

Drug Induced Colitis

What Can We Learn

About IBD

Pathogenesis and

Treatment

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No disclosures

Animal Models

- Cell based

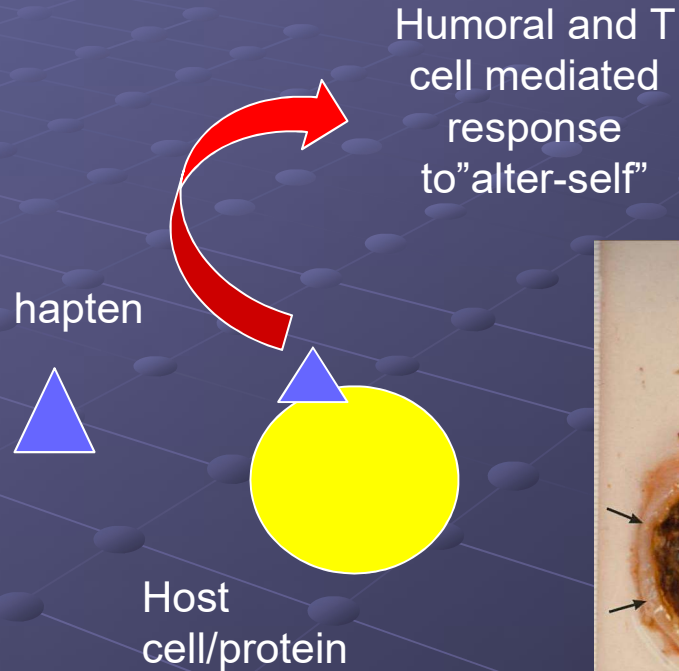
- Cell lines
- organoids

- Animal Based

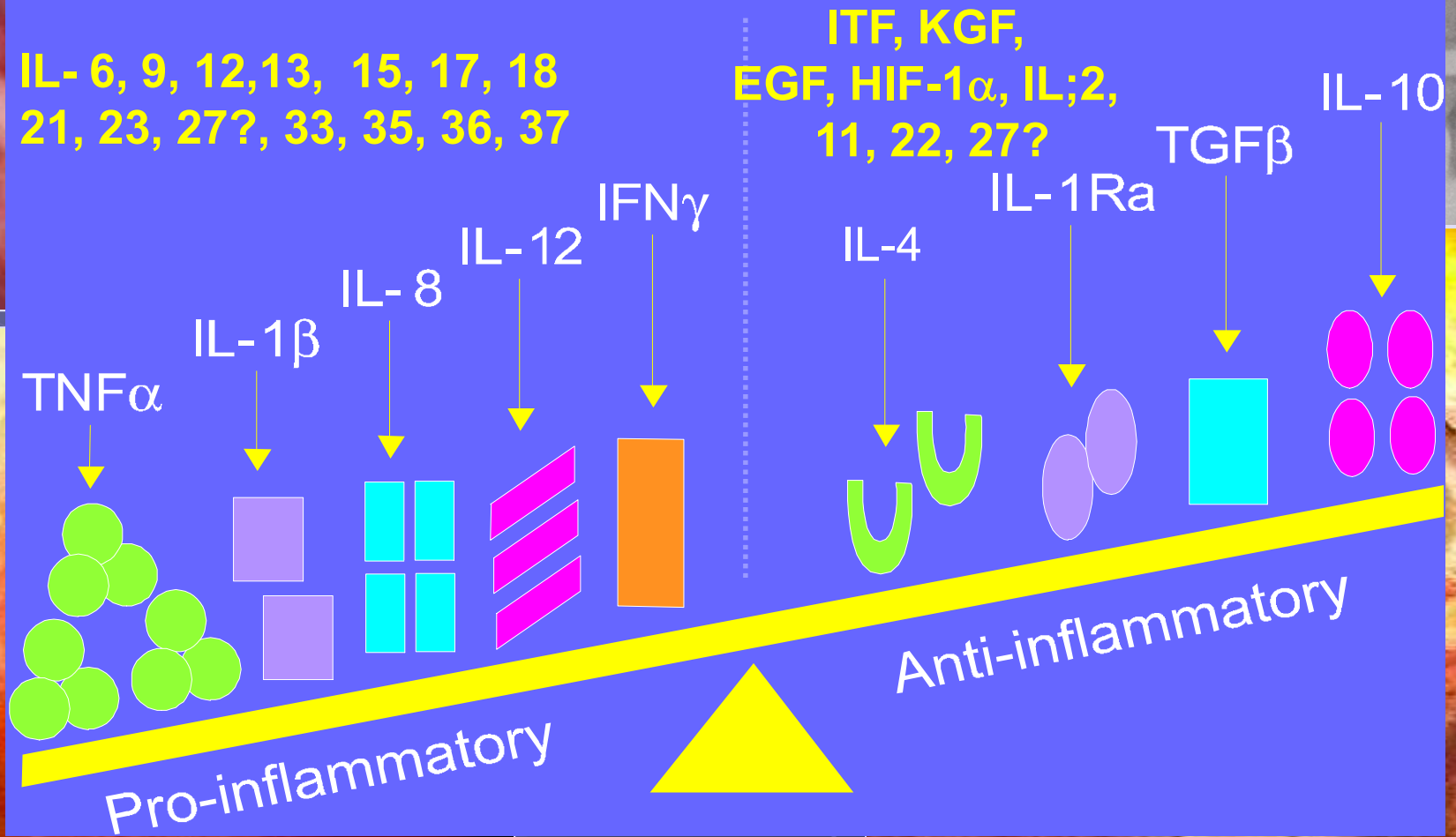
- TNBS
- DSS
- T cell transfer

- Mouse vs Humans

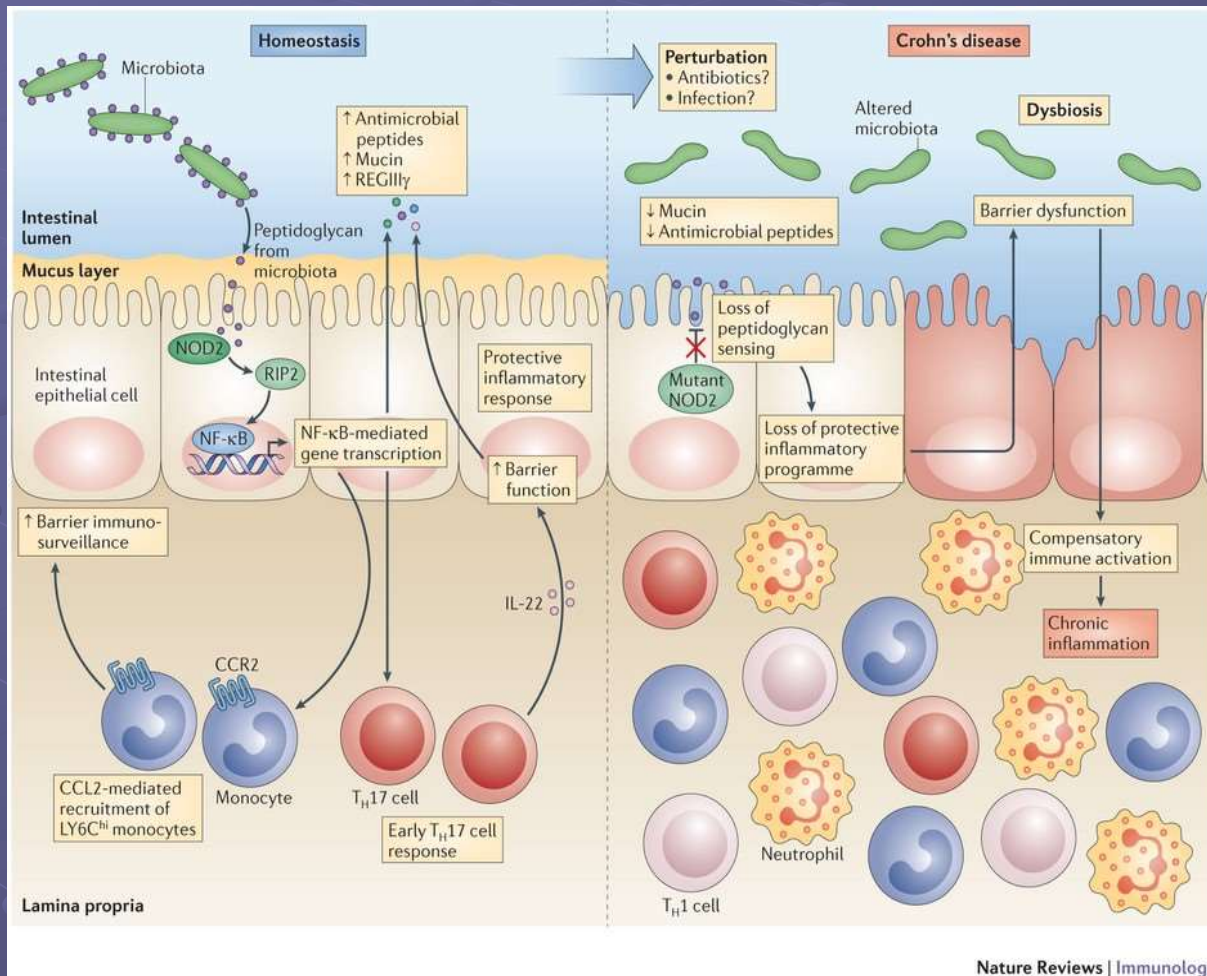
- Microbiota
- Immune cell differences



Chronic Inflammation: Imbalance in Inflammatory Mediators



Etiology and Pathogenesis of IBD; Mechanisms of Disease



- Genetic predisposition
- ↑ intestinal permeability
- NSAIDs, smoking, drugs
- ↑ antigen exposure
- Altered microbiome
- Abnormal inflammatory Responses;
 - epithelial cells
 - lymphocytes
 - cytokines and chemokines
 - lipid mediators
 - PGs, LTs
- ↓ wound repair
 - Cell proliferation and differentiation
- Altered apoptosis
- Failure to turn off inflammation

Great advances in therapy
But efficacy of most is 60%

Maybe we need a better animal
model!

