

Advancing Basic and Translational Science: Highlights From the Basic Science Workshop at the GRAPPA 2023 Annual Meeting

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ABSTRACT. Contemporary translational and clinical research advances in psoriatic disease (PsD) were highlighted at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting basic science workshop. This year's workshop focused on key topics, including the significance of the annual GRAPPA meetings as a platform for collaboration and knowledge exchange. Discussions centered around expanding our understanding of tumor necrosis factor inhibitor (TNFi) treatment in PsD and enhancing early detection strategies for PsD comorbidities, specifically for the timely intervention and management of cardiovascular (CV) comorbidities. Insights on the role of the C-C chemokine receptor type 6 (CCR6) in PsD and psoriatic arthritis were provided, suggesting that blockade of CCR6 can reduce psoriasis-like dermatitis and joint inflammation in mouse models.

Key Indexing Terms: animal models, basic research, GRAPPA, psoriasis, psoriatic arthritis

Introduction

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is dedicated to the education, support, and advancement of research in psoriatic disease (PsD). Central to GRAPPA's mission are its annual meetings, which serve as educational events gathering leading experts, clinicians, and researchers from around the globe to exchange ideas, share insights, and forge partnerships. During the basic science workshop at the GRAPPA 2023 annual meeting, like-minded researchers were encouraged to cross-pollinate ideas and drive

transformative changes in the field of PsD. GRAPPA is a pivotal forum where its members' collective dedication to studying and treating PsD converge to accelerate novel therapeutic discoveries that will improve the lives of patients with PsD.

Improving our understanding of tumor necrosis factor inhibitor treatment

Drs. M. Elaine Husni and Unnikrishnan Chandrasekharan underscored the critical importance of collaborative efforts in translational research, emphasizing the synergistic potential of integrating clinical and basic science resources to advance our understanding of PsD. By harnessing over a decade of experience with disease-specific clinical biorepositories and leveraging preclinical models such as the imiquimod (IMQ), mannan, tumor necrosis factor (TNF) transgenic mice, and TNF receptor knockout (TNFRKO) mouse models, researchers are poised to gain novel insights into PsD pathophysiology and therapeutic interventions.¹

The advent of TNF inhibitor (TNFi) therapy has revolutionized the management of immune-mediated inflammatory diseases such as psoriasis (PsO) and psoriatic arthritis (PsA) by targeting TNF signaling cascades. Despite its remarkable effectiveness for skin and joint outcomes in PsD, the treatment is not without limitations. Evidence suggests that long-term use of TNFi can induce adverse effects including opportunistic infections, reactivation of tuberculosis, and malignancies.

TNF serves as a pivotal signaling protein in orchestrating adaptive and innate immune responses by activating its receptors, TNFR1 and TNFR2. Whereas TNFR1 primarily exerts proinflammatory effects and contributes to host defense mechanisms and malignancy surveillance, TNFR2 is intricately involved in inflammation modulation, immune cell proliferation, and cell survival pathways.^{2,3} In elucidating the roles of TNFR1 and

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TNFR2 in modulating inflammatory responses and host defense mechanisms, research from the Husni laboratory provides a nuanced understanding of TNF signaling dynamics and their implications for therapeutic interventions.

The Husni laboratory used the IMQ mouse model to elucidate the differential roles of TNFR1 and TNFR2 in modulating PsD severity and inflammation (Figure 1). Notably, their findings revealed a significant reduction in PsO lesions in TNFR2KO mice compared to wild-type mice, evidenced by decreased epidermal hyperplasia, gross skin lesions, and interleukin (IL)-23 or IL-17A levels.⁴ However, this was not the case for TNFR1KO mice. Interestingly, it was found that the IMQ-induced increase in plasmacytoid dendritic cells (DCs), myeloid DCs, TNF/inducible nitric oxide synthase-producing DCs (Tip-DCs), and IL-23 expression in the draining lymph node depended on TNFR2, not TNFR1. This finding is significant, as IL-23 production by DCs can drive the differentiation of naïve T cells into Th17 and Th1 cells in lymph nodes, which subsequently infiltrate into the skin and promote psoriatic lesions.⁵ Thus, PsD and inflammation are not dependent on TNFR1 activity, but rather driven by TNFR2-dependent IL-23/IL-17 activation pathways.

