



A Selective Inhibitor of Endosomal Toll-Like Receptors, IMO-8400, Suppresses Activation of Multiple Cytokines, Th17 Response and Inflammasome Activation

Presented at American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHP) Annual Meeting

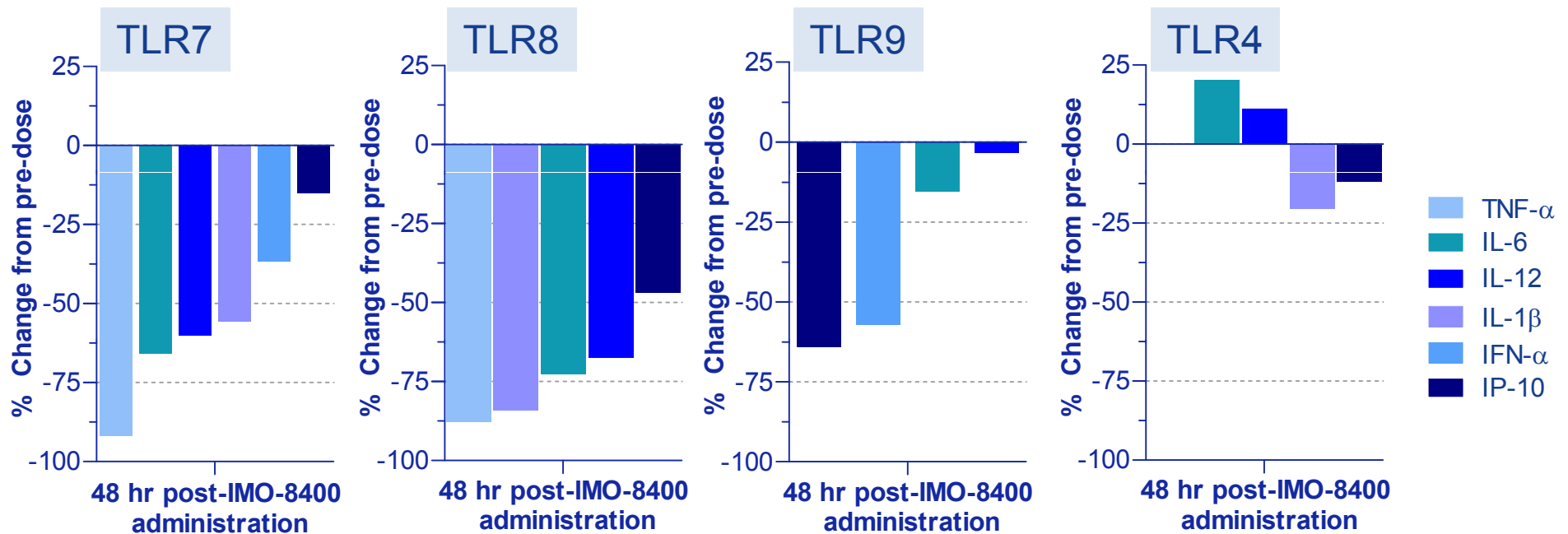
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Abstract 1068

Introduction

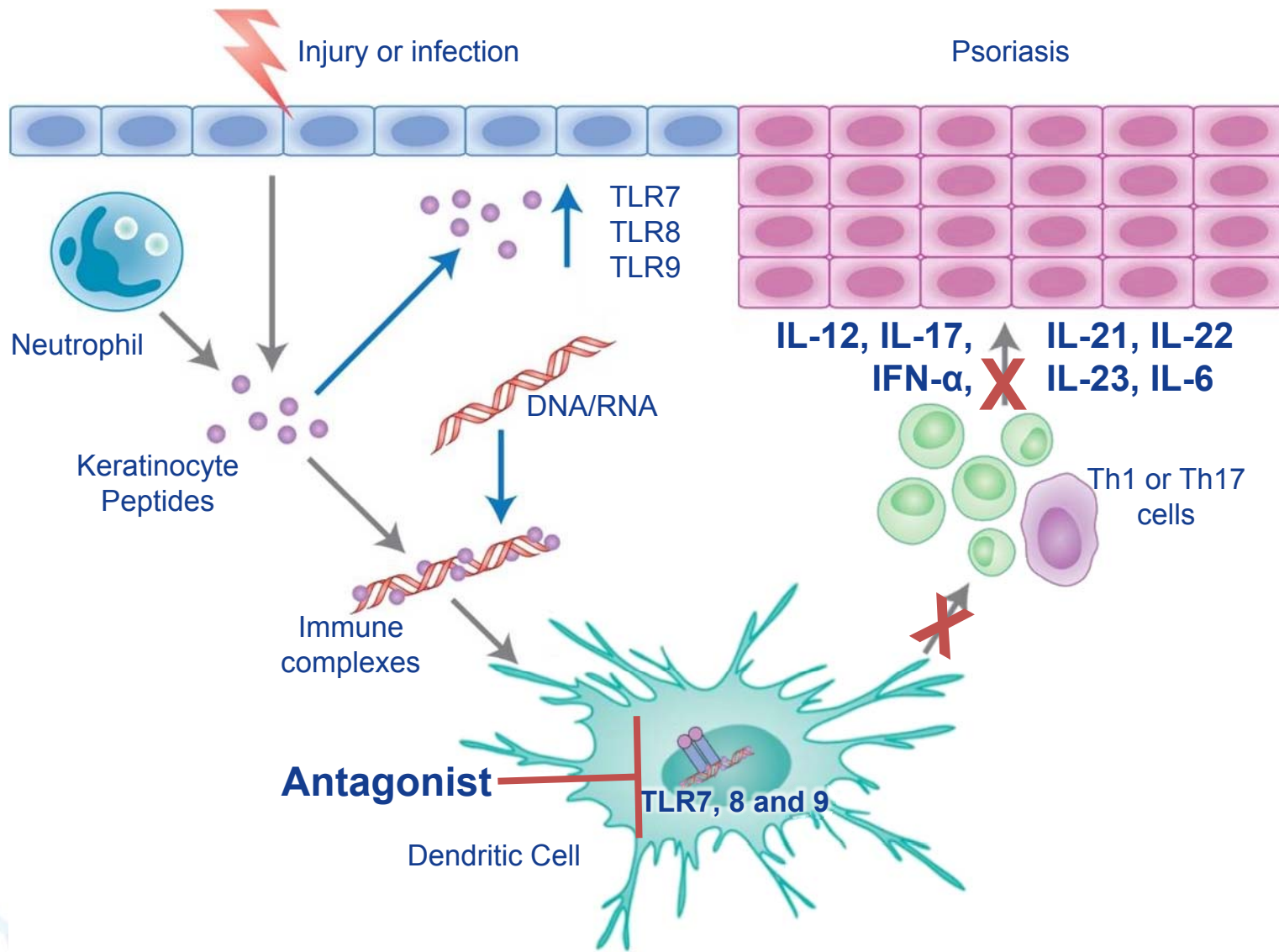
- Idera's therapeutic approach for the treatment of autoimmune diseases is to inhibit induction of disease associated cytokines and signaling cascades by modulating activation of Toll-like Receptors (TLRs) 7, 8 and 9
- We have selected Psoriasis as disease model to evaluate the efficacy of our approach
- Psoriasis is a chronic inflammatory skin disease primarily associated with a Th1 and Th17 response. The activation of inflammasomes and subsequent release of IL-1 β has also been shown to contribute to disease development
- Current therapies for psoriasis include oral and injectable drugs such as Retinoids, Methotrexate, Cyclosporine, Hydroxyurea and Biologics such as Amevive (anti-CD2 protein), Enbrel (anti-TNF α inhibitor), Remicade (anti-TNF α antibody), Stelara (anti-IL-12/23 antibody), Humira (anti-TNF α antibody) and Simponi (anti-TNF α antibody)
- We have developed novel TLR antagonists that block TLR7, 8 and 9 signaling. These antagonists improve disease outcome in autoimmune disease models by blocking interaction of immune complexes carrying self nucleic acids with TLRs, thereby preventing induction of disease associated cytokines and signaling cascades
- IMO-3100, an antagonist of TLR7 and 9 is currently in Phase 2 clinical trial in patients with moderate to severe psoriasis
- IMO-8400, an antagonist of TLR7, 8 and 9, is in clinical development for the treatment of lupus
- In this study, we evaluated the ability of IMO-8400 to control disease development in mouse models of psoriasis

