

Injectable Fiber-Hydrogel Hybrid Scaffolds for Localized Growth Factor Delivery and Modulation of Vascular and Neuronal Cell Responses

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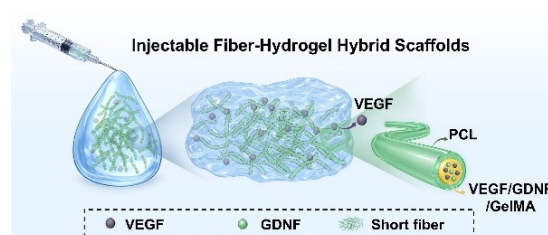
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Received: 3 July 2026; Revised: 23 September 2026; Accepted: 28 September 2026; Published: 30 September 2026

Abstract: Ischemic stroke is a leading cause of mortality and long-term disability worldwide and is characterized by neuronal loss, vascular impairment, and limited endogenous repair. Recovery after ischemic injury requires coordinated vascular and neural responses. However, the unfavorable post-stroke microenvironment, rapid loss of trophic factors, and poor retention of therapeutic proteins remain major barriers to tissue regeneration. Here, we developed an injectable hierarchical fiber-hydrogel hybrid scaffold for localized delivery of angiogenic and neurotrophic factors. Core-shell gelatin methacryloyl/polycaprolactone (GelMA/PCL) electrospun nanofibers were fabricated by coaxial electrospinning, in which vascular endothelial growth factor (VEGF) and glial cell line-derived neurotrophic factor (GDNF) were encapsulated within the GelMA core, while PCL served as the outer shell. The growth factor-loaded nanofibers were then processed into short fibers and incorporated into a VEGF-containing hydrogel matrix composed of thiol-modified hyaluronic acid/heparin and gelatin. The resulting hybrid scaffold combined an injectable hydrogel network with embedded fibrous components and provided localized release of VEGF and GDNF. In vitro studies showed that the hybrid scaffold promoted endothelial cell migration, supported endothelial cell growth, and maintained angiogenic activity under oxygen-glucose deprivation (OGD) conditions. In addition, the scaffold enhanced SH-SY5Y cell growth and supported PC12 neurite outgrowth. By integrating hydrogel-based injectable support, and localized trophic factor delivery, this scaffold provides a biomaterial platform for modulating vascular and neuronal cell responses under ischemia-mimicking conditions, which is promising for recovery after ischemic injury



Keywords: Ischemic stroke; trophic factors; localized release; core-shell short nanofibers; hybrid scaffold

1. Introduction

Ischemic stroke remains one of the leading causes of mortality and long-term disability worldwide [1,2]. The abrupt interruption of cerebral blood flow induces severe neuronal death, vascular damage, blood-brain barrier disruption, and persistent neuroinflammatory responses, ultimately leading to long-term neurological deficits [3,4]. Although thrombolytic therapy and mechanical thrombectomy have substantially improved acute stroke management, their clinical benefits are limited by narrow therapeutic windows and their inability to rebuild damaged neural tissue [5,6]. Therefore, developing regenerative strategies that promote structural and functional recovery of the injured brain is an important objective in stroke therapy.

Increasing evidence suggests that post-stroke recovery depends on coordinated reconstruction of the neurovascular unit, a dynamic microenvironment composed of neurons, endothelial cells, glial cells, and extracellular matrix components [5,7]. Within the neurovascular unit, vascular remodeling and neuronal regeneration are highly



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interdependent. Newly formed blood vessels supply oxygen, nutrients, and trophic cues that support neuronal survival and differentiation, while regenerating neural cells contribute to vascular stabilization and functional integration [8]. Accordingly, simultaneous promotion of angiogenesis and neurogenesis has emerged as a promising strategy for enhancing neurovascular repair after ischemic injury.

Growth factor-based therapies have attracted considerable attention because of their ability to regulate multiple regenerative processes. Among them, vascular endothelial growth factor (VEGF) is a potent angiogenic factor that promotes endothelial cell proliferation, migration, and vascular network formation, while glial cell line-derived neurotrophic factor (GDNF) plays a critical role in neuronal survival, neurite extension, and neural differentiation [9–15]. Despite their therapeutic potential, direct administration of growth factors is limited by rapid degradation, short biological half-life, and poor retention at the injury site [5,16]. Biomaterial-based delivery systems that protect bioactive proteins and enable localized release over a defined period are therefore highly desirable for improving therapeutic efficacy [17–19].

Hydrogels have been widely investigated for neural tissue engineering owing to their high water content, tissue-like mechanical properties, and potential for minimally invasive delivery. In particular, injectable hydrogel precursors with flowable characteristics can be readily administered into irregular defect, enabling conformal filling of the lesion site and rapid *in situ* gelation to establish a three-dimensional regenerative microenvironment [20–22]. However, hydrogels alone generally provide limited structural guidance for tissue regeneration and may show limited retention of encapsulated bioactive agents because of relatively rapid diffusion [20–22].

Electrospun fibrous materials offer tunable morphology, orientation, and composition for tissue-engineering applications. Polymeric electrospun fibers and microfibers provide versatile platforms for structural design, functionalization, and biomedical applications [23–25]. Beyond structural support, electrospun nanofibers can also be used for biomolecule delivery and release regulation [26–28]. In particular, core-shell nanofibers fabricated by coaxial electrospinning can physically isolate sensitive biomolecules within the fiber core, thereby protecting their bioactivity during fabrication and regulating release through the surrounding shell layer [29–31]. This compartmentalized structure separates the bioactive core from the protective shell and can improve protein preservation and delivery performance [32,33]. However, the continuous morphology of electrospun nanofibers limits their suitability for minimally invasive injection and their ability to conform to irregular lesion cavities. Processing nanofibers into short fibers can improve their injectability, dispersibility, and integration within hydrogel matrices [23,34,35]. Recent studies have demonstrated that incorporating short electrospun fibers into hydrogels enables hierarchical fiber-hydrogel composites that combine biomimetic fibrous architecture, structural support, and tissue-like microenvironments [36–40]. Such hybrid systems have shown promise in musculoskeletal and other soft-tissue regeneration, whereas their application in ischemic brain repair remains largely unexplored. Ischemic brain injury presents additional challenges, including irregular lesion cavities, the extremely soft mechanical properties of brain tissue, and the need for coordinated neurovascular regeneration and appropriately timed therapeutic delivery.

