

# Nanoparticle (NP) delivery of chemotherapy drugs to prostate cancer patients

## Abstract

The use of nanoparticles (NPs) for enhanced drug delivery in prostate cancer treatment has been extensively explored in many studies. However, there are serious limitations to nanoparticle delivery of drugs to prostate cancer. It has become increasingly obvious that the physicochemical properties of the nanoparticles dictate the volume of the nanoparticles needed for the drug delivery. The volume of nanoparticle used in turn determines therapeutic efficacy of the drug and the nanoparticle delivery system. In this review, we reflect on the physical chemistry of NP-mediated drug delivery to the target cell/tissue during prostate cancer treatment.

**Keywords:** prostate cancer, patients, nanoparticles, delivery system, therapeutic efficiency, drug, NP-mediated drug, biodegradable copolymers, physicochemical properties, moieties, oligonucleotides, p-glycoprotein, bio-compatibilities, 3-bromopyruvate, prostate specific antigen (PSMA)

Volume 9 Issue 5 - 2018

Toluleke Oloruntobi Famuyiwa, James Kwasi Kumi-Diaka

Department of Biological Sciences, Florida Atlantic University, USA

**Correspondence:** Toluleke Oloruntobi Famuyiwa, Department of Biological Sciences, College of Science, Florida Atlantic University, Florida, USA, Email tfamuyiwa2014@fau.edu

**Received:** August 21, 2018 | **Published:** September 10, 2018

**Abbreviations:** NP, nanoparticles; 3-BPA, 3-bromopyruvate; PLGA, poly lactic-co-glycolic acid; FDA, food and drug administration; EMA, european medicine agency; OVA, ovalbumin; TLR4, toll like receptor-4; TAA, tumor associated antigen; RNA, ribonucleic acid; CPs, control nanoparticles

## Review

Controlled drug delivery systems have attracted diverse research interests over the years.<sup>1-5</sup> This system is a useful mechanism in prostate cancer treatment. Designing nanoparticles that selectively recognize and kill prostate cancer cells in the body, remains an innovative concept.<sup>6-8</sup> The knowledge has motivated researchers to build nanoparticles with unique physicochemical properties such as, size, shape and surface chemistry. These nanoparticles are programmed with a multitude of biological and medical functions,<sup>9,10</sup> that are vital for effective treatment of prostate cancer.

Nanoparticles of biodegradable copolymers are emerging as a promising drug delivery vehicle for prostate cancer treatment. These nano-carrier systems possess diverse range of beneficial features including the significant reduction in volume of drug. These particles also have the ability to develop better pharmacokinetics.<sup>11</sup> Nanoparticles are therapeutic enhancers of anticancer drugs through passive or active targeting while reducing the lethal effects of drugs to healthy cells and tissues.<sup>12</sup>

The use of nanoparticles (NP) for prostate cancer treatment has made a revolutionary impact in the area of therapeutics.<sup>13</sup> These release systems have been shown to enhance the stability of various therapeutic agents such as tiny hydrophobic moieties, peptides, and oligonucleotides.<sup>14</sup> Due to the small size of nanoparticles, the surface area to volume ratio is very large and can lead to the release of drugs at concentrations high enough to kill prostate and other cancer cells.<sup>15</sup> The drug release mechanisms are mainly effected by pH, temperature, light, and hydrophobicity, among other factors.<sup>16</sup> The non-covalently bonded drugs have been released through hydrophobicity-induced phenomena via applying hydrophobic/hydrophilic forces to the nanocarriers.<sup>17,18</sup> The high surface area of the nanoparticles allows enhanced drug loading efficiency and targeted drug delivery with minimum leakage and toxicity.<sup>19</sup>

Nanoparticles present prolonged distribution of bioactive particles with higher body retention and permeability.<sup>20</sup> These are different types of nanoparticles, including organic nanoparticles (polymers, dendrimers, solid lipid), inorganic nanoparticles (magnetic iron oxide, quantum dots of various mineral compositions of silica), and protein-based nanoparticles (viruses and albumin).<sup>16</sup> Each type could allow distribution of bioactive molecules to the target organs of interest.<sup>20</sup> In this article, the focus is on polymeric nanoparticles.

