Cancer
Science & Therapy

Danquah, J Cancer Sci Ther 2014, 6:8
http://dx.doi.org/10.4172/1948-5956.1000286

Commentary Open Access

Polycarbonate Micelles for Cancer Therapy

Michael Danquah*

Department of Pharmaceutical Sciences, Chicago State University, 9501 South King Drive., Chicago, IL, USA

In cancer therapy a primary goal is to kill cancer cells without damaging normal ones. Following diagnosis, chemotherapy is frequently the method of treatment. Unfortunately, significant challenges associated with conventional chemotherapy limits its efficacy. First, majority of anticancer drugs presently prescribed in chemotherapy are not selective. They kill both cancerous and healthy cells resulting in systemic toxicity and life-threatening side effects. Treatments prescribed for cancer patients typically result in 1 out of 100,000 drug molecules actually reaching the disease target site [1]. Therefore even when chemotherapeutic drugs work in some cancer patients most experience adverse side effects. For instance, patients can suffer a compromised immune system during treatment and become prone to other debilitating diseases. Non-specific anticancer drug distribution also hinders therapeutic strategies employing high doses. Second, most anticancer drugs eventually succumb to multidrug resistance. Some cancer cells at the onset of therapy are intrinsically resistant due to a resistance phenotype. However, majority of cancer cells are initially responsive to chemotherapy and later become unresponsive to similar doses due to acquired resistance following repeated chemotherapy cycles [2]. Once resistance develops, systemic administration of anticancer drugs becomes ineffective. Finally, approximately a third of potent anticancer drugs is highly lipophilic and requires the use of solubilizing agents such as dimethyl sulfoxide (DMSO) and Cremophor® EL to bring them into true solution so they can be administered systemically to be clinically useful. Nonetheless, toxicity of the solubilizing agents hinder application of these anticancer drugs since they can lead to neurotoxicity, cause dose-dependent hemolysis and are harmful to the liver and kidneys [3,4]. Hence, regardless of advances made in drug discovery and therapeutic strategies (*e.g.*, combination therapy), cancer therapy is often associated with unsatisfactory results and the war on cancer must be waged differently to significantly improve the health of cancer patients. Breakthroughs in treating cancer not only require innovative ways of treating cancer but also novel concepts regarding cancer-focused drug delivery.

Nanotechnology-based therapeutics is an important tool in our armamentarium for improving efficacy and safety of cancer treatments. Key benefits from using nanotechnology-based therapeutics in cancer therapy accrue from improved drug solubility, stability, site-specificity and reduced multidrug resistance [5-7]. Several nanotechnology-based drug carriers including liposomes, polymeric micelles, polymer-drug conjugates, dendrimers and polymersomes have been extensively investigated for cancer therapy [5,8]. Among these systems, polymeric micelles are an attractive and efficient approach to deliver poorly water-soluble anticancer drugs, improve drug stability and site-specificity leading to enhance therapeutic efficacy. Polymeric micelles self-assemble from amphiphilic copolymers composed of hydrophilic and hydrophobic components into nanosized, spherical structures [9]. The hydrophobic core functions as a repository for hydrophobic anticancer drugs. Stealth properties associated with the hydrophilic corona of polymeric micelles prevent opsonization by the reticuloendothelial system (RES) and hence reduces elimination of micelles from the bloodstream resulting in increased circulation times [2]. Also, the small size ensures selective distribution to tumor cells via the enhanced permeability and retention (EPR) effect. While polymeric micelles are promising for oncology focused drug delivery, understanding key micelle properties (e.g., solubility, stability and site-specificity) and how they can be optimized is important to realizing the potential of micelles in anticancer drug delivery and consequently improved cancer therapy.

