



# Progress in CD:

An Update On The Advances  
In Crohn's Disease



*An educational program for patients, family members  
and caregivers living with Crohn's Disease*

This program is supported by  
an educational grant from



**Jonathan Braun, MD, PhD**

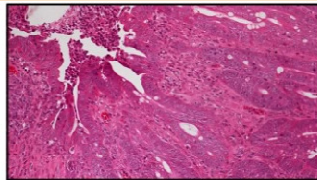
David Geffen School of Medicine at UCLA  
CCFA National Scientific Advisory Committee

## Crohn's Disease

- Chronic disease of the intestines
  - Sores (ulceration), perforation, scarring, strictures
  - All regions of intestine (especially junction of small and large intestine)
  - Abdominal pain, diarrhea, bleeding, malabsorption, abdominal infection, elevated risk of cancer



Normal



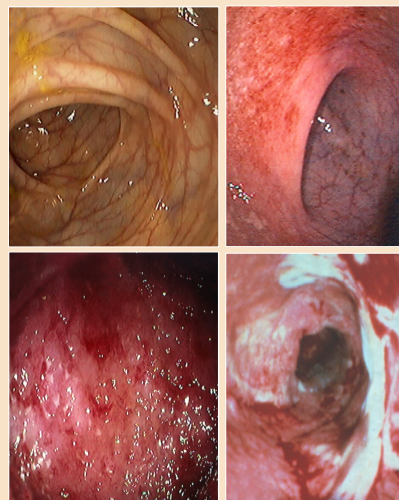
Active Disease



Treatment

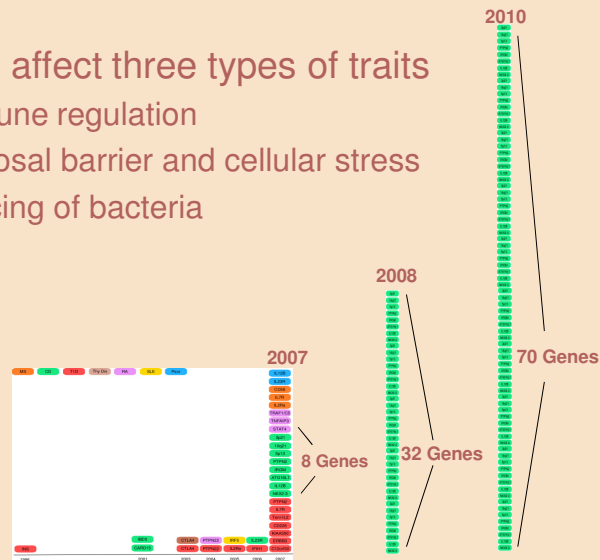
## Crohn's Disease

- Peak onset in teens
  - All ages affected
  - Growth and development problems in children
- Immune-mediated
- Family (genetic) susceptibility
- Environment affects disease risk



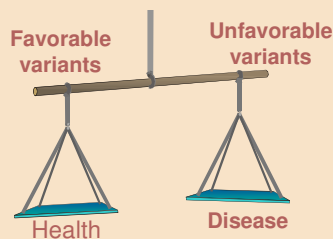
## List of Crohn's Disease Genes Is Rapidly Expanding

- Genes affect three types of traits
  - Immune regulation
  - Mucosal barrier and cellular stress
  - Policing of bacteria

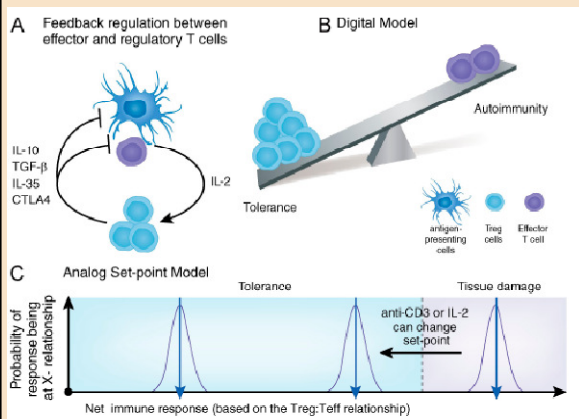


## What Do CD Genes Teach Us?

- There will be many genes when the list is complete
  - Estimated > 200
  - Single patients may have only ~5–10
  - By good fortune, unaffected siblings have slightly fewer
  - Significance: “fixing” only a few genes may be enough

