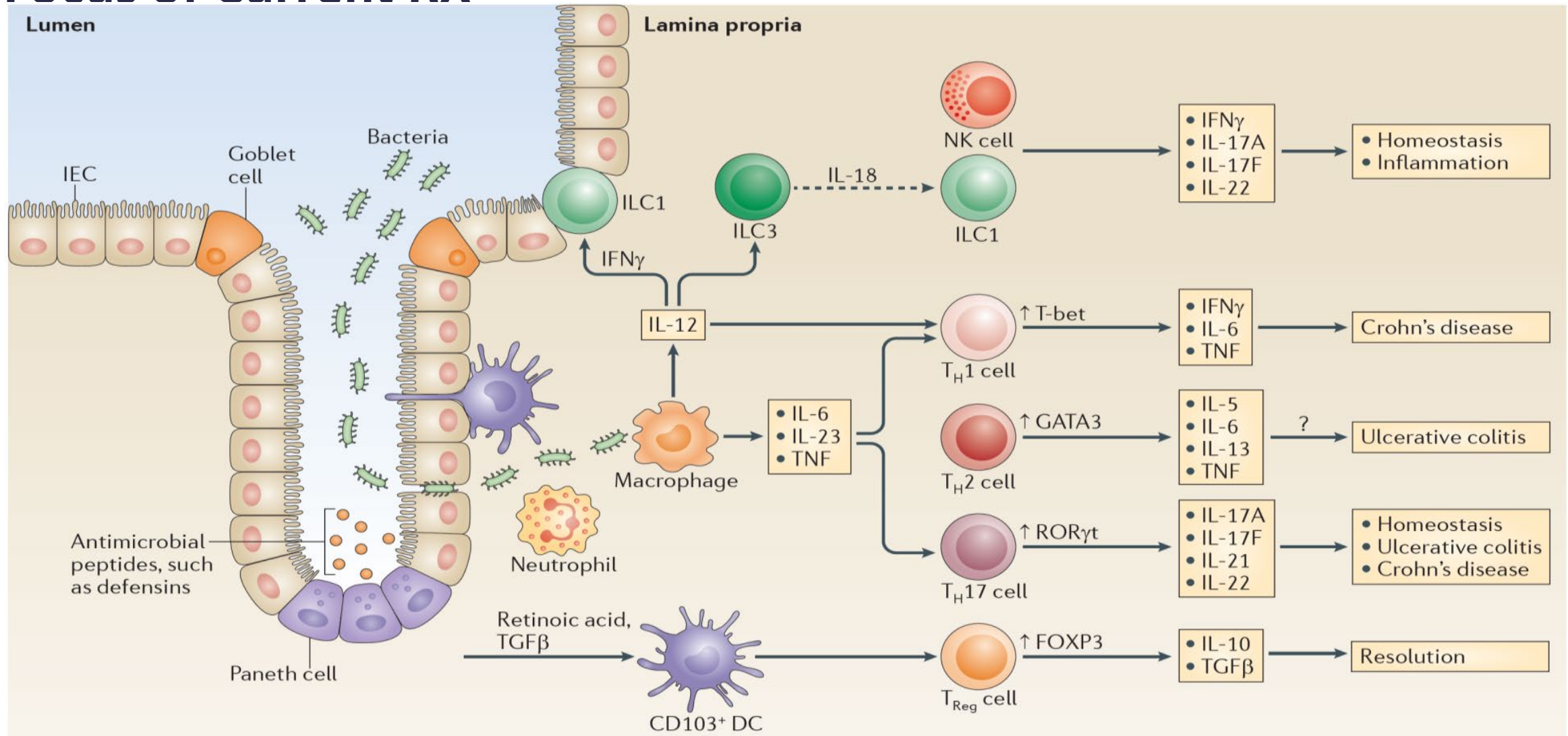
AbbVie, Boehringer Ingelheim, Ferring, Fresenius Kabi, Galapagos, Gilead, GlaxoSmithKline, InDex Pharmaceuticals, Janssen, Pandion Therapeutics, Pfizer, Takeda Pharma, Roche

