IBD: What have we learned about its causes and treatments?

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Why do only some people develop IBD?
The more junk food we eat, the more IBD we get.

A summation of events culminating in intestinal inflammation

Genetics of IBD: 163 confirmed loci

Patients With IL-10 Receptor Mutations Develop Early Aggressive CD

HSCT improves infantile IBD symptoms caused by defective IL-10 signaling

Can genes explain it all?
The case for the microbiome, virome, mycome
Environmental Factors Determine Disease Expression

Mean age at diagnosis

- Caucasian-American: 31.5
- Hispanic: 38.7
- US-born Hispanic: 26
- Foreign-born Hispanic: 43.5

Increase in IBD Incidence for Patients Exposed to *Salmonella/Campylobacter*

- Exposed:
- Unexposed

Colonization of the intestine

- Infants colonized after birth: vaginal vs C-section
- Stable flora after first three years of life
- Antibiotics have long-lived effect on microbiota
  (Jernberg, C. et al. Microbiology, 2010; 156: 3216-3223)
- Epidemiologic risk factors:
  - Breast feeding
  - Hot water
  - Antibiotics
  - Diet
Factors maintaining intestinal-microbial homeostasis

Put in our data slide

Defective GMCSF (CSF2RB) Signaling in Crohn’s Disease Patients Bearing NCF4 Risk Allele

- **Background**
  - Crohn’s disease is associated with innate immune defects and the possibility that bacterial clearance is defective
  - SNP in NADPH oxidase gene (NCF4) has been shown to confer risk for CD development and a defect in reactive oxygen production in response to GMCSF
  - The GMCSF receptor β gene (CSF2RB) lies adjacent to the NCF gene
  - GM-CSF was used with limited success to treat Crohn’s disease

- **Objective**
  - Compared EOS production, bacterial handling, and signal transduction between CD patients bearing the NCF4 risk allele and wild-type alleles

- **Results**
  - Addition of GMCSF to neutrophils from patients carrying an NCF4 mutation resulted in defective ROS production
  - The NCF4 risk allele confers a defect in CSF2RB signaling and may identify a subset of CD patients whose inflammation is influenced by impaired innate immunity
  - Benefits of GM-CSF treatment may be limited by NCF4 genetic background of patients

van der Woude CJ et al. Abstract.
Induction of Inflammation Changes the Flora: The Chicken-and-Egg Problem

- DSS disrupts epithelial barrier
- DSS-induced colitis causes a shift in the intestinal microflora towards pro-inflammatory Gram-negative bacteria
- During acute colitis E. coli increased in wt and TLR-deficient mice ($P<0.05$)


Microbial Diversity More Dependent on Type of IBD Than Genotype


Microbial Composition differs between healthy and UC discordant MZ twins

**Objective**
- Assess microbiome in 578 first-degree health relatives of CD patients enriched for genetic variations associated with increased risk for CD

**Methods**
- Analysis of relationship of microbiota with 30 of the most common disease-associated SNPs

<table>
<thead>
<tr>
<th>IL-23R rs11209026 heterozygotes</th>
<th>NOD2 risk alleles rs2066844 rs2066847</th>
<th>GTPass family M rs13361189 risk allele</th>
<th>TLR4 rs4986790 risk allele</th>
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</thead>
<tbody>
<tr>
<td>↑Bacteroides</td>
<td>↑Odoribacter</td>
<td>↑Granulolactobacillus</td>
<td>↑Streptococace</td>
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<tr>
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<td>↓Clostridium</td>
<td>↓Erysipelotrichi</td>
<td>↓Bacteroides</td>
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<td>↓Leachnospira</td>
<td></td>
<td>↑Sphingomonas</td>
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<tr>
<td>↓Subdoligranulum</td>
<td></td>
<td></td>
<td>↑Sphingomonas</td>
</tr>
</tbody>
</table>

**Conclusions**
- Differences exist in the intestinal microbiota which are associated with SNPs in IL23R, IRGM, NOD2 and TLR4
- These results from healthy FDR differ from prior studies of changes in microbiota in patients with CD, potentially indicating that genetic associations with microbiota may be difficult to evaluate in the context of established inflammation

**The type of fat intake changes the microbiota increases inflammation in the IBD-susceptible host**

- Saturated high fat diet increased sulphite-reducing sulphite-reducing pathobiont, *Bilophila wadsworthia*
Composition of Intestinal Microbiota Regulates the Intestinal Th17:Treg Balance

Faecalibacterium prausnitzii is an Anti-Inflammatory Commensal Bacterium Identified by Gut Microbiota Analysis of CD Patients

SCFA (esp acetate) Reduce Inflammation Through GPR43 Receptor

UC patients commonly flare with antibiotics
On the other hand, probiotics may be harmful.


Microbial transfer from lean humans improves insulin sensitivity in patients with metabolic syndrome.


