Engineered nanosystems and nanoconjugates with smart functionalities for targeted therapy of intractable diseases

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Nanotechnology-based medicine (Nanomedicine) has received progressive interest in treating and diagnosing intractable diseases, such as cancer. Engineered polymeric nanosystems play a pivotal role in nanomedicine as drug carriers, gene vectors, and imaging probes. This presentation focuses present status and future trends of polymeric nanosystems and nanoconjugates with smart functionalities for therapy of intractable diseases. Polymeric nanosystems of 10 to 100 nm in size can be prepared by programmed self-assembly of block copolymers in an aqueous entity. A typical example is polymeric micelle (PM) with distinctive core-shell architecture. Smart functionalities, such as pH- and/or redox potential responding properties and endosomal escaping capabilities, can be integrated into the PM structure[1]. Specific ligands may be installed on the PM surface to exert functionalities of crossing histological barriers, such as the blood-brain barrier[2]. These smart PMs loaded with various chemotherapy reagents were proven to have a significant utility in treating intractable cancers[3]. Five different formulations of the PMs developed in our group have already proceeded into clinical trials worldwide[4]. Versatility in drug incorporation is another relevant feature of polymeric nanosystems for drug delivery. Nucleic acid-based medicine, such as pDNA, mRNA, and oligonucleotides, can be self-assembled with oppositely-charged polycationic block copolymers into polyion complex (PIC) nanosystems through the ionic interaction[5,6]. Phase I clinical trial using the small-sized PIC nanocarrier loaded with siRNA has started in Japan to treat recurrent breast cancer[7].

Furthermore, smart-nanoconjugates of checkpoint blockade antibody (anti-PDL1 antibody) have been developed in our group to treat intractable glioblastoma multiforme (GBM)[8]. Anti-PDL1 antibody was decorated with glucosylated PEG to cross the blood-brain tumor barrier of GBM by recognizing glucose-transporter overexpressing on GBM capillaries. By sensing the reductive microenvironment of GBM, PEG palisades are removed from the antibody to recover its checkpoint inhibiting ability, exerting effective immune checkpoint blockade (ICB) therapy to achieve the complete remission of GBM.

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