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Versatile Hydrogel Ensembles with Macroscopic Multidimensions

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Methods allowing construction of macroscopic programmed materials in a flexible and efficient fashion are highly desirable. However, the existing approaches are far removed from such materials. A new self-healing-driven assembly (SHDA) strategy to fabricate various programmed materials by using uniform gel beads (microsize of 212 µm or millimeter size of 4 mm) as building blocks is described here. In virtue of hydrogen bonds and host–guest interactions between gel beads, a series of linear, planar, and 3D beaded assemblies are fabricated via SHDA in microfluidic channels in a continuous and controlled manner. From the perspective of practical applications, the use of gel assemblies is exploited for tissue engineering with controlled cells coculture, as well as light conversion materials toward white-light-emitting diodes (WLEDs). The SHDA strategy developed in this study gives a new insight into the facile and rapid fabrication of various programmed materials toward biological tissue and optoelectronic device.

Self-assembly enables the generation of order in nature, which also arouses great scientific and technological endeavor in synthetic materials.[1–4] Especially, small components self-organize to larger ensembles and complicate complexes across scales, using building blocks ranging from nanoscale to macroscale dimensions. In most cases, the driving forces of self-assembly are derived from magnetic force,[1,5] capillary,[6–8] electrostatic interactions,[9] surface tension,[10,11] hydrophile–lipophile balance,[12–14] or molecular recognition.[15–18] Many approaches are available for the self-assembly of molecules[19–21] and cells,[22,23] while macroscopic self-assembly, with number of reports recently, shows increasing importance because of its superiority such as precise design of building blocks and easy monitoring of assembly processes. Zamanian et al. realized the macroscopic self-assembly of cell-laden microgels by employing surface-tension forces at the liquid–air interface.[10] Qi et al. utilized DNA as programmable "glues" and shape-controlled gel as assembled units to construct prescribed structures.[24] Harada and co-workers reported a series of macroscopic self-assemblies of functional gel materials by making use of molecular recognition between host and guest moieties.[15–18] However, the currently reported macroscopic self-assemblies are limited in planar morphologies, and their use in the construction of programmed 3D ordered structures has been sparsely reported. The achievable sizes, shapes, ordered structures cannot be arbitrarily designed/controlled and the application of assemblies also remains challenging. In addition, little attention has been paid to the macroscopic self-assembly of spherical gel building blocks. If spherical gel beads can be macroscopically self-organized for programmed ordered ensembles by aid of the inherent driving force, a variety of robust soft materials and architectures would be realized, and such method could definitely provide new opportunities for assembled materials and science.

Herein, inspired by self-healing speciality of gels, we developed self-healing-driven assembly (SHDA) strategy to realize various programmed macroscopic self-organization of soft materials by using spherical gel beads as building blocks. To design smart soft materials, we initially fabricated three kinds of uniform spherical gel beads by a controllable and continuous microfluidic technique,, i.e., poly (MAH-*β*-CD-*co*-AA) and poly(VI-*co*-AA) gel beads at millimeter scale with diameter of 4 mm, and CdSe/ZnS quantum dots (QD)-loaded poly(HPA-*co*-NVP) gel beads at micrometer scale with diameter of 212 µm (MAH-*β*-CD = *β*-cyclodextrin modified with maleic anhydride, AA = acrylic acid, VI = vinyl imidazole, HPA = hydroxypropyl acrylate, and NVP = N-vinylpyrrolidone) (**Figure 1**a,b). These uniform gel beads exhibit excellent self-healing properties through hydrogen bond interactions among carboxylic groups and hydroxyl groups and host–guest interactions between *β*-CD groups and VI groups. With the aid of these inherent self-healing forces, we explored self-assembly of multidimensional-ordered architectures between these spherical gel beads for the first time. Macroscopic linear and planar structures were constructed within 5 s via interfacial SHDA, while 3D ordered materials were fabricated through layer-by-layer SHDA. Especially, we realized fabrication of oriented macroscopic assemblies (various linear, planar, 3D assemblies) via the microfluidic-assisted SHDA by simply using different channels, which guarantees ordered structure in a confined channel. By association of cell coculture with the programmed