IMO-8400 Inhibits Induction of Cytokines in NHP Mediated by TLR7, 8 or 9



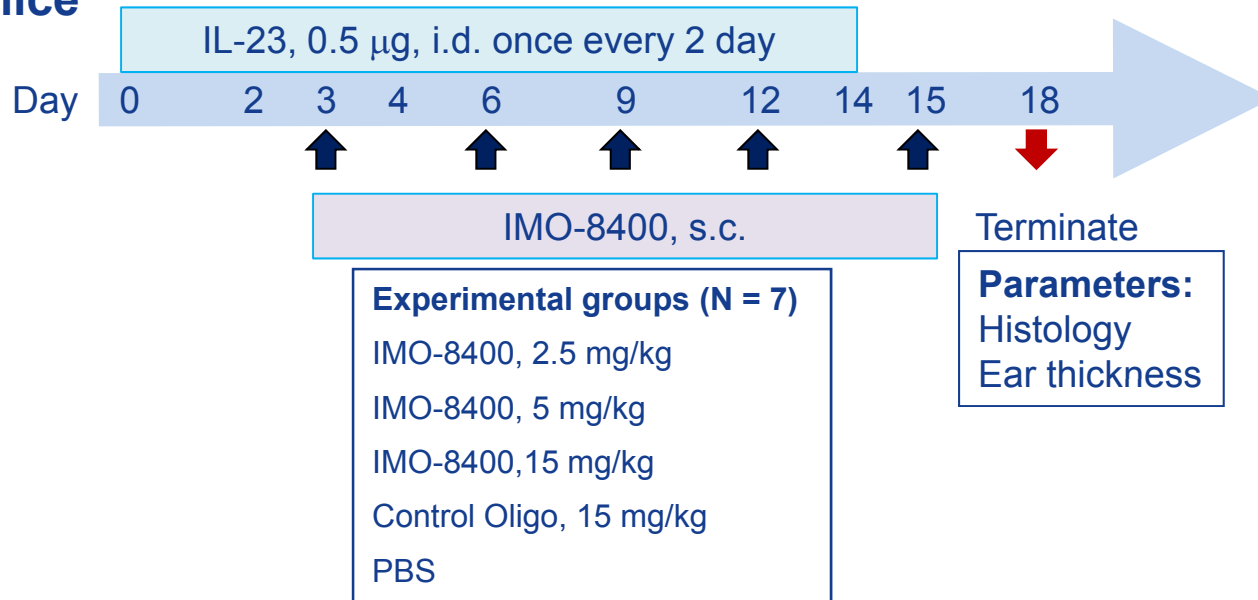
Cynomolgus macaques (N=4) were injected sc with IMO-8400 at a dose of 1.5 mg/kg
Blood was collected prior to IMO-8400 administration (pre-dose) and 48hr post dosing
PBMCs were isolated and cultured with agonist of TLR4, 7, 8 or 9
Cytokine measurements in supernatants were carried out by multiplex or ELISA assay

