OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
Biosensors & Bioelectronics

May 14-16, 2012 Embassy Suites Las Vegas, USA

Engineering multifunctional nanoparticles to selectively target multiple myeloma cells and overcome cell adhesion mediated drug resistance.

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In the continuing search for effective treatments for cancer, here we report the rational engineering of a novel multifunctional nanoparticle that combines traditional chemotherapy with cell targeting and anticellular-adhesion functionalities to selectively target multiple myeloma (MM) cells and overcome cell adhesion-mediated drug resistance (CAM-DR). Anti-cellular-adhesion evolves as a promising target in oncology. VLA-4-mediated adhesion to the bone marrow extracellular matrix and stromal cells confers MM cells with CAM-DR. In our design, we used micellar nanoparticles as dynamic self-assembling scaffolds to present VLA-4-antagonist peptides and doxorubicin conjugates simultaneously to selectively target MM cells and to overcome CAM-DR. Doxorubicin was conjugated to the nanoparticles through an pH-sensitive hydrazone bond to prevent premature release and thus non-specific toxicity. Peptides were conjugated via a multifaceted synthetic procedure for generating precisely controlled number of targeting functionalities per nanoparticle. The nanoparticles, which exhibited a size of ~20nm, were efficiently internalized by MM cells with an optimal peptide valency of 20 per micelle, and induced cytotoxicity to MM cells. Mechanistic studies revealed that nanoparticles induced DNA double strand breaks as evidenced by H2AX phosphorylation, and triggered apoptosis, which was associated with PARP and caspase-8 cleavage. Importantly, multifunctional nanoparticles were more efficacious than doxorubicin in the presence of fibronectin (IC_{50}=0.15±0.04 ⌠M and 0.42±0.09 ⌠M, respectively), and overcame CAM-DR induced by adherence of MM cells to fibronectin. Finally, in a MM xenograft model, nanoparticles preferentially homed to MM tumors, with a ~10 fold more drug accumulation when compared to doxorubicin, and demonstrated dramatic tumor growth inhibition with much reduced overall systemic toxicity. Taken together, we demonstrate the disease-driven engineering of a nanoparticle-based drug delivery system, enabling the model of an integrative approach in the treatment of MM.

Biography

Basar Bilgicer is an assistant professor in the Department of Chemical and Biomolecular Engineering, and a concurrent assistant professor in the Department of Chemistry and Biochemistry at the University of Notre Dame. After receiving his bachelor degree in chemistry at Bogazici University, he moved to Boston in 1999 to pursue his PhD in chemistry at Tufts University where he designed and studied peptides that incorporated unnatural amino acids for enhanced stability and selectivity in protein-protein association. His work, which was published in the top tier journals in his field, has been highlighted in several popular media outlets including Chemical and Engineering News. He was honored with a research excellence award as well as an outstanding academic achievement award by Tufts University. After earning his PhD degree in 2004, he moved to George Whitesides group in the Department of Chemistry and Chemical Biology at Harvard University. During this time, he focused on developing a better understanding of thermodynamics and kinetics of multivalent interactions in biological systems, specifically on association of bivalent antibodies with multivalent antigens. His research program at Notre Dame is founded on his expertise in bioengineering, biophysical chemistry, synthetic chemistry, and targeted drug delivery. As part of his research program, his group is using the principles of multivalent biomolecular interactions to design therapeutic agents with enhanced targeting selectivity in cancers such as multiple myeloma, breast and ovarian cancer.

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