CHEMICAL REVIEWS

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Review

# Hitchhiking Delivery Systems: Therapeutic Hydrogels as Advanced Tools for Immunomodulatory Applications

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Cite This: https://doi.org/10.1021/acs.chemrev.4c00923

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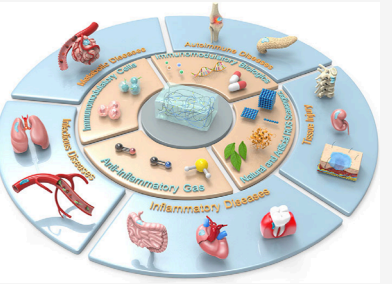
**ABSTRACT:** Recent conceptual and technological advances have underlined the importance of the human immune system in responding to dangerous threats, restoring tissue homeostasis, and mounting immunological memory. Our in-depth understanding of the immune system has also been driving the blossoming development of biocompatible macroscale biomaterials designed to prevent and treat various immune-related disorders. Hydrogels, a class of water-swollen networks with extracellular matrix-mimic characteristics, have served as promising biomaterials for guiding the immune system in biological milieus. The convergence of hydrogels and immunotherapy represents an interdisciplinary field that has driven significant advancements in both materials science and immunology. In this review, we first introduce the immune system to establish a fundamental understanding of its structure and function and then elaborate on the rational principles of hydrogel design, with a focus on passive and active mechanisms. Next, we explore a range of "hitchhiking" strategies employed to develop immunomodulatory hydrogels. State-of-the-art strategies regarding recent progress in immunomodulatory hydrogels for defense against pathological abnormalities are systematically summarized. Furthermore, the key scientific issues encountered and the hurdles faced in the development of immunomodulatory hydrogels are highlighted, aiming to show a full picture of immunomodulatory hydrogels for optimized therapeutic efficacy.

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**Received:** November 28, 2024
**Revised:** July 29, 2025
**Accepted:** July 30, 2025

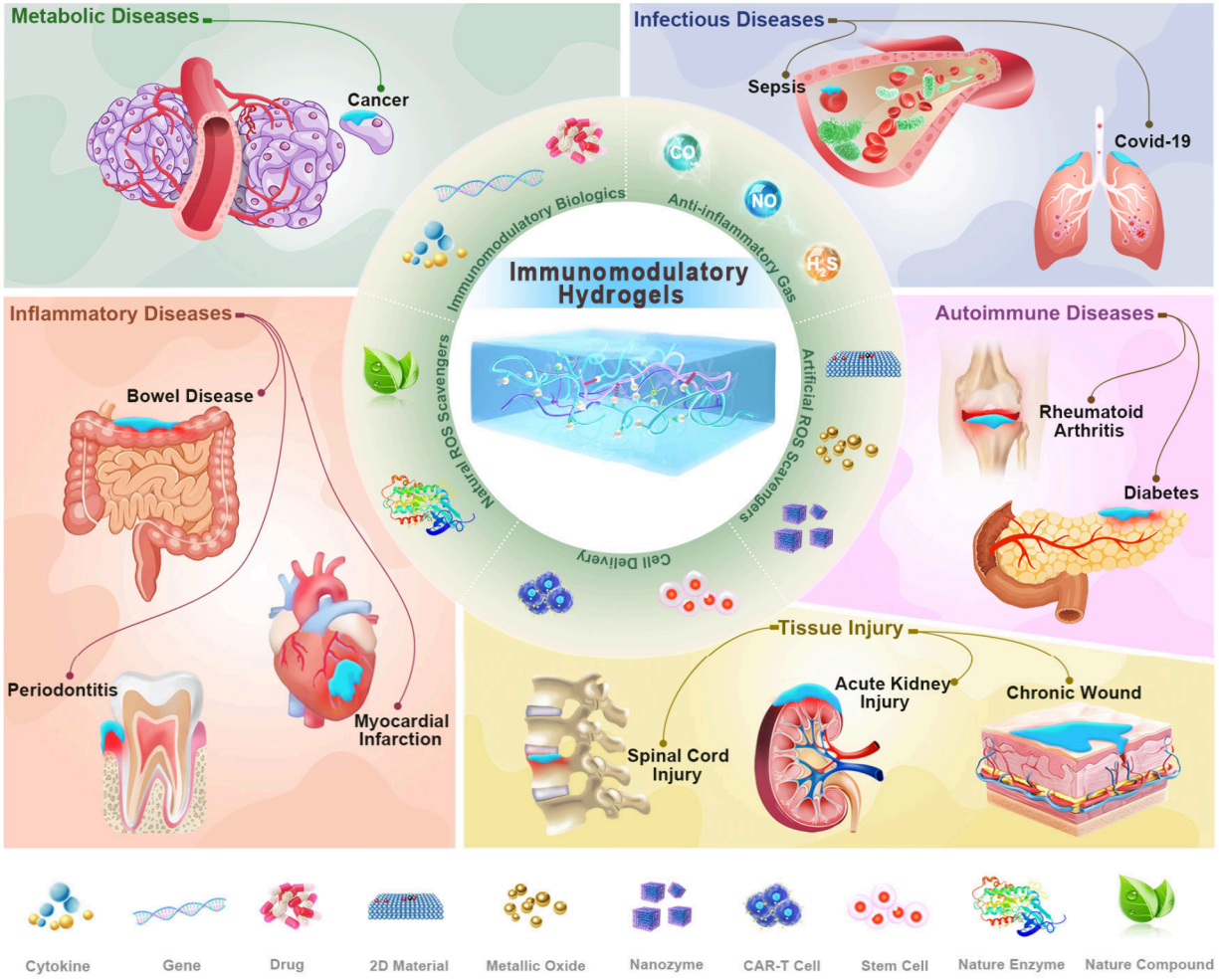


**Figure 1.** Scheme illustration of typical strategies for designing immunomodulatory hydrogels and their further application for defending against other pathological abnormalities, such as infectious diseases, metabolic diseases, autoimmune diseases, inflammatory diseases, and tissue injuries.



## 1. INTRODUCTION

In nature, all multicellular organisms are constantly exposed to a large diversity of external and internal threats, and they develop robust immune systems to adapt to and ultimately overwhelm these threats.[1,2] Looking back at human history, there has been a long fight against various challenges arising from exogenous pathogens, such as viruses and bacteria, to internal stimuli, such as tissue damage and cancer cells.[3] In the struggle for existence, the human immune system serves as the first line of defense to guard our health. Much like an intricate biological machine, this system utilizes a cascade of molecules, cells, and organs to contend with dangerous signals.[4] On the other hand, immune cells employ both redundant and antagonistic pathways to synergistically exert specialized functions, while misdirected immune responses can elicit autoimmune disease in scenarios that attack the body's own tissues.[5,6] In this regard, the human immune system plays versatile roles from the restoration of homeostasis and tolerance to defending against host invasion. Therefore, modulation of the immune system is of great promise for the management of a wide array of human disorders.

From the substantial investments witnessed in the past decade, it is clear how much effort immunologists and biomaterial scientists have devoted to designing macroscale biomaterials for immunomodulation.[7−9] In stark contrast to the systemic administration route, these biomaterials can be placed at the target location to allow for site-specific and controlled release of immunomodulatory agents into surrounding tissues.[10−13] This localized liberation of payloads is conducive to maximizing therapeutic efficacy while attenuating immune-mediated toxicity. Meanwhile, macroscale biomaterials offer a powerful delivery platform for long-term immunological memory and targeted immunomodulation, thereby achieving


https://doi.org/10.1021/acs.chemrev.4c00923
Chem. Rev. XXXX, XXX, XXX−XXX

desirable therapeutic effects during immunotherapy.[14−16] Among all the macroscale biomaterials, hydrogels have long been studied in the design of biomaterials and occupy a crucial position in steering the behavior of immune cells. As a soft and moist material, hydrogels are fabricated from polymeric macromers or arisen from the self-assembly of small molecules.[17−19] In general, the cross-linking strategies of hydrogels can be classified as covalent, noncovalent or physical cross-links.[20−22] Despite their diverse capabilities and limitations, hydrogels come in phenomenal native extracellular matrix (ECM) mimics in aspects such as water-enriched environment, inherent mechanical tenability, controllable physicochemical properties, as well as high biocompatibility.[23−25] Additionally, there are various sophisticated chemistry methods available to modify hydrogels with bioactive ligands, and advanced engineering strategies can render hydrogels with precise architectures to simulate those of soft tissues from the nano to the macroscale.[26−28] These fascinating aspects of hydrogels make them promising materials for providing a more physiologically relevant microenvironment that elicits the temporal recruitment of immune cells, suppresses proinflammatory responses, as well as facilitates tissue regeneration and repair.[29−32] Another advantage of these systems is their ability to accommodate an extensive array of immunomodulatory payloads ranging from small-molecule drugs and biomacromolecules to therapeutic cells and immunoregulatory gases. The topical delivery of immunomodulatory compounds by hydrogel can avoid the absorption barriers in oral delivery and overcome pepsin-mediated gastrointestinal (GI) degradation, alleviating concerns about low bioavailability. When therapeutic cells are encapsulated in hydrogels, the ECM-like structure of hydrogels can provide a favorable environment for cell survival and proliferation, and the manipulation of hydrogel formulation by introducing biological cues can further potentiate the transplanted cell therapeutic efficiency.[33,34] In addition to immunomodulatory molecules and cells, hydrogels can also serve as immunoregulatory gas delivery depots, as they are semipermeable, allowing the substance exchange and transportation of gases. In light of these findings, hydrogels not only steer the behavior of the immune system during immunotherapy application but also serve as suitable carriers for the delivery and concentration of immunomodulatory agents.

With the understanding that immune responses have steadily progressed, intelligent and functional hydrogels have been developed for these emerging fields, ranging from the rational design of therapeutic hydrogels to the exploitation of potential immunomodulatory applications, as illustrated in Figure 1. However, a review focused on therapeutic hydrogels as delivery systems for immunomodulation applications has not been systematically reported. Therefore, in this review, we first provide a brief overview of the immune system. Then, the fundamental design principles of hydrogels for immunomodulatory agent release are summarized, with a focus on the controlled release profiles of immunomodulatory agents in response to specific biological cues. In the subsequent sections, we highlight the development of therapeutic hydrogels as delivery platforms aimed at modulating the biological microenvironment. The term "hitchhiking" is employed to describe the unique capability of these hydrogels to synergize with and enhance the body's innate immune processes. Unlike conventional drug delivery systems, which typically release therapeutic agents passively at localized sites, hitchhiking delivery systems are engineered to engage dynamically with the immune system. These hitchhiking delivery systems can transport and release immunomodulatory agents in response to specific biological cues, effectively leveraging the body's immune response mechanisms to achieve precise and sustained therapeutic outcomes. Next, recent advances in hydrogel-based immunomodulatory delivery systems for fighting against other pathological abnormalities, such as infectious diseases, metabolic diseases, autoimmune diseases, inflammatory diseases, and tissue injuries, are presented. Finally, we elucidate the key scientific challenges encountered and the remaining opportunities in the evolution of hydrogel immunomodulatory applications. By shedding light on the importance of hydrogel-based immunomodulatory delivery systems, it is envisaged that this review will pave the way for the development of these materials and provide a deeper understanding of the relationship between macroscale biomaterials and immune-mediated diseases.

## 2. BRIEF INTRODUCTION OF IMMUNE SYSTEM

When considering how molecular pathways function during the immune response, the immune system can be categorized into two classes: the innate and adaptive immune systems.[35,36] The innate immune system serves as the first line of defense against both internal and external threats.[37,38] Taking advantage of innate immune cells, this system can mount a rapid and nonspecific response to the onslaught of perceived danger. It is known that the response of the innate immune system depends on two classes of broad molecular signatures, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[39,40] PAMPs are molecules released by microbial processes, while DAMPs are host-derived signals triggered by trauma.[41]

There are numerous cell subsets that participate in the arms of the immune system.[37,42] For example, the innate immune system is populated by neutrophils and mononuclear phagocytes, such as macrophages, dendritic cells (DCs), and monocytes, while the adaptive immune system is primarily mediated by T and B lymphocytes.[43,44] Despite significant differences in function and cell type, there is considerable feedback and interplay between these systems, intertwining their roles in modulating both the duration and intensity of the immune response.[45] Among all immune cells, neutrophils are the first to be activated at sites of tissue injury and infection, where they nonspecifically destroy pathogens through mechanisms such as phagocytosis, protease secretion, inflammatory molecule release, and the activation of neutrophil extracellular traps.[46,47] Following the initial immune response, neutrophils recruit monocytes, which differentiate into phagocytic macrophages. These macrophages initially exhibit a pro-inflammatory phenotype, enabling them to engulf dead neutrophils, pathogens, and cellular debris.[48] As the threat subsides, macrophages transition to an anti-inflammatory phenotype that promotes the restoration of homeostasis, tissue repair, and ultimately, the resolution of inflammation.[49,50] In this context, neutrophils and macrophages have been regarded as the first-line innate responders. However, they cannot recall immunological memory to recognize specific pathogens they have previously encountered.[48,51] Consequently, when faced with a second encounter of the same pathogen at a different time or location, neutrophils and macrophages will respond in the same manner as during the initial encounter.

Distinguished from the innate immune system, the adaptive immune system possesses highly specific and long-term


https://doi.org/10.1021/acs.chemrev.4c00923
Chem. Rev. XXXX, XXX, XXX−XXX

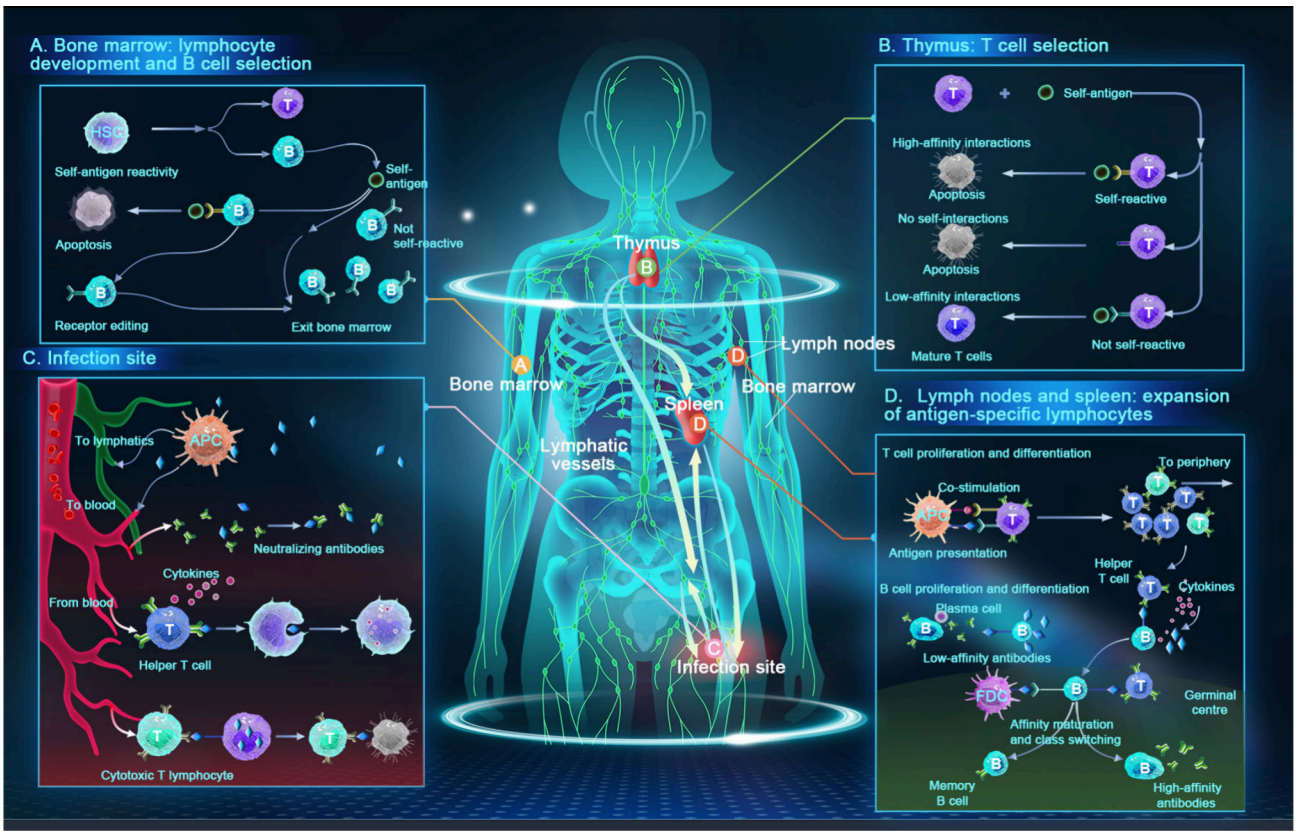


**Figure 2.** (A-D) Schematic representation of how T lymphocytes and B lymphocytes are primarily responsible for the adaptive immune system. Antigen presenting cells (APCs), follicular dendritic cells (FDCs), and hematopoietic stem cells (HSCs).

immunological memory that enables the clearance of foreign agents, and T and B lymphocytes are primarily responsible for this potent and rapid response.[38,52] B cells primarily develop and reside in the bone marrow, and once activated, they migrate to the lymph nodes and spleen.[53] A small subset of B cells that actively bind self-antigens may lead to autoimmune disease, which are either eliminated or undergo receptor editing to reduce self-reactivity (Figure 2A).[54,55] T cells originate in the bone marrow and mature in the thymus. During maturation, they interact with immunological signals presented by antigen-presenting cells, while improper binding to self-antigens may also result in autoimmune disease (Figure 2B). Once mature, T cells migrate to the lymph nodes and spleen.[56,57]

Under conditions of infection, DCs, a specialized group of antigen-presenting cells (APCs), can recognize pathogen-derived antigens and process them into short peptides. This occurs either when free antigens are present in the skin or peripheral tissue or when APCs in the periphery capture antigens and migrate to the spleen and lymph nodes.[58,59] Cytotoxic T cells can potently kill infected host cells by inhibiting viral replication. Helper T lymphocytes secrete a variety of supportive signals, including cytokines, to promote the destruction of phagocytosed bacteria (Figure 2C).[60,61] In secondary lymphoid organs, cognate peptide antigens presented by DCs can activate T cells in the setting of the major histocompatibility complex (MHC), together with the required costimulatory signals.[62,63]

After T cell activation, a set of primed T cells undergoes extensive clonal expansion and migrates to the periphery to resolve infection where they mount antigen-specific responses.[57] Additionally, B cells can produce low-affinity antibodies when antigens directly engage their receptors, while high-affinity antibodies are produced when B cells interact with helper T cells. Upon antibody production, the immune system simultaneously orchestrates an inflammatory cascade by which B cells produce specialized domains in lymph nodes known as germinal centers (GCs), where B cells interplay with helper T cells and follicular DCs.[64] B cells that have undergone phase transformation within GCs differentiate into plasma cells, which produce high-affinity antibodies to neutralize and tag pathogens. Furthermore, a subset of B cells matures into memory lymphocytes, ensuring a rapid response to future encounters with their cognate antigen (Figure 2D).[63]

## 3. DESIGN PRINCIPLES OF HYDROGELS FOR IMMUNOMODULATORY AGENT RELEASE

The release kinetics of immunomodulatory agents from the designed hydrogel network, including the pattern of release and the duration of agent availability, has a significant impact on the practical application.[65,66] Therefore, a variety of design principles should be taken into consideration to enable the controlled release of immunomodulatory agents via passive or active methods. Passive release strategies facilitate the short- and long-term release of therapeutic agents, whereas active strategies fulfill the requirements of pulsatile release patterns.[67−69]

### 3.1. Designing Hydrogels for Passive Release

Continuous passive release from hydrogels can be obtained through individual mechanisms or by combining processes such as hydrogel swelling, network degradation, and diffusion. Consequently, the passive release of therapeutic agents can be governed simply by engineering properties of hydrogels, such as


https://doi.org/10.1021/acs.chemrev.4c00923
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matrix concentration, specific interactions with agents, cross-linking density, molecular weight, hydrophilicity, and pore size distribution. The degradable performance of hydrogels has a significant influence on the release of immunomodulatory agents.[70] Hydrolytically degradable mechanisms are primarily dependent on the swelling and fluid absorption capabilities, whereas enzymatically degradable functionalities can be affected by the local concentration of enzymes at the implantation site.[71] The release behavior can be also adjusted by varying the pore size of hydrogels. The initial immunomodulatory agent release greatly depends on the size relationship between the molecules and hydrogel pores.[72] It is well-documented that the encapsulated drug release significantly increases with increased porosity, while the release does not enhance accordingly beyond a certain level of porosity.[73] When the encapsulated immunomodulatory agents are smaller than network pores, they can be released directly via diffusion. However, the release profile may be affected if the size of agents does not match the pore or mesh size of the hydrogel.[74] Moreover, immunomodulatory agents can form physical or chemical cross-links with the polymer chains of hydrogels, requiring them to "dissociate" from the hydrogel network prior to release into the surrounding environment.[75,76] The degradation of hydrogels is closely related to the sustained release of immunomodulatory agents. As the length of the hydrogel network chains increases, the degradation rate will be also accelerated.

