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Synthesis of a novel, sequentially active-targeted drug delivery nanoplatform for breast cancer therapy

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ABSTRACT

Breast cancer is the leading cause of cancer deaths among women. Paclitaxel (PTX), an important breast cancer medicine, exhibits reduced bioavailability and therapeutic index due to high hydrophobicity and indiscriminate cytotoxicity. PTX encapsulation in one-level active targeting overcomes such barriers, but enhances toxicity to normal tissues with cancer-similar expression profiles. This research attempted to overcome this challenge by increasing selectivity of cancer cell targeting while maintaining an ability to overcome traditional pharmacological barriers. Thus, a multi-core, multi-targeting construct for tumor specific delivery of PTX was fabricated with (i) an inner-core prodrug targeting the cancer-overexpressed cathepsin B through a cathepsin B-cleavable tetrapeptide that conjugates PTX to a poly(amidoamine) dendrimer, and (ii) the encapsulation of this prodrug (PGD) in an outer core of a RES-evading, folate receptor (FR)-targeting liposome. Compared to traditional FR-targeting PTX liposomes, this sequentially active-targeted dendrosome demonstrated better prodrug retention, an increased cytotoxicity to cancer cells (latter being true when FR and cathepsin B activities were both at moderate-to-high levels) and higher tumor reduction. This research may eventually evolve a product platform with reduced systemic toxicity inherent with traditional chemotherapy and localized toxicity inherent to single-target nanoplatforms, thereby allowing for better tolerance of higher therapeutic load in advanced disease states.
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1. Introduction

Globally, breast cancer is the most frequently diagnosed cancer in women and the leading cause of cancer death among women [1]. In 2012, it was estimated that 1.7 million new cases were reported and about 522,000 breast cancer deaths occurred in women. Chemotherapy plays a central role in cancer treatment, and the scientific advances in chemotherapy during the last few decades have led to significant improvements in patient survival rates. However, common anti-cancer agents demonstrate well-known limitations, such as systemic cytotoxicity, poor solubility in body fluids, and slow tumor uptake [2]. Nanotechnological advancements are being applied to overcome these problems. This report is one such effort towards targeted delivery and improved efficacy of an anti-cancer agent commonly used for the treatment of breast cancer.

The broadly-cytotoxic class of drugs 'taxanes', which includes paclitaxel (PTX) and docetaxel, is the most effective single-agent drug class used in the chemotherapy of breast cancer and the first-line therapy in the metastatic form of the disease [3,4]. PTX is used preferentially [5], with a 56% response rate against metastatic breast cancer [6,7]. Therefore, PTX was used as a model anti-cancer drug in this study.

Anti-cancer treatment involving PTX faces several limitations, including reduced bioavailability due to high hydrophobicity. Cremophor EL formulations improve solubility, but introduce severe

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side effects [6,8–10]. Further, the antitumor efficacy of many clinical anti-cancer drugs, including PTX, is limited by their non-specific, indiscriminate distribution among all tissues and the non-specific cytotoxicity to all proliferating cells (cancerous as well as normal), resulting in significant toxicity, a low therapeutic index, and a narrow therapeutic window. In particular, PTX binds to microtubules within a dividing cell during mitosis, causing kinetic stabilization through inhibition of microtubule depolymerization. The result is mitotic arrest and blockage of cell cycle progression [11–13]. This mechanism is non-specific and can produce serious unwanted consequences.

Nanotechnological advances provide for an alternative solution to enhance the bioavailability of potent anti-cancer drugs at the site of their action, while reducing drug toxicity. Shortcomings in drug delivery have given impetus to develop a targeting approach towards (i) the specific physicochemical characteristics of tumor cells and tissue, such as leaky tumor vasculature (passive targeting), and/or (ii) the biomolecules that are differentially expressed in the tumor cell or on their surface relative to the normal cells (active targeting). The targeted drug-carrying platforms that ferry the drug to the tumor increase the bioavailability of the drug at the site of action while limiting exposure to non-target tissues and organs [14,15].

While targeting of a specific molecular cue on cancer cells can prevent systemic toxicity by reducing the number of potential hits at non-cancer cells, normal tissue with similar molecular expression profiles are still exposed to the cytotoxic risk. Thus, the toxicity to non-cancerous yet similarly-expressive normal cells may remain unchanged in a single-target approach and may result in serious toxicity to one or more other vital functions [16]. Therefore, a need exists to develop a multi-targeted drug delivery platform that may be suitable to overcome physiological barriers and enhance specificity to breast cancer treatment and its efficacy [17].

