

Smart Peptide Defense Web In Situ Connects for Continuous Interception of IgE against Allergic Rhinitis

Meng-Ru Ding, Qi-Lin Liang, Huan-Ge Xu, Xiang-Dan Li,* Kuo Zhang, Zi-Jin Wei, Yong-Hong Gao, Qing-Shi Zhang, Rui Huang, Huai Yang,* Lei Wang,* and Hao Wang*



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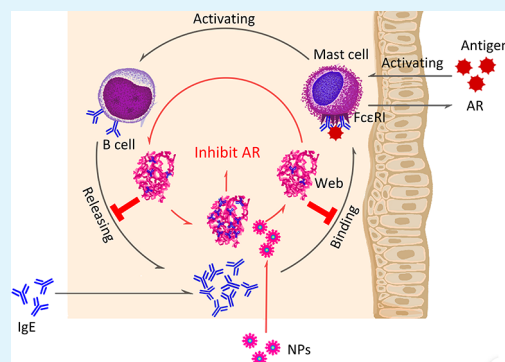
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ABSTRACT: Allergic rhinitis (AR) is a chronic inflammatory reaction by immunoglobulin E (IgE) mediators after individual contact with allergens. It affects 10–40% of the world's population and reduces the quality of life. Long-term symptoms of rhinitis can cause inflammation to spread and trigger asthma, which can harm human health. Herein, we develop a Smart Peptide defenseNse (SPIN) web technique, which in situ constructs a peptide web, trapping IgE against AR. Two candidate SPINs, SPIN-1 and SPIN-2, are designed with different IgE-binding sequences. The SPIN-1 or SPIN-2 is able to bind to IgE and transform from nanoparticles into entangled nanofibers. In turn, the web of SPIN-1 or SPIN-2 acts as a long-term trap of IgE to prevent the IgE from binding to mast cells. SPIN-1 or SPIN-2 (10 mg/kg) is able to treat AR model Balb/c mice with high efficiency and reduced symptoms of rhinitis and inflammatory factors, even better than a first-line clinical drug, cetirizine (10 mg/kg). For example, the amount of IL-4 released in the AR group (185.5 ± 6.8 pg/mL) is significantly reduced after the treatment with SPIN-1 (70.4 ± 14.1 pg/mL), SPIN-2 (86.0 ± 9.3 pg/mL), or cetirizine (112.8 ± 19.3 pg/mL). More importantly, compared with the cetirizine group (1 day), the SPIN-1 or SPIN-2 group shows long-term therapeutic effects (1 week). The SPIN web technique shows the great potential for blocking IgE binding to mast cells in vivo, attenuating AR or other allergic reactions.

KEYWORDS: self-assembly, peptide, IgE, allergic rhinitis, targeting therapy



1. INTRODUCTION

Allergic rhinitis (AR), a noninfectious inflammatory disease of the nasal mucosa, refers to the release of inflammatory mediators (mainly histamine) mediated by IgE after individual exposure to specific allergens.¹ The main symptoms are paroxysm of sneezing, nasal congestion, nasal itching, and runny nose sometimes accompanied by itching eyes and tearing. AR is a type I hypersensitivity involving mucosal inflammation that is driven by type 2 cells.² With the development of industrialization, the environment is further polluted, which can increase the risk of AR.³ AR affects 10–40% of adults in the world and perhaps a somewhat higher percentage of children.⁴

The mechanism of AR is divided into the induction phase and the effect phase.⁵ Induction phase: Antigen-presenting cells present the antigen information to T cells, which are activated to secrete IL-4, activating B cells to drive the production of IgE. IgE binds to its high-affinity receptor (FcεRI) located on the surface of mast cells in tissues. Effect phase: When the allergen comes into contact with the organism again, the multivalent antigen binds to the specific IgE on the cell surface, leading to the cross-linking of the IgE-FcεRI complex. As a result, mast cells release a large number of inflammatory factors, causing smooth muscle contraction,

increased vascular permeability, and mucus secretion. In turn, the activated mast cells enable more production by activated B cells. Treatment options for AR include allergen avoidance, immunotherapy, anti-IgE, anti-FcεRI, and pharmacologic treatments, including mast cell-stabilizing agents, antihistamines, glucocorticosteroids, leukotriene receptor antagonists, and decongestants, and other small molecule inhibitors.^{6–8} Generally, allergens are hard to avoid in daily life, and desensitization therapy is complex and time-consuming. Drug therapy has various degrees of side effects with limited relief to some degree from symptoms. Given the centrality of IgE within multiple allergic disorders, IgE has become a major target for the treatment of allergies. Omalizumab is currently the most effective anti-IgE antibody. Omalizumab binds to specific IgE with a higher affinity than IgE binds to FcεRI, leading to the high efficacy against AR.⁹ The high price of omalizumab limits its wide application.

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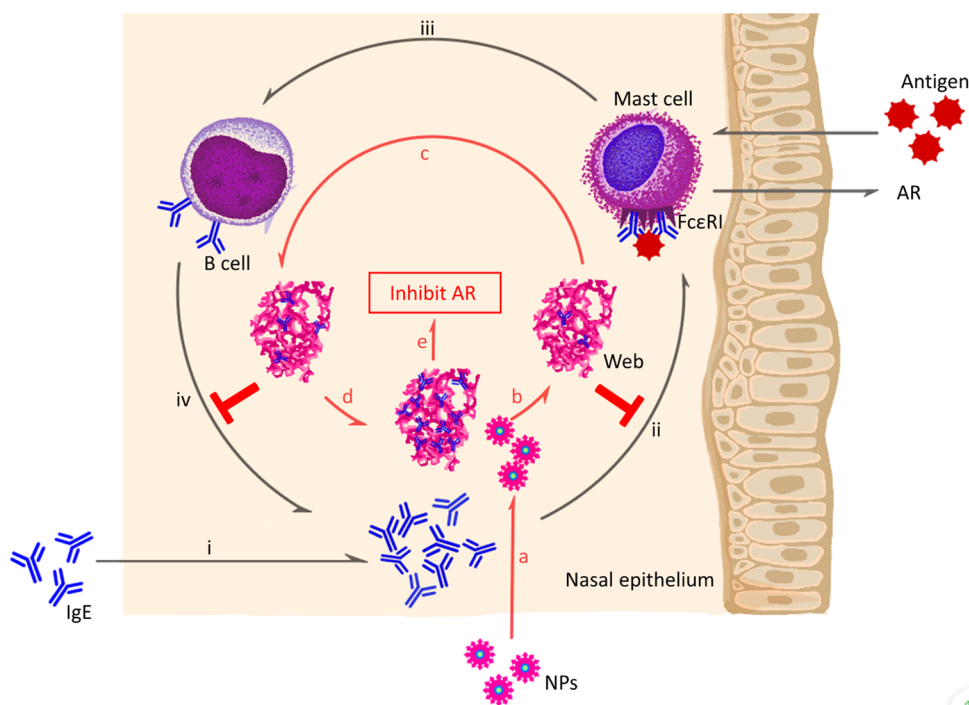


Figure 1. Schematic illustration of in situ construction of a SPIN web in the nasal mucosa to trap IgE against AR. (i) Entry of IgE from plasma cells into the nasal tissue. (ii) IgE binds to FcεRI on mast cells and allergens bind to IgE on mast cells, cross-linking IgE-FcεRI, leading to the release of inflammatory factors, such as IL-4. (iii) IL-4 in situ activates B cells. (iv) B cells in situ produce more IgE for heavier AR. (a) SPIN NPs enter the nasal mucosa. (b) IgE SPIN web opens once it encounters IgE. (c) SPIN web stuck in the nasal mucosa for a prolonged time. (d) SPIN web traps IgE and blocks IgE from binding to FcεRI on the surface of mast cells to inhibit AR.

