

Bankhead-Coley Cancer Research Program

Sayeski, Peter

*Physiology and Functional Genomics
University of Florida*

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Technology Transfer Feasibility
(1-year project)*

Project Title: Improving the Metabolic Stability of the Jak2 inhibitor, G6

Project Summary: Mutations in the Jak2 allele (one member of a pair or series of genes) result in a variety of disorders including various leukemias, lymphomas, myelomas, and the myeloproliferative neoplasms. In these diseases, cells rapidly divide and become resistant to the properties that govern normal cell growth. The current lack of effective treatments to inhibit Jak2 has greatly hampered our understanding of these diseases and left little hope for patients suffering from these disorders. Using high throughput computational analysis, we screened a drug database in order to identify novel Jak2 inhibitors. One compound in particular, herein designated as G6, was found to be a potent Jak2 inhibitor. Furthermore, it exhibits significant therapeutic effectiveness in three mouse models of Jak2-V617F mediated disease. G6 possesses a number of desirable drug-like characteristics including good aqueous solubility, high membrane permeability, high stability in plasma, and a lack of non-specific cytotoxicity. However, it is extensively metabolized by liver microsomes in vitro (a test done in glass or plastic vessels in the lab). Therefore, the purpose of this study is to identify derivatives of G6 that maintain Jak2 effectiveness, but have improved metabolic stability. As such, completion of these studies will greatly increase the commercial appeal of G6 and hence, potentially provide a new treatment for patients suffering from Jak2-mediated disorders.