MODELING PSORIASIS IN RATS FOR DRUG SCREENING AND DEVELOPMENT

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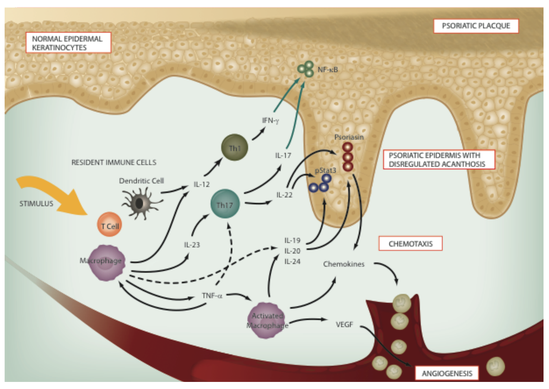
ABSTRACT

Psoriasis is the most common chronic autoimmune skin condition, effecting more than 2% of the US population and impacting roughly 125 million people worldwide. The pathogenesis of psoriasis is not wholly understood, though assumed to be a complex interplay between environmental factors, immune dysregulation and genetic susceptibility. This response triggers secretion of pathogenic cytokines IL-12 and IL-23, causing migration and differentiation of Th17 and Th1 cells. These cells release additional cytokines such as IL-22, IL-17A and IL-17F driving proliferation of keratinocytes and epidermal hyperplasia (plaque formation). With the complexity of psoriasis disease immunopathology, it has become increasingly important to model this disease, or aspects thereof, in immune competent animals. The rat is inherently more translational than mouse with closer physiology, richer behavior, more robust and repeatable assay performance, and offers the ability to do safety studies in the same strain and species as efficacy. To this end, MD Biosciences has optimized two psoriasis models in the Sprague Dawley rat.

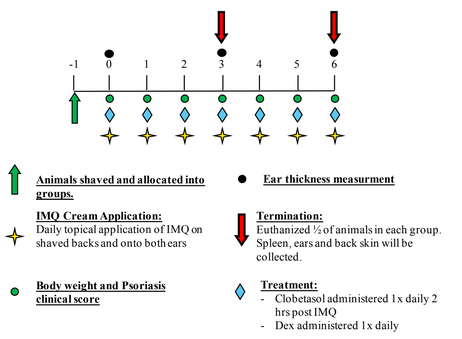
The imiquimod (IMQ) induced psoriasis model has been widely used in pre-clinical drug development. Diseased animals exhibit erythema and plaque formation shortly after the start of the study and progress through termination. IL-23 is the main pathogenic cytokine in the initiation of psoriasis disease progression and has become a lead target for the clinical treatment of psoriasis. To more specifically examine IL-23 driven psoriasis, exogenous IL-23 can be delivered directly to the dermis of rats to induce a downstream cascade of inflammatory biomarker upregulation, erythema and epidermal hyperplasia, similar to what is seen in human psoriatic plaques. The IMQ- and IL-23-induced psoriasis models are robust pre-clinical models to help develop therapeutics for psoriasis, as both models mimic specific disease pathologies.

MODEL/METHODS



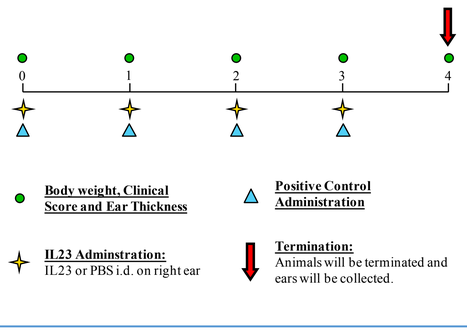
IMQ MODEL

The IMQ model utilizes imiquimod, a TLR7 agonist, to activate innate immune cells in the skin. This activation induces a cellular cascade involving IL-23/IL-17 pathways, resulting in psoriasis-like disease in the animals.

