



LATE BREAKING ABSTRACTS

95 3D Doppler imaging of inflammatory disease including Covid-19

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3D multiplanar ultrasound with Doppler and high resolution probes studied cases of inflammatory disease over 20 years including 18 months of Covid-19 inflammation.

The depth of epidermal and dermal disease was followed to guide treatment including biologics and adverse events were documented by imaging as they occurred. Toxins from heavy metals including uranium were detected and quantified as discrete focal high echoes on the 4D image reconstruction and inflammatory neovascularity was documented with the 3D Doppler histogram technology in cases of dermatomyositis, lupus, scleroderma, psoriasis and rosacea. In rosacea, the depth and density of the sebaceous glands correlated with the erythema and enthesitis of the digits and joint synovitis was associated with nail bed hyperemia in cases of psoriasis. In Covid-19 the vascular hyperemia and presence of microvessel thrombosis in the upper and lower extremities indicated worse clinical prognosis which was verified with point of care lung ultrasound observations and Doppler analysis of pleural based parenchymal pneumonitis. Breast erythematous changes included subdermal cystic components and 3 cases of inflammatory breast cancer were discovered by intradermal lymphedema after unsuccessful conventional therapies.

96 Lebrikizumab allows (interleukin) IL-13 membrane binding and subsequent internalization through IL-13 receptor alpha 2 (R α 2) [IL-13 decoy receptor]

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Lebrikizumab is a novel, monoclonal antibody that selectively targets interleukin (IL)-13 and prevents formation of the IL-13 receptor alpha 1 (R α 1)/IL-4 receptor alpha (R α) heterodimer receptor signaling complex. A previous crystal structure report showed that lebrikizumab does not interfere with IL-13/IL-13 receptor alpha 2 (R α 2) binding. In contrast, other IL-13 antibodies tralokinumab and cendakimab had been reported to inhibit IL-13 binding to both IL-13R α 1 and IL-13R α 2. We wanted to investigate whether lebrikizumab binding to IL-13 interfered with IL-13 binding to IL-13R α 2 and the subsequent internalization. Through competitive binding experiments using surface plasmon resonance, we confirmed that lebrikizumab can bind to the tralokinumab/IL-13 and cendakimab/IL-13 complexes. These data showed that lebrikizumab binds to IL-13 at a different epitope. Next, we confirmed that A375 cells only express IL-13R α 2,



but not IL-13R α 1, making these cells an appropriate model system to examine the IL-13/IL-13R α 2 interaction in the presence of lebrikizumab. Using live-cell confocal imaging, we observed that IL-13 can bind IL-13R α 2 and is internalized into the cells. Importantly, we also observed binding and internalization of the IL-13/lebrikizumab complex, while IL-13/tralokinumab and IL-13/cendakimab complexes do not bind to the receptor and get into the cells. The internalized IL-13/lebrikizumab complex colocalized with a lysosome marker, therefore indicating that it is likely to be degraded in lysosome. In summary, lebrikizumab allows IL-13 to bind and internalize through the IL-13R α 2. This mode of action differentiates it from tralokinumab and cendakimab, since lebrikizumab allows natural endogenous regulation of IL-13 levels through IL-13R α 2 (IL-13 decoy receptor).

97 Skin inflammation in Netherton syndrome: new insights from a viable Spink5 knock-out mouse model

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Netherton syndrome (NS) is a severe autosomal recessive skin disease characterized by a compromised skin barrier, hair shaft defects, chronic skin inflammation and allergy. NS is caused by loss-of-function mutations in the serine peptidase inhibitor Kazal type 5 (SPINK5) gene. Constitutive Spink5 knock-out mice reproduce the NS phenotype, but die within few hours after birth, preventing further study of disease progression. Here we describe the generation of a viable, epidermis-specific Spink5 conditional knock-out (cKO) mouse model, allowing the study of disease progression and immune system abnormalities in NS. We combined RNAseq, immunofluorescence microscopy and flow cytometry to study the skin and immune system phenotypes of Spink5 cKO mice and to compare them to those of NS patients.

Analyses of the skin transcriptome and proteome in Spink5 cKO mice revealed features of acute and chronic skin inflammation. Among the differentially expressed genes and proteins overlapping between Spink5 cKO and NS patient lesion skin, the most enriched molecular function gene ontologies were related to inflammation. This common skin inflammation signature was characterized by up-regulation of IL-36, IL-10, and IL-17 family cytokines and Th2 cell genes. Unlike NS patients, Spink5 cKO mice do not display type I IFN gene signature in the skin.