Self-assembly refers to the spontaneous formation of ordered structures from basic structural units under the interactions based on noncovalent bonds.^{10,11} Peptide assembly with defined structures can provide higher stability and better performance than the peptide itself, attracting great attention in nanomedicine.^{12,13} Recently, binding-induced fibrillogenesis (BIF) peptides that can target and bind specific receptors on cell membranes and in situ transform from nanoparticles (NPs) into nanofibers (NFs) were developed by mimicking fibronectin fibrillogenesis.¹⁴ This kind of BIF peptide can be extended to bind to intracellular proteins inside cells¹⁵ and to bind to secreted extracellular proteins.¹⁶

Here, we developed a Smart Peptide defense (SPIN) web technique, which was able to trap IgE and inhibit the binding between IgE and FcεRI against AR (Figure 1). First, we designed two SPINs, SPIN-1 and SPIN-2, both of which had one programmable self-assembling sequence, bis-pyrene-KLVFF, and two different IgE-binding peptide sequences, SILPVDAKDWIEGEG¹⁷ and HPEYAVSVLL.¹⁸ SPIN-1 or SPIN-2 in the formulation of NPs was able to bind to IgE and transform into NFs, forming a SPIN web in the nasal mucosa. In turn, the SPIN web was able to trap IgE to inhibit IgE binding to mast cells and corresponding AR. The number of sneezing events, a typical AR symptom, was up to 65.0 ± 4.0 times within 30 min in the AR mouse model. The treatment with SPIN-1 or SPIN-2 (10 mg/kg) reduced the number of sneezing events to 20.0 ± 2.4 or 26.0 ± 3.3 , respectively. Meanwhile, the number of sneezing events for the AR mouse model was reduced to 30.0 ± 5.0 when treated with the first-line anti-AR drug, cetirizine (10 mg/kg). Compared with the AR or cetirizine group, the release of inflammatory factors (histamine, IL-4, IL-5) in the SPIN-1 or SPIN-2 group was decreased significantly. A single dose of cetirizine lost efficacy

on the third day, but SPIN-1 or SPIN-2 treatment was effective for 1 week. In addition, the higher stability of the SPIN-2 web may lead to higher efficacy than that of the SPIN-1 group for a long time. The SPIN web technique is able to block IgE binding to mast cells, thus providing a promising therapeutic strategy for AR.

2. RESULTS AND DISCUSSION

2.1. SPIN-1 and SPIN-2 Form a Web Upon Binding to IgE. Two SPINs were designed as BP-K-FFVLK-SILPV-DAKDWIEGEG (SPIN-1) and BP-K-FFVLK-HPEYAVSVLL (SPIN-2) (Figures S1 and S2), which were introduced to study how the binding ability and the stability of SPIN web affected the therapeutic efficacy (Figure 2a). Due to the amphiphilic structure, SPIN-1 or SPIN-2 was able to form nanoparticles in water ($V_{\text{water}}/V_{\text{DMSO}} = 99:1$).¹⁹ The formation of SPIN-1 or SPIN-2 NPs was confirmed by UV-vis absorption (Figures S3a and S4a), fluorescence spectra (Figures S3b and S4b), and TEM observations. As shown in Figure S5, SPIN-1 and SPIN-2 were well-dispersed and were spherical NPs with diameters of 33.2 ± 4.6 and 32.5 ± 3.3 nm, respectively.

To study the formation of the SPIN web, the SPINs (30 μM) were incubated with IgE (4 $\mu\text{g}/\text{mL}$) and observed by TEM. It was found that SPIN-1 formed fibrous networks within 2 days upon incubation with IgE. Meanwhile, SPIN-1 alone was mainly NPs with few NFs on day 2 (Figures 2b and S5). Similarly, SPIN-2 NPs transformed into NFs and formed entangled fibrous networks when incubated with IgE for 2 days, but still NPs were without IgE. SPIN-2 transformed into NFs at a faster speed than SPIN-1; SPIN-2 NFs were formed in 1 day, but SPIN-1 was still NPs upon incubation with IgE (Figure S5). These results indicated that both SPIN-1 and SPIN-2 transformed into SPIN web upon binding to IgE.²⁰

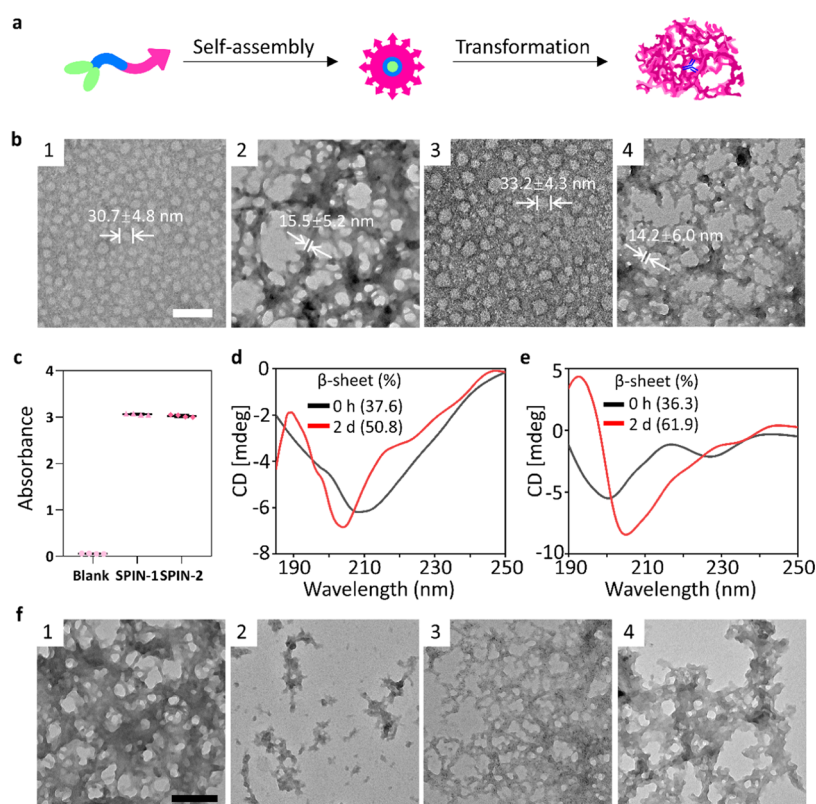


Figure 2. SPIN-1 and SPIN-2 form NPs and transform into NFs by binding to IgE with high stability. (a) Schematic illustration of SPIN-1 and SPIN-2 self-assembled into NPs, followed by fibrillogenesis to form NFs upon recognizing and binding to IgE. (b) TEM images of SPIN-1 and SPIN-2 incubated with IgE for 0 h and 2 days. Scale bar, 200 nm. TEM images of SPIN-1 (1) and SPIN-2 (3) incubated with IgE for 0 h. TEM images of SPIN-1 (2) and SPIN-2 (4) incubated with IgE for 2 days. (c) Determination of binding affinity of SPIN-1/SPIN-2 and IgE through the ELISA test. (d, e) Circular dichroism (CD) measurements of SPIN-1 (d) and SPIN-2 (e) from NPs to NFs in the presence of IgE in aqueous solutions on day 2. (f) TEM images of SPIN-1 and SPIN-2 NFs incubated with trypsin on day 3 to show the enzymatic stability. Scale bar, 200 nm. (1) SPIN-1 web + H₂O group. (2) SPIN-1 web + trypsin group. (3) SPIN-2 web + H₂O group. (4) SPIN-2 web + trypsin group.

