***Microbes, Autoimmunity & Cancer***

## Poster Presentations

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**AGAK**

**To trap a pathogen: TH17 cell-mediated extracellular traps release and their role in host defense in acne**

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Extracellular traps have been identified in different cell populations involved in providing immunity to pathogens. IL-17 producing TH17 cells are a key player in various autoimmune diseases but are also crucial for immunity against fungal and bacterial infections Here, to elucidate the antimicrobial machinery of TH17 cells, we studied the response to *Cutibacterium acnes*, a skin commensal that is resistant to IL-26, the only known TH17 secreted protein with direct antimicrobial activity. We generated *C.acnes*-specific antimicrobial TH17 clones (AMTH17) with varying antimicrobial activity against *C.acnes*, which we correlated by RNA-seq to the expression of transcripts encoding proteins that contribute to antimicrobial activity. We validated that AMTH17-mediated killing of *C. acnes* as well as the killing of other bacterial pathogens, was dependent on the secretion of several antimicrobial molecules. We found that AMTH17 cells release T cell extracellular traps (TETs) – fibrous structures composed of DNA decorated with histones that entangle and kill *C. acnes.* Within acne lesions, histone H2B and IL-17 colocalized in CD4+ T cells, in proximity to TETs in the extracellular space. Additionally, our preliminary

data indicate that the same AMTH17 cell may have more than one TET-forming mechanism. Our study identifies a functionally distinct subpopulation of TH17 cells with an ability to form TETs containing secreted antimicrobial proteins that capture and kill bacteria. Insights on the role of the skin microbes in regulating TET formation have broad implications not only in novel probiotic design for acne treatment, but also in the treatment for other chronic inflammatory skin disorders and autoimmune diseases.

**BOOTHBY**

**Early Life Inflammation Primes a Th2-Fibroblast Niche in Skin**

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Inflammation early in life can prime the immune milieu of peripheral tissues, causing lasting changes in immunologic tone that confer disease protection or susceptibility.1,2 The cellular mechanisms that incite changes in immune tone in many nonlymphoid tissues remain poorly understood.3 We find that time-limited neonatal inflammation induced by transient reduction of neonatal regulatory T cells (Tregs) causes a dramatic dysregulation of subcutaneous tissue in murine skin, accompanied by the selective accumulation of Th2 cells within a distinct microanatomic niche. Th2 cells are maintained into adulthood through interactions with a fibroblast population in skin fascia that we refer to as Th2-interacting fascial fibroblasts (TIFFs), which expand in response to Th2 cytokines to form subcutaneous fibrous bands. Activation of the Th2-TIFF niche by neonatal inflammation primes skin for altered reparative responses to wounding. We further identify fibroblasts in human skin expressing the TIFF transcriptional signature and find these cells at high levels in eosinophilic fasciitis, an orphan disease characterized by inflammation and fibrosis of the skin fascia. Taken together, these data define a novel Th2 niche in skin, functionally characterize a disease-associated fibroblast population, and suggest that early life inflammation rewires immune cell-stromal interactions to establish a durable immunological set-point in tissues.

**BOUSBAINE**

**A conserved Bacteroidetes antigen induces anti-inflammatory intestinal T lymphocytes**

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The microbiome contributes critically to the development and maturation of the immune system, especially at barrier sites, including the skin and intestine. Many of the mechanisms driving commensal microbial education of the immune system remain undefined. In the small intestine, the development of regulatory intraepithelial lymphocytes that co-express CD4 and CD8αα homodimers (CD4IELs) depends on the microbiota. However, the identity of the microbial antigens recognized by CD4+ T cells that can differentiate into CD4IELs remains unknown. We identified β-hexosaminidase, a conserved enzyme across commensals of the Bacteroidetes phylum, as a driver of CD4IEL differentiation. In a mouse model of colitis, β-hexosaminidase–specific lymphocytes protected against intestinal inflammation. Thus, T cells of a single specificity can recognize a variety of abundant commensals and elicit a regulatory immune response at the intestinal mucosa. This example of commensal-immune interaction at the intestinal mucosa may offer broader lessons for less well-studied barrier sites, such as the skin. Additionally, this work may have implications for how gut commensals influence skin-gut crosstalk and immune tone.

**BOUTEAU**

**Steady-state Langerhans cells induce Tfh and B cell responses through a type I interferon and IL-6 independent mechanism**

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The danger model of how the immune system works cannot explain why the presentation of foreign but no self-antigens by skin dendritic cells in homeostatic (no inflammation) conditions induces T-cell-dependent humoral immune responses. However, deciphering it could lead to a better understanding of how immune responses are generated and regulated and, ultimately, to developing more efficient immunotherapeutics. Here we used a well-established steady-state antigen targeting model to dissect the mechanism by which Langerhans cells (LCs) support T follicular helper (Tfh) cells and antibody responses. Using bone marrow chimeras, Cre-lox system, and blocking antibodies, we found that IL-6, which is critical in the induction of Tfh cells and antibody responses in inflammatory conditions, played no role in LC-induced adaptive immune responses at steady-state. The type I interferon signaling was also dispensable in this regard. However, our preliminary data support that induction of humoral immune responses by steady-state LCs depends on membrane-bound co-stimulatory molecules, such as ICOS/ICOS-L. Thus, these data suggest that adaptive immune responses against foreign antigens in the absence of inflammation are generated through a distinct mechanism that likely does not involve inflammatory cytokines.

**CHAKRAVARTHY**

**Role of acidic microenvironment in the activation of human CD1a-autoreactive T cells**

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Human epidermal Langerhans cells express high levels of CD1a, a lipid-antigen presenting molecule. The abundance of CD1a in normal healthy skin suggests its role in skin homeostasis and immunity. CD1a-autoreactive T cells are a subset of CD1a-restricted T cells that do not require exogenous lipids for their activation. They are found in the skin and blood of healthy individuals and their numbers are increased in inflammatory skin diseases. The constitutive high expression of CD1a, endogenous lipid antigens, and CD1a-autoreactive T cells in normal skin suggest that under normal conditions, regulatory mechanisms must be in place in order to prevent CD1a-dependent T cell activation. In this study, we focus on the role of extracellular pH in the binding between CD1a-autoreactive T cell receptors (TCRs) and CD1a-lipid complexes. Using fluorescently-labeled CD1a tetramers, we determined that a subset of CD1a-autoreactive T cells binds CD1a-lipid complexes at acidic pH (pH ≤6.5), but not/less at physiological pH (pH 7.4), suggesting a role for decreased extracellular pH in enhancing CD1a-TCR interactions. This may have implications for CD1a-dependent T cell activation in conditions where the tissue environment can be acidic such as early wound healing and malignancies. Ongoing work involves single cell TCR sequencing of pH dependent and independent T cell clones to understand the molecular basis for this acid-dependent binding. This study may have broader implications for the role of pH in TCR-target interactions.

