

UCSF Colitis and Crohn's Disease Center (Clinical)





UCSF Health COVID-19 Clinical Update

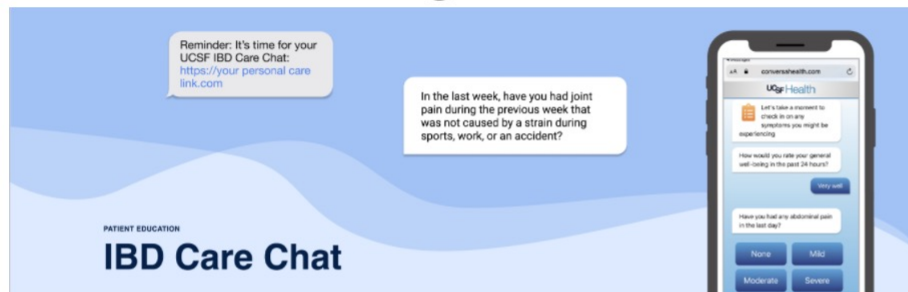
Today's Status:

	Inpatient COVID19 + Patients	Asymptomatic Case Positivity (7 day moving average)	Symptomatic Case Positivity (7 day moving average)	COVID Surge Status
UCSF Health	13	0.8%	3.7%	Green
ZSFG	5			Green

New Medications for Treatment and Prevention of COVID19 Infection

- FDA has provided Emergency Use Authorization (EUA) of an oral antiviral medication called **molnupiravir (Lagevrio)** and is reviewing data for a second oral antiviral medication called **nirmatrelvir/ritonavir (Paxlovid)** for **treatment** of COVID-19 in high-risk outpatients.
- In addition, the FDA granted an EUA for AstraZeneca's long-acting monoclonal antibody cocktail **tixagevimab/cilgavimab (Evusheld)** for **prevention** (pre-exposure prophylaxis) of COVID-19 in immunocompromised individuals who do not respond to a COVID-19 vaccine series or individuals who cannot complete vaccination for medical reasons.
- These exciting new treatments will be allocated to pharmacies and hospitals by the state in the upcoming weeks.
- At UCSF Health, we are implementing workflows for administration of each of these medications once they become available. We will provide additional information and details when we have received drug supply and can start prescribing these treatments.

IBD Care Chat: Digital Health Tool for Patients



[Faculty & Providers](#)

[Clinical Trials](#)

[Inflammatory Bowel Disease Fellowship](#)

[Updates in Inflammatory Bowel Disease National Symposium](#)

[IBD Care Chat: Digital Health Tool for Patients](#)

Purpose

This tool engages patients with inflammatory bowel disease (IBD) and allows their team to monitor health in between visits. This will lead to improved health care maintenance, earlier detection of disease activity and ideally reduction of complications such as need for steroids. Ask your doctor if you are eligible!

Benefits

- Detect early warning signs of disease activity and reduce chances of a major disease flare
- Encourage patients to get the health care maintenance they need, when they need it
- Feature constantly updated educational videos on topics such as the IBD therapies, COVID vaccine, and IBD in special populations (pregnancy, adolescents, older patients)



University of California
San Francisco

Immunology 101: How IBD medications work

Michael Kattah MD PhD

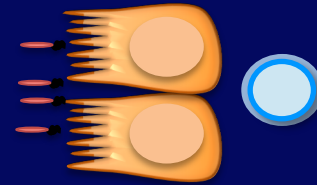
Assistant Professor

Member, UCSF Bakar ImmunoX

John V. Carbone MD Endowed Chair in Medicine

Division of Gastroenterology

UCSF



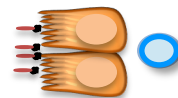
2021 UCSF IBD Town Hall

Disclosures

- **Eli Lilly Grant/Research Support**
- **Surrozen, Stemodontics/Consulting**

Outline

- **What causes IBD**
- **How IBD medications work**
 - 5-ASA (mesalamine)
 - Thiopurines (AZA/6MP) or methotrexate
 - Biologics (injection/infusion)
 - anti-TNF
 - anti-IL-12/23
 - anti-integrin
 - Newer pills, tofacitinib and ozanimod



Key Concepts

- IBD is caused by inflammation that damages the lining of the intestine (mucosa/epithelium)
- Current medications inhibit or suppress the immune system
- We currently try medications and see if they will work (best guess)
 - Eventually, detailed understanding of each person's biology will help us choose the right therapy (precision medicine)
- All immunosuppressive medications have side effects, some more than others
 - Today we are *just* discussing *how* they work, talk your MD/NP for more info

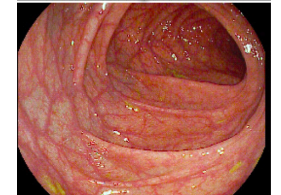


What are we trying to achieve with medications?

- What are the goals?
 - We want to improve symptoms
 - Also want to heal the lining of the intestine (mucosa)
 - Minimize side effects/risks
- If we heal the mucosa, then we can often keep patients healthy longer
 - Reduce the risk of surgery or steroids
- Frequently adjust therapy to these targets
- **Key point: not just improving symptoms, goal is to heal the mucosa**



Inflamed

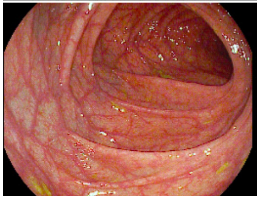


Healing

IBD: Crohn's disease (CD) and ulcerative colitis (UC)

IBD

- Chronic inflammation GI tract
- ~1% of the population
- Abd pain, bloody diarrhea
- Managed by medications and/or surgery

