CANIBD
Canadian IBD Nurses
ANNUAL CONFERENCE
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Ritz-Carlton Hotel, Toronto
Future landscape of IBD therapy

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The Cleveland Clinic Foundation
Cleveland, Ohio, USA
Conflict of interests

None
Session objectives

Review the most significant advances in our understanding of IBD pathogenesis and management over the past 10 years

Biosimilars – International perspective

IBD research:
Where are we going in the next 5-10 years?
Where will the next great breakthrough be?

“Precision medicine”

Inspirational/visionary message
## Evolution of IBD therapy: from empirical to pathophysiology-based

<table>
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<th>Year</th>
<th>Agent</th>
<th>Specificity</th>
<th>Overall efficacy</th>
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<tbody>
<tr>
<td>1940’s</td>
<td>Sulfasalazine</td>
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<tr>
<td>1950’s</td>
<td>Corticosteroids</td>
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<tr>
<td>1960’s</td>
<td>Azathioprine</td>
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<td>1970’s</td>
<td>5-Aminosalicylic acid</td>
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<tr>
<td>1980’s</td>
<td>6-mercaptopurine Metronidazole</td>
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<td>6-mercaptopurine Elemental diets</td>
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<td>1990’s (early)</td>
<td>Cyclosporine</td>
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<td>Budenoside</td>
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<tr>
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<td>Methotrexate</td>
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<tr>
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<td>Antibiotics</td>
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<td>1990’s (late)</td>
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<td>Probiotics, prebiotics</td>
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<td></td>
<td>Leukapheresis</td>
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<tr>
<td>2000’s</td>
<td>Combination therapies</td>
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</table>
Evolution of IBD therapeutic goals: from few to to multiple

**Traditional**
- Clinical response
- Clinical remission

**Current**
- Steroid-free remission
- Prevention of complications
- Prevention of dysplasia
- Avoidance of hospitalization
- Avoidance of surgery
- Good quality of life
- Sustained (deep) remission
- Achieve mucosal healing
- “Treat to target”

Ultimate goal: modification of the natural history?
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The IBD “omes” as individual therapeutic targets

Genes (Genome)

Microbiota (Microbiome)

Environment (Exposome)

Immunity (Immunome)

Where do we go from here?
Exposome-derived environmental factors: key determinants of gene function in health and disease
Microbial manipulation strategies in IBD: how effective they really are?

**Fecal transplant:** replacement of “pathogenic” microbiota with “normal” microbiota

**Antibiotics:** removal or suppression of undesirable microbes

**Prebiotics:** replenishment of beneficial microbes and probiotics

**Probiotics:** introduction of missing desirable microbes

**Defensins:** replenishment of antimicrobial peptides controlling the gut microbiota

Antibiotics in the management of IBD

**Crohn’s disease**
- **Induction of remission**
  - Ciprofloxacin\textsuperscript{70}
  - Clarithromycin\textsuperscript{72}
  - Rifaximin/rifaximin-EIR\textsuperscript{77,80,a}
- **Treatment of fistulizing disease**
  - Ciprofloxacin\textsuperscript{84,85}
  - Metronidazole\textsuperscript{86}
- **Postoperative management**
  - Metronidazole\textsuperscript{86}
  - Omidazole\textsuperscript{87}

**Ulcerative colitis**
- **Induction and maintenance of remission**
  - Ciprofloxacin\textsuperscript{88}

**Pouchitis**
- Ciprofloxacin\textsuperscript{92}
- Rifaximin\textsuperscript{84,85}
- Ciprofloxacin plus rifaximin\textsuperscript{96}
Which probiotic to use...? How effective they really are?
Fecal microbiota transplant (FMT): hope and reality

“Fecal microbiota transplant is the infusion of a fecal suspension of normal stools into the gastrointestinal tract of another person (patient) to cure a specific disease”

Aroniadis O & Brandt L. *Curr Opin Gastroenterol* 2013;29:79-84

So far, in IBD patients FMT only offers selective, donor- and recipient-dependent, transient modification of the gut microbiota with unpredictable clinical benefits
Food, food additives and xenobiotics: exposome-derived modulators of the microbiome and immunome

Artificial sweetener
Emulsifiers
Smoking
Salt (excess)

Fats

TiO₂ nanoparticles

CHRONIC INFLAMMATION
CANCER
DIABETES
CARDIOVASCULAR
PANCREATITIS
AUTOIMMUNE
DISEASES
ARTHRITIS
IBD
RENAL
DISEASE

...and almost everything else
Evolution of biologic therapies for the treatment of immune-mediated inflammatory disorders (IMIDs)

