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Title: The intimate relationships between tissue surface barriers and their saline environments create a therapeutic substrate for the surgical rescue of diseased tissue: a molecular energy conversion loop designed for surgical work.

Significant treatment advances for mammalian disease have originated from understanding tissue characteristics that relate the practitioner's ability to distinguish diseased tissue from normal tissue as correlated to biophysical mechanisms that contribute to disease burden. As an example, the fundamental cancer observation that abnormal cell growth kinetics could serve as a therapeutic substrate was required to enable substantial disease burden mitigation. Rather than resection techniques based on imperfect visual-tactile cues designed to unencumber contiguous healthy tissue function, selective targeting diseased tissue *traits* protects against the iatrogenic collateral damage of over-resection which can further impair contiguous healthy tissue from retaining and displaying differentiated phenotypes.

Pioneering research into tissue-surface based medical conditions has produced a technological breakthrough founded on this fundamental therapeutic principle of targeting diseased tissue traits to avoid over-resection and has begun to revolutionize treatment for this complex disease category; a category that constitutes a large portion of most all medical disciplines. Diseased tissue resection at these locales requires precision because tissue surfaces display the shared cell-to-matrix feature of structural stratification whereby volumetric or functional over-resection corrupts tissue elements, including intrinsic homeostatic and repair mechanisms, concentrated within the superficial layers at and around these lesions. For many conditions, this imprecision significantly provokes disease progression by eliminating contiguous tissue phenotypes and expanding lesion size toward unsalvageability. The ability to resect diseased tissue precisely, unencumbering contiguous healthy tissue function without iatrogenic impairment of its differentiated phenotype, is the necessary prerequisite to mitigate the disease burden of tissue-surface based medical conditions. This technological ability has opened a new scientific era of early intervention by enabling the therapeutic enrollment of contiguous tissue *healing* phenotypes that make lesion *reversibility* possible. Early intervention becomes more than an effort to stabilize these lesions into a transient palliative remission indifferent to resection margin accuracy; it becomes a *tissue rescue* harnessing features unique to tissue surfaces.

Tissue surfaces display a superficial-level healing phenotype because this region is required to interact most intimately with repetitive external tissue-specific stressors; without these attributes, tissue integrity would be rapidly lost to environmental perturbation. Diseased tissue surfaces manifest as forces or processes overload tissue capacity to maintain integrity; untreated, this tissue burden can ultimately lead to symptoms of disease progression. While the topographic loss of water-structured surface barrier regimes and the collagen failure of backup layered cleavage planes occur during physiologic loading, these lesions are generally self-repaired by intrinsic tissue assembly mechanisms. Although the factors by which *in vivo* self-repair becomes insufficient are complex and tissue-specific, lesions that remain reversible require targeted resection of the diseased tissue that serves as a biophysical irritant impeding regional tissue organization and assembly. This irritant changes the tissue-surface microenvironment, impeding reconstitution of damaged surface barrier regimes and altering chemomechanotransductive gene expression in contiguous tissue, progressively edging reversible lesions toward failed differentiated homeostatic resistance capacity and an unsalvageable state characterized by non-reversible phenotypic alterations.

Even though the consequences of over-resection for tissue-surface based medical conditions include disease progression, early morphologic surface changes remain an attractive therapeutic target as this setting retains the elements *in situ* for normal homeostasis and repair. Because of the resection precision required (μm - nm scale) and since tissue surfaces reside within a saline milieu, maintaining cell viability and a differentiated phenotype around a lesion site stabilized relative to its perturbation specificity requires knowledge of saline-to-tissue interfaces during disease-related changes in tissue structure-function. Accordingly, the mechanisms by which organisms construct and utilize saline charge barriers provide a therapeutic substrate at the requisite *scale* from which interventions can be devised that do not injure this barrier at normal tissue surfaces yet take advantage of its disruption at diseased tissue sites. This scale-appropriate trait-targeting challenge has been met by technology that physiochemically loads tissue surfaces in an *irrigant* manner based upon germ layer independent but charge dependent mechanisms, preparing these surfaces for selective disease-specific tissue resection systems. Concurrent with this physiochemical loading of tissue surfaces (physiochemical scalpel) are methods designed to accelerate lesion recovery by inducing advantageous cell-to-matrix modifications and stimulating differentiated tissue assembly repair functions within the retained contiguous tissue.

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Dr. Augé is a Diplomat of the American Board of Orthopaedic Surgery and Fellow of the American Academy of Orthopaedic Surgeons specializing in knee and shoulder care. He obtained his Doctorate of Medicine from Northwestern University Medical School and Bachelor of Science Cum Laude from Loyola University of Chicago focusing upon molecular genetics, chemistry, and philosophy. Dr. Augé is internationally recognized through his research, novel surgical techniques, and medical inventions being used today by many surgeons in many countries. He is currently serving as Chief Clinical Officer for NuOrtho Surgical, Inc. to advance the science of tissue preservation in order to reduce human disease burden.