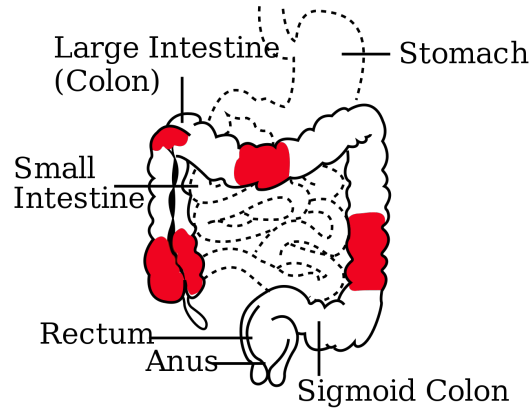


Normal



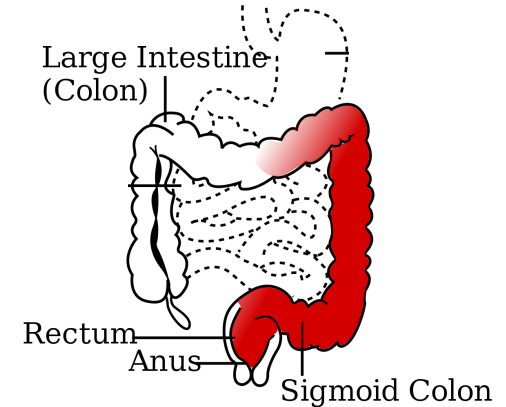
Inflamed

Crohn's Disease



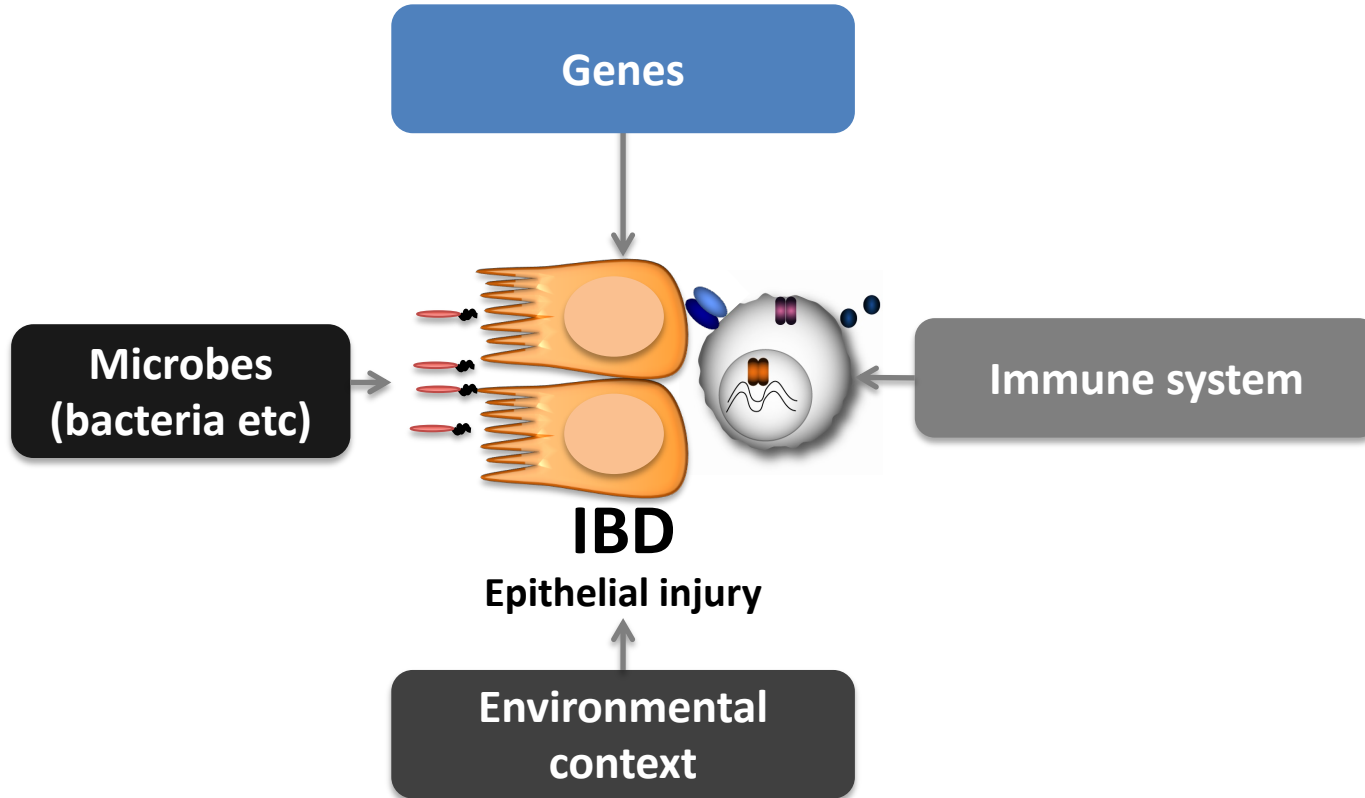
- Patchy, anywhere in the intestine
- Ileum and colon most common

Ulcerative Colitis

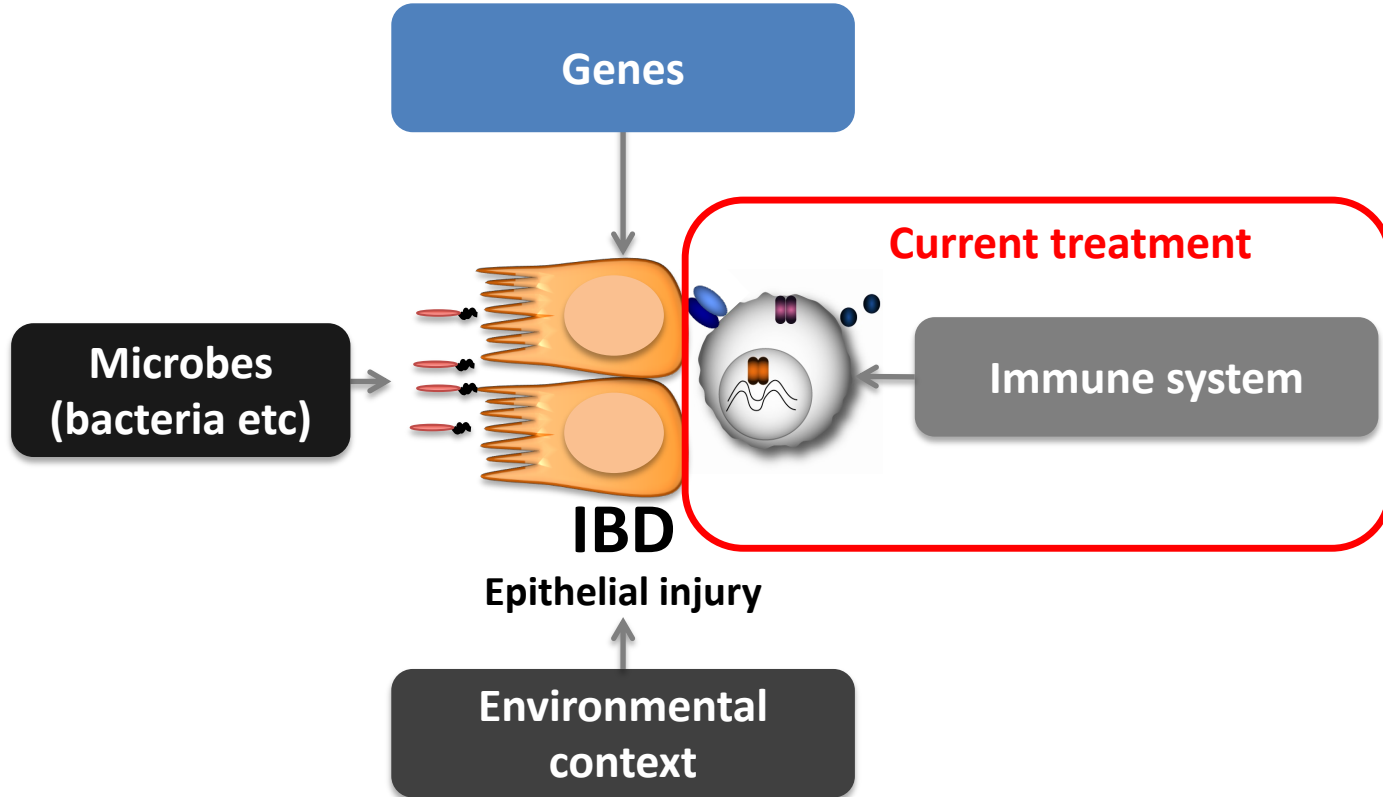


- Colon only
- Ascending from anal verge
- 25% rectum, 25% L colon
- 50% extensive

What causes IBD?