**Timeline of biologics approval**

- **2012 up to present**
  Millions of IMID patients treated with a continuously increasing number of biological agents

- **2011**
  More than 2 million patients with RA treated with anti-TNF therapies

- **1998 - 2000**
  Approval of first TNF inhibitor therapy for treatment of RA in Europe and the United States

- **1993 - present**
  Implementation of TNF-focused therapies for inflammatory disease

- **Early 1990s**
  Animal models suggest that TNF monoclonal antibody or recombinant TNF fusion protein modulate rheumatoid arthritis (RA)

- **Late 1980s**
  Discovery of role of anti–tumor necrosis factor (TNF) in inflammatory diseases

**Timeline events**

- **1980**
  - Etanercept (anti-TNF)
- **1990**
  - Infliximab (anti-TNF)
  - Adalimumab (anti-TNF)
  - Abatacept (CTLA-4 fusion protein)
- **2000**
  - Golimumab (anti-TNF)
  - Tocilizumab (anti-IL6)
- **2010**
  - **……mab** (anti-A, B, C, D, etc.)
Targeting the immunome in IBD: successful and failed biological therapies

Adapted from Kennedy N & Jones G-R. *IBD Monitor* 2012;13;79-83
Adapted from Danese S. *Gut* 2012;61:918-932
Combined biological therapy in clinical practice

• Combination **anti-TNF + an immunosuppressors** should be the rule in immunomodulator-naive patients for at least one year (both UC and CD)

• Benefits and risks should be weighted for combination therapy in the following situations:
  - Adalimumab, certolizumab pegol in CD
  - Infliximab in AZA/6-MP failures
  - Patients with previous serious infections or malignancies
Monitoring biological therapy in IBD
Algorithm for loss of response in patients using infliximab

Figure 4 Approaches to patients on infliximab in the setting of loss of response. ATI: Anti-infliximab antibody; IFX: Infliximab; TNF: Tumor necrosis factor.
Side effects and complication of IBD therapy

- **Anti-TNFs**
  - Infection
  - Heart Failure
  - Decreased clearance
  - Live vaccines

- **5-ASA**
  - Decreased GFR
  - Unable to retain topical therapy
  - Interaction with thiopurines

- **Corticosteroids**
  - Osteoporosis and hip fracture
  - Worsening psychiatric diagnosis
  - Infection
  - Glaucoma/Cataracts

- **Thiopurines**
  - Non-Hodgkin lymphoma
  - Nonmelanoma skin cancer
  - Interaction with warfarin, ACE inhibitors, NSAIDs

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Biosimilars – International perspective

IBD research:
Where are we going in the next 5-10 years?
Where will the next great breakthrough be?

“Precision medicine”

Inspirational/visionary message
Biosimilars development pipeline*

*2016
Pipeline of biosimilars for adalimumab and Infliximab*

* As of September 2016
Long term efficacy of the infliximab biosimilar CT-P13

Week 14

Week 30

Week 54
Review article: pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases


Conclusions
It is likely that biosimilars will be widely used for the treatment of IBD due to their cost savings and comparable efficacy. Nevertheless, robust post-marketing studies and pharmacovigilance are warranted in the coming years.

Aliment Pharmacol Ther 2015; 42: 1158-1169

Biosimilars in inflammatory bowel disease: ready for prime time?

Fernando Gomollón

Summary
Biosimilars in IBD are here to stay. New data are awaited to settle the controversy of extrapolation, but only the complex behavior of markets will show whether biosimilars fuel competition and extend access to biologics with significant cuts in drug costs.

Curr Opin Gastroenterol 2015; 31: 290-295
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Importance of gut selectivity for therapeutic success

Leukocyte surface

Endothelial surface

ICAM-2  ICAM-1  MAdCAM-1  VCAM-1

Natalizumab  Alicaforsen  AJM300

Vedolizumab  PF-00547659  AMG 181  Etrolizumab

Danese S & Panes J. Gastroenterology 2014;147:981-9
Inhibition of lymphocyte egression from lymph nodes by S1P receptor modulators

