

IGA Nephropathy Foundation of America

IgA Nephropathy Research Team at UAB: 2018 Progress Report

Gifts from *IGA Nephropathy Foundation of America* in 2018 provided funding for continued research concerning the causes of IgA nephropathy and assessment of approaches for treatment of the disease.

The Foundation supported in part the following research projects:

- Detection of IgG autoantibodies in glomerular deposits. We showed that patients with IgA nephropathy have IgG autoantibodies in the glomeruli (filtering units in the kidneys) specific for galactose-deficient IgA1, including patients whose kidney biopsies did not exhibit IgG by routine immunofluorescence microscopy. This finding, now with a manuscript draft prepared for submission, supports UAB team's hypothesis on the key role of IgG autoantibodies in pathogenesis of the disease.

Paper in preparation. Dr. Rizk presented results in a lecture at 15th International Symposium on IgA Nephropathy, Buenos Aires, Argentina, September 27-29, 2018. Dr. Rizk received a prize from the International IgAN Network for outstanding presentation.
- Development of a new mouse model of IgA nephropathy. Uniqueness of the human IgA system complicates studies of disease pathogenesis in experimental animals, as only humans and some primates have IgA1 with its O-glycans. To circumvent this problem, we developed a mouse model using passive administration of human immune complexes into immunodeficient mice. For the first time, these studies provided *in vivo* direct evidence for a disease-causing role of immune complexes consisting of galactose-deficient IgA1 and IgG autoantibodies. Furthermore, this mouse model may provide a basis for development of future preclinical testing of therapeutics.

Paper in revision, preliminary data used for a grant submission in July 2018.
- Assessment of composition and mechanism of action of disease-inducing immune complexes. These complexes with galactose-deficient IgA1 are in the circulating blood and deposit in the kidneys of patients with IgA nephropathy to cause damage to the filtering units (glomeruli). These studies are clarifying the features of the immune complexes in the blood of patients that induce kidney injury.

Preliminary data used for a grant submission in July 2018. Dr. Renfrow presented an invited a lecture 15th International Symposium on IgA Nephropathy, Buenos Aires, Argentina, September 27-29, 2018.
- Structural characterization of IgG autoantibodies. We have been using an IgG autoantibody derived from blood cells of a patient with IgA nephropathy to produce crystals for structure-function experiments. Our preliminary results already provide a molecular-level understanding of these IgG autoantibodies that are key for the formation of immune complexes. Defining the specific properties of the circulating autoantibodies that recognize galactose-deficient IgA1 to form immune complexes will provide information that will aid in development of future disease-specific treatment, e.g., medication(s) preventing disease-causing activities of these autoantibodies.

Preliminary data will be used for a grant submission in February 2019.

5. Studies of a Chinese traditional herbal medicine used for treatment of IgA nephropathy in China. Shen Ping decoction is an herbal medicine that has been prescribed to treat IgA nephropathy in China for decades. To investigate its pharmaceutical mechanisms, we assessed its effects in our *in vitro* model system of cultured human mesangial cells. Moreover, we have performed initial isolation and characterization of the active components. These experiments have been conducted in collaboration with Dr. Chen, the inventor of this remedy at the Shanghai University of Traditional Chinese Medicine, Shanghai, China. Moreover, The Foundation supported a 6-month stay of a visiting scientist from Dr. Chen's groups, Dr. XianWen (Judy) Zhang, at UAB in Dr. Novak's laboratory. Our studies showed that this Chinese herbal medicine blocked disease-causing activation of multiple signaling pathways. These findings thus begin to outline the mechanisms of treatment that may benefit patients with IgA nephropathy. Ongoing collaboration with the hospital in Shanghai aims to assess how the treatment impacts immune responses of the patients and whether it can reduce production or activity of autoantibodies.

Poster presented at 15th International Symposium on IgA Nephropathy, Buenos Aires, Argentina, September 27-29, 2018 and manuscript in preparation.

6. Characterization of abnormalities of cells that produce galactose-deficient IgA1. We found that specific compounds involved in responses to infections, such as cytokine IL-6, cause an abnormally strong activation of a signaling factor, called STAT3, that controls cells producing antibodies. This abnormal activation caused overproduction of galactose-deficient IgA1. It is possible that this abnormal signaling pathway may represent a new target for disease-specific therapy. Dr. Reily, Assistant Professor in Nephrology and a former post-doc in Dr. Novak's laboratory, has been working closely with our group and has developed single-cell protocols to determine the mechanisms enhancing production of an autoantigen in patients with IgA nephropathy.

Dr. Reily presented results in a lecture at 15th International Symposium on IgA Nephropathy, Buenos Aires, Argentina, September 27-29, 2018 and used preliminary data for his R03 grant submitted in October 2018.

Additional support in kind:

Dr. Reily, a member of IgA Nephropathy Research team at UAB, was in March 2018 promoted to Assistant Professor in Nephrology and received Research Acceleration Funds (\$100,000 per year for 3 years) from the School of Medicine through a request by Dr. Agarwal, Director of the Division of Nephrology. These funds enabled him to hire a technician and start developing new approaches to analyze the mechanisms enhancing production of galactose-deficient IgA1 in patients with IgA nephropathy. This additional support, together with the ongoing support from the Foundation and his K01 grant, helped to fund studies focused on *Hit 1* in IgA nephropathy, *i.e.*, production of the key autoantigen, galactose-deficient IgA1. Through better understanding of the causes leading to over-production of galactose-deficient IgA1, researchers may start designing disease-specific treatments that would impact *Hit 1*.

In summary, the Foundation's support has helped to maintain the cutting-edge academic research into the causes of IgA nephropathy by the IgA Nephropathy Research team at UAB, and enabled development and extension of ongoing studies as well as retention of staff at the time of reduced federal funding.

Publications and presentations resulting from this support are listed in a separate document.