# USTEKINUMAB and BRIAKINUMAB

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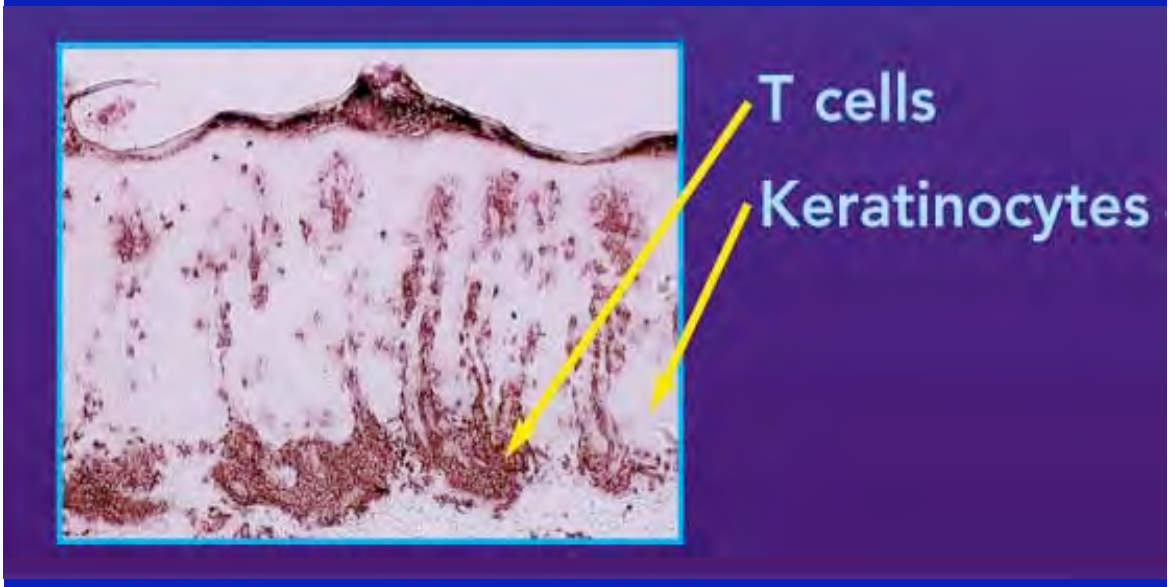
## CONFLICTS OF INTEREST

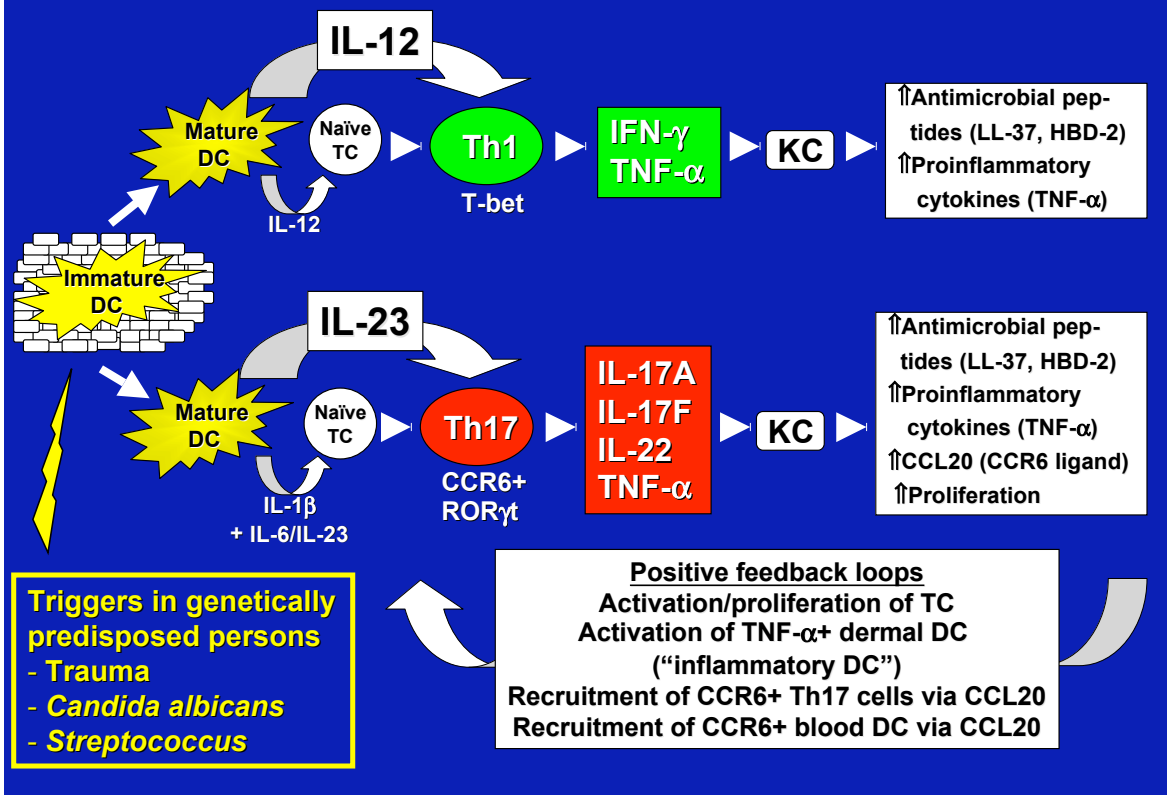
- Centocor: scientific advisor, principal investigator for clinical studies, received lab research funds
- Abbott: scientific advisor, principal investigator for clinical studies
- Lilly: principal investigator for clinical studies

