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Review

Phe−Phe-Based Macroscopic Supramolecular Hydrogel Construction Strategies and Biomedical Applications

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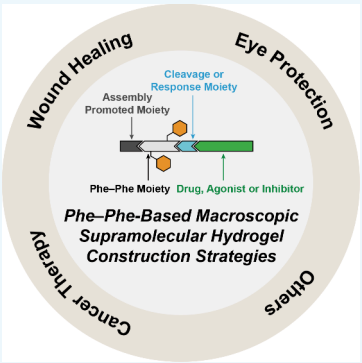
ABSTRACT: Since the phenylalanine (Phe) dipeptide moiety is referred to as an essential structure for building amyloid-β peptide from Alzheimer's disease, its wonderful assembly ability to form nanofibers has been extensively studied. Cross-linked Phe−Phe-based peptide nanofibers can construct networks, thus encapsulating the drugs to form supramolecular hydrogels. Recently, scientists have proposed a variety of Phe−Phe-based macroscopic supramolecular hydrogels and used them in biomedical applications. Therefore, we summarize the construction strategies of Phe−Phe-based macroscopic supramolecular hydrogels and list their represented biomedical applications (*e.g.*, wound healing, eye protection, cancer therapy, *etc.*) since the birth of Phe−Phe-based supramolecular hydrogels. In addition, we present the perspectives and challenges of Phe−Phe-based macroscopic peptide hydrogels.



KEYWORDS: *Assembly, Cancer therapy, Eye protection, Nanomedicine, Phe−Phe-based peptide, Supramolecular hydrogel, Wound healing*

1. INTRODUCTION

Peptide assembly has a special prominence in life science owing to every life activity depending on the assembly of peptides or proteins.[1] Therefore, analyzing and understanding the peptide assembly process is important for designing intelligent chemical biology molecules in the biomedical field. Since the phenylalanine (Phe) dipeptide sequence was confirmed to be the key assembly unit of amyloid-β (Aβ) polypeptide in Alzheimer's disease,[2] the Phe−Phe-based aggregation of peptides and proteins in pathological disorders has been widely explored. During this process, abnormal intermolecular interactions between the aromatic residues lead to the formation of disordered aggregates and thus accelerate the amyloidogenic process and induce many diseases.[3,4] The formation of phenylalanine aggregates (especially fibers) is closely correlated to amyloid-related diseases, and therefore, the controlled assembly behavior of diphenylalanine has been deeply explored. In different conditions, various ordered nanostructures including nanotubes, nanovesicles, nanosheets, and nanofibers can be obtained from programmed formation by self-assembly.[5] Among all of the nanostructures, nanofibers have been extensively studied experimentally due to their high biocompatibility and convenient hydrogel physical properties.[6−8] As the nanofibers grow, the microscopic nanofibers cross-link together to form macroscopic hydrogels. These Phe−Phe-based macroscopic supramolecular hydrogels exhibit a good elastic modulus,[9] a high drug-loading rate,[10] excellent biocompatibility,[11] and injectable characteristics,[12] whose performance is not inferior to traditional hydrogels.

Taking advantage of the modifiability of polypeptides, additional functional peptide sequences or small molecule moieties are applied to modify Phe dipeptides for developing the functions and uses of Phe−Phe-based supramolecular hydrogels. In addition, hydrogels have both hydrophilic and hydrophobic blocks, which can load or coassemble with many active molecules. Based on these foundations, many Phe−Phe-based supramolecular hydrogels have been reported and applied in various fields over the past few decades.[13,14] Specifically, Phe−Phe-based macroscopic supramolecular hydrogels have been widely used in wound healing and tissue regeneration due to their fillable properties.[15−19] Meanwhile, ophthalmologists are concerned about their excellent biosafety and high stability and have designed a series of Phe−Phe-based supramolecular hydrogels for anti-inflammatory use and eye protection.[20−23] In addition, cancer therapy and organ injury

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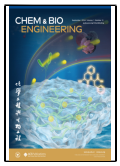

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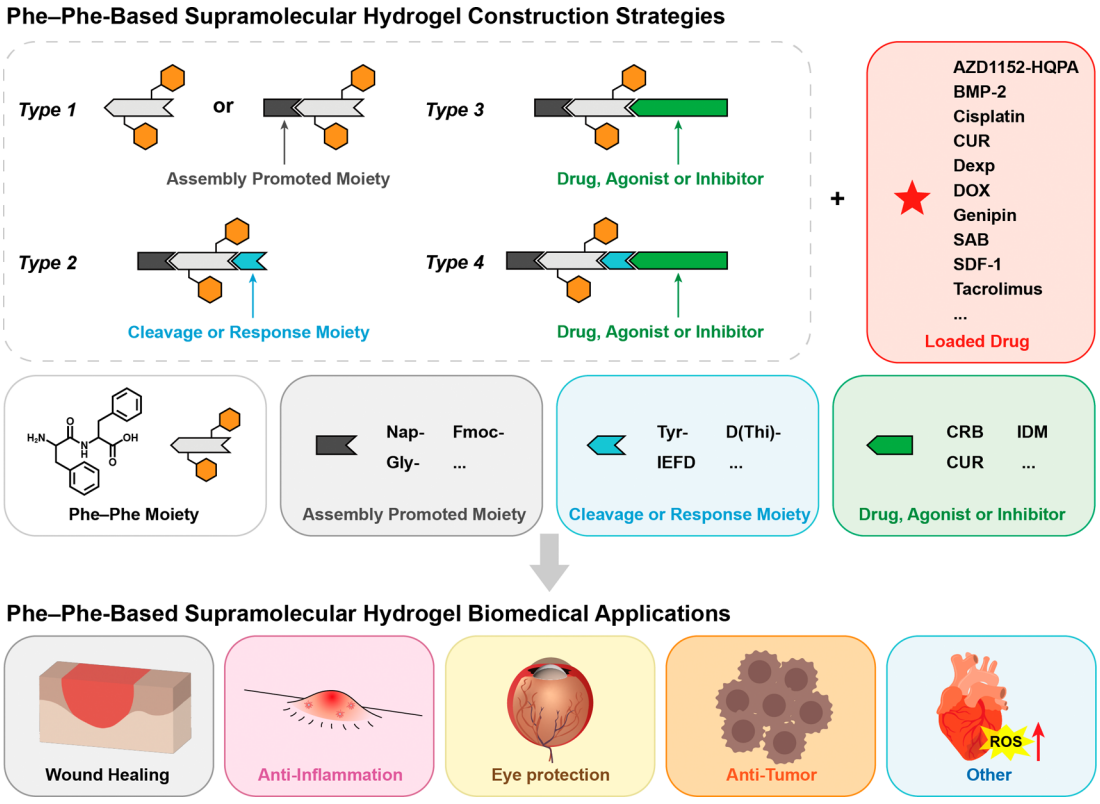
Scheme 1. Four Types of Major Phe−Phe-Based Supramolecular Hydrogel Construction Strategies, and Biomedical Applications of Phe−Phe-Based Supramolecular Hydrogels[a]



[a]Representative abbreviations in Scheme 1: BMP-2, bone morphogenetic protein-2; CUR, curcumin; Dexp, dexamethasone sodium phosphate; DOX, doxorubicin; SAB, salvianolic acid B; SDF-1, stromal cell derived factor-1; Nap, 2-naphthylacetic acid; Fmoc, 9-fluorenylmethyloxycarbonyl; Gly, glycine; D(Thi), aspartic acid decorated with thiazolidinone; IEFD, isoleucine−glutamic acid−phenylalanine−aspartic acid; CRB, chlorambucil; IDM, indomethacin.

repair are also of concern. Some Phe−Phe-based supramolecular hydrogels can smartly respond to the essential markers in specific diseases and further break down to release corresponding therapeutic drugs.[24,25] Moreover, Phe−Phe-based supramolecular hydrogels can also be used in many other aspects (such as myocardial infarction treatment,[26] ischemic stroke repair,[27] periodontal bone repair,[28] renal injury repair,[29,30] ovarian aging delay,[31] and organ transplantation overcome[32]). These Phe−Phe-based supramolecular hydrogels effectively overcome the limitations of traditional hydrogels in these biomedical applications.