The immunomodulatory agent release in hydrogels is also governed by water uptake and swelling properties. As amphiphilic macromolecular materials, hydrogels exhibit significant water absorption and swelling performance.[77−79] In general, the release capabilities of small molecule agents increase with the enlargement of the pore size of hydrogels. Meanwhile, the length of the agent release pathway increases as the hydrogel swells, which reduces the concentration gradient of the agent. According to the literature, the concentration gradient of the drug is the driving force for release, while a higher swelling rate in the hydrogel can also lead to a slower drug diffusion rate.[80] Therefore, when studying the effect of swelling on the release rate of agents, it is essential to consider changes in the volume and pore size of the hydrogel.

### 3.2. Designing Hydrogels for Active Release

To address the challenges related to passive release, on-demand delivery of immunomodulatory agents from hydrogels has been developed using active release mechanisms.[81,82] The active release of agents via hydrogels can be achieved by varying their physical and chemical properties. Such modifications enable hydrogels to respond to external or internal stimuli, thereby precisely controlling drug delivery. The release of immunomodulatory agents through external stimuli improves the capacity for target identification and enhances the accuracy and effectiveness of medication release.[8]

**3.2.1. Temperature-Responsive Release.** Temperature is a crucial physiological parameter, with abnormal fluctuations closely linked to various diseases. Over the past decades, temperature-responsive hydrogels have garnered significant attention for drug delivery.[83,84] Typically, the preparation of temperature-responsive hydrogels involves introducing thermosensitive polymer chains (or segments) into the hydrogel's three-dimensional network structure. These hydrogels generally exhibit either a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST). At the critical temperature, the interaction between the polymer chains or segments and the aqueous solution shifts, leading to transitions between dissolved and insoluble states. This results in macroscopic changes in the hydrogel, such as sol−gel transitions or volumetric expansion and contraction.[85,86] Guided by this response mechanism, a wide range of temperature-responsive smart hydrogels have been developed. For example, hydrogels based on poly(*N*-isopropylacrylamide) (PNIPAM) have an LCST of approximately 32 °C, which is close to normal physiological temperature. Therefore, PNIPAM-based hydrogels hold significant potential in biomedical applications.[87,88] Agarose-based hydrogels represent another widely studied class of temperature-responsive materials. Their three-dimensional network structure is maintained by secondary bonds, such as hydrogen bonds. At lower temperatures, hydrogen bond interactions between sugar chains strengthen, resulting in a gel state. As the temperature rises, these bonds break, causing the hydrogel to transition into a sol state.[89,90] Due to ease of chemical modification, biodegradability, biocompatibility, water solubility, and low cost, agarose-based temperature-responsive hydrogels have garnered considerable attention in drug delivery and related biomedical applications.

**3.2.2. pH-Responsive Release.** In addition to temperature, pH is another essential physiological indicator, as different tissues in the human body exhibit distinct pH values. For instance, the pH of chronic wounds ranges from 5.4 to 7.4, pancreatic juice from 7.8 to 8.4, and gastric juice from 1.0 to 3.0.[91,92] Abnormal fluctuations in pH are often closely associated with pathological conditions. Consequently, pH-responsive hydrogels have promising applications in biomedicine and therapeutic fields.[93,94] These hydrogels typically contain a high concentration of pH-responsive monomers and/or functional groups, which donate or accept protons in response to environmental pH shifts, resulting in changes in their degree of ionization. The majority of pH-responsive hydrogels are made from weak electrolytes such as sodium alginate, chitosan, albumin, sodium carboxymethyl cellulose, poly(N,N-dimethylaminoethyl methacrylate), polyethylenimine, polylysine, xanthan gum, poly(acrylic acid), and so on.[95] Additionally, certain dynamic chemical bonds, such as imine bonds, acylhydrazone bonds, and phenylboronic acid ester bonds, exhibit pH-responsive behavior. These hydrogels are suitable for controlled release of immunomodulatory agents in acidic tissue microenvironments, such as cancer and rheumatoid arthritis (RA).

**3.2.3. Phototriggered Release.** Photoresponsive materials offer several advantages, including rapid response, high precision, ease of operation, and controllability, making them highly promising for broad applications.[96,97] Photoresponsive hydrogels are polymeric networks that undergo phase transitions when stimulated by specific light wavelengths.[98,99] These hydrogels are typically modified with photosensitive chemical groups on their main or side chains, such as azobenzene, spiropyran, nitrobenzyl groups, triphenylmethane, and their respective derivatives.[100−102] Upon exposure to external light, these photosensitive groups undergo reactions such as cleavage, addition, dipole moment changes, or isomerization.[103,104] At the microscopic level, this results in the formation or dissociation of cross-linking points, while at the macroscopic level, the hydrogel exhibits changes such as sol−gel transitions, volume expansion, or contraction. Photoresponsive hydrogels offer superior spatial and temporal control compared with their counterparts. They can offer more flexibility and spatial accuracy since they permit noncontact manipulation,


https://doi.org/10.1021/acs.chemrev.4c00923
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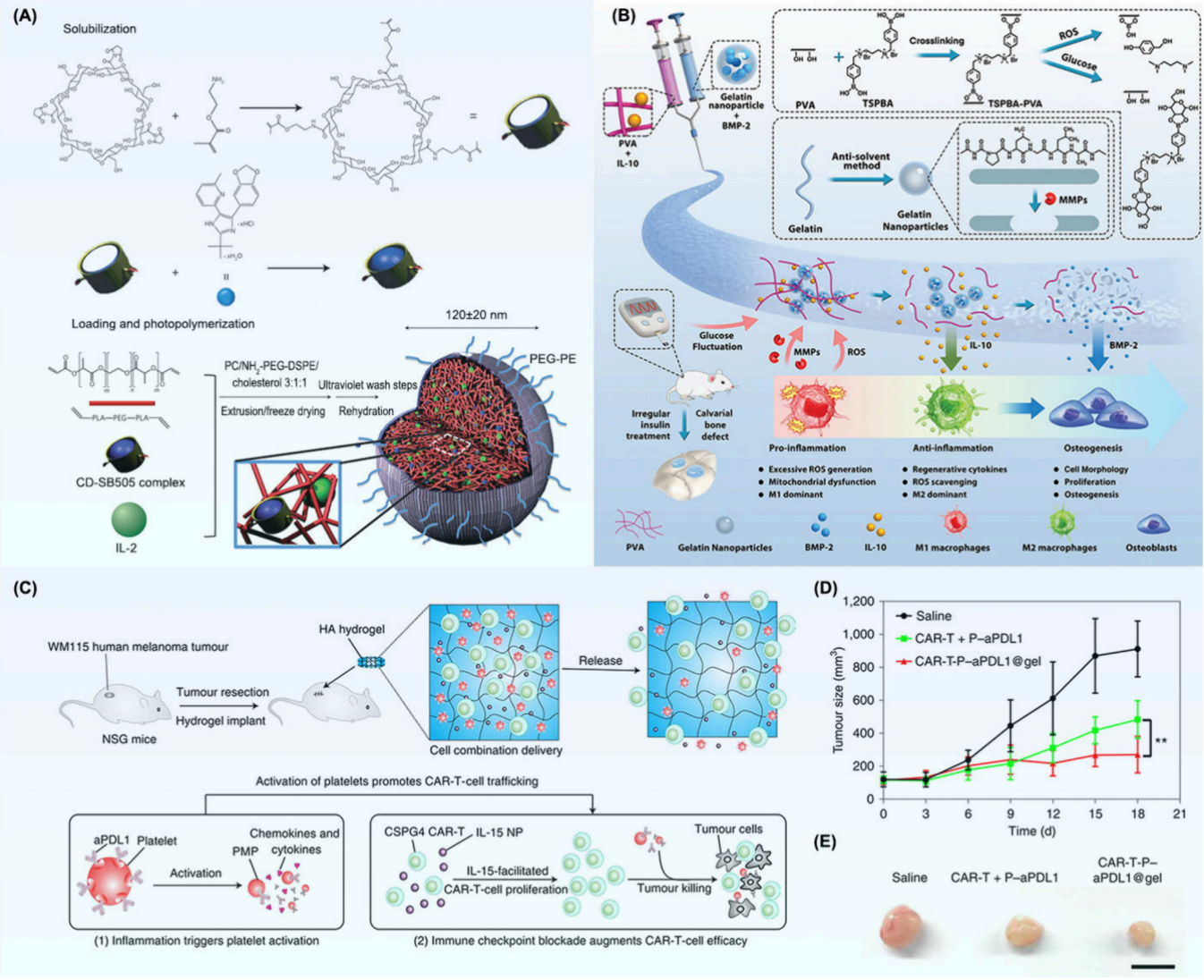


**Figure 3.** (A) Schematic diagram showing the synthesis approach for the nanoscale liposomal polymeric hydrogels and exert enhanced tumor immunotherapy efficiency. Reproduced with permission from ref 127. Copyright 2012 Springer Nature. (B) Schematic illustration showing the design rationale of logic-based diagnostic and therapeutic hydrogel for diabetic bone regeneration. Reproduced with permission from ref 129. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (C) Schematic diagram showing the implantation of multifunctional hydrogel encapsulating the cytokine IL-15 and platelets for inhibition of tumor recurrence. (D) Tumor growth curves after treatment with different experimental groups. (E) Representative images of tumors on the 18th day. Scale bar: 1 cm. Reproduced with permission from ref 131. Copyright 2021 Springer Nature.

allowing for precise illumination of targeted areas.[105] The light source used in photoresponsive hydrogels can range from ultraviolet (UV) to visible and near-infrared (NIR) light. In particular, NIR light is less harmful to human tissues compared to UV light, offering greater tissue penetration and the ability to reach deeper layers of the skin.[106,107]

**3.2.4. Redox- and Biomarker-Responsive Release.** Redox-responsive hydrogels are materials that undergo changes in volume and shape when exposed to external redox stimuli.[108,109] The presence of redox centers along the main chain, side chains, or at the ends of these hydrogels imparts them with reversible response behavior. Based on the nature of their oxidation centers, redox-responsive hydrogels can be classified into several types, including disulfide, ferrocene, conjugated polymer, tetrathiafulvalene, and transition metal-based hydrogels.[110] Given that redox reactions are widespread in biological systems, these hydrogels hold significant potential for use in immunomodulatory agent delivery.[111]

Living systems maintain a dynamic balance in the body under the action of a variety of complex biological molecules, many of which serve as key biomarkers of health status.[112] By monitoring their levels, early diagnosis and timely intervention of diseases can be achieved. Therefore, the development of hydrogel systems for biomarker responsiveness has important clinical significance.[113] For example, enzyme-sensitive hydrogels typically possess polymer networks cross-linked by enzyme-sensitive peptide linkers. After introduction of specific enzymes, such as matrix metalloproteinase 2, proteases, trypsin, and lysozyme, peptide linkages are cleaved, leading to the controlled release of encapsulated immunomodulatory therapeutics from the hydrogel.[114]

## 4. THERAPEUTIC HYDROGEL-BASED HITCHHIKING DELIVERY SYSTEMS

Hydrogels are one of the most promising carriers for the hitchhiking delivery of various immunomodulatory factors, such


https://doi.org/10.1021/acs.chemrev.4c00923
Chem. Rev. XXXX, XXX, XXX−XXX

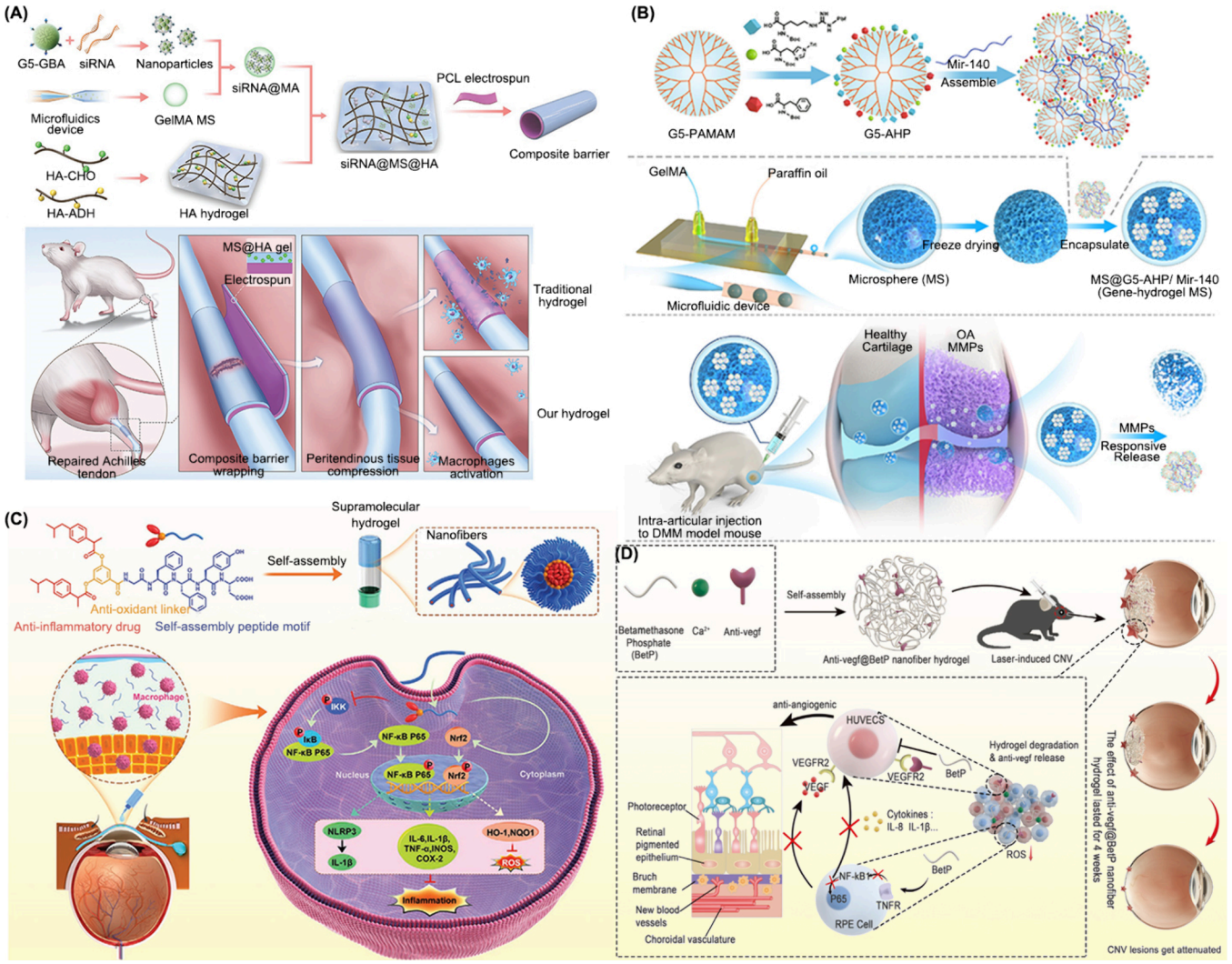


**Figure 4.** (A) Schematic depiction of the fabrication process siRNA@MS@HA hydrogel-electrospun membrane, and the application of hydrogel-electrospun membrane for prevention of peritendinous adhesion. Reproduced with permission from ref 139. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (B) Schematic representation of the preparation process of G5-AHP/miR-140 nanoparticles and gene-hydrogel microspheres, and the gene-hydrogel microspheres for local treatment of osteoarthritis. Reproduced with permission from ref 141. Copyright 2022 Springer Nature. (C) Chemical structures of 2IPF-DHB-GFFYD and its self-assemble into supramolecular hydrogels for boosting the anti-Inflammatory efficacy. Reproduced with permission from ref 145. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (D) Schematic representation of the self-assembly of betamethasone phosphate (BetP), $Ca^{2+}$, and anti-VEGF to produce supramolecular nanofiber hydrogel and promote age-related macular degeneration treatment. Reproduced with permission from ref 146. Copyright 2023 Wiley-VCH Verlag GmbH & Co.

as therapeutic proteins (e.g., cytokines and antibodies), nucleic acids (e.g., microRNAs and small interfering RNAs), and small-molecule drugs.[12,34,115] Due to their 3D polymeric networks swollen in water, hydrogels are equipped with the ability to protect, deliver, target, and precisely control the release of bioactive immunomodulatory factors.[76,116,117] Compared to traditional drug administration methods, hydrogels offer the advantage of overcoming issues such as high dosage requirements, off-target effects, and the need for repeated administration.[118,119]

## 4.1. Hitchhiking Delivery of Immunomodulatory Biologics

**4.1.1. Cytokines.** Cytokines can regulate the behavior of T cells, and the delivery of cytokines used to modulate T cells has shown great promise for immunotherapy.[120,121] Pro-inflammatory cytokines, such as interleukin (IL)-1$\beta$, IL-2, IL-12, IL-18, tumor necrosis factor-$\alpha$ (TNF-$\alpha$), and interferon-$\gamma$ (IFN-$\gamma$), can trigger both innate and adaptive immune responses. In sharp contrast, anti-inflammatory cytokines, including IL-4, IL-10, IL-11, IL-13, and transforming growth factor-$\beta$ (TGF-$\beta$), suppress the production of pro-inflammatory cytokines, thereby inhibiting inflammatory immune responses.[122,123]

Engineered hydrogels with defined structures and properties offer new opportunities for the sustained release of encapsulated cytokines or for targeted cytokine delivery to T cells. For instance, numerous studies have demonstrated that IL-2 induces and enhances T cell-specific responses in melanoma and is therefore widely employed in the treatment of advanced melanoma.[124,125] TGF-$\beta$, another pleiotropic cytokine, can inhibit cytotoxic T lymphocyte activity while promoting the expansion of regulatory T cells.[126] Fahmy et al. developed a nanoscale liposomal polymeric hydrogel that allowed for the sustained delivery of small hydrophobic TGF-$\beta$ antagonists and water-soluble IL-2 to enhance tumor immunotherapy against melanomas (Figure 3A).[127] This hybrid platform is a promising strategy to mediate antitumor activity and enhance tumor


https://doi.org/10.1021/acs.chemrev.4c00923
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immunotherapy in vivo. Similar to IL-2, IL-10 is another cytokine that has pleiotropic effects on immune regulation and inflammation.[128] In view of this property, Chen et al. reported a multiple stimuli-responsive hydrogel with logic-based diagnostic and therapeutic functions (Figure 3B).[129] The hydrogel was synthesized from the phenylboronic-acid-cross-linked poly(vinyl alcohol) (PVA) and gelatin colloids. The dynamic bonds of PVA provided responsiveness to glucose and reactive oxygen species (ROS), while the gelatin colloidal was equipped with bioactive motifs for cell affinity as well as matrix metalloproteinase-triggered degradation. Under the dynamic diabetes mellitus microenvironment, the hydrogel served as a delivery vehicle for releasing IL-10 and bone morphogenetic protein 2 (BMP-2), regulating macrophage polarization and promoting osteogenesis in diabetic bone defects. IL-15 can induce the proliferation of natural killer cells and has been demonstrated to boost the antitumor immunity of $CD8^+$ T cells in clinical settings.[130] Gu et al. proposed a biodegradable hydrogel for the delivery of chimeric antigen receptor T (CAR-T) cells, anti-PDL1-conjugated platelets, and IL-15 (Figure 3C).[131] This postsurgical local delivery system was demonstrated to modulate immune responses and enhance antitumor activity, effectively preventing cancer recurrence in a melanoma-bearing mouse model (Figure 3D, 3E).

