Future Therapies in IBD

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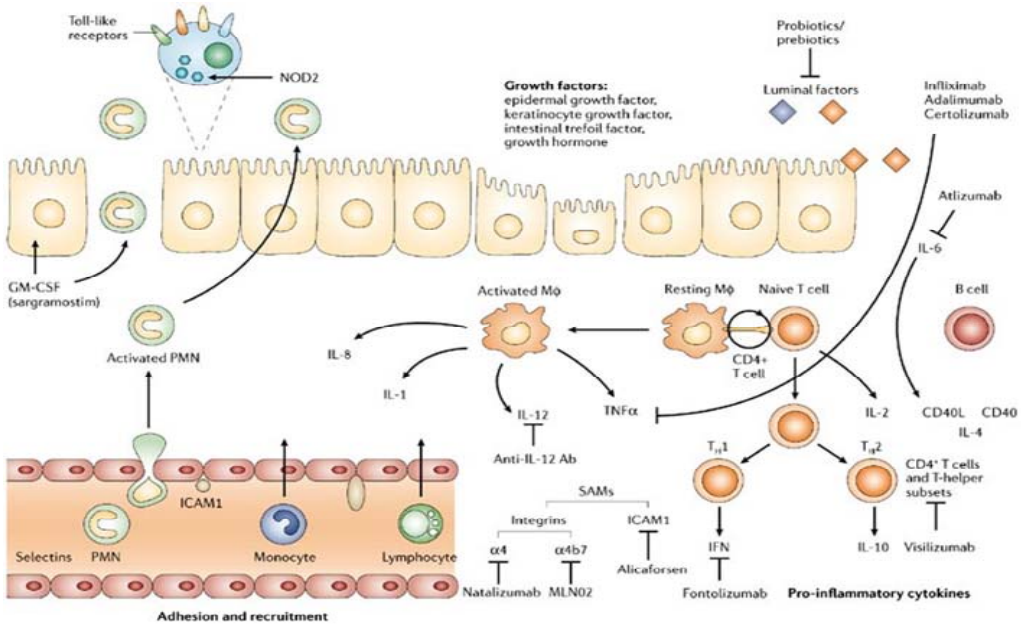


Korzenik *et al. Nature Reviews Drug Discovery* **5**, 197–209 (March 2006) | doi:10.1038/nrd1986

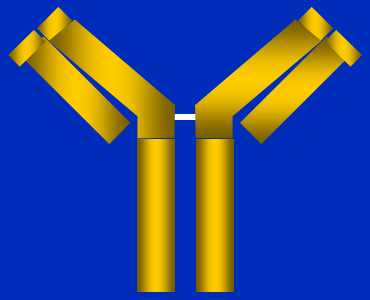
nature REVIEWS DRUG DISCOVERY

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)

Golimumab (CNTO 148)

- Fully human anti-TNFα IgG1 mAb
- In preclinical studies, golimumab 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



CNTO 148
(golimumab)

Kay et al. ACR 2006. Abstract 2123.

Fully Human Antibodies From Transgenic Mice

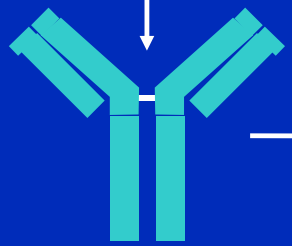
Normal Mouse

Mouse Antibody Genes Deleted

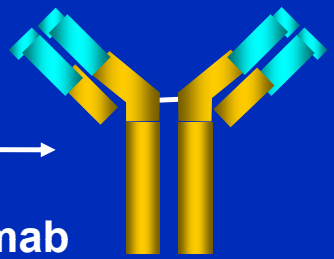
Human Antibody Genes Inserted

Human Antibody Transgenic Mouse

Immunize with TNFα

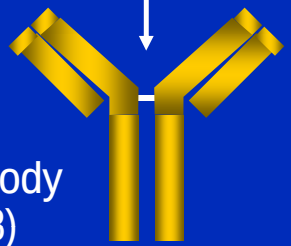


chimerize



infliximab

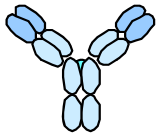
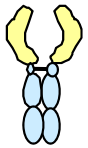
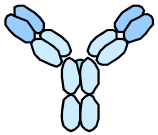
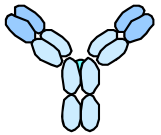
Immunize with TNFα



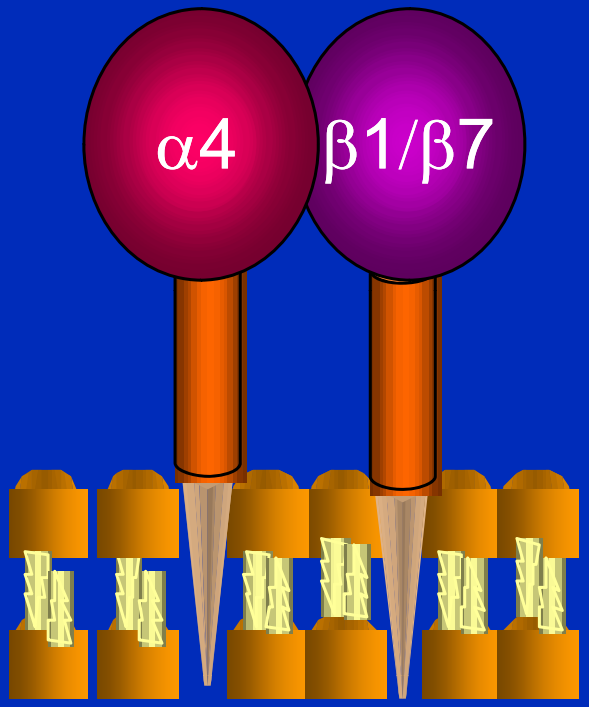
Human Antibody (CNTO 148)

Mouse Human

Physical Characteristics of Anti-TNF Biologics

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

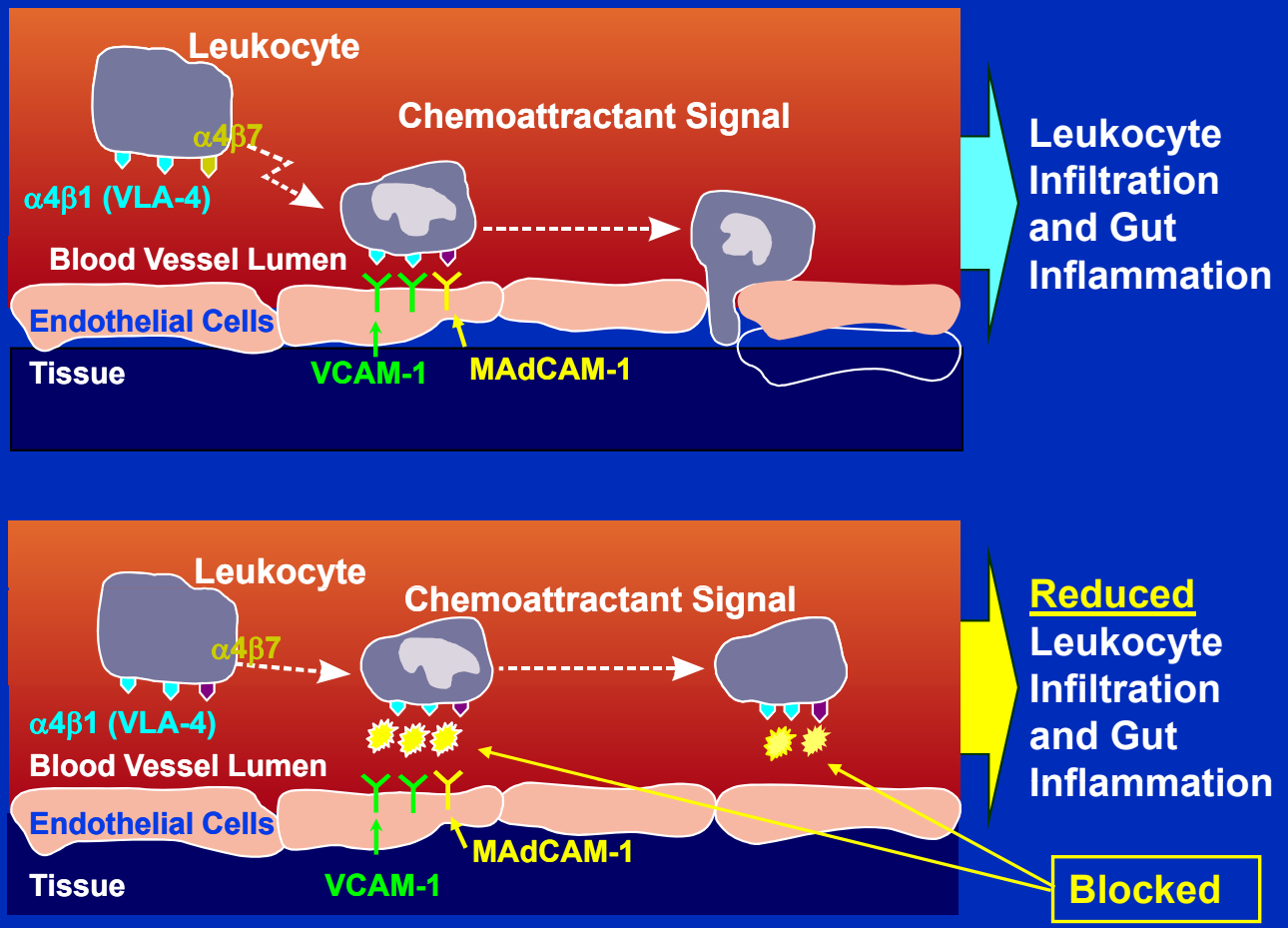
Endothelial And Leukocyte Adhesion: A4 Integrins



- 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

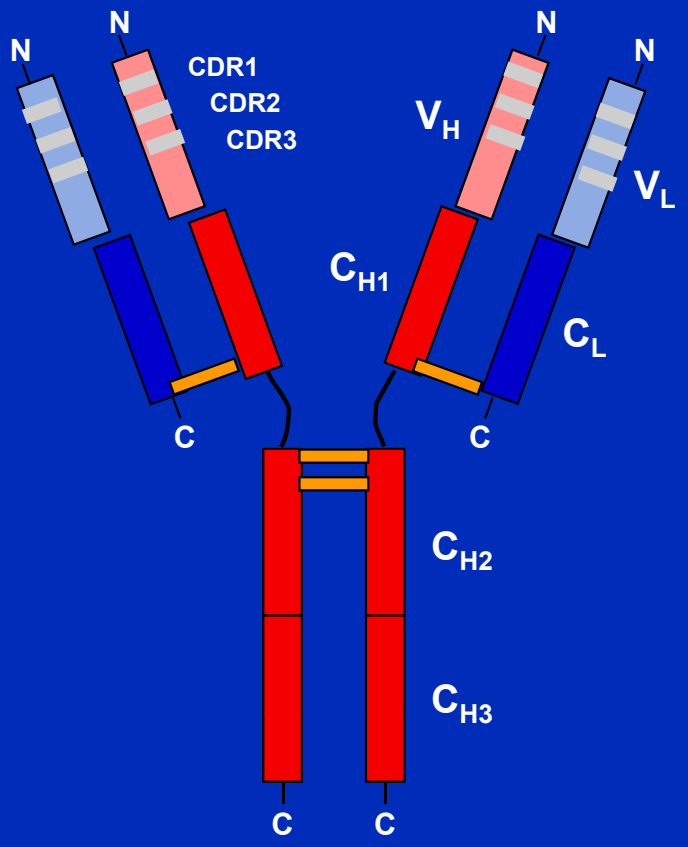
Springer TA. *Cell.* 1994;76:301–314; Butcher EC, et al. *Science* 1996;272:60–66.

