Tape-Based Tissue Adhesives: Inspiration From Nature

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The thousands of papers dedicated to tissue adhesives in both clinical and non-clinical journals demonstrate significant scientific interest in defining the mechanisms of tissue adhesion and illustrate the clinical demand for more effective adhesives. Of significant importance, the generation of adhesives for internal applications presents considerable regulatory and functional challenges compared to topical adhesives, as they cannot be easily monitored, and thus must achieve strong adhesion to a wet surface without the use of wraps (*i.e.*, gauze or tensor bandages) to protect and keep the adhesive in place.

In particular, there is a significant medical need for tough, biodegradable polymer adhesives for closing and sealing wounds or incisions that can accommodate various mechanical deformations while remaining strongly attached to the underlying tissue[1]. These materials would be particularly useful as replacement or support for sutures that are sometimes difficult to manipulate during laparoscopic or microscopic procedures, and/or could be used as patches to aid in hemostasis to improve the visibility of the operative field, or as drug delivery patches for internal use. The potential advantages of using these materials include reduction in operating time and tissue handling, and mitigation of surgical complications such as infection. Although numerous tissue adhesives exist, presently none of them can withstand high tensile strength or can be rapidly applied in a tape or sheet format that matches the compliance of underlying tissue with a programmable rate of degradation[1a, 2].

Ideally, a tissue adhesive should provide the following properties: 1) biocompatibility and biodegradability, 2) mechanical compliance with the underlying substrate (i.e. the tissue), 3) strong adhesion under wet conditions, 4) minimal inflammatory response, 5) the ability to form a watertight seal, and preferably, 6) the ability to direct the formation of reparative tissue during wound healing. However, a paradox exists: namely, strong tissue adhesion typically requires highly reactive chemistry that also promotes an intense inflammatory response. This significantly limits the potential medical applications of strongly adherent tissue glues.

Gecko-Inspired Medical Adhesives

We approached these design constraints by utilizing a novel polymer poly (glycercol sebacic acid acrylate) (PGSA) and modifying the surface to mimic the nanotopography of gecko feet that allows attachment to vertical surfaces. The mechanism of gecko adhesion was recently elucidated; [3] nearly two millennia after Aristotle first reported it. Each gecko foot is covered with as many as 500,000 fine hairs, each tipped with hundreds of projections known as spatulae. Since each spatula's length is on the order of 200-500 nm, it is possible to mimic these adhesive regions using nano/micro scale approaches. However, translation of existing gecko-inspired adhesives for medical applications is

complex, as multiple parameters must be optimized, including: biocompatibility, biodegradation, strong adhesive tissue bonding, as well as compliance and conformability to tissue surfaces. Ideally these adhesives would also have the ability to deliver drugs or growth factors to promote healing.

Intuitively, it would seem counterproductive to break up the footpad interface into patterns as this patterning reduces the contact area. Although the contact area is reduced for a patterned interface, the total contact line or perimeter, as defined by the sum contribution for each setae, can be significantly greater than that of a smooth interface provided that the patterns are properly designed. As demonstrated by previous researchers, the contact line per interfacial area is a critical length scale to maximize in order to enhance adhesion. For example, for a rectangular piece of scotch tape, it is more difficult to peel the tape lengthwise versus widthwise, while the area remains constant (the difference between the two is the length of the contact line that is being peeled at the interface). This control has been demonstrated in nature. Specifically, setae density becomes greater as the mass of the animal increases[4], in other words, the setae diameter decreases as the mass of the animal increases. This simultaneous reduction in setae diameter and an associated increase in setae density result in an enhancement in total contact line per contact area.

Previously, Chan and co-workers have identified this mechanism as "contact line splitting" and discussed the relevance of this mechanism in relation to surface chemistry of the interface of interest [5]. Since the mechanism is based on geometry, this mechanism can be applied to a variety of interfaces assuming that the pattern size-scale is commensurate with the materials-defined length scale. For example, for the gecko and many insects, the other contributions to adhesion are van der Waals attraction and capillary forces, which are on the order of 1-10 N/cm^2, and are typical values for most non-specific interfaces[6]. It is the coupling of these interactions with the mechanism of contact line splitting provided by the setae pattern geometry that affords the gecko with strong adhesion. Additionally, the hierarchical design of setae, from the macro to the nanoscale, increases the mechanical compliance of the footpad and permits the gecko foot to conform and adhere to a variety of rough terrain, maximizing interfacial contact to enhance both contact line splitting and van der waals/capillary force mechanisms of adhesion. Based on this understanding, synthetic adhesives have been designed without a chemical "glue", through utilizing a fibrillar design that enhances adhesion by the mechanism of contact line splitting and increasing mechanical compliance to improve conformability to surfaces with a variety of roughness.

Synthetic gecko patterns have been fabricated in a variety of polymers through many different top-down fabrication techniques including contact lithography[7], nanodrawing[8], photolithography followed by etching[9], micro/nano molding[10] or nanocasting using vertically aligned multiwalled carbon nanotubes[11]. The merit of top-down approaches is the inherent advantage to generate patterned surfaces with highly-defined feature length-scales. In the application of these approaches for developing tissue adhesives, such systems are particularly attractive since they are capable of generating solid-state devices that can be placed with greater accuracy (i.e. glues may leak into unwanted regions). Additionally, the fibrillar design of gecko footpad can be mimicked in polymeric

materials to enhance mechanical compliance for the interface and therefore provides good conformability to a variety of surfaces. This enhancement in compliance can improve contact with surfaces having various degrees of small-scale roughness and large-scale curvature.

