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COMMENTARY

From platelet-rich plasma to personalized implants: A commentary on "3D-printed vascularized biofunctional scaffolds for bone regeneration"

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Abstract

Bone defects require simultaneous vascularization and sustained osteoinductive signaling to achieve functional repair—two goals that conventional grafts frequently fail to meet. The study under discussion explores the use of platelet-rich plasma (PRP) as a natural, multi-factor source, embedded in a methacrylated gelatin/methacrylated alginate (GA) hydrogel and modified with laponite (Lap) to regulate growth factor release. The resulting PRP–GA@Lap bioink is co-printed with polycaprolactone to create structurally reinforced scaffolds. *In vitro*, PRP–GA@Lap stimulated bone marrow mesenchymal stem cell proliferation, migration, and osteogenic differentiation, enhanced endothelial tube formation, and polarized macrophages toward a pro-regenerative M2 phenotype. *In vivo*, hybrid scaffolds accelerated vascular ingrowth and improved bone volume, mineral density, and defect integration in rat femoral condyles. By coupling biologically broad PRP signaling with engineered release kinetics and mechanical stability, this approach offers a clinically adaptable, patient-specific strategy for complex bone repair, with strong potential for personalized regenerative therapy.

Keywords: Bone regeneration; Immunomodulation; Laponite; Platelet-rich plasma; Three-dimensional printing; Vascularization

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1. Introduction

Critical-sized bone defects pose a considerable challenge in orthopedic, craniofacial, and reconstructive surgery.[1,2] These flaws, frequently arising from significant trauma, tumor excision, infection, or congenital abnormalities, surpass the bone's natural regeneration ability and necessitate surgical intervention.[3,4] The optimal treatment must address both the anatomical and biomechanical issues in the affected region while minimizing complications at the donor site, reducing immunological responses, and limiting the necessity for revision procedures.[5] Autologous bone grafting has traditionally been considered the gold standard; however, it has significant drawbacks, including restricted tissue availability, extended surgical time, ongoing donor site pain,

and variable resorption rates.[6] Allogeneic bone grafts and synthetic substitutes address particular challenges; even so, they often fail to attain long-term integration, primarily due to insufficient graft vascularization.

Vascularization is crucial for effective bone regeneration due to the metabolic demands of newly produced bone.[7] It necessitates the continuous provision of oxygen, nutrients, and osteoinductive signals, effectively eliminating waste products. In the absence of rapid neovascularization, implanted materials may undergo fibrosis or necrosis, resulting in inadequate healing and mechanical instability.[8] In instances with considerable inadequacies, the distance to the next capillary bed is frequently inadequate for effective diffusion to maintain cellular viability, highlighting the need to develop structures that facilitate vascular ingrowth. Platelet-rich plasma (PRP) contains a broad spectrum of growth factors—such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β)—that collectively promote angiogenesis, osteogenesis, and tissue remodeling.[9–11] However, when applied directly, PRP releases its factors rapidly, limiting its long-term regenerative effect. Recent advancements in tissue engineering have concentrated on amalgamating osteogenic and angiogenic signals into a unified therapeutic framework. Additive manufacturing, also known as three-dimensional (3D) printing, has emerged as an effective method for producing patient-specific scaffolds with very precise construction.[12–14] This approach enables exact regulation of pore size, porosity, interconnectivity, and mechanical properties, all critical for bone growth and vascular infiltration. Moreover, 3D printing enhances the spatial arrangement of bioactive molecules, enabling the fabrication of scaffolds that replicate the varied biological conditions essential for natural bone regeneration.

Cao *et al.*'s study on 3D-printed vascularized biofunctional scaffolds for bone regeneration efficiently demonstrates this technology.[15] They address this limitation by incorporating PRP into a methacrylated gelatin/methacrylated alginate (GA) hydrogel, further modified with the nanoclay laponite (Lap). Lap serves as a release modulator, binding growth factors electrostatically and extending their availability for up to two weeks. This PRP–GA@Lap bioink is co-printed with polycaprolactone (PCL) to create hybrid scaffolds that combine biological activity with structural stability. The authors hypothesize that this design will promote rapid vascular ingrowth, enhance bone marrow mesenchymal stem cell osteogenesis, and establish a pro-regenerative immune environment *in vivo*. This commentary will encapsulate the principal findings, examine the methodologies and implications, and discuss potential applications of this research in clinical practice.

