THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Preventing Infections in Children Undergoing Bone Marrow Transplantation: Boosting First Responder Immune T Cell Expansion to Improve Outcomes

When cancer treatment fails in children, one of the last resorts is bone marrow transplantation. In this process, the child's entire immune system is eradicated and they are given a new immune system from a donor. Infections pose the largest risk to the child during the period when the new immune system is weak and 35% of children die in the first years after treatment. In part, this is due to the fact that the immune system takes so long to fully recover (αβ T cells are the slowest to recover). However, about 90% of children that can rapidly produce a special kind of first responder γδ T cell will survive. It is not known why some children produce greater numbers of γδ T cells or what stimulates their growth. To address this unmet need, it is necessary either to develop better antimicrobials or to improve the patient immune response. Better antimicrobials require a drug for every pathogen class and each will come with its own side effects. By contrast, enhancing the immune response has the advantage of improving outcomes towards broad classes of infections, does not require rapid pathogen identification and can be used as a preventive strategy. Using a novel approach, Paul proposes to isolate large quantities of first responder γδ T cell receptors from the skin, lungs, and gut and then place them into a unique cell line created in his lab for the high-throughput readout of T cell activation. This will enable the identification of drugs that will promote formation of these vital cells and boost immune protection against infections when children are most vulnerable. Combining the unbiased characterization of T cell receptors and the exceptional capabilities of high throughput screening, he will seek to discover a lead candidate drug that specifically triggers first responder T cell receptors to enhance the expansion of a protective T cell response. His goal will be to reduce infections after bone marrow transplantation, with a targeted 80% improvement in survival (from a 40% mortality rate to a 7% mortality rate). If Paul is successful, it will represent a major advance in bone marrow transplant care for children and potentially broaden the indications for which bone marrow transplants can be utilized.