The PARP14 inhibitor RBN-3143 suppresses skin inflammation in preclinical models

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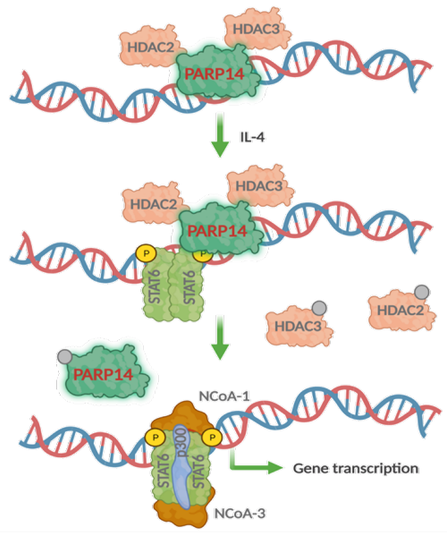
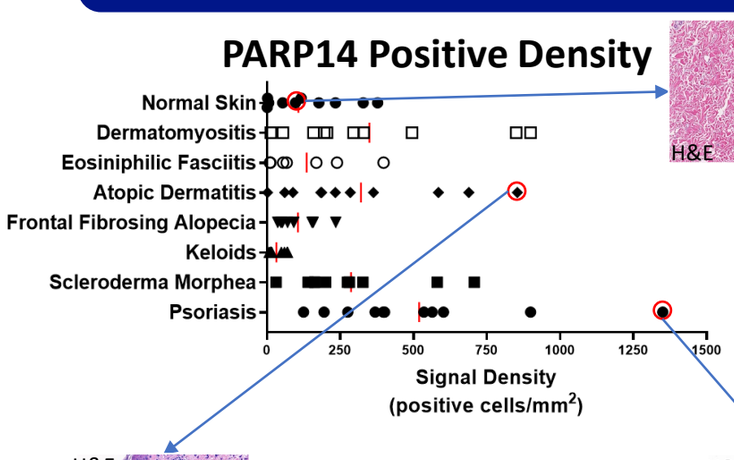
Background: PARP14 is a Mediator of Th2/Th17 Signaling Pathways and is Induced by Infections and Inflammation

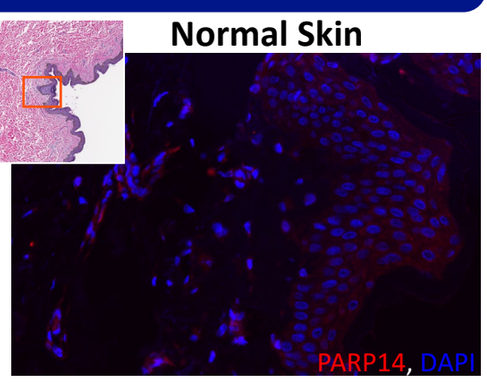
- PARP14 suppresses Th2/17-driven transcription via the recruitment of histone deacetylases (HDACs)[1]
- Interferons and TLR agonists induce PARP14 expression and activity[2]
- Active PARP14 modifies HDACs and releases transcriptional repression[1]
- PARP14 knockout mice are less susceptible to allergic lung inflammation than wild type mice[3]

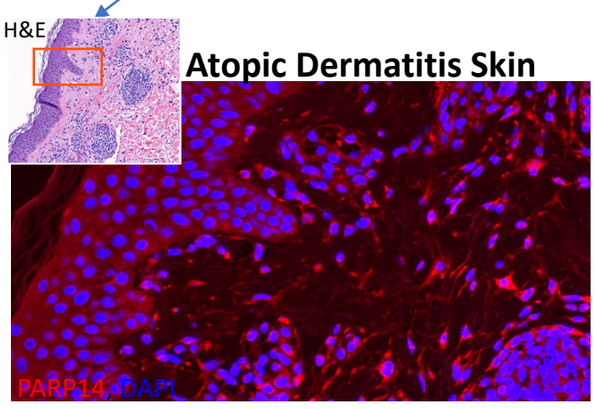


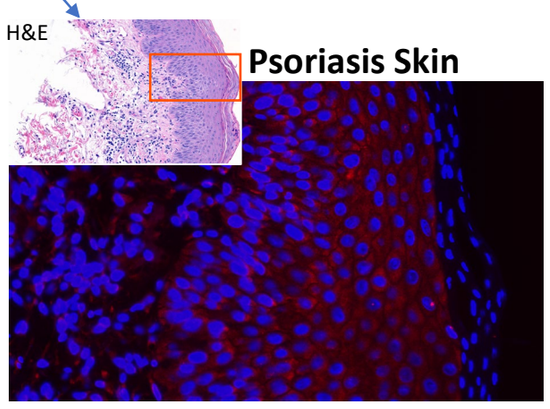
1 Mehrotra et al., J. Biol. Chem., 2011
2 Caprara et al., J. Immunol., 2018
3 Cho et al., J. Immunol., 2013