**DENG**

**Staphylococcus aureus activates pruriceptor neurons to drive itch and skin damage in topical infections**

Liwen Deng

Itch is an unpleasant sensation provoking a desire to scratch and is mediated by dorsal root ganglia (DRG) sensory neurons that innervate the skin. While itch accompanies many skin infections, the role of microbes in producing itch is unknown. Also, although the itch-scratch cycle is a known driver of skin barrier damage and inflammation, the role of scratching in promoting pathology during infection has not been studied. Staphylococcus aureus (SA) is an important human skin pathogen and carriage of this bacterium is associated with atopic dermatitis (AD), a condition characterized by chronic itch and flares of inflamed lesions. SA is also a frequent cause of itchy skin infections such as impetigo. We optimized a murine model of epicutaneous infection to measure itch behaviors and show that mice exhibit robust itch and scratching-induced skin damage during SA infection. Using this infection model, we identify V8 protease as the driver of itch. SA lacking V8 protease cannot induce itch and purified V8 is sufficient to elicit scratching. V8 protease directly activates neurons by cleaving the receptor Par1, which is expressed by both mouse and human itch neurons. We find that blocking Par1 pharmacologically or genetically could decrease V8-induced itch. Lastly, targeting Par1 prevented itch during epicutaneous infection with SA and reduced skin damage from scratching. Thus, we identify for the first time a pruritogenic bacterial factor and demonstrate the potential of targeting neuronal Par1 to treat itch and skin damage.

**ELDER**

**Integrative analysis of chromatin accessibility and gene expression implicates Th17 polarization of activated skin-homing T cells in psoriasis**

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To better define the regulatory landscape of skin-directed immunity in psoriasis, we purified mDC and eight memory T-cells subsets (CLAP/CLAN × CD4/CD8 × 0h/24h of CD3/CD28 activation) from 86 psoriasis cases and 67 controls. CD3/CD28 activation was performed on CD1c- cells, thereby removing mDCs but retaining CD14+ monocytes. Differentially expressed genes (DEGs) and differentially accessible regions (DARs) were identified using DESeq2 (FDR < 0.05 and |log2 FC| ≥ 0.585). Activation-related DEGs featured dramatic up-regulation of Th17-relevant cytokines (*IL17A, IL17F*, *IL22*, and *CCL22)*, along with similar up-regulation of the Th1 signature transcript *IFNG*. Stratified analysis showed that *IL17A, IL17F*, *IL22*, and *CCL22* were strongly upregulated in CLAP vs. CLAN from CD3/CD28-activated cells (*IL17A* 4.4-fold, padj = 3.4 x 10-55; *IL17F* 3.9-fold, 4.9 x 10-27; *IL22* 2.9-fold, 2.0 x 10-19; *CCL22* 12.1-fold, 1.6 x 10-140), with a corresponding induction of IL-17A and IL-22 proteins by flow cytometry. In contrast, *IFNG* was not increased in CLAP vs. CLAN, regardless of activation. *IL17A* and *IL17F* were overexpressed in activated T-cells from psoriasis cases vs. controls (each 1.9-fold, padj = 4.7 x 10-4). These results confirm the previously-reported monocyte requirement for Th17 expansion and identify a psoriasis-relevant nexus between skin-homing, T-cell activation, and Th17 expansion.

**GIACOMASSI**

**Epithelial activation of TLR7 promotes emergency myelopoiesis and curbs lung viral infections**

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Skin is the largest barrier site in the body and is targeted as an entry point by a number of pathogens, including single-stranded RNA viruses that are sensed by TLR7. While toll-like receptors (TLR) play a crucial role in local immune responses, the effect of TLRs activation at the epithelial barrier on the haematopoietic system and the subsequent innate immune response in other organs is unclear. We demonstrated that persistent TLR7 stimulation at the epithelial barrier (skin and gut), triggers a potent ‘emergency’ myeloid response in mouse. The monocytes egressing from the bone-marrow (BM) have an immature Ly6c-high phenotype and differentiates into Ly6C-low monocytes and tissue macrophages in multiple organs. The process is unique to TLR7 activation, and occurs independently from the canonical CCR2 and CX3CR1. Of note, these emergency monocytes displayed an impaired cytokine response to TLR7 re-stimulation, and also curbed respiratory infections by RSV and influenza virus. This study elucidates a novel pathway of emergency myelopoiesis triggered by the cutaneous activation of TLR7, recapitulating the events likely to occur in response to the encounter of single-stranded RNA viruses such as arboviruses and coronaviruses at barrier sites.

**GULATI**

**Th2 blockade with dupilumab plays a potentially tumor-suppressive role in multiple myeloma patients**

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Immunomodulatory drugs such as lenalidomide are key components of multiple myeloma (MM) therapy. However, they are frequently associated with skin toxicities that resemble atopic dermatitis, the archetypal Th2-driven disease. Dupilumab, a monoclonal antibody that specifically inhibits Th2 immunity, is a first-line treatment for atopic dermatitis, and has successfully been employed off-label to treat lenalidomide skin toxicities. The prototypic Th2 cytokines, IL-4 and IL-13, have documented roles in carcinogenesis and tumor immunosurveillance. Thus, to assess the impact of dupilumab-induced blockade of these cytokines on the underlying malignancy in MM patients, we examined MM blood markers (free kappa light chains) in three patients treated with dupilumab for lenalidomide-associated skin toxicities. All patients’ skin toxicities improved with dupilumab. In terms of MM blood markers, one patient remained stable for 19 months while on dupilumab alone and, shortly after discontinuing this agent, rapid disease progression was observed. The second patient remained in remission with dupilumab treatment for 15 months, the latter 12 of which were without concurrent maintenance therapy. The third patient was initiated on dupilumab while receiving induction therapy for MM and, with both treatments simultaneously, achieved normalization of MM blood markers. The potential tumor-suppressive role of Th2 blockade warrants further study.