Humans!

Drugs Linked to IBD Pathogenesis

- Antibiotics
- Nonsteroidal anti-inflammatory drugs
- Oral contraceptives?
- Isotretinoin (analog vit A, retinoic acid)?
- Etanercept (sTNFR, psoriasis, RhA, AK)
- Rituximab (anti-CD20 B cell NHL and RhA)
- Ixekizumab, Secukinumab, Brodalumab (anti-IL-17)
- Mycophenolate mofetil (MMF)
- **Check point inhibitors;**
 - **Ipilimumab** (anti-CTLA4).
 - **Nivolumab, Pembrolizumab** (PD-1 blocking antibodies)
 - **Atezolizumab** (PD-L1 blocking antibody)

Histologic Patterns of Injury	Medication
Mucosal Ulcerations, Erosions & Strictures	NSAIDs, Methotrexate, MMF, Checkpoint inhibitors, Nonabsorbable drugs:kayexalate, sevelamer,cholestyramine.
Increased epithelial apoptosis	MMF, Checkpoint inhibitors, Idelalisib (PI 3-kinase inhibitor, used in CLL), TNF α (etanercept, infliximab), Antimetabolites (methotrexate, capecitabine), NSAIDs. Sodium phosphate, colchicine
Ischemic colitis	Digitalis, Estrogen, Cocaine, Ergotamine, Sumatriptan Nonabsorbable drugs: Kayexalate, Sevelamer, NSAIDs, MMF.
Chronic colitis-like pattern	MMF, Checkpoint inhibitors (CTLA4>PD-1/PD-L1) Rituximab, TNF α (etanercept, infliximab), NSAIDs Idelalisib,
Focal active colitis/ self-limited colitis	NSAIDs, Sodium phosphate, MMF, Checkpoint inhibitors (CTLA4>PD-1/PD-L1),
Microscopic colitis	Proton pump inhibitors (lansoprazole), H2 receptor antagonists, Ticlopidine, NSAIDs, Statins, Carbamazepine, Flutamide, Paroxetine, Penicillin Selective serotonin reuptake inhibitors, Idelalisib

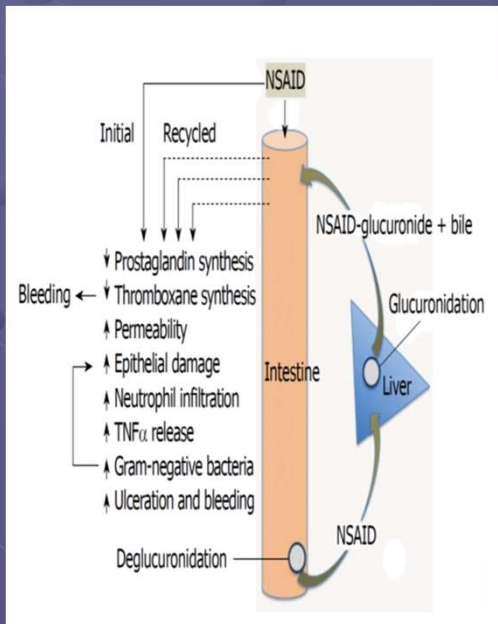


Drugs that impact barrier function

NSAID Enteropathy and Colopathy



- Small intestine is the most common site of injury and this occurs with both enteral and parenteral NSAIDs and Cox-2 inhibitors. nsNSAID>Cox-2
- Topical injury and systemic injury likely mediated via barrier injury and delayed rep



- Risk factors; Age >65, PPI and H2 blocker use
- air.
- PPIs can induce dysbiosis and cause NSAID enteropathy
- Rifaximin decreases NSAID induced injury assessed by capsule endoscopy (diclofenac/omeprazole +/- rifaximin). 43% mucosal breaks vs 20%.

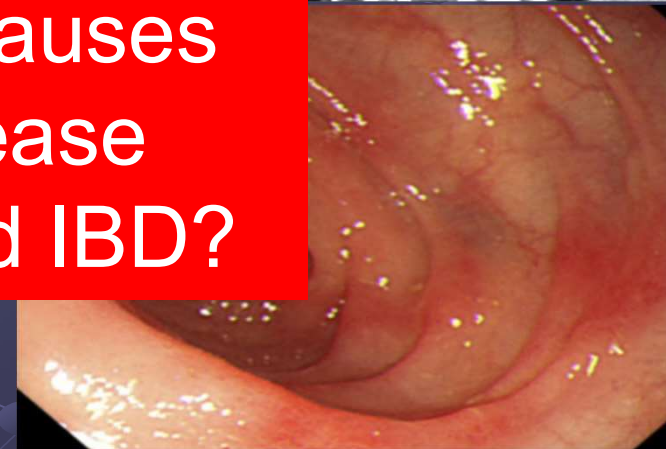
Nintedanib

small molecule tyrosine-kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet derived growth factor (PDGFR).

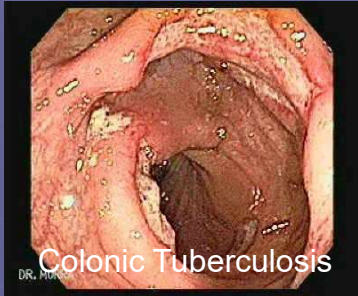
- Used in idiopathic pulmonary fibrosis systemic sclerosis, lung cancer and metastatic colon cancer.
- 30-75% develop diarrhea (in first few days)
- About 50% in both groups were also on were also on MMF.
- Gastric reports
- Main mg/d



What specialist group causes the most IBD-like disease and only that have cured IBD?



What Causes Chronic Intestinal Inflammation?



Autoimmunity Syndromes Linked with IBD

Agammaglobulinemia
Hypogammaglobulinemia
Selective IgA deficiency
Chronic granulomatous disease
NEMO syndrome (loss of NF- κ B)

IL10/R mutations
IPEX syndrome (FOXP3 mutation \downarrow Tregs)

Immune Suppression

Immune Over activation

Chemotherapy
Barrier injury and immune depletion

Drugs

GVHD

Drugs

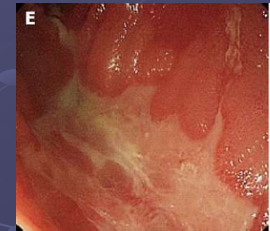
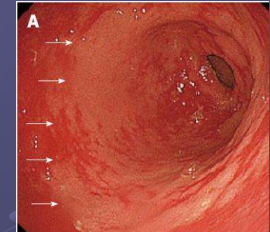
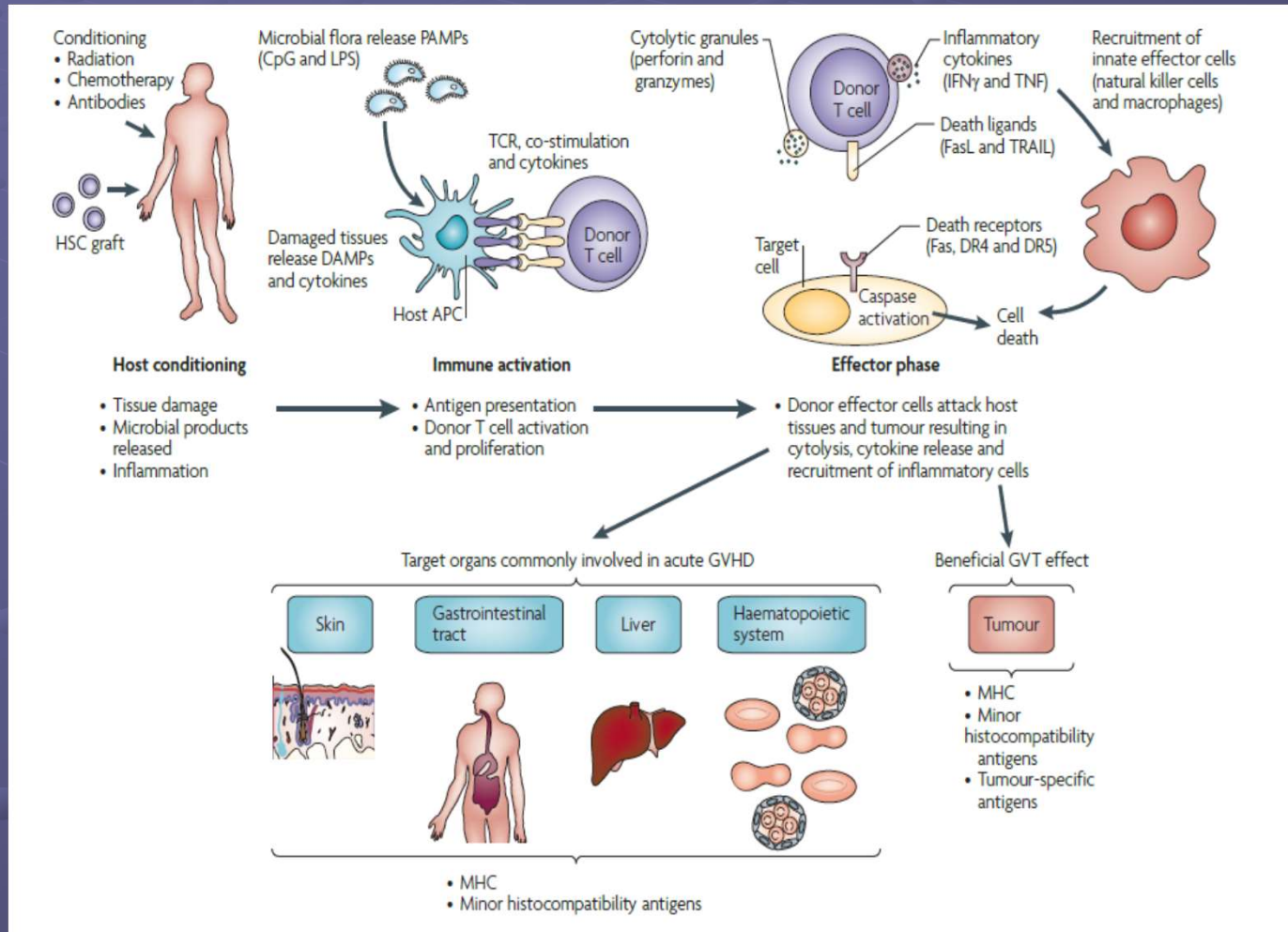
Marked Immune suppression
Increases the risk of IBD

Immune suppression is the main stay IBD therapy

What Causes Chronic Intestinal Inflammation?



