Novel Oncolytic Virus to Treat Pancreatic Ductal Adenocarcinoma

Nathan Smith[1], Sina Aslanabadi[2,3], Steven Scahill[2,3], Joycelynn Coleman-Barnett[2,3], Temitope Fadipe[4], Sudhakar Ammanamanchi[2,3], Omeed Moaven[2,3]

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

Introduction

- Pancreatic Ductal Adenocarcinoma (PDAC) is projected to become the second leading cause of all cancer deaths in the United States by 2030.
- Incidence of pancreatic cancer is not uniform, with a higher incidence in Black Americans than in any other ethnic group in the United States.
- Despite advancements in therapeutic modalities for other cancers, dense fibrotic and immunosuppressive tumor microenvironment (TME) has limited effective PDAC. treatment options and survival prognosis remains poor.
- Our research advances a novel treatment for this disease using the Vesicular Stomatitis Virus (VSV).
- For our oncolytic virus (OV) approach, we integrate one of three different transgenes into our VSV treatment: Decorin, Rexalin, or Hyaluronidase PH20.
- Each of these transgenes utilizes a different mechanism of action to help break up the desmoplastic TME allowing the virus and subsequent drug treatment therapy to penetrate deeper into the tumor.

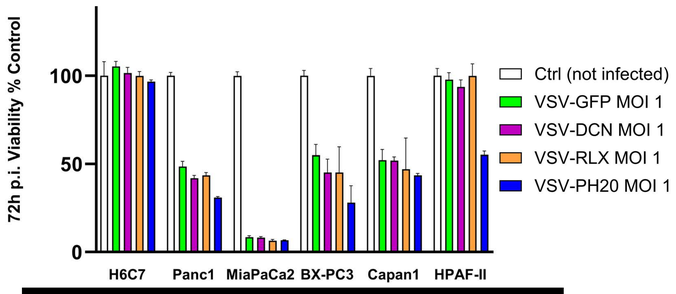

Figure 1: Cytotoxicity Effects of VSV Treatment

- Preclinical trials have shown that Ruxolitinib, a Janus Kinase (JAK) 1/2 inhibitor, can reverse some viral resistance in PDAC cell lines improving overall VSV treatment effectiveness.
- We leveraged these findings and extended our PDAC cell line studies to now include human organoids.

Objectives

- Evaluate cytotoxicity in human PDAC organoid and cell lines following VSV treatment combined with varying concentrations of Ruxolitinib.
- Evaluate effects of different transgenes (Decorin, Rexalin, or Hyaluronidase PH20) on VSV treatment results.

Methodology

- Seeded 96-well plates with a density of 5,000 cells per well.
- Infected PDAC organoids and cell lines with different VSV Multiplicity of Infection (MOI), transgenes, and concentrations of Ruxolitinib.
- Assessed cell viability by MTS assay at 3 and 6 days post infection for PDAC cell lines and patient derived organoids (PDOs), respectively.

