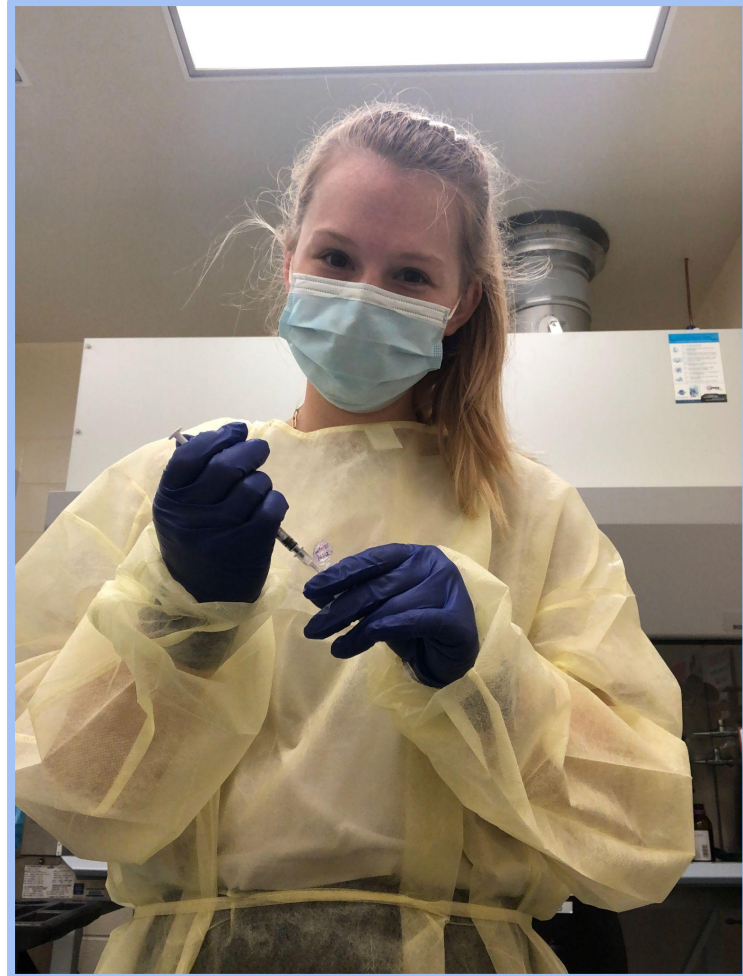


Improving Pediatric Medulloblastoma Treatments Using Palbociclib in Combination with CT-179

Molly Poole

BS in Biology and BA in Philosophy
Faculty Advisor: Dr. Timothy Gershon
Department of Neurology



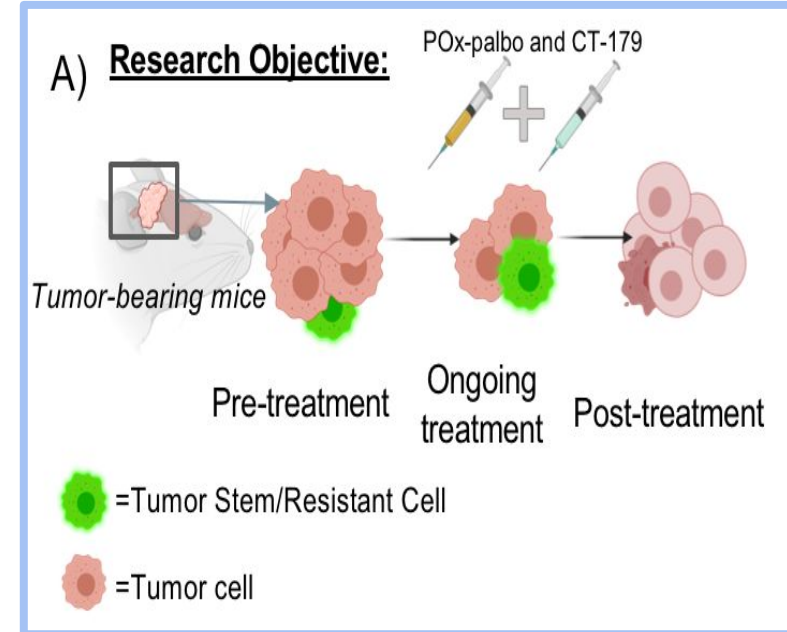
How can we improve the efficacy of palbociclib by combining it with treatments that target the S-phase of the cell cycle?