Polymeric nanoparticles (NP) show some advantages with respect to other drug delivery systems; such as more stability during storage.<sup>21</sup> Polymeric nanoparticles could reduce the multi-drug resistance that characterizes many anti-cancer drugs, by a mechanism of internalization of the drug<sup>22</sup> thereby reducing efflux from cells mediated by the P-glycoprotein.<sup>23</sup> It has been reported that gold NP attached to 3-Bromopyruvate (3-BPA) could target the mitochondrial membrane potential more selectively and precisely than treatment with 3-BPA alone.<sup>24,25</sup> Interestingly, gold NP preferentially kill cancer cells more than normal mesenchymal stem cells due to higher mitochondrial membrane potential in cancer cells compared to normal cells.<sup>24,25</sup> Furthermore, oral administration of surface modified Poly (lactic-co-glycolic acid) (PLGA) NP containing capecitabine delivers the drug to the prostate effectively and precisely than conventional treatment approach.<sup>26</sup> This drug formulation significantly improves patient condition by reducing dosing frequency of conventional treatment modality. This delivery method helps in better management of prostate cancer.<sup>26</sup> Additionally, PLGA adjuvant NP systems are reported to elicit a strong T cell immune response, using 100-fold lower doses (0.05µg) of CpG oligodeoxynucleotide antigen. In previous studies, PLGA NP systems showed significantly higher cytokine secretion (up to 10-fold), as well as a comparative antibody response to abnormal body physiology.<sup>27</sup> Inevitably, PLGA systems may be further developed for tailored drug delivery in both chemo- and immunotherapy in prostate cancer treatment regimen.

PLGA is a biocompatible member of the aliphatic polyester polymer family of biodegradable polymers. It has long been a popular choice for drug delivery applications since its approval by the Food and Drug Administration (FDA) for use in humans.<sup>28</sup> PLGA nanoparticle can transport hydrophobic drugs such as SC-514 in an aqueous environment for delivery within minutes. The drug enters

the cell just by “slight contact” with the phospholipid layer of the cell.<sup>29</sup> Biodegradable NP constructed from PLGA polymers are widely used as antigen carriers/adjuvants due to its biocompatible and biodegradable characteristics. Safety profile and use has been approved by both the US FDA and the European Medicine Agency (EMA).<sup>30</sup> PLGA offers unique advantages and properties for drug delivery purposes, like the world-wide approval for medical use, biodegradability, biocompatibility, and controlled release.<sup>26</sup> However, there are considerable challenges that must be overcome in developing PLGA-based NP systems for drug delivery application. The challenges: targeting the diseased tissue, cellular uptake together with pre-programmed intracellular trafficking, and escaping the reticuloendothelial system are not manageable by a single polymer.<sup>26</sup> The contact of PLGA nanoparticle with the body and the impact are mediated via the surface of the PLGA nanoparticles. PLGA-based NPs have poor loading capacity, and display sudden release of drugs to unwanted tissues and/or cells.

Surface modification of PLGA-particles by grafting with selected biomimetic ligands can meet some of these challenges. Surface modification can lead to a more efficacious medication. Effective medications can reduced side effects and improve patient’s treatment outcome.<sup>26</sup> Surface modification of PLGA nanoparticles can deliver the drug in a controlled manner throughout the prostate by using a much reduced dosing schedule to increase the therapeutic efficiency.<sup>26</sup> Several modifications have been utilized to overcome these problems. A pH sensitive PLGA NP system was developed for rapid release of ovalbumin (OVA) antigen in acidic environments to improve immune response.<sup>31</sup> The pH based drug release has been used for tumor targeting drug release. This release mechanism is effective because tumor tissues possess lower pH than normal tissues.<sup>32–34</sup>

