



## Multifunctional particles for melanoma-targeted drug delivery

Aniket S. Wadajkar<sup>a,b,1</sup>, Zarna Bhavsar<sup>a,b,1</sup>, Cheng-Yu Ko<sup>a,b</sup>, Bhanuprasanth Koppolu<sup>a,b</sup>, Weina Cui<sup>c</sup>, Liping Tang<sup>a,b</sup>, Kytai T. Nguyen<sup>a,b,\*</sup>

<sup>a</sup> Department of Bioengineering, University of Texas at Arlington, 500 UTA Blvd, Arlington, TX 76019, USA

<sup>b</sup> Department of Biomedical Engineering, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

<sup>c</sup> Department of Radiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

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### ABSTRACT

New magnetic-based core-shell particles (MBCSPs) were developed to target skin cancer cells while delivering chemotherapeutic drugs in a controlled fashion. MBCSPs consist of a thermo-responsive shell of poly(*N*-isopropylacrylamide-*acrylamide*-allylamine) and a core of poly(lactic-co-glycolic acid) (PLGA) embedded with magnetite nanoparticles. To target melanoma cancer cells, MBCSPs were conjugated with Gly-Arg-Gly-Asp-Ser (GRGDS) peptides that specifically bind to the  $\alpha_5\beta_3$  receptors of melanoma cells. MBCSPs consist of unique multifunctional and controlled drug delivery characteristics. Specially, they can provide dual drug release mechanisms (a sustained release of drugs through degradation of PLGA core and a controlled release in response to changes in temperature via thermo-responsive polymer shell), and dual targeting mechanisms (magnetic localization and receptor-mediated targeting). Results from *in vitro* studies indicate that GRGDS-conjugated MBCSPs have an average diameter of 296 nm and exhibit no cytotoxicity towards human dermal fibroblasts up to 500  $\mu\text{g ml}^{-1}$ . Further, a sustained release of curcumin from the core and a temperature-dependent release of doxorubicin from the shell of MBCSPs were observed. The particles also produced a dark contrast signal in magnetic resonance imaging. Finally, the particles were accumulated at the tumor site in a B16F10 melanoma orthotopic mouse model, especially in the presence of a magnet. Results indicate great potential of MBCSPs as a platform technology to target, treat and monitor melanoma for targeted drug delivery to reduce side effects of chemotherapeutic reagents.

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### 1. Introduction

Current treatment methods for melanoma, the most prevalent form of skin cancer, have several limitations, such as low target specificity, severe side effects and drug resistance [1]. Metastatic melanoma cells may invade other organs, leading to a hindered response to chemotherapeutic drugs and a decrease in patient survival rate [2]. To address some of these issues, substantial progress has been made in the development of particulate drug delivery systems. It is well established that targeted drug delivery by nanoparticles is more effective and less harmful than the conventional systematic delivery of chemotherapeutic drugs [3]. Nanoparticles are thought to be ideal carriers to efficiently deliver the drugs directly to the tumor site, thereby reducing systemic toxicity and side effects [4]. Different types of functional nanoparticles

have been designed to target or accumulate in cancer tissues via either receptor-mediated targeting or passive targeting, respectively [5], leading to an increase in therapeutic efficiency while minimizing side effects.

Conjugation of targeting moieties like antibodies, peptides or aptamers to the particles has been used to allow for active targeting of cancer cells and overcome the limitations of passive targeting [6]. For an instance, Arg-Gly-Asp (RGD)-functionalized nanoparticles have been used for both targeted drug delivery and imaging applications, especially in melanoma skin cancer [7,8]. Furthermore, Gly-Arg-Gly-Asp-Ser (GRGDS) peptides have been shown to increase the specific binding of the particles to the  $\alpha_5\beta_3$  receptors of melanoma cells [9]. Many recent works have also emphasized the development of a multifunctional cancer therapeutic system with both diagnosis and treatment capabilities by incorporating various polymers, organic and inorganic materials [10].

Several particle devices developed for melanoma cancer therapies have demonstrated varying degrees of success. These particles include hydrophobically modified glycol-chitosan nanoparticles for paclitaxel-based chemotherapy [11], magnetic-based cationic

\* Corresponding author at: Department of Bioengineering, University of Texas at Arlington, 500 UTA Blvd, Arlington, TX 76019, USA. Tel.: +1 817 272 2540; fax: +1 817 272 2251.

E-mail address: [knguyen@uta.edu](mailto:knguyen@uta.edu) (K.T. Nguyen).

<sup>1</sup> Both authors contributed equally to this work.