Hidradenitis Suppurativa Preclinical Landscape - DRAFT

Organization Name	Project Leader	Project Title	OniX Summary
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	KAPLAN, DANIEL H	Immune Functions of Cutaneous Nociceptors	**Research question:** How do TRPV1-expressing sensory neurons trigger and maintain inflammatory responses in the skin, specifically focusing on the role of mast cells, immune cell clustering, and IL-23 production by dendritic cells? **Stage:** In vitro (likely using isolated skin cells) based on the mention of optogenetics and cell types. **Drug development:** Not directly mentioned, but research aims to provide insights for potential future therapies in chronic inflammatory and autoimmune diseases.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	NAIK, HALEY	Microbial Shifts and Immune Dysregulation in Hidradenitis Suppurativa Pathogenesis	**Research question:** This study investigates the role of bacteria (C. acnes) and immune system activity (IL-17/IL-6 pathway) in Hidradenitis Suppurativa (HS). **Stage:** Early investigation (focuses on understanding the disease mechanisms) **Methods:** • Analyze the levels of C. acnes bacteria in HS lesions and surrounding areas at different disease stages. • Examine activity of genes involved in the IL-17/IL-6 immune pathway in HS skin compared to healthy skin. **Drug development:** Not the main focus, but the research aims to provide insights for developing new HS therapies in the future.
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	WHITLEY, SARAH KERN	Targeting cutaneous nociceptors to reduce Type-17 inflammation in hidradenitis suppurativa	**Research question:** Does inhibiting sensory nerve cells (nociceptors) reduce the inflammatory response (specifically Th17 cells) in Hidradenitis Suppurativa (HS)? **Stage:** Preclinical (using human cells and tissues, but not a whole organism) **Methods:** • Analyze immune cells in HS skin using spatial transcriptomics. • Investigate the effect of botulinum toxin (prevents neuropeptide release) on immune cell activity in HS skin. • Use cell cultures and genetic analysis of HS skin samples to study the role of neuropeptides in HS. **Drug development:** Not the main focus, but research aims to support the development of new therapies for HS by targeting sensory nerve cells.

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PROGENRA, INC.	SURESH, KUMAR	Development of ITCH-activating IRAK4 degraders as dual-targeting drug candidates for the treatment of rheumatoid arthritis	**Research question:** Can a new type of drug called a PROTAC be developed to target and degrade IRAK4, a protein involved in inflammation, for diseases like rheumatoid arthritis and hidradenitis suppurativa? **Stage:** Preclinical (in vitro studies and development) **Methods:** • Design and synthesize new PROTAC molecules that target IRAK4. • Test the effectiveness of these PROTAC molecules in degrading IRAK4 in cells. • Compare the new PROTACs to existing IRAK4 inhibitors. **Drug development:** This research directly aims to develop a new therapeutic drug (PROTAC) for inflammatory diseases.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	ROSENBLUM, MICHAEL DAVID	Restoring Immune Balance in Hiddradenitis Suppurativa	**Research question:** Does correcting the imbalance between regulatory T cells (Tregs) and Th17 immune cells improve Hidradenitis Suppurativa (HS)? **Stage:** Preclinical (using human tissue samples and developing an animal model) **Methods:** • Develop an assay using HS patient skin samples to study Treg and Th17 cell function. • Establish a humanized mouse model of HS. • Investigate how manipulating Treg and Th17 cells using different molecules affects inflammation in HS skin models. **Drug development:** Not the main focus, but research aims to inform potential future therapies for HS by targeting the immune system.
UNIV OF NORTH CAROLINA CHAPEL HILL	SAYED, CHRISTOPHER J	Evaluation of the Genetics of Hidradenitis Suppurativa	**Research question:** • Does genetics play a role in Hidradenitis Suppurativa (HS)? **Stage:** • In silico (analysis of existing genetic data) **Methods:** • Analyze DNA samples from 700 HS patients. • Perform a genome-wide association study (GWAS) to identify genetic variants associated with HS. • Compare patient data to existing genetic data sets (TOPMed, GSP). **Drug development:**

