

Research Update: Looking for the Answers

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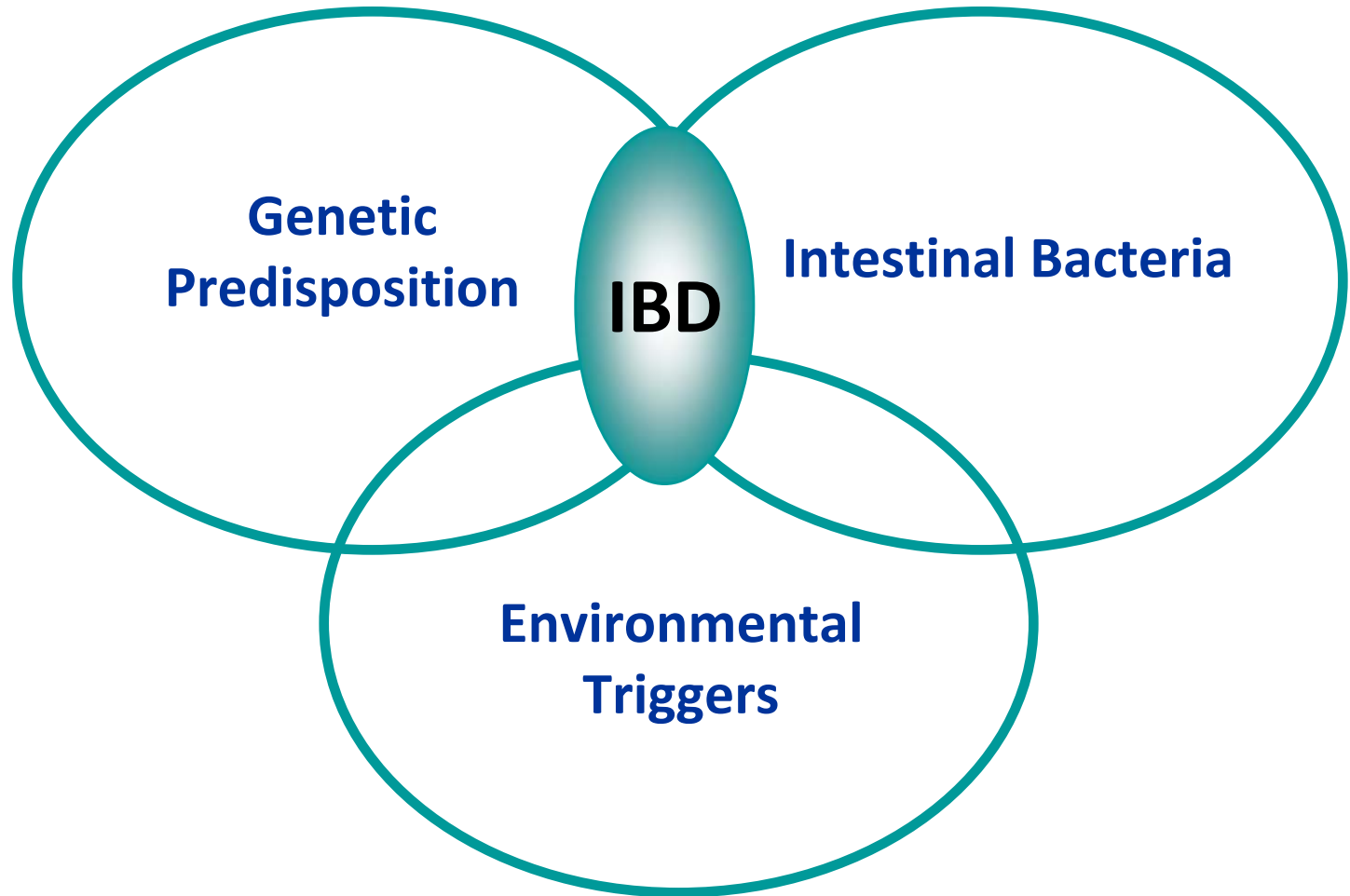


Research Support: NIH/NIDDK, CCFA, BMRP, Genentech, Centocor

Objectives

- 1) Understand the causes of IBD.
- 2) Be familiar with new therapies which are in the pipeline for IBD.
- 3) Know how to get information about clinical trials

What Causes IBD?

