IMO-8400, a novel TLR7, TLR8 and TLR9 antagonist, inhibits disease development in mouse models of psoriasis

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Introduction

Toll-like Receptosr (TLRs) 7, 8 and 9 can recognize endogenous immune complexes containing self-RNA and -DNA, respectively. In many autoimmune diseases, TLR7- and 9-mediated inflammation induced by immune complexes leads to maintenance and progression of disease.

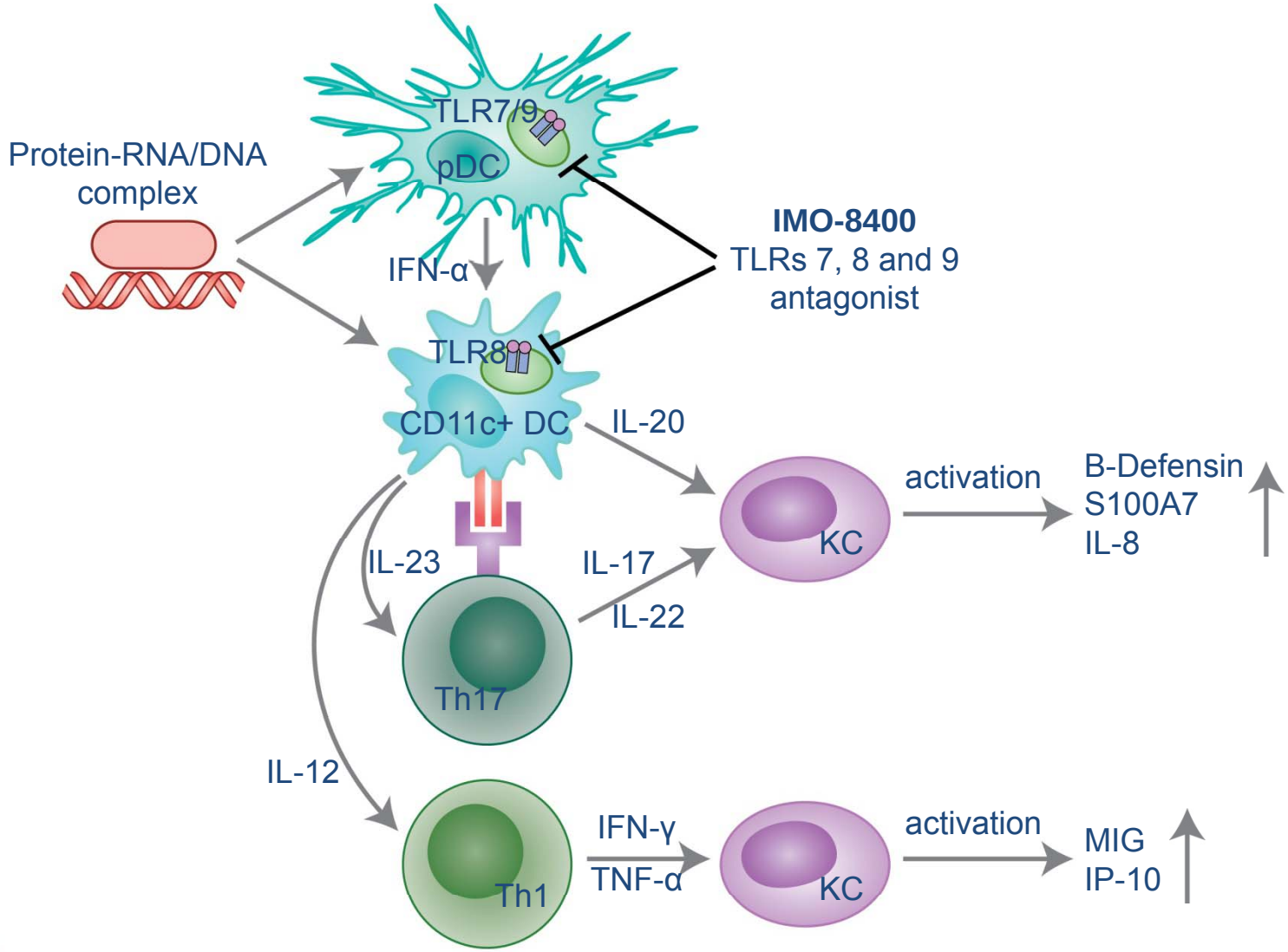
Activation of TLR7, TLR8 and TLR9 in pDC and mDC through the interaction of these receptors with the antimicrobial peptide LL37 complexed with self-RNA or DNA contributes to psoriasis development[1,2]. Therefore, inhibition of TLRs 7, 8 and 9 through the use of a TLR antagonist could provide therapeutic effect in this autoimmune disease.