PARP14 Expression is Elevated in Tissues from Patients With Inflammatory Diseases Compared to Normal Tissue



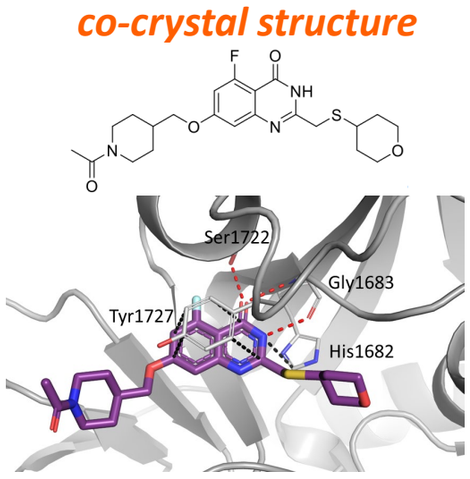




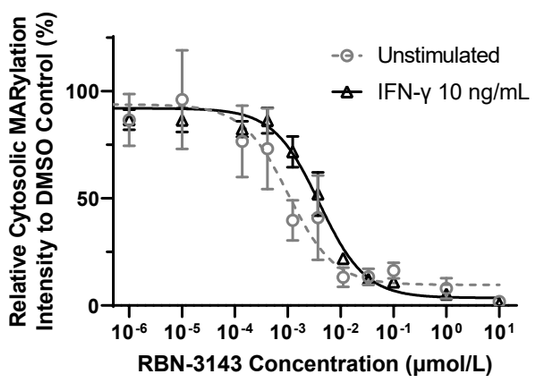


RBN-3143 is a Potent and Selective Inhibitor of PARP14

RBN-3143 and PARP14 co-crystal structure

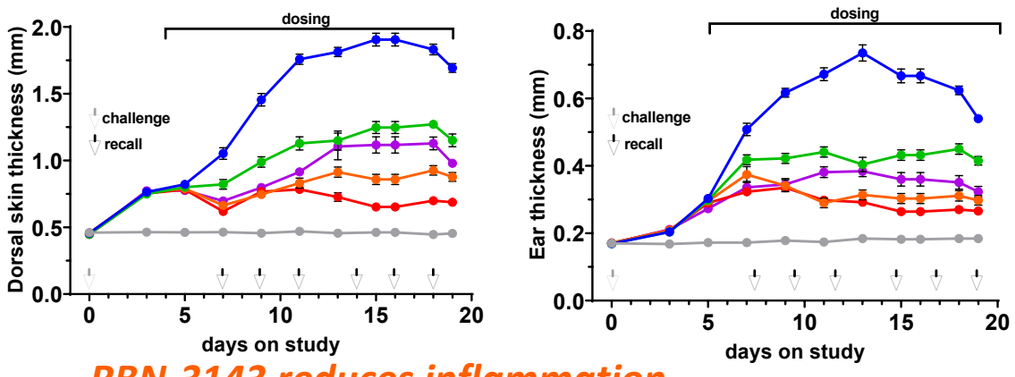


RBN-3143 is a highly potent cellular inhibitor of PARP14

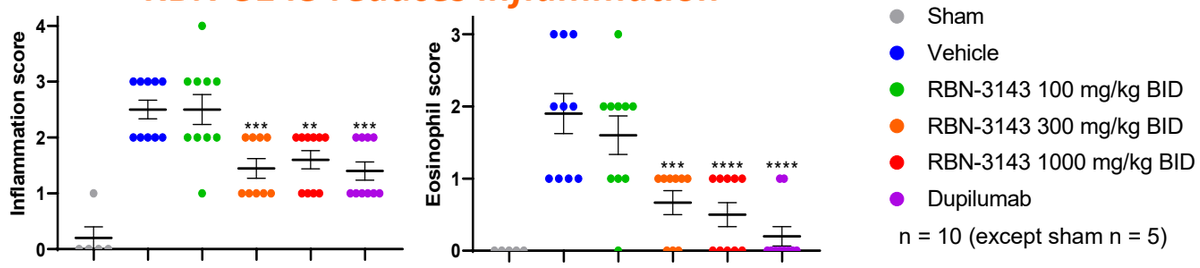


RBN-3143 Suppresses Skin Inflammation in a Mouse Model of Atopic Dermatitis Induced by Oxazolone

