Psoriasis: Therapeutic Advances Based on Increased Understanding of Disease Pathways

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Conflicts

• Research support, consulting, or lecture fees by most pharma and biotech companies with a psoriasis product or investigational agent during the past 20 years

• No patents, ownership, or financial gain from any psoriasis product or drug
Immune-Mediated Inflammatory Diseases affect at least 1:10 People Worldwide

- Skin: Psoriasis Vulgaris, Atopic Dermatitis, Alopecia Areata, Vitiligo and numerous others
- Digestive System: Crohn’s Disease, Ulcerative Colitis, and Type 1 Diabetes
- Skeletal: Rheumatoid Arthritis, Psoriatic Arthritis
- CNS: Multiple Sclerosis
- Respiratory: Asthma
- Multi-organ: Systemic Lupus, Systemic Sclerosis
Psoriasis Vulgaris

- The most successful case of molecular therapeutic targeting in a human immune-mediated disease

- With a single drug can now control psoriasis extremely well in ~80-90% of patients

- Now have drugs that directly target elements of genetic/genomic disease risk
Generations of Pathogenic Models

- 1\textsuperscript{st} - Simple T-cell model (agnostically of T-cell polarity)
- 2\textsuperscript{nd} - Polar T-cell model (IL-12/Th1 T-cells)
- 3\textsuperscript{rd} - Innate Immunity Model--Its TNF and not T-cells
- 4\textsuperscript{th} - Complex T-cell Model (Th1, Th17 & Th22 T-cells)
- 5\textsuperscript{th} - IL-23/T17 T-cell model-- Type 17 T-cells (Th17, Tc17, innate lymphocytes synthesize IL-17 under control of IL-23)
Psoriasis vulgaris

An autoimmune skin disease associated with increased systemic inflammation that impacts overall health and lifespan
Phenotypes of psoriasis

• The cellular (histologic) disease definition
• The molecular definition based on gene expression

How are these features created by immune-derived cytokines and how does targeting those cytokines with immune antagonists change the phenotypes?
Histopathology of normal appearing background skin and a psoriasis plaque (both at same magnification).
CD3+ T-cells in Psoriasis


Psoriasin (S100A7) is a protein first isolated from scales of psoriatic lesions.
HBD2 (β-defensin) and lipocalin 2 (LCN2) are anti-microbial proteins
Myeloid (CD11c+) Dendritic Cells in Psoriasis
NON-LESIONAL PSORIASIS PLAQUE
CD3 cell counts

NL

LS

0

50

100

150

200

250

300

350

CD11c cell counts

NL

LS

0

100

200

300

400

500

600

Langerin cell counts

NL

LS

0

25

50

75

100

125

8-fold average increase

p < 0.0001

7-fold average increase

p < 0.0001

no significant change

Concept of an inflammatory dendritic cell. CD11c+ DCs in psoriasis lesions had different markers and different functions from normal skin.
The evolving psoriasis transcriptome—disease road maps based on study of skin biopsies

159 genes
2001 n=24
Oestreich et al

800 genes
2003 n=24
Zhou et al

2800 genes
2008 n=26
Yao et al

4175 genes
2010 n=90
Suarez-Farinas et al
Fundamental Hypothesis:

Psoriasis vulgaris is an immune-mediated disease caused by T-lymphocytes (T-cells) and associated cytokines.
Autoimmunity is caused by inappropriate activation of one or more polar T-cell subsets
An early hypothesis proposed Th1 T-cells caused psoriasis.
Type 1 Deviation in Psoriasis

Psoriasis

Type 1 (γ-Interferon)

~ 2-3 fold expansion of Type 1 T-cells

Type 2 (Interleukin-4)

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Cytokine-driven pathogenesis

$\gamma$-IFN → human keratinocytes (in vitro)

- CXCL9
- CXCL10
- CXCL11
- IL-8
- ICAM-1
- MHC-II

Immune amplification
Cytokine-driven pathogenesis

ϒ-IFN →

human keratinocytes (in vitro)

{ CXCL9, CXCL10, CXCL11, IL-8, ICAM-1, MHC-II }

Immune amplification
In 2005 the Th17 T-cell was identified as associated with CNS autoimmunity.
Experiments in mice clearly show that IL-23 drives activation & expansion of Th17 T-cells, not Th1 T-cells.

γ-interferon
(Th1)

IL-17
(Th17)
Consistent up-regulation of p40 and p19 mRNAs (IL-23 subunits) in psoriasis plaques, as detected by real-time RT-PCR (normalized to HARP)

Lee et al JEM (2005)  

Dendritic Cells established as major producers of IL-23 in psoriasis lesions
Genetic Biomarkers of Increased Risk

O’Reilley Nat Rev Rheum (2011)
Th17 T-cells increased in psoriasis lesions

Gene expression during cyclosporine treatment

K16 mRNA

IFNg mRNA

IL-17 mRNA

IL-22 mRNA
T-cell produced cytokines act on keratinocytes to induce specific gene products

- IL-17A
- IL-17F

human keratinocytes (in vitro)

\[ S_{100}A7 \text{ (psoriasin)} \]
\[ \text{CXCL1,2,3,8} \]
\[ \text{CCL20} \]
\[ \beta\text{-defensin and other anti-microbial peptides} \]
IL-23/Th17 pathway in psoriasis

IL-23

DC

IL-23

T17

IL-17

Th17

Tc17

Tgamma-delta 17

ILC 17

KC

CCL20

Anti-microbial peptides
β-defensins
Lipocalin
LL-37
S100A7, S100A8
CXCL1, 2, 3, 5
IL-8