Small molecule drugs: an alternative to biologics

Table 1 Differences between small-molecule drugs (SMDs) and biologics

<table>
<thead>
<tr>
<th>SMDs</th>
<th>Biologics</th>
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<tbody>
<tr>
<td>Molecular weight (Da)</td>
<td>&gt;&gt;1000</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>Proteins</td>
</tr>
<tr>
<td>Location of target</td>
<td>Extracellular</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Depletion</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Distribution</td>
<td>Limited to plasma and extracellular fluids</td>
</tr>
<tr>
<td>Degradation</td>
<td>Metabolism</td>
</tr>
<tr>
<td>Serum half-life</td>
<td>Proteolysis</td>
</tr>
<tr>
<td>Antigenicity</td>
<td>Long</td>
</tr>
<tr>
<td>Drug–drug interactions</td>
<td>Potentially antigenic</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Production</td>
<td>Receptor-mediated toxicity</td>
</tr>
<tr>
<td>Cost of production</td>
<td>Biological production</td>
</tr>
<tr>
<td>Generics</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Biosimilar</td>
</tr>
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</table>
Cytokine activation of downstream signaling molecules
JAKs and STATs and respective blockers
Promotion of TGFβ1 suppressor/anti-inflammatory activity by oligonucleotide*-induced inhibition of SMAD7

*Mongersen

New IBD drugs: hopes and realities

Celgene halts mongersen trials in Crohn’s disease

October 20, 2017

Celgene announced it has discontinued two trials of drug candidate GED-0301 (mongersen) in Crohn’s disease due to disappointing results.

The company said it decided to stop the phase 3 REVOLVE trial (CD-002) and the extension trial (SUSTAIN, CD-004) based on the Data Monitoring Committee’s recommendation in October following an interim analysis of observed risks and benefits. A press release noted this analysis showed “no meaningful safety imbalances.”

SEE ALSO
Galapagos initiates phase 3 trial of filgotinib in Crohn’s...
Axsome launches phase 2/3 trial of AXS-05 for agitation in...
CDC: Nearly 500,000 C. difficile infections in US in 2011

As a result, the company said it will not begin the phase 3 DEFINE trial (CD-003) in Crohn’s disease, and will decide if it will continue developing mongersen for ulcerative colitis after reviewing full data from a phase 2 trial.

This oral antisense therapy, which is investigational and not approved for use in any country, “is an oligonucleotide that decreases Smad7 protein, thereby potentially impacting [TGF-beta 1] signaling,” according to the press release. “In patients with Crohn’s disease, abnormally high levels of Smad7 interfere with [TGF-beta 1] anti-inflammatory pathways in the gut, leading to increased inflammation.”
Increasing molecular specificity of antibody targeting

**IL-12 receptor**
- p35
- IL12-RI
- IL12-RII

**IL-23 receptor**
- p40
- p19
- IL-23R

**Ustekinumab**

**MEDI2070 Risankizumab**
The Crohn’s disease therapeutic universe

- **Chemokine receptors**
  - CCX282-B GSK
  - CCX-025 GSK

- **Immunomodulators**
  - RDP 58 Genzyme
  - Iaquimod Teva / Active Biotech
  - ZP1848 Zealand
  - Rifaximin EIR AlphaWessermann
  - NN8555 Novo Nordisk

- **JaK3 inhibitors**
  - Tasocitinib Pfizer
  - Remestemcel-L Osiris
  - PDA-001 Celgene Cellular

- **Stem cell therapies**
  - Cellerix
  - OvaSave TXCell

- **Interleukin inhibitors**
  - TNFK-005 Neovacs
  - C326 QPharm
  - SCH-900222 Merck & Co
  - Ustekinumab Centocor
  - Vidofludimus 4SC

- **CAM inhibitors**
  - Natalizumab GSK 1070806 GSK
  - Natalizumab Elan/Biogen Idec
  - Vedolizumab Millenium / Takeda

- **TNF-α inhibitors**
  - Infliximab Centocor
  - Ozoralizumab Pfizer
  - Debiaerse Neovacs

- **Registration Launched**
  - AMG 827 Amgen
  - PF-04236921 Pfizer
  - PF 05230900 Pfizer

- **Phase I**
  - PF-547659 Pfizer
  - ELND-004 Elan/Biogen Idec

- **Phase II**
  - AIN 457 Novartis

- **Phase III**
  - PF-05230900 Pfizer

Courtesy of S. Danese
The ulcerative colitis therapeutic universe

**JAK3 inhibitors**
- Tasocitinib Pfizer
- AM-3301 Amalyte
- GSK-1399686 GSK
- Dersalazine Palau

**Immunomodulators**
- RDP58 Genzyme
- DIMS-0150 InDex
- Golimumab Centocor
- Adalimumab AbbVie
- Etrolizumab Genetech
- ELND-004 Elan
- PF-547659 Pfizer
- ASP-2002 Asphelia
- LMW heparin Cosmopharm.