We have identified a first-in-class DNA-based antagonist of TLR7, 8, and 9, referred to as IMO-8400. IMO-8400 inhibitsTLR7- and 9-mediated immune responses in mice and TLR7-, 8- and 9-mediated immune responses in human cell-based assays and in non-human primates.

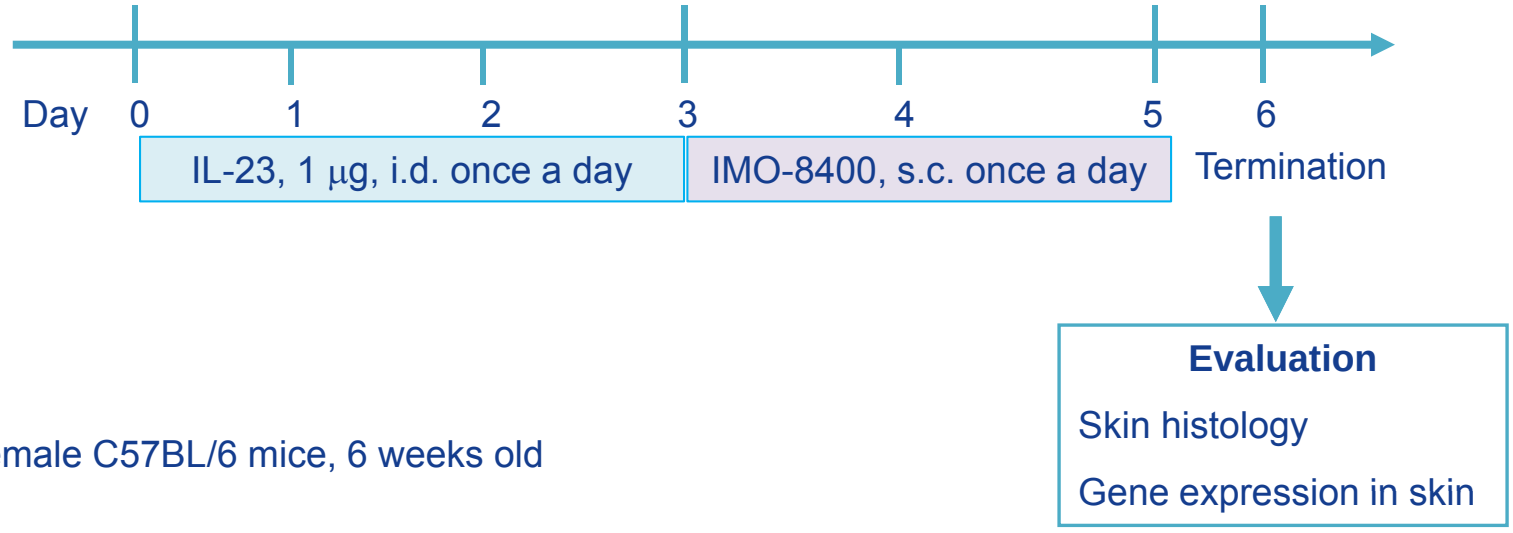
In the present study, we have evaluated IMO-8400 as a therapeutic agent in IL-23- and LL-37-induced psoriasis models in mice.

[1]Lande R, et al., Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature 449: 564-569, 2007
[2]Ganguly D, et al., Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J. Exp. Med. 206: 1983-1994, 2009

Role of TLRs 7, 8 and 9 in Psoriasis : Induction of IL-23 and IL-17 Pathways



Outline of Study Protocol of IL-23-Induced Psoriasis



Female C57BL/6 mice, 6 weeks old

Experimental groups (n = 8/group)

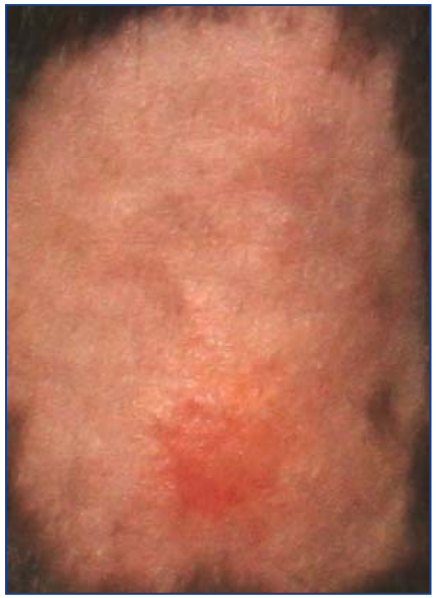
IMO-8400, 300 μg/dose (15 mg/kg)