At present, few literature reviews have systematically summarized the construction strategies of macroscopic Phe−Phe-based supramolecular hydrogels and enumerated the various applications of these supramolecular hydrogels in biomedicine. Herein, we in detail introduce the core strategies of designing functional Phe−Phe-based supramolecular hydrogels and catalog the corresponding commonly applied sights (*e.g.*, wound healing, eye protection, antitumor, *etc.*). On the other hand, we analyze the limitations and future trends of Phe−Phe-based supramolecular hydrogels. This review is expected to contribute to the in-depth understanding of the designed strategies of Phe−Phe-based supramolecular hydrogels and inspire more applications in clinical practice.

2. PHE−PHE-BASED SUPRAMOLECULAR HYDROGEL CONSTRUCTION STRATEGIES

The Phe−Phe motif as a self-assembling building block exhibits strong supramolecular interactions in an aqueous environment. In general, hydrogen bonding and $\pi-\pi$ stacking are the main driving forces for assembly of the Phe−Phe motif. Specifically, multidirectional hydrogen bonding allows the formation of noncovalent interactions of network interweaving, and $\pi-\pi$ stacking stabilizes the association. Additionally, hydrophobic interaction, electrostatic interaction, and van der Waals force also play a role in self-assembly.[33,34] Based on various chemical structures of assembled peptides, these noncovalent interactions synergistically work and balance between peptide−peptide and peptide−water interactions. For free Phe dipeptides, two phenylalanine residues mediate the intermolecular interaction between polypeptide chains into a reverse parallel β-sheet.[35] This reverse parallel structure enables the Phe dipeptides to assemble into ordered nanofibers. According to the structure of Phe−Phe, many Phe−Phe-based supramolecular hydrogels have been proposed. As shown in Scheme 1, we summarize the universal construction strategies of these Phe−Phe-based supramolecular hydrogels.

The construction strategies of Phe−Phe-based supramolecular hydrogels can be divided into four types according to complexity in design. In the first type, free Phe dipeptide and simple assembly-promoted modifications are included.

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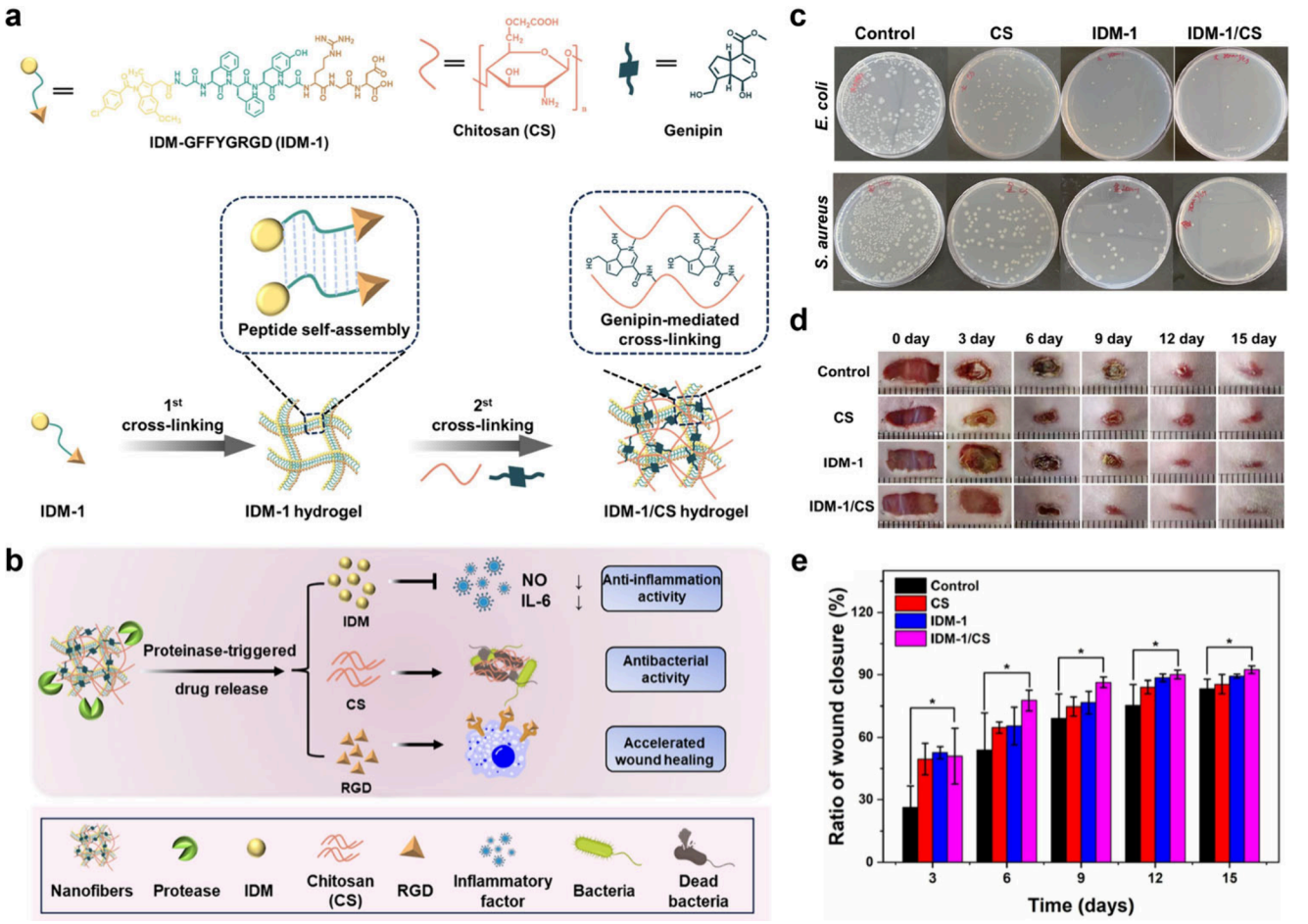

Figure 1. Diagrams displaying the formation of IDM-1 and IDM-1/CS hydrogels (a), and mechanisms for multifaceted wound management (b). (c) Images of bacterial colonies of *E. coli* and *S. aureus* after 12 h incubation with hydrogels. (d) Images of wounds at different time points. (e) The quantitative results of wound closure. Modified with permission from ref 18. Copyright 2024 Elsevier.

The protection of the terminal amine or acid group is a common and convenient approach to altering the self-assembly properties through solid-phase peptide synthesis (SPPS).[36] Many moieties can reduce charge repulsions and introduce hydrophobic contributions or $\pi-\pi$ stacking, thus facilitating the assembly of nanofibers, for example, 2-naphthylacetic acid (Nap) and the common amino protective group 9-fluorenylmethyloxycarbonyl (Fmoc).[37−42] In addition, many glycine-modified Phe−Phe supramolecular hydrogels exhibit excellent gel properties.[43] This type 1 construction strategy is easy to synthesize and obtain Phe−Phe supramolecular hydrogels with stability and biosafety.

Although this construction approach has many advantages, the type 1-constructed hydrogels lack response ability, which may induce undifferentiated drug release outside interesting locations. Hence, developing an intelligently controllable disassembly hydrogel may contribute to specific and rapid drug release. Based on these aims, several responsible components have been explored. For example, tyrosine (Tyr), an important amino acid, can be phosphorylated by certain kinases that are overexpressed at disease locations. After phosphorylation, the water solubility of the Phe−Phe-based peptides increases, thereby inducing the disassembly and rapid drug release within the disease area. All in all, the Phe−Phe−Tyr sequence is widely used to construct supramolecular hydrogels due to responsivity and controlled release.[44−46]

In the pursuit of elevated therapeutic effects, several drugs, agonists, and inhibitors have been used to conjugate with the Phe−Phe structure. This conjugated strategy can be divided into type 3 and type 4. For type 3, conjugated small molecules or peptide sequences show stable potency. Once the hydrogel is injected into the disease site, these drugs, agonists, or inhibitors can continuously play a role. However, this strategy suffers from the same issue of selectivity, which makes encapsulated drugs difficult to intelligently and quickly release in interesting locations. To address this problem, cleavage linkers were affiliated with the type 4 approach. Using specific peptide sequences that can be accurately cleaved by the corresponding enzymes, conjugated drugs can be specifically and efficiently released with complete efficiency.

