IBD is comprised of ulcerative colitis & Crohn’s disease

- Affects 1.4 million Americans
- Age of onset: 15-30 years
- Symptoms: diarrhea, abdominal pain, intestinal bleeding
- 2003-2004 costs: ~$9 billion/yr
  - CD: $8265/yr
  - UC: $5066/yr

Kappelman, Gastroenterology 2008
Histopathology & radiology

- IBD disease course:
  - Intermittent: inflammation (flare) & quiescence: mesalamine (mild/moderate), steroids & anti-TNF
  - Cycles of inflammation & repair → cumulative end organ structural damage

Normal colon  IBD colon  Late course, structural damage
Defining IBD disease mechanisms

Microbiome

Immune response

Genetics

Abraham & Cho, *NEJM* 2009
163 loci associated to IBD

GWAS meta-analyses

38,565 cases & 37,747 controls

NOD2

MHC in UC

Single-center GWAS

Immunochip 163 loci

Jostins et al., Nature 2012
Marked overlap between CD and UC loci

IBD vs. control odds ratio

CD vs. UC odds ratio

23 UC specific loci

110 IBD loci

30 CD specific loci

MHC

IL23R

NOD2

PTPN22

0.67

1.0

>1.5
Striking overlap between IBD & mycobacterial susceptibility

163 IBD loci

6/7

7 leprosy GWAS loci

7/9

9 single gene mycobacterial (Tb) genes

Anti-TNF treatment of IBD associated with re-activation of latent mycobacterial disease

NEJM 2001; 345: 1098
Gene associations correlate with *general* therapeutic targets

<table>
<thead>
<tr>
<th>Class</th>
<th>IBD associations</th>
<th>Therapeutic targets</th>
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<tbody>
<tr>
<td>Cytokines &amp; receptors</td>
<td>IL23 pathway</td>
<td>Anti-p40 (IL12/23)</td>
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<tr>
<td>Cytokine signaling</td>
<td>JAK2, TYK2</td>
<td>JAK inhibition (JAK3/1)</td>
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<td>Leukocyte trafficking</td>
<td>CCR6</td>
<td>Anti-alpha4, CCR9 targeting</td>
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</table>
Value of uncommon, loss-of-function protective alleles in *precisely* defining therapeutic targets

- PCSK9, LDL cholesterol & coronary artery disease
- IL23R (Arg381Gln) in IBD/psoriasis/ankylosing spondylitis

*Cohen JC, N Engl J Med 2006*
Collaboration!!
New *paradigms* of collaboration

- Across disciplines: genetics-immunology-microbiome
- Across diseases: overlap of loci between IBD, rheumatoid arthritis, psoriasis.....
  - How to prioritize therapeutic targets?
- Across academic functions: clinical care/quality imperatives, education & research
- Across stakeholders: academia, industry, philanthropy & patient groups
Wishlist for innovation

- Models for collaboration
- Information technologies (-omics, sequence data) & end-user understanding
  - Pharmacogenetics & rare, deleterious alleles
- Intestinal technologies:
  - Frequent & microbiome sampling
  - Dissemination of organoid, cytof technologies
  - Metabolomic sampling: salt, pH, oxygen