TUMOR PRIMING SEQUENCES COMBINED WITH NOVEL NANOPARTICLE DRUG CARRIERS FOR ENHANCED THERAPEUTIC EFFICACY IN PANCREATIC CANCER: A TRIPARTITE USA/NORTHERN IRELAND/REPUBLIC OF IRELAND CONSORTIUM

Pancreatic cancer (PaCA) has significant incidence, and is usually advanced at diagnosis. Regardless of treatment, 94% die within 2 yrs. Treatment challenges include tumor genetic heterogeneity, so that "one size fit all" treatment approaches are a dismal failure. Personalizing treatment based on patients' cancer biology is needed. Another challenge is that poor tumor blood perfusion limits delivery of effective chemotherapeutic drugs. Tumor stromal cells collaborate with malignant cells to establish a microenvironment that promotes metastasis, invasion, and treatment resistance, and therefore constitutes an additional target in PaCA treatment. We hypothesize that a specific, sequential, pharmacology-based combination approach will exploit this potential vulnerability: first, a `tumor priming' step will be employed to compromise vascular barrier properties. When vascular compromise is achieved, a persistent, intra-tumor drug depot will be established to extend pharmacological exposure of the tumor cells, even if the barrier is re-established. Nanoparticulate drug carriers containing high drug cargo loads will be employed to achieve this objective. Employing low-passage, patient-derived (PDX) tumor models, Aim 1 will investigate the tumor priming characteristics of two distinct types of agents: a stroma-modifying drug and a clinically-approved chemotherapeutic that primes by inducing tumor decompression. The key objectives are to understand the temporal interrelationships of (i) the primary pharmacological effects that lead to (ii) the tumor priming effect and (iii) enhanced nanoparticle deposition. Of particular interest is (iv) the role of discharging tumor interstitial pressure in the temporal onst (and waning) of the priming effect. A novel, quantitative pharmacological model will be developed to interrelate all these constituent effects into a predictive framework so that mathematical simulation can be used to develop testable hypotheses as to the appropriate priming and therapeutic sequence. In Aim 2 we will investigate distinct drug-containing nanoparticles for their efficacy; high drug-content sterically-stabilized liposomes (SSL) and PEGylated polymeric nanoparticles will be investigated for their therapeutic and mechanistic effects in a tumor- priming regimen. These formulations enable us to test the hypothesis that the aggregate properties of drug and carrier, rather than those of drug alone, determine the tumor pharmacological effects observed. In Aim 3 we will test the hypothesis that under tumor priming conditions, tumor clearance (efflux) of therapeutic nanoparticles can be reduced by employing a tumor- or stroma-targeting ligand, resulting in significant increases in efficacy. Cetuximab- (anti EGFR) bearing nanoparticles will provide proof-of-concept, owing to the predominance of EGFR expression in PaCA. Novel targeting ligands (such as anti-Death Receptor 5) will be explored also. These studies will provide a comprehensive understanding of the `tumor priming' phenomenon to enable their rational design, as well as a strong rationale for therapeutic combinations and agents that could rapidly transition to clinical evaluation in PaCA, a cancer of nearly uniform lethality.

Pancreatic cancer is lethal to the vast majority of patients, largely because the disease is advanced when discovered, and tumor blood flow is so low that drugs do not readily access the tumor. This project will address the `drug delivery' barrier by establishing a conceptual understanding of how `tumor priming' agents work; they attack the barrier between the blood stream and the tumor interior, creating a `window of opportunity' for delivery of a second agent. We hypothesize that nanoparticle-based drug carriers may have unique advantages that enable them to exploit tumor priming strategies more effectively and improve therapeutic outcomes; inclusion of several clinically-approved agents in our research plan will provide strong rationale for near-term clinical trials in pancreatic cancer, and we propose novel nanoparticle agents of longer-term developmental potential.