**HERBST**

**Intracellular Monitoring by Dendritic Cells – a New Way to Stay Informed – From Simple Scavenger to Active Gatherer**

Christopher Herbst

The ability of dendritic cells (DCs) to acquire antigen from their environment is critical for the induction of an adaptive immune response and the maintenance of tolerance. Despite its importance, it is tacitly assumed that DCs acquire antigen by scavenging extracellular material via endocytosis, phagocytosis, and macropinocytosis. Here, using labeled RNA and time lapse imaging, we observe DCs siphoning material directly from live neighboring keratinocytes. This contact dependent mechanism of material uptake – which we term intracellular monitoring – accounts for a large percentage of RNA transferred to DCs, and cannot be blocked by inhibitors of known antigen uptake processes. It is dependent on extracellular calcium, and can be inhibited by proteolytic degradation of membrane proteins. It is exclusive to DCs, as other cell types do not efficiently siphon RNA from neighboring cells, and common among most DCs subsets tested. Langerhans cells with a conditional gene deletion can successfully overcome their deficiency by siphoning RNA and protein from their neighbors. Such behavior reframes our understanding of DCs from mere scavengers to highly informed supervisors with extensive access to neighboring cell cytosol. Intracellular monitoring may therefore play important roles in the maintenance of tolerance, defense against infection, and detection of cancerous cells.

**KASHEM**

**Development of azathioprine associated alopecia areata in a patient with NUDT15 polymorphism**

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Fifteen-year-old previously healthy patient was diagnosed with new-onset autoimmune hepatitis. She was started on azathioprine after an unremarkable thiopurine methyltransferase (TPMT) screening. Three weeks after initiation of azathioprine, she was admitted with neutropenic fever, cutaneous herpes virus infection and mucocutaneous candidiasis. Her azathioprine was discontinued. She further presented to dermatology clinic with diffuse non scarring hair loss of the scalp and eyebrows. A scalp punch biopsy was characteristically diagnostic of alopecia areata. Given the constellation of autoimmunity and localized cutaneous infections, she was screened for autoimmune polyendocrinopathy and candidiasis but tested negative for *AIRE* mutation and no malignancy was detected by imaging. Patient’s serum was negative for anti-cytokine autoantibodies. Further TPMT testing and drug metabolite testing was negative. Patient’s hair loss resolved without any interventions, and she did not have any further skin complications in subsequent years of follow up. Given reports of severe leukopenia secondary to azathioprine and mercaptopurine being associated with *NUDT15* R139C T/T homozygous variants in numerous GWAS studies, patient was screened variation of the *NUDT15* gene. Homozygous T/T polymorphism of the *NUDT15* R139C variant was confirmed by full length PCR. Review of case studies was performed and suggested that nearly 100% of *NUTD15* R139C T/T variant patients on thiopurine therapy present with severe but transient alopecia suggestive of alopecia areata. Conversely, nearly 100% of the patients that are on thiopurine therapy that presented with early severe alopecia was found to have *NUDT15* R139C T/T variation. Analysis of population wide genome registry demonstrated *NUDT15* R139C T/\* allele frequency to be 10-30% amongst Hispanic and Asian ancestral populations but <2% of patients of African and European ancestry. Review of clinical trials databases showed underrepresentation of American ethnic minority populations in clinical trials involving azathioprine and mercaptopurine demonstrating the underpowered nature of clinical studies in capturing pharmacogenomic response differences to thiopurines by race. Mouse studies are underway to uncover the mechanistic underpinnings of azathioprine associated alopecia in patients with *NUDT15* R139C polymorphisms.

**KIM**

**A look into the skin microbiota in basal cell carcinoma**

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**Background:** Skin cancer, which encompasses melanoma, and non-melanoma skin cancer (NMSC) represents the most common form of malignancy in Caucasians and its global burden continues to rise. The pathogenesis of skin cancer is multifactorial, and while there are well-characterized environmental risk factors such as ultraviolet (UV) radiation, many remain undetermined.

**Objectives:** We aimed to identify the microbial composition and characteristics of basal cell carcinoma (BCC).

**Methods:** Patients (n=15) with BCC were included. Biopsy samples were obtained from BCC lesions and from healthy-looking contralateral skin. The extracted DNA from both lesional and nonlesional skin was analyzed using the BLAST + Search and NCBI 16S database. To determine whether groups of samples and significantly different from one another, analysis of similarity (ANOSIM) was conducted with 999 permutations. Paired t-test or paired Wilcoxon signed rank tests were conducted to find out which taxon showed a significant difference between the lesion and control regions at the genus, and species level. Similarly, paired Wilcoxon signed-rank tests were used to confirm the difference in alpha diversity between the two groups.

**Results:** We found significant difference in skin microbial composition between the sample types (BCC vs healthy-appearing skin) with a decrease in the genus Cutibacterium (p=0.0015) and increase in the genus Finegoldia (p=0.021). In the species level, there was a decrease in the relative abundance of Cutibacterium acnes (p=0.002) and an increase in Staphylococcus aureus (p=0.036) and Staphylococcus simulans (p=0.037) in BCC lesions. We observed no significant difference in alpha diversity between the groups.

**Conclusion:** Dysbiosis of the skin microbiota was observed in BCC lesions. Results provide promising information for further studies on the local skin microbiome involvement in skin cancer and may support the development of new therapeutic/ preventive strategies.

**MCCOY**

**Estimated Cost-efficacy of Biologics Compared with Narrow-Band Ultra-Violet B Light for the Treatment of Moderate to Severe Psoriasis and Atopic Dermatitis**

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**Conflicts of Interest:** Raja Sivamani is a scientific advisor for LearnHealth, Arbonne, and Codex Beauty and a Consultant/Honoraria for Burt’s Bees, Novozymes, Nutrafol, Incyte, Fotana, Abbvie, Leo, Galderma, UCB, Sun, and Regeneron Pharmaceuticals**.** The other authors report no conflicts of interest.

**Background:** Biologics are highly efficacious treatments for moderate to severe psoriasis and atopic dermatitis but there are no cost analyses comparing their efficacies in relation to cost or to the use of narrowband UVB phototherapy (NB-UVB).

Objective: We sought to estimate the cost-efficacy of all biologics and NB-UVB treatments that have been approved by the US Food and Drug Administration (FDA) for the treatment of PSO and AD.

**Methods:** A systematic review of biologics approved by the FDA for the treatment of psoriasis was performed with a primary efficacy endpoint of a 75% reduction in the Psoriasis Area and Severity Index Score (PASI 75). An additional review of biologics approved by the FDA for the treatment of atopic dermatitis was performed with a primary endpoint of a 75% reduction in Eczema Area and Severity Index score (EASI 75). Medication cost was referenced by wholesale acquisition cost (WAC). Total expenses were standardized by calculating the cost per month of treatment to achieve PASI 75 or EASI 75.