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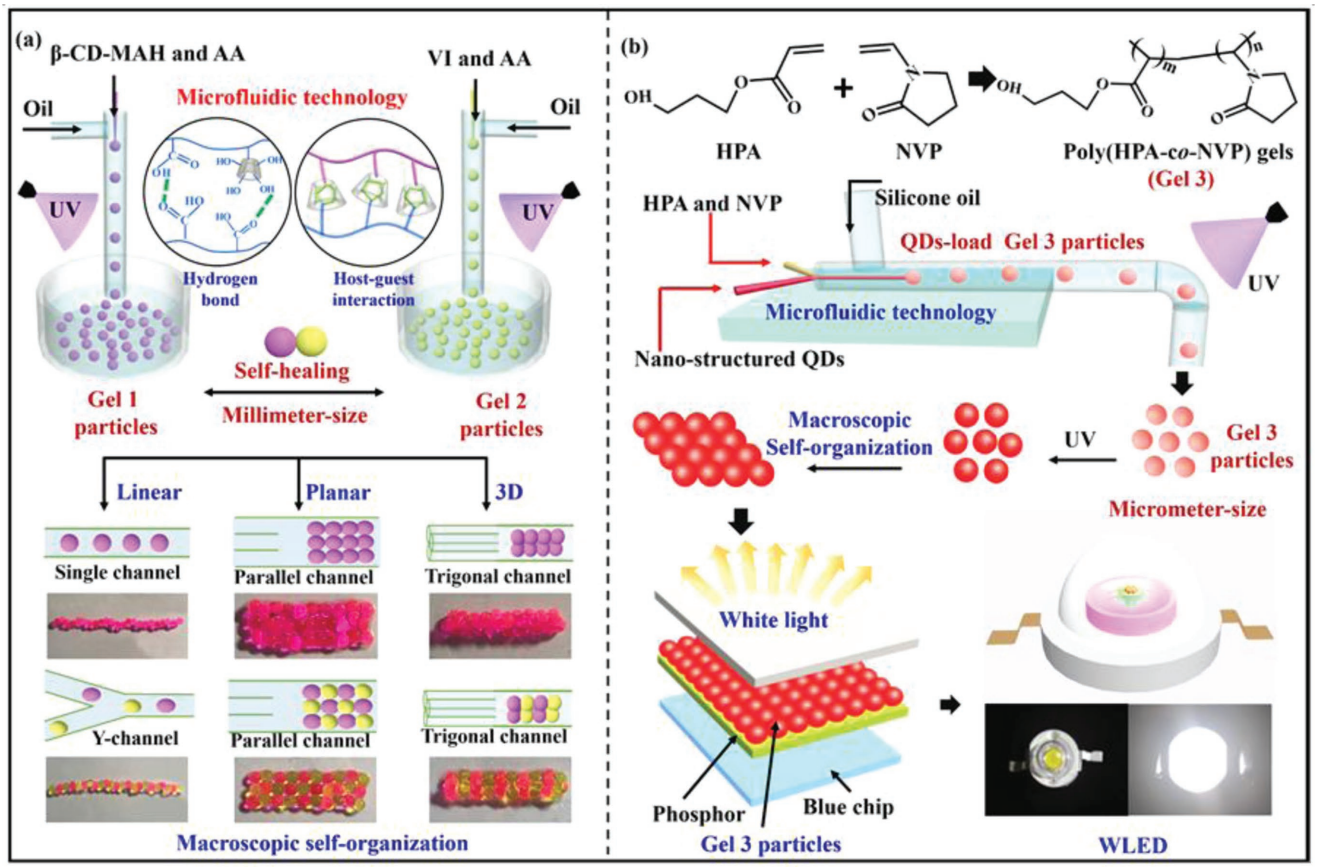

Figure 1. Schematic preparation and SHDA of self-healing gel beads. a) Construction of linear, planar, and programmed 3D ordered assemblies by using millimeter-sized self-healing Gel **1** and Gel **2** beads as building blocks via SHDA method. b) Construction of QD-loaded fluorescent architectures through SHDA and their application in WLEDs.

assembly, we confirmed that this SHDA strategy is convenient and feasible for creating 3D tissue-like materials. In addition, we accomplished SHDA by using fluorescent micron-sized gel beads to construct light conversion materials toward white-light-emitting diodes (WLEDs). This new SHDA strategy of gel beads might guide multistructure design of materials as well as promote the development of microfluidic self-assembly for diverse ordered beaded materials toward multifunctional tissue materials and LED devices.

The interfacial SHDA of gel beads to construct various linear and planar macrostructures at centimeter scale is shown in **Figure 2**. To implement macroscopic SHDA, we designed hydrogen bonds,[25,26] host–guest supramolecular forces,[27,28] and effective intermolecular interactions for self-healing of materials. We employed MAH-β-CD, VI, and AA to generate host–guest interactions between β-CD group and VI group and hydrogen interactions among carboxylic groups and hydroxyl groups. Typically, we continuously fabricated millimeter-sized poly(MAH-β-CD-*co*-AA) gel beads (named as Gel **1**, red, stained by rhodamine B) and poly(VI-*co*-AA) gel beads (named as Gel **2**, yellow, stained by fluorescein) via a microfluidic technique[29–31] with diameter of 4 mm (Figure 1a and Figures S1, S2, Supporting Information). Gel **1** exhibits self-healing property. Micro-IR spectroscopic characterizations were performed to exhibit chemical changes of carboxylic groups (≈1720 cm^{-1}) and hydroxyl groups (≈3413 cm^{-1}) before and after self-healing of Gel **1** through color variation (Figures S3 and S4, Supporting Information), which suggest that the hydrogen bonding enables the rupture interface to be welded.[25] Also, there are supramolecular host–guest assembly between Gel **1** (containing β-CD group as a host) and Gel **2** (containing VI group as a guest)[32] (Figures S5 and S6, Supporting Information). Based on these forces, we facilely carried out SHDA between Gel **1** beads or between Gel **1** and Gel **2** beads at the water/chloroform interface (Figure 2a and Figure S7, Supporting Information). These gel beads merged immediately once touched to each other (within 5 s) without any external stimulus, which stuck together firmly and could be stretched to a great extent without breaking (Figure 2b), demonstrating remarkable feasibility of this method to fabricate macroassemblies.