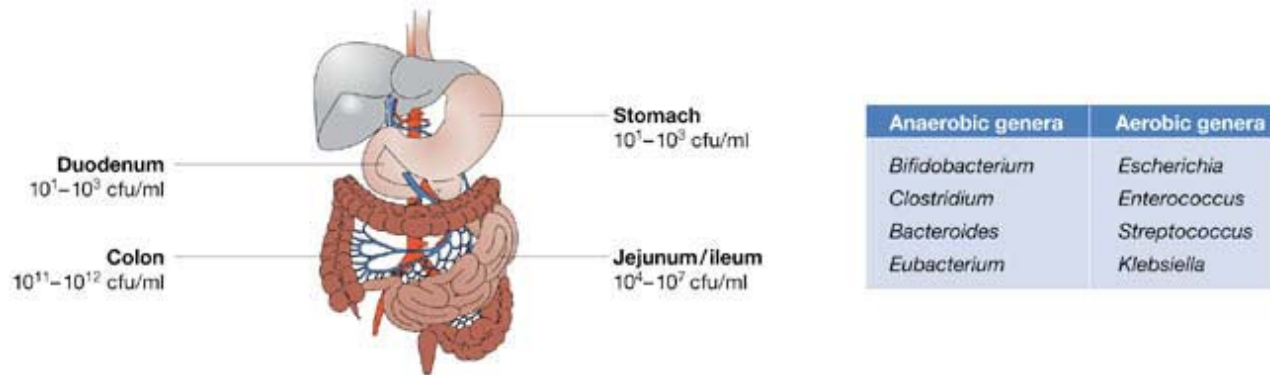


New(er) IBD Genes: 37+

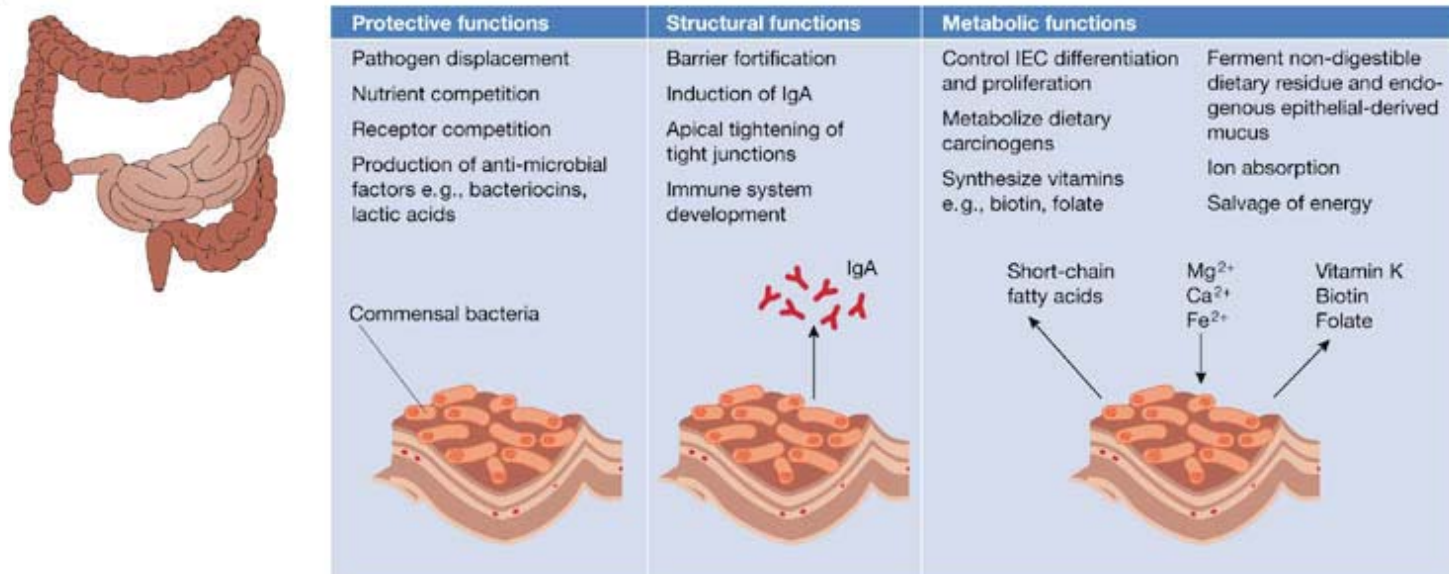
- Prevent white cells from dying
- Anti-inflammatory genes
- Bacterial sensing in very young children
- Many types of IBD: identify pathways in individual patients to target their therapy

