CHEMICAL REVIEWS

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Therapeutic Hydrogels: Properties and Biomedical Applications

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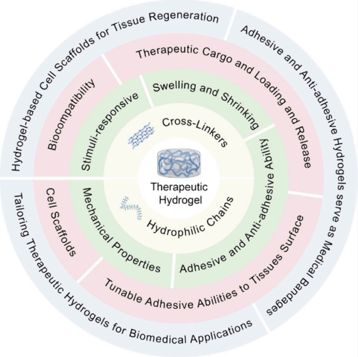
ABSTRACT: Hydrogels have emerged as versatile therapeutic platforms with immense potential for treating various diseases, due to their tunable properties and biocompatibility. Recent innovations, including injectable, self-assembling, and bioadhesive hydrogels, have broadened their biomedical applications, driven by advancements in materials chemistry. This review systematically examines the role of chemical principles in designing and customizing therapeutic hydrogels, with a focus on hydrogelation mechanisms, swelling ratios, mechanical properties, and biological interactions. By highlighting key studies in this field, this review explores how chemical chain modifications, cross-linking strategies, and cargo delivery systems have been tailored to achieve diverse functions, such as drug depots, wound dressings, antiadhesive barriers, and regenerative scaffolds. Addressing the gap in comprehensive analyses, this review underscores the integration of chemical design principles to optimize hydrogel properties for targeted therapies and discusses future opportunities to advance therapeutic hydrogel technology for a wide range of biomedical applications.



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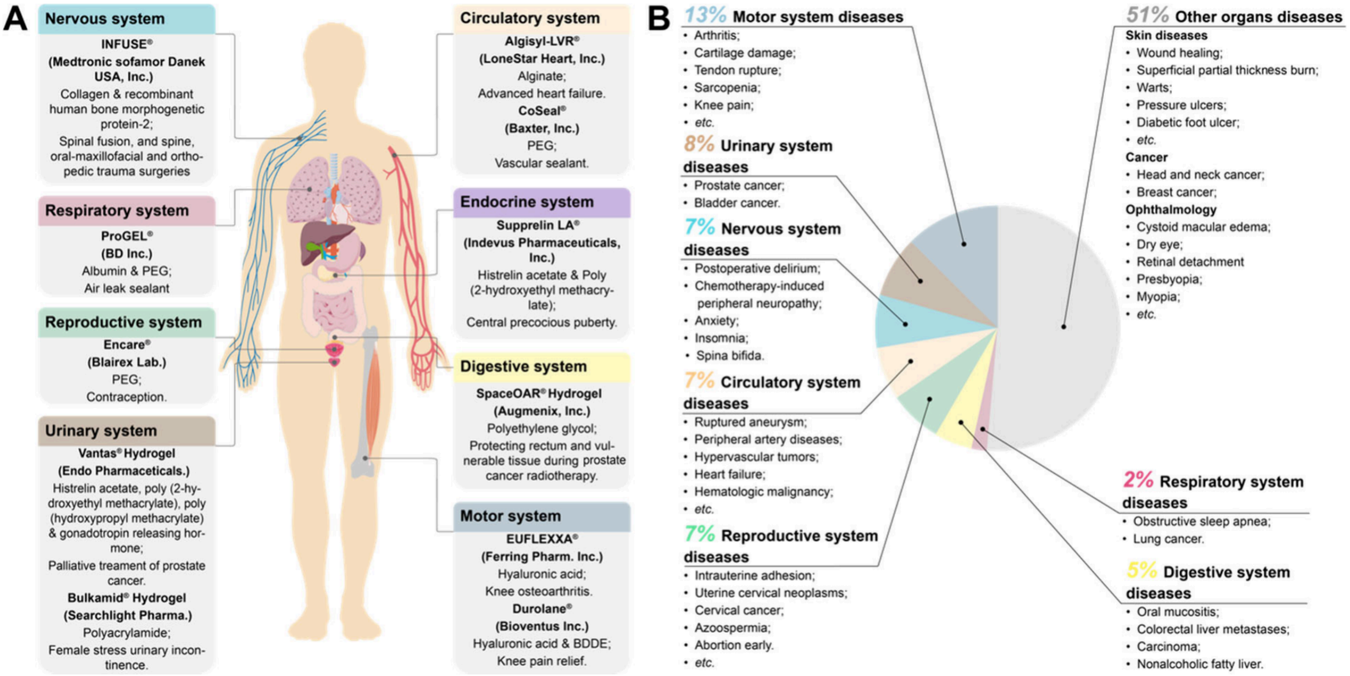

Figure 1. Development of therapeutic hydrogels for various diseases. Schematic illustration of (A) representative hydrogel-based products approved by the FDA and used across eight human physiological systems (Data source https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm) and (B) therapeutic hydrogels currently undergoing clinical trials for different disease treatments. (Data source: https://clinicaltrials.gov, searched using the term "hydrogel". Data were collected in Feb 2025).

1. INTRODUCTION

Hydrogels, composed of three-dimensional cross-linked polymeric networks, have emerged as transformative platforms in modern biomedical science, offering immense therapeutic potential.[1,2] With their intrinsic properties, including exceptional biocompatibility, adjustable mechanical characteristics, and responsiveness to various physiological stimuli, hydrogels have been widely applied in treating diverse diseases.[3,4] Approved by the FDA for use as therapeutic carriers and Class I to III medical devices (Figure 1A), hydrogels have demonstrated remarkable versatility in medical applications, ranging from localized drug delivery and wound care to tissue regeneration and bioadhesive interventions.[5,6] Moreover, their clinical significance is underscored by over 80 active clinical trials investigating their potential for addressing a wide array of medical conditions (Figure 1B and Figure 2, Tables 1-2).[7]

The broad therapeutic applicability of hydrogels is intrinsically linked to their ability to be tailored for specific medical purposes. Materials chemistry, a rapidly evolving branch of materials science, plays a pivotal role in this customization process. By strategically manipulating chemical components, chemical design principles enable the development of materials with tailored functions, making them ideally suited for advancing hydrogel technology.[8−12] As hydrophilic polymeric constructs, therapeutic hydrogels embody the synergy between materials chemistry and biomedical engineering. This interdisciplinary approach enables meticulous tuning of essential features, including mechanical properties, swelling dynamics,

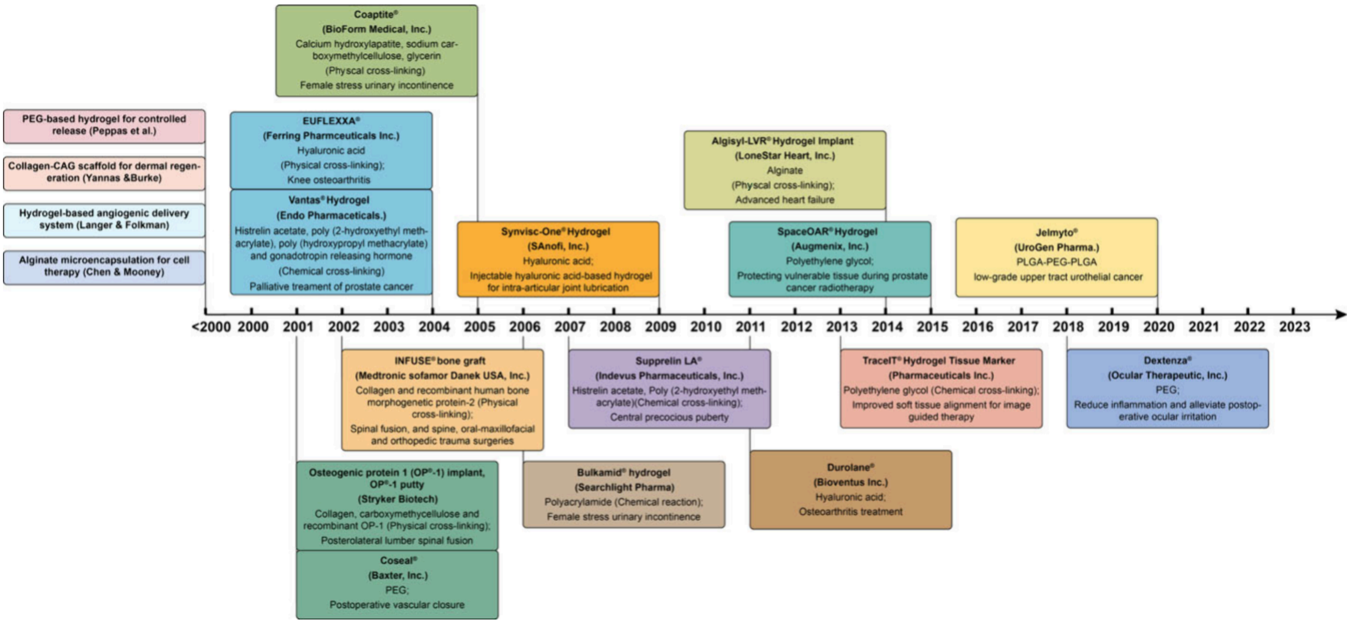

Figure 2. Timeline of hydrogel products approved for clinical use. Key clinical milestones of hydrogel-based medical products approved between 2000 and 2023. Each colored block represents a distinct product, annotated with its material composition, cross-linking strategy, therapeutic indication, and company. This timeline illustrates the evolution of hydrogel technologies from early physical gels to chemically cross-linked systems and highlights diverse applications across orthopedics, urology, oncology, and ophthalmology.

Table 1. Representative FDA-Approved Hydrogel-Based Medical Products and Their Biomedical Applications

Approval Year	Product Name	Manufacturer	Application	Indication	Key Features
1996	Seprafilm	Baxter	Adhesion prevention	Postsurgical adhesion prevention	Hyaluronic acid—based hydrogel
1997	Regranex	Smith & Nephew	Wound healing	Diabetic foot ulcers	Platelet-derived growth factor in hydrogel
1999	Floseal	Baxter	Hemostasis	Surgical bleeding control	Gelatin-thrombin matrix
2000	Gelclair	EUSA Pharma	Oral care	Oral mucositis	Bioadhesive hydrogel for pain relief
2001	Cosseal	Baxter	Surgical sealant	Prevention of leakage in vascular surgery	Synthetic hydrogel sealant
2005	DuraSeal	Integra LifeSciences	Surgical sealant	Dural closure in neurosurgery	Absorbable hydrogel sealant
2009	SynviscOne	Sanofi	Regenerative medicine	Osteoarthritis pain relief	Viscosupplementation with hyaluronic acid
2009	ProGel	Neomend	Surgical sealant	Lung surgery air leak prevention	Polyethylene glycol-based hydrogel
2011	Durolane	Bioventus	Regenerative medicine	Osteoarthritis joint pain	Hyaluronic acid—based injectable hydrogel
2013	TracelTHydrogel Tissue Marker	Pharmaceutical Inc.	Tissue regeneration	Image-guided therapy	PEG
2014	Algisy-LVRHydrogel Implant	LoneStar Heart Inc.	Heart diseases	Advanced heart failure	Alginate
2015	SpaceOAR Hydrogel	Augmenix Inc.	Cancer radiotherapy	Protecting vulnerable tissue	PEG
2018	Dextenza	Ocular therapeutic Inc.	Anti-inflammation	Alleviate postoperative ocular irritation	PEG
2020	Jelmyto	UroGen Pharma.	Urothelial cancer	Cancer therapy	PLGA—PEG-PLGA

degradation kinetics, and bioactivity, to meet a broad range of therapeutic requirements.[13−21]

To bridge this gap, this review presents an in-depth summary of recent advancements in the biomedical use of therapeutic hydrogels. It explores key principles underlying hydrogel property manipulation, with a particular focus on hydrogelation mechanisms, swelling ratios, mechanical properties, and biological interactions. By summarizing both recent and earlier representative advancements, this review highlights how chemical design principles have been leveraged to achieve specific medical functions. Moreover, it identifies the guiding methodologies and mechanisms that have driven these innovations, offering insights into future opportunities and challenges in advancing hydrogel technology.