**4.1.2. Genes.** Gene delivery is an alternative strategy used for the mediation of immune-related diseases.[132,133] This approach focuses on modulating macrophage phenotypes by increasing the expression of anti-inflammatory cytokines (e.g., IL-10 and IL-4) while reducing pro-inflammatory cytokines. Additionally, it promotes the recruitment of regulatory T cells (Tregs) to further suppress inflammation.[134] To date, various hydrogel-based gene delivery platforms have been developed. For example, small interfering RNA (siRNA), a molecule typically 20−24 base pairs in length, can specifically target and degrade mRNA to interfere with gene expression.[135−137] In this contribution, Hammond and co-workers constructed a hydrogel-based wound dressing using layer-by-layer (LbL) self-assembly technology, incorporating siRNA for therapeutic purposes.[138] This platform enabled the sustained release of siRNA for at least 2 weeks, effectively achieving target gene knockdown. In vivo experiments demonstrated that the hydrogel-based wound dressing dramatically reversed the proteolytic wound environment, and further enhanced the wound healing rate. SiRNA, a double-stranded RNA, is prone to degradation by ribonucleases, which limits its therapeutic efficacy due to low stability, insufficient transfection efficiency, and a short half-life in vivo.

To enhance the therapeutic efficiency of siRNA, Fan and co-workers integrated guanidinobenzoic acid-modified generation 5-polyamidoamine (G5-GBA) with siRNA, forming stable nanoparticles.[139] These G5-GBA/Smad3-siRNA nanoparticles were then encapsulated in matrix metallopeptidase (MMP)-2-degradable gelatin-methacryloyl (GelMA) nanoparticles using microfluidics techniques, and subsequently incorporated into a hyaluronic acid (HA) hydrogel. With the assistance of polycaprolactone (PCL) electrospun nanofibers, the self-healing hydrogel could produce a peritendinous antiadhesion membrane (Figure 4A). The siRNA nanoparticles could be released from the hydrogel matrix in response to MMP-2 activity, thus attenuating Smad3 expression and fibroblast proliferation. Significantly, the hydrogel-electrospun nanofibers enabled to blunt the inflammatory response and performed as a physical barrier to prevent peritendinous adhesion.

MiRNA, a small single-stranded noncoding RNA molecule, is regarded as a key regulator of gene expression. MiRNA functions by binding to the 3′ untranslated region of target mRNA, leading to either translational suppression or mRNA destabilization.[140] Although miRNA shares similarities with siRNA in the RNA interference pathway, miRNA specifically targets unique mRNA. In light of these findings, Annabi et al. developed an adhesive hydrogel reservoir for loading miRNA-laden nanoparticles. In this study, HA nanoparticles loaded with miR-223 successfully drove the polarization of macrophages and promoted wound remodeling in an acute excisional wound model. The sustained and controllable delivery of therapeutic miRNA has significant potential for treating osteoarthritis (OA). For instance, Cui et al. designed a multifunctional gene vector, generation 5-polyamidoamine, to form stable nanoparticles with microRNA-140.[141] These nanoparticles were then encapsulated in MMP-degradable GelMA hydrogel microspheres using microfluidics techniques. These "nano-micron" combined gene hydrogels are responsively degraded by MMP overexpression, allowing for on-demand release of miRNA complexes. Furthermore, in vivo experiments demonstrated that this composite platform effectively reduced articular cartilage degeneration and attenuated osteophyte formation. (Figure 4B).

**4.1.3. Small-Molecule Drugs.** Small-molecule drugs, such as dexamethasone, resveratrol, paclitaxel, and celecoxib, are one of the most preferred and commonly applied strategies for anti-inflammatory therapy.[142−144] Nevertheless, their effectiveness is often hindered by poor retention and low bioavailability due to rapid metabolism. More importantly, off-target toxicity remains a significant concern in clinical trials, often leading to serious side effects. To address these limitations, hydrogel-based drug delivery systems have emerged as promising solutions, offering controlled release and improved localization of these therapeutics.

For example, Li et al. employed a polyphenol, a nonsteroidal anti-inflammatory drug (NSAID), and a self-assembled peptide motif to construct a supramolecular filament hydrogel for the treatment of ocular disorders (Figure 4C).[145] The synthesized supramolecular hydrogel exhibited innovative immunomodulation of macrophages toward an anti-inflammatory phenotype. Moreover, in vivo studies showed that this hydrogel boosted therapeutic efficacy compared to the clinically employed 0.1 wt % diclofenac (DIC) sodium eyedrops. Wang et al. introduced a directed self-assembly approach using herbal small molecules to address the challenges of poor solubility and inadequate stability commonly associated with natural small molecules (Figure 4D).[146] This drug delivery platform was prepared from the supramolecular self-assembly of rhein. Interestingly, the resultant hydrogel exhibited superior antineuroinflammation over the free-drug form and essentially boosted the therapeutic efficacy. In addition, Kohane et al. investigated a steroid drug (for example, dexamethasone, betamethasone, and hydrocortisone)-based hydrogel corroborating to the supramolecular self-assembly strategies as described above.[143] It was observed that the supramolecular hydrogel possessed shear-thinning and self-healing properties. In particular, the steroid hydrogel revealed an anti-inflammatory capacity, presenting a promising approach for managing a variety of steroid-responsive diseases.

### 4.2. Hitchhiking Delivery of Immunomodulatory Cells

**4.2.1. Stem Cells.** Stem cells are multipotent progenitor cells that can be isolated from various human tissues, including adipose, umbilical cord blood, and mesenchymal bone


https://doi.org/10.1021/acs.chemrev.4c00923
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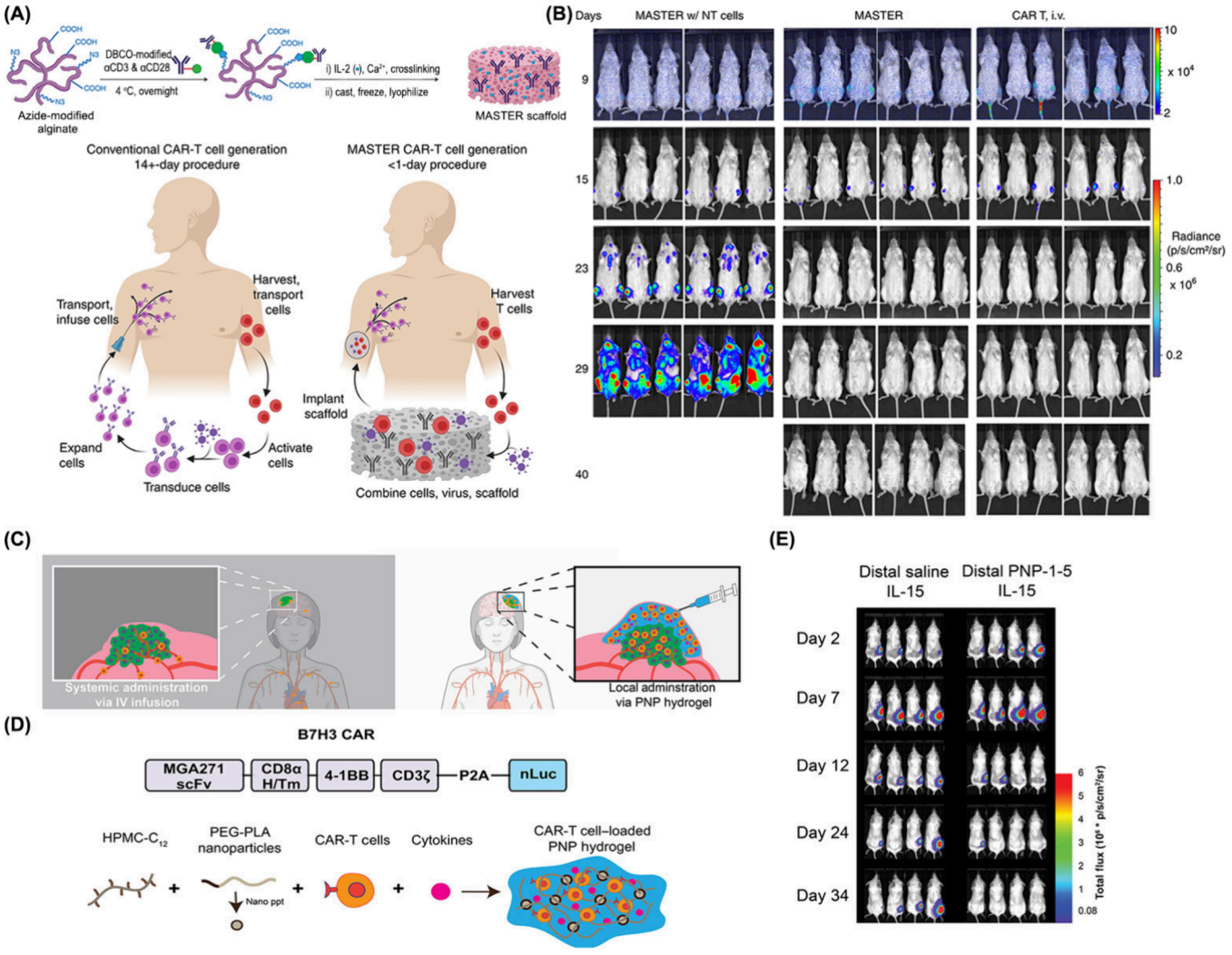


**Figure 5.** (A) Schematic showing the fabricated process of MASTER and mediated CAR-T cell generation and therapy compared with conventional CAR-T cell therapy. (B) Representative luminescent imaging of tumors after treatment with different experimental groups. Reproduced with permission from ref 174. Copyright 2022 Springer Nature. (C) Schematic showing traditional intravenous approaches compared to the developed local administration via PNP hydrogel. (D) Schematic showing the construction of B7H3 CAR applied for all studies, and the development of PNP hydrogels for encapsulation of CAR-T cells and stimulatory cytokines. (E) Representative luminescent imaging of tumors after treatment with different experimental groups. Reproduced with permission from ref 175. Copyright 2022 American Association for the Advancement of Science.

marrow.[147,148] These specialized cells possess both multilineage differentiation capability and paracrine functions, enabling them to play a crucial role in tissue regeneration within specific microenvironments.[149,150] Another important characteristic of stem cells is their immunomodulatory ability. Emerging evidence suggests that stem cells can both enhance and inhibit immune responses within their local niches.[151,152] The production of various immune-related cytokines, chemokines, exosomes, growth factors, and extracellular vesicles (EVs) underpins the immunosuppressive actions of stem cells.[153] Given their combined tissue regeneration and immune-regulatory capacities, stem cells can offer a vast array of application prospects for treating a range of inflammatory and autoimmune diseases, such as diabetes, RA, and arterio-sclerosis.[154−156]

The application of appropriate scaffold biomaterials as carriers for stem cells has yielded promising results in maintaining the immune privilege and tissue repair capacity of these cells.[157−159] As three-dimensional polymeric networks, hydrogels are characterized by their hydrophilic nature, high-water content, and good substance permeability.[160−162] These properties make hydrogels suitable for cell encapsulation in the treatment of chronic diseases and injuries.[163−165] For example, García and co-workers developed an injectable synthetic hydrogel for the activation of human mesenchymal stem cells (hMSCs). This hydrogel was chemically synthesized from maleimide-modified 4-armed PEG macromer and cysteine-functionalized N-terminal IFN-γ, enabling the activation of encapsulated hMSCs to enhance their immunoregulatory capacity.[166]

Moreover, the hMSCs loaded with IFN-γ-tethered hydrogel revealed a favorable decrease in the tendency of cytokine levels and an increase in colonic mucosal wound closure rate both in immunocompromised and immunocompetent mice. In addition to their role in chronic wound healing, stem cell-based therapies have also shown considerable therapeutic potential in treating myocardial infarction (MI). For example, to increase the survival of implanted stem cells within challenging microenvironments, Liu et al. successfully encapsulated bone marrow mesenchymal stem cells (BMSCs) into polyzwitterionic microgels and then induced a Chinese herb-cross-linked hydrogel.[167] The Chinese


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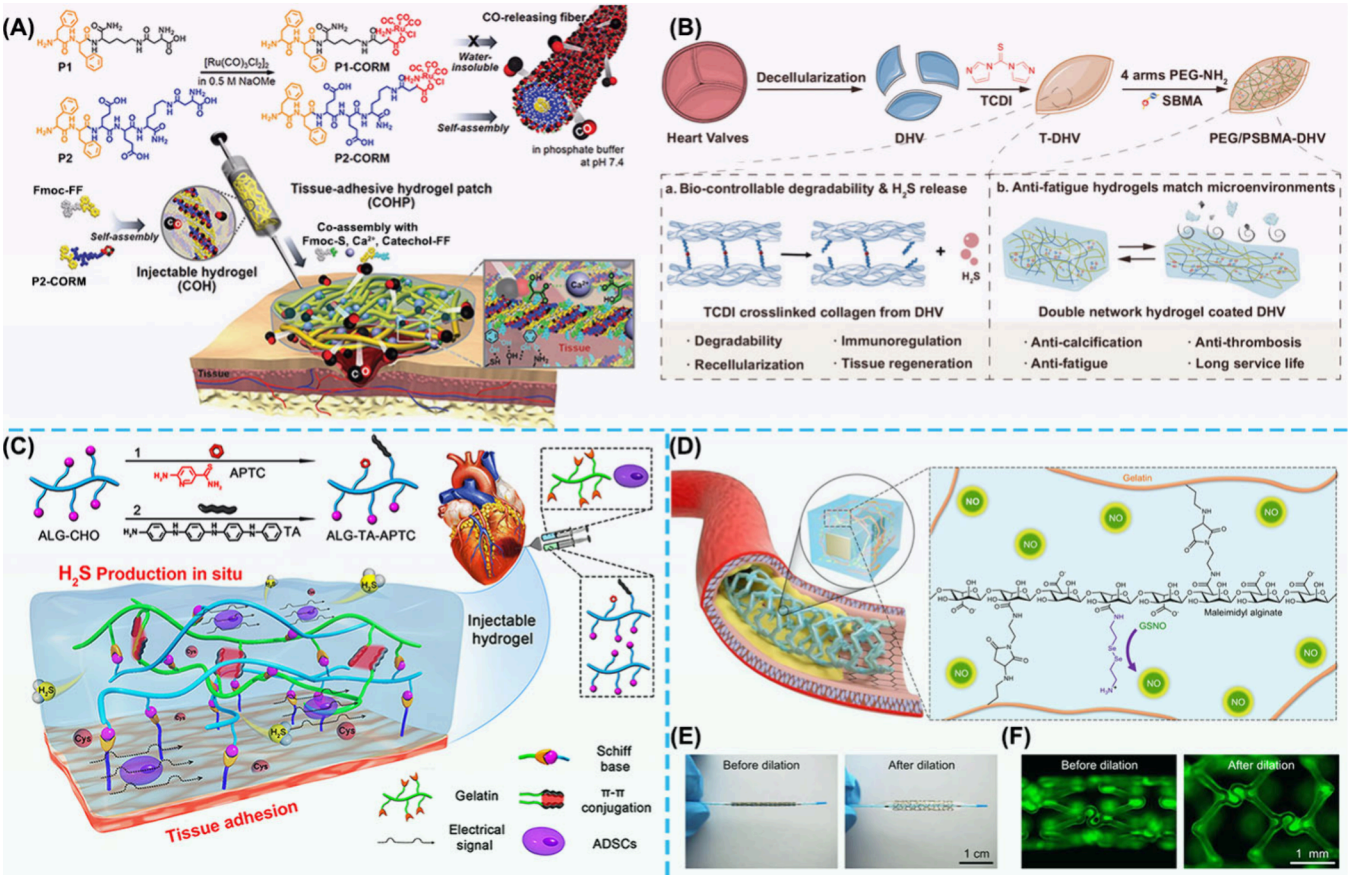


**Figure 6.** (A) Schematic displaying the formation of CO-releasing peptides and the preparation of injectable patch-like tissue adhesives. Reproduced with permission from ref 180. Copyright 2018 Wiley-VCH Verlag GmbH & Co. (B) Diagrams displaying the formation of $H_2S$-releasing hydrogel and further application for promoting heart valve regeneration via polarization of M2 macrophages. Reproduced with permission from ref 183. Copyright 2024 Springer Nature under a Creative Commons Attribution 4.0 International License. (C) Diagrams displaying the preparation of $H_2S$-releasing conductive hydrogel and further promoting cardiac repair. Reproduced with permission from ref 184. Copyright 2019 American Chemical Society. (D) Schematic illustration of the design of nitric oxide-eluting hydrogel. (E) Images of a vascular stent coated with nitric oxide-eluting hydrogel. (F) Nitric oxide-eluting hydrogel was stained with fluorescein isocyanate and observed before and after balloon dilation using fluorescence imaging. Reproduced with permission from ref 187. Copyright 2021 Springer Nature under a Creative Commons Attribution 4.0 International License.

herb-cross-linked hydrogel was found to not only scavenge uncontrolled accumulation of ROS but also ameliorate the hypoxic microenvironment, thereby enhancing the ability of BMSCs to exert anti-inflammation and angiogenesis properties in restoring infarcted myocardium. Additionally, supplementing stem cells to the defective tissue represents a feasible strategy for treating steroid-associated osteonecrosis (SAON), whereas the majority of traditional hydrogels with a static nature do not permit the infiltration of therapeutic cells. To resolve this obstacle, Bian and co-workers proposed a novel cell-infiltrating gelatin hydrogel (namely Ci-I hydrogel), which is based on multiple bonding mechanisms, including physical cross-linking, host−guest complexations, and chemical cross-linking.[168] The dynamic network of the engineered hydrogel allowed the encapsulation of stem cells and drugs, enabling them to infiltrate and migrate into the surrounding environment, thereby enhancing bone defect regeneration in a SAON animal model.