Benefits of the Gut Bacteria

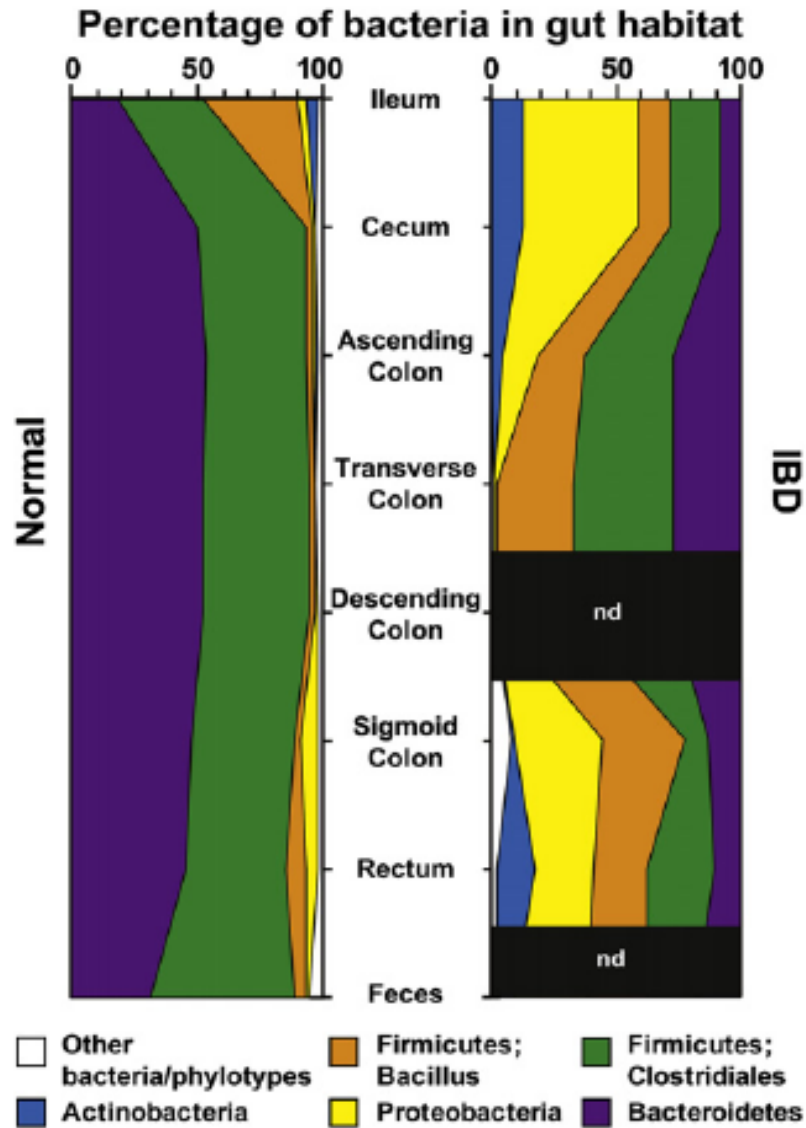
A



B



Gut Bacteria in IBD are Different