PBS

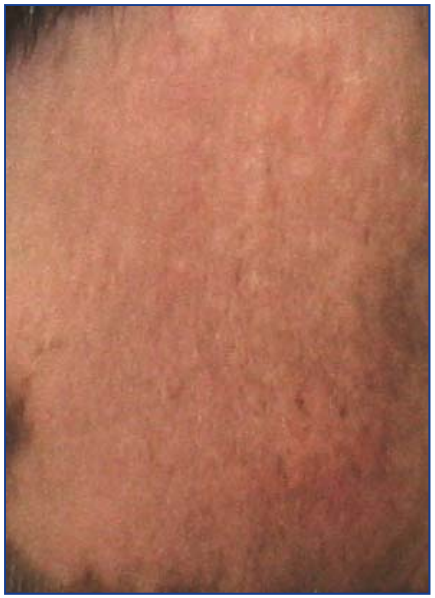
Naïve

Treatment with IMO-8400 Suppresses Skin Lesions Induced by IL-23

PBS-treated



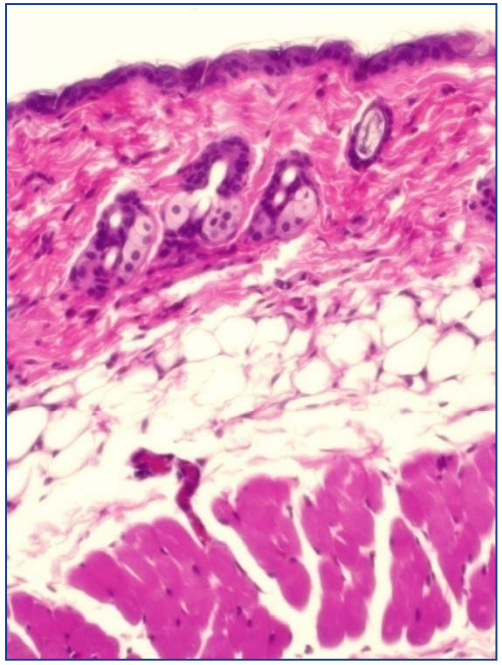
IMO-8400-treated



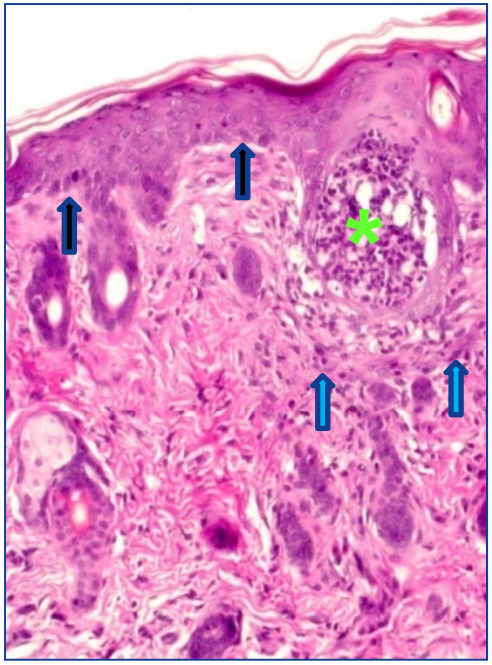
IL-23 induced various degrees of erythema and induration. IMO-8400 inhibited inflammation induced by IL-23