By systematically summarizing these advancements, this review highlights the strategic role of materials chemistry in optimizing therapeutic hydrogels. It not only elucidates the design rationale and medical applications of these materials but also provides a roadmap for future research and development. This comprehensive analysis will serve as a valuable resource for the material science, medical, and chemical communities, fostering continued exploration and innovation in the rapidly growing domain of therapeutic hydrogels in diverse biomedical applications.

2. BASIC COMPONENTS OF HYDROGELS

According to the literature, various forms of therapeutic hydrogels have been developed to achieve a broad medical applications, such as shear-thinning hydrogels for local injection,[22−27] adhesive hydrogels for injury sealing,[28] and mechanically supportive hydrogels for tendon repair[29] (Figure 3A). Despite the diverse characteristics of these therapeutic hydrogels, including swelling ratio, mechanical properties, degradation ability, and cargo-loading capacity, the fundamental building blocks remain the same: polymer chains and cross-linkers (Figure 3B).[30] This suggests that specific principles govern the combination of these basic elements to achieve unique medical functions within hydrogels, which fall under the domain of materials chemistry.[31]

Understanding the properties of these fundamental elements is essential for designing therapeutic hydrogels. As the primary structural component, selecting appropriate hydrophilic polymeric chains is a key consideration. These chains can be categorized into natural polymer chains (e.g., alginate, dextran, and chitosan) and synthetic polymeric chains (e.g., poly(vinyl alcohol) (PVA), poly(ethylene glycol) (PEG), and poly(*N*-isopropylacrylamide) (PNIPAAm)).[32,33] Modifying the chemical structure of polymeric chains allows for precise regulation of hydrogel properties; for instance, such as tethering NIPAAm or carboxyl groups into polymeric chains can impart thermal or pH sensitivity, respectively.[34] As the other key constituent of hydrogels, cross-linkers are generally categorized as either covalent or supramolecular.[34,35] The choice of cross-linker determines several key factors, including hydrogelation conditions (e.g., "click-chemistry" cross-linkers enable *in situ* gelatinized hydrogels), mechanical properties (e.g., supramolecular cross-linkers contribute to shear-thinning and self-healing abilities), and responsiveness to specific microenvironments (e.g., reactive oxygen species (ROS), pH, and enzyme).[36,37] Given the interplay between these fundamental components and the diverse medical functionalities of therapeutic hydrogels, materials chemistry plays a crucial role in uncovering the underlying principles governing their design and in rationally tailoring hydrogels for specific therapeutic applications.

2.1. Hydrophilic Chain

2.1.1. Polymeric Chain. *2.1.1.1. Natural Polymeric Chain.* Natural polymeric chains commonly used in hydrogels can be categorized into (i) polysaccharide-based chains, including chitosan, alginate, carrageenan, hyaluronic acid, starch, cellulose, and agarose, and (ii) protein-based hydrophilic chains, including silk fibroin, keratin, and collagen. Derived from natural sources, these hydrogels typically exhibit excellent biocompatibility.

Polysaccharides, as natural polymers of saccharide units connected via glycosidic bonds, display diverse structures ranging from linear chains to complex branched forms.[38] Derived from diverse natural sources, these macromolecules can be classified as homopolysaccharides or heteropolysaccharides, depending on the uniformity of their monosaccharide units.[39] The structural heterogeneity and abundant hydrophilic groups of polysaccharides allow them to absorb water and form hydrogels through chemical or physical cross-linking[40] (Figure 4A).

Derived from chitin through deacetylation, chitosan is a biocompatible, polycationic biopolymer that has become fundamental to hydrogel fabrication for its distinctive structure and versatile functionality.[41] Composed of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose units, chitosan's molecular structure offers abundant opportunities for chemical modification and functionalization.[42] These features enable the formation of hydrogels through covalent, ionic, and physical cross-linking strategies, allowing for tailored biomedical and industrial needs.

Similarly, alginate, a hydrophilic polysaccharide composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, is widely recognized for its biocompatibility, biodegradability, and structural versatility.[43] Extracted from brown algae or synthesized by bacteria such as *Azotobacter* and *Pseudomonas*, alginate's block structure enables selective interactions with divalent cations, such as Ca^{2+}, particularly at G blocks.[44] These interactions enable the formation of stable hydrogels under mild conditions, preserving the bioactivity of encapsulated molecules.

Derived from marine red algae, agarose is a biocompatible polysaccharide commonly employed in hydrogels for its excellent water absorption and resemblance to the extracellular matrix.[45] Composed of 3-linked β-D-galactopyranose and 4-linked 3,6-anhydro-α-L-galactopyranose residues, agarose forms thermoreversible gels via hydrogen bonding, eliminating the need for external cross-linking agents. Its pH-responsive properties, attributed to ionizable groups, further enhance its versatility.[46] Agarose hydrogels can be tailored through copolymerization with acrylic monomers or blending with xanthan to optimize mechanical strength and hydration properties.

Similarly, carrageenan, a sulfated polysaccharide, is highly adaptable for chemical modifications such as oxidation, carboxymethylation, methylation, and acetylation, which enhance its physicochemical properties.[47] Carrageenan hydrogels can be formed through thermos-reversible gelation, ionic cross-linking with cations like K^+ and Ca^{2+}, or photo-cross-linking using methacrylate-functionalized backbones.[48] Such strategies allow hydrogels to be engineered with customized mechanical strength and swelling characteristics.

Hyaluronic acid, a nonsulfated glycosaminoglycan, consists of repeating D-glucuronic acid and N-acetyl-D-glucosamine units linked by alternating β-1,4 and β-1,3 glycosidic bonds.[49] Renowned for its exceptional biocompatibility and biodegradability, it is widely utilized in biomedical fields. To enhance its mechanical strength and enzymatic stability, cross-linking strategies target its carboxylic (−COOH) and hydroxyl (−OH) groups using agents like methacrylic anhydride or divinyl sulfone.[50]

Starch, a plant-derived polysaccharide composed of glucose units linked by α-D-(1→4) and α-D-(1→6) glycosidic bonds, comprises two structural components: amylose and amylopectin.[51] Extracted from sources such as corn and potato, starch undergoes a gelatinization-retrogradation process during hydrogel formation, wherein heating and cooling reorganize its polymer network. Chemical modifications, such as grafting with vinyl monomers or introducing ionic groups, further enhance its physicochemical properties.[52]

Finally, cellulose, a naturally abundant polymer composed of β(1→4)-linked anhydro glucose units, is renowned for its biocompatibility, biodegradability, and mechanical robustness.

Table 2. Active Clinical Trials (2022–2025) on Therapeutic Hydrogels for Biomedical Applications

NCT	Study Title	Study Status	Conditions	Interventions	*Start Date*
NCT06839222	Knee OsteoArthritis Long-term Assessment	NOT_YET_RECRUITING	Knee Osteoarthritis (Knee OA)	DEVICE: Hydrogel OA 2%	2025-04
NCT06839716	Comparison of Ropivacaine-Poloxamer 407 Hydrogel and TAP Block for Postoperative Pain Management in Laparoscopic/Robotic Gastrectomy	RECRUITING	Gastric Cancer	PROCEDURE: Arm I (Ropivacaine-Poloxamer 407 hydrogel group)| PROCEDURE: Arm II (TAP block group)	2025-02-01
NCT06828978	Clinical and Radiographic Success Following Regenerative Pulpotomy Using Chitosan Hydrogel Versus Platelet Rich Fibrin in Mature Mandibular Molars	NOT_YET_RECRUITING	Regenerative Pulpotomy for Symptomatic Pulpitis of Mandibular Permanent Molars With Mature Apices	PROCEDURE: Full Pulpotomy	2025-Feb
NCT06826898	To Evaluate the Effectiveness of the Use of a Novel Cross-linking Hyaluronan Hydrogel on the Prevention of the Adhesion Occurrence After Anterior Talofibular Ligament Repair Surgery	RECRUITING	Anterior Talofibular Ligament Injury	DEVICE: DEFEHERE Absorbable Adhesion Barrier| DEVICE: Sham (No Treatment)	2025-03-01
NCT06778057	Clinical Performance of Three Daily Disposable Silicone Hydrogel Contact Lenses	RECRUITING	Visual Acuity	DEVICE: Test Lens 1| DEVICE: Test Lens 2| DEVICE: Test Lens 3	2024-12-29
NCT06748404	TriCalm Hydrogel in the Treatment of Immunotherapy-Related Pruritus	RECRUITING	Immunotherapy-related Pruritus	DRUG: Tricalm Hydrogel| DRUG: Triamcinolone acetonide 0.1% cream	2025-01-31
NCT06740123	Evaluation of Hydrogel Application in the Treatment of Periodontitis and Peri-implantitis	ACTIVE_NOT_RECRUITING	Periodontal Disease Stage 2| Peri-Implantitis and Peri-implant Mucositis| Periodontal Regeneration	PROCEDURE: Nonsurgical periodontal treatment and application of H42 hydrogel to the peri-implant pocket| PROCEDURE: Nonsurgical periodontal treatment of periodontal pocket| PROCEDURE: Nonsurgical periodontal treatment and application of H42 hydrogel to the periodontal pocket| PROCEDURE: Nonsurgical periodontal treatment of peri-implant pocket	2024-06-01
NCT06719089	Evaluation of the Safety and Performance of the Hydrusten Biodegradable Hydrogel Ureteral Stent	NOT_YET_RECRUITING	Urinary Lithiasis	DEVICE: Biodegradable double loop ureteral stent| DEVICE: PolyUrethane Double Loop Ureteral Stent	2025-02-01
NCT06716372	A Clinical Trial to Evaluate the Vision Correction Safety and Efficacy of DSiHy Silicone Hydrogel Soft Contact Lens	RECRUITING	Myopia| Refractive Errors	DEVICE: DSiHy Silicone Hydrogel Soft Contact Lens| DEVICE: Daily Silicone Hydrogel Contact Lenses (oB)	2024-10-07
NCT06716385	A Clinical Trial to Evaluate the Vision Correction Safety and Efficacy of MSiHy Silicone Hydrogel Soft Contact Lens	RECRUITING	Myopia| Refractive Errors	DEVICE: MSiHy Silicone Hydrogel Soft Contact Lens| DEVICE: Monthly Silicone Hydrogel Contact Lenses (oA)	2024-10-09
NCT06709612	Postsurgical Analgesia After Hernia Repair	NOT_YET_RECRUITING	Hernia| Hernia, Abdominal	DRUG: AMT-143 hydrogel containing ropivacaine| DRUG: Ropivacaine| OTHER: Placebo	2025-01-27
NCT06634719	Juveena Hydrogel System Feasibility Study for Heavy Menstrual Bleeding (HMB)	RECRUITING	Heavy Menstrual Bleeding	DEVICE: Juveena Hydrogel System	2025-02-01
NCT06584617	The Purpose of This Study is to Assess Clinical Efficacy and Safety of Berovena Intended to Promote Treatment and to Expedite Chronic Diabetic Foot Ulcer Healing	RECRUITING	Diabetic Foot Ulcer	DEVICE: Berovena| DEVICE: NU-GEL Hydrogel with Alginate	2023-05-17
NCT06558240	To Explore the Effectiveness and Feasibility of HERADERM Hydrogel Wound Dressing on Caesarean Section Surgical Site	RECRUITING	Cesarean Section| Surgical Wound|	DEVICE: HERADERM Hydrogel Wound Dressing (Sterile)	2024-Aug

