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Nano-structure Mediated Delivery of a Chemotherapeutic Agent for Improved Leukemia Treatment

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Chronic myeloid leukemia (CML) is a slow progressing blood and bone marrow disease. Currently, tyrosine kinase inhibitors (TKIs) are used to treat CML, by preventing the oncogenic function of the BCR-ABL gene, which is found in the cells of more than 95% of CML patients [1]. Bosutinib, a TKI, is effective for most patients with CML, but shows substantial toxic side effects [2]. Developing a more targeted drug delivery system using gold nanoparticles may decrease the negative side effects of Bosutinib. The aim of this project was to study the effectiveness of gold nanoparticles (AuNPs) as a platform for the delivery of Bosutinib to decrease toxicity to normal human cells and to develop a more efficient treatment for CML. Gold nanoparticles were synthesized, capped with carboxymethyl chitosan and conjugated with Bosutinib. Synthesis and conjugation was confirmed by transmission electron microscopy (TEM), UV-visible spectroscopy, and dynamic light scattering. TEM images show that the AuNPs have a typical dense and spherical morphology and are at a relatively high concentration (Figure 1A). The size of the AuNPs (n=111) was analyzed and the most abundant size was found to be 23-34 nm. The mean size was calculated to be 27.7 nm (Figure 1B). This has been found to be an ideal size for drug delivery applications [3]. In addition to viability assays, caspase assays, scanning electron microscopy, and ELISA were performed to further examine the efficiency of this drug delivery system.

Cell viability studies were performed to determine the effectiveness of the AuNP drug delivery system as compared to unconjugated Bosutinib, and its specificity to cancer cells. An MTS cell viability assay showed that K562 leukemia cells treated with Bosutinib-conjugated AuNPs had significantly lower viability than cells treated with unconjugated Bosutinib (Figure 2). This indicates that this Bosutinib-AuNP delivery system has a significantly higher toxicity to cancerous cells than unconjugated Bosutinib. In addition, Bosutinib-conjugated AuNPs are less toxic to normal cells compared to unconjugated Bosutinib (Figure 3). Human foreskin fibroblast (HFF) cells treated with unconjugated Bosutinib had a significantly lower viability than those treated with Bosutinib-conjugated AuNPs.

This study has demonstrated the high efficiency and advantages of a nano-structure mediated drug delivery method for the chemotherapeutic agent Bosutinib. Conjugating Bosutinib to AuNPs significantly increases the its ability to kill leukemia cells, while decreasing its cytotoxicity to normal human cells. The increased chemosensitivity that this drug delivery method provides will significantly improve treatment outcome and increase both patient quality of life and treatment compliancy.

References:
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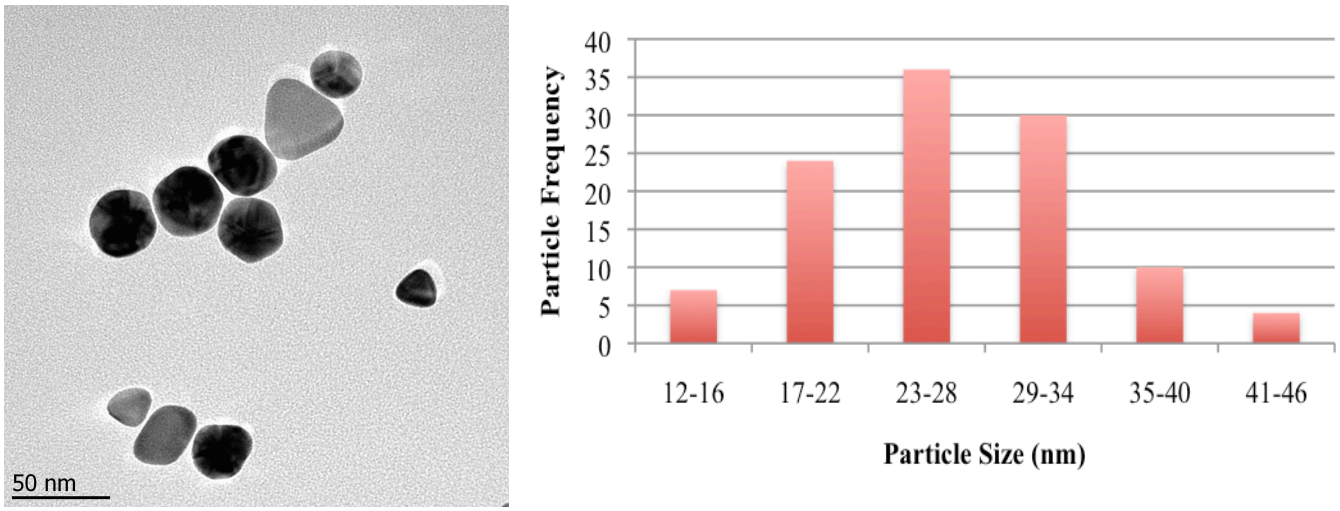

Figure 1: Analysis of gold nanoparticles stabilized with CM-Chitosan. (A) TEM image of CM-Chitosan capped gold nanoparticles. (B) Gold nanoparticle size distribution graph (n=111).

