A Highly Elastic and Antimicrobial Composite Hydrogel-Based Dressing for Wound Healing

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Statement of Purpose: More than 2% of the US population suffers from chronic wounds, which represents an estimated 20 billion dollars in health care related costs each year. Conventional wound closure methods, such as sutures, mechanical fasteners, and staples lead to increased localized stress, and tissue damage at the wound site. Furthermore, chronic wounds are highly susceptible to colonization by pathogenic bacteria, which can severely prolong the healing process. Therefore, alternative strategies for sutureless wound closure, that can also help prevent microbial infection, could potentially simplify surgical procedures and improve patient care and prognosis. Hydrogel-based dressings can be readily tailored to mimic the composition, as well as the physicochemical properties of the native extracellular matrix (ECM).[1] In addition, they can be rendered antimicrobial through the integration of different biocidal agents. However, conventional polymer-based dressings are often associated with poor mechanical properties, low biocompatibility, cytotoxicity, or weak attachment to physiological tissues. Therefore, to address this limitations, we engineered a highly elastic and antimicrobial, biocompatible hydrogel-based dressing, for the clinical management of chronic non-healing wounds.

Methods: The composite hydrogels were comprised of two biopolymers derived from native ECM proteins, namely gelatin methacryloyl (GelMA) and methacryloyl-substituted tropoelastin (MeTro). MeTro/GelMA hydrogels were formed via visible light-mediated photocrosslinking of different polymer concentrations, as well as different ratios of MeTro to GelMA. In addition, we conjugated the antimicrobial peptide (AMP) Tet213 (KRWWKWWRRC) to MeTro/GelMA hydrogels. We investigated the degree of crosslink within the hydrogels using ^{1}H-NMR, as well as the porosity of the scaffolds using SEM. Then, we characterized the *in vitro* degradation and swellability, as well as the mechanical and adhesive properties. We evaluated the bactericidal activity of MeTro/GelMA-Tet213 hydrogels against methicillin resistant *Staphylococcus aureus* and *Escherichia coli*. Lastly, we evaluated biocompatibility of MeTro/GelMA-Tet213 hydrogels via *in vitro* assays, as well subcutaneous implantation in a murine *in vivo* model.

Results: ^{1}H-NMR analysis showed that MeTro/GelMA hydrogels formed via visible-light exhibited ≈ 90% degree of crosslinking. Cyclic tensile and compressive tests demonstrated that the mechanical properties of the composite hydrogels can be modulated through variations in the total polymer concentration, as well as the ratio of MeTro to GelMA. In all instances, higher concentrations of MeTro yielded hydrogels with consistently higher extensibility and recoverability. Furthermore, the incorporation of the AMP did not significantly alter the mechanical properties of the hydrogels. Lap shear, burst pressure, and wound closure tests demonstrated that MeTro/GelMA hydrogels exhibit stronger adhesion to native tissues, when compared to commercially available tissue adhesives, such as Evicel (Ethicon, NJ) and CoSeal (Baxter, IL). In addition, the porosity, as well as the *in vitro* swellability and degradability of the hydrogels exhibited a wide range of highly tunable behaviors. *In vitro* colony forming and live/dead assays showed that MeTro/GelMA-AMP hydrogels possess stronger antimicrobial activity, when compared to zinc oxide nanoparticles. *In vitro* assays also showed that the composite hydrogels support the growth and proliferation of 3D-encapsulated mouse fibroblasts. Lastly, histological analysis of subcutaneously implanted samples demonstrated that MeTro/GelMA-AMP hydrogels do not elicit any inflammatory or cytotoxic responses *in vivo*.

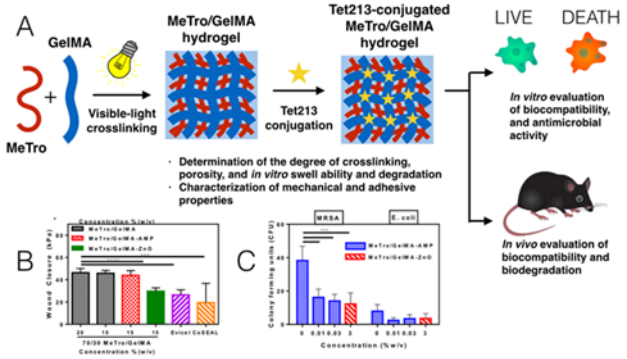

Figure 1. Schematic of the project (a), and representative wound closure (b) and antimicrobial (c) tests.

Conclusions: In this work, we introduce a new class of highly elastic hydrogel-based adhesive for the clinical management of non-healing wounds. The synergistic association of two biopolymers with distinct physicochemical properties enabled the fine-tuning of various features of the composite hydrogels. Taken together, our results demonstrate the remarkable potential of MeTro/GelMA-AMP hydrogels for the engineering of sutureless tissue adhesives, which could prevent infection and promote healing of non-healing wounds.

References: 1. Veiga AS, Schneider JP. Biopolymers. 2013 Nov;100(6):637-44. doi: 10.1002/bip.22412.