**Results:** NB-UVB ($217.00 to $1,714.00) had the lowest monthly cost to achieve a PASI 75. The adjusted monthly cost per month of treatment to achieve PASI 75, for the remaining therapies, arranged in descending adjusted monthly cost included tildrakizumab, ustekinumab, ixekizumab, secukinumab, etanercept, certolizumab, risankizumab, adalimumab, and NB-UVB. Dupilumab had a monthly cost per month ranging from $6199.00 to $6405.55 per EASI 75 for the treatment of AD. Tralokinumab’s adjusted cost per EASI 75 ranged from $3488.31 to $3986.64.

**Limitations:** Laboratory fees, office visit fees, drug rebates, and incentives, potential adverse effects, comorbidity risk reduction, ambassador programs, combination therapies, and open-label extension trials were excluded.

**Conclusion:** Our study provided useful cost-efficacy data that can impact psoriasis and atopic dermatitis treatment selection. While the biologics have shifted the landscape of psoriasis therapy, NB-UVB remains a cost-efficacious therapy for the treatment of PSO.

**MORTLOCK**

**Cytokine Profiling of Ichthyosis with Confetti**

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Ichthyosis with confetti (IWC) is a rare autosomal-dominant genetic skin condition caused by mutations which affect the proteins keratin 1 or 10. Patients with IWC have severe red, scaly skin and develop “confetti spots” of genetically reverted, histologically normal-appearing skin which grow in number and size over time. Past work on other orphan forms of ichthyosis has demonstrated increased expression of IL-17 and TNFa target genes in the skin and Th17/22 skewing in the blood, pointing to an IL-23/IL-17/IL-22 immunological signature resembling that of psoriasis. We aimed to determine whether IWC shares this immunological signature with other forms of ichthyosis by quantifying cytokine levels in IWC patient skin using RNA in situ hybridization. We also used an inducible Cre model to turn on KRT10 mutation in mice and profiled skin at multiple time points of genetic induction to dissect the role of inflammation in the pathogenesis of IWC. We found increased production of specific innate cytokines by differentiated keratinocytes in the affected skin of IWC patients. Our results may inform choice of biologic therapy in patients with this severe skin condition.

**NELSON**

**The War On MelanomaTM: *Melanoma Stands Out*TM Campaign**

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It is currently unknown whether public health campaigns regarding self-skin exams effect melanoma morbidity and mortality outcomes. The *Melanoma Stands Out*TM media campaign is a state-wide educational campaign designed as part of the wider *War on MelanomaTM* to test the hypothesis that education can improve public melanoma-specific knowledge and behaviors, and ultimately, lower melanoma mortality and stage of disease at diagnosis.

Our four-front campaign targeted the lay population, skin aware licensed professionals (e.g., cosmetology, massage therapy, etc.), primary care providers, and melanoma experts in Oregon. Lay population outreach involved a mass media ad campaign which delivered a total of 41.8 million impressions. An educational curriculum was implemented at 83 high schools reaching 11,824 students. An educational toolkit with pre- and post-education assessments was developed and offered to over 40,0000 licensed skin aware professionals. A separate educational toolkit given to 12,000 primary care providers offered a tailored education module and additional resources. Melanoma experts received 355 e-consults through the SKLIP teledermoscopy patient loaner program, resulting in 20 malignancies diagnosed.

*Melanoma Stands OutTM* was part of an expansive melanoma education campaign. Future reports will include results from our population-based survey and SEER-Medicaid data to estimate the effect on melanoma morbidity and mortality.

**OYA**

**Eribulin mesylate exerts antitumor effects via CD103**

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Eribulin mesylate (ERB) induces cell cycle arrest by binding to microtubules and inhibit tumor growth. Although ERB has also been speculated to increase immune response to the tumor, the precise mechanism is still unclear. In our study, ERB suppressed the tumor growth of MC38 in wild-type mice, whereas ERB failed to inhibit the tumor growth in Rag1-deficient mice. Moreover, depletion of either CD4+ T cells or CD8+ T cells abrogated ERB-induced antitumor effect, indicating that T cells play an important role in the ERB-induced antitumor effect. Moreover, ERB treatment increased number of tumor infiltrating lymphocytes (TILs), and expression of activation markers (CD38 and CD69), immune checkpoint molecules (LAG3, TIGIT and Tim3) and cytotoxic molecules (granzyme B and perforin) in TILs. Consistent with previous reports, ERB upregulated E-cadherin expression in MC38 both *in vitro* and *in vivo*. E-cadherin is a ligand of CD103, and binding of E-cadherin with CD103 results in activation of CD103+ T cells. ERB increased proportion of CD103+ cells in both CD4+ TILs and CD8+ TILs. ERB-induced anti-tumor effects were abrogated in CD103-deficient mice. Collectively, these results suggest that ERB exerts antitumor effects by upregulation of E-cadherin expression in tumor cells and subsequent activation of CD103+ TILs.

**PENG**

**Experimental and clinical evidence suggests that S100A7 inhibits melanoma development**

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Melanoma, the most serious skin cancer, continues to cause severe burden worldwide. The limited effective treatment options, particularly toward metastatic melanoma prompted us to identify novel molecules for either diagnostic/prognostic or therapeutic purpose. S100 calcium binding protein A7 (S100A7) is known to maintain calcium metabolism, cell proliferation, differentiation and apoptosis, production of reactive oxygen species and cytokines, and improvement of skin barrier function. However, the role of S100A7 in melanoma progression has not been explored sufficiently. Our analysis using data from The Cancer Genome Atlas Skin Cutaneous Melanoma (TCGA SKCM) dataset and Genotype-Tissue Expression (GTEx) project showed remarkable lower levels of S100A7 in SKCM tissues compared to normal skin tissues. In addition, SKCM cases with S100A7 alteration showed worse overall survival (OS) and poor disease-free survival (DFS) than patients without altered S100A7. Moreover, S100A7 expression negatively correlated with the infiltration of CD8+ T-cell in SKCM. Importantly, S100A7 addition suppressed cell growth, migration, and invasion of human skin melanoma cell line. Furthermore, the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis suggested that “glycosaminoglycan degradation” and “lysosome” might be involved in anti-tumorigenic properties of S100A7. Taken together, our study provides evidence of the anti-tumorigenic role of S100A7 in melanoma development and suggests this molecule as a compelling therapeutic target and biomarker for melanoma treatment.

