A NOVEL PRO-APOPTOTIC-BASED COMBINATION THERAPY FOR PEDIATRIC SOLID TUMOR TREATMENT

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Despite advances in pediatric oncology, solid tumors, which account for ~30% of childhood cancers, remain a leading cause of mortality due largely to late diagnosis, therapeutic resistance, and a lack of effective treatment options [1,2]. Current disease management remains suboptimal, underscoring the need for innovative therapeutic strategies to overcome these challenges. One promising approach involves nanomedicine, which offers enhanced drug delivery and efficacy. For example, in a Phase II clinical trial, ~30% of Ewing's sarcoma models responded favorably to the chemotherapeutic nanomedicine Abraxane® [NCT02945800]; however, elevated levels of anti-apoptotic proteins (targetable by BCL-2 inhibitors) correlated with treatment resistance. Although several BCL-2 inhibitors have progressed to Phase I and II clinical trials, dose-limiting toxicities, particularly thrombocytopenia, have limited their clinical use [3]. To circumvent these challenges, we propose the use of polymer therapeutics - specifically, polypeptide-based nanoconjugates - as a modular, on-demand platform for combination therapy development in pediatric solid tumors [4]. Our strategy focuses on identifying optimal drug combinations involving BCL-2 inhibitors across two primary pediatric tumor cell lines, with the goal of developing novel nanotherapeutics capable of targeted and controlled drug delivery [5].

We conducted a high-throughput combination screening of a BCL-2 inhibitor with the Prestwick Chemical Library in A673 (Ewing's sarcoma) and RH30 (rhabdomyosarcoma) cells. We administered treatments for 72 h at 2.5 µM as single agents or combined with the IC25 concentration of the BCL-2 inhibitor (as determined in preliminary cytotoxicity assays). We calculated synergy scores using the Bliss independence model, with positive hits defined by a score of ≥ 20 and combination-induced cytotoxicity of ≥ 50% relative to untreated controls. This analysis identified 16 potential hits: 6 in A673 cells and 10 in RH30 cells. Based on dose-response synergy scores (≥30 at 0.75 µM) and the presence of functional groups amenable to conjugation, we selected three lead candidates for nanoconjugate development: 2 for A673 cells and 2 for RH30 cells.

In conclusion, we present a list of FDA-approved drug candidates that enhance the anti-tumor effects of BCL-2 inhibition in pediatric solid tumor models. Our findings contribute a foundational dataset of potential therapeutic agents for further preclinical evaluation and provide a rationale for future development of combination nanotherapeutics. Ongoing efforts will focus on engineering nanoconjugates at optimized drug ratios that exhibit maximal synergy in vitro and in vivo.

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