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Design and development of IT-101, a cyclodextrin-containing polymer conjugate of camptothecin ☆

Mark E. Davis

Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA

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ABSTRACT

IT-101 (Insert Therapeutics-101) is a linear, cyclodextrin-containing polymer conjugate of camptothecin (CPT). When formulated properly, the polymer conjugate self-assembles into nanoparticles of ca. 30 nm diameter and near neutral zeta potential. The nanoparticles show long circulation half-lives in animals and humans and localize in tumors. The nanoparticles enter the tumor cells and slowly release the CPT causing them to disassemble into individual polymer chains that are sufficiently small to be cleared renally. IT-101 is currently being investigated in human clinical trials. Here, the design and development of IT-101 is described with emphasis on features distinguishing it from other polymer-containing therapeutics.

Contents

1. Introduction

Polymer-drug conjugates are a class of therapeutic entities that have members ranging from approved drugs, e.g., PEGylated proteins, to laboratory curiosities. While all polymer-drug conjugates are now being denoted as "nanoscaled" entities, only some assemble into true nanoparticles [1]. Recent reviews on nanoparticle therapeutics either in the clinic or about to reach clinical status have appeared [1, and references therein]. Here, the experimental, nanoparticle therapeutic, IT-101, that is currently being investigated in the clinic, is described. To the best of my knowledge, IT-101 is the first de novo designed, polymer-based therapeutic to reach the clinic for the treatment of cancer. This review outlines the features of the IT-101 design, and describes how they influence the behavior of this nanoparticle cancer therapeutic.

2. Design of IT-101

2.1. Design of the polymer component

The design of the IT-101 polymer included features that were aimed at addressing biocompatibility, cGMP processing and regulatory hurdles (for example with the FDA). The polymer was designed to be linear, highly biocompatible, non-biodegradable and of sufficient size to be cleared renally as a single molecule. To meet these design criteria, a new class of water-soluble, linear polymers was prepared.

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E-mail address: mdavis@cheme.caltech.edu.

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These polymers contain cyclodextrins (CDs) as part of the backbone. CDs have a long history as drug solubilizers and their properties are established in humans [2]. My co-workers and I created numerous types of water-soluble, linear polymers with CDs in their backbones [2–5]. Initially, cationic polymers were prepared for assembly with nucleic acid-based drugs [2–4]. For IT-101, a linear co-polymer of β-CD and PEG (see Fig. 1) was synthesized [5]. This highly water-soluble polymer is polyanionic and gives low toxicity in animals (MTD is greater than 240 mg/kg in mice [6]). The polymer is prepared by reacting a diaminoacid-β-CD monomer with a difunctionalized PEG (MW = 3400). The polymer has been prepared at a multi-kilogram scale and the molecular weight is purposefully controlled to give polymer molecules that are able to clear renally (ca. 70 kDa with PDI of ca. 2). In solution, the individual polymer molecules are slightly smaller than 10 nm (see Table 1 [7]), and thus, are able to filter through the kidney [8].

2.2. Conjugation of the drug (CPT) to the polymer

Camptothecin (CPT) is conjugated to the carboxylate groups on the linear, water-soluble CD polymer. To do so, CPT is functionalized to form an ester bond at the 20-hydroxyl group of the CPT in order to maintain the lactone form of the CPT while it is residing on the polymer [5]. Release of the conjugated CPT does in fact give pure CPT in the lactone form, and the release rate can be tuned by the choice of the linker chemistry [5]. Several amino acid-based linkers were investigated both in vitro [5] and in vivo [6]. Ultimately, glycine was chosen as the linker as it provided for antitumor efficacy with low toxicity [6,9,10]. When CPT is conjugated to the polymer (ca. 10 wt% CPT), the water solubility of the lactone form of CPT is increased by over three orders of magnitude. Conjugation is not limited to CPT, and other drug molecules are discussed below.