GVHD and IPEX syndrome looks like IBD



IBD and Microscopic Colitis After Solid Organ Transplant

- Risk of MC 50x increased in Txpl patients
- Significant risk of IBD post transplant
 - Mostly following liver or renal txpl.
- Drugs; are they the culprit?

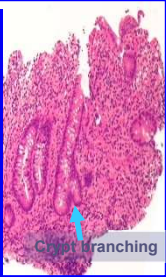
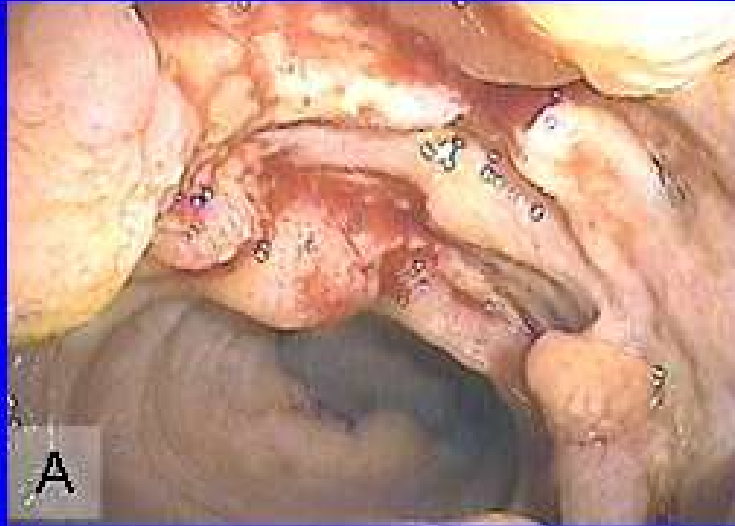
Mycophenolate Mofetil (MMF)

- One of the most common used anti-rejection drugs due to efficacy and minimal renal toxicity.
- Acts by blocking RNA/DNA synthesis in T and B cells
- Reported to cause diarrhea in 30-60% transplant patients
 - 40 pt on MMF underwent colonoscopy; 28% had IBD-like changes
- Failed as a treatment of Crohn's disease
 - Minimal efficacy
 - Exacerbation of disease in some.
 - **Now that's a good animal model**

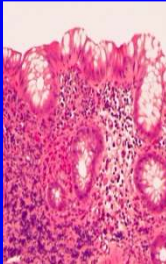
Characterization of MMF-induced Pathology

Celiac-like (MMF-Type 1 Lesion)

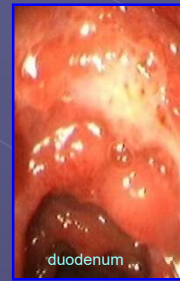
IBD-like changes (MMF-Type 4 Lesion)



GVHD-like



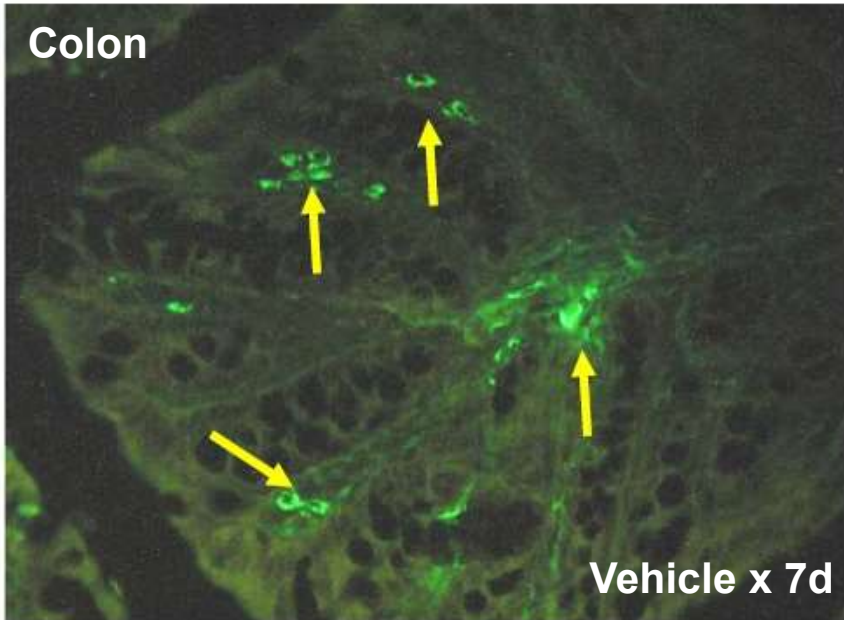
Ischemic-like





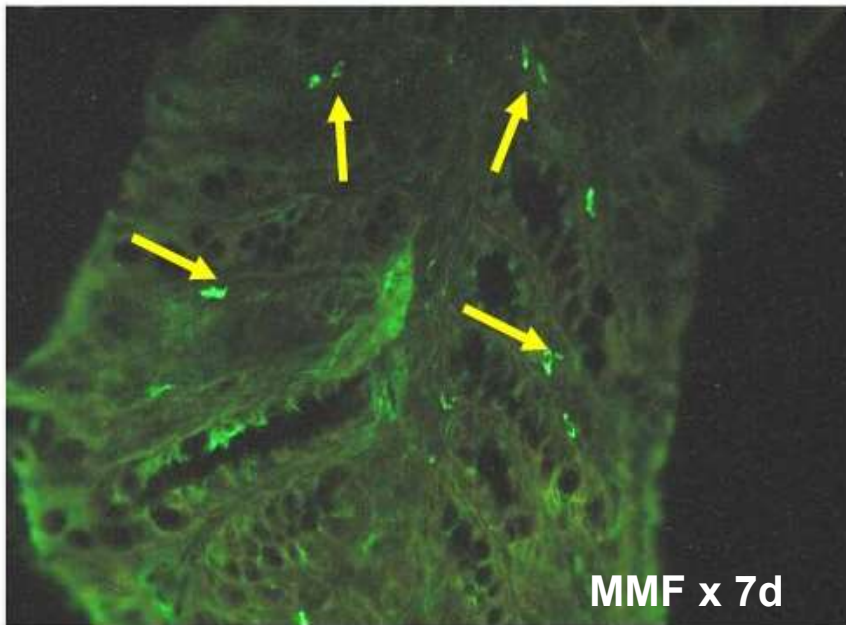
To the lab!

