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

Temitope Fadipe[1], Sina Aslanabadi[2,4], Sudhakar Ammanamanchi[2,4], Joycelynn Coleman-Barnett[2,4] and Omeed Moaven[2,3,4]

[1]Louisiana School for Math, Science, and the Arts, Natchitoches, LA, USA.
[2]Department of Interdisciplinary Oncology, Louisiana State University Health School of Medicine, New Orleans, LA, USA.
[3]Department of Surgery, Louisiana State University Health School of Medicine, New Orleans, LA, USA.
[4]LSU-LCMC Cancer Center, New Orleans, LA, USA.

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC)

- PDAC is one of the deadliest cancers and is projected to become the 2nd leading cause of cancer related deaths in the US by 2040.
- It is a highly invasive malignancy with poor prognosis and 5-year survival rate of 12%.
- PDAC exhibits a dense desmoplastic and immune suppressive tumor microenvironment enriched in fibroblasts and extracellular matrix that promotes resistance to current therapies.

Vesicular Stomatitis Virus

- Vesicular stomatitis virus (VSV) is a small, enveloped and single-stranded RNA virus.
- VSV targets PDAC through tumor-selective cytotoxicity and antitumor immune activation.
- Oncolytic VSV expressing decorin (*DCN)* may enhance virotherapy by remodeling the tumor stroma and promoting anti-tumor immunity while retaining oncolysis.
- Most PDAC cell lines are susceptible to VSV oncolysis but some exhibit VSV resistance.

KRAS Mutations & Daraxonrasib in PDAC Virotherapy

- *KRAS* mutations drive PDAC progression by promoting persistent RAS signaling with $KRAS^{G12D}$ being the most prevalent mutation.
- Daraxonrasib is a pan-*KRAS* inhibitor designed to suppress oncogenic *KRAS* signaling.
- *KRAS*-driven PDAC exhibits dysregulated signaling and antiviral responses.
- Daraxonrasib-mediated *KRAS* inhibition may restore antiviral immunity and enhance VSV-based oncolytic virotherapy.

Aim

This research evaluated the therapeutic potential of combining daraxonrasib and VSV-Decorin for improved PDAC oncolytic activity.

Methods

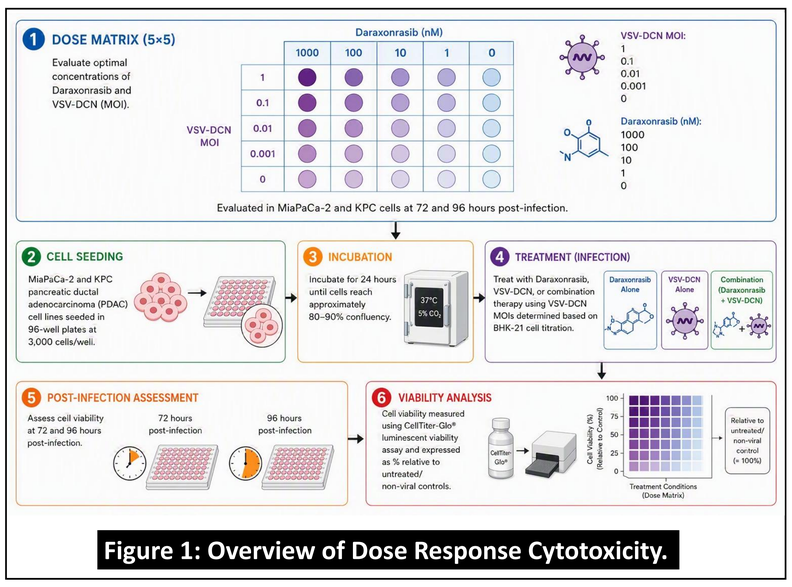

Figure 1: Overview of Dose Response Cytotoxicity.

Effective Combination Regimen

- A 3x4 treatment matrix with 2-hour daraxonrasib pre-treatment was used to determine the effective combination at 24 and 48 hours post-infection.
- MiaPaCa-2 and KPC were seeded in 96-well plates at 4,000 cells/well.
- For MiaPaCa-2, daraxonrasib concentrations were 5, 1 and 0 nM and VSV-DCN MOI of 0.1, 0.05, 0.01and 0.
- For KPC, daraxonrasib concentrations 100, 50 and 0 nM and VSV-DCN MOI of 10, 5, 1 and 0.

