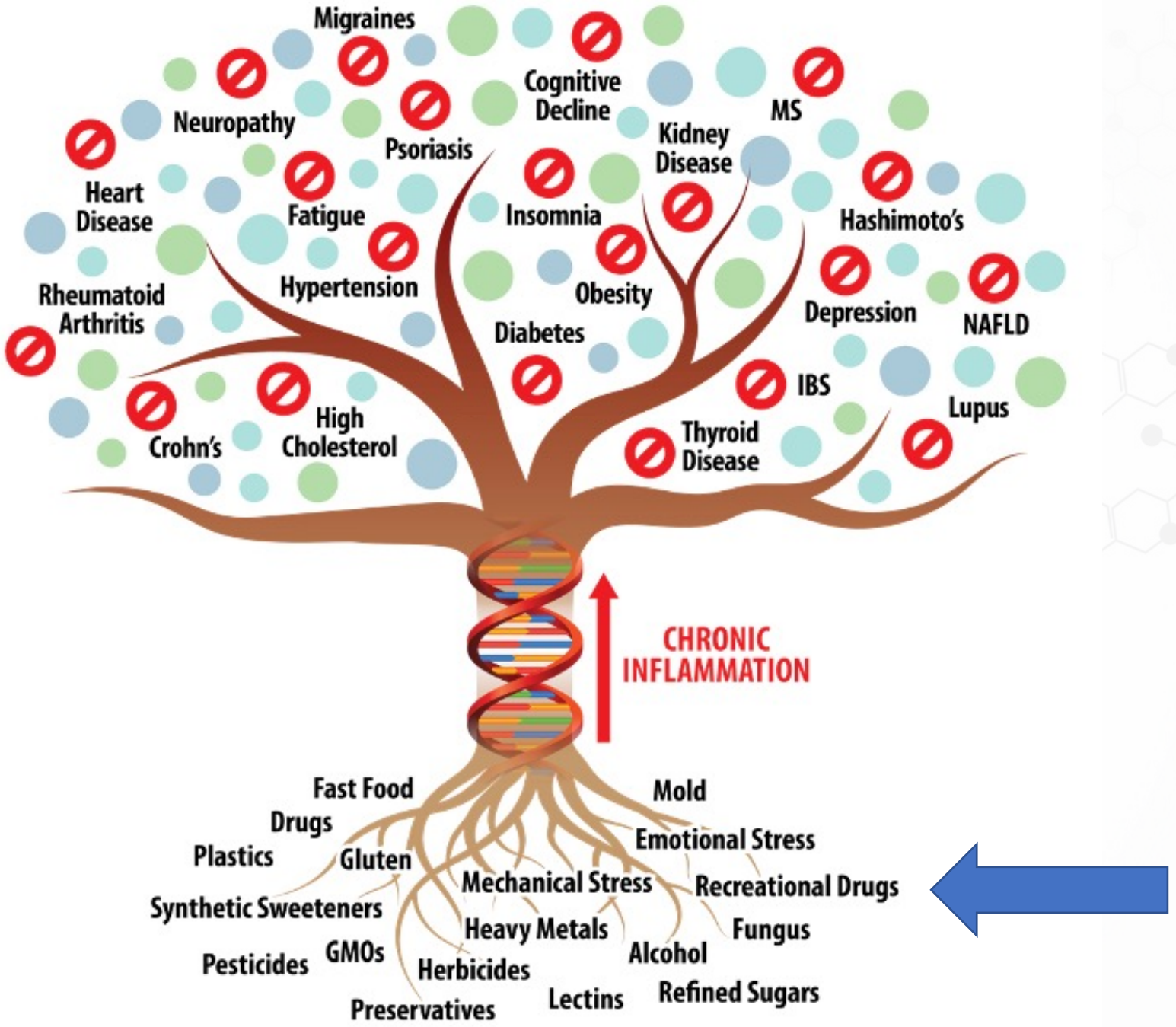
IBD and the Functional Provider Pt I

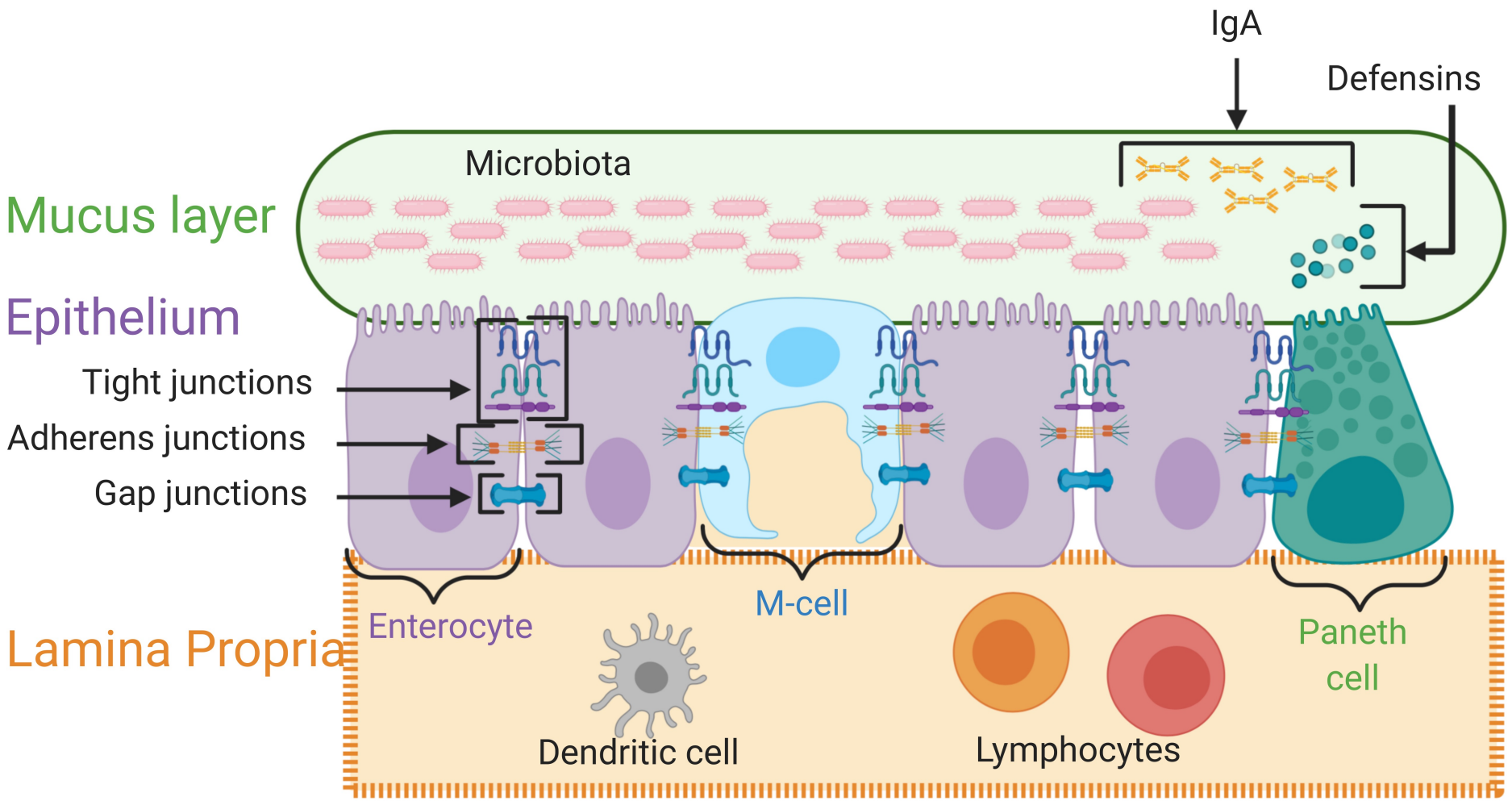
A Biogenetix Clinical Presentation

BIOGENETIX.COM

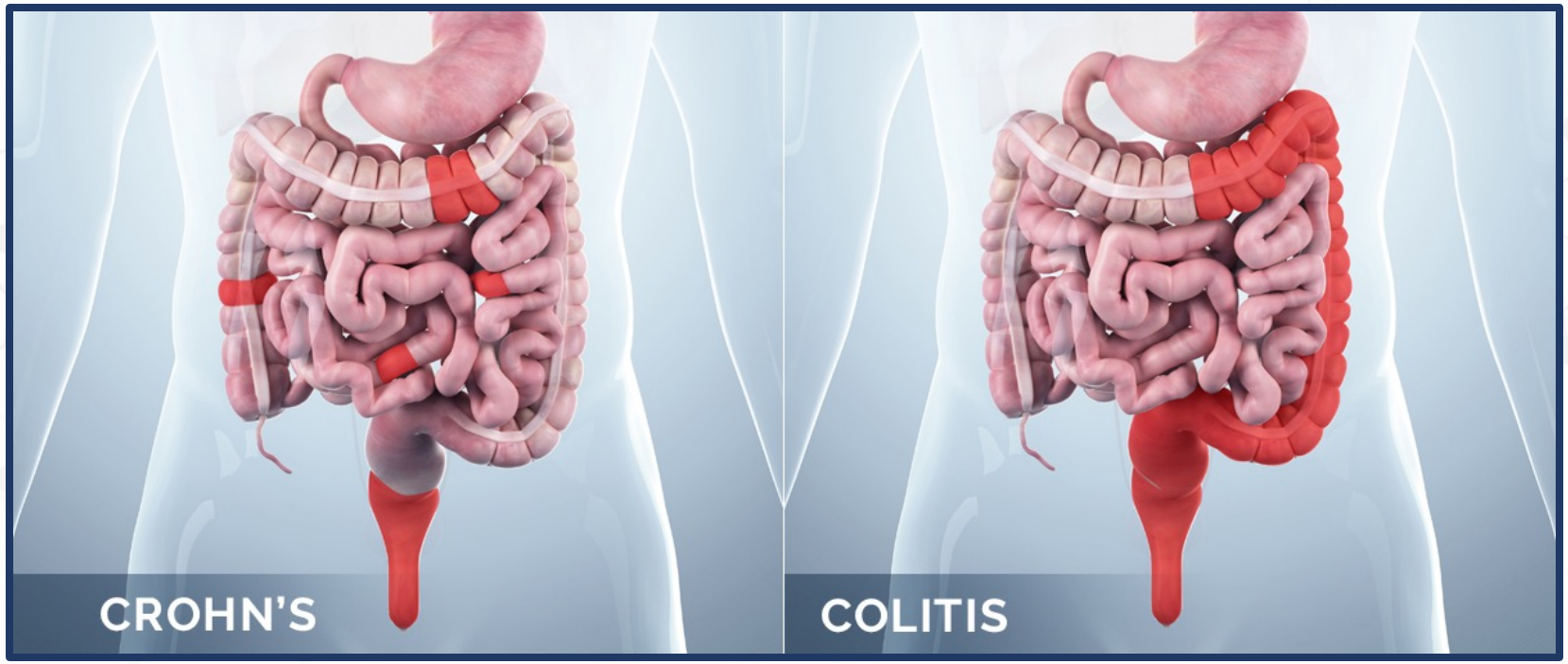
Disclaimer

- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives



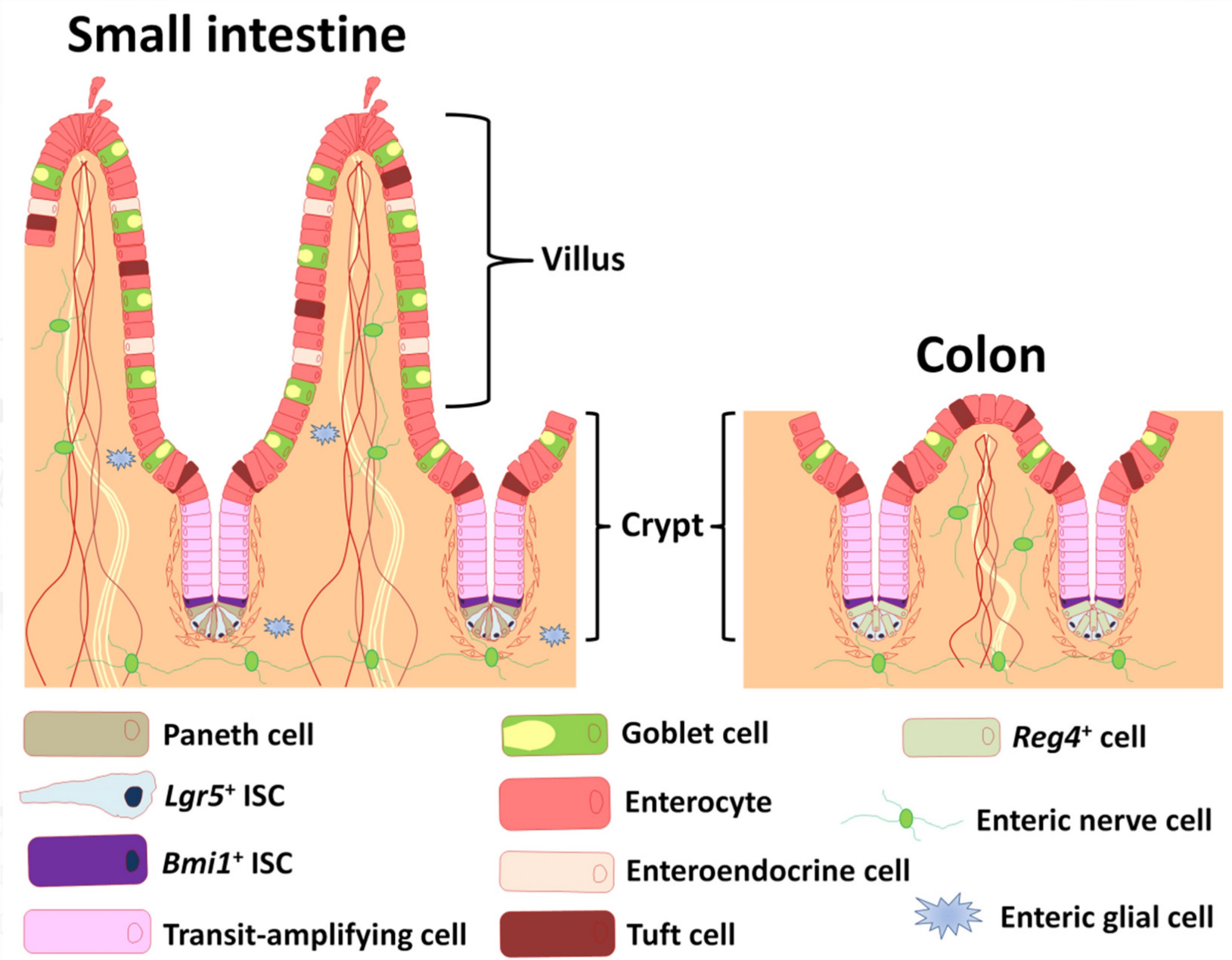
https://www.mdpi.com/microorganisms/microorganisms-08-01744/article_deploy/html/images/microorganisms-08-01744-g001.png



https://healthmatters.nyp.org/wp-content/uploads/2019/05/crohns-colitis-hero-2.jpg

	Crohn' disease	Ulcerative colitis
