THE HARTWELL FOUNDATION

2008 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **James L. Ferrara, MD, D.Sc.**
Professor
Department of Pediatrics and Internal Medicine and Immunology

Institution: **University of Michigan**

Proposal: **A Bioenergetic Strategy to Treat Graft Versus Host Disease**

Dr. Ferrara proposes to lead a translational effort to demonstrate the selective effectiveness of a novel target drug for treatment of graft-versus-host disease (GVHD) in unrelated-donor bone marrow transplantation (BMT). For many types of cancers that affect blood, bone marrow, and lymph nodes, BMT is an essential and effective therapy, but unfortunately also toxic. The donor white blood cells (lymphocytes) cause the problem. The recipient conditioning regimen prior to BMT destroys bone marrow ability to grow new blood cells and eliminates immune system cells, damaging host tissues and causing release of pro-inflammatory cytokines (signaling proteins) that activate host and donor white cells. Donor immune cells that encounter unrelated host recipient cells respond by signaling and activating white cells derived from the transplant to migrate to the encounter site. Activated lymphocytes proliferate in number and pathogenically amplify the immune response by releasing inflammatory and cellular effectors in a "cytokine storm" that produces additional organ damage and fulminant GVHD. Standard therapy is high dose corticosteroids, which will blunt the response of all lymphocytes. However, steroids are successful in only half the cases and cause multiple problems, such as infections and diabetes. Unfortunately, the incidence of GVHD will increase in the next ten years due to the increasing number of transplants performed from unrelated donors, placing pediatric patients at an even higher risk of GVHD. Given this information, Dr. Ferrara seeks to exploit how during cell proliferation the metabolic demands of pathogenic lymphocytes increase enormously, suggesting that Bz-423, a lead compound that disrupts the energy producing machinery of the cell, may, in a BMT mouse model system, preferentially kill only the activated lymphocytes responsible for the disease. Presumably, pathogenic lymphocytes are susceptible to the drug due their acquired metabolic weakness to an elevated requirement for energy, compared to normal or resting lymphocytes. If Dr. Ferrara is successful, preclinical data will lead to a Phase I trial of this entirely innovative approach to treat GVHD, benefitting children who are eligible for high risk BMT from an unrelated donor and who therefore are likely to develop GVHD.