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Engineering coordinated lymphatic–vascular responses with Haversian-mimetic IL-6-releasing scaffolds for bone regeneration

Running title: Lymphatic–vascular scaffolds for bone repair

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Abstract

Bone regeneration requires coordinated vascularization and microenvironmental remodeling; however, most bone biomaterials have primarily emphasized angiogenesis and have less explicitly addressed lymphatic-associated responses. Here, inspired by developmental bone formation and emerging evidence implicating the IL-6-CXCL12 axis in regenerative processes, we developed a biomimetic platform designed to promote bone repair accompanied by coordinated blood vascular and lymphatic-associated responses. A 3D-printed Haversian-mimetic scaffold with architecturally defined microchannels was fabricated to support guided tissue infiltration and vascular organization. To provide instructive biochemical signaling, a GelMA-based coating enabled sustained, low-dose delivery of interleukin-6 (IL-6). Developmental immunofluorescence analysis revealed pronounced spatial association between CXCL12 and osteocalcin-positive osteogenic regions, providing a biological rationale for engaging this axis as a regeneration-associated cue. In vitro studies demonstrated enhanced osteogenic differentiation and concomitant upregulation of angiogenic and lymphatic-associated markers. Transcriptomic profiling further indicated activation of gene programs associated with extracellular matrix remodeling, vascular-related signaling, and tissue regeneration. In a critical-sized defect model, the IL-6-functionalized Haversian-mimetic scaffold promoted new bone deposition and was accompanied by increased CD31-positive vascular structures, LYVE1-positive lymphatic-associated structures, and CXCL12 expression. Collectively, this work demonstrates a strategy that integrates architectural mimicry with cytokine signaling to enhance bone regeneration while explicitly evaluating lymphatic-associated responses as a design parameter for next-generation bone biomaterials.

Keywords: Lymphatic–vascular coupling; Regenerative niche; Haversian-mimetic scaffold; IL-6–CXCL12 axis; Bone regeneration

1.Introduction

Regeneration of large bone defects requires more than osteogenic stimulation; it demands reconstruction of a functional circulatory microenvironment capable of sustaining nutrient delivery, interstitial fluid balance, and regenerative signaling^{1,2}. In native bone, this microenvironment is supported by two interconnected yet distinct systems: the blood vascular system and the lymphatic system^{3,4}. While angiogenesis has long been recognized as indispensable for bone repair and has become a central focus in biomaterial design, the contribution of lymphatic vessels to skeletal regeneration has only recently gained attention³. The identification of functional lymphatic vessels within bone and their involvement in regenerative processes has expanded the traditional view of bone vascular biology, suggesting that coordinated blood and lymphatic responses may influence regenerative outcomes.

Additive manufacturing, particularly 3D printing and bioprinting, has become an increasingly important strategy for tissue repair and regeneration because it enables precise control over scaffold geometry, pore interconnectivity, and spatial organization of biological cues⁵. Compared with conventional scaffold fabrication methods, 3D printing allows patient-specific or defect-adapted constructs to be fabricated with reproducible internal architectures, which is especially relevant for bone regeneration where mechanical support, tissue ingrowth, and vascular access must be considered simultaneously⁶⁻⁸. Recent advances in 3D bioprinting have further expanded the design space of regenerative scaffolds by integrating structural, cellular, and biochemical components within engineered tissue constructs⁹.

Despite this evolving biological understanding, most bone tissue engineering strategies remain predominantly angiogenesis-centered^{10,11}. Scaffold architectures are typically optimized to facilitate endothelial infiltration and perfusion, and cytokine delivery systems are designed primarily to enhance osteogenesis or stimulate blood vessel formation^{12,13}. In contrast, lymphatic regeneration is rarely considered an explicit design parameter in scaffold engineering, and lymphatic markers are often not evaluated separately from angiogenic markers in bone biomaterial studies. Whether a

biomaterial platform can be rationally engineered to promote coordinated regeneration of both blood vascular and lymphatic networks—and thereby establish a more physiologically integrated regenerative microenvironment—remains an open question.

Although angiogenesis and lymphangiogenesis may occur in parallel during tissue repair, they represent distinct biological processes with different cellular markers and functions^{3,14}. Blood vessels primarily support oxygen and nutrient supply, whereas lymphatic vessels contribute to interstitial fluid drainage, immune-cell trafficking, and resolution of tissue edema^{3,10}. Therefore, angiogenic readouts such as VEGF or CD31 cannot fully substitute for lymphatic-associated readouts such as LYVE1 or CXCL12. Separate assessment of lymphatic-associated markers is thus necessary to determine whether a scaffold-induced regenerative response involves both vascular and lymphatic components.

From a structural perspective, native cortical bone provides an instructive organizational template through the Haversian system^{6,15,16}. This hierarchical architecture, characterized by longitudinal microchannels, spatially organizes vascular alignment and fluid transport^{7,15}. Recapitulating selected features of this structural paradigm may provide spatial guidance for tissue ingrowth, fluid exchange, and vascular distribution within engineered constructs. At the molecular level, recent work has demonstrated that IL-6–driven lymphangiogenesis enhances CXCL12-associated regenerative responses in bone, highlighting a signaling axis that links cytokine stimulation, vascular remodeling, and osteogenesis³. Integrating architectural guidance with controlled activation of this axis may therefore provide a means to enhance bone regeneration while enabling simultaneous assessment of blood vascular and lymphatic-associated responses within a biomaterial context.

In this study, we engineered a high-resolution 3D-printed scaffold that recapitulates Haversian microchannel organization and functionalized it with a GelMA-based coating enabling sustained, low-dose IL-6 release. We investigated whether combining structural vascular guidance with IL-6–associated signaling could enhance

coordinated regeneration of blood vessels and lymphatic vessels and thereby promote osteogenesis (Figure 1). Through systematic material characterization, transcriptomic profiling, and in vivo evaluation in a critical-sized defect model, we demonstrate that this integrated strategy enhances blood vascular formation, lymphatic regeneration, and new bone deposition. Our findings suggest that coordination of blood vascular and lymphatic networks can be incorporated as a rational consideration in bone biomaterial design, providing a framework for engineering more physiologically integrated regenerative systems.

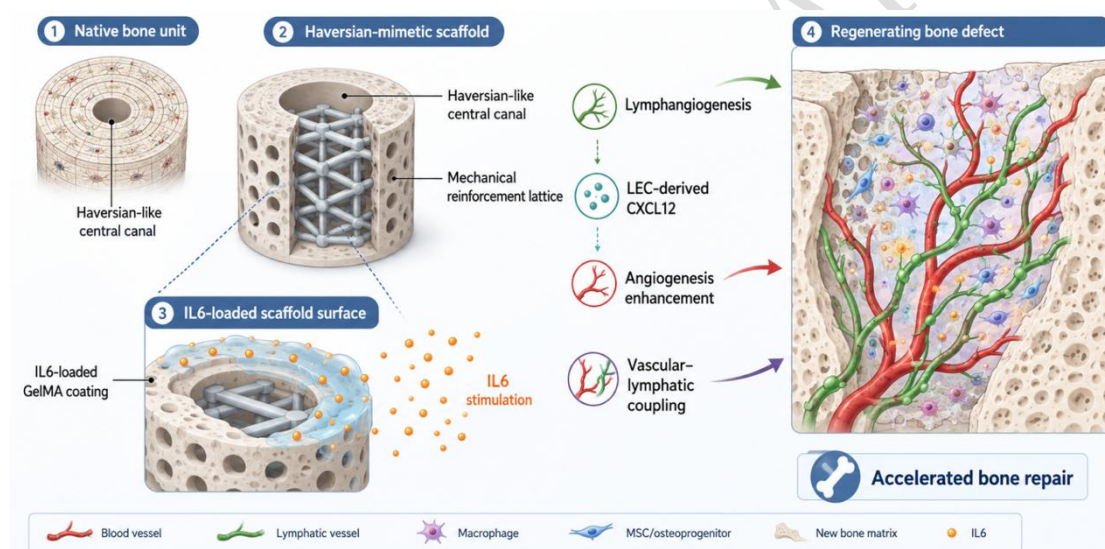


Figure 1. Schematic illustration of the Haversian-mimetic IL-6-releasing scaffold designed to promote bone regeneration with coordinated angiogenic and lymphatic-associated responses.