In this study, we developed an injectable fiber-hydrogel hybrid scaffold by incorporating VEGF/GDNF-loaded gelatin methacryloyl/polycaprolactone (GelMA/PCL) core-shell short electrospun fibers into a VEGF-containing hydrogel matrix composed of thiol-modified hyaluronic acid/heparin and gelatin. The hierarchical architecture combines an injectable hydrogel matrix with embedded short fibrous components to enable localized delivery of VEGF and GDNF. The scaffold was evaluated under oxygen-glucose deprivation (OGD) conditions for its effects on endothelial cell migration, angiogenic activity, SH-SY5Y cell metabolic activity, and PC12 neurite outgrowth. This study aimed to establish a fiber-hydrogel platform for localized delivery of angiogenic and neurotrophic factors and coordinated modulation of vascular and neuronal cellular responses under ischemia-mimicking conditions.

2. Experimental Section

2.1. Materials

PCL ($M_n = 80,000$) was purchased from Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). GelMA was obtained from EFL Biotechnology Co., Ltd. (Suzhou, China). VEGF and GDNF were purchased from Abcam (Cambridge, UK) and Wuhan Huamei Bioengineering Co., Ltd. (Wuhan, China), respectively. Human VEGF and GDNF enzyme-linked immunosorbent assay (ELISA) kits were supplied by Wuhan Huamei Bioengineering Co., Ltd. Cell Counting Kit-8 (CCK-8) and Live/Dead Cell Viability/Cytotoxicity Assay Kit were purchased from Solarbio Life Sciences (Beijing, China). Alexa Fluor 555 phalloidin, 4',6-diamidino-2-phenylindole (DAPI), and Alexa Fluor 488-conjugated secondary antibody were obtained from Thermo Fisher Scientific (Waltham, MA, USA). Anti-neurofilament 200 (NF200) antibody (1:500) was purchased from Sigma-Aldrich.

The injectable hydrogel precursor, HyStem-HP, composed of thiol-modified hyaluronic acid/heparin, gelatin, and a polyethylene glycol diacrylate (PEGDA) crosslinker, was obtained from Advanced BioMatrix (Carlsbad, CA, USA). All other reagents were of analytical grade and used as received unless otherwise stated.

2.2. Fabrication of Hybrid Scaffolds

Growth factor-loaded GelMA@PCL core-shell nanofibers were fabricated by coaxial electrospinning. Briefly, PCL and GelMA were separately dissolved in trifluoroethanol at concentrations of 10% w/v. Lithium phenyl-2,4,6-trimethylbenzoylphosphine (0.25% w/v) was added to the GelMA solution as a photoinitiator. For the preparation of VEGF/GDNF-loaded nanofibers, VEGF and GDNF were added to the GelMA core solution at a final concentration of 10 µg/mL immediately before electrospinning. During coaxial electrospinning, the GelMA solution containing VEGF and GDNF was used as the core phase, while the PCL solution was used as the shell phase. Coaxial electrospinning was performed at an applied voltage of 15 kV, with the core and shell flow rates set at 0.3 and 1.0 mL/h, respectively. The nanofibers were collected on a rotating drum collector at 1300 rpm to obtain aligned nanofibrous membranes. During the 6 h electrospinning process, the GelMA core solution containing VEGF and GDNF was freshly prepared every hour to minimize prolonged exposure to trifluoroethanol and preserve the bioactivity of the encapsulated growth factors. The collected membranes were then exposed to 405 nm light (10 mW/cm²) for 30 s to photocrosslink the GelMA core. Oxygen plasma treatment was subsequently performed at 30 W for 20 s to improve the surface hydrophilicity of the nanofibers. To visualize the separate core and shell streams during coaxial electrospinning, rhodamine B and indocyanine green (ICG) were separately incorporated into the GelMA core and PCL shell solutions, respectively, before electrospinning.

The aligned core-shell nanofibrous membranes were processed into short fiber fragments by cryosectioning. Briefly, the membranes were cut into 1.5 × 1.5 cm² pieces, embedded in optimal cutting temperature compound, and frozen at −20 °C. The frozen fiber blocks were cryosectioned into short fiber fragments with approximate dimensions of 100 × 50 µm². Residual compound was removed by repeated washing with deionized water, followed by ultrasonic dispersion for 30 min. The dispersed short fibers were then lyophilized and stored for subsequent use.

For the fabrication of the injectable growth factor-loaded hybrid scaffold, two flowable precursor solutions were prepared according to the manufacturer's protocol. The first precursor consisted of thiol-modified hyaluronic acid/heparin (10 mg) and gelatin (10 mg) dissolved in 2 mL of phosphate-buffered saline (PBS), into which soluble VEGF and VEGF/GDNF-loaded GelMA@PCL short fibers were uniformly dispersed. The second precursor contained the PEGDA crosslinker (5 mg in 0.5 mL). Upon co-injection, the two precursor solutions rapidly mixed and initiated thiol-mediated crosslinking, enabling in situ hydrogel formation after incubation at 37 °C for 20 min. The final concentrations of free VEGF and VEGF/GDNF-loaded short fibers in the hybrid hydrogel precursor were 100 ng/mL and 5 mg/mL, respectively. Pristine hybrid scaffolds containing 5 mg/mL pristine GelMA@PCL short fibers without growth factors were prepared as controls.

2.3. Characterization of Hybrid Scaffolds

The core-shell architecture of the electrospun nanofibers was characterized using transmission electron microscopy (TEM, HT7700, Hitachi, Japan). The morphology of the electrospun nanofibers, short fibers, hydrogels, and hybrid scaffolds was examined by scanning electron microscopy (SEM, S-4800, Hitachi, Japan). The fiber diameter was quantified using ImageJ by measuring 30 randomly selected fibers per sample from representative SEM images, and the results were presented as mean ± SD. Fiber alignment was independently evaluated using a fast Fourier transform-based image analysis in ImageJ. Briefly, selected regions of the SEM images were subjected to 2D fast Fourier transform to generate the corresponding Fourier spectra. The angular distribution of the Fourier intensity was subsequently analyzed to obtain the fiber orientation distribution, which was used to characterize the overall alignment of the fibrous membranes. For hydrogel-based samples, freeze-dried specimens were used to examine scaffold morphology and the distribution of short fibers within the dried matrix. The surface hydrophilicity of the nanofibers before and after plasma treatment was evaluated by water contact angle measurements using an OCA20 contact angle analyzer (Krüss, Germany).