Common site	Terminal ileum	Rectum
Distribution	Mouth to anus	Rectum
Spread	Discontinuous	Continuous
Gross feature	Focal aphthous ulcer with intervening normal mucosa, linear fissures, cobblestone appearance, thickened bowel wall, creeping fat.	Extensive ulceration pseudopolyps.
Microscopy	Non-caseating granulomas	Crypt abscesses
Inflammation	Transmural	Limited to mucosa and sub-mucosa
Complications	Strictures, string sign on barium studies, abscesses, sinus tract, obstruction, fistulas	Toxic megacolon
Extraintestinal manifestations	Uncommon	Arthritis, spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum
Cancer risk	1-3%	5-25%

https://www.researchgate.net/publication/332098556/figure/tbl1/AS:742174392070145@1553959572389/Differences-between-Crohns-disease-and-ulcerative-colitis.png



https://www.mdpi.com/1422-0067/22/20/10912

Revisiting Inflammatory Bowel Disease: Pathology, Treatments, Challenges and Emerging Therapeutics Including Drug Leads from Natural Products

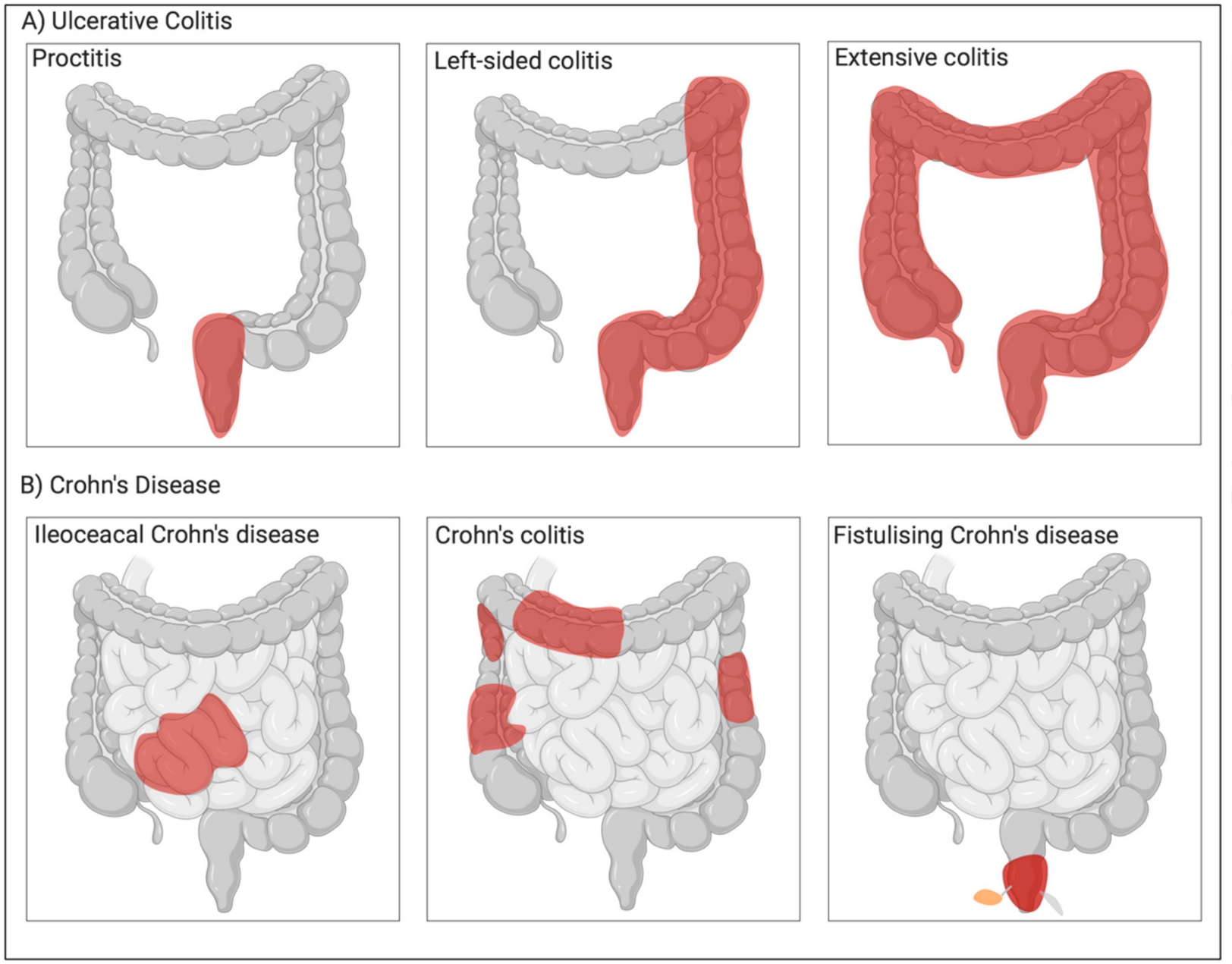
by Karma Yeshi [1], Roland Ruscher [1], Luke Hunter [2], Norelle L. Daly [1], Alex Loukas [1] and Phurpa Wangchuk [1,*]