TLR7, 8 and 9 in Psoriasis

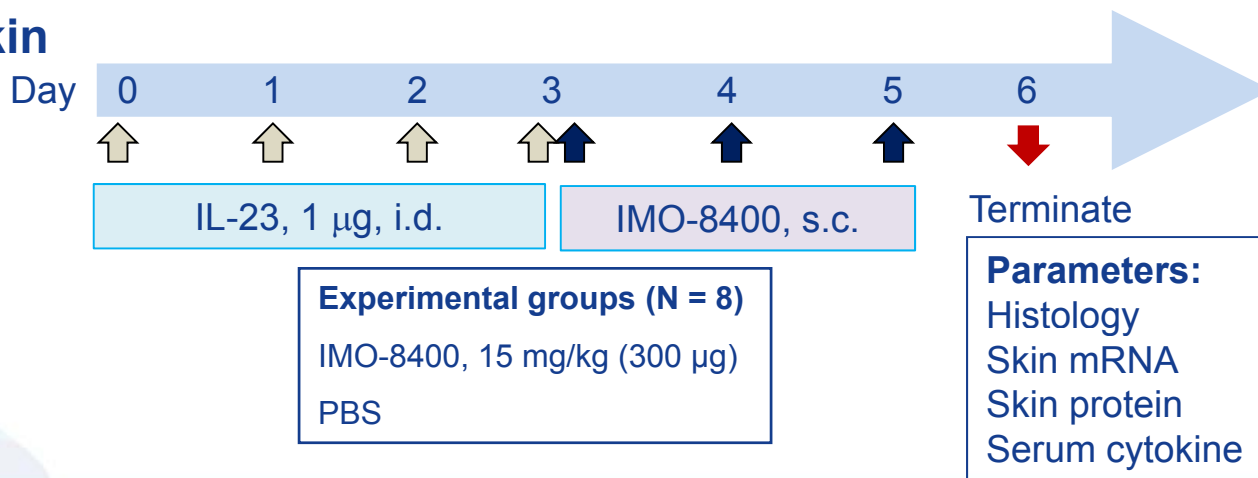


Experimental models of Psoriasis

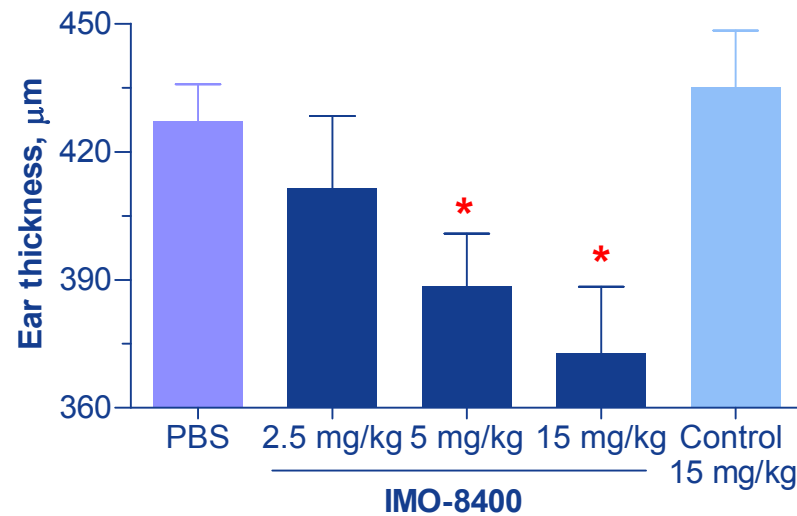
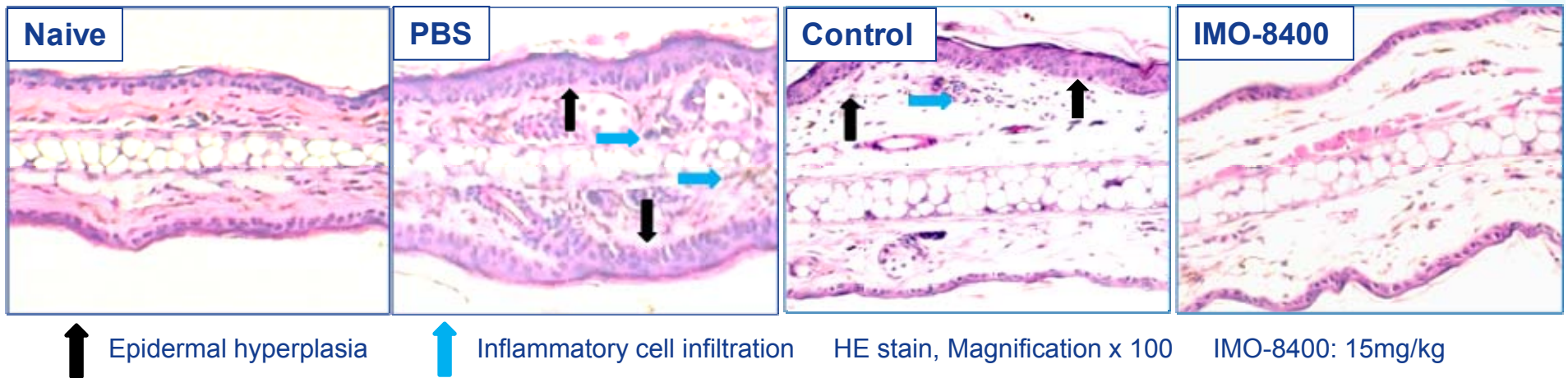
C57BL/6 mice ear