Anti-Beta 7 Mechanism of Action: Adhesion Molecule Inhibition as an IBD Therapy



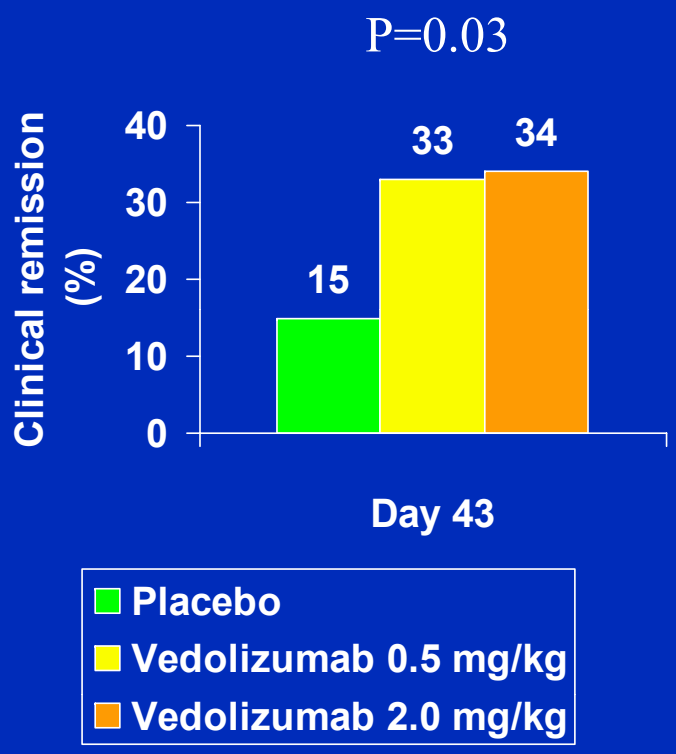
Vedolizumab (MNL-0002): A Humanized, Monoclonal Antibody (mAb) Against $\alpha 4\beta 7$ Integrins

- Targets *only* a4b7 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

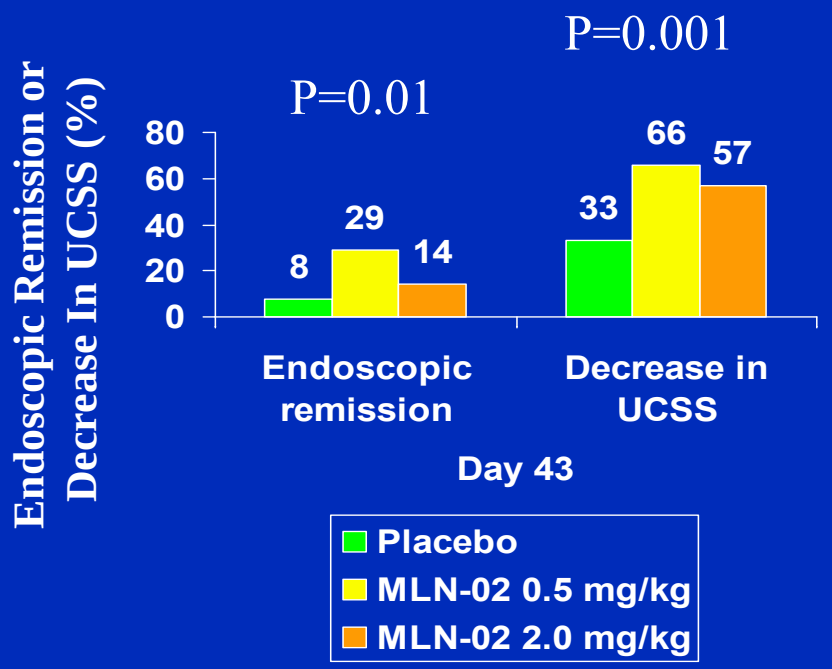
- 181 patients with active ulcerative colitis [ulcerative colitis clinical score (UCSS) ≥ 5 and modified Baron score (MBS) ≥ 2] receiving a stable dose of 5-ASA or no medical therapy
- Randomized to receive IV doses of placebo, 0.5 mg/kg, or 2.0 mg/kg vedolizumab on days 1 and 29
- The primary endpoint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



Feagan New England Journal of Medicine 2005

Vedolizumab (MLN-0002) **For Active Ulcerative Colitis Remission at Week 6**

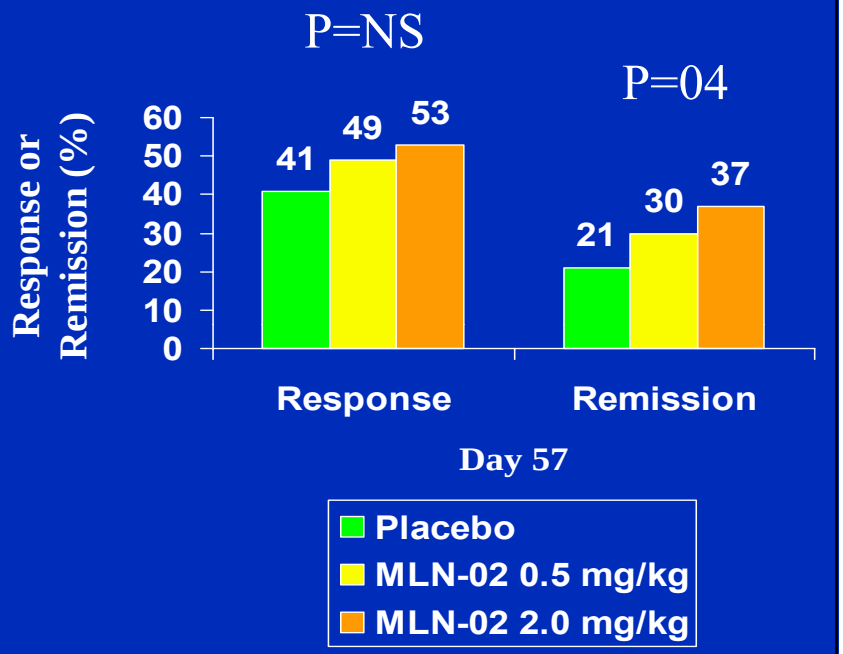
- Secondary endpoint was % endoscopic remission (MBS 0) at day 43
- Secondary endpoint was % of patients with decrease ≥ 3 UCSS points from baseline
- Serious adverse events 8% for MLM-02 and 5% for placebo, one patient with angioedema after MLN-02



Feagan N Engl J Med 2005

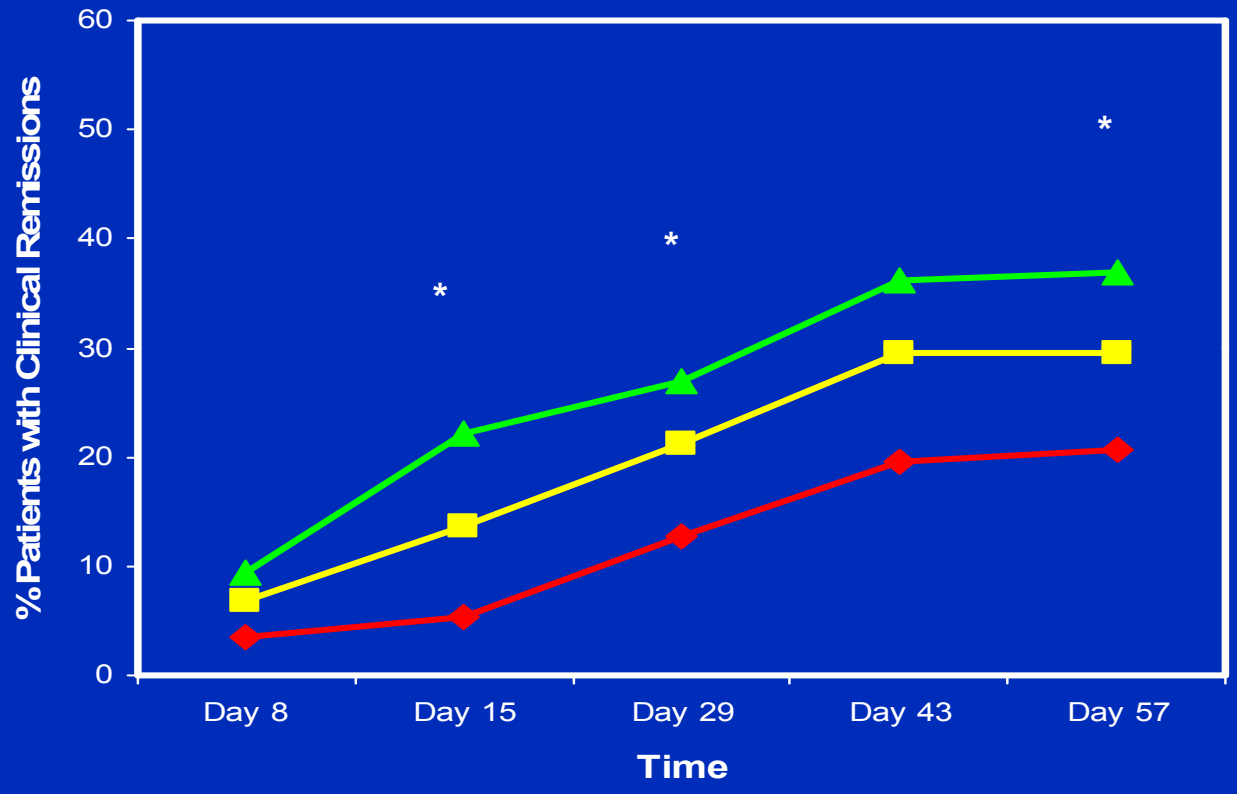
Vedolizumab (MLN-0002) For Active Crohn's Disease Response and Remission at Week 8

- 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 $\alpha 4\beta 7$ on peripheral blood lymphocytes was not consistently achieved



Feagan Gastroenterology 2008 (In Press)

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



* p-value < 0.05

ITT population

Placebo
0.5 mg/kg
2.0 mg/kg

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.