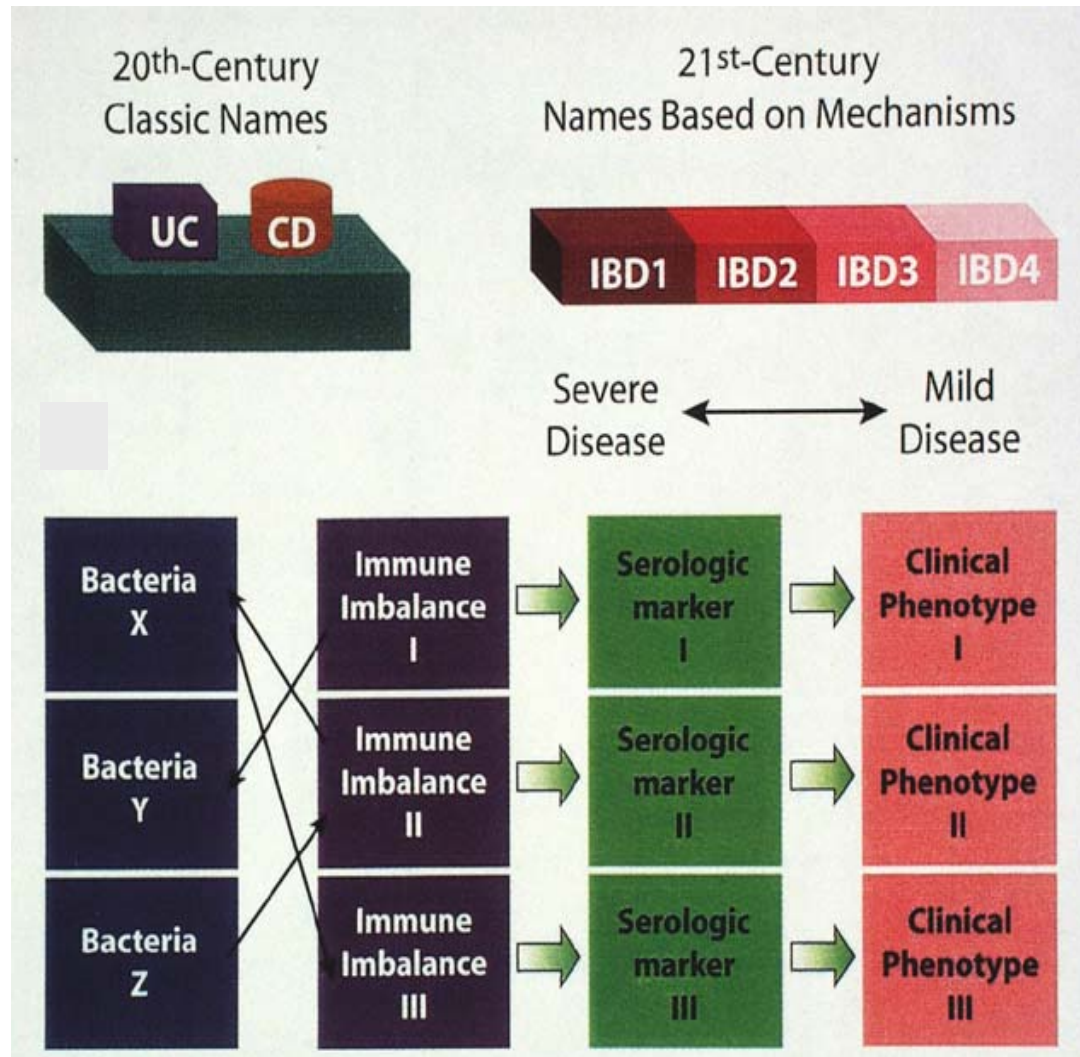


Environmental Triggers

- Stress
- Non-steroidal anti-inflammatory drugs
- Smoking
- Food or food additives?