By demonstrating the critical involvement of TNFR2-dependent IL-23/IL-17 activation pathways in driving psoriatic inflammation, the study highlights the therapeutic potential of targeting TNFR2 while preserving TNFR1, the receptor crucial for host defense. In summary, targeting TNFR2 pathways may offer promising next-generation therapeutic approaches for PsD, likely with reduced adverse effects compared to TNFi therapy.

Novel pathways and potential biomarkers of cardiovascular comorbidity in PsA

Patients with inflammatory arthritis, including PsA, have 8 to 15 years of reduced life expectancy compared to the general population, mainly due to cardiovascular (CV) comorbidities.⁶ Unfortunately, the underlying mechanisms of this comorbidity are unclear, and no early predictors or clinical guidelines exist to specifically address the management of CV comorbidities in this population. Traditional CV risk factors such as advanced age, hypertension, type 2 diabetes, and smoking do not fully account for increased CV disease (CVD) in these patients. Recent studies, including from Husni's research group, implicated aberrant L-arginine metabolism in patients with chronic inflammatory diseases at increased risk for CVD. Interestingly, their research found that decreased L-arginine levels correlated with increased cardiac fibrosis in a mouse model of PsA. These findings are significant because L-arginine is the only biological precursor of nitric oxide (NO). Therefore, lowering the bioavailability of L-arginine can decrease NO production, leading to vascular dysfunction and adverse CV events.⁷ Based on findings from human and mouse models, Drs. Husni and Chandrasekharan propose that changes in levels of L-arginine in conjunction with an increase of specific L-arginine catabolic products in circulation may function as early biomarkers of premature CVD in patients with inflammatory arthritis including PsA.⁸

In light of these findings, targeting TNFR2 and its associated pathways may be a novel therapeutic strategy for PsD, opening up new avenues for treatment development and patient care. Moreover, the investigations presented in this basic research workshop unveiled intriguing connections between irregular L-arginine metabolism and CV morbidity in PsD. These findings underscore the importance and untapped opportunities of early detection and intervention in mitigating CV risks in individuals with autoimmune disorders.

Targeting the chemokine receptor C-C chemokine receptor type 6 in PsO and PsA

Chemokines, small chemotactic cytokines, and their cognate 7-transmembrane spanning chemokine receptors play critical roles in immune trafficking to sites of inflammation, including the skin and joints. More than 20 years ago, the chemokine known as CCL20 and its sole known receptor, C-C chemokine receptor type 6 (CCR6), were identified by Homey et al as being overexpressed in human psoriatic skin.⁹ Dr. Samuel Hwang and colleagues then showed that CCR6 facilitates the adhesion of CCR6-transduced Jurkat T cells to activated endothelial cells *in vitro*.¹⁰ Consequently, it was hypothesized that CCR6 and CCL20 may be critical for the migration of immune cells into psoriatic skin since the keratinocytes and dermal endothelial cells produce CCL20, whereas certain subsets of T cells, namely those associated with Th17 inflammation, express CCR6. Hwang and collaborators showed a decade later that CCR6 knockout mice were highly resistant to psoriasisiform dermatitis triggered by intradermal injections of IL-23,¹¹ a cytokine now accepted as critical in PsO pathogenesis. Further work in the Hwang laboratory over the last decade showed (1) that murine $\gamma\delta$ T cells, which produce high levels of IL-17 in psoriatic murine models, also express high levels of CCR6; (2) that this receptor facilitates epidermal trafficking of these cells in psoriatic skin models; and (3) that blocking antibodies to CCL20 prevents IL-23-driven psoriasisiform dermatitis.^{12,13}

Dr. Hwang emphasized that the features of psoriatic skin and joint disease are highly dependent on the murine model used by investigators. He noted that skin dermatitis in the systemic IL-23 model, which is driven by a single tail vein injection of plasmid containing IL-23 DNA on a minicircle (MC) plasmid (ie, IL-23 MC model), is far greater in the B10.RIII mouse strain than in the otherwise very genetically similar and commonly used C57/BL6 strain (Figure 2). Moreover, joint inflammation is also greater in the B10.RIII strain compared to the C57/BL6 strain in the IL-23 MC model. Having a mouse model in which both skin and joint disease is triggered by a single systemic injection can be advantageous in trying to model PsO in humans, who frequently have manifestations in both organs.