**QIN**

**Pre-exposure to the mRNA-LNP platform inhibit adaptive immune responses and alters innate immune fitness in an inheritable fashion**

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The mRNA-LNP-based SARS-CoV-2 vaccine is highly inflammatory, and its synthetic ionizable lipid component responsible for the induction of inflammation has a long *in vivo* half-life. Since chronic inflammation can lead to immune exhaustion and non-responsiveness, we sought to determine the effects of pre-exposure to the mRNA-LNP on adaptive immune responses and innate immune fitness. We found that pre-exposure to mRNA-LNPs or LNP alone led to long-term inhibition of the adaptive immune responses, which could be overcome using standard adjuvants. On the other hand, we report that after pre-exposure to mRNA-LNPs, the resistance of mice to heterologous infections with influenza virus increased while *Candida albicans* decreased. Interestingly, mice pre-exposed to the mRNA-LNP platform can pass down the acquired immune traits to their offspring, providing better protection against influenza. In summary, the mRNA-LNP vaccine platform induces long-term unexpected immunological changes affecting both humoral immune responses and heterologous protection against infections. In the light of the growing list of severe side effects reported with this novel and uncharacterized platform and its subpar performance in preventing infections and virus spread, our studies highlight the need for more research to determine this platform's true impact on human health.

**RICARDO-GONZALEZ**

**Innate type 2 immunity controls hair follicle commensalism by *Demodex* mites**

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*Demodex* mites are obligate commensal parasites of hair follicles (HF) in mammals. Normally asymptomatic, inflammatory outgrowth of mites can accompany malnutrition, immune dysfunction and aging, but mechanisms restricting *Demodex* outgrowth and pathogenesis are not defined. Here, we show that control of mite HF colonization in mice requires ILC2s, IL-13, and its receptor IL-4Ra/IL-13Ra1. Epithelial HF-associated ILC2s elaborate IL-13 that attenuates HF and epithelial cell proliferation at anagen onset; in their absence, *Demodex* colonization leads to increased epithelial proliferation and replacement of gene programs for repair by aberrant inflammatory programs leading to loss of barrier function and premature HF exhaustion. Humans with rhinophymatous acne rosacea, a nasal inflammatory condition associated with a high burden of *Demodex*, had increased HF inflammatory cells with decreased type 2 cytokines, consistent with the inverse relationship seen in mice. Our studies uncover a key role for skin ILC2s and IL-13, which comprise an immune checkpoint that sustains cutaneous integrity and restricts pathologic infestation by colonizing HF mites. **Keywords:** Type 2 immunity, ILC2, innate immunity, *Demodex* mites, tissue immunity, IL-13, hair follicle stem cell, skin homeostasis, barrier function, rhinophyma

**SEVERN**

***Staphylococcus capitis* strain level diversity impacts colonization in patients with ichthyosis**

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Healthy skin is colonized by many species of Coagulase Negative Staphylococci (CoNS) that directly interact with the host. Most often, CoNS colonization is beneficial and establishes immunological tolerance, promotes tissue development, and excludes pathogens from skin. However, the vast strain level diversity within and between CoNS is increasingly appreciated as a significant factor in balancing skin homeostasis or disease. Many CoNS strains retain capacity for virulence and interspecies genetic transfer depending on environmental and host factors. It is evident from metagenomic analyses that the composition of staphylococci changes over time at the species and strain level in patients with certain skin disorders. We identified that the staphylococcal community in patients with ichthyosis, a group of keratinization disorders, profoundly shifts to favor inhabitation by the CoNS *S. capitis* compared to healthy controls. We hypothesize that strain level variation in the genetic and metabolic repertoire of *S. capitis* allows for niche specialization and expansion compared to other staphylococci. Current investigations include large scale genetic comparisons between *S. capitis* isolates from healthy and diseased skin to determine the distribution of core and accessory genes. Future work will include mechanistic assessment of unique *S. capitis* factors required for expansion and colonization of ichthyotic skin.

**SEZIN**

**Investigating the role of the gut microbiome in alopecia areata**

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Alopecia Areata (AA) is a highly prevalent autoimmune skin disease leading to hair loss in affected individuals, in which both genetic and environmental factors likely play a role. Associations between changes in the microbiome composition and many autoimmune and inflammatory diseases have been reported, however, a characterization of the role of gut microbiota in the development of AA has not been undertaken. To investigate the role of the gut microbiota to AA development *in vivo*, we depleted the gut microbiome in the C3H/HeJ mouse model of AA with antibiotics and found that antibiotic-treated mice were protected from AA. Additionally, using 16S rRNA gene sequencing (16SrRNA Seq) and untargeted metabolomics we found that AA-affected mice show overrepresentation of a single species, *Ligilactobacillus murinus (L. murinus)* as well as its metabolites lactic acid and succinic acid in the gut*.* Using *L. murinus* specific primers, we further validated our 16S rRNA Seq findings and showed that overrepresentation of *L. murinus* preceded development of clinical signs of AA, suggesting that *L. murinus* is associated with development of AA in C3H/HeJ mice. Examining the effects of microbiome on T cell composition, we uncovered that compared to untreated mice, the gut microbiota-depleted mice had decreased levels of infiltrating CD8+ T cells in the skin and a decreased abundance of effector NKG2D+ CD8+ T cells in skin draining lymph nodes (SDLNs). Effector NKG2D+ CD8+ T cells were previously shown to be required and sufficient to induce AA, suggesting that gut microbiome suppressed disease by modulating the generation of effector memory responses in SDLNs. Consistent with these findings depletion of *L. murinus* following exposure of C3H/HeJ mice to high-salt diet significantly attenuated development of AA. In contrast, monoassociation of antibiotic-depleted mice with *L. murinus* induced more aggravated disease.To establish the relevance of these observations to human AA, we performed shotgun metagenomics and compared gut microbiome composition in stool samples between AA patients and healthy controls (HCs). We discovered a striking gut dysbiosis in AA patients compared to HCs and identified species of the *Lachnospiraceae* and *Bacteroidaceae* to be overrepresented in AA. Altogether these findings suggest that gut microbiome dysbiosis contributes to the pathogenesis of AA and offer important implications for the treatment of this disease.

