Future Therapies in IBD

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Therapies for IBD: The Pipeline

- Anti-TNF
  Golimumab
- Anti-Selective Adhesion Molecule
  Anti-integrin antibodies
  Vedolizumab (anti-α4β7, MLN-002)
  Anti-β7
  Anti-MAdCAM-1
  Alicaforsen (ICAM-1 anti-sense) enemas
- Antagonist to chemokine receptor 9
  CCX282-B
- *L. lactis*-secreting Interleukin-10

- Anti-Interleukin 12/23
  ABT 874 (J695)
  Ustekinumab (CNTO 1275)
- Anti-Interleukin-17 (AIN457)
- Antagonist to Janus kinase 3 (JAK3)
  CP-690,550
- Anti-Interleukin-2 Receptor (CD25)
  Basiliximab (failed)
  Daclizumab (failed)
- Anti-CTLA-4
  Abatacept
- Sargramostim (failed)
- Visilizumab (failed)
Golimumumab (CNTO 148)

- Fully human anti-TNFα IgG1 mAb
- In preclinical studies, golimumumab was shown to be more effective at neutralizing TNFα than other anti-TNF biologics
- In development for SC and IV administration
- SC mode of administration is being evaluated for dosing once every 4 weeks

Fully Human Antibodies From Transgenic Mice

- Normal Mouse
- Mouse Antibody Genes Deleted
- Human Antibody Genes Inserted
- Transgenic Mouse
- Immunize with TNFα
- Human Antibody
- Infliximab (CNTO 148)

Mouse Human

Mouse

Human

Immunize with TNFα

Chimerize

Human Antibody

Transgenic Mouse
# Physical Characteristics of Anti-TNF Biologics

<table>
<thead>
<tr>
<th></th>
<th>infliximab</th>
<th>etanercept</th>
<th>adalimumab</th>
<th>golimumab</th>
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<tbody>
<tr>
<td><strong>design</strong></td>
<td>mouse/human chimeric mAb</td>
<td>human receptor/Fc fusion protein</td>
<td>recombinant human mAb</td>
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<td><strong>isotype</strong></td>
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<td>IgG1 (no CH1 domain)</td>
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<tr>
<td><strong>how generated</strong></td>
<td>engineered murine mAb</td>
<td>TNF RII (p75) extracellular domain fused to Fc</td>
<td>murine mAb, phage display, affinity maturation</td>
<td>Medarex HuMab transgenic mouse</td>
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<tr>
<td><strong>how produced</strong></td>
<td>murine myeloma cells</td>
<td>chinese hamster ovary cells</td>
<td>chinese hamster ovary cells</td>
<td>murine myeloma cells</td>
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<td><strong>how supplied</strong></td>
<td>lyophilized, 100 mg/vial</td>
<td>liquid, 50 mg/mL in prefilled syringe</td>
<td>liquid, 40 mg/mL in prefilled syringe</td>
<td>liquid, 100 mg/mL in prefilled syringe and lyophilized</td>
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<tr>
<td><strong>molecular wt</strong></td>
<td>149,100</td>
<td>150,000</td>
<td>148,000</td>
<td>149,700</td>
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<tr>
<td><strong>% carbohydrate</strong></td>
<td>2.2%</td>
<td>31.0%</td>
<td>2-3%</td>
<td>1.4-2.7%</td>
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Endothelial And Leukocyte Adhesion: A4 Integrins

- Leukocyte membrane glycoproteins
- β1 and β7 subunits
- Interact with endothelial ligands VCAM-1 and MAdCAM-1, and mediate leukocyte adhesion and trafficking
- Interact with extracellular ligands fibronectin, osteopontin, and thrombospondin
Anti-Beta 7 Mechanism of Action: Adhesion Molecule Inhibition as an IBD Therapy

Leukocyte adhesion molecule inhibition can reduce leukocyte infiltration and gut inflammation. The α4β7 integrin plays a key role in the adhesion process.

**Mechanism:**
- **Leukocyte** interacts with **endothelial cells** via the **α4β1 (VLA-4)** and **α4β7** integrins.
- **Chemoattractant Signal** leads to **leukocyte infiltration** into the **tissue**.
- **VCAM-1** and **MAdCAM-1** are involved in this process.