There are several polymeric materials presently employed in preparing polymeric micelles. Among them, polycarbonates are most promising since they are biodegradable, biocompatible and result in nontoxic degradation products. They are also easy to synthesize due to improvements in polymerization techniques [10]. Furthermore, the cyclic carbonate monomers used have the potential for greater functional diversity compared to cyclic ethers and esters. Therefore, functionalized polycarbonate-based polymers can be designed to exhibit desirable physicochemical properties to enhance drug delivery for safe and efficient cancer therapy. Below is a summary of how carbonate-based copolymers have been designed to specifically improve key micelle properties, a reflection on the chemical lessons this process teaches us and how engineered carbonate-based polymeric micelles have been used to enhance therapeutic approaches for treating cancer.

In the past decade, the design and application of carbonate-based polymers with well-tuned chemical composition and structures for drug-delivery has received much interest. Several studies report on the ability of polymeric micelles with a carbonate-based hydrophobic core to improve loading of anticancer drugs [10,11]. Careful review of the literature suggests two main approaches. The more common approach involves screening numerous carbonate-based polymers against a drug of interest to select the best polymer. Although eventually successful, this method is costly and labor intensive. The second approach is to tailor the carbonate-based polymer specifically for the drug of interest. Here, careful thought is given to the physicochemical properties of the drug and subsequently carbonate monomers are chemically tailored to ensure maximum compatibility between drug and carbonate-based polymer. Since this process can be performed *in silico* it is relatively cheap and less labor intensive. Using the chemical tailoring method, Danquah et al. employed a computational material science approach to improve bicalutamide loading [12]. Prior to synthesis, a series of biodegradable hydrophobic blocks possessing structural similarities with bicalutamide were screened *in silico* and a suitable hydrophobic core identified. Since drug loading is a function of the compatibility between the drug and the hydrophobic component of the polymer,

***Corresponding author:** Michael Danquah, Ph.D., Department of Pharmaceutical Sciences, Chicago State University, 9501 South King Drive, DH RM 203-24, Chicago, IL 60628, USA, Tel: (773)821-2167; Fax: (773)821-2595; E-mail: mdanquah@csu.edu

Received July 17, 2014; **Accepted** August 22, 2014; **Published** August 25, 2014

Citation: Danquah M (2014) Polycarbonate Micelles for Cancer Therapy. J Cancer Sci Ther 6: 310-313. doi:10.4172/1948-5956.1000286

it was hypothesized that theoretical approaches that can predict this compatibility can be used to expedite identification or creation of appropriate drug delivery polymers to improve drug loading. Using the Flory–Huggins interaction parameter which has been shown to be a good indicator of polymer–drug compatibility, poly(ethylene glycol)-b-poly(L-lactide) (PEG-b-PLLA) copolymer and a series of diblock copolymers designed by modifying the poly(L-lactide) (PLLA) hydrophobic core with a carbonate monomer (i.e. 5-methyl-5-benzyloxycarbonyl-1,3-dioxane-2-one) were screened *in silico* for compatibility with bicalutamide [12]. The interaction parameter between bicalutamide and PLLA was calculated to be 11.06 while the interaction parameter between bicalutamide and poly (carbonate-co-lactide) [P(CB-co-LA)] was computed to be 7.34. This decrease in the interaction parameter reflected better compatibility. Therefore, by introducing a carbonate monomer into the PLLA hydrophobic core, a potential increase in compatibility between bicalutamide and the micelle core was predicted. Experimental evidence confirmed this prediction as bicalutamide loading in poly(ethylene glycol)-b-poly(carbonate-co-lactide) [PEG-b-P(CB-co-LA)] copolymer was up to four-fold more than in PEG-b-PLLA copolymer [12]. Furthermore, PEG-b-p(CB-co-LA) micelles were used to deliver a second generation antiandrogen (CBDIV17) in vivo and found to be potent in treating prostate tumor when combined with embelin [13].