The fibrillogenesis from NPs to NFs was driven by hydrogen-bonding interactions from KLVFF with β -sheet structure formation. The following circular dichroism (CD) measurements for the β -sheet structure may provide the explanation for the faster fibrillogenesis of SPIN-2.

The binding ability of the SPIN-1 and SPIN-2 to IgE was further confirmed by the enzyme-linked immunosorbent assay (ELISA) with an enzyme-labeled plate coated with IgE.¹⁷ NHS-biotin-labeled SPIN-1 or SPIN-2 (100 μ L) was added to micropores in the plate for incubation for 2 h. The binding capability was finally determined by the absorbance of indicators at 450 nm with a microplate reader. As shown in Figure 2c, the absorbance at 450 nm of the blank hole was 0.5, but 3.1 and 3.0 for SPIN-1 and SPIN-2, respectively, showing a high affinity with the IgE of SPIN-1 and SPIN-2.

The secondary structure of proteins/peptides was determined with a CD spectrometer. We tested the secondary structure of SPIN-1 and SPIN-2 by CD during the formation of the SPIN web. Both SPIN-1 and SPIN-2 NPs had random coil structures with a negative signal at 200 nm initially, most likely because the strong hydrophobic interactions of BP units induced the fast aggregation of SPIN-1 or SPIN-2²¹ (Figure 2d,e). Then, SPIN-1 or SPIN-2 incubated with IgE for 2 days exhibited characteristic signals of the hydrogen-bonded β -sheet structure. The percentage of the β -sheet in IgE-incubated SPIN-1/SPIN-2 NPs increased from 37.6%/36.3% to 50.8%/61.9% in 2 days with morphological transformation. SPIN-2

had higher β -sheet content compared to SPIN-1. These results suggested that the SPIN-2 triggered by IgE binding exhibited stronger intermolecular hydrogen bonds, probably leading to the faster fibrillogenesis of SPIN-2. The 13.2%/25.6% increase in the β -sheet indicated more highly ordered packing structures in SPIN NFs than those in SPIN NPs. Without IgE incubation, the SPIN-1 and SPIN-2 NPs still had a random coil structure in 2 days (Figure S6a,b). The typical β -sheet sequence of KLVFF provided both hydrogen-bonding interactions and hydrophobicity,²² leading to the fibrillogenesis of SPIN-1 and SPIN-2 to form an entangled SPIN web with a β -sheet structure, which could trap IgE persistently.

FTIR spectroscopy was also carried out to measure the secondary structures of SPIN-1 and SPIN-2 during incubation with IgE.²³ The β -sheet structure is formed by the intermolecular hydrogen-bonding interactions. The hydrogen bonds formed by carbonyl and amino groups cause the stretching vibration of C=O, which can be detected by FTIR spectroscopy.²⁴ As shown in Figure S7a,b, peaks at 1636 and 1639 cm^{-1} , attributed to the stretching vibration of C=O, were observed in SPIN-1 and SPIN-2 incubated with IgE for 2 days, indicating the parallel β -sheet structure.²⁵ SPIN-1 NPs alone with the peak at 1644 cm^{-1} (0 h) and 1641 cm^{-1} (2 days) indicated that SPIN-1 NPs retained the random coil state for 2 days (Figure S7c). Similar FTIR spectra for SPIN-2 NPs alone suggested SPIN-2 NPs retained the random coil state for 2 days (Figure S7d). These results were in agreement

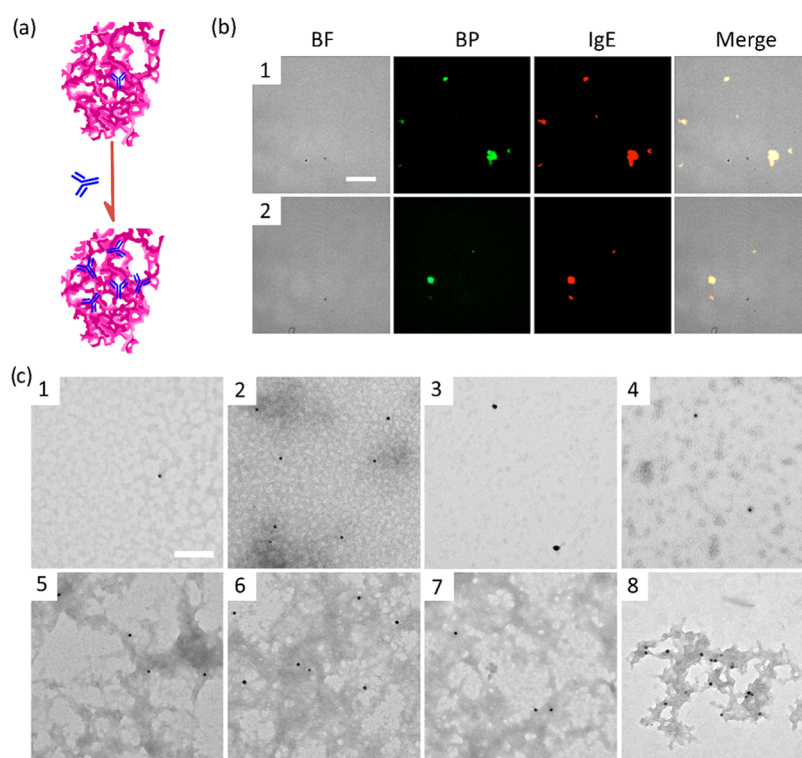


Figure 3. SPIN-1 or SPIN-2 web traps IgE. (a) Schematic illustration of SPIN-1 or SPIN-2 web trapping IgE. (b) CLSM images of SPIN-1 and SPIN-2 incubated with the Cy5-labeled IgE to show the trapping of IgE by SPIN-1 or SPIN-2 web. The green channel represents BP. The red channel represents IgE. Scale bar, 25 μm . (1) SPIN-1 group. (2) SPIN-2 group. (c) TEM images of SPIN-1 and SPIN-2 incubated with colloidal gold-labeled IgE (IgE-Au) (4 and 20 $\mu\text{g/mL}$) for 0 h and 2 days. Scale bar, 200 nm. TEM images of SPIN-1 incubated with IgE-Au of 4 (1) and 20 $\mu\text{g/mL}$ (2) for 0 h. TEM images of SPIN-2 incubated with IgE-Au of 4 (3) and 20 $\mu\text{g/mL}$ (4) for 0 h. TEM images of SPIN-1 incubated with IgE-Au of 4 (5) and 20 $\mu\text{g/mL}$ (6) for 2 days. TEM images of SPIN-2 incubated with IgE-Au of 4 (7) and 20 $\mu\text{g/mL}$ (8) for 2 days.

with CD spectra, confirming the parallel β -sheet packing of SPIN-1 and SPIN-2 during incubation with IgE for 2 days.

