Synergistic Drug Combinations for a Precision Medicine Approach to Interstitial Glioblastoma Therapy

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Statement of Purpose: Glioblastoma (GBM) is the most deadly and aggressive form of all brain malignancies. Even after receiving the current standard of care (resection, radiation, and chemotherapy), patients have a 90% chance of recurrence and a median survival of 15 months. Utilizing drugs with unique and known mechanisms of action in combination can provide an approach to address the genotypic and phenotypic heterogeneity that is prevalent to GBM and contributes to recurrence. This can be readily achieved through interstitial delivery, encapsulating drugs in a tunable and biodegradable polymer matrix that supplies the drug directly to the tumor, bypassing the blood-brain barrier. Acetalated dextran (Ace-DEX) is a biodegradable polymer with tunable degradation rates ranging from days to months. This allows for precise control of drug release kinetics. Additionally, Ace-DEX has safe, pH-neutral degradation products. Combined, these factors make Ace-DEX a promising polymer platform for rapid and sustained interstitial drug delivery. Here, we explored the synergistic effects of pairing paclitaxel (PTX), a highly potent microtubule stabilizing agent, with (1) temozolomide (TMZ), an orally administered standard-of-care chemotherapeutic, or (2) everolimus (EVR), a mTOR inhibitor which targets an aberrant pathway found in >80% of GBM mutations. We determined synergistic combinations of these drugs in vitro and observe the therapeutic efficacy of drug combination when delivered locally via biodegradable acetalated dextran (Ace-DEX) polymer scaffolds in a clinically relevant orthotopic murine model.

Methods: The effects of PTX, TMZ, and EVR on viability was determined both individually and in combination in a panel of GBM cell lines. Synergy was determined from the combination index. (Chou TC. Pharmacol. Rev. 2006. 58,621-681) Ace-DEX was synthesized and characterized as described previously. (Kauffman KJ. Appl Mater Interfaces. 2012; 4, 4149–4155.) PTX and EVR were separately formulated into Ace-DEX polymer scaffolds via electrospinning. Scaffold morphology was characterized by scanning electron microscopy. Drug release studies were carried out in vitro at 37 ˚C and pH of 7.4 to mimic physiologic conditions. Drug retained in scaffolds over time was quantified by high-performance liquid chromatography. Fluorescent and bioluminescent glioma cells were implanted in the right frontal lobe of mice and allowed to grow for 8 days, at which point the tumor was surgically resected. Drug loaded scaffolds (Ace-PTX, Ace-EVR, Ace-PTX + Ace-EVR) or blank scaffolds (Ace-Blank) were placed in the surgical cavity. Tumor recurrence was monitored non-invasively by bioluminescent imaging.

Results: PTX, TMZ, and EVR all individually reduced cell viability in the GBM cell lines (e.g. U87-MG, LN-18, LN-229, U-251, TRP, GBM8), with PTX being 20,000-fold more potent than TMZ. In vitro, PTX displayed an overall higher degree of synergy with EVR than with TMZ in all GBM cell lines and was thus chosen for synergy analysis for the in vivo studies. To keep the ratio of PTX and EVR constant and maintain the synergistic ratio, the release rates of the drug loaded Ace-DEX scaffolds were formulated to be similar. This was achieved using the tunable degradation of Ace-DEX polymer. The PTX loaded Ace-DEX scaffold (Ace-PTX) with medium polymer degradation and the EVR loaded Ace-DEX scaffold (Ace-EVR) with slow polymer degradation showed analogous release rates (~3% per day) and were explored in vivo. In the clinically relevant surgical murine model, combination therapy with Ace-PTX + Ace-EVR significantly improved progression free survival compared to each drug individually and blank scaffolds (Ace-Blank) (Fig. 1).

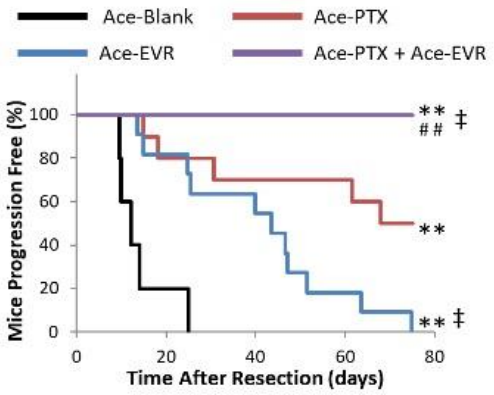

Figure 1: Kaplan Meier progression free survival curve. Statistical significance by Log-Rank test ** $p < 0.001$ with respect to Ace-Blank, ## $p < 0.001$ with respect to Ace-EVR, ‡ $p < 0.05$ with respect to Ace-PTX, *** $P < 0.001$ with respect to all other groups. Reproduced with permission from (Gurysh EG. JCR. 2020; 323, 282-292).

Conclusions: Local delivery of optimized drug combination can enhance the prognosis for patients with GBM. This method addresses GBM heterogeneity by combining drugs with unique mechanisms of action to minimize drug resistance and overcomes systemic drug delivery barriers through local administration. Our work demonstrates the value of combination interstitial therapy for synchronized local drug delivery.