Despite the growing interest in developing gecko-inspired adhesives, the adhesive strength of single gecko setae to wet surfaces has showed that the adhesive strength of the gecko surfaces depends on the hydrophobic and hydrophilic nature of substrates, and the wet adhesion strength is significantly lower than dry adhesion[7, 12]. This observation is not surprising, given the nature of the adhesive contributions of the setae interface (van der Waals and capillary forces) and their likely interaction with water rather than the substrate of interest (or blood in the case of medical adhesives). Furthermore, only a single adhesive has been optimized for a wet tissue-like environment. Specifically, important work from P. Messersmith's group has led to synthetic gecko adhesive that is effective under water with reversible, non-covalent bonding to inorganic surfaces[13]. The bond strengths of gecko-inspired adhesives are typically evaluated through sub-micron atomic force microscopy measurements which provide evidence for adhesion strength of the different pillar geometries[13]. However, it is difficult to accurately predict large area adhesion strength of patterns from single pillar measurements or functional utility if the adhesion interactions of individual pillars are coupled[13]. Unlike the gecko-inspired dry adhesives created to date (and the reversible adhesive mechanism the gecko uses for locomotion), adhesives for medical applications require strong irreversible bonds to organic substrates to avoid disruption by the movement of underlying or nearby tissues. Thus it may be more appropriate to consider a gecko-"inspired" medical adhesive than a gecko 'mimicking' adhesive, given the need for additional mechanisms that are not required for gecko adhesion to dry surfaces.

Getting back to the paradox described above, where typically strong levels of adhesion to tissue require reactive chemistry, we postulated that a gecko-inspired nanostructured surface design could be used to increase the surface contact of the reactive adhesive interface with tissue. Our goal was to use this approach to reduce the reactivity of the chemistry required to achieve strong tissue bonding without promoting an intense inflammatory response. We also postulated that the patterned surface may be useful to enhance adhesion through mechanical interlocking with the underlying compliant tissue substrate.

To develop a general platform for biocompatible tissue adhesives that can be manufactured using a variety of materials (and can accommodate temperature-sensitive drugs for drug delivery applications), we developed a materials and fabrication approach that avoids high processing temperatures or harsh chemical modifications[14]. Specifically, we have developed a biomedical adhesive that utilizes pattern morphology and specific covalent chemistry to enhance adhesion to a tissue interface, along with tailoring the specific bulk and surface material chemistry to facilitate biocompatibility and biodegradability. For the requirements of biocompatibility and biodegradability, we evaluated a candidate biodegradable elastomer that we developed[15]. The elastomer is a ephotocrosslinkable biodegradable elastomer poly(glycerol sebacate acrylate) (PGSA)

that can be cured rapidly (within minutes) at ambient temperatures to form polymeric networks with robust mechanical properties and favorable biocompatibility[16] both *in vitro* and *in vivo*. Tensile tests show control of the Young's modulus between 0.05 to 1.38 MPa, ultimate strength from 0.05 to 0.50 MPa and elongation at break between 42 and 189%. The mechanical properties of the elastomer can be tailored to match the properties of soft tissue and demonstrate the potential application of our materials, for example, to the peripheral nerve, which has a Young's modulus of approximately 0.45 MPa [17], and the thoracic aorta, which has a Young's modulus of 0.53 MPa [18].

Importantly, to promote strong adhesion to tissue (under wet conditions), additional mechanisms that are not utilized by the gecko are required[13]. As a first demonstration for creating gecko-inspired tissue adhesives, this PGSA elastomer was further modified to incorporate a thin, tissue reactive, biocompatible surface coating. Tissue adhesion was optimized by utilizing surface morphology, specifically, by varying the dimensions of the nano-scale pillars including the ratio of tip diameter to pitch and the ratio of tip diameter to base diameter. Coating these nanomolded pillars of biodegradable elastomers with a thin layer of oxidized dextran significantly increased the interfacial adhesion strength on porcine intestine tissue *in vitro* and in the rat abdominal subfascial *in vivo* environment. The oxidized dextran served as model tissue glue that enabled us to control the reactivity towards the tissue substrate through simply altering the degree of oxidation. *In vivo* characterization of implanted adhesive-tapes demonstrated minimal inflammatory response, and functional testing against tissue showed maximum shear adhesion strength on the order of 1 N/cm^2 through contributions of both morphology and chemistry. To achieve this we utilized a degree of oxidation of 14% and believe that there is significant room to increase the reactivity of the glue without compromising the minimal inflammatory response that we observed. To translate these materials to medical applications, adhesion strengths on the order of 5-15 N/cm^2 are required. We are in the process of enhancing the utility of our existing adhesives through optimizing the chemical crosslinking via reactivity of the glue, and through optimizing mechanical interlocking with tissue through use of both micrometer and nanometer hierarchical morphology.

This gecko-inspired medical adhesive approach may have potential applications for sealing wounds and for replacement or augmentation of sutures or staples. Through combined morphology and chemistry effects, we have developed a general materials paradigm for a tissue adhesive. This tape-based tissue adhesive platform may have application in medical therapies ranging from suture/staple replacements/supplements, waterproof sealants for hollow organ anastomoses, air-tight seals to prevent air leaks following lung resection procedures, mesh grafts to treat hernias, ulcers, and burns, and haemostatic wound dressings.

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