Inflammatory cell infiltrates in the skin, spleen and lymph nodes of Spink5 cKO mice were mostly represented by neutrophils, IL-17A+ cells and S100A8/9+ cells. Transcriptomic analyses of lymph nodes in Spink5 cKO mice confirmed up-regulation of IL-17 signaling during systemic inflammation and absence of Th9 response. Another feature of systemic inflammation in Spink5 cKO mice was thymic atrophy, which strongly correlated with phenotype severity.

Here we characterize a viable Spink5 knock-out model of NS and demonstrate a significant correlation of its skin transcriptome and proteome profiles to those of NS patients. Our results highlight the importance of immune response for shaping the NS phenotype in both murine models and patients, and provide a basis for exploring future therapies for NS.



98 Increased prevalence of vitamin D deficiency in black patients with Central Centrifugal Cicatricial Alopecia (CCCA)

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Individuals of African descent have increased prevalence of vitamin D deficiency. A recent study has demonstrated that Black patients in the United States with alopecia have greater than six times increased odds of severe vitamin D deficiency compared to white patients. The vitamin D receptor is expressed in the epidermal keratinocytes and the dermal papilla cells of the hair follicle (HF). Vitamin D deficiency can inhibit keratinocyte differentiation and disturb the normal HF cycle. Vitamin D deficiency has been implicated in cicatricial and non-cicatricial forms of alopecia. However, there has been no data published on vitamin D deficiency in the CCCA population. We performed a retrospective chart review of 36 Black patients diagnosed with CCCA presenting to a specialty alopecia clinic. 19 patients had serum vitamin D levels recorded in their medical record at the time of diagnosis. We defined vitamin D deficiency as less than 20 ng/mL. Patients with CCCA had nearly 17 times increased odds of vitamin D deficiency (CI: 2.271-126.9, $p=0.0058$) compared to Black patients in the general population. Prevalence of vitamin D deficiency in our cohort was 95%, compared to 71.9% of Black patients in the general population ($p<0.001$). We demonstrate a significant relationship between vitamin D deficiency and Black patients with CCCA. Future studies should investigate relationships between the severity of vitamin D deficiency and the severity of hair loss in Black CCCA patients. Further work may also examine the effect of vitamin D supplementation on CCCA disease course.

99 The molecular signature of Eosinophilic Cellulitis correlates with the efficacy of baricitinib in a refractory patient

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Eosinophilic cellulitis (EC) is a rare skin disorder characterized by fixed pruritic urticarial plaques and a dermal eosinophilic infiltrate. Pathogenesis is unclear and current paradigm stands for an IL-5 mediated delayed type hypersensitivity. However, numerous patients are resistant to standard corticosteroids, dapsone or cyclosporine treatments.

To better characterize the inflammatory pathways involved in EC, we retrospectively analyzed skin samples from 12 EC patients and 5 healthy controls, using RT-qPCR and phospho-STAT (pSTAT) immunostaining. We next explored the clinical and molecular response in one refractory patient treated with the new JAK1/JAK2 inhibitor, baricitinib.

A significant increase of mRNA transcripts related to specific markers of type 2 inflammation (IL-13 and IL-3R, but not IL-5) and eosinophil recruitment (CCL17, CCL18 and CCL26) was found in lesional skin of EC patients compared to controls. We also observed that almost all EC samples were strongly positive for pSTAT-5 and, at a lesser degree, for pSTAT-1. Comparatively, pSTAT-3 staining was negative. As pSTAT-1 and -5 are classically associated with JAK1/2 activation, we then treated one refractory EC patient with baricitinib at 4mg/day. Strikingly, skin lesions completely resolved in one month. The up-regulation of type 2



inflammation markers, notably IL-13 and IL-3, were also completely normalized in the healed skin following baricitinib treatment.

Our results therefore highlight that a unique type 2 inflammation typifies acute lesions of EC, associated with an IL-13 and IL-3 signature. They also suggest that JAK1/JAK2 inhibition could be a promising strategy to treat refractory patients.