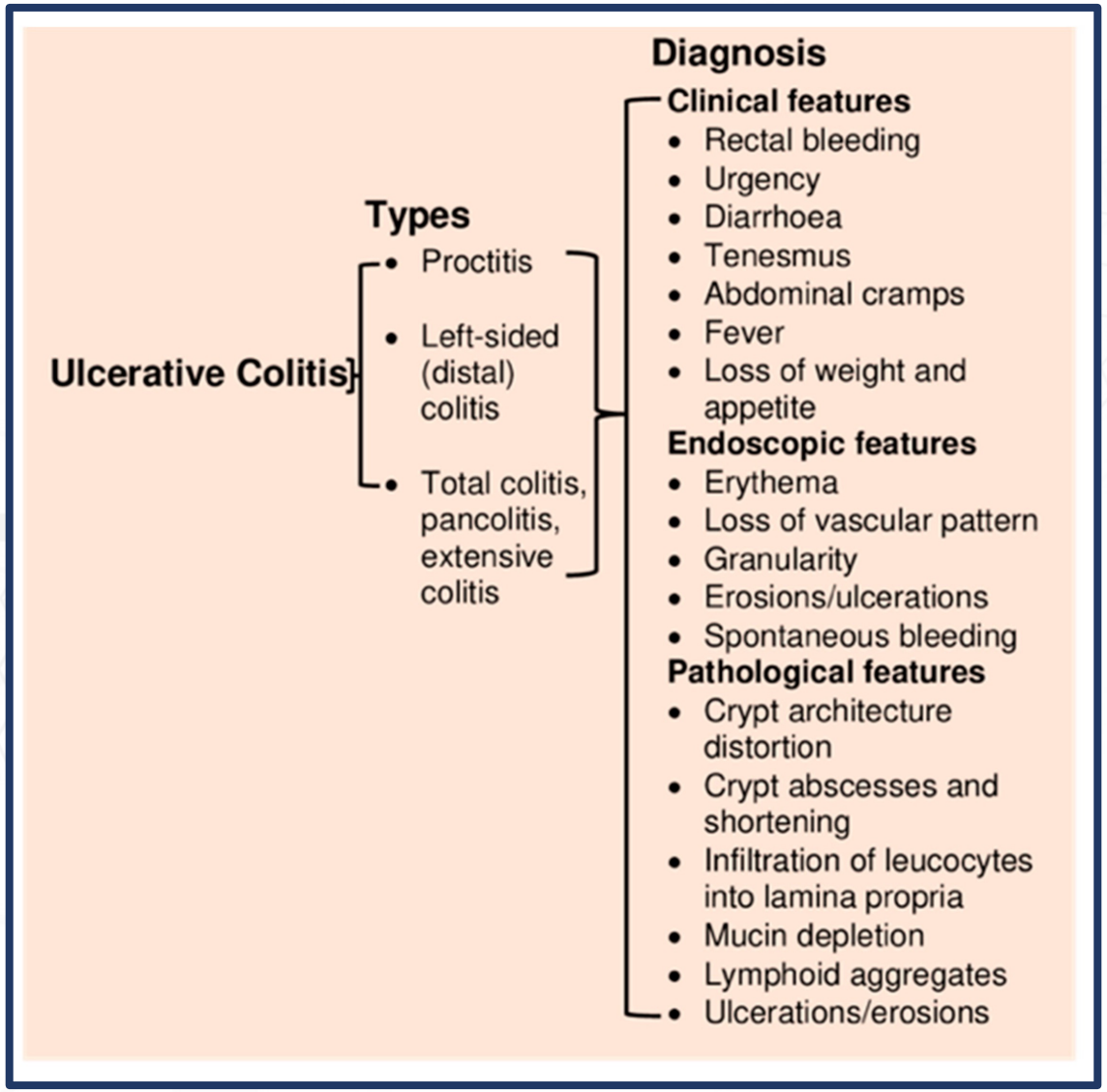
[1] Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, James Cook University, Cairns QLD 4878, Australia

[2] School of Chemistry, University of New South Wales (UNSW), Sydney NSW 2052, Australia

* Author to whom correspondence should be addressed.

Both CD and UC show heterogeneity in many clinical and pathological features. They are distinguishable by their location and nature of inflammation (**Figure 1**). Unlike UC, which attacks colonic mucosa, CD can affect any part of the gastrointestinal (GI) tract [23]. Both conditions share clinical features like extra-intestinal manifestation, but hematochezia and passage of mucus or pus are common only in UC. Fistulas, perianal disease, colonic and small bowel obstruction is common in CD. Cryptitis and crypt abscesses are observed in both UC and CD, while crypt architecture is more distorted in the case of UC [24]. Both UC and CD show relapsing intestinal inflammation. Intermediate colitis (IC) sometimes does not present distinct clinical features of either UC or CD, particularly in colectomy specimens, rendering it hard to distinguish UC from CD. Although IC is not a unique disease or distinct clinical entity, it accounts for around 10% of the total IBD cases involving the colon [25], and this figure has not changed over the last 30 years [26]. Currently, IC is usually diagnosed when a distinction between UC and CD becomes difficult. A standard positive diagnostic test for IC is not yet available.