**Inhibition:**
- **Anti-Beta 7**-targeted therapy blocks the interaction, reducing **leukocyte infiltration** and **gut inflammation**.

**Result:**
- **Reduced** leukocyte infiltration and **blocked** gut inflammation.
Vedolizumab (MNL-0002): A Humanized, Monoclonal Antibody (mAb) Against $\alpha 4\beta 7$ Integrins

- Targets *only* $\alpha 4\beta 7$ integrin
- Created by insertion of ACT-1 CDRs into human IgG1 framework
- Two amino acid substitutions abrogate Fc-receptor binding and complement fixation (ADCC)
- IV infusion over 30 – 60 minutes
Vedolizumab (MLN-0002) For Active Ulcerative Colitis
Remission at Week 6

- 181 patients with active ulcerative colitis [ulcerative colitis clinical score (UCSS) ≥ 5 and modified Baron score (MBS) ≥ 2] receiving a stable dose of 5-ASA or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg vedolizumab on days 1 and 29
- The primary endpoint was % clinical remission (UCSS score 0 or 1, MBS 0 or 1, and no blood) at day 43

Vedolizumab (MLN-0002) For Active Ulcerative Colitis

Remission at Week 6

- Secondary endpoint was % endoscopic remission (MBS 0) at day 43
- Secondary endpoint was % of patients with decrease ≥ 3 UCSS points from baseline
- Serious adverse events 8% for MLM-02 and 5% for placebo, one patient with angioedema after MLN-02

P=0.001  
P=0.01

Endoscopic Remission or Decrease In UCSS (%)

Day 43

Vedolizumab (MLN-0002) For Active Crohn’s Disease
Response and Remission at Week 8

- 185 patients with active Crohn’s disease receiving a stable dose of 5-ASA or antibiotics or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg MLN-02 on days 1 and 29
- The primary endpoint was % clinical response (decrease in CDAI of ≥70 points) at day 57
- Secondary endpoint was % remission (CDAI < 150) at day 57
- Saturation of α4β7 on peripheral blood lymphocytes was not consistently achieved

Vedolizumab (MLN-0002) For Active Crohn’s Disease
Remission Over 8 Weeks

MLN0002 induced a significantly greater clinical remission rate in patients with Crohn’s disease compared to placebo (2 mg/kg group) at days 15, 29, and 57.
Mechanistic Rationale for Anti-MAdCAM Antibody

MAdCAM
• Predominantly expressed on high endothelial venules of organized intestinal lymphoid tissue
• Binds $\alpha_4\beta_7$ integrin on lymphocytes
• Facilitates lymphocyte homing & extravasation
• ↑↑↑ expression at sites of GI inflammation

Anti-MAdCAM Antibody (PF-00547659)
• Fully human IgG2 monoclonal antibody
• Binds with high affinity & specificity to MAdCAM
• Blocks MAdCAM/$\alpha_4\beta_7$ dependent lymphocyte recruitment to gut
• Designed to reduce inflammation caused by excessive lymphocyte infiltration in GI disease
ICAM-1 is the ligand for LFA-1.

ICAM-1 antisense decreases the amount of ICAM-1 protein produced by endothelial cells, leading to decreased leukocyte adhesion, emigration, and inflammation.
AntiSense Oligonucleotides

- Synthetic oligonucleotides of single-stranded DNA
- Prevent translation of messenger RNA (mRNA) into protein
- Increase degradation of target mRNA
- Can inhibit formation of the somatic gene products encoded by human, viral, or other infectious agent genomes
Alicaforsen (ISIS-2302) Enemas Versus Placebo in Active Distal Ulcerative Colitis

Van Deventer. Alimentary Pharmacology and Therapeutics 2006
Alicaforson (ISIS-2302) Enemas Versus Mesalamine in Active Distal Ulcerative Colitis

Mean Percent Change in DAI (+/- SEM)

- BSLN
- WK3
- WK6
- WK10
- WK18
- WK30

ISIS 2302 240 mg
ISIS 2302 120 mg
Rowasa 4.0 g

P=0.17
P=0.13

Miner. Alimentary Pharmacology and Therapeutics 2006
Genetically modified L. Lactis for the Oral Delivery of Therapeutic Peptides and Proteins

