

# 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

## Program Objectives

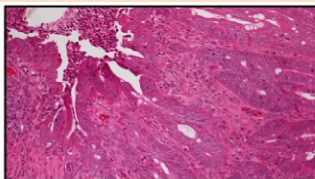
- Provide an overview of Crohn's disease
- Highlight newly uncovered genes and targets for treatment in genetic research
- Identify microbiome research and the role of bacteria in Crohn's disease
- Highlight clinical research studies in targeted groups: pregnancy and pediatrics
- Introduce CCFA Partners program and its importance in the future of research

## 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



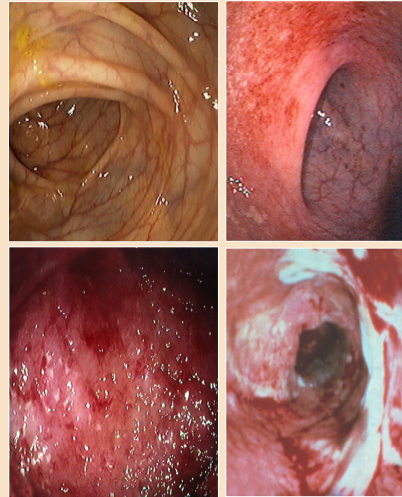
Active Disease



Treatment

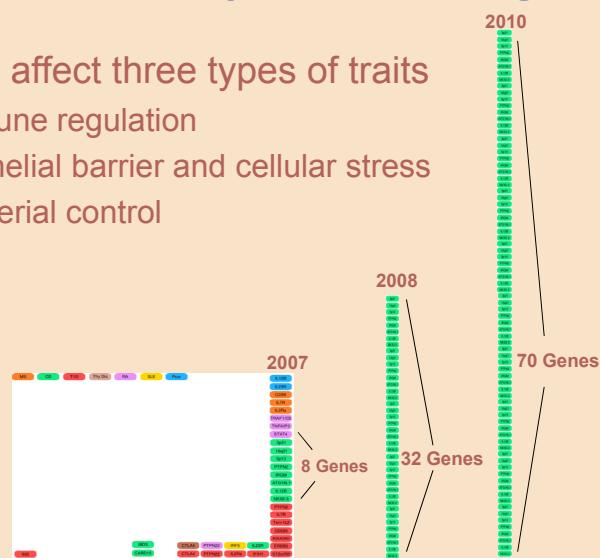
## Crohn's Disease

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



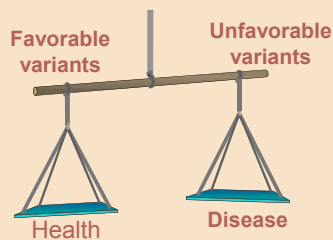
## List of Crohn's Disease Genes Is Rapidly Expanding

- Genes affect three types of traits
  - Immune regulation
  - Epithelial barrier and cellular stress
  - Bacterial control

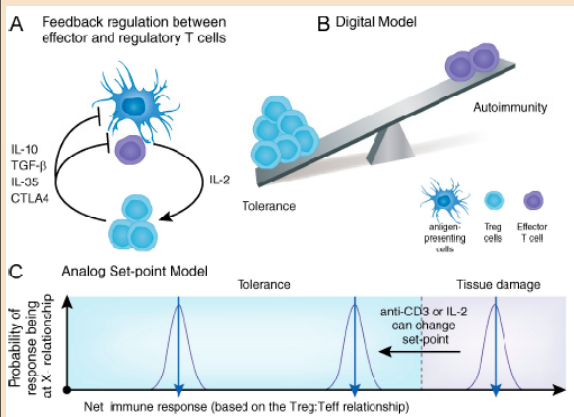


## What Do CD Genes Teach Us?

- 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



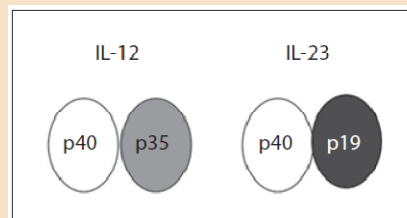
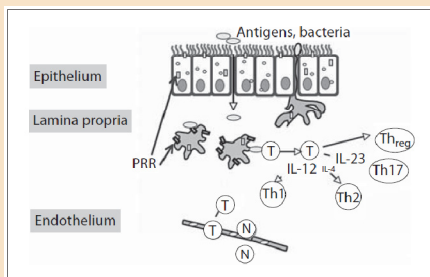
- Animal research discovers immune hormones that control colitis risk
- Examples
  - IL10 quiets inflammation
  - IL23 drives inflammation