RBN-3143 suppresses skin and ear thickening better than dupilumab in humanized hIL-4/hIL-4Rα mice

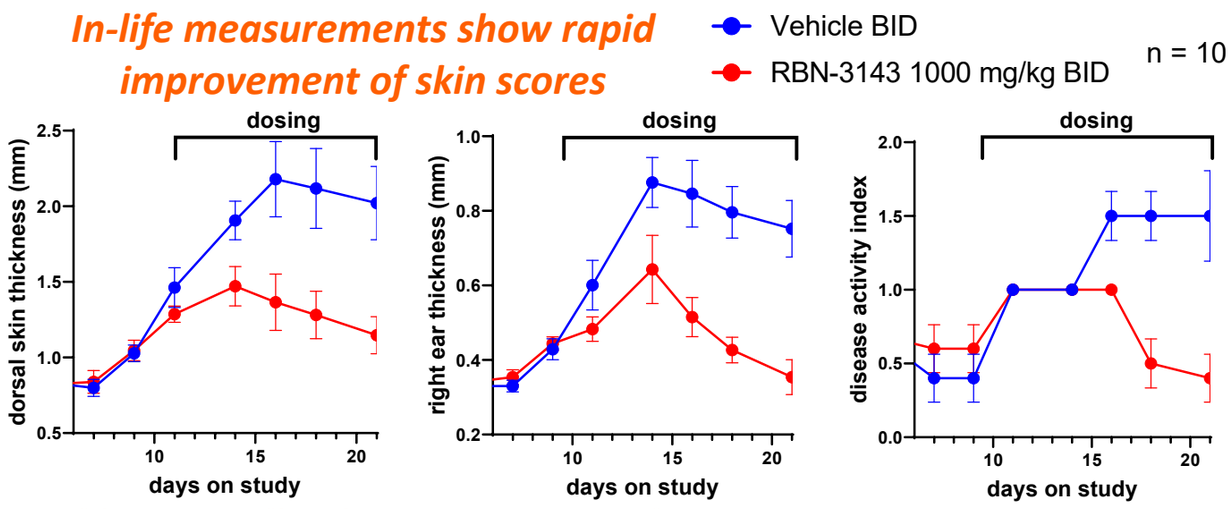


RBN-3143 reduces inflammation



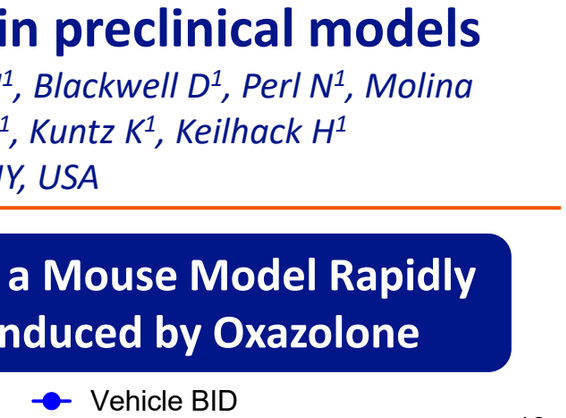
RBN-3143 Therapeutic Dosing in a Mouse Model Rapidly Improves Skin Inflammation Induced by Oxazolone

