An in Vivo Comparison of Susceptibility of Pancreatic and Breast Xenograft Models to Targeted Osmotic Lysis

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Introduction

Breast cancer is the most common cancer among women in the United States. It is diagnosed in 12 percent of women and may also affect men in rare cases. Pancreatic cancer has the highest mortality rate of all major cancers. The majority of patients are diagnosed at an advanced stage, contributing to this high observed mortality rate. Current treatments for both cancers include chemotherapy, radiation and surgery, all of which have many adverse effects. Previous studies from our lab used a novel technique that selectively lyses breast cancer cells *in vitro*. The proposed project uses this new technique called Targeted Osmotic Lysis (TOL). TOL kills cancer cells without affecting non-cancerous cells, thereby reducing adverse effects. Many types of cancers express more voltage-gated sodium channels (VGSCs) than normal tissue. TOL treatment stimulates these VGSCs while concurrently blocking sodium pumps pharmacologically. This process overloads the cancer cells with sodium, leading to the subsequent flow of water into the cells, causing them to burst (lyse). Normal cells do not lyse because they have fewer VGSCs. Because breast cancer and pancreatic cancer cells both overexpress VGSCs, we hypothesize, based on our previous experiments, that TOL will be similarly efficacious treating *in vivo* models of both pancreatic and breast cancers.

Background

TOL targets cancer cells that are known to over-express voltage-gated sodium channels (VGSCs) relative to non-cancerous cells. By stimulating VGSCs while concurrently blocking Na^+K^+ATPase (sodium pumps) pharmacologically, TOL selectively targets cancer cells. The cells are stimulated using a custom-engineered coaxial ring device, and the sodium pumps are inhibited with digoxin. This allows Na^+ to enter the cell, leading to a subsequent influx of water. Because digoxin treatment prevents the sodium pumps from removing Na^+ from the cell, water influx continues unabated, causing an osmotic lysis of the cancer cells.

Coaxial Ring is a custom-engineered device that provides stimulation using a pulse electric field (PEF).

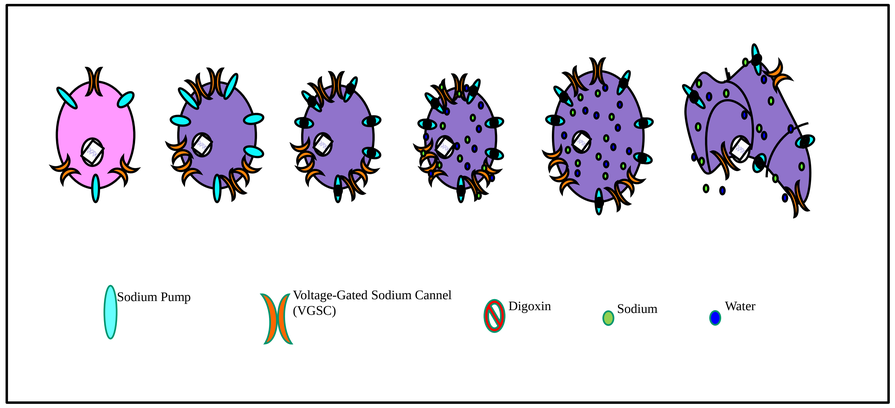
Digoxin inhibits ion-transport through Na^+K^+ATPase. It is an FDA-approved drug that at one time was widely used to treat heart failure and atrial fibrillation.

NU/J Mice an immunodeficient mouse that lacks a normal immune system and thymus gland. The nude mice are used for many different types of tumor and tissue studies. In our studies, the mice were injected subcutaneously (sc) with either human pancreatic cancer cells (PANC-1) or human triple-negative mammary gland cancer cells (MDA-MB-231).

MDA MB-231 Cells are mammary gland adenocarcinoma cells isolated from a human female.

Panc-1 Cells are ductal pancreatic carcinoma cells isolated from a human male.

