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# Progress of drug-loaded polymeric micelles into clinical studies

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ABSTRACT

Targeting tumors with long-circulating nano-scaled carriers is a promising strategy for systemic cancer treatment. Compared with free small therapeutic agents, nanocarriers can selectively accumulate in solid tumors through the enhanced permeability and retention (EPR) effect, which is characterized by leaky blood vessels and impaired lymphatic drainage in tumor tissues, and achieve superior therapeutic efficacy, while reducing side effects. In this way, drug-loaded polymeric micelles, *i.e.* self-assemblies of amphiphilic block copolymers consisting of a hydrophobic core as a drug reservoir and a poly(ethylene glycol) (PEG) hydrophilic shell, have demonstrated outstanding features as tumor-targeted nanocarriers with high translational potential, and several micelle formulations are currently under clinical evaluation. This review summarizes recent efforts in the development of these polymeric micelles and their performance in human studies, as well as our recent progress in polymeric micelles for the delivery of nucleic acids and imaging.



## 1. Introduction

Cancer has become a leading cause of death, and the number of cancer patients is predicted to double by 2050 [1]. This situation is driving a rapid increase in the demand for effective cancer treatments, and the application of nanotechnology on cancer is expected to provide significant improvements for diagnosis, treatment and management of the disease, offering lower toxicity, specific targeting and reduced treatment cost. In this way, nano-scaled carriers, which can selectively deliver reporter molecules, anticancer drugs or genes to tumor tissues, have great potential for early and efficient diagnosis, and enhanced therapeutic efficacy [2–4]. The selectivity of nanocarriers to solid tumors is based on the augmented leakiness of neovascularization of malignant tissues to macromolecules, and the retention of these macromolecules due to the impaired lymphatic drainage in tumor tissues, so called the enhanced permeability and retention (EPR) effect [5]. Thus, the *in vivo* success of such nanocarriers relies on their stability while circulating in the body, avoiding recognition by the reticuloendothelial system, as well as their effective extravasation and penetration in tumor tissues for selectively releasing their payloads [2–4].

Since the late 1980s, our group has been developing self-assembled polymeric micelles as carrier systems for delivering various bioactive molecules, such as cytostatic agents, nucleic acids, and reporter molecules, for cancer diagnosis and therapy (Fig. 1). Our polymeric micelles are prepared by self-assembly of poly(ethylene glycol)-*b*-poly(amino acid) copolymers into core-shell nanostructures [4,6], where the core is formed by the poly(amino acid) segment, which is engineered for efficiently incorporating and releasing the payload, and the poly(ethylene glycol) (PEG) block forms a dense and soft hydrophilic shell, which protects the drugs in the core, hindering the interaction with plasma proteins and cells, avoiding the recognition by macrophages and prolonging the circulation in the bloodstream [4,6]. The diameter of polymeric micelles resembles that of natural viruses and can be tuned from 10 to 100 nm [4,6], which reduces their accumulation in the organs of the reticuloendothelial system and facilitates overcoming physiological barriers, such as lymphatic transport to lymph nodes after intradermal injection [7], and extravasation, deep penetration and high accumulation in solid tumors after systemic injection (Fig. 2) [8]. This broad and increased accumulation of polymeric micelles in tumor tissues augment the efficacy of the incorporated drugs, allowing the delivery of therapeutic concentrations of drugs to most cells within tumors [4,6,8]. Moreover, after accumulating in tumors, polymeric micelles can act as intracellular Trojan horses, selectively delivering the drugs to their subcellular targets, thus, overcoming mechanisms of drug resistance and enhancing the efficiency of therapies [4,6,9]. In addition, after releasing their cargo, micelles can dissociate into the former block copolymers and be eliminated by filtration through kidneys, avoiding any long-term side effect [4,6].

Our polymeric micelles incorporating doxorubicin (Dox; NK911, Nippon Kayaku, Co.) were the first to proceed into clinical evaluation in 2001 [10], and soon after, several other micelle formulations loading anticancer agents joined human trials (Table 1). These clinical studies are demonstrating high efficacy of polymeric micelles even against intractable tumors, such as triple-negative breast cancer and pancreatic

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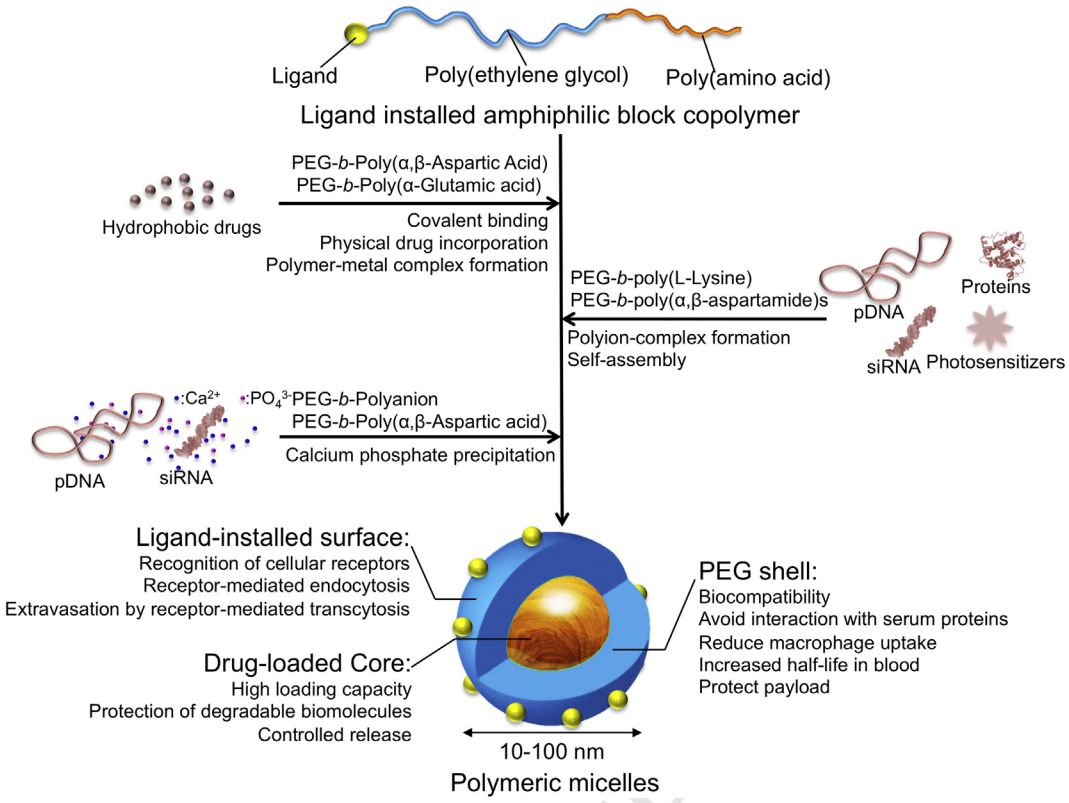