Treatment with IMO-8400 Inhibits Skin Inflammation Induced by IL-23

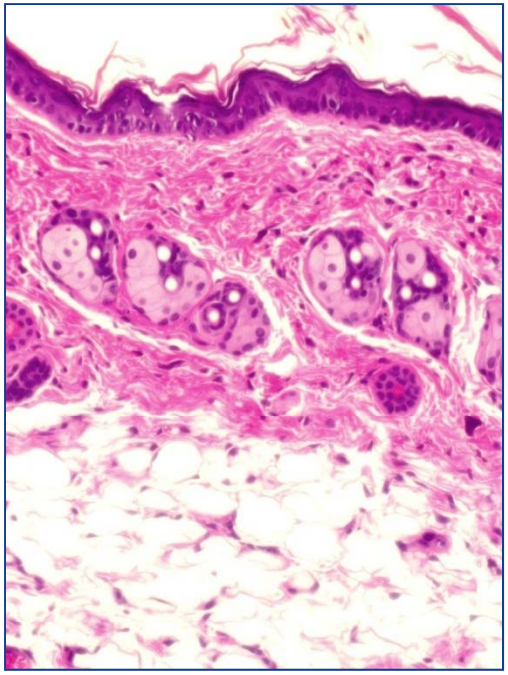
Naive



PBS-treated

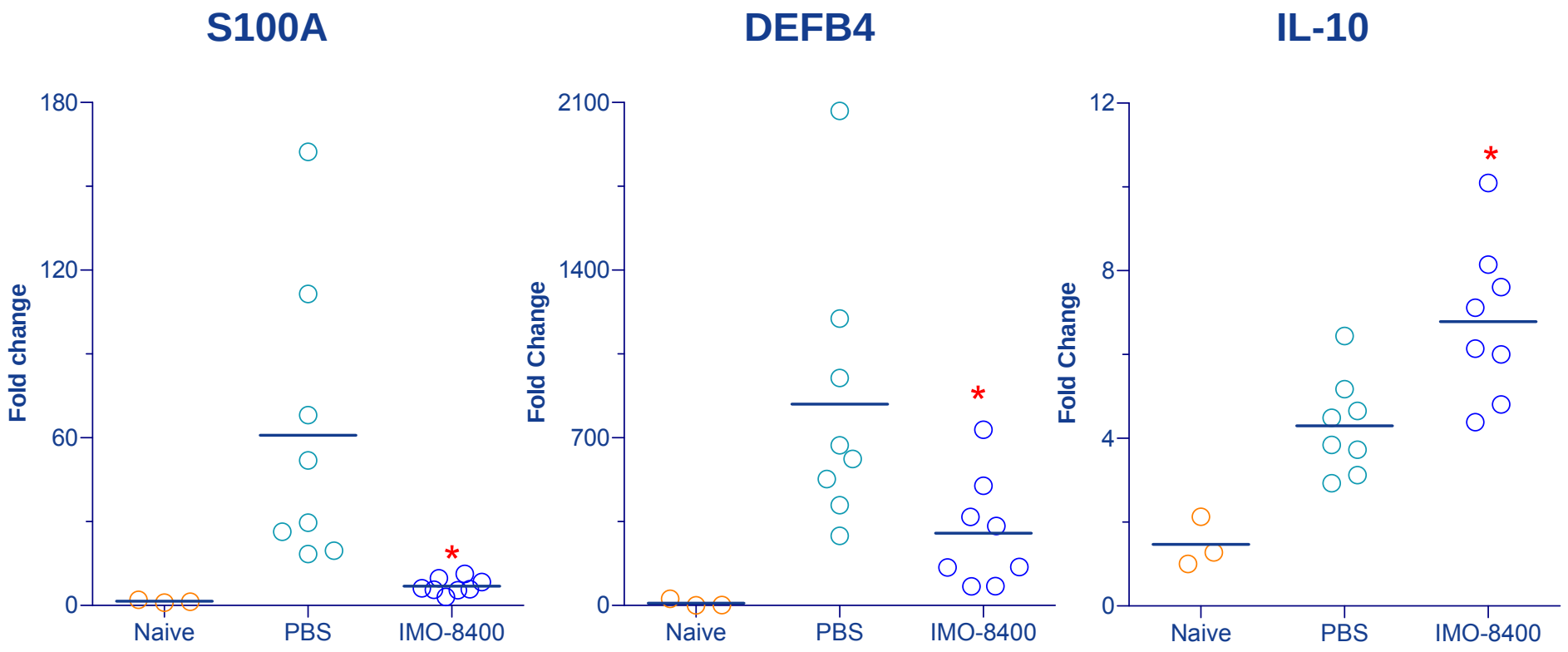


IMO-8400-treated



Epidermal hyperplasia Inflammatory cell infiltration * Abscess HE stain, Magnification x 200

