The Immune Deficiency Foundation Research Grant Awards 2018-2019

Role of Topoisomerase 2 beta in human B cell development
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B cell development in humans requires active selection for immunoglobulin maturit and elimination or attenuation of antigenic self-reactivity. The role of Top2b in B cell development and differentiation remain unknown. We recently described a presentation of complete B cell immunodeficiency, associated with facial, limb and genital anomalies. We used whole genome sequencing of affected patients and unlinked first-degree relatives from two families to identify genetic mutations in a common gene. Variant analysis revealed mutations in TOP2B. A role for Top2b in B cell development and differentiation has not previously been described.

We hypothesize that mutations in TOP2B are responsible for the immunodeficiency phenotype observed in patients due to negative effects on B cell differentiation and elimination of immature B cell populations. Disruption of the development and use of induced pluripotent stem cells from our immunodeficient patients as a model of how loss of Top2b function affects regulation of B cell development, and 2) elucidate the mechanisms of transcriptional regulation by Top2b.

These studies will provide greater insight into the mechanisms of B cell development. An understanding of the role of Top2b will have far reaching effects on our ability to treat B cell-driven diseases.

Clinical indications of early bone loss in Common Variable Immunodeficiency
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More than half of all Americans experience osteoporosis placing them at risk for bone fractures. CVI patients are therefore at increased risk of developing osteoporosis as compared to the average person of the same age. The reasons for this increased risk are varied and include exposure to corticosteroids or prednisone, poor nutrition leading to low calcium and D levels, and long-standing inflammation. We are seeking to administer a survey to IDF members with antibody deficiency as well as Duke patients. Survey data along with data from the medical charts of the Duke patients will be analyzed. This information will help us to determine what factors place CVI patients at increased risk of osteoporosis and bone fractures. We plan to use this knowledge to create guidelines for screening, especially in higher risk patients as well as outline treatment of osteoporosis in CVI patients.

This will be the largest combined study of osteoporosis in pediatric and adult CVI patients. This provides a first step toward the creation of guidelines for low bone density/osteoporosis in CVI. It will provide a platform for a prospective project of screening and treatment of low bone density/bone fractures in CVI. We would be able to provide data for a translational project examining the mechanism of low bone density/osteoporosis in CVI.

Novel genetic variants in pediatric patients with immune dysregulation
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The immune system must maintain a delicate lifelong balance between the ability to recognize a near-infinite number of pathogens and the recognition of self-tissue. Defects in this regard can result in immune dysregulation syndromes, which cause a great deal of morbidity. The immune system efficiently controls infections and eliminates cancer cells. ‘Immune dysregulation syndromes’ describe a group of rare primary immune deficiencies overlapping clinical features including lymphoproliferation, cancer, autoimmunity, and recurrent infections.

Recently our lab described a cohort of patients with gain-of-function (GOF) variants in STAT3 resulting in early onset autoimmunity and autoimmunity. Identification of this variant has led to targeted therapies for these patients.

Our laboratory is interested in understanding the molecular basis of some of these syndromes; however, a significant number of children remain undiagnosed. We will identify pediatric patients with newly discovered syndromes, and perform whole-exome sequencing to identify new genetic defects.

The long-term goal is to develop personalized therapies for these children translating our research into improved patient care.

CXR2-Dependent neutrophil chemotaxis defect in Hyper IgE Syndrome
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Hyper-IgE (IgE) syndrome (HIES), or Job's syndrome is a primary (genetic) immunodeficiency clinically characterized by eczema, cold abscesses, recurrent infections and fungal infections, eczema, characteristic facial features, skeletal abnormalities, neutrophilic migratory skin lesions, and an increased risk of bone fractures, and indolent cold abscesses.

These abscesses are called ‘cold’ for their lack of the classical features of inflammation, such as warmth, redness, tenderness and fever. Cold abscesses indicate a deficient inflammatory response, and were the original defining feature of HIES. Mutations in the STAT3 gene have been identified in almost all classic HIES patients. We do not yet understand how these mutations lead to the clinical picture seen in these patients. Recurrent infections are major cause of morbidity in HIES. Clearance of infection requires a coordinated immune response, including immune cell (e.g. neutrophil granulocyte) migration to the site of injury.

The goal of this proposal is to study STAT3-dependent neutrophil granulocyte migration to understand the immune defects in HIES. This proposal will identify critical steps in the human inflammatory response and potential therapeutic targets we currently lack to develop specific therapies for HIES.

Neurological manifestations of Common Variable Immune Deficiency (CVID)
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CVID is a condition that leaves patients susceptible to frequent and severe bacterial, fungal, viral, and parasitic infections. Patients with CVID do not produce enough antibodies to protect against these infections. In the case of bacterial infections, the immune system does not have enough antibodies to mount an effective immune response to bacterial pathogens. This can lead to recurrent infections, autoimmune complications, and immune cell accumulation in lung and gut disease that is caused by mutations that turn off a related PI3K molecule.

We have recently expanded our genetic analyses in primary immunodeficiency patients with a focus on PI3K gene mutations and have discovered a new disease involving recurrent infections, autoimmune complications, and immune cell accumulation in lung/gut disease that is caused by mutations that turn off a related PI3K molecule.

The goal of this proposal is to investigate the mechanistic link between the mutated mutations and defects in innate immunity that underlie disease. This work will help define potential therapies for PI3K related syndromes and will advance our understanding of PI3K in immune function, a topic emerging as central to a spectrum of immunodeficiency diseases.

Inherited T-BET deficiency in Mendelian susceptibility to mycobacterial disease
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Mendelian susceptibility to mycobacterial disease (MSMD) is a rare birth defect that causes recurrent infections with weakly virulent mycobacteria, including M. bovis Bacille Calmette-Guérin (BCG) vaccines and environmental mycobacteria (EM).

In this proposed study, we identified a patient with MSMD caused by T-BET deficiency. This deficiency led to a unique clinical and immunological manifestation. Our research will result in a more in-depth understanding of an immunodeficiency not caused by defects in T-BET as well as the non-redundancy immunological role of T-BET.

Currently, our research will have far-reaching translational, clinical and immunological implications. If successful, it will lead to 1) the discovery of a novel genetic effect of MSMD; 2) an improvement in our understanding of the non-redundant function of T-bet in human infection; 3) a better awareness of potential adverse effects of the BCG vaccine, one of the most widely administered vaccines worldwide; 4) the development of new genetic diagnostic criteria for clinical mycobacterial diseases; 5) advanced mycobacterial prevention, including possibly tuberculosis, in genetically susceptible populations; 6) the development of novel therapeutic avenues by restoring or supplementing immunity specific to mycobacterial infection.

The Immune Deficiency Foundation
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IDF is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.