For the conjugation of the aforementioned moieties, it is necessary to select rational and suitable reaction groups and conditions. Correct conjugated locations and appropriate linkers will affect the therapeutic effect. At the same time, the medicine should be carefully considered. Some suitable drugs can be involved in the assembly process of supramolecular hydrogels, improving the strength of the assembled nanofibers and the formed hydrogels.[17] These rationally designed Phe−Phe-based supramolecular hydrogels have been applied to address many biomedical problems, including wound healing, anti-inflammation, eye protection, anti-tumor, and more.

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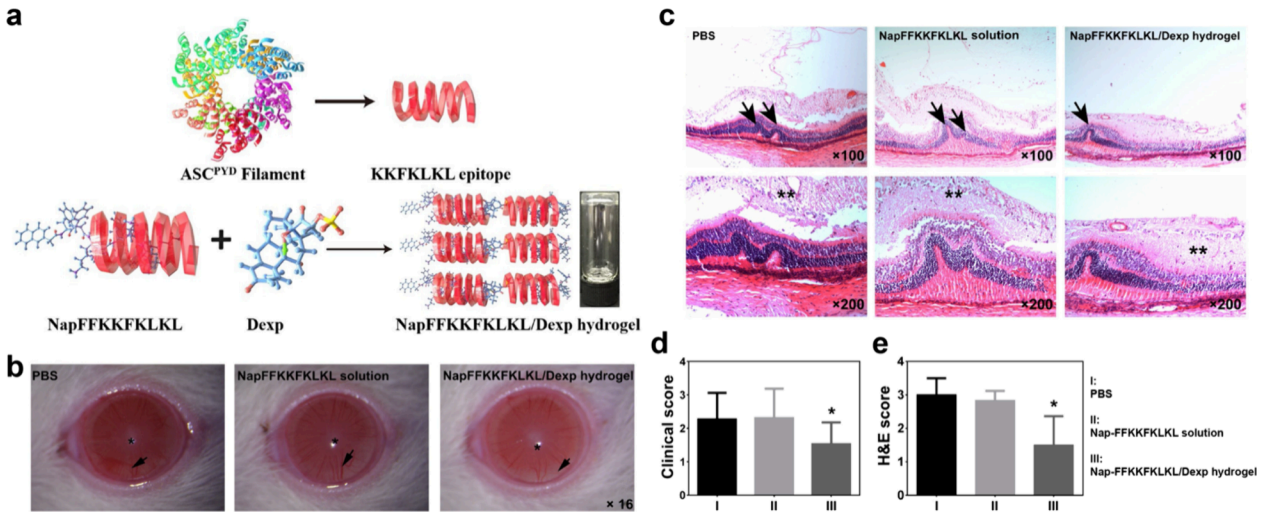

Figure 2. (a) Schematic formation of NapFFKKFKLKL/Dexp supramolecular hydrogel (2.5 mg/mL NapFFKKFKLKL and 10 mg/mL Dexp). (b) Clinical signs of EAU rats after treatment of PBS, NapFFKKFKLKL, and NapFFKKFKLKL/Dexp hydrogel on 12th day post immunization; black arrow indicates the protein exudate, and black star indicates the occlusion of pupil. (c) Histopathological observation of the retina from EUA rats treated by PBS, NapFFKKFKLKL, Dexp, and NapFFKKFKLKL/Dexp hydrogel on the 12th day post immunization. Black arrow indicates the retinal folds; black star indicates the inflammatory cell infiltration. (d) Clinical scores of EAU rats after treatment of PBS, NapFFKKFKLKL, and NapFFKKFKLKL/Dexp hydrogel on the 12th day post immunization. *$P < 0.05$ as compared to the PBS and NapFFKKFKLKL-treated group. (e) H&E score of EUA rats treated by PBS, NapFFKKFKLKL, and NapFFKKFKLKL/Dexp hydrogel on the 12th day post immunization. * $P < 0.05$ as compared to the PBS and NapFFKKFKLKL-treated group. Modified with permission from ref 21. Copyright 2021 Elsevier.

3. VARIOUS BIOMEDICAL APPLICATIONS OF PHE−PHE-BASED MACROSCOPIC SUPRAMOLECULAR HYDROGEL

3.1. Wound Healing. Wound healing is a common application scenario for hydrogels.[47,48] Supramolecular hydrogels can easily fill damaged tissues and sustainably release drugs to repair aimed at tissues. In the process of wound healing, hemostasis,[49,50] angiogenesis,[51,52] and tissue generation[53] are the mostly expectant functions for hydrogels. Hu *et al.* used Pro−His−Ser−Arg−Asn (PHSRN, a fibronectin-mimetic peptide sequence) to conjugate Nap−Phe−Phe (NapFF) to prepare NapFFPHSRN supramolecular hydrogel.[15] This hydrogel had great potential to promote F-action remoldation and enhance the zonula occludens-1 (ZO-1) expression. *In vivo*, the corneal scrape model indicated that the NapFFPHSRN structure could effectively repair the cornea by promoting re-epithelialization and recovering the corneal morphology and architecture. This mimic peptide has achieved effective injury treatment without other drugs, demonstrating the excellent therapeutic effect of Phe−Phe-based supramolecular hydrogels.

Although Phe−Phe-based hydrogels can serve as an effective matrix providing a growth platform for wound healing, there is still room for improvement in efficiency. Silk fibroin (SF) is a protein extracted from *Bombyx mori* cocoons with the abilities of proliferation and differentiation, showing the potential for tissue repair, and thus is widely applied in supramolecular hydrogels.[54] In 2021, Wang *et al.* focused on a peptide sequence Ser−Val−Val−Tyr−Gly−Leu−Arg (SVVYGLR, derived from osteopontin, with the potential to induce adhesion, migration, and tube formation of endothelial cells) and synthesized its phosphorylated structure to be conjugated with Nap−Phe−Phe to obtain NapFFSVVYpGLR.[16] Upon the alkaline phosphatase (ALP) addition, NapFFSVVYpGLR could be converted to NapFFSVVYGLR (SV) and form a supramolecular hydrogel by hydrogen bonding, $\pi-\pi$ stacking, and hydrophobic interactions. To enhance the assembly effect, SF was used to take part in coassembly, and thus, a stable hydrogel (SV-SF) could be prepared. This hydrogel framework provided a platform for stimulating collagen deposition and expression of angiogenesis-related genes/proteins for repairing the skin by promoting vascular regeneration and repairing epidermization. Similarly, Cheng *et al.* combined a native extracellular matrices (ECMs)-derived binding ligand Arg-Gly-Asp (RGD) fragment with NapFF to construct a NapFFRGD supramolecular hydrogelator.[17] Upon mixing the NapFFRGD solution and SF solution, SF gel could be obtained in a few seconds. Next, the author incorporated vascular endothelial growth factor (VEGF) into SF gel. Upon subcutaneous injection, the smart hydrogel showed enhanced adhesion and angiogenesis. Totally, SF is considered to be an ideal structure to help Phe−Phe-based hydrogels improve the speed of wound healing. In addition, the discovery of other suitable matrices may contribute to the widespread application of Phe−Phe-based hydrogels in wound healing.

