THE HARTWELL FOUNDATION

2008 Individual Biomedical Research Award

Review of Proposed Research

Investigator: **David C. Lyden, MD, Ph.D.**
Associate Professor
Department of Pediatrics, Cell and Developmental Biology

Institution: **Cornell University**

Proposal: **Bone Marrow-Derived Stromal Cell Contribution in Medullablastoma**

Dr. Lyden proposes a transformative approach to reduce the reoccurrence of cancer. As a clinician, he specializes in meduloblastoma. It is the most common brain cancer in children, representing 20% of all childhood brain tumors. Highly malignant and metastatic, meduloblastoma most often arises in the cerebellum and spreads into the central nervous system. Aggressive radiotherapy after surgery in combination with short-term, intense chemotherapy has increased the overall five-year survival rate among high-risk patients to 70 percent. Patients who survive the course of therapy are subject to long-standing and devastating side effects, including those that contribute to growth impairment, a loss of motor abilities, memory impairment, diminished learning capability and shifts in personality. Because of the chemotherapy, surviving patients are often partially or completely deaf. Despite timely therapy, approximately 40 % to 50% of children with medulloblastoma will have recurrent disease, almost invariably associated with a poor prognosis. Current therapies focus on killing dividing tumor cells, although other cells also seem to be essential for growth of the developing tumor. In particular, Dr. Lyden has focused on certain bone marrow-derived stem cells (BMDC) that are at the invasive front and associated with the medulloblastoma blood capillaries (perivascular niche), pointing out that the BMDC seem to "attract" cancer stem cells; encouraging them to reside in conditions favorable to selectively maintain and expand their population. By this mechanism, he proposes the cancer stem cells are resistant to conventional therapy and can direct their developmental potential toward reappearance of the cancer at future sites of metastasis. Even more important, Dr. Lyden describes secreted microparticles released by BMDC that are capable of promoting the exchange of genetic information with medulloblastoma cells, suggesting they may represent a novel molecular system for horizontal cell-to-cell regulation. If the microparticles can traverse the blood-brain barrier and promote the survival and growth of cancer stem cells in the perivascular niche for tumor recurrence, the implications would be profound. If successful, Dr. Lyden will derive specific site-directed therapies for meduloblastoma that target the BMDC, including strategies to counteract the microparticles and thereby, reduce reoccurrence of the cancer.