Colon



Vehicle x 7d

Untreated

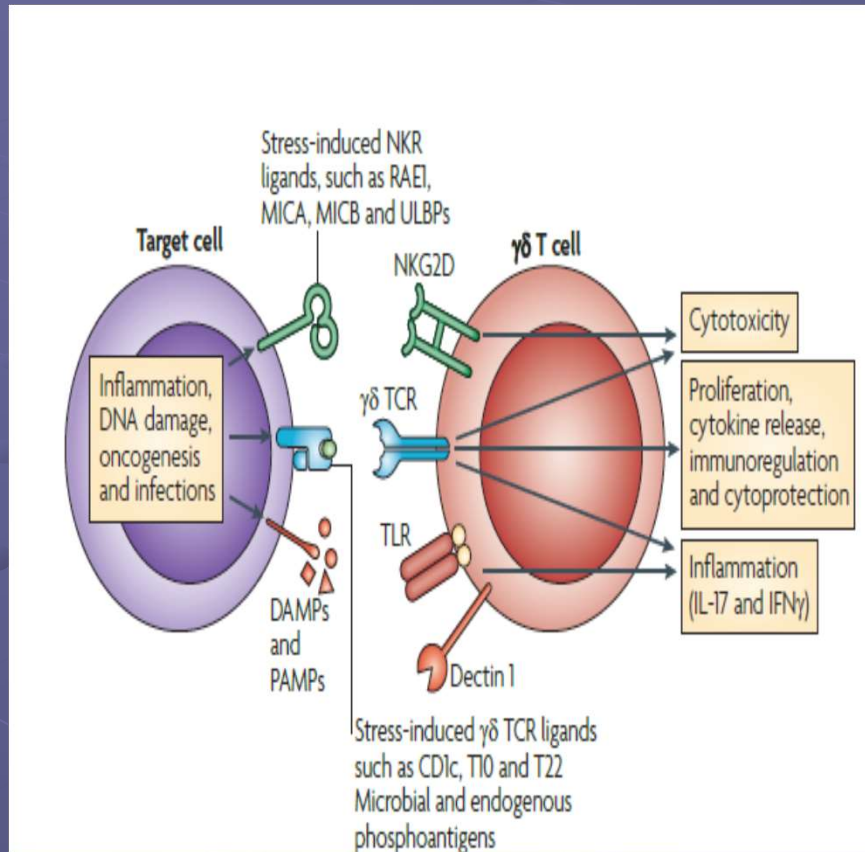


MMF x 7d

7 days MMF

MMF
Decreases
Gamma Delta
T cells in the
Intestine

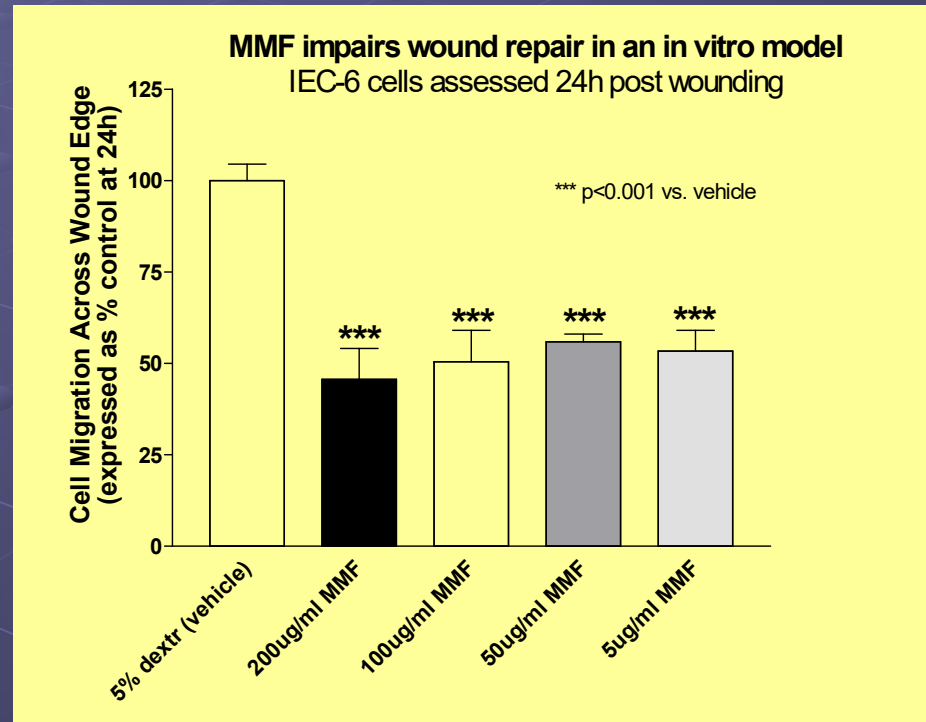
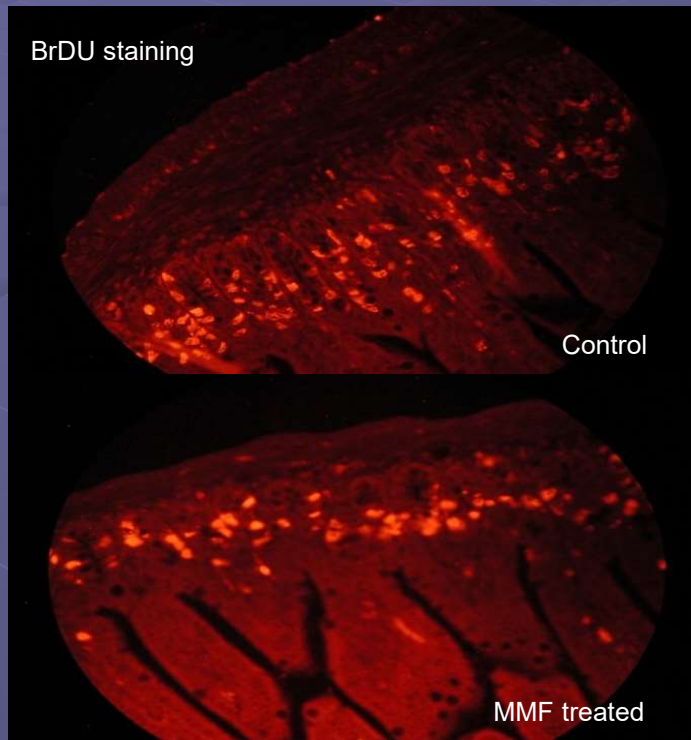
γ/δ T cells



- “The front line” of the mucosal defense
- \uparrow Celiac disease, UC and Crohn’s disease.
- Cytolytic, Immune regulatory functions
 - Can express Th 1 cytokines such as IFN- γ
 - Can produce anti-inflammatory cytokines and thus can downregulate the inflammatory response
 - Can produce KGF
 - \uparrow wound repair increased IEL proliferation
- Appears to play an essential protective role intestinal injury.
- γ/δ $-/-$ mice have crypt villous atrophy similar to that seen in celiac disease

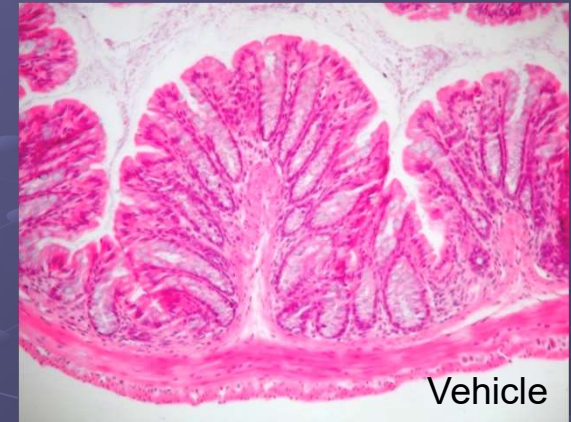
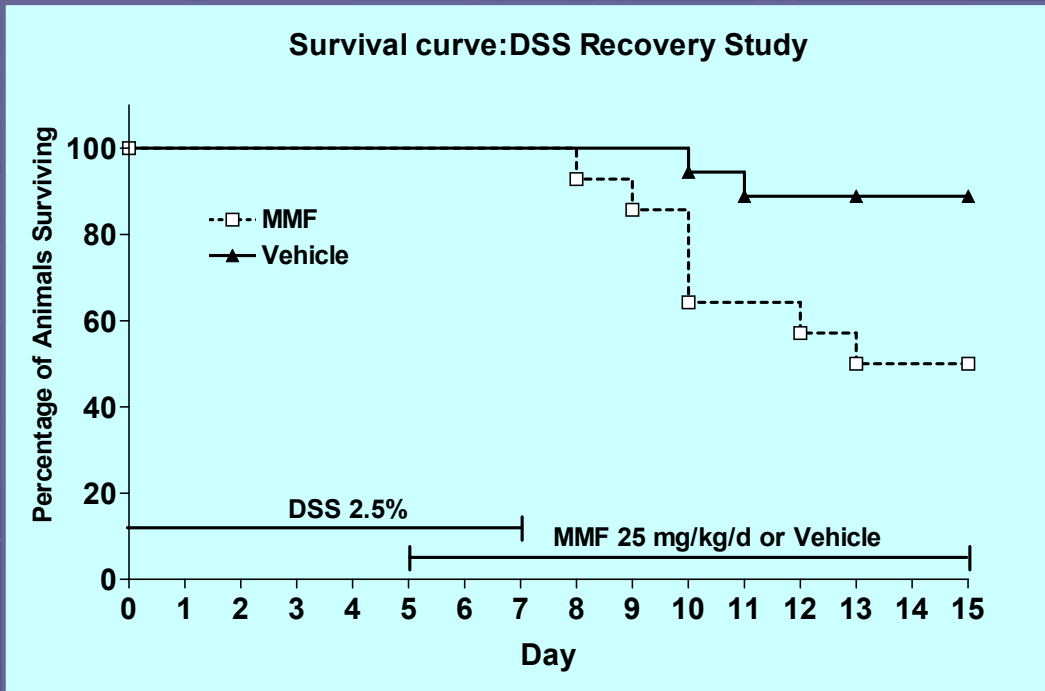
MMF decreases epithelial cell proliferation and impairs wound repair