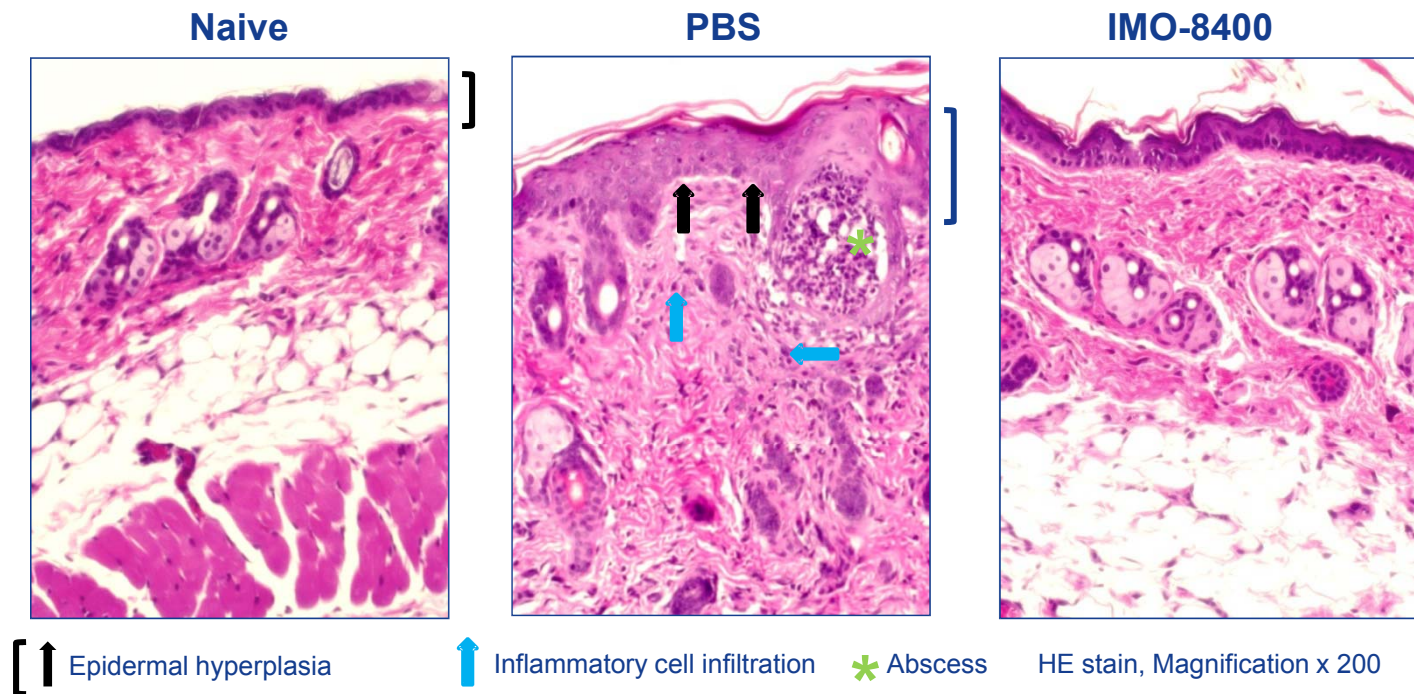
C57BL/6 mice dorsal skin



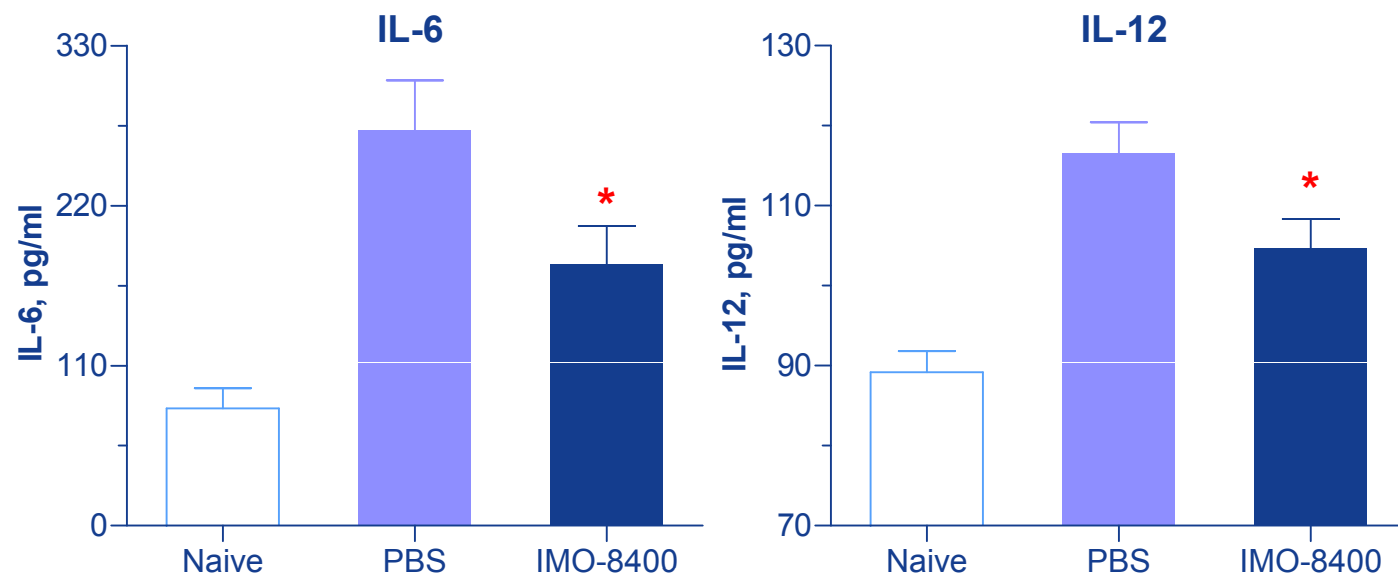
IMO-8400 Suppresses IL-23-Induced Ear Thickness Increase