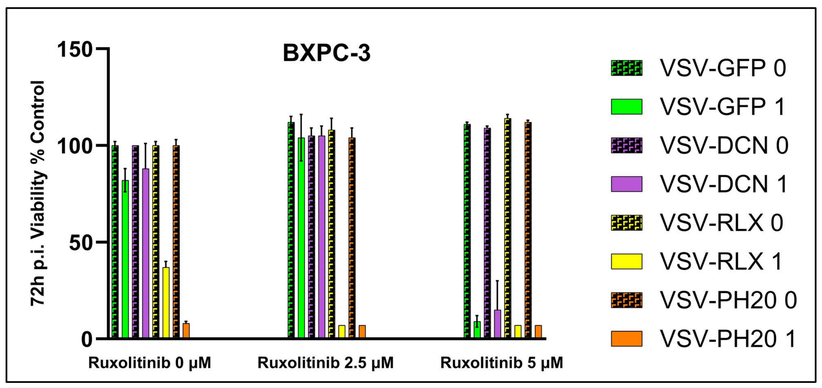

Figure 2: BXPC-3 Cell Viability with VSV-Ruxolitinib Treatment

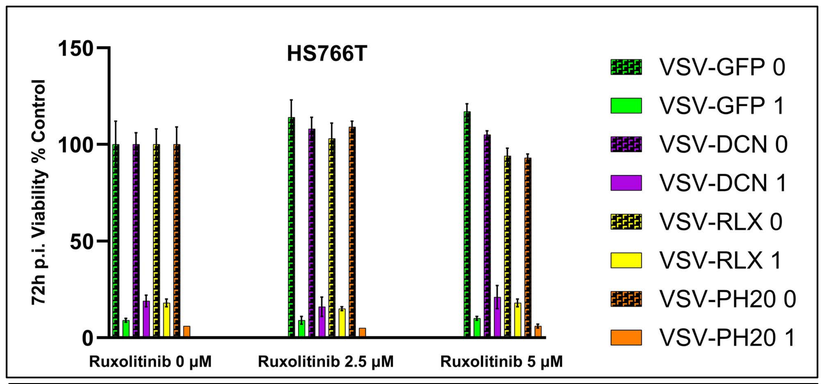

Figure 3: HS766T Cell Viability with VSV-Ruxolitinib Treatment

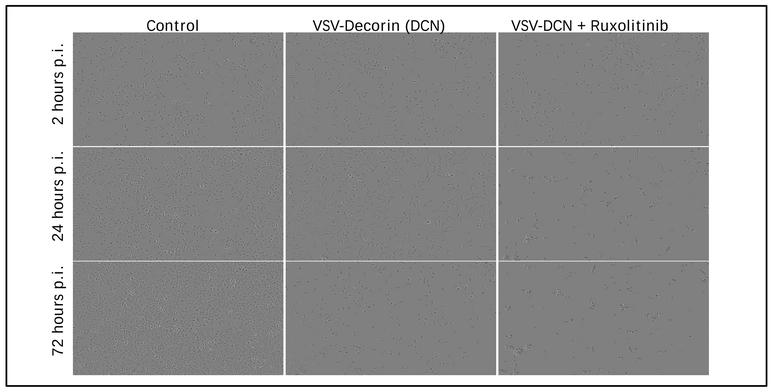

Figure 4: HS766T Density: VSV-DCN & VSV-DCN + Ruxolitinib Treatment

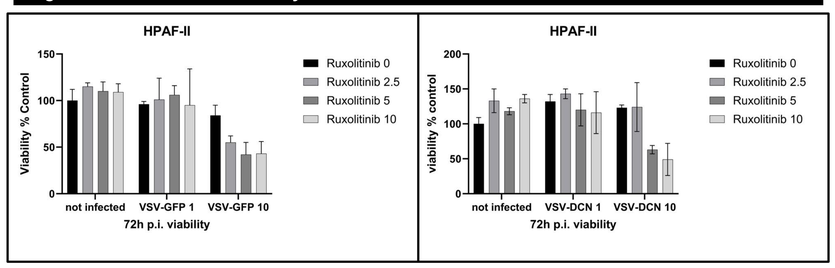

Figure 5: HPAF-II (Human) Cell Viability with VSV-Ruxolitinib Treatment

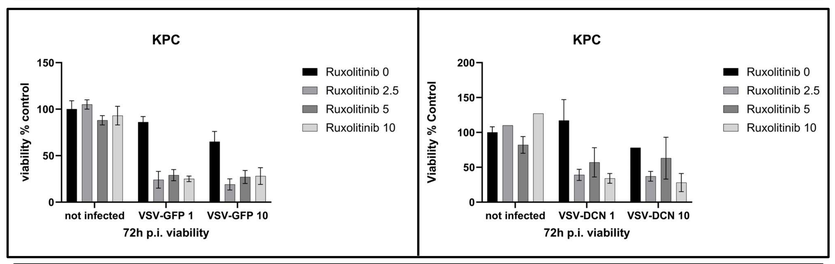

Figure 6: KPC (Murine) Cell Viability with VSV-Ruxolitinib Treatment

Results

- We observed that our OV treatment approach had no effect on normal, non-cancerous, human pancreatic cells (H6C7), validating non-cancerous, human pancreatic cells (H6C7), reaffirming oncotropism and an important safety signal.
- VSV treatment significantly decreased the viability of PDAC in permissive cell lines (Mia PaCa2).
- For modestly resistant PDAC cell lines (Panc1, BX-PC3), our VSV treatment approach was still effective in reducing cytotoxicity.
- However, in the resistant PDAC cell line (HPAF-II) only the VSV-PH20 showed an appreciable reduction in cytotoxicity in the absence of Ruxolitinib.
- With the addition of Ruxolitinib, our treatment approach was effective against resistant PDAC cell lines with the effectiveness increasing with increased MOI and Ruxolitinib concentration.
- For our organoids (hMIA), a MOI of 10 and Ruxolitinib concentration of 5 uM significantly decreased the viability of pancreatic cancer and practically eliminated the patient-derived organoid completely.

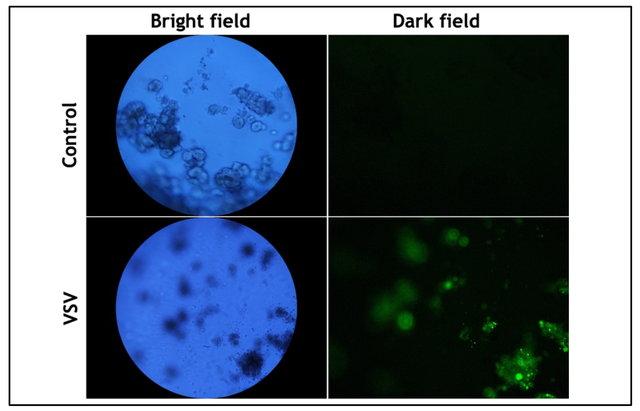

Figure 7: PDO Viability with VSV-GFP + Ruxolitinib

- We now plan to expand our studies to include a larger number of patient-derived organoids.

Conclusion

- This study demonstrated that VSV treatment bioengineered with transgenes targeting ECM, combined with Ruxolitinib is a highly effective approach for decreasing the viability of pancreatic cancer in viral-permissive, viral-resistant, and human patient-derived organoids.
- This OV therapeutic approach offers tremendous potential as an effective treatment option for PDAC, which could significantly improve the current survival prognosis for this devasting and deadly disease.

References

- Hartupee C, Nagalo BM, Chabu CY, Tesfay MZ, Coleman-Barnett J, West JT, and Moaven O (2024). Pancreatic Cancer Tumor Microenvironment is a Major Therapeutic Barrier and Target. Front. Immunol. 15:1287459. doi: 10.3389/fimmu.2024.1287459
- Hastie, E., Cataldi, M., Moerdyk-Schauwecker, M. J., Felt, S. A., Steuerwald, N., and Grdzelishvili, V. Z. (2016). Novel Biomarkers of Resistance of Pancreatic Cancer Cells to Oncolytic Vesicular Stomatitis Virus. Oncotarget, 7(38), 61601–61618. https://doi.org/10.18632/oncotarget.11202

This research project was supported by the following organizations: Robert A. Winn Clinical Investigator Pathway Program (Winn CIPP), VCU Massey Comprehensive Cancer Center, Bristol Myers Squibb Foundation, Louisiana State University (LSU) Health Sciences Center (HSC), and LSU LCMC Cancer Center