2. Materials and Methods

2.1 Scaffold fabrication, physicochemical characterization, and IL-6 loading

The Haversian-mimetic scaffold was designed using computer-aided design (CAD) software to recapitulate the hierarchical organization of native cortical bone, incorporating a central longitudinal canal surrounded by an interconnected lattice framework. The digital model included longitudinal microchannels intended to guide

vascular infiltration and fluid exchange. Scaffolds were fabricated using a digital light processing (DLP)-based high-resolution 3D printing system with a polyurethane acrylate (PUA) photopolymer resin. DLP printing was selected because it allows rapid layer-by-layer photopolymerization with relatively high printing resolution and good geometric fidelity, which are advantageous for fabricating microchannel-containing scaffolds with reproducible internal architectures. Compared with material extrusion, DLP can better preserve fine architectural features without filament collapse, while avoiding the high processing temperature or powder-related constraints associated with powder bed fusion techniques. Printed constructs were washed to remove uncured resin and post-cured under ultraviolet light to ensure complete polymerization. The scaffold geometry was designed as a self-supporting interconnected lattice. No additional sacrificial or removable support structure was required during printing. After printing, the constructs were washed to remove uncured resin from the internal channels and then post-cured under ultraviolet light.

For cytokine functionalization, a post-printing GelMA coating strategy was used rather than directly mixing GelMA with PUA resin. This design separated the mechanically supportive printed scaffold from the bioactive cytokine-delivery layer, thereby preserving the printability and structural fidelity of the PUA scaffold while avoiding potential IL-6 exposure to the organic resin environment and prolonged photopolymerization process. GelMA was dissolved in PBS containing photoinitiator and mixed with recombinant rat IL-6. The scaffold surface was immersed in the solution and photo-crosslinked to form a thin hydrogel coating enabling sustained cytokine release. IL-6 release kinetics were evaluated by incubating scaffolds in PBS at 37 °C and quantifying released IL-6 at designated time points using ELISA.

Mechanical properties were assessed via uniaxial compression testing, and stress–strain curves were recorded. The compressive behavior was used to evaluate whether the scaffold could maintain structural stability during handling and implantation. Because the present scaffold was designed primarily for a rat cranial defect model rather

than immediate load-bearing human bone replacement, the mechanical results were interpreted in the context of defect support and space maintenance rather than direct equivalence to native human cortical bone. Degradation behavior was evaluated by incubating scaffolds in PBS at 37 °C for up to 28 days, followed by measurement of remaining dry mass. Surface morphology and structural fidelity were examined using scanning electron microscopy.

2.2 Cell culture, cytocompatibility, and osteogenic differentiation

Rat bone marrow–derived mesenchymal stem cells (MSCs) were cultured in α -MEM supplemented with fetal bovine serum and antibiotics under standard conditions. Lymphatic endothelial cells (LECs) were cultured in endothelial growth medium according to the manufacturer's instructions.

For scaffold cell-seeding experiments, a defined number of MSCs was carefully seeded onto each pre-wetted scaffold and allowed to attach under static culture conditions before additional medium was added. To improve cell retention within the large-pore scaffold, the initial attachment period was performed using a small medium volume. Cell attachment and distribution were subsequently evaluated by fluorescence imaging. Cytocompatibility was evaluated using CCK-8 assays and Live/Dead staining after MSCs were cultured with scaffolds or scaffold extracts. For osteogenic differentiation studies, MSCs were co-cultured with scaffolds under osteogenic induction conditions. Alkaline phosphatase (ALP) staining and activity assays were performed at early time points, while mineralized matrix formation was assessed by Alizarin Red S staining at later stages. Immunofluorescence staining for COL1, OCN, VEGF, and CXCL12 was conducted following fixation, permeabilization, and incubation with specific primary and fluorescent secondary antibodies.

2.3 Lymphatic functional assays and co-culture experiments

To assess lymphatic-associated responses, LEC tube formation assays were performed on Matrigel-coated plates using conditioned media from different experimental groups. Tube length and branch points were quantified using ImageJ

software. For co-culture studies, MSCs and LECs were cultured in a transwell system to evaluate paracrine interactions. CXCL12 protein expression was analyzed by immunofluorescence and quantified by image analysis.

Gene expression analysis was performed using quantitative real-time PCR (qRT-PCR). Total RNA was extracted using TRIzol reagent, reverse-transcribed to cDNA, and amplified using SYBR Green chemistry. Relative expression levels were calculated using the $2^{-\Delta\Delta C_t}$ method with GAPDH as the internal control.

2.4 RNA sequencing and bioinformatic analysis

To evaluate early transcriptional responses to IL-6 stimulation, MSCs were treated with IL-6 for 24 h, and total RNA was extracted for high-throughput sequencing. Differentially expressed genes were identified using standard bioinformatic pipelines with thresholds of $q\text{-value} < 0.05$ and $|\log_2 \text{fold change}| > 1$. KEGG pathway enrichment and Gene Ontology analyses were conducted to identify significantly enriched biological processes and signaling pathways. Hierarchical clustering, volcano plots, and enrichment visualizations were generated using R software.

2.5 In vivo bone defect model and tissue analysis

All animal experiment operation procedures had been reviewed and approved by the Tab of Animal Experimental Ethical Inspection of Southeast University, with reference number SEU-IACUC-20260220146. A rat critical-sized bone defect model was established under anesthesia. Scaffolds were implanted into the defect sites according to experimental grouping. At predetermined time points, specimens were harvested for imaging and histological analysis.

Micro-computed tomography (micro-CT) was performed to assess new bone formation. Bone volume fraction (BV/TV), trabecular thickness (Tb.Th), and trabecular number (Tb.N) were quantified using dedicated analysis software. For histological evaluation, specimens were fixed, decalcified, embedded, and sectioned for hematoxylin and eosin (H&E) and Masson's trichrome staining. Immunofluorescence

staining for OCN, CD31, CXCL12, and LYVE1 was conducted to evaluate osteogenic maturation and vascular–lymphatic responses *in vivo*.

2.6 Statistical analysis

All experiments were performed with at least three independent replicates. Data are presented as mean $\pm$ standard deviation (SD). Statistical comparisons were performed using one-way ANOVA followed by appropriate post hoc tests. A value of $p < 0.05$ was considered statistically significant.

3. Results

To establish a developmental rationale for engaging CXCL12-associated signaling in our regenerative design, we first mapped the spatial distribution of CXCL12 during fetal skeletal development. A whole-section histological overview of the mouse fetus (Figure 2A) was used to identify developing skeletal regions and anatomical context. We then performed immunofluorescence staining to visualize CXCL12 relative to osteogenic activity, using osteocalcin (OCN) as a marker of osteogenic differentiation (Figure 2B). As shown in Figure 2B, CXCL12 signal was enriched in developing skeletal tissues and exhibited a close spatial association with OCN-positive osteogenic regions. Notably, within ossification centers—where active bone formation occurs—CXCL12 and OCN signals appeared highly coincident. The magnified insets in Figure 2B further highlight that CXCL12-positive staining is concentrated within, or immediately adjacent to, OCN-enriched areas at the ossification front, indicating a strong developmental correlation between CXCL12 expression and sites of active osteogenesis. Together, these developmental observations suggest that CXCL12 is prominently present within osteogenic microenvironments during bone formation. While this sectioning analysis is descriptive and does not imply causality, it provides a biologically grounded starting point for leveraging the IL-6–CXCL12 axis—previously implicated in regeneration-associated lymphangiogenic responses—to guide the design of an engineered scaffold in which osteogenic, angiogenic, and lymphatic-associated

responses can be evaluated in parallel.