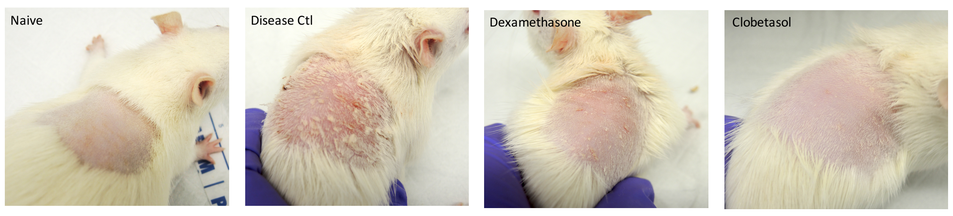


rrIL-23 MODEL

In the IL-23 model, animals are injected with rrIL-23 protein, bypassing the need for the initial stimulus (i.e. IMQ). IL-23 activates the IL-17 pathways and cellular processes resulting in dermal and epidermal alterations similar to psoriasis disease.



IMQ MODEL RESULTS



Psoriasis Score					
Plaques	Grade	Erythema	Grade	Punctate redness/scabbing	Grade
Normal	0	Normal	0	No red dots	0
Very few plaques (cover about 5-10% of the back area).	1	Slight	1	Very few (1-10) red dots present on the entire back	1
Several plaques (cover about 20%-30% of the back area).	2	Moderate	2	Red dots are diffuse and cover ~50% of the back (10-25 red dots)	2
Moderate plaques (cover about 50% of the back area).	3	Marked	3	Red dots cover the entire back and are more concentrated (>25 red dots)	3
Spread plaques (cover over 90% of the back area).	4	Extreme	4		
Plaques are no longer detected, however the skin is irritated and no fur is growing on the skin	5				

Figure 1: Gross images of disease progression and clinical score rubric. Animals were treated with IMQ daily on both the shaved back skin and on the right ear. Animals were left untreated or dosed daily with 1mg/kg dexamethasone or 50mg clobetasol. Animals were monitored daily for clinical score parameters per Psoriasis scoring table.

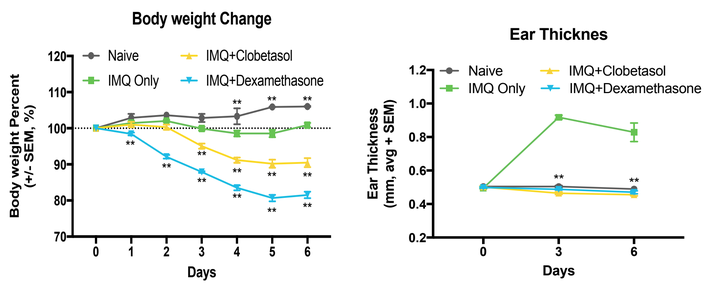


Figure 2: Psoriasis Clinical assessments. Animals were treated as above and monitored for daily bodyweight compared to starting weight. Ear thickness was assessed as a proxy for skin thickening. IMQ only animals developed significant ear inflammation compared to naïve and treated animals. **p<0.01, Two-way ANOVA, multiple comparisons.

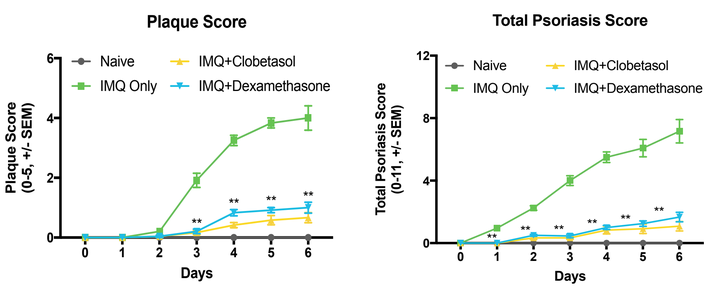
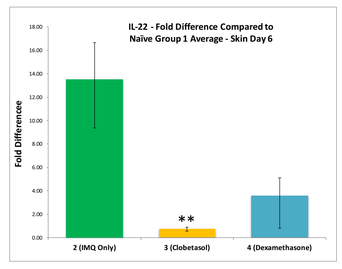
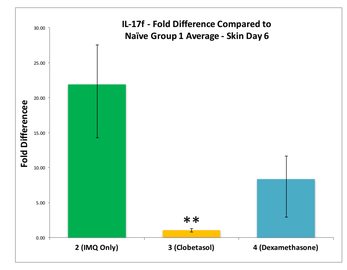


Figure 3: Psoriasis Clinical assessments. Animals were treated as above and monitored daily for assessment of psoriasis disease development based on table above. IMQ only animals developed significant plaques and overall disease compared to naïve and treated animals. **p<0.01, Two-way ANOVA, multiple comparisons.