MMF decreases epithelial cell proliferation



- Dependent on KGF

MMF Delays Recovery

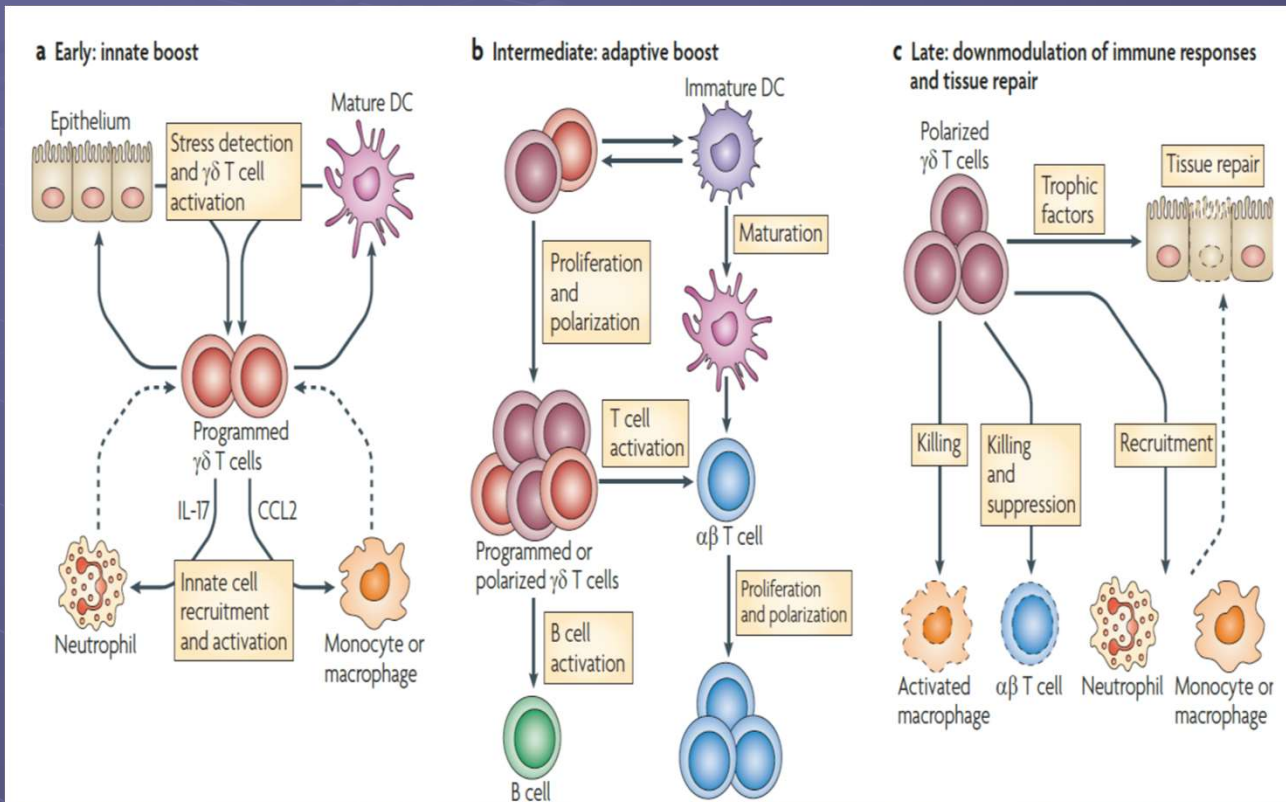


What do we see in patients?

65 yo male renal txpl, abd pain, diarrhea, anemia



MMF induces colitis via depleting γ/δ T cells



MMF-induced intestinal injury is dependent on microbiota.

New era for cancer therapy



2018 Nobel Prize in Medicine Awarded to 2 Cancer Immunotherapy Researchers



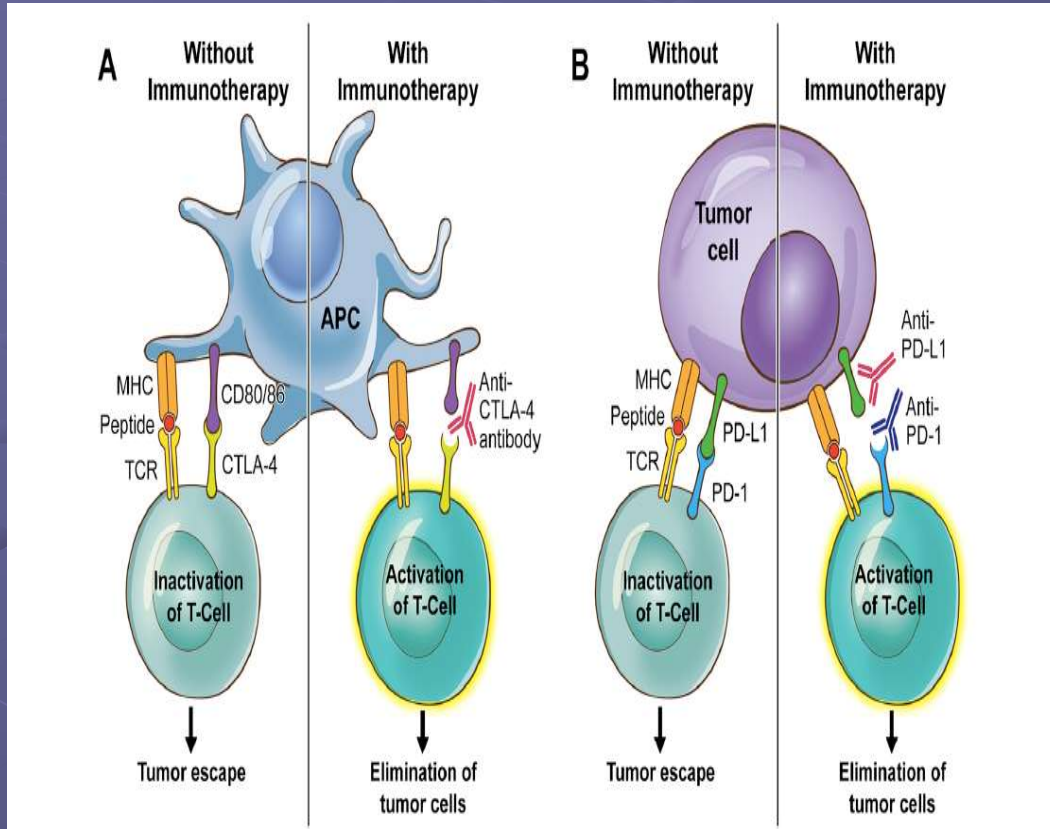
The Nobel Prize for Physiology and Medicine was awarded to James P. Allison, left, and Tasuku Honjo on Monday for their work on cancer research. Jonathan Nackstrand/Agence France-Presse — Getty Images

Nobel Prize for developing Immune check-point inhibitors for cancer therapy.

Inflammatory Bowel Disease Mimickers

Dr Franck Carbonnel
Mentoring in IBD

Role of CTLA-4 and PD-1



Blockade of these pathways upregulate T cell activation and tumor killing.