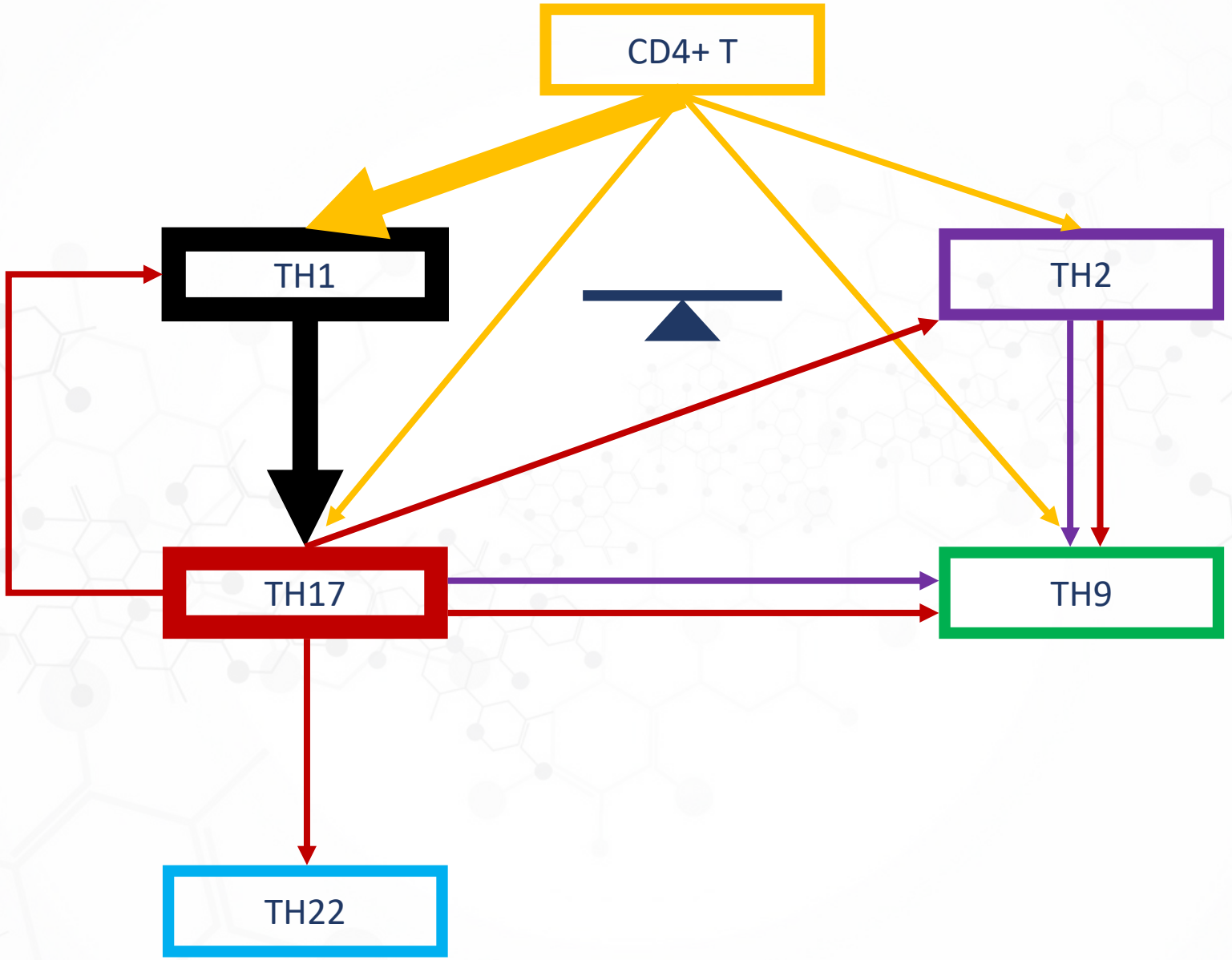


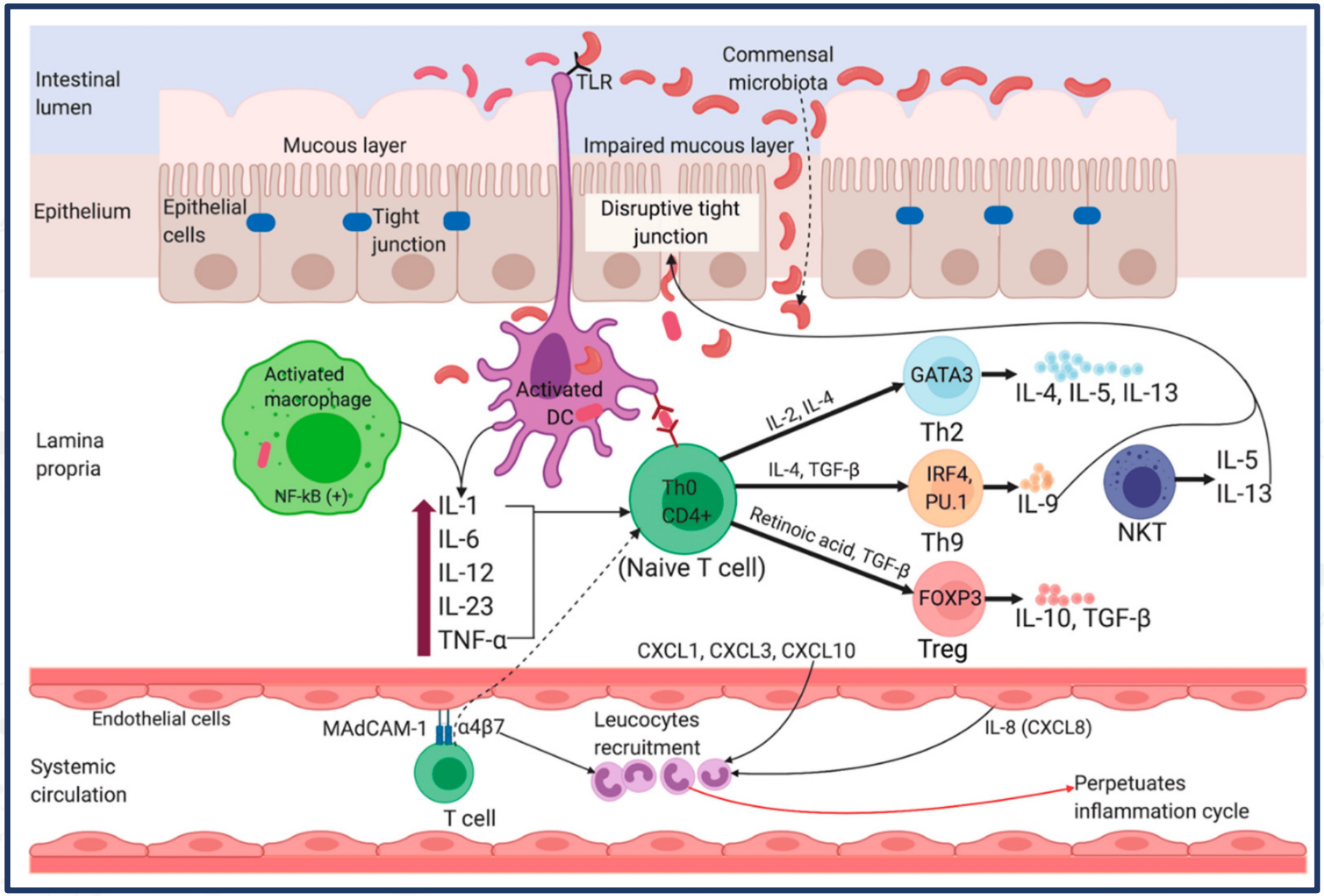


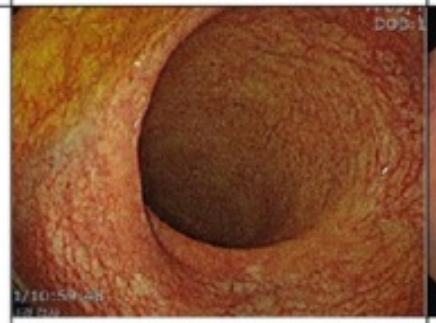
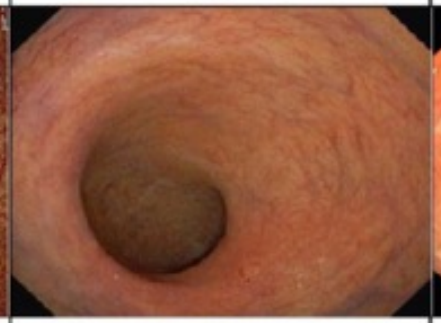
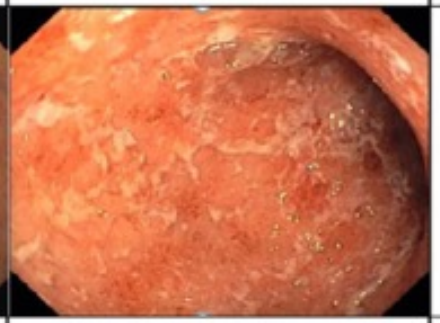
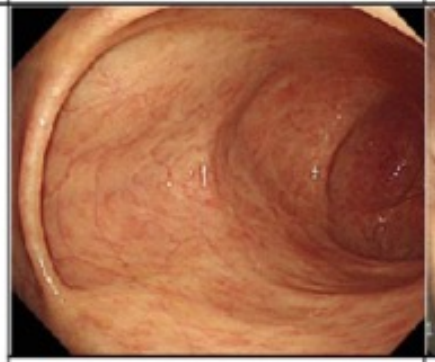
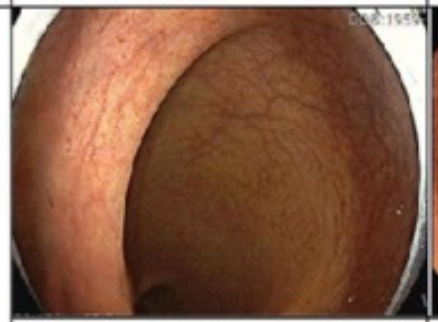
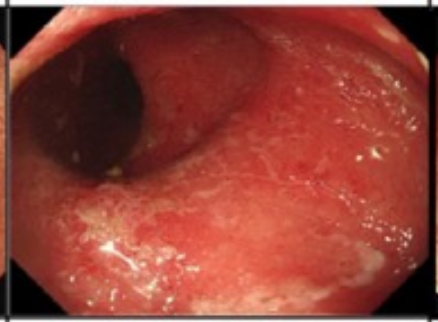
Revisiting Inflammatory Bowel Disease: Pathology, Treatments, Challenges and Emerging Therapeutics Including Drug Leads from Natural Products

by Karma Yeshi [1], Roland Ruscher [1], Luke Hunter [2], Norelle L. Daly [1], Alex Loukas [1] and Phurpa Wangchuk [1,*]

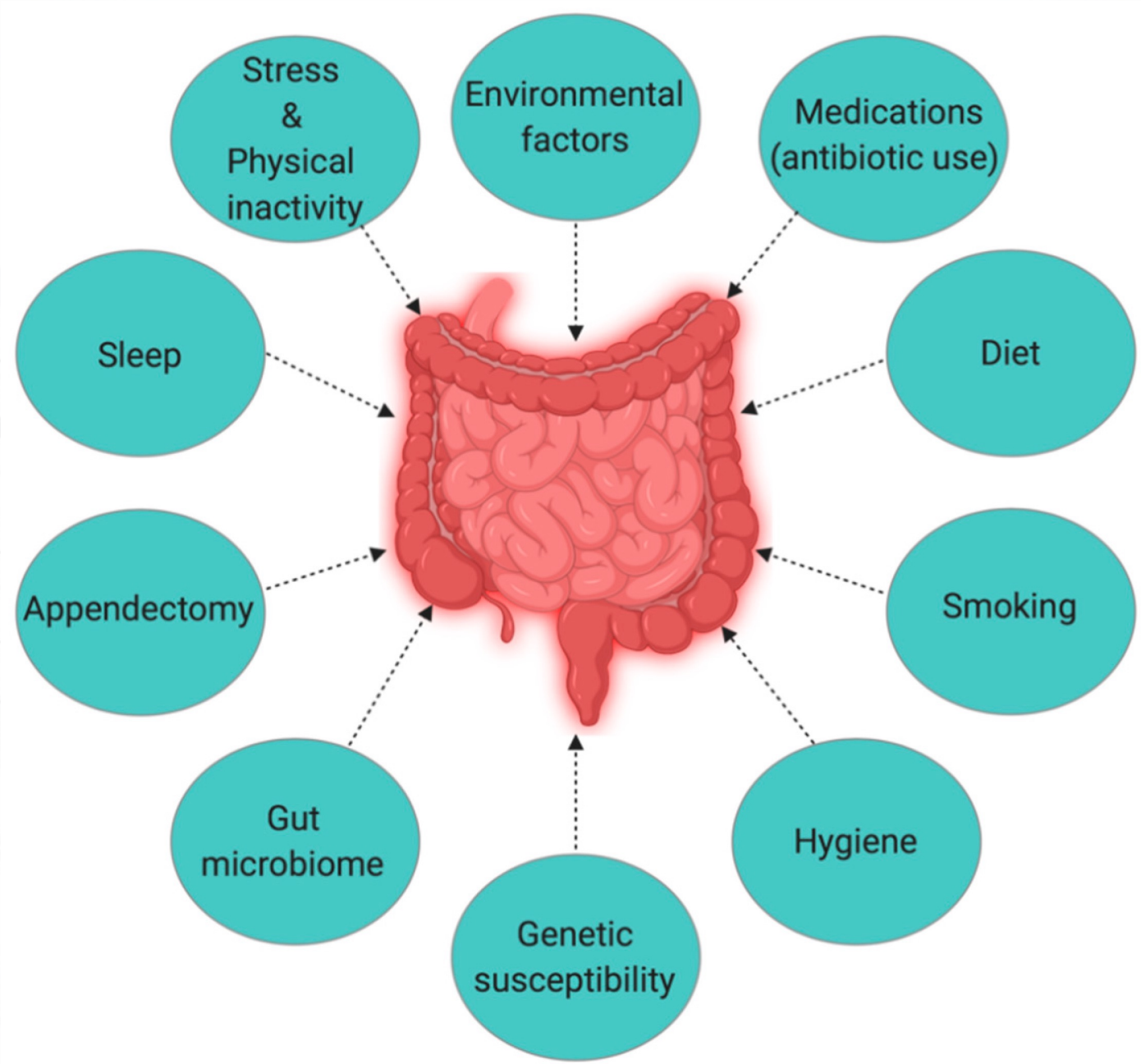
The pathogenesis of UC and CD is considerably distinct from each other. The change in luminal microbial diversity (dysbiosis), impairment of epithelial, and mucus layer barrier via disruption of tight junctions are strongly implicated in the pathogenesis of UC. Figure 3 shows an overview of the pathophysiology of UC. Although UC patients exhibit lower diversity of Firmicutes and a higher proportion of Gamma-proteobacteria and Enterobacteriaceae [32], and sulfite reducing deltaproteobacteria [33], whether such changes are intestinal inflammation-driven or vice versa remains controversial. Interleukin (IL)-13 produced by T helper type 2 (Th2) cells and non-classical natural killer T cells (NKT cells) also mediates UC [34,35,36] as it synergizes with tumor necrosis factor alpha (TNF-α) to regulate the