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A High Molecular Weight Biodegradable Gelatin-Doxorubicin Conjugate

Lead Inventor

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Unmet Need

A major challenge in cancer chemotherapy is the selective delivery of small molecule anti-cancer agents to cancer cells. Doxorubicin (DOX) is a potent antineoplastic agent that is effective against a wide range of solid tumors and lymphomas but it is also associated with an irreversible cardiomyopathy above cumulative doses of 550 mg/m2. This and other toxic side effects make the drug a good candidate for localized drug delivery. DOX has been investigated in several macro-molecular delivery systems such as liposomes synthetic copolymers of N-(2-hydroxypropyl) methacrylamide (HPMA), other synthetic water-soluble polymers, micelles, polysaccharides, as well as block copolymer vesicles (or polymersomes). Such delivery systems have demonstrated preferential accumulation in solid tumors compared to healthy tissue due to the enhanced permeation and retention effect (EPR) The resulting therapeutic advantages include an enhanced antitumor effect and reduced systemic toxicities. Also, maximum tolerated doses of 5 to 10-fold greater than the free drug and the ability to overcome drug resistance have been reported. These and similar delivery systems, however, have produced concerns.

Gelatin is the denatured and partially hydrolyzed product of collagen. It has been used as a macromolecular carrier to deliver several drugs including amphotericin B, methotrexate, and tumor necrosis factor. It also has been shown to have cell uptake. Its high molecular weight and bio-degradability are attractive properties for use as a carrier in a DOX macromolecular delivery system. A sufficiently high molecular weight (e.g., 40 kDa or higher) can avoid glomerular filtration by the kidney leading to an extended circulation time and greater tumor accumulation by the EPR effect. Once the gelatin conjugate accumulates within the interstitial space of a tumor, its susceptibility to degradation by metalloproteinases such as cathepsin B would reduce the conjugate size and allow it to be taken up into tumor cells by endocytosis leading to accumulation in the subcellular lysosome compartment. In this acid environment, the acid sensitive conjugate bond will release the drug very close to its site of action so that its cytotoxic effect will occur only within the cell.

Despite the interest in the art in synthesizing a high molecular weight gelatin-DOX conjugate, there are numerous synthetic challenges, particularly related to the degradation of high molecular weight gelatin during synthesis. Accordingly, there is an unmet need in the art for high molecular weight gelatin-DOX conjugates and methods of production.

Opportunity

High molecular weight gelatin-DOX conjugates to increase efficacy of delivery of small molecule anti-cancer agents to cancer cells. This localization is also expected to minimize toxic side effects of this cancer drug because it is not released until it reaches the tumor and its cells.

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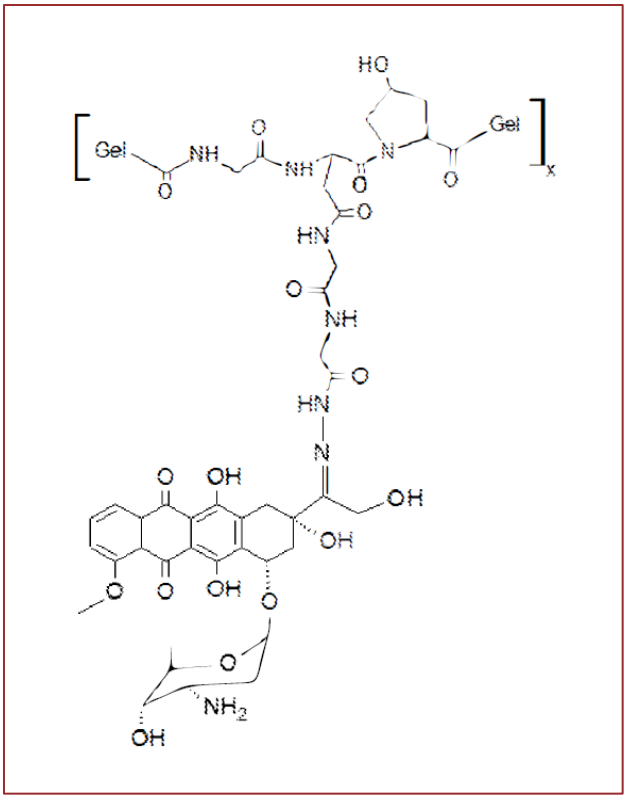
Unique Attributes

- The invention is based, in part, on a novel synthesis methodology that can produce high molecular weight gelatin-DOX conjugates.
- In one aspect, the invention provides a high molecular weight compound comprising gelatin and DOX (i.e., a high molecular weight gelatin-DOX conjugate), where the gelatin is covalently linked to DOX through a cleavable linker.

Clinical Applications

Potential new treatment for triple negative (TNBC) breast cancer since conjugate cell uptake does not require receptors common in other types of breast cancer but absent in TNBC.



Stage of Development

Preclinical Studies

Intellectual Property

US Patent No. 10,265,413
Also published as CA2966598A, 1EP03215116B1, WO2016077083A1

Collaboration or Licensing Opportunity

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

References and Publications

- Wu, DC et al.; *Preparation, Drug Release, and Cell Growth Inhibition in a Gelatin – Doxorubicin Conjugate*. Pharmaceutical Research, August 2013, Volume 30, Issue 8, pp 2087–2096.
- Alvi, M, and Ofner, CM III; *The Intracellular Distribution of Doxorubicin and a Gelatin-Doxorubicin Conjugate for Tumor Targeting in a Triple Negative Breast Cancer Cell Line*. Accepted poster for the 2017 annual meeting of American Association for Pharmaceutical Scientists (AAPS, November 12-15, San Diego, CA).
- Alvi, M et al.; *Lysosomal Targeting and Cytotoxicity of a Gelatin-Doxorubicin Conjugate in MCF7 Breast Cancer Cells*. (In Preparation).

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