100 Deciphering circulating CLA⁺Tregs in atopic dermatitis patient with scRNAseq reveals disease specific signatures.

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Regulatory T cells (Treg) play an important role in controlling inflammatory disease. Genetic defect on generation or function of Treg induced atopic dermatitis like skin lesion in mice and humans, suggesting its central role in disease pathophysiology. However, limited cell numbers in circulation and difficulties of isolating immune cells from human skin hampers its exploration. Herein, we sorted TCR $\alpha\beta$ +CD4+CD25+CD127^{low}CLA⁺ cells, in which Tregs migrated from skin are enriched, from PBMCs of a total of 10 patients and control and proceed the scRNAseq. Expectedly, Proportions of CLA⁺ Treg from T cell compartment increased in atopic dermatitis. MKI67⁺ proliferating CLA⁺ Treg increased across atopic dermatitis patients suggesting clonal expansions of Tregs to control the inflammation were still active in the chronic phase. Helios negative peripheral Tregs(pTreg) proportions were not increased across the patients compared to healthy control suggesting thymic Treg(tTreg) rather than peripheral converted pTreg plays more important roles in controlling the disease in atopic dermatitis. In summary, scRNAseq CLA⁺ Treg from atopic dermatitis patients unveiled disease specific Tregs in the circulation.

101 Inhibition of tissue resident memory-T cells as a therapy for contact hypersensitivity

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Background: Systemic therapy for eczema targets the immune system during active inflammation. Disease inevitably returns to previously involved but healed skin due to the persistence of tissue resident memory T (Trm) cells responding to autoantigens/allergens. The survival of Trm cells is regulated by IL-7 and IL-15. We present a novel mouse model of recurrent contact hypersensitivity (CHS) and suggest a novel approach to the treatment of inflammatory skin diseases by inhibiting Trm cells thereby establishing long-term disease remission.

Methods: C57BL/6 mice were epicutaneously sensitized on the abdomen with the allergen 2,4-dinitrofluorobenzene (DNFB) (day -5). Mice were initially challenged on the right ear on day 0 with DNFB to create an allergic response, and then re-challenged on days 30 and 60. The ear swelling, as a measure of CHS response, was measured every 12 hours for 96 hours post challenge. The ear skin was harvested 2 days (inflamed skin) and 15 days (healed skin) after each DNFB ear re-challenge (days 32, 45, 62 and 75).



Results: Serial DNFB challenges produced progressively stronger peak CHS responses, with a significant increase at 2- months (2-months vs. 1-month re-challenge; 12.0 vs. 8.8 μ in, n=24, *P<0.05). The total number of Trm cells and the number of IL-15-receptor positive Trm cells significantly increased in healed skin compared to inflamed skin (15-days vs. 2-days post 2-months re-challenge; 67857 vs. 10493 total Trm cells; 45290 vs. 16528 IL-15-receptor Trm cells; n=6, *P<0.05). There were significant increases in total Trm cell number, IL-7- and IL-15-receptor positive Trm cells in skin at 2-months compared to 1-month DNFB re-challenge (67857 vs. 15767 cells; 11360 vs. 3528; 45290 vs. 6710, respectively; n=6, *P<0.05).

Conclusions: Repeat CHS inflammation via serial DNFB challenges lead to accumulation of Trm cells expressing IL-7 and IL-15-receptors in healed skin. We suggest that inhibition of IL-7/IL-15-receptors during disease quiescence to reduce Trm cell numbers, may be a novel strategy to prevent dermatitis recurrence and maintain long-term remission.

102 Dupilumab significantly improves clinical scores in pediatric moderate to severe atopic dermatitis: A real-world, single-center study