2. Discussion

Incorporating Lap into PRP–GA hydrogel significantly altered the material's physical and biological performance. Adding Lap improved mechanical stiffness, reduced swelling, and slowed degradation, enabling the scaffold to maintain its form during early healing. Importantly, enzyme-linked immunosorbent assays confirmed that Lap extended the release of key PRP-derived growth factors—including VEGF, platelet-derived growth factor-BB, and TGF-β—from a rapid burst to a steady release profile lasting up to 14 days. This timing aligns well with the physiological sequence of fracture healing, in which angiogenic and osteogenic signals must persist during the early and mid-stage repair.

Bone marrow mesenchymal stem cells cultured on PRP–GA@Lap hydrogel showed increased proliferation and migration compared to PRP–GA and GA controls. Osteogenic differentiation was also enhanced, as evidenced by elevated alkaline phosphatase activity at day 5, upregulation of osteogenic markers (Runt-related transcription factor 2, osteocalcin), and greater mineralized matrix deposition at day 14. On the vascular side, human umbilical vein endothelial cells exposed to PRP–GA@Lap-conditioned media displayed robust proliferation, chemotaxis, and tube formation—indicating that the sustained release of PRP factors effectively supports angiogenesis. Macrophage polarization assays revealed a clear shift toward the M2 (pro-regenerative) phenotype when cultured with PRP–GA@Lap hydrogel. Expression of M1 markers (inducible nitric oxide synthase, C–C chemokine receptor type 7) decreased, while M2 markers (arginase 1, CD206) increased, suggesting that the scaffold actively modulates the immune environment to favor tissue repair and integration.

Hybrid scaffolds composed of PRP–GA@Lap bioink and PCL were tested in rat subcutaneous implantation and femoral condyle defect models. In subcutaneous sites, the PRP–GA@Lap/PCL group showed more mature and perfused blood vessels (alpha-smooth muscle actin$^+$, CD31$^+$) than controls. In femoral condyle defects, micro-computed tomography analysis demonstrated greater bone volume fraction and bone mineral density in the PRP–GA@Lap/PCL group, along with more complete defect bridging. Histological staining confirmed the presence of well-integrated new bone with active vascularization throughout the regenerated area.

Cao *et al.*'s[15] work represents a deliberate shift in bone tissue engineering strategy—from reliance on single recombinant growth factors to a multi-factor, endogenously derived bioactive system. By using PRP as the biological payload, the authors circumvent some cost

and safety issues associated with supraphysiologic doses of bone morphogenetic protein 2 or VEGF, while retaining a physiologic breadth of angiogenic and osteogenic cues. The integration of Lap as a release modulator is particularly noteworthy. Instead of relying on covalent tethering or synthetic carriers, Lap achieves sustained factor delivery through electrostatic interactions, preserving bioactivity and avoiding additional chemical modifications that might complicate regulatory approval. However, this approach also raises critical questions. The inherent variability of PRP composition between donors—affected by age, comorbidities, and preparation method—could introduce inconsistent scaffold performance, potentially impacting reproducibility and standardization. Furthermore, the current study focused on short-term endpoints in small animal models; it remains unclear whether the same immunomodulatory and regenerative benefits will persist in long-term, load-bearing, or large-defect scenarios. Looking forward, this strategy could evolve into a personalized, autologous scaffold platform if integrated with point-of-care PRP preparation and on-demand 3D printing. Future studies should aim to map the correlation between specific PRP factor release profiles and *in vivo* regenerative outcomes, potentially enabling predictive tailoring of scaffold formulations for individual patients. Additionally, combining PRP's multi-factor environment with gene-edited cells or responsive biomaterials could further refine temporal control over healing processes. By framing growth factor delivery as a kinetic engineering problem rather than a single-factor supplementation challenge, this work opens a compelling avenue for more physiologically aligned and clinically adaptable bone regeneration therapies.

3. Conclusion

The use of PRP–GA hydrogel modified with Lap, combined with PCL structural reinforcement, presents a well-integrated solution to the dual challenges of vascularization and osteoinduction in bone regeneration.[15] Sustained release of multiple endogenous growth factors from PRP supports a coordinated sequence of endothelial, osteogenic, and immunomodulatory events, leading to superior tissue integration and functional repair in preclinical models. Although further studies are needed to optimize PRP concentration, Lap content, and long-term mechanical performance—especially in load-bearing environments—this platform demonstrates strong translational potential. Its reliance on autologous PRP, combined with a modular and customizable 3D-printing process, makes it an attractive candidate for clinical application in complex bone defect repair. By engineering the release kinetics rather than relying solely on single-factor delivery, Cao *et al.*'s[15] work offers a biologically nuanced and technically practical pathway toward next-generation bone tissue scaffolds.

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Conflict of interest

Hyun-Do Jung is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, the author declares no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

This is a single-author article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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