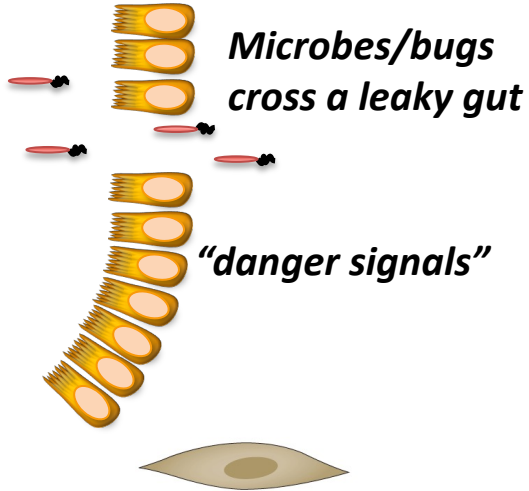


What causes IBD?

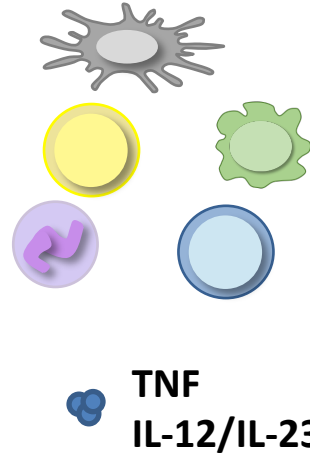


Why is the intestine inflamed in IBD?

Damage mucosa/lining

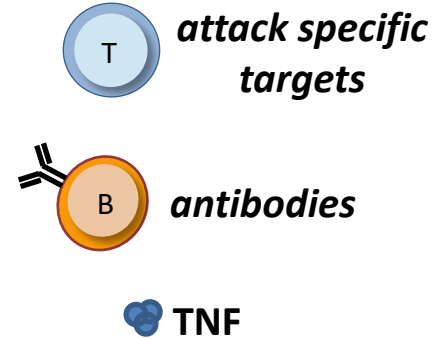


"Innate" immune activation



Secrete proteins called "cytokines"
that increase inflammation
"pro-inflammatory"

Adaptive immune activation



Tissue damage
Ulceration
Scar tissue

FDA-approved medications for CD & UC

FDA-approved	Crohn's Disease	Ulcerative Colitis
anti-TNF (Infliximab, Adalimumab)	✓	✓
anti-TNF (Certolizumab)	✓	
anti-TNF (Golimumab)		✓
anti-integrin (anti- $\alpha 4\beta 7$ Vedolizumab)	✓	✓
anti-integrin (anti- $\alpha 4$ Natalizumab)	✓	
anti-p40 (anti-IL12/23 Ustekinumab)	✓	✓
JAK1/3 inhibitor (Tofacitinib/Xeljanz) small molecule		✓
S1P modulator (Ozanimod/Zeposia) small molecule		✓

- ***Lots of options!and more on the way!***
- ***We will discuss how they work***
- ***Will not get into details about risks/benefits/side effects for each medication, just how they work***

Patient

- Young patient with ulcerative colitis
 - Moderate colitis involving whole colon
 - Started on mesalamine and prednisone
 - Persistent symptoms, also started on azathioprine



A horizontal timeline arrow points to the right. A vertical line drops from the start of the arrow to a box containing the text '5-ASA', 'Prednisone', and 'Azathioprine'. Further along the arrow, there is a circular inset image showing a colonoscopic view of inflamed, ulcerated colonic mucosa.

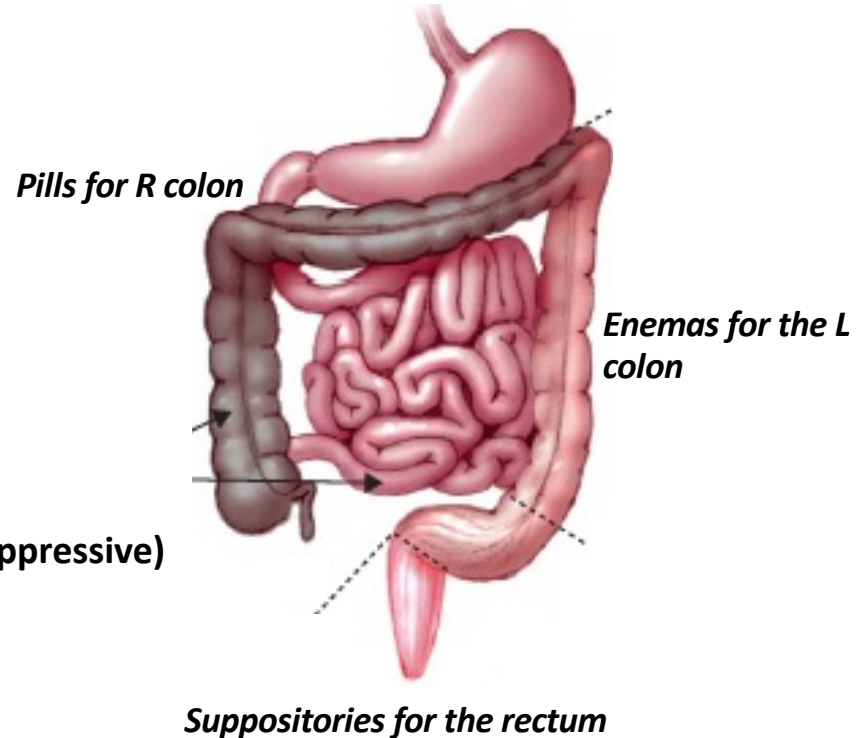
5-ASA
Prednisone
Azathioprine



How do 5-ASA and thiopurines work?

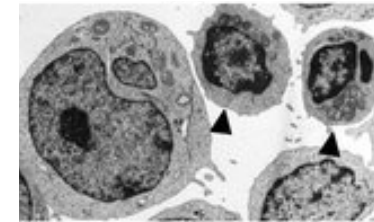
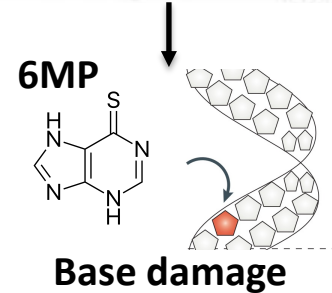
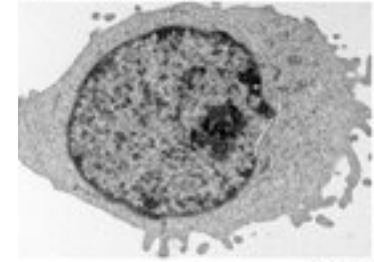
5-ASA agents (aminosalicylates)

- **Common versions**
 - Mesalamine (Lialda, Pentasa, Apriso)
 - Balsalazide
 - Sulfasalazine
- **Pills, suppository, or liquid enema**
 - Been around since 1940s, work for UC (not CD)
 - Absorbed by colon epithelial cells
 - Inhibit inflammatory cytokines locally
 - Low systemic activity (not particularly immunosuppressive)
 - Decrease expression of inflammatory genes
 - Inhibit inflammatory chemicals in colon



Antimetabolites (thiopurines, MTX)