expression of genes responsible for the formation of tight junction entero-epithelial cells [37]. IL-13 also disturbs the membrane integrity by increasing the rate of cell apoptosis (which intensifies upon exposure to TNF-α), and by changing the protein composition of the tight junctions [38]. An impairment of tight junctions increases gut permeability, leading to an enhanced influx of luminal antigens. Antigen-presenting cells (APC) such as macrophages and dendritic cells become activated upon recognizing non-pathogenic bacteria (commensal microbiota) through Toll-like receptors (e.g., Toll-like receptor 2 (TLR2) and TLR4) [39]. Activated APCs in turn initiate differentiation of naïve $CD4^+$ (cluster of differentiation 4) T-cells into different subsets of effector T helper cells such as Th2, Th9, and regulatory T cells (Treg) in UC. In the inflamed lamina propria of UC patients, the expression of IL-4, which is a signature cytokine of Th2 cells, is dominated by high-level expression of other Th2-associated cytokines such as IL-5 and IL-13, and the Th2 master transcription factor GATA binding protein 3 (GATA3) [40]. Thus, UC is predominantly a Th2-mediated immune disorder, but considering the low-level expression of IL-4, the role of Th2 cells as a whole in UC remains inconclusive. IL-9-producing Th9 cells are also associated with UC as they prevent mucosal wound healing and disrupt protective functions of the mucus layer [41].


