Project Description

Kidney cancer is one of the most common and one of the deadliest of all human cancers, with over 60,000 new cases being diagnosed per year and claiming approximately 15,000 lives yearly. For patients with metastatic kidney cancer, five year survival rates are well below 50% highlighting the fact that new and better treatments are urgently needed. To achieve this, we must first understand the specific molecular pathways that are altered in kidney cancer and which are relied upon by the tumor cells for their continued growth and survival. The WISE project I am proposing builds upon a new discovery in my lab that has identified a vital contribution for the oxidative branch of the pentose phosphate pathway for maintaining kidney cancer cell viability, proliferation, and tumorigenesis in vivo. Briefly, we have used a bioinformatics approach to mine the landmark NIH-funded TCGA gene expression dataset to identify several genes in the pentose phosphate pathway whose expression is significantly increased in cancer vs. normal kidney tissue samples. Our own metabolomics analysis has confirmed that deregulation of this biochemical pathway is a cardinal feature of the disease. Furthermore, using genetic RNA interference-based knockdown approaches in human clear cell renal cell carcinoma (the main subtype of malignant kidney cancer) cells in culture, we have verified that kidney cancer cells indeed require a functionally intact pathway to drive tumor growth, thereby revealing a new anti-cancer approach that may have a profound therapeutic benefit for patients with this deadly disease. The WISE student will initiate a project that will expand on these findings by seeking to decipher why and how deregulation of the pentose phosphate pathway contributes to kidney cancer development and progression. Specifically, the student will perform experiments aimed at understanding whether activation of the pentose phosphate pathway fuels tumorigenesis in a manner dependent upon increased production of cellular reducing equivalents (NADPH), increased production of
nucleotides (e.g. ATP, GTP, CTP, UTP), or by driving increases in production of both classes of molecules. Upon completion of the project, the student will have acquired expertise in sterile tissue culture techniques, state-of-the-art molecular biology approaches such as lentivirus-mediated knockdown or knockout using RNA interference and/or CRISPR/Cas9 genome editing, and biochemical endpoint assays to measure relevant biomolecules. Furthermore, the student will have the opportunity to contribute to a project that is likely to culminate in a scientific publication.