Feagan Gastroenterology 2008 (In Press)

Mechanistic Rationale for Anti-MAdCAM Antibody

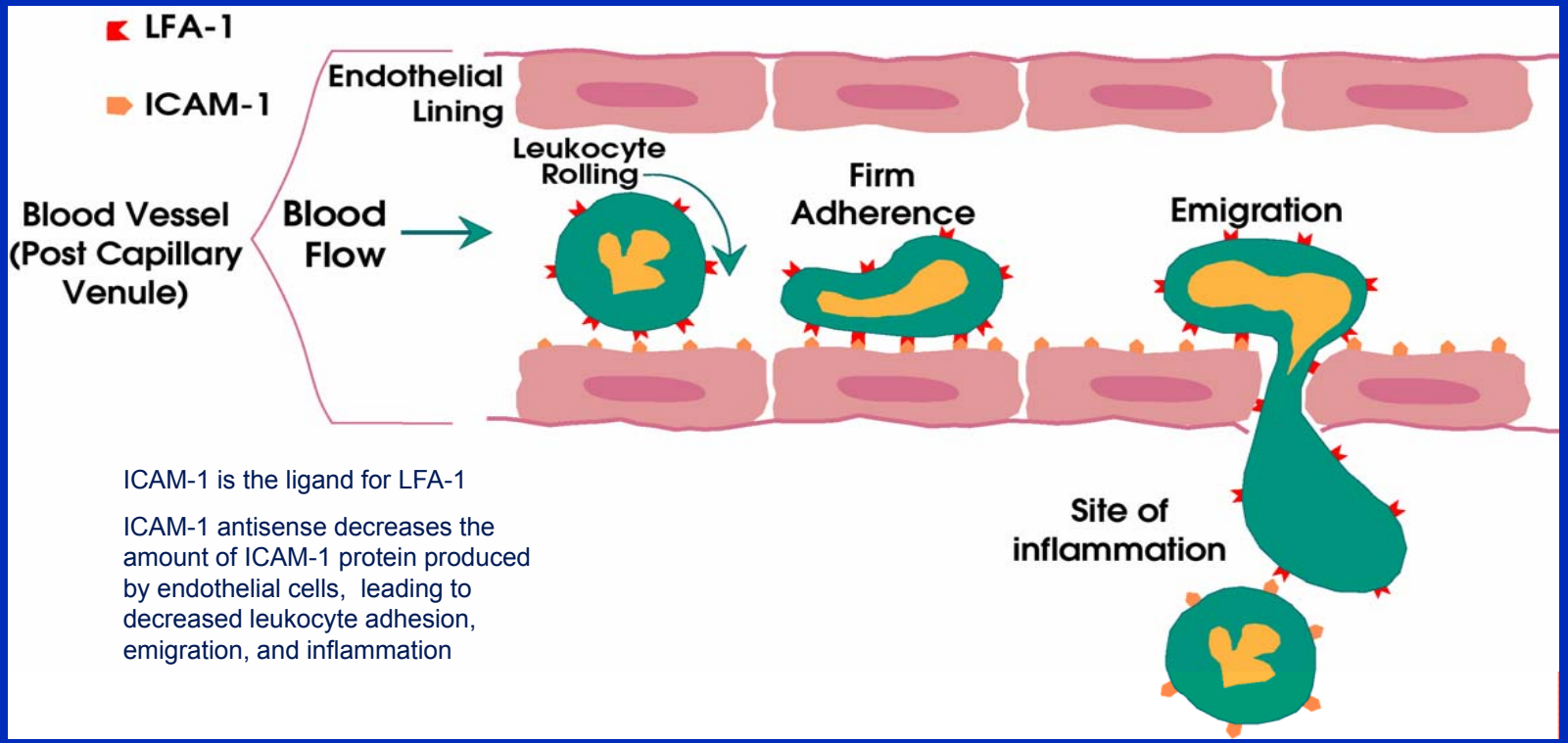
MAdCAM

- 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/α4β7 dependent lymphocyte recruitment to gut
- Designed to reduce inflammation caused by excessive lymphocyte infiltration in GI disease

Role of ICAM-1 in Leukocyte Emigration



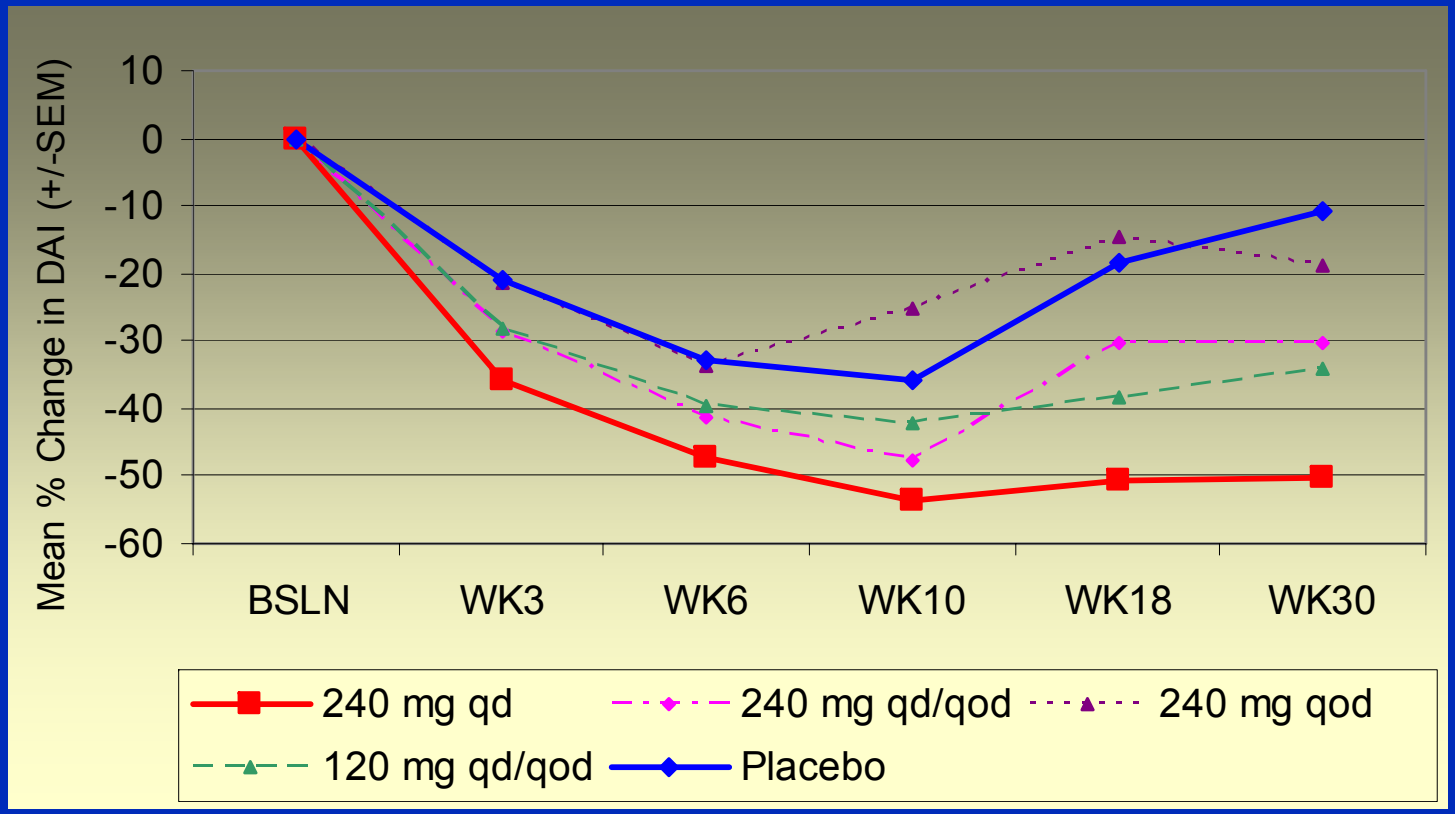
ICAM-1 is the ligand for LFA-1

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

AntiSense Oligonucleotides

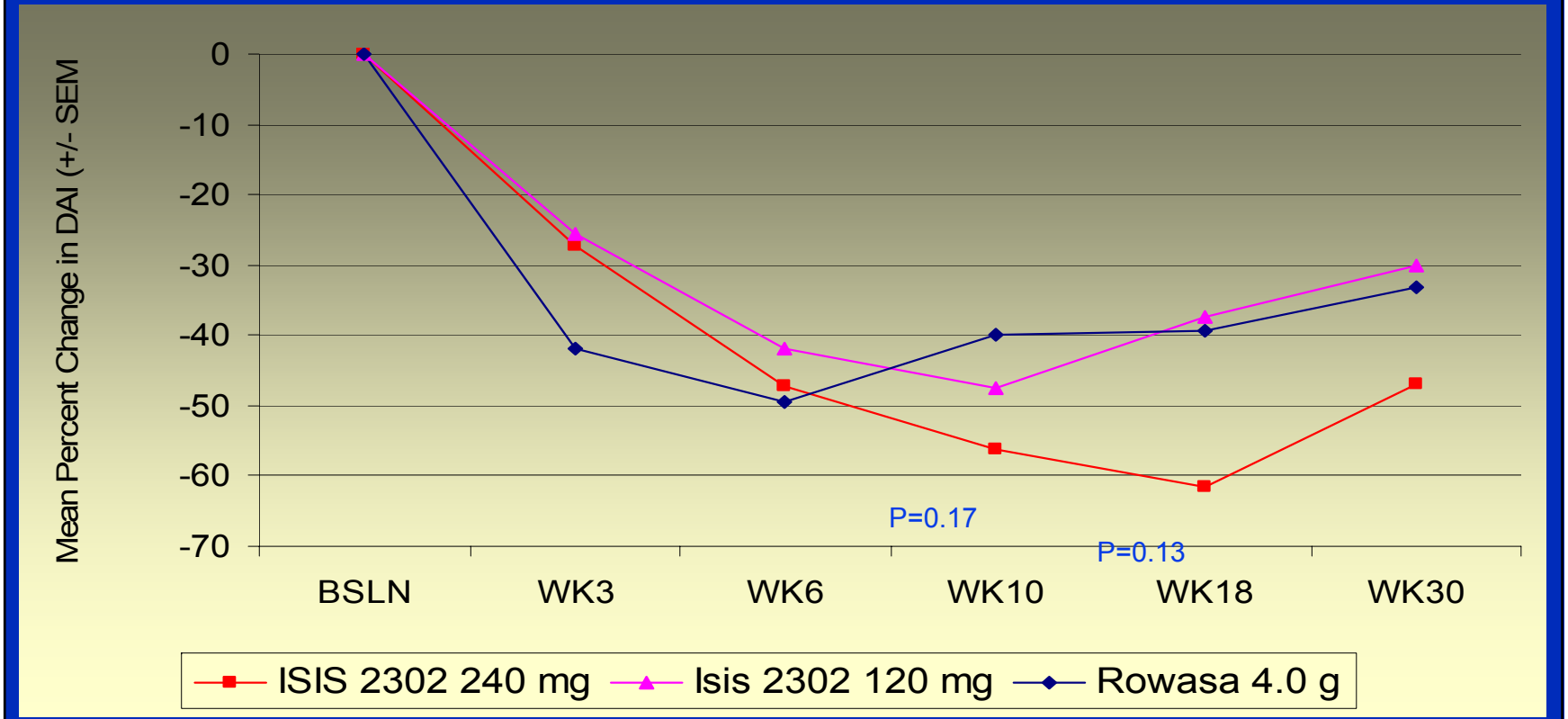
- Synthetic oligonucleotides of single-stranded DNA
- Prevent translation of messenger RNA (mRNA) into protein
- Increase degradation of target mRNA
- Can inhibit formation of the somatic gene products encoded by human, viral, or other infectious agent genomes

Alicaforsen (ISIS-2302) Enemas Versus Placebo in Active Distal Ulcerative Colitis



Van Deventer. Alimentary Pharmaocology and Therapeutics 2006

Alicaforsen (ISIS-2302) Enemas Versus Mesalamine in Active Distal Ulcerative Colitis

