Award ID:
DP150064

Project Title:
Novel Separase Inhibitors to Treat Refractory Breast Cancer

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Currently there is no good therapy for two subtypes of human breast cancers (BC) which have aggressive disease phenotype, often resulting in high mortality. They include the triple negative BC (TNBC), and the endocrine resistant Luminal B subtypes. According to the American Cancer Society, in 2013, there were 232,340 new cases of invasive BC (15,000 in the State of Texas) and 39,620 BC-related deaths in the US. Since 15-20% of the total BC comprises of TNBC and 20% of Luminal B subtypes, it can be estimated that in 2013, ~100,000 women had these deadly forms of BC which contribute to majority of the BC-related deaths. Our goal is to develop a new class of drugs targeted for these hard-to-treat tumors which is safe and effective with least side effect. Towards that goal we have identified a novel target called Separase, an enzyme important for cell division. Separase is an oncogene which is overexpressed in >60% of BC, 50% of TNBC, and 65% of Luminal-B BC tumors, and its overexpression strongly correlates with high incidence of relapse, metastasis, and a lower 5-year overall survival rate. Overexpression of Separase induces aggressive mammary tumors in mice. We hypothesize that modulation of Separase enzymatic activity constitutes a new therapeutic strategy for targeting resistant, Separase-overexpressing tumors, particularly the hard-to-treat TNBC. Using a high throughput screen, we have identified five novel small molecular inhibitors of Separase, which we named Sepin 1-5. Our studies indicate that Sepin-1 is not only well tolerated by the animals, but also highly effective in inhibiting the growth of Separase-overexpressing human TNBC xenografts in mice. Encouraged by these studies, we propose here: 1) to perform FDA required preclinical studies to bring Sepin-1 to the clinic, 2) to further develop highly effective Sepin-1 analog using medicinal chemistry approaches, and 3) to characterize the mechanisms of Sepin action at the molecular level.