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Dupilumab has proven safe and effective in clinical trials of patients with moderate-to-severe atopic dermatitis (AD). However, real-world studies in the pediatric population are lacking. We conducted a chart review from November 2017 to August 2021 of patients ≤ 18 years old treated with dupilumab for AD at Mount Sinai Department of Dermatology. Eighty-nine patients [50 females (56%), 39 males (44%); 42 European American (47%), 14 African American (16%), 15 Asian American (17%), 16 Hispanic/Latin American (18%), and 2 two races (2%)] were included. Subjects' age at treatment initiation ranged from 6 to 18 years old, with a mean age of 12.6 ± 2.9 years. Mean treatment duration was 1.3 ± 0.9 years. The longest treatment course reported in the cohort was 3.8 years. Percent decreases in AD clinical scores between baseline and follow-up visit 2 were 81.3% in BSA, 61.9% in IGA, and 77.9% in EASI. A linear mixed-effects model showed a statistically significant decrease in AD clinical scores between baseline and follow-up visit 1, baseline and follow-up visit 2, and follow-up visits 1 and 2: BSA (P<0.001, P<0.001, P<0.05 respectively), IGA (P<0.001 all comparisons), and EASI (P<0.001 all comparisons). Eleven patients (12%) achieved complete AD clearance following a mean treatment duration of 7.4 ± 6.9 months. Conjunctivitis (n=6) and joint pain (n=2) were the most common adverse events. No serious adverse events were reported. Our results support the safety and utility of dupilumab in pediatric moderate-to-severe AD in a real-world clinical setting.



103 Changes in the molecular profile of lesional skin and blood of patients with generalized pustular psoriasis treated with spesolimab are associated with clinical response

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Generalized pustular psoriasis (GPP) is a rare, chronic inflammatory skin and systemic disease characterized by acute onset of disseminated pustular eruptions. GPP is associated with significant morbidity, and GPP flares can be life-threatening if untreated. The pathogenesis of GPP involves dysregulated interleukin (IL)-36 signaling. Spesolimab, a monoclonal antibody that targets the IL-36 receptor, was efficacious in patients experiencing a GPP flare. In the Effisayil™ 1 study, spesolimab resulted in rapid pustular and skin clearance within 1 week versus placebo in patients experiencing a GPP flare. We identified 5208 gene transcripts that were differentially expressed (2861 decreased, 2347 elevated) in lesional versus non-lesional skin biopsies (adjusted p-value ≤ 0.05 , log₂ fold change ≥ 1) at baseline. These included genes associated with the IL-36 family (IL36A, IL36B, IL36G), neutrophilic recruitment (CXCL1, CXCL6, CXCL8), proinflammatory cytokines (IL6, IL19, IL20), and skin inflammation (DEFB4a, S100A7, S100A8, S100A9). A significant number of genes in lesional skin were modulated 1 week after (324 decreased, 622 increased; adjusted p-value ≤ 0.05 , log₂ fold change ≥ 1) and 7–8 weeks after (1115 decreased, 1425 increased; adjusted p-value ≤ 0.05 , log₂ fold change ≥ 1) a single dose of spesolimab (900 mg intravenously). Patients who achieved the primary endpoint (GPP Physician Global Assessment pustulation subscore of 0 by Week 1) demonstrated significant changes from baseline in differentially expressed genes in lesional skin. Histopathological changes in select biomarkers (NE, K16, beta defensin 2, IL-17C) were observed in lesional versus non-lesional skin pre- versus post-treatment at Week 8. There were also reductions in serum biomarker levels, including IL-17C, IL-20, TGF- α , IL-24, CCL4, CCL19, IL1-RN, and CCL20, which were sustained until Week 12 and correlated with primary endpoint achievement. In summary, the clinical efficacy of spesolimab in patients with a GPP flare in the Effisayil™ 1 study was associated with modulation of key pathogenic pathways in skin and blood, highlighting the importance of inhibiting the IL-36 pathway in GPP treatment.



104 A Novel Scale to Assess Disease Severity in Patients with Alopecia Areata

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Alopecia areata (AA) is common, chronic, autoimmune disease characterized by patchy hair loss on the scalp, face, and body. It is a disease with a wide spectrum of clinical presentations in both children and adults [1]. At present, the categorization of AA (developed in 1902) includes patchy AA, alopecia totalis, alopecia universalis, and alopecia ophiasis. This categorization is suboptimal, as it only vaguely describes the severity of disease unless there is 100% hair loss in the scalp or the whole body. Consequently, the vast majority of AA cases that have 0% to 99% scalp involvement are labeled patchy AA regardless of prognosis, facial/body hair involvement, and treatment response [2]. This paper presents a new proposed scale to describe disease severity in patients with AA. An advisory group of 22 AA clinical experts from the USA collaborated to delineate the clinical assessment of the disease. A modified Delphi process was utilized to determine which factors AA experts assess when considering AA disease severity. 11 factors were assessed via survey, including response to treatment, eyebrow/eyelash involvement, and psychosocial impact of disease. A consensus vote was held to determine the final AA severity statement, with all experts agreeing to adopt the scale. The scale categorizes AA severity first by percentage of scalp involvement. It then defines several qualifiers that can adjust its severity and help to more descriptively categorize each patient with AA. This scale captures key features that AA experts use in clinical practice. It will aid clinicians in appropriately assessing severity in patients with this common disease.