**TNF-α inhibitors**
- LT-02 Lipid Theragent cgGmbH
- Anrakinumab Millenium
- Vedolizumab Pfizer

**CAM inhibitors**
- LT-02 Bio-Pharma
- Pur-0110 PurGenesis Technologies Inc

**Protein kinase inhibitors**
- GSK-1607586 ChemoCentryx GSK
- BBIC ProteMed Inc
- Sotrastaurin Novartis
- HMPL-004 Hutchinson
- Enkorten Farmacj
- CyCol Sigmoid Pharma
- HE-3286 Harbor BioSciences

**Chemokine receptors**
- MDX-1100 Medarex

**Interleukin inhibitors**
- LT-02 Bio-Pharma

**Antioxidants/barrier function**
- Vidofludimus 4SC

Courtesy of S. Danese
The most advanced treatments for IBD are still suboptimal

**Induction of clinical remission**

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<tr>
<th>Treatment</th>
<th>Remission</th>
<th>Non remission</th>
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<tbody>
<tr>
<td>Crohn’s disease</td>
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<td>Adalumimab</td>
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<td>Golimumab</td>
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<tr>
<td>Ulcerative colitis</td>
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<td>Tofacitinib*</td>
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**Maintenance of clinical remission**

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<th>Treatment</th>
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<td>Vedolizumab</td>
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<tr>
<td>Ulcerative colitis</td>
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<td></td>
<td>Tofacitinib*</td>
<td>47</td>
</tr>
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</table>

*OCTAVE Sustain

Adapted from Courtesy of Dr. M. Gassull
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“Precision medicine”

Inspirational/visionary message
“What is precision medicine?”

According to the Precision Medicine Initiative of the NIH, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"
IBD: a complex disease with a lopsided therapeutic approach

Genes (Genome)

Microbiota (Microbiome)

Environment (Exposome)

Immunity (Immunome)

<5%

<10%

~90%
Complex diseases require complex therapies

1. Drugs, by and large, work at a molecular level, just as diseases originate from molecular malfunctions

2. Malfunctions differ from person to person owing to variations and changes in the person’s genome and environment

3. Current approaches might have reached their limits and we need new thinking to drive drug discovery and use

4. Systems biology-based treatments are likely to be of increasing value because most diseases undergo multiple molecular changes as they progress

5. Complex diseases cannot be treated effectively by modulating a single target

6. Combining drugs that act on different targets within a network could be more efficacious than treating diseases with one drug
IBD is a highly complex disease: multiple molecules, multiple interactions, multiple effects

- **DNA** → **RNA** → **Protein**

  - **Genome**
    - SNPs
    - Mutations
  - **Transcriptome**
    - Coding RNAs
    - Non-coding RNAs
  - **Proteome**
    - Metabolome

- **Epigenome**
  - DNA methylation
  - Chromatin modifications

Credit: Courtesy of Dr. D. Iliopoulos
Multiple IBD “omics” data integration: genome, exposome, microbiome, immunome, etc.

Mathematical model

Organize information in networks

Identification of the central regulators (○) of IBD pathogenesis

Courtesy of Dr. D. Iliopoulos
CSB technology platforms

High throughput drug discovery platform

- An integrated robotic system for pharmaceutical discovery
- Collection of >500,000 compounds
- Ability to test ~200,000 compounds in a single screen in 7 days
- A single laboratory would perform the same analysis in 2 years

Courtesy of Dr. D. Iliopoulos
Omics accelerated drug discovery

Kraljevic S et al. EMBO Reports 2004;5:837-842
A systems biology approach to IBD therapy

1. Collection of clinical, biochemical, genetic, molecular, etc. data

2. Data integration by mathematical modeling

3. Networks Identification

4. Drug discovery & development platform

5. Targeting IBD molecular networks
   - Patient stratification
   - Therapeutic response

6. Precision IB therapies

Courtesy of Dr. D. Iliopoulos
The future of IBD: a therapeutic approach based on systems biology

- Exposome
- Omics analysis
- Genome
- Omics analysis
- Gut microbiome
- Omics analysis
- Immunome
- Omics analysis
- Multiomics integration of IBD networks

Precision Rx:
- Correct target identification
- Absolute specificity
- Potentially curative
Thank you!