To evaluate injectability at different gelation times, the two precursor solutions were mixed and incubated at 37 °C for 0, 10, and 20 min. At each time point, the hybrid hydrogel was loaded into a syringe and manually extruded through a 26 G needle, and the injection process was photographed. The rheological properties of the gelled hybrid hydrogel (d = 5 mm) were characterized using a rotational rheometer.

The degradation behavior of the nanofibers and hybrid scaffolds was evaluated in PBS at 37 °C under gentle shaking. PCL nanofibers and growth factor-loaded core-shell nanofibers (Fiber-GF) were prepared as circular

samples with a diameter of 15.6 mm. Pristine hydrogels and hybrid scaffolds were prepared with a volume of 350 μL . Each sample was immersed in 500 μL PBS and collected at predetermined time points. After washing with deionized water, the samples were lyophilized and weighed. The remaining mass was calculated as the percentage of dry weight relative to the initial dry weight.

To investigate the release of VEGF and GDNF, hybrid scaffolds with a volume of 100 μL were incubated in 100 μL PBS at 37 °C. At predetermined time points (2, 4, 6, 8, 10, 12, and 14 days), the release medium was completely collected and replaced with an equal volume of fresh PBS. The concentrations of VEGF and GDNF in the collected media were quantified using ELISA kits according to the manufacturers' instructions, and cumulative release was calculated by summing the amounts measured at each time point. The final cumulative released amount was considered the total releasable amount of each growth factor from the scaffold and was used to determine the corresponding dose for the free growth factor control groups.

2.4. In Vitro Evaluation of Angiogenic Activity under OGD Conditions

An OGD model was established to simulate ischemic injury in vitro. Briefly, human umbilical vein endothelial cells (HUVECs) were cultured in glucose-free medium and placed in an anaerobic chamber with less than 1% O_2 for 1 h before subsequent experiments. After OGD treatment, cells were assigned to four groups: untreated control group (Blank), free VEGF group (Free-VEGF), scaffold without growth factors group (Scaffold), and growth factor-loaded hybrid scaffold group (Scaffold-GF). The Free-VEGF group was treated with free VEGF at a dose equivalent to the total releasable amount from 100 μL of the Scaffold-GF scaffold (19.6 ± 3.2 ng per 100 μL scaffold). Scaffold extracts were prepared by incubating scaffolds with a volume of 100 μL in 500 μL serum-free DMEM for 24 h, followed by filtration through a 0.22 μm membrane. For the scratch assay, OGD-treated HUVECs were seeded into 24-well plates at a density of 1×10^4 cells per well and cultured until a confluent monolayer formed. A linear wound was generated using a sterile 200 μL pipette tip, and different scaffold extracts were then added. After 24 h of incubation, cells were fixed with 3% glutaraldehyde, permeabilized with 0.1% Triton X-100, blocked with 1% bovine serum albumin, and stained with Alexa Fluor 555 phalloidin and DAPI. The remaining wound area was quantified using ImageJ.

For cell growth analysis, sterilized scaffolds (100 μL) were placed in 24-well plates, and OGD-treated HUVECs were seeded at a density of 1×10^4 cells per well. Cell growth was evaluated on days 1, 3, 5, and 7 using the CCK-8 assay. Cell viability and cytocompatibility were further assessed by Live/Dead staining on day 7 using calcein-AM and propidium iodide, followed by fluorescence microscopy.

For the tube formation assay, Matrigel was diluted with serum-free DMEM at a volume ratio of 1:1 on ice and added to 24-well plates. After 45 min at 37 °C, OGD-treated HUVECs were seeded onto Matrigel at a density of 3×10^4 cells per well and then incubated with different scaffold extracts prepared as described in the scratch assay. After 4 h, capillary-like networks were imaged using optical microscopy. Total number of junctions, total vessel length, and vessel percentage area were quantified using ImageJ.

2.5. In Vitro Evaluation of Neural Cell Growth and Differentiation under OGD Conditions

SH-SY5Y and PC12 cells were used to evaluate the neuroprotective and neuroregenerative effects of the hybrid scaffold under ischemia-mimicking conditions. Briefly, cells were cultured in glucose-free medium and placed in an anaerobic chamber with less than 1% O_2 for 1 h before subsequent experiments. After OGD treatment, cells were assigned to four groups: untreated control group (Blank), free GDNF group (Free-GDNF), scaffold without growth factors group (Scaffold), and growth factor-loaded hybrid scaffold group (Scaffold-GF). The Free-GDNF group was treated with free GDNF at a dose equivalent to the total releasable amount from 100 μL of the Scaffold-GF scaffold (9.9 ± 1.8 ng).

For cell growth analysis, SH-SY5Y neuroblastoma cells were cultured in DMEM supplemented with 10% fetal bovine serum at 37 °C. After OGD treatment, scaffolds (100 μL) were placed in 24-well plates, and SH-SY5Y cells were seeded at 1×10^4 cells per well. Cell growth was assessed on days 1, 3, and 5 using the CCK-8 assay. Cell viability and cytocompatibility was evaluated by Live/Dead staining on day 5 and observed using fluorescence microscopy.

For neuronal differentiation, OGD-treated PC12 cells were seeded into 24-well plates and cultured in differentiation medium containing nerve growth factor (NGF) at 50 ng/mL. To evaluate the effects of growth factors released from the scaffolds while minimizing direct physical contact between the scaffolds and PC12 cells, 200 μL of the hybrid scaffold was placed in the upper chamber of each Transwell insert. After 10 days of co-culture, cells were fixed and immunostained with anti-NF200 antibody, followed by Alexa Fluor 488-conjugated

secondary antibody. Cell nuclei were counterstained with DAPI. Neurite outgrowth was visualized using confocal laser scanning microscopy and quantitatively analyzed using ImageJ.

2.6. Statistical Analysis

All experiments included at least three parallel samples, and data are presented as mean $\pm$ standard deviation (SD). Statistical analyses were performed using GraphPad Prism 10. Comparisons between two groups were performed using Student's *t*-test. Comparisons among more than two groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparisons test. Statistical significance was defined as $p < 0.05$.