Viruses, worms, fungi.
**Enterovirus infection and gut inflammation in Type I diabetic patients**

<table>
<thead>
<tr>
<th>ISH+</th>
<th>ISH-</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>57</td>
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<tr>
<td>CD3</td>
<td>64</td>
<td>49</td>
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<tr>
<td>Ab</td>
<td>64</td>
<td>51</td>
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<tr>
<td>γδ</td>
<td>66</td>
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<td>γδ/CD3</td>
<td>0.24</td>
<td>0.17</td>
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<tr>
<td>HLA-DR</td>
<td>62</td>
<td>37</td>
</tr>
<tr>
<td>IgA deposits</td>
<td>54</td>
<td>31</td>
</tr>
</tbody>
</table>

Increased T-cell and antibody mediated gut inflammation in virus +ve (ISH +ve) samples


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**Defective Autophagy Increases Inflammatory Response and Decreases Paneth Cell Function**

- ATG16L1 associated with ileal involvement
- Murine norovirus required for mouse pathology

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**Recognition of fungi is protective of colitis**

Iliyan D. Iliev et al. Science 336, 1314 (2012);
Trichuris trichiura infection induces IL-22 and reduces symptomatic colitis

- Ulcerative colitis
- Increased IL-22+ after infection
- Ulcerated epithelium,crypt abscesses, neutrophil infiltration
- Resturation of glands, goblet cells, intact mucosal surface, no infiltration


Mucosal immune responses

Innate and Adaptive Immunity Are Linked

TLRs, NODs

- TLRs, toll-like receptor
- NOD, NOD protein

0–6 hours
- Immediate responses
- Innate immunity
- Broad action

1–5 days
- Longer-term mobilization
- Adaptive immunity
- Antigen-specific

KILL PATHOGENS CLEAR INFECTION

- Cytokines and chemokines
  - Release of antimicrobials
  - Recruitment of cells
  - Localized inflammation

PRIME
ACTIVATE
MODULATE

Abnormal Mucosal Immune Responses in IBD

Crohn’s-like Ulcerative colitis-like

Conserved innate and adaptive immune effector modules in the gut

Differentiation of T helper Cells

Janus Kinase Pathway

- Jak-STAT pathway genes highly associated with IBD
- Janus kinase inhibitor
  - Targets a specific intracellular signaling cascade-JAK/STAT pathway
  - The JAK family binds multiple cytokine receptors including:
    - IL2/IL4/IL7/IL9/IL12 (JAK3)
    - IFNs
  - Tofacitinib is JAK3 inhibitor used for psoriasis and rheumatoid arthritis.


IL-12 and IL-23 Cytokines and Receptors Are First Cousins

IL-12

IL-23

p40 p35

Anti-p40 Mechanism of Action

IL-12

Ustekinumab
Briakinumab

IL-23

p40 p35

Anti-p40 Mechanism of Action

IL-12

Ustekinumab
Briakinumab

IL-23

p40 p35
Ustekinumab

- Ustekinumab (UST) is a fully-human IgG1 monoclonal antibody that targets the p40 subunits of both human interleukin-12 and interleukin-23
- Anti-interleukin-12/23 therapy with UST has shown efficacy in psoriasis and has been evaluated in multiple sclerosis


Ustekinumab: human IgG1 anti-p40
Subgroup Analysis in Patients with Prior Infliximab Experience

<table>
<thead>
<tr>
<th>Week 8</th>
<th>Population 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion of patients with 70 point drop or 25% decrease in CDAI (%)</td>
</tr>
<tr>
<td>Week 2</td>
<td>SC and IV placebo (N=27)</td>
</tr>
<tr>
<td></td>
<td>SC and IV UST (N=22)</td>
</tr>
<tr>
<td>0</td>
<td>26</td>
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<tr>
<td>20</td>
<td>55</td>
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<td>80</td>
<td>59</td>
</tr>
<tr>
<td>100</td>
<td>59</td>
</tr>
</tbody>
</table>

p=0.046 p<0.001 p=0.004 p=0.022


A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2b Study of Ustekinumab, a Human Monoclonal Antibody to IL-12/23p40, in Patients With Moderately to Severely Active Crohn’s Disease: Key Results Through Week 22 From the Certifi Trial

Sandborn WJ et al. Abstract 592
**Design**

- **Design**
  - Phase 2b randomized, double-blind, placebo-controlled study
- **Objective**
  - Assess the efficacy of ustekinumab in patients with CD
- **Patients (N=526)**
- **Treatment**
  - IV placebo
  - IV UST 1, 3, 6 mg/kg
  - At week 8, patients who received IV UST induction and were either responders (≥100 CDAI decrease) or non-responders at week 6 were re-randomized separately to maintenance therapy with 90mg UST or PBO SC at weeks 8 and 16, and then followed through week 22
  - Responders to IV PBO received PBO SC at weeks 8 and 16 and non-responders received UST 270 mg SC at week 8 and UST 90 mg SC at week 16
- **Primary end point**
  - Response (≥100 CDAI decrease) at Week 6