Table 2. continued

NCT	Study Title	Study Status	Conditions	Interventions	*Start Date*
			Surgical Wound Infection| Wounds and Injuries		
NCT06552611	Noninvasive Electrical Spinal Cord Stimulation To Restore Upper Extremity Function in Multiple Sclerosis	RECRUITING	Multiple Sclerosis	COMBINATION_PRODUCT: Transcutaneous electrical spinal cord stimulation + therapy| OTHER: Occupational Therapy	2024-08-08
NCT06551766	The Application of Photosensitive Hydrogel in Intranasal Endoscopic Dacryocystorhinostomy	RECRUITING	Chronic Dacryocystitis	DEVICE: Photosensitive hydrogel| DEVICE: 6-0 absorbable stitches	2023-03-01
NCT06544200	Intraoperative Air Leak Management After Minimally Invasive Lung Segmental Resection	RECRUITING	Lung Cancer Stage I| Lung; Node| Air Leak From Lung	DEVICE: Polymeric Hydrogel Matrix	2023-07-15
NCT06542757	Evaluation of Tumor Control Based on Serial Multiparametric MRI and Post-Treatment Biopsies For Patients Treated With Dose Intensification to the Dominant Intra-Prostatic Lesion (DIL) Using Ultra-Hypofractionated, MR-Guided Radiotherapy	NOT_YET_RECRUITING	Prostate Cancer	RADIATION: 1.5 T Elekta Unity MR-Linac system| DEVICE: Hydrogel rectal spacer (SpaceOAR)	2024-08-12
NCT06530017	Clinical Trial to Evaluate the Ingested, Space Occupying Hydrogel Capsules for Simple Obesity Treatment	NOT_YET_RECRUITING	Simple Obesity	DEVICE: Ingested, Space Occupying hydrogel capsules| DEVICE: placebo	2024-07-31
NCT06508151	Neovaginoplasty Using Photoinduced-imine-cross-link Hydrogel in MRKH Patients	NOT_YET_RECRUITING	Mayer Rokitansky Kuster Hauser Syndrome	PROCEDURE: neovaginoplasty and vaginal mold spreaded with photoinduced-imine-cross-link hydrogel| PROCEDURE: neovaginoplasty and vaginal mold	2024-08-01
NCT06492811	Efficacy and Safety of a Hydrogel Containing Cascade Catalytic Enzymes in the Treatment of Diabetic Wounds	ACTIVE_NOT_RECRUITING	Diabetic Wound	DRUG: GAT@F nanoenzyme hydrogel complex	2024-04-01
NCT06469736	Comparison Between Ureterorenoscopy with Lithotripsy Alone Versus Combination with Hydrogel for Kidney Stone Removal	RECRUITING	Nephrolithiasis| Lithotripsy, Laser| Ureteroscopy	PROCEDURE: Standard of Care Ureterorenoscopy| PROCEDURE: Standard of Care Ureterorenoscopy with MediNiK	2024-07-01
NCT06451614	SpaceIT Hydrogel System for Perirectal Spacing	RECRUITING	Prostate Cancer	DEVICE: SpaceIT Hydrogel System| DEVICE: Commercially available Boston Scientific Spacer	2024-10-30
NCT06447311	Assessing the Clinical Efficacy of Hyaluronic Acid Hydrogel in Papilla Augmentation: A Clinical Study.	RECRUITING	Gingival Destruction	OTHER: Hyaluronic acid gel	2023-04-10
NCT06445699	Photodynamic Therapy With Hydrogel Dressing for Chronic Wounds	RECRUITING	Photodynamic Therapy	OTHER: Photodynamic therapy| OTHER: Hydrogel dressing	2023-01-01
NCT06433284	Comparative Study of Decellularized Human Amniotic Membrane Hydrogel and Inverted Internal Limiting Membrane Flap in Idiopathic Large Macular Holes	NOT_YET_RECRUITING	Macular Holes	PROCEDURE: 25-gauge pars plana vitrectomy with inverted flap technique and SF6 tamponade| PROCEDURE: 25-gauge pars plana vitrectomy with complete internal limiting membrane peeling with amniotic membrane hydrogel filling and SF6 tamponade	2025-01-01
NCT06421454	Clinical Trial for the Evaluation of Melatonin in the Treatment of Pressure Ulcers	NOT_YET_RECRUITING	Pressure Ulcer	DRUG: Melatonin| DRUG: Hydrogel	2024-09-01
NCT06135259	Topical Erythropoietin Hydrogel in Management of Oral Lichen Planus	NOT_YET_RECRUITING	Oral Lichen Planus	DRUG: erythropoietin| DRUG: Triamcinolone acetonide	2024-05-20
NCT06084546	Geko, KM40C Hydrogel Skin Adhesion Trial (XW-3)	NOT_YET_RECRUITING	Leg Ulcer	DEVICE: geko, X-W3	2023-Dec
NCT06039774	Mangostin Hydrogel Film With Chitosan Alginate Base for Recurrent Aphthous Stomatitis (RAS)	RECRUITING	Recurrent Aphthous Stomatitis	DRUG: Mangostin Hydrogel Film With Chitosan Alginate Base|	2023-12-04

Table 2. continued

NCT	Study Title	Study Status	Conditions	Interventions	*Start Date*
				DRUG: Placebo	
NCT06028763	Development of Biomedical Technology for the Treatment of Ankle Cartilage Using Injectable Biocomposite Hydrogel	RECRUITING	Ankle Osteoarthritis	PROCEDURE: Injection of biocomposite hydrogel into ankle's cartilage lesion under arthroscopic control| PROCEDURE: Microfracture of ankle's cartilage lesion under arthroscopic control	2023-07-01
NCT06011551	HYDRAFIL-D: HYDRogel Augmentation for Intervertebral Lumbar Discs	RECRUITING	Degenerative Disc Disease (DDD)	DEVICE: The ReGelTec HYDRAFIL, System| OTHER: Conservative Care Management	2024-Jan
NCT05967325	SVF Combined With Functional Self-assembling Peptide Nanofiber Hydrogels in the Treatment of Spinal Cord Injury	RECRUITING	Safety Issues	PROCEDURE: Stromal Vascular Fraction (SVF) combined with Functional self-assembling peptide nanofiber hydrogels	2023-07-15
NCT05902390	The Long-term Benefit of Hydrogel Spacer in Reducing Rectal Radiation Dose in Cervical Cancer Radiation Therapy	RECRUITING	Uterine Cervical Neoplasms	DEVICE: hydrogel spacer	2023-06-01
NCT05898074	Role of Novel RADA16 Hydrogel in Endoscopic Skull Base Surgery	RECRUITING	Skull Base Neoplasms| Cerebrospinal Fluid Leakage| Nasal; Hypertrophy, Mucous Membrane (Septum)	DEVICE: Non-Absorbable Packing (Silastic Splint)| DEVICE: PuraGel (RADA16) Hydrogel	2023-10-09
NCT05853224	An Interventional Study to Evaluate the Safety and Performance of Cross-linked Hyaluronic Acid Hydrogel	RECRUITING	Dermal Filler| Volume Deficiency of the Midface	DEVICE: Cross-linked Hyaluronic Acid (CLHA) Hydrogel with and without Lidocaine	2022-04-02
NCT05690906	Evaluate the Effect of ReSpace, Hydrogel on Reducing Rectal Radiation Dose in Radiotherapy for Cervical Cancer	RECRUITING	Uterine Cervical Neoplasms	DEVICE: ReSpace| DEVICE: gauze packing	2022-07-12
NCT05679232	Hydrogel Coating to Reduce Postsurgical Infection After Joint Arthroplasty	RECRUITING	Arthritis| Traumatic Arthritis| Avascular Necrosis	DEVICE: Hydrogel coating| PROCEDURE: Control	2022-12-06
NCT05597852	Using Rectal Hydrogel Spacer for Salvage SABR in Prostate Cancer	RECRUITING	Prostate Cancer	DEVICE: SpaceOAR	2021-11-30
NCT05411484	Investigation of Laser Assisted Drug Delivery of NanoDOX	ACTIVE_NOT_RECRUITING	Wounds and Injury	DRUG: NanoDO Hydrogel| DEVICE: CO2 Ablative Fractional Laser	2023-11-29
NCT05394662	Safety and Effectiveness of Juveena Hydrogel System Following TCGP At High-Risk for Intrauterine Adhesions	ACTIVE_NOT_RECRUITING	Intrauterine Adhesion	DEVICE: Juveena Hydrogel System	2022-08-11
NCT05364502	(HALT) Embrace Hydrogel Embolic System (HES) Study of Embolization in Peripheral Arterial Bleeds	RECRUITING	Arterial Bleeding in Solid Organs and Peripheral Arteries	DEVICE: Embrace HES including Instylla, Delivery Kit and Instylla, Microcatheter	2022-12-12

Its hydroxyl-rich structure promotes stable intra- and intermolecular hydrogen bonding; however, its insolubility in water and most organic solvents necessitates chemical or physical modification.[53] Cellulose derivatives, such as carboxymethyl cellulose (CMC) and methylcellulose, are commonly cross-linked with agents like epichlorohydrin or aldehydes to produce hydrogels with tunable swelling and mechanical properties. Additionally, hybrid hydrogels incorporating cellulose with polymers like chitosan or alginate, exhibit enhanced mechanical strength and functionality.[53]

Proteins, naturally occurring macromolecules composed of amino acid residues linked by peptide bonds, are defined by their unique sequences encoded in genetic materials.[54] Due to their complex structures, proteins are typically isolated from natural sources. Their hydrophilic functional groups enable water binding, making them ideal candidates for hydrogel formation. As a result, protein-based hydrogels are highly water-absorbent, supporting diverse biomedical applications (Figure 4B).

Silk fibroin, a natural protein mainly sourced from *Bombyx mori* silkworms, offers notable benefits such as low cost, owing to its longstanding role in textiles, and ease of large-scale extraction from silk industry byproducts.[55] Silk fibroin hydrogels can be formed through methods such as pH adjustments, ultrasonication, or the introduction of organic solvents.[56] However, the inherently slow gelation process often necessitates modifications, including temperature elevation, increased protein concentration, or calcium ion incorporation, to accelerate gelation kinetics.[57] The β-sheet structure of silk fibroin provides stability and slow degradation, though additional cross-linking is often required to enhance mechanical properties and tunable biodegradability.

Keratin, a fibrous protein abundant in animal hair, wool, nails, and horns, exhibits greater stability and enzymatic resistance compared to other proteins.[58] Classified into α-helix and β-sheet conformations, keratin is primarily sourced from wool, though human-derived keratin is increasingly favored due to its reduced immunogenicity.[59] Keratin-based hydrogels stand out for their excellent mechanical robustness, biological stability, and capacity to create porous structures that support cell growth and tissue regeneration.[60] Notably, keratin hydrogels exhibit higher storage and loss moduli than collagen-based hydrogels, even without cross-linking, underscoring their intrinsic mechanical robustness.[60] Their stability, ease of rehydration, and potential for long-term storage via lyophilization make keratin-based hydrogels commercially attractive. Despite these advantages, further research is needed to fully explore their potential and optimize their applications in regenerative medicine and biomaterials engineering.

Collagen, the primary protein in human connective tissues, plays a crucial role in biomaterial development due to its biocompatibility, biodegradability, and structural similarity to the extracellular matrix.[61] Predominantly type I collagen, with its well-defined triple-helix structure, is sourced from bovine skin, rat tendons, and fish scales.[62] Collagen-based hydrogels can be prepared under cell-friendly physiological conditions, where polymerization is modulated by temperature, pH, ionic strength, and collagen concentration.[63] Higher collagen concentrations and pH levels enhance hydrogel mechanical properties, while chemical and irradiation-based cross-linking further improve mechanical strength and degradation resistance.[64] These hydrogels exhibit tunable viscoelastic properties and pore structure, which are critical for optimizing mechanical performance and cellular interactions.[65] Moreover, the fiber architecture, including diameter, density, and orientation, regulates key cellular behaviors including morphology, migration, and gene expression.