Spectrum of Inflammatory Bowel Diseases



IBD: Treatment Goals

- Clinical remission: no disease activity
- Excellent quality of life
- Normal growth and development
- Prevent surgeries and hospitalizations
- Minimal side effects
- Acceptable financial cost

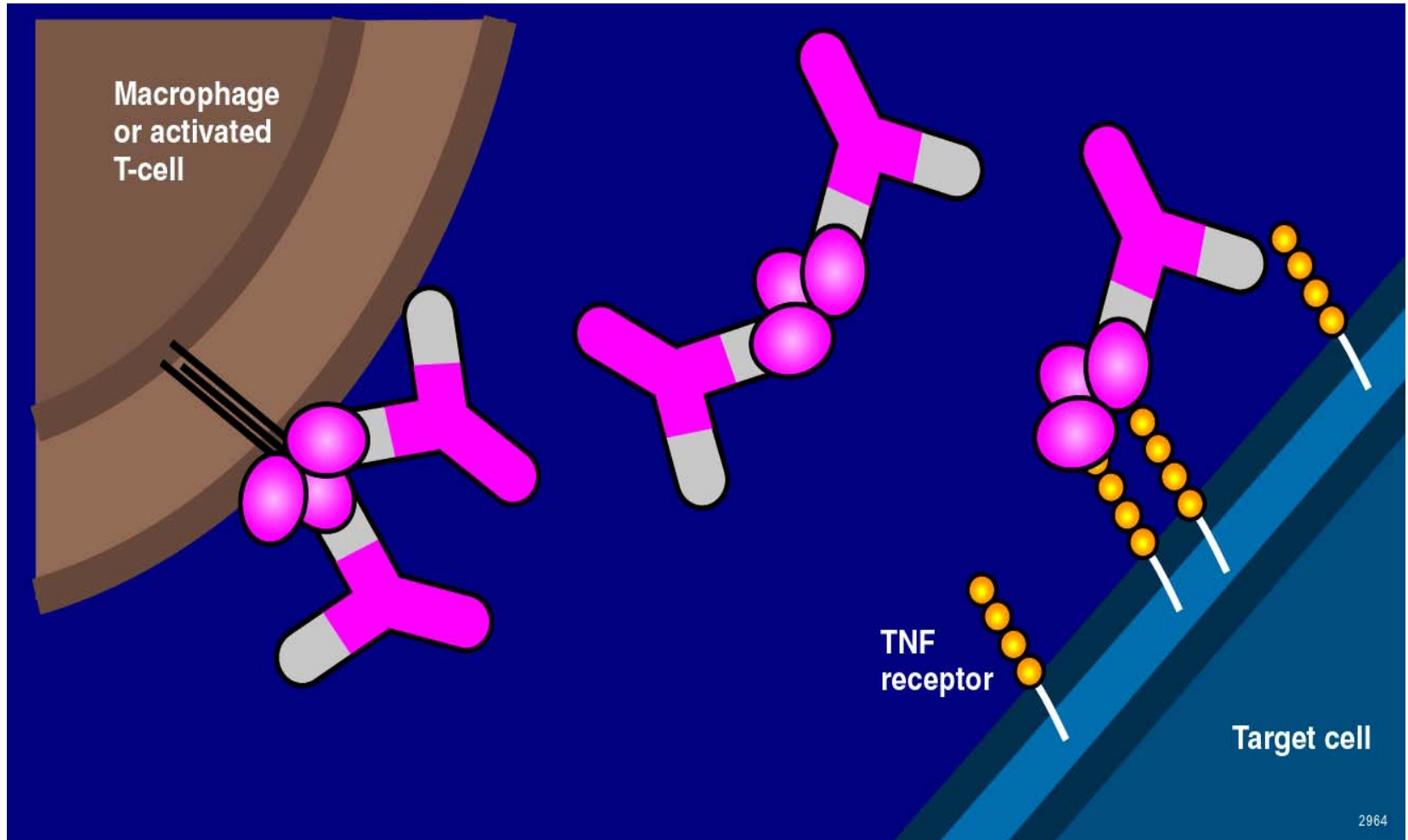
The SONIC Trial

- Infliximab and/or azathioprine for Crohns in adults
- Remission and intestinal healing
- Higher rate of remission and intestinal healing with combined therapy
- Longer term outcomes?
- Can you change to one medication at some point?

IBD: New Therapies

- New agents are being tested in over 100 clinical trials : www.ccfa.org, www.clinicaltrials.gov
- Biologics: targeted blockade of specific inflammatory mediators
- Growth factors: agents which promote tissue repair and/or normal growth
- Tolerance: agents which promote anti-inflammatory mediators
