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Ashley Elliott<sup>1</sup> , Tejpal Gill<sup>2</sup> , Jaehwan Kim<sup>3</sup> , Maria S. Shutova<sup>4</sup> , Oliver FitzGerald<sup>5</sup> ,  
Stephen R. Pennington<sup>5</sup> , Madeleine Rooney<sup>1</sup> , Atul Deodhar<sup>2</sup> , Siba P. Raychaudhuri<sup>6</sup> ,  
Wolf-Henning Boehncke<sup>4</sup> , Kurt de Vlam<sup>7</sup> , Vinod Chandran<sup>8</sup> , and Wilson Liao<sup>9</sup> 

**ABSTRACT.** Research progress from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) pilot award program was presented and discussed at the GRAPPA 2023 annual meeting. Topics included identification of protein biomarkers associated with enthesitis in psoriatic arthritis (PsA), the role of *HLA-B27* on gut microbial dysbiosis in PsA, single-cell profiling of synovial fluid vs psoriatic skin lesions in PsA, and the role of mechanotransduction in hyperactivation of transforming growth factor- $\beta$  via  $\alpha V\beta 6$  integrin in psoriatic epidermis.

*Key Indexing Terms:* biomarker, GRAPPA, mechanotransduction, microbiome, psoriasis, psoriatic arthritis

## Introduction

Part of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)'s mission is to encourage and support early-stage psoriatic disease (PsD) researchers. Each year, key advances from GRAPPA pilot award program projects are presented at GRAPPA's annual meeting. Professors Wilson Liao, Vinod Chandran, and Kurt de Vlam moderated the presentations at the 2023 annual meeting. Dr. Ashley Elliott spoke about his use of mass spectrometry-based proteomics to identify protein biomarker candidates in patients with PsA with enthesitis. Dr. Tejpal Gill discussed dissecting the effect

of *HLA-B27* on the immunopathogenic mechanisms underlying PsA. Dr. Jaehwan Kim spoke about comparing the synovial fluid of PsA and the skin of psoriasis (PsO) using single-cell RNA sequencing. Finally, Dr. Maria Shutova discussed molecular mechanisms of mechanotransduction in psoriatic epidermis relevant to the Koebner phenomenon.

## Protein biomarkers associated with enthesitis in PsA

Elliott presented his biomarker discovery approach in PsA. It is known that the presence of enthesitis in PsA may provide clues to disease pathogenesis, aid diagnosis, and contribute to poor prog-

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<sup>1</sup>A. Elliott, MB Bch BAO, MSc, PhD, M. Rooney, MD, Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK; <sup>2</sup>T. Gill, PhD, A. Deodhar, MD, Division of Arthritis and Rheumatic Diseases, Oregon Health & Science University, Portland, Oregon, USA; <sup>3</sup>J. Kim, MD, PhD, Department of Dermatology, University of California Davis, Davis, California, and Dermatology Section, Veterans Affairs Northern California Health Care System, Mather, California, and Laboratory for Investigative Dermatology, the Rockefeller University, New York, New York, USA; <sup>4</sup>M.S. Shutova, PhD, W.H. Boehncke, MD, University of Geneva, Department of Pathology and Immunology, and University Hospitals of Geneva, Division of Dermatology and Venereology, Geneva, Switzerland; <sup>5</sup>O. FitzGerald, MD, S.R. Pennington, PhD, School of Medicine, UCD Conway Institute for Biomolecular Research, University College Dublin, Dublin, Ireland; <sup>6</sup>S.P. Raychaudhuri, MD, Department of Dermatology and Rheumatology, University of California Davis, Davis, and Dermatology and Rheumatology Section, Veterans Affairs Northern California Health Care System, Mather, California, USA; <sup>7</sup>K. de Vlam, MD, PhD, Department of Rheumatology, University Hospital, and Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium; <sup>8</sup>V. Chandran, DM, PhD, Departments of Medicine, Laboratory Medicine and Pathobiology and Institute of Medical Science, University of Toronto, and Schroeder Arthritis Institute, Krembil Research

Institute, University Health Network, Toronto, Ontario, Canada; <sup>9</sup>W. Liao, MD, Department of Dermatology, University of California San Francisco, San Francisco, California, USA.