Pathogenesis of IBD

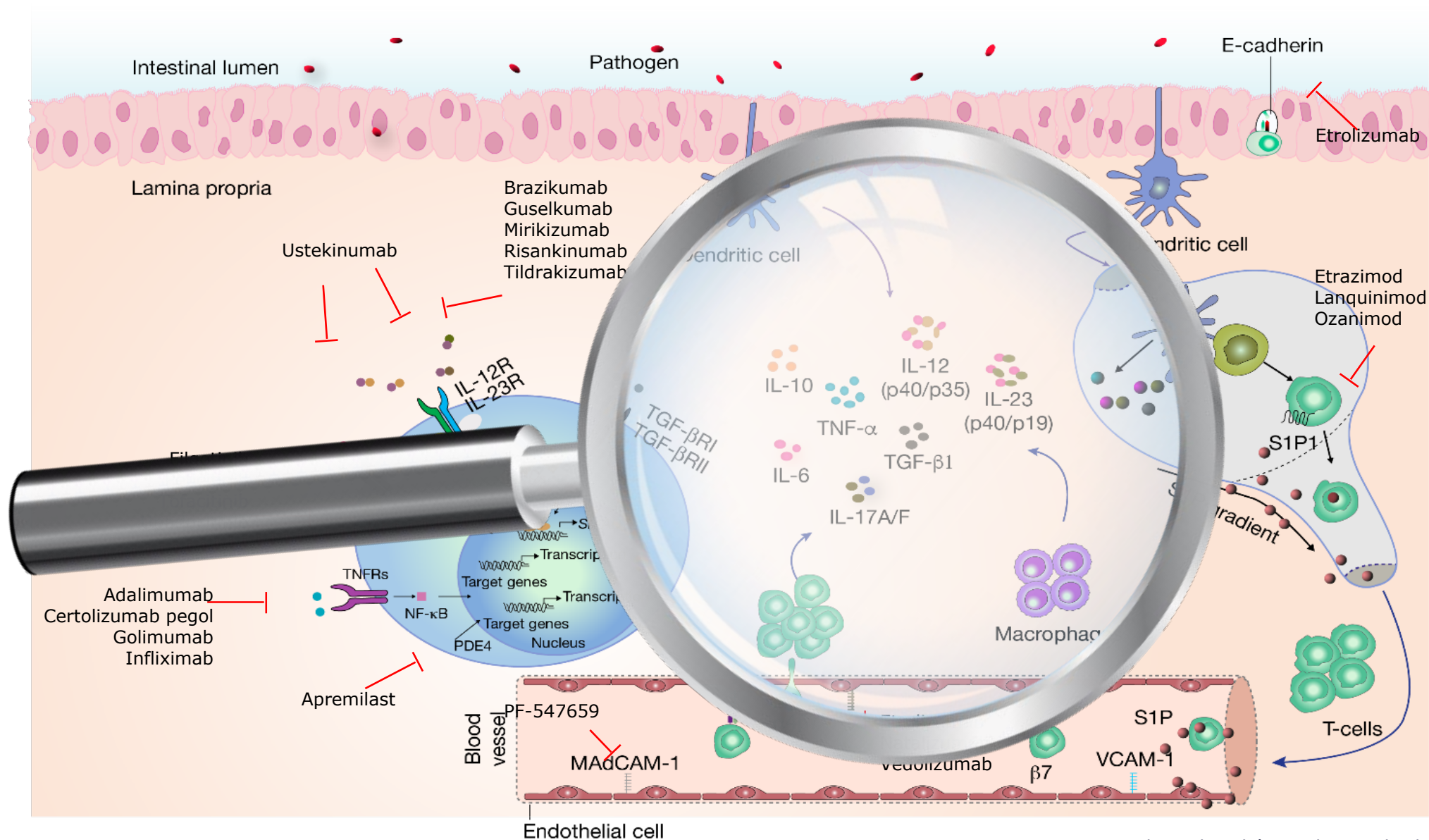


Multiple cytokines are involved in the pathogenesis of IBD

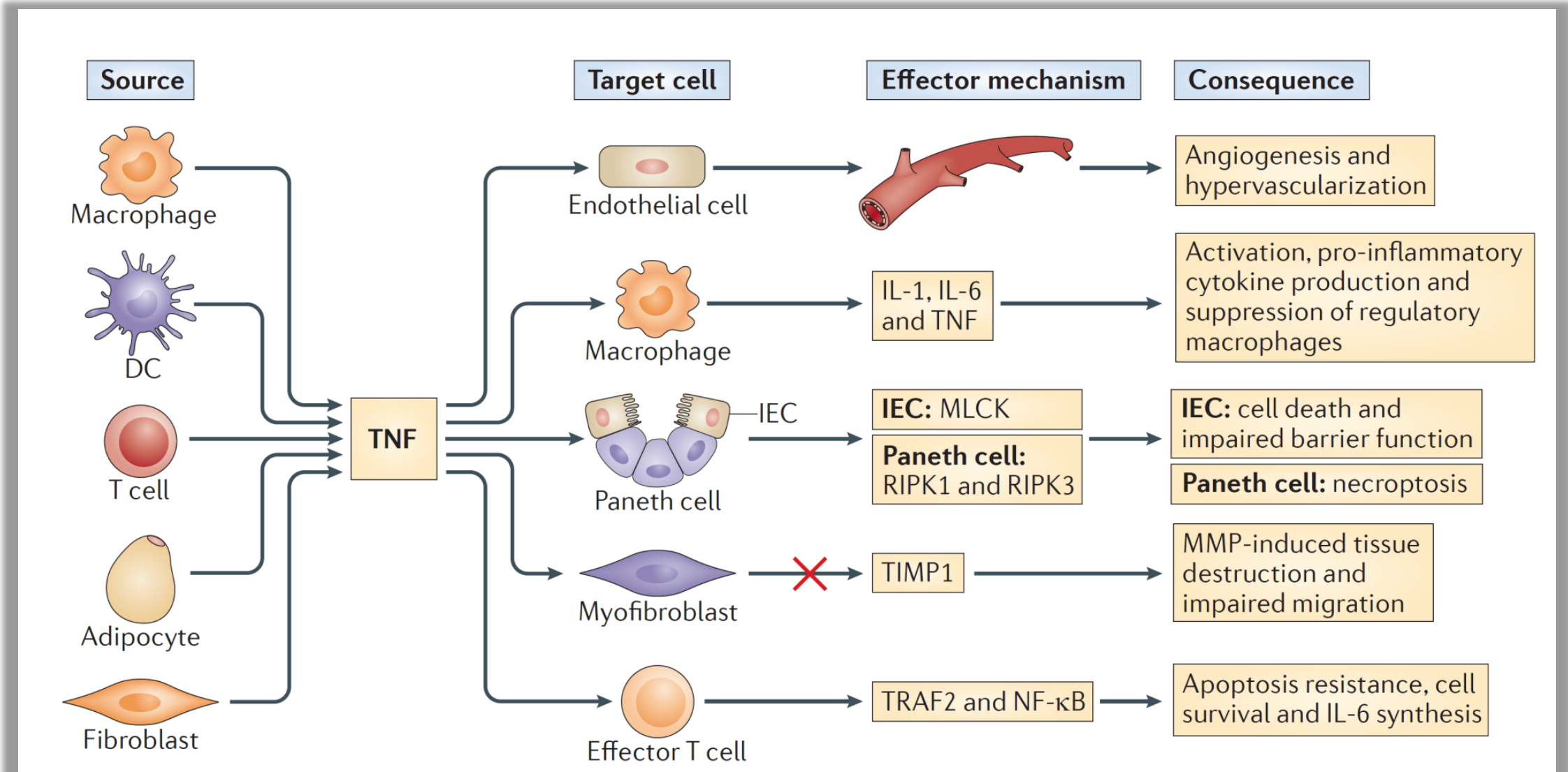
Focus of Current RX



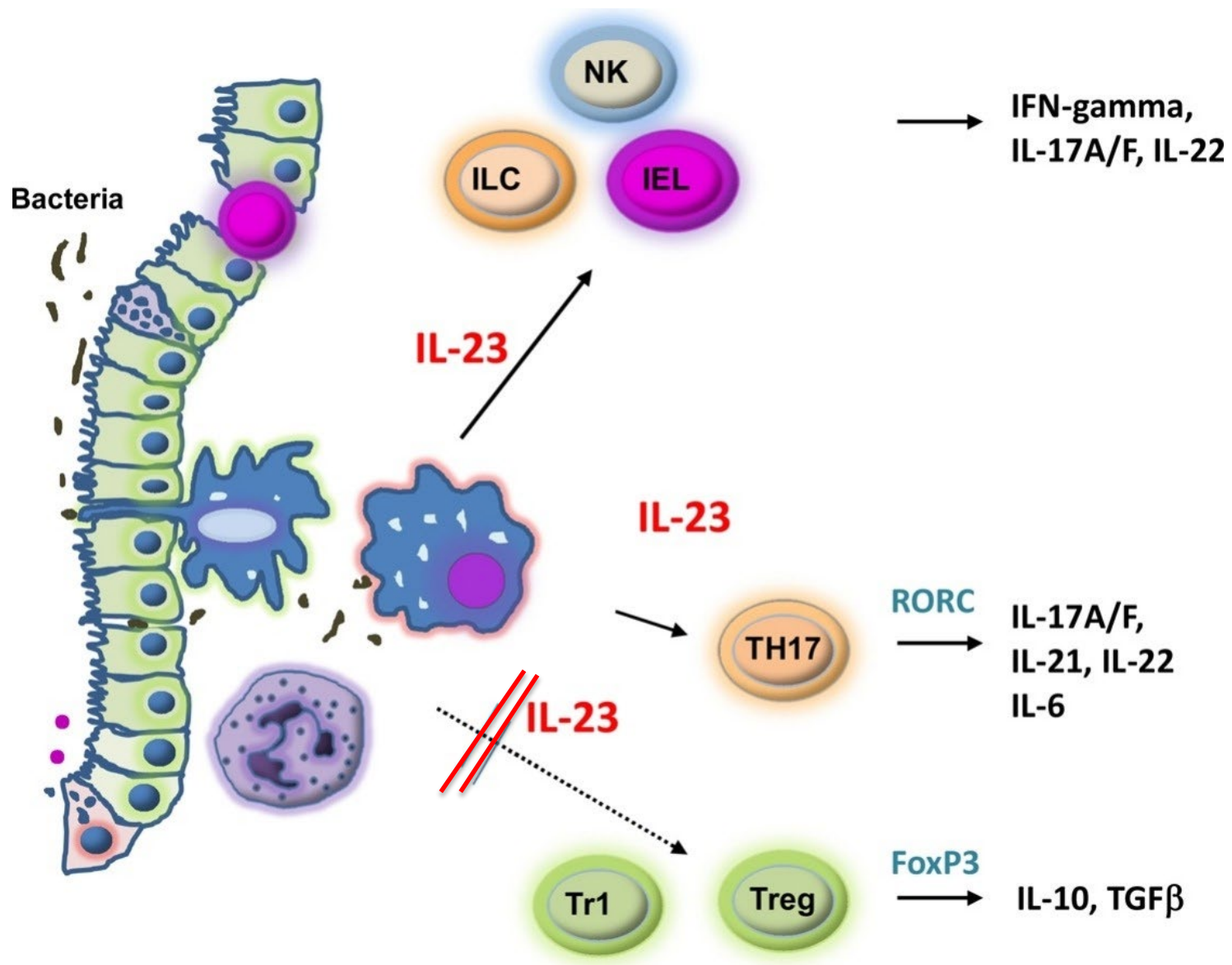
Immunopathogenesis of IBD and therapeutic targets