**Ustekinumab for Crohn’s disease: blocks IL-12/IL-23**

- Clinical Response and Remission at Weeks 6 and 8


**Briakinumab (Anti-interleukin 12/23p40, ABT874) for Treatment of Crohn's Disease**

Briakinumab was not effective for induction or maintenance of remission

- Placebo
- Briakinumab 400 mg
- Briakinumab 700 mg

(12-week responders only)
Th17 cells are characterized by the production of IL-17A, IL-17F and IL-22

Redundancy in the IL-17/IL-17 Receptor signaling pathway

Clinical trials of IL-17 antagonists

- Novartis AIN457 (secukinumab) anti-IL-17A Ab failed
- Amgen: AMG 827 is a fully human monoclonal antibody that blocks signaling via the interleukin-17A receptor
- Clinical trial stopped due to increased flares of Crohn’s disease in treated group!
Secukinumab (anti-IL-17A) in Crohn’s disease

Unpublished Hueber et al.

Innate lymphoid cells (ILC) maintain anatomical containment of GALT resident bacteria


Jak-STAT pathway genes highly associated with IBD

Janus kinase inhibitor – Tofacitinib is JAK3 inhibitor used for psoriasis and rheumatoid arthritis.

A Humanized Mouse Model to Assess Mucosal Homeostasis

- Background
  - Understanding of human immune cell function in intestinal mucosa has been hampered by lack of a robust in vivo model.

- Methods
  - Engraftment of human CD4+ T cells into immunodeficient murine hosts.

- Results
  - Mice with adoptively transferred human T cells can develop IBD with activation of T cells (OKT3) or the chemical TNBS.
  - This does not happen in mice that are immunodeficient but do not get the human T cells.

- Conclusions
  - Human CD4 T cells adoptively transferred into humanized NSG mice can be used to mimic inflammatory bowel disease and can be used to test therapeutic interventions.

Phase 2 Study of CP-690,550, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis
Sandborn WJ et al. Abstract 594

Phase 2 Randomized Study of CP-690,550, an Oral Janus Kinase Inhibitor, in Active Crohn’s Disease
Sandborn WJ et al. Abstract 745

Janus Kinase Pathway

- Janus kinase inhibitor
  - Targets a specific intracellular signaling cascade-JAK/STAT pathway.
  - The JAK family binds multiple cytokine receptors including:
    - IL2/IL4/IL7/IL9/IL12 (JAK3)
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- Tofacitinib is JAK3 inhibitor used for psoriasis and rheumatoid arthritis.
Drug 2: Tofacitinib (UC/CD)

- Janus Kinase Inhibitor
  - Targets a specific intracellular cascade-JAK/STAT (influences DNA transcription/production of inflammatory cytokines)
  - To compare: most current conventional therapies bind to circulating cytokines (anti-TNF) and block interaction to receptor
  - Mechanism undergoing investigation in RA, IBD, organ transplantation, psoriasis

Design

- Design
  - Two separate, phase 2 clinical studies
- Objectives
  - Evaluate the efficacy and safety of CP for induction of response and remission in patients with moderate-to-severe active UC
  - Evaluate the efficacy and safety of CP in patients with moderate-to-severe CD
- Patients
  - Moderate-to-severe active UC (N=189)
  - Moderate-to-severe CD (N=139)
- Treatments
  - UC: CP-690,550 0.5, 3, 10, 15, mg BID or placebo (8 weeks)
  - CD: CP 1, 5, 15 mg BID or placebo (4 weeks)
- Primary end point
  - UC: Clinical response rate (decrease in Mayo score ≥3 points and ≥30%; decrease in rectal bleeding subscore ≥1 point or absolute subscore ≤1) at week 8
  - CD: Percentage of patients with CDAI score reduction of ≥70 points at week 4

Key Results in Ulcerative Colitis (Week 8)

- No additional details provided in the image.
Key Results in Crohn’s Disease (Week 4)

- Patients (%)
  - PBO (n=34)
  - 1 mg BID (n=36)
  - 5 mg BID (n=33)
  - 15 mg BID (n=35)

Normal Host: Leukocyte Surveillance

Immune Defect in IBD: Increased Leukocyte Migration and Activation
**Diapedesis in IBD**

- Leukocyte
- Endothelial cell

**Minimizing Diapedesis**

- Glycoproteins and Glycolipids
- L-Selectin
  - $\alpha_4\beta_7$
  - $\alpha_4\beta_1$