**SUBUDHI**

**Deciphering the Role of Epithelial HIF1**⍺ **in Inflammatory Disease**

Ipsita Subudhi

Psoriasis (PsO) is a debilitating inflammatory skin disease that manifests with demarcated scaly patches or plaques driven by unchecked immune responses and epithelial hyperplasia. Type 17 proinflammatory cytokines, such as interleukin (IL)-23 and IL-17, signal into epithelial cells to drive epidermal pathology in PsO. Understanding the pathological programs intrinsic to PsO epithelium could lead to therapeutic alternatives that target localized pathology with minimal adverse effects. Our lab has identified the transcription factor hypoxia inducible factor 1⍺ (HIF1⍺) as a novel transcriptional effector of IL-17A in epithelial tissue repair. Yet, the role of this transcription factor in type 17 pathologies such as PsO and its specific transcriptional targets are poorly understood. We find that epidermal HIF1⍺ is robustly activated and upregulated in human and mouse PsO lesions and correlates with epidermal pathology and T cell-mediated inflammation. Spatial transcriptomics analysis revealed that HIF1⍺ is expressed by suprabasal epidermis containing differentiated epithelial cells, and its expression coincides with expression of IL-17receptorC (IL-17RC). Accordingly, IL-17ReceptorA (IL-17RA) knockout mice had both diminished epidermal pathology and HIF1⍺ expression. Topical inhibition or epithelial-specific knockdown of HIF1⍺ abrogated epidermal and immune pathology. We are now examining the transcriptional targets of inflammatory HIF1⍺ by integrating CUT&RUN sequencing with bulk RNA-sequencing to test their specific contributions toward disease pathology. Altogether, these studies reveal a role for inflammatory HIF1⍺ in PsO that can be leveraged to treat hyperproliferative conditions underwritten by Type 17 inflammation.

**VAN STRAALEN**

**Hippo pathway drives excessive fibrosis in Hidradenitis Suppurativa**

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Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease characterized by a massive immune cell infiltrate and extensive fibrosis. We aimed to elucidate the role of fibroblasts in HS pathophysiology through scRNA-sequencing of chronic, lesional and healthy control skin samples (both n=8).

Fibroblast subclustering revealed 6 subsets of which the *SFRP4+* and *CXCL13+* subsets were specifically derived from HS samples. The *SFRP4+* subset was identified as myofibroblasts displaying prominent pro-fibrotic characteristics. Activation of this subset was found to be driven by key HS-associated cytokines (IFNγ, IL-1β, and TNF). Analysis of the expression of transcription factors within the *SFRP4+* subset identified several upregulated components of the Hippo pathway. To determine the functional relevance of the Hippo pathway, primary dermal fibroblasts were stimulated with TRULI (promoting the Hippo pathway) and verteporfin (inhibiting). TRULI treatment led to a significant increase in pro-fibrotic markers in HS fibroblasts (*ACTA2* and *COL1A1*) on mRNA and protein level, and enhanced proliferation and gel contraction. Verteporfin treatment downregulated pro-fibrotic markers, proliferation, migration, and gel contraction.

Overall, these results identify a central role for the Hippo pathway in myofibroblast activation in HS and provide pre-clinical evidence that modulation of this pathway can reverse the pro-fibrotic phenotypes of HS myofibroblasts.

**WHITLEY**

**Local IL-23 is required for proliferation and retention of skin-resident memory Th17 cells**

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The cytokine IL-23 is critical for development and maintenance of autoimmune inflammation in nonlymphoid tissues, however the mechanism through which IL-23 supports tissue-specific immunity remains unclear. In mice, we found that circulating memory T cells were dispensable for anamnestic protection from *C. albicans* skin infection, and tissue resident memory (TRM) cell-mediated protection from *C. albicans* reinfection required IL-23. Administration of anti-IL-23R antibody to mice following resolution of primary *C. albicans* infection resulted in loss of CD69+ CD103+ tissue resident Th17 (TRM17) cells from skin and clinical anti-IL-23 therapy depleted TRM17 from skin of psoriasis patients. IL-23 receptor blockade impaired TRM17 cell proliferation but did not impact apoptosis susceptibility or tissue egress. CD301b+ dermal dendritic cell (dDC)-produced IL-23 was required for TRM17 maintenance in skin after *C. albicans* infection, and CD301b+ dDCs were necessary for TRM17 expansion during the development of imiquimod dermatitis. This study demonstrates that locally produced IL-23 promotes *in situ* proliferation of cutaneous TRM17 to support their longevity and function and provides mechanistic insight into the durable efficacy of IL-23 blockade in the treatment of psoriasis.

**YANG**

**Transcriptional profiling of colonization response of 3D human skin organoids to genetically diverse staphylococcal strains**

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The skin microbiome is increasingly recognized as important for skin health. *Staphylococcus* species (e.g., *epidermidis, haemolyticus, capitis, hominis,* and others), are ubiquitous colonizers of human skin and modulate cutaneous immunity, skin barrier, and microbial community homeostasis. However, such skin-microbe interactions—whether beneficial or pro-disease—can be specific to species, also subspecies, or strain-level. Here, we used 3D human skin organoids (reconstructed human epidermis, RHE) to investigate effects of genetically diverse staphylococcal strains’ colonization on transcription in host epithelium. Network analyses of RNA-seq data of RHE colonized with one of 10 strains each of *S. aureus*, *haemolyticus*, or *lugdunensis* vs. water (vehicle control) showed species-driven clusters and strain differences, vis a vis global transcriptional response. Targeted analyses, examining gene subsets involved in skin innate immune function (e.g., antimicrobial peptides, pro-inflammatory cytokines and chemokines) showed strain-level differences in expression level and tendency within gene sets of this functional class. A target analysis of skin barrier functional gene sets including keratin network, barrier development, aryl hydrocarbon signaling, and other genes involved in barrier also showed notable strain-level differences. Pathway analysis confirmed these strain-specific effects. Our results suggest that host-microbe interactions between genetically diverse staphylococcal strains and the epidermis may differentially affect skin-specific processes.

