

IL-23-INDUCED PSORIASIS MODEL

Psoriasis is a chronic immune-mediated inflammatory skin disease, multifaceted in pathogenesis:

- Involves interplay between genetic predisposition, immune system dysregulation, and environmental triggers
- Characterized histologically by epidermal thickening resulting from hyperproliferation of keratinocytes, immune cell infiltration into the skin, and parakeratosis
- Pathology associated with cytokine dysregulation and the JAK and STAT signaling pathways, with the primary driver being the IL-23/IL-17 pathway
- Therapeutic treatments exist; however, significant challenges persist: treatment adverse effects and resistance to conventional therapies

The IL-23-induced psoriasis model is translational into the clinic, bearing significant hallmarks of the human disease.

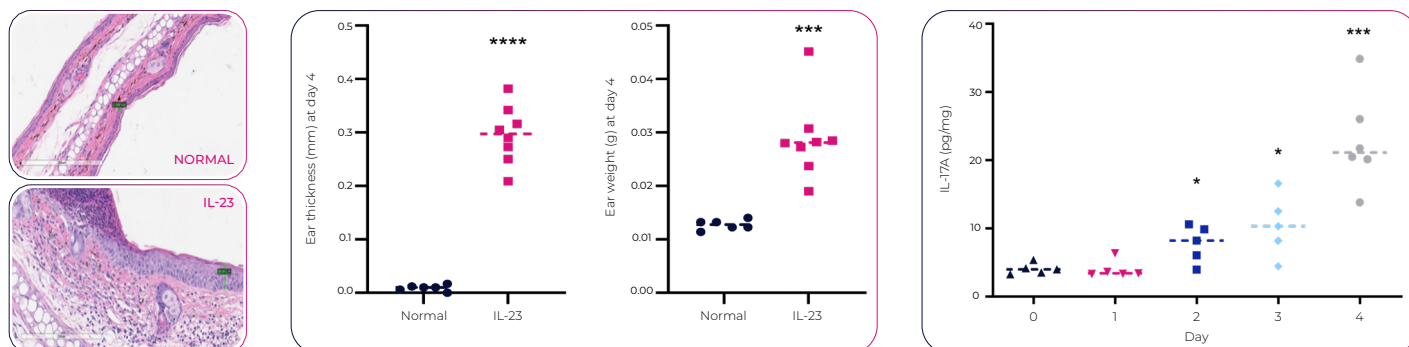
PRECLINICAL *IN VIVO* MODELS

Model	Development of Phenotype	Pros	Cons	Scientific Readouts
Recombinant IL-23-induced Model	Daily intradermal injection of rIL-23	<ul style="list-style-type: none"> • Activation of the IL-23/IL-17 pathway produces many of the hallmarks of psoriasis • Single cytokine used • Published transcriptomic data suggest that this model more closely resembles human disease • Validated model that is fast and reproducible 	<ul style="list-style-type: none"> • Significant differences between human and mouse skin – mouse models do not mimic all aspects of disease • Limited inflammation observed due to activation of a single pathway • Cost of rIL-23 	<p><i>In Vivo</i></p> <ul style="list-style-type: none"> • Daily bodyweight and ear caliper measurements • Digital images* • Ear skin macroscopic observations <p><i>Ex Vivo</i></p> <ul style="list-style-type: none"> • H&E staining of ear sections*
IMQ (Aldara)-induced Model	Application of Aldara/IMQ (TLR 7/8 agonist) leads to IL-23 production by dendritic cells thereby driving IL-17A-dependent skin inflammation	<ul style="list-style-type: none"> • More enhanced inflammation observed • Topical application • Relatively inexpensive • Validated model that is fast and reproducible 	<ul style="list-style-type: none"> • Complexity in mechanism of action of Aldara <ul style="list-style-type: none"> - Vehicle used augments inflammation in a non-TLR dependent manner 	<ul style="list-style-type: none"> • Epidermal and dermal thickness* • Ear weight • Histopathological assessment (parakeratosis, neutrophilic abscess, cellularity)* • Cytokine analysis* • mRNA level of cytokines*

*available on request.
Extra cost may apply to additional services.