IMO-8400 Inhibits Dorsal Skin Lesions Induced by IL-23

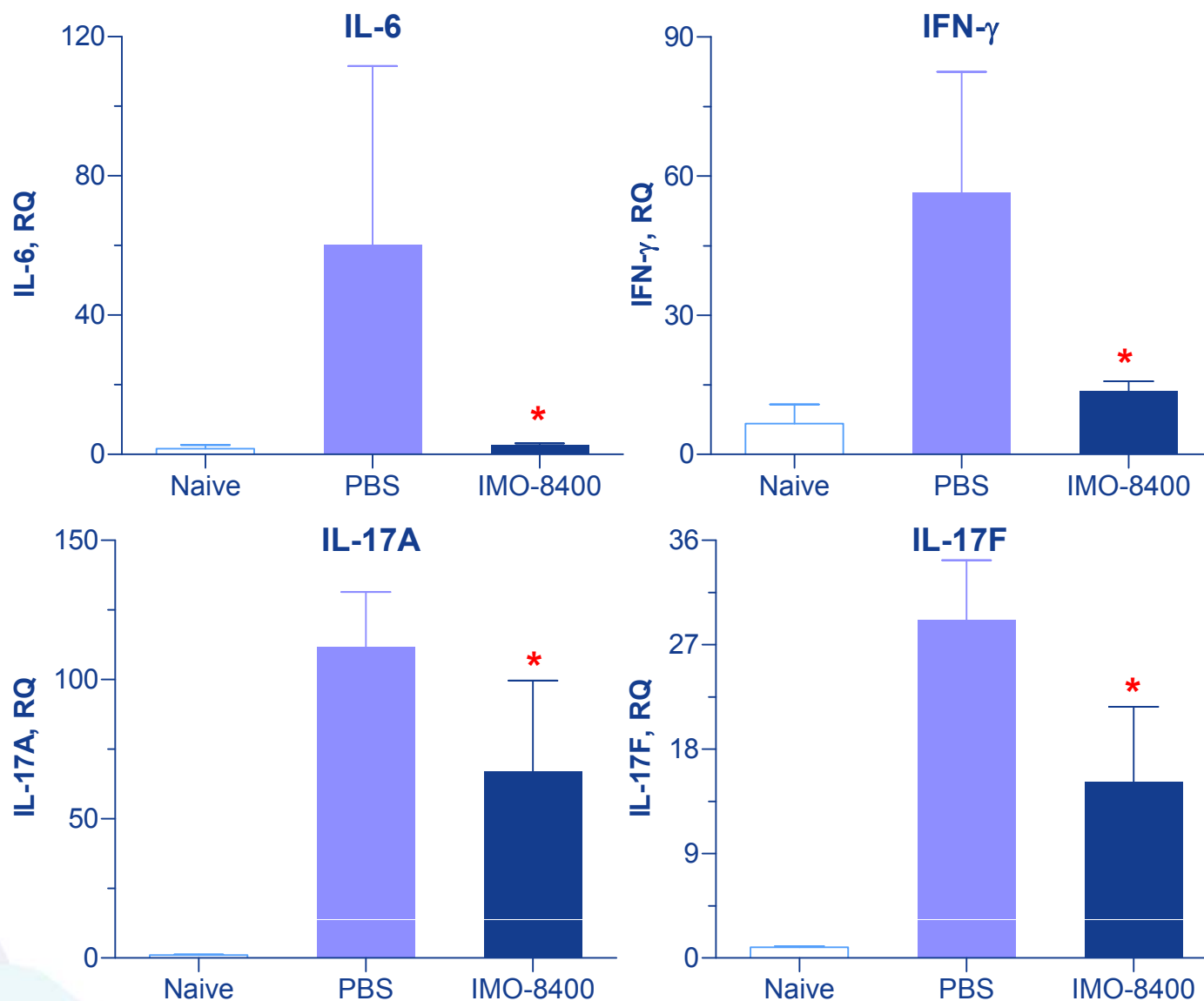


IMO-8400 Inhibits Cytokine Production



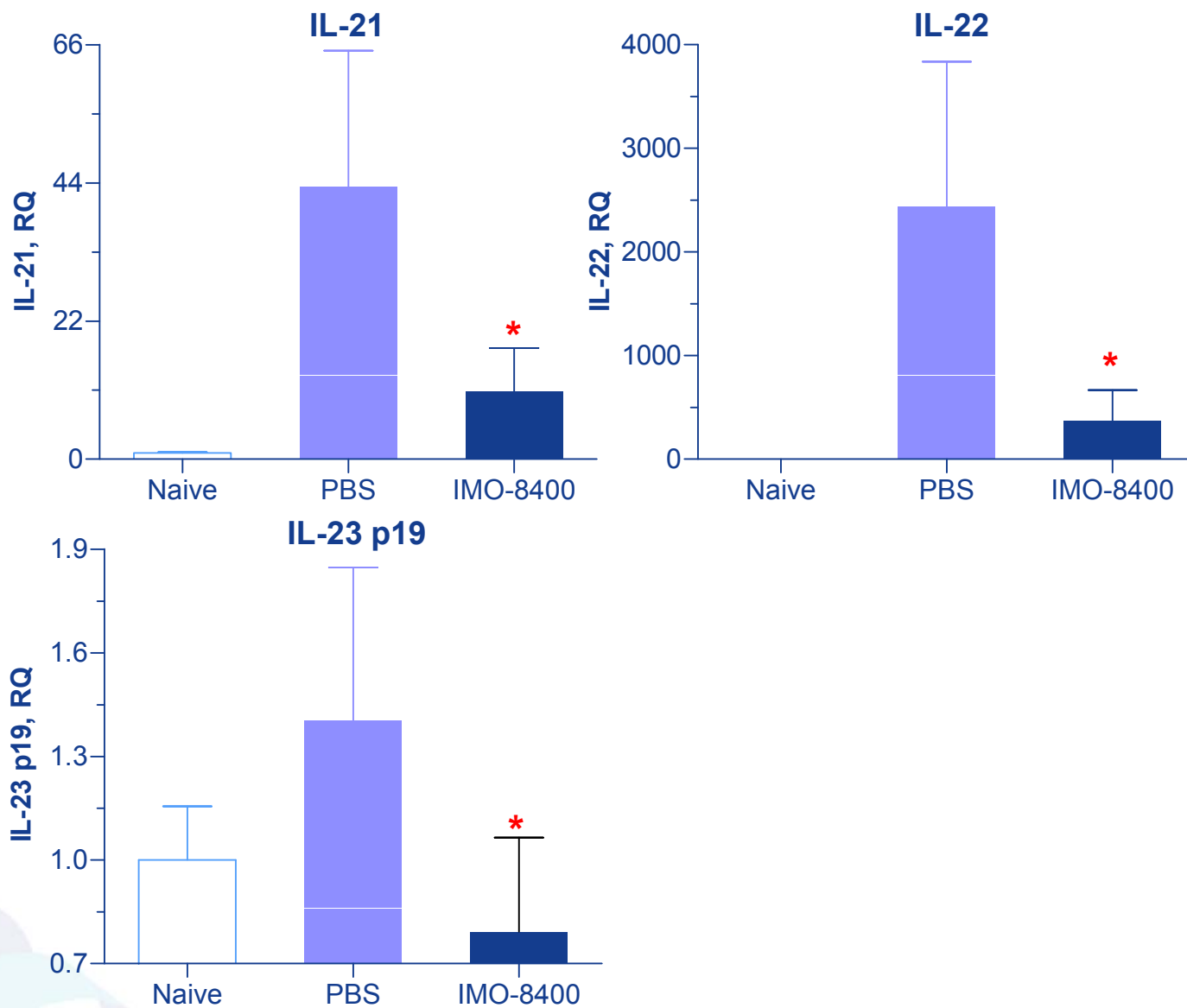
* $P < 0.05$ vs PBS group by two-tailed Student's t test; Serum levels of cytokines were measured by ELISA

