THE HARTWELL FOUNDATION

2022 Individual Biomedical Research Award

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Leveraging Shared Patterns of Immune Dysfunction to Target Primary Immune Regulatory Disorders

One in 1200 Americans have an inborn error of immunity that leads to frequent and severe infections, autoimmunity, and cancer. A subset of these conditions, with many different causative genes, are known as primary immune regulatory disorders (PIRD). Diagnosis and treatment of inborn errors remain a significant challenge for pediatricians because the diversity of potential underlying causes arise from a constellation of genetic errors: more than 450 genes have been identified, which when mutated impair immune function. Problematically, there are simply too many possibilities to target individual therapies for each inborn error. Uniquely, PIRD all share overactivation of a single signaling pathway that negatively impacts immune T cell function. With complex and difficult-to-manage clinical phenotypes that generate significant morbidity and mortality, PIRD are remarkable for the breadth of their impacts on immune health. Most significant, PIRD are characterized by a state of immune dysregulation caused by chronic T cell hyperactivation that is typical of chronic infection and cancer, degrading T-cell function to exhaustion. My hypothesis is that the mimicry of chronic infection via amplified T cell receptor signaling leads to amplified mTOR signaling (an essential serine/threonine protein kinase in a critical signaling pathway that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, metabolism, and transcription) and ultimately, T cell exhaustion. To identify shared patterns of poor immune function in PIRD, I propose a novel strategy of targeting the disrupted immune pathway(s) rather than a specific gene. Rather than focus on differences between PIRD, I will target similarities, focusing on one shared dysfunctional state: *immune exhaustion*. In this regard, I have developed a set of diagnostic panels to measure impaired immune cell function. The tests recognize altered RNA expression as well as the quantity and quality of signaling in PIRD patient immune cells and have enabled me to generate preliminary evidence substantiating patterns of T cell exhaustion in a subset of the disorders. To clarify the drivers of T cell exhaustion in PIRD, I propose to evaluate “retuning” of the identified dysfunctional pathways responsible for T cell exhaustion in cell culture, using existing approved medications. If I am successful in identifying shared patterns of immune dysfunction in primary immune regulatory disorders, it will facilitate precision diagnosis, making it possible to target drug therapy to improve the health and quality of life of affected children.