

# Ultrasound-responsive Nanoparticles for Neurotherapeutic Delivery

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Neurodegenerative diseases cause incurable neuronal damage and often result in fatality. A major challenge in treating neurodegenerative diseases is the inability to deliver drugs to the brain due to the blood-brain barrier (BBB). To circumvent this problem, ultrasound-responsive nanoparticles were designed and tested as a potential solution for localized drug delivery to the brain. Liposomes, used as drug delivery vehicles, were conjugated to microbubbles ( $\mu$ Bs) and treated with focused ultrasound (FUS). FUS causes  $\mu$ Bs to cavitate and liposomes to burst, temporarily disrupting the BBB and allowing drugs to enter the brain. Liposome-conjugated  $\mu$ Bs were prepared and tested for neurotherapeutic viability. Both  $\mu$ Bs and liposomes were prepared using synthetic lipids with functionalized PEG linkages for self-conjugation. Liposomes were evaluated by encapsulating fluorescent dye and/or MRI contrast agent. Viability was analyzed using fluorescence microscopy, MRI, mathematical analysis, FUS, and particle sizing. Fluorescence microscopy demonstrated successful conjugation of liposomes onto  $\mu$ Bs. MRI demonstrated that liposomes readily released encapsulated content when treated with FUS and heat; there was a 338% increase in R1 values between treated and untreated samples. However, mathematical analysis indicated that content release was only 24% efficient. Particle sizing over three weeks showed stable liposomes with a standard deviation of  $\pm 10$  nm from initial diameters. This indicates secure shelf life and viability in medical applications. Future work includes increasing delivery efficiency of drug-encapsulated liposomes and in vivo experiments. This study is a step towards the use of liposome-conjugated  $\mu$ Bs as a targeted, noninvasive drug delivery method to the brain.