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

Paige Goderis, Gabrielle Vontz, Zhipin Liang, Connor Kent, Lei Liu, Caiyue Li and Qiang Shen

Department of Interdisciplinary Oncology, Louisiana State University Health Sciences Center, LSU-LCMC Health Cancer Center, New Orleans, LA.

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.

MTT Assays

- CYD0618 shows improved potency against TNBC cells in vitro compared to oridonin.
- HJC0152 exhibits comparable potency against TNBC to niclosamide.

ADP/ATP Ratio

- 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

- While niclosamide largely targets mitochondrial ATP production, HJC0152 inhibits both mitochondrial oxidative phosphorylation and glycolysis.

Future Directions

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

Acknowledgements

- This project was completed under the support of the Summer Undergraduate Cancer Research Experience (SUCRE) through the Louisiana Cancer Research Center (LCRC) and LSUHSC-N.O.
- This project was also supported in part by NIH/NCI R01CA226001 and R01CA231150 to Q.S.
- The derivative compounds used in this study were designed and synthesized in collaboration with Dr. Jia Zhou at the University of Texas Medical Branch.

This research project was supported by the LSU-LCMC Health Cancer Center.