Current therapies for treatment of chronic myelogenous leukemia (CML) do not eliminate leukemic stem cells (LSCs), leading to relapse of the disease. Discovery of alternative therapies to target LSCs is essential. We have recently reported a more effective method to ablate LSCs using a class of endogenous fatty acid-derived prostaglandin (PGs) metabolites that contain a cyclopentadieneone structure, including PGJ_2 and PGJ_3 (Hedge and Kaushal et al., 2011). We hypothesize that PGJ_2 and PGJ_3 promote programmed cell death (apoptosis) of LSCs by binding to the G-protein coupled receptor (GPCR), prostaglandin D2 (DP receptor) on the surface of the LSCs. An intricate signaling cascade following ligation of the DP receptor by PGJ_2 or PGJ_3 leads to the activation of apoptotic pathways. As a proof of principle experiment, we propose to use genetic methods, such as shRNA, to silence the expression of the DP receptor to complement the use of DP receptor antagonists. We propose a set of experiments to detect the efficiency of the knockdown of the gene expression and to utilize these LSCs for further characterization of the receptors' role in leukemia progression in well established and relevant rodent models.