**4.2.2. Immune Cells.** Adoptive cell therapy (ACT) shows great promise for cancer treatment that has effectively controlled symptoms in a significant number of patients suffering from hematologic malignancies.[169,170] During ACT procedures, immune cells are harvested from a patient's tumor tissue, engineered to express specific receptors for enhanced recognition, expanded in vitro, and then infused back into the patient for cancer treatment. CAR-T cells are precisely designed to target antigens that are overexpressed on cancerous cells.[171] This strategy has demonstrated unprecedented success in treating various B cell malignancies, and several CAR-T cell-based therapies have received approval from the U.S. Food and Drug Administration.[172,173]

Despite its promising therapeutic potential, the successful acquisition of therapeutic cells requires high costs, complex, and labor-intensive manufacturing procedures. Additionally, the engineering process for CAR-T cells may encounter challenges such as heterogeneous composition, compromised engraftment, and unsatisfactory persistence in vivo. To deal with these problems, Brudno and colleagues developed a lyophilized hydrogel scaffold for T cell engineering and release (Figure 5A, 5B).[174] This implantable scaffold was fabricated from the electrostatic interaction between alginate and calcium ions, and its macroporosity facilitates homogeneous cell distribution.

To enhance T cell activation and expand its efficiency, cyclooctyne-conjugated anti-CD3 and anti-CD28 antibodies were immobilized on the polymeric chains via click chemistry with azide-modified alginate, and the cytokine IL-2 was encapsulated within the three-dimensional network. Notably, this bioinstructive implantable scaffold simplified CAR-T cell manufacturing in vivo and decreased the operating period to just


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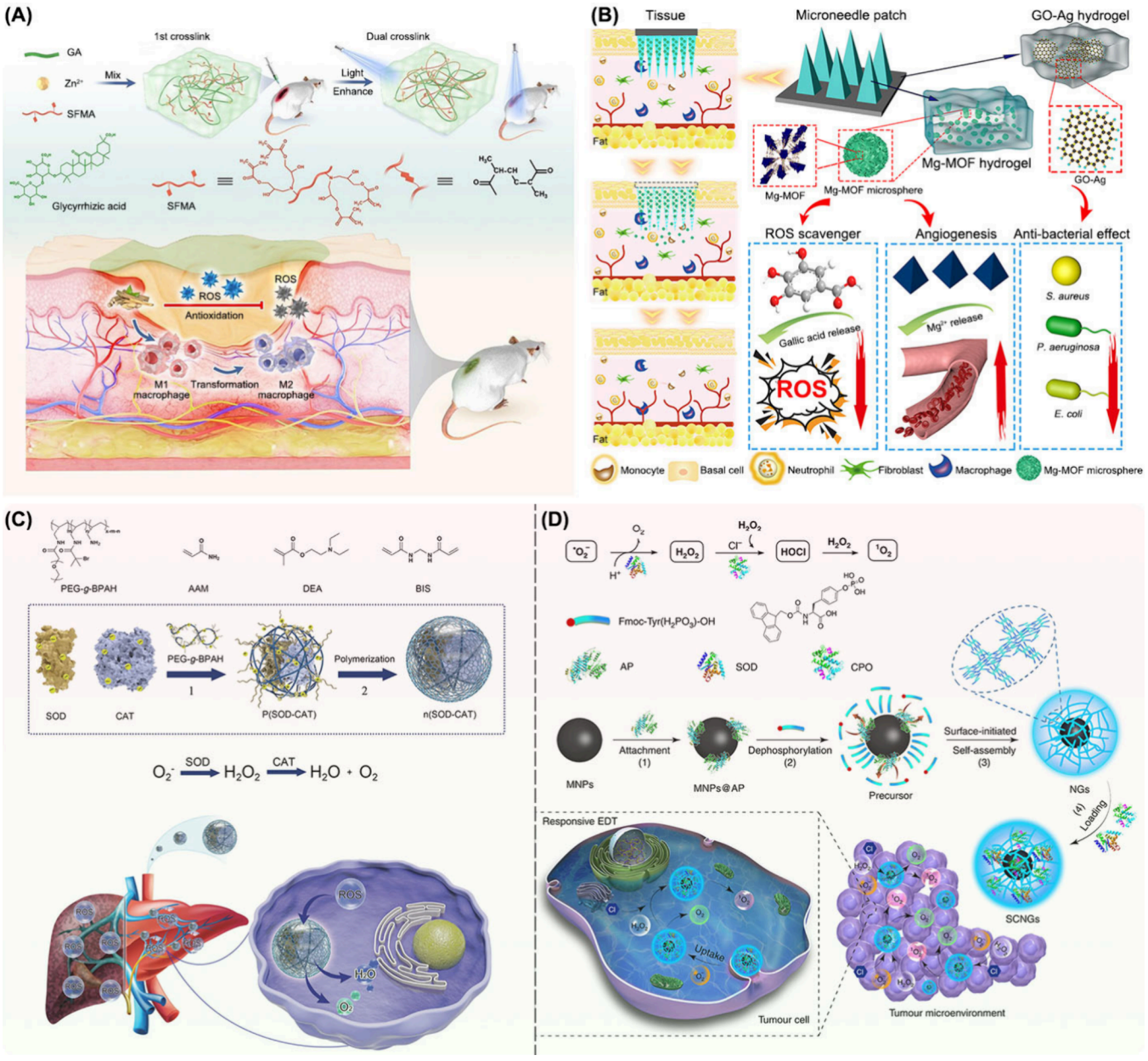


**Figure 7.** (A) Schematic representation of the photoenhanced glycyrrhizic acid hybrid hydrogel with immunoregulatory properties for promoting diabetic wound healing. Reproduced with permission from ref 191. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (B) Schematic representation of magnesium organic framework-based microneedle patch for accelerating diabetic wound closure rate. Reproduced with permission from ref 194. Copyright 2021 American Chemical Society. (C) Schematic illustration of the preparation of enzyme-polymer nanocomplexes and further application for ischemia and reperfusion injury in liver transplantation. Reproduced with permission from ref 197. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (D) Design principle of the enzyme dynamic therapy and the application for singlet oxygen elevated cancer therapy. Reproduced with permission from ref 200. Copyright 2019 Springer Nature under a Creative Commons Attribution 4.0 International License.

1 day. The lyophilized hydrogel scaffold allowed for the in vivo release of completely functional engineered CAR-T cells and further restrained distal tumor growth in a mouse xenograft model of lymphoma. This multifunctional scaffold represented a translational route for reprogramming and delivering therapeutic cells. In another study, Appel et al. proposed a transient injectable hydrogel that functioned as a CAR-T cell reservoir for promoting the treatment of solid tumors (Figure 5C-5E).[175] The biocompatible formulation and mild formation characteristics of the hydrogel enabled it to encapsulate CAR-T cells and cytokines, and further created a stimulatory inflammatory microenvironment for CAR-T cell expansion and activation. It was demonstrated that this type of transient injectable stimulatory hydrogel could provide a desirable microenvironment for regulating CAR-T cells, significantly enhancing the efficacy of eliminating solid tumors in mice.

### 4.3. Hitchhiking Delivery of Anti-Inflammatory Gases

**4.3.1. Carbon Monoxide.** The targeted delivery of anti-inflammatory gases, such as carbon monoxide (CO), hydrogen sulfide ($H_2S$), and hydrogen ($H_2$) presents a promising strategy for managing various inflammatory diseases. As an endogenous gaseous signaling molecule, CO exerts substantial therapeutic functions in hypertension management, bacterial inhibition, atherosclerosis, and stroke.[176,177] In addition, CO at a


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physiological level has been recognized as an effective anti-inflammatory agent, as it can selectively inhibit the expression of pro-inflammatory cytokines and enhance the production of anti-inflammatory cytokines.[178,179] In light of this, CO-releasing materials have gained great attention for gas-mediated therapy. For instance, Lee and colleagues reported an efficient and convenient CO-releasing patch based on the supramolecular self-assembly of a CO-releasing diphenylalanine (FF)-peptide hydrogel and a corresponding tissue-adhesive hydrogel (Figure 6A).[180] This CO-releasing hydrogel patch demonstrated cytoprotective and anti-inflammatory capacities in the $H_2O_2$-damaged cardiomyocytes. In another study, the same group presented a visible light-cross-linkable supramolecular CO-releasing hydrogel that exhibited superior mechanical strength and stability. Noticeably, this hydrogel was suitable for the site-specific and controlled release of CO, thus providing anti-inflammatory functions for oxidatively stressed cardiomyocytes.

**4.3.2. Hydrogen Sulfide.** $H_2S$ is a gas transmitter that can downregulate levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-$\alpha$, demonstrating a significant anti-inflammatory effect and promoting the growth and migration of epidermal/endothelial cells.[181,182] For instance, Wu et al. developed a one-step chemical cross-linking technique using 1,1'-thiocarbonyldiimidazole. In this system, 1,1'-thiocarbonyldiimidazole cross-linking controlled the immunological microenvironment and sped up tissue remodeling by creating cleavable thiourea and thiocarbamate connections that eventually released $H_2S$ during breakdown (Figure 6B).[183] In vitro and in vivo experiments showed that this novel $H_2S$-releasing hydrogel significantly promoted the M2 polarization of macrophages and further accelerated heart valve regeneration.

In addition to its role in macrophage polarization during wound healing, $H_2S$ exhibits protection against oxidative stress in the cardiovascular system. Despite its remarkable therapeutic effect, the application of $H_2S$ in the cardiovascular systems is limited, due to its short half-life and difficult-to-control release. To deal with this, Liu et al. used a cell-loaded conductive hydrogel with the modification of a macromolecular $H_2S$ prodrug, 2-aminopyridine-5-thiocarboxamide (Figure 6C).[184] This conductive hydrogel was able to slowly and continuously release $H_2S$, and thus effectively reverse the hostile microenvironment in the MI zone. The proposed ADSC-loaded conductive hydrogels with $H_2S$-releasing behavior were highly effective for downregulation of inflammatory factors and restoration of cardiac functions. Therefore, this work presents a promising tactic for MI treatment.

**4.3.3. Nitric Oxide.** As a versatile biomolecule, NO also plays a pivotal role in inhibiting platelet aggregation, preventing thrombosis, and modulating the inflammatory response.[185,186] In this regard, NO has been widely investigated for its potential in treating cardiovascular diseases. For example, Wu and colleagues developed a nitric oxide-eluting (NOE) hydrogel coating for vascular stents (Figure 6D-6F).[187] This hydrogel consisted of alginate and gelatin, wherein the organoselenium species were conjugated to alginate, allowing for the sustainable production of NO. After optimizing the formula, the NOE hydrogel exhibited tough mechanical properties, selectively benefiting the adhesion of endothelial cells, and inhibited smooth muscle cell formation. When the NOE hydrogel was coated on the surface of vascular stents, it was observed that the NOE hydrogel could suppress inflammation and neointimal hyperplasia. These results demonstrated the translational potential of this NOE hydrogel coating for the treatment of cardiovascular diseases.

### 4.4. Hitchhiking Delivery of ROS Scavengers

The mitigation of overexpressed ROS is promising for alleviating organismal inflammation. To address oxidative stress, various natural and synthetic ROS scavengers have been incorporated into hydrogels, offering an effective approach to managing these hostile environments.

**4.4.1. Natural ROS Scavengers.** The application of natural ROS scavengers can neutralize or redistribute harmful factors (e.g., ROS) at dysfunctional tissue sites, and has been extensively developed as a powerful tool for preventing and treating immune-related diseases.[188,189] For example, glycyrrhizic acid (GA) is a natural compound that derived from the root of the licorice plant. It has been demonstrated that GA and its derivatives are effective inhibitors of ROS accumulation and possess intrinsic immunoregulatory activity, making them a valuable tool for alleviating inflammation-related tissue injuries.[190] In light of these findings, Shen and colleagues reported a photoenhanced GA hydrogel scaffold with immunoregulatory capabilities (Figure 7A).[191]

This hybrid hydrogel was synthesized through the self-assembly of GA and $Zn^{2+}$ salts, and subsequently incorporated into methacrylated silk fibroin (SF), achieving good injectability and outstanding mechanical strength. Due to the anti-inflammatory effects of GA, the resultant hydrogel exerted regulatory functions on macrophage phenotypes, providing a potential wound dressing for diabetic wound treatment and improving wound healing quality in multiple ways. Gallic acid, classified as a phenolic acid, can effectively capture the uncontrolled accumulation of ROS, therefore, it downregulates ROS-induced inflammation in macrophages.[192,193] For example, Huang et al. designed biocompatible and porous metal−organic frameworks (MOFs) through the self-assembly of gallic acid and $Mg^{2+}$ salts. The Mg-MOF nanoparticles were then entrapped in graphene oxide (GO)-silver nanocomposites-loaded poly($\gamma$-glutamic acid) hydrogel (Figure 7B).[194] Notably, gallic acid could be slowly released in acidic microenvironments and act as a ROS-scavenger for immunomodulation. Furthermore, the multifunctional MOF-based hydrogels were engineered into microneedle patches, enabling transdermal delivery and combination therapy to promote diabetic wound healing.

In addition, a variety of natural ROS scavengers in the human body play critical roles in maintaining redox homeostasis. For example, superoxide dismutase (SOD) breaks down superoxide into hydrogen peroxide ($H_2O_2$), while catalase (CAT) converts $H_2O_2$ into water and oxygen.[195,196] Taking advantage of the cascade reactions of CAT and SOD, Lu et al. designed a nanogel capable of stabilizing nanocomplexes of these enzymes, enabling efficient elimination of intracellular ROS and reducing ROS-related damage (Figure 7C).[197] The remarkable immunological characteristics of these cascade enzyme-based nanogels make them attractive for the amelioration of ischemia-reperfusion injury and pathogen-induced liver injury. As a robust peroxidase, chloroperoxidase (CPO) catalyzes the conversion of $H_2O_2$ into singlet oxygen ($^1O_2$) and exhibits superior resistance to oxidative inactivation.[198,199] Building on this, Wang et al. designed and developed a core−shell supramolecular hybrid nanogel incorporating both SOD and CPO for the effective reduction of ROS in tumor tissue and production of $^1O_2$, ultimately inducing apoptosis in hypoxic tumor cells (Figure 7D).[200] This


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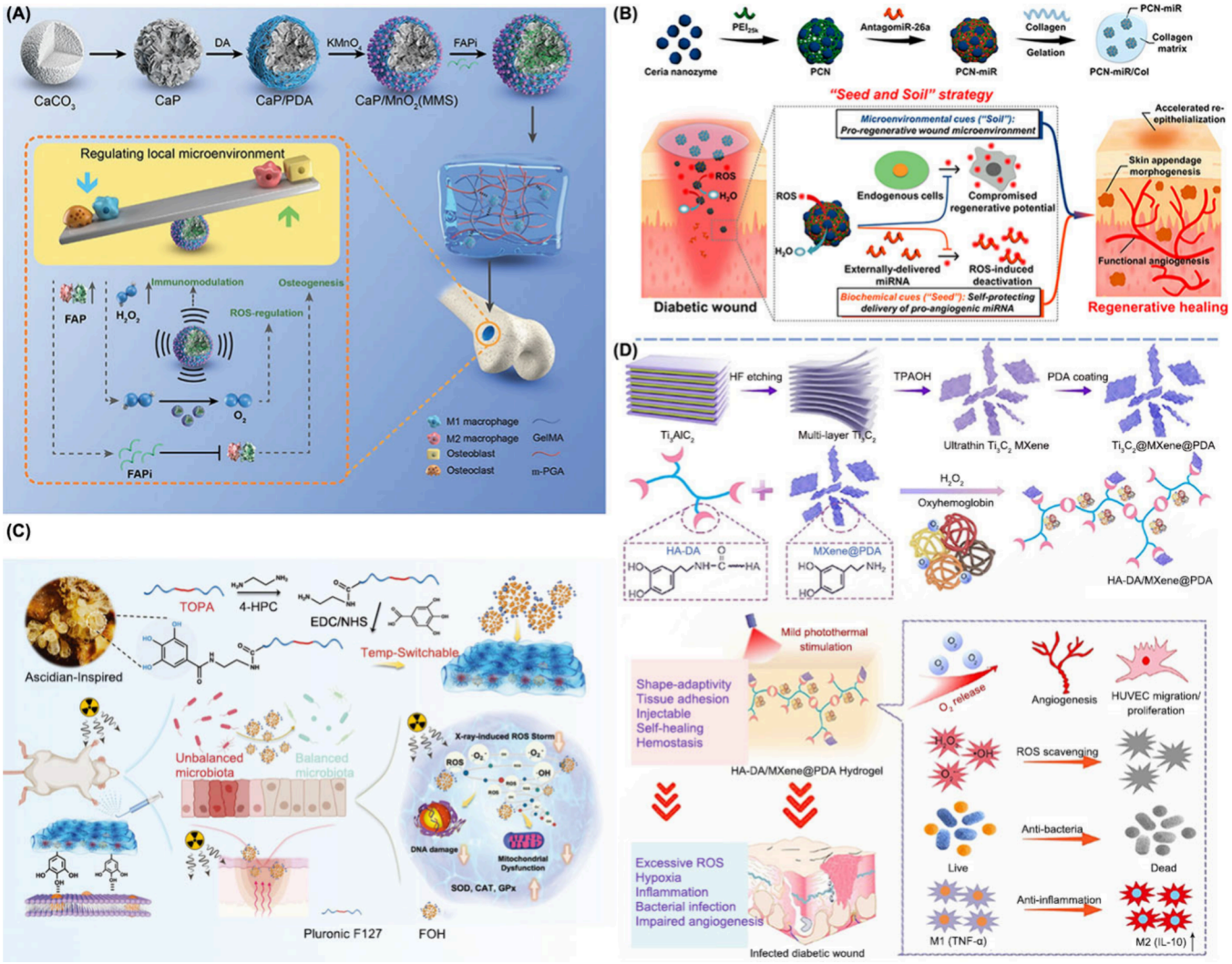


**Figure 8.** (A) Schematic representation of the synthesized process of the nanocomposite hydrogel loading CaP/$MnO_2$-coated FAPi and the application for osteoporotic bone defect regeneration mechanism. Reproduced with permission from ref 207. Copyright 2022 Wiley-VCH Verlag GmbH & Co. (B) Synthesis diagram of the PCN-miR/Col hydrogel for functional angiogenesis and infected diabetic wound healing by modulating the overexpressed-ROS microenvironment. Reproduced with permission from ref 208. Copyright 2019 American Chemical Society. (C) Schematic representation of the fullerenol/temperature-switchable hydrogel for protecting against oral mucositis under radiation-induced ROS microenvironment. Reproduced with permission from ref 209. Copyright 2023 Wiley-VCH Verlag GmbH & Co. (D) Schematic illustrations of the fabricated process HA-DA/MXene@PDA hydrogel and further application for the treatment of infected diabetic wound healing. Reproduced with permission from ref 215. Copyright 2022 American Chemical Society.

work provides a novel therapeutic strategy for tumor elimination without the need for external energy activation.

