Dr. Laura Geraldino-Pardilla

Title: Anti-Citrullinated Peptide Antibodies: Surrogate Markers Of Cardiac Dysfunction And/Or Atherosclerosis In Rheumatoid Arthritis Patients?

The **overarching** goal of this work is to provide a novel tool for early detection and therapeutic decision making for RA patients at high risk for CV events. Rheumatoid arthritis (RA) is an autoimmune disease affecting ~1% of the population. Despite the significant advancements in RA treatment, standardized mortality rates still remain up to 3 times higher than in the general population. Cardiovascular (CV) disease, including myocardial infarctions and heart failure, represents the leading cause of excess deaths in RA populations. Anti-citrullinated peptide antibodies (ACPA) are highly specific for RA, and occur in 60-70% of patients. Our group has shown a strong correlation of ACPA titers with an unusual cardiac phenotype in RA – i.e., low left ventricular (LV) mass by cardiac MRI (CMR). Moreover, we have recently confirmed the presence of citrullinated substrates in autopsied myocardia of RA patients, and preliminary data from our collaborators at Stanford University also indicate the presence of citrullinated substrate(s) in atherosclerotic plaques of non-RA patients. These data strongly suggest that autoreactivity to citrullinated peptides may constitute a critical link between autoimmunity and the increased prevalence and incidence of atherosclerosis and myocardial dysfunction. However, the identity and specificity of the peptides undergoing citrullination are unknown.

My hypothesis is that autoreactivity to one or more specific citrullinated peptides will be highly associated with low LV mass and/or coronary artery atherosclerosis in patients with RA. In the proposed studies, we will investigate and identify circulating autoantibodies to specific citrullinated peptides in RA patients using ELISA arrays, and correlate these with measures of left ventricular function/structure by CMR (Aim 1) as well as with a measure of coronary atherosclerosis, coronary artery calcium (CAC), assessed by cardiac CT (Aim 2). We will use sera from Dr. Bathon's ESCAPE-RA I (Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis) cohort. This represents a very unique cohort of RA patients with extensive phenotyping for subclinical cardiovascular disease (i.e., CMR, cardiac CT and carotid ultrasound) and RA disease characteristics, and for whom we have stored serum and plasma samples from 3 visits over 30 months. Identifying the specific peptide(s) against which the anti-CCP reactivity is directed will constitute an indirect, but important, advance in understanding the pathophysiology of accelerated CV disease in RA, given that direct evaluations of RA myocardial and vascular tissues are nearly impossible. If this hypothesis is confirmed, our findings could have multidisciplinary implications and potentially translate into changes in current medical practice. The results derived from this study will support my planned K23 where I will validate these findings and expand with pertinent studies.