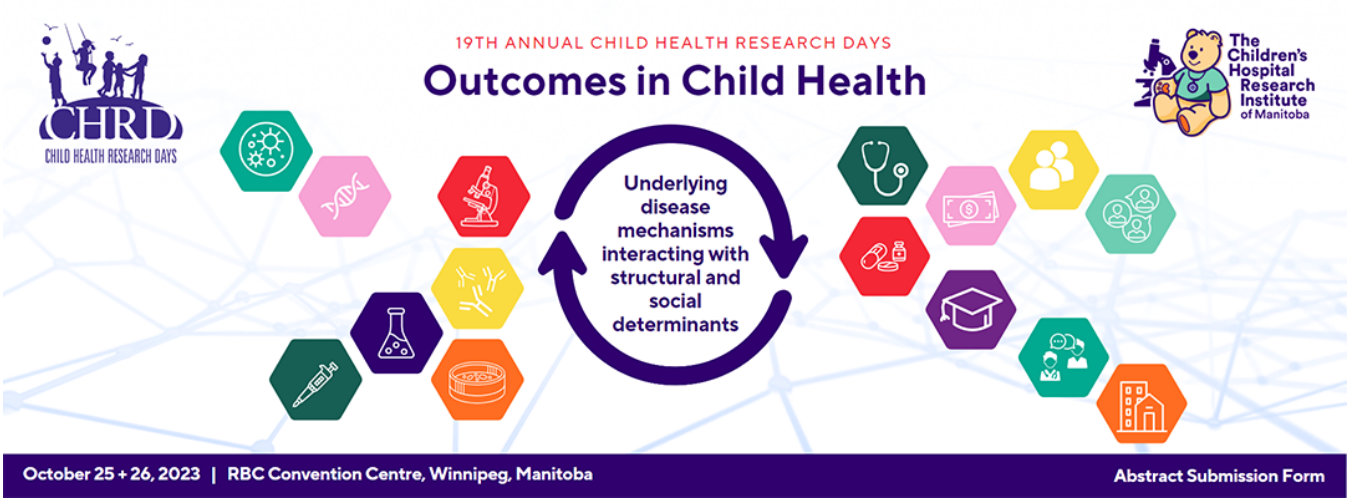

CHRD 2023: Abstract Submission Form

Submitter Name
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Presenter Name
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Presenter Status
Masters Student

Research Category
Basic Science

Role in the project
Perform Experiments
Analyze Data
Write Abstract

Title
Exploring New Targeted Therapies for Sonic Hedgehog (SHH) Medulloblastoma

Background
Medulloblastoma (MB) is the most common malignant primary pediatric brain tumor. Up to 40% of patients succumb to their disease while survivors are left with cognitive and physical delays following treatment. Novel, targeted therapies that reduce toxicity and improve survival are needed. The Ogilvie lab identified CD271, a neurotrophin receptor that is present specifically in SHH-MB. CD271 is diagnostic and prognostic in SHH-MB, providing a specific therapeutic target. CD271 can be targeted by a novel small molecule known as NSC49652.

Objective
The goal of this study is to determine whether NSC49652 will significantly decrease tumorigenic properties in vitro while also decreasing tumor growth in vivo.

Methods
Concentrations of NSC were evaluated with cells derived from the human UI226 and DAOY OE SHH-MB cell lines. Self-renewal was assessed using the tumorsphere assay for two passages. Trypan blue staining was used as an indicator of cell viability.

In vivo studies were performed by culturing UI226 cells and injecting them into the cerebellum of immunodeficient mice. Following tumor engraftment, NSC49652 was administered at a concentration of 200mg/kg, for 5-days on, 2-days off until endpoint was reached. Tumor growth and survival was assessed.

Results
NSC49652 treatment results in a significant reduction in tumorigenic properties in vitro following NSC49652 treatment. NSC significantly reduces tumorsphere number ($p < 0.03$), size ($p < 0.0001$), viability ($p < 0.02$), and migration ($p < 0.03$) in a dose-dependent manner in UI226 and DAOY OE SHH-MB cells.

In vivo toxicity studies demonstrate that NSC49652 is well-tolerated at a concentration of 200mg/kg, significantly reduces tumor volume ($p = 0.0019$) and significantly increases survival time ($p = 0.0012$).

Conclusion
NSC holds promise as a targeted therapy for SHH-MB by reducing tumorigenic properties in vitro and in vivo.

