Novel Toll-Like Receptor Antagonists Strongly Decrease Expression of IL-23-induced Psoriasis Profile Genes in a Mouse Model

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Collaborative Project with Idera Pharmaceuticals, Inc.

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**Toll-like Receptors: Inflammation Regulators and a Therapeutic Target in Autoimmunity**

**Endosomal Toll-like receptors (TLRs)**

- TLR3, 7, 8, and 9 are endosomal receptors for nucleic acids.
- Activation of TLRs in dendritic cells leads to cytokine synthesis and enhanced T-cell stimulation capacity.
- In autoimmune and inflammatory diseases, it is believed that host RNA/DNA activates TLRs and leads to uncontrolled inflammation.
- IMO-3100 and IMO-8400 are synthetic oligonucleotides of novel construct that mimic the natural ligands of endosomal TLRs and act as selective antagonists.
Inhibition of Immune Induction by Targeting TLRs

Autoimmune Disease Activators

Immune Complexes

Dendritic Cell

TLR7, 8 & 9

IMO-3100 (TLR7 & 9 antagonist)

IMO-8400 (TLR7, 8 & 9 antagonist)

Inhibition of Immune Induction

Th1 and Th17 cells

IL-12, IL-23, TNF-α, IL-17, IFN-α, IL-1β

Inflammatory Cascade
Mouse IL-23 Psoriasis Model Study Design

C57BL/6 mice dorsal skin

Day 0 1 2 3 4 5 6

Terminate

IL-23, 3 µg, i.d.
PBS, s.c.
IMO-3100, s.c.
IMO-8400, s.c.
Antagonists, 15 mg/kg

n = 5
IL-23–driven inflammation in C57BL/6 Model

- Erythema and induration at IL-23 injection site (day 6)
- Focal parakeratosis/scale
- Epidermal hyperplasia
- Lymphocytic infiltration
- Dermal edema

Normal mouse skin

IL-23 injected mouse skin
IL-23 transcriptome on Murine Affymetrix Arrays (FDR<0.05, FCH>2): 3500 genes modulated

2346 probes up (1726 unique genes)
2762 probes down (1775 unique genes)

About 34% of Psoriasis transcriptome is in IL23-Mouse model by these FCH criteria
A genomic method was developed by Swindell et al. (2011) to compare mouse inflammation models to psoriasis.
Swindell approach uses a gene rank approach to compare transcriptome of mouse skin with psoriasis (Gudjonsson data base of psoriasis)

**IL-23 injection model**

- **(A) K5-Tie2**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes

- **(B) IMQ**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes

- **(C) K14-AREG(E)**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes

- **(D) K14-AREG(T)**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes

- **(E) K5-Stat3C**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes

- **(F) K5-TGF**
  - Psoriasis Increased Genes
  - Psoriasis Decreased Genes
Mouse IL-23 Psoriasis Model Study Design

C57BL/6 mice dorsal skin

Day 0        1            2              3             4              5           6

Terminiate

IL-23, 3 µg, i.d.  PBS, s.c.  IMO-3100, s.c.  IMO-8400, s.c.

Antagonists, 15 mg/kg

n = 5  n = 5  n = 5
TLR Antagonist Activity in Mouse IL-23 Psoriasis Model – Dermal Histology

Naive

PBS-treated

IMO-8400-treated

↑ Epidermal hyperplasia

↑ Inflammatory cell infiltration

HE stain, Magnification x 200
Overall genomic effects viewed by a principal components analysis (PCA)
IL-23 transcriptome (Saline vs Normal)@FDR<0.05, FCH>2:
3500 genes modulated
2346 probes up (1726 unique genes)
2762 probes down (1775 unique genes)

Treatment Effect
FDR<0.05, FCH>2

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>Up</th>
<th>Down</th>
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<tbody>
<tr>
<td>IL23.IMO3100vsSaline</td>
<td>833</td>
<td>1155</td>
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<tr>
<td>IL23.IMO8400vsSaline</td>
<td>1380</td>
<td>1110</td>
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More genes upregulated when TLR8 also antagonized
Which inflammatory pathways are modulated by TLR7/9 or TLR 7/8/9 antagonism?

- Strong reduction in IL-17A mRNA (>12-fold), along with reduced β-defensin, CXCL1, CXCL2, CXCL3, Lipocalin 2, and other IL-17 pathway molecules, including the IL-21 receptor and IL-12 Rβ1 (part of IL-23R).
- IL-6 reduced by 98-fold (upstream regulator of Th17 T-cell development)
- IFN-γ reduced (8-fold IMO-3100, 11.5-fold IMO-8100), along with IFN pathway genes like CXCL9, as well as IL-12 Rβ1 (part of IL-12R)
- IL-1 reduced (6-fold IMO-3100; 12-fold IMO-8400) with reduction in NFkB mRNA
Psoriasis vulgaris is now understood to be an IL-17 induced inflammatory disease in which upstream regulation by IL-23 is essential.

Results of IMO-3100 in Phase 2a trial in psoriasis vulgaris (with 4 weeks of treatment) to be presented in May at the International Investigative Dermatology meeting.

Ability of IMO-3100 to modulate psoriasis-related genes in skin biopsies of treated patients is now under investigation.