Heat-Targeted Drug Delivery using the COMBAT BRS Device for Treating Bladder Cancer

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Introduction and objective: Mild bladder hyperthermia (~43°C) can be used to improve intravesical drug delivery, to trigger payload release from systemically-administered thermally-sensitive liposomes, and to elicit immune responses. In this study we assess a novel conductive bladder heater, the COMBAT BRS device, in a live porcine bladder model to assess its ability to function as a heat-targeted drug delivery platform for use in bladder cancer.

Methods: Eleven 60 kg female swine were anesthetized and catheterized with a 3-way 16 French catheter. A multidimensional and multiparametric thermal monitoring system (fiberoptic microprobes, semiconductor germanium thermistors, custom designed/fabricated thermistor strips, and infrared cameras) was surgically implanted for high resolution 3D bladder temperature mapping. The COMBAT BRS device was used to heat the bladders to ~43°C for 2 hours. Pigs received intravesical mitomycin C (MMC, 2 mg/mL), systemic thermally-sensitive liposomes containing doxorubicin (Dox), or both. Pharmacokinetic testing was done by measuring MMC and Dox levels in blood and tissues (bladder, lymph nodes, liver, kidney, spleen, heart, and lung) by liquid chromatography tandem-mass spectrometry (Agilent 1200 - Applied Biosciences/SCIEX API 5500 QTrap). Data acquisition and quantification was performed by Analyst 1.6.2 software.

Results: Heat mapping showed consistent intravesical temperatures of 42.9°C (±0.14) and a transmural gradient of 1.5°C across the detrusor, resulting in full thickness bladder heating >41°C. Adjacent organ and core body temperature increased only minimally, well below safety thresholds. Mean bladder tissue MMC level was 0.9 μM. Mean tissue Dox level was 117.2 μM in the bladder and 6.7 μM in the heart, a 17-fold difference. Liver, kidney, spleen, lung, and LN tissue all contained significantly lower Dox levels than the bladder.

Conclusions: The COMBAT BRS device effectively heated the entire bladder wall to acceptable target temperatures and with excellent temperature safety parameters. COMBAT BRS was able to effectively trigger the release of Dox from systemically-administered thermally-sensitive liposomes, resulting in bladder Dox levels far exceeding levels required for anti-neoplastic effects, while concurrently minimizing unwanted drug delivery to other organ sites. Heat-targeted drug delivery has the potential to make systemic chemotherapy much more effective while also dramatically improving safety.