Targeting Colon Cancer Cells Using PEGylated Liposomes Modified With a Fibronectin-Mimetic Peptide

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The ability to target cancer cells using an appropriate drug delivery system can significantly reduce the associated side effects from cancer therapies and can help in improving overall quality of life post cancer survival. Integrin $\alpha5\beta1$ is expressed on several types of cancer cells, including colon cancer, and plays an important role in tumor growth and metastasis. Thus, the ability to target the integrin $\alpha5\beta1$ using an appropriate drug delivery nano-vector can signficantly help in inhibiting tumor growth and reducing tumor metastasis. In this study we have designed functionalized stealth liposomes (liposomes covered with polyethylene glycol (PEG)) that specifically target the integrin $\alpha5\beta1$. The PEG provides a steric barrier allowing the liposomes to circulate in the blood for longer duration and the functionalizing moiety, the PR_b peptide specifically recognizes and binds to integrin $\alpha5\beta1$ expressing cells. PR_b is a novel peptide sequence, designed in our lab, that mimics the cell adhesion domain of fibronectin, and includes four building blocks, RGDSP (the primary recognition site for $\alpha5\beta1$), PHSRN (the synergy site for $\alpha5\beta1$), a (SG)5 linker, and a KSS spacer. In this study, we demonstrate that by optimizing the amount of PEG and PR_b on the liposomal interface we can engineer nano-vectors that bind to CT26.WT, HCT116, and RKO colon cancer cells in a specific manner and are internalized through $\alpha5\beta1$-mediated endocytosis. Stealth liposomes functionalized with an RGD containing peptide bind to colon cancer cells and internalize, but they have much lesser efficiency than PR_b-targeted stealth liposomes, and more importantly they are not as specific since many integrins bind to RGD. PR_b-targeted stealth liposomes are as cytotoxic as free 5-Fluorouracil (5-FU) and exert the highest cytotoxicity on CT26.WT cells compared to RGD-targeted stealth liposomes and non-targeted stealth liposomes. In order to further increase the efficacy of the system we have designed peptide-functionalized stealth liposomes that are pH-sensitive and exhibit triggered release under mild acidic conditions present in endocytotic vesicles. The proposed targeted delivery system has the great potential to deliver a therapeutic load directly to colon cancer cells, in an efficient and specific manner.

A Novel Combination Therapy for Post-Operative Arrhythmias

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Atrial fibrillation (AF) is a common heart rhythm disorder, effecting about 20% of cardiac surgical patients. While often benign, it leads to a prolonged hospital stay, and potentially to malignant arrhythimas. Many anti-arrhythmic drugs have been used to both prevent and treat post-operative AF and other post-operative arrhythmias; however, they have potentially harmful side-effects (e.g., hypotension, pulmonary fibrosis). Cardioversion is often the therapy of last resort to restore a perfusable rhythm. We propose a novel, innovative concept that allows for local pharmacological and electrical therapy of the heart. We have shown in animal models that such delivery increases the efficacy of the therapy and reduces side effects. Several variations of the device have been conceived and prototypes are currently being developed. The simplest version is a multi-port infusion catheter incorporated into a temporary pacing lead. Placement of the device would be trivial for surgeons, who routinely place temporary pacing leads prior to closing the chest. Removal of the device post-operatively would be equally simple. More complex iterations include an expandable wick to maintain the infused drug in a desired location. Designs may also include epicardial defibrillation capabilities, which would lower the energy required for defibrillation. To demonstrate proof of principle, cadaver and animal investigations were performed. In a fresh cadaver, a sternotomy and pericardiotomy was performed. A catheter was placed in the pericardium, and an infusion of radio-opaque contrast was administered under fluoroscopy. The majority of the contrast collected near the pulmonary veins, which are often the origin of atrial arrhythmias. To evaluate the efficacy of drugs administered into the pericardium as compared with drugs administered through the conventional route (intravenously), animal studies in swine were performed. Results demonstrated that pericardially administered metoprolol had a greater and more lasting effect on heart rate than when given intravenously. Additionally, during pericardial delivery myocardial contractility was better preserved. Only trace amounts of metoprolol were found in the circulation. Thus pericardial delivery may enhance certain therapeutic effects of drugs while limiting side effects. Currently, studies are underway to evaluate the efficacy other pharmacologic agents delivered into the pericardium. Should our animal studies continue to show promising results, we anticipate moving into clinical trials. Development and refinement of prototype delivery devices will also continue as we pursue this promising new therapy for post-operative arrhythmias.