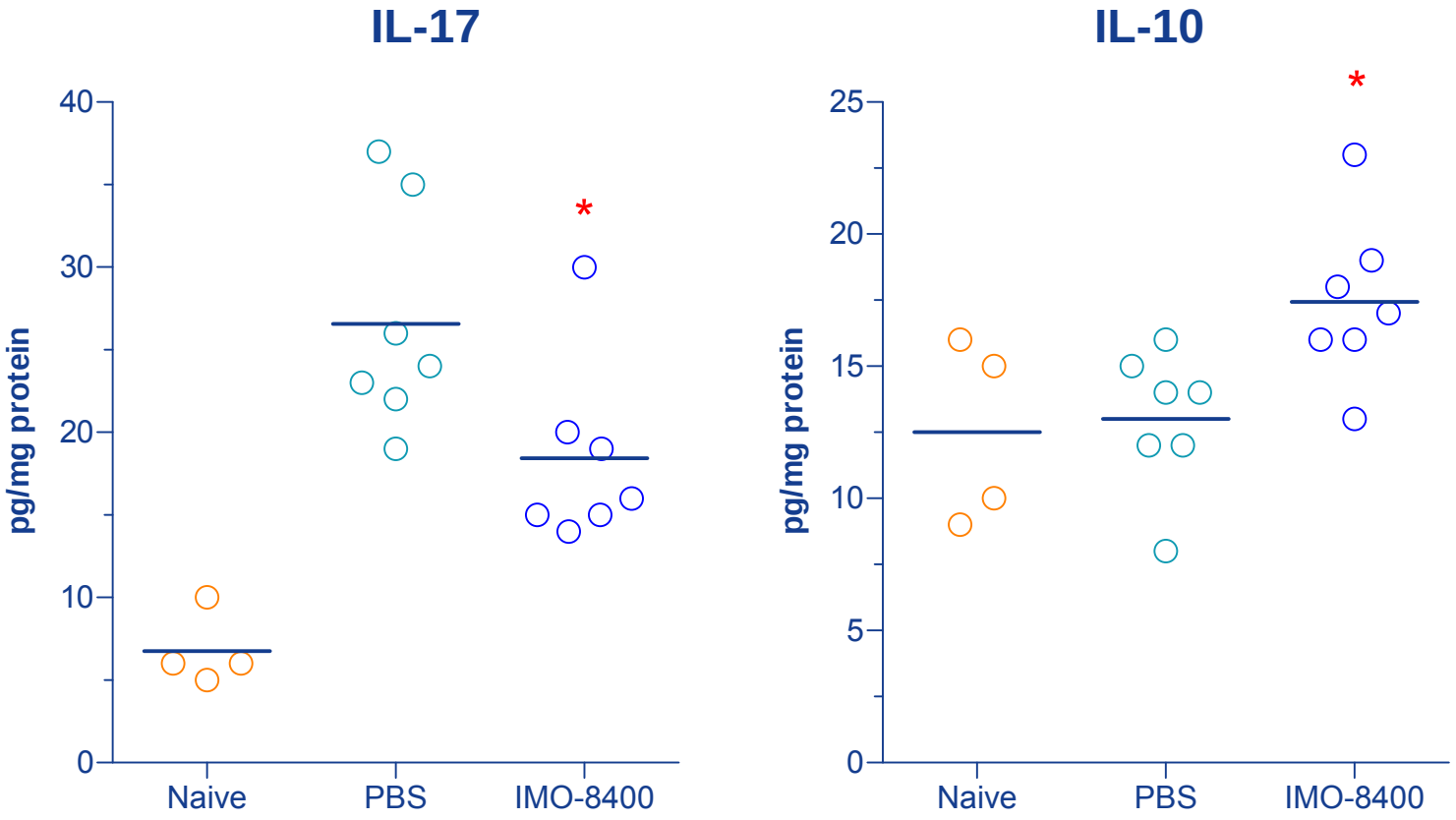
Treatment with IMO-8400 Impacts Gene Expression in IL-23-Injected Skin



* P < 0.05 vs PBS group

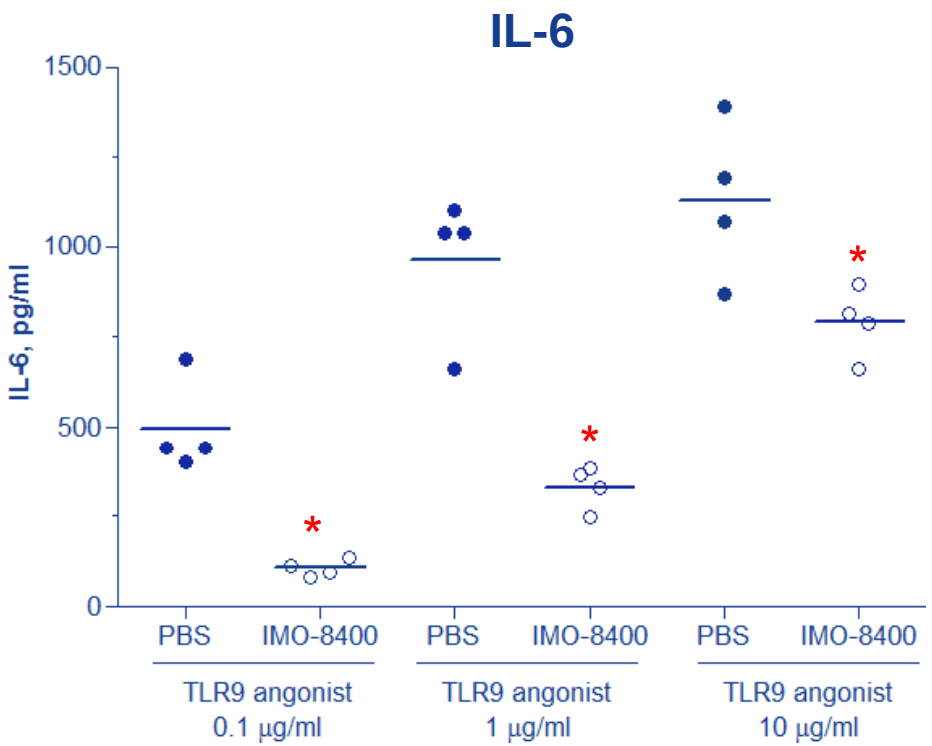
Expression of S100 and β-defensin (DEFB4) genes is up-regulated in lesions of psoriasis patients; IMO-8400 significantly suppressed expression of both genes. Gene expression was determined by quantitative real-time PCR