3. Results and Discussion

3.1. Fabrication and Characterization of Injectable Fiber-Hydrogel Hybrid Scaffolds

VEGF/GDNF-loaded GelMA@PCL core-shell nanofibers were fabricated by coaxial electrospinning, using the VEGF/GDNF-containing GelMA solution as the core phase and the PCL solution as the shell phase. In this configuration, the hydrophilic GelMA core provided a compartment for protein encapsulation, while the PCL shell maintained the fibrous morphology and was expected to retard the outward diffusion of the loaded proteins. As shown in the inset of Figure 1a, rhodamine B and ICG were used to visualize the core and shell streams within the coaxial needle, respectively, illustrating their spatially separated configuration during electrospinning. The TEM image further showed the core-shell structure of the resulting nanofibers (Figure 1a). SEM observation further confirmed the formation of continuous and uniform nanofibers, with an average diameter of 940 ± 180 nm (Figures 1b and S1). The as-spun nanofibers exhibited a water contact angle of 120.5° , reflecting the hydrophobic nature of the PCL-rich surface. After oxygen plasma treatment, the water contact angle decreased to 53.4° , indicating improved surface wettability (Figure S2).

The electrospun nanofiber membranes were then processed into short fibers by cryosectioning followed by ultrasonic dispersion. Optical microscopy confirmed that the resulting GelMA@PCL short fibers had an average length of 58.5 ± 20.2 μ m, allowing their homogeneous dispersion within the thiol-modified hyaluronic acid/heparin and gelatin precursor (Figure 1c). The injectable system comprised two precursors: a thiol-modified hyaluronic acid/heparin and gelatin solution containing soluble VEGF and short fibers, and PEGDA crosslinker solution. Upon co-injection, the two flowable precursor solutions rapidly mixed and underwent thiol-mediated crosslinking, enabling rapid in situ gelation to form a stable fiber-hydrogel hybrid scaffold. The morphology of the hydrogel-based scaffolds was examined by SEM after freeze-drying. The pristine HyStem-HP hydrogel exhibited a porous interconnected morphology (Figure 1d). After incorporation of short fibers, the hybrid scaffold maintained a similar porous architecture, with short fibers distributed throughout the hydrogel matrix (Figure 1e).

The injectability of the hybrid hydrogel was evaluated at 0, 10, and 20 min after mixing the two precursor solutions (Figure S3a). The hydrogel could be injected through a 26 G needle at all tested time points, including after gelation at 37°C for 20 min. Rheological analysis of the gelled hydrogel further showed shear-thinning behavior, with viscosity decreasing as the shear rate increased (Figure S3b). These results demonstrate that the hybrid hydrogel remained injectable through a 26 G needle under the tested conditions.

The mass retention of different scaffold components was evaluated in PBS at 37°C . PCL nanofibers showed minimal mass loss over 30 days, whereas Fiber-GF showed approximately 24% mass loss during the same period (Figure 1f). This mass decrease was mainly associated with the hydrated GelMA core and the release or loss of encapsulated components, while the PCL shell remained relatively stable. For the hydrogel-based samples, the pristine HyStem-HP hydrogel retained $29.2 \pm 6.0\%$ of its initial mass after 30 days, whereas the hybrid scaffold retained $47.1 \pm 12.9\%$ due to slower degradation of the embedded nanofibers (Figure 1g).

Each 100 μ L of hybrid scaffold contained 19.6 ± 3.2 ng of VEGF and 9.9 ± 1.8 ng of GDNF, confirming the successful incorporation of both types of growth factors in the scaffold. The release profiles of VEGF and GDNF from the hybrid scaffold were further quantified by ELISA. Both growth factors showed an early release phase during the initial incubation period, followed by a marked decrease in release rate at later time points (Figure 1h,i). VEGF release reached 19.6 ± 3.2 ng by day 8 and was no longer detectable at day 10, whereas GDNF release remained detectable through day 10, reaching 9.9 ± 1.8 ng, but was no longer detectable at day 12. The resulting release profile from the hydrogel matrix and embedded core-shell short fibers may provide locally available angiogenic and neurotrophic cues during the initial cellular response to ischemic injury.

