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"Exploring the Mechanisms of Anticancer Agents with Improved Solubility Against Triple Negative Breast Cancer"

Triple-negative breast cancer (TNBC) presents significant challenges in treatment and prevention due to its aggressive properties, lack of actionable targets and high rates of resistance. A hallmark of TNBC is its dependence on aberrant glycolytic pathways, characterized by the Warburg Effect, where cancer cells downregulate oxidative phosphorylation in the mitochondria and preferentially produce energy through aerobic glycolysis in the cytosol. This reliance on aberrant pathways offers an opportunity to target TNBC with novel small molecular inhibitors. The Shen Lab investigates mitochondrial and metabolic targets for TNBC to develop innovative anticancer small molecules from synthetic compounds and natural products.

Oridonin, a natural diterpenoid derived from the Eastern herb Rabdosia rubescens, is known for its anticancer and anti-inflammatory properties. While these qualities are ideal for potential cancer therapies, oridonin has not been utilized in clinical settings due to its low potency and limited bioavailability. Our lab has previously developed a highly soluble derivative of oridonin, CYD0618, that has increased potency against breast cancer in both cell culture experiments and xenograft mouse models. In parallel studies, our lab also works on niclosamide, an FDA-approved synthetic anthelmintic drug that has promising anticancer effects but similar limitations like low potency and limited solubility in the gut. To address these issues, we developed a niclosamide derivative, HJC0152, that exhibits improved water solubility, bioavailability, and anti-proliferative effects against TNBC. While both CYD0618 and HJC0152 have improved potency and bioavailability compared to their parent compounds, the mechanisms of action of these derivatives against breast cancer remain understudied.

In this project, we evaluated the effects of CYD0618 and HJC0152 on TNBC viability and metabolism using MTT assays, ADP/ATP ratio measurements and Seahorse analysis. We determined that HJC0152 inhibits both glycolysis and oxidative phosphorylation but CYD0618 may target other oncogenic processes that are not related to glucose metabolism. In the future, our lab plans to identify the direct targets of both compounds using proteomics-based approaches like degradation-based protein profiling. The results of this project contribute to understanding the mechanisms of promising anticancer agents and provide a foundation to optimize these compounds for future clinical testing.