Feng and coworkers used a similar approach to improve the drug loading of embelin by grafting dodecanol onto the carbonate hydrophobic backbone. It was postulated that the structural similarity between dodecanol and the alkyl chain component of embelin may translate to superior drug loading [14]. The poly(ethylene glycol)-*block*-poly(2-methyl-2-carboxyl-propylene carbonate-graft-dodecanol) [PEG-PCD] lipopolymer they synthesized significantly improved embelin loading compared to the unmodified poly(ethylene glycol)-*block*-poly(2-methyl-2-carboxyl-propylene carbonate) [PEG-b-PBC]. Interestingly, hydrophobic chain length of PEG-PCD copolymer did not enhance embelin loading when increased from a degree of polymerization of six to twenty-nine. Importantly, embelin-loaded PEG-PCD micelles demonstrated dose-dependent inhibition of C4-2 prostate cancer cells [14]. It is noteworthy that the carbonate-based copolymers discussed above did not only improve anticancer drug solubility but also yielded a smorgasboard of useful chemical lessons. The study by Danquah et al. addressed the question of how drug-polymer interaction and polymer solubility interplay to affect drug loading [12]. It was observed that as the carbonate content increases, the interaction between bicalutamide and the copolymer increases but the solubility of the copolymer decreases. Therefore, the trade-off between drug–polymer interaction and polymer solubility influenced the extent of bicalutamide loading and it was important to determine the optimum balance between the two competing forces. At carbonate content of up to 20 mol%, the influence of drug–polymer interaction was dominant leading to improved bicalutamide loading. In contrast, at 40 mol% carbonate content, the effect of decreased copolymer solubility dominated contributing to the observed reduction in drug loading. Nonetheless, experimental evidence showed the PEG-b-P(CB-co-LA) and PEG-PCD copolymers to be promising materials for facilitating monotherapy and combination therapy strategies for treating cancer [12,14].

Amphiphilic copolymers possessing a carbonate hydrophobic block have been developed to improve micelle stability. Poor *in vivo* stability has limited clinical application of polymeric micelles due to premature dissociation and ensuing untimely drug release. To address this, chemical and physical crosslinking have been advocated and investigated to improve thermodynamic and kinetic stability of polymeric micelles. Low critical micelle concentration (CMC) values reflect superior thermodynamic stability. Therefore, strategies are employed to alter properties of amphiphilic copolymers that can affect the CMC (e.g., chain length and chemical composition). For instance, tailoring the hydrophobic core to contain aromatic moieties improved micelle stability through π–π interactions and decreased CMC values. As Danquah et al. point out, introduction of carbonate moieties promoted self-assembly of copolymers and cmc values of PEG-b-P(CB-co-LA) copolymers were up to ten-fold lower than PEG-b-PLLA [12]. It has also been shown that PEG-PBC, PEG-PCC and PEG-PCD demonstrate comparatively low cmc values.[14] This suggests copolymers composed of PEG and a carbonate based hydrophobic block tend to be thermodynamically stable. Once in the blood, polymeric micelles loose kinetic stability through interaction with plasma proteins. Recent efforts have been devoted to developing copolymers which are kinetically stable. Hu et al. prepared micelles by covalently crosslinking double bonds introduced into the carbonate containing hydrophobic polymer block [15]. The resulting core-crosslinked micelles maintained their mechanical integrity even when diluted several-fold below cmc. Using PEG-b-poly(acryloyl carbonate)-b-polycaprolactone (PEG-b-PAC-b-PCL) triblock copolymer, Yang et al. [16] recently reported preparing interface crosslinked micelles. The double bonds in the acryloyl carbonate were photo-crosslinked once micelles were prepared using UV light and a photoinitiator. The crosslinked system was observed to be more potent than the non-crosslinked system in treating human hepatoma in mice when used to deliver paclitaxel. In a notable study, Danquah and coworkers synthesized and evaluated core-crosslinkable copolymer methoxy poly(ethylene glycol)-b-poly(carbonate-co-lactide-co-5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-one) and core-corona interface crosslinkable copolymer methoxy poly(ethylene glycol)-b-poly(acryloyl carbonate)-b-poly(carbonate-co-lactide) copolymers for delivering bicalutamide to treat prostate cancer (Figure 1). In this study, crosslinked micelles exhibited enhanced stability against extensive dilution with water (up to 1000-fold below cmc) and in the presence of physiological simulating serum concentration. Also, bicalutamide-loaded crosslinked micelles were observed to be more effective compared to non-crosslinked micelles in inhibiting proliferation of LNCaP prostate cancer cells. In practice, the flexibility associated with polycarbonate copolymers allows engineering of physically stabilized, shell-, core- and interface-crosslinked micelles to improve stability. However, physically stabilized micelles are susceptible to destabilization caused by blood components and shell-cross linked micelles can suppress mobility of the hydrophobic chains. Therefore, attention should be focused on developing functionalized carbonate polymers that facilitate easy and efficient core- and interface-crosslinking. This will expedite development of more stable polymeric micelles to enhance drug delivery and cancer therapy.