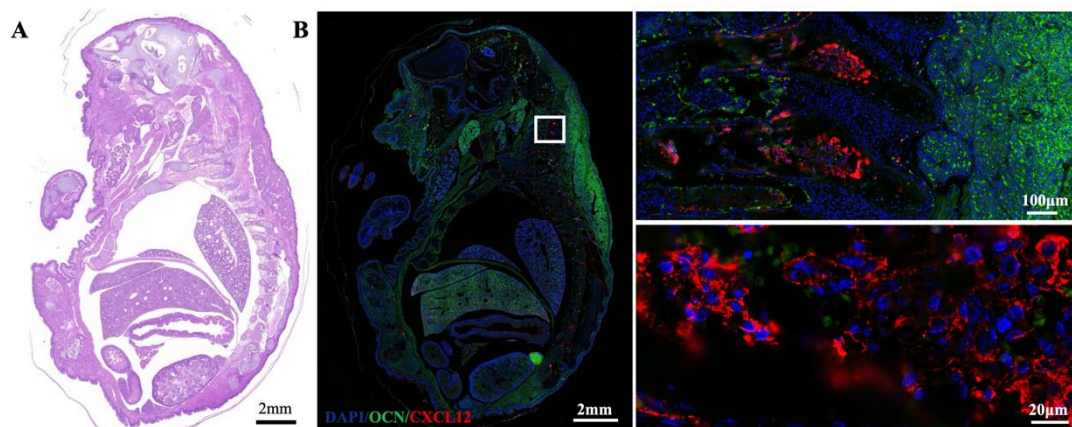


Figure 2. CXCL12 expression spatially correlates with osteogenic regions during fetal bone development. (A) Whole-section histological overview of a mouse fetus. (B) Immunofluorescence staining for CXCL12 (red) and OCN (green) with DAPI (blue). CXCL12 is enriched within ossification centers and spatially associated with OCN-positive regions. Insets show higher-magnification views of the boxed area.

To translate the developmental association of CXCL12 with osteogenic regions into an engineered regenerative platform, we designed a Haversian-inspired scaffold incorporating selected structural features of native cortical bone. As shown in Figure 3A–B, the scaffold incorporates a central canal surrounded by an interconnected lattice framework, resembling selected aspects of the Haversian unit and providing longitudinal microchannels that may facilitate tissue ingrowth, fluid exchange, and vascular infiltration. The construct was fabricated via high-resolution 3D printing of a polyurethane acrylate-based polymer, and the printed structures faithfully reproduced the designed geometry (Figure 3C–E). Both cross-sectional and longitudinal views confirmed precise formation of the central canal and peripheral channels, while scanning electron microscopy further verified the structural fidelity and internal lattice integrity. The resulting constructs exhibited uniform morphology and structural continuity, demonstrating reliable translation from digital model to physical scaffold.

Mechanical and functional properties were subsequently evaluated to ensure suitability for regenerative application. Uniaxial compression testing revealed stable load-bearing behavior with progressive stress increase under strain, indicating effective

stress distribution within the reinforced lattice architecture (Figure 3F). Degradation analysis over 28 days showed gradual mass reduction while maintaining overall structural integrity (Figure 3G), suggesting controlled material stability. To introduce biochemical signaling, the scaffold surface was coated with GelMA for IL-6 loading. The cumulative release profile demonstrated sustained IL-6 delivery over time, with GelMA coating moderating release kinetics compared to uncoated controls (Figure 3H). Together, these results establish a structurally defined and mechanically supportive platform capable of controlled cytokine presentation, enabling subsequent investigation of osteogenic, angiogenic, and lymphatic-associated responses.

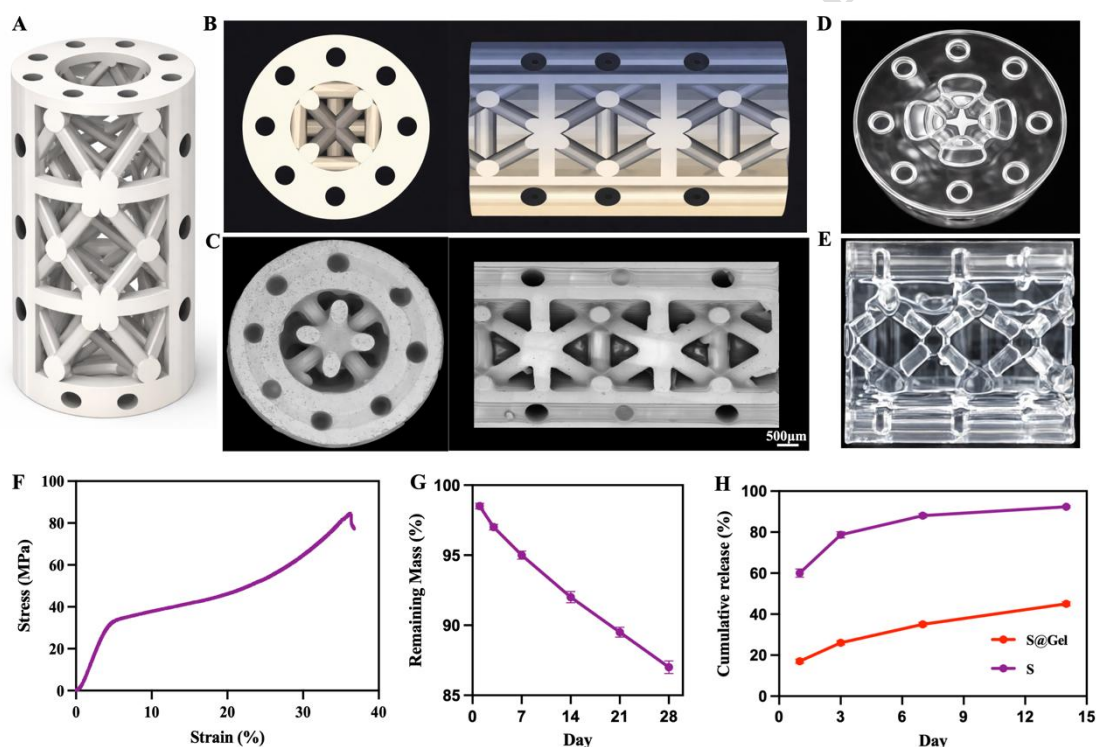


Figure 3. Design, fabrication, and physicochemical characterization of the Haversian-mimetic scaffold with controlled IL-6 delivery. (A) Three-dimensional digital model of the Haversian-mimetic scaffold featuring a central canal and surrounding reinforced lattice architecture. (B) Cross-sectional and longitudinal views of the designed scaffold illustrating the longitudinal microchannels and interconnected internal framework. (C) Representative images and scanning electron microscopy (SEM) micrographs of the 3D-printed polymer scaffold confirming accurate structural replication of the digital model. (D, E) Photographs of the fabricated scaffold demonstrating macroscopic morphology and structural integrity. (F) Compressive stress-strain curve of the polymer scaffold showing stable load-bearing behavior under increasing strain. (G) Degradation profile of the scaffold over 28 days, presented as remaining mass percentage. (H)

Cumulative IL-6 release profile from scaffolds with or without GelMA coating, indicating sustained cytokine delivery enabled by the hydrogel layer.

