# THE HARTWELL FOUNDATION

## 2011 Individual Biomedical Research Award

### Review of Proposed Research

**Investigator:** **Jing Yang, Ph.D.**
**Assistant Professor**
**Departments of Pharmacology and Pediatrics**

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

**Proposal:** **Targeting Neural Crest Migration Program to Treat Ewing's Sarcoma Metastasis**

Cancer is the leading cause of disease-related death in children and is the second leading cause of all deaths to children, behind automobile accidents. One such cancer, called Ewing's sarcoma (EWS), is a malignant tumor that commonly appears in a bone. It usually occurs between 10-20 years of age (more than 200 cases per year) and is more common in males. About 25% of pediatric patients present with clinically detectable metastatic disease (secondary cancerous growth) in the lung and/or in bone. There are currently no known causes of the disease or methods of prevention. Because most patients with clinically apparent localized disease at diagnosis may also have occult metastatic disease, multidrug chemotherapy as well as local disease control with surgery and/or radiation therapy is applied for all patients. Despite aggressive therapy and marked improvement in survival among patients with local disease during the past 40 years (50% cure rate), almost no improvement has been seen in patients with metastatic disease (80% mortality). The main reason for the failure to treat metastatic EWS is due to the complete lack of understanding of what molecular pathways regulate metastasis. Recently however, Ewing sarcoma-specific gene expression profiling suggested that a specialized group of embryonic stem cells (neural crest cells) may be the origin of EWS. Neural crest cells are highly motile cells derived from neural epithelial cells and migrate extensively throughout the body during embryogenesis with the potential to give rise to many different cell types. Several genes involved in neural crest formation have been implicated in promoting cancer. Jing hypothesizes that a group of genes that regulate the generation and function of neural crest cells, which normally are shut off after they have completed their functions, are reactivated to allow EWS cells to metastasize. She has determined that expression of the TWIST1 gene is associated with metastasis and poor survival in affected sarcoma patients. The gene encodes a transcription factor (protein) required for neural crest migration and may very well be a marker for distant metastasis and prognostic for poor survival. Therefore, Jing proposes to identify and describe the signaling pathways regulating EWS metastasis and thus identify target drugs that will block metastasis with higher specificity and fewer side effects than conventional therapy. If her approach is successful, it would reduce morbidity from ineffective conventional therapies and prolong the lives of countless children affected with metastatic EWS.