An Inflammation-responsive Hydrogel for Drug Delivery for Treatment of Ulcerative Colitis

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Statement of purpose: Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract. Current treatment of IBD relies on non-specific anti-inflammatory drugs such as 5-aminosalicylates, corticosteroids, or immunosuppressants, which may result in debilitating side effects in long-term use, and a biological therapy using anti-tumor necrosis factor (TNF) monoclonal antibody that is often limited by a loss of efficacy [1]. A major hurdle in the treatment of IBD is the lack of an effective vehicle to precisely deliver the therapeutics to inflamed intestinal tissue for higher local drug concentration, less systemic absorption, and therefore less adverse effect. We have developed a self-assembled hydrogel system for corticosteroids delivery in IBD treatment. We designed this hydrogel to achieve 1) site-specific drug delivery to the inflamed intestinal tissue; and 2) drug release in response to the level of inflammation within the microenvironment. Importantly, this hydrogel is made of a material listed as "Generally Recognized as Safe" by the Food and Drug Administration (FDA).

Methods: The assembly of the gel was described as before with modifications [2]. Dexamethasone (Dex) was used as a model drug in the experiments. The amount of Dex released from different medium, including PBS, culture medium from unactivated macrophages, culture medium from lipopolysaccharide (LPS) activated macrophages and lipase, was quantified by HPLC. To demonstrate enhanced adherence of the hydrogel to inflamed colon, a fluorescent dye was encapsulated in the hydrogel for imaging purpose. Colon was dissected from mice with colitis and healthy controls, and then incubated with the dye-loaded hydrogel for 30 minutes, respectively. After washing, the fluorescence in the colon was quantified by EVOS fluorescence microscope. The principal *in vivo* mouse model was T-bet$^{-/-}$Rag2$^{-/-}$ Ulcerative Colitis (TRUC) mouse model, which develops spontaneous microbiota-driven colitis with a strong resemblance to human UC [3,4]. Dex-loaded hydrogel was administered to mice via enema. The retention of Dex in the colon was quantified at 24 h post-enema. The colon tissue was collected and homogenized. Dex was extracted from the homogenate, and subsequently quantified. The therapeutic efficacy of Dex-loaded hydrogels was examined using histopathology scores after treatment in comparison with free Dex and untreated mice.

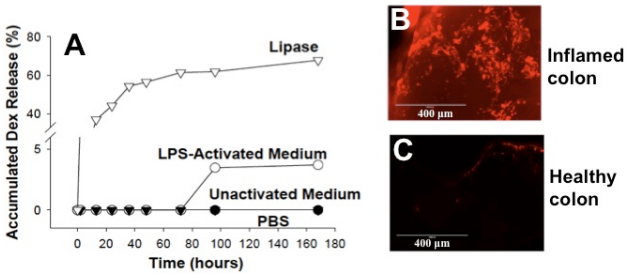

Figure 1. (A) Enzyme-responsive release of Dex from the hydrogel following incubation in lipase or media from activated macrophages. (B) Dye-loaded hydrogel microfibers selectively adhered to the inflamed colon compared to (C) healthy colon *ex vivo*.

Results: We developed an inflammation responsive hydrogel microfiber system to encapsulate high amounts of drug using Dex as a model drug, and demonstrated enzymatically-triggered release of the encapsulated drug (**Figure 1A**) and enhanced adherence to the inflamed colon tissue (**Figure 1B**). Studies using a murine colitis model showed that drug-loaded inflammation responsive hydrogels administered via enema extended availability of drug in the colon compared to drug alone (**Figure 2A**). Histopathology scores showed the drug-loaded hydrogel significantly inhibited the inflammation in the colon compared to drug alone or untreated mice with colitis (**Figure 2B**).

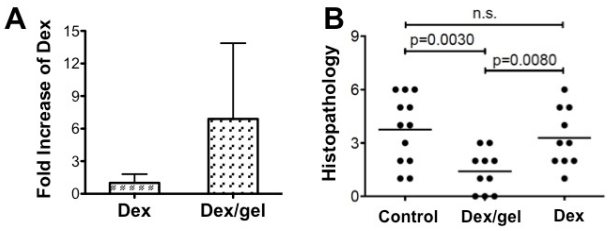

Figure 2. **(A)** Dex-loaded hydrogel showed a 6.8 fold higher Dex retention in the colon of mice with colitis than using Dex alone at 24 h post-enema. **(B)** Histopathology score showed that Dex-loaded hydrogel improved the treatment efficacy of Dex in comparison with using Dex alone (p=0.0080) and untreated mice with colitis (p=0.0030).

Conclusions: This site-specific, inflammation-responsive delivery approach harnesses the advantages of local drug delivery (reduced systemic toxicity) while overcoming existing limitations (need for frequent drug administrations). These studies have established a proof of concept in pre-clinical UC mouse models that should serve as useful data for future studies towards clinical implementation.

References: [1] Abraham C and Cho JH, N. Engl. J. Med., 2009; 361(21): 2066-2078. [2] Vemula PK, et al., J. Biomed. Mater. Res., 2011, A 97(2): 103-110. [3] Garrett WS, et al., Cell, 2007, 131(1): 33-45. [4] Ermann J, et al., Proc. Natl. Acad. Sci. USA, 2011, 108(17): 7137-7141.