THE HARTWELL FOUNDATION

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Modulating Immune Cell Dysregulation in Autoimmune-Associated Uveitis

Uveitis is a serious condition brought on by inflammation of the middle layer of the eyeball that may develop rapidly and cause lasting damage to the eye. While the cause may be an acute infection, about half of all cases are of unknown origin and presumed to be an early manifestation of systemic childhood autoimmune disease. Among children, the most frequent cause of uveitis is juvenile idiopathic arthritis (JIA). With approximately 7,000 children in the United States affected by JIA-associated uveitis, outcomes may be severe; 30-40% of patients experience substantial loss of vision and often blindness. Remarkably, despite its isolation as an immunologically privileged site from the rest of the body's immune system, the eye is the first organ to succumb to autoimmune disease; and while chronic uveitis accounts for approximately 15% of all cases of total blindness in the United States, little is known about the altered response of immune cells in the eyes to the systemic immune response. Steroid eye drops are the front-line therapy for treating uveitis, but long-term use has significant adverse side effects, such as glaucoma, retinal detachment and macular edema. Systemic immunosuppressive therapies have limited efficacy and are not well tolerated, causing infection, cancer and infertility. Moreover, systemically treating uveitis disregards any putative beneficial role for the intact immune system in maintaining eye health. To address this vision-threatening childhood disease, Shayn offers a new paradigm: cells comprising our immune system do not all behave “badly” in autoimmune disease and as such, do not categorically need to be restrained by immunosuppressive drugs. In 2013 she identified two distinct populations of immune cell macrophages in healthy versus pathological retinal eye tissue: those with degenerative activity (M1) and those with regenerative capabilities (M2). She hypothesizes that during chronic childhood uveitis the balance between M1 and M2 favors degenerative macrophages and ultimately, impaired vision. She suggests it may be possible however, to control the ratio of these immune cell macrophages by using a class of drugs that targets sphingosine-1-phosphate receptor subtypes (S1P1 and S1P3) on the macrophage cell surface. Using a mouse model of childhood uveitis she will examine the dynamic relationship between degenerative and regenerative macrophages in the eye and seek to identify drugs that can modulate S1P receptor subtype signaling. A rabbit model will be used to substantiate future human clinical trials for drugs that can be delivered in the form of eye drops. If Shayn is successful, re-setting the balance between degenerative and regenerative changes in uveitis has the potential to restore health and prevent blindness in an estimated 20,000 affected children.