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Daraxonrasib and Oncolytic Vesicular Stomatitis Virus as Combination Treatment for Pancreatic Ductal Adenocarcinoma

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest cancers and is projected to become the second leading cause of cancer-related deaths in the United States by 2040. PDAC is characterized by a dense desmoplastic and immunosuppressive tumor microenvironment enriched in cancer-associated fibroblasts and extracellular matrix that promote tumor progression and resistance to current therapies. Vesicular stomatitis virus (VSV) is a small, enveloped and single-stranded RNA virus belonging to the Rhabdoviridae family. VSV has emerged as a promising therapeutic platform for PDAC due to its preferential tumor cell cytotoxicity and ability to stimulate anti-tumor immune responses. Engineered VSV expressing therapeutic genes may further enhance efficacy through stromal remodeling and immune activation. However, VSV resistance remains a challenge in PDAC models. *KRAS* mutations, particularly $KRAS^{G12D}$, drive PDAC progression through persistent RAS signaling. Daraxonrasib, a pan-*KRAS* inhibitor, suppresses oncogenic *KRAS* signaling and may modulate antiviral pathways to enhance VSV-based oncolytic virotherapy in *KRAS*-driven PDAC. This research evaluated the therapeutic potential of combining daraxonrasib and VSV-Decorin for improved PDAC oncolytic activity.

Methods: This study utilized an *in vitro* model of MiaPaCa-2 and KPC cell lines to evaluate the therapeutic potential of daraxonrasib and VSV-Decorin (VSV-DCN) as combination treatment for PDAC. A 5×5 dose matrix was used to determine the optimal daraxonrasib concentration and VSV-DCN multiplicity of infection (MOI) at 72 and 96 hours post-infection. Subsequently, a 3×4 treatment matrix with a 2-hour daraxonrasib pretreatment was used to determine the effective combination regimen at 24 and 48 hours post-infection. Cells were seeded in 96-well plates and treated after 24 hours and 80 – 90% confluency. Cell viability was assessed using the CellTiter-Glo® luminescent assay and expressed as a percentage relative to untreated/non-viral controls. All experiments were performed in triplicate.

Results: The results showed that the effective combination treatment for MiaPaCa-2 is daraxonrasib 1 nM and VSV-DCN at MOI of 0.1 and for KPC is daraxonrasib 100 nM and VSV-DCN at MOI of 10, both at 48 hours.

Conclusion: This study showed that the combination of daraxonrasib and oncolytic VSV expressing decorin demonstrates promising therapeutic potential for virotherapy of PDAC.