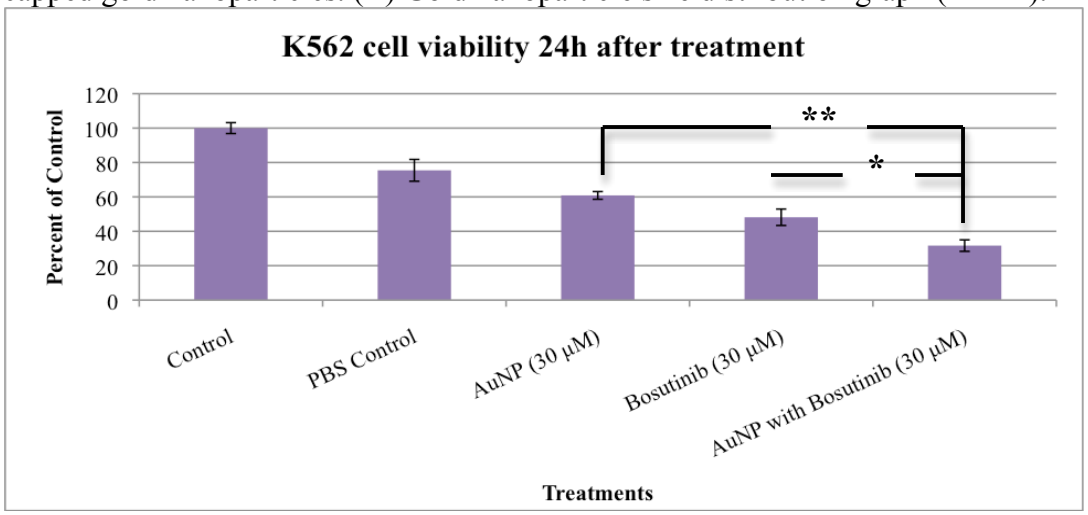

Figure 2: MTS cell viability assay of K562 cells after Bosutinib, AuNP and conjugated AuNP treatment. Data represented as mean ± s. d. * denotes $p<0.01$ (n=4) compared to unconjugated Bosutinib; ** denotes $p<0.001$ (n=4) compared to AuNP.

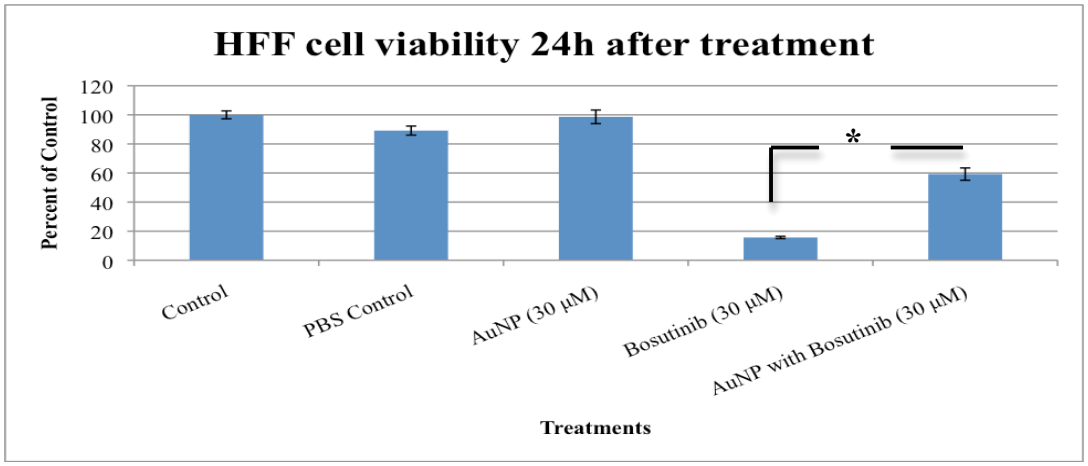

Figure 3: MTS cell viability assay of HFF cells after Bosutinib, AuNP and conjugated AuNP treatment. Data represented as mean ± s. d. * denotes $p<0.001$ (n=4) compared to unconjugated Bosutinib.

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