THE HARTWELL FOUNDATION

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Machine Learning to Identify Biological Markers for Allergic Disease

Allergic diseases are disorders of the immune system initiated in early life as a result of sensitization to environmental allergens. Once allergen sensitization is established, therapy is primarily focused on management of symptoms. Asthma is one such common disorder, in which allergens cause swelling of the airways, create difficulty in breathing, produce wheezing, coughing and tightness in the chest. With no cure, asthma can be deadly. In the United States, more than 6 million children have asthma, which has been increasing in all age, sex and racial groups since the early 1980's. Notable exceptions are those children reared in close proximity to farm animals, particularly Amish children, who have increased exposure to diverse microbes and bacterial organisms yet seem to have remarkable protection against allergic disease. A popular theory known as the *hygiene hypothesis* has evolved to explain this phenomenon and suggests exposure to diverse bacteria in early life is necessary for the development of a normal immune system. The working hypothesis is that there is a window of opportunity within the first 100 days of an infant's life where microbe-based treatments may be useful in preventing the latent development of chronic allergic asthma. In this regard, there is supporting evidence using gene expression profiling that the blood immune profiles and gut microbiota are different for non-farm vs farm children. However, the particular biological molecules that can safely confer protection against asthma for millions of children at risk remains unknown. To address this unmet need, I propose to identify the early life gastrointestinal microorganism population at the species level (metagenomic sequencing) in birth cohorts from 50 farm, 50 non-farm and 50 Amish stool samples, which will enable identification of immune modulating bacteria and candidate bacterial products of metabolism (metabolites like short-chain fatty acids). Because beneficial microbial effects may occur in part via stimulation of immune cells by specific metabolites, I will characterize immune cell composition from their cord blood stimulated with candidate metabolites. This approach will also enable identification of cell components of the immune system that can be used as a biomarker for children who are potentially at-risk for asthma or protected from asthma; as well as potential asthma biomarkers and the immune cells in which they are differentially expressed. Using computational tools like machine learning, I will develop a prediction algorithm to determine if a child is likely to get allergic disease. If I am able to define the origins of protection from allergies, metabolites from beneficial bacteria will be used in clinical trials to evaluate their protective effect for the millions of children raised in non-farm environments who would otherwise suffer from allergic disease. If clinical translation is successful, the result would be a therapeutic intervention to prevent the development of allergic asthma in children.