Another modification to improve the drug release is the bio-molecular supported process.<sup>35</sup> This method is commonly grouped into three parts: ligand exchange mediated release,<sup>36</sup> enzymatic release,<sup>37,38</sup> and chemical reduction-based release.<sup>39</sup> Delivery of dual or triple antigens in PLGA-NPs, co-delivery of Toll Like Receptor-4 (TLR 4) ligand and Tumor Associated Antigen (TAA) using PLGA-based NPs,<sup>40</sup> may occur through ligand exchange mediated release mechanism. Hydrophilic or hydrophobic interactions by heating, may occur through chemical reduction mechanism. This latter interaction permits encapsulated drugs to diffuse out of the matrix and into the target cell or organ.<sup>16</sup>

The major considerations in determining the method for drug delivery are the parameters that influence bio-compatibilities and bioactivities of nanoparticles. Particle size is one of the most important parameters that determine bio-compatibilities and bioactivities of nanoparticles. Particle size has a direct relevance to the stability of drug formulations.<sup>26</sup> The delivery efficiency of PLGA nanoparticle is impacted by all the drug releasing factors aforementioned.

Recommendations to augment delivery efficiency of PLGA nanoparticles to prostate cancer include; surface functionalization of PLGA NPs with the A10 2’-fluoropyrimidine ribonucleic acid (RNA) aptamers (that recognize the prostate-specific membrane antigen (PSMA) on prostate cancer cells) and biotin to modify the surface of PLGA nanoparticles.<sup>41</sup> Biotin is a small molecule that can induce efficient receptor-mediated endocytosis.<sup>42</sup> Growing evidence suggests a role for biotin in cell signaling, gene expression, and chromatin remodeling, together with its potential involvement in inhibiting prostate cancer cell proliferation.<sup>43</sup> Previous work indicated that molecular modification of PLGA nanoparticles with biotin did not

change the process of nanoparticle nucleation and growth in solution. There was no evidence of change in shape, size or aggregation of biotinylated nanoparticle compared to the control nanoparticles (CPs).<sup>44</sup> This observation further justifies the suggested use of biotin to functionalize PLGA nanoparticle.

In conclusion, clinical effectiveness of nanoparticles has many limitations.<sup>45</sup> A central strategy for addressing all of these issues is to increase the delivery efficiency and specificity of the drug on the targeted tumor. If delivery efficiencies increase from 1% to 10%, the volume of nanoparticles needed to release the same concentration of drug decrease from 90ml to 9ml.<sup>45</sup> The lower the volume of nanoparticles used in prostate cancer treatment the lesser the chances that healthy tissues and cells will be impacted with toxicities. The reduction in the volume of nanoparticles in contact with healthy cells and tissues implies increase therapeutic efficiency of the drug and the nanoparticle delivery system.

## Acknowledgements

None.

## Conflict of interest

Author declares that there is no conflict of interest.