- Based on living, food-grade, lactic acid bacteria
- Lactococcus lactis: non-invasive, non-colonizing food bacterium
- Genetically engineered to secrete therapeutic proteins and peptides
- Containment system to prevent survival outside the human body

*Lactococcus lactis*
AG011 in IBD
Product Profile

- AG011: delivering human Interleukin-10 (hIL-10) – a potent anti-inflammatory cytokine for the treatment of UC and CD
- Targeted topical delivery of IL-10 in the intestinal tissues, allowing optimal target tissue bioavailability and no systemic exposure
- Superior tolerability and safety profile
- More convenient dosing (oral capsules) – good patient compliance
Role of AG011 in IBD

Treatment promotes mucosal healing; by inhibiting pro-inflammatory mediators and promoting anti-inflammatory T cells.

- Anti-inflammatory
  - TNFα
  - IL-1β
  - IL-6

- Promotes IgA secretion
- Epithelial barrier

- Inhibits Antigen recognition
- Inhibits T Cell driven inflammation

- Promotes T reg function
- Promotes long lasting immune suppression

AG011/IL-10
Phase 1 clinical study: LL IL-10 in Crohn’s Disease

Individual patient data: CDAI scores and CRP levels

1 Week treatment – 4 weeks monitoring
Interleukin 12/23/17 Pathways in Crohn`s Disease:

**Biology of Interleukins 12 and 23**

- **Stimulus**
  - TLR?

- **Antigen Presenting Cell**
  - IL-12
  - IL-23

- **CD4+ TCR**
  - Ag (Th1)
  - MHCII
  - IL-23R
  - IL-12Rβ1
  - β2

- **IFNg (Th1)**
  - IL-17 (Th17)

**Anti-IL-12/23**

- CNTO 1275 (ustekinumab) and ABT 874 are fully human IgG1 monoclonal antibodies
- Bind the p40 subunit of human IL-12/23
- Prevent IL-12 and IL-23 from binding IL-12Rb1
- Normalize IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production
- In development in Crohn’s disease and psoriasis
IL-12 and IL-23

IL-12

p40 (CNTO1275)

anti p40

anti p35

IL-12Rβ1

p35

IL-12Rβ2

anti p19

IL-12Rβ1

IL-23

p40

p19

IL-23R
ABT-874 Antibody Properties

- Fully human anti-IL-12p40 antibody
- Derived by phage-display technology
- Selective for IL-12/IL-23 (p40) amongst a panel of cytokines
- High affinity ($K_d=97 \text{ pM}$)
- Very potent in vitro neutralization ($IC_{50}=5 \text{ pM}$)
- Neutralizes IL-12 induced responses in vivo in animals
Anti–Interleukin-12/23 Monoclonal Antibody (J695, ABT-874) for Active Crohn’s Disease

**Phase II Trial**
- Cohort 1: n=40
- Cohort 2: n=39
- Active CD (CDAI 250-450)
- 7 weekly SQ injections of J695 1 or 3 mg/kg or placebo
- Clinical remission = CDAI <150 pts at week 7
- Clinical response = ↓ in CDAI ≥100 pts at week 7

Ustekinumab (CNTO 1275) for Active Crohn’s Disease: Clinical Response Through Week 8

Response: ↓CDAI scores of ≥25% & ≥70 points

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
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<td>SC and IV placebo (N=53)</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>40</td>
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<tr>
<td>SC and IV Ustekinumab 1275</td>
<td>41</td>
<td>53</td>
<td>53</td>
<td>49</td>
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Primary Endpoint

p=0.335
p=0.02
p=0.019
p=0.337

Sandborn
Gastroenterology 2008
Ustekinumab (CNTO 1275) for Active Crohn’s Disease: Subgroup Analysis in Patients with Prior Infliximab Experience

Clinical Response Through Week 8

Response: ↓ CDAI scores of ≥25% & ≥70 points

![Graph showing clinical response through week 8](image)

- Week 2: SC and IV placebo (N=27) - 26, SC and IV Ustekinumab 1275 (N=22) - 55
- Week 4: SC and IV placebo (N=27) - 15, SC and IV Ustekinumab 1275 (N=22) - 59
- Week 6: SC and IV placebo (N=27) - 19, SC and IV Ustekinumab 1275 (N=22) - 59
- Week 8: SC and IV placebo (N=27) - 26, SC and IV Ustekinumab 1275 (N=22) - 59

Sandborn
Gastroenterology 2008
Inflammatory Bowel Disease – Blockade of IL17A Reduces Colitis in Murine Models

Blocking IL-6 and IL-17 significantly reduced intestinal inflammation, by 50% in T cell transfer model of IBD.