Working with Brian Volkman at the Medical College of Wisconsin, Hwang and colleagues engineered a unique dimeric molecule composed of 2 CCL20 molecules bound by a disulfide bridge. This molecule, called the "CCL20 locked dimer" (Figure 3A), was able to bind to the CCR6, but engaged the receptor in a manner that did not trigger chemotaxis, and prevented native CCL20 from inducing chemotaxis in

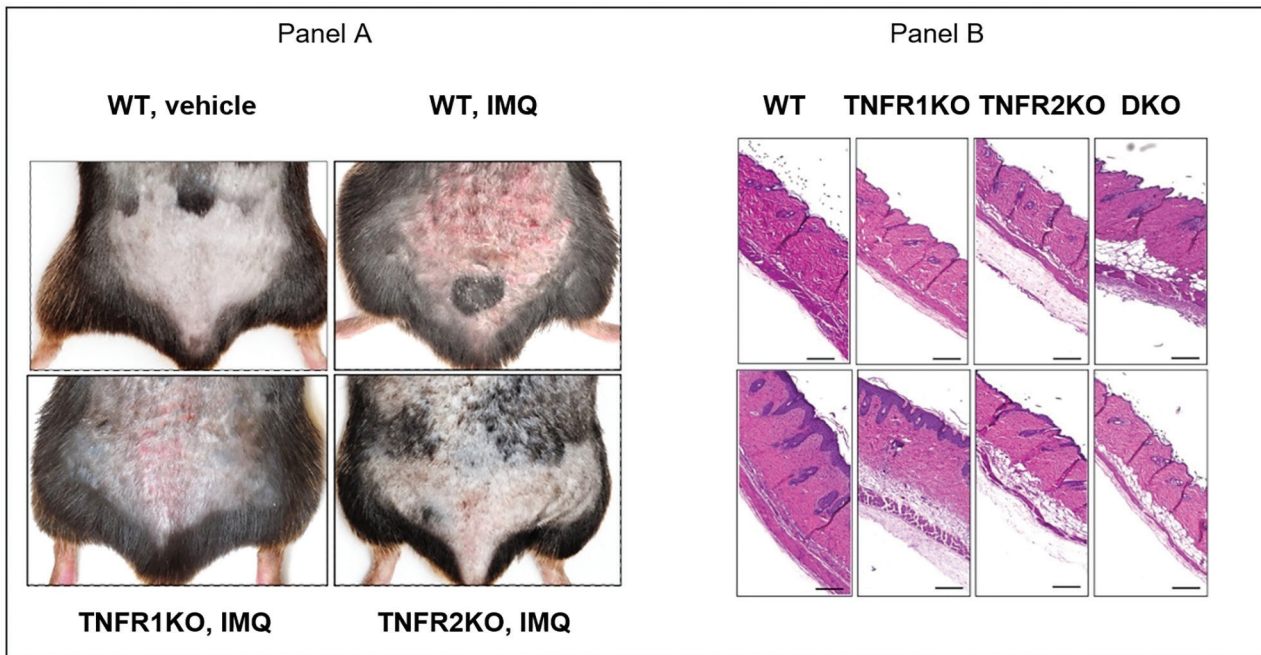


Figure 1. The IMQ-induced psoriasis-like inflammation is reduced in TNFR2KO mice (A) at the morphological level, and (B) at the histological level (scale bar = 125 μ m). IMQ: imiquimod; KO: knockout; TNFR: tumor necrosis factor receptor; WT: wild-type.