**Key Adhesion Molecule Interactions**

- E-Selectin
- P-Selectin
- MAdCAM-1
- VCAM-1
- $\alpha_4$-Integrins: required for firm adhesion to and migration across endothelium
- Natalizumab
- Vedolizumab
- Upregulated by cytokines
- Anti-MAdCAM

MAdCAM-1 = mucosal addressin cell adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1

**ENCORE: Remission in Anti-TNF Failures**

- Placebo (n=82)
- Natalizumab (n=86)

**Rationale for vedolizumab**

- Ligand for \( \alpha_4\beta_7 \) is MAdCAM
- Animal models show that MLN-02 selectively blocks trafficking of \( \alpha_4\beta_7 \)-positive lymphocytes to the gut
- Striking benefit in cotton top tamarin model

**Vedolizumab: A Monoclonal Antibody For IBD**

- Humanized IgG1
- Targets only \( \alpha_4\beta_7 \) integrin
- 30 min IV infusion
- No Fc-receptor binding or complement fixation (ADCC)
Rutgeerts PJ et al. Abstract 91
Vedolizumab: 1-year Results for CD

• Methods
  – Patients: Active CD and intolerance or inadequate response to immunomodulators or TNF antagonists
  – After 2 induction doses of vedolizumab, patients randomized to vedolizumab 300 mg IV every 8 weeks, 300 mg IV every 4 weeks, or placebo until week 52
• Results
  – CDAI decreased until Week 52 in patients taking vedolizumab
  – Corticosteroid-free remission and durable clinical remission rates significantly higher in patients taking vedolizumab

MLN-002 (vedo) induces clinical remission in ulcerative colitis

Week 6

Overall P=0.030

Response to a humanized anti-α4β7 Ab (MLN-002) in active ulcerative colitis

MLN-002 (vedo) induces clinical remission in Crohn’s disease

Week 8

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percent of Patients in Remission on Day 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12/58 (21%)</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>19/62 (30%)</td>
</tr>
<tr>
<td>2.0 mg/kg</td>
<td>24/65 (37%)</td>
</tr>
</tbody>
</table>

*p=N/S
*p=0.044


MLN02 Phase 2 Study in Active Crohn’s Disease

- Patients with active CD (N=185)
  - Stable doses of 5-ASA or antibiotics or no medical therapy
  - Randomized to IV placebo, 0.5 mg/kg, or 2.0 mg/kg MLN02 on days 1 and 29
- Primary endpoint: response (≥ 70 pt decrease in CDAI) at day 57
- Secondary endpoint: remission (CDAI <150) at day 57
- Saturation of α4β7 on peripheral blood lymphocytes was not consistently achieved

Placebo
MLN02 0.5 mg/kg
MLN02 2.0 mg/kg

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percent Response</th>
<th>Percent Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>MLN02 0.5 mg/kg</td>
<td>46</td>
<td>30</td>
</tr>
<tr>
<td>MLN02 2.0 mg/kg</td>
<td>53</td>
<td>37</td>
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</table>

*p=N/S
*p=0.04


Vedolizumab in ulcerative colitis

<table>
<thead>
<tr>
<th>Groups</th>
<th>Response</th>
<th>Remission</th>
<th>Mucosal Healing</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>25</td>
<td>20</td>
<td>45</td>
</tr>
</tbody>
</table>

Known and theoretical side-effects of vedolizumab

• Approximately 1200 subjects have received vedolizumab over 10 years
  – Many in combination with corticosteroids or immunomodulators
  – No increase in peripheral lymphocytosis
• Well tolerated to date; SAEs same as placebo
• No cases of PML

PF-00547,659 (anti-MAdCAM IgG2 antibody) in active ulcerative colitis

Effects on Immune System

• No peripheral lymphocytosis or increase in circulating eosinophils, basophils or monocytes
• No depletion of lymphocytes, or other cell types
• No evidence of cytokine release (TNFα, IL-2, IL-6, IFNγ)
• No effect on IgA, IgG, and IgM levels
Chemokines recruit inflammatory cells to intestine

CCX282-B (Traficet-EN) is a Chemokine Receptor Antagonist of CCR9: Results in Moderate to Severe CD

Response at Week 12

- CCX282-B: p=0.039, 61% (47%) and p=0.020, 59% (45%)
- Placebo: 270 points, 210 points

Slide 78

T.3    CCX282
       Maria Abreu, 24/06/2009

T.4    Maria Abreu, 01/05/2010
**Combination strategies to inhibit leukocyte trafficking to the intestine**

- CCR9 blockade
- Anti-integrin

**IBD pathogenesis**

- **Crohn's disease-like**
  - Colonization (bacteria, viruses, fungi, worms)
  - Crohn's activating infections
  - Crohn's specific genes (Nod2)

- **Ulcerative colitis-like**
  - Loss of protective flora
  - Core genes regulating inflammation, epithelial barrier, autophagy, etc

**Finding the Right Mechanism for the Right Patient**

- The Future is Bright