CD4+ T
TH1
TH2
TH17
TH9
TH22
(Dermatologic)



Score	0	1	2	3
Vascular pattern				
	Normal	Patchy obliteration	Obliterated	
Bleeding				
	No visible blood	Mucosal	Luminal mild	Luminal moderate
Erosion and ulcers				
	No visible erosion	Erosions	Superficial ulcer	Deep ulcer

https://www.researchgate.net/publication/362345186/figure/fig1/AS:1185024674136066@1659543307354/Endoscopic-features-of-each-descriptor-in-ulcerative-colitis-endoscopic-index-of-severity.png



https://www.mdpi.com/2077-0383/9/5/1273

Revisiting Inflammatory Bowel Disease: Pathology, Treatments, Challenges and Emerging Therapeutics Including Drug Leads from Natural Products

by Karma Yeshi [1], Roland Ruscher [1], Luke Hunter [2], Norelle L. Daly [1], Alex Loukas [1] and Phurpa Wangchuk [1,*]

[1] Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, James Cook University, Cairns QLD 4878, Australia

Diet influences the composition of the microbiota and their metabolic activity in the human gut [86]. There is a growing concern that the western diet, rich in fats and sugars, is responsible for the change in the diversity and metabolic activity of human gut microbiota, thereby contributing to the increasing incidence of IBD [87,88]. The increase in the abundance of *Bilophila wadsworthia* due to an animal-based diet can facilitate the growth of microorganisms that can trigger IBD [87,88]. Moreover, *B. wadsworthia* also produces hydrogen sulfide that can cause damage to intestinal tissues [86]. Long-term dietary pattern influences the development of IBD [89]. For instance, the intake of fruits decreases the risks of developing CD [90], although the underlying mechanism is yet to be understood. Smoking is one of the contradictory factors linked to IBD. While smoking is harmful to CD patients, reports show beneficial in UC [63]. The positive effect of smoking in UC is evident from the "Boston Drugs Surveillance Program" [91], "UC patients in Birmingham, England" [92], and "Oxford Family Planning Association Contraceptive Study" [93]. Additionally, the transdermal treatment of active UC patients with nicotine patches also showed better remission compared to the placebo group [94]. However, it is still controversial, and more research is required to determine if nicotine is one of the active components of cigarette smoking that is responsible for the beneficial effects on the UC disease course.

Revisiting Inflammatory Bowel Disease: Pathology, Treatments, Challenges and Emerging Therapeutics Including Drug Leads from Natural Products

by Karma Yeshi [1], Roland Ruscher [1], Luke Hunter [2], Norelle L. Daly [1], Alex Loukas [1] and Phurpa Wangchuk [1,*]

[1] Centre for Molecular Therapeutics, Australian Institute of Tropical Health and Medicine, James Cook University, Cairns QLD 4878, Australia

[2] School of Chemistry, University of New South Wales (UNSW), Sydney NSW 2052, Australia

3.5. Sleep Deprivation, Stress, and Physical Inactivity

Inadequacy of sleep and psychological distress are additional intrinsic factors known to associated with inflammation and the inflammation system. Sleep disturbances are said to be common in IBD patients [95,96]. Some studies [97,98] have reported that symptoms of depression and anxiety cause clinical recurrence in IBD patients. However, stressful life events are not associated with the onset of inflammatory disease [99]. Alteration of sleep pattern or circadian rhythms [100] and insufficient sleep (<6 h/day) [96] has a direct impact on disease course and severity. A study involving 136 Japanese IBD patients found sleep disturbances as a potential risk factor of disease flare-up for both UC and CD within one year [95], but a similar kind of study (3173 IBD patients with sleep disturbances) conducted by Ananthakrishnan et al. [101] could observe an increased risk of disease flares only in CD within 6 months. A positive correlation between psychological distress and IBD flare-ups [102,103] indicates the need for timely psychological therapy in IBD patients.