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



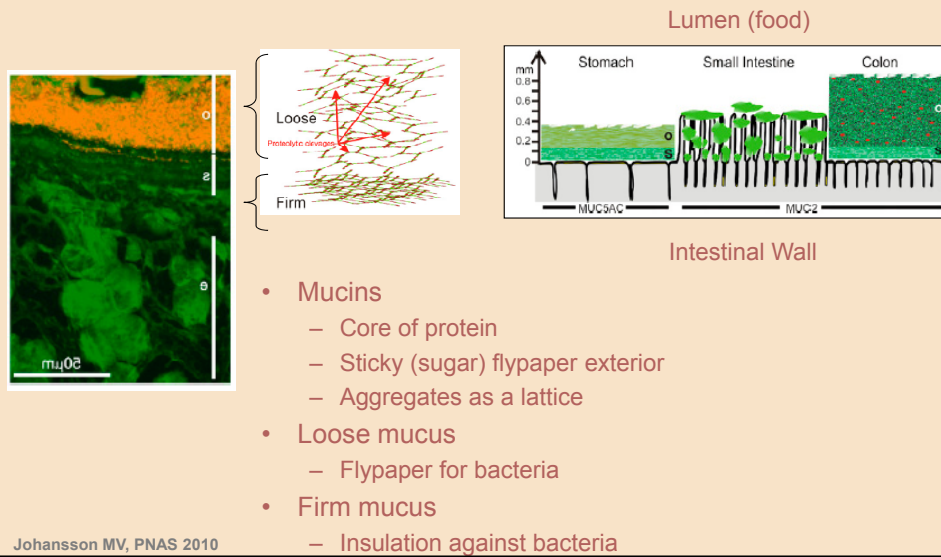
- Team Leader, Dr. Scott Snapper
  - CCFA Research Initiatives Chair
  - Glocker EO. *N Engl J Med*, 2009
- Treatment implications
  - IL10 hormone won't correct
  - Stem cell replacement gave complete remission
  - Future: identify compensatory hormone

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

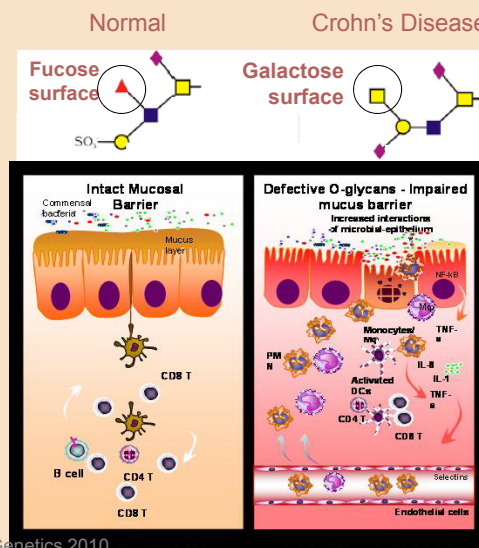


- Human genetics
  - An overactive IL23 receptor gene variant is present in 90% of Crohn's patients
- Strategy: Block the IL23 receptor
  - IL12 and IL23 receptors *both* can be targeted via shared p40
- First success: phase 2 clinical trial (Mannon et al. *N Engl J Med*. 2004)
- Ustekinumab phase 3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