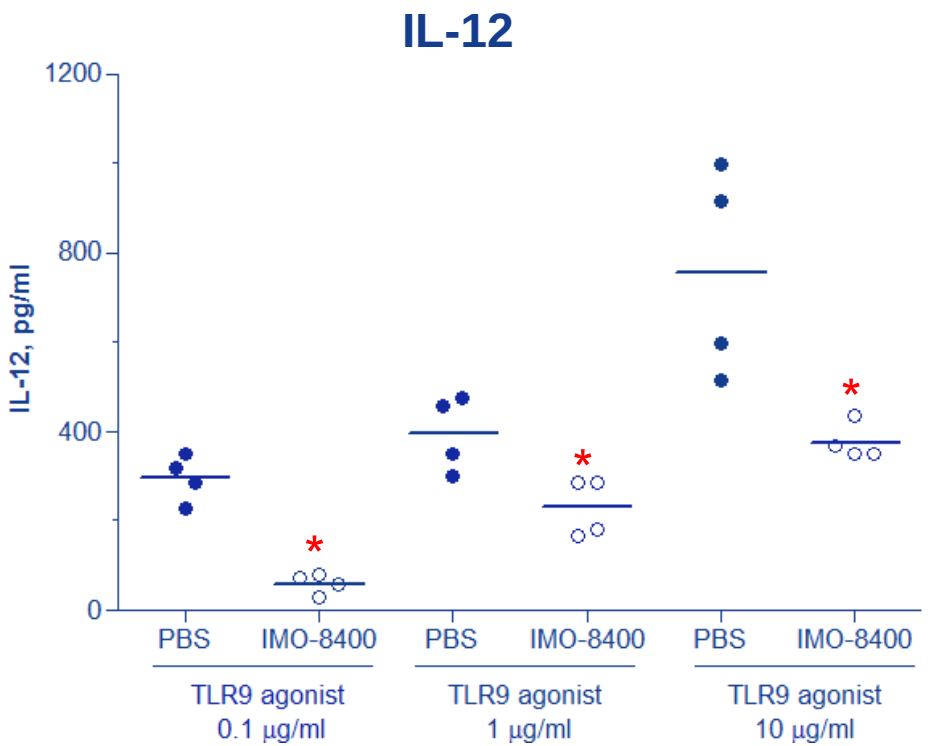
Treatment with IMO-8400 Reduces IL-17 and Increases IL-10 Levels in IL-23-Injected Skin