2.1.1.2. Synthetic Polymer Chain.

2.1.1.2.1. Synthetic Polymers from Free Radical Polymerization.

Free radical polymerization is a highly versatile and widely used technique for hydrogel synthesis, involving the key stages of initiation, propagation, and termination (Figure 4C). In this process, initiators such as ammonium persulfate (APS) generate radicals that activate the polymerization of monomers.[66] Typically conducted in aqueous solutions or organic solvents at mild temperatures (room temperature to 70 °C), free radical polymerization is compatible with a broad spectrum of monomers, enabling scalable and straightforward synthesis.[67] The reaction rate can be modulated through adjustments in initiator concentration and temperature. Advanced techniques, such as Atom Transfer Radical Polymerization (ATRP) and Reversible Addition−Fragmentation Chain Transfer (RAFT) polymerization, provide precise control over polymer molecular weight and polymerization kinetics.[68] This approach enables the synthesis of various polymers, including poly(acrylic acid) (PAA), poly(acrylamide) (PAAm), poly(*N*-isopropylacrylamide) (PNIPAm), poly(methacrylic acid) (PMAA), and poly(acryloyl morpholine) (PAM), each exhibiting distinct properties that can be tailored for specific applications.

Owing to carboxyl group ionization, PAA hydrogels exhibit pH sensitivity and swell under alkaline conditions, while incorporating acrylamide improves their mechanical strength.[69] PAAm hydrogels, typically formed using cross-linkers such as *N*,*N*′-methylenebis(acrylamide) (MBAA), exhibit high water retention but are typically nondegradable unless modified.[70] PNIPAm hydrogels, synthesized with MBAA as a cross-linker, exhibit thermos-responsive properties, transitioning from hydrophilic to hydrophobic at their lower critical solution temperature (LCST) of approximately 34 °C.[71] PMAA hydrogels exhibit pH responsiveness, expanding in acidic environments, making them suitable for targeted drug delivery.[72] Moreover, PAM hydrogels, derived from acryloyl morpholine, are notable for their chemical stability, biocompatibility, and low toxicity, which renders them highly suitable for drug delivery and tissue scaffold applications.[73] Together, these polymers demonstrate the versatility of free radical polymerization in creating hydrogels adaptable to diverse biomedical and industrial needs.

2.1.1.2.2. Synthetic Polymers from Ring-Opening Polymerization.

Ring-opening polymerization (ROP) is an effective method for synthesizing biodegradable polymers by opening cyclic monomers, enabling for the formation of hydrogels with precise control over their structure and properties[74] (Figure 4D). Typically conducted in an inert atmosphere at 100−200 °C, and using catalysts like tin(II) octanoate, ROP enables the production of high-molecular-weight polymers from monomers such as lactones and lactides.[75] The process requires anhydrous conditions and careful control of the catalyst but offers significant flexibility in tuning polymer properties, including molecular weight and copolymer composition, through adjustments in catalyst type, monomer concentration, and reaction time.[76]

Polymers commonly produced through ROP, such as poly(lactic-*co*-glycolic acid) (PLGA), poly(caprolactone) (PCL), poly(L-lactic acid) (PLLA), and poly(butylene

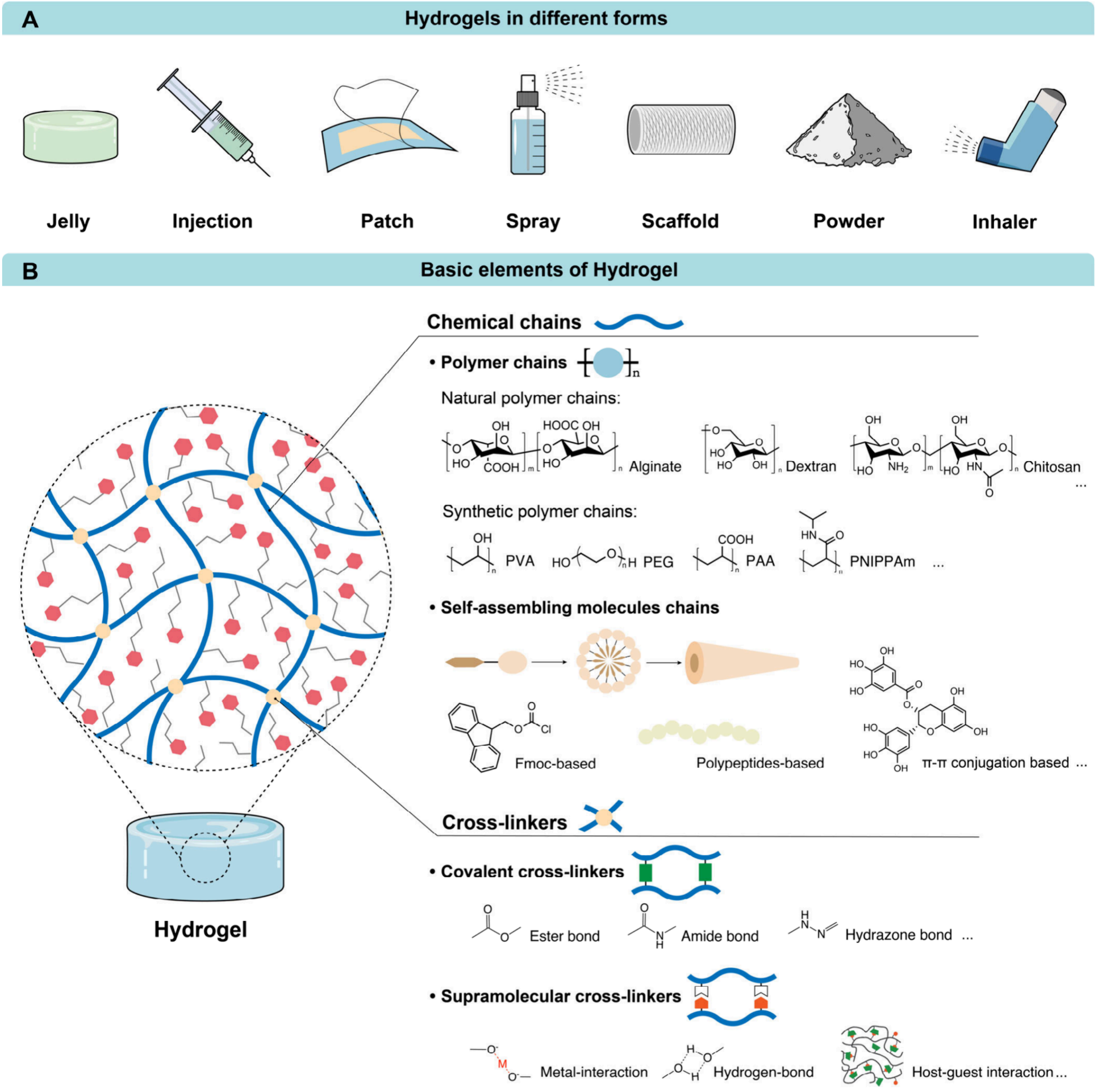

Figure 3. Basic structures of therapeutic hydrogels. In this schematic, the red hexagonal unit represents a chemically functionalized polymer subunit (e.g., acylated PEG or methacrylated HA), while the gray linker denotes a representative cross-linking moiety such as a hydrazone bond, disulfide bond, or enzymatically cleavable peptide linker. (A) Therapeutic hydrogels exist in various forms, including jelly, injectable solution, patch, sprayable solution, scaffold, powder, and inhalable hydrogel. (B) Fundamental components of hydrogels, consisting of polymeric chains and cross-linkers, which form the hydrogel network.

succinate) (PBS), exhibit distinct mechanical properties and degradation behaviors, rendering them appropriate for diverse biomedical uses. PLGA hydrogels, in particular, break down into biocompatible products, and their degradation rate can be finely tuned by adjusting the lactic-to-glycolic acid ratio, making them well-suited for controlled drug release and tissue engineering.[77] PCL hydrogels, derived from ε-caprolactone, exhibit slower degradation and can be modified with hydrophilic polymers like PEG to enhance water absorption, making them suitable for long-term soft tissue applications.[78] Hydrogels made from L-lactide-derived PLLA exhibit high mechanical strength and can be customized through cross-linking for bone and cartilage tissue engineering.[79] PBS hydrogels, synthesized from butylene succinate, offer a balance of flexibility and controlled biodegradability for tissue engineering applications. Additionally, PPF-based hydrogels, synthesized from propylene fumarate, are UV-cross-linkable and exhibit high mechanical strength, making them particularly effective for load-bearing applications such as bone repair.[80] Collectively, these ROP-derived polymers highlight the versatility of the method in producing hydrogels with customizable properties for a variety of biomedical needs.

2.1.1.2.3. Synthetic Polymers from Step-Growth Polymerization. Step-growth polymerization is a versatile synthetic method that involves the reaction of bifunctional or multi-functional monomers, forming macromolecules through a stepwise process[81] (Figure 4E). The process utilizes functional groups like hydroxyl, amine, or carboxyl, and is usually performed in bulk or solution at high temperatures (100−300 °C) with catalytic assistance.[82] Compared to chain-growth polymerization, step-growth polymerization generally exhibits a slower rate, which accelerates as monomer conversion increases. Achieving high molecular weights necessitates extended reaction times and precise control of monomer functionality, stoichiometry, and conversion rates.[83]

Polymers synthesized via step-growth polymerization include poly(ethylene glycol) (PEG), polyphosphazenes, polyphosphoesters (PPEs), polyanhydrides, and poly(*β*-amino esters), each demonstrating distinct properties suitable for hydrogel formation. PEG, also known as poly(ethylene oxide) (PEO), forms hydrophilic and biocompatible hydrogels through chemical cross-linking or photopolymerization, enabling applications in drug delivery and tissue scaffolding.[84] Polyphosphazenes, synthesized by modifying side groups on a phosphorus−nitrogen backbone, offer tunable degradation rates, making them suitable for controlled drug release and tissue engineering.[85] Additionally, PPEs degrade into nontoxic byproducts, facilitating their use in biodegradable hydrogels for drug delivery systems.[86] Polyanhydrides, synthesized via the condensation of diacid monomers, exhibit predictable degradation kinetics, making them ideal candidates for controlled-release applications.[87] Poly(*β*-amino esters), derived from amines and diacrylates, possess tunable degradation profiles, allowing their use in temporary tissue scaffolds and drug delivery systems.[88] Collectively, these polymers exemplify the versatility and precision of step-growth polymerization in designing hydrogels with tailored physicochemical properties for diverse biomedical applications.

2.1.1.2.4. Synthetic Polymers from Copolymerization. Copolymerization, the polymerization of two or more distinct monomers, enables precise control over polymer properties by adjusting monomer composition and sequence within the polymer chain[89] (Figure 4F). Depending on the relative reactivity of the monomers, this process can produce random, alternating, block, or graft copolymers.[89] Typically conducted via solution or emulsion polymerization, copolymerization employs radical, ionic, or condensation mechanisms under carefully regulated conditions. The reaction rate and polymer composition are influenced by the reactivity ratios of the comonomers and the chosen polymerization method, requiring careful control of the monomer feed ratio and reaction parameters.[90]

Notable copolymers synthesized through this approach include poly(lactide-*co*-caprolactone) (PLCL) and poly(ethylene-*co*-vinyl alcohol) (EVOH), each exhibiting unique properties tailored for specific hydrogel applications. Produced by copolymerizing lactic and glycolic acids, PLGA hydrogels offer tunable degradation and mechanical properties through adjustment of the monomer ratio, making them ideal for applications in drug delivery and tissue engineering.[90] PLCL hydrogels, derived from lactide and caprolactone, provide a balance of flexibility and controlled degradation, ideal for soft tissue engineering and vascular grafts.[91] Poly(aspartic acid-*co*-lactic acid) hydrogels exhibit pH sensitivity and degrade into nontoxic byproducts, rendering them particularly useful in responsive drug delivery systems.[92] These examples underscore the versatility and utility of copolymerization in designing hydrogels with tailored physicochemical properties, enhancing their applicability across diverse biomedical fields.