Following structural and physicochemical characterization, we next evaluated the cytocompatibility of the engineered scaffold. CCK-8 analysis revealed comparable cell viability among the control, scaffold-only (S), and IL-6-functionalized scaffold (S@Gel-IL6) groups (Figure 4A), indicating that neither the printed polymer nor the GelMA-based IL-6 coating induced cytotoxic effects. Consistently, live/dead staining demonstrated a predominance of viable cells across all groups with minimal dead cell signals (Figure 4B). To assess cellular interaction with the three-dimensional construct, mesenchymal stem cells (MSCs) were co-cultured with the scaffolds (Figure 4C). Fluorescence imaging confirmed cell attachment and distribution along the scaffold surface and within the lattice framework (Figure 4D, E), suggesting that the scaffold architecture provides a permissive microenvironment for cell adhesion and colonization. However, these fluorescence images primarily provide qualitative evidence of cell attachment and distribution, and quantitative cell-seeding efficiency should be further evaluated in future studies. We subsequently examined osteogenic differentiation of MSCs cultured with the scaffolds. Alkaline phosphatase (ALP) staining revealed increased enzymatic activity in the S group compared with control, which was further enhanced in the S@Gel-IL6 group (Figure 4F). Quantitative analysis confirmed significantly elevated ALP activity in the IL-6-functionalized scaffold (Figure 4H), indicating early-stage osteogenic activation. At later stages, Alizarin Red S (ARS) staining demonstrated increased mineralized matrix deposition in scaffold-treated groups, with the S@Gel-IL6 group exhibiting the most pronounced calcium nodule formation (Figure 4I). Corresponding quantification further verified enhanced mineralization in the IL-6-functionalized condition (Figure 4J). Together, these findings demonstrate that the Haversian-mimetic scaffold supports cell viability and promotes osteogenic differentiation, with sustained IL-6 delivery further enhancing osteogenic outcomes.

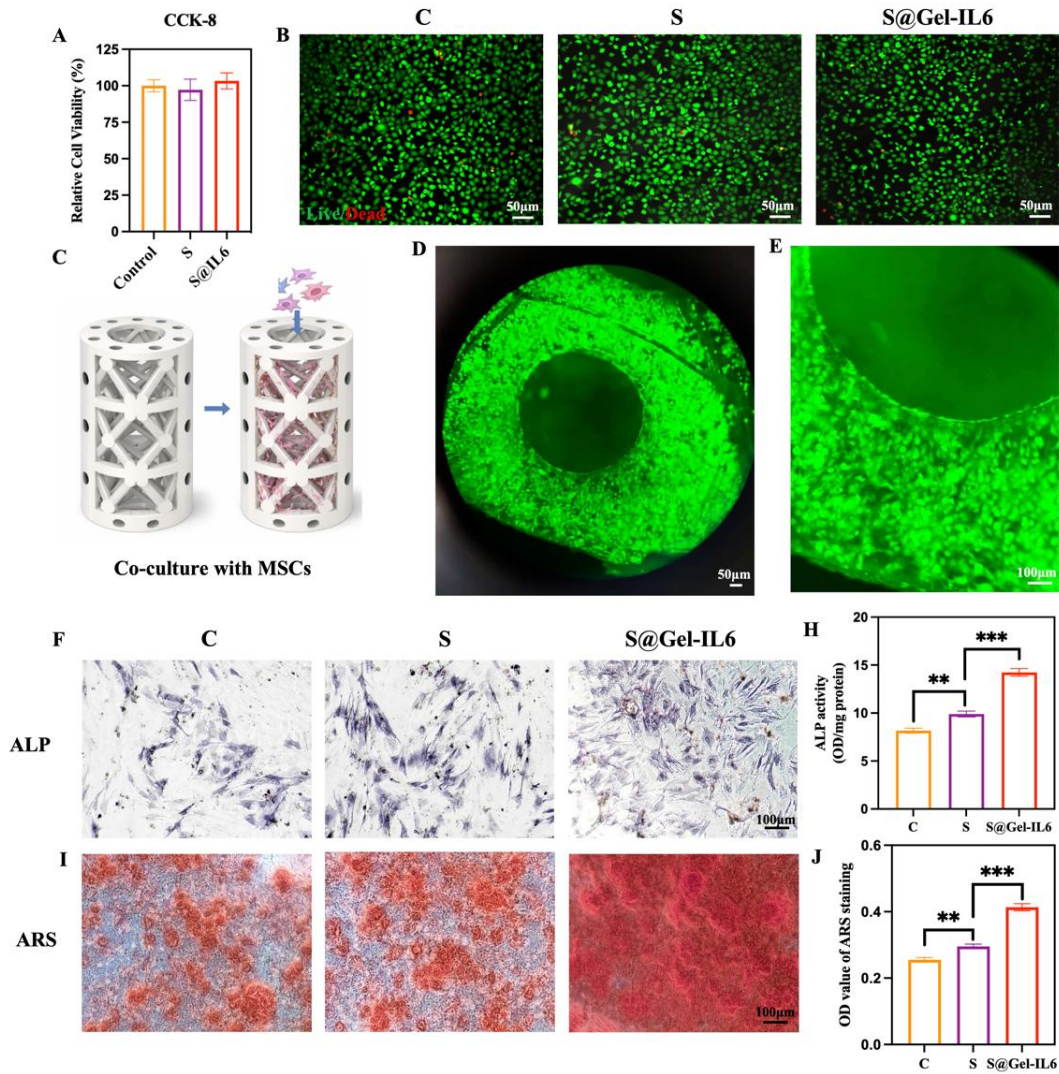


Figure 4. Cytocompatibility and osteogenic differentiation of the Haversian-mimetic IL-6-functionalized scaffold. (A) CCK-8 assay showing relative cell viability of mesenchymal stem cells (MSCs) cultured under control (C), scaffold-only (S), and IL-6-functionalized scaffold (S@Gel-IL6) conditions. (B) Live/dead staining of MSCs in different groups, indicating predominant viable cells (green) with minimal dead cells (red). (C) Schematic illustration of MSC co-culture with the 3D scaffold. (D, E) Fluorescence images showing MSC adhesion and distribution on the scaffold surface and within the internal lattice structure. (F) Alkaline phosphatase (ALP) staining of MSCs cultured with different scaffolds. (H) Quantitative analysis of ALP activity normalized to total protein. (I) Alizarin Red S (ARS) staining showing mineralized matrix deposition. (J) Quantification of ARS staining. Data are presented as mean $\pm$ SD. Statistical significance is indicated as ** $p < 0.01$ and *** $p < 0.001$.

Building upon the observed enhancement of osteogenic differentiation, we next examined whether the engineered scaffold could modulate vascular- and lymphatic-associated signaling pathways. Immunofluorescence staining demonstrated elevated

expression of osteogenic markers COL1 and OCN, as well as the angiogenic marker VEGF, in the S@Gel-IL6 group compared to control and scaffold-only groups (Figure 5A–F). Quantitative analysis confirmed significantly increased fluorescence intensity in the IL-6-functionalized condition. Consistently, quantitative PCR analysis revealed upregulation of osteogenic genes (OPN, COL1) and vascular-associated genes (VEGF, CD31) in the S@Gel-IL6 group (Figure 5G–J), indicating simultaneous enhancement of osteogenic and angiogenic marker expression.

We further investigated lymphatic-associated responses. mRNA analysis showed significantly increased expression of CXCL12 and the lymphatic endothelial marker LYVE1 in the S@Gel-IL6 group (Figure 5O–P). Functional assessment using lymphatic endothelial cell (LEC) tube formation assays revealed enhanced capillary-like network formation in the S@Gel-IL6 condition, with increased total tube length and branch points compared to controls (Figure 5K–L). Moreover, co-culture experiments with LECs demonstrated elevated CXCL12 protein expression in the S@Gel-IL6 group, as confirmed by immunofluorescence staining and quantitative analysis (Figure 5M–N). Collectively, these findings suggest that controlled IL-6 delivery within the Haversian-mimetic architecture promotes osteogenic and angiogenic responses while also enhancing lymphatic-associated activity and CXCL12-related signaling. These results support the need to evaluate lymphatic-associated responses separately from angiogenic responses in scaffold-mediated bone regeneration.