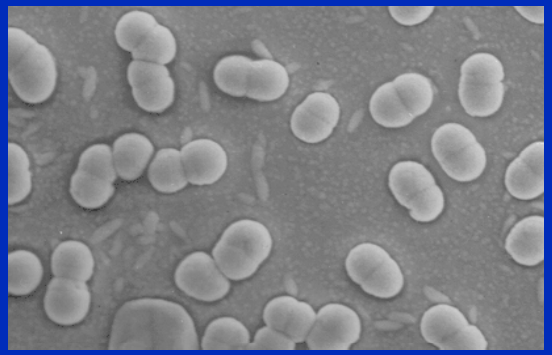


Miner. Alimentary Pharmacology and Therapeutics 2006

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

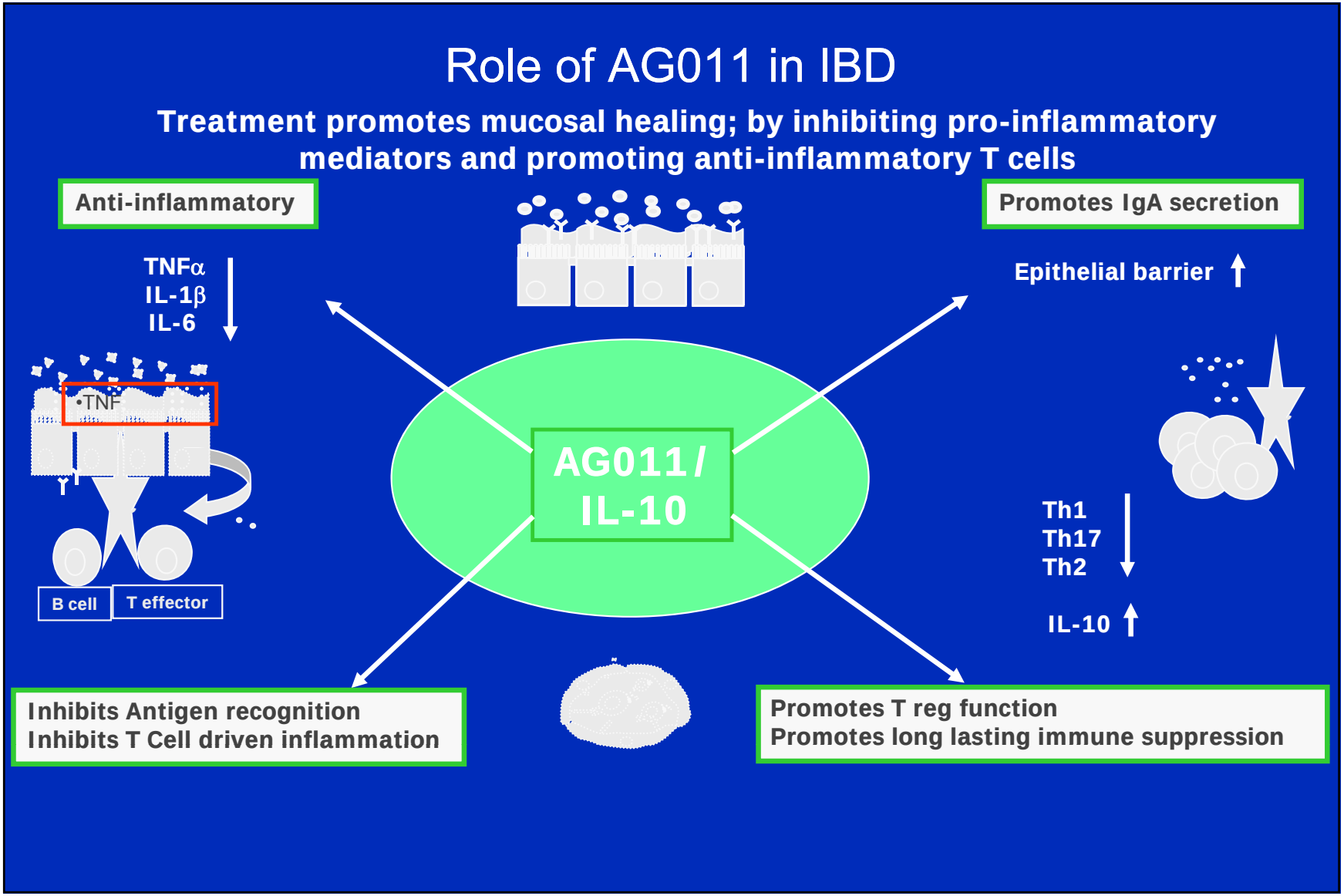


AG011 in IBD
Product Profile

- 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

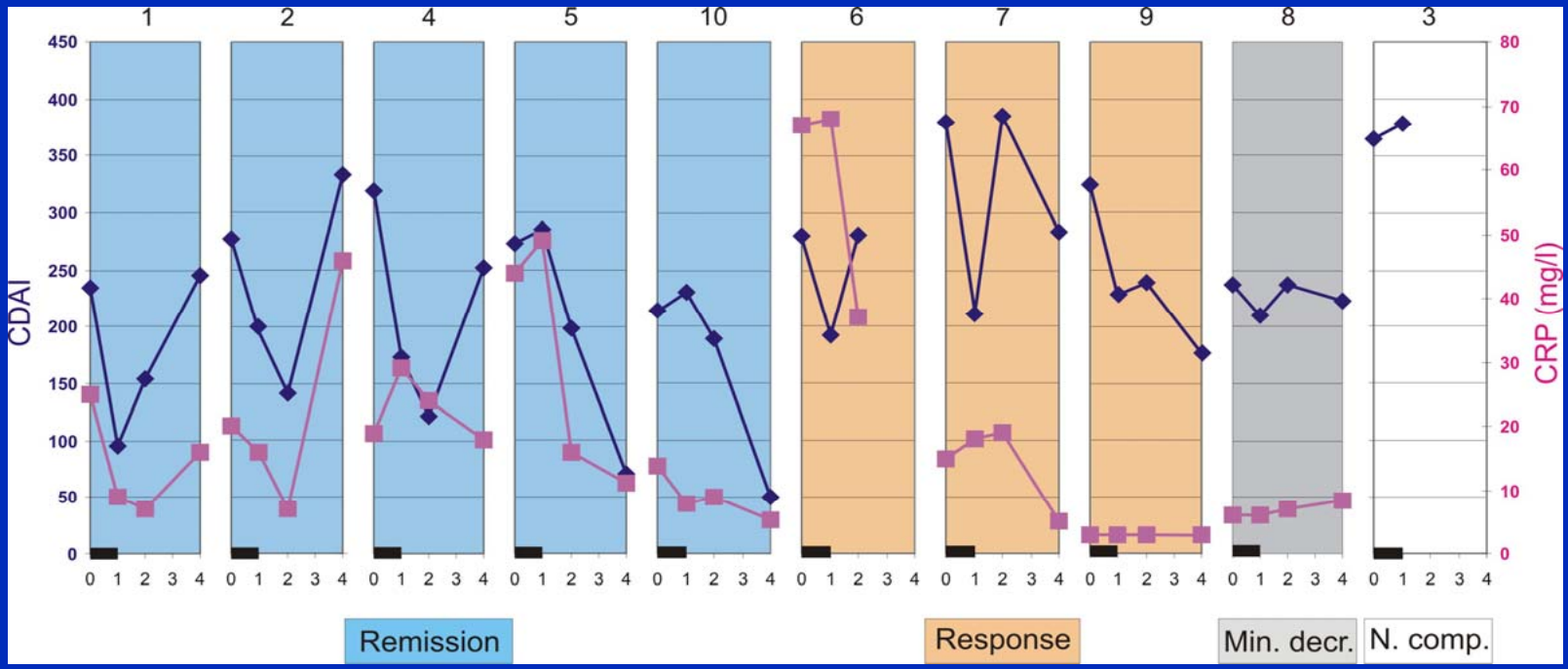
Treatment promotes mucosal healing; by inhibiting pro-inflammatory mediators and promoting anti-inflammatory T cells



Phase 1 clinical study: LL IL-10 in Crohn's Disease

Individual patient data: CDAI scores and CRP levels

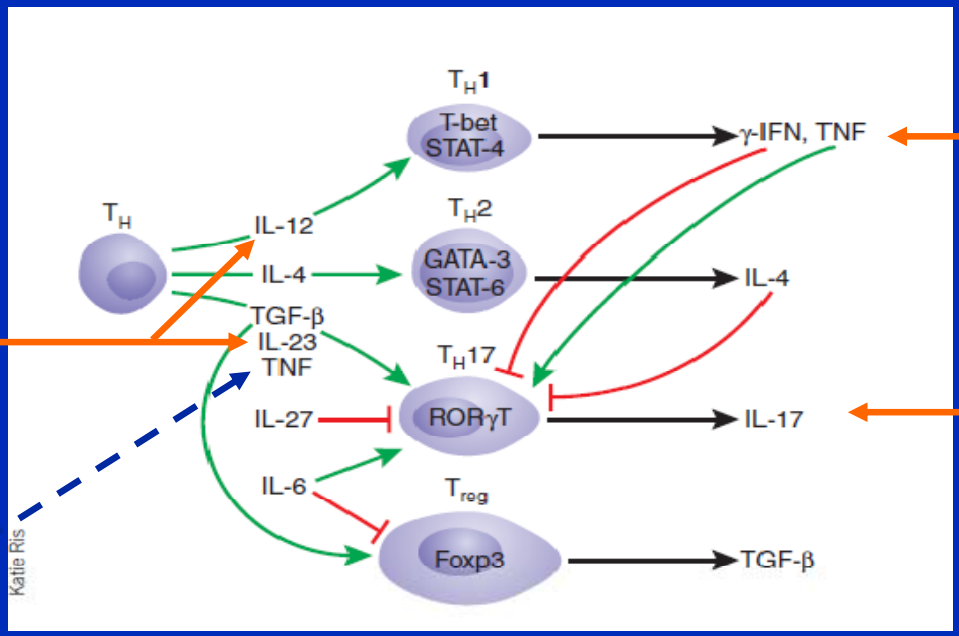
1 Week treatment – 4 weeks monitoring



CDAI<150

CDAI -D70

Interleukin 12/23/17 Pathways in Crohn`s Disease:



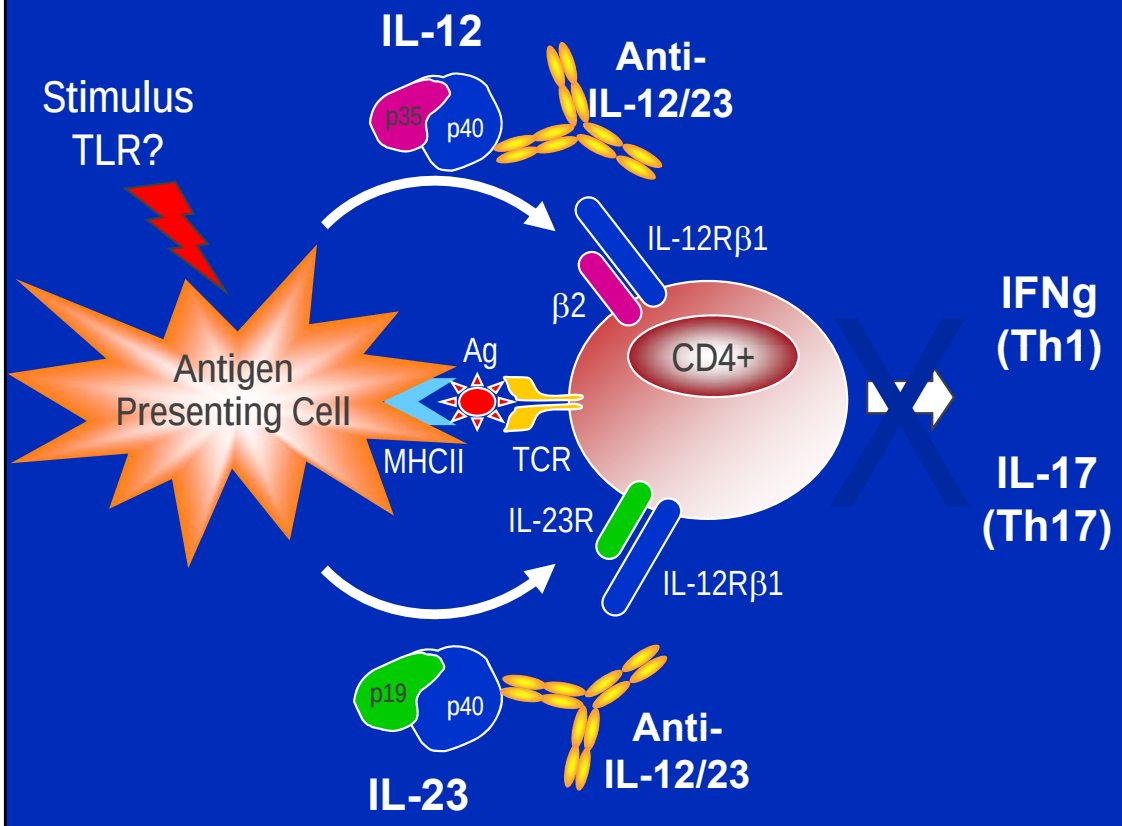
Infliximab
Adalimumab
Certolizumab

CNTO 1275
(Ustekinumab)
ABT-874

Anti-Interleukin 12
AIN457

Adopted from Steinman L, Nat Med 13:144 (2007), Ivanov I, Cell 126;1121 (2006), Tato CM Nature 441:166 (2006)