We focused on proof of this concept, and therefore we investigated the new SHDA method toward various macroassembly by using Gel **1** beads (Figure 2c) or Gel **1** and Gel **2** beads (Figure 2d,e). It should be noted that these self-organized assemblies exhibit macroscopic scale, for example, 1.6 cm for linear architectures formed by four gel beads. These sizes are obeyed by the following mathematical formula: L (cm) = $a \times 0.4$, where L is the length size and a is the gel bead number in length direction; W (cm) = $b \times 0.4$, where W is the width size and b is the gel bead number in width direction.

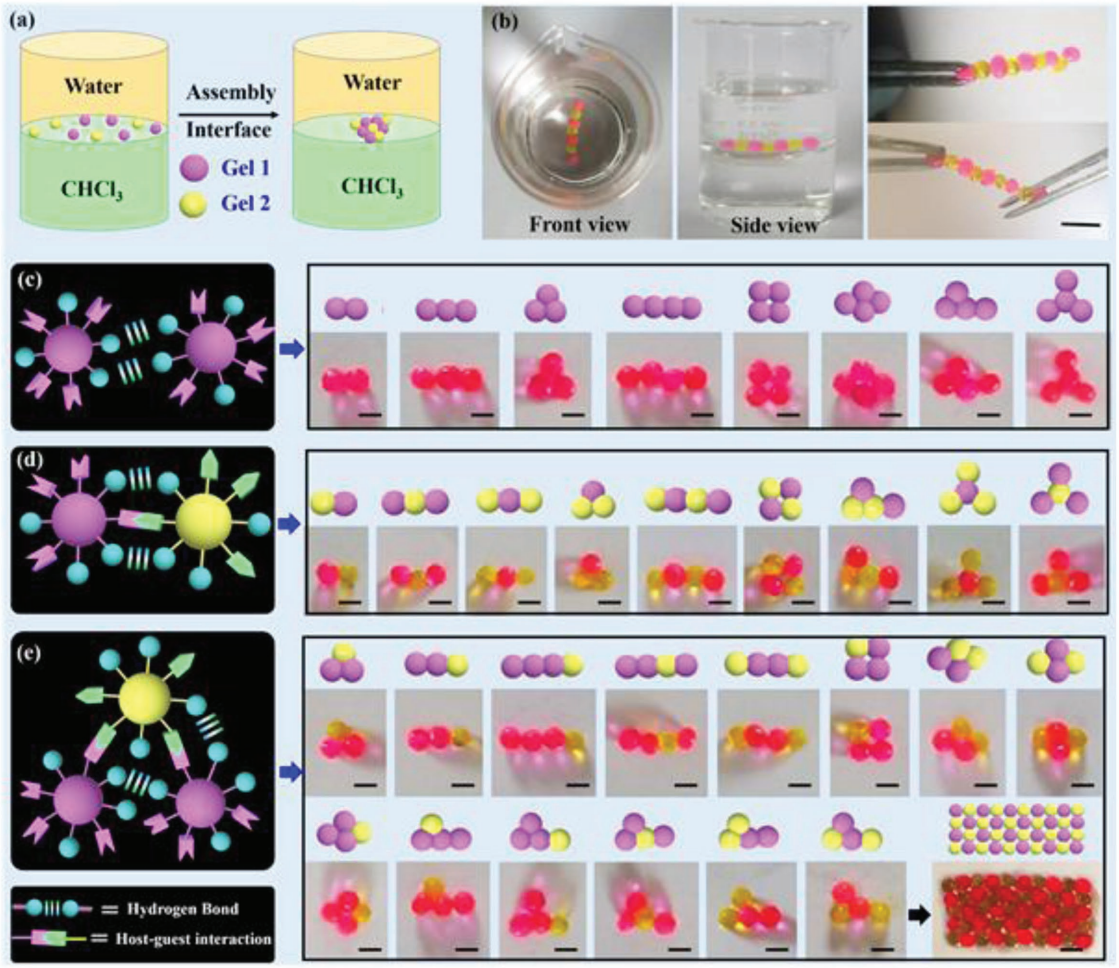

Figure 2. Interfacial SHDA for construction of linear and planar assemblies. a) Schematic illustration of the SHDA of Gel **1** and Gel **2** beads at water/chloroform interface. b) Photographs demonstrate linear assemblies formed at water/chloroform interface. The scale bar indicates 1.0 cm. Diverse linear and planar assembled patterns formed via a certain number of c) Gel **1** beads and d,e) Gel **1** and Gel **2** beads. The scale bar indicates 4.0 mm.

We further investigated the macroassembly and disassembly of gel beads toward homogeneous or heterogeneous architectures under different pH values. For instance, the homogeneous architecture formed by Gel **1** beads stuck together firmly at low pH (pH = 3) but dissociated when immersed into urea solution (pH = 10) (Figure S8, Supporting Information). At low pH value, the terminal carboxyl groups are protonated, which facilitate the formation of hydrogen bonds with other terminal-carboxyl groups across the interface, hence allowing the gel beads to be coupled; while at a high pH value (pH > 7), the terminal carboxyl groups are deprotonated, leading to the dissociation of assemblies. This phenomenon confirms that the SHDA of Gel **1** beads is originated from hydrogen interactions.[26] For heterogeneous architectures formed by Gel **1** and Gel **2** beads, they are exceedingly stable no matter at low pH (pH = 3) or urea solution (pH = 10) (Figure S9, Supporting Information), revealing strong synergistic effect of supramolecular interaction and hydrogen-bonding between these two beads. This interfacial SHDA of gel beads offers the advantages, such as flexibility, high efficiency, and visualization, to facilely construct macroscopic programmed materials with diverse linear and planar structures. The uniform gel beads fabricated by microfluidic technique also allow to produce these programmed materials in a controlled fashion.

