# THE HARTWELL FOUNDATION

## 2007 Individual Biomedical Research Award

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### JNK Signaling at the Crossroads of Immunity and Tolerance: Molecular Control of Childhood Diabetes

Each year over 15,000 children are diagnosed with type-1 diabetes in the US — more than 40 children every day. It is currently a disease with no cure, due principally to the fact that it is a cell-mediated autoimmune disorder responsible for destroying the islet cells of the pancreas; cells, which provide the body's primary source of insulin. Effectively, an inappropriate immune response apparently occurs when T-cells become inexplicably sensitized to antigens associated with the insulin producing cells of the pancreas, attack, and destroy the islet cells. The outcome of the autoimmune response is critically dependent upon induction of T cell immunity or tolerance; but how the cell fate decision between T cell immunity and tolerance occurs is not entirely clear. Normally, cell-mediated immune responses are important in defense against pathogens, including some acquired allergies. Unfortunately, there are no appropriate animal constructs available to address signaling for the cell fate decision. In this regard, Dr. Chi proposes that one of the central intracellular pathways in this process, the JNK pathway, may be the signal for T-cell "inactivation" and therefore, could be a pivotal regulator of this process. To explore whether manipulation of the JNK pathway in animal models will alter the pathogenesis of type 1 diabetes, he has recently generated an innovative and remarkable genetic mouse model, removing all of the important components of the JNK pathway, as well as the essential negative regulators of JNK activity, from the mouse genome. His intent is to determine whether JNK is a key cell fate determinant in T cells and whether the JNK pathway might be an important drug target for type-1 diabetes. If successful, the results will also have enormous potential application for other autoimmune pathology affecting children, including treatment of graft rejection and possibly, for directed tumor immunotherapy.