Results

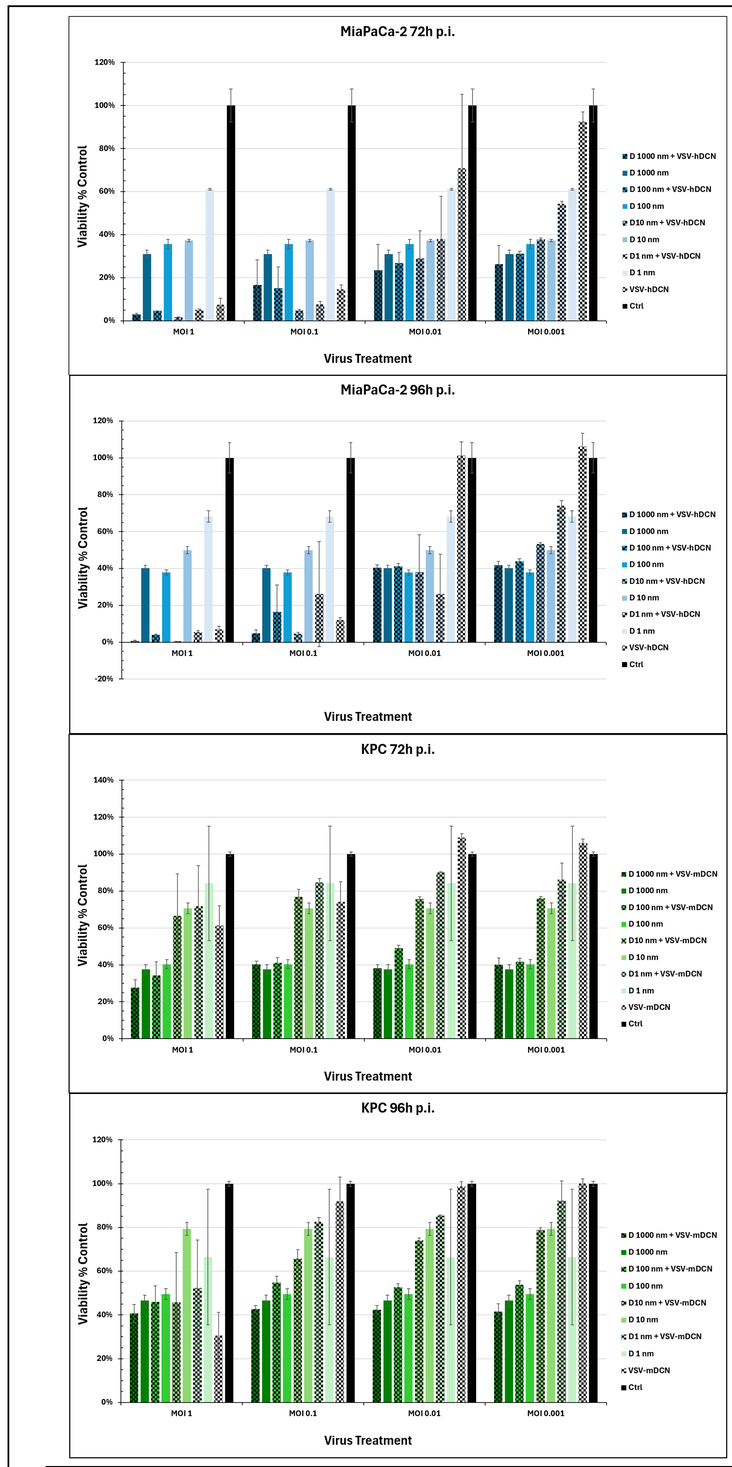

Figure 2: Dose-response Analysis of Daraxonrasib and VSV-DCN Combination Treatment in PDAC cell lines.

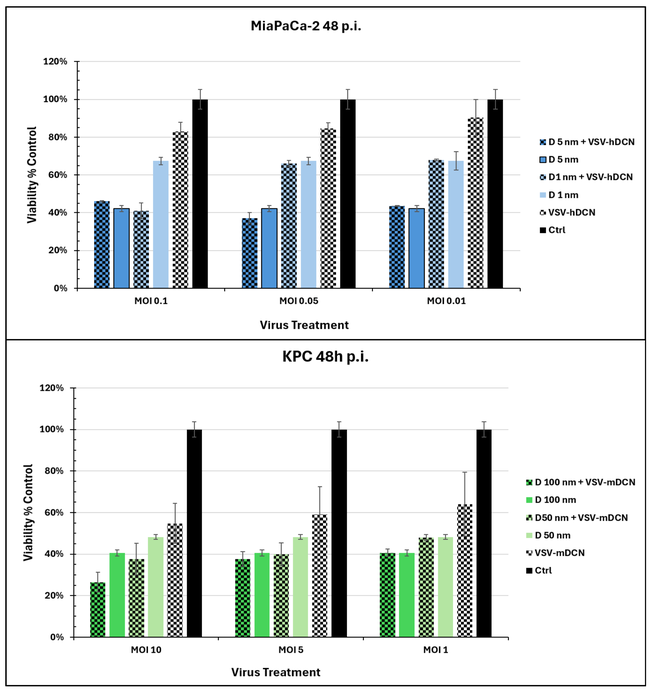

Figure 3: Optimization of Daraxonrasib and VSV-DCN Combination Treatment in PDAC cells.

Summary of 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.

Outlook

- Virus pre-treatment with combination treatment.
- Gene expression studies of interferon stimulating genes by qPCR.
- Organoids based experiments and *in vivo* studies with animal models.

Conclusion

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

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