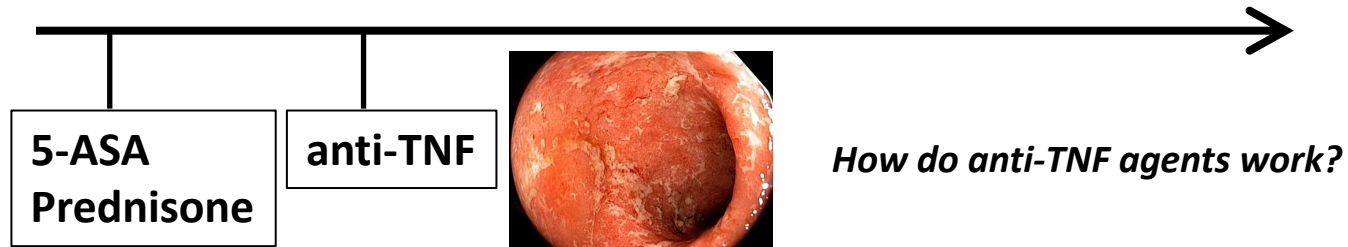
- Purine antagonists
 - thiopurines (azathioprine/imuran, 6-mercaptopurine)
- Folate antagonist
 - methotrexate
- Affect some of the signaling molecules inside cells, inhibits activation
- *Interfere with nucleic acid synthesis (DNA, RNA)*
- DNA damage inhibits B and T cell proliferation
 - Apoptosis “programmed cell death”
 - DNA damage can rarely increase the risk of certain WBC cancers
- We used these more in the past to treat IBD
- *Now, we often use at low dose in combination with injection/infusion medication, prevent “rejection”, neutralizing antibodies*



Inflammatory cells die

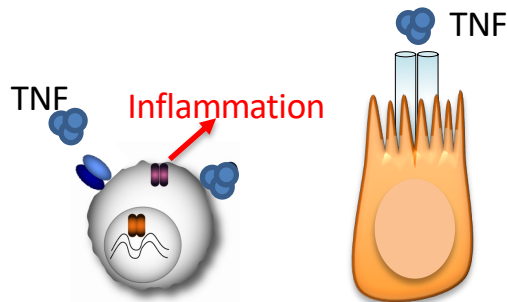
Patient

- Young patient with ulcerative colitis
 - Moderate colitis involving whole colon
 - Flare while on mesalamine and azathioprine
 - Admitted, start her on Infliximab (anti-TNF)



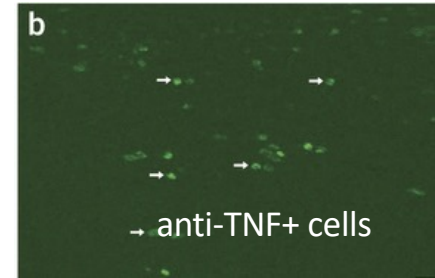
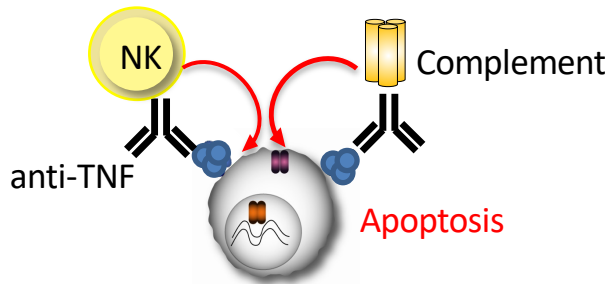
Anti-Tumor Necrosis Factor (TNF)

- Infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), certolizumab pegol (Cimzia), others
 - Some are infusions, some injections
- Still among the most frequently prescribed and most effective treatments
 - CD & UC
 - Used to treat other autoimmune conditions
- Blocking TNF makes sense
 - TNF is pro-inflammatory
 - TNF directly kills IECs->*ulcer*

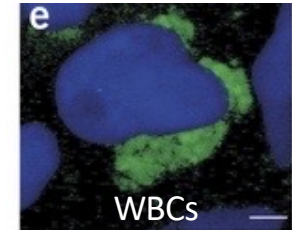


Anti-TNF-> death of inflammatory cells

- Anti-TNF kills/eliminates cells that are driving inflammation
 - Cells coated with anti-TNF antibody get killed
 - Those cells also kill themselves “apoptosis”/programmed cell death
- Can see this, sprayed mucosa with fluorescent anti-TNF⁵
 - Look with special colonoscope
 - Visualize inflammatory WBCs stained and eliminated by the anti-TNF



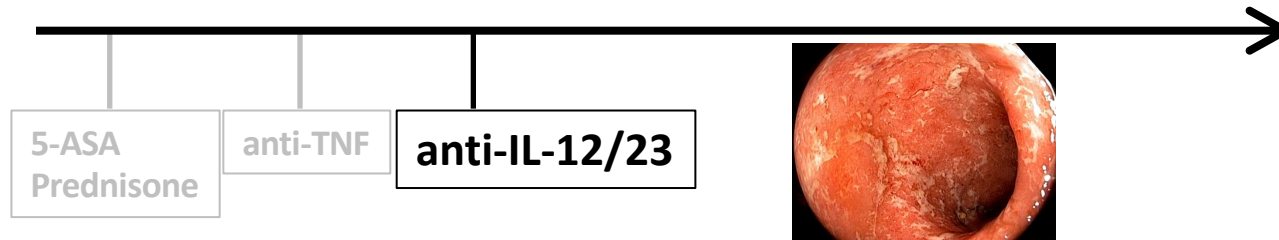
CLE images



microscopy

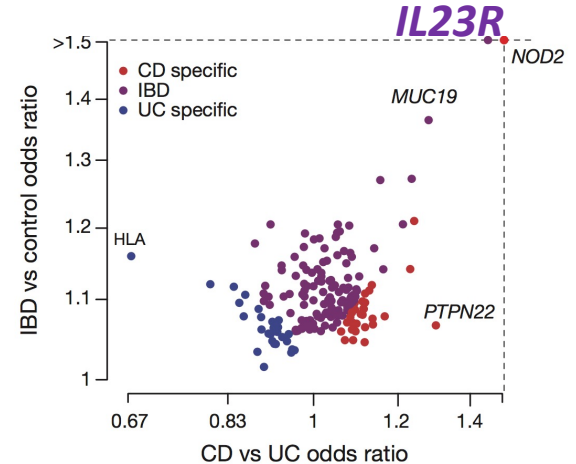
Patient

- **Young patient with ulcerative colitis**
 - Moderate colitis involving whole colon
 - Flare while on mesalamine and azathioprine
 - Ultimately did not respond to Infliximab
 - **Start anti-IL12-23**

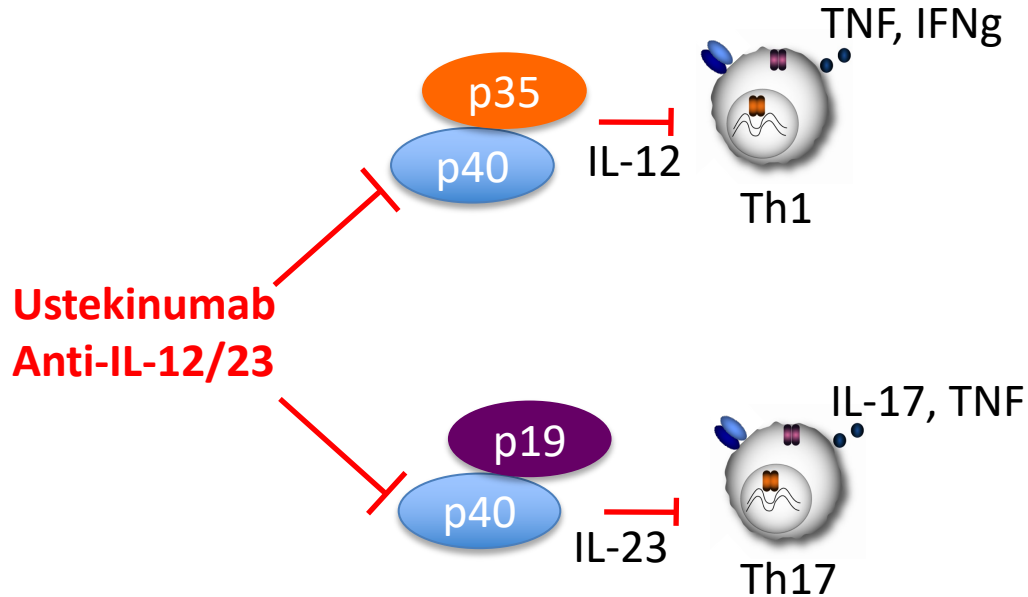


Anti-Interleukin 12/23 (Ustekinumab)