Copolymers containing carbonate hydrophobic core have been functionalized to co-deliver anticancer drugs and nucleic acids. Co-delivery of anticancer drugs and nucleic acids to cancer cells has garnered interest since it is a good strategy to overcome multidrug resistance. For instance, nucleic acids may be used to silence drug resistant genes allowing the co-delivered anticancer drug to be more therapeutically effective. In one study, Mahato's group designed a self-assembling carbonate-based copolymer conjugated with gemcitabine and a tumor suppressor miRNA-205. Co-delivery of gemcitabine

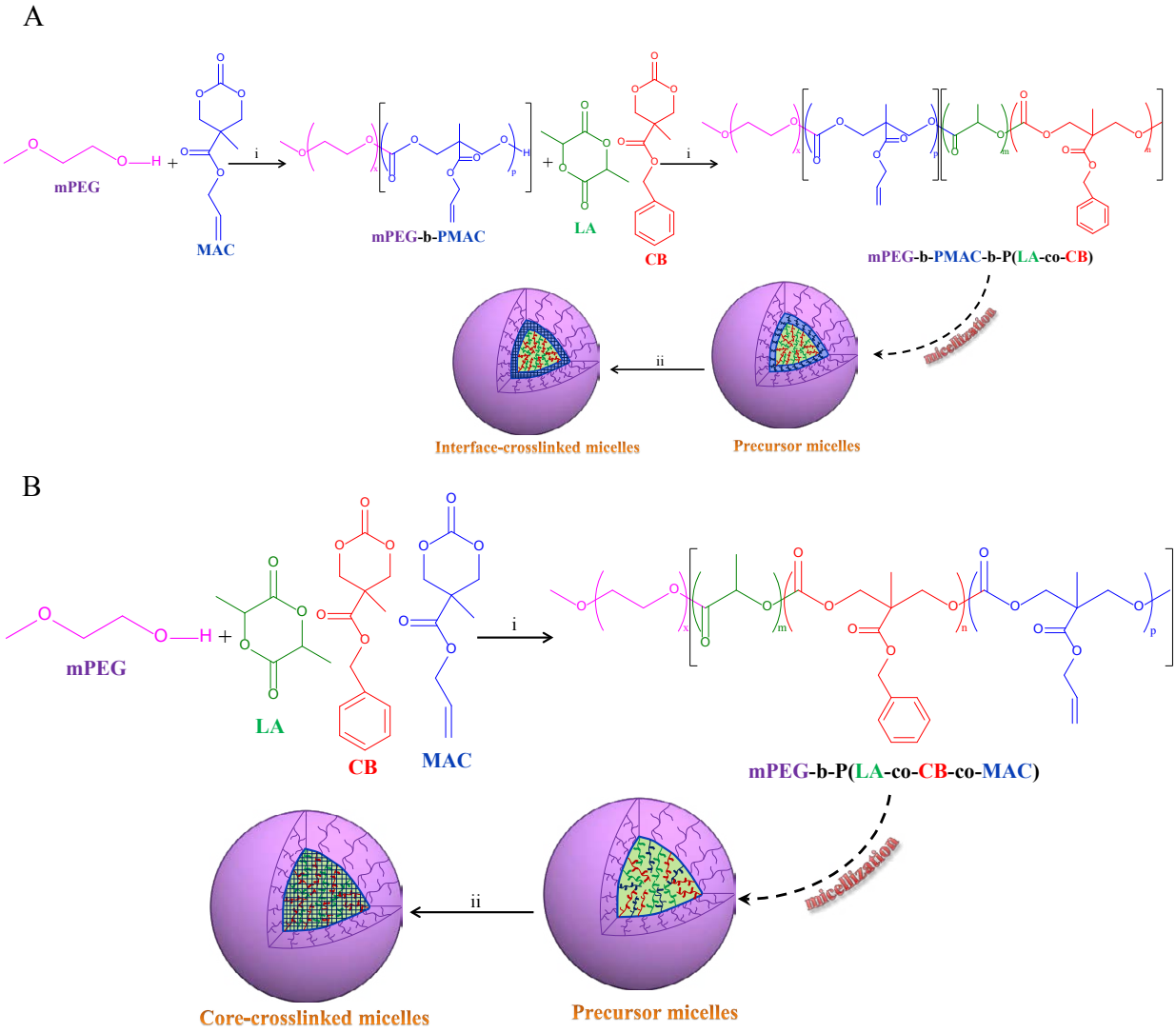

Figure 1: Synthesis method for preparation of lactic acid and carbonate-based crosslinked micelles. Conditions: (i)DBU, CH_2Cl_2, RT, 3 h. (ii) AIBN, 60 °C. (A) Core-crosslinked micelles. (B) Interface-crosslinked micelles [13]. Reproduced with permission from Danquah et al. Pharm Res 29: 2079–2091, 2012.

and miRNA-205 effectively reversed chemo-resistance, invasion and migration in gemcitabine resistant MIA PaCa-2R and CAPAN-1R pancreatic cancer cells and significantly inhibited tumor growth *in vivo* [17].

Gene therapy is a promising strategy for treating cancer. However, its clinical potential has been limited due to inefficient nucleic acid delivery. Early cationic polymeric gene delivery systems contained polyethylenimine (PEI) and poly(L-lysine) which are not biodegradable and extremely cytotoxic. Polycarbonates functionalized with cationic moieties have been investigated as potential nucleic acid delivery platforms. In a recent study, Ong and coworkers synthesized