2.1.1.2.5. Synthetic Polymers from Condensation Polymerization. Condensation polymerization occurs when monomers with complementary reactive groups, such as carboxyl and hydroxyl, undergo covalent bonding, releasing small byproducts like water or methanol.[93] This process typically requires a precise stoichiometric balance between the monomers and is typically conducted at elevated temperatures (≥200 °C) in the presence of catalysts to facilitate bond formation and drive the reaction to completion.[94] Due to the gradual nature of the polymerization, achieving high molecular weights often necessitates extended reaction times and efficient removal of byproducts to shift the equilibrium toward polymer formation. Molecular weight control in condensation polymerization is governed by maintaining stoichiometric balance, optimizing reaction temperature, and continuously extracting byproducts. Despite its relative complexity compared to other polymerization methods, this approach enables the synthesis of a wide range of high-performance polymers with tailored properties. Notable examples include polyurethane (PU), valued for its mechanical strength and flexibility; poly(butyl methacrylate) (PBMA), known for its optical clarity and impact resistance; poly(ethylene imine) (PEI), widely used for its high cationic charge density in biomedical and gene delivery applications; and poly(dopamine) (PDA), recognized for its strong adhesion properties and biocompatibility. These polymers exemplify the versatility of condensation polymerization in producing materials with diverse mechanical, chemical, and biological functionalities, supporting applications in coatings, biomedical engineering, adhesives, and advanced material development.

2.1.1.3. Strategies for Choosing the Polymeric Chains for Hydrogels. While natural polymers provide superior bioactivity and are ideal for soft tissue applications, their widespread clinical translation is constrained by several critical issues. First, batch-to-batch variability arising from their biological origin can compromise reproducibility in material performance and regulatory compliance. Second, their mechanical weakness, especially in hydrated states, often limits their application in load-bearing tissues or prolonged implantation. Third, natural polymers like collagen and hyaluronic acid degrade quickly in vivo due to enzymatic activity, which benefits short-term tissue remodeling but limits their suitability for long-term structural support. In contrast, synthetic polymers enable fine-tuning of molecular weight, degradation kinetics, and functional group density but generally lack biological signaling and can produce nonphysiological or inflammatory byproducts (such as acidic PLGA monomers), potentially affecting tissue compatibility.

To reconcile these trade-offs, hybrid hydrogels that combine natural and synthetic polymers have emerged as a promising design strategy. Systems such as collagen−PEG, gelatin−methacrylate−alginate, or HA−PCL blends aim to integrate the bioactivity and cell-adhesiveness of natural components with the tunable mechanics and stability of synthetic backbones.[95−97] However, achieving homogeneous dispersion and interpenetration of the two networks remains challenging. Natural polymers often aggregate or phase separate when mixed with synthetic chains due to disparities in solubility, chain conformation, and gelling kinetics. This leads to structural heterogeneity, compromising the consistency of degradation, mechanical integrity, and cell interaction.

Recent advances have introduced interpenetrating polymer networks (IPNs) and sequential cross-linking strategies to mitigate phase separation. For instance, natural polymers can

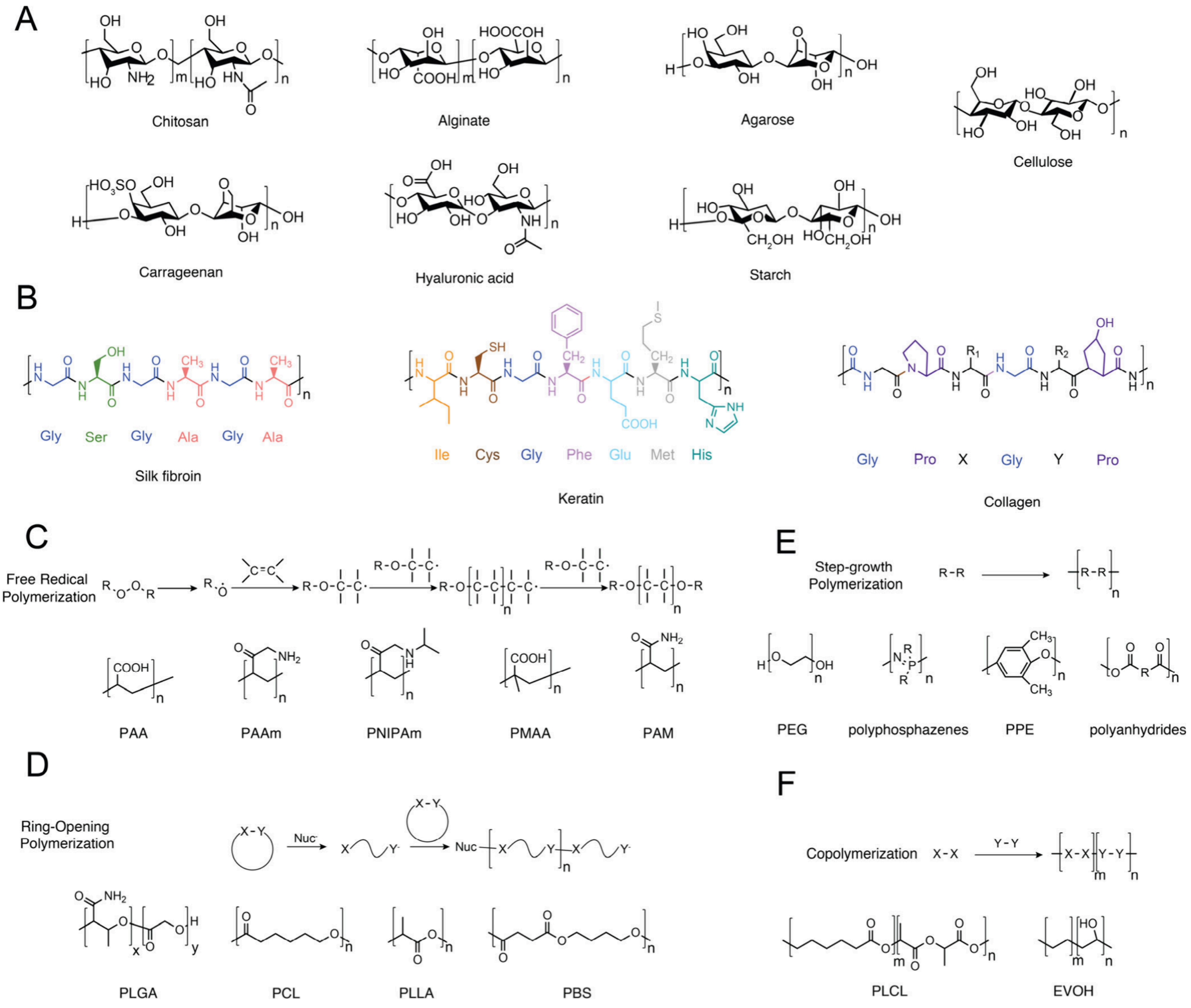

Figure 4. Chemical structures of natural and synthetic polymeric chains. (A) Polysaccharide-based polymeric chains. (B) Protein-based polymeric chains. (C) Polymeric chains synthesized via free-radical polymerization. (D) Polymeric chains synthesized via ring-opening polymerization. (E) Polymeric chains synthesized via free-radical polymerization. (F) Copolymer-based polymeric chains.

be physically entrapped within a precross-linked synthetic network, or sequentially polymerized to preserve component-specific functionalities.[98] Nonetheless, such systems often require multistep synthesis, UV irradiation, or use of cross-linkers that may affect biological viability, thus raising concerns regarding manufacturability and cytotoxicity.

Another frontier in polymer design and consideration involves dynamically assembling systems, particularly supramolecular hydrogels built from peptides, block copolymers, or host−guest interactions. These materials rely on noncovalent forces (e.g., hydrogen bonding, $\pi-\pi$ stacking, electrostatics, or inclusion complexation) to form reversible, stimuli-responsive networks. Examples include RADA16 peptide nanofibers, Fmoc-based systems, and cyclodextrin−adamantane inclusion complexes.[99,100] Such systems allow fine control over nanostructure and enable injectability, self-healing, and bioresponsiveness, which are highly desirable in minimally invasive therapies.

However, despite their elegance, dynamically assembled hydrogels often suffer from limited mechanical robustness, uncontrollable degradation kinetics, and lack of long-term structural fidelity. Moreover, their sensitivity to environmental fluctuations (pH, ionic strength, temperature) makes them prone to instability in physiological conditions.[101] Questions also remain regarding their scalability, sterilization compatibility, and regulatory classification, particularly due to their use of novel components or complex self-assembly mechanisms.

In summary, the integration of natural and synthetic building blocks, whether through hybrid interpenetrating networks or modular supramolecular architectures, holds tremendous potential for creating functionally adaptive hydrogels. Nevertheless, achieving structural homogeneity, translational scalability, and regulatory tractability remains an ongoing challenge. Future directions may involve computationally guided design, machine-learning-based formulation prediction, and bio-orthogonal click-compatible modules to realize hydrogel systems that are both sophisticated in function and practical in manufacture.

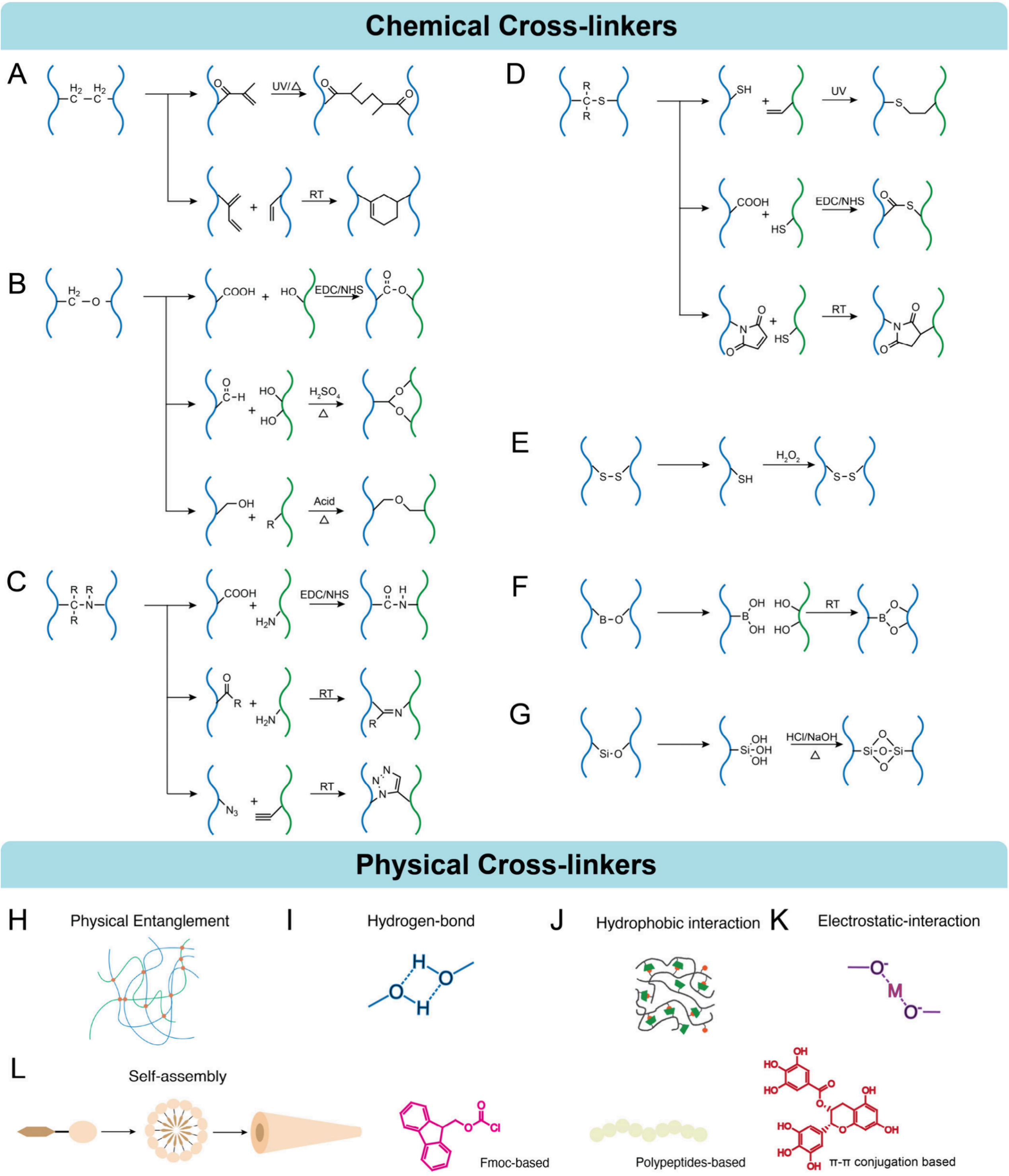

Figure 5. Chemical and physical cross-linkers. (A) C−C bonded-based cross-linkers. (B) C−O bonded-based cross-linkers. (C) C−N bonded-based cross-linkers. (D) C−S bonded-based cross-linkers. (E) S−S bonded-based cross-linkers. (F) B−O bonded-based cross-linkers. (G) Si−O bonded-based cross-linkers. (H) Physical entanglement; (I) Hydrogen-bond; (J) Hydrophobic interactions; (K) Electrostatic-interaction; (L) Self-assembly based cross-linkers.