- Ustekinumab (Stelara) FDA-approved for CD and UC
 - Inhibits BOTH IL-12 and IL-23
- Receptor IL-23 is one of the genes that increases risk IBD



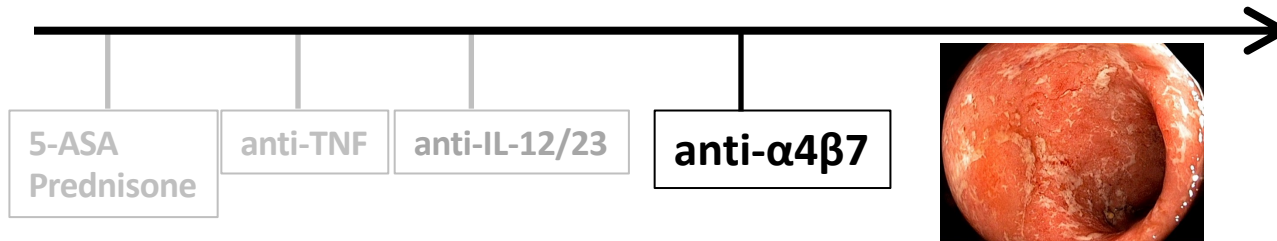
Anti-IL-12/23



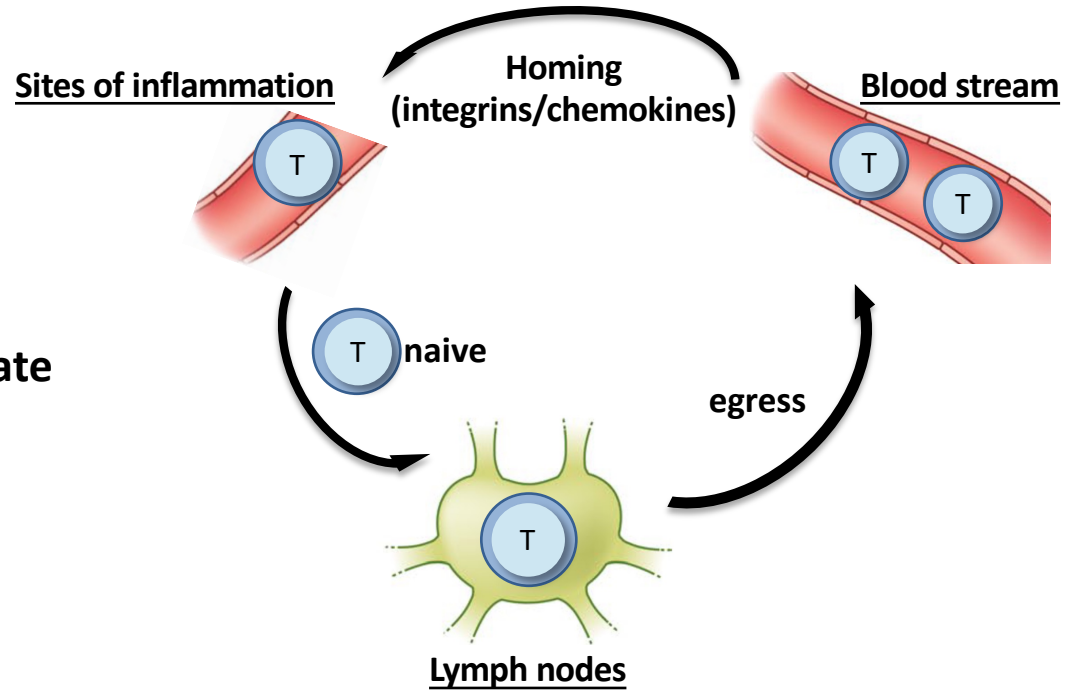
- *Blocking these cytokines inhibits certain types of inflammatory T cells, lymphocytes*
- *Inhibits the cytokines they make*
- *Reduces T cell-mediated tissue damage*
- *The lining “epithelium” of the intestine can heal*

Patient

- **Young patient with ulcerative colitis**
 - **Moderate colitis involving whole colon**
 - **Flare while on mesalamine and azathioprine**
 - **Ultimately did not respond to Infliximab or Ustekinumab**
 - **Start Vedolizumab**