The second set of experiments were focused on constructing 3D materials by SHDA method. We mixed the number of Gel **1** beads (or Gel **1** and Gel **2** beads) in the petri dish filled with n-hexane solution. By vigorously stirring, the associations between these gel beads occurred immediately (within 5 s) to form 3D macroscopic architectures (**Figure 3**a and Figure S10, Supporting Information). As described above, because of synergistic effect of hydrogen-bonding and host–guest supramolecular interactions, the 3D macroscopic architecture stuck firmly to sustain intensive stretch without breaking. However, the randomness of this self-organization results in these 3D architectures with irregular and disordered morphologies. Besides, we designed an ear mould via the 3D-printing technique[33] to fabricate 3D programmed ear-like organ materials by organizing self-healing Gel **1** beads. As shown in Figure 3b, the assembly displayed a perfect ear-shape with size up to 10 × 5 cm. The SHDA strategy developed herein holds the promise for integration of various heterogeneous self-healing beads, which can carry and

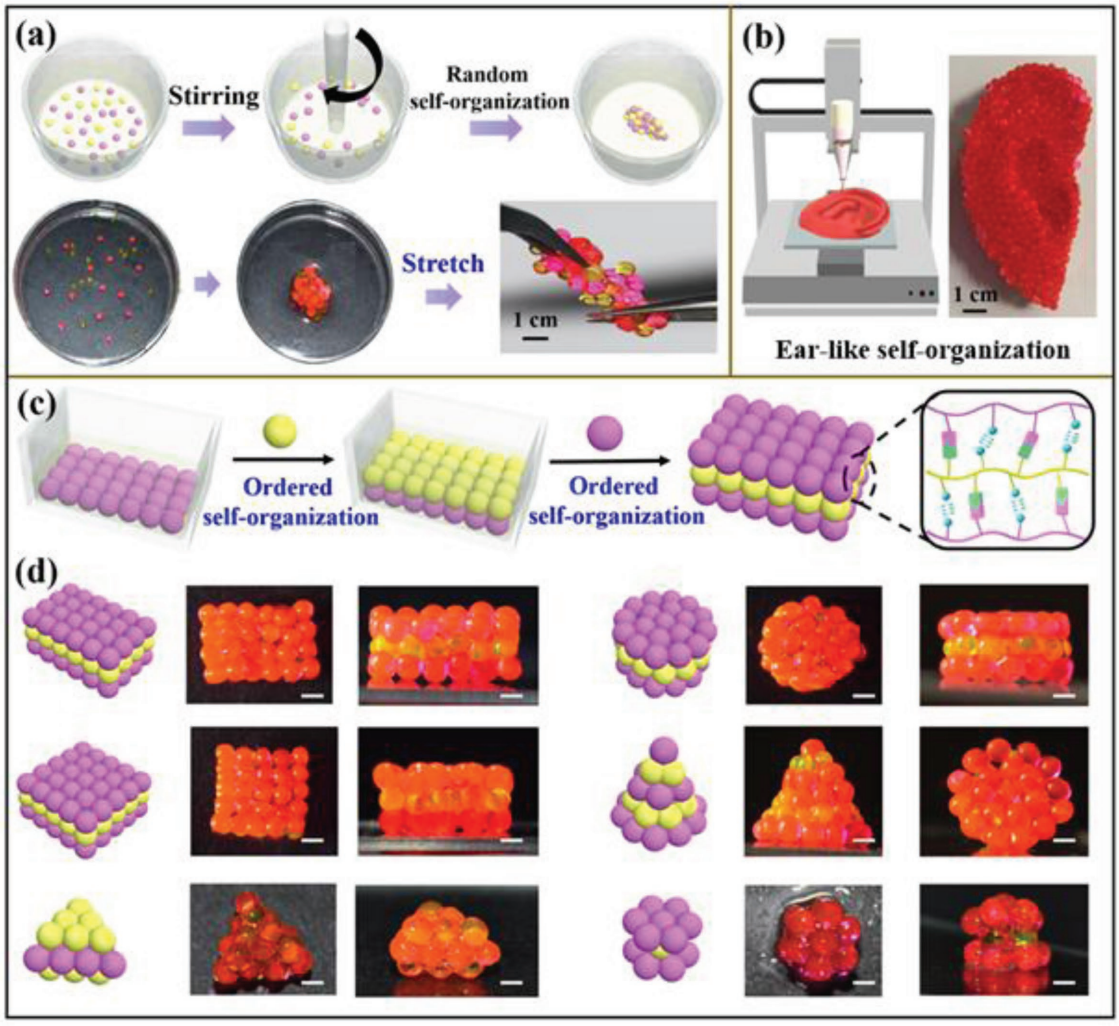

Figure 3. SHDA for construction of programmed 3D assemblies. a) Random self-organization of Gel **1** and Gel **2** beads in the petri dish. b) Ear-like organ materials formed via SHDA. The scale bar indicates 1.0 cm. c) Schematic illustration of the layer-by-layer SHDA procedure of Gel **1** and Gel **2** beads in the specific mould to form programmed 3D ordered structures. d) Photographs show diverse ordered 3D structures formed via macroscopic layer-by-layer SHDA. The scale bar indicates 4.0 mm.

exchange information with each other. If different cell-laden gel beads are used as building blocks in the SHDA method, it is conceivable that organ materials might be achieved. Compared with the reported computer-aided 3D organ printing of heterogeneous cell-laden gel,[34] the SHDA toward organ generation provides distinct advantages of rapidness, convenience, and flexibility.

