

PKM2 is a promising novel target in atopic dermatitis

Tom Ashton¹, Sabine Broc¹, Gareth Davies¹, Martin Domville¹, Eva Palsson-McDermott^{1,2}, Oscar Barba¹, Mark Whitmarsh¹, Lisa Pierre¹, Ravi Rao¹, Luke O'Neill^{1,2}, Iain Kilty¹

¹Sitryx Therapeutics Ltd, 101 Bellhouse, Oxford Science Park, Oxford, UK OX4 4GA

²School of Biochemistry and Immunology, Trinity Biomedical Science Institute, Trinity College Dublin, Ireland

Introduction

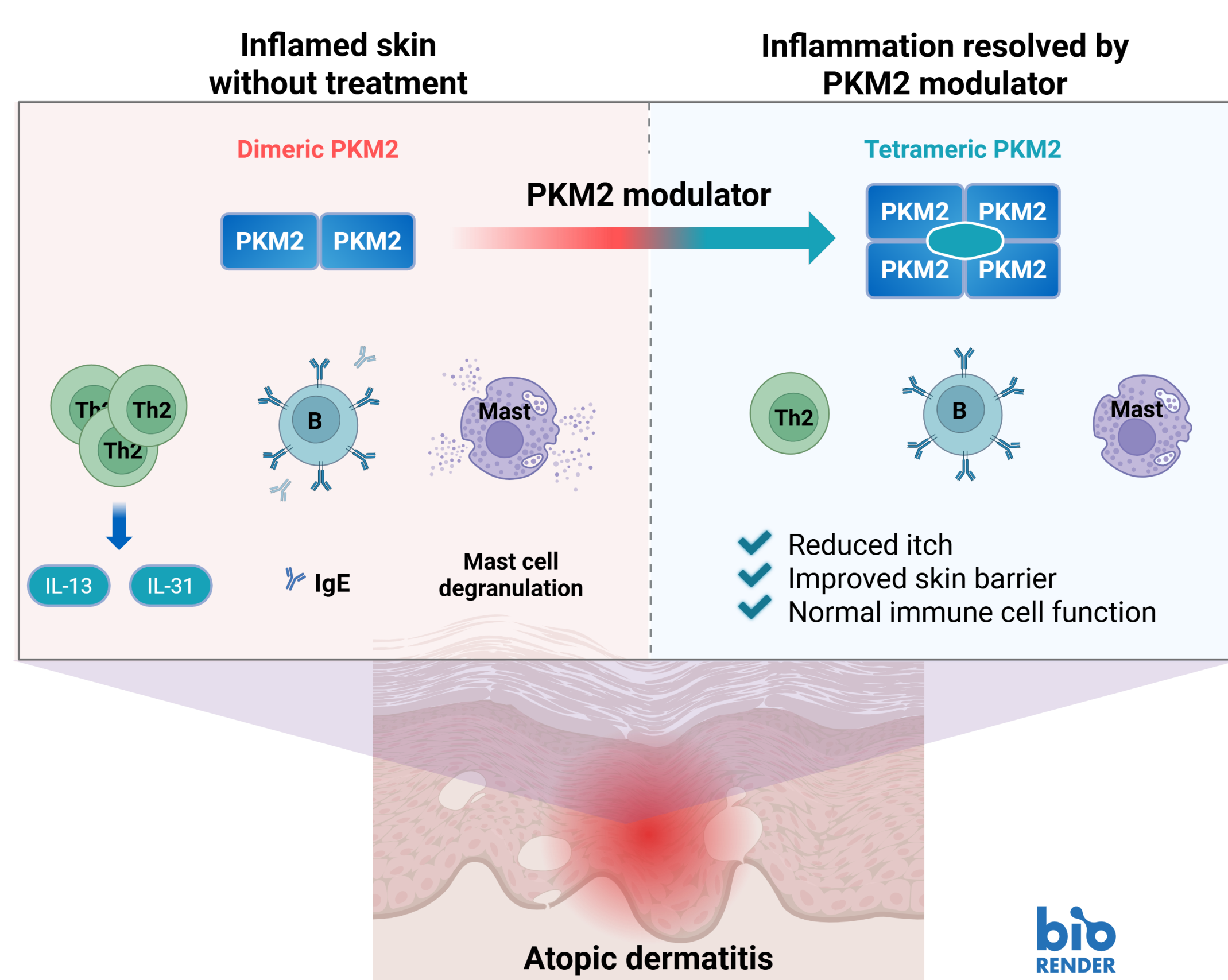
Atopic dermatitis (AD) is a complex, chronic inflammatory, non-contagious skin disease with high unmet need and no curative treatment options. Pyruvate kinase M2 (PKM2) is a key enzyme in the central metabolic pathway of glycolysis and is specifically upregulated in inflammatory tissues. Here we describe PKM2 as a novel target in AD and demonstrate efficacy of novel PKM2 modulators in the DNFB and oxazolone induced contact dermatitis mouse models of inflammatory skin disease. Efficacy is also demonstrated in IgE-induced passive cutaneous anaphylaxis and cortistatin-14 induced mast cell mouse models. A Sitryx PKM2 modulator, SYX-5219, has recently entered into a clinical trial for AD.