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Address correspondence to Prof. W. Liao, Department of Dermatology, University of California San Francisco, Box 0808, San Francisco, CA 94143, USA. Email: wilson.liao@ucsf.edu.

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nosis.<sup>1</sup> Ultrasound (US) is an invaluable tool in assessing enthesal disease, but it requires training, which is time consuming. We investigated whether enthesitis may be measured by changes in serum proteins and, as such, allow us to better understand, diagnose, and treat the condition. We aimed to use mass spectrometry-based proteomics to identify protein biomarker candidates that may be associated with enthesitis in patients with PsA.

Serum was collected as part of a prospective observational study from patients with PsA who fulfilled the Classification for Psoriatic Arthritis (CASPAR) criteria and were aged  $\geq 18$  years. All patients were biologic-naïve and due to commence biologic treatment. We used the validated Madrid Sonographic Enthesitis Index (MASEI)<sup>2</sup> to assess US-confirmed enthesitis, with a score  $\geq 18$  signifying significant enthesitis and  $< 18$  determined to be nonsignificant. The samples were analyzed using targeted mass spectrometric multiple reaction monitoring (MRM) analysis with  $> 200$  candidate biomarker proteins. The MRM data were analyzed in 3 ways: (1) raw with no normalization; (2) normalization to 7 stable isotope-labeled peptide spike-ins (SIL7), correcting for fluctuations in sample injections/mass spectrometry loading; and (3) normalization to a set of endogenous peptides that represent total serum protein abundance (TSPA7), correcting for different amounts of total serum across samples. Univariate analyses and multivariate machine learning random forest (RF) modeling were performed.

Eighty samples were analyzed. Twenty-nine patients had a MASEI score  $< 18$  (36%) and 51 had a score  $> 18$  (64%). We identified 35 candidate protein biomarkers from both the multivariate and univariate datasets (Table). RF multivariate analysis of all data revealed a set of peptide signatures with the ability to differentiate between MASEI scores  $< 18$  vs  $\geq 18$ . From the peptide data, the testing and training area under the curve generated were 0.789 (95% CI 0.65-0.93) and 0.953 (95% CI 0.92-0.98) for the raw RF model, 0.83 (CI 0.74-0.94) and 0.972 (95% CI 0.96-0.99) for the TSPA7 RF model, and 0.845 (95% CI 0.72-0.97) and 0.966 (95% CI 0.94-0.99) for the SIL7 RF model, respectively. In conclusion, we have identified a panel of serum proteins within this small cohort that are associated with enthesitis in PsA. Verification of these findings in a larger independent dataset is the next required step.

### Characterizing the effect of *HLA-B27* on gut microbial dysbiosis in PsA

Gill presented on the role of the genetic factor *HLA-B27* on the gut microbiome. PsA is a chronic immune-mediated inflammatory disease of the synovial joints and entheses in association with PsO. There is a strong link between the genetic risk factor *HLA-B27* and PsA, with up to 50% of patients with axial PsA carrying the *HLA-B27* allele.<sup>3</sup> Despite this strong genetic association, there is a paucity of data on the effect of *HLA-B27* on disease development in comparison with patients with PsA who are *HLA-B27* negative. Recent studies from our group have revealed that the *HLA-B27* allele is associated with a decrease in the gut microbial diversity in healthy individuals and patients with axial spondyloarthritis (axSpA), which is a prototypic spondyloarthritis. Further, patients with axSpA and

*HLA-B27*-positive healthy individuals have an altered mucosal IgA response to gut microbes.<sup>4</sup> Therefore, in this study, we aimed to dissect the effect of *HLA-B27* on the immunopathogenic mechanisms underlying PsA.