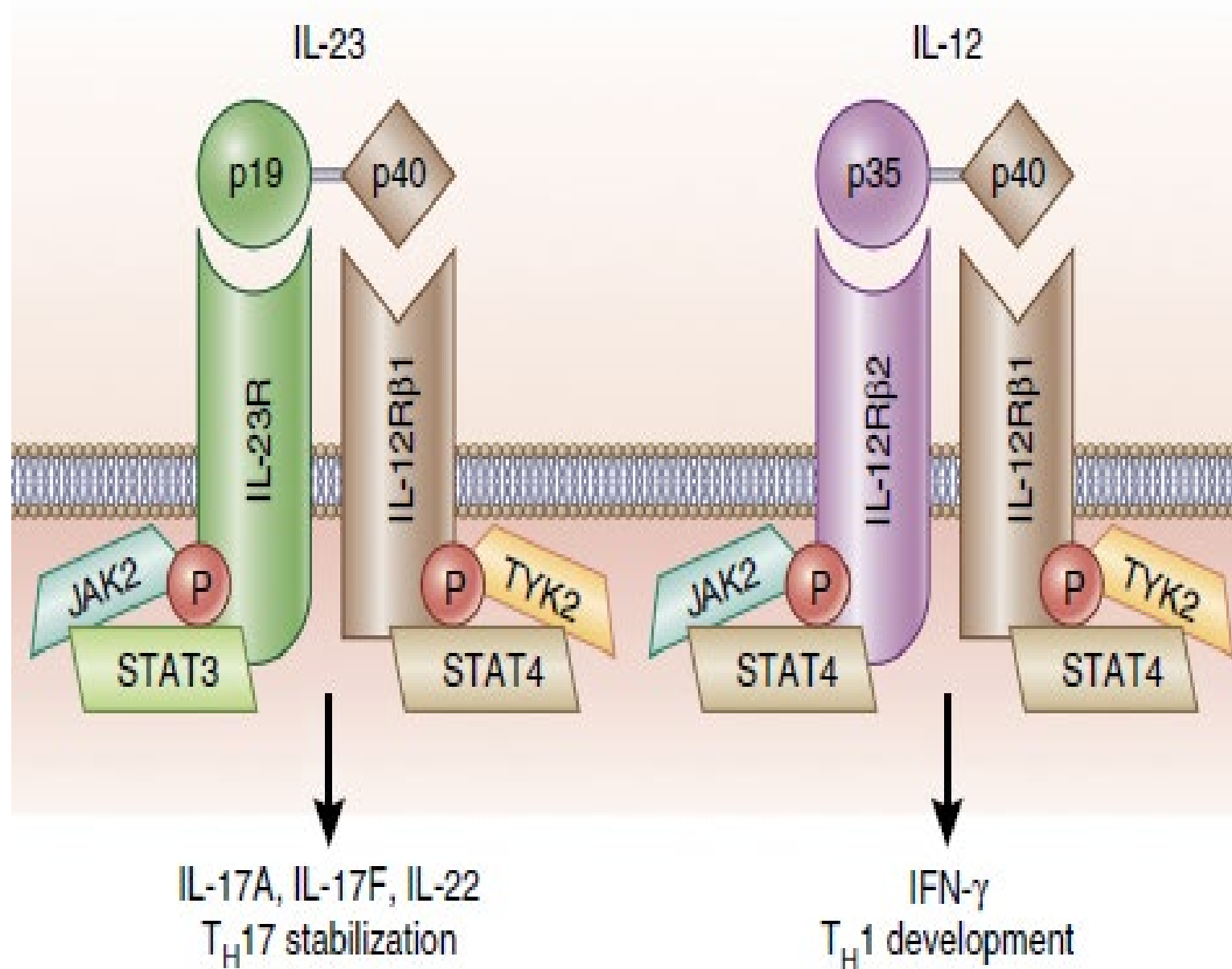
Central role of TNF in mediating inflammation



The pro-inflammatory role of IL-23 in IBD

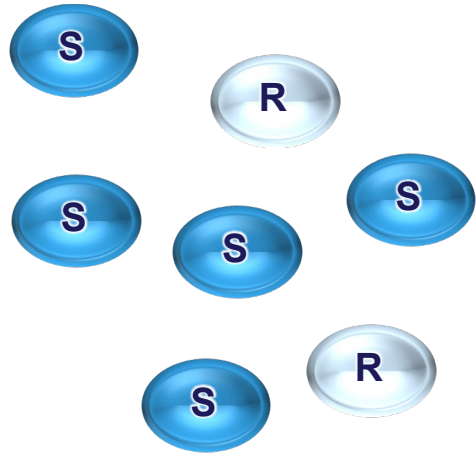


Differentiating the IL-23 from the IL-12 signaling pathway



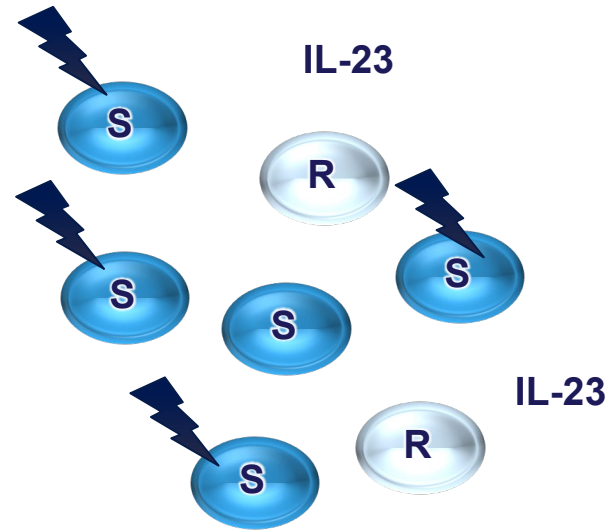
IL-23 mediates molecular resistance to anti-TNF therapy in CD

CD Immune T Cell Infiltrate



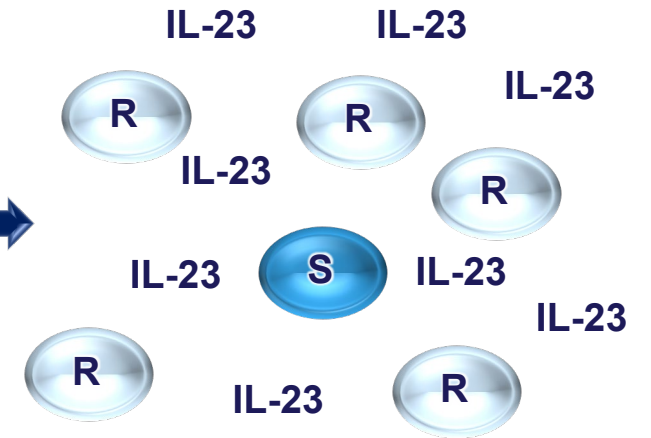
S: Anti-TNF sensitive mTNF⁺ Cell
R: Anti-TNF resistant IL-23R⁺ Cell