Methods

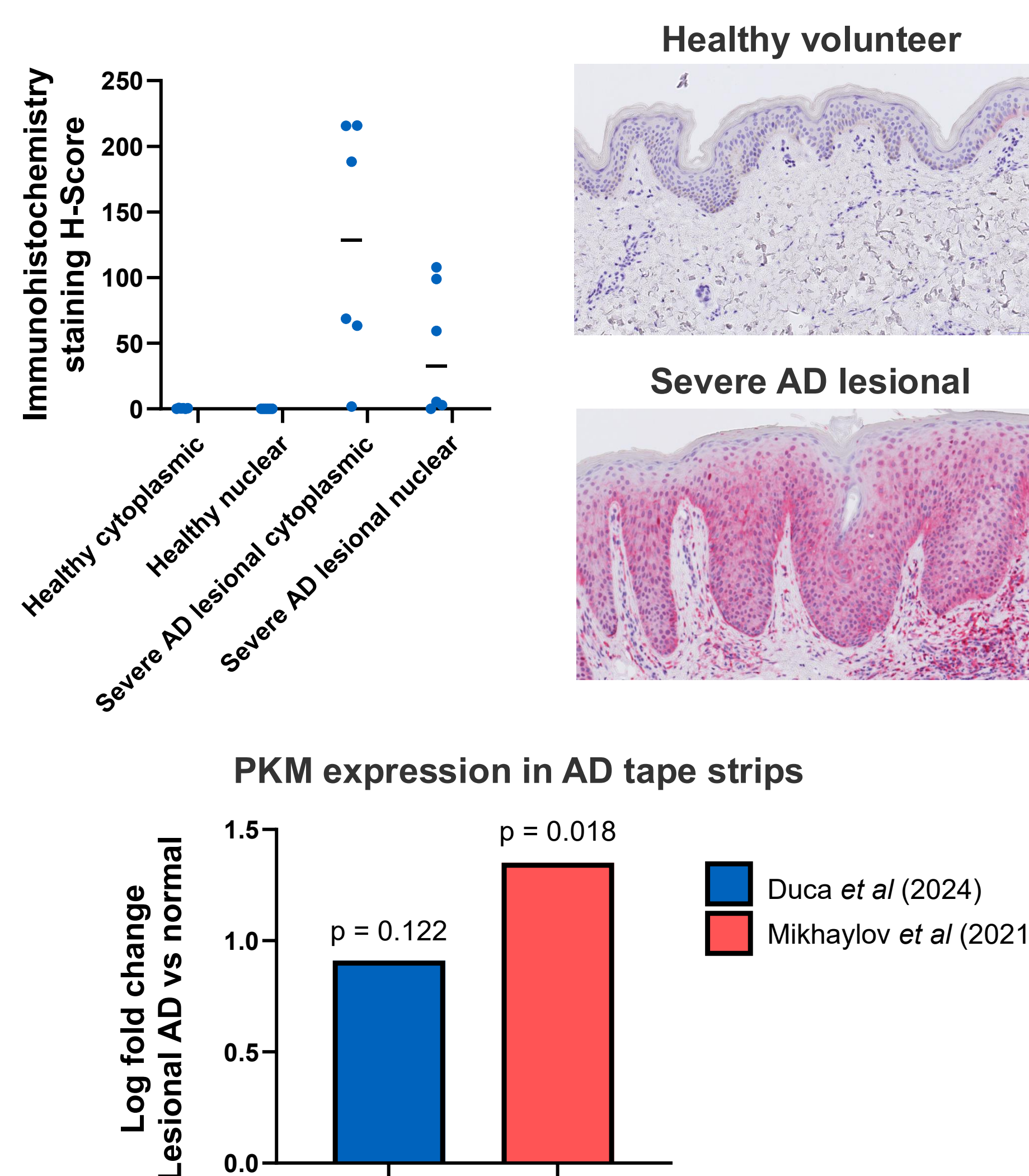
PKM2 expression was studied in human healthy skin and AD skin using immunohistochemistry (PKM2 Ab Cell Signalling, 4053S) and RNAseq. The *in vitro* pharmacology of PKM2 modulators, SYX-PKM-A and SYX-PKM-B, was studied using biochemical assays (Bio-Techne, 7244-PK-020) and pyruvate kinase activity (Abcam assay, ab83432) in human CD4+ T cells. The *in vivo* pharmacology of PKM2 modulators was determined in murine models. 2,4-dinitrofluorobenzene (DNFB) or oxazolone were used to induce contact dermatitis. IgE or cortistatin-14 were used to induce mast cell degranulation. Efficacy was measured using ear thickness, excoriation score, RNAseq from ear tissue, cytokine analysis from ear tissue (IL-1 β , IL-4, IL-6, IL-13, IFN γ , IL-17a, IL-31 Luminex) or skin Evans' blue quantification. ANOVA with Dunnett's post-test * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