## References

1. Pakulska MM, Miersch S, Shoichet MS. Designer protein delivery: From natural to engineered affinity-controlled release systems. *Science*. 2016;351(6279):aac4750.
2. Lu Y, Aimeetti AA, Langer R, et al. Bioresponsive materials. *Nat Rev Mater*. 2016;2.
3. Raavé R, van Kuppevelt TH, Daamen WF. Chemotherapeutic drug delivery by tumoral extracellular matrix targeting. *J Control Release*. 2018; 274:1–8.
4. Meléndez-Ortiz I, Varca GHC, Lugão AB, et al. Smart Polymers and Coatings Obtained by Ionizing Radiation: Synthesis and Biomedical Applications. *Open J Polym Chem*. 2015;5(3):17–33.
5. Koshy ST, Zhang DKY, Grolman JM, et al. Injectable nanocomposite cryogels for versatile protein drug delivery. *Acta Biomater*. 2018;65:36–43.
6. Peer D, Karp JM, Hong, et al. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol*. 2007;2:751–760.
7. Rao W, Wang H, Han J, et al. Chitosan-Decorated Doxorubicin-Encapsulated Nanoparticle Targets and Eliminates Tumor Reinitiating Cancer Stem-like Cells. *ACS Nano*. 2015;9(6):5725–5740.
8. Min Y, Caster JM, Eblan MJ, et al. Clinical Translation of Nanomedicine. *Chem Rev*. 2015;115(19):11147–11190.
9. Nel AE. Understanding biophysicochemical interactions at the nano-bio interface. *Nat Mater*. 2009;8:543–557.
10. Albanese A, Tang PS, Chan WC. The Effect of Nanoparticle Size, Shape, and Surface Chemistry on Biological Systems. *Annu Rev Biomed Eng*. 2012;14:1–16.
11. Zhang H, Chen T, Jiang J, et al. Selenium-containing allophycocyanin purified from selenium-enriched *Spirulina platensis* attenuates AAPH-induced oxidative stress in human erythrocytes through inhibition of ROS generation. *J Agric Food Chem*. 2011;59(16):8683–8690.
12. Chen T, Wong YS. In vitro antioxidant and antiproliferative activities of selenium-containing phycocyanin from selenium-enriched *Spirulina platensis*. *J Agric Food Chem*. 2008;56(12):4352–4358.