PD-1 blocking antibodies

- Nivolumab
- Pembrolizumab

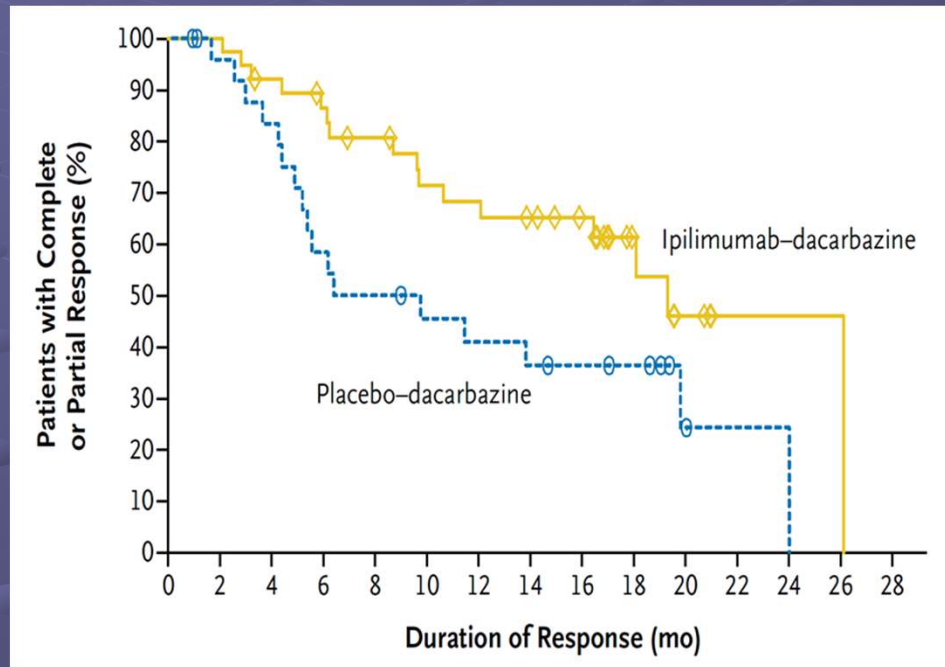
PD-L1 blocking antibody

- Atezolizumab

CTLA4 Ab: Ipilimumab

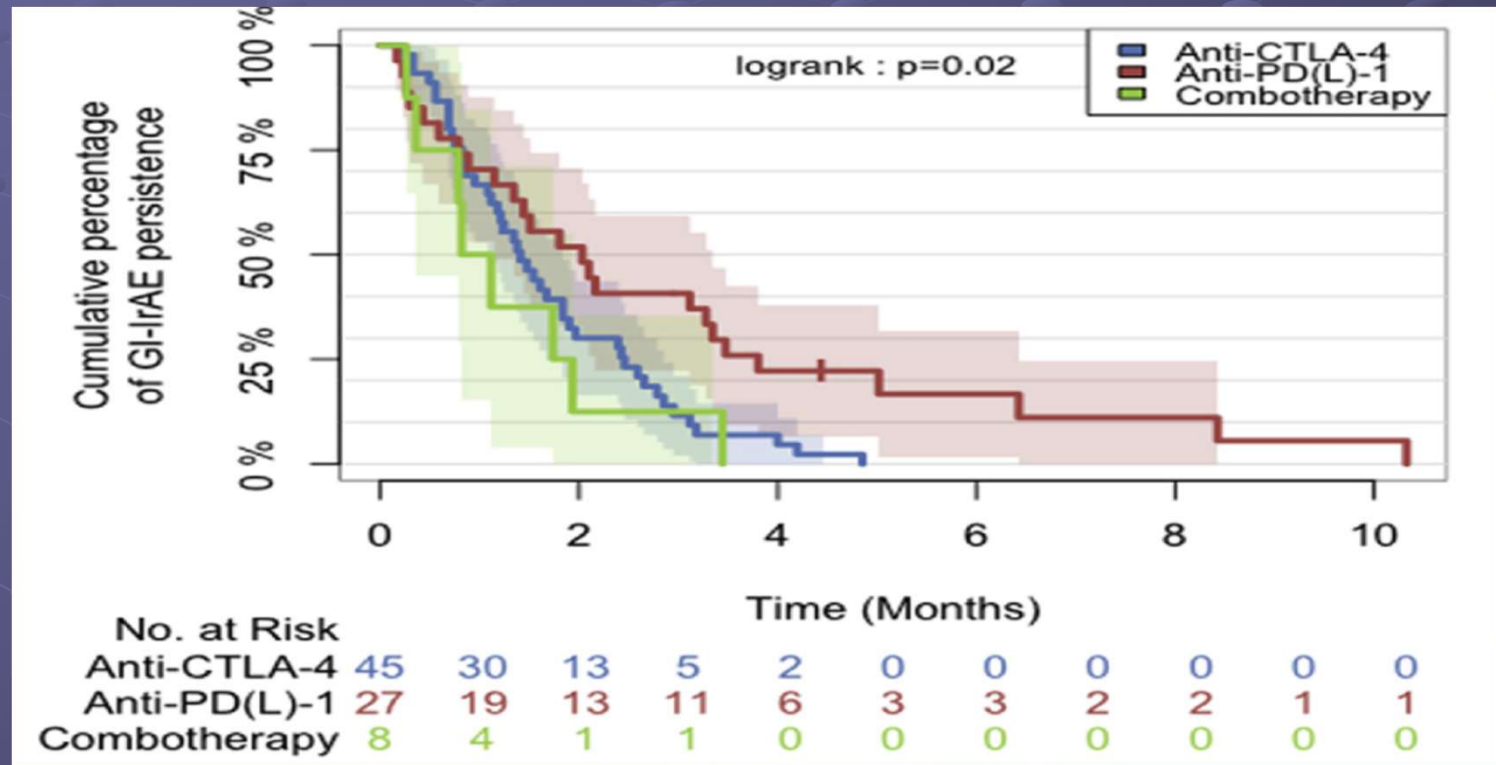
(Soularue, Gut 2018)

ipilimumab (anti CTLA4) markedly improves survival in melanoma



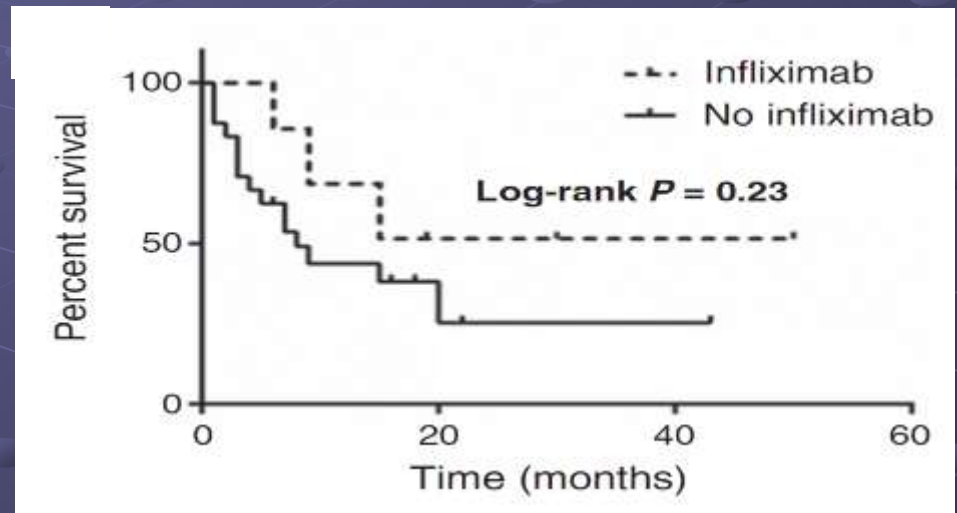
**Robert et al.
NEJM 2011**

Colitis is more severe in those on CTLA4/PD-1 combination therapy followed by CTLA4 then PD inhibitors.



When given for ICI-colitis; infliximab does not worsen malignancy

- ◆ Retrospective study : 113 patients ipilimumab
- ◆ Diarrhea n = 32 (28%)
 - ◆ Steroids n = 29/32
Median survival = 7 months
 - ◆ Infliximab n = 7/32
Median survival not reached



Arriola et al. Clin Cancer Res 2015

Germfree mouse studies found that intestinal microbiome is required for some chemotherapy agents to act.

Coley's toxin

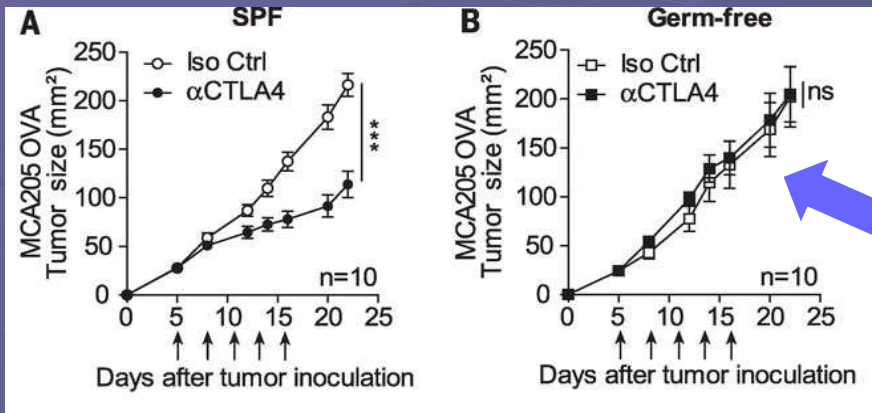
Sometimes referred as MBV for mixed bacterial vaccine, Coley's toxin was the first attempt to use immunotherapy and hyperthermia against cancer. William B. Coley MD, a bone surgeon at MSK from 1893 to 1936 developed interest when his first patient, a young girl died from metastatic sarcoma.



Coley's Toxin Treatment Results for 210 Patients

Disease	Any response	Durable CR
Soft tissue sarcomas	63% (66/104)	52% (54/104)
Lymphomas	52% (26/50)	38% (19/50)
Osteosarcoma	33% (1/3)	0% (0/3)
Ovarian carcinoma	75% (3/4)	25% (1/4)
Cervical carcinoma	100% (2/2)	50% (1/2)
Testicular carcinoma	44% (8/18)	33% (6/18)
Renal carcinoma	50% (3/6)	50% (3/6)
Multiple myeloma	100% (1/1)	100% (1/1)
Colorectal carcinoma	50% (1/2)	0% (0/2)
Breast carcinoma	43% (6/14)	14% (2/14)
Melanoma	67% (4/6)	17% (1/6)
Total	58% (121/210)	42% (88/210)

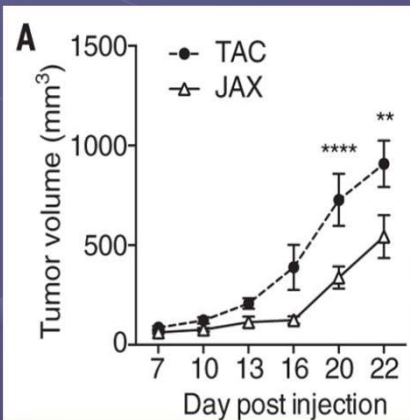
Microbiota Regulates immune checkpoint inhibitor tumor response!



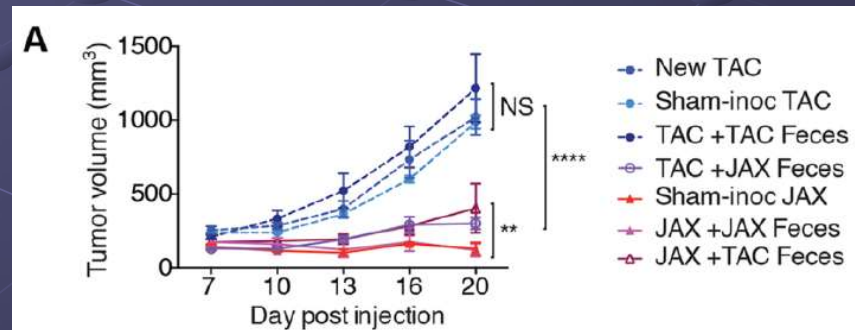
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota.
Science. 2015 November 27; 350(6264): 1079–1084

Germ free mice lost response to anti-CTLA4 (sarcoma model)

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015; 350(6264): 1084–1089;



