RHEUMATOLOGY RESEARCH FOUNDATION

SUMMER RESEARCH SERIES

ADVANCES IN THE TREATMENT OF INFLAMMATORY ARTHRITIS

FRIDAY, AUGUST 13TH
2:00 - 4:30 PM EDT

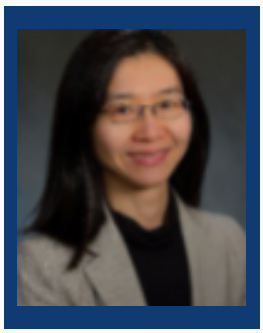
Cong-Qiu Chu, MD, PhD
Oregon Health & Science University

Novel Treatment Strategies Targeting Synovial Stroma for Rheumatoid Arthritis

Innovative Research Award

Therapy for rheumatoid arthritis (RA) has significantly improved the quality of life in these patients. However, even those most efficacious biological drugs are unable to cure the disease and have a therapeutic ceiling of response at around 70%. The common mechanisms of action of these highly targeted and effective drugs are inhibition of inflammatory components and immune cells. Other mechanisms underlying the persistence of inflammation in RA have not been explored but open alternative avenues for targeted therapy. RA is primarily an inflammation of the synovium. RA synovium shares similarities to tumor tissue, namely, RA synovium proliferates and invades adjacent cartilage and bone leading to joint destruction. The tumor like feature of RA synovium is largely contributed by fibroblast-like synoviocytes (FLS). In a healthy joint, synovium is a thin loosely organized connective tissue without a basal membrane. Instead, synovium is bordered by a lining layer which comprises of resident FLS and cells of monocyte in origin. In RA, synovium grows enormously and invade into cartilage and bone. This is the result of expansion of FLS in the lining and sublining layers and infiltration of immune and inflammatory cells. FLS build a stromal network which harbors immune and inflammatory cells. Moreover, FLS actively interact with immune cells and inflammatory cells lead to persistent inflammation of the synovium with new vessel formation and ectopic lymphoid follicles. In addition, RA FLS can also produce inflammatory cytokines participating inflammatory process. Thus, RA FLS are a potential target for alternative therapy which may induce long-lasting therapeutic effect. Here in murine RA models, we propose two strategies to ablate FLS by targeting fibroblast activation protein (FAP) which is specifically expressed by FLS, thereby disrupting the stromal structure of the tumor-like synovium: 1) We will immunize arthritic mice with DNA based vaccines against FAP to generate cytotoxic T cell immunity; 2) We will use engineered chimeric antigen receptor (CAR) T cells against FAP to treat mice with arthritis. Both vaccines and CAR T cells are novel approaches to therapy of arthritis by targeting these non-immune cells. These strategies are highly translational into clinical trials for development of novel and potential long-lasting therapies for RA.

Laura F. Su, MD, PhD
University of Pennsylvania



Self-reactive CD4+ T Cells Drive Autoantibody Production in Ectopic Lymphoid Aggregates in Rheumatoid Arthritis

Innovative Research Award

Rheumatoid arthritis (RA) is a debilitating disease that causes inflammation and deforming joint destruction. RA afflicts 1.5 million people in the United States and is becoming increasingly more common as the average age of the U.S. population increases. It is also one of the most expensive illnesses to treat and results in billions of dollars in increased health care spending. A hallmark of RA is the production of autoantibodies. Approximately 70% of RA patients generate rheumatoid factor (RF) and autoantibodies to cyclic citrullinated antigens (anti-CCP). While cognate interactions with the follicular helper subset of CD4+ T cells (Tfh) are broadly required for B cell differentiation and antibody affinity maturation, the specific mechanisms that promote autoreactive antibody formation in RA and other autoimmune diseases remain poorly understood. Recent studies have demonstrated an abnormal accumulation of autoantibody producing B cells with a distinct phenotypic profile in RA patients. These B cells belong to a broader effector B cell population generally referred to as age-associated B cells (ABC). ABCs arise with age and accumulate in the setting of autoimmunity and chronic infection. A dominant feature of ABCs is the expression of the transcription factor T-bet. Using HIV infection as a model to study chronic inflammation, we have observed an accumulation of T-bet+ B cells in inflamed primary human lymph nodes. Notably, we found T-bet expression in B cells correlated with the abundance of a distinct CXCR5- CD4+ T cell population characterized by up-regulation of activation markers and high PD-1 and ICOS expression. These CXCR5- CD4+ T cells that we identified in HIV-infected LNs phenotypically resemble a previously described circulating population of CXCR5- CD4+ T cells that has been implicated in the formation of ectopic lymphoid aggregates in the synovial tissues of RA patients. Whether CXCR5-PD-1+CD4+ T cells contribute to autoantibody production in RA is unknown. In the proposed study, we will use precise cellular tools and high dimensional imaging modalities to test the hypothesis that the CXCR5-PD-1+ phenotype is enriched for autoreactive CD4+ T cells that drive ectopic autoantibody production in inflamed synovium of RA patients.