# PROMINENT T CELL INFILTRATION ADJACENT TO HYPERPROLIFERATIVE KERATINOCYTES IN PSORIASIS

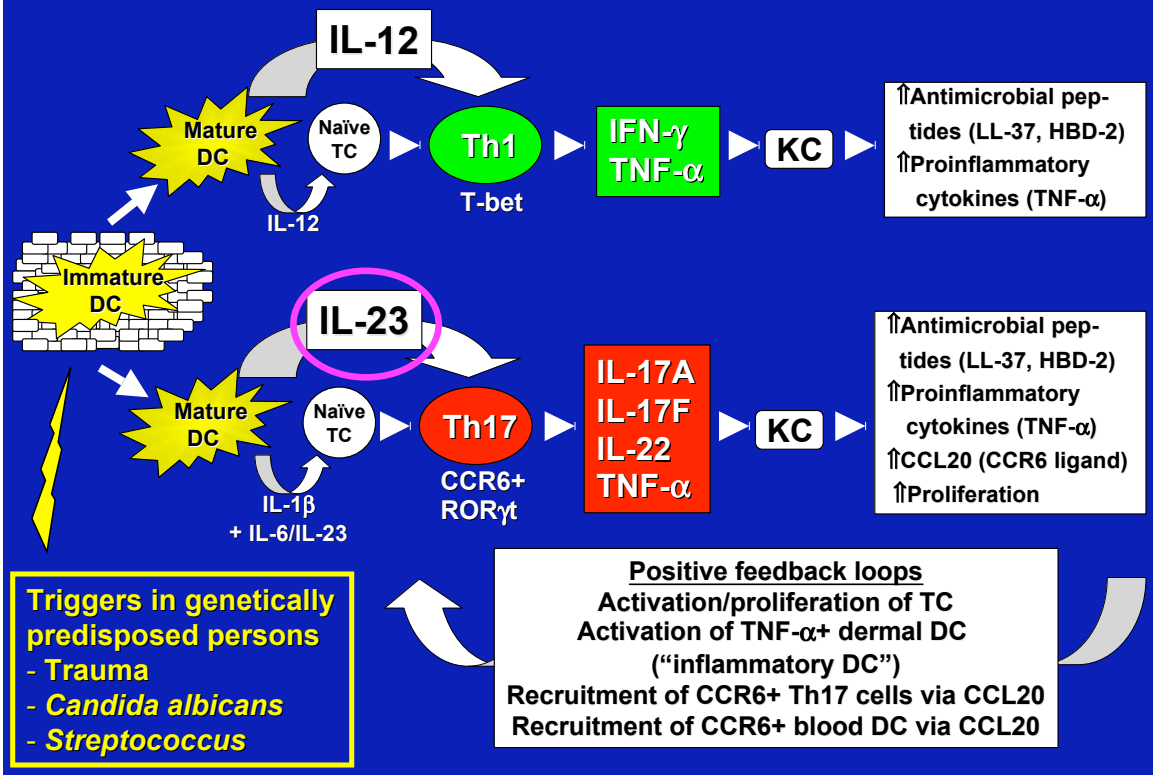



REF: Jim Krueger, Rockefeller Univ.

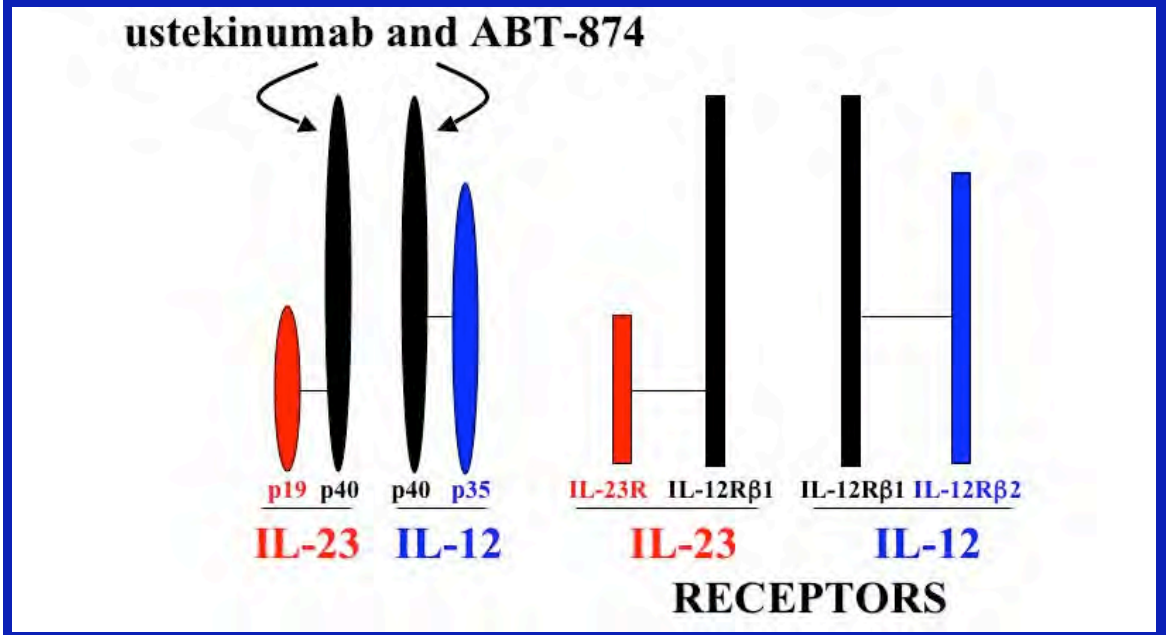
## DC ACTIVATION ⇒ TC ACTIVATION ⇒ KC ACTIVATION



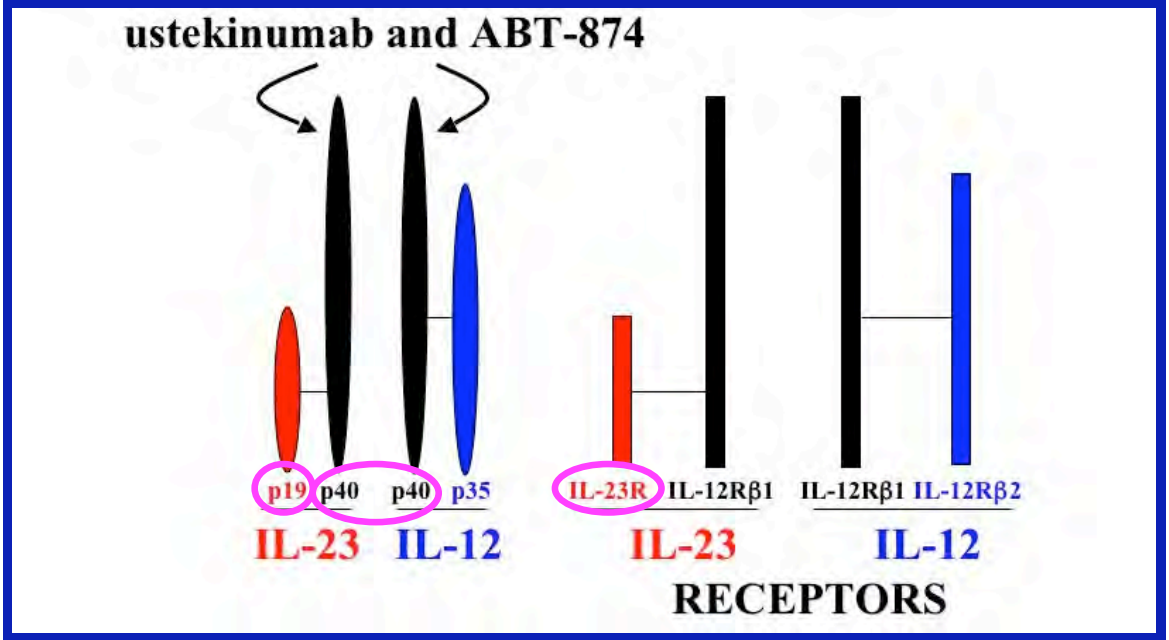
## DC ACTIVATION ⇒ TC ACTIVATION ⇒ KC ACTIVATION



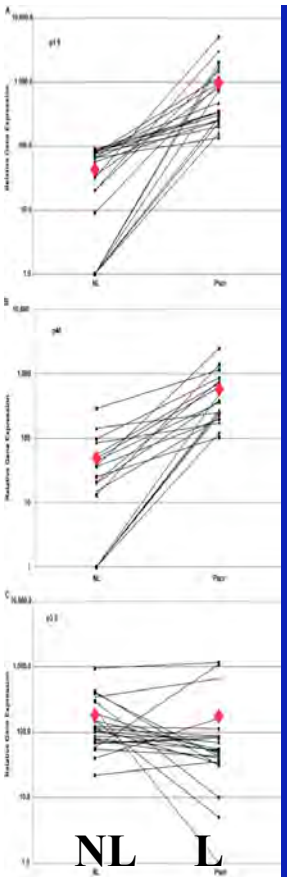

## IL-23 AND IL-12 SHARE THE p40 SUBUNIT, YET EACH HAVE THEIR OWN UNIQUE SUBUNIT



## POLYMORPHISMS IN *p19*, *p40*, AND *IL-23R* LINKED TO PROTECTION OF AND SUSCEPTIBILITY TO PSORIASIS




REF: Nair et al, Nat Genet, 2009




p19

IL-23

p40

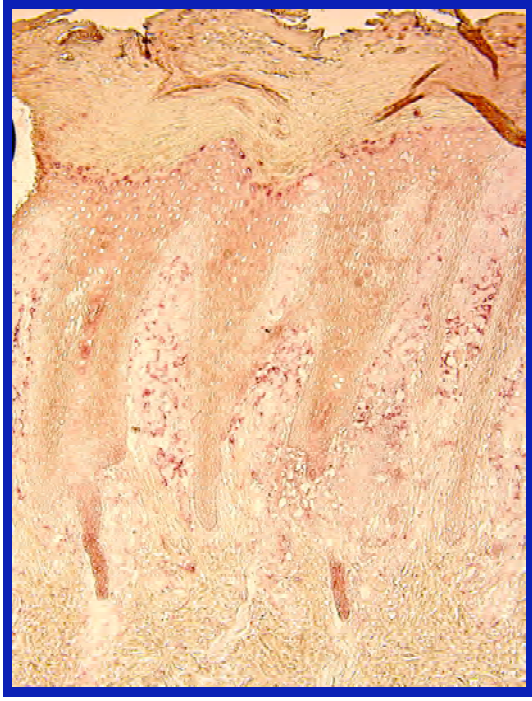
IL-12

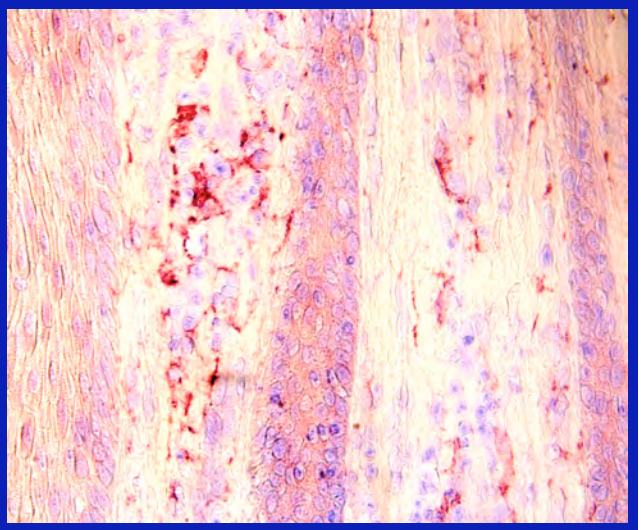
p35

**INCREASED IL-23, BUT NOT IL-12, mRNA PRODUCTION IN LESIONAL PSORIASIS**

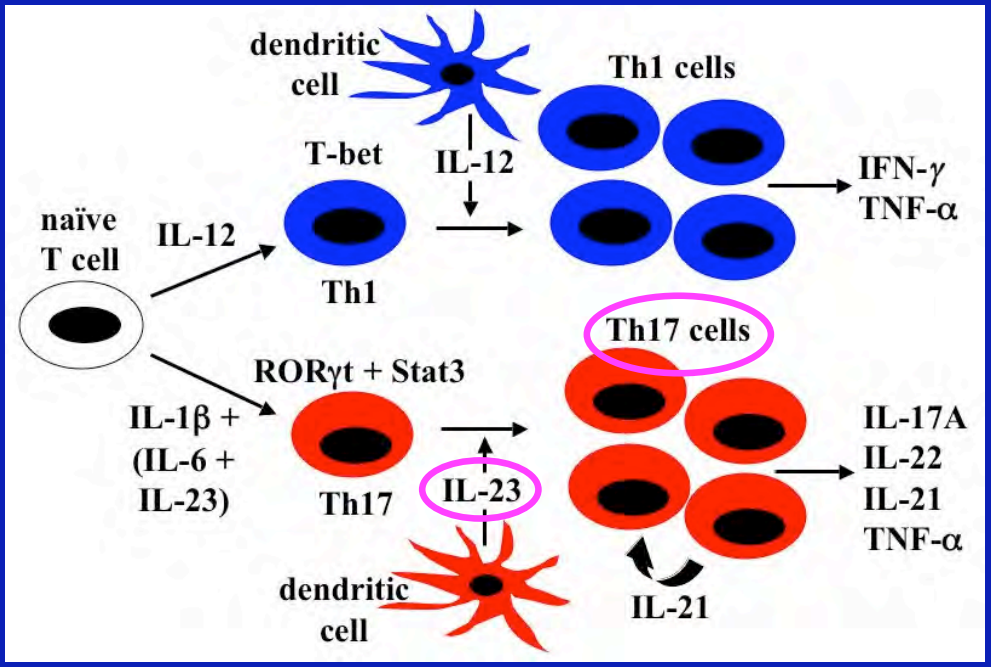
REF: Lee et al, J Exp Med, 2004

# IL-23 POSITIVE DENDRITIC CELLS IN PSORIASIS

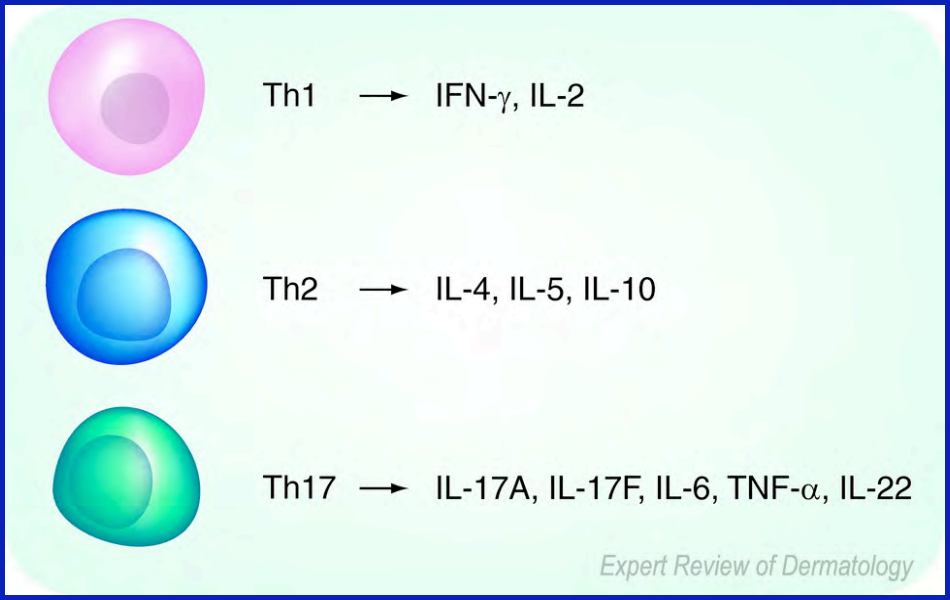




# IL-23 IS CRITICAL FOR THE SURVIVAL AND PROLIFERATION OF Th17 CELLS

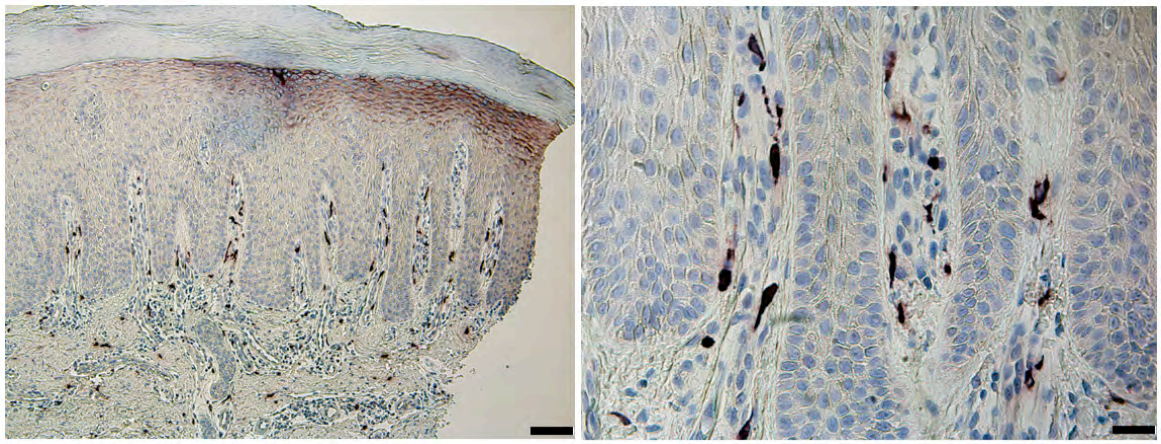


# Th17 CELLS ARE DISTINCT FROM Th1 AND Th2 CELLS



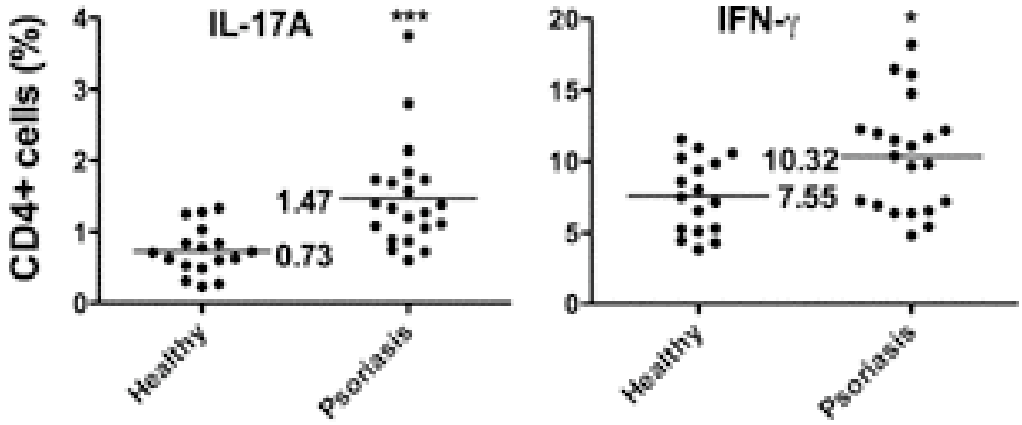

REF: Blauvelt, Expert Rev Dermatol, 2007

# IL-17A+ LEUKOCYTES IN PSORIASIS



REF: Harper et al, J Invest Dermatol, 2009

## ⇑CIRCULATING IL-17A+ AND IFN-γ+ CD4+ CELLS IN PSORIASIS




Kagami et al, submitted

## T CELLS AND PSORIASIS (older data)

- Many of the CD4+ and CD8+ T cells are type 1 T cells: Th1 and Tc1 cells (i.e, they secrete IFN-γ)
- Thus, psoriasis is a "Th1 disease"

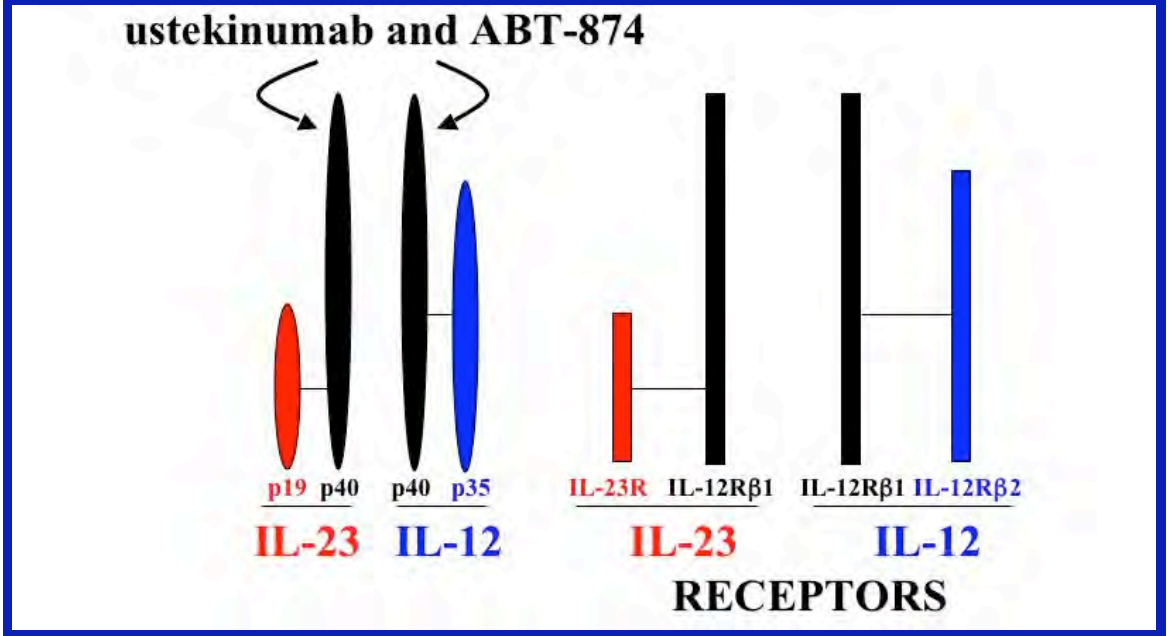
# T CELLS AND PSORIASIS (newer data)

- Many of the CD4+ T cells are Th17 cells (i.e, they secrete IL-17A) plus new genetics/mouse data
- Thus, psoriasis is a "Th17 disease"
- Or, more conservatively: psoriasis is a "mixed Th1/Th17 disease"
- If "mixed," what is primary and what is secondary?
- Data in mice suggest that IL-12/Th1 cells and IL-23/Th17 cells counter-regulate one another

# THERAPUETIC IMPLICATIONS:

## DRUGS THAT BLOCK IL-23 (e.g., ustekinumab and briakunumab)

## USTEKINUMAB AND BRIAKINUMAB (ABT-874) TARGET p40, THE SUBUNIT SHARED BY IL-23 AND IL-12

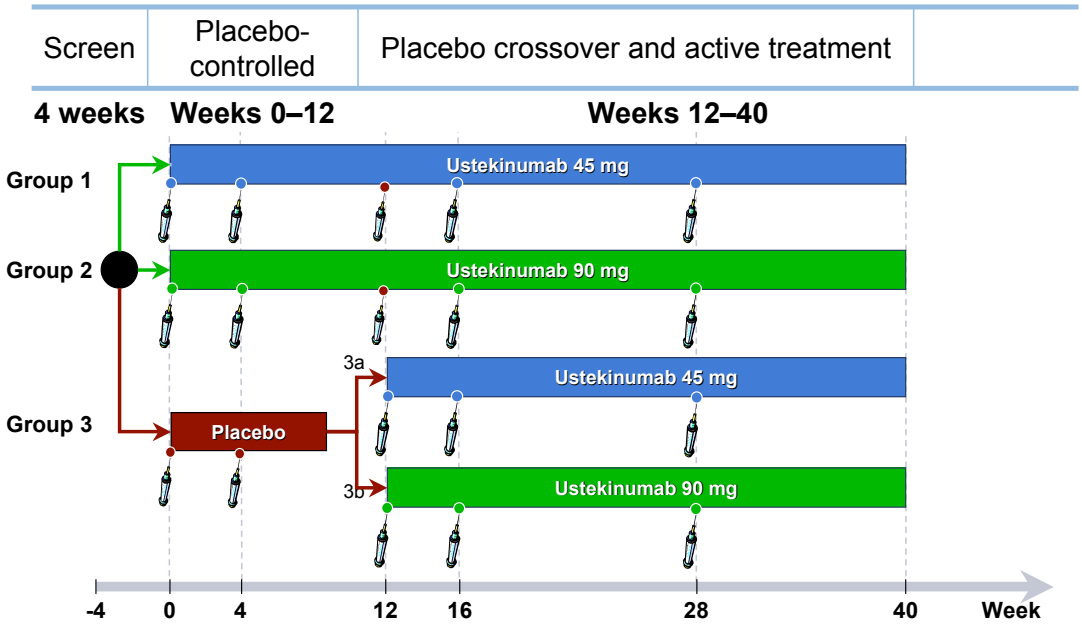



## ANTI-IL-23/12 MONOCLONAL Abs UNDER EVALUATION FOR PSORIASIS AND OTHER DISEASES

| | Ustekinumab (approved in Canada and Europe) | Briakinumab |
|---|---|---|
| Structure | Fully human monoclonal IgG1 Ab | Fully human monoclonal IgG1 Ab |
| Type | Transgenic | Phage display |
| Half-life | 20 days[1] | Unpublished |
| Published clinical data | Psoriasis (3 ph III)[2-4]<br>Psor. arthritis (ph II)[5]<br>Crohn's disease (ph II)[6]<br>Multiple sclerosis (ph II)[7] | Psoriasis (ph II)[8] |

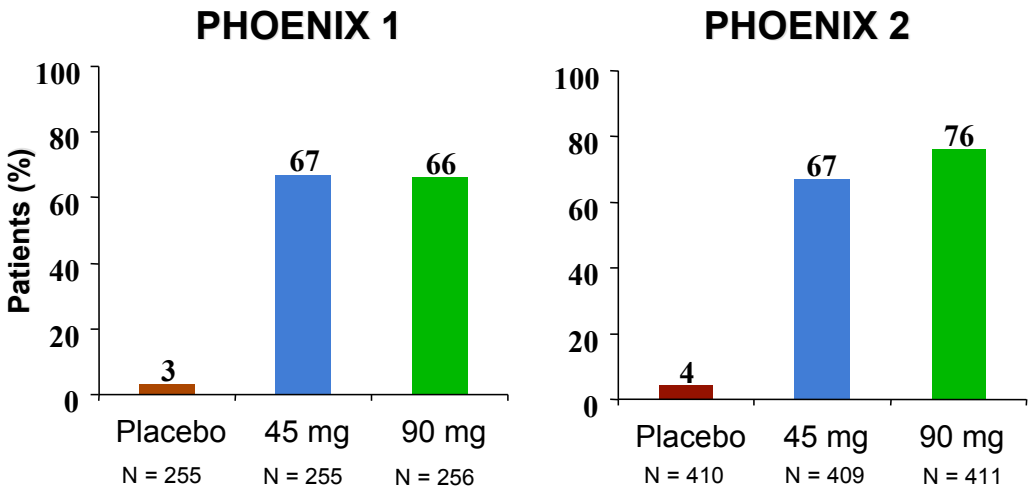
1. Gottlieb AB, et al. *Curr Med Res Opin* 2007;23:1081; 2. Leonardi CL, et al. *Lancet* 2008;371: 1665; 3. Papp KA, et al. *Lancet* 2008;371:1675; 4. Griffiths C, et al. EADV 2008; 5. Gottlieb AB, et al. ACR 2007; 6. Peyrin-Biroulet L, et al. *Lancet* 2008;372:67; 7. Segal BM, et al. *Lancet Neurol* 2008; 7:796; 8. Kimball AB, et al. *Arch Dermatol* 2008;144:200

# PHOENIX 1 & 2: STUDY DESIGN




**REFS: Leonardi et al, Lancet, 2008; Papp et al, Lancet, 2008**

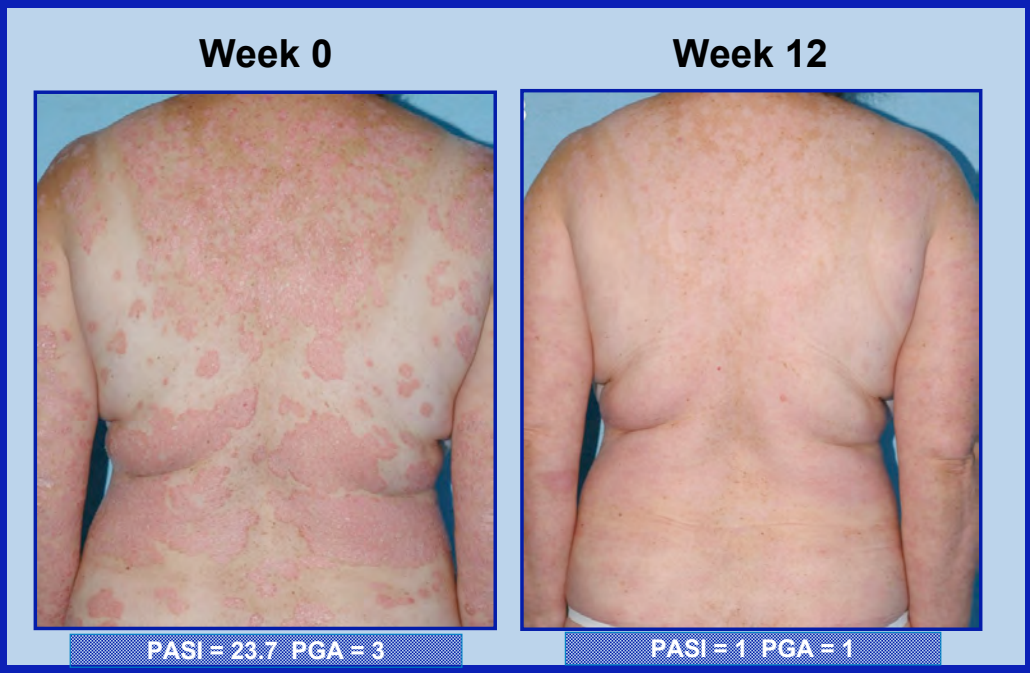
# USTEKINUMAB PASI 75 RESPONSES AT WEEK 12 (AFTER DOSES AT WEEKS 0, 4)




**p < 0.001 vs placebo for each dose comparison**

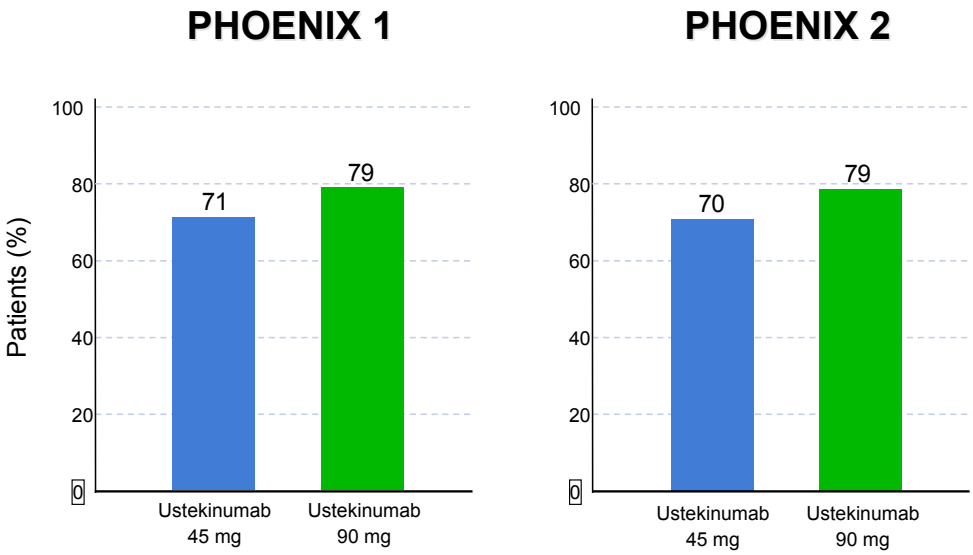
**REFS: Leonardi et al, Lancet, 2008; Papp et al, Lancet, 2008**

## SIGNIFICANT EFFICACY AFTER TWO INJECTIONS



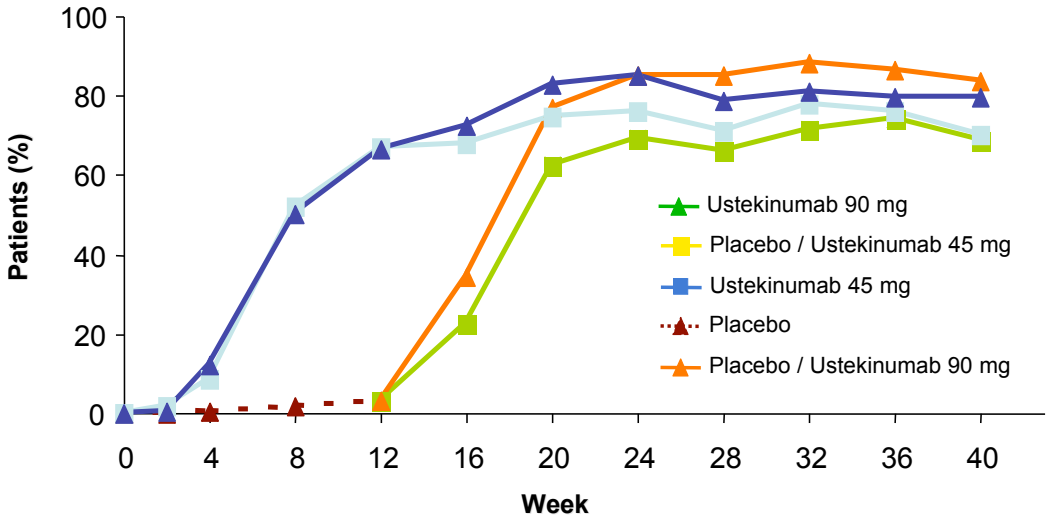

Images courtesy of the PHOENIX 2 Investigators

## USTEKINUMAB PASI 75 RESPONSES AT WEEK 28 (AFTER DOSES AT WEEKS 0, 4, 16)




REFS: Leonardi et al, Lancet, 2008; Papp et al, Lancet, 2008

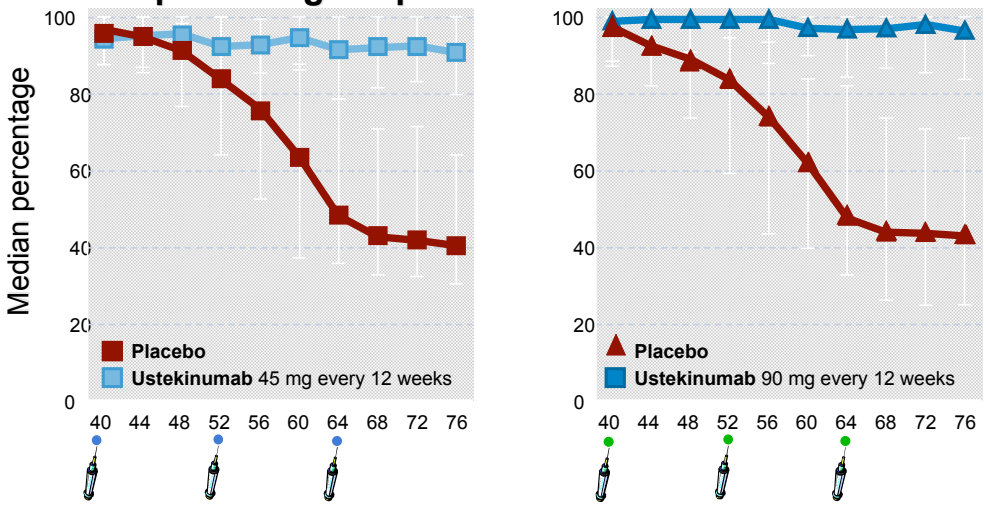
# USTEKINUMAB PASI 75 RESPONSES THROUGH WEEK 40




**REF: Leonardi et al, Lancet, 2008**

# MAINTENANCE TREATMENT WITH USTEKINUMAB IS EFFECTIVE WITH EVERY 12 WEEKS DOSING

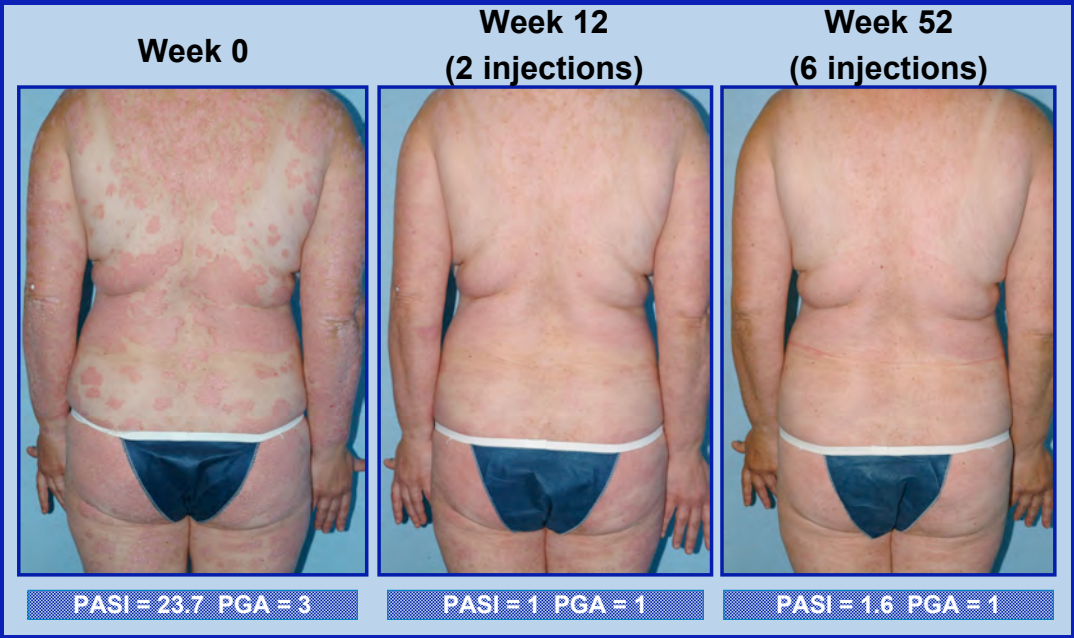
**Median percentage improvement from baseline in PASI score**




***All patients randomised to maintenance therapy or treatment interruption at week 40.**

**REF: Leonardi et al, Lancet, 2008**

## TYPICAL CLINICAL RESPONSE TO USTEKINUMAB

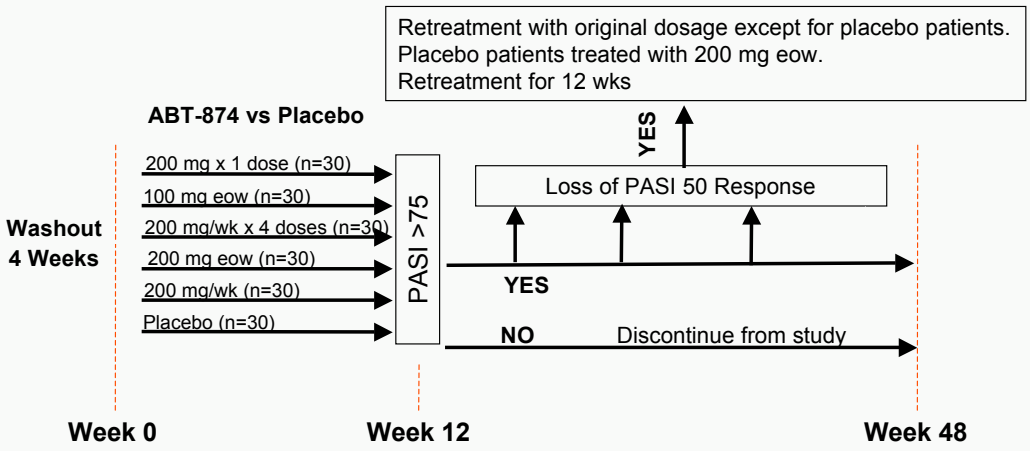



Images courtesy of the PHOENIX 2 Investigators

# SUMMARY OF PASI 75 RESULTS FOR USTEKINUMAB AND BRIAKINUMAB

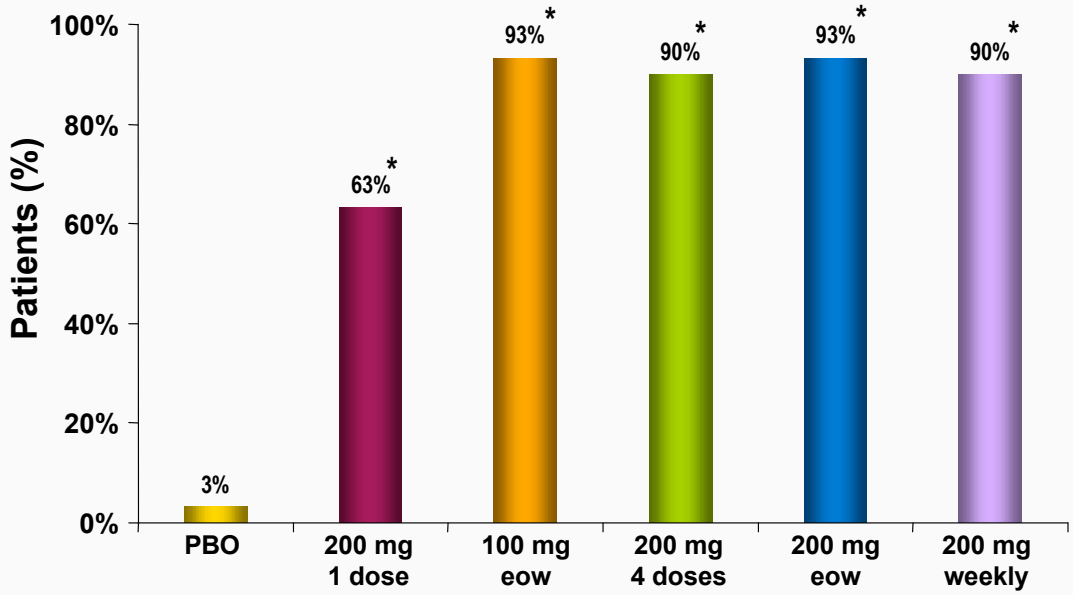
| DRUG AND CONDITIONS | PASI 75 (%) |
|---|---|
| Ustekinumab (phase II): week 12, low dose | 52 |
| Ustekinumab (phase II): week 12, low-medium dose | 59 |
| Ustekinumab (phase II): week 12, medium-high dose | 67 |
| Ustekinumab (phase II): week 12, high dose | 81 |
| Ustekinumab (phase III): week 12, 45 mg | 67 |
| Ustekinumab (phase III): week 12, 90 mg | 66-76 |
| Ustekinumab (phase III): weeks 20-24, 45 mg | 75-76 |
| Ustekinumab (phase III): weeks 20-24, 90 mg | 84-85 |
| Briakinumab (phase II): week 12, low dose | 60 |
| Briakinumab (phase II): week 12, low-medium dose | 90 |
| Briakinumab (phase II): week 12, medium dose | 87 |
| Briakinumab (phase II): week 12, medium-high dose | 90 |
| Briakinumab (phase II): week 12, high dose | 87 |