2.2. Cross-Linkers

2.2.1. Chemical Cross-Linker. *2.2.1.1. Carbon−Carbon (C−C) Bonds.* Hydrogels with carbon−carbon (C−C) cross-links with bond energies of approximately 348 kJ mol^{-1}, are typically synthesized via vinyl polymerization or acrylate copolymerization, yielding robust and chemically stable network structures[102] (Figure 5A). Vinyl monomers can undergo radical polymerization, commonly with cross-linkers like N,N'-methylenebis(acrylamide) (MBA), providing a versatile approach compatible with various initiation methods.[103] A common approach involves incorporating photoinitiators into a prepolymer solution containing vinyl monomers and cross-linkers. Upon UV exposure, radicals are generated, initiating polymerization and network formation.

Alternatively, redox initiation with peroxydisulfate and N,N,N′,N′-tetramethylenediamine (TEMED) enables rapid hydrogel.

Synthesis under ambient temperatures, accelerating cross-linking efficiency with minimal external input.[104] Acrylate cross-linking provides another effective method for establishing stable C−C bonded hydrogel networks.[105] Through radical copolymerization of acrylate groups, this approach enables the formation of dense and highly customizable networks. Poly(ethylene glycol) diacrylate (PEGDA), a widely used cross-linker with multiple acrylate functionalities, facilitates precise mechanical tuning, making it suitable for applications requiring controlled elasticity and strength. Initiation through UV light or chemical initiators such as benzoyl peroxide induces in situ polymerization of acrylate monomers and cross-linkers, producing hydrogels optimized for applications in soft tissue engineering, drug delivery, and regenerative medicine.[106,107]

For applications requiring dynamic or reversible behavior, the Diels−Alder reaction offers a thermo-reversible approach for C−C cross-linking.[108] This reaction relies on the cycloaddition between diene and dienophile groups, such as furan and maleimide, forming covalent bonds that can be reversibly dissociated under mild heating.[109] The unique thermoresponsiveness of Diels−Alder cross-links enables the fabrication of hydrogels with self-healing and adaptive properties, making them highly suitable for reconfigurable materials and self-repairing tissue scaffolds.

For applications demanding enhanced structural stability and mechanical robustness, particularly in high-stress environments, high-energy irradiation techniques such as gamma or electron beam exposure provide an efficient means for C−C cross-link formation.[110] These irradiation methods generate radicals via homolytic scission of polymer chains, facilitating cross-linking even in polymers lacking unsaturated bonds. Additionally, in aqueous systems, water radiolysis generates hydroxyl radicals, which further interact with polymer backbones to create highly durable networks.[111] Irradiation-induced cross-linking produces hydrogels with outstanding mechanical strength, well-suited for load-bearing biomedical uses and other long-term stable applications.

2.2.1.2. Carbon−Oxygen (C−O) Bonds. Hydrogels featuring carbon−oxygen (C−O) bonds, with bond energies around 358 kJ mol^{-1}, are commonly synthesized through esterification reactions between carboxylic acids and alcohols, forming biodegradable linkages within the polymer network[109] (Figure 5B). This approach is widely utilized in poly(lactic-*co*-glycolic acid) (PLGA) and poly(caprolactone) (PCL) hydrogels, providing structural integrity while enabling controlled degradability.[112] Typically conducted at elevated temperatures (100−200 °C) in the presence of acidic or basic catalysts, ester bonds undergo gradual hydrolysis under physiological conditions. This controlled degradation makes ester-based hydrogels suitable for applications requiring transient mechanical support or sustained drug release, including biodegradable implants and tissue scaffolds.

Ether-bonded hydrogels are synthesized through dehydration or condensation reactions between hydroxyl groups, forming hydrolytically stable networks ideal for long-term applications. Commonly utilized in poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) hydrogels, these ether linkages are catalytically driven, often by acids such as sulfuric acid, at elevated temperatures (above 100 °C) to create durable hydrogel matrices.[113] The inherent resistance of ether bonds to hydrolytic degradation makes these hydrogels particularly well-suited for implantable medical devices requiring prolonged structural integrity.

For applications requiring targeted degradability, acetal bonds introduce pH-sensitive linkages within hydrogels.[114,115] Acetal bonds are typically formed via mild acid-catalyzed reactions between aldehydes and diols, facilitating hydrogel degradation in acidic environments.[116] This acetalization mechanism is particularly advantageous for drug delivery systems targeting acidic microenvironments, such as tumor sites, where selective hydrolysis enables controlled release, thereby enhancing therapeutic precision.

2.2.1.3. Carbon−Nitrogen (C−N) Bonds. With bond energies of approximately 272−285 kJ·mol^{-1}, C−N bonds significantly contribute to the structural integrity, stability, and functional performance of hydrogels in biomedical contexts[117] (Figure 5C). Owing to their strength and durability, they are highly suited for creating resilient, long-lasting networks that support tissue scaffolds, drug delivery platforms, and other applications demanding both mechanical integrity and biocompatibility.[118]

Among the C−N bonds commonly utilized in hydrogel chemistry are amide, imine, hydrazone, and triazole linkages, each offering distinct reactivity, stability, and responsiveness to environmental cues. Amide bonds, formed through condensation between carboxylic acids and amines, are frequently facilitated by coupling agents such as 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS), which enhance reaction efficiency under mild conditions while preserving the bioactivity of integrated biomolecules.[119] The inherent stability of amide bonds makes them suitable for applications requiring robust and durable networks, such as tissue scaffolds and drug delivery systems.[120] Furthermore, their formation under ambient, buffered conditions ensure compatibility with sensitive biological molecules, enabling stable cross-linking and long-term structural integrity in biomedical environments.

In addition to amide bonds, imine bonds, also known as Schiff bases, represent a unique class of C−N linkages in hydrogels, formed via the condensation reaction between primary amines and aldehydes.[121] This reaction, typically conducted under mildly acidic conditions, yields pH-sensitive, reversible bonds that impart dynamic responsiveness to hydrogel networks.[122] Imine-based hydrogels leverage this reversibility to adapt to environmental pH changes, making them particularly suited for self-healing materials and drug delivery systems where controlled release is triggered by specific pH shifts, thereby enhancing therapeutic efficacy in targeted applications.[123]

Expanding on the pH-responsive nature of imine bonds, hydrazone bonds add further versatility by introducing both injectability and enhanced reversibility to hydrogel networks.[124] These bonds are formed through the reaction of hydrazides with aldehydes or ketones under mild, near-neutral conditions, supporting in situ gelation—a property particularly advantageous for biomedical applications such as wound healing and drug delivery.[125] Hydrazone-linked hydrogels facilitate the development of dynamic, responsive matrices that can be modulated or degraded as needed, making them highly suitable for biomedical environments requiring flexibility, degradability, and controlled therapeutic release.

Complementing the responsive characteristics of imine and hydrazone bonds, triazole bonds formed via "click" chemistry provide an exceptionally stable and bioorthogonal cross-linking approach.[126] Triazole linkages are generated through azide−alkyne cycloaddition, either via copper-catalyzed azide−alkyne cycloaddition (CuAAC) or, in the absence of a catalyst, through strain-promoted azide−alkyne cycloaddition (SPAAC).[127] The robust nature of triazole bonds makes them ideal for in vivo applications where nonreactivity with biological molecules and resilience to hydrolysis are essential. Such stability ensures the sustained structural integrity needed for tissue engineering and targeted drug delivery, where durability and biocompatibility are paramount.[128]

2.2.1.4. Carbon−Sulfur (C−S) Bonds. C−S bonds, with bond energies around 272−285 kJ mol^{-1}, play a pivotal role in hydrogel design by offering a balance between stability and redox responsiveness[129] (Figure 5D). This adaptability is particularly advantageous in applications such as controlled drug delivery, tissue engineering, and regenerative medicine. These linkages enable hydrogels to respond dynamically to redox changes, tailoring degradation and functionality to physiological conditions for enhanced therapeutic outcomes.

Thioether bonds, commonly formed via thiolene or thiolyne reactions, provide structurally stable C−S linkages under mild reaction conditions.[130] Their durability and stability make them particularly suited for photopolymerizable hydrogels, where resilience is critical.[131] This stability underpins their suitability for long-term biomedical applications, where redox stability and sustained structural integrity are required.

Thioester bonds offer degradability through hydrolytically or reductively cleavable O=C−S linkages, synthesized by reacting carboxylic acids with thiols.[132] This bond type imparts dynamic responsiveness, allowing hydrogel degradation or controlled release in response to environmental triggers like redox changes. Such responsiveness makes thioester-linked hydrogels valuable in regenerative medicine and tissue engineering, where transient scaffold structures and controlled therapeutic release are essential.[133]

Sulfhydryl-maleimide bonds, formed through the highly specific reaction between maleimide groups and thiols, generate stable thioether linkages that enable precise bioconjugation.[134] This specificity supports targeted therapeutic applications by allowing active agents to be strategically incorporated within the hydrogel matrix, enhancing delivery efficacy. These linkages, being both bioorthogonal and robust, minimize biological interference, making them well-suited for in vivo applications requiring precise delivery.[135]

2.2.1.5. Disulfide (S−S) Bonds. Disulfide bonds (S−S), with bond energies around 240−270 kJ mol^{-1}, provide reversible cross-linking within hydrogel networks, enabling redox-responsive behavior ideal for controlled drug delivery and tissue engineering applications[136] (Figure 5E). These bonds are typically formed through the oxidative coupling of thiol groups under mild oxidative conditions, such as exposure to oxygen or hydrogen peroxide, which facilitates the conversion of −SH groups into disulfide linkages. This redox-sensitive cross-linking mechanism enables the design of hydrogel networks that degrade in response to specific environmental cues, allowing for tunable stability and adaptability.[137]

In biomedical applications, disulfide-cross-linked hydrogels take advantage of the reducing environments characteristic in cellular interiors and tumor sites, where elevated levels of intracellular glutathione (GSH) cleave the disulfide linkages, triggering controlled hydrogel degradation.[138] This degradation pathway enables targeted release of encapsulated therapeutics at redox-active sites, thereby enhancing delivery precision and therapeutic efficacy within regions with high reducing potential, such as tumor microenvironments or inflamed tissues.[139] Thus, disulfide bonds offer a versatile strategy for engineering hydrogel systems that combine structural integrity with environmentally triggered degradability, optimizing them for dynamic biomedical applications.

2.2.1.6. Boronic Acid-Diol (B−O) Bonds. With bond energies near 536 kJ·mol^{-1}, boronic acid−diol (B−O) interactions impart hydrogels with distinctive pH and glucose sensitivity, which is highly advantageous for applications like glucose sensing and insulin delivery.[140] (Figure 5F). These dynamic bonds form through reversible covalent interactions between boronic acid and diol groups, yielding stable boronate esters under physiological conditions.[141] The bonds' sensitivity to acidic pH allows for controlled dissociation, enabling tunable hydrogel degradation and release of encapsulated agents.

Typically, B−O cross-links are generated by combining boronic acid-functionalized polymers with diol-containing polymers under mild aqueous conditions, which facilitates in situ gelation.[142] In glucose-sensitive systems, boronate ester bonds within the hydrogel competitively bind to glucose, leading to their selective dissociation and subsequent release of therapeutic agents, such as insulin.[143] This competitive binding mechanism renders boronic acid−based hydrogels highly suitable for environments where glucose levels modulate drug release.