To further elucidate the early molecular responses induced by IL-6 stimulation, we performed transcriptomic sequencing of mesenchymal stem cells (MSCs) treated with IL-6 for 24 h and compared them with untreated controls. This analysis aimed to identify signaling pathways potentially underlying the enhanced osteogenic, angiogenic, and lymphatic-associated responses observed in the scaffold system. Differential expression analysis revealed substantial transcriptional reprogramming following IL-6 stimulation (Figure 6A). Using a cutoff of $q\text{-value} < 0.05$ and $|\log_2 \text{fold change}| > 1$, a distinct set of upregulated and downregulated genes was identified. Notably, several

genes associated with extracellular matrix remodeling, cytokine signaling, and cell–cell interaction were significantly altered. Hierarchical clustering analysis demonstrated clear separation between IL-6–treated and control samples, indicating consistent transcriptomic divergence between the two groups (Figure 6C).

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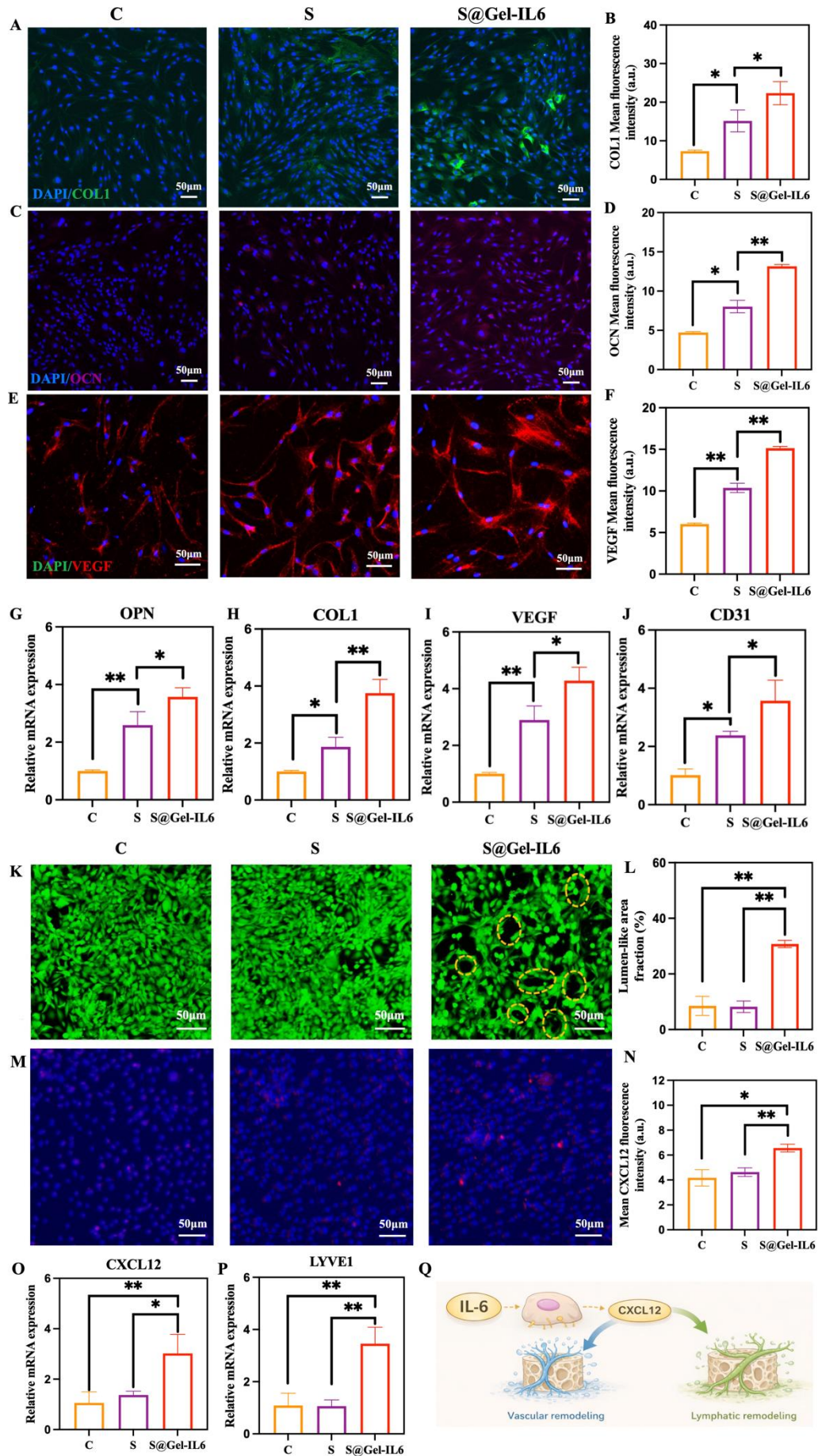


Figure 5. IL-6-functionalized Haversian-mimetic scaffold enhances osteogenic, angiogenic, and lymphatic-associated responses in vitro. Immunofluorescence staining of COL1 (green), OCN (red), and VEGF (red) in MSCs cultured under control (C), scaffold-only (S), and IL-6-functionalized scaffold (S@Gel-IL6) conditions, with nuclei counterstained by DAPI (blue), along with corresponding quantitative fluorescence intensity analyses (A–F). Relative mRNA expression levels of osteogenic markers (OPN, COL1) and vascular-associated markers (VEGF, CD31) were determined by qPCR (G–J). Lymphatic endothelial cell (LEC) tube formation assays were performed to evaluate lymphangiogenic activity, with representative images and quantitative analysis of total tube length and branch points shown in (K–L). CXCL12 protein expression in LEC co-culture systems was assessed by immunofluorescence staining and quantitative analysis (M–N). Relative mRNA expression levels of CXCL12 and the lymphatic marker LYVE1 are presented in (O–P). (Q) Schematic illustration summarizing the coordinated enhancement of osteogenic, angiogenic, and lymphatic-associated responses induced by the IL-6-functionalized Haversian-mimetic scaffold. Data are presented as mean $\pm$ SD. Statistical significance is indicated as * $p < 0.05$ and ** $p < 0.01$.

Pathway enrichment analysis of upregulated genes revealed significant enrichment in focal adhesion, regulation of actin cytoskeleton, ECM–receptor interaction, PI3K–Akt signaling, MAPK signaling, and cytokine–cytokine receptor interaction pathways (Figure 6B). These pathways are closely related to cell adhesion dynamics, extracellular matrix organization, and vascular-associated signaling. Of particular relevance, JAK–STAT signaling—an established downstream pathway of IL-6—was significantly enriched, confirming effective activation of IL-6-responsive transcriptional programs. Gene ontology and functional annotation further indicated enrichment of extracellular space, extracellular matrix organization, positive regulation of cell migration, and response to hypoxia categories (Figure 6D), processes that are highly relevant to vascular remodeling and regenerative microenvironment adaptation. Importantly, genes implicated in chemokine signaling and stromal regulation, including CXCL12, were upregulated following IL-6 stimulation (Figure 6C, O). This transcriptional shift aligns with our in vitro findings showing enhanced CXCL12 expression and lymphatic-associated responses in the IL-6-functionalized scaffold system. Collectively, these transcriptomic data suggest that IL-6 induces coordinated activation of extracellular remodeling, vascular-related signaling, and chemokine-associated pathways in MSCs,

providing mechanistic support for the observed enhancement of vascular–lymphatic coupling and osteogenesis in the engineered scaffold context.