Figure 3c indicates the scheme of layer-by-layer SHDA under a cuboid-shaped mould for fabrication of programmed 3D ordered architectures. Specifically, we firstly paved two layers of gel beads onto the bottom of a cuboid-shaped mould with several ordered pores; one layer is Gel **1** beads, and the other is Gel **2** beads. And then the Gel **1** beads were poured onto the top of two layers as the third layer. SHDA occurred between these three layers. By analogy, we believe that programmed 3D ordered sandwich-structured materials alternately arranged by Gel **1** and Gel **2** beads could be generated (Figure 3d and Figure S11, Supporting Information). The sizes of these ordered architectures are up to centimeter scale in all three dimensions. For example, the cuboid assembly size is $2.4 \times 1.6 \times 1.2$ cm. Analogous to the linear and planar structures, we can easily control and calculate the size of these ordered assemblies according to the uniform gel beads number. It should be noted that the whole assembly process was accomplished within 5 min. Three-layer programmed architecture could hold up weights above 100 g (Figure S12, Supporting Information) with tensile strength up to 0.032 Mpa. In contrast to the self-healing time (usually 2–24 h),[25,26] this SHDA method displays greatly high assembly efficiency within several minutes to fabricate programmed 3D architectures.

The interfacial and layer-by-layer SHDA described above provide a fast pathway to achieve beaded assemblies. However, both methods sustain vital defects of neither randomness or complexity. Herein, we aimed to realize programmed assembly[35–37] by the new SHDA strategy. To conduct the SHDA in a precisely continuous and controlled manner, a microfluidic device comprising different types of channels was designed for various assemblies (Figure S13, Supporting

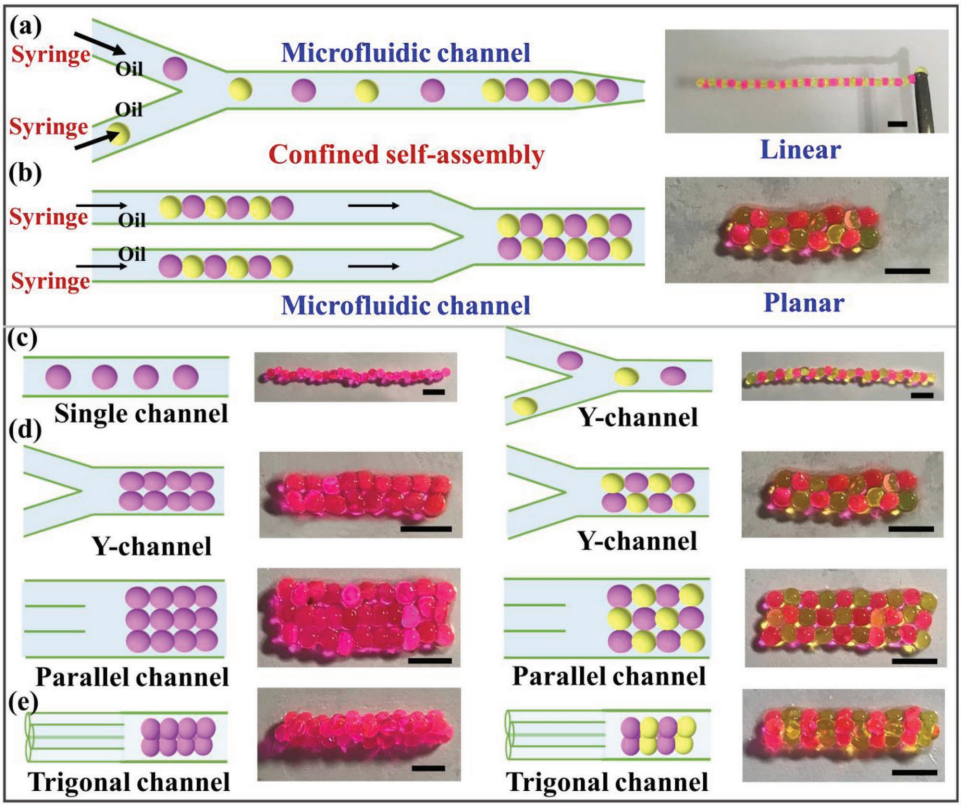

Figure 4. Microfluidic-assisted SHDA for construction of programmed linear, planar, and 3D assemblies. a) Schematic fabrication of linear assemblies alternately arranged by Gel **1** and Gel **2** beads in Y-type channel (diameter 4.5 mm). b) Schematic fabrication of ordered planar assemblies with two rows in Y-type channel (inlet diameter 4.5 mm; outlet diameter 9 mm). c) Linear, d) planar, and e) 3D architectures formed in different types of channels. The scale bar indicates 1.0 cm.