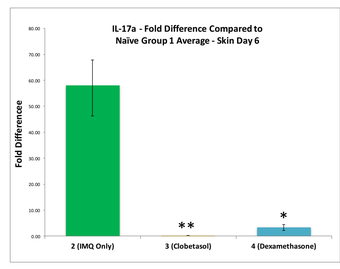
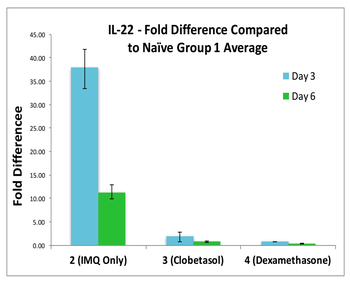
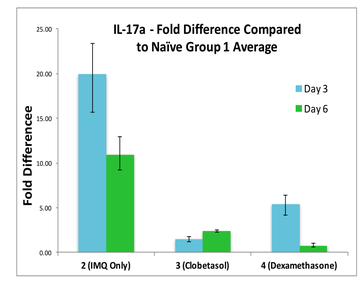


Figure 4: Biomarker Assessments. qPCR was performed on back skin samples from animals on day 6. Samples were normalized to housekeeping gene, HPRT1 and naïve controls. IMQ induced robust biomarker production. All markers were significantly decreased in treated animals compared to IMQ controls.





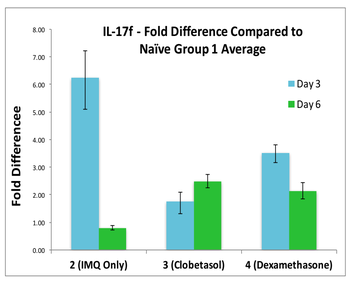


Figure 5: Biomarker Assessment. qPCR was performed on ear samples from day 3 and day 6. Samples were normalized to housekeeping gene, HPRT1 and naïve controls. IMQ induced biomarkers in the ear mimicked thickness, peaking day 3 and residing by day 6.

IL-23 MODEL RESULTS

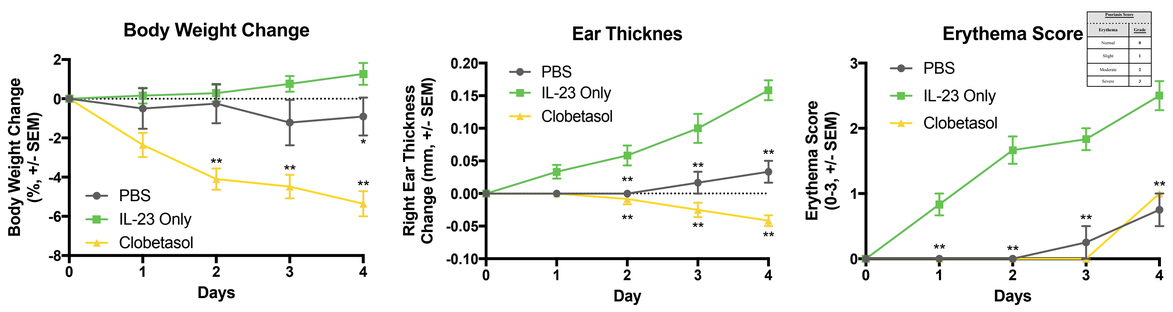


Figure 6: Model parameter verification and clinical assessments. Animals were injected i.d. on the R ear with either PBS or rrIL-23 protein. Body weight, ear thickness and erythema were monitored daily during the course of disease. **p<0.01, Two-way ANOVA, multiple comparisons.