a gene delivery vehicle using organocatalytic ROP of haloalkyl functionalized cyclic carbonates, followed by quaternization with bis-tertiary amines. The subsequent cationic polycarbonates demonstrated well-defined molecular weights, narrow polydispersities and condensed DNA at low N/P (nitrogen to phosphate) ratios. Additionally, the polycarbonate delivery system exhibited minimal cytotoxicity at the optimal N/P ratios and showed high luciferase expression efficiencies in HepG2, HEK293, MCF7 and 4T1 cancer cell lines [18]. In another study, Seow and Yang developed a series of COOH-functionalized polycarbonates synthesized via an organocatalytic ring opening polymerization. The polymers were conjugated with different chain length aliphatic amines (triethylenetetramine, tetraethylenepentamine or pentaethylenehexamine) onto the polycarbonate backbone using DIC/NHS chemistry. These amine-functionalized polycarbonates were able to condense DNA and facilitate efficient luciferase expression in HEK293, HepG2 and 4T1 cancer cell lines [19]. In both studies the cytotoxicity of the polycarbonates delivery vehicles was much less compared to PEI. Most studies reported in the literature focus on functionalizing carbonates with only cationic moieties to improve nucleic acid condensation. However, successful nucleic acid delivery also requires efficient transfection and intracellular release. Therefore, polycarbonates designed for nucleic acid delivery to treat cancer should also be functionalized with lipid chains and pKa modulators to ensure high transfection efficiency and intracellular release, respectively.