# BRIAKINUMAB PHASE II STUDY DESIGN




**REF: Kimball et al, Arch Dermatol, 2008**

# BRIAKINUMAB PASI 75 RESPONSES AT WEEK 12




**REF: Kimball et al, Arch Dermatol, 2008**

ITT-NRI
*p<0.001 vs placebo

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## PHOENIX 1 & 2: SUMMARY OF USTEKINUMAB SAFETY/TOLERABILITY

- Safety profiles seen in Phoenix 1 were consistent with those seen in Phoenix 2, and together they support a favorable safety profile through 1 year of treatment
  - Well-tolerated when administered up to 52 weeks
  - AEs, serious AEs, and infection rates at 52 weeks comparable to those seen at Week 12
  - Most commonly reported AEs (≥ 5% of ustekinumab-treated patients): nasopharyngitis, upper respiratory tract infection, headache
  - No cases of active tuberculosis
  - No anaphylactic or serum sickness-like reactions
  - Mild injection-site reactions

REFS: Leonardi et al, Lancet, 2008; Papp et al, Lancet, 2008

## WHAT IS THE NORMAL FUNCTION OF Th17 CELLS?

- Mouse studies suggest that Th17 cells are important in fighting extracellular bacterial infections, especially at mucosal surfaces
- Th17 cytokines induce anti-microbial peptide production and epithelial thickening at mucosal surfaces
- Individuals deficient in Th17 cells are susceptible to *C. albicans* and *S. aureus* infections (i.e., those with Job's/hyper-IgE syndrome and chronic mucocutaneous candidiasis)

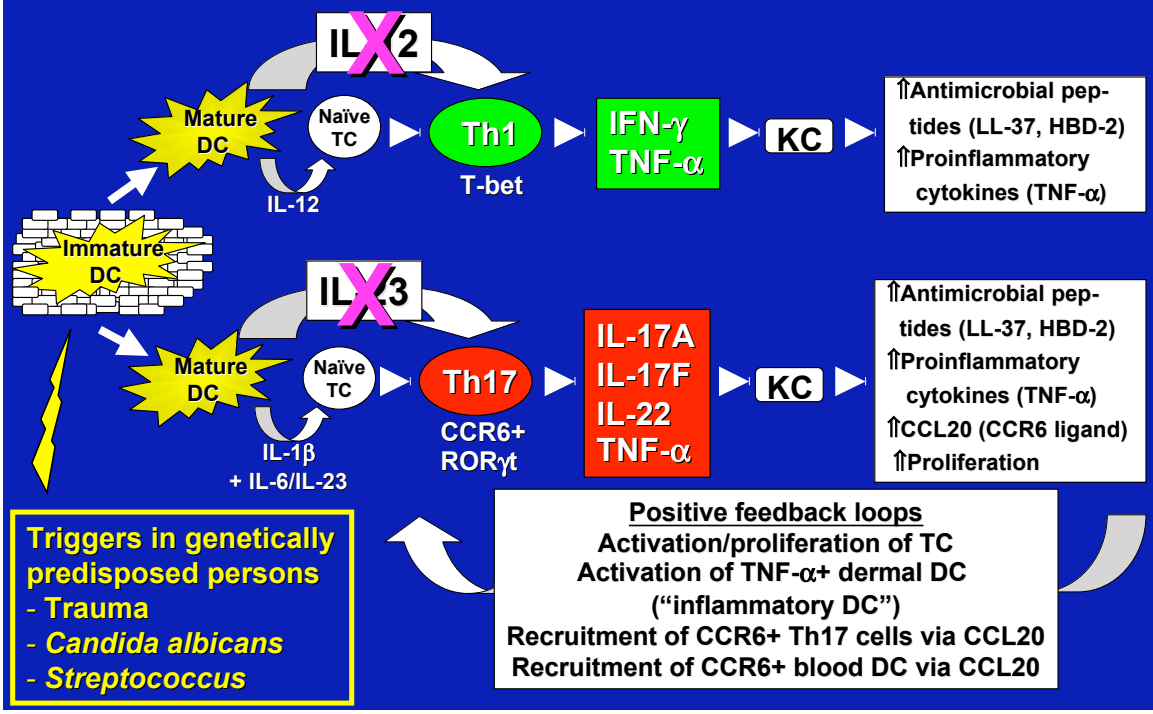
## USTEKINUMAB BRIAKINUMAB: MAJOR ADVANCES IN PSORIASIS THERAPY

- **Efficacy**: 67-90% clear or near clear in both short-term and long-term studies
- **Safety**: minimal issues with over 3.5 years of use in over 3,000 patients
- **Convenience**: given as SC shot once every 1-3 months
- **Cost**: approximately $18,000 per year in Canada

## STATUS OF DRUGS THAT BLOCK THE IL-23/Th17 INFLAMMATORY PATHWAY

- **Ustekinumab (Stelara®)**: long-term (>3.5 years) phase III studies on-going; approved in Canada and Europe; expected to be FDA-approved soon
- **Briakinumab**: phase III studies began late 2007
- **Anti-p19 mAbs** that target only IL-23 and not IL-12: phase I studies underway
- **Anti-IL-17 mAbs**: phase II studies underway

## USTEKINUMAB AND BRIAKINUMAB BLOCK p40, AND THUS BLOCK BOTH IL-23 (Th17 GROWTH FACTOR) AND IL-12 (Th1 GROWTH FACTOR)




THANKS!