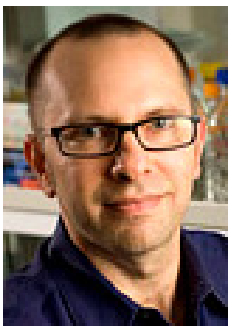
THE HARTWELL FOUNDATION

2009 Individual Biomedical Research Award

Review of Proposed Research



Investigator: **Peter J. Murray, Ph.D.**
Associate Member
Infectious Diseases and Immunology

Institution: **St. Jude Children's Research Hospital**

Proposal: **Tumor Associated Macrophages: Molecular and Functional Dissection in Models of Childhood Solid Tumors**

Dr. Murray proposes to determine if tumor-associated macrophages are struggling to fight the cancer or paradoxically, are actually helping cancer cells survive and proliferate. The association of these inflammation-inducing cells with solid tumors is directly linked to tumor progression through a variety of mechanisms, including survival and proliferation of malignant cells, formation of new blood vessels, inhibition of immune responses, and response to hormones and chemotherapeutic agents. By contrast, the signals that drive inflammation in tumors, the interaction between inflammatory and tumor cells, and the outcomes in terms of cancer progression, remain largely unknown. Macrophages were first observed in tumors a century ago, leading to the notion that cancers may be a type of inflammation distinct from the normal inflammatory processes that macrophages (a type of white blood that ingests foreign material) use to control infectious agents. Macrophages arise from bone marrow stem cells and blood monocytes, and populate most organs, where they fulfill both specialized and generalized surveillance functions. A generalized function of all macrophages is the recognition of pathogens and the subsequent production of mediators that signal both tissue damage (inflammation) and the development of antibodies (acquired immunity). Most evidence suggests that events during tumor development attract macrophage progenitor cells to continuously seed the tumor. The signals to attract these cells are unknown, but could include tumor-derived chemo-attractants, or the many dead and dying cells present within rapidly growing tumors. Regardless of the mechanism, most solid tumors contain variable amounts of macrophages. Dr. Murray hypothesizes that tumor-associated macrophages contribute to the cancer process in multiple ways, including the production of trophic factors (supporting growth), pro-angiogenic factors (supporting the appearance of new blood vessels), and matrix modification factors (controlling the cellular environment). He has developed several tumor models (neuroblastomas, retinoblastomas and transplantable solid tumors) necessary to characterize and track populations of inflammatory macrophages in human tumor samples. Using this approach, he proposes to determine if macrophages should be activated or silenced to control tumor growth. If successful, Dr. Murray's contributions will provide a roadmap to manipulate the inflammatory response in cancer, generating momentum in an area poised to make an impact in the management of pediatric tumors.