Results

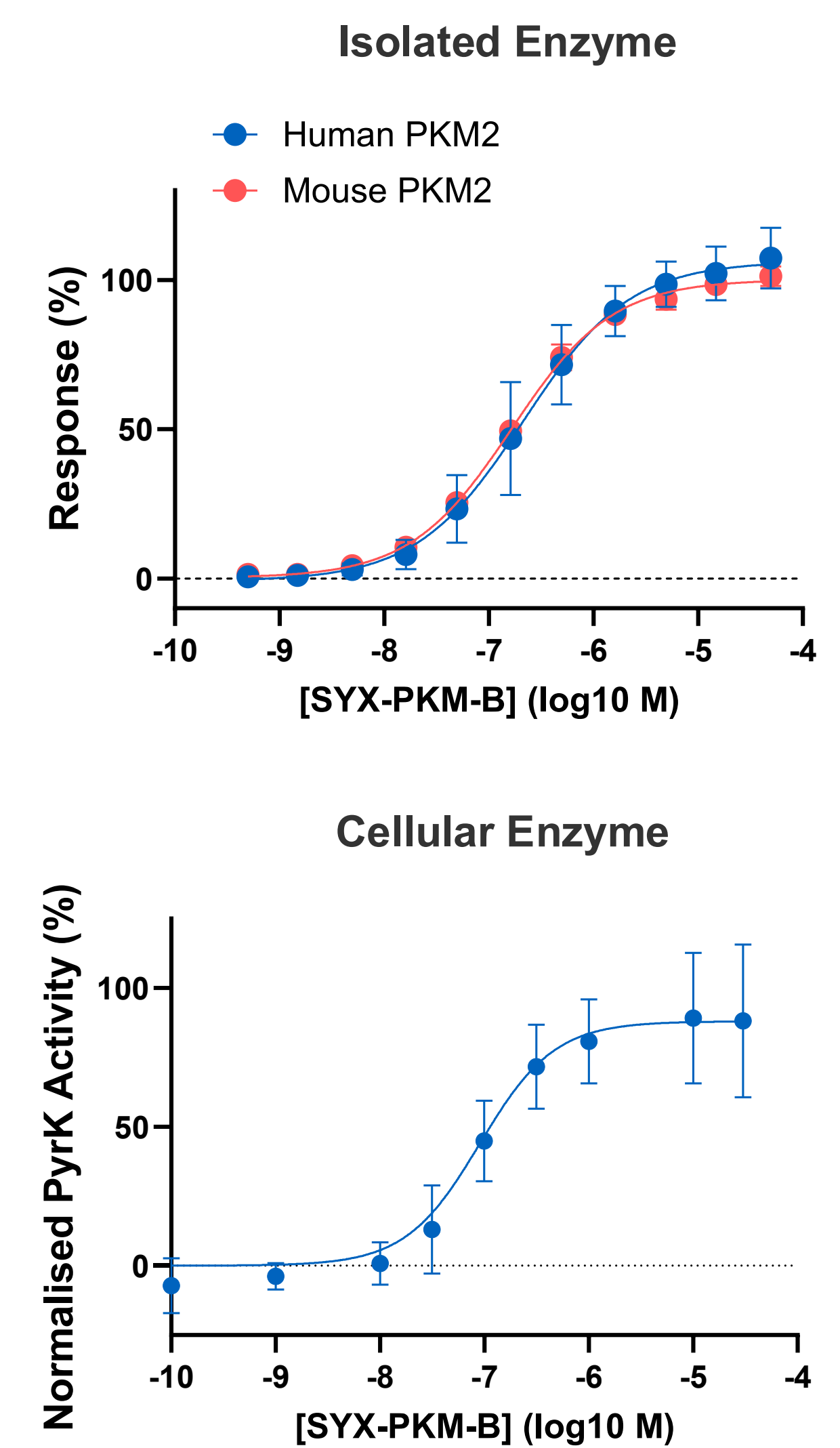
1. Resolution of inflammation in atopic dermatitis with a PKM2 modulator



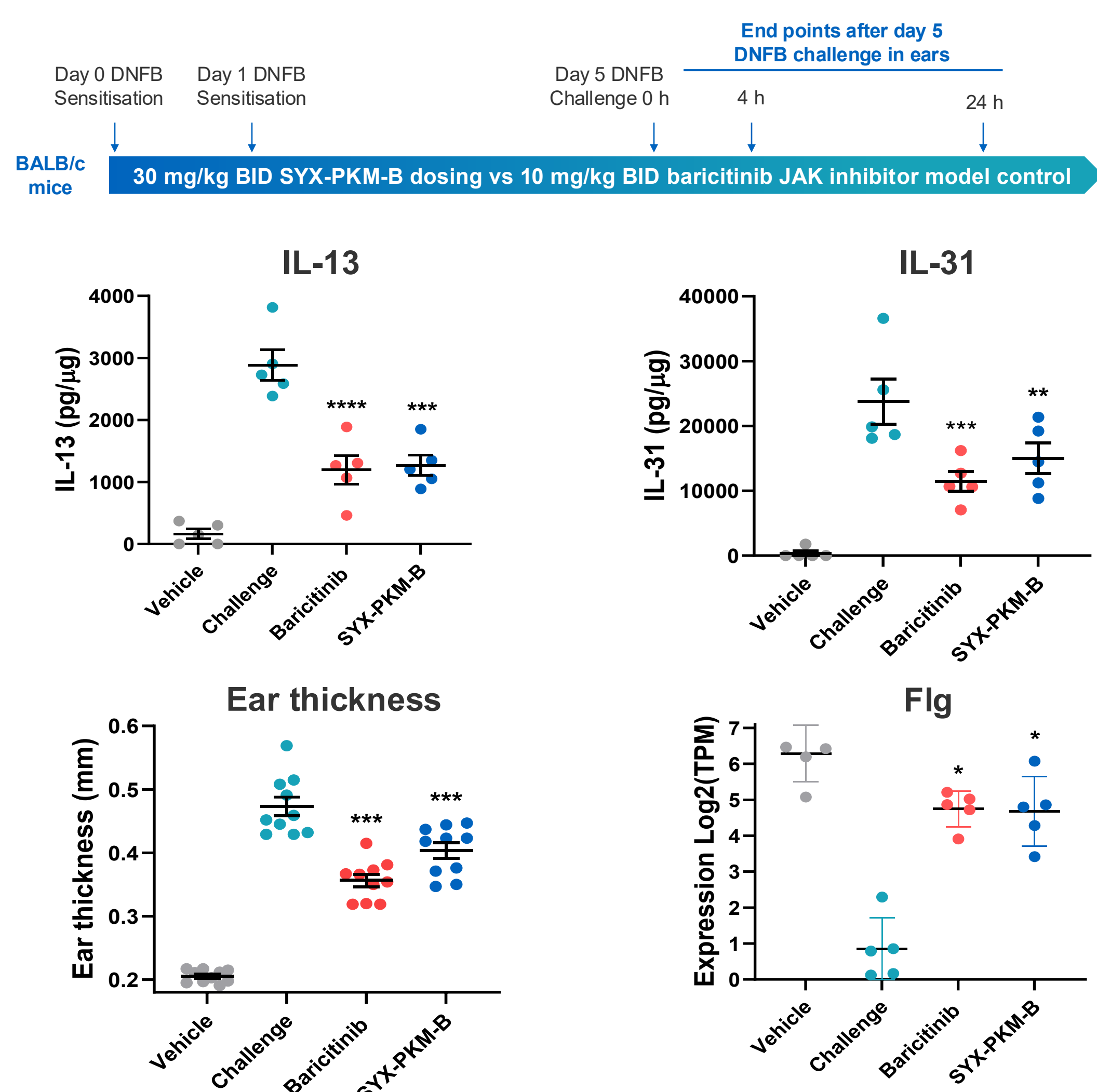
2. Induction of PKM2 in AD lesional tissue