The inhibition efficacy of IgE binding to Fc ϵ RI for AR therapy by the SPIN web in the nasal mucosa was possibly ascribed to the trapping ability as well as the retention time in vivo. Therefore, the enzymatic stability of the SPIN web was evaluated, which was positively related to the retention time of the SPIN-1 or SPIN-2 web in vivo. We first incubated SPIN-1 and SPIN-2 with IgE for 2 days to prepare the SPIN-1 and SPIN-2 web, which were divided into two equal portions. One was mixed with trypsin (final concentration of 2 mg/mL) and the other portion was mixed with the same amount of H_2O , both of which were incubated at 37 $^\circ\text{C}$ for 5 days and were observed by TEM on days 3 and 5. As shown in Figure 2f, the morphology of the SPIN-1 web + H_2O group exhibited fibrous networks, and the SPIN-1 web + trypsin group exhibited broken short NF aggregates on day 3. In addition, the SPIN-1 web was further degraded into shorter NFs incubated with trypsin for 5 days (Figure S8). Meanwhile, SPIN-2 web showed a similar degradation trend once incubated with trypsin, but at a much slower speed. The SPIN-2 web incubated with trypsin still retained the fibrous network on day 3 and became short NF aggregates on day 5. These results showed that SPIN-2 exhibited higher enzymatic stability than SPIN-1. The high stability was possibly attributed to the high β -sheet contents (61.9%) in the SPIN-2 web than that in the SPIN-1 web (50.8%). The SPIN-1/SPIN-2 webs were further incubated with serum at 37 $^\circ\text{C}$ for 3 days and were observed by TEM on days 1 and 3. As shown in Figure S9, the SPIN-1 web + serum group exhibited a fibrous network on day 1 and

broken short NF aggregates on day 3, indicating high serum stability. Meanwhile, the SPIN-2 web showed high serum stability with a degradation trend similar to the SPIN-1 web once incubated with serum.

2.2. SPIN Web Traps IgE and Prevents IgE from Binding to Mast Cells. SPIN-1 or SPIN-2 self-assembled into NPs, followed by fibrillogenesis to form NFs upon recognizing and binding to IgE, and the fibrous networks trap IgE (Figure 3a). The BP fluorescent unit in SPIN had the characteristics of the AIE effect, which showed strong green fluorescence at 420–550 nm. To study whether the SPIN web was able to trap IgE, SPIN-1 or SPIN-2 (30 μM) was incubated with Cy5-labeled IgE (34 $\mu\text{g/mL}$) for 4 h and observed with a confocal laser scanning microscope (CLSM) (Figure 3b). It was found that the entire red fluorescence merged well with green fluorescence, implying that IgE was trapped by the SPIN-1 web. Similarly, the SPIN-2 web was also able to trap IgE.

Could the trapping of IgE by the SPIN web inhibit the binding of IgE to mast cells? At present, mast cell lines that are widely used include the human mast cell line, i.e., HMC-1 cells and LAD2 cells. Due to the abundant expression of Fc ϵ RI, LAD2 cells are more suitable for the study of IgE-mediated type I hypersensitivity.²⁶ Therefore, LAD2 cells were selected as the model cell to study the inhibition of IgE binding to mast cells by SPIN-1 or SPIN-2 web, respectively. LAD2 cells were incubated with IgE and SPIN-1/SPIN-2 for 4 h and were observed by CLSM. As shown in Figure S10, IgE (red) still merged with SPIN-1 (green). There was no green or red fluorescence on LAD2 cells. These results indicated that the

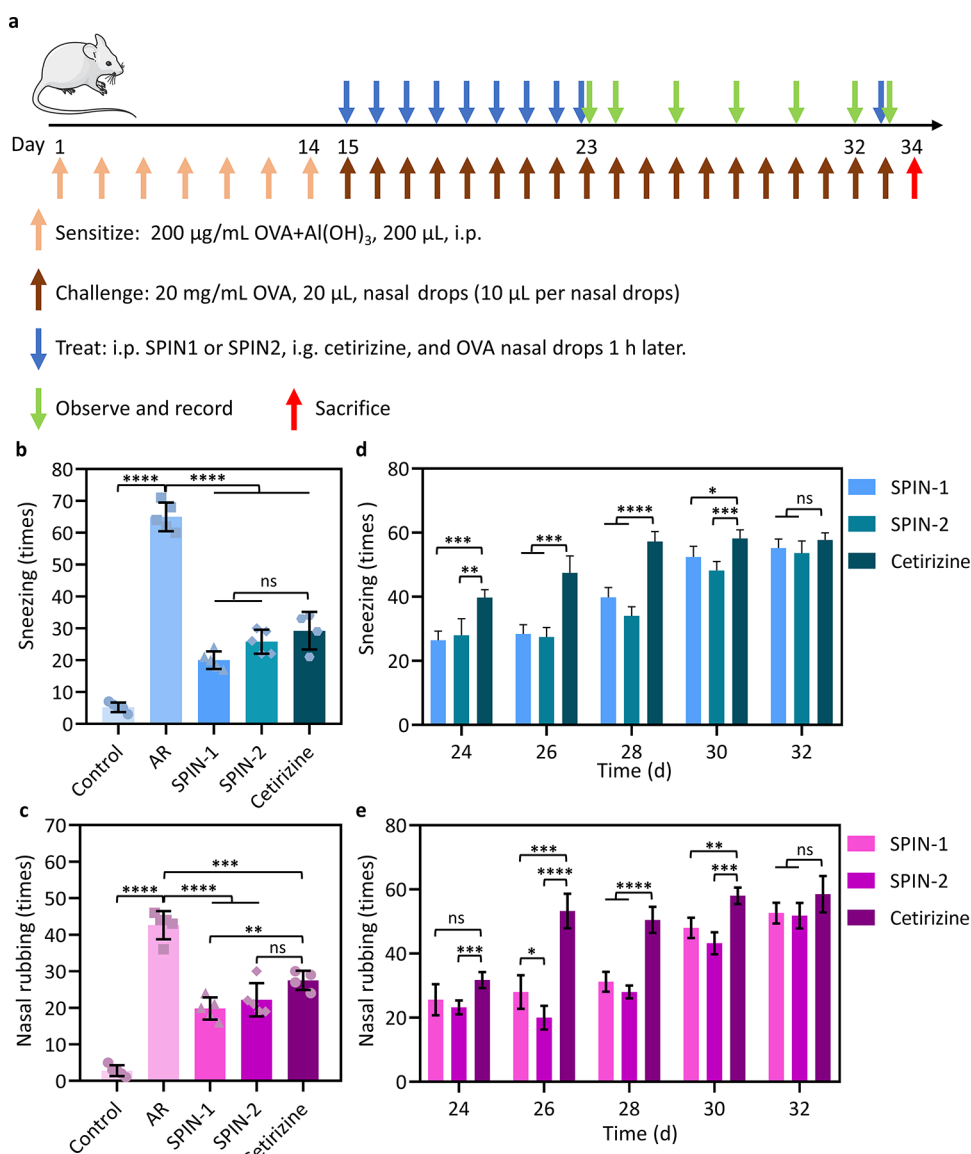


Figure 4. SPIN-1, SPIN-2, and cetirizine reduced the allergic symptoms of AR in vivo. (a) Schematic diagram of the OVA-induced AR model and treatment. i.p. represents intraperitoneal injection, i.g. represents intragastric administration. (b, c) Counts of sneezing (b) and nasal rubbing (c) of each mouse in all groups for 30 min on the 23rd day. (d, e) Counts of sneezing (d) and nasal rubbing (e) of SPIN-1, SPIN-2, and cetirizine groups on the 24, 26, 28, 30, and 32 days. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

SPIN-1 web could trap IgE and thereby prevent IgE from binding to LAD2 cells and so did SPIN-2 for the inhibition of IgE binding to LAD2 cells.