2.3. Assembly/disassembly of the IT-101 nanoparticle

The CPT conjugated polymer is a multivalent polymer that when placed in aqueous media self-assembles into a multi-strand nanoparticle (Table 1). CPT can form inclusion complexes with β-CD and does so in a multivalent fashion to assemble the IT-101 nanoparticle. Fig. 2 shows a cryo-TEM photograph of IT-101. The particle size is ca. 30–40 nm (confirmed by DLS), and in PBS, the nanoparticles of this size have a zeta potential of ca. −2 mV (not all the carboxylate groups are reacted at 10 wt% CPT). The size and surface charge were targeted in the design as appropriate for in vivo use (near neutral surface charge to minimize macrophage uptake, and sizes appropriate for inhibiting renal clearance but sufficient for tumor localization and movement throughout the tumor [7]). The nanoparticles assemble from polymer conjugates via multiple interactions (must be the case to provide sufficient strength to resist disassembly by dilution). It is believed that the primary mechanism for assembly is interstrand CPT↔β-CD inclusion complex formation (although CPT↔CPT interaction may also occur). The reasons for this are: (i) release of the drug by treatment with NaOH gives individual polymer strands, (ii) addition of drug solubilizing agents such as DMSO do not disassemble IT-101, and (iii) addition of soluble adamantane (AD) compounds such as AD–PEG disassemble (presumably by displacing the CPT from the β-CD in IT-101). Thus, the IT-101 nanoparticles are sufficiently large to avoid renal clearance, but the disassembled nanoparticles can give individual polymer strands (Table 1) that can clear via the kidney (see Fig. 3 for schematic). This assembly–disassembly mechanism is unique amongst all polymer drugs to IT-101. It is of importance since regulatory agencies require characterization of drug and drug fragments. For IT-101, only the nanoparticle and parent polymer (no polymer fragments since it is not biodegradable) require characterization.

Table 1
Properties of individual polymer strands and IT-101 in aqueous solutions [7].

Parameter	Individual cyclodextrin polymer strand	IT-101
Particle size	8 nm	36 nm
PDI	0.323	0.277
Zeta potential	Not determined	−1.81 +/− −0.79 mV

The individual strands (do not contain CPT) and IT-101 both had polymer strands of MW = 67 kDa and a polydispersity index (PDI) of 2.1.

2.4. Proposed in vivo function

The overall design of IT-101 involved a systems approach to provide a multifunctional therapeutic. The design concepts involved

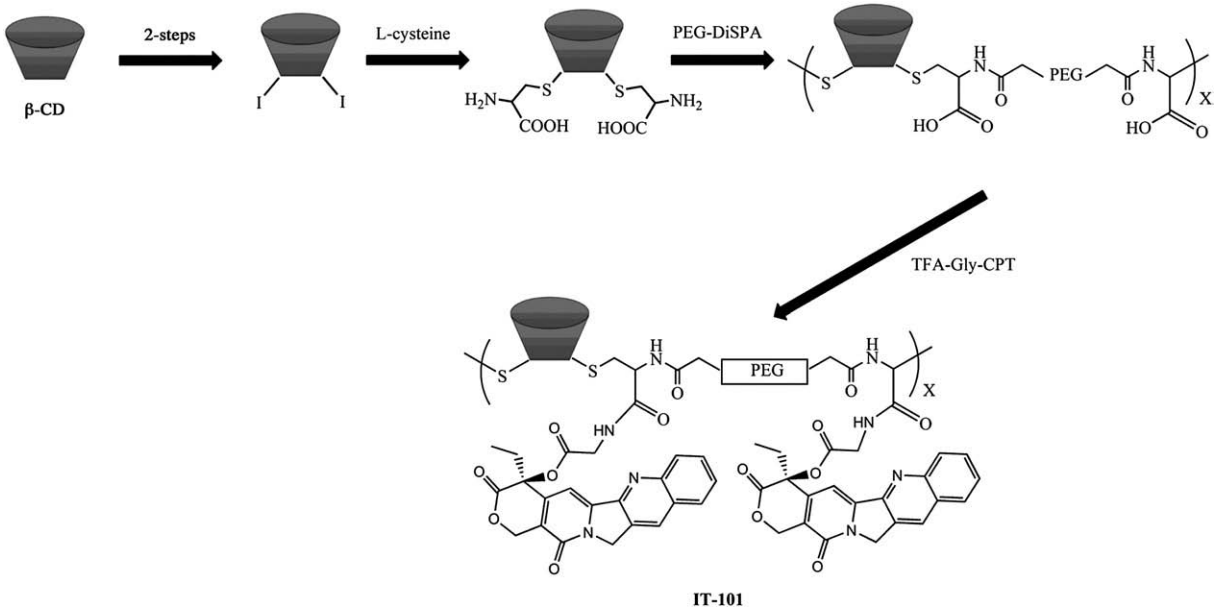

Fig. 1. Schematic diagram of the synthesis steps involved in preparing the polymer-CPT conjugate of IT-101. PEG-DISPA: poly(ethylene glycol) dipropanoic succinimide. *X* is the number of repeat units in the polymer and can be controlled by the synthesis procedure.