Information). For homogeneous linear Gel **1** assemblies, we designed a long single channel (diameter 4.5 mm) with a holder at the end. With methylsilicone oil flowing, Gel **1** beads were continuously pushed forward and gathered at the end of the channel, forming linear arranged assembles (Movie S1, Supporting Information). Y-type channel (diameter 4.5 mm) was utilized for linear assemblies alternately arranged by Gel **1** and Gel **2** beads. Typically, Gel **1** beads and Gel **2** beads moved forward in sequence under the control of microfluidic device, and formed heterogeneous linear architectures (**Figure 4**a,c and Movie S2, Supporting Information). By adjusting Y-type channel's inlet and outlet diameter (inlet diameter 4.5 mm; outlet diameter 9 mm), keeping both inlet flow rates the same, ordered planar assemblies with two rows could be achieved, as shown in Figure 4b and Movies S3, S4 in the Supporting Information. Similarly, taking advantage of three parallel channels, we obtained planar architectures with three rows of gel beads (Figure 4d). In addition, 3D ordered assemblies could also been controllably fabricated using trigonal channels (Figure 4e). By prolonging the length of channels and employing parallel channels, the SHDA is easily available for large-scale production of gel assemblies, as verified in Figure S14 in the Supporting Information. This microfluidic-assisted SHDA offers the following advantages: 1) The microfluidic technique offers a powerful platform for SHDA in a controllable and continuous fashion, which also could be developed to large-scale self-assembly. Moreover, the 3D structures of assemblies can be done with higher production rate. 2) The self-assembly of gel beads in a confined channel guarantees 3D ordered structure assemblies. 3) By simply designing different types of channels and controlling sequence of gel beads, various ordered linear, planar, and 3D architectures could been achieved, which might guide the multistructure design of materials as well as promote the development of microfluidic self-assembly.

Unlike Whitesides' work[38] about self-assembly of millimeter-scale polyhedra via capillary forces, the SHDA method developed in this study focused on self-healing interactions toward programmed materials. Interestingly, Harada and coworkers[15–18] successfully produced macroscopic materials by molecular recognition method. However, the continuous and controllable macroscopic self-assembly has not been reported yet. In this case, we employed spherical self-healing gel beads as building blocks (micron-sized and millimeter-sized) to construct functional assemblies, which has been sparsely reported yet. More importantly, by simply designing different channels, we realized oriented microfluidic-assisted SHDA for programmed assemblies (various linear, planar, 3D assemblies), while the reported literatures about hydrogel ensembles are limited in planar morphologies.

From a practical standpoint, the programmed architecture fabricated via SHDA provides identical shapes and dimensions for 3D tissue-like constructs of multiple cell types. Therefore,

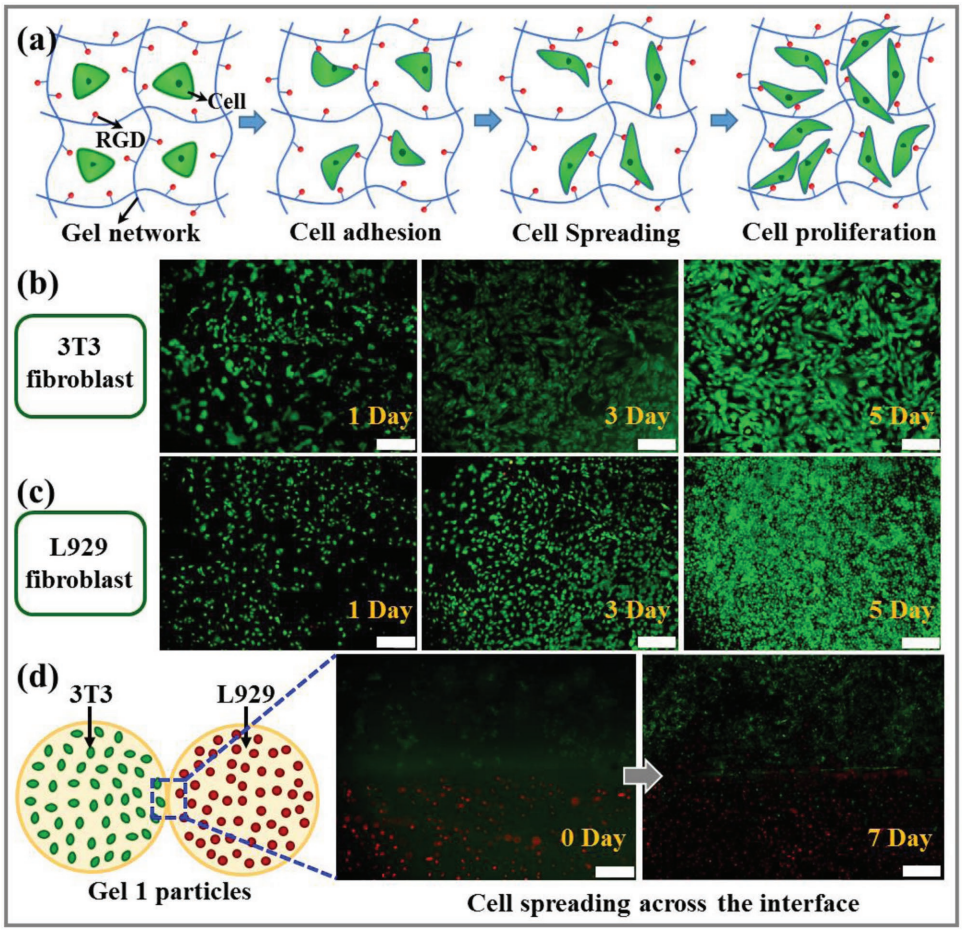

Figure 5. Gel assembly toward tissue-like constructs. a) Schematic illustration of cells culturing on Gel **1** matrices. b,c) MTT assay and Live/Dead cell assay of 3T3 (b) and L929 (c) fibroblast on Gel **1** after 1, 3, and 5 day, respectively. The seeding density is 1×10^5 cells cm^{-2}. d) The coculture of 3T3 and L929 cells using Gel **1** assembly to generate 3D tissue-like constructs. The scale bar indicates 100 μm.