Revisiting Inflammatory Bowel Disease: Pathology, Treatments, Challenges and Emerging Therapeutics Including Drug Leads from Natural Products

by Karma Yeshi [1], Roland Ruscher [1], Luke Hunter [2], Norelle L. Daly [1], Alex Loukas [1] and Phurpa Wangchuk [1,*]

3.6. Appendectomy

Appendectomy (i.e., surgical removal of the appendix) and its association with the development of UC and CD is a scarcely explored area of research [104]. Few studies involving both humans as well as animal models showed evidence for a role of the appendix in gastroenterology. T-cell receptor-α mutant mice (TCR-$\alpha^{-/-}$) appendectomized at a young age (3–5 weeks old) contained more mesenteric lymph node (MLN) cells compared to the placebo group (sham-operated TCR- $\alpha^{-/-}$ mice), indicating that the appendix could be an important site for priming MLN cells involved in causing IBD [105]. Similarly, Mombaerts et al. also found that an increase in the number of MLN cells in TCR-$\alpha^{-/-}$ mice is related to the development of IBD [106]. A few studies and case reports have also shown the positive effect of appendectomy on the clinical course of UC in human subjects. A study of IBD patients in Australia confirmed that appendectomy before diagnosis delays disease onset of both UC and CD and results in fewer flare-ups in the case of UC when compared with patients without prior appendectomy [107]. A case report from Korea also confirmed that a patient with UC experienced a more extended period of remission after appendectomy [108]. However, the therapeutic relationship between CD and appendectomy remains inconclusive. [30].

3.7. Antibiotic Use

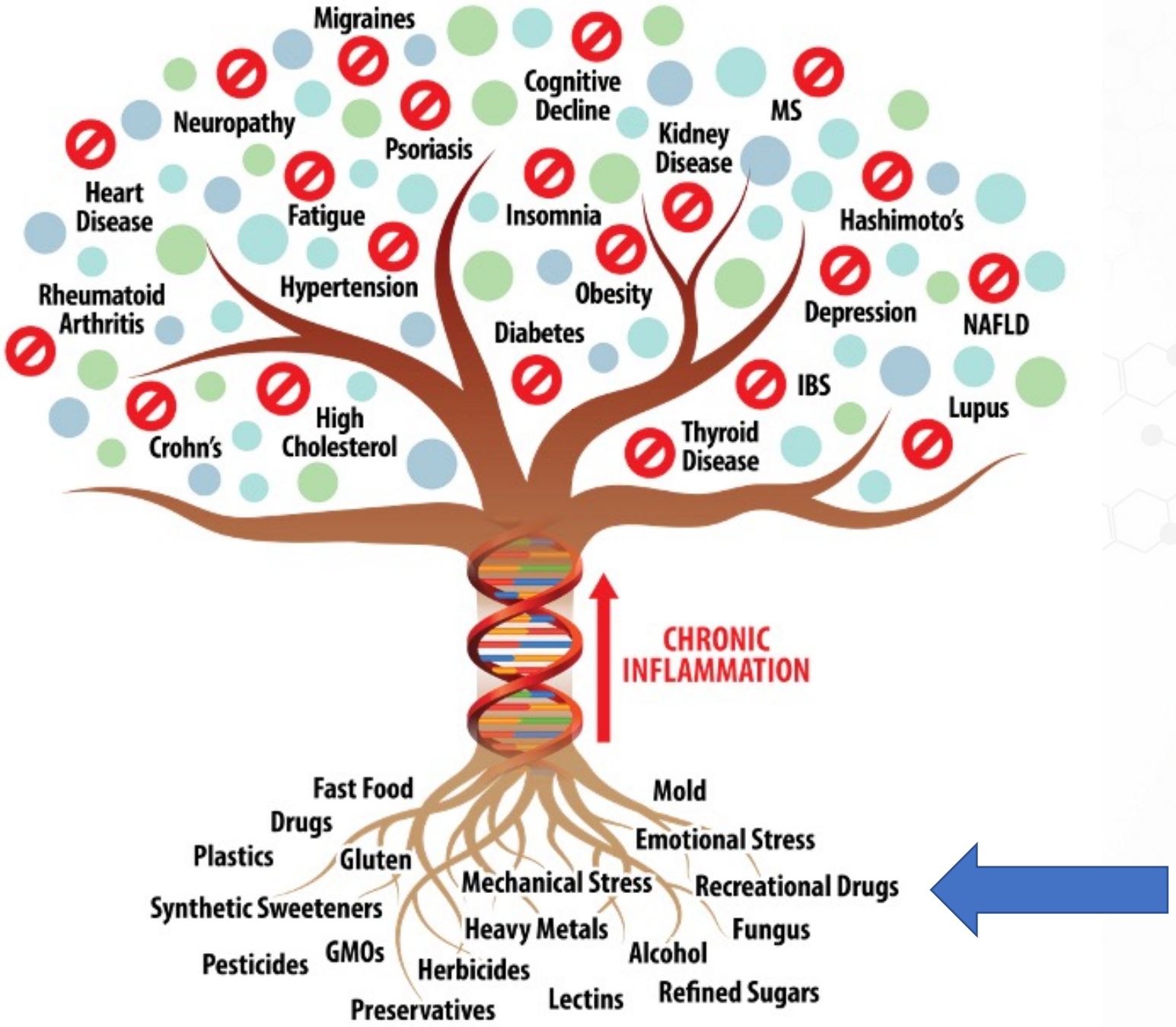
A leading hypothesis in the etiology of IBD is the alteration in the human gut microbiota that triggers abnormal inflammatory responses, including IBD. Multiple factors are assumed to be responsible for inducing gut dysbiosis. Childhood exposure to antibiotics is one among them [109]. Children exposed to antibiotics at an early stage [109,110,111,112] and adults who had medication for acute gastroenteritis [113] possess higher risks for IBD. The frequency of use of antibiotics and the age at the time of use may have a varying effect as risks for IBD tend to decrease with increasing age at the time of exposure [114]. Regular intake of non-steroidal anti-inflammatory drugs like aspirin showed a strong positive correlation with only CD [115].

Dx: Ulcerative Colitis

1. What is your current lifestyle/environment?
2. What does the microbiome landscape look like?
3. Any identifiable food triggers (labs, experience, or otherwise)?

SAD → Modern Med:
- Low Meat
- Heavy vegetable
- Moderate fruit
- Complex carbohydrates

→ AIP → Carnivore


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives