ABSTRACTS | Epidermal Structure and Barrier Function

253 RNA-seq profiling of tape strips from infants with atopic dermatitis show profound barrier and immune abnormalities

J Kreitinger1, N Wageling1, K Fields2, K Rodan2, J Craw2, T Falla2, C Crane2 and the presence of the selective PAR2 agonist (SLIGKV-NH2) or reverse peptide as control. T J scale clinical trials, where skin biopsies are not possible.

alterations in early AD in infants, and provide a minimally invasive strategy for defining innate immunity (IL1A/B) (FDR (IL13, IL31, IL4R, CCL17), JAK signaling (JAK2/3), Th17 (IL8, IL19, IL36A/G, S100s), and inflammatory genes were shared by lesional and non-lesional skin versus controls, including data for the first time shows that dupilumab is effective in NS patients.

254 AKR1B10 inhibition in keratinocytes as a strategy to improve retinaldehyde efficacy and increase endogenous aTRA

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Retinoic acid (RA) is a potent regulator of numerous physiological processes in the skin and controls keratinocyte proliferation and differentiation. The RA biosynthesis pathway is tightly regulated by enzymes that increase intracellular RA through oxidation of retinoldehyde to RA and decrease intracellular RA through reduction of retinaldehyde (RAL) to retinol (ROL), respectively. Aldo-keto reductase enzymes (AKRs), specifically AKR1B10, is responsible for the reduction of RAL to ROL thereby acting to limit the synthesis of intracellular RA. This makes the selective inhibition of AKR1B10 a highly promising mechanism for increasing endogenous RA. We hypothesized that a select panel of natural fatty acids and synthetic compounds evaluated through molecular docking studies would reduce AKR1B10 activity and increase intracellular aTRA. Using healthy adult keratinocytes, we found that AKR1B10 RNA and protein is significantly upregulated differentiated keratinocytes, and AKR1B10 inhibitors modulate keratinocyte expression of differentiation and proliferation markers. Further studies using molecular docking simulations have identified optimized orientation of AKR1B10 ligands to generate potential adduct structures with increased AKR1B10 binding affinity, and LC/MS was used to measure the concentration of retinoids in keratinocytes following AKR1B10 inhibitor exposure. Together, this in-depth understanding of structural features and bioassay validation enables specific AKR1B10 inhibitors to increase endogenous aTRA.

255 Keratinocytes isolated from dark or light pigmented skin showed different degrees of tight junction impairment after PAR2 activation in-vitro

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Protease activated receptor 2 (PAR2) is a transmembrane receptor with a tethered extracellular amino-terminal small peptide which acts as an activating ligand after cleavage. In the skin, PAR2 has extensively documented effects in promoting Th2-inflammation, skin barrier impairment and pruritus. Increased PAR2 expression was found in epidermal nerve fibers and keratinocytes in Atopic Dermatitis (AD) skin. In this study we aim to investigate the effect of PAR2 on Tight Junction (TJ) function and composition in primary human keratinocytes (PHK) isolated from dark or light pigmented foreskin. PHK were differentiated in high-Ca+2 media in isolated from dark or light pigmented foreskin. PHK were differentiated in high-Ca+2 media in

256 Treatment of Netherton syndrome with dupilumab

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Netherton syndrome (NS) is a rare autosomal-recessive disease that is caused by loss-of-function mutations in the SPINK 5 gene encoding for the serine protease inhibitor lymphoepithelial Kazal type inhibitor (LEKTI). LEKTI opposes the function of several epidermal serine proteases including kallikrein 5 (KLK5), kallikrein 7 (KLK7) and kallikrein 14 (KLK14). This results in an activation of the PAR2-TSLP axis and an increase of other Th2 polarizing mediators including CCL-17 and CCL-22. This presumably spurred a Th2 response consequently leading to increased IgE levels. In NS effective treatment options are missing. In contrast, in atopic dermatitis treatment with dupilumab an antibody directed against the alpha unit of the IL-4 receptor leads to a remarkable success in controlling disease activity which is reflected in decreased IgE levels. Thus, dupilumab represents a worthwhile treatment strategy in NS. Three adult patients with genetically confirmed NS were individually treated with dupilumab 300mg injections every other week for 32 weeks. EASI scores at baseline were 30.0, 29.0 and 18.2. Clinical improvement was observed as early as at week 8 leading to continuously improved EASI scores (w32: -55.82%+/-16.69). In line, IGA scores enhanced in all three patients. DLQI clearly improved with ongoing dupilumab treatment. Serum IgE levels declined steadily (w32: -60.93%+/- 8.57). In contrast, LDH serum levels and blood eosinophil count were unchanged. Further analysis of serum cytokines are underway. Decrease of serum IgE levels clearly correlated with both EASI and DLQI reduction intra- and inter-individually. Similarly, EASI improvement correlated with DLQI reduction. In summary, these data for the first time shows that dupilumab is effective in NS patients.