I. INTRODUCTION

1.1 Background

Atypical teratoid rhabdoid tumor (ATRT) is a rare pediatric central nervous system (CNS) tumor class of devastating prognosis, with under a year of overall survival (OS) (Fleming et al., 2012). Despite the established signatures and molecular subclassifications, there remains no designated therapies for ATRT. Current standard of care relies on intensive and multimodal combinations of surgical resection, conventional and high-dose chemotherapies and irradiation (Lau et al., 2015). These unfortunately fail to prolong patient survivals to adulthood while costing them major toxicities and long-term developmental deficiencies (Lafay-Cousin et al., 2015, Slavc et al., 2014). Furthermore, therapeutic advances are yet undermined by the shortage of ATRT disease models and trial subjects which limits data reproducibility (Ginn & Gajjar, 2012). A novel therapeutic discovery approach that overcomes the aforementioned limitations is therefore urged.

High-throughput drug screening (HTS) assays vast numbers of compounds at microscales to potentiate the identification of a therapeutic candidate, and is hence an increasingly popular means of cancer drug discovery (Avery et al., 2010; Bialkowska & Yang, 2012; Lin et al., 2019; Vulin et al., 2022; Xie et al., 2016). Drug hits obtained in this short period have the potential to represent a therapeutic strategy for the actual disease population when given sufficiently large disease model cohorts. The Childhood Cancer Model Atlas (CCMA) currently holds the world's largest ATRT cell line collection and therefore exemplifies a superior subject cohort to support high-throughput drug screening on ATRT (Sun et al., 2023). Furthermore, the aforementioned publication revealed that pediatric tumor groups exhibit indistinct drug sensitivity unlike adult tumors, leading to the establishment of the Australian Library of Paediatric Anti-Cancer Agents (ALPACA)—a pediatric cancer-targeted drug library containing nearly 500 pediatric cancer-effective agents—which

optimizes high-throughput drug screens for pediatric tumors by focusing on pediatric-relevant groups of agents.

1.2 Scope, aim and objectives

Given these platforms, this study employs high-throughput drug screening against ALPACA on the CCMA's ATRT cohort to identify novel therapeutic opportunities for ATRT, with specific objectives of 1) identifying common cellular pathways or targets among ATRT-cytotoxic compounds, 2) identifying compounds selectively cytotoxic against ATRT and 3) identifying compounds selectively cytotoxic against ATRT Group 1 or 2.

1.3 Hypothesis

This study hypothesizes that the ALPACA screening shall reveal particular cellular pathways, targets or drugs ATRTs are vulnerable to.