**4.4.2. Artificial ROS Scavengers.** Given the respective and collective drawbacks associated with natural enzymes, such as high production costs, sensitivity to environmental conditions, and low operational stability, significant efforts have been made to develop artificial enzymes as ROS scavengers. Among these, metal-based nanomaterials stand out as representative artificial nanozymes that possess antioxidant-enzyme-mimetic catalytic activity.[201−203] In comparison with conventional antioxidant molecules or enzymes, metal-based nanomaterials exhibit beneficial intrinsic properties, including good biocompatibility, facile synthesis, and enhanced catalytic performance.[204−206] Based on these considerations, the combination of metal-based nanozymes and hydrogels offers vast application prospects for treating various oxidative-stress-associated diseases. For example, ROS accumulate uncontrollably in bone defects of patients with osteoporosis, which makes bone regeneration difficult and remains a significant challenge. To address this situation, Han and colleagues proposed a multifunctional nanocomposite hydrogel that overcame the limitation of overexpressed $H_2O_2$ and modulated immune reactions (Figure 8A).[207] In this system, the multifunctional hydrogels were loaded with redox-modulatory manganese dioxide ($MnO_2$)-coated calcium phosphate microspheres, which served as an $H_2O_2$-activated oxygenerator and released fibroblast activation protein inhibitor (FAPi). Treatment of osteoporotic bone defects with these hydrogels significantly enhanced M2 macrophage polarization and accelerated bone formation. Overaccumulation of ROS is also a hallmark of impaired diabetic wounds, and the selective elimination of ROS using nanozyme-decorated hydrogels holds great promise for promoting diabetic foot ulcers (DFUs) healing. Ling et al. developed a polyethylenimine functionalized ceria nanocluster reinforced self-protecting hydrogel to reshape the hostile oxidative microenvironment of diabetic wounds (Figure 8B).[208] The results suggested that this nanozyme-


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reinforced self-protecting hydrogel not only converted detrimental ROS into $H_2O$ but also prevented encapsulated miRNAs from ROS-induced damage.

Apart from the aforementioned metal-based nanozymes, some carbon-based nanomaterials can also act as ROS scavengers. For example, Gu and colleagues introduced fullerenol nanoparticles into an ascidian-inspired temperature-switchable hydrogel to protect against oral mucositis and maintain the homeostasis of oral microbiota under the radiation-induced ROS storm (Figure 8C).[209] They demonstrated that the antioxidant activity of fullerenol nanoparticles enabled them to effectively scavenge ROS and attenuate the proinflammatory status. In vitro and in vivo studies showed that this fullerenol-immobilized hydrogel protected the proliferation and migration of mucosal epithelial cells in the oxidative microenvironment following radiation-induced oral mucositis. Moreover, antioxidative polymer-based nanomaterials are another category of synthetic nanomaterials with ROS-scavenging performance that have been integrated into hydrogel networks. These polymer-based nanomaterials typically fall into two main classes. One representative example is the polymer nanomaterial containing phenol groups. It is generally considered that the $H_2O_2$-scavenging performance of phenol groups originates from their ability to accelerate the decomposition of $H_2O_2$. Free radical trapper-containing polymer nanomaterials are another type of ROS-scavengers, and they have been investigated for combination with hydrogels.

Two-dimensional (2D) materials possess flexible sheet-like structures, high surface-to-volume ratios, and good biocompatibility.[210,211] This type of material has been integrated with hydrogels as ROS scavengers. GO, a typical 2D hydrophilic nanosheet, has garnered growing interest in biomedical applications due to its ability to scavenge ROS and mitigate ROS-mediated oxidative damage in tissue injuries.[212,213] In view of these features, Guo et al. designed and developed a pH/glucose dual responsive GO-decorated hydrogel dressings to promote diabetic foot wound closure.[214] It was observed that the engineered multifunctional hydrogels could significantly reduce inflammation and promote wound closure since the introduction of polydopamine coated reduced GO. MXene nanosheets known for their capacity to eliminate harmful ROS such as $H_2O_2$, hydroxyl radical (•OH), and superoxide anion ($O_2^{-\bullet}$), have also been leveraged for the management of oxidative stress-related diseases. In view of these antioxidant properties, Fan and colleagues presented a MXene nanosheet-anchored injectable hydrogel to eliminate accumulated ROS in DFUs (Figure 8D).[215] In this system, the MXene nanosheet could regulate macrophage polarization from M1 to M2 and maintain intracellular redox homeostasis. Similarly, molybdenum disulfide ($MoS_2$) nanosheets have demonstrated various antioxidant enzyme activities, such as CAT, SOD, and peroxidase. Chu et al. developed a $MoS_2$ nanosheet decorated hydrogel to ameliorate oxidative stress and promote wound healing.[216] The network of hydrogel was produced from the copolymerization of *N*-isopropylacrylamide, acrylamide, and acryloyl Pluronic 127. The key to achieving both antibacterial and antioxidant functions was the presence of polydopamine modified $MoS_2$, which was desirable for the elimination of ROS and further alleviation of oxidative stress in the wound healing process.

## 5. THERAPEUTIC HYDROGEL-BASED DELIVERY SYSTEMS FOR IMMUNOMODULATORY APPLICATIONS

### 5.1. Therapeutic Hydrogel-Based Delivery Systems for Infectious Diseases

**5.1.1. Sepsis.** Sepsis is one of the most life-threatening diseases, primarily arising from a severe inflammatory response to infection.[217] This syndrome can lead to multiple organ dysfunction due to the release of inflammatory cytokines into the bloodstream.[218] Without proper supportive care, patients with sepsis may develop a range of symptoms, including fever, hypourocrinia, systemic hypotension, impaired blood coagulation, increased vascular permeability, and potentially death. According to reports, the mortality rate for severe sepsis and septic shock ranges from 30 to 41%, in which the figure is higher than that of MI and stroke. Moreover, sepsis is highly related to Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To address these lethal effects of sepsis, an effective therapeutic platform should be developed.[219,220]

The neutralization of specific cytokines represents a promising therapeutic strategy that has been extensively exploited for the intervention of sepsis.[221] In this regard, Shea et al. proposed an abiotic hydrogel nanoparticle (HNP) for late-stage sepsis management. This HNP was synthesized by incorporating N-*tert*-butylacrylamide, acrylic acid, and/or N-(3-aminopropyl)-2-methylacrylamide hydrochloride into PNIPAM-based HNPs. After optimization of the formula, the HNPs could selectively capture and neutralize all variants of histones, which play as a major role in sepsis lethality. The authors further demonstrated that intravenous injection of HNPs could prevent murine sepsis induced by a lethal dose of histones by inhibiting platelet aggregation and migration into the lungs, resulting in near-complete survival in the murine sepsis model. The highly therapeutic efficacy of HNPs in murine sepsis makes them promising for sepsis therapy in clinics.

Targeting multiple mediators presents another viable treatment strategy to lower mortality in sepsis. Luo et al. reported a telodendrimer nanotrap (TDNT) that scavenged multiple inflammatory mediators through hybrid, multivalent, and synergistic interactions.[222] In this system, the TDNT was conjugated to a size-exclusive hydrogel resin, enabling simultaneously selective capture of sepsis-related biomolecules, including lipopolysaccharides, cytokines, and damage or PAMPs in the bloodstream. In particular, the distinctly charged moieties of TDNT endowed it with the ability to selectively capture multiple negative pro-inflammatory cytokines and positive anti-inflammatory cytokines. In vivo experiments indicated that the optimized TDNT therapy achieved nearly 100% survival, as evidenced by a significant alleviation of infection and hyper-inflammation. This remarkable therapeutic treatment makes this TDNT technology suitable for enhancing the survival of sepsis.

**5.1.2. COVID-19.** COVID-19, caused by SARS-CoV-2, has presented an unprecedented healthcare crisis, particularly in its severe forms, which can lead to significant morbidity and mortality.[223,224] With the evolution of viruses and the emergence of new variants, there are ever-increasing fears that such variants may augment pathogenesis by evading the immunity produced from previous infection or vaccination or by triggering a more severe disease. Given the magnitude of the influence of COVID-19, it is imperative to develop robust and


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Chem. Rev. XXXX, XXX, XXX−XXX

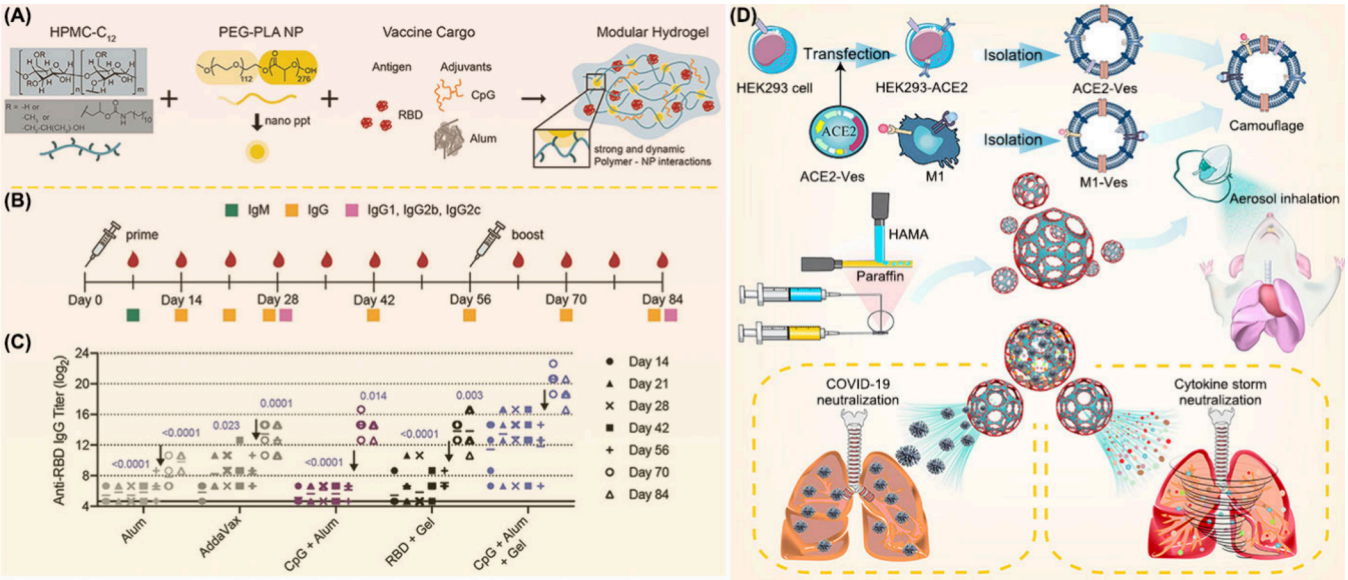


**Figure 9.** (A) Schematic illustration of the fabricated process of polymer−nanoparticle hydrogel. The dynamic multivalent noncovalent interactions between dodecyl-modified hydroxypropylmethylcellulose (HPMC-$C_{12}$) and poly(ethylene glycol)-*b*-poly(lactic acid) (PEG−PLA) result in the physical cross-linking of hydrogels that act as a vaccine cargo (RBD, CpG, and Alum). (B) Flowchart of animal experiments for immunizations and blood collection. (C) Antibody titers before and after boosting (arrow) from different experimental groups, and the hydrogel exhibited a higher level of the anti-RBD IgG titer compared with other bolus vaccines. Reproduced with permission from ref 228. Copyright 2021 Wiley-VCH Verlag GmbH & Co. (D) Design rationale and application of the inhaled ACE2-engineered microfluidic hydrogel nanoparticles for neutralizing COVID-19 and eliminating cytokine storms. Reproduced with permission from ref 231. Copyright 2022 Elsevier.

effective strategies to combat the virus and mitigate its devastating health and financial burdens.[225,226]

Conventional SARS-CoV-2 vaccine platforms, including DNA-based and mRNA-based vaccines, face several challenges, such as limited effectiveness, prolonged research timelines, side effects, and high expense.[227] Therefore, there is a pressing need for the rational design of robust and rapidly manufactured vaccines. The receptor-binding domain (RBD) of the SARS-CoV-2 spike protein mediates viral infection by selectively binding to the human angiotensin converting enzyme 2 (ACE2) receptor. Different from conventional vaccine candidates, the RBD is highly stable and efficient to manufacture.

In addition, considerable research has demonstrated that RBD is a target for neutralizing antibodies. Despite its appealing therapeutic activity, the application of RBD as a COVID-19 subunit vaccine is limited owing to its poor immunogenicity. On account of this problem, Appel et al. proposed an injectable polymer−nanoparticle (PNP) hydrogel depot designed for the prolonged release of a RBD subunit vaccine together with CpG/Alum adjuvant (Figures 9**A**-9**C**).[228] According to the results of the lentiviral SARS-CoV-2 pseudovirus assay, this hydrogel-based vaccine could arouse stronger neutralizing responses as compared to bolus vaccines. This creative work was able to attain a PNP hydrogel depot for the delivery of RBD subunit vaccines and in turn, improved the immunogenicity of RBD. Consequently, this synergistic strategy offers valuable insights into improving the efficacy of RBD subunit vaccines against SARS-CoV-2.

Cell-membrane-based therapeutic platforms are another feasible therapeutic intervention for SARS-CoV-2 infection.[229,230] By inheriting associated functions of source cells, this membrane engineering approach can enhance targeting specificity and modulate broad-spectrum inflammation. As a typical paradigm, Cui et al. tactfully fabricated an inhaled microfluidic hydrogel microsphere-based therapeutic platform that remarkably decreased the effectiveness of SARS-CoV-2 infection and alleviated proinflammatory cytokines (Figure 9D).[231] In this system, HEK293-ACE2 cells were genetically engineered to express ACE2 receptors and then isolated in the ACE2-overexpressing cell membranes. These cell membranes were subsequently fused with the membranes of pro-inflammatory macrophages. To enhance the accumulation of the bioactive cell membranes in the respiratory system, they were attached to inhaled microfluidic hydrogel microspheres. Both in vitro and in vivo experiments demonstrated that the inhaled ACE2-engineered hydrogel nanoparticles could elicit potent neutralizing responses and alleviate hyper-inflammation of lymph nodes and the spleen. This noninvasive technology offers promise for the management of patients with severe COVID-19.

### 5.2. Therapeutic Hydrogel-Based Delivery Systems for Metabolic Diseases

Compared to radiation therapy and conventional chemotherapy, cancer immunotherapy generally induces fewer side effects and targets cancer cells by activating tumor-specific immune responses.[232−234] However, the systemic delivery of immune cells and immunomodulatory drugs often requires high doses or multiple injections, which can lead to significant side effects. Hydrogels have been developed as efficient and controlled delivery systems for the localized distribution of cells and immunomodulatory drugs, offering the ability to modulate anticancer immune responses both systemically and locally while also suppressing tumor growth.

Immunomodulatory hydrogels exert a superior promise for cancer therapy by virtue of their ability to deliver single or multiple immunotherapeutic agents, such as immunomodulatory factors, antibodies, vaccines, and exogenous immune cells.[235−237] Gu et al. harnessed a sprayed immunotherapeutic hydrogel for postsurgical cancer treatment (Figure 10A).[238] In


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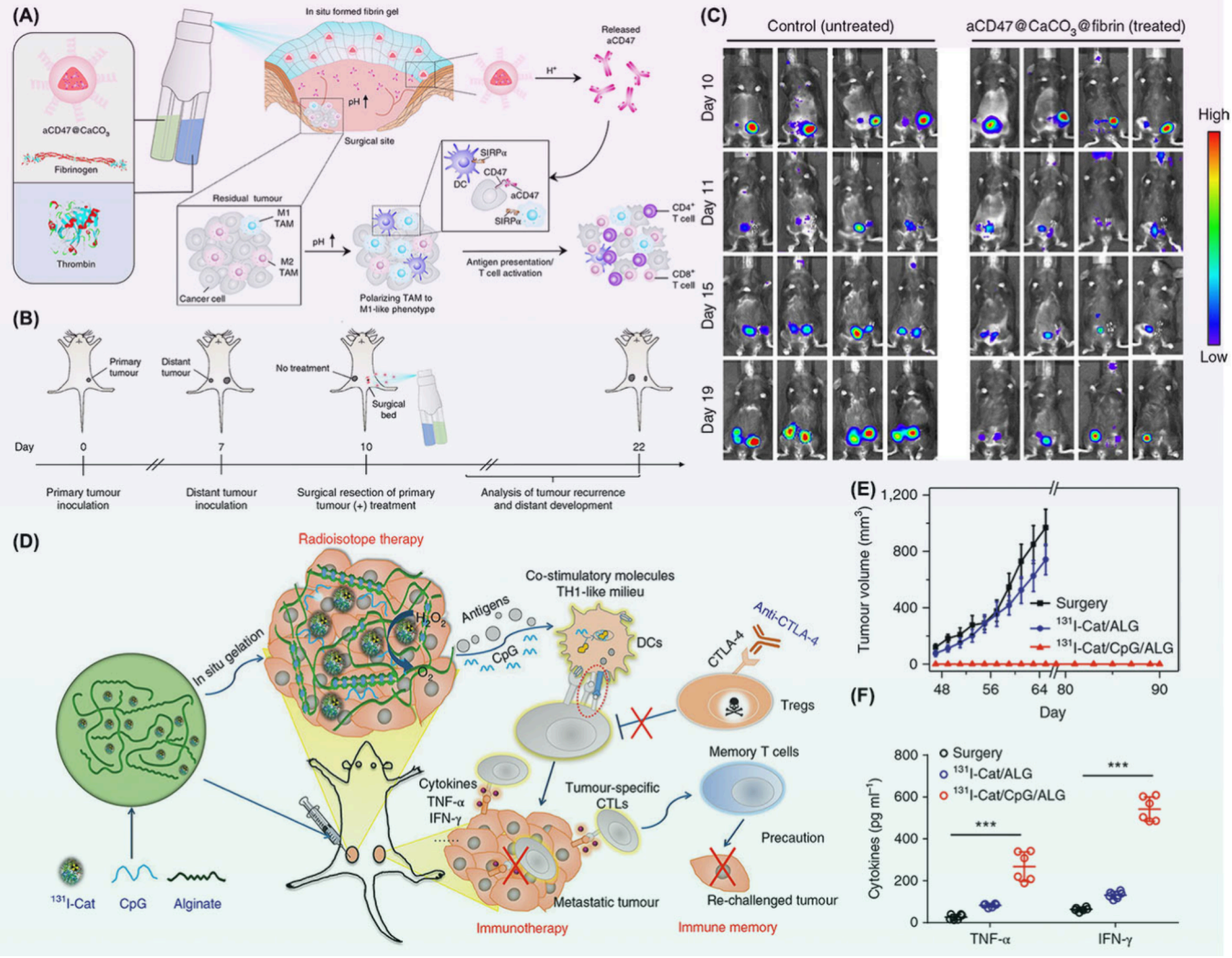


**Figure 10.** (A) Schematic illustration of the in situ sprayed hydrogel loading aCD47@$CaCO_3$ nanoparticles in the postsurgery tumor bed. (B) Flowchart of aCD47@$CaCO_3$@fibrin therapeutic effect in vivo experiment of a mouse model. (C) Representative luminescent imaging of B16F10 tumors after being treated with local aCD47@$CaCO_3$@fibrin on 10th day. Reproduced with permission from ref 238. Copyright 2019 Springer Nature. (D) Mechanism of the combination of checkpoint blockade with the $^{131}$I-Cat/CpG/ALG-based RIT for induction of antitumor immune responses. (E) Tumor growth curves after being treated with local aCD47@$CaCO_3$@fibrin at different time points. (F) Cytokine levels in serum of mice after treated with local aCD47@$CaCO_3$@fibrin on 5th day. Reproduced with permission from ref 242. Copyright 2018 Springer Nature.

this design, anti-CD47-containing $CaCO_3$ nanoparticles were introduced into a fibrinogen solution, and an immunotherapeutic hydrogel was fabricated at the tumor sites after being mixed with thrombin solutions. CD47, a transmembrane protein, inhibits phagocytosis by binding to signal regulatory protein $\alpha$ (SIRP$\alpha$). Recent studies have shown that CD47 is overexpressed in a plethora of tumors, and inhibiting the CD47-SIRP$\alpha$ pathway is a promising strategy to promote tumor cell phagocytosis. Additionally, $CaCO_3$ nanoparticles could sustainably release CD47 and serve as a proton scavenger to adjust the acidic tumor microenvironment. This bioresponsive immunotherapeutic hydrogel was shown to trigger macrophage-mediated cancer cell clearance and T cell-induced cancer cell destruction, effectively preventing tumor recurrence in an incomplete tumor resection mouse model (Figure 10B, 10C).