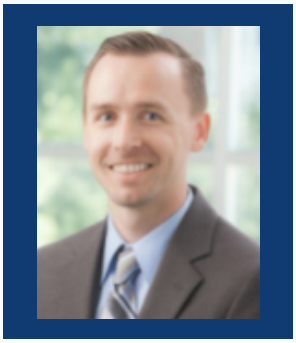
Erika Darrah, PhD
Johns Hopkins University

The Role of Citrullination in the Processing and Presentation of Autoantigens in Rheumatoid Arthritis

Innovative Research Award

Citrullinated proteins are hallmark targets of the immune response in rheumatoid arthritis (RA) with approximately 80% of patients making anti-citrullinated protein antibodies (ACPAs). CD4+ T cells that preferentially recognize citrullinated versions of self-peptides have also been identified. Citrullinated proteins are generated via the post-translational deimination of arginine residues by the peptidylarginine deiminase enzymes (PADs), and PAD-inhibition has shown therapeutic promise in pre-clinical models of RA. Despite the wide-spread acceptance of citrullinated antigens as key drivers of RA pathogenesis, it remains unknown how citrullinated antigens become immunologic targets. The strong association of RA development with a specific group of MHC class II alleles called the â€œshared epitopeâ€ (SE) alleles, particularly in patients with ACPAs, suggests that CD4+ T cells are critical for disease development. A growing body of evidence suggests that even minor modifications to self-proteins, such as citrullination, may play a role in their targeting by the immune system. These changes have been shown to alter the way self-proteins are processed and presented by the MHC class II antigen processing machinery, leading to the presentation of neo-epitopes. A newly described form of neutrophil death, called leukotoxic hypercitrullination (LTH), induced by host and bacterial pore-forming molecules, has been shown to trigger wide-spread protein citrullination and may act as a pro-inflammatory source of citrullinated autoantigens in RA. Preliminary data revealed that neutrophils dying via LTH induced activation of antigen presenting cells including upregulation of co-stimulatory and MHC class II molecules. This proposal aims to define the consequences of protein citrullination on antigen processing at the molecular level using proteolytic mapping and a novel natural antigen processing assay (NAPA). NAPA harnesses the power of an individualâ€™s cellular antigen processing machinery and will serve as a unique platform to interrogate the effect of citrullination on the processing and presentation of well-defined RA autoantigens. This proposal will also determine if neutrophils dying by LTH are a pro-inflammatory source of RA autoantigens and will provide a cellular model to interrogate the efficacy of current and emerging therapeutics on this process. These studies have the potential to define fundamental mechanisms by which citrullinated proteins become immunogenic targets in patients with RA and elucidate some of the most proximal factors responsible for RA initiation. This may inform the design of novel therapies aimed at blocking the generation of immunogenic peptides or selectively inhibiting antigen-specific immune responses.

Bryant R. England, MD
University of Nebraska Medical Center &
Nebraska-Western IA VA Health Care System



Epidemiology of Multimorbidity in Rheumatoid Arthritis
Scientist Development Award

Multimorbidity, the presence of two or more chronic conditions, poses a tremendous threat to health by increasing the risk of hospitalization, disability, and mortality. Although associated with similarly poor long-term outcomes and predisposing to the development of many

individual chronic diseases, there has been little study of multimorbidity in the context of rheumatoid arthritis (RA). Thus, while strategies to reduce multimorbidity development and progression in RA are needed, significant knowledge gaps limit the development of effective management approaches. In this proposal, we will conduct a comprehensive epidemiologic study of multimorbidity in RA. In Specific Aim 1, we will use large administrative and electronic health record enabled datasets to characterize the prevalence, incidence, and progression of multimorbidity compared to matched general population and diseased controls, with an emphasis on multimorbidity risk surrounding the period of RA onset. In Specific Aim 2, we will use novel bioinformatics methods to identify multimorbidity clusters in RA patients and compare their prognostic value for important health-related outcomes – hospitalization, mortality, and healthcare utilization. Together, this will establish a requisite foundation of knowledge referent to multimorbidity in RA including the derivation of clinically informative RA multimorbidity clusters. The results will inform future multimorbidity outcome measure development as well as pharmacoepidemiologic and comparative effectiveness studies in the multimorbid RA population. Coupled with a robust research training plan, the proposed investigation will be completed under the guidance of a highly-productive team of senior investigators and will support the applicant's development into an independent investigator with the necessary skillset to lead future clinical and translational research efforts.