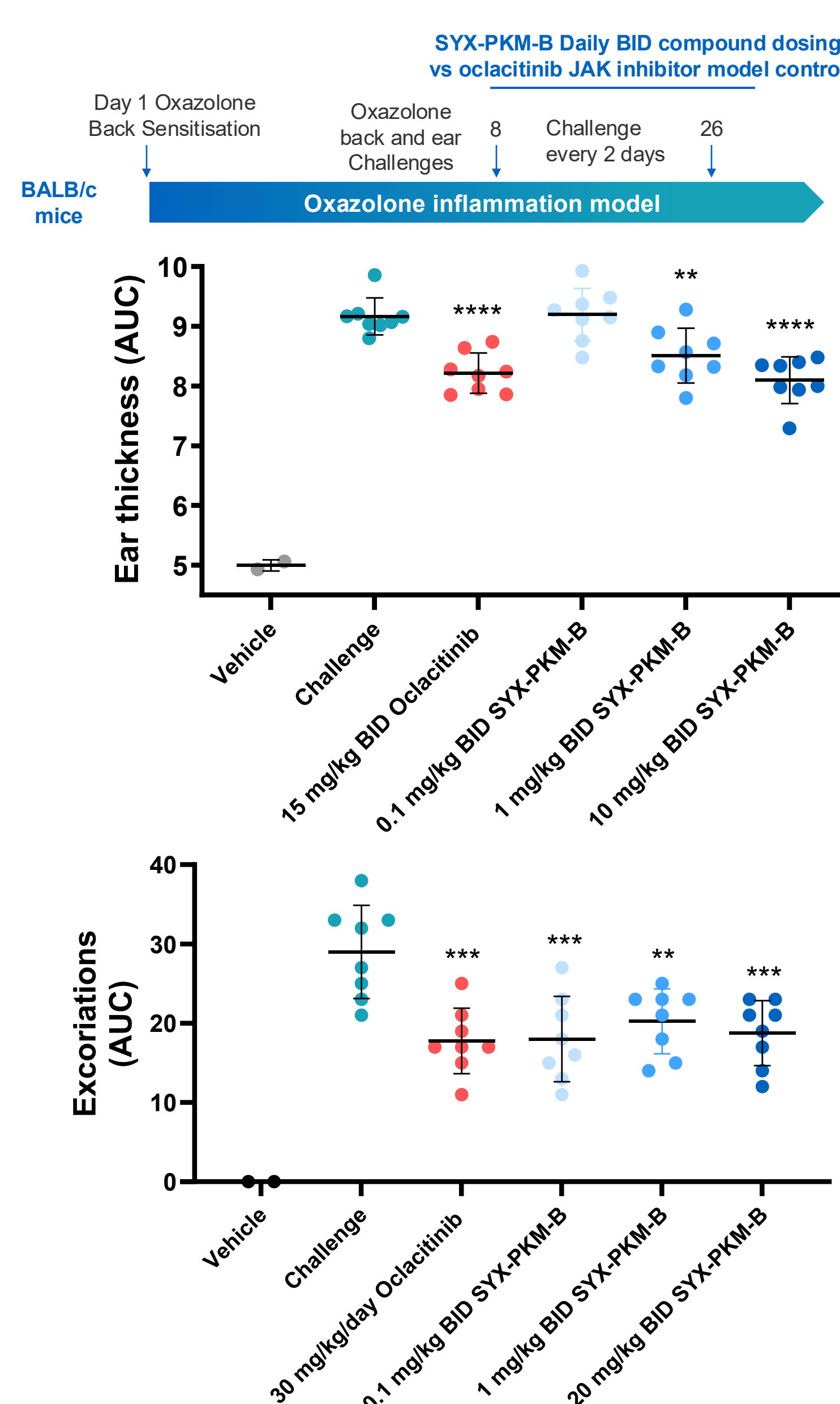
3. PKM2 modulators activate PKM2



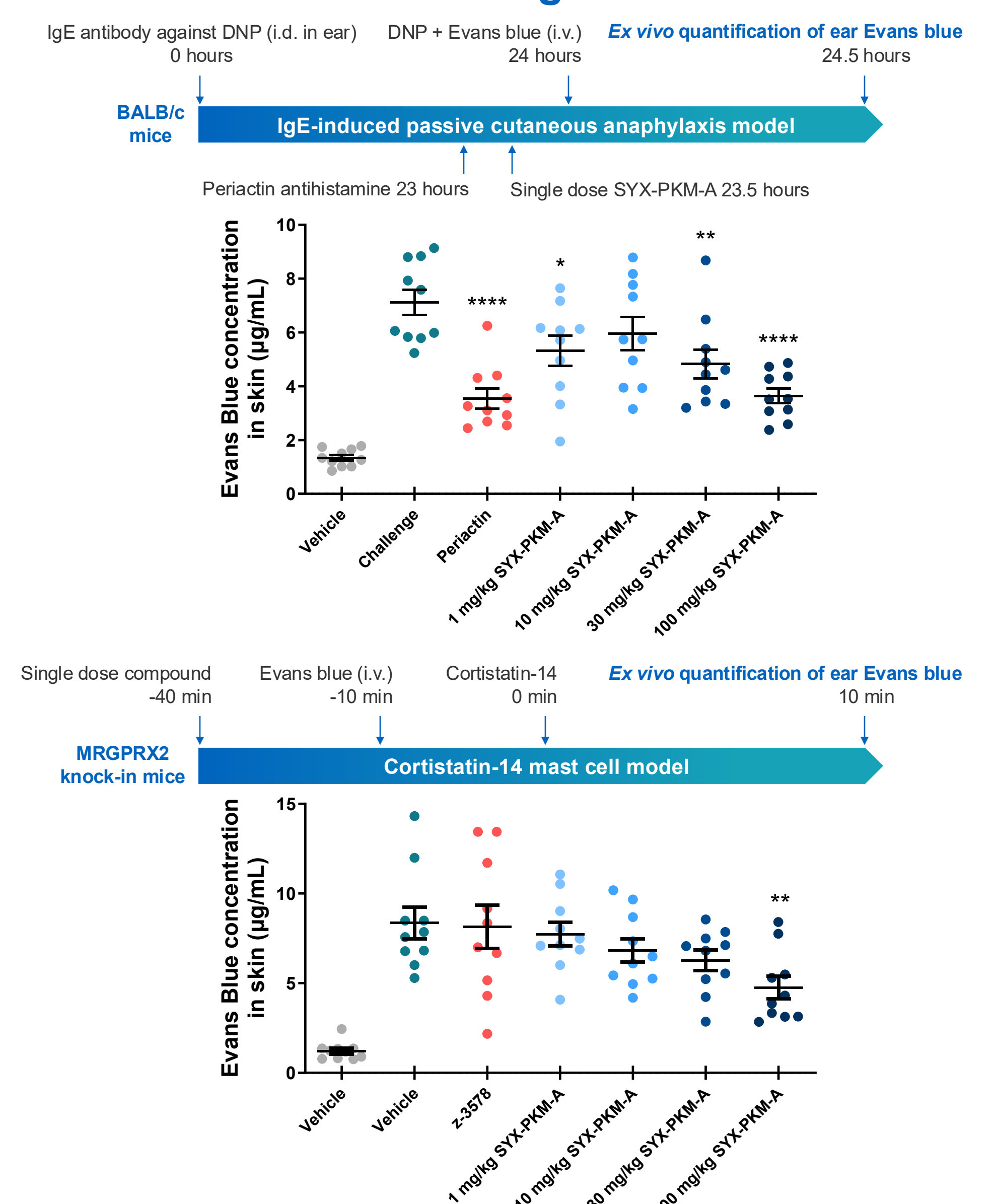
4. PKM2 modulators positively impact AD markers in a DNFB skin inflammation model



5. PKM2 modulation positively impacts skin thickness and excoriations



6. PKM2 modulation inhibits mast cell degranulation



1. E. D. Duca *et al.*, *Allergy*. **79**, 80–92 (2024).
2. D. Mikhaylov *et al.*, *Dermatitis*. **32**, S71–S80 (2021).

Conclusions

PKM2 is overexpressed in lesional AD skin. Novel small molecule PKM2 modulators, developed as a potential AD therapeutic, activate PKM2 in isolated enzyme and cellular assays. PKM2 modulation impacts inflammation, itch and barrier function in several murine models of inflammatory skin diseases. Furthermore, PKM2 modulation decreases mast cell degranulation in IgE-induced and cortistatin-14 induced mast cell models. Taken together, the studies show that PKM2 modulation inhibits several important mechanisms underlying AD pathology. PKM2 modulator, SYX-5219, has recently entered clinical trials in AD (Scan QR code). PKM2 modulation offers an oral, targeted, disease-modifying anti-inflammatory approach, targeting a critical enzyme that regulates cell metabolism. This PKM2 modulator could address the major unmet needs of AD where there are limited treatment options under the current standard of care.

