First-in-class Anti-tumor Dextran-based Dual Drug Conjugate

Overview

Drug Name	CQ-527
Description	Docetaxel (DTX) is a semisynthetic chemotherapeutic agent commonly used against a wide range of cancers, but the effectiveness of treatment is limited in clinic due to the its low water solubility, nonselective biodistribution, systemic toxicity, and severe allergic reactions. A novel dextran-based conjugate is design to overcome these drawbacks. CQ-527 is a dual-drug conjugate formed by independent covalent binding of DTX and docosahexaenoic acid (DHA) to dextran via individual linkers. In vivo studies showed that CQ-527 accumulated in tumor tissues and significantly reduced DTX concentration in normal tissues, and it exhibited superior antitumor activity.
Target	Tubulin
Drug Modality	Small molecule
Indication	Cancer
Product Category	Chemotherapeutic agent
Mechanism of Action	Inhibition of tubulin polymerization to induce cancer cell apoptosis
Status	Preclinical
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for CQ-527. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

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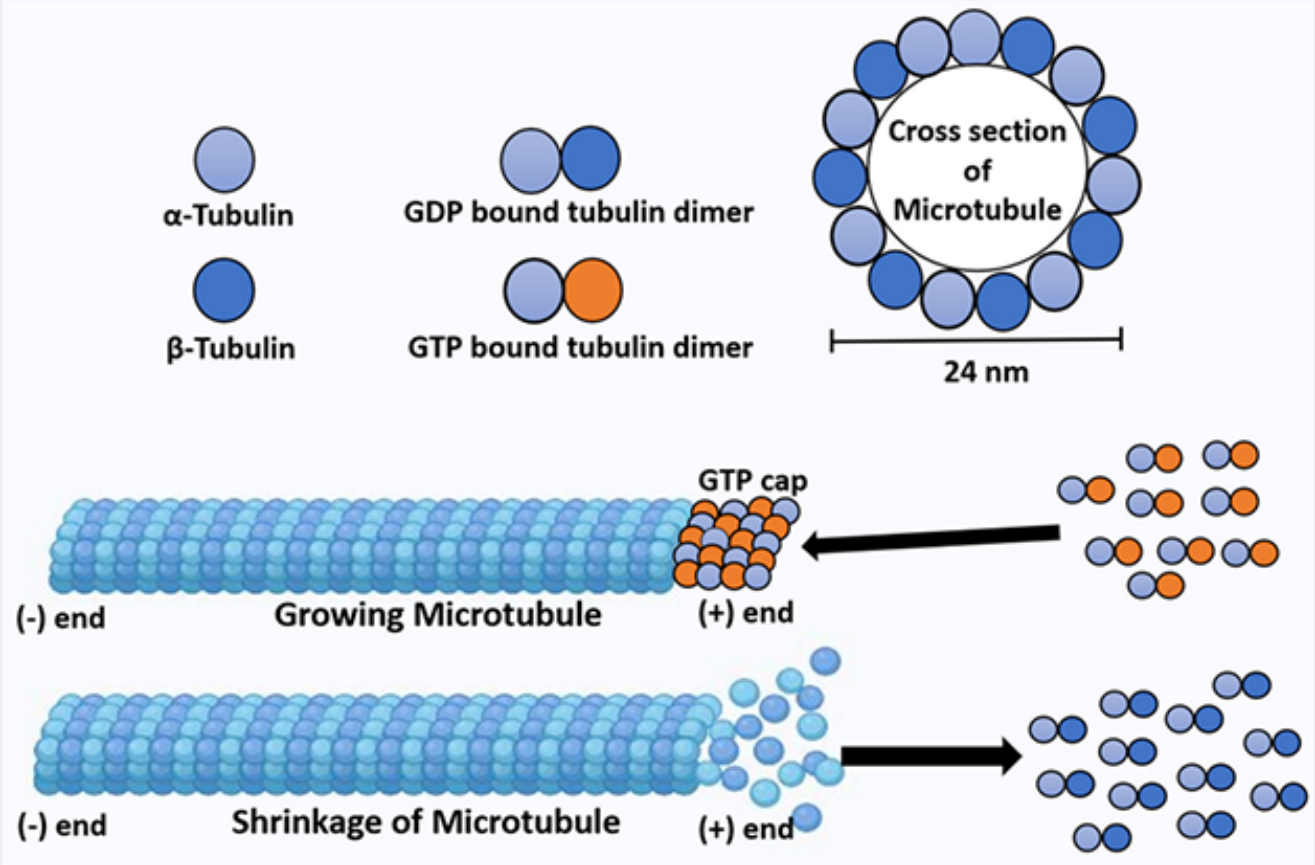
Tubulin

Tubulins are cytoplasmic proteins that are divided into three classes: alpha, beta, and gamma. Alpha and beta tubulins form heterodimers that polymerize into cylindrical microtubule fibers, which are found in almost all eukaryotic cell types and are involved in cellular processes such as mitosis, cell signaling, and motility. Beta tubulin binds GTP and hydrolyzes GTP to GDP. This process of hydrolysis is associated with tubulin polymerization and microtubule formation. Alpha tubulin also binds GTP but does not have GTP/GDP hydrolysis activity. However, alpha tubulin can be modified by addition of a C-terminal tyrosine residue, which affects polymerization rates. Disruption of microtubule formation and consequent arrest of the mitotic process is currently a successful strategy for the treatment of cancer. Some antimitotic agents act by overstabilizing GDP-bound tubulin in the microtubule, while others block microtubule formation and destroy mitotic spindles.



