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Doxorubicin and *BikDD* delivery to AU565 breast cancer cell line by targeted polymeric nanocarriers

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Breast cancer is the most common cancer type among women with a 25.1 percent incidence worldwide. It is a major public health problem with no current effective treatment thus more target-specific therapeutic methods are needed. Peptide 18, a tumor homing peptide, shown to have high potential in targeting breast cancer cells was used in labeling the polymeric nanocarrier constructs formulated poly(2-ethyl-2-oxazoline)-b-poly(L-lactide) (PEtOx-b-PLA) based polymers. These polymers have high biocompatibility and biodegradable characteristics. Toxicology studies showed that these polymeric nanocarriers did not affect the cell survival of human endothelial cells (HUVEC), hepatocytes (HEPG2), mesenchymal stem cell, human osteoblasts (hFOB1.19), kidney (HEK293) and fibroblasts cell lines, characterizing these constructs with minimal toxicity. Target specificity and cellular uptake of peptide 18 labeled polymeric nanocarriers were determined via flow cytometry and confocal microscopy. Our results showed that these targeted polymeric nanocarriers possessed higher binding affinity to AU565 breast cancer cell line compared to healthy epithelial MCF10A breast cell line. Pro-apoptotic *BikDD* gene and doxorubicin drug were loaded to these targeted polymeric nanocarriers. In order to examine *BikDD* gene delivery by targeted polymeric nanocarriers in AU565 cells, qPCR and western blotting was conducted. The increased Bik mRNA and protein expression levels in these AU565 cells suggest the high effectiveness of the targeting polymeric nanocarriers. The apoptotic activity of pro-apoptotic *BikDD* gene and doxorubicin delivery by peptide 18 labeled polymeric nanocarriers to AU565 cells was detected using Annexin V/PI staining and Caspase 3 colorimetric assay. Our results showed an enhanced apoptotic rate in AU565 cells. Following *in vitro* studies, the delivery of doxorubicin using polymeric nanocarriers were analyzed in CD-1 nude mice animal model. The animal study suggested that doxorubicin delivery by peptide 18 labeled polymeric nanocarriers significantly decreased tumor volume by 3 fold when compared to the 2 fold decrease recorded for doxorubicin alone. However, there was no significant difference in tumor volume of CD-1 nude mice treated with *BikDD* gene loaded into peptide 18 labeled polymeric nanocarriers. Our results suggest that this targeted therapy may potentially become a substitute for the conventional approaches. This project is funded by TUBITAK (213M726-231M760).

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