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"Evaluation of Oridonin derivatives with PROTACs against triple-negative breast cancer"

Oridonin, a natural kaurene-type diterpenoid enriched in the traditional Chinese medicinal herb *Rabdosia rubescens*, is a promising anticancer agent that has been shown to improve survival rates of cancer patients. Although oridonin exhibits antiproliferative capabilities including induction of apoptosis and cell cycle arrest, its low potency against aggressive cancers including triple-negative breast cancer (TNBC) and poor bioavailability limit its incorporation into standard chemotherapeutic regimens. To improve oridonin's chemotherapeutic efficacy, several derivatives containing a thiazole ring were previously synthesized and assessed. Oridonin derivative compound CYD0618 was identified as a potent anticancer agent inhibiting cancer growth both in vitro and in vivo.

CYD0618 was shown to directly bind and inhibit STAT3, a transcription factor that transduces several cytokines and growth factors. Upon ligand binding, STAT3 is phosphorylated, dimerizes, and is transported into the nucleus where the dimer binds DNA to regulate the expression of genes related to proliferation, survival, and transformation of epithelial cells. The STAT3 signaling cascade is constitutively active in ~70% of human cancers, including breast cancer. Thus, CYD0618 is an attractive foundation for the development of broad spectrum anticancer agents. Previously developed experimental STAT3 inhibitors block STAT3 dimerization upstream of DNA binding. However, these inhibitors show poor clinical activity due to low specificity and basal biological activity of monomeric STAT3. Currently, there is a lack of FDA-approved STAT3 inhibitors for clinical use. Recently, PROteolysis TArgeting Chimera (PROTAC) technology has been developed to induce proteasomal degradation of drug targets. PROTAC modifications of experimental STAT3 inhibitors have been explored to improve potency through STAT3 specific degradation, however none has reached clinical phase testing. Thus, in an attempt to improve anticancer activity of CYD0618, our group has designed several novel CYD0618-based derivatives containing PROTAC modifications.

In this project, we propose to characterize the anticancer properties of these CYD0618-PROTAC derivatives by testing their effects on proliferation, colony formation, and migration in TNBC cells and tumors. In preliminary assessments, our data shows that a number of CYD0618-PROTAC derivatives exhibited a range of efficacy compared to parent compound CYD0618. Specifically, we identify two novel PROTAC STAT3 inhibitors, PW965 and PW1087, which show potent antiproliferative activity and serve as potential chemotherapeutic agents. We will further determine the interactions between CYD0618-PROTACs and STAT3, and their effects on cellular motility and tumor growth of TNBC xenografts.