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Nanomedicine in Cancer

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Nanotechnology in biomedical research has emerged as an interdisciplinary science that has quickly found its own niche in clinical methodologies including imaging, diagnostic, and therapeutics. The nano-based technology is expected to expand multi-directionally to provide unmet needs in medicine and has potential to generate unprecedented innovations that will bring breakthrough treatments to various human diseases, including cancer. Broadly accepted but generalized definition of cancer nanotechnology is that man-made particles that are size about 100 nm in a dimension. According to the size based definition, many different nano-scale delivery platforms fall into this category and various materials have been used for the construction, including liposomes [1], polymer-based platforms [2,3], dendrimers [4] [5], metal nanoparticle [6,7], nanocrystal [8], silicon- and silica-based nanoparticle [9-11] and others. The major advantage of nanomedicine is multifunctionality that allows for delivery of large amounts of payload such as therapeutics or imaging contrast, active targeting, timed release, and stealth effect for avoidance of uptake from phagocytes. Consequently, a single nanoparticle can be implicated under multiple methods to perform multi-task and can be utilized to serve multiple functions.

Therapeutic efficacy of nanotechnology based particles has been evaluated in clinical trials worldwide, and approximately 90 clinical trials for cancer treatments are currently underway. (clinicaltrial.gov). An excellent example of multifunctionality of nanotechnology has been achieved by encapsulating doxorubicin in PEGylated liposome to significantly prolong circulation half-life (Doxil® marketed and distributed in the U.S. by Ortho Biotech Products, L.P., Bridgewater, NJ, and Caelyx® distributed outside the U.S. by Schering-Plough Corporation; Kenilworth, NJ). Long-circulation time of liposomes by the STEALTH® principle is taken for granted today as one of the functionality that nanoparticles can acquire for drug delivery. Doxorubicin and other anthracyclines are one of the most commonly used anti-cancer therapeutics for multiple cancer types. However, antracyclines causes an irreversible cardiac toxicity (congestive heart failure) perhaps due to redox formation, and antracycline associated cardiac toxicity is cumulative over the life-time across all antracyclines. The efficacies of Doxil containing regimen are similar to that of conventional doxorubicin treatment, but the nanoparticle-mediated deliveries have superior post-treatment clinical data profiles for cardic toxicity [12,13]. Currently, this regimen is most widely used for breast and ovarian cancer treatments as a single agent or in combination with other agents. The most notable advantage of the PEGylated liposome-mediated delivery method is in the serum half-life since the PEGylated-liposomal formulation extends the half-life to longer than 50 hours, consequently improving a quality of life on patients undergoing the therapy [1]. Furthermore, Doxil significantly reduces the total uptake by mononuclear phagocytes, in turn increases the plasma half-life when compared with conventional drug delivery methods or that of non-PEGylated liposomal doxorubicin. Albumin-bound paclitaxel (Abraxane®) is another example of an application of nanotechnology. Albumin-bound paclitaxel was developed to overcome this challenge by reducing toxicity profile of conventional paclitaxel that is used with cremophor that causes hypersensitivity reaction and neurotoxicity [14]. For imaging, iron oxide nanoparticles (combidex®) in a conjunction with magnetic resonance imaging (MRI) provides important staging information.

While the field of nanomedicine is expected to bring the major breakthrough for cancer therapy and imaging, the FDA approved nanoplatforms have not reached to a comprehensive multi-functionality yet and still lacking ability to target tumor, which compromises the efficacy and leads to adverse effect. While active targeting has been the major asset for multifunctional nanoparticles, the vast majority of FDA approved nano delivery systems relies on passive targeting (i.e., enhanced permeation and retention (EPR) effect) through leaky vessels, which is a hallmark of tumor vasculature. However, increased interstitial fluid pressure (IFP) contributes to decreased transcapillary transport as well as retention of the nanoparticles in the tumors. It is well established that the IFP is increased in most solid tumors due to blood vessel leakiness, lack of lymphangiogenesis, interstitial fibrosis and a contraction of the interstitial space mediated by stromal fibroblasts [15,16] [17]. While IFP is fairly uniform throughout the necrotic core of solid tumors, IFP is significantly less near the periphery of the tumor mass [18-20]. For this reason, nanoparticles accumulate within the periphery. The IFP is about 0 mmHg in most normal tissues but it increases to 14 to 30 mmHg in tumor [21]. Therefore, it presents an obstacle to treatment as it leads to a decrease in the uptake of drugs or therapeutic molecules into a tumor.