Table/Figure File
Figure 1_merged (2).pdf

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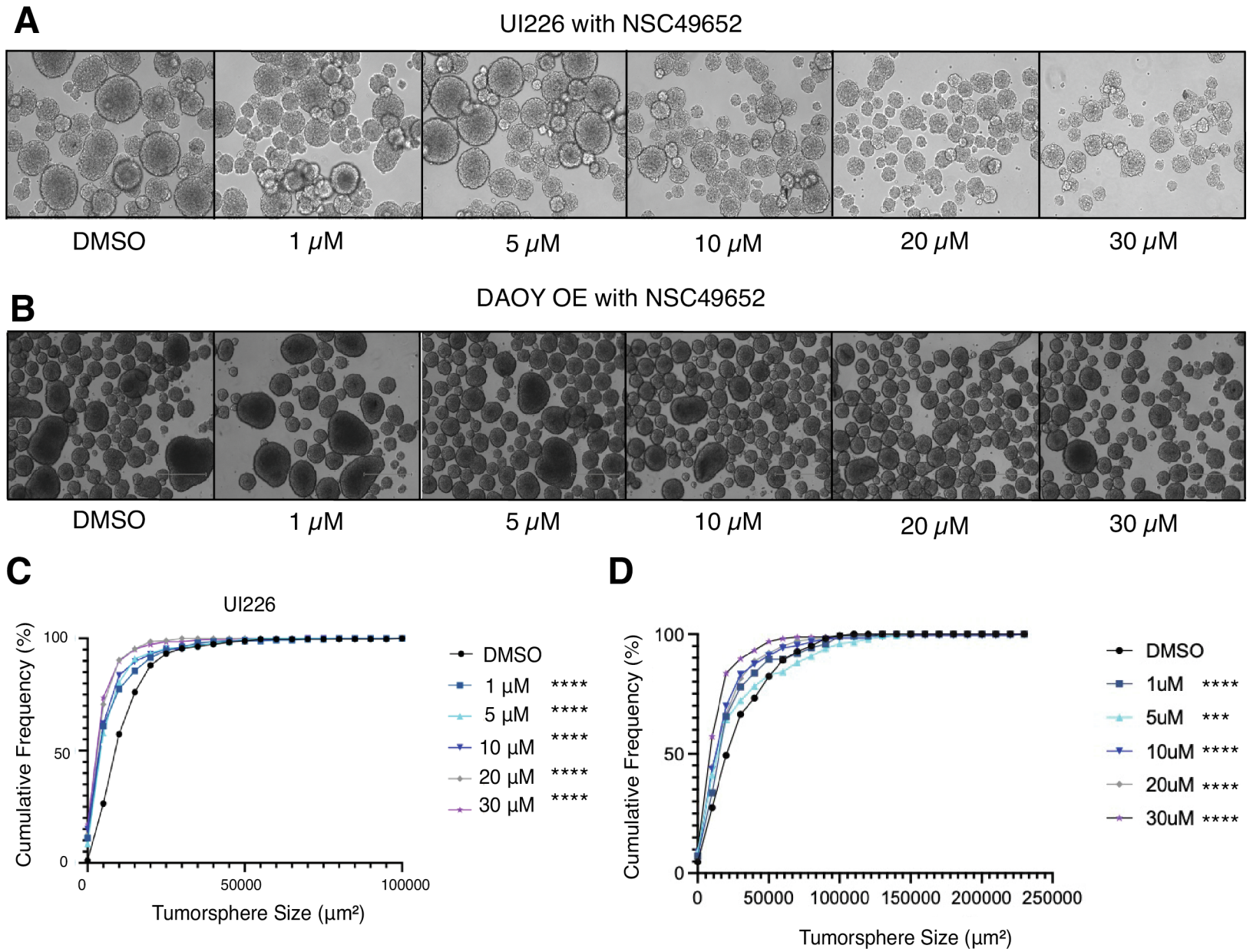