* P < 0.05 vs PBS group. Cytokine levels were determined by ELISA

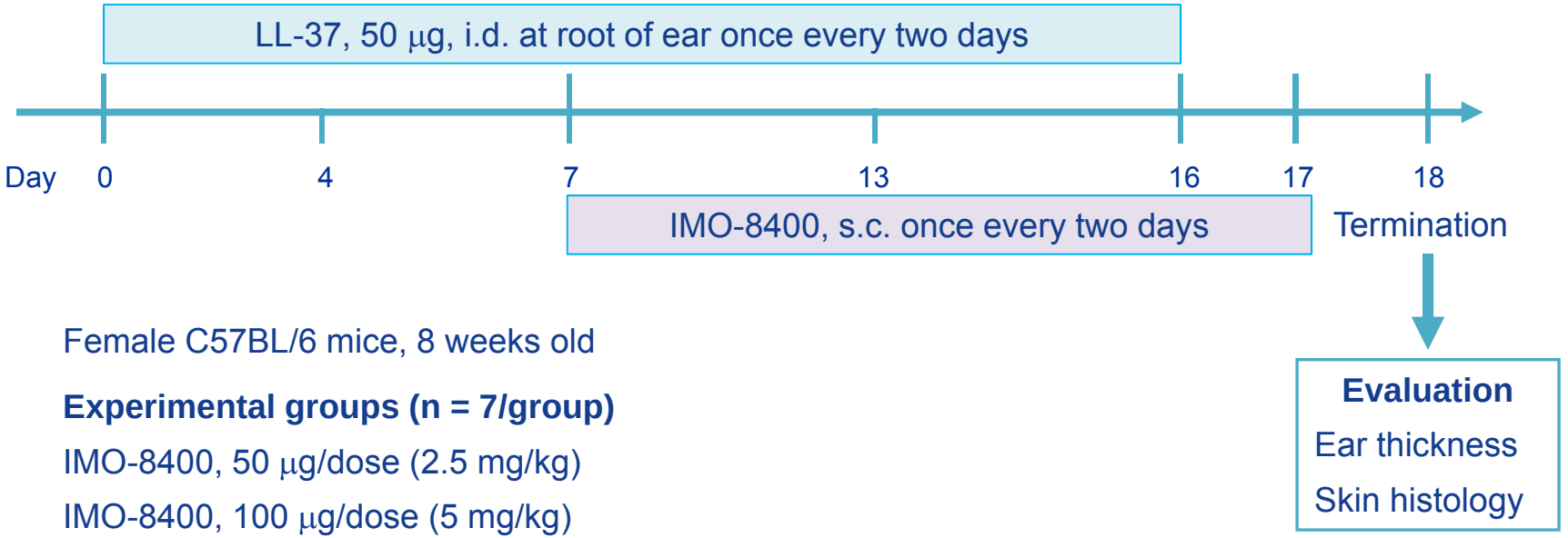
Splenocytes From IMO-8400-Treated Mice Show Reduced Response to TLR9 Agonist Stimulation





*P < 0.05 vs PBS. Cytokine levels were determined by ELISA.

Outline of Study Protocol of LL-37-Induced Psoriasis



Female C57BL/6 mice, 8 weeks old

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IMO-8400, 50 μg/dose (2.5 mg/kg)

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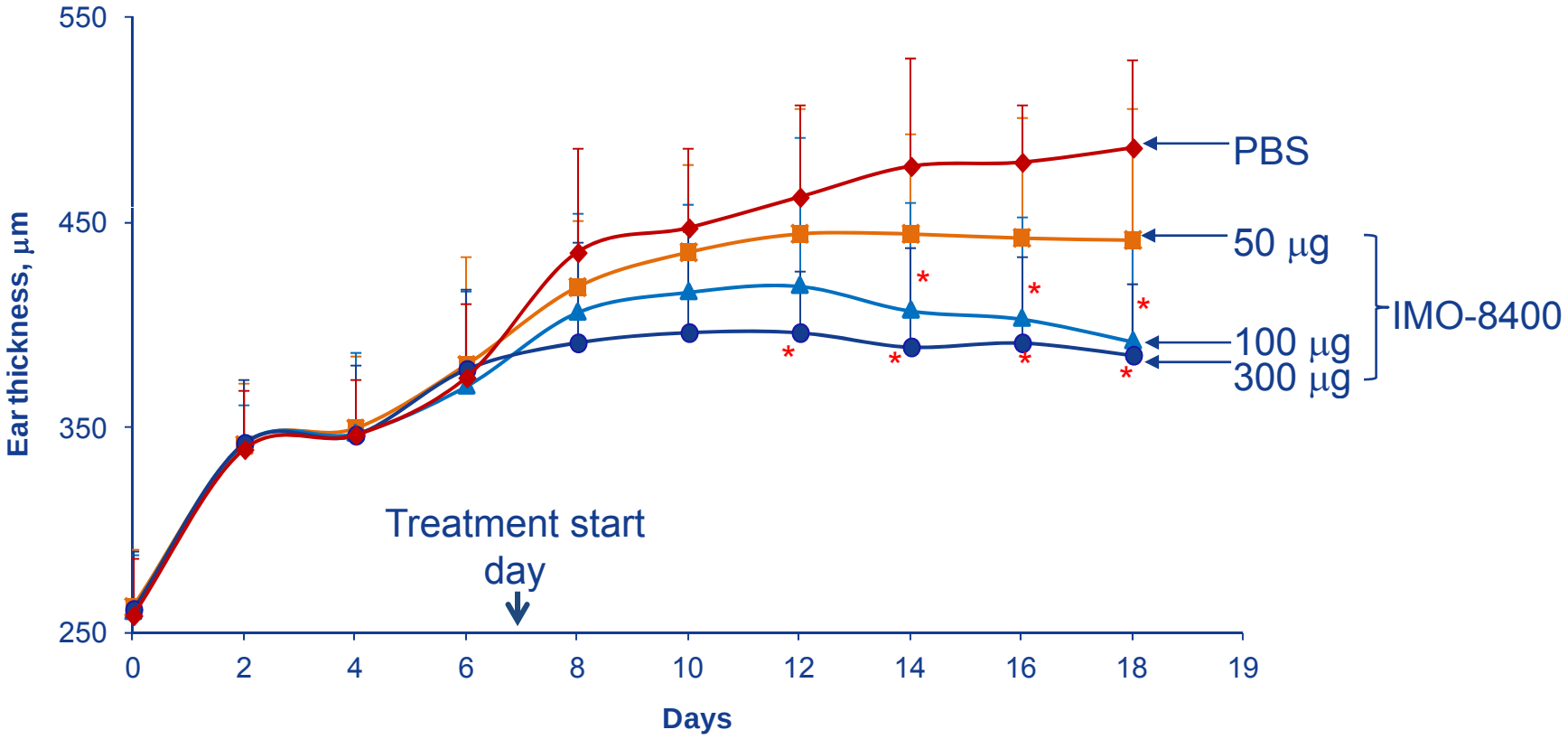
IMO-8400, 300 μg/dose (15 mg/kg)