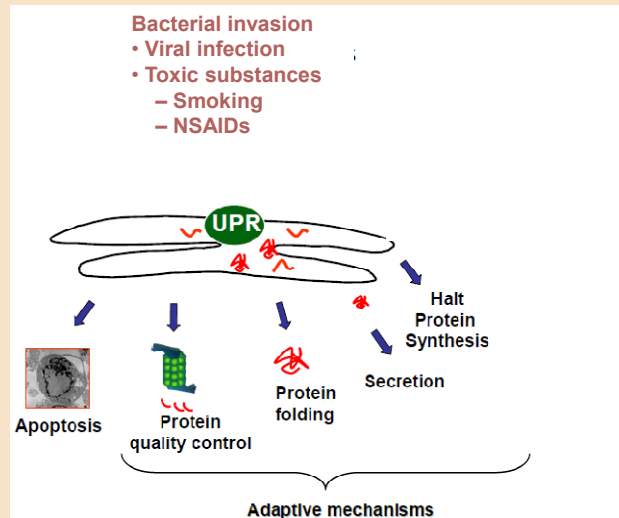
# Barrier Control and Epithelial Stress The News About Mucus



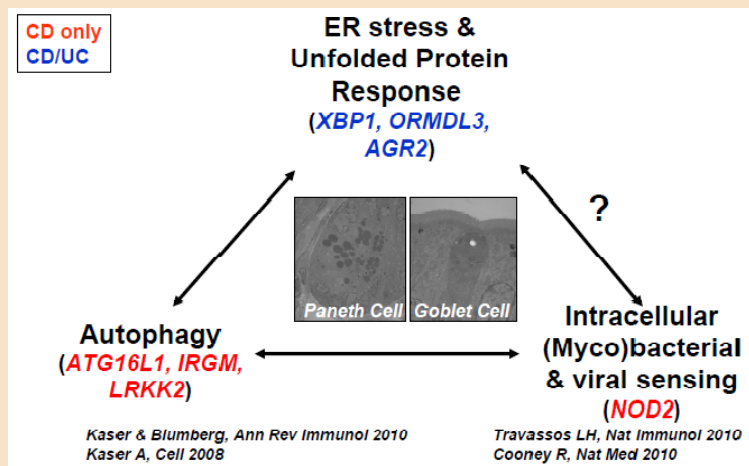
# Deficiency of the *FUT2* Enzyme Gene: Loss of the Fucose “Flypaper” in Crohn’s Disease



# Cellular “Stress” and Crohn’s Disease

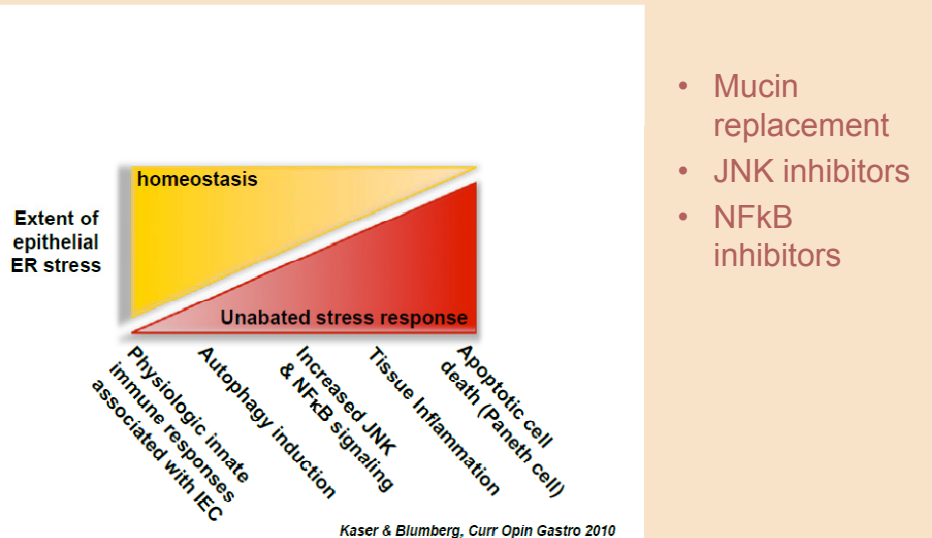


# Crohn’s Disease Risk Due to Variants of Cellular Stress and Bacterial Control Genes



## Stress Therapy for Crohn's Disease

Compensatory targets for deficits in ER stress and control of bacteria



## CCFA Genetics Initiative (Second Phase)

- 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 genes that:
    - 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

