Polysaccharide-Based Tissue Adhesives for Closure of Surgical Wounds

Sujata K. Bhatia, **Samuel D. Arthur**, **H. Keith Chenault**, **Garret D. Figuly**, **Sharon L. Haynie** and **George K. Kodokian**, Materials Science and Engineering, DuPont Central Research & Development, Experimental Station, E328, P.O. Box 80328, Wilmington, DE 19880-0328

Reliable closure of surgical wounds remains one of the great unsolved challenges of clinical medicine. Despite refinements in suturing and stapling techniques for wound closure, physicians continue to struggle with the problem of leakage from internal wounds. For example, gastrointestinal wound closures have a leakage rate of 3-15%, resulting in dire clinical consequences (infection, hemorrhage, etc.) and a 2-3% mortality rate for patients undergoing gastrointestinal surgeries. There is great demand for tissue adhesives to augment or replace sutures and staples for internal wound repair.

Several types of tissue adhesives have been developed and commercialized, but these adhesives have generally not been successful due to biocompatibility or performance problems; for example, cyanoacrylate-based adhesives release toxic degradation products, and fibrin sealants exhibit poor adhesion and pose a risk of viral infection. We have developed the ActaMax™ sealant family of hydrogel tissue adhesives, formed by reacting an oxidized polysaccharide with a water-dispersable multi-arm polyether amine. Specifically, we have developed tissue adhesives composed of two components: dextran aldehyde and multi-arm PEG amine, which undergo a Schiff base reaction to form a crosslinked hydrogel (Figure 1). This two-component tissue adhesive system crosslinks in water, cures rapidly (<1 min) at room temperature, adheres to moist tissue, and degrades hydrolytically. The adhesive is non-cytotoxic to fibroblasts, and does not induce inflammatory activation of macrophages. The adhesive is also advantageous in that it does not pose a risk of viral contamination, and is based on polymers with a long history of clinical use as plasma expanders (dextran) and drug delivery agents (PEG).

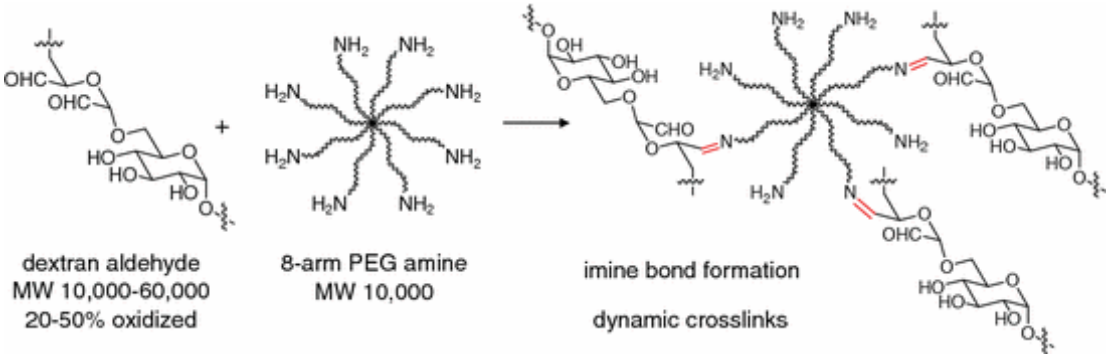

Figure 1. Foundation chemistry for polysaccharide-based tissue adhesives. The oxidized polysaccharide dextran aldehyde reacts with an 8-arm star PEG amine to form a crosslinked hydrogel network.

