450f Dendritic Nanoparticles for Controlled Release of Anticancer Drugs

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Targeted drug delivery using drug carriers responsive to biological stimuli has been proposed as an attractive strategy for cancer treatment. Considerable progress has been made in an attempt to develop drug carriers, including low molecular weight pro-drugs, liposome and micro- and nano-particulates, with varying degrees of clinical success. Several issues remain regarding developing drug carrier used for caner treatment: the limited therapeutic activity and insolubility of current anticancer drugs and inaccessibility and heterogeneity of the tumor. Ceramide is a potent, anti-mitogenic, lipid-derived, second messenger that inhibits the proliferation and/or induces apoptosis in various cell types. However, the delivery of natural and cell-permeable ceramide analogs, including C6-ceramide (C6), to cancerous cells is impeded by the hydrophobicity of these bioactive lipids, resulting in reduced efficacy and limited potential as chemotherapeutic agents.

In this work, we have developed novel dendritic nanoparticles for thermally targeted and sustained drug delivery for cancer chemotherapy using C6. The dendritic nanoparticles sensitively change solubility in response to temperature stimuli, and hydrolytically degrade with time. The cellular uptake of fluorescein-labeled dendrimers by human MDA-MB-231 breast adenocarcinoma cells was significantly enhanced under hyperthermic conditions. The dendritic nanoparticles displayed prolonged C6-release kinetics, while released C6 was shown to inhibit the proliferation of MDA-MB-231 cells. In alignment with long-term objectives, it can be envisioned that these “biosmart” strategies have the potential to significantly impact clinical therapy of breast cancer and other neoplastic diseases.