Biomimetic Adhesive Coatings for Soft Tissue Repair

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Biologic and synthetic scaffolds or meshes are commonly used in surgical procedures including hernia repair, tendon and ligament repair, cardiovascular surgery, dural sealing and certain dental procedures. These prosthetic materials are fixated through the use of sutures, staples or tacks. While these mechanical fixation devices have been successfully used to immobilize prosthetic meshes, they also lead to complications. In hernia repair, for example, current mechanical fixation methods that are based on perforation may be the source of neural irritation and persistent pain.[1, 2] Fixation tacks may also work loose and migrate around the abdomen causing further problems. The use of tissue adhesives for mesh fixation is a relatively new approach that can potentially reduce pain and other complications, simplify and shorten surgical procedures, and reduce healthcare costs.[3, 4] However, currently available tissue adhesives lack adequate adhesive strength and safety profiles, and require complex preparatory procedures which may complicate surgical work flow.

In developing novel bioadhesives with improved properties, we were inspired by the adhesive protein secreted by marine mussels that enables them to anchor to a wide range of surfaces in wet, saline, turbulent environments.[5] These mussel adhesive proteins (MAPs) are secreted in liquid form but can quickly harden to form adhesive plaques that bind tenaciously to

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various substrates. One unique structural feature of MAPs is the presence of 3,4-dihydroxy-phenylalanine (DOPA), which is believed to fulfill a dual role as a surface adhesion promoter and a crosslinking precursor.[6]

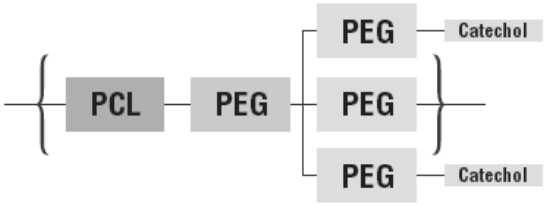

Figure 1. General architecture of the adhesive polymers.

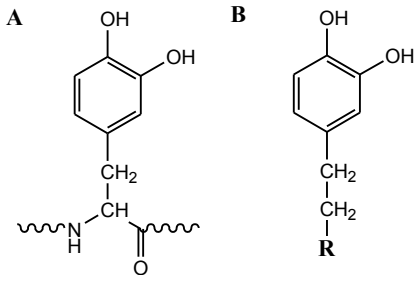

Figure 2. Chemical structures of **A**) DOPA and **B**) dopamine (**R** = NH_2) or DOHA (**R** = COOH).

We developed a series of new adhesive polymers (**Medhesives**) that are synthetic mimics of MAPs. **Figure 1** and **Table 1** show the polymers' general structure and chemical composition, respectively. These amphiphilic block copolymers are constructed from hydrophilic polyethylene glycol (PEG) and hydrophobic polycaprolactone (PCL) of known biocompatibility. PEG allows the adhesive polymer to remain relatively hydrophilic to achieve good "wetting" or adhesive contact with a biologic substrate. The hydrophobic PCL segments increase cohesive strength, prevent rapid dissolution of the adhesive in water, and reduce the degradation rate. These polymers are modified with 2 DOPA derivatives, dopamine and 3,4-dihydroxyhydrocinnamic acid (DOHA) as shown in **Figure 2**, which act as the adhesive moiety for interfacial binding and for solidifying the adhesive when an oxidant is introduced.

When these adhesive polymers were coated onto biologic meshes (**Figure 3**), the resulting bioadhesive constructs exhibited significant adhesive strength to wetted soft tissue (bovine

Table 1. Composition of the adhesive polymers.

Adhesive Polymer	Polymer Composition (wt%)				Catechol Type	GPC	
	^{1}H NMR			UV-vis		Molecular Weight (M_w)	PD*
	PEG	PCL	Catechol	Catechol			
Medhesive-054	84.0	13.4	2.6	3.1 ± 0.30	DOHA	98,000	2.8
Medhesive-096	76.6	20.6	2.8	3.4 ± 0.11	Dopamine	66,000	4.4

* Polydispersity (PD) = Weight average molecular weight (Mw) / number average molecular weight (Mn)