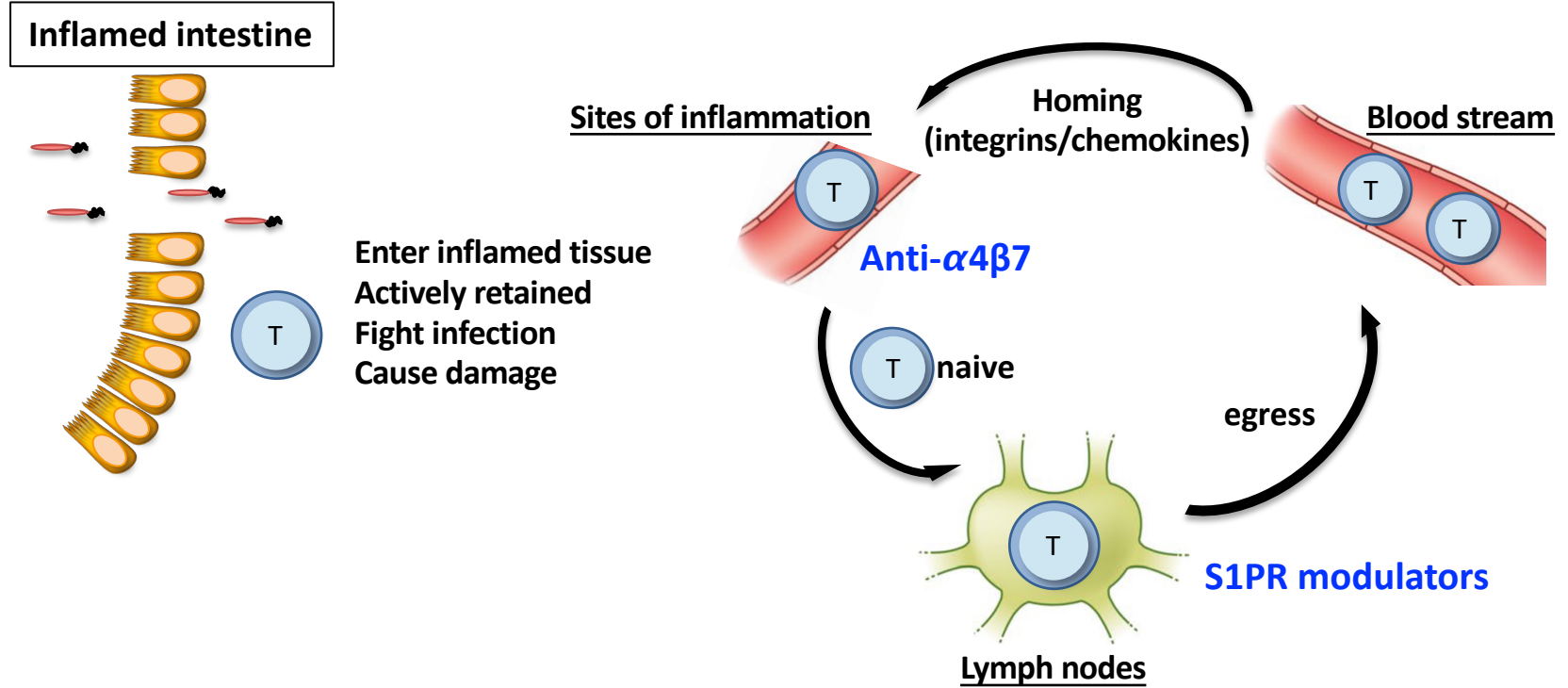


Immune cell trafficking



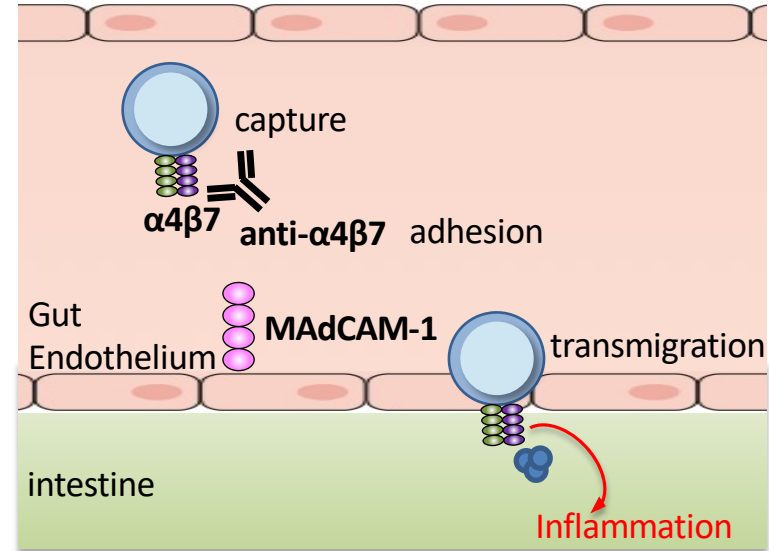
WBCs/Immune cells actively circulate

Immune cell trafficking



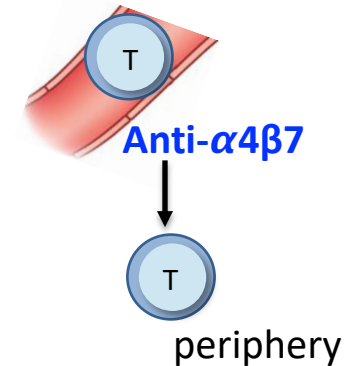
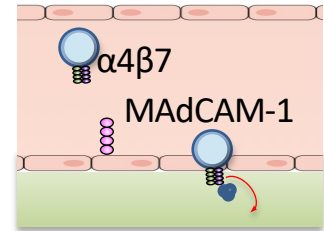
Anti-integrin/anti-adhesion therapy

- Immune cells (WBCs) circulate blood
- Home to site of inflammation
- Then they stop and enter the tissue
- *How do they know where to go?*
- $\alpha 4\beta 7$ binds to protein expressed exclusively blood vessels in the gut
 - Like a molecular “address” or zip code
- *Anti- $\alpha 4\beta 7$ selectively blocks intestinal migration*
- Inflammatory cells can’t get into intestine



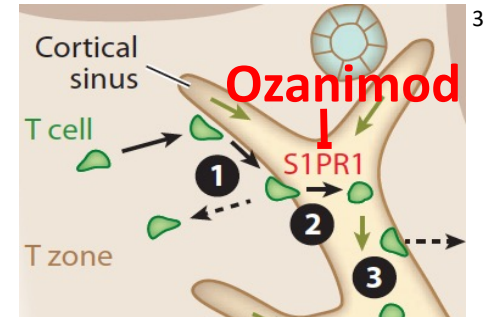
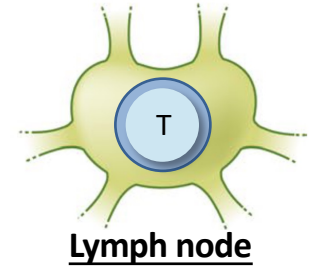
Anti-integrin/anti-adhesion therapy

- **Vedolizumab blocks WBCs from entering intestine**
 - Can still go to other sites, can respond to distant infections
 - Gut selectivity improves safety
- But, also means it is not the best for patients with inflammation elsewhere (e.g. arthritis/joint inflammation)
- Approved for UC and CD, acts more slowly than anti-TNF in CD
 - Selectively blocks new cells from coming in
 - May not affect “resident” inflammatory cells already there
 - Slower response, tends to work better for UC than CD



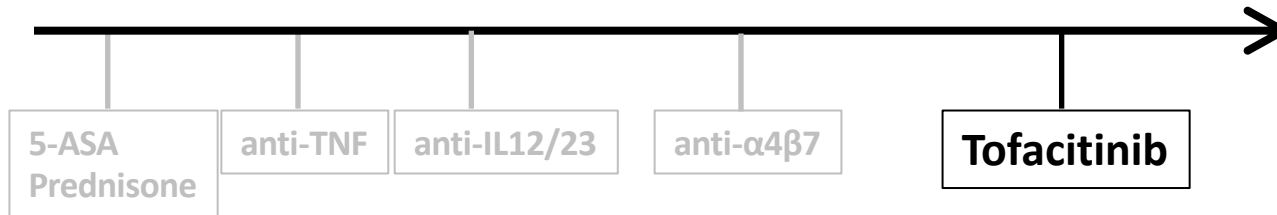
How does Ozanimod fit in?

- Ozanimod/Zeposia FDA-approved for UC², in development CD³
 - Pill, a "small molecule", not injection or infusion
- How does this work?
 - Sphingosine 1-phosphate (S1P) lipid/fat that helps white blood cells *leave* a lymph node
 - Ozanimod disrupts this signal
 - Traps lymphocyte in the lymph node
 - Hotel California of meds, WBCs check in, can never leave
- *S1PR modulators are another way to interfere with immune trafficking, reduce cells going to the gut*



