# Engineering a highly elastic bioadhesive hydrogel for sealing soft and dynamic tissues

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**Statement of Purpose:** Pulmonary air-leaks are common entanglements post lung resection, leading to prolonged hospital stay and high healthcare cost. Despite recent advances in the development of surgical sealants, there are currently no clinically approved products offering combined properties of high elasticity, low toxicity, and strong tissue adhesion in wet and highly dynamic environments. In this work, highly adhesive and elastic bioadhesives based on gelatin-methacrylol catechol (GelMAC) and poly (ethylene glycol) diacrylate (PEGDA) were developed, which can be potentially used to stop air leakages after lung surgery and support new tissue formation to repair the wound. Due to its highly tunable nature, the engineered bioadhesives can also be used for various applications such as anastomoses, cardiovascular surgeries, and wound closure.

**Methods:** Inspired by the natural mussel adhesive mechanism, an efficient synthetic method was designed to chemically conjugate the catechol motifs (i.e. dopamine) to porcine gelatin backbone. Next, the gelatin-catechol compound was functionalized with methacrylic anhydride to form a highly adhesive and photocrosslinkable biomaterial named gelatin-methacrylol catechol (GelMAC) [1]. To form the composite bioadhesives, GelMAC/PEGDA prepolymer solution was prepared by mixing different ratio of two polymers to form bioadhesives at final 20% polymer concentration. An optimized concertation of photocrosslinking reagents (0.1 mM Eosin Y, 1% N-vinylcaprolactam and 1.5% Triethanolamine) was then added to the prepolymer solution. Ferric ion solution (2.5 µM $Fe^{3+}$) was added to the mixture to crosslink the network. The mixture was then exposed to a visible light (450-550 nm) for 240 sec for a second step crosslinking. The adhesive strengths of the hydrogels to porcine lung tissue were evaluated using a standard wound closure test [2]. Uniaxial tensile tests were performed by using an Instron mechanical tester to measure the extensibility of the hydrogels. Finally, the burst pressure and sealing ability of the hydrogels were tested in an *ex vivo* porcine lung incision model.

**Results:** The result of wound closure test demonstrated that adhesion of GelMAC/PEGDA hydrogels decreased with increasing PEGDA concentration. Also, there was no significant change in the adhesive strength of GelMAC/PEGDA hydrogels with and without $Fe^{3+}$ ion solution (2.5 µM) (**Fig 1a**). Moreover, the results of tensile test showed that addition of PEGDA improved the elasticity of the hydrogels (**Fig 1b**). For example, 50/50 GelMAC/PEGDA hydrogel exhibited a 2-fold higher elasticity than pure GelMAC sealant at 2.5 µM $Fe^{3+}$ concentration (**Fig 1b**). We used an *ex vivo* lung incision model to measure the burst pressure of the engineered 50/50 GelMAC/PEGDA bioadhesive containing ferric ions ((GelMAC/PEGDA)-Fe). A 1 cm-wide circular defect was created as shown in **Fig 1ci-ii**. The bioadhesive prepolymer solution was then applied at the defect site and was photopolymerized immediately to seal it (**Fig 1ciii-iv**). The lung was then connected to a ventilator and the pressure was increased stepwise over time until the burst point (**Fig 1d**). The average burst pressure values were found to be 1.83 ± 0.14 kPa, 1.93 ± 0.31 kPa, and 1.95 ± 1.42 kPa for GelMAC-Fe, (GelMAC/PEGDA)-Fe, and Coseal, respectively (**Fig 6e**). According to these results, (GelMAC/PEGDA)-Fe bioadhesive exhibited a similar sealing ability to the clinically available Coseal surgical sealant.

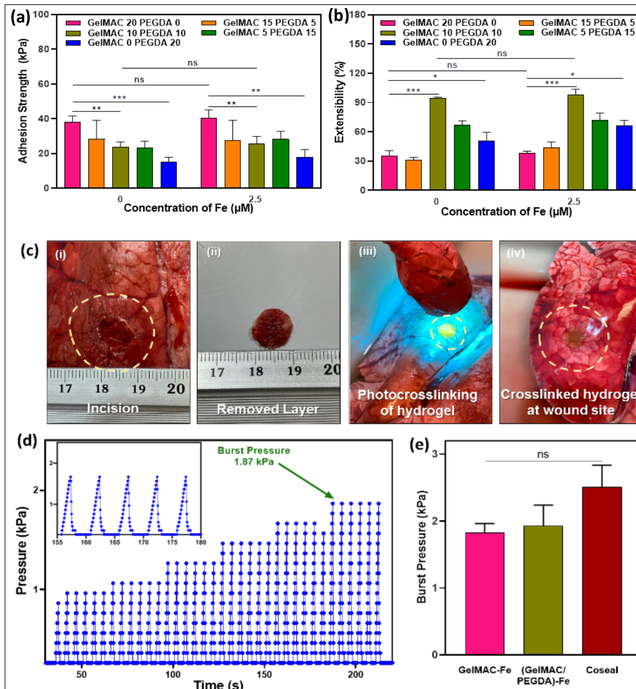


**Fig 1. Adhesion, extensibility, and *ex vivo* burst pressure of GelMAC/PEGDA bioadhesives. (a)** Adhesion strength, and **(b)** Extensibility of GelMAC/PEGDA bioadhesives at varying ratios of GelMAC/PEGDA with/without ferric ions ($n \geq 4$). **(c-d)** *Ex vivo* test to evaluate the sealing capability of the bioadhesive: **(c)** Creating incision, injecting hydrogel and photocrosslinking in situ, **(d)** a representative graph depicting the stepwise pressure increasing over time during testing, and **(e)** burst pressure values for of GeMAC-Fe, (GelMAC/PEGDA)-Fe, and Coseal. Error bars indicate standard error of the means, asterisks mark significance levels of $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***), and $p < 0.0001$ (****)

**Conclusions:** In this study, we developed an elastic visible light crosslinked surgical sealant. The engineered hydrogel demonstrated adequate elasticity and mechanical properties, and high adhesion to the wet surfaces. Therefore, it can be used for sealing internal elastic organs such as the lung, heart, and blood vessels.

**References:** [1] A. Assmann et al., Biomaterials. 2017;140:115-27; [2] E. Shirzaei Sani et al., ACS Biomaterials Science & Engineering. 2018;4:2528-254.