Here, we describe the design of a multi-core drug delivery platform that offers the possibility of multi-focused targeting of breast cancer tissue and cells. The inner core of this construct consists of a PTX delivery device that releases PTX following the action of a proteolytic enzyme upregulated in breast cancer cells. We have previously described the synthesis of such a prodrug [18]. Intended to release PTX in the presence of cathepsin B overexpression (as is the case in many cancer cells, but not normal tissue), it is designed by the conjugation of PTX to the terminal amino groups of the polyamidoamine (PAMAM) dendrimers through the cathepsin B-cleavable tetrapeptide, Glycine-Phenylalanine-Leucine-Glycine (GFLG). This prodrug, referred to as PGD (Fig. 1), demonstrated successful cytotoxic and antitumor efficacy [18]; yet by design, the conjugate possesses a single-level targeting capability only, limiting its potential due to the aforementioned cytotoxic effects seen in such platforms.

Encapsulation of the PGD in a liposomal outer core allows for the development of a sequentially-targeted multicore architecture (Fig. 2). Liposomes are phospholipid (PL) bilayered vesicles with a membrane mimicking architecture, including a hollow structure to allow for the enclosure of drug warheads. Several liposomal compositions have evolved to include evasion of the reticuloendothelial system (RES) [19,20] and active targeting to cell surface receptors [21,22]. In this study, we have designed a formulation that includes polyethylene glycol (PEG)-based RES evasion and folate receptor (FR)-targeting. To introduce active targeting in the liposomes, the distal end of PEG was conjugated to folate, one of the most widely studied small molecules as a cancer cell targeting moiety. Folate is essential for rapid cell division and growth, and has a high binding affinity for FR ($Kd = 10^{-9}$ M). In cancers, since FRs are overexpressed on tumor cells, the folate moiety enables the targeted delivery of therapeutic agents to tumors [23].

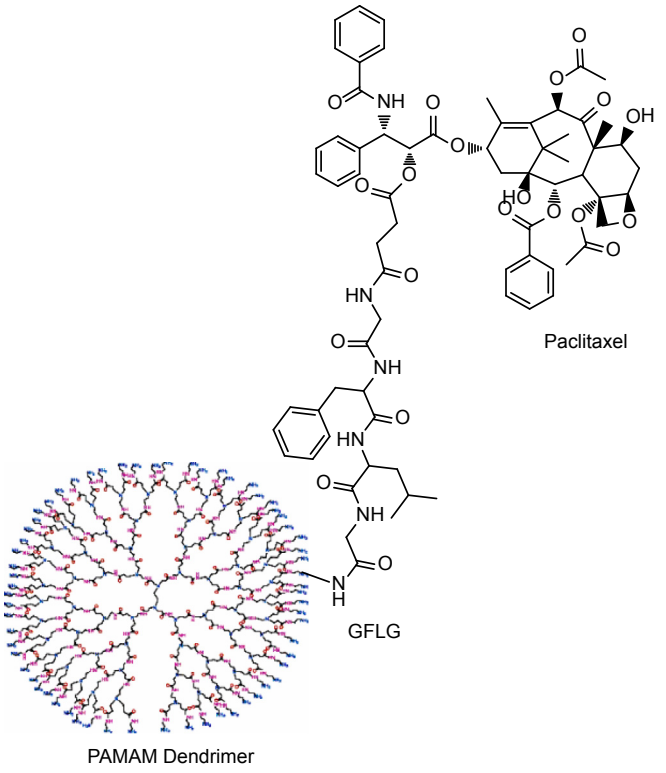

Fig. 1. Structure of paclitaxel-GFLG-PAMAM dendrimer (PGD) conjugate (image components not to scale).

While paclitaxel-based liposomal formulations that target FRs exist [24], they display strong limitations: (i) active targeting at a single-level only and (ii) component leakage before reaching target site [25].

To overcome disadvantages of both the dendrimer and liposome platforms yet exploit their advantages, the dendrosome construct was designed to sequentially exploit its potential for (i) long-term circulation, (ii) protection of the inner core prodrug from the circulatory biological environment until it reaches the target site, (iii) passive targeting to take advantage of the enhanced permeation and retention (EPR) effect in tumor tissue caused by chaotic and leaky vasculature along with dysfunctional lymphatic drainage, (iv) active targeting of upregulated FRs on rapidly dividing cancer cells for internalization of prodrug in cancer cells, and (v) further active targeting of cathepsin B, a highly upregulated enzyme in many breast cancer cells to liberate the active agent PTX from its dendrimer-based prodrug. It was expected that the sequential active targeting is achieved such that inner core targeting is not activated until outer core targeting requirements are met. Thus, the overall goal was to improve the therapeutic efficiency of the active agent and to achieve increased targeting specificity using two molecular differences between cancer and normal cells instead of just one.

Therefore, this report describes the design and synthesis of the above dendrosome architecture (hereafter referred to as FR-targeting PGD dendrosomes), its physicochemical characterization, and subsequent evaluation through *in vitro* and *in vivo* experiments. The device was evaluated with respect to traditional FR-targeting PTX liposomes for improved efficacy in treating cancer cells and reduced toxicity against normal cells. Confirmation of increased treatment efficacy by FR-targeting PGD dendrosomes was evaluated by investigating tumor growth reduction in xenograft mice models of breast cancer.

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