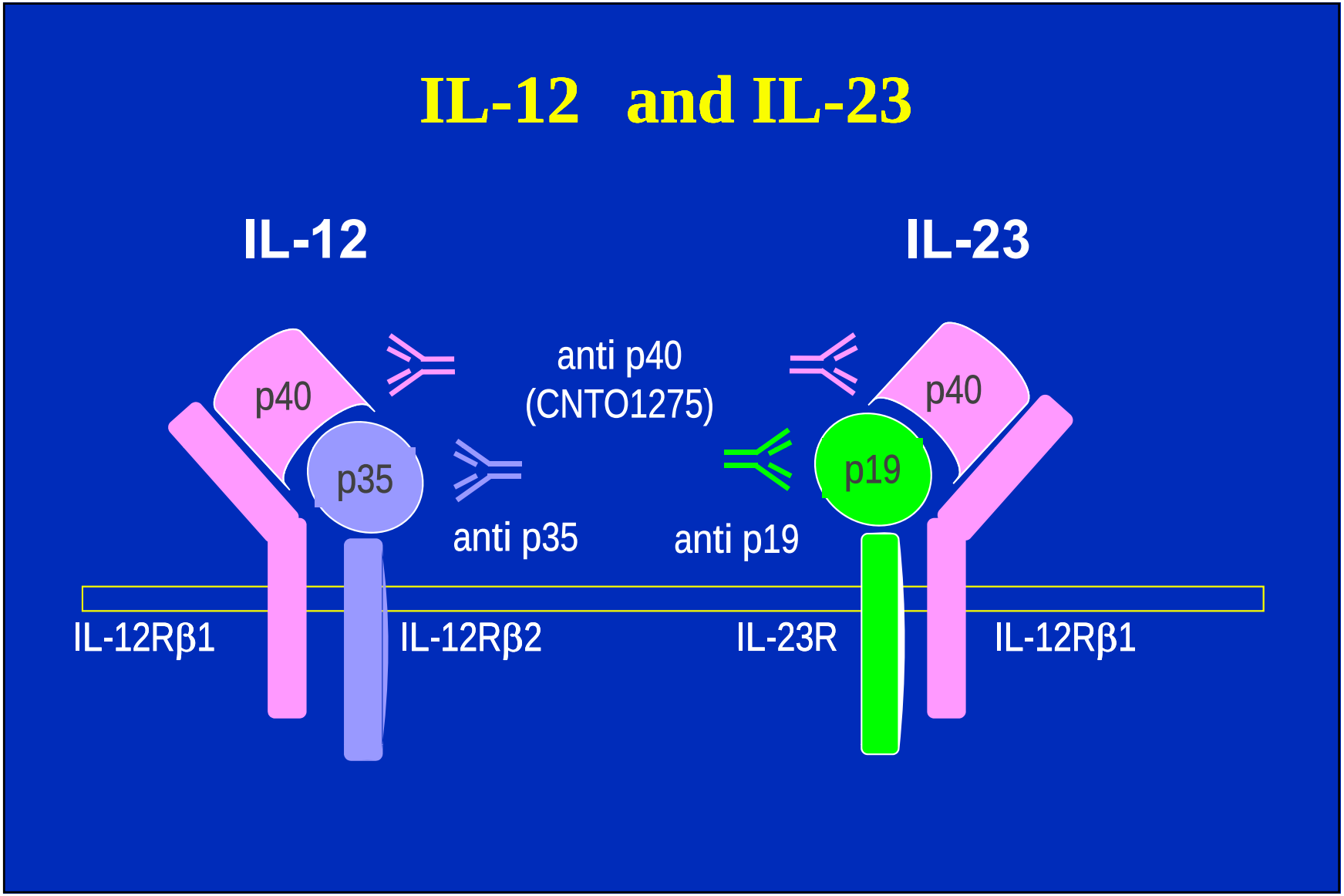
Biology of Interleukins 12 and 23



Anti-IL-12/23

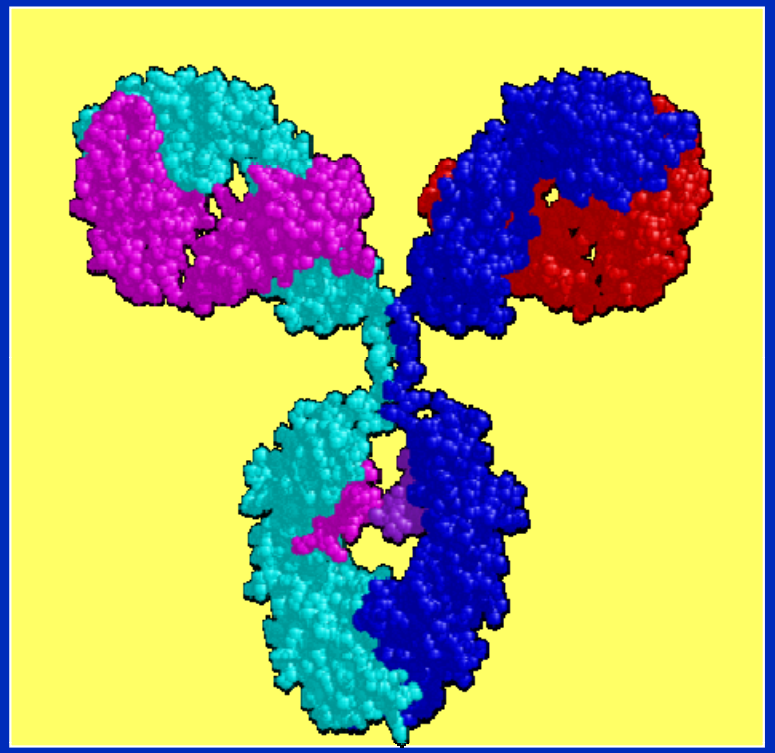
- CNTO 1275 (ustekinumab) and ABT 874 are fully human IgG1 monoclonal antibodies
- Bind the p40 subunit of human IL-12/23
- Prevent IL-12 and IL-23 from binding IL-12Rb1
- Normalize IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production
- In development in Crohn's disease and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

IL-12 and IL-23



ABT-874 Antibody Properties

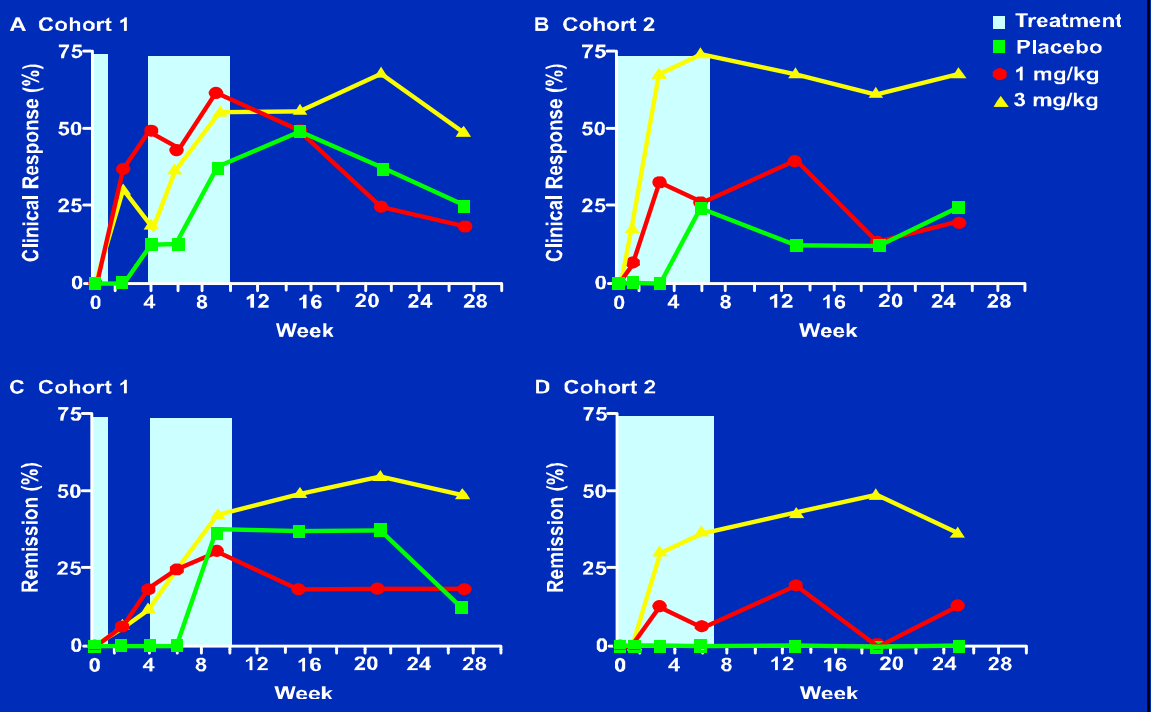
- Fully human anti-IL-12p40 antibody
- Derived by phage-display technology
- Selective for IL-12/-23 (p40) amongst a panel of cytokines
- High affinity (K_d=97 pM)
- Very potent *in vitro* neutralization (IC_{50}=5 pM)
- Neutralizes IL-12 induced responses *in vivo* in animals



Anti–Interleukin-12/23 Monoclonal Antibody (J695, ABT-874) for Active Crohn's Disease