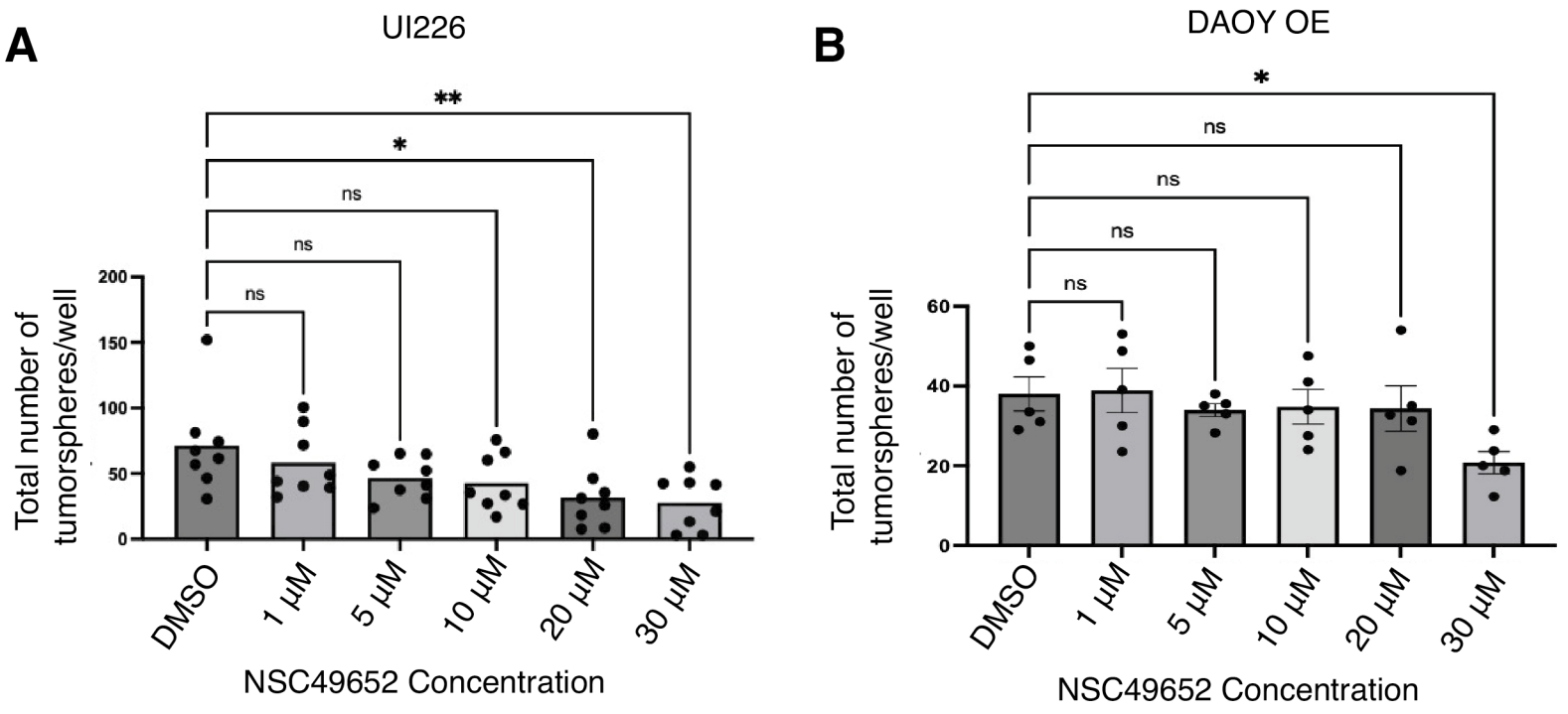
Figure 1. Treatment with NSC49652 decreases tumorsphere size.



