Massey Cancer Center Pilot Project Program

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Title: Development of small-molecular inhibitors of the oncogenic transcriptional co-repressor CtBP

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Lay Abstract:

Many cancers turn off the expression tumor suppressor genes, which leads to inappropriate cell survival and cell migration/invasion. C-terminal binding protein (CtBP) is a transcriptional co-repressor protein that helps turn off expression of multiple tumor suppressor genes including PTEN, E-cadherin, and BH3 proteins such as Bik. CtBP is upregulated in multiple types of cancers including 64% of colon cancer tumors, 92% of breast cancer tumors, and 83% of ovarian cancer tumors. We have previously demonstrated that inhibition of the dehydrogenase enzymatic activity of CtBP reverses the cancer phenotype in cancer cells and animal models, and that inhibition of CtBP is non-toxic to normal tissues. In this project we propose to develop tumor-selective CtBP inhibitors with improved potency using a combination of computational approaches, compound synthesis, and evaluation in assays with recombinant CtBP and cancer cells. We expect that these CtBP inhibitors will restore the expression of tumor suppressor genes such as PTEN, E-cadherin, and Bik in tumor cells, which will lead to apoptosis, growth inhibition, and inhibition of migration. Once CtBP inhibitors have been developed, they can be utilized as primary or adjunctive therapies in various cancers where CtBP is upregulated. As these CtBP inhibitors will be tumor-selective, they should have fewer off-target effects and a more favorable side-effect profile as compared to many current oncology drugs.