Abstract No: PO-25

L-asparaginase encapsulated poly-l-lysine-graft-poly(ethylene) glycol polymer nanoparticles for therapeutic delivery

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Therapeutic proteins have shown to be effective against a variety of diseases. Unlike traditional small-molecule chemotherapeutics, protein therapeutics can be actively targeted towards malignant cells using cell surface receptors and/or other markers specifically associated with or overexpressed on tumors versus healthy tissue. L-asparaginase (L-ASNase) is a therapeutic enzyme that is widely used for the treatment of hematopoietic diseases such as acute lymphoblastic leukemia and lymphomas since 1970. L-ASNase can destroy asparagine dependent tumors by degrading circulating L-asparagine and destroying malignant cells. L-ASNase has intrinsic drawbacks such as low stability, short circulating lifetime, and low catalytic activity under physiological conditions due to it being a therapeutic enzyme and essentially a protein drug. Immunogenicity of L-ASNase is another major problem with high frequency of hypersensitivity reactions due to the bacterial origin of this protein. ASNase delivered after pegylation (poly(ethylene)glycol)-ASNase) has been shown to improve clinical outcome of this therapy. However, the safety and efficacy of this therapy in older adults is less well established and has shown toxicity in clinical trials. Much effort has been devoted to developing methods to avoid such side effects as well as to increase its in vivo half-life. This research is focused on synthesis, optimization, and characterization of L-ASNase encapsulated nanoparticles for successful delivery of the therapeutic protein. Poly-L-lysine-graft-poly(ethylene) glycol copolymer (PLL-g-PEG) was successfully synthesized and characterized using ^{1}H NMR spectroscopy. L-ASNase encapsulated nanoparticles were formed through electrostatic interaction of the cationic backbone of the PLL-g-PEG copolymer and negatively charged L-ASNase. Average hydrodynamic diameter of these nanoparticles was 114.5 ± 5.66 nm, and they had a zeta potential of 0.436 ± 0.258 mV. Polyacrylamide gel electrophoresis (PAGE) was used to analyze the extent of L-ASNase encapsulation. According to PAGE data, there were no free proteins present in our nanoparticle formulations. These therapeutic nanoparticles are stable in solution at physiological pH conditions up to more than three months and long-term particle stability studies are in progress. L-ASNase catalytic activity experiments are currently in progress to evaluate how encapsulation could affect protein function and will also be presented.

Keywords: Encapsulation, L-asparaginase, Nanoparticles, Protein, Therapeutic delivery

Acknowledgment
This work was supported by Western Carolina University under the research grant of Provost's Scholarship Development Awards.