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			• Not the main focus, but research aims to identify genes involved in HS which could inform future treatment development.
NORTHWESTERN UNIVERSITY AT CHICAGO	BUDUNOVA, IRINA	Role of healthy skin molecular phenotype in the switch to specific skin diseases	**Research question**: Investigating the molecular mechanisms underlying the disparity in susceptibility to different inflammatory skin diseases between African American (AA) and White Non-Hispanic (WNH) populations. **Stage**: In vitro (3D human skin equivalent cultures made from human primary keratinocytes seeded on collagen matrix). **Methods**: The study utilized extensively validated RNA-seq analysis to compare gene expression in healthy AA versus WNH skin, focusing on proinflammatory signaling. Additionally, 3D human skin equivalent cultures were treated with pro-inflammatory cytokines to simulate the effects of inflammatory skin diseases like atopic dermatitis (AD) and psoriasis. The research aimed to delineate the initial significant stages of the molecular switch towards specific inflammatory skin diseases using in vitro skin models and comprehensive molecular analysis techniques. **Drug development**: The study aimed to identify how different molecular phenotypes of healthy skin in AA and WNH populations define the switch towards either pro-AD or pro-psoriasis signaling. By using in vitro skin models and advanced molecular analysis methods, the research sought to understand the molecular mechanisms that trigger the shift towards specific inflammatory skin diseases, with the goal of developing personalized prevention approaches for different minority populations.
BOSTON UNIVERSITY MEDICAL CAMPUS	BOTCHKAREV, VLADIMIR A	Genome transposable elements as drivers of inflammation in understudied skin types	**Research question**: Investigating the role of transposable elements (TEs) in driving inflammatory skin responses in individuals with understudied skin types, particularly focusing on African American (AA) individuals. Stage: In vitro (3D skin equivalent cultures and experimental in vitro models of skin inflammation). **Methods**: The study involves comparative analyses of transposable element expression in human epidermal keratinocytes from understudied skin types and non-Hispanic White (NHW) skin. Correlation of TE expression with gene expression patterns and DNA/histone modifications will be conducted. Additionally, the effects of inhibitors targeting dsRNA and dsDNA pathways on the expression of inflammation-associated genes in epidermal keratinocytes will be investigated.

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			Drug development: The research aims to explore a novel strategy for managing inflammatory skin diseases in individuals with understudied skin types by inhibiting TE transcription with nucleoside reverse transcriptase inhibitors. By elucidating the role of TEs in regulating inflammation, the study seeks to provide insights into potential therapeutic targets for modulating TE activities to address skin inflammatory responses in this population.
EMORY UNIVERSITY	ORENSTEIN, LAUREN ANNE VIGIL	Pain in Hidradenitis Suppurativa: Adolescent Phenotypes and Perspectives	**Research question**: This research aims to investigate pain mechanisms in adolescent patients with hidradenitis suppurativa (HS), a chronic inflammatory skin disease, and develop targeted interventions to reduce pain and prevent chronic opioid use in this population. **Stage**: in vivo (adolescent patients with HS). **Methods**: The study will adapt techniques to understand pain mechanisms in adolescents with moderate-to-severe HS, utilizing comprehensive assessments including clinical disease activity, systemic inflammation, and sensory profiles through quantitative sensory testing. Semi-structured interviews with adolescents and their parents/guardians will explore unmet needs in HS pain management. A Stakeholder Panel will be formed to develop recommendations for interventions addressing pain and suffering in adults and adolescents with HS using Intervention Mapping methodology. **Drug development**: This competitive revision to a K23 career development award will equip Dr. Lauren Orenstein to conduct studies focusing on HS pain in adolescent patients. The research will involve multi-site recruitment, research in pediatric populations, and engagement with adolescent stakeholders. Mentoring will be provided by experts in pediatric dermatology and adolescent populations. The study aims to fill knowledge gaps related to HS pain in adolescents, optimize pain measurement, and develop family-centered interventions to alleviate pain and prevent long-term opioid use. This prospective cohort study represents a unique opportunity to address pain management in adolescents with HS and lay the groundwork for future intervention development proposals.
PENNSYLVANIA STATE UNIV	NELSON, AMANDA MARIE	Adherens Junction dysfunction in	**Research question**: The research aims to investigate the role of E-cadherin (E-cad) and p120 catenin (p120) loss in keratinocytes in the pathogenesis of Hidradenitis Suppurativa (HS) and its contribution to the inflammatory process and disease severity.