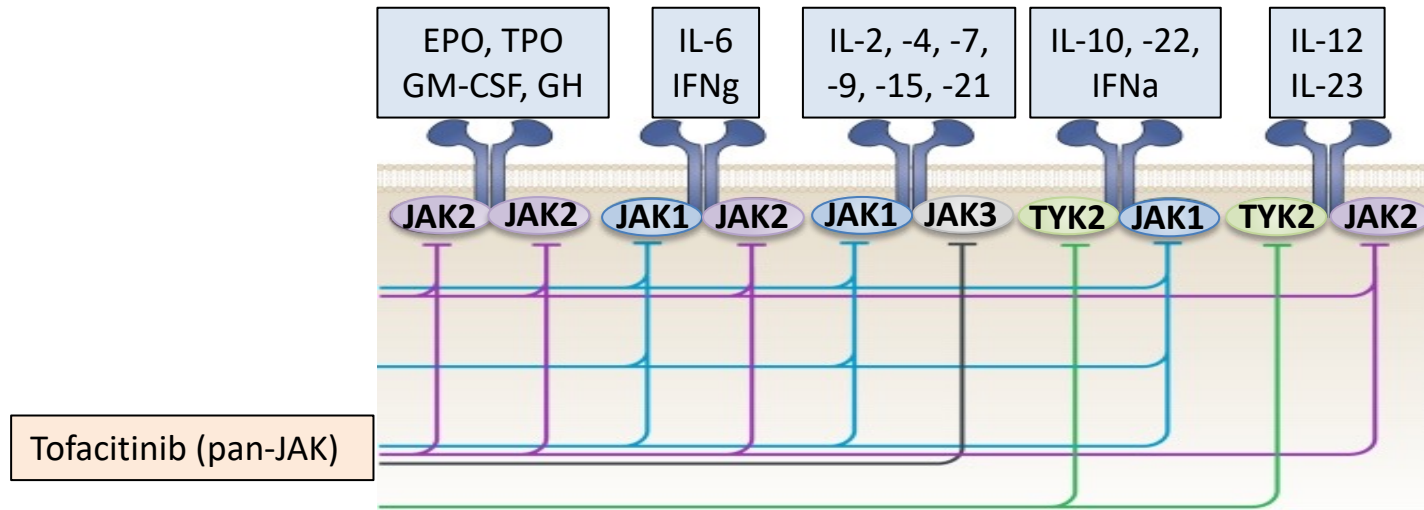
Patient

- **Young patient with ulcerative colitis**
 - **Moderate colitis involving whole colon**
 - **Flare while on mesalamine and azathioprine**
 - **Ultimately did not respond to Infliximab, Ustekinumab, or Vedolizumab**
 - **Start Tofacitinib**
 - **After 16 weeks, she feels great, and achieves remission**



Tofacitinib Janus Kinase (JAK) inhibitor

- Janus kinases (JAKs)
- Proteins inside of cells, they transmit signals to the cell about surrounding inflammation
- Different inflammatory signals use different combinations of JAK proteins to communicate



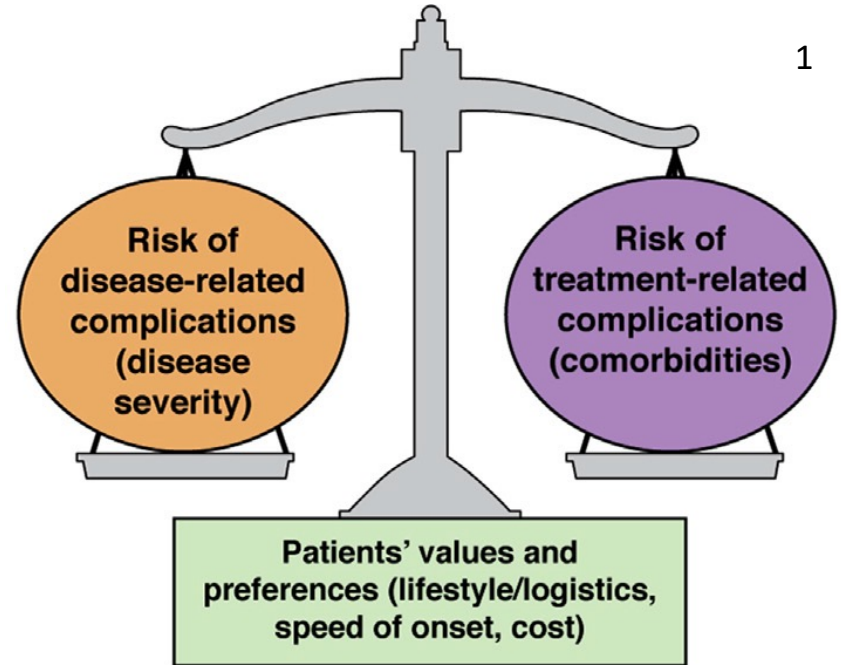
Tofacitinib Janus Kinase (JAK) inhibitor

- Tofacitinib (pan-JAK inhibitor)
- Pill (small molecule), not a protein
- *Inhibits multiple pathways at the same time*
 - No neutralizing antibodies, starts and stops quickly
 - Good option for patients failed injection/infusion medications
 - FDA-approved UC 2018
 - Not better than placebo for CD (we do use it sometimes)
 - Inhibits multiple pro-inflammatory cytokines
- *Hopefully, more options soon*

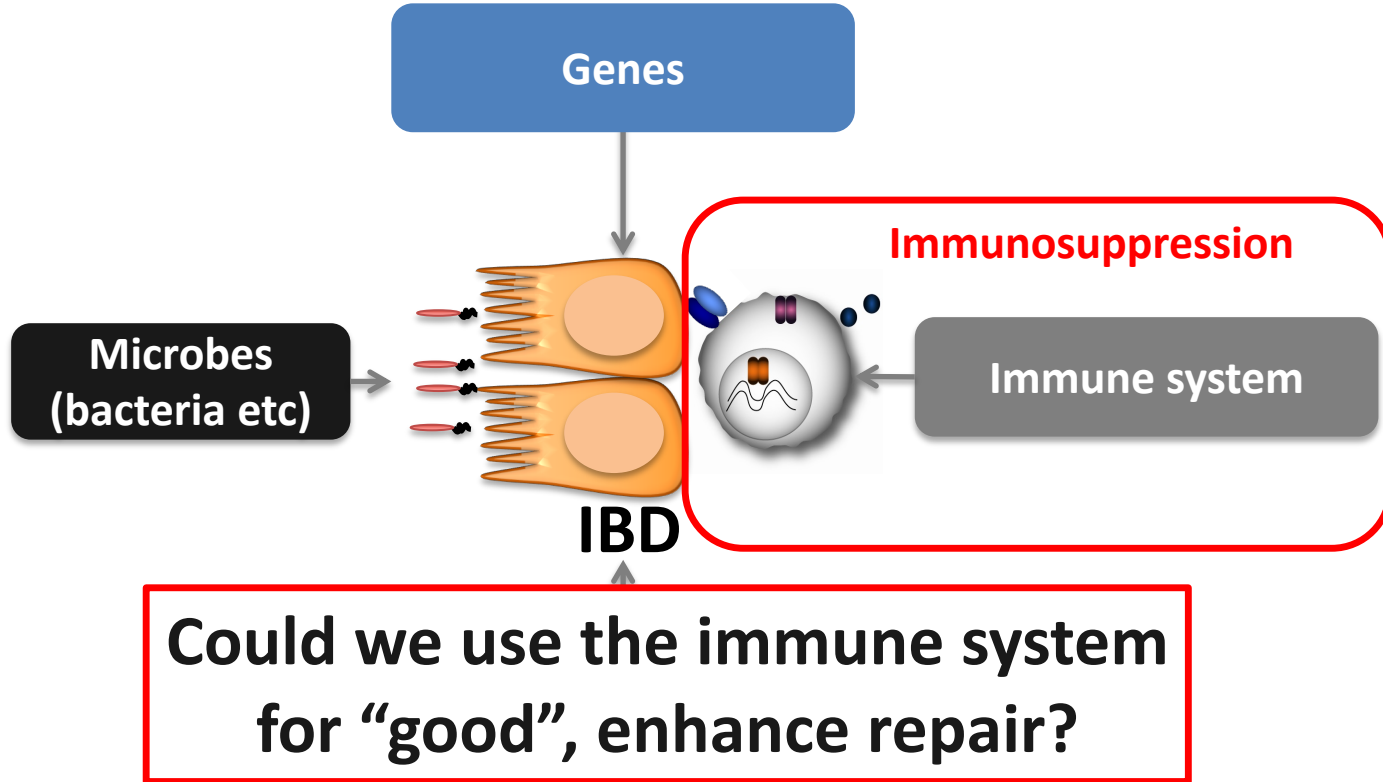
Cytokines	JAKs
IL-2, -4, -7, -9, -15, -21	JAK1 JAK3
IL-6, IFN γ	JAK1 JAK2
IFN α IL-10, IL-22	JAK1 TYK2
IL-12, IL-23	JAK2 TYK2
EPO, TPO, GM-CSF	JAK2 JAK2

How to choose the right therapy?

