Physiological barriers to drug delivery and therapy-induced molecular selection pressures preclude durable improvements in survival for many cancer patients. It is increasingly evident that the most effective treatments will involve cooperative regimens that target multiple non-overlapping pathways, while minimizing systemic toxicities. Photodynamic therapy (PDT) improves the therapeutic index of traditional and emerging treatments by exploiting photochemically-triggered mechanisms that prime tumor cells and enhance drug delivery. Leveraging biomedical engineering and pharmacoengineering approaches, this presentation describes the development of PDT-based regimens that overcome barriers to effective treatment. A focus is on enhancing the efficacy of camptothecin analogues and platinum-based chemotherapies, which are commonly used to manage cancers, but suffer from significant toxicities, poor drug penetration, and resistance. Capturing the distinct mechanisms and non-overlapping toxicities of PDT in rationally-designed combinations leads to synergistic tumor reduction in 3D models, and durable tumor control in vivo. The mechanistic basis of these improved outcomes will be presented: (1) Photo-initiated damage to sub-cellular targets (e.g. mitochondria/ER and bcl-2) to increase the susceptibility of tumor cells to chemotherapeutic insult; (2) Stromal and vasculature disruption to significantly improve drug delivery and penetration, increasing intra-tumoral chemo accumulation by >10-fold; and (3) Mitigation of chemotherapy-induced enrichment of cellular stemness markers (e.g. CD44, CXCR4) for prolonged survival. Results will be discussed in the context of establishing a Research Program involving imaging and therapeutic applications of light, bioengineered 3D models and animal models for cancer, and molecular targeted drug delivery to inhibit tumor survival pathways.