Responsive and Chemoselective Tissue-Specific Adhesive Materials

Natalie Artzi, Nuria Oliva[a,b], Sagi Shitreet[a,c], Maria Carcole[a,b] David Alperstein[c], and Elazer R. Edelman[a,d]

From the [a]Harvard–MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, [b]Department of Chemistry, Institut Quimic de Sarria`, Universitat Ramon Llull, Barcelona, Spain 08017; [c]Ort Braude College, Karmiel, Israel 21982 and [d]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.

Statement of Purpose: Nature regulates tissue-tissue interfacial stress with subtle variations in surface chemistry. We examined and used these changes to help understand tissue-material interactions and to develop tissue-specific adhesives. Chemical differences drive gastrointestinal (GI) tract physiology. The spectrum of contractility and persitalsis, pH and surface chemistry across the GI bed allow for a profound modulation of nutrition, inflammation, infection etc. We hypothesized that within regions of the small intestine, variation in chemical composition supports diverse functionality and could be harnessed for specific adhesion. We used natural GI surface chemistry to create adhesive materials that interact differentially with specific tissues to create more effective GI wall sealants. Leakage of gut content is a frequent surgical complication that can result in local infection and systemic sepsis, peritonitis and often the need for reoperation.

We designed tissue responsive adhesive materials by matching material and tissue properties. We used aldehyde-amine chemistry to determine if alterations in tissue surfaces (amine density in duodenum, jejunum and ileum) could affect interactions with materials of varied (aldehyde content and density) composition. A two component material based on dextran aldehyde and dendrimer amine provides cohesive gel through aldehyde-amine crosslinking, and adhesive interface by dextran aldehyde selective reaction with tissue amines. Material amines absorb excess non-reactive aldehydes and thus prevent toxicity.

Methods: Adhesive mechanics to excised rat tissues (duodenum, ileum and jejunum) were measured by uniaxial mechanical testing of tissue-material interfaces. Fluorescently labeled dendrimer:dextran was applied to tissues stained with propidium iodide to identify cellular structures against the fluorescent material background (Fig. 1), and quantified using digital image analysis. The aldehyde affinity of various soft tissues was determined through quantification of the conjugation of aldehyde-coated fluorescent microspheres to soft tissue surfaces (Fig. 1). *In vivo* biocompatibility was examined at 7 and 30 days after subcutaneous implantation and assessed for inflammatory response. Molecular simulation and pair correlation function was used to determine internal reactions.

Results: Adhesive strength varied dramatically with material chemistry and is tissue-specific. The nature of the tissue:material interface changed when the same material was applied to the three small intestinal regions (Figure 1). The interfacial regime is determined by the intermediate material structure resulting from concurrent dextran aldehyde reactivity with dendrimer and tissue amines. The morphology of the adhesive regime varied with tissue and reflected the strength of adhesion; appearing discontinuous on the duodenum and jejunum, and continuous and dense over ileum. Changes in material density at the interface on a micro-scale correlated with macro scale measurements of adhesion strength using tensile stress. These changes also correlated with variation in amine density on the three tissue surfaces measured by the affinity of aldehyde-coated fluorescent microspheres to these tissues, with ileum tissue possessing the greatest apparent aldehyde affinity (Fig 1). These data support the notion that both tissue and material functional groups influence aldehyde-mediated adhesive interactions, providing a functional basis for tissue-specific sealant design. The tissue response to subcutaneous material implants was used to evaluate the *in vivo* biocompatibility of dendrimer:dextran materials and the influence of material aldehyde content on tissue response. Materials were implanted into a subcutaneous pocket in mice survived for 7 or 30 days. Tissue-specific adhesive materials based on star PEG:dextran constructs with varied aldehyde content show aldehyde-dependant toxicity[1]. Substitution of star PEG by dendritic molecule imparts negligible toxicity irrespective of aldehyde content in 3T3 fibroblasts in vitro, and in vivo. Dendritic molecules whose size and functionality can be controlled on the nanoscale allows for better dendrimer-dextran reaction yield, resulting in internal consumption of non-reactive aldehydes which minimizes toxicity.

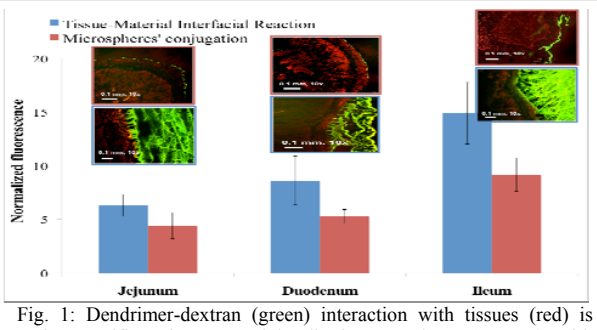

Fig. 1: Dendrimer-dextran (green) interaction with tissues (red) is region-specific. Tissue-material adhesion correlates (R=0.99) with microsphere conjugation to tissues representing tissue amine density.

Conclusions: Current adhesive materials force a choice between adhesion strength and biocompatibility, and for all materials make no distinction on the basis of target tissue. We examined tissue:material interactions and mimicking nature designed materials whose adhesion was titrated to environment. Amine groups are ubiquitous on tissues and their density varies from tissue to tissue. By providing a chemical key in the form of tethered aldehydes for specific tissue locks (tissue amines), we modulated adhesion while maintaining biocompatibility. The concepts and tools employed can help create and evaluate a family of selective biomaterials for a range of applications and clinical needs.

References:

[1] Artzi N, Shazly T, Baker AB, Bon A, Edelman ER. Adv mat 4;21(32-33):3399-403.