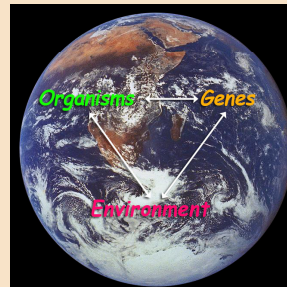
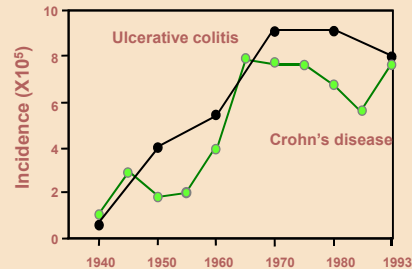
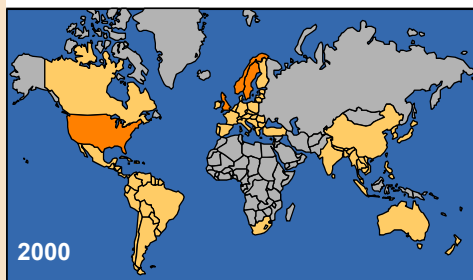
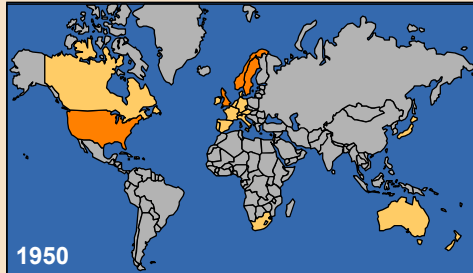
## PIANO

### 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.ccfa.org/trials](http://www.ccfa.org/trials) (Search: PIANO)

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



## Individual Variation in Microbial Composition

### CCFA Microbiome Initiative

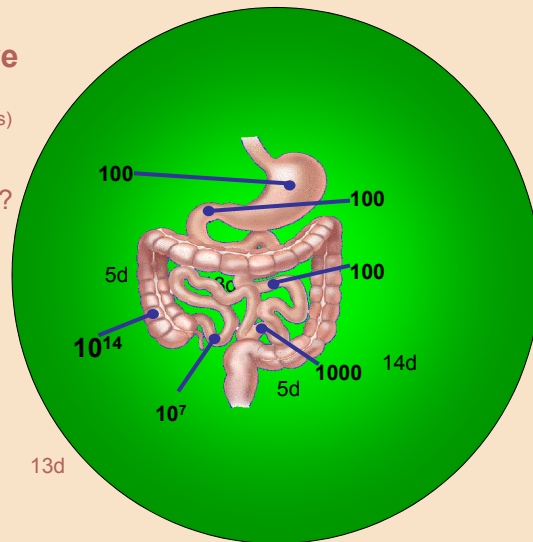
#### First Phase

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)

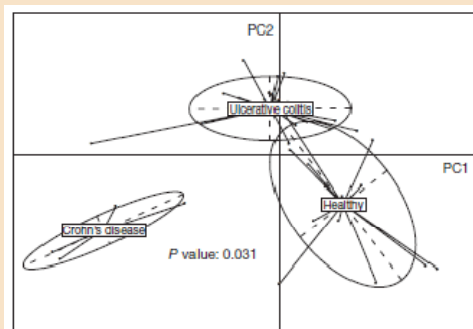


Your Intestinal Bacteria  
(10–100 trillion cells)

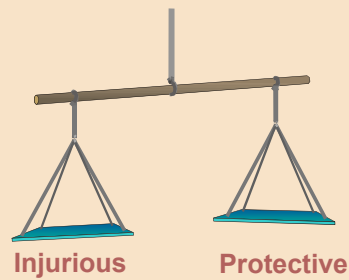


## Clinical Implications of Intestinal Bacteria

- **Hundreds of candidates**
  - Mother effect
  - Many species for each function
  - Genetics of response to bacteria
  - *Which are relevant for individual patients?*