Anti-TNF Therapy



Induction Apoptosis
Selection Pressure

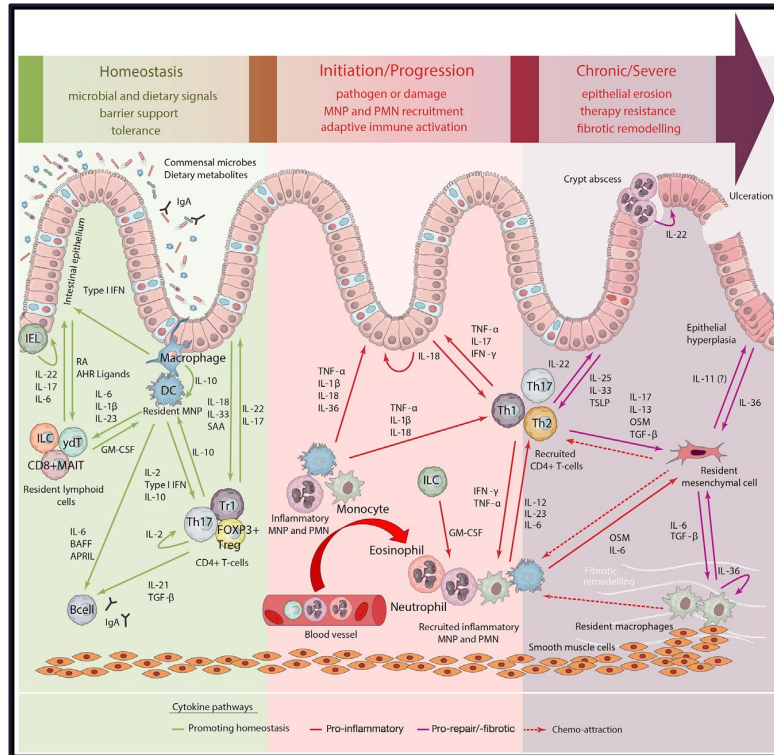
Molecular Resistance



Expansion IL-23R⁺ Cell
New Immunophenotype
Non-response anti-TNF

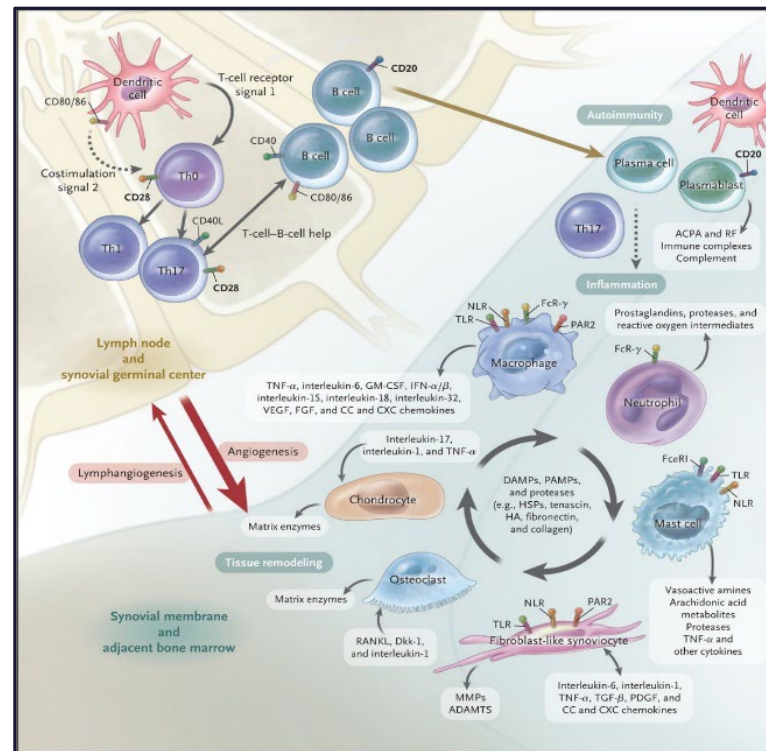
Cytokine networks fuel inflammation in the gut/joints/skin