it is necessary to investigate their 3D cell cultures as potential candidates of tissue organs. Herein, we incorporated specific cellular adhesion recognition sites (arginine-glycine-aspartic-cysteine acid peptide [RGDC])[39–41] into gel beads to enhance the spreading and proliferation of cells. Firstly, we implemented MTT assay and Live/Dead assay to investigate the viability of 3T3 fibroblasts in Gel **1** matrices. The number of 3T3 fibroblasts generally increase in both systems of Gel **1** and the tissue culture polystyrene dish (TCPS) (control) determined on days 1, 2, and 3 (Figures S15 and S16, Supporting Information). Compared with the control, no cytotoxicity was observed upon the introduction of Gel **1**, demonstrating excellent biocompatibility of the gel matrices. Then, we observed the proliferation and distribution of 3T3 and L929 fibroblast in Gel **1**. As shown in **Figure 5**a–c, during the entire test period, both 3T3 and L929 fibroblasts displayed a rapid proliferation rate. Extension was observed after 1 day incubation, demonstrating that the cells were starting to spread. The spreading cells were increasing visually with formation of localized cell aggregates, which gradually grew into and finally filled up the space of the gel. Based on the remarkable biocompatibility and structure feature, we aimed to create 3D tissue-like organ materials with multiple cell types using the gel assembly. 3T3 and L929 fibroblasts that labeled with green CMFDA and red CM-DiI cell trackers, respectively, are seeded in individual Gel **1** beads of the assembly. As expected, the cocultured cells could proliferate and migrate across gel borders to interact with neighboring cells after 7 days (Figure 5d). Thus, we created cell-laden tissue-like structures with controlled cell distribution, which is similar to the reported literature.[10] The results indicate the successful construction of organogenic tissue materials by association of cell coculture with programmed macroscopic assembly via SHDA, which may guide the construction of engineered tissues in a simple and flexible fashion.

Another advantage of SHDA method is that it allows various function and information to be integrated together into one system. We herein introduced fluorescent QDs[42–44] in gel beads to achieve programmed photoelectric materials via SHDA, allowing them to connect with the outside world for wide practical applications. However, the presence of AA might easily cause fluorescence quenching of CdSe/ZnS QDs. Considering favorable compatibility with QDs, we employed another self-healing system poly(HPA-*co*-NVP) gel (Gel **3**) reported in our previous work to construct micron-sized QD-loaded Gel **3** beads via a microfluidic device. Schematic preparation is shown in **Figure 6**a. By adjusting the velocities of discontinuous and