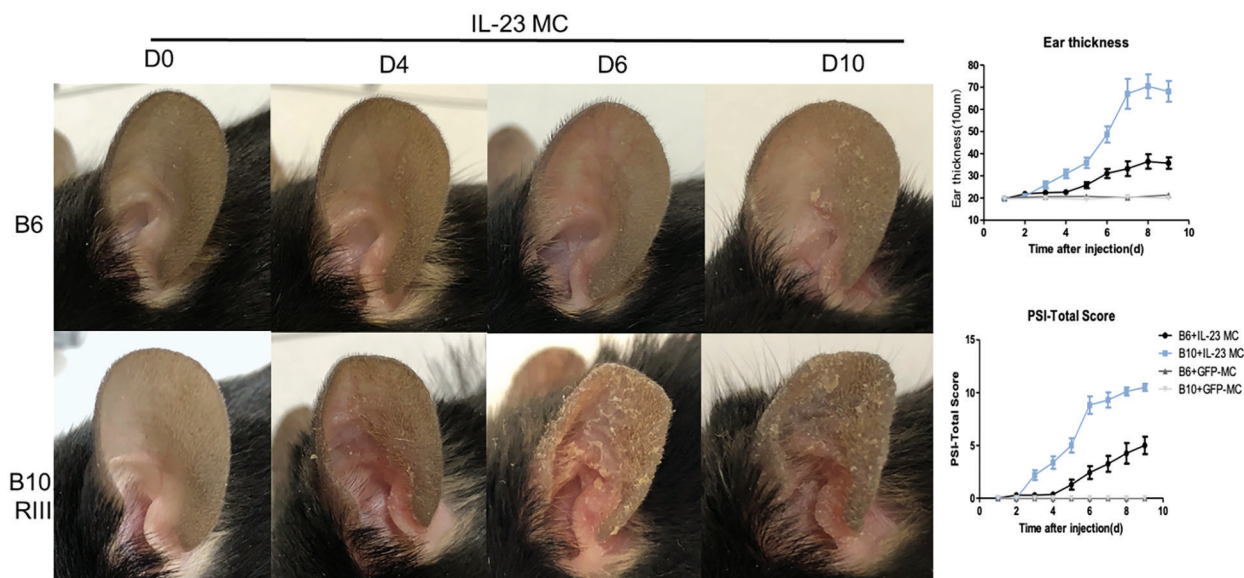


Figure 2. Increased psoriasiform skin disease in B10.RIII mice compared to closely related C57/BL6 (B6) mice. Mice were injected with IL-23 MC plasmid DNA via hydrodynamic tail vein injection. Systemic levels of IL-23 are achieved within hours and sustained over 30 days. Photos indicate days after initial injection. Ear thickness was measured with microcalipers at indicated time. PSI is a combined measure of redness and scaling. Unpublished data (Hwang lab, 2023). GFP: green fluorescent protein; IL: interleukin; MC: minicircle; PSI: psoriasis skin index.

CCR6-bearing cells.¹⁴ This collaborative group demonstrated that the locked dimer could ameliorate psoriasiform dermatitis in mice in several relevant models, including a systemic IL-23-driven model (Figure 3B).^{14,15} Strikingly, in the IL-23 MC model in B10.RIII mice, the locked dimer ameliorated symptoms at both skin and joints in a preventive as well as therapeutic

manner,¹⁵ raising the possibility that targeted therapy directed against CCR6 might be a new strategy for the treatment of Th17 diseases, including PsO and PsA.¹⁶

