

# World DNA and Genome Day

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**Title: Addressing the large world-wide disease burden of osteoarthritis through targeted induction of biosynthetic gene expression: early intervention engineered to reverse articular cartilage lesions.**

Osteoarthritis results in whole joint-organ disease persuaded by articular cartilage integrity failure. Because damaged cartilage serves as a biologic-mechanical irritant that causes symptoms and advances disease, treatment efforts designed for its removal remain an intuitive and important focus intended to maintain articular cartilage integrity and alleviate disease burden. Yet, lesion stabilization has been constrained by surgical interventions resulting in volumetric or functional over-resection that expand lesion size and provoke disease progression. Despite past attempts to minimize over-resection, only recently has its elimination been enabled. Transformative discoveries of this magnitude are often initially plagued by doubts about their practical value; for osteoarthritis, these value assessments are additionally confounded by articular cartilage's reputation as a tissue type with a perceived poor healing capacity, even though this *reputation* may be largely due to the retention of damaged tissue as a biophysical irritant in the context of the historical inability to avoid scale-appropriate over-resection.

Articular cartilage is a highly differentiated and stratified tissue that retains a large portion of its adult healing phenotype at its surfaces. Because cartilage lesions can progress slowly, reflecting retained contiguous differentiated homeostatic resistance capacity against the degree to which diseased tissue burden becomes overwhelming, eliminating over-resection is often viewed as a *tissue rescue* designed to unencumber contiguous tissue function and minimize downstream morbidity. To preserve superficial healing properties heretofore fully eliminated as collateral damage, surgical resection requires " $\mu\text{m}$  level" precision; further, normal tissue surface barrier regimes are structured at the "nm level", presenting a challenging venue to guard against iatrogenic injury. Consequently, surgical precision necessitates a unique "physicochemical scalpel" technological approach that includes replacing traditional surgical visual-tactile cues with treatment endpoints translated from comparative explant microhistology. Although treatment endpoint cue evolution can influence new technology adoption rates, cartilage management education toward a *cognitive map* is being encouraged by socioeconomic pressures supportive of over-resection as unnecessary, harmful, and liability-laden. As it is difficult to imagine informed patients forgoing the opportunity to preserve their tissue longer, either by replacing cartilage lesions with larger ones or simply waiting for diseased tissue to overwhelm contiguous differentiated homeostatic resistance capacity, the rapidly emergent obsolescence of over-resection also reflects consumer pressures.

The benefits of tissue rescue to unencumber contiguous tissue function are considerable; yet prior to surmounting the over-resection treatment barrier that enabled tissue rescue, lesion *reversibility* was clinically inaccessible. Since contiguous differentiated homeostatic resistance capacity can give way to the burden of damaged cartilage, tissue rescue seeks not only to unencumber contiguous tissue, but also to permit-enroll its intrinsic homeostatic and repair capabilities to avoid irreversible phenotypic alteration. Uniquely, articular cartilage's superficial zone reveals: molecular production specificity like clusterin, versican, lubricin, phospholipid, and contractile actin isoforms; chondrocyte spatial reorganization in response to focal partial-thickness lesions; control of zonal reorganization; appositional growth; chondroproliferation; chondrocyte colony formation; and a side population source of mesenchymal progenitor cells that express stem cell markers, progenitor cell signaling mediators, and monolayer expansion behavior while maintaining a chondrogenic phenotype. Because articular chondrocytes display significant phenotypic plasticity and high anabolic capacity, improving their environment by targeted diseased tissue resection is an effective means toward stabilizing contiguous chondrogenic phenotype(s), including the interruption of early phenotypic disease adaptations-alterations. As reversibility for some lesions may require phenotypic shifts, even a redifferentiation of osteoarthritic chondrocytes such as that induced by physiologic loading a healthier site, an important early post-treatment therapeutic desire is transient upregulation of focal chondrocyte biosynthetic activity reflective of differentiated tissue assembly repair mechanisms.

Inducing *in situ*, targeted, appropriate, and differentiated biosynthetic cellular function within contiguous tissue subadjacent to diseased locales, thereby recruiting local chondrocytes to aid lesion recovery, requires the ability to access genomic control mechanisms that govern tissue assembly and display promoter domain-segment threshold responsiveness slightly above micro-environmental perturbation noise. As such, *in vivo* transcription initiation technology based upon *charge/mass ratio* dependent acceleration characterizes a revolution of vision and enabled possibility for cartilage. Because of the enormous health gains to be realized by reducing osteoarthritis disease burden, the goal of unencumbered contiguous tissue *and* lesion reversibility becomes an effort difficult to ignore, despite cartilage lesion heterogeneity that may require nuanced device design.

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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.

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