Background and Significance

Medulloblastoma is the most common malignant pediatric brain tumor and current surgical, chemotherapeutic, and radiative treatments pose the risk of recurrence as well as severe, long-term neurological deficits. Because medulloblastoma is a heterogeneous tumor with four distinct subgroups, current research involves developing less toxic and more personalized therapeutic treatment options. Palbociclib is a current drug used to treat breast cancer, however in order to extend this therapeutic treatment to medulloblastoma the blood-brain barrier must be considered. To address this physiological barrier, we developed the novel nanoparticle formulation of palbociclib (POx-palbo). Mice treated with this formulation showed prolonged survival and an early cell-cycle arrest of tumor cells in the G1 (growth) phase, but this effect wears off by 24 hours. Additionally, monotherapy of POx-palbo fails to cure medulloblastoma due to resistance. Thus, combination strategies are needed to aid in the increased cell-cycle arrest in medulloblastoma cells and target resistance. Here, we use an OLIG2 inhibitor, CT-179 to address both resistance to POx-palbo and increase cell-cycle arrest.

Hypothesis

In order to investigate the proposed question, we hypothesize that that POx-palbo in combination with CT-179, an OLIG2 inhibitor, will irreversibly arrest the cell-cycle and aid in the therapy of medulloblastoma.



Results: Our results suggest that CT-179 combined with POx-palbo increases tumor cell cycle arrest by halting a higher number of cells in the G0 (resting) phase than either treatment alone (Fig. 1). This combinational effect, continues to be statistically significant after both 6 and 24 hours, although there are fewer cells in the resting phase at the longer time point due to decreased efficacy of POx-palbo at this stage. Overall, this treatment method continues to be promising because it targets resistant tumor cells, pushing a higher number into cell cycle arrest.

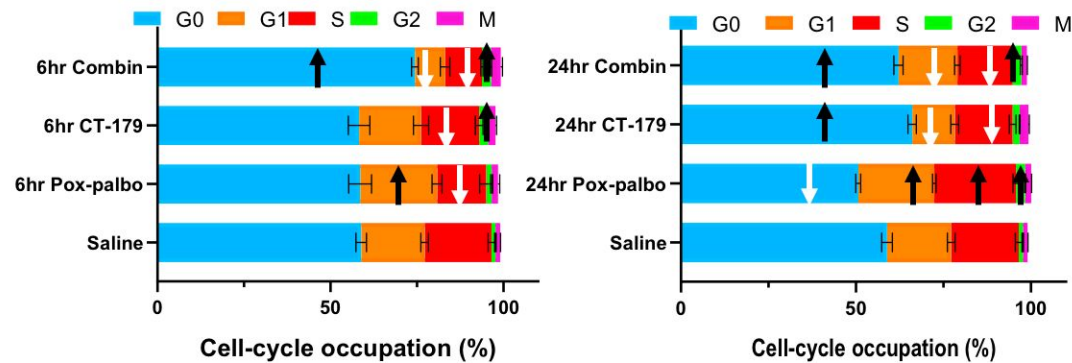


Figure 1. Combinational treatment at 6 hours shows significantly more tumor cells halted in the G0 phase than CT-179 and POx-palbo alone. This remains true for the 24 hour time point, but there are fewer halted cells due to decreased POx-palbo efficacy at 24 hours. The arrows indicate an increase or decrease in cell cycle occupation compared to the saline control.

Importance: These results are extremely relevant to the scientific community because they show that combinational drug therapies are useful treatment plans to combat drug resistance. Speaking to the general audience, current chemotherapeutic and radiative treatments for pediatric brain tumors result in neurological trauma that leads to deficits and developmental delays. Finding less intensive, but ultimately more effective treatment plans is of the utmost importance to saving children's lives and improving future well-being.