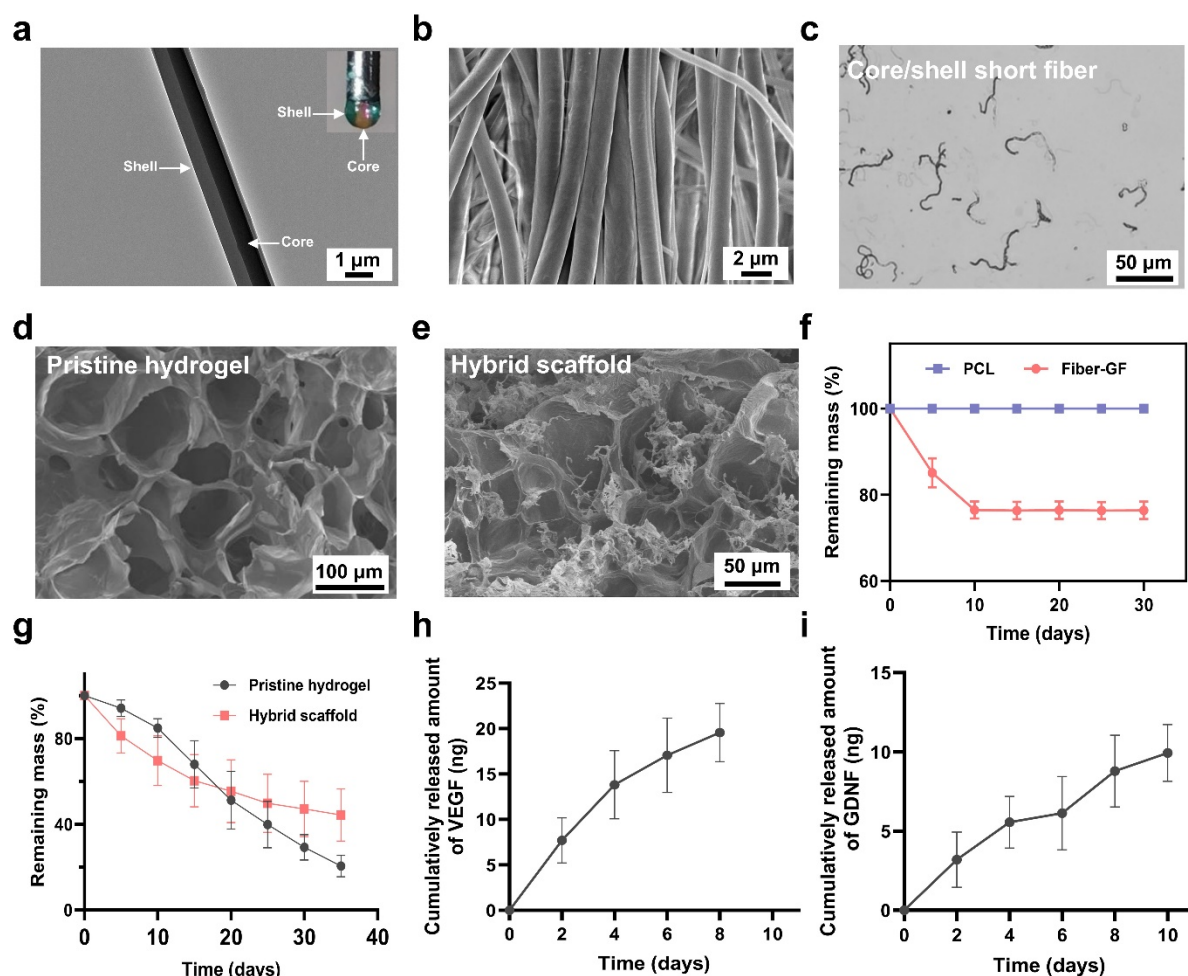


Figure 1. Characterization of GelMA@PCL short fibers and hybrid scaffolds. (a) TEM image of GelMA@PCL core-shell nanofibers, with the inset showing the spatially separated core and shell streams within the coaxial needle labeled with rhodamine B and ICG, respectively. (b) SEM image of GelMA@PCL core-shell nanofibers. (c) Optical microscopy image of GelMA@PCL short fibers. (d,e) SEM images of freeze-dried (d) pristine HyStem-HP hydrogel and (e) GelMA@PCL short fiber/HyStem-HP hybrid scaffold, respectively. (f) Mass retention profile of PCL nanofibers and Fiber-GF in PBS at 37 °C. (g) Mass retention profiles of pristine hydrogel and hybrid scaffold in PBS at 37 °C. (h,i) Cumulatively released profiles of (h) VEGF and (i) GDNF from the hybrid scaffold, respectively. Data are presented as mean $\pm$ SD ($n = 3$).

3.2. Regulation of Endothelial Cell Migration, Growth, and Tube Formation under OGD Conditions

Endothelial cell migration is an early event during angiogenesis and is important for vascular remodeling after ischemic injury. To evaluate the effect of the hybrid scaffold on endothelial migration under ischemic conditions, HUVECs were first subjected to OGD for 1 h and then assigned to the Blank, Free-VEGF, Scaffold, and Scaffold-GF groups. The cells were treated with basal culture medium, free VEGF-containing medium, scaffold extract, or Scaffold-GF extract, respectively, and their migratory response was evaluated using a scratch assay. After incubation for 24 h, HUVECs in the Blank group showed limited migration into the scratched area, indicating impaired endothelial cell motility after OGD treatment (Figure 2a). In contrast, the Free-VEGF, Scaffold, and Scaffold-GF groups showed reduced remaining wound areas, suggesting improved cell migration after treatment. The Scaffold group also reduced the remaining wound area compared with the Blank group, indicating that the scaffold extract itself provided a favorable environment for HUVECs migration. Quantitative analysis showed that the Scaffold-GF group exhibited the smallest remaining wound area, reaching $10.1 \pm 0.6\%$, while the Free-VEGF group showed a comparable value of $11.4 \pm 1.1\%$ (Figure 2b). These results indicate that the VEGF-containing hybrid scaffold extract retained pro-migratory activity under OGD conditions.

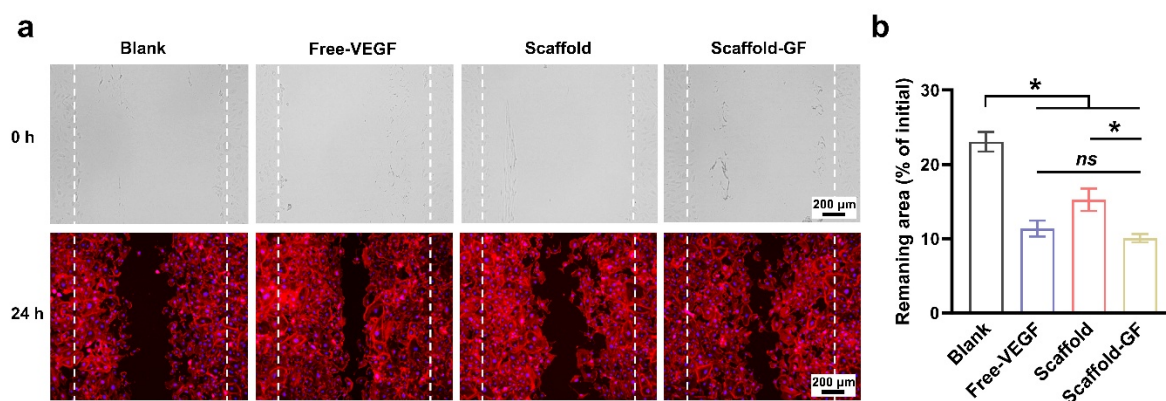


Figure 2. Effect of hybrid scaffolds on HUVECs migration under OGD conditions. **(a)** Representative images of the scratch assay by OGD-treated HUVECs after incubation with basal culture medium, free VEGF-containing medium, scaffold extract, or Scaffold-GF extract at 0 and 24 h. F-actin was stained with phalloidin, and nuclei were stained with DAPI. White dashed lines indicate the initial scratch boundaries. **(b)** Quantification of the remaining wound area after 24 h. Data are presented as mean $\pm$ SD ($n = 3$). Statistical significance was analyzed using one-way ANOVA followed by Tukey's multiple-comparisons test. * $p < 0.05$; n.s., not significant.