Phase II Trial

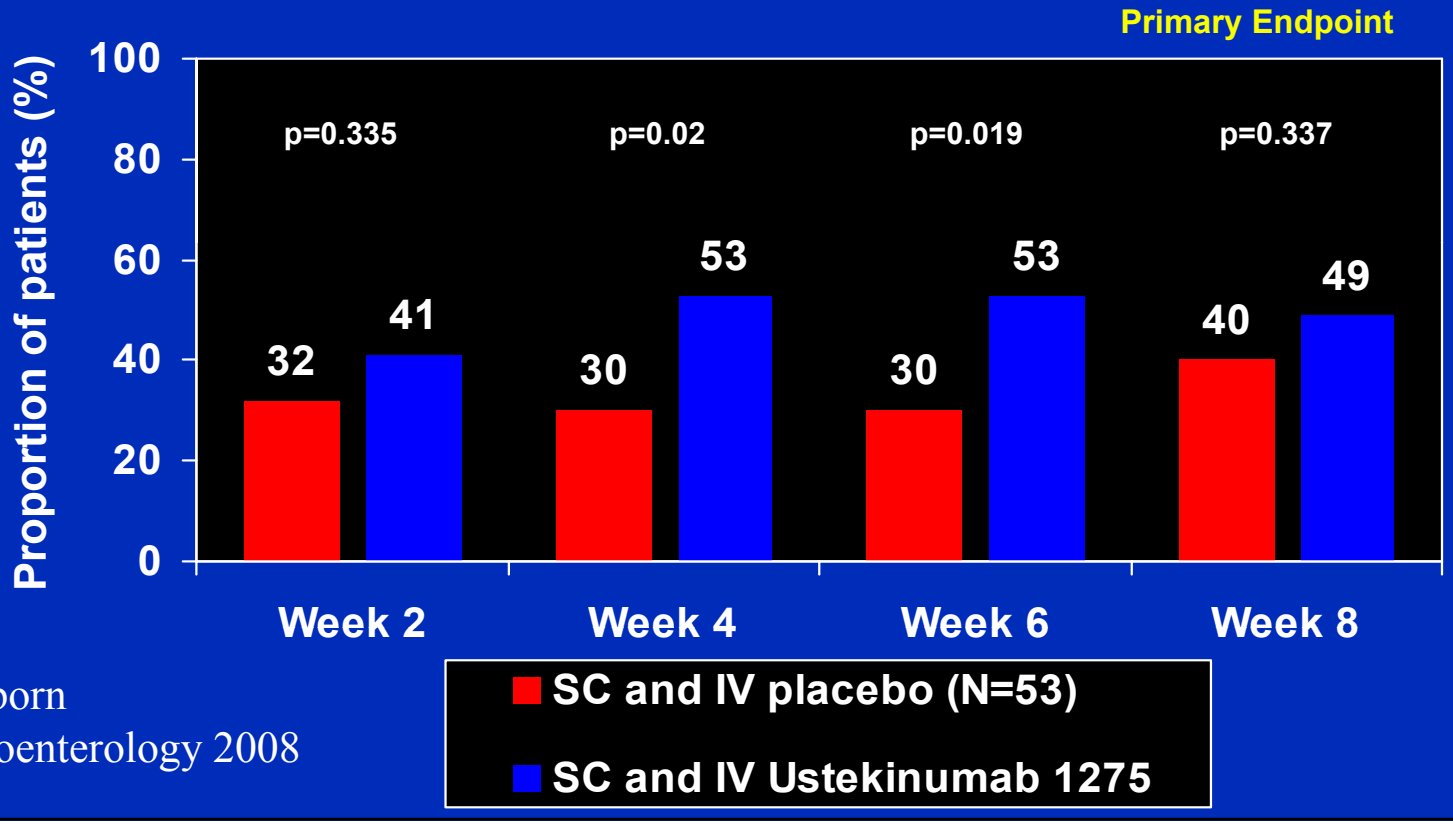
- Cohort 1: n=40
- Cohort 2: n=39
- Active CD (CDAI 250-450)
- 7 weekly SQ injections of J695 1 or 3 mg/kg or placebo
- Clinical remission = CDAI <150 pts at week 7
- Clinical response = ↓ in CDAI ≥100 pts at week 7



Mannon PJ, et al. *NEJM.* 2004;351:2069-2079.

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

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

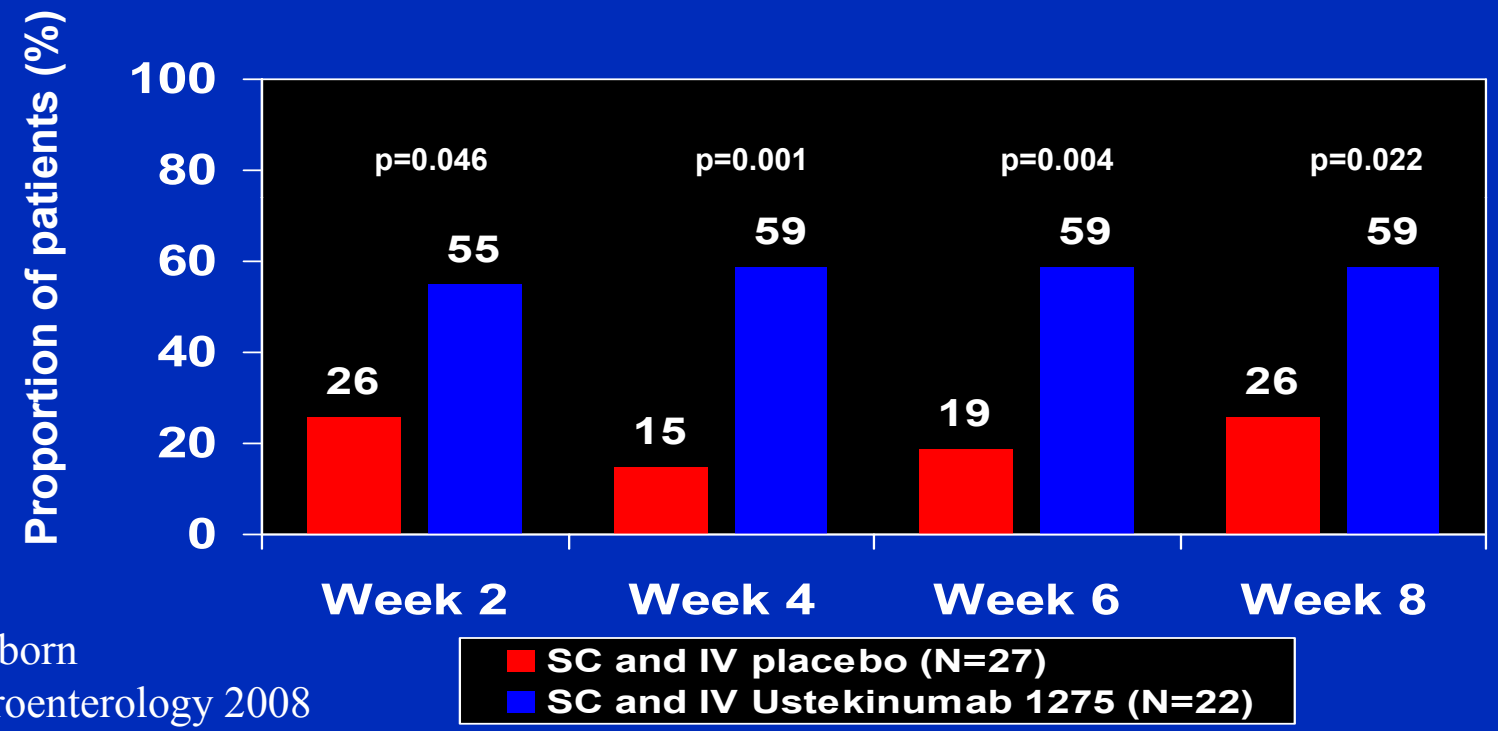


Sandborn
Gastroenterology 2008

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



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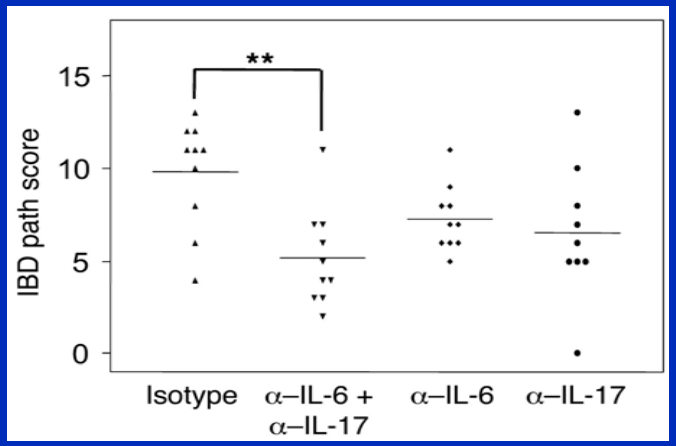
Inflammatory Bowel Disease – Blockade of IL17A Reduces Colitis in Murine Models

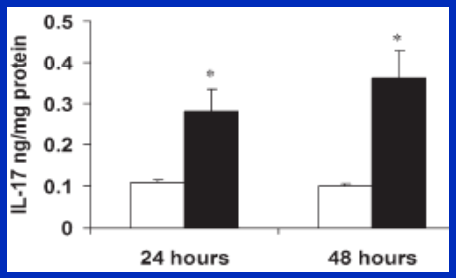
Blocking IL-6 and IL-17 significantly reduced intestinal inflammation, by 50% in T cell transfer model of IBD.

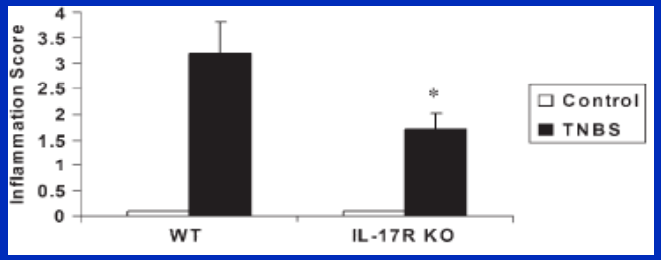


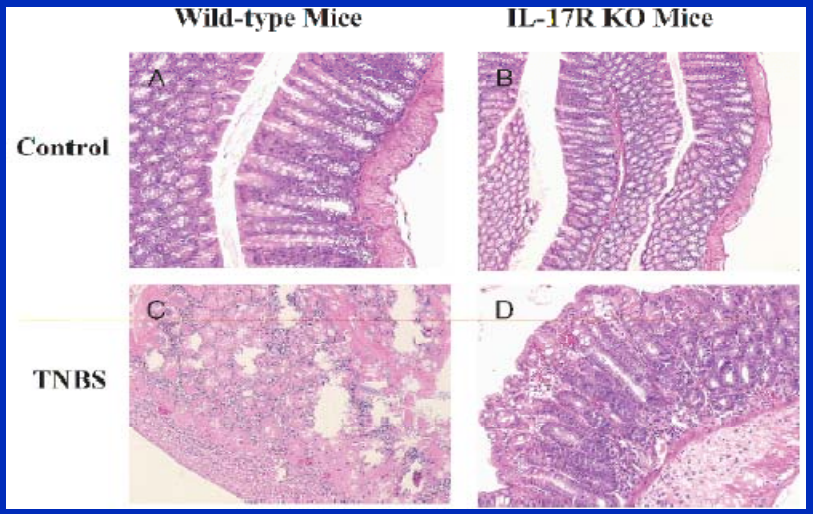
Recipient mice were dosed i.p. with isotype, anti–IL-6, anti–IL-17, or anti–IL-6 plus anti–IL-17 Abs (2 mg/mouse) a day prior to T cell reconstitution. *Rag*-KO mice were reconstituted with sorted splenic CD4+CD45RBhi (naive) T cells (5×10^5 cells/mouse) from diseased *IL-10*–KO mice and treated daily 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).