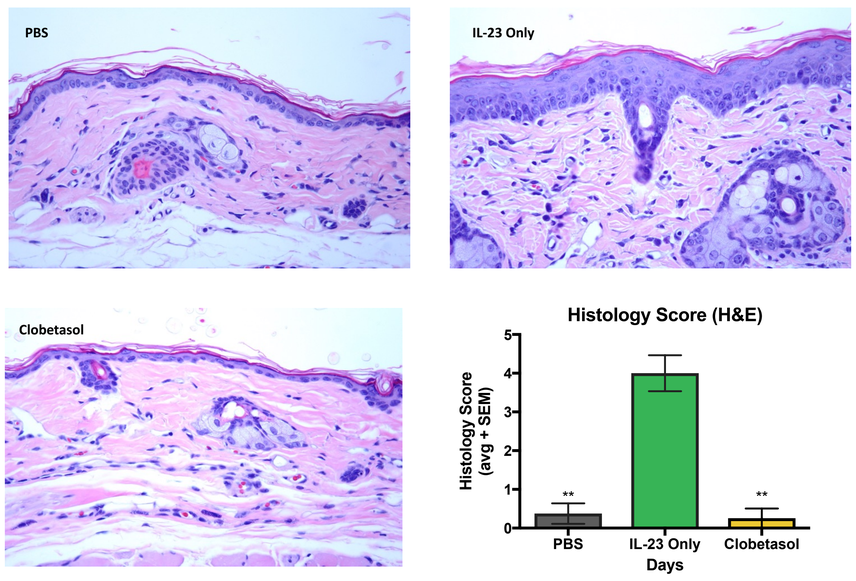


Figure 7: Histology (H&E). Ear samples from day 4 were harvested and stained for H&E disease severity. Slides were scored by a pathologist and representative images and cumulative data shown. Parameters include epidermal exudates, erosion, epidermal hyperplasia and inflammation. Scoring was based on the following scale 0 = no finding; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe. Based on H&E scoring, IL-23 induced significant disease that was reduced upon clobetasol treatment. **p<0.01, One-way ANOVA, multiple comparisons.

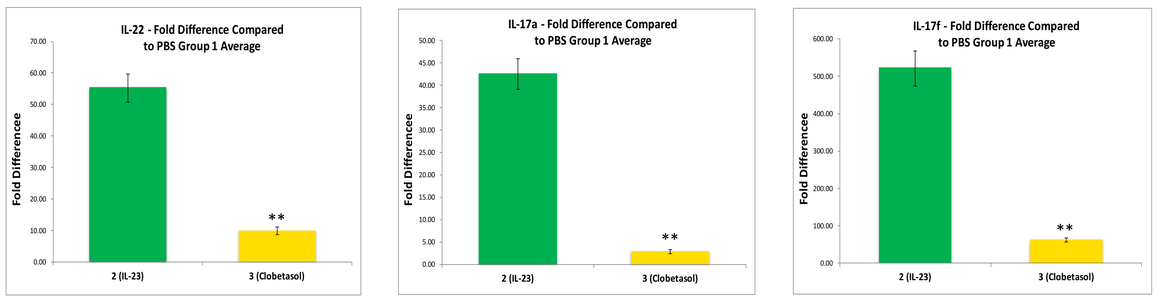


Figure 8: Biomarker Assessments. qPCR was performed on ear samples from animals on day 4. Samples were normalized to housekeeping gene, HPRT1 and PBS injection controls. IL-23 induced robust biomarker productions. All markers were significantly decreased in treated animals compared to IL-23 only controls. **p< 0.01, T-Test.

CONCLUSIONS

IMQ Model

- Daily application of IMQ resulted in plaque-like lesions accompanied with erythema, that progressed over the course of the study.
- Application of IMQ to the ears resulted in skin thickening (epidermal hyperplasia), a known clinical symptom of psoriasis.
- IMQ-only animals exhibited a cytokine signature similar to that seen in plaque psoriasis, including upregulation of IL-22, IL-17A and IL-17F in the diseased skin.
- IMQ-diseased animals treated with topical and systemic corticosteroids had decreased clinical symptoms and biomarker signatures.
- The biomarker signature within the skin of the ear correlated to clinical symptoms (skin thickening).

IL-23 Model

- Daily i.d. injection with the psoriatic cytokine, rrIL-23, resulted in epidermal thickening (ear thickness) and erythema.
- Histological assessments of the diseased ear mimicked gross pathology as seen by increased epidermal hyperplasia, erosion and subacute tissue inflammation.
- rrIL-23 i.d. injections resulted in upregulation of a psoriatic cytokine signature including IL-22, IL-17A, and IL-17F.
- Treatment with topical corticosteroid significantly inhibited clinical symptoms, histological changes and psoriatic cytokine upregulation.

- **In total these data suggest that the IMQ and rrIL-23 induced psoriasis-like skin inflammation models in rats can be used to evaluate lead drug candidates. Candidates may include cytokine targeting drugs, (i.e. anti-IL17A) or anti-inflammatories**.

CONTACTS