The effect of the scaffold on endothelial cell growth was further evaluated using the CCK-8 assay. As shown in Figure 3a, the optical density (OD) value increased gradually from day 1 to day 7 in all groups. On days 3, 5, and 7, the Free-VEGF, Scaffold, and Scaffold-GF groups showed higher OD values than the Blank group. The increased OD value in the Scaffold group suggests that the scaffold matrix itself may contribute to the cellular response. This effect may be associated with the presence of gelatin and hyaluronic acid/heparin, which have been reported to support cell–matrix interactions and cellular activity [41–43]. The Scaffold-GF group showed a further increase in the OD value compared with the Scaffold group, suggesting an additional effect of the released growth factors. Live/Dead staining at day 7 showed predominantly viable cells with few dead cells in all groups, indicating good cytocompatibility of the scaffolds (Figure 3b).

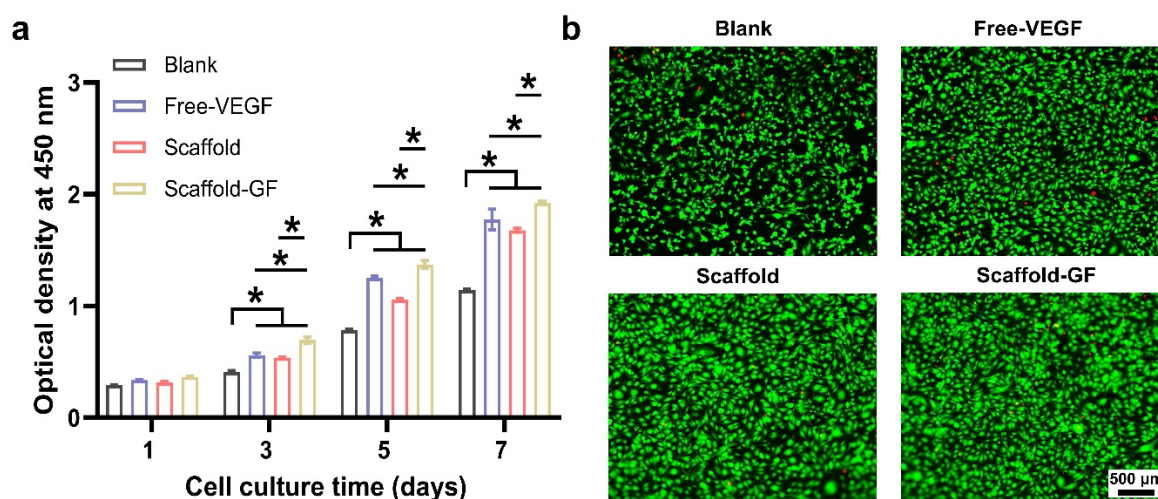


Figure 3. **(a)** OD values of HUVECs cultured with different scaffolds for 1, 3, 5, and 7 days, measured using the CCK-8 assay. **(b)** Live/Dead staining of HUVECs at day 7 (green: live; red: dead). Data are presented as mean $\pm$ SD ($n = 3$). At each time point, statistical significance among groups was analyzed using one-way ANOVA followed by Tukey's multiple-comparisons test. * $p < 0.05$.

Functional angiogenic activity was evaluated using a Matrigel tube formation assay. After OGD treatment, HUVECs were seeded on Matrigel and incubated with basal culture medium, free VEGF-containing medium, scaffold extract, or Scaffold-GF extract. After 4 h of incubation, HUVECs in the Free-VEGF and Scaffold-GF groups formed more evident capillary-like networks than those in the Blank and Scaffold groups (Figure 4a). Quantitative analysis showed that total number of junctions, total vessel length, and vessel percentage area were increased in the Free-VEGF and Scaffold-GF groups compared with the Blank and Scaffold groups (Figure 4b). No significant difference was observed between the Free-VEGF and Scaffold-GF groups, although Free-VEGF

showed a slight trend toward higher tube formation parameters. This result is reasonable because the tube formation assay is a short-term assay in which soluble VEGF can directly stimulate endothelial network formation. The comparable response in the Scaffold-GF group indicates that the scaffold-derived growth factors retained angiogenic bioactivity under OGD conditions.