DISCUSSION

At the GRAPPA 2023 annual meeting, Drs. Husni and

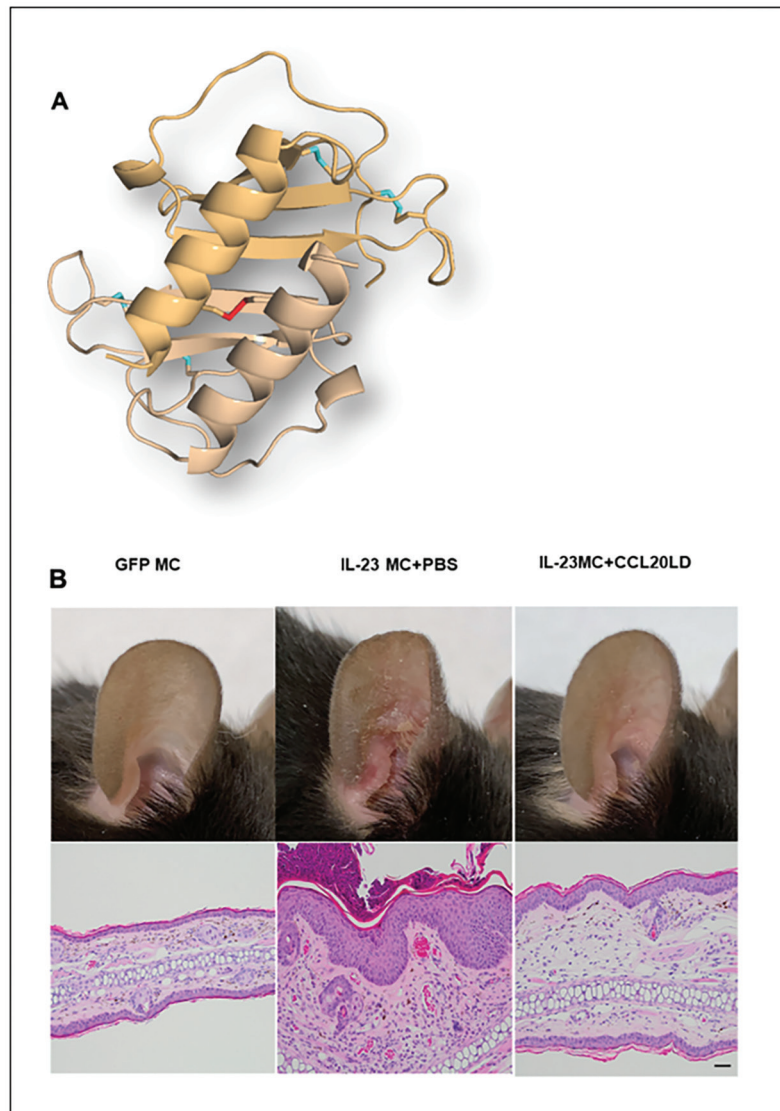


Figure 3. (A) CCL20 locked dimer structure (red indicates disulfide bridge) and (B) reduction of psoriasiform dermatitis by locked dimer treatment. In (B), mice were injected with IL-23 MC on day 0 and then treated with either CCL20LD or PBS by intraperitoneal injection at day 7 for 7 more days.¹³ CCL20LD: CCL20 locked dimer; GFP: green fluorescent protein; IL: interleukin; MC: minicircle; PBS: phosphate buffered saline.

Chandrasekaran presented the intricate mechanistic role of TNFR2 in PsO and PsA, illuminating potential therapeutic strategies centered around targeting TNFR2 and its associated pathways and offering promising avenues for treating PsD with potentially lower adverse effects compared to TNFi. Their investigations using both mouse models and human samples revealed that abnormal L-arginine metabolism may be an early indicator of CV comorbidity in patients with PsA. Research conducted by the Hwang laboratory showed that inhibiting CCR6 through a novel locked peptide dimer antagonist can significantly lower psoriasiform dermatitis and PsA-like joint inflammation. These findings from the 2 research groups together point toward the unfolding of more targeted therapeutic approaches to address PsD and associated CV comorbidities.

The enthusiasm and engagement demonstrated by attendees underscore a collective commitment to advancing basic and translational research in PsD and associated CV comorbidities. As we reflect on the insights shared and discussions sparked during the GRAPPA 2023 basic research workshop, we anticipate the emergence of new collaborations and discoveries that will drive future innovation and improve outcomes for patients with PsD. We look forward to fostering a vibrant community of researchers dedicated to unraveling the complexities of these conditions and translating discoveries into tangible clinical benefits.

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