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HERSHEY MED CTR		Hidradenitis Suppurativa	**Stage**: in vitro culture models, murine models, and samples from human subjects, including keratinocytes, blood, and suction blister fluid from both normal subjects and HS patients. **Methods**: The study will rigorously investigate how the loss of E-cad and p120 in HS keratinocytes influences HS pathophysiology and how inflammatory mediators induce adhesion loss in keratinocytes. Two synergistic aims will be pursued: Aim 1 will focus on understanding the contribution of E-cad and p120 loss to HS pathogenesis in keratinocytes, while Aim 2 will explore how inflammatory mediators impact adhesion molecules in keratinocytes. Results will be correlated with subject demographics and clinical data to identify associations with biological variables. **Drug development**: The research seeks to elucidate the mechanism by which keratinocytes contribute to the pathogenic cycle of inflammation and tissue disruption in HS. Understanding these new pathomechanisms is crucial for developing future therapeutic approaches to improve the treatment of this debilitating disease. By investigating the role of E-cad and p120 in HS pathophysiology, this study aims to pave the way for more effective and targeted therapies for HS patients.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	LIAO, WILSON	Elucidating Systemic Inflammation in Hidradenitis Suppurativa using Single Cell Omics and Machine Learning	**Research question**: The study aims to investigate dysregulated pathways in the circulating immune system of patients with Hidradenitis Suppurativa (HS) using single-cell technology and advanced bioinformatic and machine learning methods. **Stage**: in vitro (circulating immune cells from HS patients). **Methods**: The research will utilize single-cell technology along with novel bioinformatic and machine learning approaches to identify dysregulated pathways in the circulating immune system of individuals with HS. By focusing on immune cells, the study seeks to advance understanding of the immunobiology of HS and discover new therapeutic targets for intervention. **Drug development**: Hidradenitis Suppurativa is a debilitating skin disease associated with significant physical and emotional morbidity, as well as systemic inflammation and increased risk of comorbidities. By investigating dysregulated pathways in the immune system of HS patients, this research aims

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			to uncover novel biologic pathways that can be targeted for therapeutic interventions, potentially leading to improved treatment strategies for this underrecognized condition.
COLUMBIA UNIVERSITY HEALTH SCIENCES	PETUKHOVA, LYNN	Establishing the contributions of monogenic etiologies to hidradenitis suppurativapathogenesis	Research question: The study aims to investigate the role of inborn errors of immunity (IEI) in the pathogenesis of Hidradenitis Suppurativa (HS) and their potential implications for targeted interventions and individualized screening. **Stage:** in vivo (human participants with HS). **Methods:** The research will involve generating exome data to identify IEI in individuals with HS, followed by diagnostic analysis and validation of mutations. Additionally, burden testing with exome data and genome-wide association studies will be conducted to identify IEI genes, pathways, and cell types relevant to HS. Large HS cohorts with diverse ancestries will be leveraged for this investigation, collaborating with clinical experts in HS treatment and industry partners involved in HS clinical trials. **Drug development:** Hidradenitis Suppurativa is a challenging inflammatory skin disease with significant unmet medical needs, especially in terms of new treatments. By exploring the potential role of IEI in HS pathogenesis, this study aims to identify subsets of HS patients with IEI, determine the prevalence of IEI in HS, and uncover IEI pathways relevant to HS patients without IEI. These findings could provide insights for drug repurposing in HS and enhance strategies for managing pathological inflammation associated with this debilitating condition.
UNIVERSITY OF IOWA	GURUNG, PRAJWAL	Elucidating cellular and molecular mechanisms regulating SHP1-mediated inflammatory skin disease	**Research question**: The study aims to investigate the mechanisms of IL-1α production and its regulation in inflammatory skin diseases, particularly focusing on neutrophilic dermatoses. **Stage**: in vivo (Ptpn6spin mutant mice model of neutrophilic dermatosis). **Methods**: The research utilizes a mouse model of neutrophilic dermatosis to explore IL-1α-mediated inflammatory skin disease, independent of inflammasome and IL-1β, but requiring IL-1α and potentially driven by RIPK1. The study aims to elucidate the roles and regulation of IL-1α in inflammatory disease, with a focus on upstream events that control IL-1α production. Preliminary findings suggest that microbiota may influence IL-1α expression by radioresistant cells, contributing to disease development. Two main aims are proposed: Aim 1 will