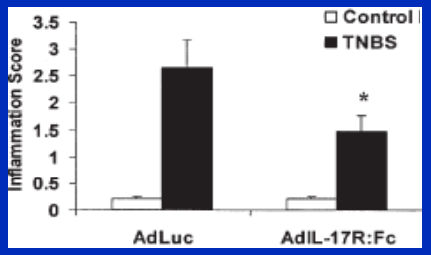
(Yen et al., J Clin Invest 2006;116:1310)

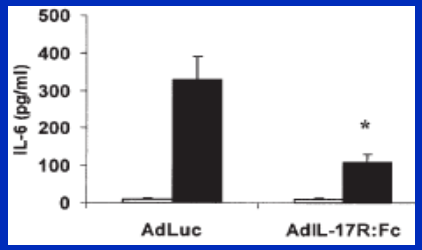
Inflammatory Bowel Disease – Blockade of IL17A Reduces Colitis in Murine IBD Models



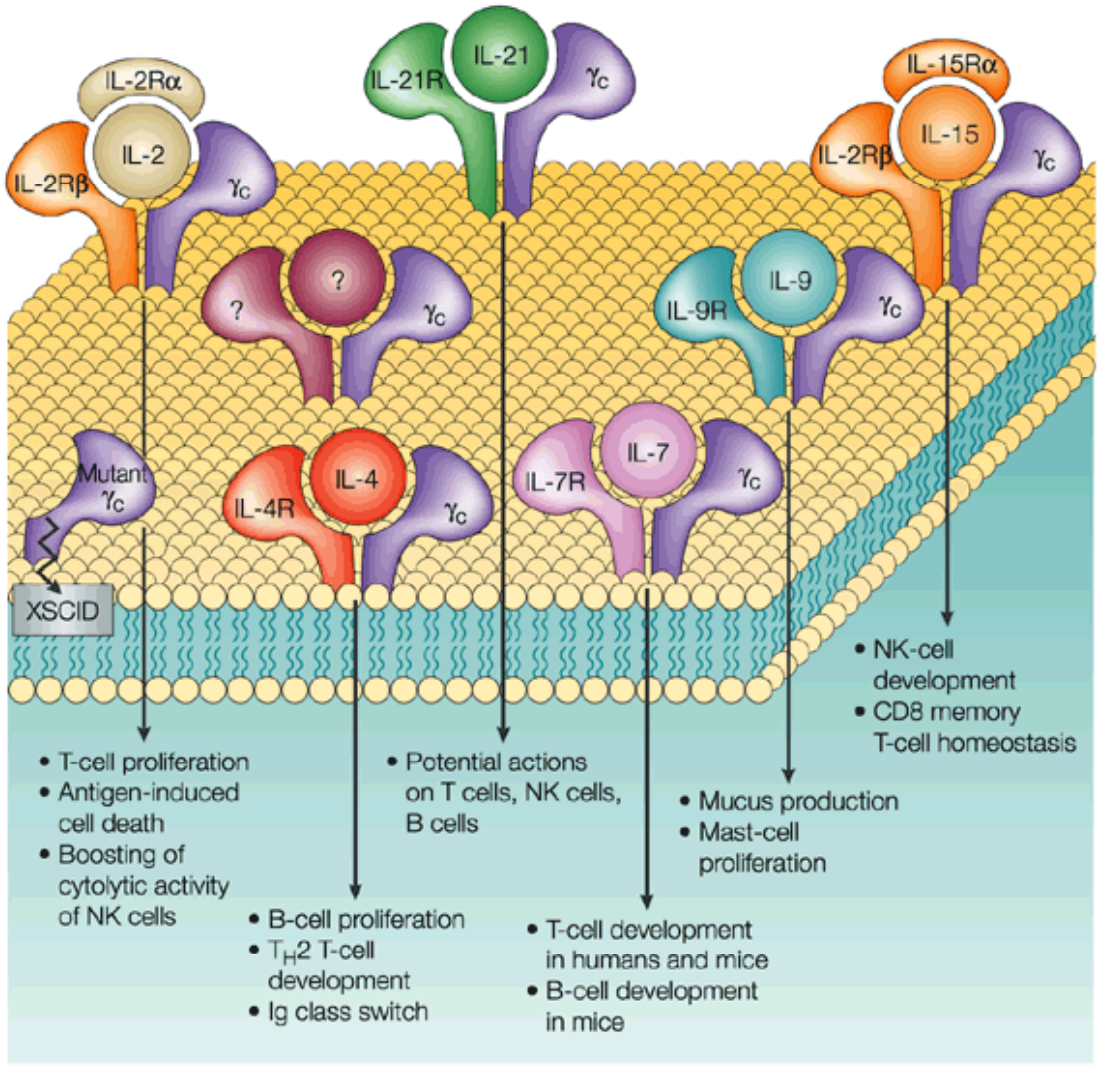








A soluble IL-17R:Fc fusion protein antagonizes colitis, and tissue IL-6 induction. (Zhang et al., Inflamm Bowel Dis 2006;12:382)

