GRANT SNAPSHOT

2009 Pancreatic Cancer Action Network – AACR Pilot Grant

Grantee:	Jiayuh Lin, PhD
Institution:	Research Institute at Nationwide Children's Hospital, Columbus, OH
Research Project:	Dual Inhibitors Target JAK2/STAT3 for Novel Pancreatic Cancer Therapy
Award Period:	July 1, 2009 – June 30, 2011
Amount:	$200,000

Biographical Highlights

Dr. Lin received his B.S. in biology and microbiology from FU-JEN Catholic University in Taiwan, and earned a PhD in genetics and molecular biology from University of Delaware. After completing postdoctoral studies in cancer biology at Princeton University, he joined the faculty of University of Michigan. Currently, Dr. Lin is a principal investigator at the Research Institute at Nationwide Children's Hospital and an Associate Professor at Ohio State University Medical Center, Columbus.

Dr. Lin's laboratory focuses on the molecular mechanisms of Signal Transducer and Activator of Transcription (STAT) and p53 pathways in cancer. He has developed novel compounds that inhibit STAT3 activity and has been testing them in pancreatic cancer cells since 2008. These compounds, named FLLL31 and FLLL32, work by preventing two STAT3 molecules from pairing up with each other, a decisive step during STAT3 activation, making them very potent STAT3 inhibitors. Compared to other STAT3 inhibitors, these compounds have distinct advantages because they are not peptides or nucleotides and are not easily metabolized. This keeps them stable and produces long-lasting anti-cancer effects. They also are very small, and can therefore easily enter the cells to find their targets. Preliminary work using these novel compounds on pancreatic cell lines and tumor models demonstrates that they effectively inhibit STAT3 activity and cause cancer cells to die quickly in experimental models.

Project Overview

The funded project provides an opportunity for Dr. Lin to expand his work on molecular inhibitors of pancreatic cancer-specific proteins and will be the first time that the therapeutic potential of the small molecular compound FLLL32 and its analogues will be systematically tested in tumor cells and animal models. Persistent activation in Janus kinase 2 (JAK2) and Signal Transducer and Activator of Transcription 3 (STAT3) have been implicated in pancreatic cancer. STAT3, for example, exists in both normal and tumor cells. In normal cells, it plays a critical role in cell survival and its activities are tightly regulated. However, in many types of cancers, including pancreatic cancer, STAT3 is frequently observed to be constantly activated. The persistent "on" mode of STAT3 is critical for cancer cells to survive and become resistant to chemotherapy. The development of drugs that inhibit STAT3 activity may therefore be a promising way to treat pancreatic cancer and make cancer cells regain sensitivity to chemotherapy. FLLL32, a recently developed compound, is believed to be more potent than other major STAT3 and JAK2 inhibitors and has the added advantage of retaining low toxicity in normal human cells.

The study also will explore the potential utility of using curcumin as a lead compound for drug development. Curcumin, the primary bioactive compound isolated from the dietary spice turmeric, is known to be an effective antioxidant and has been shown to inhibit several targets closely associated with cancer cell growth, including JAK2 and STAT3. The goal is to provide ample pre-clinical evidence of the potential efficacy of these pharmacological compounds and should establish the basis for future clinical study, with the ultimate goal of treatment and improved survival for pancreatic carcinoma.