Injectable, Biofunctionalized, Tissue-Mimicking Collagen for Bone Regeneration

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A. Overview/Abstract

Bone possesses an innate capacity to self-heal; however, certain fractures fail to mend in the expected timeframe—resulting in a nonunion that requires additional clinical intervention. When bone loss is extensive—as in tumor resection or high-energy trauma—these critical-sized defects often cannot fully regenerate via the body's natural processes. Patients with nonunion or critical-sized defects can face lengthy rehabilitation, elevated healthcare costs, and an increased risk of complications, underscoring the need for novel regenerative strategies. Although autologous bone grafting remains the gold-standard treatment for large defects, it is limited by donor-site morbidity, inadequate graft volume, and inconsistent healing outcomes. Allogeneic grafts and metal fixations introduce additional hurdles such as immune responses, infection risks, and suboptimal integration. Tissue engineering approaches have therefore gained traction, employing biomaterial scaffolds combined with stem cells and growth factors to form a three-dimensional, pro-regenerative microenvironment.

Recent attention has turned to porous hydrogels and injectable microgels. These platforms can be administered via minimally invasive procedures, adapt to irregular shapes, and be engineered for local release of angiogenic and osteogenic cues. Yet, despite these advantages, current microgel systems rely predominantly on synthetic polymers that lack intrinsic osteoconductive properties and often present close-packed, granular architectures that do not replicate the fibrous bone extracellular matrix. The complexity of microgel fabrication, along with their limited capacity to emulate native tissue organization and composition, highlights the pressing need for more biomimetic yet user-friendly scaffolds.

To address these challenges, we have developed a novel tissue-engineered collagen scaffold designed to more closely mimic the structure and composition of native bone ECM. This method build upon our previously established technique termed TRACE (TRACE (Tunable Rapid Assembly of Collagenous Elements), which assembles Type I collagen into continuous, porous bundles that support cell infiltration and nutrient transport. Unlike synthetic microgels, these collagen bundles form a fibrous, physiologically relevant network that aligns well with the natural architecture of human tissues. Collagen's low immunogenicity, inherent cell-binding motifs, and osteoconductive properties further enhance its suitability for bone tissue engineering. Our in vitro data have demonstrated endothelial cells form well-developed vascular networks within the collagen bundles, while pilot animal studies showed that the scaffold supports robust host cell infiltration in vivo.

Building on these promising outcomes, our overarching goal is to optimize and validate this collagen-based injectable scaffold for clinically relevant bone defect repair. First, we will refine this scaffold to be both shear-thinning and paste-like, enabling injection through a syringe or cannula. We will then adopt mild crosslinking strategies that allow stable integration of pro-angiogenic (VEGF) and pro-osteogenic (BMP-2) factors and consistent growth factor release. Next, we will systematically evaluate angiogenesis and bone formation in vitro, measuring cell infiltration, microvessel development, and osteogenic differentiation. Finally, we will perform pilot in vivo studies using rodent models of critical-sized bone defects, assessing neovascularization, new bone mass, and mechanical integrity over time. This research will generate pivotal data for future large-animal studies and federal funding proposals, ultimately guiding the translation of our technology into a minimally invasive, biomimetic solution for patients afflicted by complex fractures and nonunion injuries.