Award ID:
DP150069

Project Title:
Oral Stat3 Inhibitor as Targeted Treatment for Triple-Negative Breast Cancer

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

An estimated 230,480 new cases of invasive breast cancer will be diagnosed in the US in 2014. Of these, ~40,000 will suffer breast cancer relapse. The breast cancers in half of those that relapse will lack the three breast cancer markers that help guide therapy and are referred to as triple-negative breast cancer (TNBC). There currently are no effective treatments for patients with TNBC. We and other groups have demonstrated that TNBC tumors contain small numbers of cancer cells that persist after standard chemotherapy and cause tumor relapse. We showed that these persisting cancer cells express a new tumor marker, termed Stat3 that is essential for their survival and growth. These findings suggested to us that development of an agent that targets Stat3 for use in combination with standard chemotherapy will overcome chemotherapy resistance and dramatically reduce relapses in patients with TNBC. We successfully developed a small, drug-like compound (C188-9) that binds to Stat3 with high affinity and that potently inhibits its activation in cancer cells. Mice bearing tumors transplanted from patients whose tumors were chemotherapy resistant demonstrated shrinkage of their tumor when the mice were treated with a combination of chemotherapy plus C188-9. We also showed that C188-9 is safe when given by mouth to mice, rats, and dogs and achieves high levels in the blood and tumors of these animals. In addition, we identified a process for producing C188-9 that follows standard guidelines for producing a drug for patient use. In this proposal, we wish to continue developing C188-9 into a treatment for patients with TNBC. Towards this end, we propose studies that will: 1) determine the fraction of TNBC patients in whom C188-9 will reverse resistance to first-line chemotherapy, 2) identify biomarkers that are predictive of tumor response, and 3) identify the first safe and pharmacokinetically suitable oral dose and frequency of C188-9 for administration to cancer patients.