Targeted Osmotic Lysis



Methods and Material

Methods for in vivo experiment

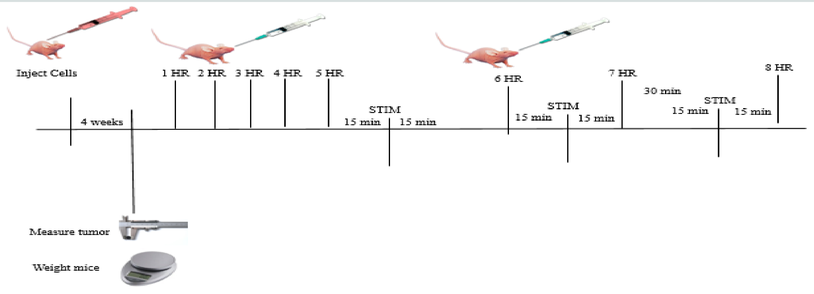
- Culture the Cells
- Harvest the Cells
- Inject Mice with Cancer
- Weight mice and measure tumors
- Inject drug, and vehicle
- Stimulate mice with Coaxial Ring Device
- Weight mice and measure tumors
- Sacrifice the Mice
- Expose all organs and tumor to the fixative
- Send to the Pathologist

Coaxial Ring Device

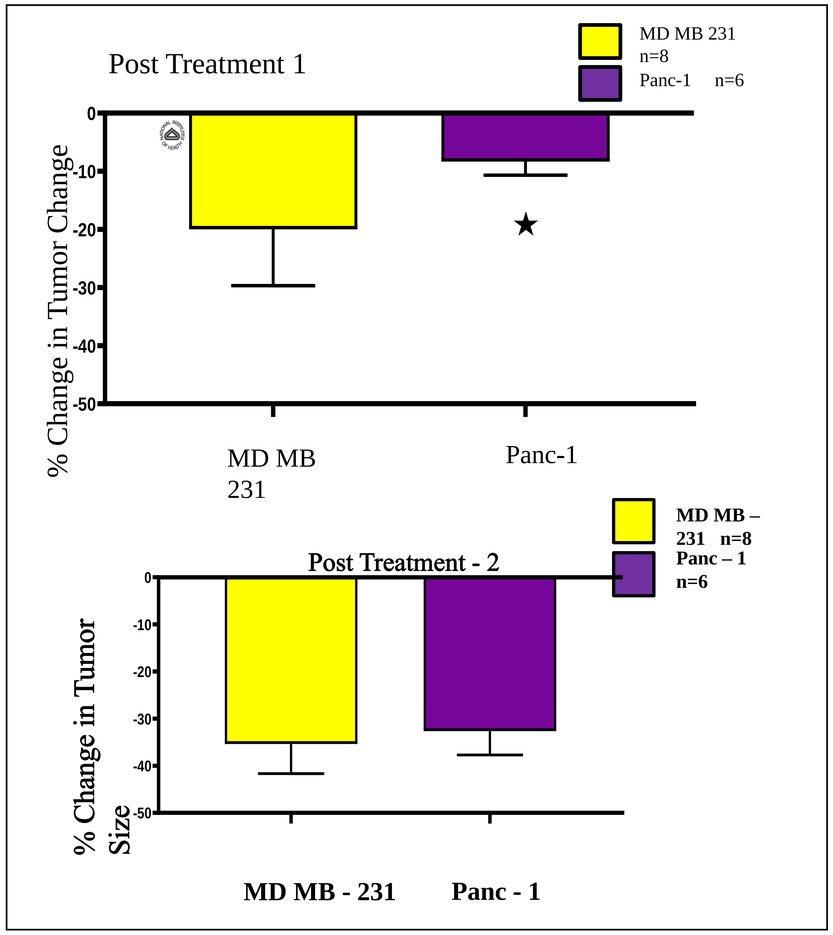
Materials

- T25 Flask
- T75 Flask
- Needles
- Calipers

Experimental Design



Results



Conclusion

- Panc-1 & MD MB-231 cells have decreased tumor size after TOL treatment
- TOL decrease tumor size in a murine model of breast cancer and pancreatic cancer, however the decrease in the tumor size for pancreatic cancer has a different profile when compared to the breast cancer model.

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