Q2 **Fig. 1.** Self-assembled polymeric micelles from PEG-*b*-poly(amino acid) copolymers represent a versatile platform for incorporating various bioactive molecules through the controlled interaction of the payloads and the core-forming segments. The relative small size and the PEG shell are remarkable advantages for operating at the biological interface.

cancer, and the reduction of side effects associated with the incorporated drugs [11]. In this article, we have reviewed the works for developing these micelles' systems and their recent clinical performance. Moreover, we have also included our recent progress and preclinical observations on polymeric micelles for nucleic acid delivery and imaging, as well as the impact of ligand installation on the targeting efficiency of micelles.

## 2. Polymeric micelles in clinical trials

### 2.1. Doxorubicin (Dox)-loaded micelles (NK911)

Dox is a potent anthracycline widely used for the treatment of several malignancies, but presents serious adverse effects, such as heart damage, which restrict the working dosage [12]. Several carrier approaches have been considered for delivering Dox to solid tumors, including N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers covalently conjugating Dox *via* enzymatically cleavable glycyl–phenylalanyl–leucyl–glycine spacers [13], which was the first polymeric drug conjugate to proceed into clinical trials (PK1) [14], Dox-loaded liposomes (Myocet) and PEGylated Dox-loaded liposomes (Doxil/Caelix), which have been approved by the US Food and Drug Administration (FDA) for the treatment of Kaposi's sarcoma [15], and ovarian [16] and breast cancer [17]. Our polymeric micelles incorporating Dox were originally developed in the late 1980s by using PEG-*b*-poly(α,β-aspartic acid) copolymer conjugated with Dox through amide bonds (Fig. 3A), which was engineered for physically entrapping Dox *via* π–π stacking [18,19]. Thus, the physically loaded Dox serves as an agglomerant in the core of micelles, augmenting the stability of the micelles and reducing the critical micelle concentration, allowing the preservation of the micelles upon dilution. Moreover, because Dox can self-associate into dimers [20], these micelles not only incorporated Dox monomers, but also Dox dimers, which were found to further stabilize the micellar nanostructure [21]. However, because these dimers are not clinically approved, the micelle formulation was optimized to include only Dox monomers, while maintaining their high stability in blood and high antitumor efficacy [22]. In preclinical studies, these micelles showed longer blood circulation, with a 29-fold higher area under the drug concentration *versus* time curve (AUC) in plasma than free Dox, and higher accumulation in tumors due to the EPR effect (3.4-fold higher than that of free DOX), leading to a stronger antitumor effect than the free drug in mice models of sarcoma and lung, breast, and colon cancer [22]. This optimized formulation was the first micelles to proceed into clinical trials under the name NK911 in 2001 (Fig. 3B).

Phase I clinical trials of NK911 in 23 patients with solid tumors were performed at the National Cancer Center Hospital, Tokyo, Japan [11]. This study specified the toxicity profile, maximum-tolerated dose (MTD), the pharmacokinetics and the recommended dose of intravenously administered NK911. The administration schedule was once every 3 weeks using an infusion pump at a rate of 10 mg $min^{-1}$ of Dox equivalent. The results showed that NK911 was well tolerated, producing only moderate nausea and vomiting at Dox dosages usually causing myelosuppression, and infusion-related reactions were not observed. The predominant hematological toxicity was neutropenia at 67 mg $m^{-2}$, while non-hematological toxicities, such as alopecia, stomatitis, and anorexia, were mild. The recommended dose was determined to be 50 mg $m^{-2}$ every 3 weeks and the MTD was 67 mg $m^{-2}$ due to grade 4 neutropenia. The plasma AUC of the NK911 at the recommended dose (3.2 μg h $ml^{-1}$) was higher than that of free Dox (1.6 μg h $ml^{-1}$) (Table 2), but lower than Dox-loaded PEGylated liposomes (902 μg h $ml^{-1}$), probably because PEGylated liposomes do not release the encapsulated Dox [23]. In addition, one partial response was observed in a patient with metastatic pancreatic cancer [11]. This clinical trial established valuable criteria for studying drug-loaded polymeric micelles in humans, while the translational success of NK911 provided a philosophy for constructing micelles for clinical



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