Ty Louis Campbell Foundation Invests in New Targeted Therapies for Ewing Sarcoma

Kimberly Stegmaier, M.D., Dana-Farber Cancer Institute

Despite improvements in the treatment of many pediatric cancers, cure rates for high-risk pediatric solid tumors remain largely unchanged. Ewing sarcoma, the second most common pediatric cancer involving bone in children and young adults, is one important example. Long-term survival for patients with metastatic disease is less than 30%, and for patients who relapse, the prognosis is even more dismal. Our laboratory has used cutting-edge chemical genomics approaches to identify new drug candidates for this disease. We screened over 1,000 cancer cell lines, a subset of which was Ewing sarcoma, and identified a new drug class that is highly active in Ewing sarcoma cells. This new drug class targets proteins called CDK 7, 12, and 13. These proteins are important in the expression of genes in the cell and also in the control of DNA damage.

The first-in-class CDK 7/12/13 inhibitor, THZ1, was discovered and developed by a Dana-Farber Cancer Institute (DFCI) chemist. We have teamed up with him and his laboratory to study the activity of these novel compounds in Ewing sarcoma. In our preliminary studies, we have demonstrated that the most important target of these compounds in Ewing sarcoma cells is CDK12. Next, we have shown that all of our Ewing sarcoma cell lines that express the critical EWS/FLI cancer-promoting protein are sensitive to THZ1 and to a newer, more specific CDK 12/13 inhibitor called THZ531. In fact, we believe that it is the expression of EWS/FLI that contributes to the extreme sensitivity of these cells to THZ1 and THZ531. These Ewing sarcoma cells undergo cell death with drug treatment, and we have demonstrated in two mouse models of Ewing sarcoma that THZ1 dramatically impairs the growth of the Ewing sarcoma tumors and prolongs the survival of the mice.

Our next steps will be to test these compounds in novel models of Ewing sarcoma developed directly from patient tumors, called patient-derived xenograft (PDX) models, thought to more faithfully predict response to drug treatment in human patients. Second, we will test an exciting drug combination with THZ1 and THZ531 in Ewing sarcoma cells in the laboratory and in Ewing sarcoma mouse models. Third, we will determine the mechanisms behind why the EWS/FLI cancer-promoting protein makes Ewing sarcoma cells so exquisitely sensitive to these compounds.

There is a Boston-based company that is developing CDK 7/12/13 inhibitors for testing in clinical trials for patients with cancer. If our studies are successful, they will form the preclinical data to support the testing of this drug class in children with Ewing sarcoma in first generation single agent trials and in drug-drug combinations in second generation clinical trials.