We further confirmed that the SPIN web did trap IgE through the immune colloidal gold technique (GICT). SPIN-1 or SPIN-2 (30 μM) was incubated with 4 and 20 $\mu\text{g/mL}$ of colloidal gold-labeled IgE (IgE-Au) for 2 days. As shown in Figure 3c, SPIN-1 or SPIN-2 NPs bound to the IgE-Au initially. There was IgE-Au on the fibrous network on day 2. In contrast, SPIN-1 or SPIN-2 incubated with colloidal gold still exhibited NPs for 2 days, and there were no obvious interactions between SPIN-1 or SPIN-2 and Au (Figure S11). These results revealed that SPIN-1 or SPIN-2 could bind to IgE and perform fibrillogenesis. The SPIN-1 or SPIN-2 web in turn trapped IgE with high efficiency, regardless of the concentrations of IgE-Au (4 or 20 $\mu\text{g/mL}$).

To verify the cytocompatibility of SPIN-1 and SPIN-2 (Figures S12 and S13), we evaluated the effects of a series of

concentrations of SPIN-1 and SPIN-2 (1.56–200 μM) on the average survival rates of LAD2 and HUVECs using the CCK-8 assay. The results showed that even at 200 μM , SPIN-1 and SPIN-2 still had good cytocompatibility with LAD2 and HUVECs. The hemolysis rates of SPIN-1 and SPIN-2 at a series of concentrations were lower than the international standard upper limit of 5%, indicating that SPIN-1 and SPIN-2 had no significant effect on the hemolysis of red blood cells. Based on the above results, the SPIN-1 and SPIN-2 showed good biocompatibility, and the work concentration ranged up to 200 μM .

2.3. SPIN-1 and SPIN-2 Inhibit AR in the Mouse Model. A schematic illustration of the mouse model and administration is shown in Figure 4a.²⁷ Mice were randomly divided into five groups ($n = 5$), including the AR group, the SPIN-1 group, the SPIN-2 group, the cetirizine hydrochloride group, and the control group. A mouse model of AR was constructed by sensitizing and challenging the mice. Mean-

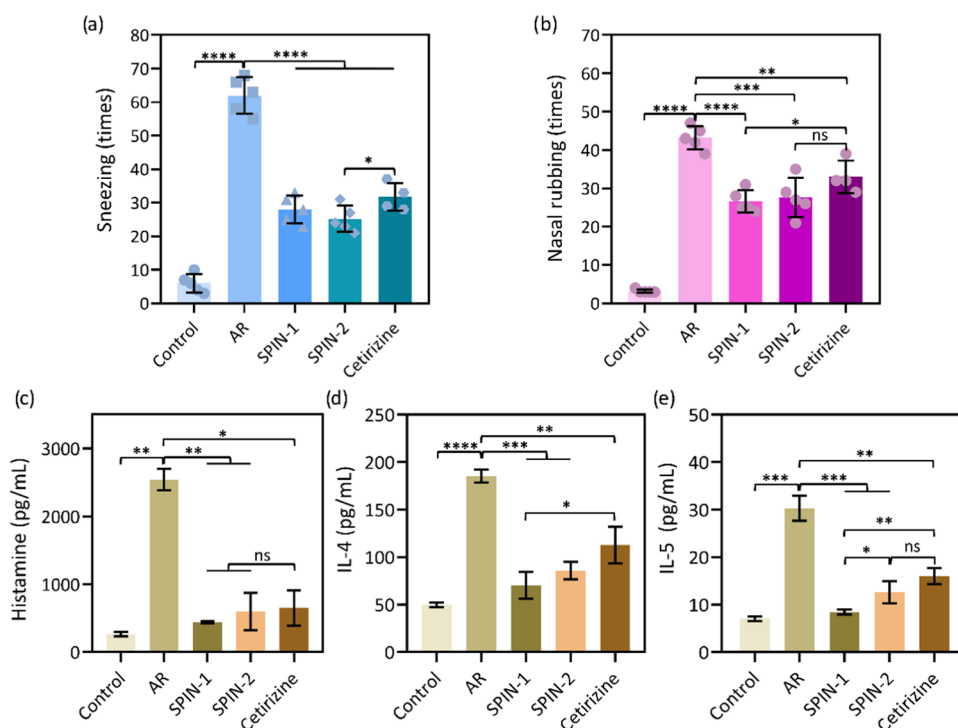


Figure 5. SPIN-1, SPIN-2, and cetirizine ameliorated AR symptoms and reduced inflammation factors in the AR mouse model. (a, b) Number of sneezing (a) and nasal rubbing events (b) of each mouse in all groups for 30 min on the 33rd day after treatment and challenge. (c–e) Amount of histamine (c), IL-4 (d), and IL-5 (e) in the serum of each mouse on day 34. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

while, the AR mice were treated with an intraperitoneal injection (i.p.) of SPIN-1 (10 mg/kg), an i.p. injection of SPIN-2 (10 mg/kg), and an intragastric administration (i.g.) of cetirizine (10 mg/kg). Sneezing and nasal rubbing are typical symptoms of AR. The sneezing and rubbing events of mice in each group were recorded within 30 min on day 23 to calculate the allergic symptom scores of each group and evaluate the relief degree of allergic symptoms by treatment with SPIN-1, SPIN-2, and cetirizine. According to the biological behavior scoring standard,²⁸ the scores of the AR group were higher than 5, indicating the successful modeling (Figure S14). Compared with the AR group (65.0 ± 4.0), the number of sneezing events in the SPIN-1 group (20.0 ± 2.4), the SPIN-2 group (26.0 ± 3.3), and the cetirizine group (30.0 ± 5.0) was significantly reduced ($p < 0.0001$) (Figure 4b). As shown in Figure 4c, the number of nasal rubbing events in the AR group was 43.0 ± 3.4 , being significantly higher than those in the SPIN-1 group (20.0 ± 2.7 , $p < 0.0001$), the SPIN-2 group (22.0 ± 4.0 , $p < 0.0001$), and the cetirizine group (27.0 ± 2.0 , $p < 0.001$). In addition, the number of sneezing and nasal rubbing events in both SPIN-1 and SPIN-2 groups was significantly lower than that in the cetirizine group. These results exhibited that SPIN-1, SPIN-2, and cetirizine could reduce the allergic symptoms of AR and that the treatment efficacy of the SPIN-1 and SPIN-2 groups was higher than that of the cetirizine group.

To study the duration of the drug effect of SPIN-1, SPIN-2, and cetirizine, the number of sneezing and nasal rubbing events was recorded for 9 days (from day 24 to 32) post intranasal stimulation without medication. As shown in Figure 4d,e, the number of sneezing and nasal rubbing events in the cetirizine group was close to that in the AR group on day 26 (the 3rd day), which was on day 32 (the 9th day) for SPIN-1 and SPIN-2 groups. On days 24, 26, 28, 30, and 32, the

number of sneezing and nasal rubbing events in the cetirizine group was significantly higher than that in the SPIN-1 and SPIN-2 groups. These results showed that SPIN-1 and SPIN-2 SPIN web had long-term retention effects for up to 1 week, probably due to the high stability. The SPIN-2 web with higher stability showed better therapeutic efficacy than the SPIN-1 web, further indicating that the stability was responsible for the long-term therapeutic effect.

On day 33, the biological behavior of each mouse was recorded for 30 min after the last administration and intranasal stimulation (Figure 5a,b). The results again confirmed that SPIN-1, SPIN-2, and cetirizine could reduce the allergic symptoms of AR, and the treatment effect of the SPIN-1 and SPIN-2 groups was better than that of the cetirizine group.