Preliminary results revealed a decrease in the fecal microbial diversity in patients with PsA in comparison to healthy controls (Figure 1A), as shown by previous studies in patients with PsA.<sup>5</sup> Patients with PsA also exhibit a significant increase in the relative abundance of the genus *Prevotella*, with a concomitant decrease in the relative abundance of the *Bacteroides* genus (data not shown). However, this decrease in microbial diversity and altered microbial community structure in patients with PsA was not affected by the presence or absence of *HLA-B27* allele (Figure 1B).

Since gut microbial function is redundant, we further analyzed the fecal metabolic profile to determine the effect of *HLA-B27*. Interestingly, we found that many inflammatory fecal metabolites, such as stearyl-L-carnitine, were significantly increased in patients with PsA ( $P < 0.001$ ) in comparison with healthy controls. Upon stratification of their *HLA-B27* status, these differences were more pronounced in patients who were *HLA-B27* negative (Figure 1C). In tandem, we also observed a decrease in antiinflammatory metabolites, such as evoxine (Figure 1D) in patients with PsA ( $P < 0.001$ ) in comparison to healthy controls. When stratified by their *HLA-B27* status, we found that *HLA-B27* was associated with decreased levels of evoxine in both patients with PsA and healthy controls. Increased levels of inflammatory metabolites and/or decreased antiinflammatory or antioxidative metabolites are a hallmark of many immune-mediated inflammatory diseases, including *HLA-B27*-associated axSpA. To examine whether these altered metabolites were associated with gut inflammation, we measured the plasma levels of calprotectin, a marker of gut inflammation. Indeed, we found that patients with PsA have significantly elevated levels of calprotectin in comparison with healthy controls regardless of their *HLA-B27* status.

Taken together, our preliminary data suggest that *HLA-B27* affects gut microbes and their metabolic profile; however, disease status might exert a greater effect that may mask certain, but not all, *HLA-B27*-associated changes. The *HLA-B27*-negative cohort had more patients with axial PsA, which might affect these outcomes. Future studies will involve increased sample size to determine the effect of *HLA-B27* as well as disease phenotype (axial vs peripheral) to determine the role of microbial community structure and function underlying PsA pathogenesis. In conclusion, dissecting the effects of host genetics on gut microbes/metabolites in PsA is the first step toward disease stratification and identification of novel biomarkers for precision medicine and has the potential to drive innovative PsA research.

### Comparative single-cell genomic profiling of synovial fluid vs skin lesions in PsA

Kim presented his single-cell profiling work. Although cytokines of the interleukin (IL)-23/Type 17 (T17) cell axis have attracted attention as therapeutic targets for both PsA and PsO, treatment responses to biologic agents targeting the T17 cells

Table. Proteins related to the peptide sequences for both the univariate analysis and multivariate analysis for all 3 datasets.

Raw		TSPA7		SIL7	
Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
SHBG	SHBG	SHBG	SHBG	SHBG	SHBG
Angiotensinogen		Angiotensinogen		Angiotensinogen	Angiotensinogen
Antithrombin III		Antithrombin III	Antithrombin III	Antithrombin III	
DBP	VitD recombinant protein	DBP	DBP	DBP	
CBG		CBG	CBG	CBG	
Calumenin		Calumenin		Calumenin	Calumenin
ANGPTL3	ANGPTL3	ANGPTL3		ANGPTL3	
GPX3		GPX3	GPX3	GPX3	
	PEDF	PEDF	PEDF		PEDF
PI-G PLD	ANT3	PI-G PLD	TR $\beta$	PI-G PLD	ANT3
IGFALS	HRG	IGFALS	Agglutinin-like protein	IGFALS	HRG
AHSG		AHSG	PHLD	AHSG	
Apo-AI		Apo-AI	B2M	Apo-AI	
CPN1		CPN1	Complement factor B	CPN1	
Tenascin-X		Tenascin-X	C4BPA	Tenascin-X	
HSP90- $\beta$		HSP90- $\beta$	IGJ chain	HSP90- $\beta$	
Protein S100-A8		Complement factor H	ACT	CRP	
		IGHV3-7	HCII	Prothrombin	
		SAP	Cadherin 13		
			DmX-like protein		