Genetically identical mice with different microbiome respond differently

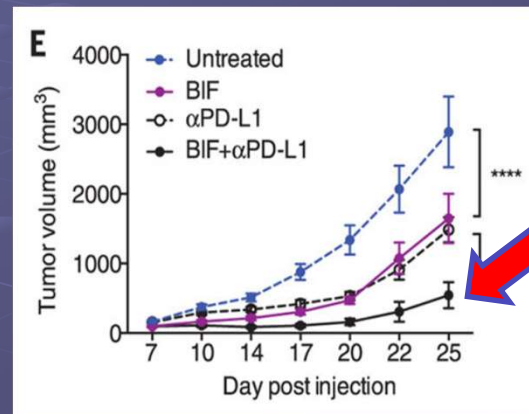
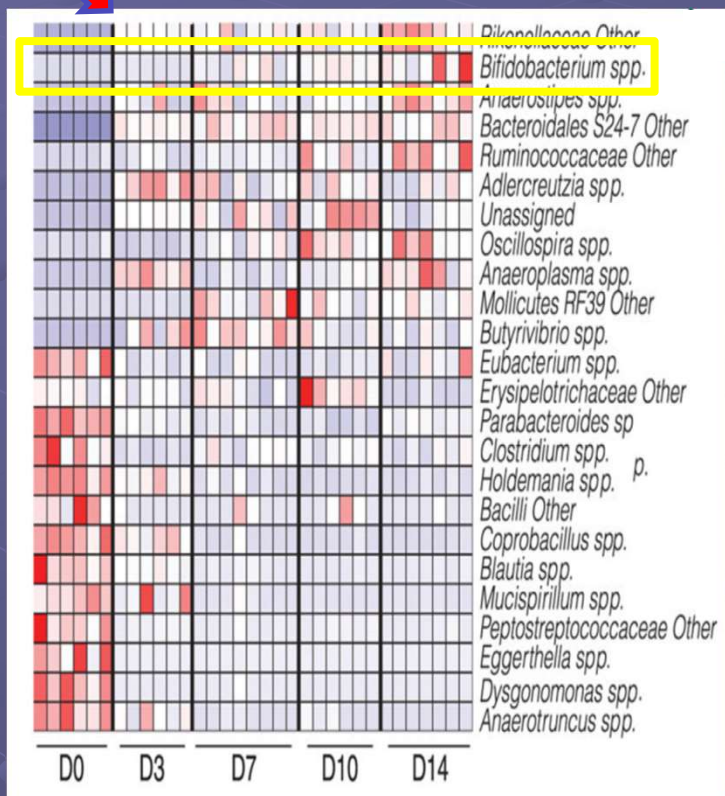


Differences eliminated with FMT

Bifidobacterium mediates the tumor resistance and response to PD-L1 Therapy

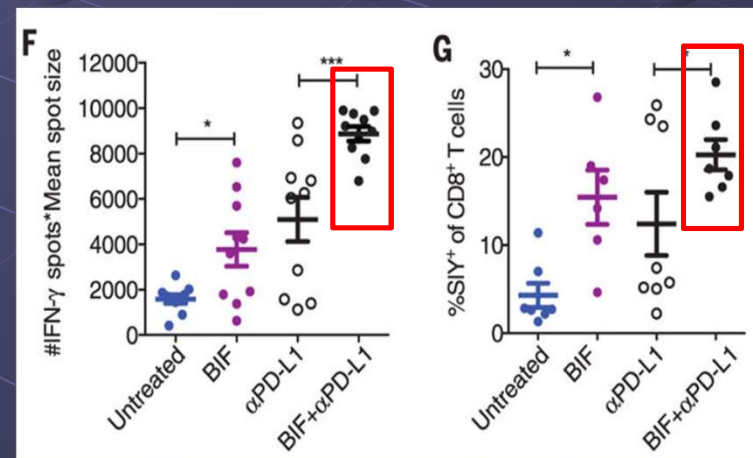
When TAC mice were fed JAX feces the main change in microbiome was \uparrow Bifidobacterium (BIF)

JAX Feces

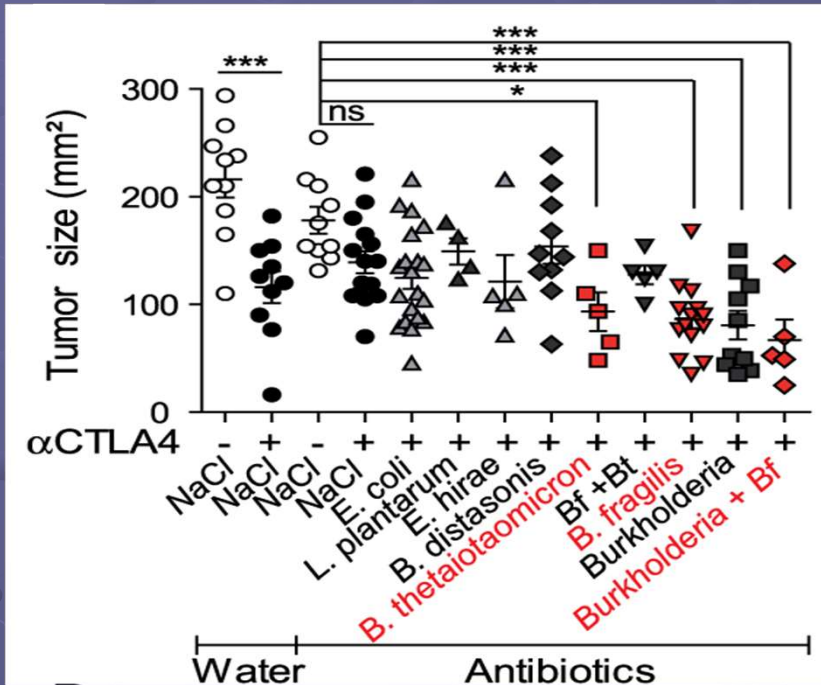


Bifidobacterium (BIF) reduced tumor growth and increased response to PD-L1 therapy

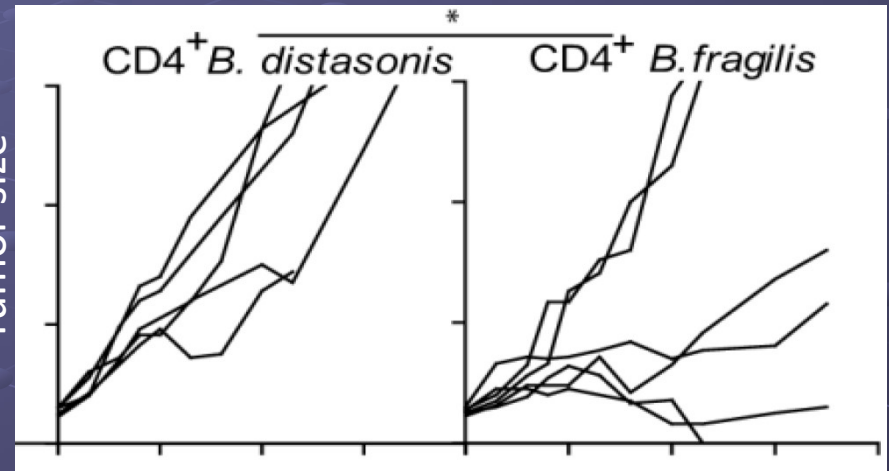
Response to PD-L1 was associated \uparrow IFN γ and CD8⁺ cells



Anti-CTLA4 efficacy need SPECIFIC bacteria



GF tumor-bearing mice treated with anti CTLA-4 and fed with specific bacteria



Memory T cell responses against Bt and Bf and anticancer efficacy of CTLA-4 blockade.

T cells harvested from spleens of mice exposed to CTLA-4 Ab and restimulated with *Bf* versus *B. distasonis* were infused intravenously in MCA205 tumor-bearing GF mice

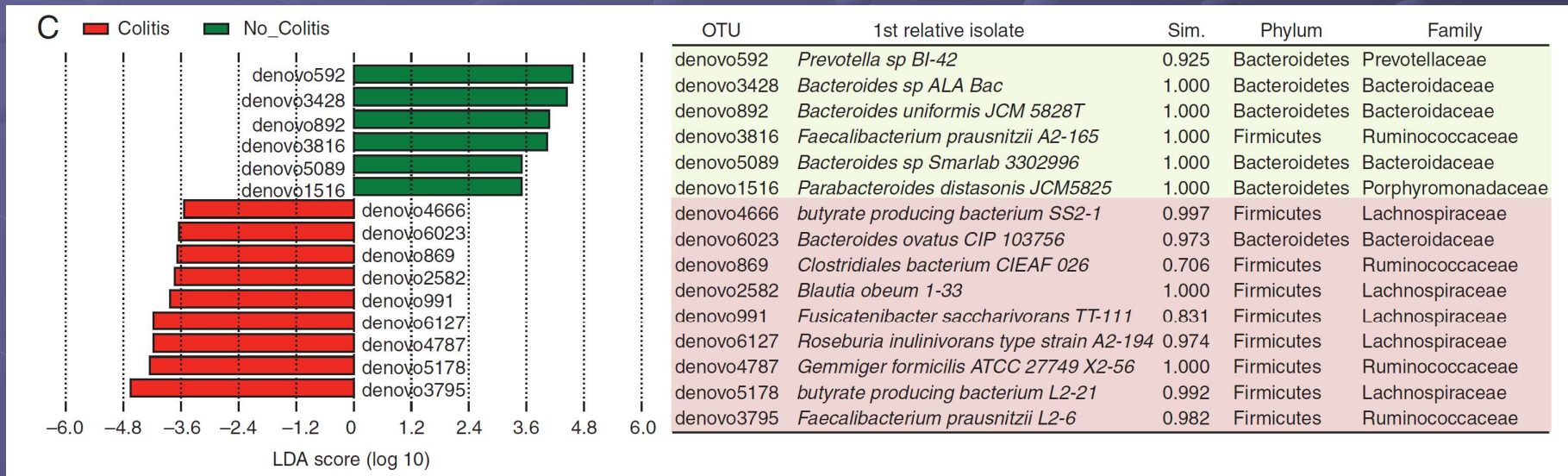
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

- Efficacy of CTLA-4 blockade is influenced by the microbiota composition (*B. fragilis* and/or *B. thetaiotaomicron* and *Burkholderiales*)
- The microbiota composition affects interleukin 12 (IL-12)–dependent T_H1 immune responses
- These bacteria are recognized by the pyrin–caspase-1 inflammasome (IL-1, IL-18) and synergizing with TLR2/TLR4 signaling pathways.
- Other pathways that maybe involved is short chain fatty acid synthesis, butyrate produced by bacteria are known to regulate the immune system.