- Stem cells: may promote tissue repair and have anti-inflammatory effect

Antibody Blockade of Tumor Necrosis Factor



Ustekinumab – anti-IL-12/IL-23

- IL-12/23 pathway may drive white cell activation in some patients
- Early clinical trial showed improved symptoms in adults with Crohns
- Better responses in patients who had been on infliximab

Low Dose Naltrexone

- Opioid blocker
- May increase natural opioid (enkephalin and endorphin) levels
- May reduce inflammation and promote tissue healing
- Clinical responses in one previous small study in Crohn's

Growth Hormone

- Reduced symptoms and improved growth in children with Crohn's
- Biomarker predicted higher long-term response
- Organize a multi-center study

Restoring Immune Tolerance

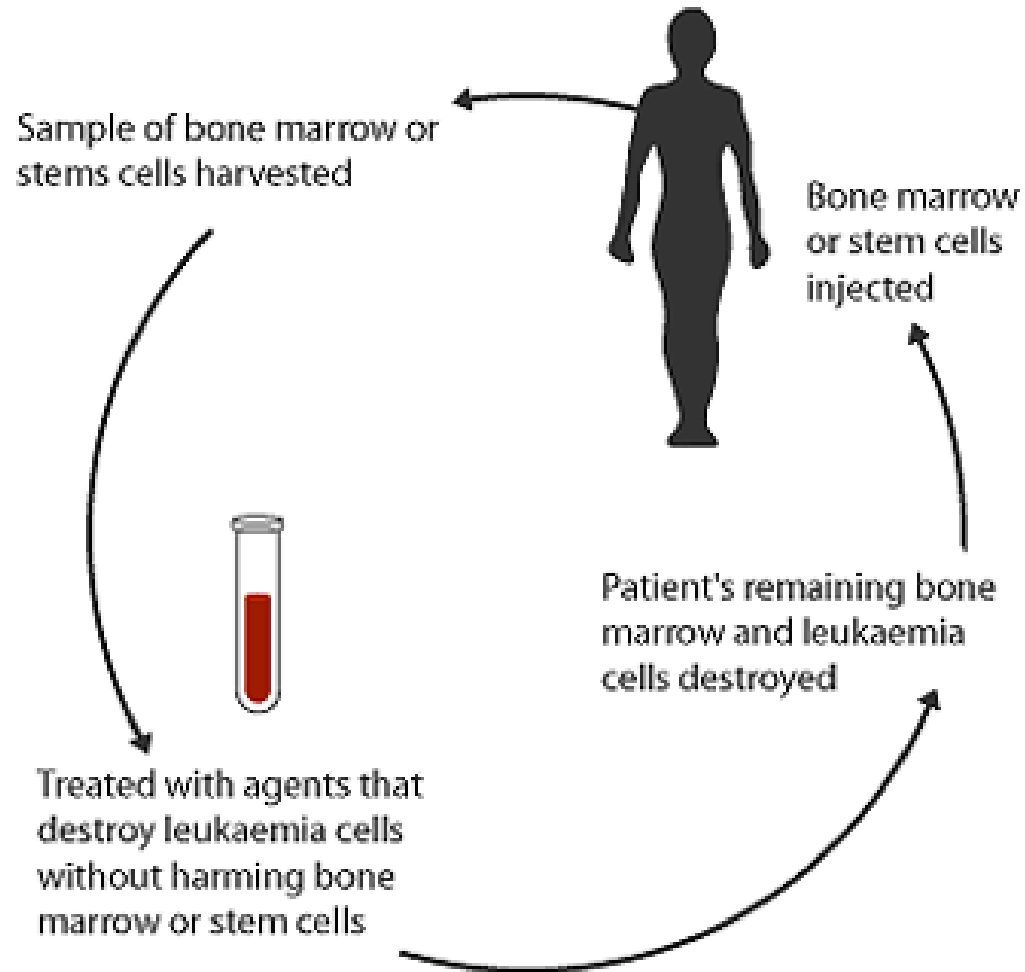
Modulate white cell activation:

- Abatacept/CTLA4-Ig –adults with Crohns/Colitis
- Interferon – adults with colitis
- Vitamin D – children with Crohns
- Turbo-probiotics – bacteria engineered to make anti-inflammatory protein IL-10

Resetting the Gut Immune System

- Autologous Hematopoietic Stem Cell Transplantation
- Conditioning regimen: very strong medications to eliminate most of the white cells causing IBD
- Replace immune system with patients own immune stem cells
- Promising early studies with a controlled trial now

Autologous Hematopoietic Stem Cell Transplantation

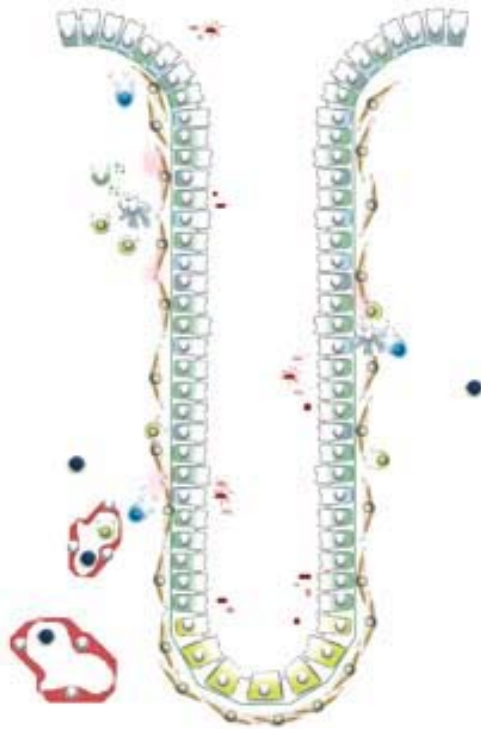


Mesenchymal Stem Cell Transplant

- Mesenchymal stem cell infusion for the induction of remission in adults with Crohn's disease
- Heal intestine or turn off immune cells with these mesenchymal stem cells
- Promising early studies with a controlled trial now

Stem Cells for IBD

Hematopoietic Stem Cells



“Reboot” the Immune System

Mesenchymal Stem Cells



Heal the Damaged Intestine
Modulate the Immune System



Hematopoietic Stem Cells
Mesenchymal Stem Cells

Targeted Individualized Therapy

- Identify treatment responders versus non-responders at diagnosis
- Predict the type of treatment which is most likely to work
- Test for early responses which will predict long term remission
- Avoid rare, significant side effects
- Optimize frequency of remission with minimal number of medications & side effects

Advances in IBD Research

- **Much Better Genetic Understanding**
- **Better Understanding of the Bacteria**
- **Improved Use of Current Medications**
- **More Options for “Biologic” Therapy**
- **Stem Cells**
- **Personalized Approach**