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			investigate the role of microbiota in regulating IL-1α-mediated skin inflammation and identify the specific cell population responsible for IL-1α production. Aim 2 will delve into the molecular mechanisms of SHP1-mediated disease induction, focusing on myelopoiesis, IL-1α signaling, and RIPK1/TAK1 pathways to regulate skin inflammation. **Drug development**: By exploring the regulation of IL-1α production and its impact on inflammatory skin diseases using a mouse model of neutrophilic dermatosis, this study aims to uncover novel biomedical targets within these inflammatory pathways. The research seeks to advance understanding of the mechanisms underlying IL-1α-mediated skin inflammation and potentially identify new therapeutic targets for neutrophilic dermatoses.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO	SCHARSCHMIDT, TIFFANY CRAWFORD	Functional Dissection of Regulatory Myeloid Cells in Microbe-Immune Crosstalk in Skin	**Research question**: The study aims to investigate the role of type 2 conventional dendritic cells (cDC2s) in mediating immune tolerance to skin commensal bacteria and promoting skin homeostasis. **Stage**: in vivo (mouse models, gnotobiotic models, transgenic mouse models) and ex vivo systems to study human skin immune cell function. **Methods**: The research will focus on understanding how commensal bacteria influence the mature-regulatory (mreg) phenotype of cDC2s and their ability to support skin homeostasis through commensal-specific immune tolerance. By utilizing engineered skin commensal bacteria mutants, high-dimensional single-cell analyses, and novel tools to measure cDC2 priming of bacteria-specific CD4+ T cells, the study aims to elucidate how host receptor pathways respond to bacterial ligands to promote immune homeostasis. The investigation will also explore differences in these responses in the context of skin disease, specifically hidradenitis suppurativa. **Drug development**: Establishing and maintaining local immune homeostasis is crucial for the proper functioning of barrier tissues, with a key role played by regulatory T cells (Tregs) and cDC2s in mediating immune tolerance to skin commensals. The proposed research will employ innovative approaches to define the role of cDC2s in cutaneous immune regulation, identify bacterial molecules and host pathways involved in these processes, and enhance understanding of how host-commensal interactions support skin homeostasis. The results from this study have the

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			potential to inform future therapeutic strategies targeting host-commensal interactions in skin diseases.
NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES	KAPLAN, MARIANA	Systemic Autoimmunity	**Research question:** This research branch does not focus on a single research question. However, the overall focus is on the role of neutrophils and neutrophil extracellular traps (NETs) in various diseases. **Stage:** In vitro (human neutrophils) and in vivo (not mentioned in the abstract). **Methods:** • Studying sex differences in neutrophil biology. • Analyzing how NETs damage tissues in various diseases. • Investigating mitochondrial dysfunction in neutrophils and its connection to autoimmune diseases. • Identifying neutrophil heterogeneity and its role in health and disease. • Examining the role of type III interferons in lupus. • Using sophisticated imaging and functional assays to assess vascular abnormalities in lupus patients. • Utilizing gene expression approaches (RNA sequencing, ATAC sequencing, single cell RNA sequencing) to understand cellular heterogeneity. • Investigating the genetics of childhood lupus. • Studying neutrophil dysregulation in COVID-19. **Drug development:** The research branch identifies potential therapeutic targets but doesn't develop drugs themselves. Examples include improving mitochondrial function in lupus and the use of PPAR-gamma agonists for vascular function in lupus patients.

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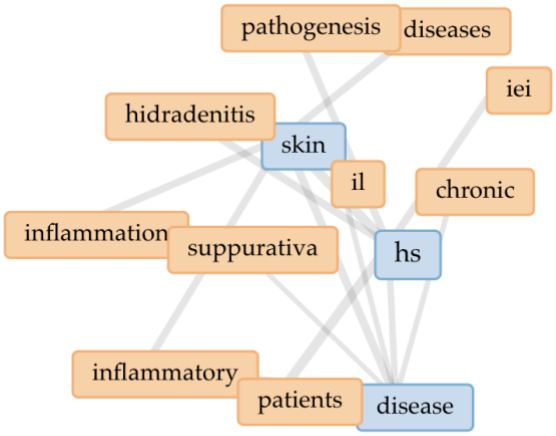

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