- Many factors play a role...
- How severe is your disease?
 - More severe->more effective medication
 - Less severe->fewer side effects
- What is your risk of needing surgery/steroids?
- What are your treatment goals?
- Do you prioritize efficacy or safety?
- What other diseases do you have?
- Do you have logistical hurdles that would favor an injection vs infusion vs pills?
- Are you contemplating pregnancy soon?
- What will insurance cover?
- Discuss options with your Gastroenterologist

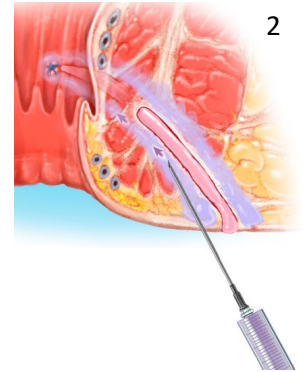
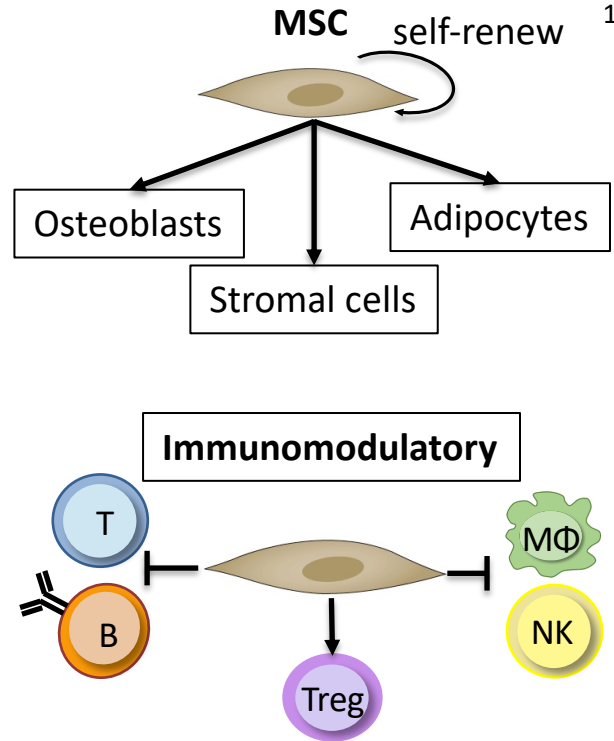


IBD Pathogenesis



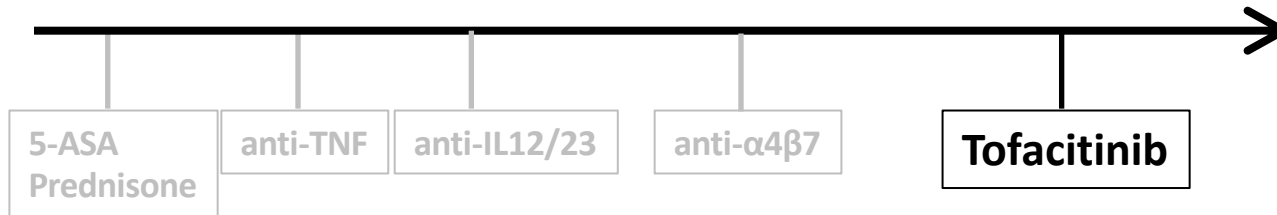
Promoting healing

- Mesenchymal stem cells
 - Self-renew
 - Also help make new connective tissue
- Immunomodulatory
 - *Suppress inflammation*
- Fistulas are tracts/tunnels from intestine-to skin
 - *Promote fistula healing*
 - Trials of this approach to treat fistulas
- Other approaches in development to help healing in the intestine...

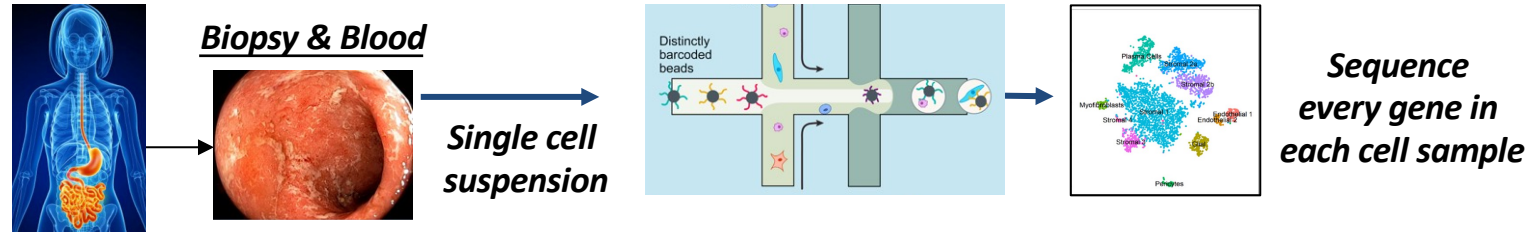


Patient

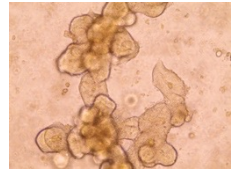
- Young patient with ulcerative colitis
 - Moderate colitis involving whole colon
 - Flare while on mesalamine and azathioprine
 - Ultimately did not respond to Infliximab, Ustekinumab, or Vedolizumab
 - Start Tofacitinib
 - After 16 weeks, she feels great, and achieves remission
 - *Had to try 5 medications over a few years before we found the one that worked!*



One day, we hope to find best treatment faster



- Collective understanding of human immune system growing (single cell sequencing)
- We can sequence all of the genes inside cells, study hundreds of proteins on the surface of every cell, and we can study how they interact in tissue
- Generating a detailed “cellular atlas” of IBD
- Can grow “organoids” 3D miniature guts we can study in the lab
- *Hope technologies like this will help identify new pathways for patients*
- *Unprecedented power to understand disease in each patient*
- *One day pick the most effective medicine with fewest side effects for each individual*
- *Promise of “precision medicine” in the future*



“organoids”

Summary & Looking Forward...

- Knowledge of immune system and tools for treating IBD are expanding
- Future: microbiome, IECs, other non-immune cells, promote healing
- Understanding of immune system->precision medicine
 - In the future, prioritize the right treatment upfront
- Lots of research at UCSF and other centers to improve treatment
- *If you would like to learn more*
 - <https://www.ucsfhealth.org/clinics/colitis-and-crohns-disease-center>
 - <https://gastroenterology.ucsf.edu/colitis-and-crohns-disease-center/clinical-trials>



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Najwa El-Nachef MD



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