Besides fastening angiogenesis in the wound area, hemostasis is also an important issue.[49,50] Zheng *et al.* proposed an indomethacin (IDM, a nonsteroidal anti-inflammatory drug)-Gly-Phe-Phe-Tyr-Gly-Arg-Gly-Asp (IDM-1) hydrogelator.[18] As shown in Figure 1a, IDM-1 gelators cross-link with each other to form IDM-1 hydrogel. Then, by doping with chitosan (CS) and genipin (GEN, a cross-linker for hydrogel), IDM-1/CS hydrogel was obtained. Upon cleavage by protease, IDM could be effectively released and then render anti-inflammatory efficacy by downregulating nitric oxide (NO) and interleukin-6 (IL-6). Here, CS showed its antibacterial activity in the disease area, and the RGD sequence could bind with integrin receptors to accelerate wound healing. IDM-1/CS hydrogel exhibited the least amount of bleeding *in vitro*. Likely inhibiting effects could be seen in both *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) groups treated with IDM-1/CS hydrogel (Figure 1c). Thus, the IDM-1/CS hydrogel has the fastest

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wound healing speed in Figure 1d and 1e, indicating the excellent IDM-1 design for accelerating wound healing.

Apart from hemostasis and angiogenesis, hydrogels in scar hyperplasia also achieve some improvements.[55] Salvianolic acid B (SAB) is one of the water-soluble active components of *Salvia miltiorrhiza* (a traditional Chinese medicine),[56] showing great potential in inhibiting apoptosis, oxidation, inflammation, and fibrosis and, meanwhile, promoting blood circulation and angiogenesis. Huang *et al.* utilized the NapFFKYp peptide sequence to prepare **1** solution and mixed it with SAB solution to obtain **1**&SAB hydrogel.[19] The results indicated that **1**&SAB hydrogel could effectively promote wound healing and reduce scar hyperplasia.

To sum up, Phe−Phe-based macroscopic hydrogels can be effectively filled and cover the damaged area of the wound and hemostasis. By designing recognizable substrates in injury locations or conjugating/coassembly with various specific drugs, peptide hydrogels can fasten angiogenesis and inhibit scar hyperplasia to improve the efficiency of wound healing.

3.2. Eye Protection. Eyes, as the window to see the world, should be given more attention in our daily lives. With the development of biomedical engineering, scientists regard hydrogels as important agents for eye protection.[57] Reducing inflammation in the eye is one of the key factors in design. For example, Lin *et al.* designed IDM-Nal-Nal-Asp for high selectivity of cyclooxygenase-2 (COX-2) and enhanced anti-inflammatory effect in eyes.[58] In addition, Li's group integrated antioxidant 3,5-dihydroxybenzoic acid, ibuprofen (IPF, a nonsteroidal anti-inflammatory drug), and Gly−Phe−Phe−Tyr−Asp (GFFYD) to synthesize 2IPF-DHB-GFFYD supramolecular hydrogel for reducing the cytokine production in lipopolysaccharide (LPS)-activated macrophage RAW264.7 cells.[20] Recently, peptide sequence KKFKLKL was found as a key peptide epitope with the ability to be anchored to the surface by interacting with the negative-charged domain of apoptosis-associated speck-like protein (ASC).[59,60] On this basis, Li's group rationally raised NapFFKKFKLKL hydrogelator (Figure 2a).[21] Specifically, this nonapeptide could be coassembled with dexamethasone sodium phosphate (Dexp, a powerful corticosteroid, which is widely used for anti-inflammation[61]) to form NapFFKKFKLKL/Dexp supramolecular hydrogels. The experimental results demonstrated that the NapFFKKFKLKL/Dexp hydrogel had a stable rate of release of Dexp (Figure 2b) and good biocompatibility. After that, experimental autoimmune uveitis (EAU) rat models were established to verify the effects of anti-inflammation and eye protection. The results in Figure 2c indicate that the NapFFKKFKLKL/Dexp hydrogel group could significantly attenuate the clinical symptoms of ocular inflammation on day 12 following a single intravitreal injection, while the PBS or NapFFKKFKLKL solution group had more inflammatory occlusion and iris congestion. Meanwhile, there was the existence of numerous infiltration areas of inflammatory cells in exudates in the anterior chamber with certain pupil vitreous cavities. Remarkably downregulated clinical and hematoxylin-eosin staining (H&E) scores indicated the optimal anti-inflammatory and best eye protection effects.

Except for the vitreous body, the cornea is another virtual eye structure participant in transparency and avascularity.[62] Effectively balancing the factors of angiogenesis and antiangiogenesis can maintain the vascularity of the cornea.[63] However, this balance can be broken down upon the various external stimuli, which may induce corneal neovascularization (CoNV), with the help of vascular endothelial growth factor (VEGF).[64] Although bevacizumab has been shown to have the ability to improve vision,[65] there are still some injured patients who have unsatisfactory treatment. In 2021, Chen *et al.* utilized an 11-peptide sequence HRHTKQRHTALH (HRH, which can bind to VEGFR for antiangiogenesis) to fabricate Nap-HRHTKQRHTALH (NapFFHRH).[22] NapFFHRH could be assembled into nanofibers, which can inhibit cell proliferation and migration. Meanwhile, the vascular endothelium cell formation was inhibited *in vitro*, and significant vascular growth restriction was seen in the rats with alkali burn-induced CoNV treated with NapFFHRH hydrogel *in vivo*.

Mucin is a highly glycosylated protein that serves to inhibit the adhesion of the eyelid epithelium, inflammatory cells, and the cornea surface. Its primary function is to prevent the attachment of pathogenic substances and other debris to the eye's epithelial surface as well as to hinder the tight adhesion of the outer layer of mucus in the tear film to the eye surface. Liu *et al.* compared the eye protection potential of various numbers of lysine or aspartic acid conjugated NapFF.[23] The results indicated that NapFFKK supramolecular hydrogelator, acting as a cationic peptide, can interact with ocular mucin. This interaction leads to increased retention and adhesion on the corneal surface. As a result, it shows promise as an ocular drug carrier that can address the challenges associated with delivering therapeutics in the eye, such as physiological obstacles and clearance mechanisms.

In summary, in order to protect the eyes, a variety of short peptide sequences are used to conjugate with the Phe−Phe structure to self-assemble into macroscopic hydrogels. These smart peptides can significantly enhance the effectiveness of eye protection through specific properties at various locations in the eye.

3.3. Cancer Therapy. Cancer is a highly lethal disease, and many strategies surrounding cancer therapy have been proposed.[66−68] Recently, there has been increased interest in functional hydrogels for cancer therapy. Compared with traditional hydrogels, supramolecular hydrogels show potential in biodegradability,[69] molecular recognition ability,[70] stimulus response ability,[71,72] self-assembly ability,[73] *etc.* Sustainable and controllable drug release is regarded as an important feature of Phe−Phe-based supramolecular hydrogels for cancer therapy. Wang *et al.* designed Nap-$G_DF_DF_D$Yp-CHO peptide as a pH-responsive supramolecular hydrogel precursor.[74] In this molecule, the aldehyde group (−CHO) could react with the amino group in the doxorubicin (Dox) by Schiff bases. The CHO−Dox−gel could be obtained upon ALP addition, which showed the pH-controllable Dox release.

In normal hydrogels, agglomerations happen among drug delivery.[75] To solve this problem, Cao *et al.* synthesized Fmoc-Gly-Phe-Phe-Gly (Fmoc-GFFG) to construct supramolecular hydrogels.[76] Specifically, the host−guest interaction between Fmoc and the sulfobutylether-β-cyclodextrin (SBE-β-CD) moiety enhanced the storage modulus (G'). Meanwhile, 10-hydroxycamptothecin (HCPT) could be encapsulated in SBE-β-CD by host−guest interaction. Thus, the Fmoc-GFFG/SBE-b-CD@HCPT hydrogels were prepared. Compared with other drug carriers, this hydrogel could reduce HCPT agglomeration and prolong the retention time in the target area. This work smartly used the spatial structure of β-CD to disperse the HCPT and provide an excellent strategy for drug delivery.