Proteins in blue are those in all datasets, green are those in all univariate datasets and at least 1 multivariate dataset, yellow are those in all multivariate datasets and at least 1 univariate dataset, red are those in all univariate datasets, and pink are those in 2 multivariate datasets. All proteins correspond to an increase in abundance with a lower MASEI score. ACT:  $\alpha$ -1-antichymotrypsin; AHSG:  $\alpha$ -2 Heremans Schmid glycoprotein; ANGPTL3: angiopoietin-related protein 3; ANT3: adenine nucleotide translocase 3; Apo-AI: apolipoprotein AI; B2M:  $\beta$ 2 microglobulin antigen; C4BPA: complement component 4 binding protein  $\alpha$ ; CBG: corticosteroid-binding globulin; CPN1: carboxypeptidase N catalytic chain; CRP: C-reactive protein; DBP: vitamin D binding protein; GPX3: glutathione peroxidase 3; HCII: heparin cofactor 2; HRG: histidine-rich glycoprotein; HSP: heat shock protein; IGHV3-7: immunoglobulin heavy variable 3-7; IGFALS: insulin-like growth factor-binding protein complex acid labile subunit; IGJ: immunoglobulin J; MASEI: Madrid Sonographic Enthesitis Index; PEDF: pigment epithelium-derived factor; PHLD: Pleckstrin homology-like domain; PI-G PLD: phosphatidylinositol-glycan-specific phospholipase D; SAP: serum amyloid P component; SHBG: sex hormone-binding globulin; SIL7: 7 stable isotope-labeled peptide spike-ins; TR $\beta$ : thyroid hormone receptor  $\beta$ ; TSPA7: total serum protein abundance; VitD: vitamin D.

are very different between PsA and PsO. By blocking IL-17A, 83% of patients achieved a 75% improvement in the Psoriasis Area and Severity Index [PASI75]), whereas only 35% to 50% of patients achieved a 20% improvement in American College of Rheumatology response criteria (ACR20) for PsA. To understand the divergent skin-joint response to IL-23/T17 cell axis cytokine blockers, we are studying the synovial fluid of PsA and the skin of PsO with single-cell RNA sequencing techniques, taking a 2-step strategy. For the first step of the project, we profiled single-cell gene expression profiles of immune cell subsets in the skin of PsO and characterized how the single-cell transcriptome of immune cell subsets changed after systemic IL-17A blockade. For the second step of the project, we are currently comparing the differences in single-cell transcriptomes between PsA and PsO within the clusters of immune cell subsets.

The results of the first step showed that systemic IL-17A blockade depleted 100% of IL17A<sup>+</sup> T-cells and 95% of IL17F<sup>+</sup> T-cells in psoriatic skin. The expression of IL-17-driven inflammatory mediators (*IL36G*, *S100A8*, *DEFB4A*, and *DEFB4B*) in suprabasal keratinocytes and the expression of *IL23A* in dendritic cell subsets in psoriatic skin were also downregulated by systemic IL-17A blockade. Thus, systemic IL-17A inhibition blocks the entire feed-forward amplification loops of the IL-23/

T17 cell axis in psoriatic skin. For the ongoing second project, we observed that interferon gamma gene (*IFNG*) expression was higher in psoriatic skin compared to the synovial fluid of PsA, but the expression of interferon-induced genes (*MX1*, *IFIT3*, *ISG15*, and *RSAD2*) was higher in the synovial fluid of PsA compared to psoriatic skin. In addition, we observed that the synovial fluid of PsA had a cluster of mononuclear phagocytes that was not observed in psoriatic skin, and the synovial fluid of PsA also had more B cells and plasma cells than psoriatic skin. In our ongoing research trajectory, we aim to continue single-cell transcriptome experiments with more PsA synovial fluid samples to directly compare T cell subset transcriptomes between the synovial fluid of PsA and the skin of PsO. We hope we can present more findings in future GRAPPA meetings.