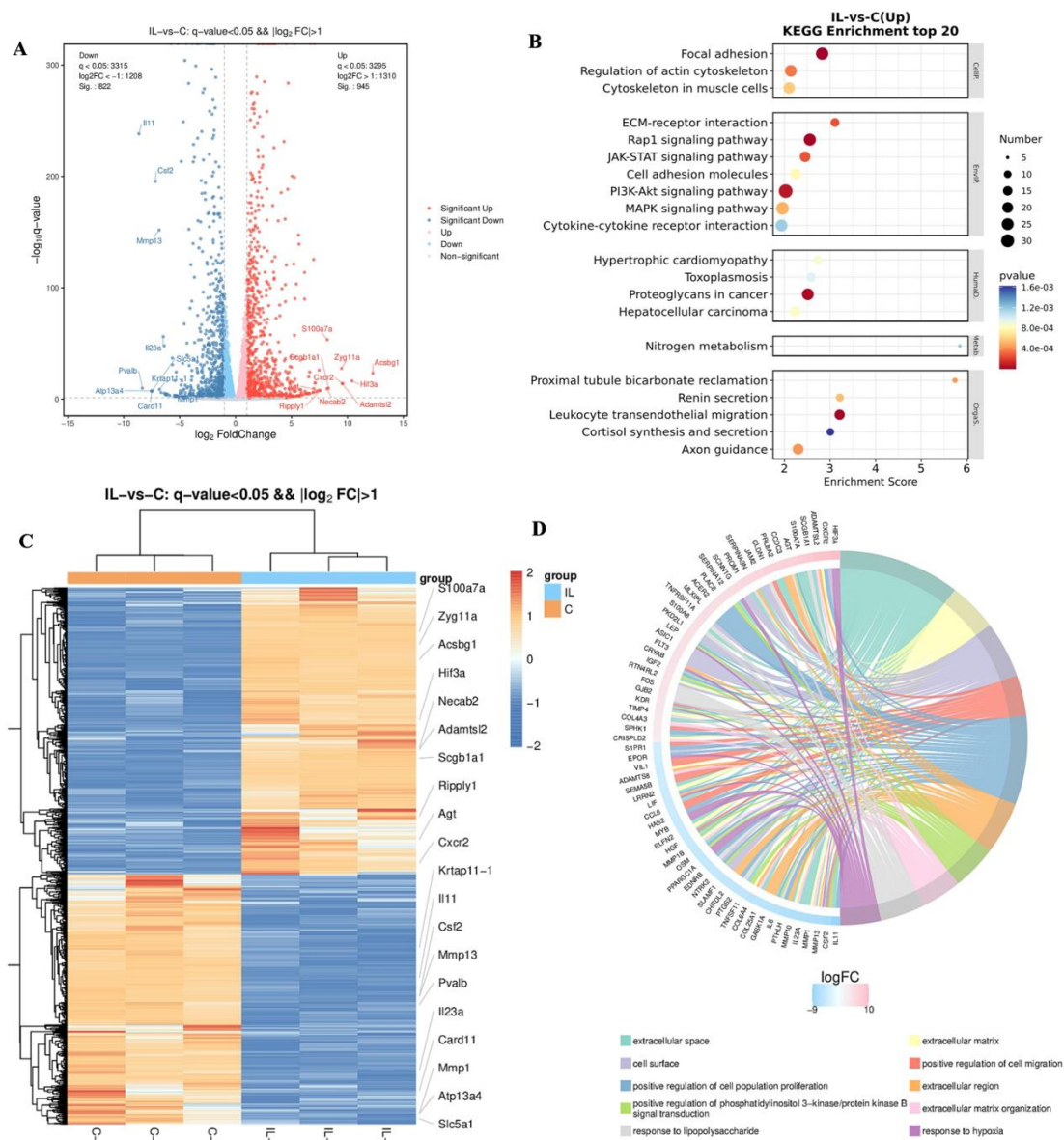


Figure 6. Transcriptomic profiling reveals IL-6-induced transcriptional reprogramming in mesenchymal stem cells. Volcano plot showing differentially expressed genes between IL-6-treated MSCs (24 h) and untreated controls (q-value < 0.05, |log₂ fold change| > 1), with upregulated genes in red and downregulated genes in blue (A). KEGG pathway enrichment analysis of upregulated genes highlights focal adhesion, ECM–receptor interaction, PI3K–Akt signaling, MAPK signaling, JAK–STAT signaling, and cytokine–cytokine receptor interaction pathways (B). Hierarchical clustering heatmap demonstrates clear separation between IL-6-treated and control samples (C). Functional annotation and gene ontology enrichment analyses indicate significant enrichment in extracellular matrix organization, extracellular space, positive regulation of cell migration, and response to hypoxia-related categories (D). Data represent three biological replicates per group.

Encouraged by the *in vitro* enhancement of osteogenesis and the activation of vascular- and lymphatic-associated programs, we next evaluated regenerative efficacy in a rat critical-sized bone defect model. Micro-CT reconstruction revealed limited defect bridging in the control group, whereas implantation of the Haversian-mimetic scaffold (S) promoted detectable bone ingrowth within the defect region. Notably, the IL-6-functionalized scaffold (S@Gel-IL6) exhibited the most substantial new bone formation, with increased mineralized tissue occupying the defect area in both 3D reconstructions and sagittal sections (Figure 7A–B). Quantitative micro-CT analysis further confirmed significantly higher bone volume fraction (BV/TV), trabecular thickness (Tb.Th), and trabecular number (Tb.N) in the S@Gel-IL6 group compared with the control and scaffold-only groups (Figure 7C–E), indicating accelerated bone regeneration and improved trabecular microarchitecture.

Histological analyses corroborated the imaging findings. H&E staining showed sparse tissue filling and limited osteoid/bone-like structure formation in the control defects, while scaffold implantation supported more organized tissue infiltration and defect remodeling. In the S@Gel-IL6 group, denser tissue occupancy and more mature reparative morphology were observed within the defect region (Figure 7F). Masson's trichrome staining further demonstrated increased collagen-rich matrix deposition and more advanced maturation of newly formed tissue in scaffold-treated groups, with the most pronounced remodeling and matrix organization in the S@Gel-IL6 group (Figure 7G). Collectively, these results demonstrate that the combination of a Haversian-inspired scaffold architecture and sustained IL-6 presentation enhances bone regeneration *in vivo*, consistent with the pro-regenerative transcriptional and *in vitro* phenotypic responses observed earlier. Because a pore-size- and porosity-matched non-Haversian structural control was not included, the independent contribution of the Haversian-inspired geometry should be interpreted cautiously.