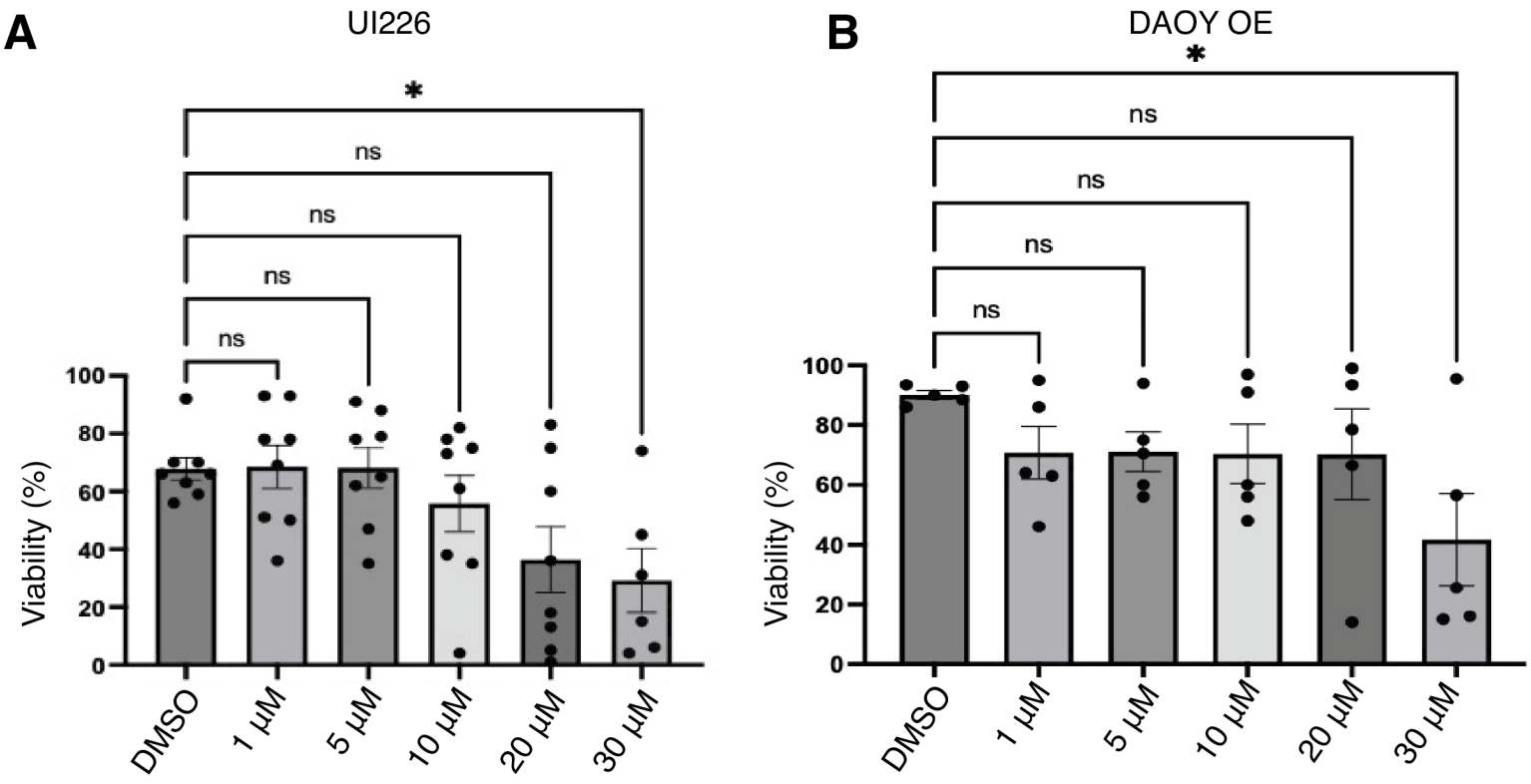
A. Images of the treated UI226 tumorspheres used to determine the cumulative frequency. All spheres measured using FIJI. **B.** Images of the DAOY OE tumorspheres used to determine the cumulative frequency. All spheres measured using FIJI. **C.** Cumulative frequency distribution of tumorsphere size for the UI226 tumorspheres following treatment with NSC49652. Tumorsphere size differences were analyzed using the Kolmogorov-Smirnov test. $p < 0.0001$ for all levels of treatment. **D.** Cumulative frequency distribution of tumorsphere size for the DAOY OE tumorspheres following treatment with NSC49652. Tumorsphere size differences were analyzed using the Kolmogorov-Smirnov test. $p < 0.0001$ for 1 μM and 10 μM-30 μM. $p = 0.0001$ at 5 μM.

Figure 2. Treatment with high concentrations of NSC49652 significantly decreases the total number of tumorspheres.



A. The total number of UI226 spheres present after multiple passages decreases with NSC49652 treatment, suggesting a decrease in self-renewal capacity. One-way ANOVA used with Dunnett's multiple comparisons test. $p = 0.0110$ at the 20 µM concentration and 0.0046 at the 30 µM concentration. **B.** The total number of DAOY OE spheres present after multiple passages also decreases with NSC49652 treatment, again suggesting a decrease in self-renewal capacity. One-way ANOVA used with Dunnett's multiple comparisons test. $p = 0.0357$ at 30 µM.

Figure 3. Treatment with NSC49652 significantly decreases cell viability at the 30 µM concentration.



Tumorsphere viability was assessed with trypan blue. **A.** UI226 tumorsphere viability decreases significantly after treatment with a 30 µM concentration of NSC49652. One-way ANOVA with Dunnett's multiple comparisons test. $p = 0.0181$ at 30 µM. **B.** DAOY OE Tumorsphere viability decreases significantly after treatment with a 30 µM concentration of NSC49652. One-way ANOVA with Dunnett's multiple comparisons test. $p = 0.0161$ at 30 µM.