Further, to increase tumor recognition ability, many intelligently detachable Phe−Phe-based supramolecular hydro-

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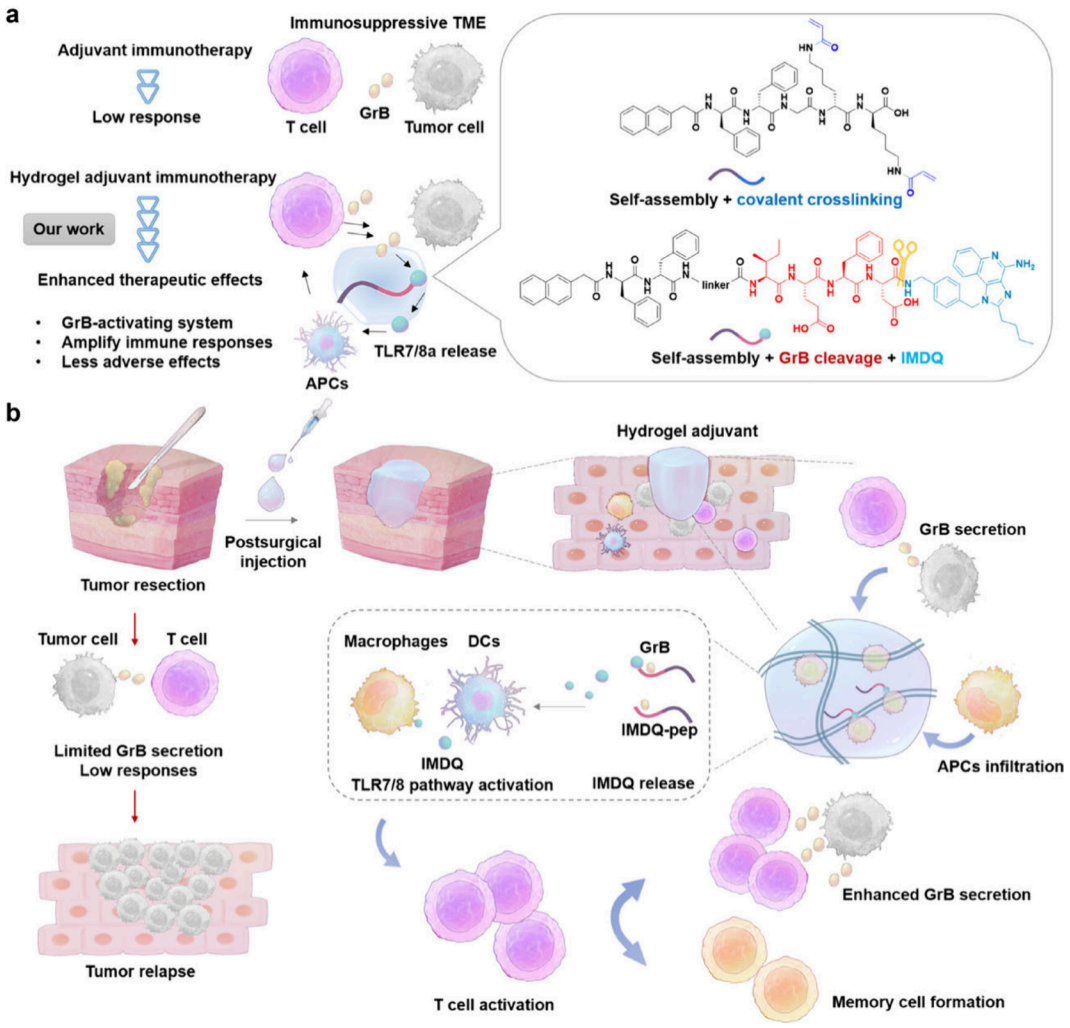

Figure 3. Composition of hydrogel adjuvant, and schematic mechanism for adjuvant-mediated postsurgical immunotherapy. (a) The structure of the peptide scaffold and GrB responsive IMDQ−peptide conjugate. (b) By filling the surgical cavity with the hydrogel, it creates a localized inflammatory depot for infiltration of APCs. The localized release of IMDQ responses to GrB allow for immune activation while minimizing immune-related toxicity, which are crucial for further enhancing GrB secretion and establishment of long-term immunological memory to improve personalized postsurgical immunotherapy. Modified with permission from ref 98. Copyright 2024 American Chemical Society.

gelators have been proposed. Usually, kinases are widely present as important biomarkers in different stages of cancer.[77] Many hydroxyl or phenolic hydroxyl-based groups can be phosphorylated after being recognized by kinases, which may greatly enhance the water solubility of hydrogelators and thus lead to the disassembly of supramolecular hydrogels.[78,79] In 2023, Xu *et al.* referred to Nap-Phe-Phe-Arg-Arg-Lys-Ser-OH (**S**), which could coassemble with AZD1152-HQPA (**AZD**, an aurora kinase B inhibitor) to form **Gel S/AZD**.[78] Skillfully, aurora kinase B (AURKB) is an important biomarker widely present in cervical cancer, and RRKS tetrapeptide is the ideal sequence substance for AURKB. After intratumoral injection, **Gel S/AZD** could disassemble with the help of AURKB in the cervical cancer cells, and then, **AZD** was released to inhibit AURKB by decreasing phosphohistone H3 (pH3, AURKB downstream protein) expression for inducing cell cycle disorder and apoptosis. Similarly, Hua *et al.* designed a Nap-Phe-Phe-Glu-Glu-Leu-Tyr-Arg-Thr-Gln-Ser-Ser-Ser-Asn-Leu-OH (**Nap-S**) supramolecular hydrogel to coassemble with a salt-inducible kinase 2 (SIK2) inhibitor HG-9-91-01 for suppressing metastasis of ovarian cancer.[79]

Besides depending on coated drugs, many functional Phe−Phe-based supramolecular hydrogelators have been designed. Liu's group developed a cyclen-conjugated FFFK peptide framework (FFFK-cyclen) for achieving enhanced cell endocytosis by protonation of cyclen under normal conditions.[80] At the same time, FFF can provide the hydrophilic site to drive the peptide assembling into nanofibers and accumulate in the tumor cells. In detail, his team selected chlorambucil (CRB, an aryl nitrogen mustard agent[81,82]) to conjugate with FFFK-cyclen to induce stronger tumor cellular DNA damage, as tested by histone H2AX phosphorylated on serine 139 (γ-H2AX) experiments. Then, they modified HCPT with FFFK-cyclen for constructing HCPT-FFFK-cyclen nanofibers.[83] Compared with free HCPT, these nanofibers exhibited significantly increased nuclear accumulation. Interestingly, cyclens might consume ATP in tumor cells, allowing ATP-dependent drug efflux, and achieving stronger chemotherapeutic efficiency.

Although chemotherapy has achieved considerable success, multidrug resistance (MDR) still significantly hinders the efficacy of drugs, primarily due to P-glycoprotein (P-gp).[84] Except for common P-gp inhibitors, including verapamil,[85]

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vitamin E,[86] cyclosporin A,[87] and small interfering RNA,[88] it has been confirmed that nitric oxide (NO) has chemosensitization effects by decreasing the P-gp expression levels and thus overcomes MDR.[89,90] Surrounding generation of NO, Zhang *et al.* proposed a NapFFGEE-JSK hydrogelator to load Dox for overcoming MDR of breast cancer.[91] The obtained hydrogel could release Dox in acidic conditions by destroying the electrostatic binding point between NapFFGEE-JSK and Dox. Meanwhile, NO prodrug JSK can be activated by glutathione (GSH) and glutathione *S*-transferase (GST) and release NO. The hydrogel treatment demonstrated an anticipated synergistic antitumor effect on drug-resistant breast cancer in the experimental results. Additionally, Wang et al. used a nonsteroidal anti-inflammatory drug (NSAID) naproxen (Npx)-conjugated $_DF_DF_DE_DY$ structure to coat cisplatin for boosting the radiosensitization effect to solve the problem of the limited radiotherapeutic effects.[92]