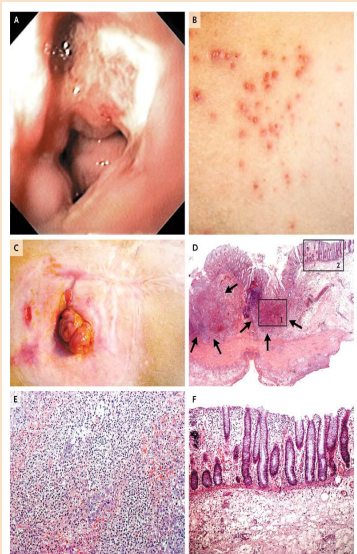


## Immune Regulation: Hormones Controlling the Balance of Inflammation



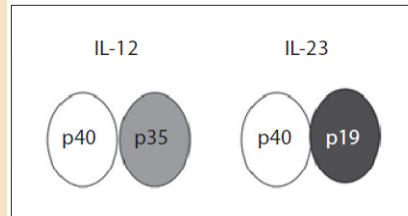
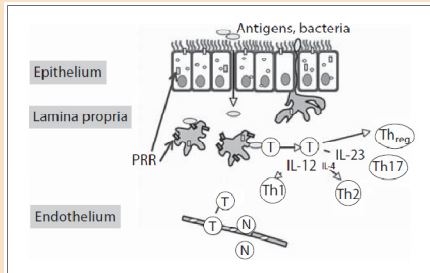
- Animal research discovers immune hormones that control colitis risk
- Examples
  - IL10 quiets inflammation
  - IL23 drives inflammation

## Early Onset (<1 y/o) Aggressive Crohn's Disease Due to a Rare Mutation in the IL-10 Hormone Receptor



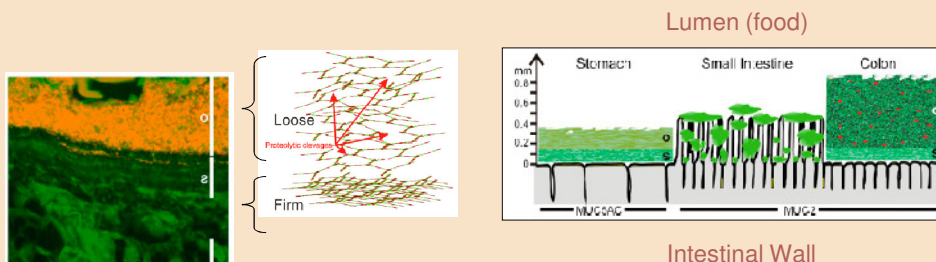
- Team Leader, Dr. Scott Snapper
  - CCFA Research Initiatives Chair
  - Glocker EO. *N Engl J Med*, 2009
- Treatment implications
  - IL10 hormone won't correct
  - Stem cell replacement gave complete remission
  - Future: identify alternative hormone

## Targeting the IL-12/IL-23 Pathway in Crohn's Disease



- Human genetics
  - An overactive IL23 receptor gene variant is present in 90% of Crohn's patients
- Strategy: Block the IL23 receptor
  - IL12 and IL23 receptors *both* can be targeted via shared p40
- First success: phase 2 clinical trial (Mannon et al. *N Engl J Med.* 2004)
- Ustekinumab phase 3 trials underway

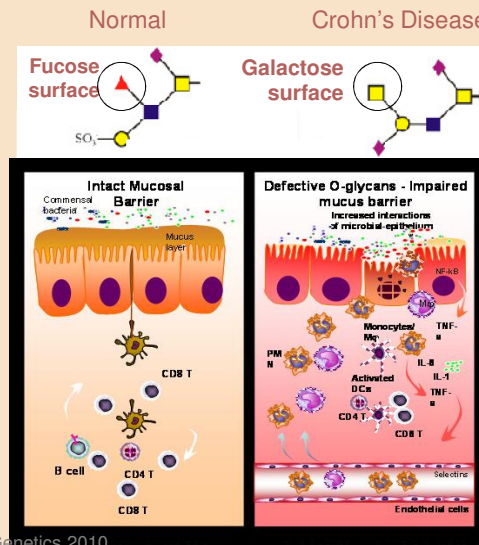
## Barrier Control and Epithelial Stress The News About Mucus



