

## Focused Ultrasound – Mediated Insulin Delivery Through Nano-network

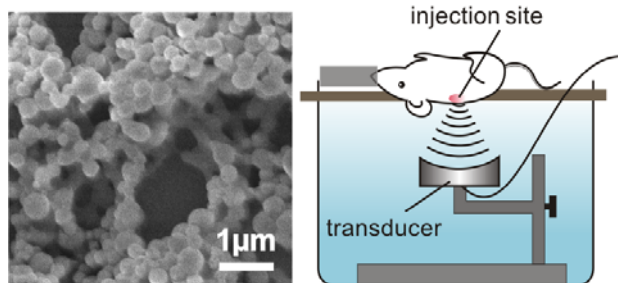
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**Statement of Purpose:** An on demand, non-invasive and portable insulin delivery method that can achieve pulsatile insulin release and effective regulation of blood glucose is highly desirable for type 1 and advanced type 2 diabetes management<sup>[1]</sup>. We report that integration of an injectable nano-network with a focused ultrasound system (FUS) can remotely regulate insulin release both *in vitro* and *in vivo*<sup>[2]</sup>.



**Figure 1.** Characterization of the PLGA based NN encapsulating insulin. The SEM image of formed NN with 3D porous structure. Scale bar: 1  $\mu\text{m}$ . And Focused ultrasound (FUS) -mediated regulation of blood glucose (BG) levels *in vivo*. Schematic of the experimental apparatus. Anesthetized mice were immobilized on a stage over a water bath.

**Methods:** We prepared insulin-loaded nano-network by a double emulsion-based solvent evaporation method. Poly(lactic-co-glycolic acid) (PLGA) was selected as a matrix material due to its prominent biocompatibility and biodegradability. To acquire oppositely charged nanoparticles, two natural polysaccharides, chitosan (positively charged) and alginate (negatively charged) were respectively applied as surfactants during the emulsion procedure to coat PLGA cores. Further these two kinds of nanoparticles were mixed together to form cohesive gel like nano-network through electrostatic force. To demonstrate the pulsatile release profile triggered by Focused Ultrasound System (FUS), we

performed multiple FUS treatment over time *via* optimized FUS condition.

**Results:** By serving as a synthetic insulin reservoir, the nano-network consisting of adhesive PLGA nanoparticles significantly promoted insulin release upon intermittent FUS triggers. Remarkably, a maximum of 80-fold increase in the insulin release rate was observed when the nano-network was exposed to the irradiation of ultrasound for 30 sec. *In vivo* studies validated that this method provided repeatable and spatiotemporal regulation of blood glucose levels in Type 1 diabetic mice (Figure 2).

**Conclusions:** We have developed a novel means of ultrasound-triggered controlled drug delivery based on the use of an injectable NN. The gel-like 3D scaffold of NN can be effectively triggered to release insulin upon FUS-mediated administration. This system provides an unprecedented useful tool for noninvasive, rapid and pulsatile regulation of BG levels for diabetes treatment. It also can be extended to deliver other drugs, therapeutic proteins, or peptides in an intermittent and spatiotemporal release fashion. Furthermore, this method can be integrated with an ultrasound imaging system<sup>[3]</sup> for noninvasively monitoring degradation of the drug-contained formulation and facilitating the subsequent administration.

### References:

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