13. Ahmed EA, Omar HM, elghaffar SKA, et al. The antioxidant activity of Vitamin C, DPPD and l-cysteine against Cisplatin-induced testicular oxidative damage in rats. *Food Chem Toxicol.* 2011;49(5):1115–1121.
14. Carey PB, Frenkel GD. Selenium compounds prevent the induction of drug resistance by cisplatin in human ovarian tumor xenografts in vivo. *Cancer Chemother Pharmacol.* 2000;46(1):74–78.
15. Li S, Zhou Y, Wang R, et al. Selenium sensitizes MCF-7 breast cancer cells to doxorubicin-induced apoptosis through modulation of phospho-Akt and its downstream substrates. *Mol Cancer Ther.* 2007;6(3):1031–1038.
16. Chaudhary S, Umar A, Mehta SK. Surface functionalized selenium nanoparticles for biomedical applications. *J Biomed Nanotechnol.* 2014;10(10):3004–3042.
17. Kumi-Diaka J, Merchant K, Haces A, et al. Genistein-selenium combination induces growth arrest in prostate cancer cells. *J Med Food.* 2010;13(4):842–850.
18. Gang J, Park SB, Hyung W, et al. Magnetic poly epsilon-caprolactone nanoparticles containing Fe<sub>3</sub>O<sub>4</sub> and gemcitabine enhance anti-tumor effect in pancreatic cancer xenograft mouse model. *J Drug Target.* 2007;15(6):445–453.
19. Jayaprakash V, Marshall JR. Selenium and other antioxidants for chemoprevention of gastrointestinal cancers. *Best Pract Res Clin Gastroenterol.* 2011;25(4–5):507–518.
20. Pu W, Wang D, Zhou D. Structural Characterization and Evaluation of the Antioxidant Activity of Phenolic Compounds from *Astragalus taipaihanensis* and Their Structure-Activity Relationship. *Sci Rep.* 2015;5:13914.
21. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: Rationale for development and what we can expect for the future. *Adv Drug Deliv Rev.* 2001;47(1):3–19.
22. Davda J, Labhasetwar V. Characterization of nanoparticle uptake by endothelial cells. *Int J Pharm.* 2002;233(1–2):51–59.
23. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. *Adv Drug Deliv Rev.* 2002;54(5):631–651.
24. Baltazar F, Pinheiro C, Morais-Santos F, et al. Monocarboxylate transporters as targets and mediators in cancer therapy response. *Histol Histopathol.* 2014;29(12):1511–1524.
25. Marrache S, Dhar S. The energy blocker inside the power house: mitochondria targeted delivery of 3-bromopyruvate. *Chem Sci.* 2015;6(3):1832–1845.
26. Sun SB, Liu P, Shao FM, et al. Formulation and evaluation of PLGA nanoparticles loaded capecitabine for prostate cancer. *Int J Clin Exp Med.* 2015;8(10):19670–19681.
27. Diwan M, Elamanchili P, Cao M, et al. Dose sparing of CpG oligodeoxynucleotide vaccine adjuvants by nanoparticle delivery. *Curr Drug Deliv.* 2004;1(4):405–412.
28. Mccall RL, Sirianni RW. PLGA Nanoparticles Formed by Single- or Double-emulsion with Vitamin E- TPGS Video Link. *J Vis Exp.* 2013;82:51015.
29. Hofmann D, Messerschmidt C, Bannwarth MB, et al. Drug delivery without nanoparticle uptake: delivery by a kiss-and-run mechanism on the cell membrane. *Chem. Commun.* 2014;50(11):1369–1371.
30. JC, LSB, ID. Engineering the lymph node microenvironment via intranodal controlled release vaccine depots. *J Immunol.* 2012:188.
31. Danhier F, Ansorena E, Silva JM, et al. PLGA-based nanoparticles: An overview of biomedical applications. *J Control. Release.* 2012;161(2):505–522.
32. Dhar S, Daniel WL, Giljohann DA, et al. Polyvalent oligonucleotide gold nanoparticle conjugates as delivery vehicles for platinum(IV) warheads. *J Am Chem. Soc.* 2009;131(41):14652–14653.
33. Qu X, Yao C, Wang J, et al. Anti-CD30-targeted gold nanoparticles for photothermal therapy of L-428 Hodgkin's cell. *Int J Nanomedicine.* 2012;7:6095–6103.
34. Leones R. Luminescent DNA- and agar-based membranes. *J Nanosci Nanotechnol.* 2014;14(9):6685–6691.
35. Xi H, Cun D, Xiang R, et al. Intra-articular drug delivery from an optimized topical patch containing teriflunomide and lornoxicam for rheumatoid arthritis treatment: Does the topical patch really enhance a local treatment? *J Control Release.* 2013;169(1–2):73–81.
36. Shukla R, Bansal V, Chaudhary M, et al. Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview. *Langmuir.* 2005;21(23):10644–10654.
37. Rojo J, Díaz V, de la Fuente JM, et al. Gold glyconanoparticles as new tools in antiadhesive therapy. *Chem BioChem.* 2004;5(3):291–297.
38. Lv H, Wu P, Wan W, et al. Electrochemical durability of heat-treated carbon nanospheres as catalyst supports for proton exchange membrane fuel cells. *J Nanosci Nanotechnol.* 2014;14(9):7027–7031.
39. Pernodet N, Fang X, Sun Y, et al. Adverse effects of citrate/gold nanoparticles on human dermal fibroblasts. *Small.* 2006;2(6):766–773.
40. Hamdy S, Molavi O, Ma Z, et al. Co-delivery of cancer-associated antigen and Toll-like receptor 4 ligand in PLGA nanoparticles induces potent CD8<sup>+</sup> T cell-mediated anti-tumor immunity. *Vaccine.* 2008;26(39):5046–5057.
41. Chan JM, Valencia PM, Zhang L, et al. Polymeric nanoparticles for drug delivery. *Methods Mol Biol.* 2010;624:163–175.
42. Chen S, Zhao X, Chen J, et al. Mechanism-based tumor-targeting drug delivery system. Validation of efficient vitamin receptor-mediated endocytosis and drug release. *Bioconjug Chem.* 2010;21(5):979–987.
43. Zempleni J. Uptake, Localization, and Noncarboxylase Roles Of Biotin. *Annu Rev Nutr.* 2005;25:175–196.
44. Gagliardi M, Bertero A, Bifone A. Molecularly Imprinted Biodegradable Nanoparticles. *Sci Rep.* 2017:7.
45. JA Stefan Wilhelm, Anthony J Tavares, Qin Dai, et al. Analysis of nanoparticle delivery to tumours. *Perspectives (Montclair).* 2016.