Antibiotic therapy reduces IC tumor activity

Microbiota is a colitis predictor of colitis?

Stool sampled before CTLA-4 therapy



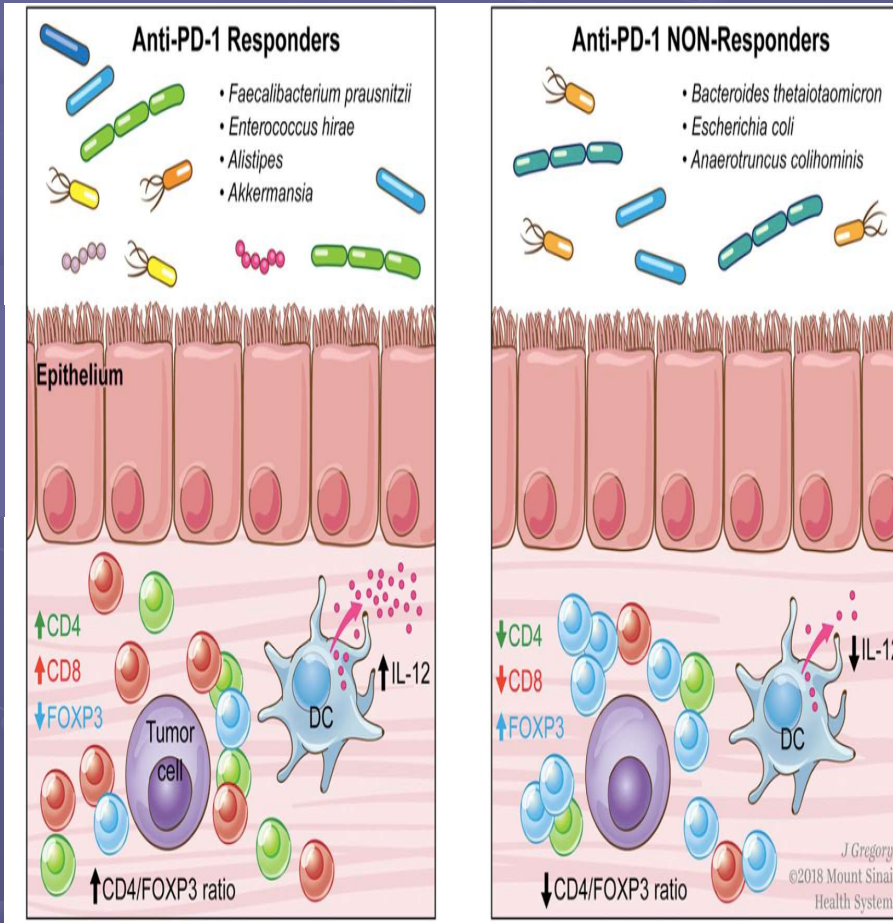
- Some specific OTUs may help predict immune-mediated colitis associated with ipilimumab in melanoma patients

Table 2. Gut bacteria and association with a response, toxicity, or both, with immune checkpoint inhibitors.

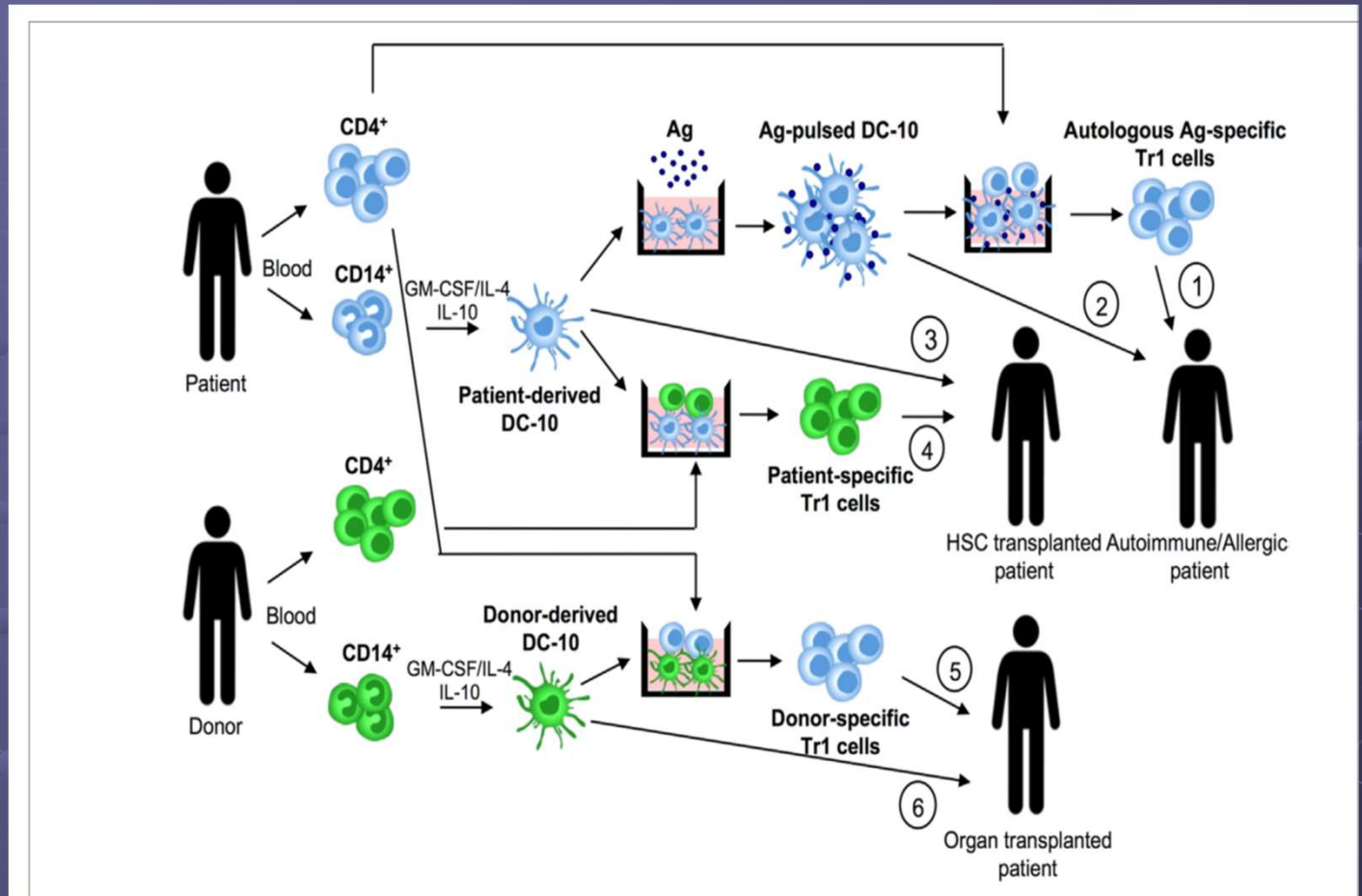
Bacteria	Tumor type studied	Impact on ICI efficacy/toxicity	Proposed mechanism of immune modulation
<i>Bifidobacterium</i> ^{33,35}	Melanoma patients and mouse models	Promotes anti-PD-1 and anti-PD-L1 efficacy	Enhance the activation of dendritic cells Increase CD8 ⁺ T cells
<i>Bacteroides</i> ³²	Sarcoma, melanoma and colon cancer (mouse models)	Promotes anti-CTLA-4 efficacy	Induce T helper 1 immune responses in tumor-draining lymph nodes Promote maturation of intratumoral dendritic cells
<i>Bacteroidetes</i> ³⁷	Melanoma (patients)	Decreased colitis secondary to anti-CTLA-4	Stimulate T-regulatory cell differentiation
<i>Ruminococcaceae, Faecalibacterium</i> ³⁴	Melanoma (patients)	Increased response to anti-PD-1	Increased antigen presentation Improved effector T cell function
<i>Bacteroidales</i> ³⁴	Melanoma (patients)	Decreased response to anti-PD-1	Impaired systemic and antitumor responses mediated by limited intratumoral lymphoid and myeloid infiltration Weakened antigen presentation capacity
<i>Enterococcus faecium, Klebsiella pneumoniae, Veillonella parvula, Parabacteroides merdae, Lactobacillus, Collinsella aerofaciens</i> ³⁵	Melanoma (patients)	Increased response to anti-PD-1	Increased frequency of dendritic cells and greater T helper cell responses Decreased frequency of regulatory T cells
<i>Ruminococcus obeum, Roseburia intestinalis</i> ³⁵	Melanoma (patients)	Decreased response to anti-PD-1	Increase in CD8 ⁺ tumor-infiltrating lymphocytes
<i>Akkermansia muciniphilia</i> ³⁶	NSCLC and RCC (patients) ¹	Increased response to anti-PD-1	Induce dendritic cell secretion of IL-12

¹NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.

Summary



- Increased TH1 (INF γ , IL2, TNF β , IL-12), Th17 and TH2 (IL4, 5, 9, 13, 25, 33) cytokines.
- Decreased Tregs.
- Altered memory T cells
- CD8+ T cells at the tumor interface is the main source of PD-1.
- Antitumor response is mediated by the microbiome.
 - Healthy microbiome better tumor response less colitis
- Main therapy for GI related toxicity
 - Steroids
 - Anti-TNF
 - Anti-adhesion (vedolizumab)
 - FMT in future!



A 3D grid of spheres on a blue background. The spheres are arranged in a regular pattern, creating a perspective effect that recedes into the distance. The background is a solid, dark blue color.

Humans are better models!

Thank you!