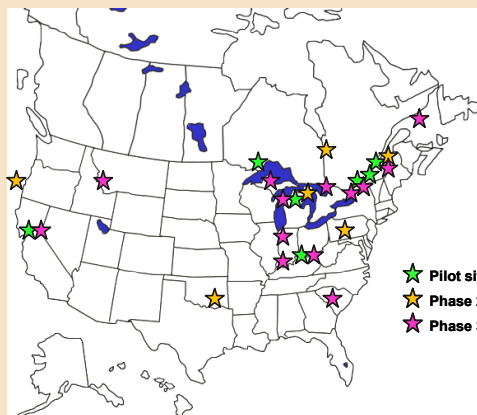


- **Selectively alter the balance**
  - Diet and prebiotics
  - Probiotics
  - Antibiotics
  - Engineered bacteria (IL10, KGF2)

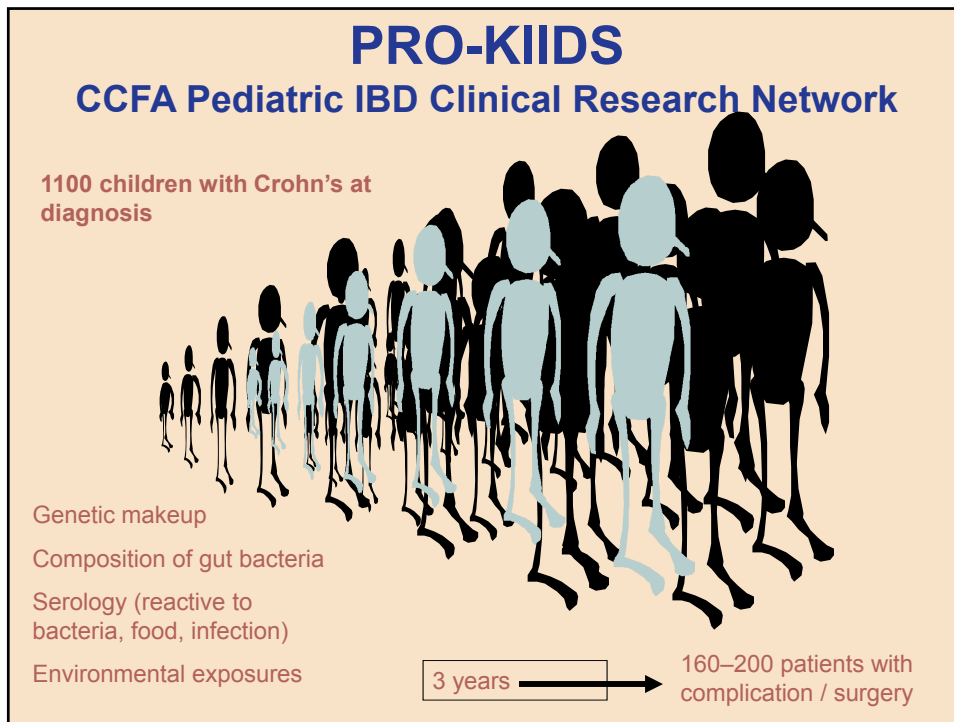


## PRO-KIIDS

### CCFA Pediatric IBD Clinical Research Network



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



## 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
  - Antibiotics, probiotics, prebiotics and immunologic treatments
- Effect of dietary manipulations on bacterial microbial composition
- Creating a dashboard for patients to monitor and adjust their bacteria

## 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)

## Summary

- Overview of Crohn's disease
- Genetic research
  - 70 genes identified
  - New targets for treatment uncovered
    - Immunoregulation
    - Mucin barrier
- Microbiome research
  - 1000 core bacterial species
  - Good and bad bacteria in Crohn's disease
    - Depends on genetics
    - New targets for diet, probiotics, and antibiotics
- Clinical research
  - Trials underway
  - Pregnancy in IBD and Neonatal Outcomes (PIANO)
  - Pediatric Research – Pediatric Network
- Patients as Partners program

## **Questions & Answers**

## **Program Evaluation**

[www.RMEI.com/CCFAevaluation](http://www.RMEI.com/CCFAevaluation)