Application number/Title: 1618 - Interaction of genetics and environment in triggering anti-PLA2R autoantibody in membranous nephropathy: a paradigm for initiation of autoimmunity

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Keywords provided by the Applicant PI to describe the research project:

anti-pla2r, autoimmunity, genetics, infection, kidney, proteinuria

Application Lay Summary:

Primary Membranous Nephropathy (MN)is a rare chronic, kidney disease, generally affecting men and women aged 40-70yrs (2:1 ratio). Individuals present with heavy proteinuria (loss of large amounts of serum protein in the urine) with 80% of cases seropositive for an autoantibody, anti-phospholipase receptor 1 (anti-PLA2R), which damages the podocyte, the cell responsible for maintaining the glomerular filtering unit. This project seeks to understand how genetic predisposition to MN and environmental factors e.g.infection, occupational chemical exposure interact to initiate this specific autoantibody (anti-PLA2R)that damages the glomerular filter to cause proteinuria. Understanding the mechanism by which anti-PLA2R autoantibodies are produced will improve the prognosis and treatment options for patients with MN. Recently we identified the two genes DQA1 and PLA2R that account for the susceptibility to MN (NEJM 2011)and have developed an ELISA to quantitate anti-PLA2R in clinical management(Kid Int 2013). We defined the major epitope recognised by anti-PLA2R (JASN 2015). In this study, we will identify potential MN cases in the prodromal and active disease state based solely on genetic risk and proteinuria data from UK Biobank. The whole cohort will be assessed for genetic risk markers of PLA2R and DQA1 and by protein/creatinine ratio (P/C). Known cases of diabetic nephropathy will be excluded. The cohort will be classified by genotype (none, one or two pathological alleles)for each of PLA2R and DQA1. All genotypes will be classified for urine Protein/Creatinine ratio. We will classify the 9 genotype combinations based on demographic data and investigate these groups for environmental exposure to chemical exposure based on occupation, geography and smoking history. The classification will

identify the spectrum of MN cases, prodromal to overt disease. The full cohort will be included for data analysis of genetic markers and urine analysis (protein/creatinine ratio). We would exclude patients with high Hb1c (diabetic proteinuria).

We would require data on demographics, smoking history, occupational chemical/infection exposure for all cases. This will enable us to determine the phenotype of each of the 9 genotypes.