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

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Introduction

Triple-negative breast cancer (TNBC) poses significant challenges in treatment due to its aggressive nature, lack of targeted therapy options, and high resistance rates. TNBC's metabolic dependency on aberrant glycolytic pathways, termed the Warburg effect, provides a potential avenue to develop novel targeted therapies. The Shen Lab investigates mitochondrial and metabolic targets for TNBC to develop innovative anticancer small molecules from synthetic compounds and natural products. Our lab has previously developed a highly soluble derivative of natural product oridonin, CYD0618, that has increased potency against breast cancer in both cell culture experiments and xenograft mouse models. In parallel studies, the lab developed HJC0152, a derivative of FDA-approved anthelmintic niclosamide, that exhibits improved solubility and bioavailability. Despite improvements in potency and bioavailability, specific mechanisms of action of CYD0618 and HJC0152 against breast cancer are 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. Results from this project will contribute to understanding the mechanisms of promising anticancer agents and provide a foundation to optimize these compounds for future clinical testing.

CYD0618

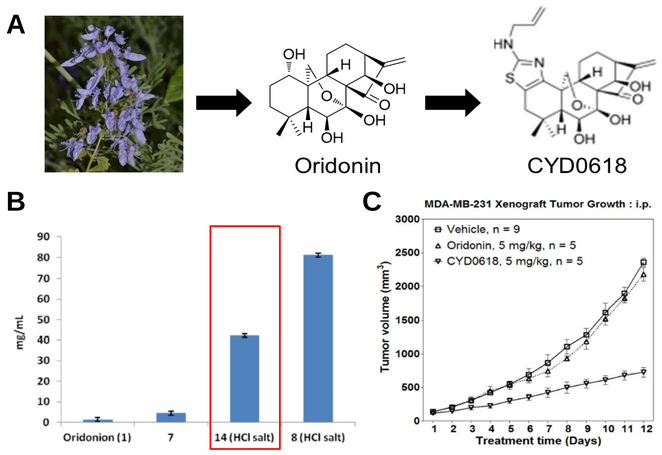


Figure 1A: CYD0618 is a derivative of natural product oridonin.

Figure 1B: CYD0618 exhibits increased solubility compared to parent compound oridonin.

Figure 1C: CYD0618 inhibits tumor growth in a xenograft TNBC mouse model.

HJC0152

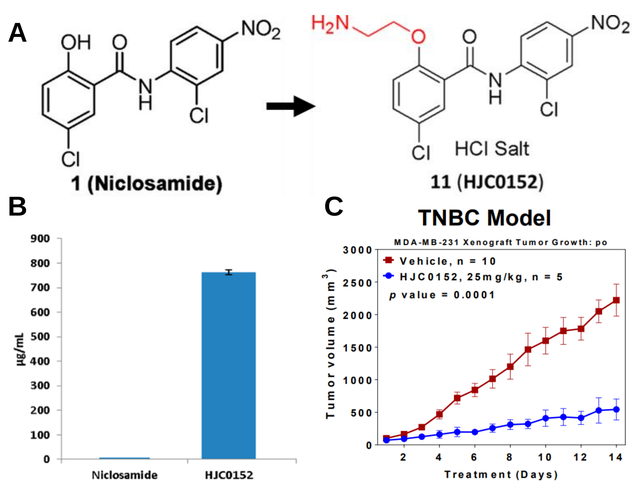
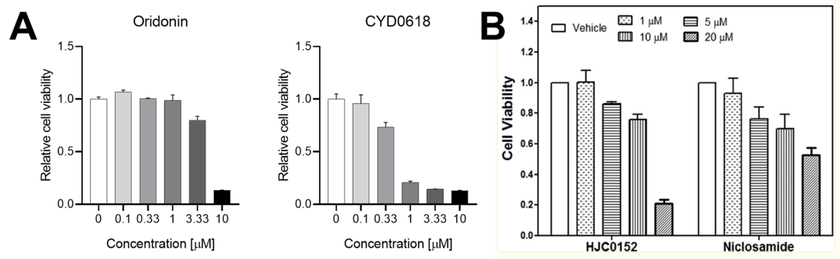


Figure 2A: HJC0152 is a derivative of FDA-approved drug niclosamide.

Figure 2B: HJC0152 exhibits increased solubility compared to parent compound niclosamide.

Figure 2C: HJC0152 inhibits tumor growth *in vivo*.

MTT Assays



Compound	Oridonin	CYD0618
IC_{50} (μM)	6.32	0.38

niclosamide	HJC0152
0.79	1.64

Figure 3A: CYD0618 shows improved potency against TNBC cells *in vitro* compared to oridonin.