GUT



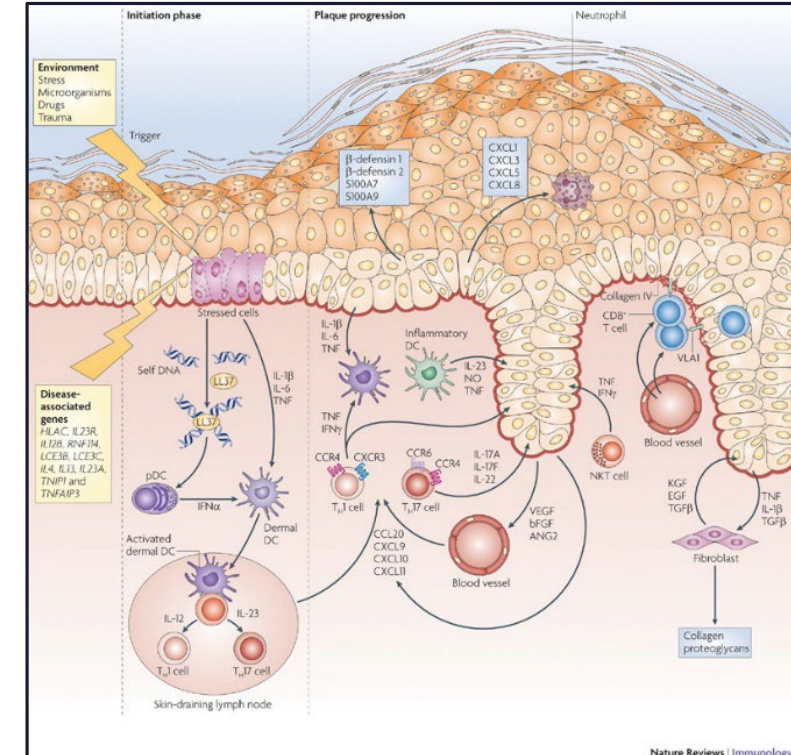
IBD

JOINTS



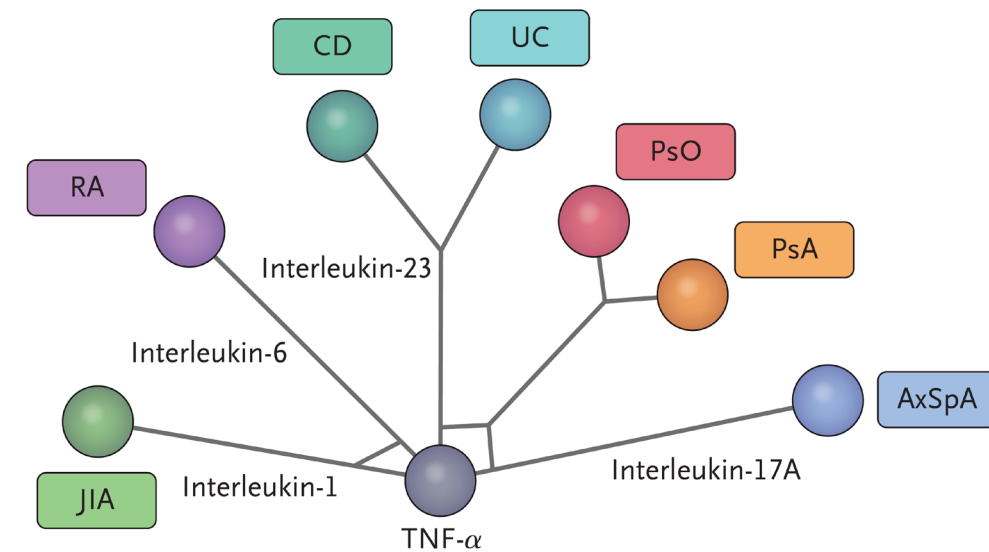
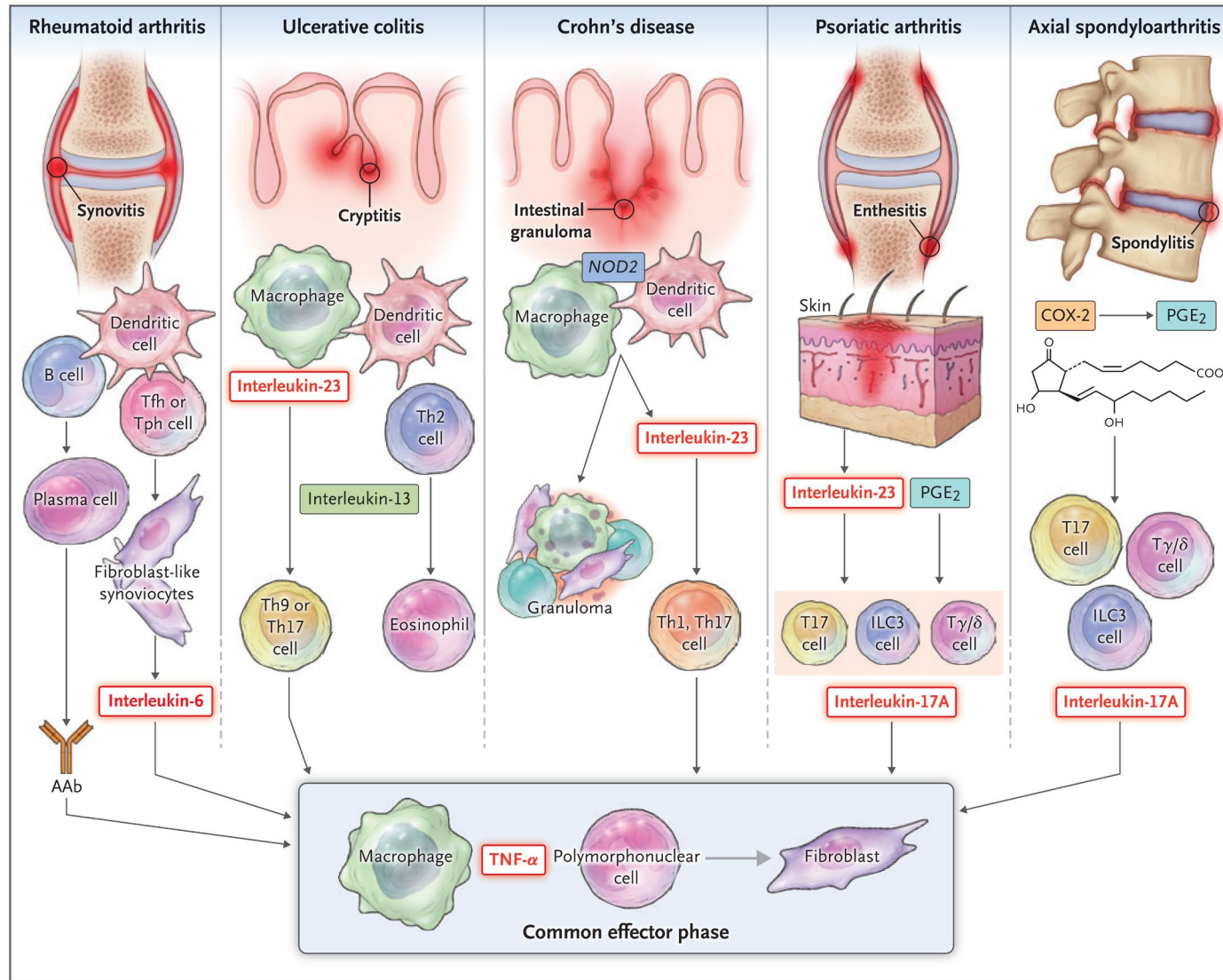
Rheumatoid arthritis

SKIN

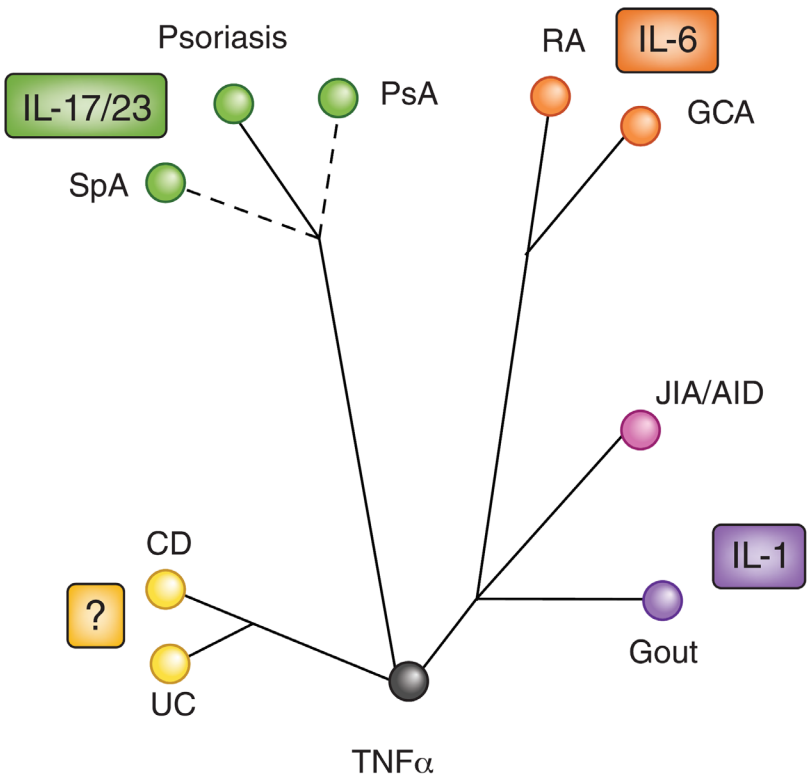


Psoriasis

Resolution of chronic inflammatory diseases: Universal and tissue-specific concepts



Resolution of chronic inflammatory diseases: universal and tissue-specific concepts



CID	TNF	IL-6R	IL-1	IL-12/23	IL-17A
Rheumatoid arthritis					
Giant cell arthritis					
JIA/AID					
Gout					
Crohn's disease					
Ulcerative colitis					
Psoriasis					
Psoriatic arthritis					
Ankylosing spondylitis					
Multiple sclerosis					