IMO-8400 Inhibits Expression of Multiple Cytokines



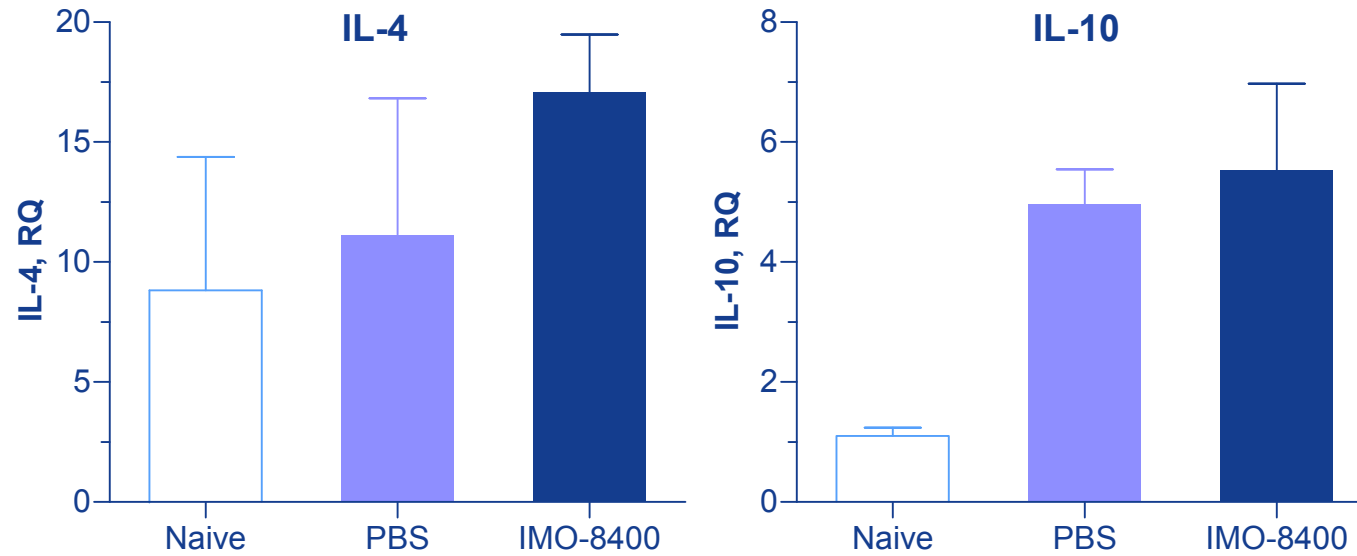
*, $P < 0.05$ vs PBS group by two-tailed Student's t test