The foundation chemistry based on dextran aldehyde and PEG-amine allows fine-tuning of sealant properties to meet surgeon needs for specific clinical targets. ActaMax™ sealant demonstrates strong tissue adhesion (as strong as or better than that of all current commercial internal sealants in a burst pressure test). Additionally, ActaMax™ sealant demonstrates tissue adhesion that is substantially stronger than that of fibrin, the leading incumbent sealant. Our sealant is well-tolerated in short-term and long-term intestinal painting studies; the sealant remains on the target site with no injury to adjacent tissue. A multi-organ scouting study demonstrated that ActaMax™ tissue adhesive was efficacious in a variety of clinical procedures (Figure 2) including aortic graft, aortic puncture, aortic anastomosis, graft puncture, cardiac painting, cardiac puncture, coronary artery incision, intestinal anastomosis, liver lobectomy, splenectomy, lung lobectomy, and hernia patch attachment. ActaMax™ tissue sealant is a versatile bioadhesive platform that can be utilized in multiple surgical applications.

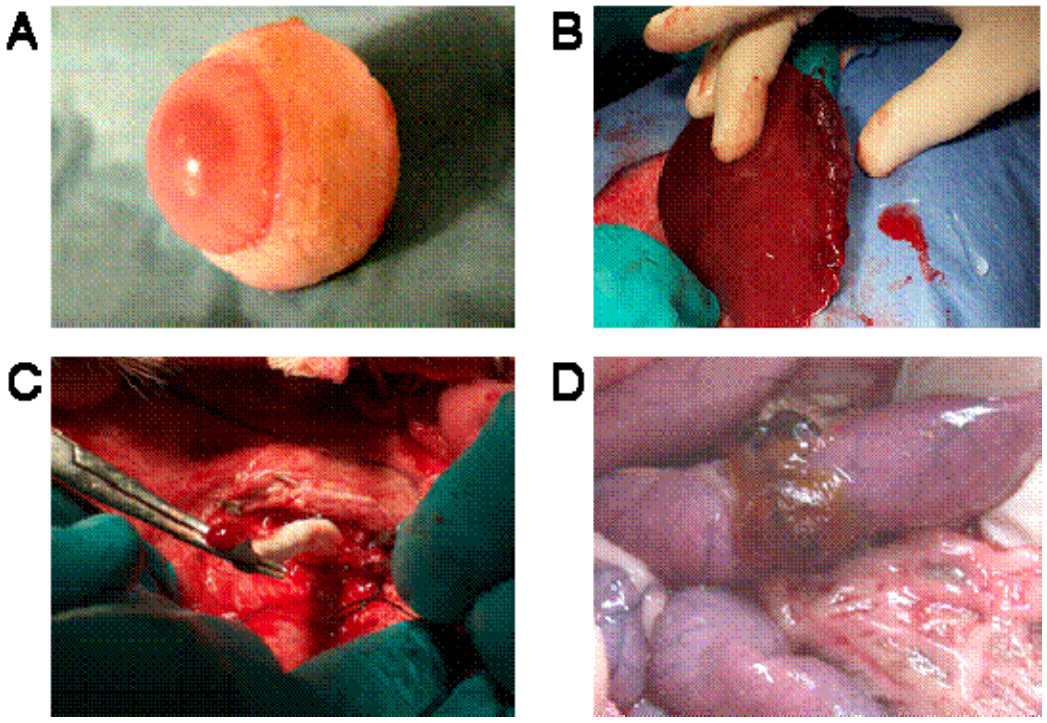

Figure 2. Use of ActaMax™ tissue adhesive for (A) cataract incision closure; (B) hemostasis following liver lobectomy; (C) vascular anastomosis closure; and (D) gastrointestinal anastomosis closure.

References:

S. K. Bhatia, S. D. Arthur, H. K. Chenault, G. K. Kodokian, “Interactions of Polysaccharide-Based Tissue Adhesives with Clinically Relevant Macrophage and Fibroblast Cell Lines,” *Biotechnology Letters* (2007), 29:1645-1649.

S. K. Bhatia, S. D. Arthur, H. K. Chenault, G. D. Figuly, G. K. Kodokian, “Polysaccharide-Based Tissue Adhesives for Sealing Corneal Incisions,” *Current Eye Research* (2007), 32:1045-1050.