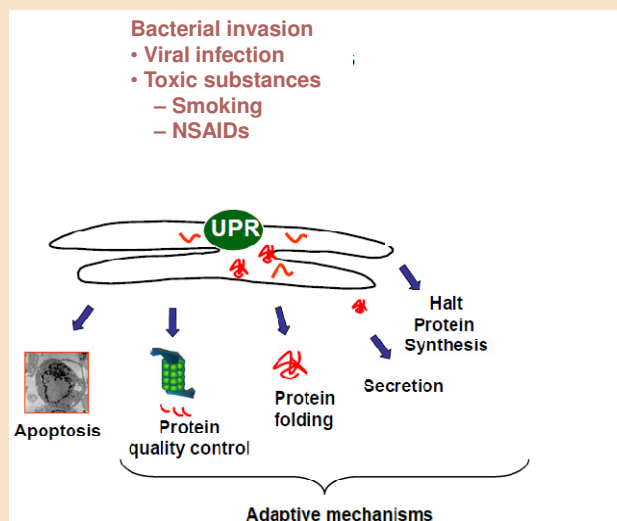
- Mucins
  - Core of protein
  - Sticky (sugar) flypaper exterior
  - Aggregates as a lattice
- Loose mucus
  - Flypaper for bacteria
- Firm mucus
  - Insulation against bacteria

Johansson MV, PNAS 2010

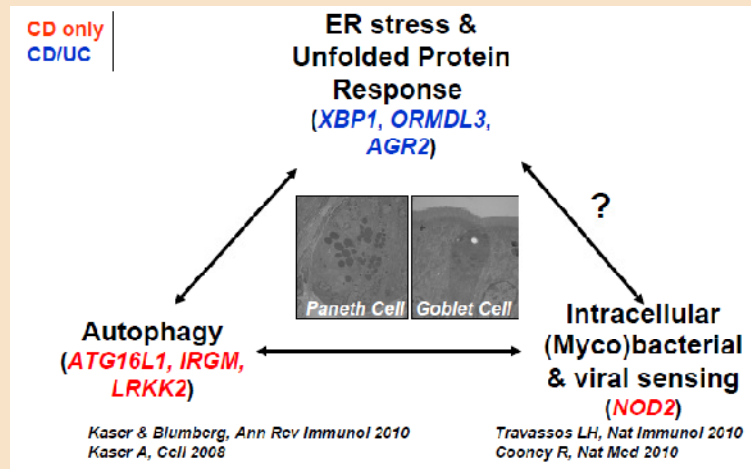
## Deficiency of the *FUT2* Enzyme Gene: Loss of the Fucose “Flypaper” in Crohn’s Disease



## Cellular “Stress” and Crohn’s Disease

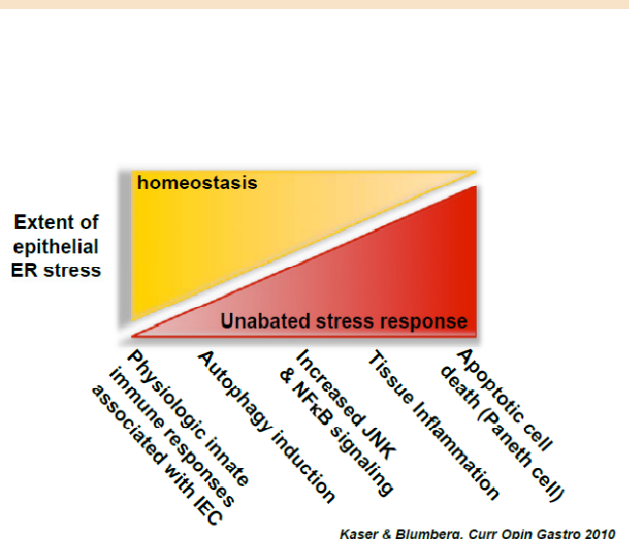


## Crohn's Disease Risk Due to Variants of Cellular Stress and Bacterial Control Genes



## Stress Therapy for Crohn's Disease

Compensatory targets for deficits in ER stress and control of bacteria



- Mucin replacement
- JNK inhibitors
- NFκB inhibitors

## CCFA Genetics Initiative

- First phase (inception, 2000)
  - Creation of first international team
  - DNA bank from patients
  - Discovery of original IBD genes
- Second phase (inception, 2011)
  - Create a gene testing toolkit for patients and doctors
  - Find the clinically most important genes:
    - Affect response to treatment
    - Determine disease severity
  - Identify genes suitable for treatment strategies

## 80 Agents in the Clinical Trial Pipeline

- Homing blockers
  - Natalizumab (approved, 2008)
  - Vedolizumab (phase III, 2009)
- IL12 and 23 blockers
  - Ustekinumab (phase III, 2009)
- Adult mesenchymal stem cells
  - Control inflammation, promote tissue repair, prevent scar formation
  - Prochymal (phase III, 2009)
- Combination of TNF blockers and methotrexate
  - More frequent response and better maintenance for fistulizing Crohn's
  - Concern: infection and cancer risk
  - CCFA Clinical Alliance trial to clarify best patients for combination therapy



