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ASN Carl W. Gottschalk Research Scholar Grant
Title: GWAS-based Pathogenesis Model of IgA Nephropathy

Immunoglobulin A Nephropathy (IgAN) is a major cause of kidney disease worldwide. It is one of the leading causes of kidney failure among Asians, and the most common form of primary glomerular disease among Europeans. The affected individuals develop characteristic IgA-containing antibody complexes that deposit in the kidney producing tissue injury. Similar to other immune-mediated disorders, IgAN is a genetically complex trait. Not much is known about its pathogenesis and the treatment options are presently limited.

We have recently completed a genome-wide association study of IgAN in 20,574 individuals. In this large international study, we identified 15 inherited genetic factors that were strongly associated with disease risk. We observed that the worldwide distribution of these factors closely paralleled the variation in disease occurrence across continents. We also discovered that individuals who were born with a greater number of risk alleles had an earlier onset of kidney disease, and thus were at a higher lifetime risk of reaching end stage kidney failure. Moreover, our findings identified that genetic defects in the immune system responsible for defense against mucosal infections were central to the disease process.

Based on our findings, we propose a novel pathogenesis model for IgAN. We hypothesize that the disease arises as a consequence of sequential hits to the immune system, and we identified a candidate genetic factor for each putative hit. The first part of this proposal will relate the newly discovered genetic factors to immunologic disease features, specific kidney biopsy findings, and clinical parameters of disease severity and progression. These studies are expected to refine the pathogenesis model and will be critical in enhancing the diagnosis and classification of IgAN.

The second part of the proposal aims to define the missing link between the newly discovered genetic factors and clinical disease features. We aim to address this gap through integration of DNA and immunological profiles of patients with a powerful RNA profiling of IgA-producing cells. Completion of the proposed studies will provide the knowledge that is necessary to translate the genetic findings into clinical applications. Most importantly, the identification of disease-causing pathways and their key molecular drivers will open doors to new therapeutic approaches. The drugs that are specific to the disease process are likely to be more effective and less toxic compared to the presently available treatments.