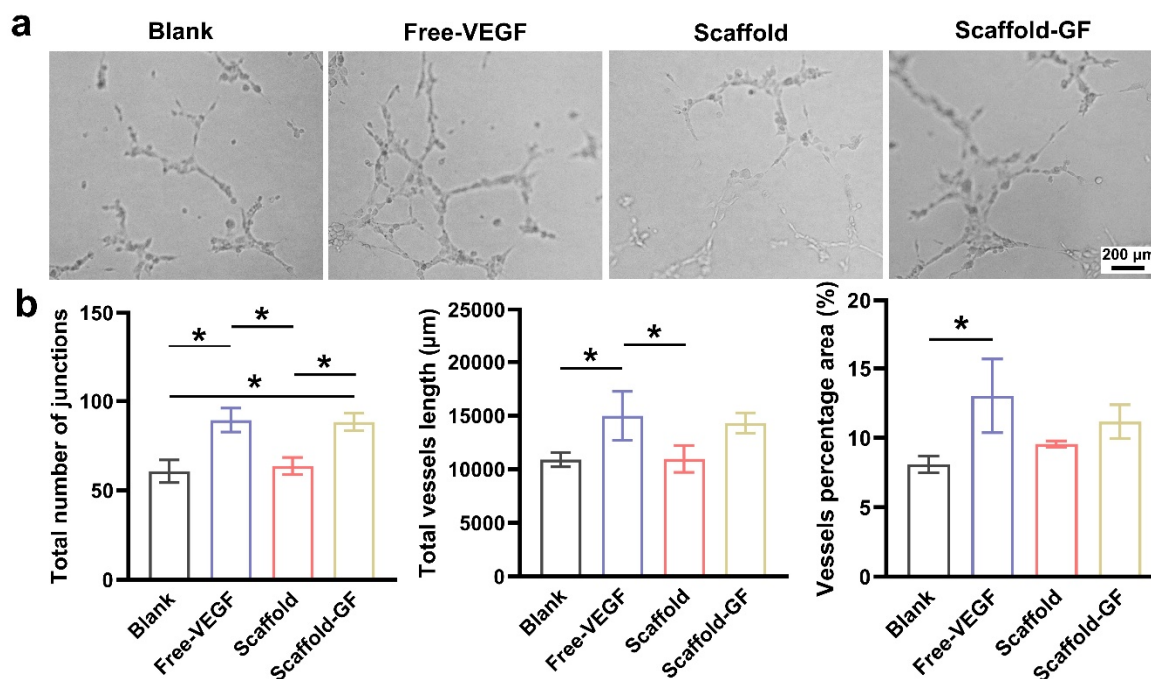


Figure 4. Effect of hybrid scaffolds on HUVECs tube formation under OGD conditions. (a) Representative images of capillary-like networks formed by OGD-treated HUVECs on Matrigel after incubation with basal culture medium, free VEGF-containing medium, scaffold extract, or Scaffold-GF extract for 4 h. (b) Quantitative analysis of total number of junctions, total vessel length, and vessel percentage area. Data are presented as mean ± SD (n = 3). Statistical significance was analyzed using one-way ANOVA followed by Tukey's multiple-comparisons test. * $p < 0.05$.

3.3. SH-SY5Y Cell Growth and PC12 Neurite Differentiation under OGD Conditions

Supporting neuronal cell survival and neurite outgrowth is important for neural repair after ischemic injury. To evaluate the effect of the hybrid scaffold on neuronal cell behavior, SH-SY5Y cells were subjected to OGD for 1 h and then treated with basal culture medium (Blank), free GDNF-containing medium (Free-GDNF), pristine scaffold (Scaffold), or growth factor containing scaffold (Scaffold-GF), respectively. Cell growth was evaluated on days 1, 3, and 5 using the CCK-8 assay. As shown in Figure 5a, the OD values increased over time in all groups. On days 3 and 5, the Free-GDNF group showed higher OD values than the Blank and Scaffold groups. The Scaffold-GF group exhibited the highest OD values among the tested groups, suggesting a favorable effect of the growth factor-loaded scaffold on SH-SY5Y cell growth under OGD conditions. Live/Dead staining on day 5 showed predominantly viable cells with few dead cells in all groups, indicating no obvious cytotoxicity toward SH-SY5Y cells (Figure 5b).

PC12 cells were used to evaluate neuronal differentiation and neurite outgrowth. After OGD treatment, PC12 cells were cultured in NGF-containing differentiation medium, while different scaffolds were placed in Transwell inserts to minimize direct scaffold–cell contact and assess the effects of released GDNF on neurite outgrowth. After 10 days of co-culture, NF200 immunostaining showed neurite extension in all groups, with more pronounced neurite outgrowth in the Free-GDNF and Scaffold-GF groups than in the Blank and Scaffold groups (Figure 6a). Quantitative analysis showed that the average neurite lengths in the Scaffold-GF and Free-GDNF groups were $181.7 \pm 48.8 \mu\text{m}$ and $185.3 \pm 58.5 \mu\text{m}$, respectively, which were higher than those in the Blank group ($123.8 \pm 28.4 \mu\text{m}$) and Scaffold group ($137.0 \pm 44.6 \mu\text{m}$) (Figure 6b). No significant difference in average neurite length was observed between the Scaffold-GF and Free-GDNF groups. A similar trend was observed for the longest neurite length. These results indicate that GDNF-containing treatments supported neurite outgrowth of OGD-treated PC12 cells in the presence of NGF, and Scaffold-GF achieved a comparable effect to free GDNF treatment.

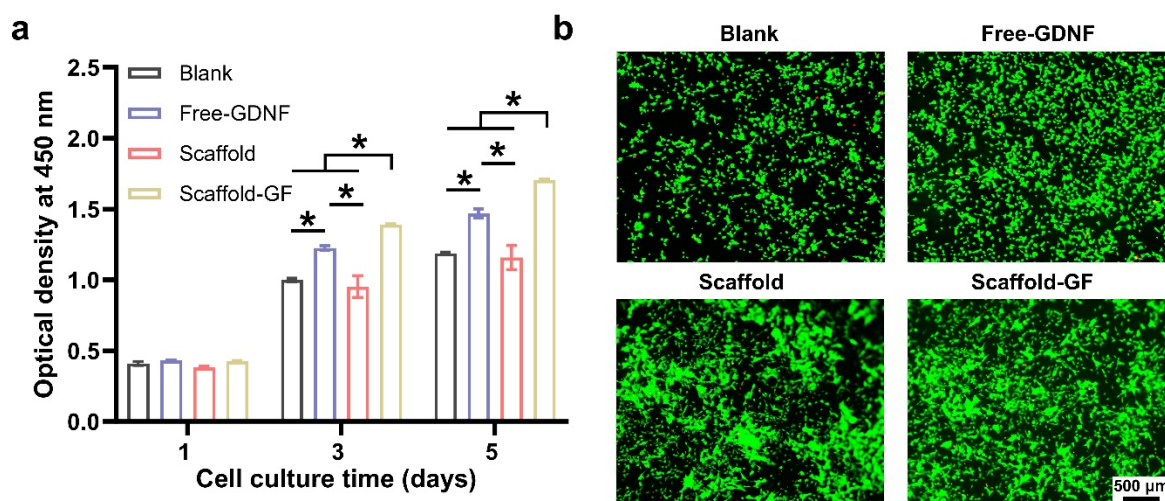


Figure 5. Effect of hybrid scaffolds on SH-SY5Y cell growth and viability under OGD conditions. (a) OD values of SH-SY5Y cells cultured with different treatments for 1, 3, and 5 days, measured using the CCK-8 assay. (b) Live/Dead staining of SH-SY5Y cells on day 5. Green fluorescence indicates live cells, and red fluorescence indicates dead cells. Data are presented as mean $\pm$ SD ($n = 3$). At each time point, statistical significance among groups was analyzed using one-way ANOVA followed by Tukey’s multiple-comparisons test. * $p < 0.05$.