The ability of boronic acid-diol bonds to respond to biochemical cues, including pH and glucose, enhances the adaptability of these hydrogels for controlled drug delivery. This feature makes B−O bonded hydrogels promising for dynamic biomedical applications, particularly for responsive therapeutic delivery in diabetes management, where precision and responsiveness are critical.

2.2.1.7. Silicon−Oxygen (Si−O) Bonds. Silicon−oxygen (Si−O) bonds, with bond energies around 799 kJ mol^{-1}, provide exceptional stability and durability within hydrogel networks, contributing to robust structural integrity and resistance to degradation in harsh environments[144] (Figure 5G). As some of the strongest covalent bonds in hydrogel systems, Si−O linkages are well-suited for applications demanding long-term stability, including implantable devices and tissue scaffolds.[145]

Si−O bonds are typically formed through condensation reactions between silanol (Si−OH) groups or via sol−gel processes involving alkoxysilanes. In the sol−gel method, silane precursors hydrolyze to form reactive silanol groups, which subsequently undergo condensation to create Si−O−Si cross-links, resulting in a robust three-dimensional network. This process is usually conducted under mild conditions, such as room temperature and neutral to mildly acidic pH, making it compatible with sensitive biomolecules that may be incorporated into the hydrogel matrix.

In biomedical applications, Si−O-bonded hydrogels exhibit outstanding mechanical strength and stability, essential for load-bearing implants and tissue engineering constructs.[145] Their resistance to enzymatic degradation and hydrolytic breakdown allows these hydrogels to maintain their structural integrity over extended periods, supporting prolonged therapeutic efficacy in vivo.[146] Consequently, Si−O cross-linking strategies are increasingly used to develop hydrogel systems that require both mechanical robustness and bioinert properties for long-lasting biomedical performance.

2.2.2. Physical Cross-Linker.

Chemical covalent bonds such as C−C, C−N, and Si−O provide stability to hydrogels through irreversible cross-links, ensuring robust structural integrity. In contrast, physical cross-linking introduces reversible, dynamic interactions, which enable hydrogels to form tunable and responsive networks.[147] Noncovalent forces, such as physical entanglement, hydrogen bonding, hydrophobic and electrostatic interactions, and self-assembly, enable hydrogels to respond to environmental stimuli, repair themselves, or undergo degradation when required.[148]

Each physical cross-linking mechanism imparts distinct properties to the hydrogel network: physical entanglement forms mechanically interlocked structures; hydrogen bonding enhances both strength and flexibility; hydrophobic interactions stabilize the network structure in aqueous environments; electrostatic interactions offer responsiveness to ionic strength or pH; and self-assembly facilitates the formation of hierarchically organized structures. Collectively, these physical cross-linking strategies significantly broaden the versatility of hydrogels, enhancing their suitability for a wide range of biomedical and industrial applications.

2.2.2.1. Physical Entanglement. Physical entanglement provides an effective strategy for developing stable and flexible hydrogel networks without the need for covalent cross-linking[149] (Figure 5H). By intertwining polymer chains, this mechanism forms mechanically robust networks that resist deformation while preserving reversible properties.[150] Various types of physical entanglement contribute to the structural integrity of hydrogels, offering key advantages such as enhanced mechanical stability and self-healing capability.[151] The interwoven polymer chains impart elasticity, allowing the hydrogel to recover from mechanical disruptions. Additionally, the ability to tailor properties by adjusting polymer composition, molecular weight, and entanglement density enhances the versatility of this cross-linking strategy. Notable examples of physically entangled hydrogels include poly(vinyl alcohol) (PVA) hydrogels, which formed via freeze−thaw cycles, and agarose-based hydrogels, which undergo gelation upon cooling.[152,153] However, despite these advantages, physically entangled hydrogels typically exhibit lower mechanical strength than covalently cross-linked counterparts and may experience structural instability under swelling conditions or prolonged aqueous exposure.

2.2.2.2. Hydrogen Bonding. Hydrogen bonding, with bond energies ranging from 4 to 50 kJ mol^{-1}, serves as a dynamic yet structurally supportive mechanism for hydrogel systems, balancing reversible interactions with mechanical stability[154] (Figure 5I). These noncovalent bonds form between hydrogen bond donors (e.g., hydroxyl or amine groups) and electron-rich acceptors (e.g., oxygen or nitrogen atoms), facilitating cohesive networks that respond to external stimuli and environmental fluctuations.[155]

Hydrogen-bonded hydrogels are commonly synthesized using polymers with functional groups capable of multiple hydrogen-bonding interactions, such as urethane and carboxylic groups.[156] Poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAA) are frequently employed in these systems due to their ability to establish hydrogen-bonding networks that confer self-healing properties, enabling hydrogels to restore their integrity following mechanical disruption.[157] This self-healing property is advantageous in biomedical applications, particularly for wound healing and tissue engineering, where material resilience is essential.

The mechanical properties of hydrogen-bonded hydrogels can be precisely tuned by adjusting the density and type of hydrogen-bonding groups in the network, allowing for control over elasticity and stiffness to meet specific application requirements.[158] However, these hydrogels generally exhibit lower mechanical strength than covalently cross-linked counterparts and may suffer from structural instability under prolonged hydration, as excessive water uptake disrupts hydrogen bonds within the network.

2.2.2.3. Hydrophobic Interaction. To expand the range of hydrophobic interactions, with bond energies around 0.4−4 kJ mol^{-1}, in hydrogel networks, diverse hydrophobic components can be integrated, each offering unique properties suited to specific applications[159] (Figure 5J). In hydrogels, hydrophobic interactions are driven by the natural tendency of hydrophobic segments to aggregate, minimizing water exposure and forming physically cross-linked domains.[159] Unlike covalent bonds, these interactions are reversible and responsive to environmental changes, endowing the hydrogel networks with adaptive properties. Such adaptability is crucial for drug delivery, tissue engineering, and soft robotics, where dynamic responses are essential.

One common approach is to use amphiphilic copolymers, such as Pluronic block copolymers (poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide)).[160] The hydrophobicity of the PPO segments drives these copolymers to form micelles spontaneously in aqueous media.[160] This self-assembly can be thermally controlled, as the PPO segments become increasingly hydrophobic at elevated temperatures, forming a thermo-responsive network that enables controlled drug release based on temperature changes.[161] Moreover, multiblock copolymers like PLGA-*b*-PEG create networks featuring distinct hydrophobic domains, which improve mechanical strength and allow precise adjustment of network characteristics.[162] This tunability is especially useful for applications such as tissue scaffolding, where specific mechanical characteristics are essential.

Hydrogels based on hydrophobic interaction are also notable for their self-healing capabilities due to the reversible nature of these noncovalent associations.[163] This self-healing property allows the hydrogel network to recover its structure after mechanical disruptions, making it ideal for injectable hydrogels that need to adapt to irregular tissue shapes.[164] By adjusting the concentration and type of hydrophobic segments, the mechanical strength and gelation behavior of these hydrogels can be customized, providing versatility across different biomedical applications.

However, a key challenge associated with hydrophobic interaction-based hydrogels is their sensitivity to high hydration levels. Excessive water uptake can disrupt hydrophobic domains, compromising the structural integrity of the network. This limitation highlights the need for careful design, particularly in applications demanding long-term mechanical stability in fully aqueous environments.

2.2.2.4. Electrostatic Interaction. Electrostatic interactions provide a versatile cross-linking mechanism in hydrogel networks by leveraging ionic attractions between oppositely charged components to form dynamically tunable matrices[165] (Figure 5K). These interactions confer reversibility and environmental responsiveness, enabling the hydrogel to adapt to variations in pH, ionic strength, and electric fields.[166] Such adaptability makes electrostatically cross-linked hydrogels particularly valuable in applications requiring environmental sensitivity, including drug delivery, biosensing, and tissue engineering.

A common strategy to integrating electrostatic interactions involves using polyelectrolytes—polymers with charged functional groups along their chains. For instance, physically cross-linked networks can be formed by complexing cationic polymers like chitosan with anionic polymers such as alginate or hyaluronic acid.[167] These polyelectrolyte hydrogels exhibit tunable mechanical properties, with stiffness and swelling behavior modulated by ionic interactions and the surrounding ionic environment.[168] The inherent sensitivity of these ionic bonds enables rapid hydrogel responses to environmental change, making them ideal for biosensors and responsive drug delivery applications.

In drug delivery applications, electrostatic interactions enable controlled spatial release of therapeutics. By adjusting the charge density of the hydrogel matrix or encapsulated drugs, release profiles can be fine-tuned to respond to specific biological stimuli, such as pH gradients within biological tissues.[169] This capability is particularly advantageous for targeted drug delivery, allowing for preferential drug release in acidic or inflamed regions, such as tumor microenvironments.

However, electrostatic cross-linked hydrogels are susceptible to fluctuations in ionic strength and pH, which can destabilize ionic cross-links and compromise mechanical integrity. This limitation necessitates precise design considerations, particularly for applications exposed to physiological conditions, to ensure structural stability and long-term functionality.

2.2.2.5. Self-Assembly. Self-assembly offers a sophisticated mechanism for hydrogel cross-linking, wherein molecular components spontaneously organize into structured networks driven by noncovalent forces such as hydrogen bonding, hydrophobic interactions, π-π stacking, and van der Waals forces[170] (Figure 5L). This bottom-up approach enables the formation of well-defined architectures with tunable properties, making self-assembled hydrogels highly adaptable for applications requiring precise structural and functional properties.

Self-assembly is widely employed in hydrogel formation using amphiphilic molecules, peptide-based systems, and supramolecular polymers. Amphiphilic molecules, such as block copolymers with hydrophilic and hydrophobic segments, spontaneously arrange into micelles or nanostructures in aqueous environments, forming physically cross-linked network.[171] Peptide-based self-assembly, often using short peptide sequences or peptide amphiphiles, enables the formation of nanofibers or nanostructures through specific molecular interactions, imparting biocompatibility and bioactivity to the hydrogel.[172] Supramolecular polymers, assembled via host−guest interactions such as cyclodextrin−adamantane pairing, exhibit dynamic and reversible networks well-suited for responsive hydrogels.[172]

The self-assembly process allows control over hydrogel properties, including mechanical strength, porosity, and degradation rate, through precise manipulation of the molecular components. This tunability enables the design of hydrogels for a broad range of applications, such as controlled drug release, tissue engineering scaffolds, and soft robotics, where adaptability and responsiveness are essential.[173] However, the stability of self-assembled hydrogels may be influenced by environmental conditions, including temperature, pH, and ionic strength, which can disrupt the noncovalent interactions underlying the network.[174] Consequently, careful consideration of these factors is necessary to ensure the functional integrity of self-assembled hydrogels, particularly in biomedical applications where environmental fluctuations are common.[175]

Despite these challenges, the intrinsic responsiveness of self-assembled systems provides unique advantages, allowing them to dynamically adapt to changing conditions—an essential feature for applications in interactive and stimuli-responsive environments.[176]

2.2.3. Strategies for Choosing the Cross-Linkers of Therapeutic Hydrogel. Choosing an appropriate cross-linking strategy for therapeutic hydrogels requires consideration beyond basic chemical compatibility. As the cross-linking mechanism defines the fundamental architecture of the hydrogel network, it directly influences key material attributes such as structural integrity, injectability, dynamic responsiveness, and interactions with biological environments. These attributes, in turn, determine how well the hydrogel performs under specific therapeutic conditions.

Covalent cross-linking offers superior mechanical strength and durability, making it advantageous for applications that require long-term implantation or load-bearing support, such as bone regeneration or surgical sealants. For instance, photo-cross-linkable PEGDA-based hydrogels produce highly stable and tunable networks suitable for intraoperative use, though they require UV exposure and photoinitiators, which may introduce cytotoxicity.[177] On the other hand, chemically dynamic covalent bonds, such as imine, hydrazone, or disulfide linkages, enable shear-thinning, self-healing, and controlled degradation, and are particularly well-suited for injectable drug delivery or immunomodulatory matrices, though they may suffer from limited mechanical resilience.

