Self-healing, Injectable Photo-Zwitterionic Hydrogels for Chronic Diabetic Wounds

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Statement of Purpose: Complications of diabetes, including impaired wound healing, represent a significant clinical issue, with the annual cost of lower extremity ulcers alone exceeding $1.5 billion annually.[1] Despite the enormous impact that diabetic wounds have on patients, an effective clinical strategy has yet to be developed. Here we report on the development of a novel biomaterial wound dressing (**Fig. 1a,b**) that contains therapeutic nanoparticles which are released to the wound in a sustained manner over time (**Fig. 1c**). This biomaterial system improves the quality and speed of repair tissue, as evidenced in an *in vivo* diabetic mouse wound healing model (**Fig. 2**). To synergistically target oxidative stress/reactive oxygen species (ROS) and chronic inflammation, we have designed and synthesized novel cerium oxide nanoparticles (CNPs) that possess ROS scavenging properties and have conjugated them with miRNA-146a to target inflammation. The CNPs are released from novel, photo-polymerized zwitterionic (ZW) hydrogels. These gels exhibit many of the ideal mechanical characteristics that are desired for wound dressing materials, including stretchability, self-healing, and low biofouling.

Methods: Zwitterionic hydrogels were prepared using a combination of sulfobetaine methacrylate (SBMA), hydroxyethyl methacrylate (HEMA), polyethylene glycol dimethacrylate (PEGDMA), and a photoinitiator. The ZW gel solutions were transferred to 1 cc syringes and polymerized with light at 405 nm to yield an injectable gel. The mechanical and physical properties were characterized, and protein adsorption to the hydrogels was quantified. For *in vitro* release studies, gels were soaked in PBS which was collected for released CNP quantification

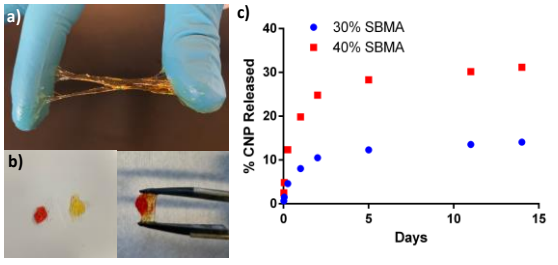

Figure 1. *Photograph of* ***a)*** *stretching and* ***b)*** *self-healing behavior of ZW hydrogels.* ***c)*** *In vitro release of FITC-labeled CNPs.*

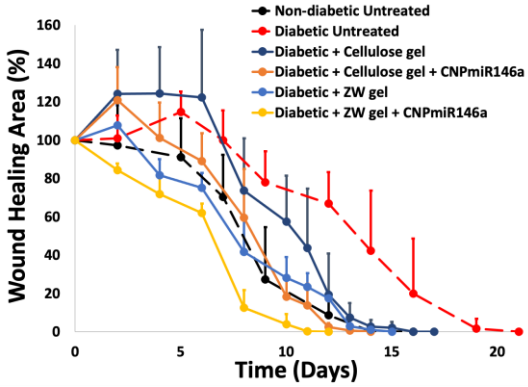

Figure 2. *In vivo wound healing rate in diabetic mouse model*

at various timepoints. 12-week-old homozygous diabetic (Db/Db) mice were used for wound healing studies. 8-mm wounds were created on the backs of the mice and empty or CNP-miR146a-laden ZW gels were administered one time. The wound surface area was measured every other day until full closure and compared with untreated non-diabetic and diabetic mice, as well as cellulose gels +/- CNP-miR146a.

Results: ZW hydrogels could be fabricated with a wide range of mechanical characteristics, ranging from sticky, stretchy, injectable self-healing gels (**Fig. 1a,b**), to solid and brittle pellets, dependent on the composition of ZW monomer and crosslinker. ZW gels also exhibited sustained release of FITC-labeled CNPs over the span of two weeks (**Fig. 1c**). Db/Db mice treated with the ZW gels alone had improved wound healing when compared to a control cellulose gel, and ZW gel in combination with CNP-miR146a exhibited a significant improvement in wound healing time in diabetic mice over time, shortening the healing time by days (**Fig. 2**).

Conclusions: Zwitterionic hydrogels can be fabricated with variable mechanics and sustained release of FITC-CNPs *in vitro*, and they increase the rate of wound healing in a diabetic mouse wound healing model.

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References: 1) Harrington, C. *et al. Diabetes Care* 23, 1333–1338 (2000)