IMO-8400 Inhibits Expression of Multiple Cytokines



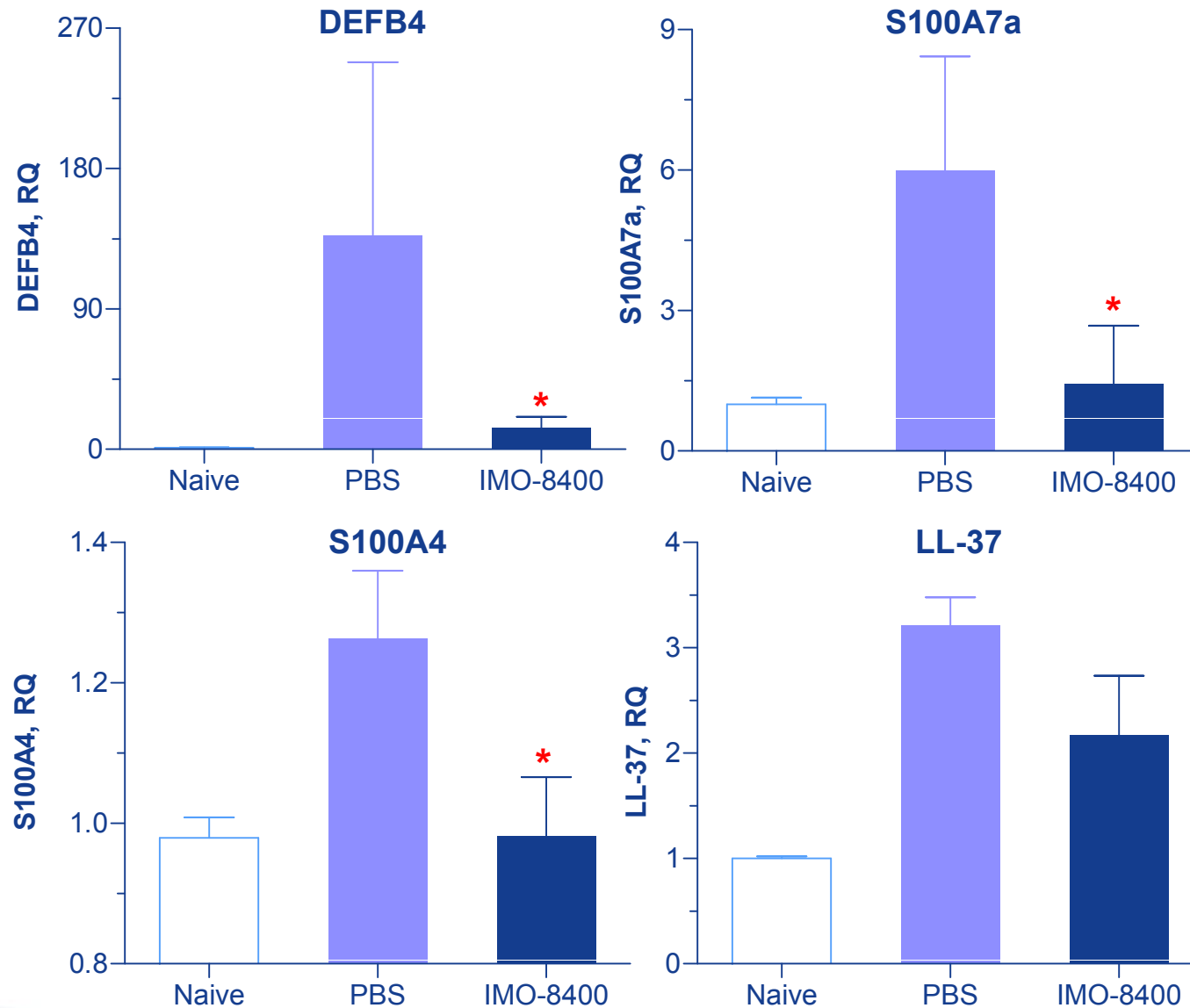
*, $P < 0.05$ vs PBS group by two-tailed Student's t test; mRNA levels of cytokines in skin were measured by qPCR

IMO-8400 Does Not Affect Th2 Cytokines



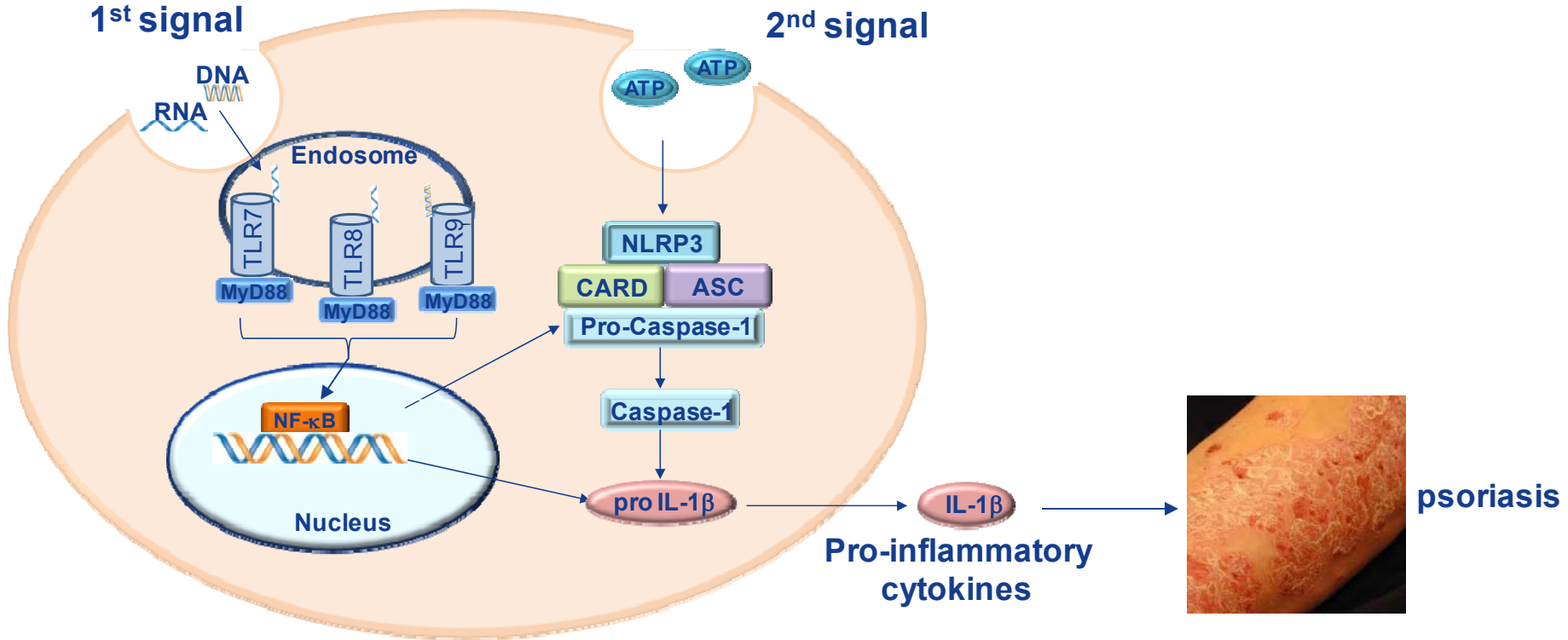
mRNA levels of cytokines in skin were measured by qPCR