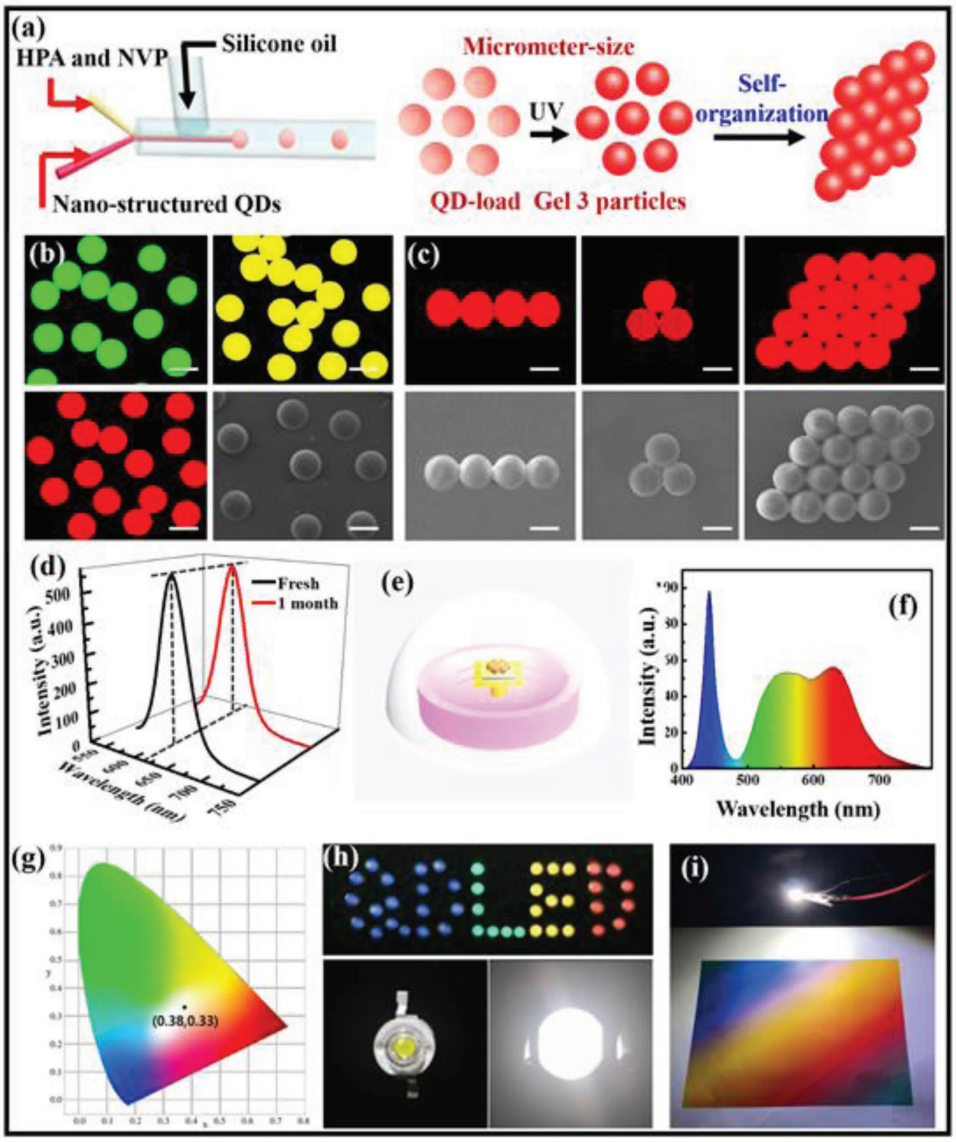

Figure 6. SHDA for fluorescent assemblies toward WLEDs. a) Schemic illustration of the fabrication of Gel **3** beads via a microfluidic device. b) Fluorescence pictures of micrometer-sized QD-loaded Gel **3** beads with emission light of 531 nm (green), 582 nm (yellow), and 631 nm (red) and SEM images. c) Fluorescence pictures and SEM images of aggregates using micron-sized QD-loaded Gel **3** beads as building blocks. The scale bar indicates 200 µm. d) 3D plot showing the fluorescence spectra of Gel **3** beads doping by QD-631 nm over time. e) Schematic preparation of WLED. f) EL spectra of the as-prepared WLED device. g) CIE color coordinate graph of the WLED device. h) Photographs of the WLED device under daylight with power off and on. i) Photographs of the WLED lighting pictures.

continuous phase, Gel **3** beads with micrometer size of 212 µm were controllably obtained (Figure S17, Supporting Information). Figure 6b shows uniform micron-sized Gel **3** beads doping with 531, 582, and 631 nm QDs, respectively. Photoluminescence emission spectra and time-resolved fluorescence decay indicate the successful construction of fluorescent nanocomposites with good optical properties (Figures S18 and S19, Supporting Information).[45,46] These micrometer-sized QD-loaded Gel **3** beads can also serve as building blocks to realize SHDA, which imparts the character of favorable arrangement and photostability (Figure 6c,d). The intermolecular hydrogen bonds between hydroxyl moieties of HPA and pyrrolidone moieties of NVP[25] facilitate the self-organization of Gel **3** beads. The size of these programmed fluorescent assemblies can be up to millimeter scale and also can been precisely calculated as described above. We finally utilized the red-emitting assembly along with yellow phosphors as light conversion materials to fabricate WLEDs (Figure 6e). The electroluminescence (EL) spectrum of WLED shows three peaks centered at 440, 560, and 632 nm, corresponding to the emission of blue light chip, YAG-05 yellow phosphors, and red QD-loaded gel assembly, respectively (Figure 6f). The Commission Internationale de L'Eclairage (CIE) color coordinate of the WLED is (0.38, 0.33) (Figure 6g), falling in the white gamut, and approaching to the coordinate of pure white-light emission (0.33, 0.33). Figure 6h,i demonstrates the realization for white illumination of the

constructed WLED. All these results illustrate that the SHDA of QD-loaded gel beads is instructive for the construction of promising fluorescent materials toward optoelectronic devices.

In summary, we proposed a new SHDA strategy for constructing programmed macroscopic assemblies in a bottom-up fashion by using self-healing gel beads via microfluidic technique. Driven by the inherent hydrogen bonds or supramolecular interactions between these gel beads, we achieved diverse linear and planar assemblies by the interfacial SHDA at water/trichloromethane interface within 5 s. We also fabricated 3D ordered architectures through layer-by-layer SHDA method within 5 min. Significantly, by utilizing different microfluidic channels, we realized oriented macroscopic linear, planar, and 3D beaded self-assemblies in a controllable manner by microfluidic-assisted SHDA for the first time. Specially, the size of gel beads used for macroscopic assembly could be tunable from 212 μm to 4 mm by adjusting the velocities of discontinuous and continuous phase. And the size of assemblies could be precisely controlled and calculated due to the excellent uniformity of gel beads. We explored the application of tissue-like structures by coculture of different cell types in the gel assembly. Moreover, for the potential of light conversion materials toward optoelectronic device, we constructed programmed fluorescent QD-loaded gel assemblies via SHDA method. The excellent optical properties of these fluorescent architectures satisfy vigorous advances for WLEDs. On a practical level, the SHDA of self-healing gel beads developed in this study provide a new perspective for construction of novel structures and functional structures in a simple, flexible, and efficient pathway.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

macroscopic self-assembly, microfluidic technique, self-healing gel beads, tissue-like material, white LEDs

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