Immunomodulatory hydrogels are a promising treatment modality, and their antitumor efficacy can be further enhanced by combining them with other therapeutic strategies, such as phototherapy, radiotherapy, and chemotherapy.[239−241] For example, Liu et al. designed an in situ gelation strategy for combined tumor treatments (Figure 10D).[242] In this platform, CpG oligonucleotide and CAT labeled with the therapeutic $^{131}$I radioisotope were introduced into a sodium alginate solution. After injection of the above solution into local tumors, the mixture of $^{131}$I-Cat, CpG oligonucleotide, and polysaccharide underwent a sol-to-gel transformation in response to endogenous $Ca^{2+}$. On account of CAT's elimination of tumor endogenous $H_2O_2$, the hypoxic status within the tumor was alleviated, enabling more effective radioisotope therapy (RIT) at relatively low radiation doses. Furthermore, CpG, an immune adjuvant, activates robust pro-inflammatory immune responses. Similar to the function of the vaccine, the local RIT together with clinical T-lymphocyte-associated protein-4 (CTLA-4) checkpoint-blockade therapy not only eradicated subcutaneous tumors but also generated long-term immune memory protection in treated mice (Figure 10E, 10F).


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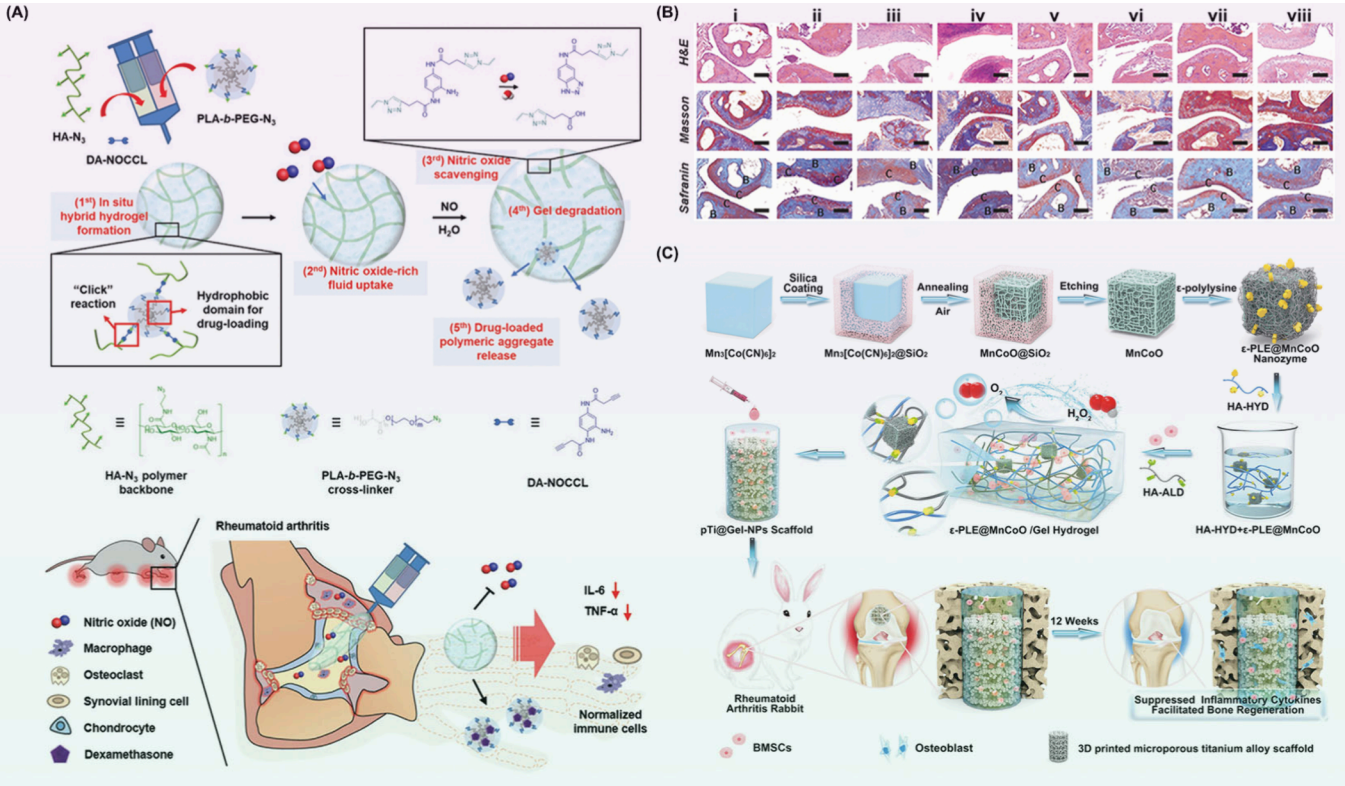


**Figure 11.** (A) Schematic showing the chemical structure of the polymeric aggregate-embodied hybrid NO-scavenging "click" hydrogel and exert therapeutic performance for rheumatoid arthritis. (B) Histological staining of the joint tissue via H&E, Masson, and Safranin staining. Scale bar: 100 $\mu$m. Reproduced with permission from ref 254. Copyright 2021 Wiley-VCH Verlag GmbH & Co. (C) Schematic representation of the formation of the nanozyme-reinforced hydrogel as a stem cell scaffold for the management of rheumatoid arthritis. Reproduced with permission from ref 258. Copyright 2022 Springer Nature under a Creative Commons Attribution 4.0 International License.

## 5.3. Therapeutic Hydrogel-Based Delivery Systems for Autoimmune Diseases

**5.3.1. Rheumatoid Arthritis.** RA is a progressive arthritic disease that severely lowers quality of life and imposes a substantial global socioeconomic burden.[243−245] A well-established hallmark of RA is the infiltration of T-cells into the synovial layer, which activates macrophages, monocytes, and synovial fibroblasts through cell−cell interactions. This activation further triggers the secretion of various pro-inflammatory cytokines, including TNF-$\alpha$, IL-6, and IL-1. The released pro-inflammatory cytokines can further elicit hyperplastic synovium and lesion formation or aggravation.[246−248] Without appropriate intervention, this disease can progress into impaired joint functions, considerable disability, and eventually early death.[249−251] Currently, the treatments predominantly focus on the inflammatory response, and immunomodulatory hydrogels have been envisioned as powerful tools for modulating the immune system in RA therapy.

Hydrogels are of particular interest for the precise delivery of bioactive substances due to their ability to respond to specific pathological environments, making them a promising therapeutic platform for RA management.[252,253] For example, Kim et al. investigated how hydrogels embodied with NO scavenging and sequential drug-releasing properties to treat RA in a mouse model (Figure 11A).[254] NO is a crucial pro-inflammatory mediator, whereas its overexpression enhances the levels of inflammatory cytokines.[255] Here, polymeric hydrogel aggregates were developed rationally by the integration of an azide-functionalized HA backbone and a dialkyne-functionalized NO-cleavable cross-linker. The hydrogel precursor solution could be intra-articularly injected and transformed into a gel via azide−alkyne "click" cycloaddition reaction, yielding self-healing capability for the on-demand release of dual drugs in response to NO concentration. This polymeric hydrogel could scavenge NO at the site of inflammation and exhibit anti-inflammatory properties, thus remarkably mitigating RA symptoms (Figure 11B).

Another promising strategy for alleviating the symptoms of RA is the use of stem cells. Stem cells are multipotent progenitor cells that can be derived from both embryonic and various adult tissues. Notably, certain stem cell populations have been shown to secrete a diverse array of growth factors, chemokines, and cytokines, thereby exerting regulatory effects on inflammatory processes.[256] Due to their anti-inflammatory properties, stem cells are widely investigated for RA treatment.[257] For example, Zhao et al. proposed a nanozyme-reinforced hydrogel as a $H_2O_2$-driven oxygenerator to manipulate BMSCs for RA treatment (Figure 11C).[258] Inspired by the structure of animal bone, the composite scaffold was composed of a soft self-healing hydrogel and stiff 3D-printed porous metal scaffolds. This structure allowed for targeted delivery of BMSCs, and this stem cell-based therapy exerted inhibition of inflammatory cytokines as well as the reconstruction of articular cartilage and subchondral bone.

**5.3.2. Type 1 Diabetes.** Type 1 diabetes (T1D) is a severe autoimmune disease in which the hyperactive immune response leads to the destruction of insulin-producing pancreatic $\beta$-cells, resulting in insulin deficiency. Despite significant progress, the development of specific therapeutic strategies to reverse T1D remains challenging.[259,260] Currently, exogenous insulin in-


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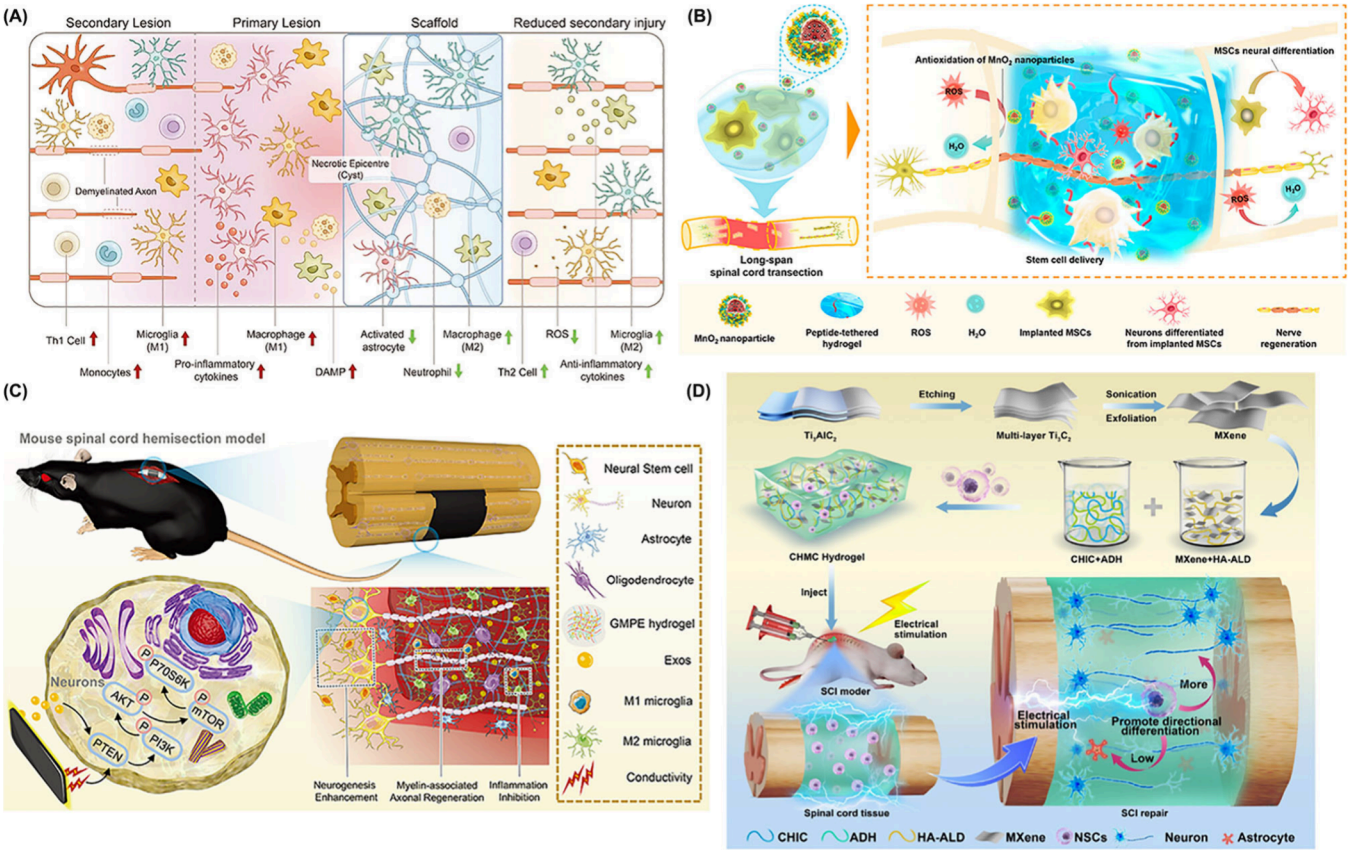


**Figure 12.** (A) Mechanism of biomaterial-based treatment methods that steer the behavior of immune-relative cells. Reproduced with permission from ref 277. Copyright 2021 Wiley-VCH Verlag GmbH & Co. (B) Schematic showing the $MnO_2$ nanoparticle-modified hydrogel accelerates spinal cord regeneration through regulating the oxidative microenvironment. Reproduced with permission from ref 278. Copyright 2019 American Chemical Society. (C) Schematic representation of GM/PPy/exosomes hydrogel promotes spinal cord regeneration via regulating inflammation and enhancing NSCs therapeutic effect. Reproduced with permission from ref 280. Copyright 2022 Wiley-VCH Verlag GmbH & Co under a Creative Commons Attribution 4.0 International License. (D) Schematic showing the MXene-modified CHM hydrogel combined with electrical stimulation accelerates spinal cord regeneration. Reproduced with permission from ref 281. Copyright 2023 Elsevier.

jections serve as the mainstay of treatment for T1D, and traditional administration of insulin with the usage of syringe pumps, injection syringes, microneedles, and other equipment will be difficult to avoid hypoglycemic and hyperglycemic events. Therefore, the development of an alternative insulin delivery system that can overcome the disadvantages of traditional administration is highly desirable for improving T1D treatment.[261,262]

The advancement of hydrogels inspires us to design long-term autonomous insulin delivery systems for improving diabetes care. With their 3D polymer networks, hydrogels can be engineered to deliver insulin and continuously release it in response to pathological microenvironments. This approach reduces diabetic pain and the risk of infection associated with traditional injections.[263,264] According to the type of glucose-responsive elements, hydrogel-based insulin delivery systems can be generally classified into phenylboronic acid, glucose oxidase (GOx), and concanavalin A (Con A)-functionalized immunomodulatory hydrogels. For example, Gu et al. developed a degradable cross-linked hydrogel-based microneedle array patch.[265] This painless microneedle array patch consisted of a core−shell structure, where the core contained GOx to produce $H_2O_2$ and trigger insulin release, while the shell component was modified with CAT to relieve the risk of $H_2O_2$-related inflammation. When applied to a type 1 diabetic mouse model, this core−shell microneedle array patch provided sustained and effective insulin delivery, maintaining blood glucose levels within the normal range.

Insulin is a peptide hormone that is considered to have intrinsic shortcomings such as poor stability, high cost, and difficulties in storage. To circumvent these limitations, significant efforts have been made to explore insulin-mimic substances.[266,267] In a study reported by Yang and colleagues in 2022, they inadvertently found that a tetrapeptide hydrogel (Nap-GdFdFdY) shared the same peptide sequence as both autoantigens proinsulin and insulin, potentially simulating multiple important autoantigens involved in T1D.[268] In a nonobese diabetic (NOD) mouse from T1D development, it was shown that the Nap-GdFdFdY hydrogel could preserve pancreatic islet morphology while suppressing immune cell infiltration. Further experiments demonstrated that the Nap-GdFdFdY hydrogel played a facilitative role in increasing peripheral T regulatory cell proliferation and thus offered the possibility to systematically modulate immune system behavior in the treatment of T1D.

## 5.4. Therapeutic Hydrogel-Based Delivery Systems for Tissue Injury

**5.4.1. Spinal Cord Injury.** Spinal cord injury (SCI) is one of the most disastrous diseases that is associated with the dysfunction of motor and sensory systems, and an increased risk of paralysis and death.[269,270] Once SCI occurs, multiple


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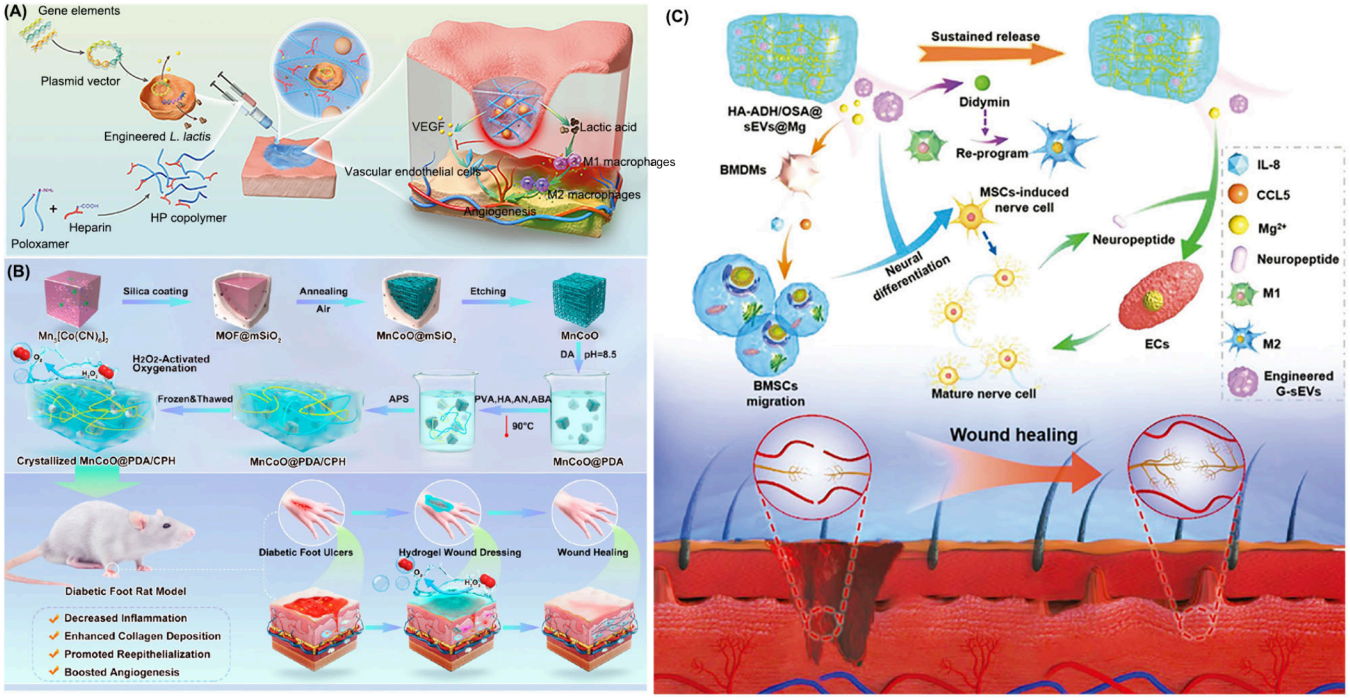


**Figure 13.** (A) Design and synthesis of living hydrogel for promoting blood vessel formation and elimination inflammation in diabetic wounds. Reproduced with permission from ref 300. Copyright 2021 Wiley-VCH Verlag GmbH & Co. (B) Design and synthesis of MnCoO@PDA/CPH hydrogels with $H_2O_2$-activated oxygenation property for diabetic wound management. Reproduced with permission from ref 301. Copyright 2023 American Chemical Society. (C) Design and synthesis of multifunctional HA-ADH/OSA@Mg@sEVs hydrogel and its application for diabetic wound healing. Reproduced with permission from ref 302. Copyright 2023 Wiley-VCH Verlag GmbH & Co.

types of immune cells, including macrophages, neutrophils, microglia, and lymphocytes (Figure 12A), are recruited into the traumatic lesion site and secrete excessive inflammatory cytokines and excitatory neurotransmitters.[271,272] According to reports, the long-term immune and inflammatory cascades play a crucial role in secondary injury and delay neural repair.[273,274] Therefore, modulation of the immune microenvironments of SCI offers a vast prospect for reducing secondary injury and accelerating SCI regeneration. Recently, soft and hydrated hydrogels are of particular interest for SCI treatment, due to their similarity to native nerve tissue, permissive microenvironment, transmission of electrical signals, and guidance cues for endogenous axonal regeneration.[275,276] It is of particular interest for hydrogels to perform immunomodulatory ability and promote the spontaneous regeneration of the spinal cord at the lesion site.[277] Even so, the simple transplantation of hydrogel may be far from satisfactory to fully achieve SCI regeneration. To deal with it, Gao and co-workers developed a $MnO_2$ nanoparticle-dotted hydrogel for the encapsulation of mesenchymal stem cells (MSCs) (Figure 12B).[278] This hydrogel network originated from the hydrazide-modified HA and aldehyde-modified HA with PPFLMLLKGSTR peptide. To eliminate the uncontrolled accumulation of ROS in the lesion microenvironment, $MnO_2$ nanoparticles were introduced into the hydrogel matrix. Thereby, this $MnO_2$ nanoparticle-dotted hydrogel could serve as a suitable carrier for MSCs and hinder the inflammatory response, which improved the efficiency of stem cell-based therapy and better served as an implant candidate for facilitating SCI repair.