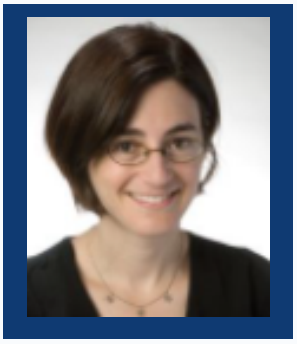
Kentaro Yomogida, MD
Washington University in St. Louis

Plasticity of Innate Lymphoid Cells and their Potential Pathological Roles in Juvenile Idiopathic Arthritis
Tobé and Stephen E. Malawista, MD Endowment in Academic Rheumatology

My project is to delineate the contributions of innate lymphoid cells (ILCs) to the pathogenesis of juvenile idiopathic arthritis (JIA). ILCs are recently discovered lymphocytes without rearranged antigen receptors and are classified into three groups based on cytokine response, cytokine production and master transcription factors; T-bet+ILC1s secrete IFN- γ; GATA3+ ILC2s produce IL-5 and IL-13; RORγt+ILC3s produce IL-17 and IL-22 as well as GM-CSF and TNF- α. While each group of ILCs has distinct phenotypical features, past reports have demonstrated their plasticity. ILC2 is known to produce IL-17 and IFN- γ in inflammatory conditions and ILC3 can acquire phenotypes resembling ILC1 (ex-ILC3). Although ILC3 is known to convert to ILC1, mechanisms and biological impact of ILC3 plasticity remain to be elucidated. In humans, ILC3 plasticity has been demonstrated only in vitro, and its presence has not yet been validated in vivo. Recent study revealed abundance of ILC3s in synovial fluid from patients with spondyloarthritis and psoriatic arthritis suggesting potential pathological roles of ILC3s in inflammatory arthritis. However, little is known on the mechanisms by which ILC3s may cause pathology: they could mediate damage through secretion of IL-17, IL-22, TNF- α or GM-CSF. Alternatively, ILC3 is known to acquire phenotypical features of ILC1

(ex-ILC3) and conversion into ILC1s may exacerbate pathology. Our preliminary studies demonstrate that activated ILC3s become ex-ILC3 in both human and mouse and murine ILC3 conversion is strongly enhanced in models of autoimmunity. In addition, we identified the cell surface markers that profile ILC3s, converting ILC3s and ILC1s in human for the first time. Here, my project is dissected into three parts: first, I am examining the mechanisms regulating ILC3 plasticity and generating mouse models in which plasticity is blocked. Second, I am establishing the impact of ILC3s and their plasticity in mouse models of arthritis. Finally, I am investigating the impact of ILC3s and their plasticity on JIA patients.

Sarah Ringold, MD, MS
Seattle Children's Hospital



Disease Recapture after Drug Discontinuation and Flare in JIA

Innovative Research Award

Background: The use of conventional disease-modifying antirheumatic drugs (DMARDs) and biologic medications has significantly improved disease control for children with juvenile idiopathic arthritis (JIA), resulting in increasing numbers of children attaining remission. Ongoing treatment after achieving disease control comes with multiple downsides, including the considerable costs of biologic medications, missed school and work for infusions, toxicity risks, side effects, the psychological burdens of repeated injections, and the uncertain risks of future adverse drug effects, particularly malignancies. As a result, stopping medication for remission is a priority for many patients, families, and clinicians. An important part of the decision-making around stopping treatment is understanding whether restarting medications can promptly and fully control flares that follow medication discontinuation. Very few data regarding disease recapture for children with JIA have been published. This lack of data contributes to the uncertainty surrounding outcomes associated with medication discontinuation and makes decisions about medication discontinuation particularly challenging for patients, families, and providers. This proposal will address this gap in knowledge, with the goal of generating data about recapture rates and predictors that can be incorporated into the decision-making process. The primary aims addressed by this project will be: 1) to measure rates of successful recapture for patients who are tapering or have discontinued their DMARD or biologic medications due to well-controlled disease and 2) to identify clinical and laboratory variables associated with successful or unsuccessful recapture. Biospecimens will be collected on a subset of patients to generate preliminary data regarding biomarkers associated with successful or unsuccessful recapture.

Approach: This will be an observational study using collected by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) patient registry. The registry currently includes data from over 5,000 children with JIA from more than 60 centers in North America. Clinical data and biospecimens will also be collected for a subset of children that will include children

enrolled into the Understanding Childhood Arthritis Network (UCAN). Data will be analyzed from 300 children restarting medications for disease flare experienced while tapering or after stopping medications, to determine the proportion of patients who were able to achieve clinical inactive disease within 6 months. Possible predictors of disease recapture, including age, JIA category, and disease duration, will be assessed to identify variables associated with either successful or unsuccessful recapture. Biospecimens will be collected for 75 children and analyzed using methods, including machine-learning techniques, currently in use by UCAN.

Anticipated results and future directions: This proposal will generate much needed information for providers and families to make more informed decisions about the risks and benefits of continued medication use versus withdrawal. The data collected during the study period will identify children with lower rates of successful recapture who may benefit from alternative management strategies, such as dose reduction instead of complete discontinuation. This study will lay the groundwork for future research on biologic predictors of recapture and facilitate the development of personalized regimens for both discontinuing and re-initiating treatment following flare once initial remission is achieved.

We hope you will join us. Registration is required.

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