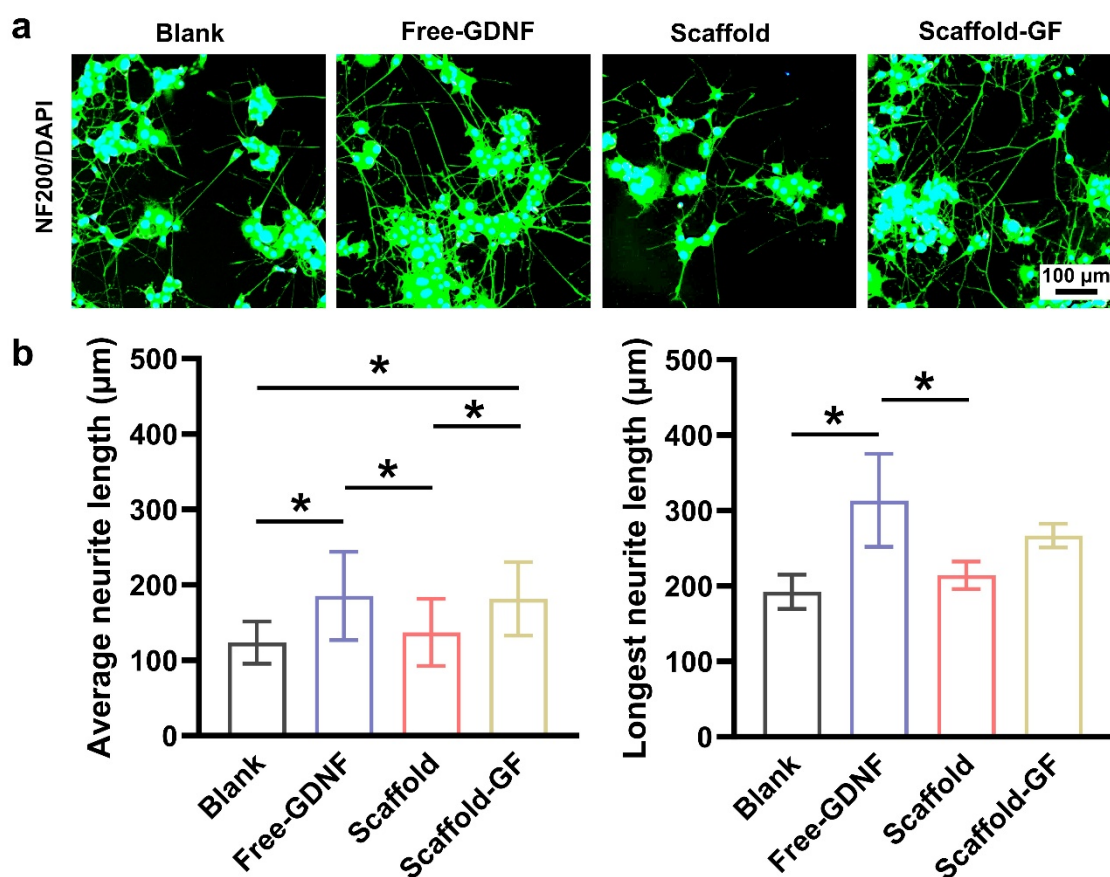


Figure 6. Effect of hybrid scaffolds on PC12 neurite outgrowth under OGD conditions. (a) Representative fluorescence images of PC12 cells showing neurite extension after co-culture with different scaffolds in a Transwell system. NF200, green; DAPI, blue. (b) Quantitative analysis of average neurite length and longest neurite length. Data are presented as mean $\pm$ SD ($n = 3$). Statistical significance was analyzed using one-way ANOVA followed by Tukey’s multiple-comparisons test. * $p < 0.05$.

Taken together, these findings suggest that the hybrid scaffold can modulate endothelial and neuronal cell responses under ischemia-mimicking OGD conditions. Nevertheless, the present study is limited to an in vitro

OGD model and therefore does not fully capture the complex pathophysiological environment of ischemic brain injury. Further animal studies will be required to determine whether these cellular responses translate into therapeutic benefit and to assess scaffold retention, degradation, and biological performance *in vivo*.

4. Conclusions

In this study, we developed a hierarchical fiber-hydrogel hybrid scaffold by incorporating VEGF/GDNF-loaded GelMA@PCL short nanofibers into a VEGF-containing hyaluronic acid/heparin and gelatin hydrogel matrix. The scaffold combined a hydrogel network with embedded fibrous components and provided localized release of angiogenic and neurotrophic factors mainly during the early incubation period. The core-shell short fibers improved the structural retention of the hydrogel scaffold while serving as additional growth factor reservoirs. Under OGD conditions, the hybrid scaffold promoted HUVECs migration, supported endothelial cell responses, and maintained angiogenic activity in a tube formation assay. It also enhanced SH-SY5Y cell growth and supported PC12 neurite outgrowth in the presence of NGF. These results suggest that the hybrid scaffold can modulate vascular and neuronal cell responses in an ischemia-mimicking microenvironment. This work provides a biomaterial platform for the design of injectable materials aimed at neurovascular repair.

Supplementary Materials: The following supporting information can be downloaded at: <https://media.sciltp.com/articles/others/2609301642414796/MI-26070026-SI.pdf>. Figure S1. (a) Diameter distribution of GelMA@PCL core-shell nanofibers obtained from SEM images and (b) fiber orientation distribution determined by fast Fourier transform-based analysis of SEM images. Figure S2. Water contact angle measurements of Fiber-GF before and after plasma treatment. Figure S3. Injectability of the hybrid scaffold. (a) Representative images showing extrusion through a 26 G needle at 0, 10, and 20 min after precursor mixing. (b) Shear-thinning behavior of the hybrid hydrogel after gelation at 37 °C for 20 min.

Author Contributions: L.R., K.M., W.D., F.T., J.X.: conceptualization; L.R., K.M., W.D., K.H., J.H., J.Q.: methodology; K.H., J.H., J.Q.: software; F.T., J.X.: data curation; L.R., K.M.: writing—original draft preparation; L.R., K.M., W.D.: visualization, investigation; F.T., J.X.: supervision; J.Q., F.T., J.X.: validation; L.R., K.H., J.H., J.Q., F.T., J.X.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work is supported by the Fundamental Research Funds for the Central Universities (buctrc202312), Interdisciplinary Research Center of Beijing University of Chemical Technology (No. XK2025-05), Talent Introduction Research Initiation Fund (2022-T-02), and the Opening Foundation of State Key Laboratory of Organic-Inorganic Composites (oic-202601002 and oic-202602035).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies: During the preparation of this work, the authors used ChatGPT to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article

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