**ARCHER**

**Neutrophil-intrinsic TNF receptor signaling orchestrates host defense against *Staphylococcus aureus***

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*Staphylococcus aureus* is the leading cause of skin and soft tissue infections and has become a major health burden due to the emergence of antibiotic-resistant strains. Tumor necrosis factor (TNF) is a proinflammatory cytokine that is induced upon *S. aureus* exposure and whose inhibition is associated with increased risk of *S. aureus* infections in humans. However, the contribution of TNF and cognate receptors, TNFR1 and TNFR2, to host defense against *S. aureus* skin infections is unclear. Therefore, we used an *in vivo* mouse model of *S. aureus* skin infection whereby TNF, TNFR1, or TNFR2 deficient mice and wildtype (wt) mice were intradermally injected with bioluminescent *S. aureus*. TNF, TNFR1, and TNFR2 deficient mice exhibited significantly increased bacterial burdens and skin lesions compared to wt mice. Furthermore, we identified neutrophils (PMNs) as the predominant TNFR1 and TNFR2 expressing cells. We discovered that TNFR1 was crucial for PMN recruitment and skin abscess formation, whereas TNFR2 was critical for NOX2 activation and PAD4-dependent neutrophil extracellular trap formation. Taken together, these findings indicated that TNF orchestrated immunity against *S. aureus* via PMN-intrinsic TNFR1 and TNFR2 signaling, which has implications in the development of novel immune-based therapies against *S. aureus* and potentially other bacterial infections.

**CHEN**

**Defining the functional properties of commensal-induced T cells by redirecting them against a non-native antigen**

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Certain bacterial colonists induce a highly specific T cell response. A hallmark of this encounter is that adaptive immunity develops pre-emptively, in the absence of an infection. However, the functional properties of colonist-induced T cells are not well defined. This limits our ability to understand anti-commensal immunity and to harness it therapeutically. We address both challenges by engineering the skin bacterium *Staphylococcus epidermidis* to express tumor antigens anchored to secreted or cell-surface proteins. Upon colonization, engineered *S. epidermidis* elicits tumor-specific T cells that circulate, infiltrate diverse local and metastatic tumors, and exert cytotoxic activity. These therapeutic effects occur without inflammation. Our therapeutic method also synergizes with immune checkpoint blockade to treat established melanoma in mice without evidence of autoimmunity. Thus, the immune response to a skin colonist can promote cellular immunity at a distal site without evidence of local inflammation. And this response can be redirected against a target of therapeutic interest by expressing a target-derived antigen in a commensal.

**DENG**

**Reprogramming tumor microenvironment by a second-generation recombinant modified vaccinia virus Ankara**

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Immune checkpoint blockade (ICB) therapy has brought hope to many cancer patients, but the response rate is low in many cancer types and acquired resistance to ICB can develop over time. Oncolytic or non-oncolytic viruses are promising therapeutic agents for advanced cancers. Modified vaccinia virus Ankara (MVA) is an attenuated replication-deficient poxvirus approved as a vaccine against smallpox and monkeypox. Our first-generation recombinant MVA has shown promising antitumor efficacy in multiple murine tumor models due to the deletion of the E5R gene (encoding an inhibitor of the DNA sensor cGAS) from the MVA genome and the insertion of two membrane-anchored transgenes – Flt3L and OX40L, which leads to the activation of the host innate and adaptive antitumor immunity. Here in this study, we engineered our second-generation recombinant MVA (MQ833) with the deletion of two more viral immune evasion genes – E3L and WR199, and the insertion of IL12 anchored to the extracellular matrix to mitigate toxicity. Intratumoral (IT) delivery of MQ833 resulted in an 80-100% cure in the mouse B16-F10 melanoma model, which is dependent on both the cytosolic DNA and dsRNA-sensing pathways mediated by STING and MDA5, and the IFN signaling pathway mediated by STAT2. Single-cell RNA sequencing analysis revealed that IT MQ833 injection reprogrammed the tumor microenvironment into an immune-stimulating state, by activating CD8+ and CD4+ T cells, depleting regulatory T cells and M2 macrophages, recruiting and activating neutrophils, and polarizing M1 macrophages. Interestingly, IT MQ833 treatment cured 70% of B2M knock-out melanomas. Since the loss of MHC-I is the most common mechanism of tumor resistance to ICB, our results support the use of MQ833 for ICB-resistant tumors.

**FENG**

**Cosegregation Analysis in Variant Classification and Gaps in Genetic Testing for Melanoma**

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Classifying germline variants as pathogenic or benign is crucial for interpreting clinical genetic testing results. The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) have developed guidelines for variant classification. Cosegregation analysis, measuring how often a germline variant and a disease are transmitted together in a pedigree, is a powerful component of the ACMG/AMP guidelines. We analyzed simulated and real-life pedigree data to evaluate different strategies for cosegregation analysis. We demonstrate that critical considerations in conducting cosegregation analysis include the choice of algorithm, penetrance model, the level of risk elevation, pleiotropy, variation in disease risk conferred by different pathogenic variants of the same gene, population, and birth year. Based on the results, we propose a web tool named COOL (Cosegregation Online, http://BJFengLab.org/), which implements an accurate Bayes factor-based cosegregation analysis. The potential usage of COOL in the genetic testing for melanoma will be discussed. We look forward to establishing collaborations in closing the gaps in cosegregation analysis on melanoma-associated genes.

**KORALOV**

**Clonal evolution and microbial triggers in Cutaneous T Cell Lymphoma pathogenesis**

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Cutaneous T cell lymphomas (CTCLs) are a heterogeneous group of non-Hodgkin’s lymphomas characterized by chronic inflammation and accumulation of malignant T cells in the skin. Among lymphomas, CTCL is uniquely characterized by the striking dermal tropism of transformed T cells—at the primary barrier between our bodies and the outside environment. Triggers of CTCL initiation and progression are poorly understood. Because little is known about the transcriptional and genomic relationship between skin- and blood-residing malignant T cells in CTCL we sought to interrogate malignant clones in matched skin and blood from patients with advanced CTCL. Our multimodal single-cell analysis (ECCITE-seq) revealed clonal evolution at a transcriptional and genetic level within the malignant populations of individual patients. Transcriptional analysis revealed that skin microenvironment in CTCL promoted a distinct signature within skin resident tumor cells that supported rapid proliferation and evolution of the malignant clone.

Next, we examined the role of skin pathobionts in CTCL disease progression using a novel animal model of this malignant disease. Analysis of germ-free vs. conventional animals revealed that skin pathobionts promote disease progression in our pre-clinical model of CTCL. Taken together, these studies suggest that skin microbiota plays a central role in the pathogenesis of CTCL.