But does not explain epidermal hyperplasia
The Th22 T-cell subset is also activated in psoriasis and IL-22 is a keratinocyte mitogen.
IL-22 promotes acanthosis and impairs terminal differentiation

- Confirms effect of IL-22 on acanthosis of epidermis
  (Sa et al J Immunology 2007)

*Parakeratosis

Three immune axes are activated in psoriasis

However IL-23/Type-17 axis drives the disease phenotype

Figure adapted from: Nestle FO, et al. N Engl J Med. 2009;361:496-509
IL-17 Signaling

Ligand/Receptor Combinations

Anti-IL-17 Receptor Antibody AMG 827 Leads to Rapid Clinical Response in Subjects with Moderate to Severe Psoriasis: Results from a Phase I, Randomized, Placebo-Controlled Trial
Kim A Papp, Cathy Reid, Peter Foley, Rod Sinclair, David H Salinger, Gary Williams, Hua Dong, James G Krueger, Chris B Russell and David A Martin


Data first presented at Society for Investigative Dermatology in 2010
Double-blind, placebo controlled study with a single dose of AMG827

Placebo (n=4)
350mg SC (n=8)
700mg IV (n=8)

Key inclusion criteria:
Moderate to severe plaque PsO ≥ 6 mos, PASI score ≥ 10, BSA≥10, eligible to receive phototherapy or systemic therapy

Key exclusion criteria:
Any prior use of biologics; recent use of systemic steroids or calcineurin inhibitors
AMG 827 (anti-IL-17R mAb) Led to Rapid Improvement in PASI Scores

![Box plot showing PASI improvement from baseline on Day 15 and Day 43 for different treatment groups.]

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<th>PGA clear or minimal</th>
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<td>PBO</td>
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<tr>
<td>700 mg</td>
<td>8/8</td>
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AMG 827 (700 mg) Rapidly Reduced Histological Abnormalities in Psoriasis Skin

Epidermal Thickness

K16 mRNA

Ki67 cell counts

Non-lesional
Day 1 Pre-dose
Day 15
Day 43

H&E

K16

Ki67
mRNA Array Reveals Major Differences in Lesional vs Non-lesional Psoriasis Skin: Pre-dose samples

AMG 827 Treatment Reversed Gene Expression Across 1000’s of Genes in PsO Skin

PreDose

Day 15 (n=8)
Signature: ~500

Day 43 (n=8)
Signature: ~500

Day 8 (n=4)
Signature: ~2000

Day 43 (n=3)
Signature: ~1000

Log Intensity (RNA expression)
IL-23/Th17 pathway in psoriasis

Role of IL-17A probed with ixekizumab
Expression of IL-17 Target Genes (RT-PCR)

Lipocalin 2

Interleukin 8

β-defensin 2

CXCL1

log2(expression/hARP) = mRNA expression (RT-PCR) normalized to the housekeeping gene human acidic ribosomal protein gene (hARP)
Genes Modulated by ixekizumab (FCH>6)– very rapid effects and much faster response than etanercept

LS= Lesional Skin Biopsies at Baseline
NL= Non-Lesional Skin Biopsies at Baseline
Proportion of Patients with PASI 75

Weeks

Proportion of Patients

Placebo SC (n=8)
LY 150 mg SC (n=8)
High Efficacy of IL-17 antagonists in Phase 3 Studies

• Secukinumab (anti-IL-17A) superior to ustekinumab in CLEAR study, 87% PASI75 in JUNCTURE study
• Ixekizumab (anti-IL-17A) superior to etanercept in UNCOVER study, 90% PASI75 in best performing dosing group
• Brodalumab (anti-IL-17 Receptor, A subunit) superior to ustekinumab in AMAGINE-3 study, 86% PASI75 in AMAGINE-2 Study, best performing dose group

Amgen has terminated brodalumab partnership with AstraZeneca. Brodalumab and ixekizumab are not currently licensed for therapeutic use. 
4. ‘Amgen and AstraZeneca announce positive results from third and final pivotal Phase III study of Brodalumab in patients with moderate-to-severe plaque psoriasis’ press release. Available at:
Does IL-23 drive the Th17 pathway?

IL-23 (p40/p19) activates keratinocytes, plasmacytoid Dendritic cells, and macrophages, leading to the production of IL-1β, IL-6, TNF-α, and IFN-γ.

IL-12 (p40/p35) activates T1 cells, leading to the production of IFN-γ and TNF-α.

IL-17A/F and IL-21 activate Th17 cells, leading to the production of IL-22.

IL-22 activates keratinocytes, leading to the production of cytokines such as IL-17A/F, IL-21, CXCL8, CXCL9, and CCL20.

Figure adapted from: Nestle FO, et al. N Engl J Med. 2009;361:496-509
Disease Profile Neutralized by CNTO 1959 (Guselkumab)

- Disease profile (lesional vs. non-lesional skin) – 1224 transcripts
- High dose* brought the expression level back to normal at Week 12

A PASI75

![Graph showing PASI75 over time for different dosages of risankizumab and ustekinumab.]  

B PASI90

![Graph showing PASI90 over time for different dosages of risankizumab and ustekinumab.]  

Papp et al. NEJM 376:1551 (2017)
Take Home Message

• Psoriasis is driven by a polar T-cell (Th17/Tc17) axis, regulated by IL-23

• Keratinocytes amplify the response

• All therapies that improve psoriasis directly or indirectly lower expression or signaling of this immune-response axis