Drugs targeting this cytokine have EMA approval for this disease

Preliminary data on clinical efficacy

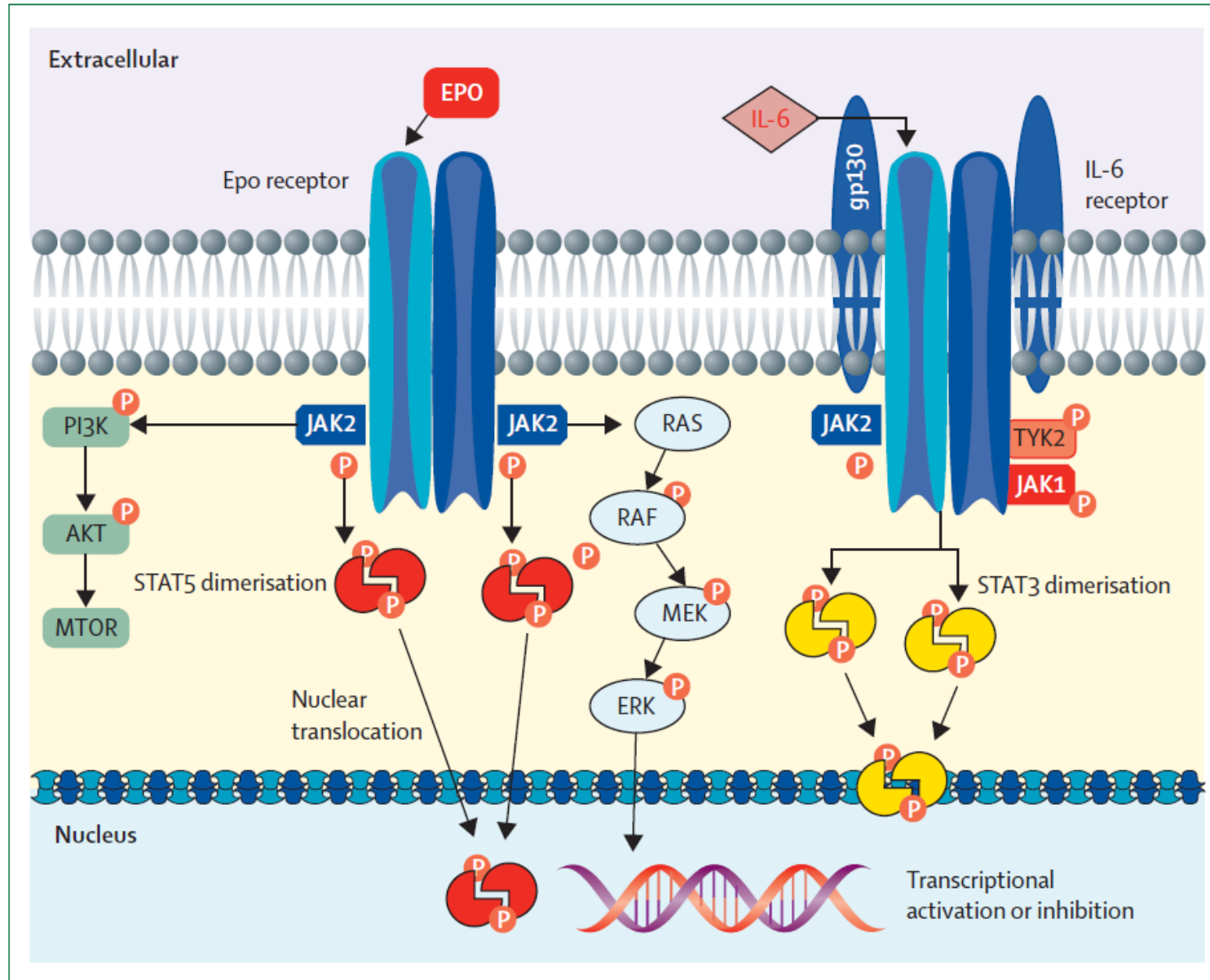
No/mild clinical efficacy or no data on efficacy

Disease-aggravating effect

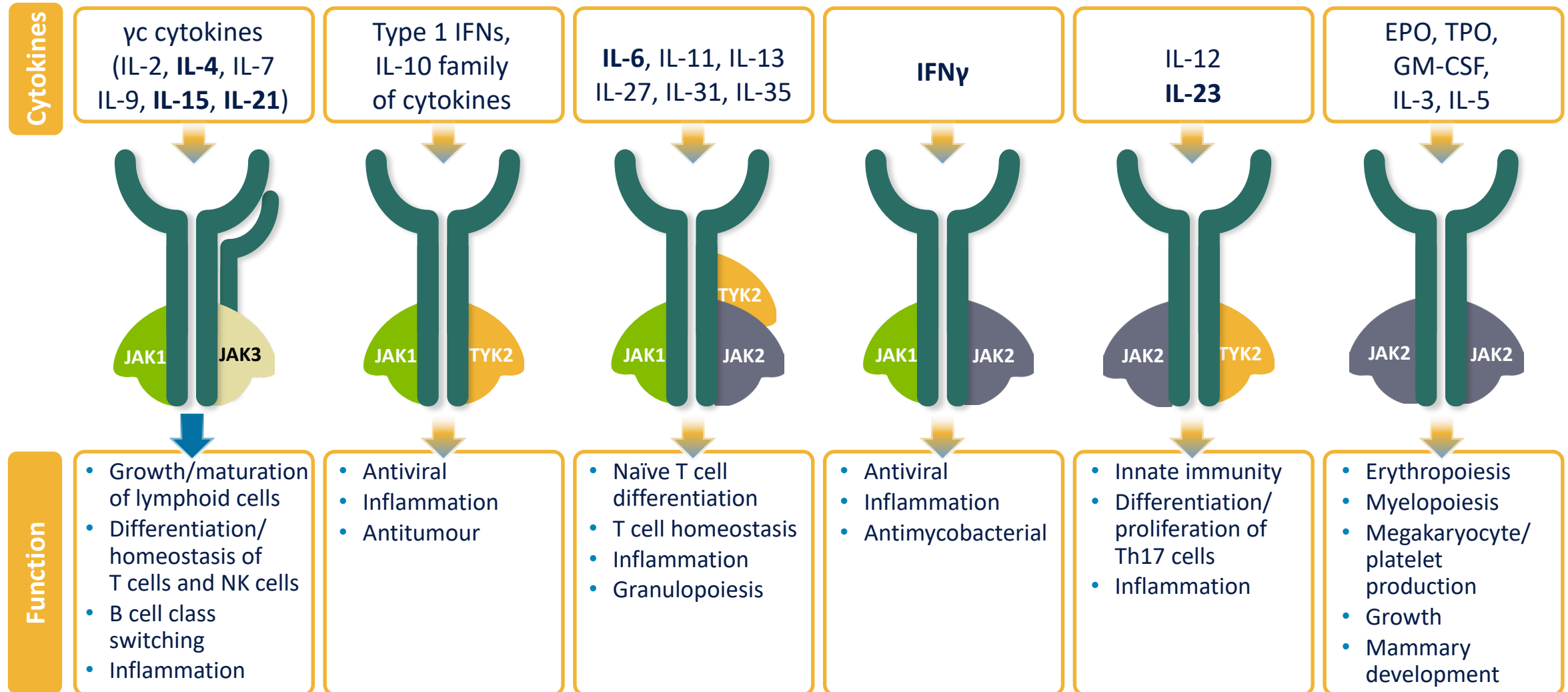
Cytokine inhibition of similar cytokine dependence



