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"Use of Oncolytic Viruses to Treat Pancreatic Ductal Adenocarcinoma"

Pancreatic ductal adenocarcinoma (PDAC) is projected to become the second leading cause of all cancer deaths in the United States by 2030. Further, the 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, the challenging tumor microenvironment (TME) has limited effective PDAC treatment options and survival prognosis remains extremely poor. Our research advances a novel and effective 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. In addition, 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.

We seeded a 96-well plate at a density of 5,000 cells per well. We then infected the PDAC organoids and various viral resistant and permissive PDAC cell lines with different VSV Multiplicity of Infection (MOI), transgenes, and concentrations of Ruxolitinib. We then assessed the cell viability by MTS assay at three days and six days post infection for the PDAC cell lines and patient-derived organoids (PDO), respectively. Importantly, we first saw that our OV treatment approach had no effect on our normal, non-cancerous, human pancreatic cells (H6C7). That was an encouraging result that validates oncotropism and safety of our approach. We also saw that our VSV treatment significantly decreased the viability of PDAC in permissive cell lines (Mia PaCa2) even in the absence of added transgenes or Ruxolitinib. For modestly resistant PDAC cell lines (Panc1, BX-PC3), our VSV treatment approach was still effective in reducing cytotoxicity even in the absence of Ruxolitinib. However, in our highly 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 now 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 PDO completely. We now plan to expand our studies to include a larger number of patient-derived organoids.