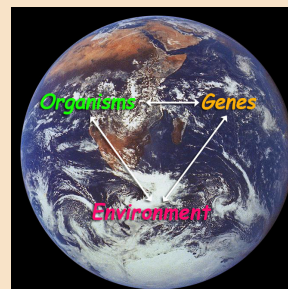
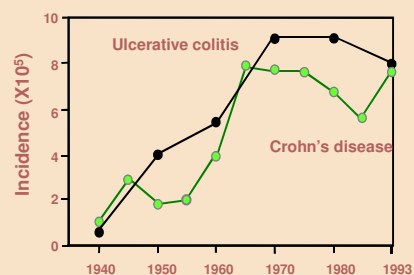
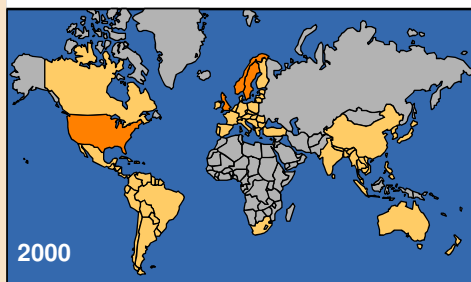
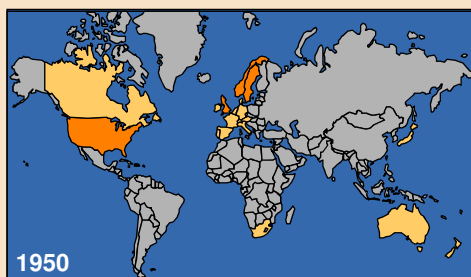
## PIANO

### Pregnancy in Inflammatory Bowel Disease And Neonatal Outcomes

- CCFA-initiated clinical study
  - Leader: Uma Mahedevan, UCSF
- 413 patients divided into 4 groups
  - No immunosuppression; AZA/6MP; Biologics; Combination
- Medication use not associated with increased risk of:
  - Any complication
  - Preterm birth, low birth weight
  - Cesarean section
  - Congenital anomalies: 17 anomalies/15 births
- Biologics: increased risk of NICU stay
- Combination: increased risk of infection at 1 year of age

Join the registry: [www.cffa.org/trials](http://www.cffa.org/trials) (Search: PIANO)

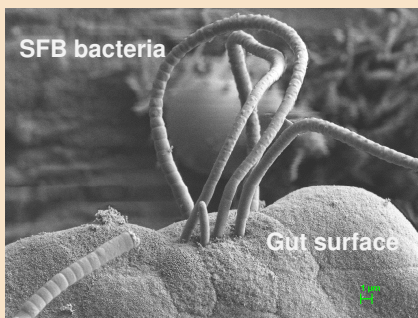
### The Inflammatory Bowel Disease Epidemic Changing, Diets, Lifestyles, and Biosphere



## Injurious and Protective Bacteria at the Intestinal Surface Associated With Crohn's Disease

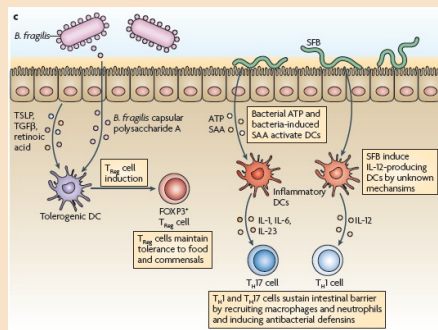
**Bad bacteria candidates**  
 Elevated in patients and in flares  
 Products damage intestine

Adherent/invasive *E. coli*  
 Segmented filamentous bacteria  
 Lachnospiraceae (CBir)



**Good bacteria candidates**  
 Reduced in patients and in flares  
 Products protect intestine

*Faecalibacterium prausnitzii*  
*Lactobacillus* spp.  
*Bacteroides fragilis*



## Individual Variation in Microbial Composition

### CCFA Microbiome Initiative

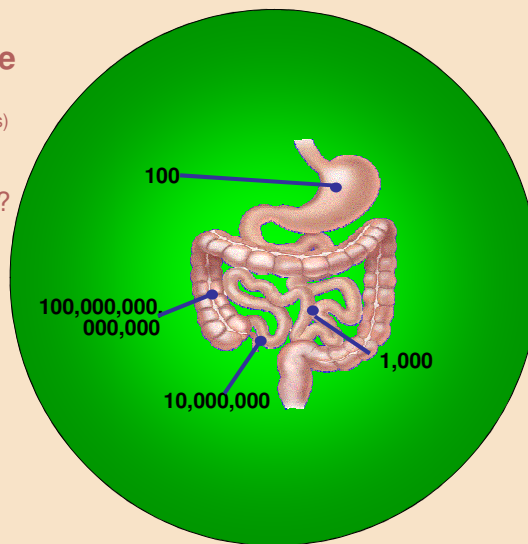
First Phase

Jeffrey Gordon (Washington University, St. Louis)  
 Rob Knight (University of Colorado)