IMO-8400 Inhibits Expression of Anti-Microbial Peptides

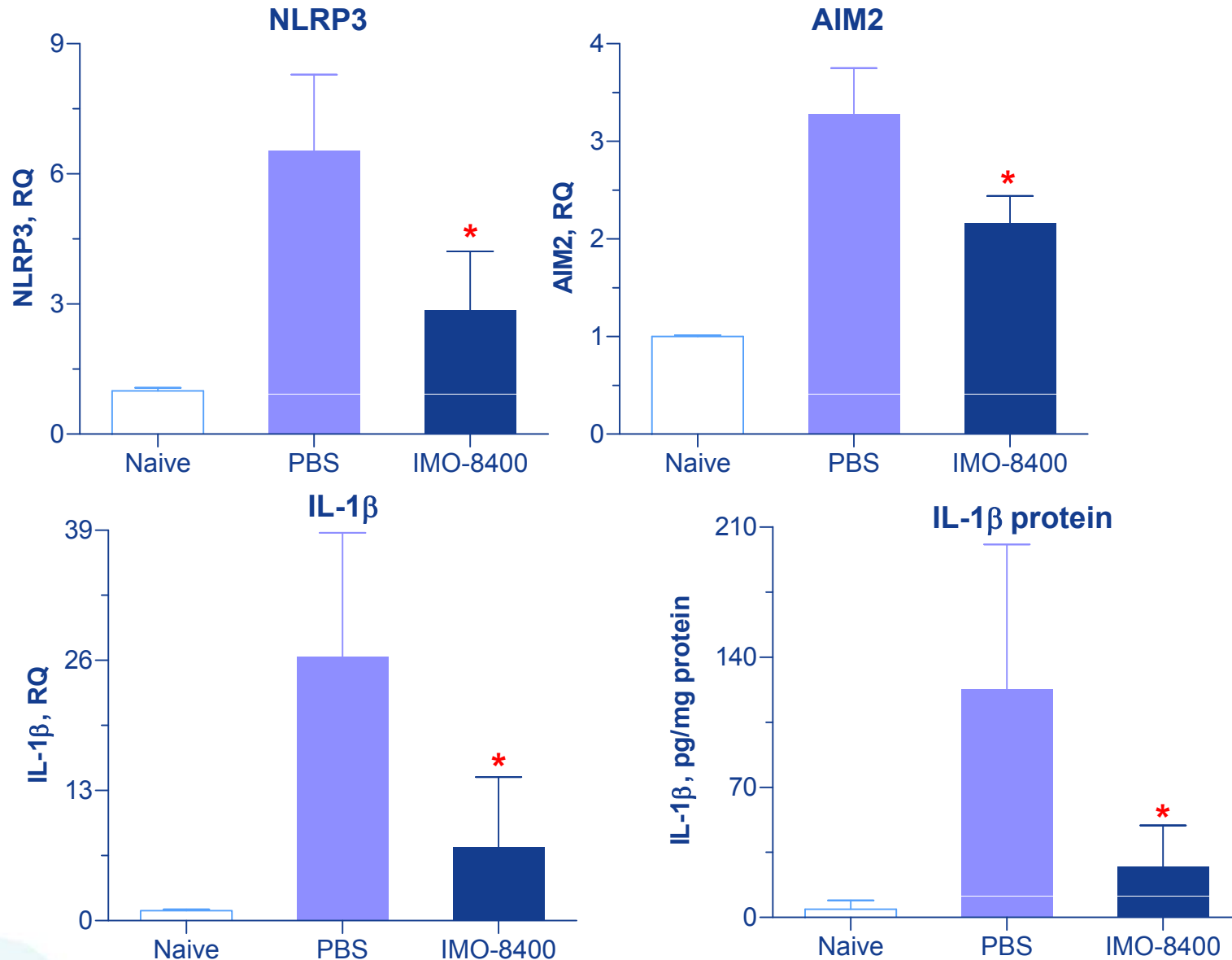


* , $P < 0.05$ vs PBS group by two-tailed Student's t test; mRNA levels of anti-microbial peptides in skin were measured by qPCR

Inflammasome Pathway in Psoriasis



IMO-8400 Inhibits Inflammasome Activation



* , $P < 0.05$ vs PBS group by two-tailed Student's t test; mRNA expression levels of inflammasome in skin were measured by qPCR; IL-1 β levels in skin were measured by ELISA.

Conclusion

- IMO-8400, an antagonist of TLR7, 8 and 9 exerts a therapeutic effect in mouse models of psoriasis induced by IL-23
 - Ameliorates disease pathology
 - Inhibits expression of Th1 cytokines such as IL-12, IL-6 and IFN- γ
 - Inhibits expression of genes associated with the IL-23/Th17 axis
 - Does not affect expression of Th2 cytokines IL-4 and IL-10
 - Inhibits expression of psoriasis-associated anti-microbial peptides such as DEFB4, S100A4 and S100A7a
 - Inhibits inflammasome activation
- IMO-3100, a TLR7 and 9 antagonist in Phase II clinical trial for the treatment of moderate to severe psoriasis is equally effective as IMO-8400 in IL-23- induced psoriasis model

Summary

- Antagonist blocks TLR activation thereby affecting the signaling cascade that controls the expression of multiple cytokines
- Inhibition of TLR activation ultimately results in the simultaneous blockade of many cellular events
- Blockade of TLR activation is not expected to perturb triggering of downstream signals mediated by other cellular events
- Mechanism of action of the antagonist is significantly different from that of immunosuppressants or monoclonal antibodies utilized for the treatment of psoriasis and other autoimmune diseases