**KULKARNI**

**A novel MIF modulator as a melanoma therapeutic**

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Macrophage migration inhibiting factor (MIF) is expressed by both immune and tumor cells and MIF overexpression is increasingly implicated in worse outcomes in melanoma patients and thus is a novel therapeutic target. The cognate receptor for MIF is CD74 and binding activates multiple pro-growth pathways. Targeting MIF activity may be a promising therapeutic strategy in melanoma. We have developed the novel third generation DRQ class of biologic compounds that are potent inhibitors of MIF binding to CD74 and have shown promise in preclinical models of melanoma. In melanoma models, MIF was highly expressed and its production downregulated by DRQ. DRQ also significantly controlled tumor growth in two localized intradermal melanoma tumor models when compared with vehicle control. DRQ exerted its effects by increasing immune infiltration into the tumor microenvironment, in particular increasing CD8+ T lymphocyte infiltration. RNA seq data demonstrated that DRQ decreased ERK and STAT3 expression. Furthermore, rechallenge experiments demonstrated the generation of persistent and specific immune anti-tumor memory responses. These results provide support for modulation of MIF activity as a novel therapeutic strategy for melanoma and suggest that DRQ could be a novel class of melanoma-active biologic agents to fill a critical unmet therapeutic need.

**LU**

**Extensive Lymphocyte Clonal Expansion Occurs in the Tertiary Lymphoid Structures in Hidradenitis Suppurativa**

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Hidradenitis suppurativa (HS) is a severe chronic inflammatory disease of human apocrine gland-bearing skin. Treatment of HS is extremely challenging due to limited understanding of the critical inflammatory mechanisms underpinning its pathogenesis. The mechanisms responsible for sustaining the chronic inflammation and rapid recurrence after surgical removal or biologics treatment remain elusive. Using single cell and spatial transcriptomics, we demonstrate the presence of tertiary lymphoid structures (TLSs) with clearly defined B and T cell zones and that the lymphocyte proliferation occurs exclusively in TLSs adjacent to the tunnels in HS lesions. Further, through V(D)J clonal analyses, we showed that polyclonal expansions of IL17A+ and IFNG+ cells occur predominantly in the TLSs, as well as that extensive clonal expansion plasma cells sharing common VHJH usage across patients systemically circulate in the body. We further identified the distinct populations of inflammatory fibroblasts that provide critical cytokines for the formation of TLSs and exhibit features similar to fibroblastic reticular cells (FRCs) and marginal reticular cells (MRCs) in the secondary lymphoid organs. Mechanistically, we show that HS lesional fibroblasts can be stimulated to upregulate cytokines to recruit immune cells and that complex immune-mesenchymal interactions contribute to their local aggregation. Our work provides significant advance in understanding the local immune milieu that supports the amplification of humoral immune responses in HS.

**PETUKHOVA**

**Monogenic mutations implicate STAT1 in hidradenitis suppurativa pathogenesis.**

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Hidradenitis suppurativa (HS) is a prevalent and debilitating skin disease with many unmet needs. Genes that underlie rare monogenic etiologies demonstrate greater success as drug targets. HS gene discovery has been limited. Transcriptomic studies show that upregulated STAT1 has a prominent role in HS pathogenesis, supporting previous evidence implicating activators of STAT1 (TNFα, microbial signals, IFNγ). Patients with heterozygous STAT1 gain-of-function (GOF) mutations can develop clinical features that overlap with HS (abscesses, colitis, autoimmunity, SCC). Thus, we hypothesize that some HS patients may carry rare monogenic GOF mutations in STAT1. To test this, we analyzed sequence data for STAT1 in 219 HS cases and 10,863 healthy controls; experimentally validated mutations; and investigated phenotype coherency. We identified 5 cases (2.3%) with 4 different STAT1 mutations, while only 0.13% of controls were carriers (p=3x10- 5). Functional analysis of PBMCs from HS carriers of STAT1 mutations (I83M, T450M, V712I) showed enhanced short-term cytokine-mediated STAT1 phosphorylation compared to non-carrier healthy controls (IL6 p=.019; IL-27 p=.01). Ex vivo total STAT1 expression was higher in T-cells from HS carriers (p=.006); as was IL-27 activated PBMC expression of STAT1 target genes SOCS1 and CXCL9. These molecular phenotypes, along with some clinical phenotypes of the mutation carriers (histories of viral and fungal infections, dental abscesses, thyroid dysfunction, asthma, and spondylitis), are consistent with those observed in well characterized STAT1GOF patients. Taken together our data indicate that rare STAT1GOF variants may underlie risk for HS, provide a rationale for ongoing investigation into JAK-STAT inhibition as a potential HS treatment, and invite a precision medicine approach to HS management.

**ZHOU**

**Nasal and gut dysbiosis are associated with more advanced disease in cutaneous T-cell lymphoma**

Madeline J. Hooper1, Francesca L. Veon1, Tessa M. LeWitt1, Yanzhen Pang1, George Chlipala2, Leonid Feferman2, Stefan Green3, Jaehyuk Choi MD PhD1, Michael B. Burns4, Joan Guitart1, Xiaolong A. Zhou1

1Department of Dermatology, Northwestern University, Chicago, IL, USA 2Research Informatics Core, Research Resources Center, University of Illinois at Chicago, Chicago, IL, USA 3Genomics/Microbiome Core Facility, Rush University Medical Center, Chicago, IL, USA 4Department of Biology, Loyola University Chicago, Chicago, IL, USA Cutaneous T-cell lymphoma (CTCL) progression has been linked to *Staphylococcus aureus* skin infections, but the nasal and gut microbiomes of this condition remain largely unexplored. Dysbiosis in these reservoirs have been linked to skin disease, cancer, and immune dysregulation. We aimed to characterize the nasal and gut microbiota associated with CTCL.

Nasal and stool swabs from CTCL patients (53 nasal, 38 stool) and matched healthy control (HC; 20 nasal, 13 stool) individuals were analyzed using 16S gene amplicon sequencing. CTCL and HC nasal microbiota were significantly distinct from each other (PERMANOVA R2=0.031, p=0.005, genus) with enriched *Roseomonas, Catenococcus*, *Vibrio*, *Marinobacter, Allorhizobium-Neorhizobium-Pararhizobium-Rhizobium*, and *Acinetobacter* communities in patient samples (p<0.002). Increased relative abundance of these taxa was associated with increased skin disease burden. *Tuf2* sequencing to investigate nasal *Staphylococcus* species revealed no group differences in relative abundance (including *S. aureus* and *S. epidermidis*). Gut microbial α-diversity was lower in advanced CTCL patients versus HC (p=0.015). Loss of *Eggerthellaceae* and *Lactobacillaceae* (p<0.02, family level) differentiated patients with high skin disease burden.

Alterations in the CTCL nasal and gut microbiomes are associated with disease severity. Further study of these microbial signatures may improve the mechanistic understanding of CTCL-microenvironment interactions and yield novel therapeutic targets.