Wounds are created in soft and hard tissue through surgery or disease. As the wound heals, the tissue is held in place using sutures or staples for soft tissue or plates, pins, or screws for hard tissues. These fixation methods inherently damage the surrounding healthy tissue. Surgical adhesives are a non-damaging alternative to these methods. In order to be effective, surgical adhesives must be biocompatible, adhere strongly in a moist environment, and have mechanical properties similar to those of the native tissue.

To address the design criteria for surgical adhesives, we look to nature to find inspiration from compounds that provide these properties. Mussels use catechol-based molecules to adhere to surfaces in wet and turbulent environments. Incorporating catechols into polymer systems can provide adhesion even in moist biological environments. Mimics of elastomeric proteins from soft tissue can be used as backbones for soft and flexible adhesive systems. In particular, elastin-inspired proteins have a well-defined modular sequence that allows for a range of design choices. In this work, we explored the behavior of elastin- and mussel-inspired natural and synthetic polymers in biologically relevant environments.

First, the cytocompatibility of a catechol-containing poly(lactic acid) (cPLA) hard tissue adhesive was studied. The cPLA polymer was reacted with iron- or periodate-based crosslinkers and compared to PLA. Fibroblasts grown directly on cPLA or cultured with leachate from cPLA had high viability but slower growth than cells on PLA. The periodate crosslinker was significantly cytotoxic, and cells grown on cPLA crosslinked with periodate had reduced metabolism and slowed growth. Cells grown on or in leachate from iron-crosslinked cPLA had similar viability, metabolism, and growth to cells on or in leachate from cPLA. The iron-crosslinked cPLA is a promising cytocompatible adhesive for hard tissue applications.

Second, two elastin-like proteins (ELP) were developed that had pH-sensitive properties in solution and when crosslinked into hydrogels. Both ELPs had a large number of ionizable tyrosine and lysine residues, and one design also had a large number of ionizable histidine and aspartic acid residues. The stiffness of the hydrogels was maximized at pH values near the isoelectric point of the protein. The stoichometric ratio of crosslinker used affected hydrogel stiffness but did not significantly alter the pH-sensitivity of the gel. The crosslinked gel shrank when swelled at physiological pH. The pH-sensitive mechanical properties of hydrogels made from the two ELPs did not vary significantly. The tyrosine and lysine residues in one ELP were also chemically blocked through acetylation to lower the isolectric point of the protein. The acetylated hydrogels had maximum stiffness at a pH near the isoelectric point of the acetylated ELP. The stiffness of both the native and acetylated gels were within the range of soft tissue. Through a combination of crosslinker ratio and chemical modification, the pH-responsive properties of the elastin-inspired hydrogels could be tuned.

Finally, adhesive proteins were created that were inspired by both elastin and mussels. An ELP was modified to include catechol groups (mELP). The ELP and mELP were optimized for adhesive use in a soft tissue system. A warm and humid environment was used to study the adhesion of these proteins on pig skin. Iron and (hydroxymethyl)phosphine crosslinkers increased the adhesive strength of both proteins, and periodate increased the adhesive strength of mELP. The adhesive strengths of the proteins were maximized when mELP was mixed with iron or when either protein were mixed with (hydroxymethyl)phosphine crosslinkers. These maximized adhesives were 12-17 times stronger than a commercially available sealant. In addition, the iron and mELP adhesive formulation achieved high

adhesive strengths even when cured for only ten minutes. This adhesive formula shows promise for adhesive applications on soft tissue.