Aliphatic polycarbonates have been studied for site-specific

micellar drug delivery applications. Polymeric micelles possess a large surface area that can accommodate a wide variety of functional groups permitting conjugation of targeting moieties. Wen et al. reported an HOOC-PEG-b-P(CB-co-LA) copolymer conjugated with Luteinizing-hormone-releasing hormone (LHRH) peptide for site-specific delivery to treat prostate cancer [20]. Since LHRH receptors are overexpressed in prostate cancer cells, LHRH peptide was hypothesized to be an effective targeting ligand. Wen and coworkers selected LHRH with a super active amine group. This strategy allowed the authors to successfully conjugate the LHRH peptide to HOOC-PEG-b-P(CB-co-LA) copolymer using EDC/DMAP coupling. Importantly, LHRH conjugated micelles demonstrated higher cellular uptake, cytotoxicity, and apoptosis in LNCaP and C4-2 prostate cancer cells compared to non-targeted micelles. Also, antiandrogen loaded LHRH-PEG-b-P(CB-co-LA) micelles suppressed prostate tumor growth *in vivo*. Interestingly, LHRH conjugation did not affect thermodynamic stability, antiandrogen drug loading and drug release profile when formulated into micelles. In another study, Suriano et al. synthesized functional trimethylene carbonate (TMC) derivatives bearing carbohydrate targeting ligands. The goal was to develop a delivery system that exploited carbohydrate-binding lectins overexpressed in cancer cells. In one example, they synthesized galactose functionalized polycarbonate block copolymers to formulate doxorubicin-loaded site-specific micelles. These micelles selectively targeted the asialoglycoprotein receptor (ASGP-R) positive HepG2 cells resulting in enhanced cytotoxicity [21]. Unlike Wen et al., Suriano and coworkers used a one-pot, two-step process sequential polymerization approach to prepare their carbohydrate-functionalized polycarbonate block copolymers. Poly trimethylene carbonate block (PTMC) was first synthesized by ring opening polymerization using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) catalyst, a thiourea TU co-catalyst and benzyl alcohol as initiator. Subsequently, a carbohydrate-functionalized carbonate monomer was added to the reaction mixture to form the second block. While the approaches used by Wen and Suriano are different, it is clear that the versatile nature of carbonate-based copolymers offers many opportunities to develop multifunctional polymeric micelles that can be employed in targeted delivery of anticancer agents and tumor imaging to improve cancer therapy.

In summary, polycarbonate micelles clearly hold immense potential as drug delivery platforms for cancer therapy. Advances in polymerization techniques and functional cyclic carbonate monomers have led to renewed interest in polycarbonates as biomaterials for oncology focused drug delivery applications. Extensive studies in tailoring carbonate monomers to enhance micellar drug loading, improve stability and site-specificity have yielded important chemical lessons. However, successful clinical translation of polycarbonate based micelles will necessitate improvements on many fronts. The trial and error approach of screening several carbonate monomers for possible improvements in key micelle properties must give way to a more rational approach. Computational methods should be refined to highly predict physicochemical properties of polycarbonate polymers, subsequent key micelle properties and biological performance. Once this is achieved, material design rules may easily be established and drug delivery systems routinely customized for a specific drug or person to ensure effective cancer therapy.