### The role of mechanotransduction in hyperactivation of transforming growth factor- $\beta$ via $\alpha$ V $\beta$ 6 integrin in psoriatic epidermis

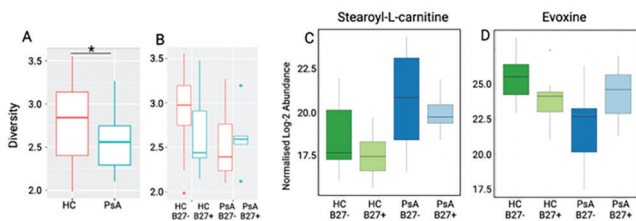
Shutova presented on her work investigating mechanotransduction in psoriatic epidermis. Mechanical stress has long been known as a pathogenic factor that can trigger skin inflammation. In the manifestation of the Koebner phenomenon, psoriatic lesions can appear on previously healthy areas following trauma

or mechanical intervention. However, the precise molecular mechanisms mediating these effects remain elusive.

The cells sense mechanical input through adhesion receptors and convert it into signaling cascades during the process of mechanotransduction, which is crucial for adequate gene expression, differentiation, secretion of mediators, barrier function, and others.<sup>6</sup> Recently, we found that inflammatory conditions that mimic PsO upregulate mechanotransduction-signaling cascades in epidermal keratinocytes. In our *in vitro* model, stimulation of human keratinocytes with a cocktail of cytokines, called M5 (IL-17A, IL-22, tumor necrosis factor- $\alpha$ , IL-1 $\alpha$ , oncostatin M), activated the Rho-GTPase pathway, leading to increased intracellular contractile forces of the actomyosin cytoskeleton anchored to transmembrane mechanosensitive adhesion receptors.<sup>7</sup> Interestingly, one of these receptors ( $\alpha$ V $\beta$ 6 integrin) can also mediate activation of transforming growth factor (TGF)- $\beta$ , which is secreted from cells in inactive form bound to latency-associated peptide (LAP). External or intracellular pulling forces promote  $\alpha$ V $\beta$ 6 binding to LAP and physical release of active TGF- $\beta$ . Growing evidence suggests that the upregulated TGF- $\beta$  signaling is implicated in PsO pathogenesis<sup>8-10</sup>; however, the role of the epidermis in TGF- $\beta$  activation and its implications for PsO are unknown.

In the beginning of this project, we found that  $\alpha$ V $\beta$ 6 integrin is overexpressed at the mRNA and protein levels in psoriatic epidermis and upon *in vitro* stimulation of keratinocytes with M5 cytokines. We also detected high TGF- $\beta$ 1 mRNA levels by RNAscope, as well as activation of Smad2/3 transcription factor downstream of TGF- $\beta$  in lesional epidermis. Next, we measured functional integrin activation by the ability of cytokine-stimulated cultures to bind a synthetic LAP tagged with GFP,<sup>11</sup> which allows precise tracking of degree and subcellular location of the active  $\alpha$ V $\beta$ 6 pool. LAP binding was increased in keratinocyte cultures stimulated with either M5 cocktail or with IL-26, which is produced by Th17 cells at the onset of PsO and has been recently shown to induce TGF- $\beta$  expression from keratinocytes.<sup>10</sup>

To investigate whether mechanical perception of keratinocytes affects integrin-dependent TGF- $\beta$  activation, we used 2