The amount of inflammatory factors, such as IL-4, IL-5, and histamine, directly indicates the degree of allergic reaction.²⁹ The concentrations of histamine, IL-4, and IL-5 in the serum of all of the mice were determined using the ELISA kit on day 34. Compared with the control group, concentrations of histamine, IL-4, and IL-5 were significantly increased after ovalbumin (OVA) sensitization and challenge in the AR group (Figure 5). After the treatment with SPIN-1, SPIN-2, and cetirizine, serum histamine, IL-4, and IL-5 were significantly reduced compared with the AR group, indicating that SPIN-1, SPIN-2, and cetirizine could effectively diminish allergic responses. The amount of histamine in the AR group was about 5 times higher than that in both the SPIN-1 and SPIN-2 groups. The amount of IL-4 released in the AR group was about 3 or 2 times higher than that in the SPIN-1 or SPIN-2 group (Figure 5c). As for IL-5, the amount in the AR group was 4 or 3 times higher than that in the SPIN-1 or SPIN-2 group. In addition, SPIN-1 and SPIN-2 showed better efficacy than cetirizine. For example, the amount of IL-4 ($p < 0.05$) in SPIN-1 groups was significantly lower than that in the

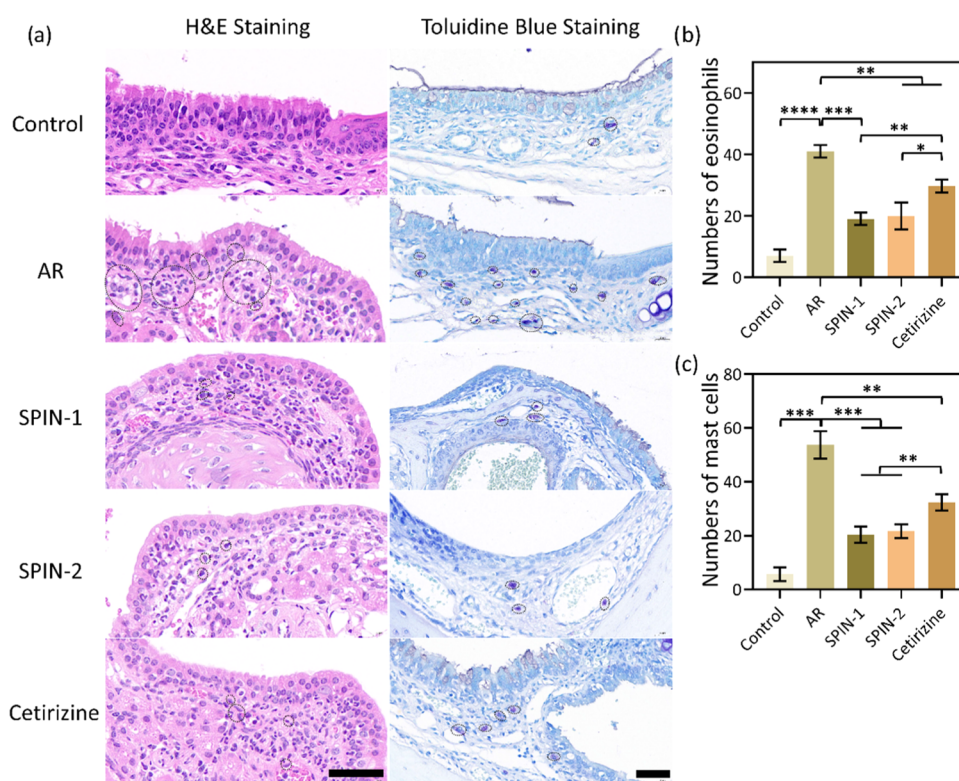


Figure 6. SPIN-1, SPIN-2, and cetirizine ameliorate the recruitment of eosinophils and mast cells in intranasal tissues. (a) Histological sections of the nasal cavity stained with H&E and toluidine blue. The circled regions in the image of H&E staining and toluidine blue staining denote infiltrated eosinophils and mast cells, respectively. (b) Numbers of eosinophils in intranasal tissues. (c) Numbers of mast cells in intranasal tissues. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Scale bar, 50 μm .

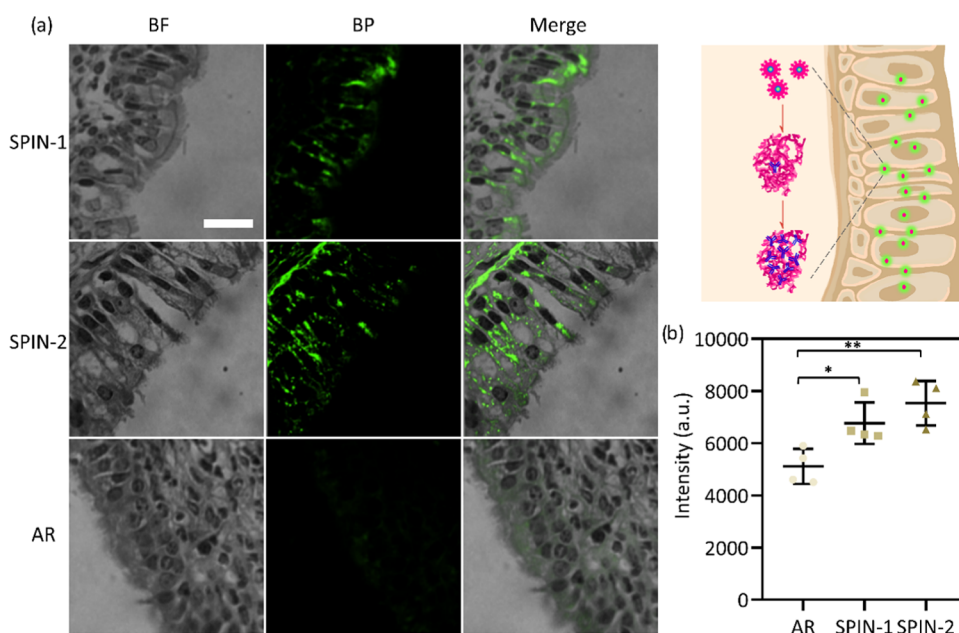


Figure 7. Accumulation and retention of SPIN-1 and SPIN-2 in the nasal mucosa. (a) CLSM images of the nasal mucosa in SPIN-1, SPIN-2, and AR groups, and the schematic illustration of SPIN web formation for trapping of IgE. The Green channel represents BP. (b) Quantification of the fluorescence intensity in confocal images of the nasal mucosa in SPIN-1, SPIN-2, and AR groups. * $p < 0.05$, ** $p < 0.01$. Scale bar, 20 μm .

cetirizine group (Figure 5d), and the amount of IL-5 ($p < 0.01$) in the SPIN-1 group was significantly lower than that in the cetirizine group (Figure 5e).

2.4. Histopathological Analysis in the Nasal Cavity of SPIN-1, SPIN-2, and Cetirizine. The representative charac-

teristics of AR significantly increased the recruitment and infiltration of inflammatory cells such as eosinophils and mast cells in the nasal mucosa.³⁰ Histopathological analysis in the nasal cavity was further investigated to evaluate the therapeutic effect of SPIN-1, SPIN-2, and cetirizine. All of the mice were

sacrificed on day 34 to harvest the nasal cavity samples, which were stained with H&E and toluidine blue, and were observed under a light microscope. As shown in Figure 6, the infiltration of eosinophils ($p < 0.0001$) and mast cells ($p < 0.001$) after sensitization and challenge with OVA was significantly increased compared to the normal group. SPIN-1, SPIN-2, and cetirizine treatment significantly decreased eosinophils and mast cell infiltration compared with the AR group. Moreover, the numbers of eosinophils and mast cells in the SPIN-1 or SPIN-2 group were significantly lower than those in the cetirizine group.

