

## Engineered strategies to overcome therapeutic resistance in solid tumors



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Characterization of the microenvironments in tumors is an essential step in the development of treatments to overcome therapeutic resistance. The metabolic heterogeneity of microenvironments within tumors causes significant resistance to standard cancer therapies. Fortunately these microenvironments are unique to tumors and are a distinguishing attribute that can be specifically targeted. Our laboratory is developing bacterial vectors that are specifically targeted to quiescent cells and therapeutically unresponsive regions of tumors. Motile bacteria, specifically *Salmonella typhimurium*, can actively penetrate tissue beyond the limits of passive diffusion. To quantify bacterial accumulation in tumors we have developed cylindroids, an *in vitro* culture technique that mimics the microenvironment gradients in tumors and can be observed microscopically. We have also used isotopic labeling, NMR spectroscopy, and metabolic flux analysis to quantify the intracellular mechanisms that control cell survival and death in tumors. In addition, we have created a mathematical model of the cell populations in tumors based on nutrient diffusion and intracellular metabolism diffusion to predict the therapeutic susceptibility of tumors based on individual cell physiology. Current results indicate that 1) *S. typhimurium* actively chemotax toward serine secreted by quiescent cells and ribose released from necrotic tissue, 2) Genetically modified *S. typhimurium* expressing a radiation inducible cytotoxic peptide doubles median mouse survival from 14 to 26 days, 3) Cell death in tumors is more dependent on oxygen than glucose availability, and 4) An optimal diffusion coefficient exists for therapeutic molecules. The results from this work will enable the generation of diagnostic tools that can predict the effectiveness of cancer therapies. Improved characterization of the microenvironments of tumors will enable development of specifically targeted therapeutics, including bacterial vectors that can overcome therapeutic resistance.



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Refreshments will be served at 3:45 PM