Recipent mice were dosed i.p. with isotype, anti–IL-6, anti–IL-17, or anti–IL-6 plus anti–IL-17 Abs (2 mg/mouse) a day prior to T cell reconstitution. Rag-KO mice were reconstituted with sorted splenic CD4+CD45RBhi (naive) T cells (5 × 10^5 cells/mouse) from diseased IL-10–KO mice and treated daily with 1 mg/mouse IL-23 protein. Subsequent rounds of Ab were administered weekly for 6 weeks. The graph shows the path scores from 2 independent but identical experiments. Horizontal bars represent the median value for each group. **P < 0.05, compared with isotype Ab (unpaired Student’s t test).

(Yen et al., J Clin Invest 2006;116:1310)
Inflammatory Bowel Disease – Blockade of IL17A Reduces Colitis in Murine IBD Models

A soluble IL-17R:Fc fusion protein antagonizes colitis, and tissue IL-6 induction. (Zhang et al., Inflamm Bowel Dis 2006;12:382)
JAK3/\(\gamma_c\) inhibitors will block signalling by six cytokines.

Receptors signalling through JAK3:
- IL-2
- IL-4
- IL-7
- IL-9
- IL-15
- IL-21
CP-690,550 (JAK 3 Inhibitor) Efficacy in Phase 2b Rheumatoid Arthritis Study
Week 12 Results

Week 12 Results

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<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
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<td>23.9</td>
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<tr>
<td>1 mg BID</td>
<td>49.3</td>
<td>30.9</td>
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<td>3 mg BID</td>
<td>58.8</td>
<td>36.6</td>
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<tr>
<td>5 mg BID</td>
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<td>10 mg BID</td>
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<td>25.3</td>
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<tr>
<td>15 mg BID</td>
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<td>20 mg QD</td>
<td>60.0</td>
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* p ≤ 0.005 vs placebo
** p ≤ 0.0001 vs placebo
CTLA4 Negatively Regulates T-cell Activation

CTLA4 expressed following T-cell activation

CTLA4 binds to CD80/86 with higher avidity than CD28, and inhibits co-stimulation
Abatacept (CTLA4-Ig, Orencia): A Human Recombinant Fusion Protein

CTLA4 (CD152)
A human trans-membrane protein

Fusion Protein

IgG1
A human antibody
Sargramostim (GMCSF) for Crohn’s Disease

- Gut inflammation phenotypically similar to Crohn’s disease occurs in chronic granulomatous disease, glycogen storage disease, and Chediak-Higashi syndrome
- 124 patients with active CD; concomitant treatment with steroids, immunosuppressives; infliximab not permitted
- Sargramostim 6 ug/kg or placebo SQ daily for 8 weeks

Rationale

**OKT3 and Immunosuppression**

- **Immunosuppression**
  - T-cell receptor modulation
  - T-cell clearance
  - Unresponsiveness

- **Activation**
  - Proliferation
  - Release of cytokines
  - Toxic effects:
    - Fever
    - Chills
    - Pulmonary distress, etc.

- Fc receptor-mediated T-cell activation contributes to toxicity but is not required for immunosuppression

Visilizumab: Severe Active Steroid-Refractory Ulcerative Colitis

Clinical Activity
Percent of Subjects in Response
MTWSI <10 with 3 point decline

Targan Gastroenterology 2005 Abstract
Conclusions

- Agents targeted against multiple targets including beta 7 integrin, the p40 subunit of interleukin 12/23, interleukin 17, chemokine receptor 9, JAK3, CTLA4, etc hold great promise for the future.