PBS

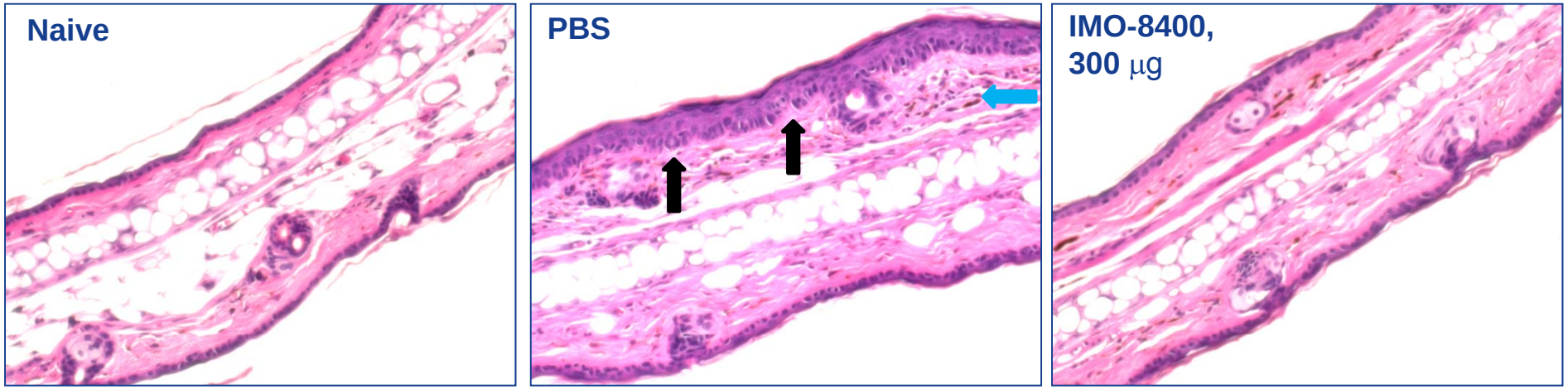
Naïve

Treatment with IMO-8400 Suppresses Ear Thickness Increase Induced by LL-37



* P < 0.05 vs. PBS group

Treatment with IMO-8400 Reduces Skin Inflammation Induced by LL-37



Epidermal hyperplasia

Inflammatory cell infiltration

HE stain, Magnification x 100

Summary

- IMO-8400 is a first-in-class antagonist of TLR7, 8 and 9
- In IL-23-induced psoriasis model, IMO-8400 suppressed
  - Psoriatic lesions, epidermal hyperplasia and inflammatory cell infiltration
  - DEFB4 and S100A gene expression and IL-17 protein levels
  - TLR9-mediated immune responses in splenocytes
- IMO-8400 treatment increased IL-10 gene expression and protein levels in skin
- In LL-37-induced psoriasis model, IMO-8400 reduced
  - Ear thickness, epidermal hyperplasia and inflammatory cell infiltration
- IMO-8400 is in development for treatment of autoimmune diseases