THE HARTWELL FOUNDATION

2024 Nominee Individual Biomedical Research Award

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Targeted Immunotherapies to Prevent Solid Organ Transplant Rejection

For children with end-stage organ failure, a transplant is often their last hope. However, pediatric transplants come with unique challenges, such as the age of the donor organ relative to the age of the recipient. A main reason for the long-term failure of heart, lung, and kidney transplants is an inflammatory immune response that causes blood vessels in the transplanted organ to narrow and function improperly. This problem is especially common in transplanted hearts, where it is known as cardiac allograft vasculopathy (CAV). While the origin and mechanisms of CAV are still under investigation, it exhibits characteristics of atherosclerosis, including cholesterol accumulation and inflammation in the blood vessel walls. To prevent the body from rejecting a transplanted organ, the current standard of care involves the use of potent immunosuppressive medications to weaken the immune response, along with statins to lower cholesterol levels that can contribute to the development of CAV. The incidence of CAV, however, has remained unchanged over the past 30 years, suggesting that complex immune-mediated risk factors are involved in CAV progression in children. Therefore, given the lack of effective treatments for CAV, there is a critical need to develop novel therapeutic approaches that can reduce, delay, or prevent the condition and extend the lifespan of transplanted organs. Rather than mitigating non-immune risk factors or broadly inhibiting immune pathways as maintenance therapies, I propose to introduce a regulatory protein that has nuanced effects on the immune system. To address the inflammation underlying cardiovascular diseases, I developed a platform to target immunomodulatory proteins in atherosclerotic plaques, reducing inflammation in the apolipoprotein E knockout (apoE-/-) model of murine atherosclerosis that shares many similarities to CAV. Specifically, I engineered a fusion protein in which one domain is an antibody fragment that binds to low-density lipoprotein cholesterol and the other domain is the anti-inflammatory protein IL-10. I have shown that this construct binds circulating cholesterol in the bloodstream of mice, hitchhikes a ride to atherosclerotic lesions, and locally suppresses vascular inflammation. To evaluate the effect of this novel engineered protein in reducing inflammation in the context of heart transplantations, I propose a cell model in vitro that simulates the transplantation process, as well as mouse models of heart transplantation. My targeted approach will reduce toxic side effects associated with broad-spectrum immunosuppressants while modulating the immune environment of the vasculature, shifting it from a pro-inflammatory to a pro-regenerative state. If successful, this strategy will change the paradigm following transplantation from systemic immunosuppression to localized therapy, ultimately improving both quality of life and rejection-free survival for pediatric organ transplant recipients.