Microtubules formed by the joining of α-tubulin and β-tubulin subunits (DOI:10.1007/s12035-024-04053-3)

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Drug Modality

Small Molecule

Among the various classes of antimitotic agents, taxanes are the most widely used in the treatment of cancers. Among them, docetaxel is a semisynthetic compound. Despite the remarkable efficacy of docetaxel, it has important limitations including low water solubility, nonselective biodistribution, and systemic toxicity. Dextran is a natural polysaccharide composed of α-1, 6-glycosidic linkages in the main chain and α-1, 3-glycosidic linkages in the side chain. Due to its desirable physicochemical properties such as water solubility, biocompatibility, biodegradability and non-immunogenicity, dextran is an attractive drug delivery system. CQ-527 is a dual-drug conjugate consisting of docosahexaenoic acid (DHA) and docetaxel, each linked to dextran through separate linkers. The polysaccharide-based DHA/DTX conjugate exhibited enhanced water solubility, prolonged plasma half-life, and selective tumor targeting in in vivo studies. DHA is a long-chain omega-3 polyunsaturated fatty acid, which is involved in many physiological processes. Importantly, DHA can induce cell cycle arrest, apoptosis, autophagy, and tumor growth inhibition through a variety of mechanisms. Therefore, DHA can enhance the therapeutic effect of Dextran-DHA-DTX conjugates. In tumor xenograft mouse models, the treatment of CQ-527 showed stronger tumor inhibition with less weight loss compared with DTX treatment.

Indication

Cancer

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells divide uncontrollably, and invade other organs and tissues of the body to form metastatic tumors. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018. Lung, prostate, colorectal, stomach, and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical, and thyroid cancer are the most common among women. Lung cancer is the most prevalent and costly malignancy in the world, as well as the most frequent cause of cancer-related mortality worldwide in men and women combined. According to the International Agency for Research

on Cancer, in 2020, female breast cancer pulled ahead of lung cancer as the most commonly diagnosed malignancy worldwide, accounting for 11.7% of all incident cancer cases that year. The cancer burden continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals, families, communities and healthcare systems.

Mechanism of Action

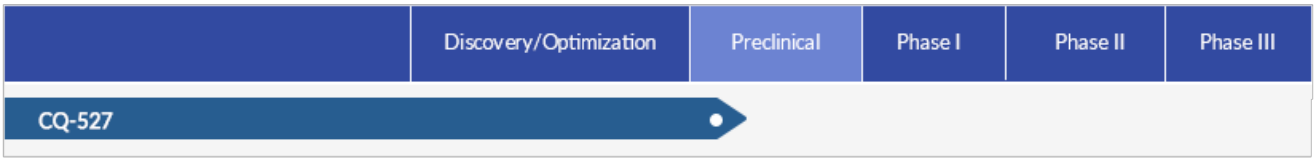
Inhibition of Tubulin Polymerization

Microtubules are the backbone of the cytoskeleton and are essential for maintaining cell morphology, intracellular transport, reproduction, and neurotransmission. Docetaxel in CQ-527 stabilizes tubulin polymerization by binding to β-tubulin subunits of microtubules in cancer cells, leading to cell cycle arrest in G2/M phase and inhibition of mitosis. Stabilization of microtubules disrupts the dynamic reorganization of microtubules into spindles, leading to the formation of abnormal bundles, which inhibits cell proliferation causing cancer cell death. Docosahexaenoic acid (DHA) can inhibit tumor growth synergistically with docetaxel and can sensitize tumor cells to chemotherapy. In addition, Dextran is a natural and excellent biomaterial for drug delivery application due to its water solubility, biocompatibility, biodegradability, and non-immunogenicity.

Status

The Status of CQ-527

CQ-527 is a polysaccharide-based dual drug conjugate with a novel structure and unique mechanism, which is designed by a proprietary technology platform.



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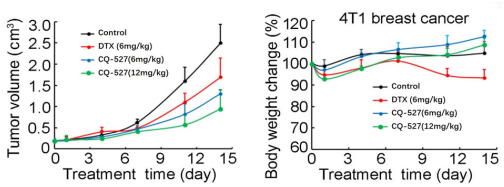

Antitumor Efficacy of CQ-527 in Breast Cancer-bearing Mice

CQ-527 is evaluated in BALB/C mice with 4T1 breast cancer cells. When compared with the group of 6 mg/kg DTX treatment, treatment with the 6 mg/kg CQ-527 conjugate had 21.3% higher anti-tumor effect. The treatment with CQ-527 did not lead to a decrease in body weights; however, 6 mg/kg DTX treatment led to a significant reduction in body weights.

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