Recently, immunotherapy has become crucial in cancer treatment. Since Luo *et al.* noticed that D-tetrapeptide-based hydrogel ($NapG_DF_DF_DY$) could stimulate $CD8^+$ T cells in 2017,[93] many Phe−Phe-based supramolecular vaccines have been created.[94,95] Yang's group screened represented NSAID structure (such as flurbiprofen (Fbp), carprofen (Car), Npx, ketoprofen, oxaprozin, fenoprofen, ibuprofen, and fenbufen) conjugated tetrapeptide ($G_DF_DF_DY$).[96] The results demonstrated that Fbp- and Car-modified tetrapeptide (termed Fbp-gel and Car-gel, respectively) might show promise as effective cancer adjuvants. Then, Wang and co-workers designed $FbpG_DF_DF_DY_DX$-ss-ERGD (X represents E, S, or K amino acid) as precursors to prepare $FbpG_DF_DF_DY_DX$-SH hydrogels. By coating ovalbumin (OVA), $FbpG_DF_DF_DY_DK$-SH hydrogels showed the strongest mechanical properties and the best antitumor immune response ability. In addition, Wang *et al.* used Fbp-$G_DF_DF_DY_DK(\gamma E)_2$-$NH_2$ to coassemble with OVA for promoting dendritic cell (DC) maturation, enhancing antigen accumulation and retention in the lymph nodes, and eliciting the secretion of cytokines.[97]

Although immunotherapy has achieved some success, it still has some limitations such as limited responses, patient heterogeneity, nontargeted distribution, and immune-related adverse effects that need to be addressed. Recently, Wang's group designed a programmable hydrogel adjuvant for filling surgically resected tissues to boost the secretion of granzyme B (GrB) and enhance immunotherapy response.[98] As shown in Figure 3a, **NapffGk(aa)k(aa)** was first synthesized for cross-linking into a hydrogel by photoinduced covalent bond generation with the help of vinyl groups from **aa** monomer. In addition, the author designed Napff-$(PEG_3)_2$-IEFD-IMDQ (**IMDQ-pep**) for stimulating immune response. In this molecule, IMDQ (imidazoquinoline) is a kind of Toll-like receptor 7/8 (TLR7/8) agonist from antigen-presenting cells (APCs) for cancer immunotherapy, and IEFD is considered to be a good peptide substance of GrB. By mixing the **NapffGk(aa)k(aa)** with **IMDQ-pep** and tumor cells undergoing immunogenic cell death (ICD), the **IC + IP**@Gel was prepared upon ultraviolet (UV) irradiation. This hydrogel adjuvant established a localized inflammatory area, promoting the infiltration of DCs and macrophages (Figure 3b). Additionally, **IMDQ-pep** had the ability to respond to low doses of GrB and locally release IMDQ to rebuild the immune microenvironment and enhance immune responses.

For cancer therapy, rapid and intelligent drug release are key issues in designing Phe−Phe-based macroscopic hydrogels. As a result, many antitumor drugs are added to supramolecular hydrogels, and disassembled peptide structures are thought to be modified with the Phe−Phe-based structures. Additionally, D-type amino acids are considered to be a good choice for enhancing the cytotoxicity of polypeptides and have potential in immunotherapy.

3.4. Other Applications. Phe−Phe-based supramolecular hydrogels not only show great potential in wound healing, eye protection, and cancer treatment but also hold a compelling position in many other biomedical applications. Here, we list represented works in various applications of Phe−Phe-based macroscopic supramolecular hydrogels.

Myocardial Infarction Treatment. Heart disease is closely related to human health, among which myocardial infarction is a critical heart disease with high mortality.[99] To cure this disease, Gross *et al.* yielded a cell-permeable peptide YGRKKRRQRRRGSGRAITILDTEKS (V1-Cal) with significant treatment effects toward myocardial infarction.[26] However, V1-Cal has a short half-life, which limits its further applications. To address this problem, Wang *et al.* used a classical NapFFY supramolecular hydrogelator to coassemble with V1-Cal to obtain V1-Cal/NapFFY hydrogel (Figure 4a),

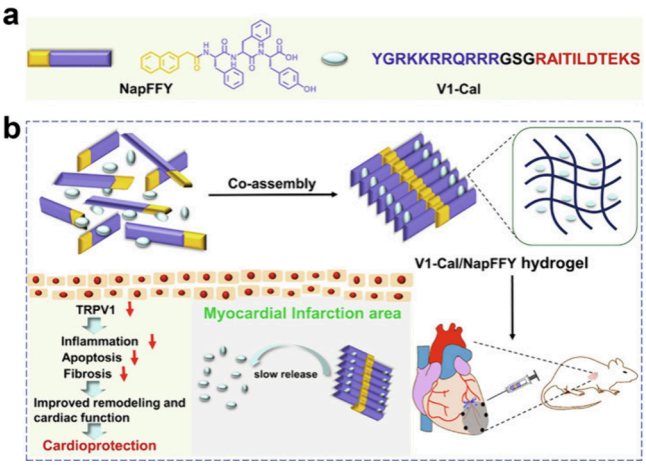

Figure 4. (a) Chemical structure of NapFFY hydrogelator, and peptide sequence of V1-Cal. (b) Schematic illustration of a supramolecular hydrogel V1-Cal/NapFFY improving cardiac function of a rat MI model by myocardial injection. Modified with permission from ref 26. Copyright 2022 Elsevier.

which could reduce the activation of transient receptor potential vanilloid 1 (TRPV1, which plays an essential role in myocardial ischemia), decrease apoptosis, and release inflammatory factors (Figure 4b). *In vivo* experiments indicated that the V1-Cal/NapFFY hydrogel could effectively inhibit ventricular remodeling after myocardial infarction and improve cardiac function.

Ischemic Stroke Repair. Brain disease is also an important disease. Stroke is one of the most important reasons for death and long-term disability worldwide, threatening the lives of patients.[100] Ischemic stroke is a devastating brain−blood circulation disorder mainly induced by acute, persistent cerebral ischemia and hypoxia, which cause over 85% of strokes.[101] Depending on the great treatment potential of curcumin (Cur, the main polyphenolic compound extracted from *Curcuma longa*, with the ability for anti-inflammation, antiapoptosis, and neuroprotection) and edaravone (EDV, that can scavenge free radical), Jia and co-workers designed an

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EDV/Cur/NapFFY hydrogel (Figure 5a and 5b).[27] *In vivo* experimental results demonstrated that **EDV/Cur/NapFFY** hydrogel could repair brain plasticity and promote functional recovery in the photothrombotic mouse model.

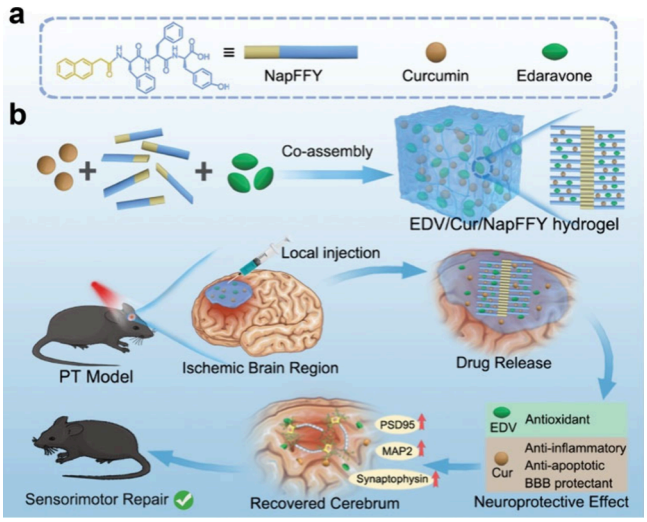

Figure 5. (a) The preparation process of EDV/Cur/NapFFY hydrogel. (b) Schematic illustration of the EDV/Cur/NapFFY hydrogel promoting nerve recovery in a stroke mice model. Modified with permission from ref 27. Copyright 2023 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Periodontal Bone Repair. Periodontal disease is a kind of inflammation that may eventually lead to periodontal bone destruction. Reconstruction of the periodontal bone environment is an ideal treatment approach for dentists. To date, utilizing biomaterials to deliver bioactive factors for recruiting stem cells and promoting their proliferation and differentiation has been a promising strategy for periodontal bone regeneration. As shown in Figure 6a, Tan *et al.* selected NapFFY hydrogel to load stromal cell-derived factor-1 (SDF-1) and bone morphogenetic protein-2 (BMP-2) to prepare **SDF-1/BMP-2/NapFFY** hydrogel for treating periodontal bone destruction.[28] Among them, SDF-1 can stimulate the homing of endogenous bone marrow mesenchymal stem cells (BMSCs) and periodontal ligament stem cells (PDLSCs) to the defect areas, and BMP-2 induces the differentiation of BMSCs into osteoblasts and improves new bone formation (Figure 6b). The maxillary critical-sized periodontal bone defect rat models exhibited a superior bone regeneration rate of 56.7% bone volume fraction, demonstrating the strong repair ability of the designed hydrogel.