JAK-STAT signalling via EPO and IL6 receptors



Cytokines that signal via the JAK-STAT pathway have a multitude of functions



The Janus Kinase inhibitor Family of drugs

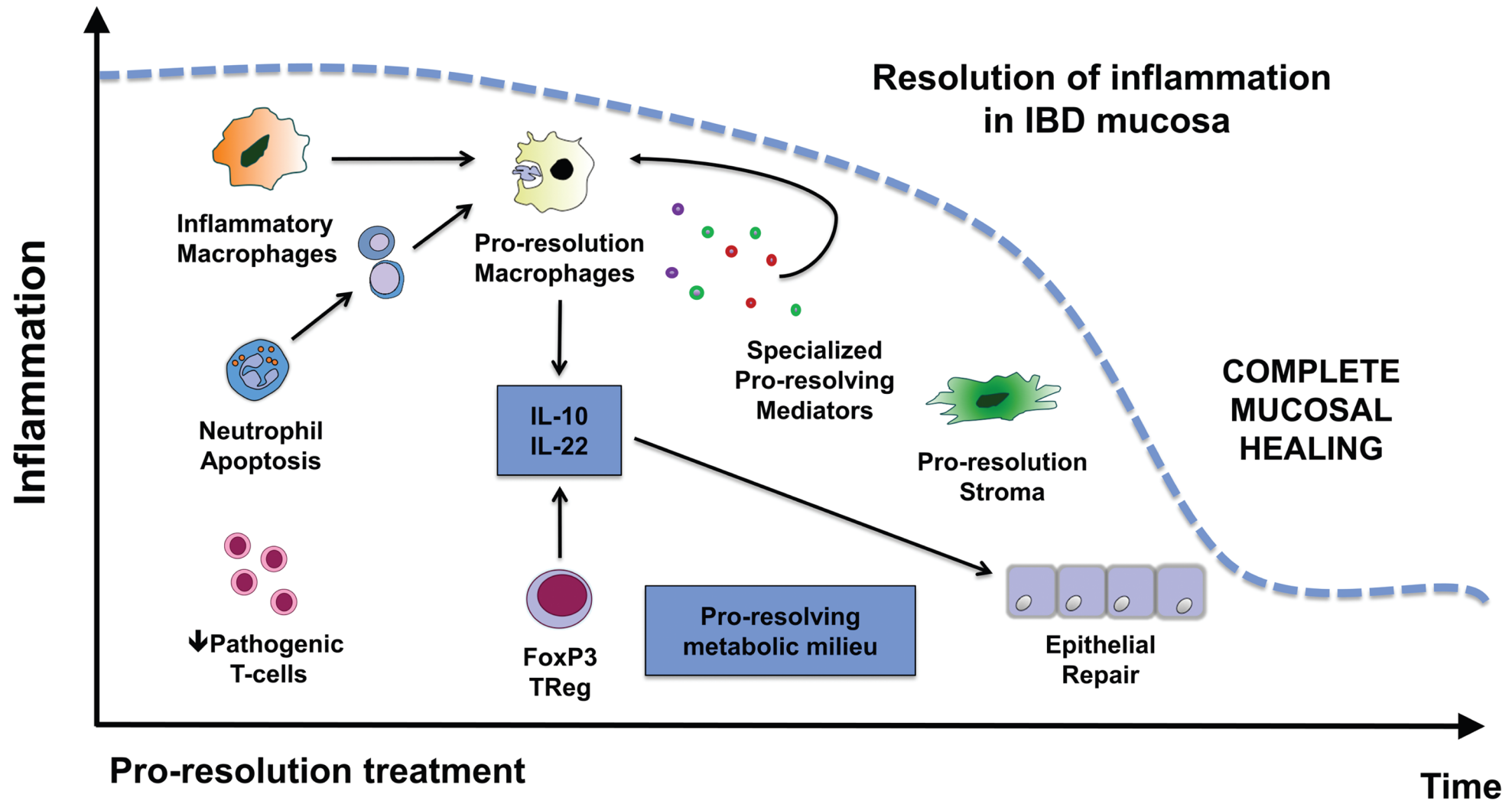
Panel 1: Drug selectivity profiles

Drug (suggested selectivity against Janus kinase [JAK] family members)

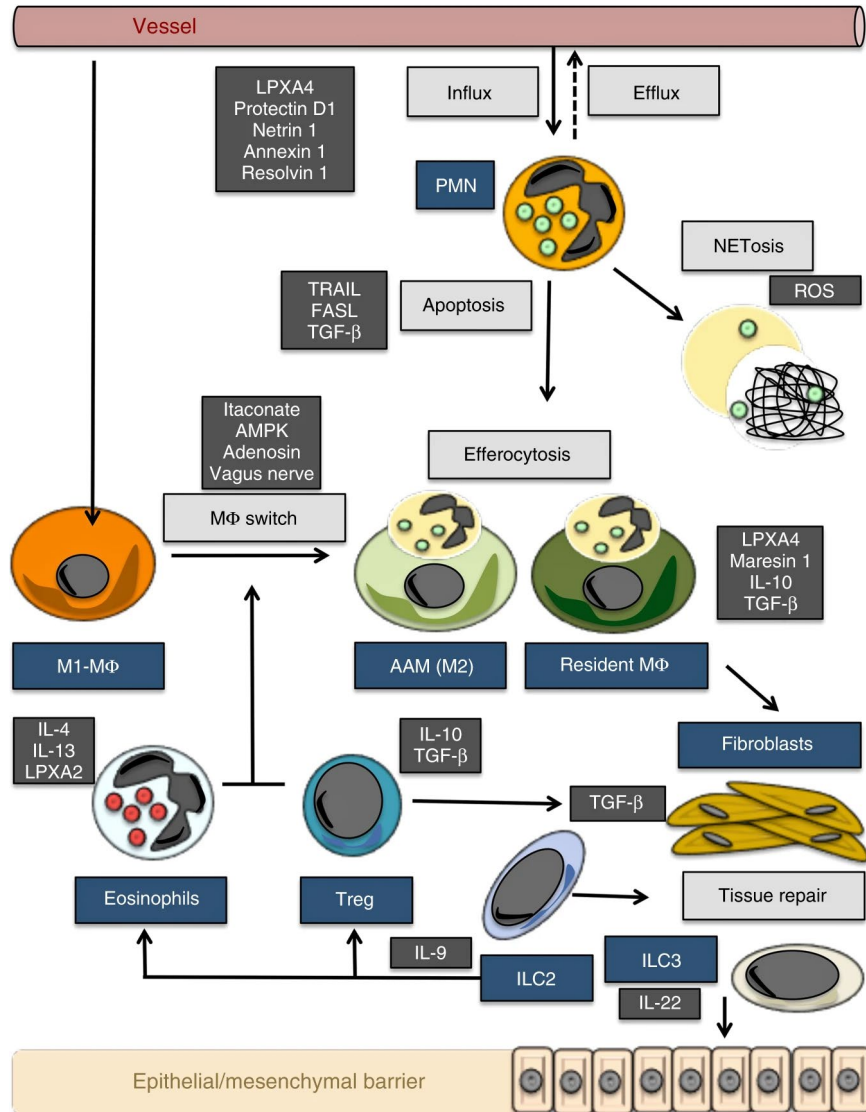
- Ruxolitinib (JAK1 and JAK2 > JAK3 > TYK2)
- Baricitinib (JAK1 and JAK2, and moderate activity against TYK2)
- Tofacitinib (JAK3 > JAK2 > JAK1)
- Fedratinib (JAK2)
- Momelotinib (JAK1 and JAK2)
- Pacritinib (JAK2 > JAK1 and JAK3)
- Fligotinib (JAK1 > JAK2 > JAK3 and TYK2)
- Upadacitinib (JAK1 > JAK2 and JAK3)
- Itacitinib (JAK1)
- Decernotinib (JAK3)
- Peficitinib (all JAK proteins)
- Deucravacitinib (BMS-986165; TYK2)
- Abrocitinib (JAK1)
- NDI-031301 (TYK2)
- Ritlecitinib (PF-06651600; JAK3)

Promoting resolution of inflammation in IBD

IS MUCOSAL HEALING an ATTAINABLE GOAL OF Rx?