- What types of bacteria live in us?
- What do they do for us?
- Create a toolkit and dashboard

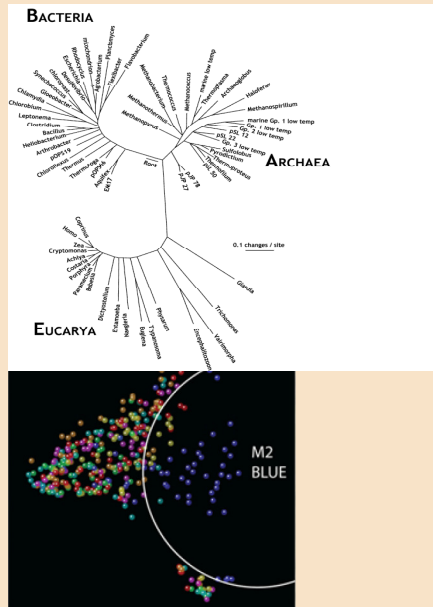


You  
 (1 trillion cells)



Your Intestinal Bacteria  
 (10–100 trillion cells)

## CCFA Microbiome Initiative (First Phase)

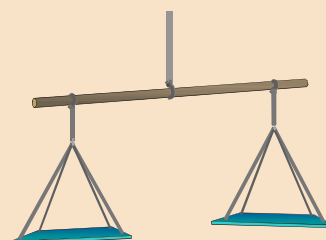


- 200 species per person
- Little species overlap between people
- Mother effect: species are shared by siblings
- However, a mosaic of *functions* are shared between people
- Toolkit: QIIME online (<http://qiime.sourceforge.net>)

## CCFA Microbiome Initiative (Second Phase)

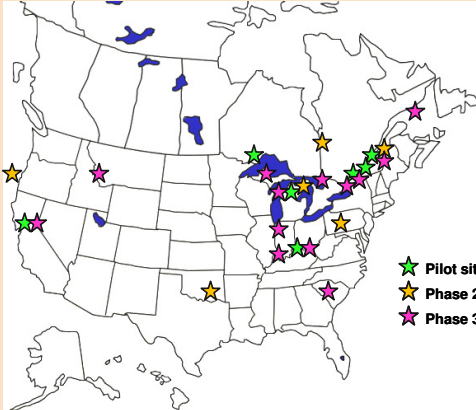
- Determine full bacterial composition in individual IBD patients
- Alterations in bacterial functions in individual IBD patients
- Effect of IBD-related genes on intestinal bacteria
- Test strategies to alter intestinal bacteria
- Effect of dietary manipulations on bacterial microbial composition
- Creating a dashboard for patients to monitor and adjust their bacteria

- **Selectively alter the balance**
  - Diet and prebiotics
  - Probiotics
  - Antibiotics
  - Engineered bacteria (IL10, KGF2)



## PRO-KIIDS

### CCFA Pediatric IBD Clinical Research Network




- Total CCFA commitment – \$5.2 million
- 38 US and Canadian Centers
- 1100 children new with Crohn's
- Identify predictors of early complications & surgery

## PRO-KIIDS

### CCFA Pediatric IBD Clinical Research Network

1100 children with Crohn's at diagnosis



Genetic makeup  
 Composition of gut bacteria  
 Serology (reactive to bacteria, food, infection)  
 Environmental exposures

3 years → 160–200 patients with complication / surgery

## CCFA Partners

- A new program to enlist patient and family participation in activities to further increase our understanding of Inflammatory Bowel Diseases (IBD)
- A long-term patient registry to participate in IBD research
- Broaden participation and inform registry members of upcoming studies and trials
- Increased patient involvement for more rapid research progress by shortening the time required to compile sufficient research data to complete the project(s)
- The investigators of CCFA Partners are:
  - Lloyd Mayer, MD (Chair, National Scientific Advisory Committee)
  - Bruce Sands, MD, MS (Chair, Clinical Research Alliance)
  - James D. Lewis, MD, MSCE (Vice-Chair, Clinical Research Alliance)
  - Sunanda Kane, MD (Chair, Patient Education Committee)
- Contact
  - [info@ccfa.org](mailto:info@ccfa.org)

## Questions & Answers