The Immune Deficiency Foundation Research Grant Awards 2018- 2019

2018

Role of Topoismerase 2 beta in human B cell development

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B cell development in humans requires active selection for immunologic maturity and elimination or inactivation of autoreactive cells, yet many details regarding this selection 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 unaffected 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 immunoclinical phenotype observed in patients due to negative effects on B cell differentiation, and elimination of immature B cells. Here, we propose the development and use of induced pluripotent stem cells from our immunodeficient patients to 1) examine 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 in B cells will have far reaching effects on our ability to treat B cell-driven diseases.

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-limitless number of pathogens and tumor antigens while at the same time learning to limit immune activation and recognition of self-tissues. When this balance is successful, the immune system efficiently controls infections and eliminates cancer cells. "Immune dysregulation syndromes" describe a group of rare primary immunodeficiencies with 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 leading to early-onset autoimmunity and immunodeficiency. 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 immune dysregulation 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.

CXCR2-Dependent neutrophil chemotaxis defect in Hyper IgE Syndrome

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Hyper-immunoglobulin E (IgE) syndrome (HIES), or Job's syndrome is a primary (genetic) immunodeficiency clinically characterized by high serum concentration of IgE, bacterial and fungal infections, eczema, characteristic facial features, skeletal findings, including 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 and mortality 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 lacking to develop specific therapies for HIES.

Novel signaling aberrations in a novel primary immunodeficiency disorder

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Identifying and understanding the molecular causes of inherited immune disorders are important scientific goals because of the potential to not only solve and better treat disease in these individuals but also to provide key insights into fundamental human biology. Our prior work has helped achieve this in a group of primary immunodeficiency patients with mutations that activate a pathway called PI3K, which is now being inhibited in clinical trials in this disease.

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 inherited mutations and defects in innate immunity that underlie disease. This work will help define potential new therapies for this disease and related disorders and will advance our understanding of PI3K in immune function, a topic emerging as central to a spectrum of immune diseases.

2019

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. CVID patients are thought to have an increased risk of developing osteoporosis compared to the average person of the same age. The reasons for this are many and include exposure to corticosteroids or prednisone, poor nutrition leading to low calcium and vitamin 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 understand what factors place CVID 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 CVID patients.

This will be the largest combined study of osteoporosis in pediatric and adult CVID patients. This provides a first step toward the creation of guidelines for low bone density/osteoporosis in CVID. It will provide pilot data for a prospective project of screening and treatment of low bone density. Additionally, it will contribute to preliminary data for a translational project examining the mechanism of low bone density/osteoporosis in CVID.

PIDD in patients with persistent post-rituximab hypogammaglobulinemia

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Rituximab is a drug that temporarily depletes B cells. It is used in the treatment of autoimmune disorders and lymphoma. For most, the IgG levels rebound to normal levels within 1-2 years. However, several patients are more than five years post rituximab treatment who still need immunoglobulin replacement as their own body cannot produce enough.

Few case reports suggest that there might be a true underlying primary immune defect in these patients. Increasingly, autoimmune manifestation and lymphoma are recognized as a presenting manifestation of defects in immune regulation. We hypothesize that rituximab in these patients with underlying genetic predisposition accelerates the development of low immunoglobulin and immune deficiency state thereby unmasking the underlying immune defects years earlier than it would have.

We propose to systematically study these patients to characterize their disease manifestations, immune abnormalities, and genetic basis. Understanding the biology and genetic basis could help in ascertaining long-term prognosis, could aid in the initiation of targeted therapies and consideration for definitive treatment such as bone marrow transplant if a genetic defect is identified.

Neurological manifestations of Common Variable Immune Deficiency (CVID)

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CVID is a condition that leaves patients susceptible to frequent and serious infections, as the immune system does not effectively or appropriately fight off infections. Paradoxically, in CVID, the immune system also sometimes attacks the body when it should not, causing autoimmune disease as well.

We have diagnosed an increasing number of patients with CVID in the Neurology clinic -- but there is little to no understanding of how frequently patients with CVID develop neurologic symptoms or diseases, and if the development of these neurologic conditions is coincidental or related to CVID. There are known CVID-associated autoimmune conditions affecting virtually every system of the body except the neurologic system, which further raises the suspicion that there are under-recognized associated neurologic diseases. This lack of recognition of neurologic comorbidity could potentially lead to increased suffering amongst CVID patients.

We further propose to analyze this information to find the most common neurologic diseases, and form categories of neurologic disease associated with CVID. We will then, using a panel of experts, formulate and publish guidelines for the evaluation and diagnosis of the most common neurologic conditions in the CVID population.

Inherited T-BET deficiency in Mendelian susceptibility to mycobacterial disease

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Mendelian susceptibility to mycobacterial disease (MSMD) is a rare disorder that can lead to severe infection 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 caused by T-BET deficiency as well as the non-redundancy immunological role of T-BET. Collectively, the proposed research will have far-reaching translational, clinical and immunological implications.

If successful, it will lead to 1) the discovery of a new genetic etiology of MSMD; 2) an improvement in our understanding of the non-redundant function of T-bet in human infection in 3) a better awareness of potential adverse effects of the BCG vaccine, one of the most widely administrated 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.

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.