Although stem cells possess therapeutic potential for SCI, their allogeneic transplants suffer from problems of low survival efficiency and immunogenicity in vivo.[279] As EVs, exosomes have recently garnered great attention for cell-free SCI treatment. Particularly, MSC-derived exosomes are equipped with anti-inflammatory abilities and offer promise for SCI therapy. For example, Ning developed an electroconductive hydrogel to mimic the aqueous microenvironment of the spinal cord, encapsulating BMSC-derived exosomes within the hydrogel to synergistically promote SCI repair (Figure 12C).[280] In vitro experiments showed that this cell-free therapeutic platform could modulate microglial M2 polarization via specific signaling pathways and promote neuronal and oligodendrocyte differentiation of neural stem cells (NSCs) while preventing astrocyte differentiation. Furthermore, the transplantation of BMSC-derived exosomes within the electroconductive hydrogel demonstrated evident motor function regeneration in an SCI mouse model, resulting in greatly efficient recovery of the central spinal cord tissue. In a study reported by Lin and colleagues in 2023, a MXene-decorated hydrogel (CHM) was found to regulate the differentiation trajectory of NSCs (Figure 12D). When combined with electrical stimulation (ES), this hydrogel-based biomimetic 3D soft scaffold effectively promoted spinal cord injury (SCI) repair and inhibited glial scar formation. The integration of a spinal cord−mimicking 3D soft scaffold with ES thus offers a promising therapeutic approach for the treatment of SCI.[281]

**5.4.2. Chronic Wound Healing.** Wound healing is a complex and tightly regulated biological process involving a diverse array of biomolecules, cellular components, signaling pathways, and ECM synthesis.[282,283] In the context of acute wounds, macrophages exhibit phenotypic plasticity, transitioning from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, a shift that facilitates the natural process of skin regeneration.[284,285] However, in chronic wounds, the balance between pro-inflammatory and anti-inflammatory macrophage phenotypes is markedly disrupted, leading to


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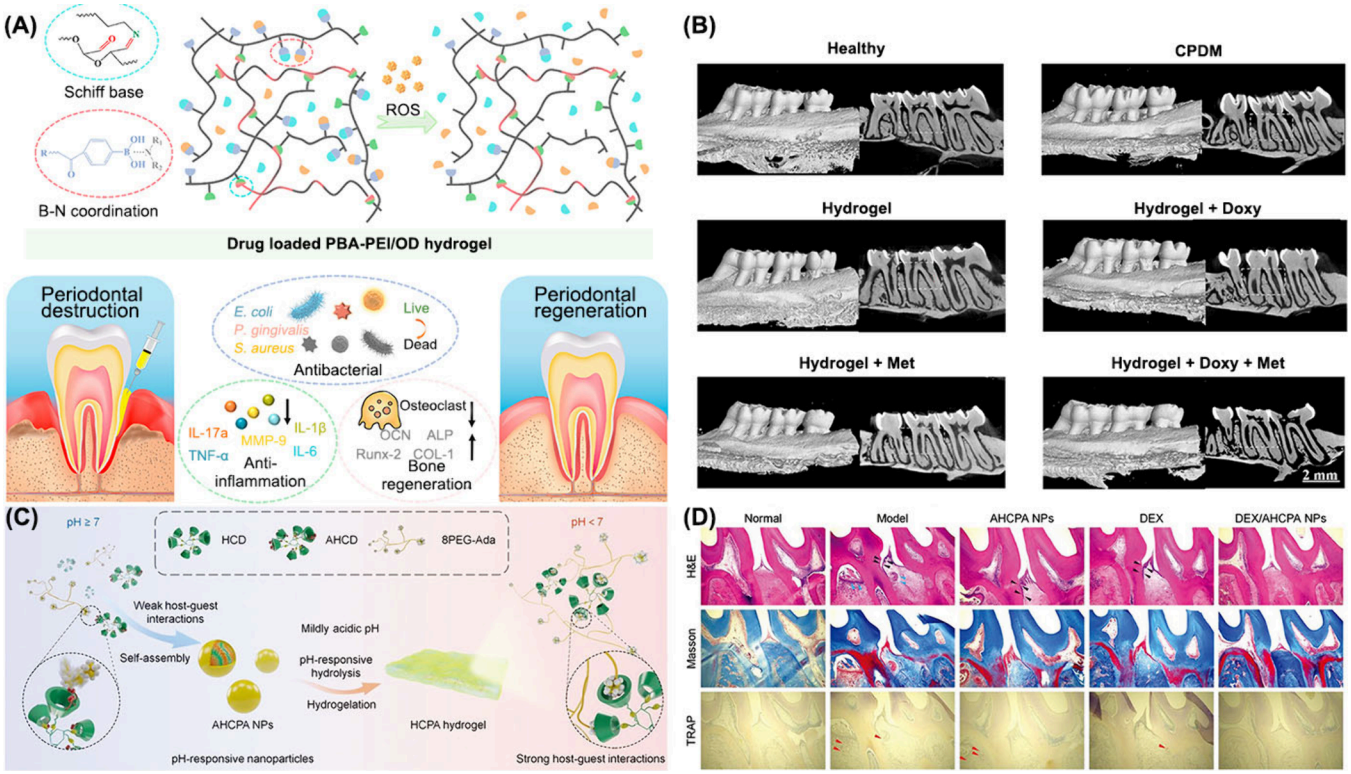


**Figure 14.** (A) A sketch displaying the fabricated procedures of ROS-responsive PBA−PEI/OD hydrogel and its loaded drug for treating inflammation and regeneration of the periodontium. (B) Typical Micro-CT images of maxillary alveolar bone after treatment of different experimental groups. Reproduced with permission from ref 316. Copyright 2022 Elsevier. (C) Schematic showing the facile development of pH-triggerable hydrogel-transforming nanoparticles. (D) Representative histological sections of the periodontal tissues were stained with H&E, Masson, and TRAP, respectively. Reproduced with permission from ref 318. Copyright 2022 Wiley-VCH Verlag GmbH & Co.

persistent inflammation and impaired tissue repair. As a result, macrophages play a critical role in orchestrating both the quality and temporal dynamics of the wound healing process.[286,287]

Given the importance of macrophages in wound healing, considerable hydrogel dressings have been made to control macrophage function and have shown possibilities to stimulate inflammatory pathways.[288−290] Hydrogels have some unique advantages of high biocompatibility, good degradability, tunable structure, and similarity to the native ECM. Additionally, their exceptional ability to retain moisture helps create an optimal environment for wound healing and minimizes scar formation.[291−293] Recently, hydrogels have elicited the great interest of many researchers to find breakthroughs in the management of wounds.[294−296] In particular, hydrogel-based wound dressings have been employed to precisely deliver bioactive molecules, effectively regulating local inflammation in chronic wounds.[297−299] This strategy could combat the threat of possible side effects of bioactive molecules compared with direct use, and potentially eliminate the problem of antibiotic resistance.

As an example, Deng and co-workers constructed a heparin poloxamer thermos-responsive hydrogel incorporating engineered living Lactococcus (L. lactis) (Figure 13A).[300] This engineered hydrogel not only produced and protected vascular endothelial growth factor (VEGF) to enhance angiogenesis, but also exhibited a strong ability to secrete lactic acid, which further facilitated the polarization of macrophages toward an anti-inflammatory phenotype. This bacteria-activated multifunctional hydrogel effectively regulated the hostile wound microenvironment and provided a highly efficient strategy for enhancing diabetic wound repair by targeting macrophages for anti-inflammatory action In another work, Zhao et al. demonstrated that a biomimetic nanozyme-decorated MnCoO@PDA/CPH hydrogels with $H_2O_2$-activated oxygenation properties (Figure 13B).[301] Significantly, the developed hydrogels dramatically modulated the polarization of macrophages toward the M2 phenotype, which in turn accelerated blood vessel formation and collagen deposition, thus promoting diabetic wound healing. Liu et al. reported a hydrogel-based whole-course repair system for promoting diabetic wound healing (Figure 13C).[302] This hydrogel could be preloaded into a syringe for subsequent in situ local injection, enabling long-term wound coverage. Moreover, it promoteed accelerated wound healing through the synergistic effects of magnesium ions ($Mg^{2+}$) and engineered small extracellular vesicles (sEVs), achieving a mutually supportive cycle of neurogenesis-angiogenesis even under an immune-microenvironment.

**5.4.3. Acute Kidney Injury.** Acute kidney injury (AKI) is a heterogeneous disease featured with a decline in the glomerular filtration rate.[303] The worldwide incidence of AKI is rapidly increasing, and its prevalence has been estimated to surpass 50% of the critically ill population in the intensive care unit. In the pathological conditions of AKI, the microarchitecture and permeability of blood vessels are seriously destroyed, leading to reduced blood flow and $O_2$ delivery. This disruption leads to overexpression of ATP, ROS, and NO, which in turn trigger hypoxia and oxidative stress.[304,305] In addition, the destruction of the microvascular endothelium induces endotheliocyte activation accompanied by the accumulation of markers on


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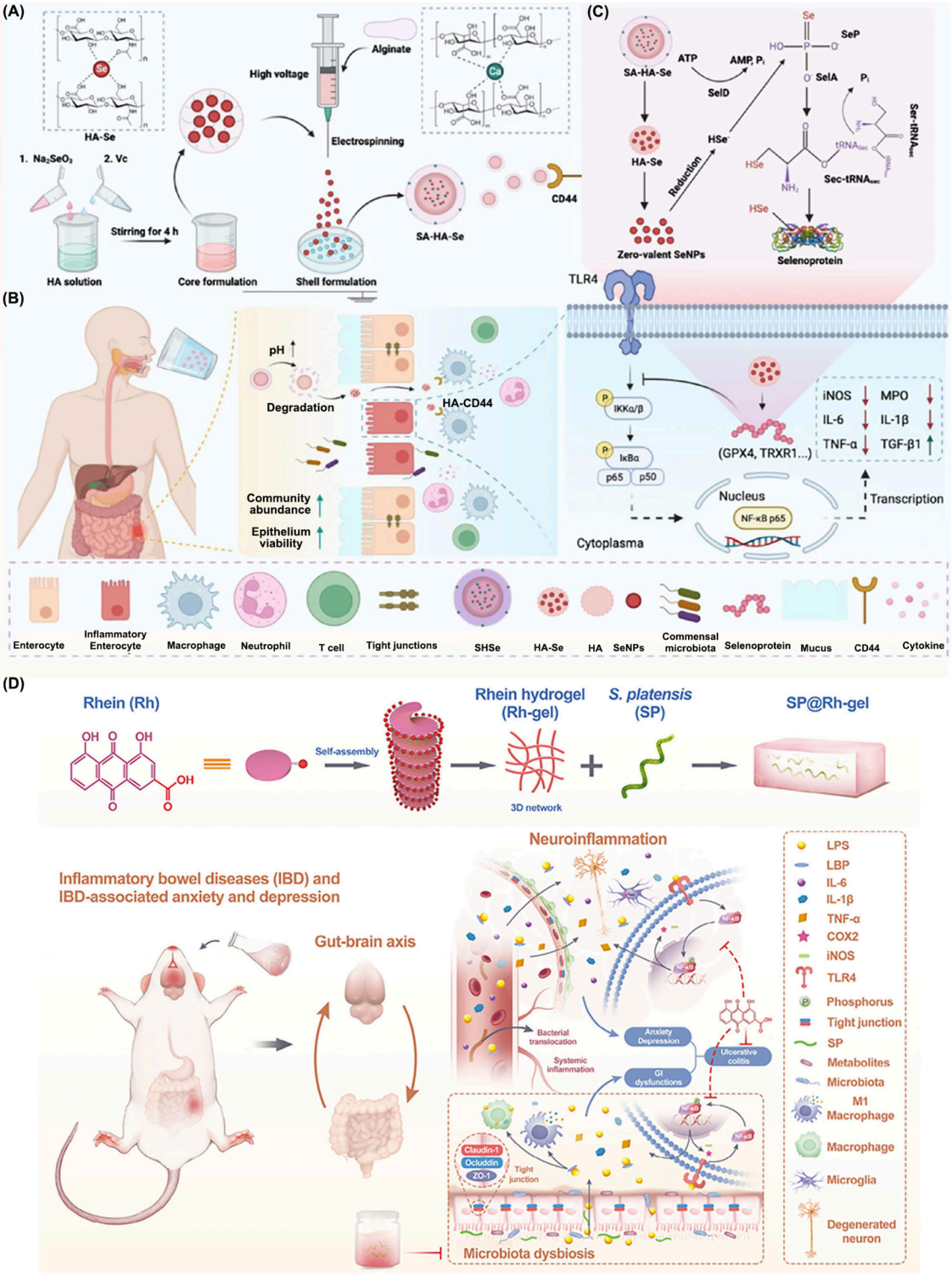


**Figure 15.** (A) Schematic illustration of the fabricated process of the SHSe hydrogel microbeads. (B) Mechanism of the inflammation-targeting hydrogel releases the drug at a target of inflamed mucosa. (C) A potential mechanism involves the in situ production of selenium-containing proteins through SeNPs. Reproduced with permission from ref 324. Copyright 2023 American Chemical Society. (D) Schematic showing the microalgae-based hydrogels are orally administrated for IBD and associated anxiety and depression. Reproduced with permission from ref 327. Copyright 2024 Wiley-VCH Verlag GmbH & Co.

the cell surface, resulting in impaired tissues and intensive inflammatory responses.[306,307]

Immunomodulatory hydrogels provide a feasible solution for the management of inflammatory microenvironment in AKI. EVs derived from mesenchymal stem cells (MSC-EVs), designated as exosomes, are produced in the endosomal compartment of most eukaryotic cells.[308] Compared with stem cell-based therapies, MSC-EVs treatments have been recognized as powerful tools for AKI management due to their attractive advantages of low immunogenicity, evitable tumor-


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igenicity, easy storage, and simple operation.[309,310] For example, Chen et al. reported a biocompatible, self-assembled Arginine-Glycine-Aspartate (RGD) peptide hydrogel.[311] The designed RGD hydrogel could bind to integrins on MSC-EVs, and further ameliorate the stability and retention of the grafted MSC-EVs. When systemically administered to mouse models of AKI, the RGD hydrogel together with MSC-EVs effectively repaired renal function and diminished tubular injury as well as improved proliferation, antifibrosis, antiapoptosis, and pro-autophagy capabilities through modulating a series of inflammatory responses.

### 5.5. Therapeutic Hydrogel-Based Delivery Systems for Inflammatory Diseases

**5.5.1. Periodontitis.** Periodontitis is defined as a bacterially induced chronic inflammatory condition affecting over 30% of adults in the world.[312,313] This prevalent disease significantly triggers the immuno-inflammatory destruction of the periodontium and can further develop into loss of tooth support and eventually tooth loss if left untreated.[314,315] According to recent studies, polymicrobial dysbiosis is the primary factor in the onset of periodontitis, while dysregulation of the host innate immune system plays a critical role in its progression.[316,317] Considering these findings, immunomodulatory hydrogels have been utilized to augment therapeutic effects and attenuate disease progression.

In a representative study, Li and colleagues employed an injectable bioresponsive hydrogel for the ROS-triggered delivery of drugs to treat chronic periodontitis (Figure 14A).[316] The hydrogel was formed from Schiff bases between oxidized dextran (OD) and phenylboronic acid-modified poly(ethylene imine) (PBA−PEI), with the incorporation of the anti-inflammatory doxycycline and the antihyperglycemic agent metformin. The hydrogel displayed strong adhesiveness toward gingival tissue, impressive antibacterial activity, and good biocompatibility. When applied to a diabetic rat model with chronic periodontitis, the hydrogel achieved significant therapeutic efficacy as evidenced by suppressed inflammation and promoted bone repair (Figure 14B). Given the complex physiological and pathological microenvironment of periodontitis, immunomodulatory hydrogels with stimuli-responsive properties have shown superior advantages.[317] For example, another research team designed and synthesized a functional hydrogel by taking advantage of the cyclodextrin as a host material and a multivalent guest polymer (Figure 14C).[318] Under acidic microenvironments, pH-responsive nanoparticles can self-assemble into a bulk hydrogel through proton-driven hydrolysis of the host material, the production of a hydrophilic multivalent host compound, and the synchronous augment host−guest interactions. As proof of concept, hydrogel-transformable nanoparticles loaded with the anti-inflammatory drug dexamethasone were injected locally into a periodontitis rat model. After 21 days of treatment, the transformable nanotherapy group showed a significant reduction in bone loss on the buccal side and markedly reduced inflammatory infiltration, as confirmed by histological staining (Figure 14D).