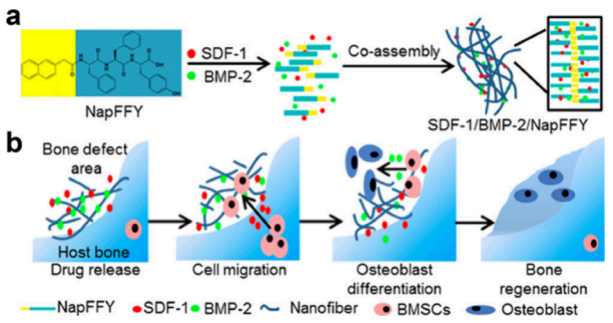

Figure 6. (a) Schematic illustration of the formation process of the SDF-1/BMP-2/NapFFY hydrogel. (b) Schematic illustration of promoted periodontal bone regeneration by the SDF-1/BMP-2/NapFFY hydrogel in the bone defect area. Slowly released SDF-1 from the hydrogel will recruit BMSCs to the defect area; then, BMP-2 will promote BMSCs to differentiate into osteoblasts, resulting in the initiation of the periodontal bone regeneration process. Modified with permission from ref 28. Copyright 2019 American Chemical Society.

Renal Injury Repair. Acute kidney injury (AKI) has high mortality and morbidity rates in the world, which may further induce chronic kidney disease (CKD).[102] Among the reasons for AKI, renal ischemia/reperfusion (I/R) injury is a common and important reason. In general, low concentrations of nitric oxide (NO), high reactive oxygen species (ROS) release, and developed endothelial injury are the important characteristics of renal I/R injury.[103,104] For effectively repairing renal I/R injury, Najafi *et al.* proposed a Fmoc-FF hydrogel to encapsulate *S*-nitroso-*n*-acetyl penicillamine (SNAP) for renal I/R injury.[29] The results indicated that obtained FmocFF-SNAP could sustainably release NO over 7 days, decrease inducible nitric oxide synthase (iNOS) expression, and increase endothelial nitric oxide synthase (eNOS) expression for promoting endothelial tissue regeneration and alleviating renal I/R injury. In addition, considering the good storage ability of the supramolecular hydrogel, Zhang *et al.* synthesized a Biotin-GFFYGRGD supramolecular hydrogel scaffold to carry extracellular vesicles derived from mesenchymal stem cells (MSC-EVs) for improving the therapeutic efficacy in renal repair.[30]

Ovarian Aging Delay. Premature ovarian failure is a common ovarian disease. Inhibiting mammalian target of rapamycin (mTOR) is regarded as an effective treatment approach. Shi *et al.* designed Nap-Phe-Phe-Asp-Arg-Leu-Tyr-OH (Nap-FFDRLY) to coassemble with Ala-Glu-Ala-Ala-Leu-Tyr-Lys-Asn-Leu-Leu-His-Ser-OH (which can competitively inhibit the autophosphorylation of receptor tyrosine kinases (RTKs)), as shown in Figure 7a.[31] The obtained hydrogel effectively delayed ovarian aging by decreasing mTOR activity, stimulating estrogen and progesterone secretion from the ovary, and developing more antral follicles for reproduction.

Overcoming Organ Transplantation Rejection. In clinical practice, transplant rejection is a big problem in organ transplantation. Tacrolimus (Tac) can effectively inhibit T cells by administration in the clinic.[105] However, direct administration of Tac may induce many side effects, including chronic allograft nephropathy, diabetes mellitus, arterial hypertension, and neurotoxicity. Wu *et al.* rationally referred to Nap−D-Phe−D-Phe−Glu−Tyr−OH for coassembling with tacrolimus to form Tac-coassembled nanofibers (Figure 7b).[32] *In vivo* experiments confirmed that the median survival time of liver transplantation rats treated with Tac-coassembled nanofibers or the same dose of Tac is 22 or 13 days, suggesting the potential to overcome organ transplantation rejection of Nap−D-Phe−D-Phe−Glu−Tyr−OH hydrogel.

4. CONCLUSION AND OUTLOOK

In this review, we summarize major Phe−Phe-based supramolecular hydrogel construction strategies and introduce their common biomedical applications, such as wound healing, eye protection, anti-inflammation, cancer therapy, myocardial infarction treatment, ischemic stroke repair, periodontal bone repair, renal injury repair, ovarian aging delay, and overcoming organ transplantation rejection. Table 1 clearly lists and

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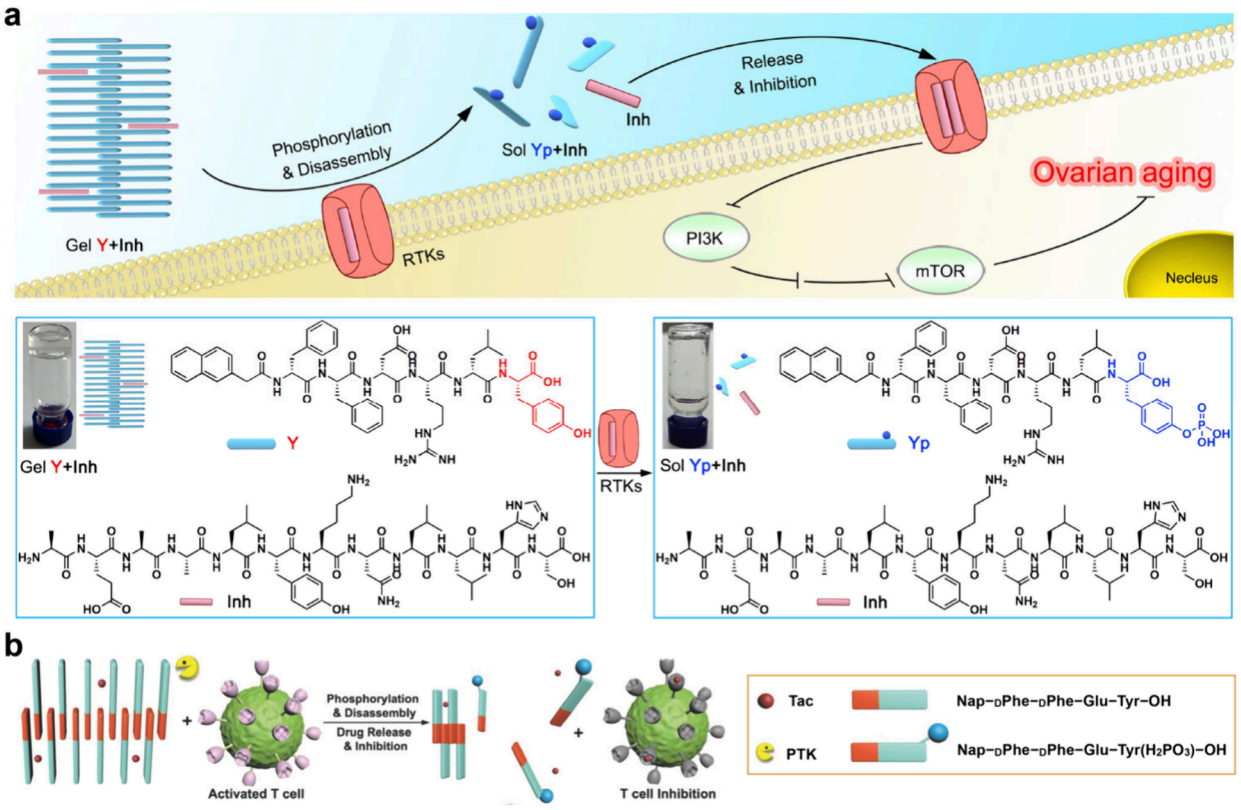