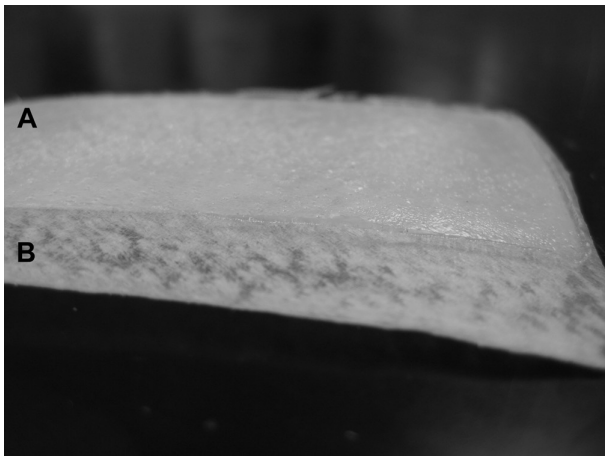

Figure 3. Photograph of adhesive film (3×8 cm) coated on a 6×8 cm biologic scaffold. **A** and **B** indicate adhesive-coated and uncoated regions, respectively.

pericardium). For both lap shear and burst strength adhesion tests (**Figures 4** and **5**, respectively), both **Medhesive-054** and **Medhesive-096** significantly outperformed the fibrin glue, Tisseel. Additionally, both **Medhesive-054** (615 ± 151 mm Hg) and **Medhesive-096** (526 ± 49 mm Hg), were able to withstand pressures that were well above reported physiological intra-abdominal pressures (64–252 mm Hg),[7] demonstrating that the bioadhesive constructs can potentially be used in hernia repair. Although Dermabond exhibited the highest shear strength, cyanoacrylate-adhered meshes were reported to have reduced tissue integration combined with a pronounced inflammatory response.[8] Additionally, cyanoacrylate adhesive significantly reduced the elasticity of the mesh and abdominal wall, and impaired the biomechanical performance of the re-

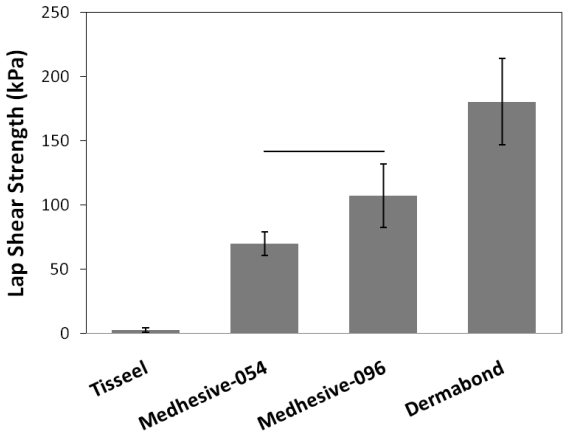

Figure 4. Maximum shear adhesive strength for adhesive joints formed using adhesive-coated bovine pericardium. Solid line represents statistical equivalence ($p > 0.05$).

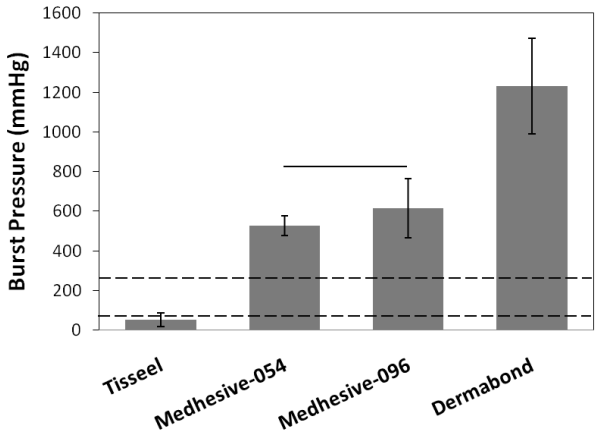

Figure 5. Pressure required to burst through adhesive joint sealed with adhesive-coated bovine pericardium. Dashed lines represent reported abdominal pressure range. Solid line represents statistical equivalence ($p > 0.05$).

pair. Due to the release of toxic degradation products (formaldehyde), cyanoacrylates are not approved for general internal applications in the US.[9, 10]

In summary, we combined a novel polymer design, biomimetic approach and biofunctional materials to address a substantial clinical need. Two new adhesive polymers were synthesized and coated onto a biologic mesh, which can potentially simplify hernia surgical repair procedures while reducing persistent patient discomfort associated with current mesh fixation methods. With further development, a pre-coated bioadhesive mesh may represent a new strategy to simplify soft tissue repair while eliminating chronic pain associated with currently available mesh materials and fixation methods.

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