**5.5.2. Bowel Disease.** Inflammatory bowel disease (IBD) is a representative chronic inflammatory disorder.[319,320] This disease can have a destructive impact on the GI tract and lead to a high risk of colorectal cancer if not properly managed. To date, the precise etiology of IBD remains elusive, and clinical medication primarily targets immune regulation with anti-inflammatory drugs and immunosuppressive agents.[321,322] Despite many advances that have been made, there are only a small percentage of patients who have managed to achieve sustained clinical remission. This is largely due to the high toxicity associated with cytokine inhibition, poor therapeutic efficacy, and the need for frequent dosing, which negatively impacts patient compliance.[323] Thus, alternative anti-inflammatory strategies that overcome these limitations are urgently needed for more effective IBD management.

Immunomodulatory hydrogels are promising candidates for the treatment of IBD as they can serve as reservoir of disease-associated active substances at the site of inflammation, thereby augmenting local drug availability with a high safety profile. In a typical study conducted by Tao and co-workers, oral hydrogel microbeads were designed for the in site mediatization of selenoprotein production (Figure 15A).[324] Selenoprotein is essential for immune cells and the control of inflammation. However, effective oral delivery of selenoprotein poses significant difficulty because it is a protein medication that is readily denatured or broken down in the stomach's acidic environment. In this study, the hydrogel microbeads were synthesized by coating selenium nanoparticles modified by hyaluronic acid with the calcium alginate hydrogel's protective shell (Figure 15B). The authors demonstrated that hydrogel microbeads could mediate selenoprotein production in the colon and then modulate intestinal inflammation by inhibiting the secretion of proinflammatory cytokines, lowering neutrophil and monocyte counts, and raising immune Treg cell levels. Additionally, HA-Se could optimize the composition of the gut microbiota by boosting probiotic populations and suppressing harmful bacterial communities (Figure 15C).

As mentioned above, intestinal immune homeostasis and the polymicrobial microenvironment are key contributors to the pathogenesis and progression of IBD.[325,326] Compared to the general population, patients with IBD are more susceptible to anxiety, depression, and other psychiatric illnesses. In another study, Zhou et al. designed microalgae-based hydrogels to modulate gut immunity and reduce associated anxiety and depression.[327] These microalgae-based hydrogels were obtained from the integration of *Spirulina platensis* and the rhein hydrogel (Figure 15D). The microalgae-loaded hydrogels could be administered to colitic mice via enema, and it was found that this system neutralized proinflammatory cytokines and promoted the M2-mediated immune response, providing a strong antibacterial effect. In a dextran sulfate sodium (DSS)-induced colitis mouse model, the colon-targeted hydrogel nanoparticles demonstrated significant therapeutic effects by regulating intestinal inflammation, altering flora composition, and facilitating tissue repair. Moreover, microalgae-based hydrogels dramatically alleviated anxiety- and depression-like behaviors (Figure 15D).

**5.5.3. Myocardial Infarction.** MI, a common ischemic heart disease characterized by occluded coronary arteries, brings millions of mortalities and disabilities worldwide.[328,329] Once MI occurs, a series of complex inflammatory cascades take place in the myocardium, including the early stage polarization of monocytes and the subsequent reduction in inflammatory cytokines, growth factors, and chemokines during the reparative phase. Especially, macrophages undergo a transformation from the pro-inflammatory-type M1 phenotype into the anti-inflammatory-type M2 phenotype, which promotes myocardium tissue regeneration.[330,331] Whereas, excessive and prolonged inflammatory responses can result in abnormal healing and ventricular remodeling.[332,333] In this regard,


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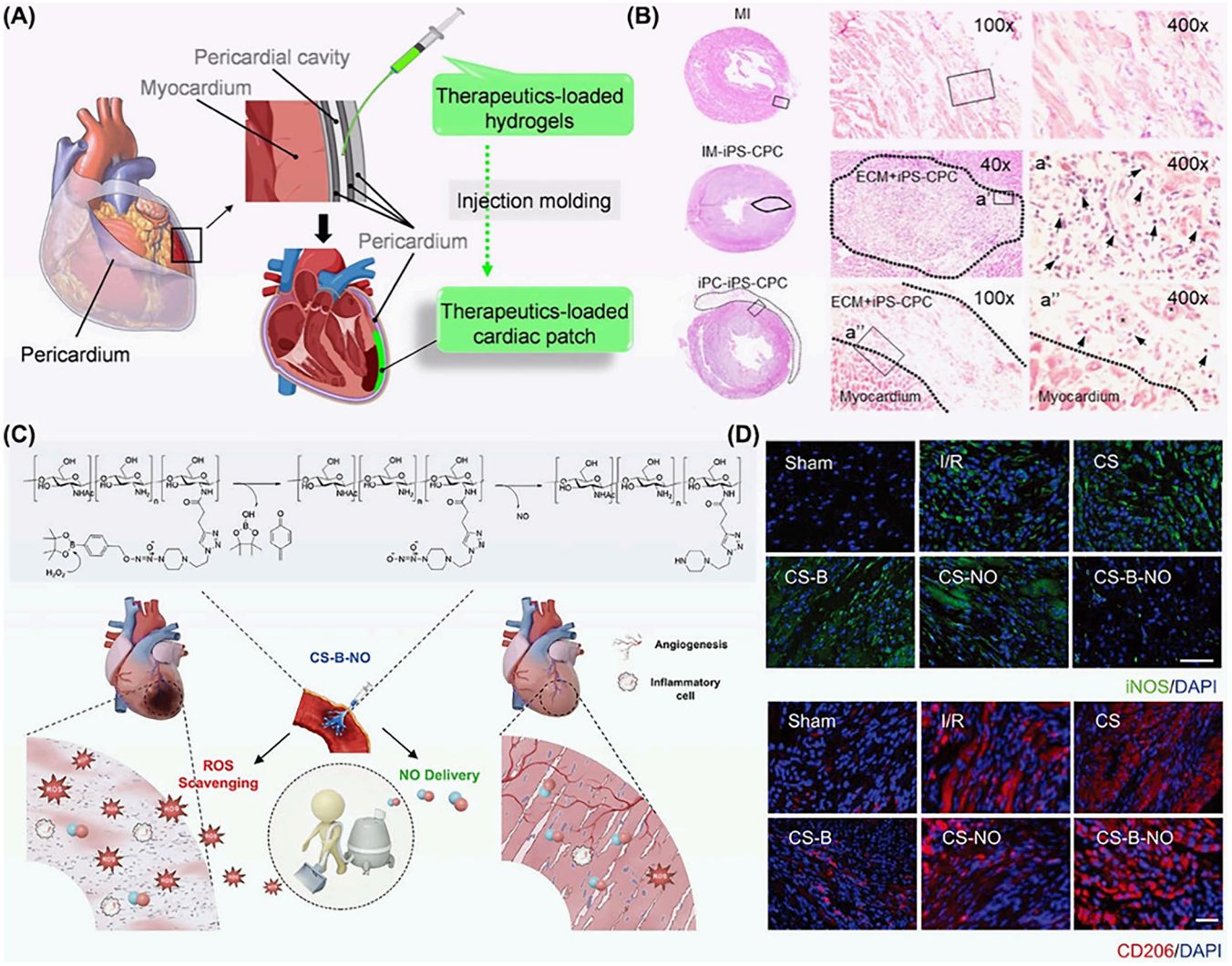


**Figure 16.** (A) Schematic description of intrapericardial injection of hydrogel and in situ construction of cardiac patch. (B) Representative histological sections of cardiac tissue stained by H&E demonstrating the formation of a cardiac patch. Reproduced with permission from ref 338. Copyright 2021 Springer Nature under a Creative Commons Attribution 4.0 International License. (C) Schematic representation of the preparation of CS-B-NO hydrogel and its application for treating I/R heart injury. (D) Immunofluorescence staining of iNOS (M1 macrophage) and CD206 (M2 macrophage). Reproduced with permission from ref 346. Copyright 2022 Wiley-VCH Verlag GmbH & Co under a Creative Commons Attribution 4.0 International License.

orchestrating the inflammatory response at the MI site ascends to the therapeutic efficiency of MI treatment.

There is an ever-increasing interest in utilizing immunomodulatory hydrogel-based cardiac patches to restore cardiac function following MI.[334−337] For example, Cheng et al. investigated a decellularized ECM hydrogel to deliver MSC-EVs or stem cell-derived cardiac progenitor cells for myocardial repair (Figure 16A).[338] The therapeutic hydrogel could be injected into the pericardial cavity and then in situ to form a cardiac patch. In rodent models of MI, the delivered therapeutics released from the biocompatible hydrogel could penetrate through the myocardium and mitigate the immune response (Figure 16B). Therefore, this safe and feasible intervention could greatly improve cardiac functions post-MI and was highly promising for further translation. In addition, miRNAs have been demonstrated to exert protective effects on the cardiovascular system by promoting angiogenesis, while the phagocytosis of certain micro/nanomaterials has been linked to inflammation modulation.[339,340] In view of these findings, Yang et al. synthesized an injectable hydrogel incorporating functionalized mesoporous silica nanoparticles (MSNs) loaded with microRNA-21−5p.[341] Results demonstrated that this delivery system harnessed the synergistic therapeutic efficacy of inflammation suppression and angiogenesis enhancement in a preclinical pig model.

Gas-based therapies utilizing $H_2S$, $H_2$, NO, and CO have also been explored for the management of various immune-related diseases. The delivery of anti-inflammatory gases plays a pivotal role in MI treatment.[342,343] For example, NO, a vital messenger, exerts pleiotropic effects in maintaining cardiovascular homeostasis. Evidence supports the involvement of three NO synthase (NOS) isoforms in anti-inflammatory actions, vascular activity, and vascular protection.[344,345] In addition, NO molecule can weaken the adhesion and activation of leukocytes in the injured endothelium, therefore benefiting the reduction of the overexpressed ROS and restoring the cardiac maladaptive repair.

Several NO-releasing hydrogels have been fabricated for controlled NO delivery in MI treatment. For example, Zhao et al. proposed a hydrogel simultaneously embodied with NO-generation and ROS-capture properties (Figure 16C).[346] This


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hydrogel was prepared from chitosan grafted with boronate-protected diazeniumdiolate (CS-B-NO). The engineered hydrogel could produce NO triggered by ROS input and thus regulate ROS/NO disequilibrium, leading to the inhibition of oxidative stress and the inflammatory response (Figure 16D). In vivo investigations validated that administration of CS-B-NO could reduce cardiac damage, promote cardiac remodeling, and restore cardiac function in a mouse model of MI.

## 6. CONCLUSIONS AND FUTURE PERSPECTIVES

Recent extensive exploration and in-depth understanding of the human immune system have driven researchers to harness this vital system for the prevention and treatment of many diseases.[347,348] With the concurrent advances in immunology, biochemistry, materials science, and therapeutic methodology, the development of immunomodulatory biomaterials has been progressing steadily and aims to regulate spatiotemporal behaviors of the immune system in the biological milieu.[349,350] As one of the most unique biomaterials, immunomodulatory hydrogels open a novel avenue for countering numerous and diverse immune-related disorders, offering enormous opportunities for guarding human health.[351,352] In this review, we first introduce the immune system to better understand the relationship between biomaterials and the immune network. Subsequently, the fundamental design principles of hydrogels for immunomodulatory agent release are summarized. Furthermore, we systematically and comprehensively introduce the advanced "hitchhiking" strategies employed in the construction of immunomodulatory hydrogels, and recent progress on immunomodulatory hydrogels for defending against a variety of immune-related disorders is systematically summarized.

Despite these advancements, up to now, there are still some unsettled challenges associated with the clinical use of immunomodulatory hydrogels. The biosafety of immunomodulatory hydrogels remains a critical concern in their practical application.[106,353] Hydrogels endowed with immunoregulatory capabilities hold great promise, yet their potential for cytotoxicity necessitates careful evaluation. For instance, immunomodulatory hydrogels have emerged as a potent strategy for tumor therapy by enhancing the patient's immune response. While this approach circumvents the widespread damage associated with conventional chemotherapy and radiotherapy, it may still induce off-target effects in surrounding healthy tissues. Importantly, only a limited subset of patients experiences substantial benefits from immunotherapy, and the risk of severe immune-related adverse events must not be overlooked in light of the anticipated therapeutic benefits.[352] Therefore, the application of immunomodulatory hydrogels in immunotherapy presents a double-edged sword. While these hydrogels can potentiate immune responses, their close interaction with the immune system necessitates rigorous evaluation of their immunotoxicity. The development of standardized methodologies to assess the potential immunotoxicity of hydrogels is critical for ensuring safety and efficacy. In addition, several key challenges remain, including inefficient clearance from the body, unintended interference with intracellular signaling pathways, and the risk of triggering undesired inflammatory responses. These factors pose substantial barriers to the translation of immunomodulatory hydrogels from preclinical studies to clinical practice and must be systematically addressed to advance their therapeutic potential.

The immunomodulatory capabilities of hydrogels are highly associated with their chemical composition and can be influenced by their structural and compositional features. Nevertheless, batch-to-batch diversity in terms of molecular weight and architecture of polymeric hydrogels may inevitably create obstacles for clinical translation.[354] From an immunological standpoint, immunomodulatory biomaterials employ a multitude of interactions between innate and adaptive immunity that work together throughout the whole body. The pathological environment of an individual is complex, variable, and heterogeneous. Hence, predictions cannot be made from the treatment effect due to the variations of immunomodulatory hydrogel formulation as well as the heterogeneous immune response among patients.

Another important consideration to take note of is that the mechanisms by which immunomodulatory hydrogels interact with the immune system are not yet fully understood. A deeper understanding of the interactions between biomaterials and immune pathways is essential for developing hydrogels that can effectively modulate immune cell behavior or promote biomaterial-tissue integration. Meanwhile, immunomodulatory hydrogels have achieved enormous improvements in guarding human health, however, the majority of immunotherapy-related studies have relied on in vitro models or animal testing before progressing to human applications. Despite the positive outcomes in these models, the development of in vitro systems that more accurately mimic human immune responses remains a significant challenge, hindering the rapid advancement of clinical applications.

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### Notes

The authors declare no competing financial interest.



https://doi.org/10.1021/acs.chemrev.4c00923
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## Biographies

Yue Zhao received her Ph.D. degree in polymeric chemistry and physics under the supervision of Prof. Quan Lin at the State Key Laboratory of Supramolecular Structure and Materials, Jilin University. She is currently a postdoctoral scholar and works with Prof. Yanli Zhao. Her research is centered on design, preparation, and biological application of biomimetic intelligent polymer hydrogel materials.

Shanliang Song obtained his Ph.D. degree in polymeric chemistry and physics, supervised by Prof. Quan Lin at the State Key Laboratory of Supramolecular Structure and Materials, Jilin University. Subsequently, he pursued postdoctoral research at the Center for AIE Research at Shenzhen University under the mentorship of Profs. Dong Wang and Ben Zhong Tang. Currently, he serves as a postdoctoral scholar in the group of Prof. Bin Liu at the National University of Singapore. His primary research focus is on designing and developing NIR-II aggregation-induced emission probes and photosensitizers for applications in surgical navigation and photodiagnosis, and therapy of tumors.

Junmin Zhang received his Ph.D. in Organic Chemistry from Sun Yat-sen University (P. R. China) in 2010. He then underwent a postdoctoral training in Nanyang Technological University (Singapore) from 2010 to 2014. From March 2014 until now, he is an associate professor and group leader of chemistry in Shenzhen University (P. R. China). His research interests include green organic synthesis & catalysis, asymmetric synthesis, functional materials and applications.

Xiangzhong Ren received the master's degree from National University of Defense Technology in 1998 and the Ph.D. degree from Sichuan University in 2007. He was appointed as a full professor at the College of Chemistry and Environmental Engineering in Shenzhen University in 2009. His research interests include the cathode and anode materials of lithium-ion batteries, nanocatalysts of metal-air battery, nanocomposites, and their related properties.

Yanli Zhao is currently the Lee Soo Ying Professor at the School of Chemistry, Chemical Engineering and Biotechnology in Nanyang Technological University, Singapore. His research is focused on the development of integrated systems for diagnostics and therapeutics, as well as porous materials for energy storage and catalysis.

## ACKNOWLEDGMENTS

This research work was supported by the National Natural Science Foundation of China (22105131), the Guangdong Basic and Applied Basic Research Foundation (2022A1515011677), and the Singapore National Research Foundation under Its Competitive Research Programme (NRF-CRP26-2021-0002).

## ABBREVIATIONS

2D, two-dimensional; ACE2, angiotensin converting enzyme 2; ACT, Adoptive cell therapy; AKI, acute kidney injury; APCs, antigen-presenting cells; BMSCs, bone marrow mesenchymal stem cells; BMP-2, bone morphogenetic protein 2; CAR-T, chimeric antigen receptor T; CAT, catalase; CS-B-NO, chitosan grafted with boronate-protected diazeniumdiolate; CO, carbon monoxide; Con A, concanavalin A; COVID-19, coronavirus disease 2019; CPO, chloroperoxidase; CTLA-4, clinical T-lymphocyte-associated protein-4; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; DFUs, diabetic foot ulcers; DIC, diclofenac; DSS, dextran sulfate sodium; ECM, extracellular matrix; EVs, extracellular vesicles; FAPi, fibroblast activating protein inhibitor; GA, glycyrrhizic acid; G5-GBA, guanidinobenzoic acid-modified generation 5-polyamidoamine; GCs, germinal centers; GelMA, gelatin-methacryloyl; GI, gastrointestinal; GO, graphene oxide; GOx, glucose oxidase; HA, hyaluronic acid; $H_2$, hydrogen; $H_2O_2$, hydrogen peroxide; $H_2S$, hydrogen sulfide; HSCs, hematopoietic stem cells; hMSCs, human mesenchymal stem cells; IFN-$\gamma$, interferon-$\gamma$; IBD, inflammatory bowel disease; IL, Interleukin; LCST, lower critical solution temperature; LbL, layer-by-layer; L. lactis, living Lactococcus; MI, myocardial infarction; MHC, major histocompatibility complex; $MnO_2$, manganese dioxide; MMP, matrix metallopeptidase; MOFs, metal−organic frameworks; $MoS_2$, molybdenum disulfide; MSNs, mesoporous silica nanoparticles; NIR, near-infrared; NO, nitric oxide; NOE, nitric oxide-eluting; NOS, NO synthase; NOD, nonobese diabetic; NSAID, nonsteroidal anti-inflammatory drug; NSCs, neural stem cells; OA, osteoarthritis; OD, oxidized dextran; PAMPs, pathogen-associated molecular patterns; PBA, phenylboronic acid; PBA−PEI, phenylboronic acid-modified poly(ethylene imine); PCL, polycaprolactone; PNIPAM, poly(*N*-isopropylacrylamide); PNP, polymer−nanoparticle; PVA, poly(vinyl alcohol); RBD, receptor-binding domain; RA, rheumatoid arthritis; RIT, radioisotope therapy; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAON, steroid-associated osteonecrosis; SCI, spinal cord injury; SF, silk fibroin; SIRP$\alpha$, signal regulatory protein $\alpha$; $^1O_2$, singlet oxygen; siRNA, small interfering RNA; SOD, superoxide dismutase; T1D, Type 1 diabetes; TDNT, telodendrimer nanotrap; TGF-$\beta$, transforming growth factor-$\beta$; TNF-$\alpha$, tumor necrosis factor-$\alpha$; Tregs, regulatory T cells; UCST, upper critical solution temperature; UV, ultraviolet; VEGF, vascular endothelial growth factor; •OH, hydroxyl radical; $O_2^{-\bullet}$, superoxide anion

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