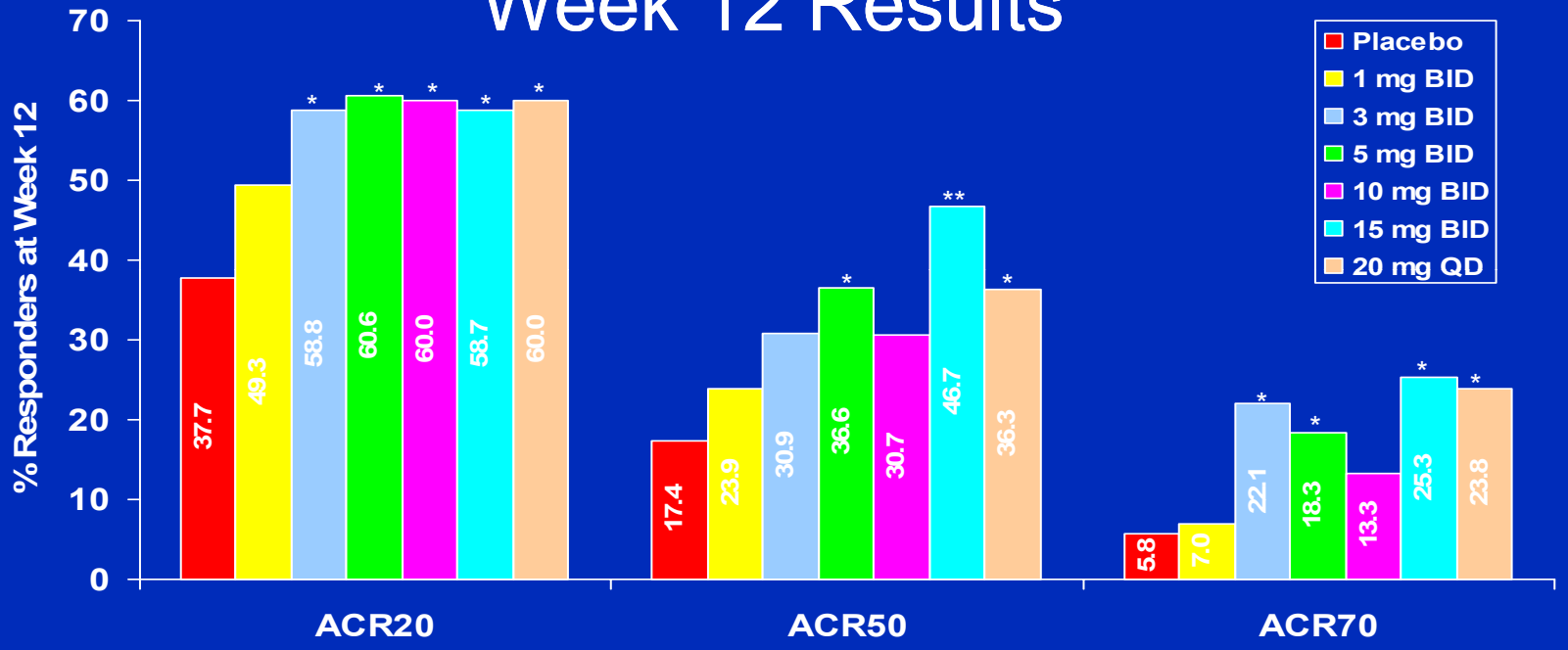


JAK3/γc inhibitors will block signalling by six cytokines

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

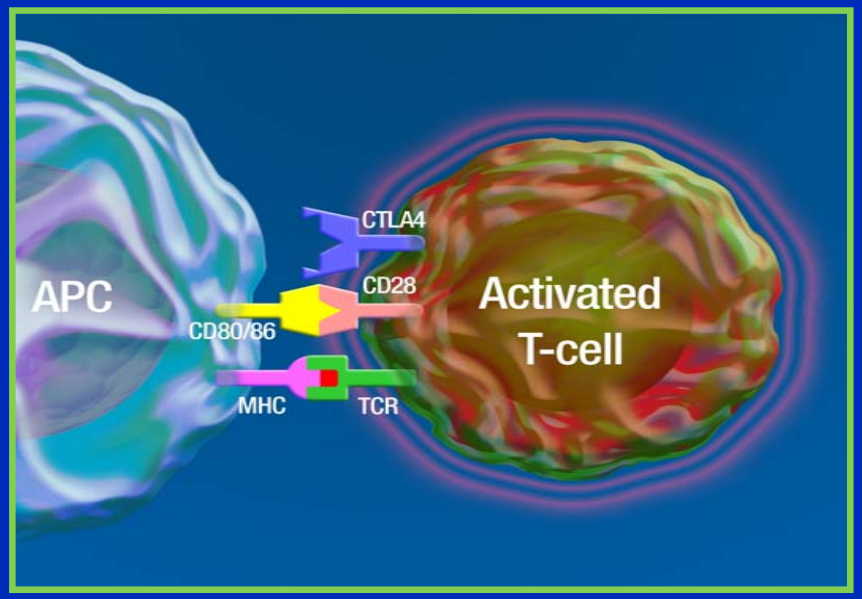


* p ≤ 0.005 vs placebo

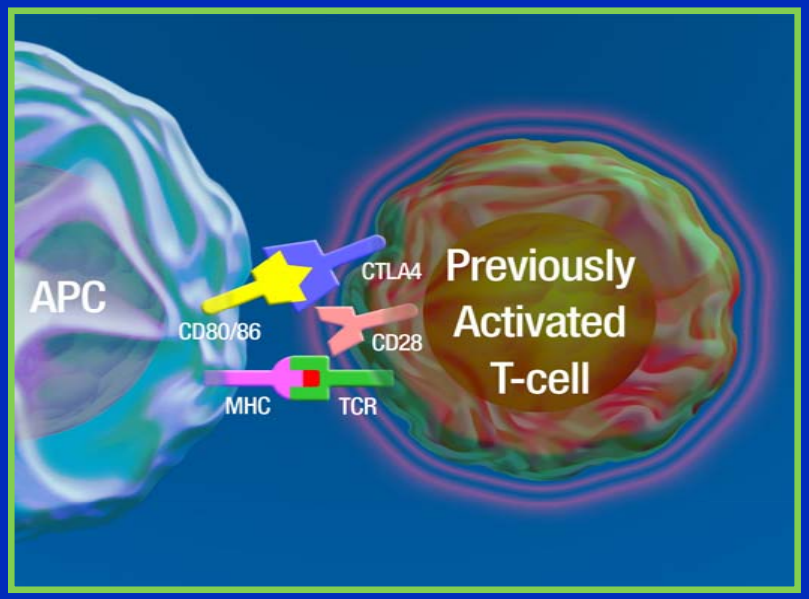
** p ≤ 0.0001 vs placebo

ACR/ARHP October 2008

CTLA4 Negatively Regulates T-cell Activation

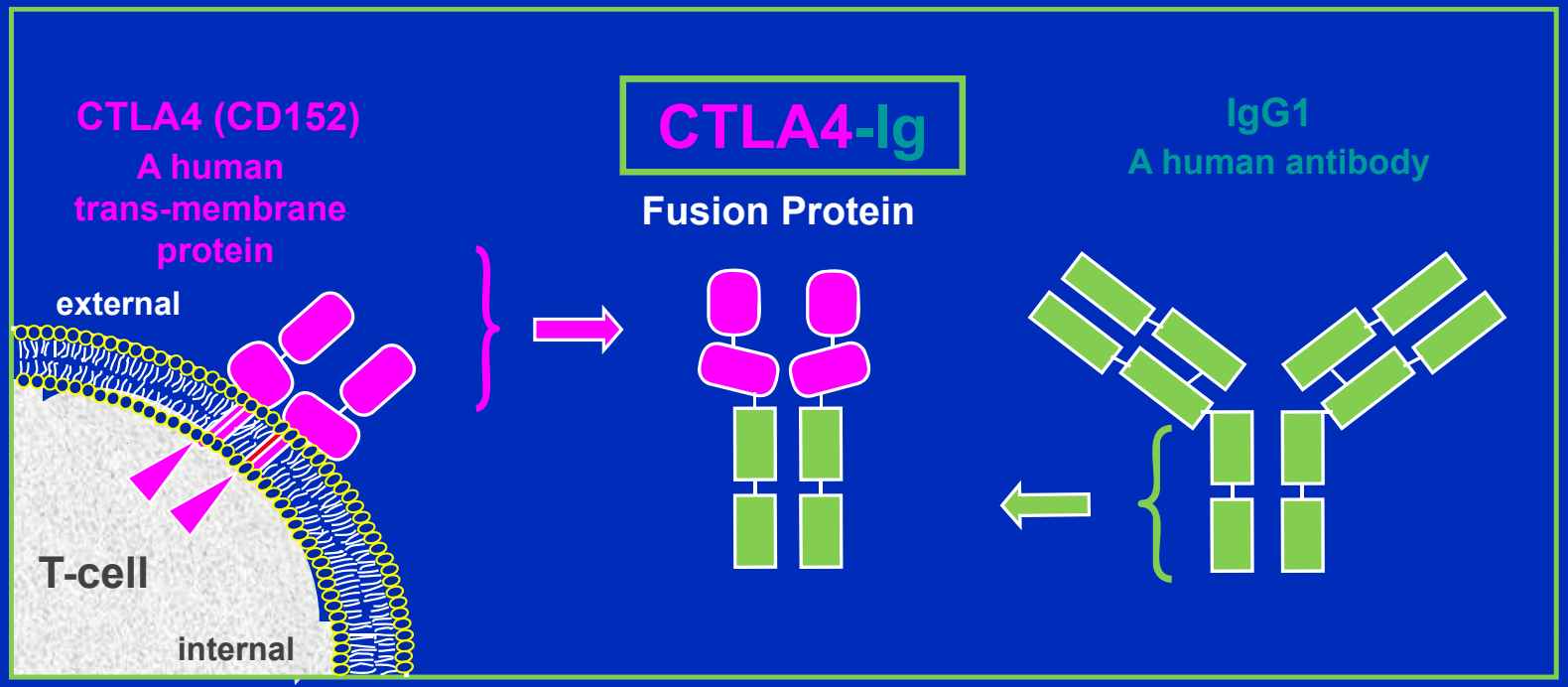


CTLA4 expressed following T-cell activation



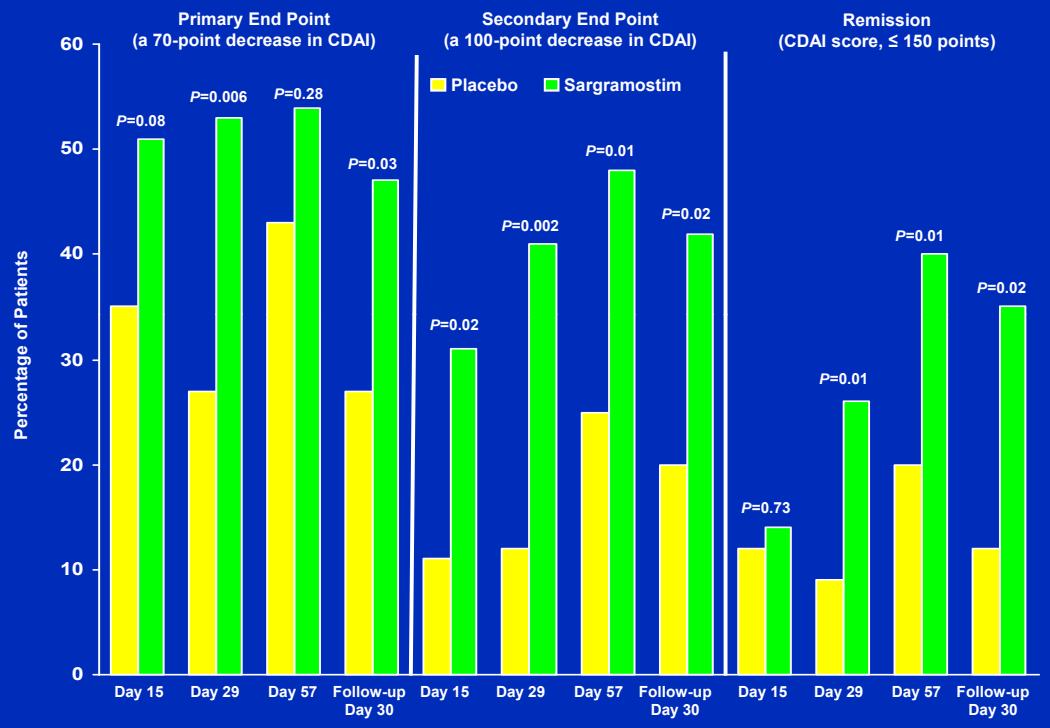
CTLA4 binds to CD80/86 with higher avidity than CD28, and inhibits co-stimulation

Abatacept (CTLA4-Ig, Orencia): A Human Recombinant Fusion Protein



Sargramostim (GMCSF) for Crohn's Disease

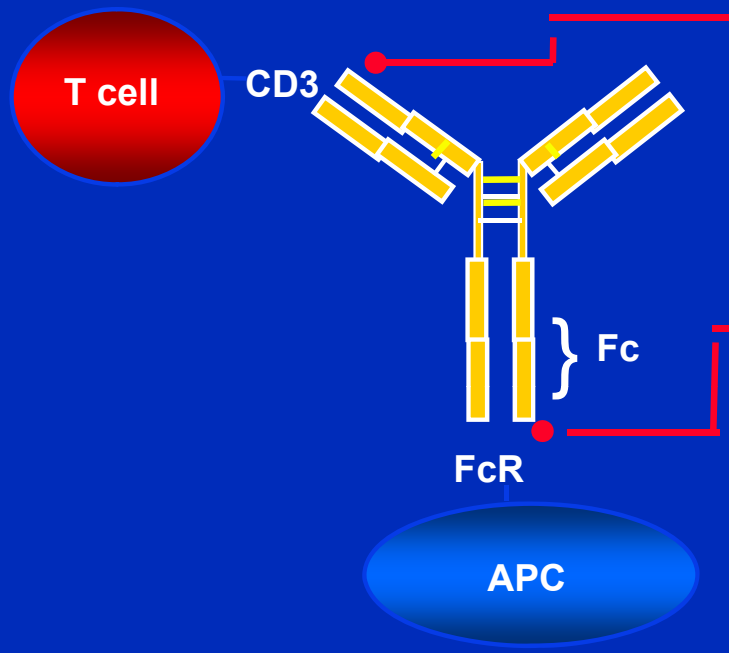
- Gut inflammation phenotypically similar to Crohn's disease occurs in chronic granulomatous disease, glycogen storage disease, and Chediak-Higashi syndrome
- 124 patients with active CD; concomitant treatment with steroids, immunosuppressives; infliximab not permitted
- Sargramostim 6 ug/kg or placebo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



Korzenik JR, et al. *NEJM.* 2005;352:2193-2201.

Rationale

OKT3 and Immunosuppression



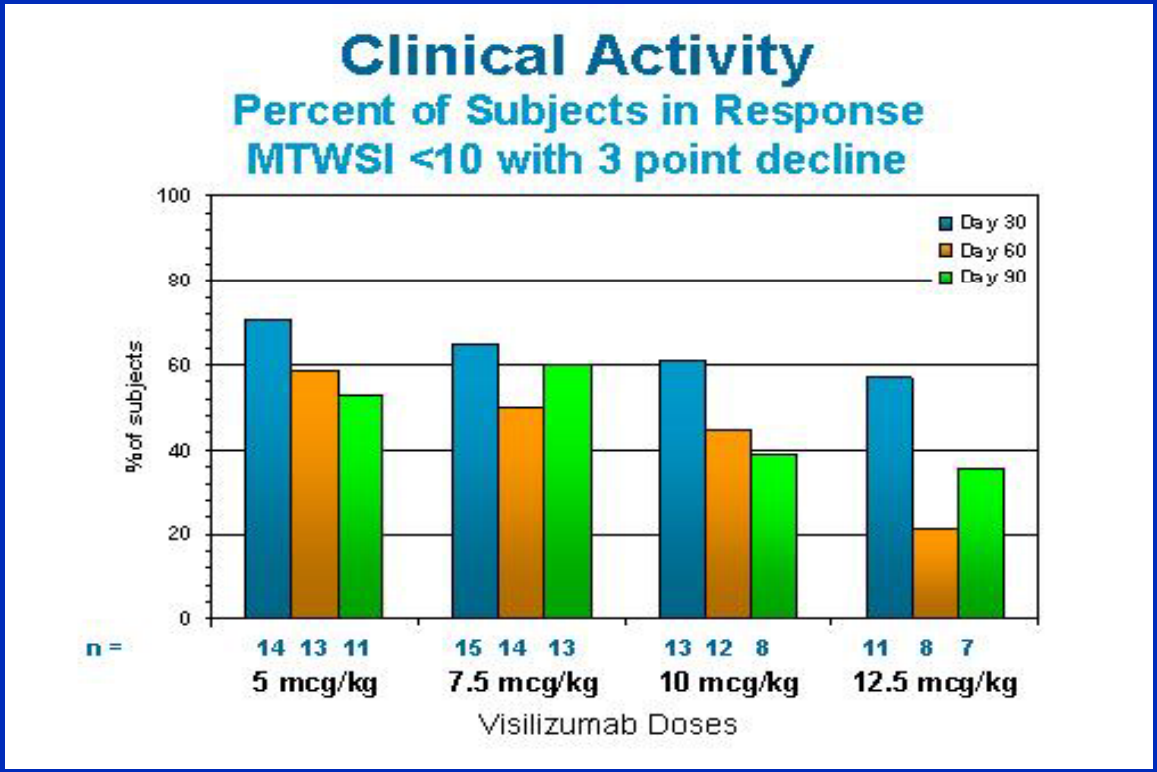
Immunosuppression
- T-cell receptor modulation
- T-cell clearance
- Unresponsiveness

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**

Alegre M-L, et al. *J Immunol*. 1995;155:1544-1555.

Visilizumab: Severe Active Steroid-Refractory Ulcerative Colitis



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