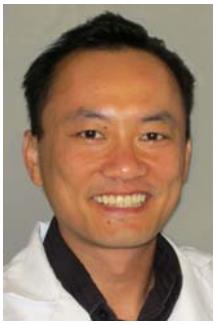
THE HARTWELL FOUNDATION

2010 Individual Biomedical Research Award

Review of Proposed Research



Investigator: **Jack Bui, MD, Ph.D.**
Assistant Professor
Department of Pathology

Institution: **University of California, San Diego**

Proposal: **Using Regressor Tumors to Treat Childhood Sarcomas**

In the United States, cancer is the leading cause of disease-related death in children less than 20 years old. There is a critical need to develop innovative cancer therapeutics for this population; but so far a cure has been elusive in spite of the resources that have been expended. Ironically, we may only have to look within ourselves for the cure. Specifically, spontaneous remission from terminal cancer has been documented and is thought to occur via the body's own immune system attacking and destroying the cancerous cells. Although such remissions are quite rare and have been estimated to occur in as few as 1 in 100,000 patients, it is likely that immune system removal of cancer cells occurs in many individuals not diagnosed because this immunological defense mechanism has protected them. In a paradigm shift, Jack proposes to understand how spontaneous remission of terminal cancer can be duplicated. He wants to understand how immune cells are activated to destroy tumor cells. Based on preliminary experiments in a mouse model, he has generated two distinguishable types of sarcoma tumor cell lines, one type that when transplanted into genetically identical, wild-type mice are rejected by the immune system (termed regressors) or the second type, which grow as tumors (termed progressors). Sarcoma "regressor" cells do not survive in immune-competent mice because as regressor cells they activate the immune system and are rejected. Jack has also found that some regressor sarcoma cells can be used to stimulate the immune system to reject certain progressor sarcoma cells. Regressors have general characteristics of tumors but appear to be enriched in genes that can stimulate the immune system to eliminate the cancer. Using microarray analysis, he has identified the gene for a known, but not understood cytokine (chemical involved in growth and regulation) as a major participant in tumor rejection — a potent modulator of immune function that is produced by the sarcomas that undergo spontaneous remission. Effectively, Dr. Bui may have found a regimen to treat established sarcomas in mice, enabling the mice to be resistant to subsequent challenge by sarcoma tumors and exhibit sustained remission. His working hypothesis is that the certain genes expressed in regressor cancer cell lines can be used to therapeutically stimulate the immune system to eradicate cancers like sarcoma. If his proposed research is successful, then the current five-year survival of children with sarcoma (30-70%, depending on the stage and type) can be expected to be significantly improved using his approach. Similarly, it may be possible to identify other regressor cell genes for other cancers, which may be deployed as a new class of anti-cancer therapeutics.