In-life measurements show rapid improvement of skin scores

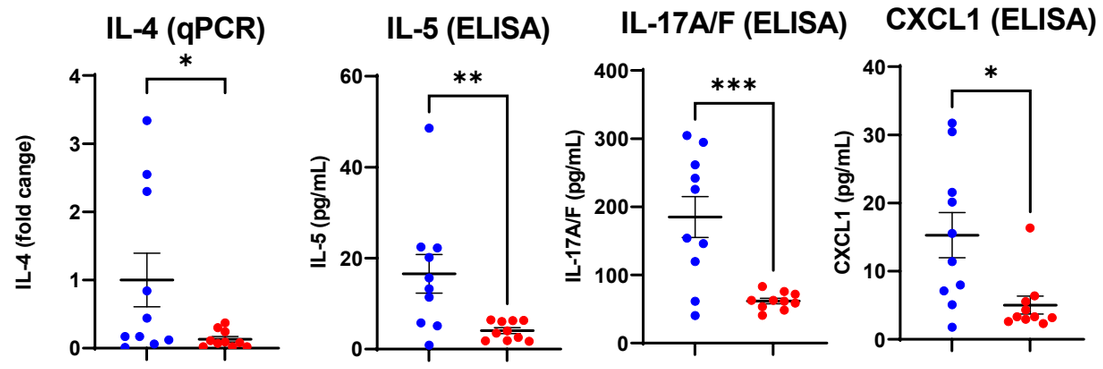


Skin Normalization Demonstrated by Histopathology

Ear Morphology

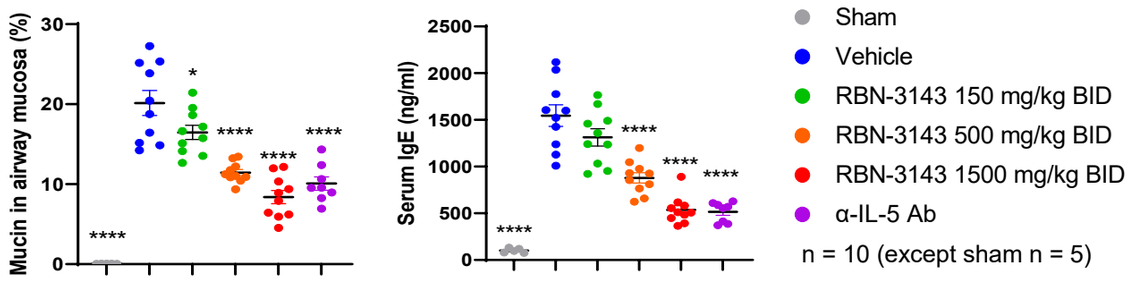


Inflammatory cytokines are reduced in the skin

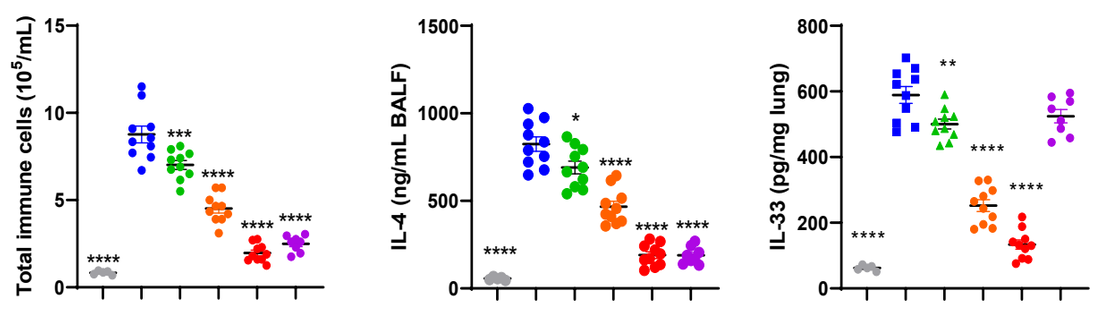


RBN-3143 Suppresses Allergic Lung Inflammation in a Steroid-Resistant Mouse Model Induced by Alternaria

RBN-3143 suppresses airway mucin and serum IgE



RBN-3143 suppresses immune cells, cytokine, and alarmin accumulation in the lungs



Summary: RBN-3143 is a Novel Treatment for Inflammatory Diseases

- PARP14 expression is induced by interferon and elevated in tissues from patients with inflammatory diseases
- RBN-3143 is a potent, selective inhibitor of PARP14 with an IC_{50} < 5 nM and > 300x selectivity over other PARPs in vitro
- In preclinical models of inflammation RBN-3143 suppresses markers of disease in line or better than clinically approved targets
- In an atopic dermatitis mouse model, RBN-3143 improves skin and ear morphology and histopathology, and reduces inflammatory cytokines
- RBN-3143 is safe and well-tolerated in preclinical models and is currently in a Phase I clinical trial in atopic dermatitis patients (NCT05215808)

Thank you to McKenna Montminy for data generation.

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