“Over my many years as a general internist, despite my subspecialty, one of the most challenging of adult chronic diseases is systemic lupus erythematosus (SLE). The etiology is perplexing, manifestations highly variable and therapeutic approaches non-specific and unpredictably successful. I chose this area of science and medicine published in the JCI for this month’s Newsletter because it demonstrates some promise for BIIB059, a humanized monoclonal antibody that binds blood DC antigen 2 (BDCA2), a pDC-specific receptor that inhibits the production of IFN-I and other inflammatory mediators. This appears applicable for the dermatological and possibly other systemic manifestations of SLE. Stay tuned as I’m sure more will follow this first-in-human trial.”

Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus

Richard Furie,† Victoria P. Werth,‡ Joseph F. Merola,§ Lauren Stevenson,*, Taylor L. Reynolds,*, Himanshu Naik,*, Wenting Wang,*, Romy Christmann,*, Agnes Gardet,*, Alex Pellerin,*, Stefan Hamann,*, Pavan Auluck,*, Catherine Babey, Parul Gulati,*, Dania Rabah, and Nathalie Franchimont*

Division of Rheumatology, Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York, USA. †Department of Dermatology, Perelman School of Medicine, University of Pennsylvania and Corporal Michael Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA. ‡Department of Dermatology and Department of Medicine, Division of Rheumatology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA. *Bogen, Cambridge, Massachusetts, USA.

BACKGROUND. Plasmacytoid DCs (pDC) produce large amounts of type I IFN (IFN-I), cytokines convincingly linked to systemic lupus erythematosus (SLE) pathogenesis. BIIB059 is a humanized mAb that binds blood DC antigen 2 (BDCA2), a pDC-specific receptor that inhibits the production of IFN-I and other inflammatory mediators when ligated. A first-in-human study was conducted to assess safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) effects of single BIIB059 doses in healthy volunteers (HV) and patients with SLE with active cutaneous disease as well as proof of biological activity and preliminary clinical response in the SLE cohort.

METHODS. A randomized, double-blind, placebo-controlled clinical trial was conducted in HV (n = 54) and patients with SLE (n = 12). All subjects were monitored for adverse events. Serum BIIB059 concentrations, BDCA2 levels on pDCs, and IFN-responsive biomarkers in whole blood and skin biopsies were measured. Skin disease activity was determined using the Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A).

RESULTS. Single doses of BIIB059 were associated with favorable safety and PK profiles. BIIB059 administration led to BDCA2 internalization on pDCs, which correlated with circulating BIIB059 levels. BIIB059 administration in patients with SLE decreased expression of IFN response genes in blood, normalized Mca expression, reduced immune infiltrates in skin lesions, and decreased CLASI-A score.

CONCLUSIONS. Single doses of BIIB059 were associated with favorable safety and PK/PD profiles and robust target engagement and biological activity, supporting further development of BIIB059 in SLE. The data suggest that targeting pDCs may be beneficial for patients with SLE, especially those with cutaneous manifestations.

TRIAL REGISTRATION. ClinicalTrials.gov NCT02106892.
Jesse Davidson, MD MPH MSc is an Assistant Professor in the Department of Pediatrics. He received his medical degree from Duke University School of Medicine, his Masters of Public Health from the University of North Carolina, Chapel Hill, and his Masters of Clinical Science from the University of Colorado. Dr. Davidson practices as a pediatric cardiac intensivist and echocardiographer in the Section of Cardiology and serves as an Associate Medical Director for the Research Institute at Children’s Hospital Colorado.

Dr. Davidson’s research focuses on the mechanisms, diagnosis, and therapy of multi-organ dysfunction following pediatric cardiac surgery. In his fellowship, Dr. Davidson identified a prominent decrease in soluble alkaline phosphatase following infant cardiac surgery that was tightly associated with short term post-operative outcomes. Based on these findings, he was awarded an AHA Career Development Award followed by a K23 from the NHLBI to validate these findings. This work also identified extracellular adenine nucleotides and endotoxin as potential biologic targets of alkaline phosphatase. Dr. Davidson then collaborated with Suzanne Osorio-Lujan, DVM, PhD and James Jaggers, MD to develop a porcine model of infant cardiac surgery with cardiopulmonary bypass funded by grants from the Department of Defense and the American Heart Association. This model serves as a platform both for additional mechanistic work and for preliminary testing of bovine alkaline phosphatase infusion to prevent post-operative multi-organ injury.

Dr. Davidson has also begun to apply metabolomic approaches to congenital heart disease research in a series of collaborations with Jelena Klawitter, PhD and Benjamin Frank, MD. This team recently published findings on the profound metabolic shift experienced by infants undergoing cardiac surgery and are currently applying this systems biology approach to multiple aspects of congenital heart disease including single ventricle pulmonary vascular development (American Heart Association), acute kidney injury, and acute lung injury.