These results showed that SPIN-1, SPIN-2, and cetirizine could reduce the allergic symptoms of AR, and the treatment efficacy of the SPIN-1 and SPIN-2 groups was higher than that in the cetirizine group. In addition, SPIN-1 and SPIN-2 web had long-term retention effects for up to 1 week. To further confirm our hypothesis that SPIN-1 or SPIN-2 formed a SPIN web in the nasal mucosa for highly efficient and long-term effect, nasal cavity samples were observed by CLSM (Figure 7a). The green fluorescence intensity of the SPIN-1 group ($p < 0.05$) and the SPIN-2 group ($p < 0.01$) was significantly stronger compared with the AR group (Figure 7b), indicating the accumulation of the SPIN-1 and SPIN-2 web in the nasal mucosa. The higher fluorescence intensity of the SPIN-2 group was in agreement with the higher stability of the SPIN-2 web than that of the SPIN-1 web, which was possibly related to better long-term therapeutic efficacy than that of SPIN-1.

The heart, liver, spleen, and kidney tissue slices of all of the mice were stained with H&E (Figure S15). There were no obvious changes between normal saline, AR, SPIN-1, SPIN-2, and cetirizine groups, indicating the good biocompatibility of SPIN-1 and SPIN-2.

3. CONCLUSIONS

The study demonstrated a SPIN web technique for trapping IgE against AR. Both SPIN-1 and SPIN-2 peptides were able to target and bind to IgE and in situ transform from NPs into NFs to form a SPIN web. In turn, the resultant SPIN web can capture IgE and prevent IgE from binding to mast cells, leading to the inhibition of AR. Compared with clinical first-line anti-AR drug cetirizine, SPIN-1 and SPIN-2 exhibited better therapeutic effects, proven by alleviation of typical AR symptoms, reduction of inflammatory cytokines in serum, and infiltration of representative proinflammatory cells in nasal tissue. More importantly, SPIN-1 and SPIN-2 exhibited long-term inhibition of AR for up to 1 week, which was 1 day for cetirizine, probably due to both high efficiency and long retention of the SPIN web. Specifically, SPIN-2 with higher enzymatic stability had better long-term inhibition effects than SPIN-1. Taken together, the SPIN web technique could serve as a long-lasting antiallergic medicine for the treatment of AR.

4. MATERIALS AND METHODS

4.1. Materials. O-benzotriazol-1-yltetramethyluronium hexafluorophosphate (HBTU) and amino acids were purchased from GL Biochem, Shanghai, China. *N,N*-Dimethylformamide (DMF), *N*-methylmorpholine (NMM), ninhydrin, phenol, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), hydrazine hydrate, trifluoroacetic acid (TFA), triisopropylsilylhydride (TIS), diethyl ether, dimethyl sulfoxide (DMSO), and hexafluoroisopropanol (HFIP) were purchased from Aladdin, Beijing, China. DMF was dehydrated with molecular sieves. Other reagents were used as received without further purification. The Human IgE protein was purchased from Abcam, and the human mast cell LAD2 cell line was purchased from Otwo

Biotech, Shenzhen, China. A cell counting kit (CCK-8) was purchased from Beyotime Institute of Biotechnology, Shanghai, China. Colloidal gold nanoparticle solution was purchased from Psaitong Co., Beijing, China. A mouse IL-4 ELISA Kit, IL-5 ELISA Kit, and ELISA Kit were purchased from Beijing Feimo Biotechnology, Beijing, China.

4.2. Synthesis of Peptides. SPIN-1 and SPIN-2 were synthesized through standard solid-phase peptide synthesis techniques using Fmoc coupling chemistry. Fmoc-Gly-Wang resin (loading: 0.326 mM/g) or Fmoc-Leu-Wang resin (loading: 0.326 mM/g) was utilized as the solid phase and was swelled in anhydrous DMF for 6 h. DBU (2%) in anhydrous DMF was utilized for the deprotection of the Fmoc group. The Kaiser test was used to detect the presence of primary amino groups. Then, the amino acid was activated by HBTU after being dissolved in an anhydrous DMF/NMM (19:1, v/v) mixed solution. The process was repeated until BP-COOH was linked to the resin. The final production was cleaved through a mixture of TFA (95%, v/v), TIS (2.5%, v/v), and water (2.5%, v/v) for 3 h in an ice bath before being filtered to obtain the peptide solution. The solution was evaporated with N_2 , precipitated in cold diethyl ether, and centrifuged before being dried in a vacuum oven. The molecular structures were confirmed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS, Autoflex III).

4.3. Preparation and Characterization of SPIN-1 and SPIN-2 NPs. SPIN-1 and SPIN-2 peptides were dissolved in DMSO (30 μ M) separately. The SPIN-1 or SPIN-2 solution in DMSO (10 μ L) was further mixed with water with the final water content of 99% to prepare SPIN-1 or SPIN-2 NPs, which were characterized by UV-vis and fluorescence measurements.

4.4. Transmission Electron Microscopy. TEM observation was performed on an HT-7700 TEM (HITACHI, Tokyo, Japan). An NPs/NFs solution (10 μ L, 30 μ M) was dropped on a copper mesh for 15 min, and most of the solution was removed with a filter paper. Uranyl acetate (10 μ L) was employed as a dye for 5 min. Deionized water (10 μ L) was used to wash for 1 min and removed with a filter paper. The copper mesh was then stored for measurements.

4.5. CD and FTIR Spectra. The CD spectra of SPIN-1 and SPIN-2 (10 μ M) were collected at room temperature using a CD spectrometer (JASCO-1500, Tokyo, Japan) with a cell path length of 1 mm. The measurements were implemented between 185 and 250 nm with a resolution of 1.0 nm and a scanning speed of 500 nm/min. For each measurement, three spectra were collected and averaged. SPIN-1 and SPIN-2 with a concentration of 30 μ M were freshly prepared and used for FTIR measurement. The FTIR spectrum was recorded on a spectrometer (Spectrum One, PerkinElmer Instruments Co., Ltd.).

4.6. Confocal Laser Scanning Microscopy. Confocal measurement was performed on a Z-760 laser scanning confocal microscope (Zeiss). The SPIN-1 or SPIN-2 solution (30 μ M, 100 μ L) was incubated with Cy5-labeled IgE for 4 h for CLSM observation. The SPIN-1 or SPIN-2 solution (30 μ M, 100 μ L) was incubated with both Cy5-labeled IgE and LAD2 cells for 4 h for CLSM observation.

4.7. Immune Colloidal Gold Technique. The colloidal gold solution (1 mL, 20 nm) was adjusted to pH 9.0 with potassium carbonate (~ 10 μ L, 0.01 M). IgE (1 mg/mL, 20 μ L) was diluted to 100 μ g/mL with borate buffer (0.05 M, pH 9.0, 180 μ L). The colloidal gold solution and IgE were mixed uniformly under stirring for 10 min, and stabilizer bovine serum albumin (final concentration 1%) was further added to the mixture. Then, the mixture was centrifuged at a low speed (2000 rpm, 20 min), and the aggregated colloidal gold particles in the bottom were discarded. The resultant supernatant was centrifuged at high speed (12 000 rpm, 1 h) at 4 $^{\circ}$ C. The sample in the bottom was redissolved in phosphate buffer (0.01 M, pH 7.4) to obtain the IgE-Au solution (40 μ g/mL) and stored at 4 $^{\circ}$ C. SPIN-1 or SPIN-2 NPs in aqueous solution were incubated with IgE-Au (final concentration of 4 or 20 μ g/mL). The samples were prepared at 0 h and 2 days for TEM measurements. The SPIN-1 or SPIN-2 NPs were directly incubated with the colloidal gold solution in parallel as controls.