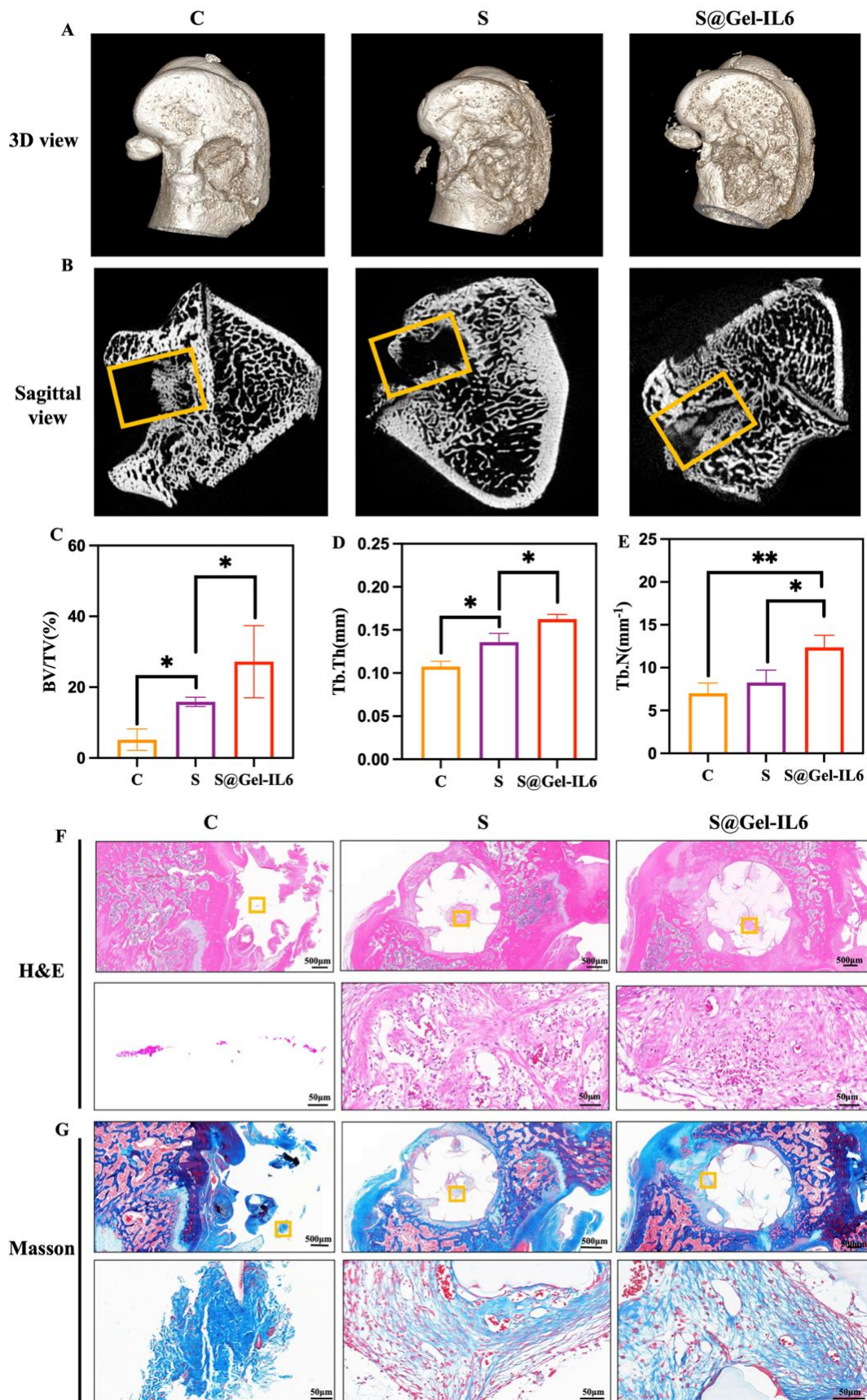


Figure 7. In vivo bone regeneration and microarchitectural improvement induced by the IL-6-functionalized Haversian-mimetic scaffold. (A) Representative three-

dimensional micro-CT reconstructions of bone defects in control (C), scaffold-only (S), and IL-6–functionalized scaffold (S@Gel-IL6) groups. (B) Sagittal micro-CT views of the defect region with highlighted areas indicating newly formed bone. Quantitative micro-CT analyses of bone volume fraction (BV/TV) (C), trabecular thickness (Tb.Th) (D), and trabecular number (Tb.N) (E) are shown. (F) Hematoxylin and eosin (H&E) staining of defect regions demonstrating tissue infiltration and reparative morphology. (G) Masson’s trichrome staining showing collagen-rich matrix deposition and maturation of newly formed tissue.

To further evaluate whether the enhanced bone regeneration observed *in vivo* was associated with coordinated vascular and lymphatic responses, immunofluorescence staining of osteogenic and vascular-related markers was performed in defect sections. As shown in Figure 8, OCN staining revealed increased osteogenic activity in the scaffold-treated groups compared with the control, with the S@Gel-IL6 group displaying the strongest signal within the defect region, indicating enhanced maturation of newly formed bone tissue. Consistent with the micro-CT and histological observations, CD31 staining demonstrated increased vascular structures in the scaffold groups, particularly in the S@Gel-IL6 group, suggesting improved angiogenic remodeling within the regenerating tissue. Notably, CXCL12 expression was also markedly elevated in the S@Gel-IL6 group, supporting the *in vitro* findings that IL-6 stimulation promotes CXCL12-associated signaling. In addition, LYVE1-positive lymphatic structures were more frequently detected in the S@Gel-IL6 group compared with the control and scaffold-only groups, indicating enhanced lymphatic involvement during tissue regeneration. Together, these results suggest that IL-6 functionalization of the Haversian-mimetic scaffold promotes osteogenesis accompanied by enhanced vascular and lymphatic responses in the defect microenvironment.

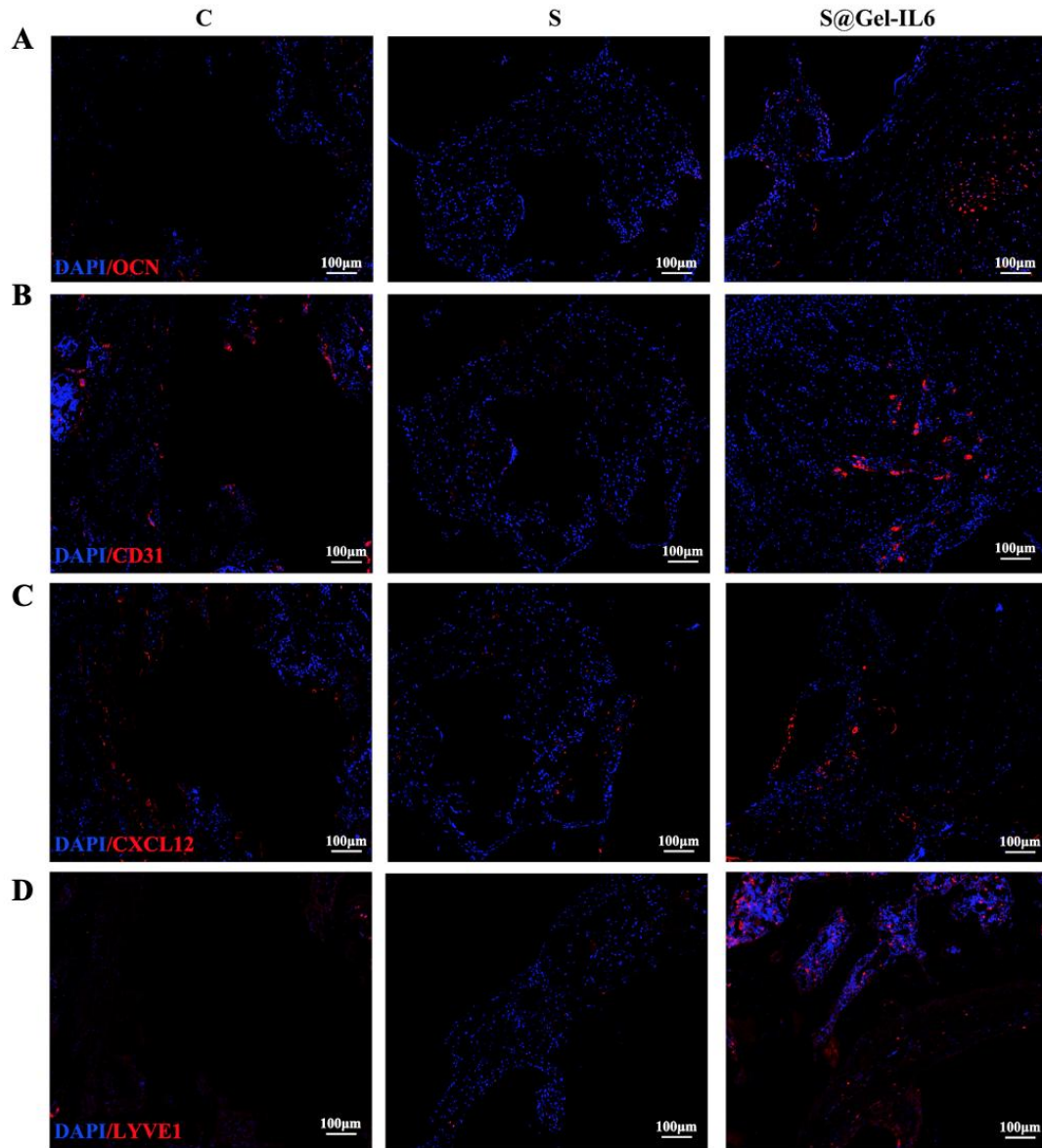


Figure 8. Immunofluorescence analysis of osteogenic, vascular, and lymphatic markers in the defect region. Representative immunofluorescence staining of OCN (A), CD31 (B), CXCL12 (C), and LYVE1 (D) in bone defect sections from control (C), scaffold-only (S), and IL-6-functionalized scaffold (S@Gel-IL6) groups. Nuclei were counterstained with DAPI (blue), showing enhanced osteogenic, vascular, and lymphatic-associated signals in the S@Gel-IL6 group.

