Examining the Anti-Proliferative Properties of DUB Inhibitors in Primary Mesothelioma Cells

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INTRODUCTION

Ubiquitin is a key protein in many biological processes and typically marks proteins for degradation. Deubiquitinating (DUB) enzymes remove the ubiquitin mark and can affect downstream biological processes by changing the ubiquitination of a specific set of proteins. They are frequently overexpressed in cancers[1]. DUB inhibitors block the deubiquitylation of proteins leading to an excess of ubiquitinylated proteins. Prior research has noted the efficacy of DUB inhibitors in immortalized cell lines[2]. Here we demonstrate that the DUB inhibitor PR-619 is significantly anti-proliferative for *primary* malignant pleural mesothelioma cells, regardless of cancer subtype (epithelioid and sarcomatoid).

RESEARCH METHODS

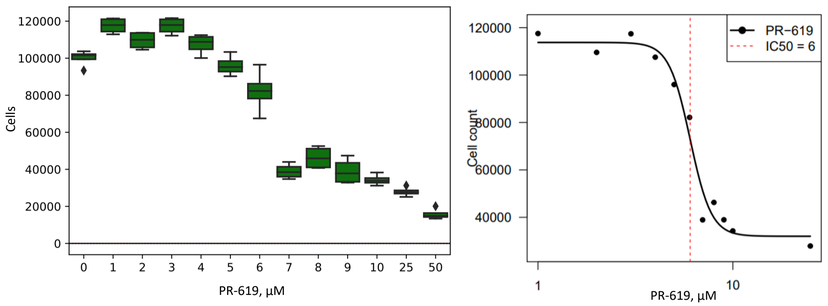
Three different cell lines of two different primary MPM subtypes were tested:

- M3T (Epithelioid)
- M24 (Sarcomatoid)
- M12T (Epithelioid)

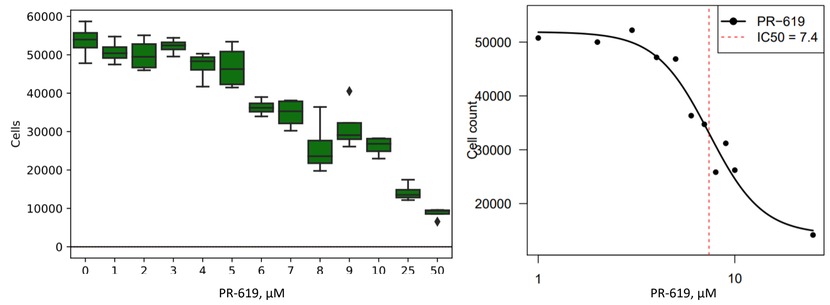
Each cell line was screened with PR-619 and compared to a standard curve in order to calculate the IC50 values, which represent the concentration of drug required to inhibit a biological function to 50% of its typical capacity.

RESULTS

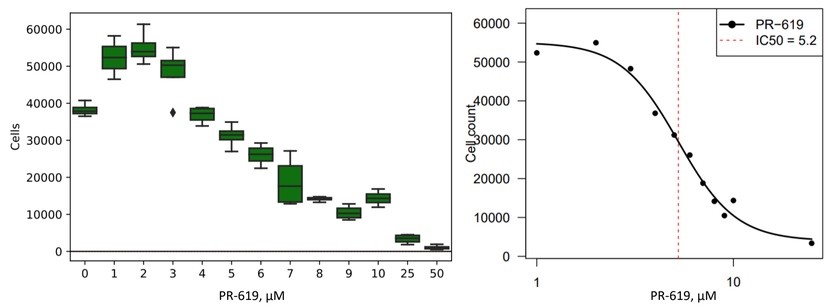
These figures show how increasing levels of PR-619 lead to a decrease in cell counts after 72 hours of treatment. The IC50 values are also calculated for each sample in micromolars.



M3T IC50: 6 µM



M12T IC50: 7.4 µM



M24 IC50: 5.2 µM

FUTURE DIRECTIONS

We are currently performing this drug screening analysis on other MPM cell lines from different patients. We are also in the middle of assessing other drug types, including those that influence ubiquitination levels of proteins. Ultimately, the IC50 values of all drugs and combinations will be compared with Cisplatin and Pemetrexed, two drugs commonly used in chemotherapy, to see if any of the drugs have a synergistic effect.

NEW SKILLS

Previously in the Plaisier lab I conducted primarily computational research. This semester I was trained in and used primarily experimental research techniques including culturing MPM cell lines, designing experiments, making protocols, calculating concentrations, and performing experiments where I collected and interpreted data.

REFERENCES

[1] Morrow, J. K., Lin, H. K., Sun, S. C., & Zhang, S. (2015). Targeting ubiquitination for cancer therapies. Future medicinal chemistry, 7(17), 2333–2350. https://doi.org/10.4155/fmc.15.148
[2] Kuo KL, Liu SH, Lin WC, et al. The Deubiquitinating Enzyme Inhibitor PR-619 Enhances the Cytotoxicity of Cisplatin via the Suppression of Anti-Apoptotic Bcl-2 Protein: In Vitro and In Vivo Study. Cells. 2019;8(10):1268. Published 2019 Oct 17. doi:10.3390/cells8101268

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