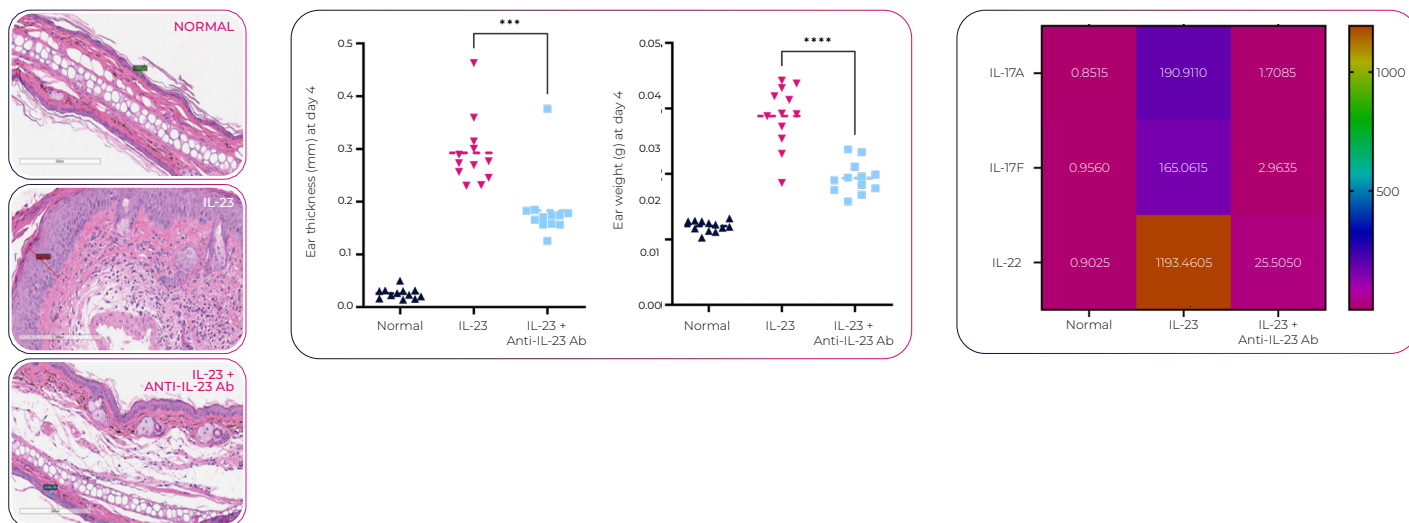
IL-23-INDUCED PSORIASIS MODEL VALIDATION DATA

- Mouse
 - SPF female C57BL/6J aged 6-8 weeks
- Model
 - Psoriasis induced by daily intradermal injections of rIL-23 into the mouse ear for 4 consecutive days
- Test article administration
 - Oral, intraperitoneal, intravenous, subcutaneous, or topical (other routes available on request)
- Statistically significant increase in ear thickness, ear weight, and IL-17A in the ear pinna of mice on days 2, 3, and 4



IL-23-INDUCED PSORIASIS MODEL VALIDATION DATA

- Anti-IL-23 was administered via i.p. or s.c. route 4 hours prior to IL-23 injection on day 0 and 2
- Blocking of IL-23 resulted in a statistically significant decrease in ear thickness and ear weight, with a corresponding decrease in the levels of IL-17A, IL-17F, and IL-22 in the ear pinna of mice on day 4 (measured by both ELISA and mRNA expression analysis)



SUMMARY

The utilization of *in vivo* models represents a critical approach in studying the underlying mechanisms of disease. The IL-23 induced model leads to histopathological changes that are characteristic of human disease, thereby offering a highly relevant and clinically translatable framework for assessing therapeutic efficacy of anti-psoriasis therapies.

The IL-23 induced psoriasis model is a cost-effective, fast, validated model with prior tested data from anti-inflammatory compounds.

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