A possible solution for aforementioned challenges might be an active targeting strategy, which can be achieved via grafting target-specific ligand on the surface of the nanoparticles for specific recognition of the surface receptor of the target cells at the diseased site. This strategy is similar to an antibody based biological therapies in attempt to target the surface receptor that is differentially expressed on the surface of the cancer cell or tumor components. To address this, many attempts have been made to increase the effectiveness of active targeting of nanoparticles to target cancer cells or tumor microenvironment. For example, nanoparticles were conjugated with Her2 antibody to target HER2+ cancer cells and increase internalization into the cells for superior delivery of payload [22,23]. Despite these efforts, these delivery strategies still primarily require extravasation of delivery carriers from discontinuous vessels where the size of openings varies depending on the stage and location of the tumor [24,25]. Furthermore, given the importance of tumor stroma in tumor survival and metastasis, successful delivery of anti-neoplastic agent to the tumor is unlikely to be lethal enough since the vast majority of tumor stroma component are terminally differentiated and resistant to this class of agent. Therefore, development of nanoparticles conjugated with ligand that selectively targets stromal component and loaded with payload

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that exerts cells killing effect specifically to the stromal cells are equally important. Another unique attempt of active targeting is a cell based delivery of non-cytotoxic nanoparticles. This strategy uses immune cells or stem cells that have ability to recognize and move toward the tumor environment against high IFP. Since the most of immune cells are highly phagocytic, nanoparticles are likely to be internalized into the cells without killing a host cell. It is critical to develop a protocol to control the degree of nanoparticle internalization to remain the cell motility high.

In this article, we want to emphasize an urgent necessity in the development of active targeting strategies for the enhancement of therapeutic efficacy with minimal toxicity. In the field of nanotechnology, a number of nano- micro-particles made by variety of materials have been developed for the delivery of drug and contrast agents. For successful active targeting, the field urgently needs novel ligands for unique surface receptor that allows for conjugation to the nanoparticles in a highly controlled fashion. While humanized monoclonal antibodies is the mainstay for the development of active targeting nanoparticles today, the cost for manufacturing the humanized monoclonal antibody conjugated nanoparticles maybe the major bottleneck for the clinical translation. As alternative of antibody, a variety of new class of ligands have been developed to date including aptamer, peptide, chemically synthesized ligands. Chemical synthesis can be cost ineffective procedures if multiple synthesis and purification are required. Peptide ligand that is short enough to escape from antigen presentation is also great alternative for easy and cost-effective synthesis and conjugation. In fact, RGD cyclic peptide has shown excellent targeting effect when conjugated with nanoparticles [26-29], though the conjugation of such to the nanoparticles accelerates the clearance and shorten the serum half-life of nanopartcles [30]. Aptamers are emerging class of ligands and structurally distinct RNA and DNA oligonucleotides that can form tertialy structure and can bind proteins at high (nM) affinity. They have been extensively studied as therapeutics, diagnostics, and more recently as biosensors [31-34]. The major disadvantage of aptamer is the serum stability, and many attempts have been made to stabilize the oligonucleotide against nucleases. Thiophosphate oligonucleotide aptamers (thioaptamers) are suitable candidate ligands for active targeting due to their unique chemical properties including high affinity binding, nuclease resistance, ease of synthesis and chemical modification, cost-effective synthesis, and lack of immunogenicity. For example, rencently developed methods for combinatorial selection of thioaptamers from random or high-sequence-diversity libraries are based on tight binding to the target protein. Through a collaborative effort, we have successfully indentified high affinity thioaptamers to E-selectin and CD44 for the targeted delivery to the inflamed tumor vasculature and cancer cells [35,36]. Our previous works have demonstrated that E-selectin thioaptamer (ESTA) conjugated liposomes result in effective targeting to the tumor vasculature without shortening the serum half-life [37]. Furthermore, a conjugation of ESTA to porous silicon particles also improved the targeting effect to the bone marrow where E-selectin expresses constitutively [38]. The field of nanomedicine has proved a feasibility of active targeting using different types of ligand as well as nanoparticles. To this end, we emphasize a need of novel ligand beyond antibodies that targets different tumor component including those in the tumor microenvironment to achieve comprehensive cancer treatment.

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