1. You H.R., Kim S.J. Factors associated with severity of alopecia areata. *Ann Dermatol.* 2017.
2. Wambier C.G., King B.A. Rethinking the classification of alopecia areata. *J Am Acad Dermatol.* 2019.

105 Successful treatment of pityriasis rubra pilaris with anti-inflammatory mediterranean diet and low-dose vitamin A

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A 32-year old Caucasian male with a history of irritable bowel syndrome presented to a general dermatology clinic for a two-week history of erythematous plaques and papules characterized by pruritus and scale on the face, chest, abdomen, back, axillae, groin and hands (Figure 1). The patient reported gastrointestinal upset and was later found to have eosinophilia and increased eosinophils in the duodenal lamina propria on EGD. The patient's stool was negative for ova and parasites. Labs revealed hypovitaminosis A and D. A comprehensive serology panel was negative for HIV, syphilis, hepatitis, ANA, anti-centromere, anti-smooth muscle, anti-RNP, anti-Smith, anti-DNA, anti-Sjogren, anti-JO-1, anti-chromatin, anti-ribosomal P, and anti-smRNP. A chest x-ray did not reveal pulmonary masses. Biopsies taken from the left upper and lower back revealed psoriasiform spongiosis with follicular inflammation and



fibrosis, consistent with pityriasis rubra pilaris (PRP). The patient was started on triamcinolone 0.1% cream, over-the-counter vitamin D, vitamin C, and probiotics without improvement 10 days later. At the next visit, the patient underwent holistic medical consultation that included counseling on the anti-inflammatory Mediterranean diet, use of moisturizers, and daily vitamin A (10,000 IU) supplementation. One month later, the patient showed significant improvement, with resolution of his face, chest, and back rash (Figure 2) and relief of skin pain, burning, and pruritus. Vitamin A levels checked at the time were within normal limits. This case highlights PRP-induced eosinophilia and is the first to note the utility of the anti-inflammatory Mediterranean diet and low-dose vitamin A for treatment of PRP.

106 Proliferative Verrucous Leukoplakia Masquerading as Oral Lichen Planus

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Dermatologists encounter patients with white lesions in the mouth which are frequently diagnosed as oral lichen planus (OLP). While erosive OLP may undergo malignant transformation, there are other diagnoses including leukoplakia and proliferative verrucous leukoplakia (PVL), which tend to have higher rates. Patients go undiagnosed and undertreated because demographics differ from traditional oral squamous cell carcinoma, and inconsistencies in published diagnostic criteria. Biopsied lesions may exhibit lichenoid changes, resulting in referral to Dermatology.

A 68-year-old female presented to the dermatology clinic for evaluation of a 7-year history of oral lesions, which had been diagnosed as OLP several years prior. There was no prior use of tobacco products. She applied topical clobetasol gel for years with minimal improvement. She denied pain, dysphagia, ocular symptoms, or involvement of skin or genitals. On exam, she had confluent sheets of white lacy plaques involving the right buccal mucosa and upper gingiva with plaques into the left lower vestibule, sparing the left buccal mucosa. A biopsy of a plaque on the right revealed a strip of mucosa surfaced by markedly orthokeratotic, atrophic stratified squamous epithelium with an abrupt change of adjacent parakeratin to orthokeratin. The hyperorthokeratosis and features of mild dysplasia were consistent with PVL.

Oral PVL has high rates (~50%) of neoplastic transformation, characterized by slowly progressive, white proliferations on the gingiva, buccal mucosa or tongue. PVL first appears as simple hyperkeratosis and evolves over months to years emerging multifocally and recalcitrant to therapies. Lesions do not always exhibit a white, verrucous appearance and may range from smooth to erythematous, nodular or ulcerated. PVL occurs frequently in women in their sixth or seventh decade. There is no association with tobacco or alcohol use, and no validated biomarkers to predict malignant transformation. Initial biopsies are often unremarkable, revealing keratosis of unknown significance or lichenoid changes. Differential diagnoses include OLP which may prompt evaluation by Dermatology.