Targeting interconnected mechanisms of resolution



Targeting immune cell recruitment

Clearance of inflammatory cells

Neutrophil death and removal

Modulating macrophage function to proresolving

Exploiting proresolving macrophage products

Promoting proresolving immune cells

Accelerating epithelial cell growth/regeneration

Clearance of the inciting stimuli

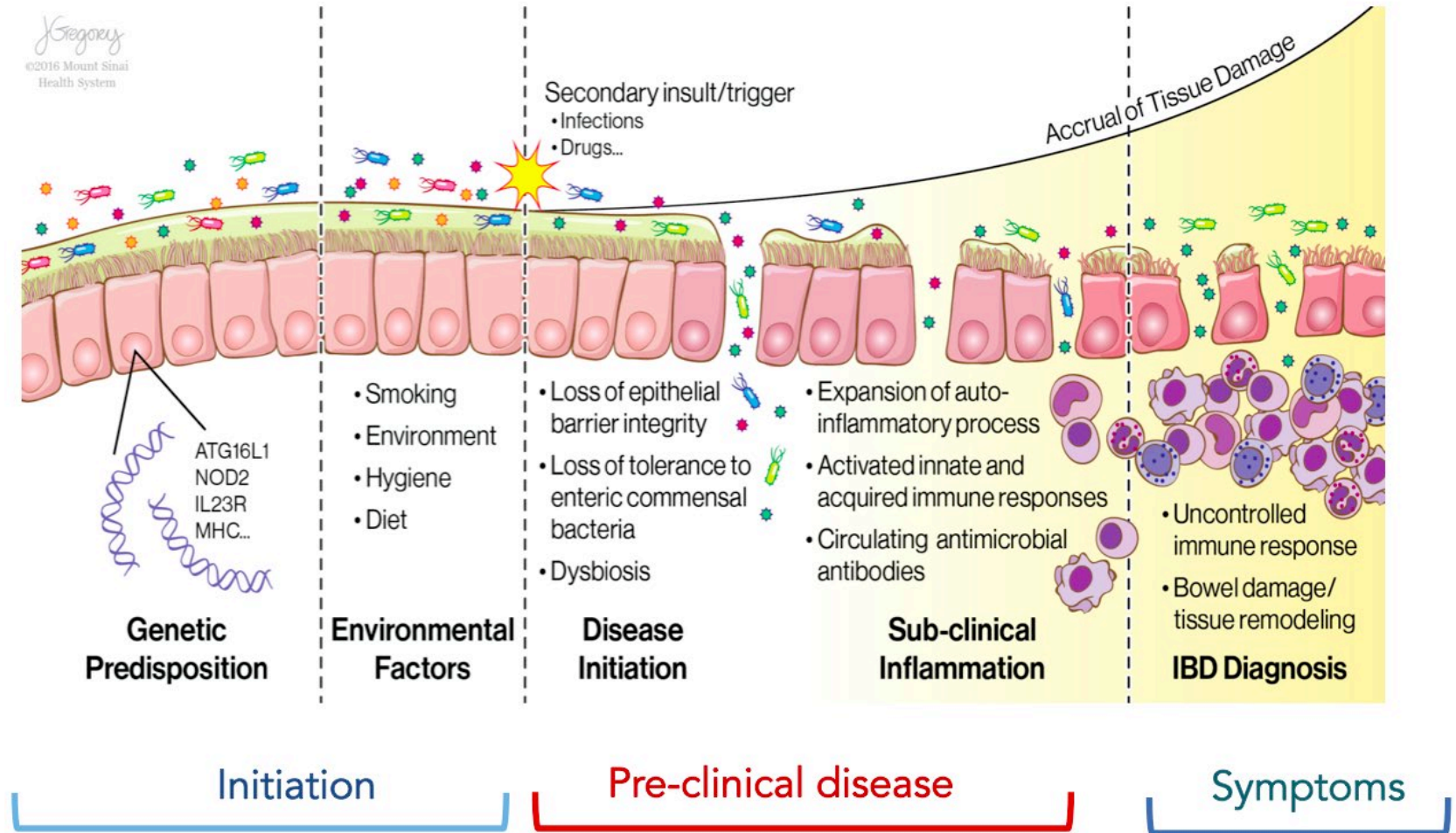
Pre-Disease Continuum of Crohn's Disease

What are EVENTS that precede disease?

Which are/is Trigger?

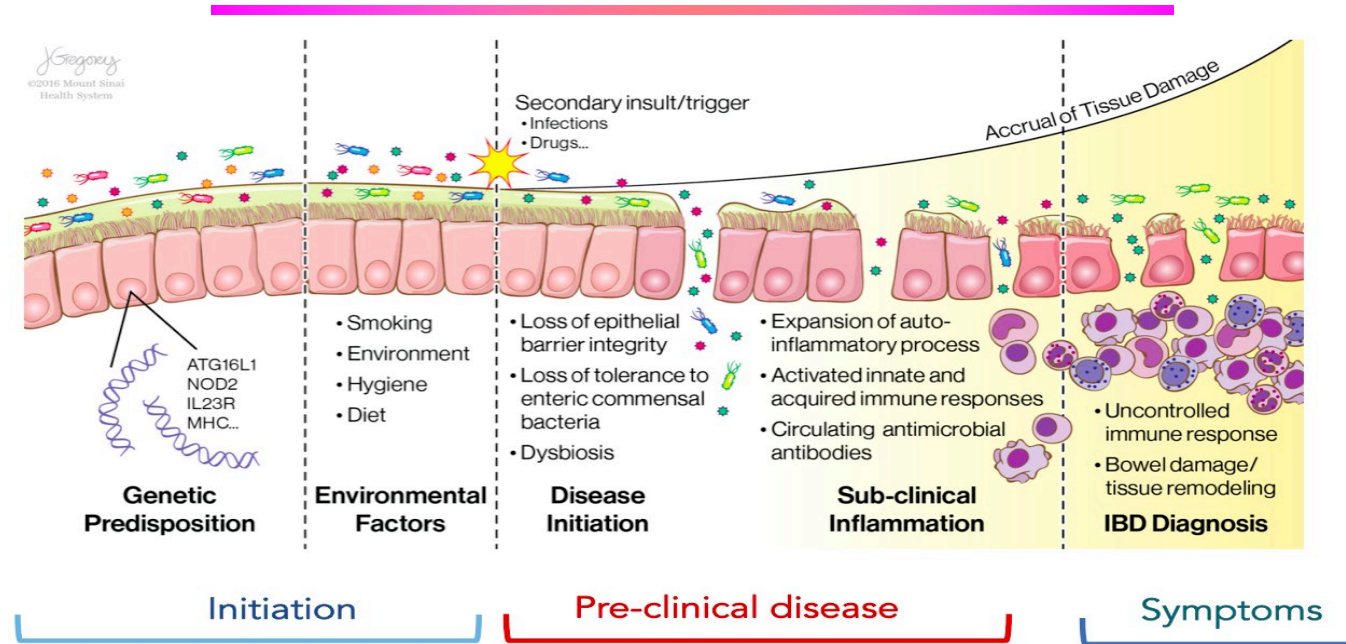
What is timing of these EVENTS?

What is relationship and interactions between EVENTS?



Pre-Disease Continuum of Crohn's Disease

Timing and Interaction of Biomarkers



Torres et al Gut 2016





Thank You