

Bankhead-Coley Cancer Research Program

Wu, Jie

*Molecular Oncology
H. Lee Moffitt Cancer Center and Research Institute*

*2006 Program
Bridge (1-year project)*

Project Title: Targeting Shp2 for New Cancer Therapeutics and Tools for Chemical Biology

Project Summary: Nearly 1.4 million Americans will be diagnosed with cancer and 564,830 will die of the disease this year. The alarming cancer death rate is largely due to the lack of efficacious anticancer drugs. Indeed, most chemotherapy drugs have major side effects and are not effective at curing the most devastating cancers. Thus, there is a pressing need to develop more efficacious and less toxic anticancer drugs. The discovery of anticancer drugs has historically relied on the search for compounds that stop cells from dividing, which act upon on all dividing cells regardless if they are cancerous or not. This proposal aims to develop new drugs that specifically target cancer cells. Protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) are enzymes that control the phosphorylation of tyrosine residues in key signaling proteins. Abnormal protein tyrosine phosphorylation is a well-established molecular basis of human cancer. Imatinib, Sprycel, Gefitinib, Tarceva, and Herceptin are examples of anticancer drugs developed recently to target PTKs. While PTP research has lagged behind PTKs, studies by this team and others have revealed that some PTPs cooperate with PTKs to control cancer development and are therefore important new anticancer drug targets. Shp2, the subject of this grant, is a PTP that relays oncogenic signal of PTKs such as HER2 in breast cancer. Shp2 is also hijacked by the oncogenic bacteria *H. pylori* to cause gastric cancer. Significantly, Shp2 mutations have been found in various types of human leukemias and solid tumors, such as juvenile myelomonocytic leukemia (JMML), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), neuroblastoma, lung cancer, colon cancer, and melanoma. All Shp2 mutations found in human malignancies are gain-of-function mutations that result in constitutively active Shp2. Thus, this research team postulates that Shp2 is a novel target for cancer therapy. The overall goal of the current study is to develop Shp2 inhibitors as new drugs for treatment of Shp2-related human cancer and as invaluable reagents for laboratory research to understand how Shp2 mediates cancer development. To achieve this goal, it is necessary to identify lead compounds of Shp2 inhibitors from chemical libraries, select the best candidates, and optimize them through chemical synthesis of their analogs. In Specific Aim I, the team will synthesize analogs of a lead compound originally identified from a National Cancer Institute chemical library to improve its properties. They will also evaluate primary hits found in their new 20,000-compound library screen to identify lead compounds that are the most specific, most potent, and able to enter cells. Analogs of the best lead compounds will be made to further improve their properties. Chemical synthesis will be assisted by advanced computer modeling. To achieve this goal, promising Shp2 inhibitors will be tested in preclinical models of human cancer. Specific Aim II of this study is to establish suitable human cancer models in animals for testing Shp2 inhibitors and validating Shp2 as a target for cancer therapy. This will be accomplished by determining 1) if depletion of Shp2 in human cancer cells impairs tumor growth and 2) if mice transplanted with human white blood cells containing a

Bankhead-Coley Cancer Research Program

mutated Shp2 develop leukemia. With better lead compounds and preclinical models on hand, the research team will be able to significantly improve their federal grant application to secure necessary funding to continue developing Shp2 inhibitors into new cancer therapy. This collaborative, multidisciplinary study is highly innovative in that it represents the first systemic effort to develop Shp2 inhibitors for cancer therapy. Positive outcomes of this study will lead to an entirely new class of anticancer drug that targets a PTP and will shift the paradigm of anticancer drug design towards targeting specific PTPs. Eventually, the new drug will be commercialized, using a scientific and business model that has led to the licensing of three new anticancer drugs (two in the State of Florida) from the H. Lee Moffitt Cancer Center.