Title: Synergy of ZEN3694 and VIP152 for dual transcriptional targeting of BET and CDK9 in patient derived organoid models of pancreatic cancer

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Link to Poster Abstract AACR 2024:
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Scientific Abstract:

Background: Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer related mortality in the United States, largely due to ineffective systemic therapy. While novel KRAS target strategies are in development, few agents have been investigated to target the transcriptional machinery for global inhibition of expression. Recent small molecule inhibitors targeting transcription (i.e., CDK7) have shown preliminary evidence of disease control; however, combination therapies have lagged, likely due to uncertainty in clinical toxicity. Text mining analysis suggests combination BET and CDK9 inhibition may be promising against PDAC. Here, we present preclinical evidence of synergistic activity for the combination of bromodomain and extraterminal (BET) inhibitor (ZEN3694) and CDK9 inhibitor (VIP152) using patient derived cancer organoids (PCOs).

Methods: Dose response curves were generated for ZEN3694 and VIP152 to assess their single agent activity against PCOs using a low volume format. ZEN3694 was treated continuously while VIP152 was removed after 24h to mimic pharmacokinetics with assay endpoint at 144h. Synergy assays were designed using a combination dose titration grid. Viability was determined in all assays using 3D CellTiter Glo (CTG, 50% v/v). Synergy scores were produced using SynergyFinder 3.0 including Zero Interaction Potency (ZIP), Bliss Independence (Bliss), Highest Single Agent (HSA), and Loewe Additivity (Loewe). Western blot analysis was performed against global markers of active RNA polymerase II (phosphorylation at serine 2, 5, 7) and antiapoptotic protein, BCL xL, and MCL 1.

Results: ZEN3694 was observed to have a single agent IC50 in the single uM range across 3 independent PDAC PCO lines (PDAC1 3.7uM, PDAC2 1.1uM, PDAC3 2.9uM). VIP152 showed significant potency in the same 3 PDAC PCO lines (PDAC1 140.2nM, PDAC2 30.5nM, PDAC3 43.4nM). The combination of ZEN3694 and VIP152 was found to have increased therapeutic activity with double digit synergy scores across all reference models: PDAC1 (Loewe 17.3, HSA 19.8, ZIP 20.2, and Bliss 17.2) and PDAC2 (Loewe 34.7, HSA 28.3, ZIP 19.7, and Bliss 19.6). Western blots of protein collected from organoids treated for 48h showed on target activity, including decrease in the phosphorylation of Rbp1 (Ser 2, Ser 5, and Ser 7) compared to both control and single agents and decreased expression in antiapoptotic proteins (MCL 1 and BCL xL).

Conclusion: Here, we show the activity of dual transcription targeting with BET and CDK9 inhibition in patient derived pancreatic cancer organoid models. The combination of ZEN3694 and VIP152 has in vitro synergy in PDAC PCO models with on target activity. Ongoing work is validating this

combination in animal models to assess toxicity, in vivo activity, and RNA expression profiling to understand transcriptional pathway dependency and therapeutic resistance.

Written Lay Abstract:

The pancreas is an organ that sits behind the stomach and is important for digestion and making insulin to control blood sugar levels. One type of cancer in the pancreas is called pancreatic ductal adenocarcinoma (PDAC). The chance of surviving PDAC is low because treatment for this type of cancer is not very effective right now. Scientists are looking for ways to better treat this type of cancer in the pancreas, but they are not sure how safe these treatments will be in people.

Studying how treatments work on cancer cells in a lab helps us understand how safe they will be when given to someone with cancer. In this study, the research team studied how well two treatments work together to treat cancer cells in a lab setting (not inside a person).

The research team found that the two treatments worked better against the cancer cells when used at the same time compared to when just one was used. The next step for this research will be to test the two treatments together in animals to see how well they work against cancer in the pancreas and to see if they may be safe for humans.

Visual Lay Abstract:

Treating Pancreatic Cancer

What Did We Study?

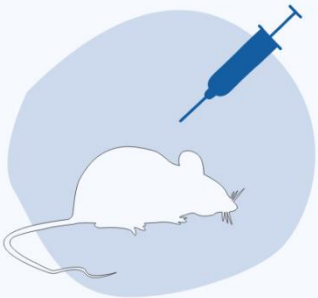
- Many people die from pancreatic cancer
- Cancer in the pancreas is hard to treat
- We tested two treatments in cells, first on their own, then together

What Did We Learn?

- On their own, the treatments did not work well
- Together, the treatments worked well against cancer

What's Next?

- Test both treatments together in animals
- See if they are safe for humans to use next



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