USTEKINUMAB and BRIAKINUMAB

Andrew Blauvelt, M.D.
Professor, Dept. of Dermatology and Dept. of Molecular Microbiology & Immunology
Oregon Health & Science University
Chief, Dermatology Service
Veteran’s Affairs Medical Center
Portland, Oregon

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.

Triggers in genetically predisposed persons:
- Trauma
- Candida albicans
- Streptococcus

Positive feedback loops:
- Activation/proliferation of TC
- Activation of TNF-α+ dermal DC ("inflammatory DC")
- Recruitment of CCR6+ Th17 cells via CCL20
- Recruitment of CCR6+ blood DC via CCL20

DC ACTIVATION ⇒ TC ACTIVATION ⇒ KC ACTIVATION

IL-12
Mature DC
Naive TC
IL-12
Th1
T-bet
Th17
IFN-γ
TNF-α
KC
IL-17A
IL-17F
IL-22
TNF-α
KC

Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)

Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)
CCL20 (CCR6 ligand)
Proliferation

Immature DC
IL-23
Mature DC
IL-1β
IL-6/IL-23
Naive TC
Th17
CCR6+
RORγt

Recruitment of CCR6+ blood DC via CCL20
Triggers in genetically predisposed persons:
- Trauma
- Candida albicans
- Streptococcus

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

Positive feedback loops:
- Activation/proliferation of TC
- Activation of TNF-α+ dermal DC ("inflammatory DC")
- Recruitment of CCR6+ Th17 cells via CCL20
- Recruitment of CCR6+ blood DC via CCL20

IL-12

IL-23

Th1

Th17

IFN-γ

TNF-α

KC

Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)

Mature DC

Immature DC

TC

T-bet

CCR6+

RORγt

IL-17A

IL-17F

IL-22

IL-17A

IL-17F

IL-22

TNF-α

KC

⇑

Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)
CCL20 (CCR6 ligand)
Proliferation

Mature DC

IL-1β + IL-6/IL-23

Naive TC

IL-12

IFN-γ

TNF-α

KC

⇑

Proinflammatory cytokines (TNF-α)

CCL20 (CCR6 ligand)
Proliferation

Mature DC

Mature DC

IL-23

IL-12

urekinumab and ABT-874

IL-23

IL-23

IL-12

IL-12

RECEPTORS
POLYMORPHISMS IN $p_{19}$, $p_{40}$, AND $IL-23R$ LINKED TO PROTECTION OF AND SUSCEPTIBILITY TO PSORIASIS

Ref: Nair et al, Nat Genet, 2009

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**

Th1 → IFN-γ, IL-2

Th2 → IL-4, IL-5, IL-10

Th17 → IL-17A, IL-17F, IL-6, TNF-α, IL-22


**IL-17A+ LEUKOCYTES IN PSORIASIS**

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

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ustekinumab (approved in Canada and Europe)</th>
<th>Briakinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Fully human monoclonal IgG1 Ab</td>
<td>Fully human monoclonal IgG1 Ab</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 days&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Published clinical data</td>
<td>Psoriasis (3 ph III)&lt;sup&gt;2-4&lt;/sup&gt;</td>
<td>Psoriasis (ph II)&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Psor. arthritis (ph II)&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crohn’s disease (ph II)&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis (ph II)&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

PHOENIX 1 & 2: STUDY DESIGN

<table>
<thead>
<tr>
<th>Screen</th>
<th>Placebo-controlled</th>
<th>Placebo crossover and active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>Weeks 0–12</td>
<td>Weeks 12–40</td>
</tr>
</tbody>
</table>

**Group 1**
- Placebo crossover and active treatment
- Ustekinumab 45 mg

**Group 2**
- Placebo crossover and active treatment
- Ustekinumab 90 mg

**Group 3**
- Placebo crossover and active treatment
- Ustekinumab 45 mg
- Ustekinumab 90 mg

**PHOENIX 1 & 2: STUDY DESIGN**

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

**PHOENIX 1**
- Placebo: N = 255
- 45 mg: N = 255
- 90 mg: N = 256

**PHOENIX 2**
- Placebo: N = 410
- 45 mg: N = 409
- 90 mg: N = 411

Patients (%)

% 100

0 20 40 60 80 100

Placebo 45 mg 90 mg

Placebo 45 mg 90 mg

p < 0.001 vs placebo for each dose comparison

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

PHOENIX 1

PHOENIX 2

MAINTENANCE TREATMENT WITH USTEKINUMAB IS EFFECTIVE WITH EVERY 12 WEEKS DOSING

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

**TYPICAL CLINICAL RESPONSE TO USTEKINUMAB**

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 12 (2 injections)</th>
<th>Week 52 (6 injections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI = 23.7 PGA = 3</td>
<td>PASI = 1 PGA = 1</td>
<td>PASI = 1.6 PGA = 1</td>
</tr>
</tbody>
</table>

Images courtesy of the PHOENIX 2 Investigators

---

**SUMMARY OF PASI 75 RESULTS FOR USTEKINUMAB AND BRIAKINUMAB**

<table>
<thead>
<tr>
<th>DRUG AND CONDITIONS</th>
<th>PASI 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab (phase II): week 12, low dose</td>
<td>52</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, low-medium dose</td>
<td>59</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, medium-high dose</td>
<td>67</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, high dose</td>
<td>81</td>
</tr>
<tr>
<td>Ustekinumab (phase III): week 12, 45 mg</td>
<td>67</td>
</tr>
<tr>
<td>Ustekinumab (phase III): week 12, 90 mg</td>
<td>66-76</td>
</tr>
<tr>
<td>Ustekinumab (phase III): weeks 20-24, 45 mg</td>
<td>75-76</td>
</tr>
<tr>
<td>Ustekinumab (phase III): weeks 20-24, 90 mg</td>
<td>84-85</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, low dose</td>
<td>60</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, low-medium dose</td>
<td>90</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, medium dose</td>
<td>87</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, medium-high dose</td>
<td>90</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, high dose</td>
<td>87</td>
</tr>
</tbody>
</table>
**BRIAKINUMAB PHASE II**

**STUDY DESIGN**

Retreatment with original dosage except for placebo patients. Placebo patients treated with 200 mg eow. Retreatment for 12 wks.

<table>
<thead>
<tr>
<th>Washout 4 Weeks</th>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABT-874 vs Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg x 1 dose (n=30)</td>
<td>YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg eow (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg wk x 4 doses (n=30)</td>
<td>YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg eow (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg wk (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=30)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Loss of PASI 50 Response**

**YES**

**NO** Discontinue from study

REF: Kimball et al, Arch Dermatol, 2008

---

**BRIAKINUMAB PASI 75 RESPONSES AT WEEK 12**

 Patients (%)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>PBO</th>
<th>200 mg 1 dose</th>
<th>100 mg eow</th>
<th>200 mg 4 doses</th>
<th>200 mg eow</th>
<th>200 mg weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
<td>63%*</td>
<td>93%*</td>
<td>90%*</td>
<td>93%*</td>
<td>90%*</td>
</tr>
</tbody>
</table>

* p<0.001 vs placebo

REF: Kimball et al, Arch Dermatol, 2008

ITT-NRI
### SUMMARY OF PASI 75 RESULTS FOR USTEKINUMAB AND BRIAKINUMAB

<table>
<thead>
<tr>
<th>DRUG AND CONDITIONS</th>
<th>PASI 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab (phase II): week 12, low dose</td>
<td>52</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, low-medium dose</td>
<td>59</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, medium-high dose</td>
<td>67</td>
</tr>
<tr>
<td>Ustekinumab (phase II): week 12, high dose</td>
<td>81</td>
</tr>
<tr>
<td>Ustekinumab (phase III): week 12, 45 mg</td>
<td>67</td>
</tr>
<tr>
<td>Ustekinumab (phase III): week 12, 90 mg</td>
<td>66-76</td>
</tr>
<tr>
<td>Ustekinumab (phase III): weeks 20-24, 45 mg</td>
<td>75-76</td>
</tr>
<tr>
<td>Ustekinumab (phase III): weeks 20-24, 90 mg</td>
<td>84-85</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, low dose</td>
<td>60</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, low-medium dose</td>
<td>90</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, medium dose</td>
<td>87</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, medium-high dose</td>
<td>90</td>
</tr>
<tr>
<td>Briakinumab (phase II): week 12, high dose</td>
<td>87</td>
</tr>
</tbody>
</table>

### 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

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)

---

Triggers in genetically predisposed persons
- Trauma
- *Candida albicans*
- *Streptococcus*

Positive feedback loops
- Activation/proliferation of TC
- Activation of TNF-α+ dermal DC ("inflammatory DC")
- Recruitment of CCR6+ Th17 cells via CCL20
- Recruitment of CCR6+ blood DC via CCL20

Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)
Antimicrobial peptides (LL-37, HBD-2)
Proinflammatory cytokines (TNF-α)
CCL20 (CCR6 ligand)
Proliferation
THANKS!