References

1. Jain RK (1999) Transport of molecules, particles, and cells in solid tumors. Annu Rev Biomed Eng 1: 241-263.
2. O'Connor R (2007) The pharmacology of cancer resistance. Anticancer Res 27: 1267-1272.
3. Luke DR, Kasiske BL, Matzke GR, Awni WM, Keane WF (1987) Effects of cyclosporine on the isolated perfused rat kidney. Transplantation 43: 795-799.
4. Onetto N, Canetta R, Winograd B, Catane R, Dougan M, et al. (1993) Overview of Taxol safety. J Natl Cancer Inst Monogr : 131-139.
5. Danquah MK, Zhang XA, Mahato RI (2011) Extravasation of polymeric nanomedicines across tumor vasculature. Adv Drug Deliv Rev 63: 623-639.
6. McCarroll J, Teo J, Boyer C, Goldstein D, Kavallaris M, et al. (2014) Potential applications of nanotechnology for the diagnosis and treatment of pancreatic cancer. Front Physiol 5: 2.
7. Minko T, Rodriguez-Rodriguez L, Pozharov V (2013) Nanotechnology approaches for personalized treatment of multidrug resistant cancers. Adv Drug Deliv Rev 65: 1880-1895.
8. Sharma A, Jain N, Sareen R (2013) Nanocarriers for diagnosis and targeting of breast cancer. Biomed Res Int 2013: 960821.
9. Jhaveri AM, Torchilin VP (2014) Multifunctional polymeric micelles for delivery of drugs and siRNA. Front Pharmacol 5: 77.
10. Xu J, Feng E, Song J2 (2014) Renaissance of Aliphatic Polycarbonates: New Techniques and Biomedical Applications. J Appl Polym Sci 131.
11. Chen W, Meng F, Cheng R, Deng C, Feijen J, et al. (2014) Advanced drug and gene delivery systems based on functional biodegradable polycarbonates and copolymers. J Control Release .
12. Danquah M, Fujiwara T, Mahato RI (2010) Self-assembling methoxypoly(ethylene glycol)-b-poly(carbonate-co-L-lactide) block copolymers for drug delivery. Biomaterials 31: 2358-2370.
13. Danquah M, Duke CB 3rd, Patil R, Miller DD, Mahato RI (2012) Combination therapy of antiandrogen and XIAP inhibitor for treating advanced prostate cancer. Pharm Res 29: 2079-2091.
14. Li F, Danquah M, Mahato RI (2010) Synthesis and characterization of amphiphilic lipopolymers for micellar drug delivery. Biomacromolecules 11: 2610-2620.
15. Xiuli H, Xuesi C, Zhigang X, Shi L Xiabin J (2007) Synthesis and characterization of amphiphilic block copolymers with allyl side-groups. Journal of Polymer Science Part A: Polymer Chemistry 45: 5518-5528.
16. Yang R, Meng F, Ma S, Huang F, Liu H, et al. (2011) Galactose-decorated cross-linked biodegradable poly(ethylene glycol)-b-poly(epsilon-caprolactone) block copolymer micelles for enhanced hepatoma-targeting delivery of paclitaxel. Biomacromolecules 12: 3047-3055.
17. Mittal A, Chitkara D, Behrman SW, Mahato RI (2014) Efficacy of gemcitabine conjugated and miRNA-205 complexed micelles for treatment of advanced pancreatic cancer. Biomaterials 35: 7077-7087.
18. Ong ZY, Fukushima K, Coady DJ, Yang YY, Ee PL, et al. (2011) Rational design of biodegradable cationic polycarbonates for gene delivery. J Control Release 152: 120-126.
19. Seow WY, Yang YY (2009) Functional polycarbonates and their self-assemblies as promising non-viral vectors. J Control Release 139: 40-47.
20. Wen D, Chitkara D, Wu H, Danquah M, Patil R, et al. (2014) LHRH-Conjugated Micelles for Targeted Delivery of Antiandrogen to Treat Advanced Prostate Cancer. Pharm Res .
21. Suriano F, Pratt R, Tan JP, Wiradharma N, Nelson A, et al. (2010) Synthesis of a family of amphiphilic glycopolymers via controlled ring-opening polymerization of functionalized cyclic carbonates and their application in drug delivery. Biomaterials 31: 2637-2645.

Citation: Danquah M (2014) Polycarbonate Micelles for Cancer Therapy. J Cancer Sci Ther 6: 310-313. doi:10.4172/1948-5956.1000286