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GRAPPA 2019 Research Recipient Awards Report

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ABSTRACT. A summary of the research conducted by the recipients of the 2019 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Research Awards is presented. Dr. Alla Ishchenko's project was "Role of Metabolomics in Diagnosis, Disease Severity, and Progression in Psoriasis and Psoriatic Arthritis: A 2-year Prospective Pilot Study" and Dr. Zhenrui Shi's project was "Preclinical Analysis of CCR6 and CCL20 in Mouse and Human Joints, Respectively, as Targets of Therapeutic Intervention in Psoriatic Arthritis."

Key Indexing Terms: cytokines, GRAPPA, psoriasis, psoriatic arthritis

At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2020 annual meeting, we were pleased to include a session highlighting progress made by recipients of the 2019 GRAPPA Research Awards. The recipients were Dr. Alla Ishchenko, whose project was "Role of Metabolomics in Diagnosis, Disease Severity, and Progression in Psoriasis and Psoriatic Arthritis: A 2-year Prospective Pilot Study" and Dr. Zhenrui Shi, whose project was "Preclinical Analysis of CCR6 and CCL20 in Mouse and Human Joints, Respectively, as Targets of Therapeutic Intervention in Psoriatic Arthritis." The presentations were outstanding and well received. GRAPPA is proud to highlight the progress made by these promising investigators, and we wish them well as they advance in their careers. Below is a summary of their reports.

"Role of Metabolomics in Diagnosis, Disease Severity and Extent of Damage in Patients with Psoriatic Arthritis: A 2-year Prospective Study" by A. Ishchenko, R.J. Lories, and K. de Vlam. The concept of psoriatic disease includes psoriasis and psoriatic arthritis (PsA), viewed as an entity, with shared genetic background and overlapping pathophysiology. Both are frequently associated with metabolic disturbances, cardiovascular morbidity, and mortality. There is growing evidence that these comorbidities and psoriatic disease share changes in common pathways. Hence, we have formulated the hypothesis of bidirectional effect between metabolic problems, and psoriasis and PsA, suggesting not only that psoriatic disease predisposes to cardiovascular and metabolic morbidity but also that through shared pathways, metabolic comorbidities directly influence the severity and progression of psoriatic disease.

The objectives of the study are to determine specific metabolic profile in treatment-naïve patients with PsA and psoriasis, to identify "clusters" within patients with PsA based on their metabolic signature, to determine the change in metabolic profile of psoriasis and PsA patients during the follow-up period, and to understand the effect of the metabolic signature of the disease with metabolic disturbances associated with PsA and psoriasis.

This is a pilot longitudinal 2-year prospective observational study with an aim to recruit 30 consecutive adult patients with newly diagnosed and treatment-naïve PsA, fulfilling ClASsification for Psoriatic ARthritis criteria (CASPAR) classification criteria, and 30 patients with psoriasis, naïve to systemic treatment. Besides demographic, clinical, and laboratory data collected at baseline, at 1 year and 2 years of follow-up, blood samples will be used for metabolomics analysis of serum and plasma. Nuclear magnetic resonance spectroscopy will be used to perform metabolomic analysis. We will use an untargeted approach and analyze a wide range of metabolites to determine alterations in metabolic pathways to identify patterns specific for PsA and psoriasis. Exploratory analysis including dimensionality reduction based on multidimensional scaling and principal component analysis will be performed. The collected data will be correlated with clinical and radiographic information.

"Preclinical Analysis of CCR6 and CCL20 in Mouse and Human Joints, Respectively, as Targets of Therapeutic Intervention in Psoriatic Arthritis" by Z. Shi with S.P. Raychaudhuri and S.T. Hwang. PsA develops in about 30% of psoriasis patients[1]. Despite many recent advances, there is still a need for new

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therapeutic approaches that target the immunopathology of psoriasis and PsA.

Chemokines and their receptors are critical for governing cell movement and interaction. The chemokine receptor CCR6 marks a subset of T cells expressing interleukin (IL)-17 and has a key role in the recruitment of these cells into inflammatory sites[2]. The chemokine/chemokine receptor pair CCL20/CCR6 is thought to be highly involved in psoriatic skin disease[3], but its role in PsA is still vague.

We previously engineered a novel CCL20 variant, a CCL20 locked dimer (CCL20LD), that blocks CCR6-dependent cell migration and prevents the development of psoriasiform dermatitis (PsD) in an IL-23 intradermal injection mice model[4]. Hydrodynamic delivery of minicircle (MC) DNA vectors devoid of bacterial DNA resulted in rapid and persistent, systemic high-level transgene expression *in vivo*. In using an IL-23 MC-based murine model, which develops features of both PsD and PsA[5,6], we were able to show that CCL20LD not only ameliorates skin inflammation, but joint inflammation as well (under review). These preliminary data suggest that CCR6/CCL20 could be a key player in the pathogenesis of both psoriatic skin and joint inflammation, and that CCL20LD could be therapeutically effective in human psoriasis and PsA.

To further investigate CCR6/CCL20 as a therapeutic target for PsA, we first determined whether CCL20 is expressed or upregulated in PsA joint fluid aspirates. To this end, we chose an antibody array that detects multiple kinds of cytokines and chemokines simultaneously (AAH-CYT-5-2, Raybiotech), and then screened the presence of chemokines and cytokines in synovial fluid (SF) from a small cohort of patients with PsA or osteoarthritis (OA). As expected, levels of most chemokines were higher in SF from patients with PsA as compared to patients with OA. It was striking, however, that the fold change of CCL20 in PsA compared to OA patient samples was the highest among all 17 measured chemokines (CCL2, CCL4, CCL5, CCL7, CCL8, CCL11, CCL17, CCL20, CCL22, CXCL1, CXCL5, CXCL6, CXCL8, CXCL9, CXCL10, CXCL12, CXCL13). Moreover, the intensity of CCL20 was positively correlated with IL-6 intensity in patients with PsA, but not in patients with OA.

Next, we investigated if CCR6 expression was increased in the IL-23 MC mouse model that recapitulates some clinical and immunological features of both psoriasis and PsA. IL-23 MC given to the mice led to enhanced accumulation of CCR6-positive γδ T cells in the ear skin, cervical skin draining lymph nodes, ankle joints, and popliteal lymph nodes. Moreover, we also observed an increased infiltration of CCR6-positive γδ T cells in the Achilles tendon from IL-23 MC mice. To summarize, we showed that CCL20 was highly upregulated in PsA SF.

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