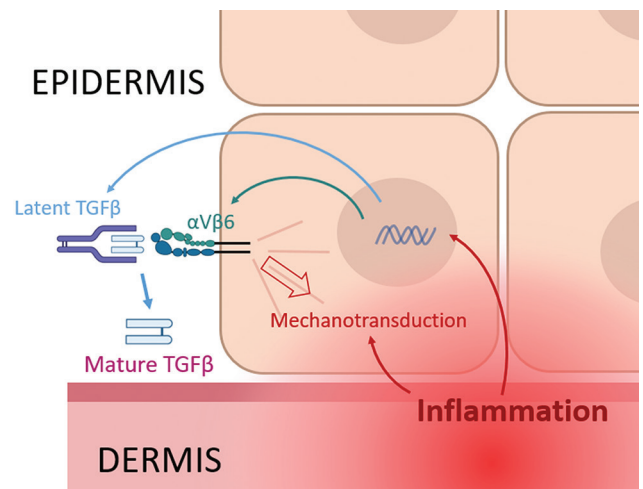
**Figure 1.** Effect of *HLA-B27* on the gut microbiome and metabolome in PsA. (A) Alpha diversity of gut microbes as measured by the Shannon Index in patients with PsA and HCs. (B) Alpha diversity of gut microbes as measured by the Shannon Index in patients with PsA and HCs, stratified by their *HLA-B27* status. (C) Patients with PsA have a significant increase in the inflammatory gut metabolite Stearoyl-L-Carnitine in comparison with HCs when stratified by the *HLA-B27* status. (D) Patients with PsA have a significant decrease in the antiinflammatory gut metabolite evoxine as compared with HCs when stratified by the *HLA-B27* status. \*  $P < 0.05$ . Figure made using Biorender. HC: healthy control; PsA: psoriatic arthritis.

complementary approaches. First, we inhibited the transmission of mechanical forces in epidermal cultures using the myosin inhibitor blebbistatin and found that it significantly decreased LAP binding in the cytokine-stimulated cultures. Second, we stimulated keratinocytes mechanically by growing them on a silicon plate under a cyclic stretch. Stretched cultures exhibited increased LAP binding, even in the absence of the cytokine stimulation.

Based on these data, we propose a model where increased mechanotransduction in psoriatic epidermis has a functional relevance for the  $\alpha$ V $\beta$ 6-dependent activation of TGF- $\beta$  (Figure 2). Similar to intracellular forces, external mechanical stimulation can facilitate induction of TGF- $\beta$  signaling in susceptible skin. This study provides new insights into the mechanistic pathways underlying the Koebner phenomenon and new strategies for a much-needed innovative topical therapy for PsO.

## Discussion

These presentations highlighted innovative approaches for investigating the pathogenesis of PsD. Using mass spectrometry-based proteomics paired with serum samples from US-evaluated patients with PsA, Elliott identified several promising biomarkers for enthesitis. As enthesitis can be an early manifestation of PsA, these biomarkers could be investigated further for their diagnostic and prognostic potential. Gill showed that patients with PsA have decreased gut microbial diversity and altered bacterial metabolites compared to healthy controls, and in some cases these differences were further affected by *HLA-B27* status. Her work highlights the heterogeneity of PsA and the importance of future work to identify PsA endotypes. Kim used single-cell RNA sequencing to show the effect of biologic therapy on immune cell subsets in psoriatic skin, and further identified differences in immune cell composition and gene expression in synovial fluid compared to skin in patients with PsA. This work may help elucidate the connection between PsO and PsA. Finally, Shutova identified a key role for TGF- $\beta$  and  $\alpha$ V $\beta$ 6 in psoriatic epidermis, influenced by mechanical forces, which helps elucidate how physical environmental cues are sensed by



**Figure 2.** Model of mechanotransduction in psoriatic epidermis via TGF- $\beta$  and  $\alpha$ V $\beta$ 6. TGF- $\beta$ : transforming growth factor- $\beta$ .

cells. Altogether, the work presented highlights the significant progress of early-stage investigators into PsD, made possible by the support of their scientific mentors and funding from the GRAPPA pilot awards program.

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