Figure 3B: HJC0152 exhibits comparable potency against TNBC to niclosamide.

ADP/ATP Ratio

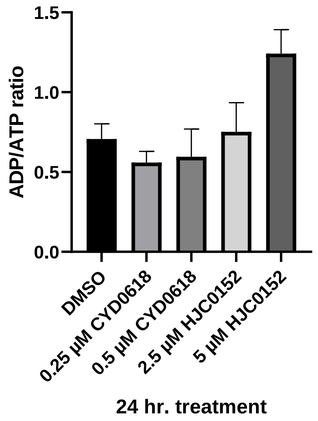


Figure 4: HJC0152 treatment increases the ADP/ATP ratio in TNBC cells in a dose dependent manner, while CYD0618 does not significantly impact the ADP/ATP ratio.

Seahorse Analysis

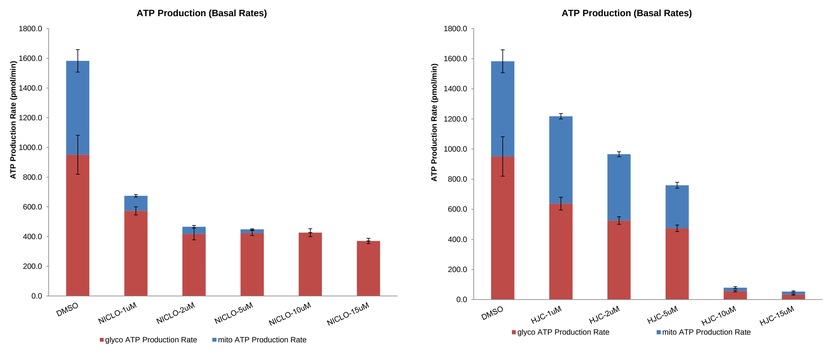


Figure 5: While niclosamide largely targets mitochondrial ATP production, HJC0152 inhibits both mitochondrial oxidative phosphorylation as well as glycolysis.

Conclusions

- CYD0618 is derivative of oridonin that exhibits improved solubility and potency against TNBC.
- HJC0152 is a derivative of niclosamide that exhibits improved solubility and bioavailability.
- Both CYD0618 and HJC0152 inhibit TNBC growth *in vitro* and *in vivo*.
- HJC0152 inhibits ATP production through both mitochondrial phosphorylation and glycolysis.
- CYD0618 and HJC0152 are promising anticancer agents that warrant further investigation for clinical applications.

Future Directions

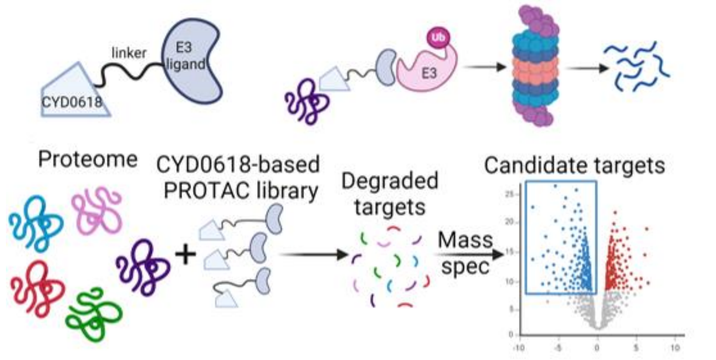


Figure 6: Degradation based protein profiling (DBPP) uses molecular degraders to identify direct protein targets of small molecules.

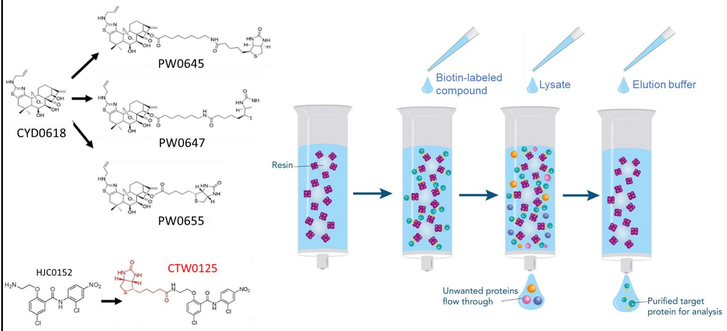


Figure 7: Biotin-labeled tool compounds will be used to identify direct protein targets via affinity chromatography.

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- The derivative compounds used in this study were designed and synthesized in collaboration with Dr. Jia Zhou at the University of Texas Medical Branch.

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