4. Discussion

Bone regeneration has traditionally been conceptualized as the restoration of mineralized tissue supported by angiogenesis^{13,17,18}. However, accumulating biological evidence suggests that the skeletal microenvironment is regulated by a more complex circulatory architecture comprising both blood vascular and lymphatic systems³. While

angiogenesis has been extensively incorporated into scaffold design, lymphatic involvement has rarely been considered an explicit engineering parameter¹⁹. In this study, we sought to bridge this gap by integrating biological insight from IL-6-associated lymphatic responses with selected structural design principles derived from native Haversian architecture. Rather than simply adding another bioactive ingredient to a scaffold, our design aimed to combine spatially organized tissue-guiding architecture with a cytokine cue linked to CXCL12-associated regenerative signaling. Our findings suggest that this integrated strategy enhances bone repair and is accompanied by both angiogenic and lymphatic-associated responses.

A central conceptual advance of this work lies in repositioning lymphatic–vascular coordination as a design consideration in bone biomaterials. Rather than treating osteogenesis and angiogenesis as independent endpoints^{20–22}, we aimed to reconstruct a regenerative microenvironment in which structural guidance and cytokine signaling act synergistically. The Haversian-inspired architecture provided a spatially organized scaffold framework with longitudinal microchannels that may facilitate tissue ingrowth, fluid exchange, and vascular infiltration. However, because the present study did not include a pore-size- and porosity-matched non-Haversian structural control, we do not attribute the biological outcome solely to the Haversian-like geometry^{6,15}. Concurrently, sustained low-dose IL-6 delivery activated transcriptional programs associated with extracellular matrix remodeling, focal adhesion, and vascular-related signaling pathways, including JAK–STAT and PI3K–Akt cascades^{23–26}. Transcriptomic profiling revealed enrichment of extracellular matrix organization, cytokine–cytokine receptor interaction, and migration-associated pathways, indicating that IL-6 stimulation primes mesenchymal stem cells toward a pro-regenerative, remodeling-competent state rather than simply inducing lineage differentiation²⁷. This interpretation may also explain why the scaffold-drug group showed broader regenerative effects than the scaffold-only group, including enhanced CXCL12 expression and lymphatic-associated readouts, rather than only stronger osteogenic staining. Importantly, the transcriptional

upregulation of CXCL12 following IL-6 stimulation provides a molecular link between cytokine signaling and vascular–lymphatic coordination. Previous biological studies have demonstrated that IL-6–driven lymphangiogenesis can promote CXCL12-associated regenerative responses in bone^{3,14,28}. Our data extend this insight into a biomaterial framework by showing that IL-6 functionalization enhances CXCL12 expression in vitro and in co-culture systems, accompanied by increased lymphatic endothelial tube formation. While the present study does not establish a direct causal pathway between IL-6, CXCL12, and lymphangiogenesis within the defect environment, the convergent in vitro, transcriptomic, and in vivo observations collectively support the notion that IL-6–associated signaling contributes to coordinated vascular remodeling²². Importantly, the lymphatic-associated evaluation in this study should not be regarded as a redundant extension of angiogenic assessment. Although angiogenesis and lymphangiogenesis may coexist during tissue repair, CD31/VEGF-positive angiogenic responses do not necessarily indicate the formation or activation of LYVE1-positive lymphatic-associated structures. Blood vessels and lymphatic vessels perform different functions in the regenerative microenvironment, including perfusion, immune-cell trafficking, interstitial fluid balance, and inflammatory resolution²⁹. Therefore, the separate assessment of LYVE1 and CXCL12 provides additional information that cannot be inferred solely from angiogenic markers. The enhanced expression of CD31 and LYVE1 in vivo further suggests that both blood vascular and lymphatic components are engaged during scaffold-mediated regeneration.

At the tissue level, micro-CT and histological analyses demonstrated that the IL-6–functionalized Haversian-mimetic scaffold significantly improved trabecular microarchitecture and matrix deposition compared with scaffold-only controls. These outcomes are consistent with a model in which structural guidance facilitates organized tissue infiltration, while cytokine-mediated signaling enhances extracellular remodeling and vascular integration^{5,8,30}. Rather than acting as a simple osteoinductive cue, IL-6 appears to function as a microenvironmental modulator that amplifies

regenerative coordination. This interpretation is supported by the observed enrichment of extracellular matrix–related gene categories and focal adhesion pathways, which are critical for cell–matrix interaction and tissue organization during repair^{31,32}. The integration of architecture and signaling represents a key strength of the present design. Many scaffold strategies rely solely on geometric optimization or growth factor supplementation; however, native bone regeneration is inherently a multi-scale process involving structural hierarchy and dynamic molecular signaling⁵. By combining Haversian-mimetic microchannels with controlled cytokine presentation, this study illustrates how biologically informed cues can be embedded within a physically defined scaffold to approximate aspects of physiological regeneration. In this context, lymphatic–vascular coordination emerges not as an isolated biological phenomenon but as an actionable engineering dimension.

Several limitations should be acknowledged. First, although enhanced CXCL12 expression and lymphatic-associated responses were observed, direct causal validation through pathway inhibition (e.g., VEGFR3 or CXCR4 blockade) was not performed and warrants future investigation^{33,34}. Second, functional assessment of lymphatic drainage capacity was not directly evaluated, and future studies incorporating tracer-based analyses could further clarify the role of lymphatic integration in defect resolution^{35,36}. Third, optimization of IL-6 dosage and temporal release kinetics may further refine the balance between regenerative stimulation and inflammatory activation^{37,38}. Addressing these questions will help delineate the precise contribution of IL-6–mediated signaling within complex regenerative microenvironments³³. In conclusion, this work demonstrates that biologically inspired cytokine signaling can be integrated with Haversian-mimetic architectural design to enhance coordinated vascular–lymphatic responses and bone regeneration. By translating insights from lymphatic-associated bone biology into a material-based platform, we highlight the potential of incorporating lymphatic–vascular coordination as a rational design consideration in next-generation bone biomaterials³⁹. Such an approach may advance

scaffold strategies from isolated enhancement of angiogenesis toward more physiologically integrated regenerative systems.

5. Conclusion

In conclusion, we engineered a Haversian-mimetic scaffold integrating structural guidance with sustained IL-6 delivery to promote coordinated regeneration of bone, blood vessels, and lymphatic components. By translating insights from IL-6-associated lymphatic biology into a material-based strategy, this work demonstrates that combining architectural mimicry with controlled cytokine signaling enhances osteogenesis, vascular remodeling, and CXCL12-associated pathways both in vitro and in vivo. Beyond improving regenerative outcomes, our findings suggest that lymphatic-associated evaluation, together with angiogenic assessment, should be incorporated into the design and interpretation of bone biomaterials, providing a framework for engineering more physiologically integrated regenerative microenvironments.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

All animal experiment operation procedures had been reviewed and approved by the Tab of Animal Experimental Ethical Inspection of Southeast University (reference number: SEU-IACUC-20260220146).

Consent for publication

Not applicable.

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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