Figure 7. (a) Schematic illustration of RTK-instructed disassembly of hydrogel Gel Nap-FFDRLY (**Y**) + Inh for RTKs/PI3K signaling pathway inhibition. RTK-instructed disassembly of Gel **Y** + Inh, and chemical structures of hydrogelator **Y**, its corresponding phosphate **Yp**, and a RTK inhibitor Inh. Photographs: Gel **Y** + Inh (left frame) and Gel **Y** + Inh incubated with SCFR (one type of RTKs) at 37 °C for 3 h (right frame). Modified with permission from ref 31. Copyright 2021 Elsevier. (b) Schematic illustration of activated T-cell-responsive disassembly of Tac-coassembled nanofiber to release the drug for T-cell inhibition. Modified with permission from ref 32. Copyright 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

classifies recent Phe−Phe-based supramolecular macroscopic hydrogels and their biomedical applications.

These responsive Phe−Phe-based supramolecular constructions provide a highly biocompatible option for effectively delivering or releasing drugs. A noncovalent interaction drives assembly blocks into nanofibers, thus forming supramolecular hydrogels and achieving self-healing properties through their dynamical reversibility. In addition, Phe−Phe-based supramolecular hydrogels are programmable by various functional moieties as shown in Scheme 1, which provides personally customized choices for different disease treatments. Through programmed design, these Phe−Phe-based supramolecular hydrogels acquire abilities of being adjustable mechanically, responsive disassembly, injectable properties, *etc.* Due to the multiple functions and flexibility, these peptide-based supramolecular hydrogels have shown powerful chemobiological applications, for example, effective enzyme activity protection,[106] strong T cell activation,[93] and promoted peripheral T regulatory cell (Treg) population.[107] These applications enrich the biomedical advancement of Phe−Phe-based supramolecular hydrogels and may inspire more improvements in the future. Phe−Phe-based supramolecular hydrogels have been proven to have long-term stability in the body,[107] and related research has proven the effective and rapid pharmacokinetics of Phe−Phe-based supramolecular hydrogels *in vivo*, which is similar to some small molecules metabolizing through the reticuloendothelial system,[108] indicating the wonderful biosafety of these macroscopic hydrogels.

Phe−Phe-based supramolecular hydrogels still face limitations in clinical use, including stability, expense, and fabrication. Overcoming these problems is one of the future development trends of Phe−Phe-based supramolecular hydrogels. First, the stability of supramolecular hydrogels is unreliable. Noncovalent interactions can form supramolecular hydrogels without bond changes, while they are also limited by complex body conditions that may easily influence the assembly balance, resulting in the leakage of coated drugs. Hence, developing Phe−Phe-based peptide structures with stronger noncovalent interactions may extend or control the retention time and release time of loaded agents and drugs. Another possible strategy is to use ᴅ-Phe instead of ʟ-Phe to achieve long-term biostability. ᴅ-Phe rarely serves as the primary unit of naturally occurring proteins, allowing higher resistance from endogenous protease proteolysis *in vivo*. Meanwhile, ᴅ-Phe also possesses a similar assembly ability to act as building blocks in biomedical applications.[109] Second, the cost of supramolecular hydrogels is higher than that of traditional ones and therefore limits systematic applications. The excellent and multiple properties of customized molecules depend on the introduction of cofactors through complex synthesis, thus increasing the cost and difficulty. Therefore, exploring low-cost Phe−Phe-based supramolecular hydrogels is also a virtual trend in the future. Third, the operation of hydrogel formation is complex for doctors and nurses. Although the heating−cooling process and pH-induced gelation are easy to be learned and carried out, it clearly not

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Table 1. Summary of the Structures and Applications of Phe−Phe-Based Supramolecular Hydrogels

hydrogelator	loading drugs	respond condition	application	ref
NapFFPHSRN			wound healing	15
NapFF-SVVYGLR	silk fibroin		wound healing	16
NapFFRGD	silk fibroin/VEGF		promotes capillary regeneration	17
IDM-GFFG-RGD	genipin		wounding healing and hemostasis	18
NapFFKYp	SAB		scar hyperplasia inhibition	19
Fmoc-FFYp	poly(ketoprofen-*co*-vinylimidazole) NPs		anti-inflammation	12
2IPF-DHB-GFFYD			anti-inflammation	20
NapFFKKFKLKL	Dexp		eye protection and anti-inflammation	21
NapFF-HRHTKQRHTALH			eye protection	22
NapFFKK	mucin		eye protection	23
NBD-βA-$G_DF_DF_DY$	Anti-HER2 affibody		cancer therapy	10
NapGFFYGD(Thi)		H_2O_2	drug release	72
Nap_DF_DFY-CHO	Dox	acid condition	cancer therapy	74
Fmoc-GFFG	SBE-β-CD/HCPT		cancer therapy	76
NapFFRKS	AZD1152-HQPA		cancer therapy	78
NapFFEELYRTQSSNL	HG-9-91-01	SIK-2	metastasis suppression	79
CRB-FFFK-cyclen			cancer therapy	80
CRB-FFE-YSV			cancer therapy	81
CRB-$G_DF_DF_DY$			cancer therapy	82
HCPT-FFFK-cyclen			cancer therapy	83
NapFFGEE-JSK	Dox	GSH/GST and acid condition	cancer therapy	91
Npx-$_DF_DF_DE_DY$	cisplatin		cancer therapy	92
Nap-$G_DF_DF_DY$			cancer therapy	93
Nap-$G_DF_DF_DY$	T0901317		cancer therapy	94
NapGFFYp-OMe($_{D/L}$)			vaccine	95
Fbp/Car-$G_DF_DF_DY$			cancer therapy	96
Fbp-$G_DF_DF_DY_DK(rE)_2$-NH_2	OVA/HBSAg		cancer therapy	97
Nap_DF_DF-$(PEG_3)_2$-IEFD-IMDQ	$Nap_DF_DFG_DK(aa)_DK(aa)$	GrB	immunotherapy	98
NapFFY	V1-Cal		myocardial infarction treatment	26
NapFFY	Cur/EDV		ischemic stroke repair	27
NapGFFY	silk fibroin	Ca^{2+}	bone repair	54
NapFFY	SDF-1/BMP-2		periodontal bone repair	28
Fmoc-FF	SWAP		renal ischemia/reperfusion injury alleviation	29
Biotin-GFFYGRGD	EVs		renal injury repair	30
NapFFDRLY	RTK inhibitor	RTKs	ovarian aging delay	31
NapFFEY($_{D/L}$)	tacrolimus		organ transplantation overcome	32

suitable for clinical emergency use. Finally, unnecessary immune response should be reduced. Yang's group has confirmed that D-type Phe−Phe-based supramolecular hydrogelators could effectively activate immunity in the bodies, which can be beneficial for immunotherapy.[93,94,96] For the treatment of inflammation-related disease, excessive immunity is detrimental. Hence, how to balance or control immune response should be considered, which may be more precise in treating various diseases. After overcoming these limitations, we believe that developing intelligent Phe−Phe-based supramolecular hydrogels will greatly influence the field of biomedical applications and provide more customized functions for clinical treatment.

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Notes

The authors declare no competing financial interest.

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