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Bone microenvironment targeted nanoparticles for metastatic prostate cancer treatment

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Purpose: The most common site of metastatic prostate cancer is the bone. These metastatic lesions are difficult to treat and often result in off target cytotoxicity from current chemotherapeutics. We hypothesize that targeted nanoparticles (NPs) designed to deliver chemotherapeutics to cancer lesions in the bone microenvironment could improve treatment and the side effect profile that results from non-discriminate action of cytotoxic agents. We have designed a novel targeted nanotherapeutic system to target the bone microenvironment in an effort to more efficiently deliver chemotherapeutics to the site of metastasis. The core of the NPs are composed of poly (D,L-lactic-co-glycolic acid) (PLGA) biodegradable polymer. The PLGA NPs have been loaded with the microtubule inhibitor, cabazitaxel. The surface of the NP has been conjugated with an amino-bisphosphonate through a BS3 (bis(sulfosuccinimidyl) suberate) linker system, which allows for high affinity binding to the hydroxyapatite structure of the bone.

Materials & Methods: NPs were formulated using a modified water-in-oil-in-water double emulsion solvent evaporation technique. The physiochemical properties of the NPs were characterized. *Ex vivo* bone binding studies were performed. Cytotoxicity was tested in C4-2B and PC3 cell lines as well as in 3D tumor spheroids. Finally, NPs were tested for efficacy in an intraosseous tumor model of metastatic prostate cancer in athymic nude male mice.

Results: NPs were made with favorable physiochemical characteristics: mean hydrodynamic diameter of 236.8 nm ± S.D. 1.19 and mean polydispersity of 0.121 ± SEM 0.003. Cellular cytoxicity assay showed that C4-2B cells were more sensitive to the free cabazitaxel, the non-targeted NPs, and the targeted NPs compared to PC-3 cells. We did not see any appreciable difference between the targeted NPs and equivalent treatment of free cabazitaxel in 3D assays. *In vivo* analysis showed that both the non-targeted and targeted NPs were more effective than free cabazitaxel at reducing tumor burden. Additionally, targeted-NPs improved bone morphology at tumor lesions and were superior in behavioral tests.

Conclusions: In this project, we have engineered a bone targeted NP formulation for metastatic prostate cancer. We have determined the chemical and physical characteristics of this system and tested the *in vitro* cytotoxicity. Finally, we have shown the efficacy of these targeted NPs in an intraosseous model of bone metastatic prostate cancer.

Biography

Jamboor Vishwanatha, PhD, Regents Professor and Vice President for Diversity and International Programs, and Director of the Texas Center for Health Disparities at the University of North Texas Health Science Center at Fort Worth. He is a Principal Investigator of the National Research Mentoring Network, a NIH Common Fund initiative to provide mentorship, networking and professional development for a diversified biomedical and behavioral workforce. He received his PhD in Biological Sciences from the University of South Carolina in 1983. His research is in cancer molecular biology, experimental therapeutics and nanotechnology. His laboratory is investigating genetic markers that predict development of aggressive prostate and breast cancers, and nanotechnology-based therapies for breast and prostate cancers. He is actively involved in mentorship and networking programs to diversify the biomedical research workforce, and has mentored numerous undergraduate and graduate students from under represented groups in biomedical sciences. As the Director of Texas Center for Minority Health, Education, Research and Outreach (Texas Center for Health Disparities), a Center of Excellence funded by the National Institutes of Health, he has directed health disparity research, education and community outreach programs. For the past 11 years, he has organized the Annual Texas Conference on Health Disparities that attract national speakers and participants. He serves on the external advisory committees for University of Puerto Rico-Cayey, PR; St. Mary's University, San Antonio, Texas; Alabama State University, Montgomery, Alabama; and Savannah State University, Savannah, Georgia.

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