4.8. Cytotoxicity. Human Umbilical Vein Endothelial Cells (HUVECs) were seeded in 96-well plates (1×10^4 cells/well) and incubated overnight for adhesion. Then, HUVECs were incubated with SPIN-1 or SPIN-2 NPs with a series of concentrations at 37 °C in a humidified environment containing 5% CO₂ for 24 h. LAD2 cells were seeded in 96-well plates (1×10^6 cells/well) and incubated with SPIN-1 or SPIN-2 NPs with a series of concentrations at 37 °C in a humidified environment containing 5% CO₂ for 24 h. Afterward, 100 μ L of culture medium with a 10% CCK-8 solution was added to each well and incubated for 4 h. The absorptions of each well were measured using a Microplate reader at a test wavelength of 450 nm, and the reference wavelength was 600 nm. Cell viability was calculated from the obtained data.

4.9. OVA-Induced AR Mouse Model and Subsequent Treatments. Twenty-five female Balb/c mice (6 weeks of age) were provided by Stanford (Beijing) Biotechnology and kept under specific pathogen-free conditions (No. 110324211103996121). They were randomly divided into five groups ($n = 5$), including the AR group, the SPIN-1 group, the SPIN-2 group, the cetirizine hydrochloride group, and the control group. The cetirizine hydrochloride group was referred to as the cetirizine group. Animal experiments were carried out under guidelines for the Care and Use of Laboratory Animals of NIH. The protocol was approved by the Institutional Animal Care and Use Committee of the National Center for Nanoscience and Technology, China.

4.9.1. Basic Sensitization. Mice in AR, SPIN-1, SPIN-2, and cetirizine groups were intraperitoneally injected with the mixture of OVA dissolved in Imject Alum (100 μ L, OVA concentration, 200 μ g/mL) every other day for 14 days. Mice in the control group received an intraperitoneal injection of 100 μ L of normal saline every other day for 14 days.

4.9.2. Treatment. One hour before the intranasal challenge from day 15 to day 23, SPIN-1 and SPIN-2 groups were treated with an intraperitoneal injection of SPIN-1, SPIN-2, cetirizine group was treated with an intragastric administration of cetirizine hydrochloride every day, respectively. Doses of drugs, SPIN-1, SPIN-2, and cetirizine hydrochloride of the three groups were all 10 mg/kg. AR and control groups were treated with an intraperitoneal injection of normal saline.

4.9.3. Challenging. Mice in AR, SPIN-1, SPIN-2, and cetirizine groups were further excited by nasal drops of 20 μ L of OVA solution of normal saline (10 μ L per nasal drop) with a final concentration of 20 mg/mL. Nasal drops were continued to be administered every day from the 15th to the 23rd day for excitation. Mice in the control group were given normal saline (20 μ L) as a nasal drip every day from the 15th to the 23rd day.

The behavior of mice was observed right after intranasal challenge on days 23, 24, 26, 28, 30, and 32. The number of sneezing and snatching events was recorded within 30 min for each mouse.

Finally, mice in AR, SPIN-1, and SPIN-2 groups were intraperitoneally injected with normal saline, SPIN-1, and SPIN-2, respectively, and the cetirizine group was intragastrically administered cetirizine, followed by intranasal challenge 1 h later, and observed for 30 min on day 33.

4.10. Enzyme-Linked Immunosorbent Assay (ELISA). Orbital venous blood of mice 24 h after the last stimulation was taken from each mouse on day 34. Serum was obtained by centrifugation for the ELISA test to determine the amounts of histamine, IL-4, and IL-5. The mice were then sacrificed, and the organs (heart, liver, spleen, and kidney) were collected for further hematoxylin and eosin (H&E) stain analyses.

4.11. Statistical Analysis. Data were analyzed using the GraphPad Prism8 software statistics package. Data were given in the form of mean $\pm$ standard deviation (SD). Differences between groups were analyzed with Student's *t*-test. It was considered that if the value of *p* is less than 0.05, there is a statistically significant difference between these groups. The level of significance was defined as **p* < 0.05, ***p* < 0.01, ****p* < 0.001, and *****p* < 0.0001.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsami.2c07092>.

Molecular structures and MALDI-TOF-MS spectrum of SPIN-1 (Figure S1); molecular structures and MALDI-TOF-MS spectrum of SPIN-2 (Figure S2); UV-vis spectra and fluorescence spectra of SPIN-1 (Figure S3); UV-vis spectra and fluorescence spectra of SPIN-2 (Figure S4); TEM images of SPIN-1 and SPIN-2 treated with/without IgE at different points in time (Figure S5); CD spectra of SPIN-1 and SPIN-2 in the absence of IgE (Figure S6); Fourier transform-infrared spectra of SPIN-1 and SPIN-2 (Figure S7); TEM images of SPIN-1 and SPIN-2 NFs incubated with trypsin (Figure S8); CLSM images of SPIN-1 or SPIN-2 incubated with the Cy5-labeled IgE and LAD2 (Figure S9); TEM images of SPIN-1, SPIN-2, and mixture of SPIN-1 and colloidal gold or SPIN-2 and colloidal gold (Figure S10); cell viability and hemolysis rate of SPIN-1 (Figure S11); cell viability and hemolysis rate of SPIN-2 (Figure S12); anaphylaxis symptom score of mice in each group (Figure S13); H&E staining of the heart, liver, spleen, and kidney tissue slices (Figure S14) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Xiang-Dan Li – Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education & Hubei Key Laboratory of Catalysis and Materials Science, South-Central Minzu University, Wuhan 430074, P. R. China; Email: lixiangdan@mail.scuec.edu.cn

Huai Yang – Key Laboratory of Polymer Chemistry and Physics of Ministry of Education, Peking University, Beijing 100871, P. R. China; Email: yanghuai@mater.ustb.edu.cn

Lei Wang – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China; orcid.org/0000-0003-1405-9815; Email: wanglei@nanoctr.cn

Hao Wang – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China; orcid.org/0000-0002-1961-0787; Email: wanghao@nanoctr.cn

Authors

Meng-Ru Ding – Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education & Hubei Key Laboratory of Catalysis and Materials Science, South-Central Minzu University, Wuhan 430074, P. R. China; CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China

Qi-Lin Liang – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China

Huan-Ge Xu – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials

and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China

Kuo Zhang – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China; orcid.org/0000-0003-3687-3172

Zi-Jin Wei – Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education & Hubei Key Laboratory of Catalysis and Materials Science, South-Central Minzu University, Wuhan 430074, P. R. China; CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China

Yong-Hong Gao – CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China; orcid.org/0000-0003-2575-7694

Qing-Shi Zhang – Key Laboratory of Catalysis and Energy Materials Chemistry of Ministry of Education & Hubei Key Laboratory of Catalysis and Materials Science, South-Central Minzu University, Wuhan 430074, P. R. China; CAS Center for Excellence in Nanoscience, CAS Key Laboratory for Biomedical Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology (NCNST), Beijing 100190, P. R. China

Rui Huang – School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, P. R. China

Complete contact information is available at:

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Notes

The authors declare the following competing financial interest(s): H. W., L. W., and M.R. D. are the co-inventors of a pending patent. The remaining authors declare that they have no competing interests.

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

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