CureJM Grant Recipient:

Dr. Chack-Yung Yu, Nationwide Children's Hospital, OH

Lay Summary

Juvenile dermatomyositis (JDM) is the most common form of inflammation in the muscles and skin in children. Many children with JDM have had the disease for a long time. The illness starts with patients' immune systems erroneously attacking their tissue. Many patients with JDM have antibodies that bind to cellular proteins in the muscles or skin, leading to sores and injury.

An important group of immune proteins, the Complement System, is engaged in the destructive process in JDM. Complement proteins normally do the job of defending our bodies from infections. In JDM patients, the complement system receives false signals from certain antibodies and white blood cells, while the complement ends up being self-destructive.

Our team believes specific gene changes in the complement system make some children more likely to develop JDM. The antibodies that bind to skin and muscle cells in patients with JDM are known as myositis-related autoantibodies. Some myositis-related autoantibodies may trigger the activation of complement proteins to cause harmful effects.

Our goal is to study changes in immune cells and proteins over time in different phases of JDM. These phases include pre-treatment, when the disease is well-controlled, and during disease flares.

The research team proposes the following three specific study objectives:

The *first objective* is to investigate how genetic factors contribute to a higher probability of developing JDM. Our team has early data suggesting that low levels of an immune protein known as **complement C4** play an important role in setting up the "risky stage" for some children to be more prone to the developing skin and muscle diseases.

The *second objective* is to study how myositis-related autoantibodies in JDM regulate the activation of the complement protein related to self-destruction. Our team will work out how changes in complement C4 gene numbers, gene sequences and their protein products are triggered by myositis-related autoantibodies.

The *third objective* is to study how a specific group of white blood cells known as T-cells contribute to cellular immune response and tissue injuries.

Key People

Dr. Chack Yang Yu

My research interests have been focused on genetic and structural variations of immune response genes, particularly those of the complement system, among healthy subjects and patients with autoimmune (AI) diseases and diabetes. My research team has led the charge in establishing the phenomenon of multi-allelic gene copy-number variations (CNVs) and gene size dichotomy for human complement C4. A low copy number of total C4 or C4A is a prevalent risk factor for systemic lupus erythematosus (SLE) and idiopathic inflammatory myopathies (IIM) with medium effect size. We are utilizing our expertise in decoding the genetic complexity of complement C4 to other innate immunity loci with copy number variations among racial groups and patients with AI disease. We aim to untangle the roles of innate and adaptive immunity genes on the predisposition of AI disease to discover useful biomarkers that help early diagnoses and minimize disease relapses.

Samantha Coss, MD. PhD.

Since completing my Ph.D., I have since completed my MD through Ohio State's NIH-funded MSTP and graduated into the Pediatric Residency at Nationwide Children's Hospital. Here at Nationwide Children's, I have provided an array of medical care to a diverse population of patients, including patients with autoimmune disorders. As a part of the Rheumatology inpatient team and outpatient clinic, I am passionate about rheumatology and autoimmune diseases. I am particularly driven to understand the biological underpinnings of autoimmune disease to target more effective treatments.

Impact of Grant Funding

This Cure JM grant will allow us to study the genetic diversity of innate immune response genes in differentiating the risk, progression, and complications of juvenile dermatomyositis. We will be able to interpret the genetic risk factors of JDM in a large collection of patients with the disease. We are enthusiastically motivated by the implications of this project, and we have the passion, dedication, expertise, and support to complete this important research.

Ultimately, this project may provide new markers to predict disease status and guide treatment and management.