In contrast, physically cross-linked hydrogels offer better injectability and reversibility but often suffer from poor mechanical robustness. Ionic cross-linking (e.g., alginate-Ca^{2+} systems) is rapid and cytocompatible, which suits wound dressings or cell encapsulation, but may undergo ion exchange *in vivo*, leading to premature dissolution.[178] Thermoresponsive polymers such as PNIPAAm enable sol−gel transitions at physiological temperatures, making them attractive for injectable drug delivery depots, but their lack of permanent structure and limited biodegradability may hinder long-term use.

Hybrid networks that combine physical and covalent interactions (e.g., dual cross-linked gelatin−methacrylate−alginate systems) can leverage the strengths of both approaches—offering improved mechanical integrity alongside dynamic remodeling capabilities.[179] These are particularly suitable for applications like cardiac patches, cartilage repair, or load-sensitive soft tissue scaffolds, where long-term functionality must coexist with biointegration.[179]

Self-assembling hydrogels represent an emerging category of physically cross-linked systems that form through noncovalent interactions such as hydrogen bonding, π−π stacking, host−guest interaction, or peptide-driven nanofiber assembly. These materials often exhibit injectability, reversible network formation, and responsiveness to physiological stimuli. For example, β-sheet forming peptides like RADA16 or Fmoc-diphenylalanine can spontaneously assemble into ECM-mimetic networks that support angiogenesis and neural tissue repair.[180] Host−guest systems utilizing cyclodextrins and

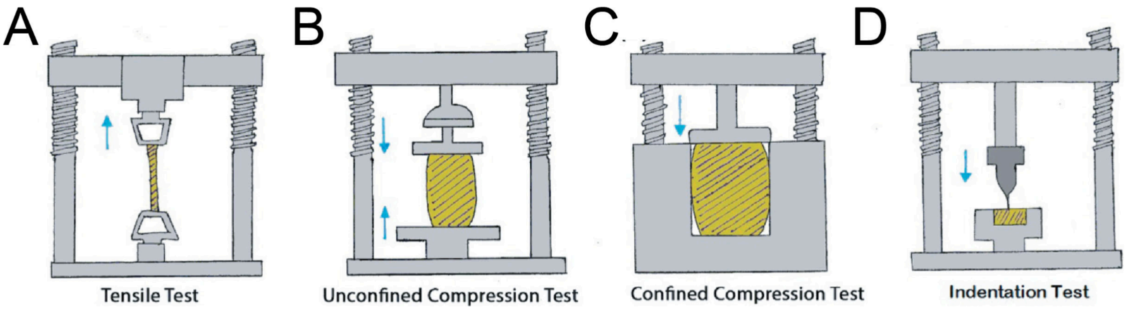

Figure 6. Mechanical testing methods for therapeutic hydrogels. (A) Tensile Test—measures the material's response to uniaxial tension, assessing its strength and elasticity. (B) Unconfined Compression Test—evaluates material strength under uniaxial compressive stress without lateral constraints. (C) Confined Compression Test—tests compressive strength with lateral constraints to simulate more realistic loading conditions. (D) Indentation Test—determines hardness and localized mechanical properties by measuring resistance to indentation.[173] Reproduced with permission from ref 173. Copyright 2017 Elsevier.

hydrophobic guests enable shear-thinning, self-healing hydrogels ideal for localized drug release or immunotherapy.[180] Although these systems offer excellent biocompatibility and functional responsiveness, they generally exhibit lower mechanical strength than covalently cross-linked systems and may require reinforcement or secondary stabilization for use in load-bearing tissues.

The optimal cross-linking strategy must be tailored to the therapeutic objective. Factors such as gelation time, delivery route (e.g., injectable vs preformed), mechanical demands of the implantation site, and desired degradation behavior should guide the selection.[181] A critical understanding of these trade-offs allows for rational hydrogel design that aligns with both biological demands and clinical constraints.

3. PHYSICOCHEMICAL PROPERTY OF HYDROGELS

3.1. Mechanical Property

The mechanical properties of hydrogels—stiffness, toughness, and resilience—are critical for their functionality in biomedical applications[173] (Figure 6). These properties are influenced by factors such as cross-linking type and density, polymer composition, and network architecture.[178] Hydrogels with covalent cross-links offer excellent mechanical stability, ideal for load-bearing applications. Conversely, physically cross-linked hydrogels, based on reversible interactions like hydrogen bonding and hydrophobic effects, exhibit enhanced flexibility and self-healing properties.[179]

3.1.1. Stiffness. Stiffness, characterized by the elastic modulus, is a crucial parameter in hydrogel design, directly influencing both mechanical function and cellular responses.[173] In biomedical applications, hydrogel stiffness must often replicate the mechanical properties of target tissues: softer hydrogels are preferred for neural and soft tissue engineering, whereas stiffer hydrogels are required for cartilage and bone regeneration, where greater structural support is necessary.[182] Hydrogel stiffness significantly affects cell behavior, influencing adhesion, proliferation, and differentiation, making it a key consideration in regenerative medicine.[183]

To quantify hydrogel stiffness, mechanical testing is performed to determine parameters such as the compressive modulus, Young's modulus, or shear modulus. These values are typically derived from stress–strain curves, where stiffness is represented by the slope of the linear region.[184] Various experimental methods are employed for this purpose, including:

Compression Testing: In this approach,[185] a uniaxial compressive force is applied to the hydrogel sample, with the compressive modulus E_c calculated from the stress–strain relationship as

$$Ec = \sigma/\epsilon$$

where σ is the stress (force per unit area) and ϵ is the strain (change in length relative to the original length). Compression testing is particularly relevant for load-bearing applications, such as cartilage replacement, where mechanical integrity under compression is critical.

Rheometry: Rheometry assesses the viscoelastic properties of hydrogels by measuring the storage modulus G' (elastic response) and loss modulus G'' (viscous response) under oscillatory shear stress:[186]

$$G' = \frac{\tau 0}{\gamma 0}\cos\delta / G'' = \frac{\tau 0}{\gamma 0}\sin\delta$$

where τ is the shear stress amplitude, $\gamma 0$ is the strain amplitude, and δ is the phase angle. Rheometry is particularly useful for soft hydrogels in dynamic biological environments, as it captures both stiffness and viscoelasticity, providing insights into hydrogel behavior under physiological conditions.

3.1.2. Toughness. Toughness is a fundamental parameter in hydrogel design, defining the material's capacity to absorb energy and resist fracture under mechanical stress. Unlike stiffness, which characterizes rigidity and resistance to deformation, toughness reflects the ability of a hydrogel to endure mechanical loads without structural failure.[187] In biomedical applications, toughness is essential for maintaining mechanical integrity and long-term functionality under physiological forces and repetitive stress.[188] Hydrogels designed for applications such as cartilage replacements, wound dressings, and load-bearing scaffolds require enhanced toughness to withstand dynamic mechanical environments and prevent failure.

Quantitatively, toughness is measured as the total energy a material can absorb before fracturing, represented by the area under the stress–strain curve obtained through mechanical testing.[189] Key parameters include fracture energy, which measures the energy required to propagate a crack per unit area, and tensile strength, the maximum stress the material can endure before rupture.[190] Standard methods for assessing hydrogel toughness include uniaxial tensile testing, which assesses energy absorption and fracture resistance; tear testing, which quantifies crack propagation resistance; and indentation testing, which measures localized toughness in softer hydrogels. Additionally, cyclic loading tests are employed to quantify toughness by evaluating fatigue resistance and energy dissipation over repeated mechanical cycles.[191] Tough hydrogels exhibit minimal permanent deformation across cycles, a desirable property for biomedical applications involving repetitive stress.[192]

Understanding and quantifying toughness is pivotal for tailoring hydrogels to meet the mechanical demands of diverse biomedical applications. By optimizing parameters such as polymer chain composition, cross-linking density, and the incorporation of reversible or sacrificial bonds, hydrogels can achieve an ideal balance of durability and flexibility, ensuring their reliability and performance in dynamic physiological environments.[193]

3.1.3. Strength.

Strength, a critical mechanical property of hydrogels, defines their capacity to withstand applied forces without permanent deformation or failure.[1] This parameter is essential in biomedical applications such as cartilage repair, vascular grafts, and tissue engineering scaffolds, where maintaining structural integrity under physiological loads is essential.[194] Adequate strength ensures the hydrogel can endure mechanical stress while supporting cell growth and tissue regeneration.[195]

Strength is quantitatively assessed through stress−strain curves obtained from mechanical testing methods, including tensile, compressive, and shear tests. Key metrics include tensile strength, which represents the maximum stress a material can endure during stretching, and compressive strength, which indicates the material's capacity to bear compression without structural failure.[195] Young's modulus, derived from the slope of the linear region of the stress−strain curve, provides an indirect measure of both stiffness and strength.[196] Compression testing is particularly relevant for load-bearing hydrogels, such as those mimicking cartilage, while shear testing assesses deformation resistance in layered structures, which are critical for dynamic tissue environments.[197]

By refining mechanical evaluation techniques and tailoring hydrogel formulations to meet application-specific mechanical requirements, strength can be optimized to ensure both mechanical reliability and functionality under diverse physiological conditions.

3.1.4. Viscoelasticity.

Viscoelasticity, a fundamental property of hydrogels, describes their dual capacity to behave as both elastic solids and viscous fluids under deformation.[198] Unlike purely elastic materials, which recover their shape instantaneously, viscoelastic materials exhibit time-dependent strain, characterized by a combination of immediate elastic recovery and delayed viscous flow.[198] This dual nature is essential in applications requiring energy absorption and dissipation, such as cartilage substitutes, soft tissue scaffolds, and wearable sensors, where materials must endure repetitive stresses without failure.

Quantifying viscoelasticity relies on rheological methods, particularly oscillatory rheometry, which measures the storage modulus (elastic component) and loss modulus (viscous component). The ratio of these moduli, expressed as the loss factor (tan δ), indicates the relative dominance of viscous or elastic behavior. A higher loss factor signifies increased viscous dissipation, whereas a lower value denotes elastic dominance.[199] Additionally, Dynamic Mechanical Analysis (DMA) provides further insights into viscoelastic responses under varying frequencies and amplitudes, enabling the assessment of material performance under dynamic physiological conditions, such as in joint tissues or artificial muscles.[200]

By optimizing the polymer network structure, cross-link density, and molecular interaction, hydrogels can be precisely engineered to achieve tailored viscoelastic profiles. Such control ensures their adaptability to diverse biomedical applications requiring specific combinations of flexibility, resilience, and energy dissipation.

3.1.5. Self-Healing Ability.

In hydrogels, self-healing describes their innate capacity to autonomously repair structural damage by reestablishing mechanical integrity via reversible interactions in the polymer network.[201]

This property is vital for tissue engineering, drug delivery, and wearable devices, where durability and resilience are needed to endure physiological stresses and prolong functionality.[206] The self-healing mechanisms primarily rely on reversible bonding interactions, including hydrogen bonds, hydrophobic interactions, dynamic covalent bonds (e.g., imine, disulfide), and host−guest chemistry. These dynamic interactions enable the hydrogel network to repeatedly form and break connections under physiological conditions, facilitating efficient structural repair.[206]

The extent and efficiency of self-healing are commonly evaluated using mechanical and rheological tests. Tensile or compression testing assesses the recovery of strength or modulus after damage, providing a direct measure of mechanical property restoration.[207] For example, a high recovery percentage in tensile strength indicates a superior self-healing ability. Additionally, rheological analyses, such as monitoring the recovery of the storage modulus after stress relaxation, characterize the time-dependent healing kinetics of hydrogels.[208] These methods offer insight into both the speed and completeness of the healing process, which are critical parameters for matching specific biomedical application needs.

Engineering the self-healing capacity of hydrogels involves the precise tuning of reversible interactions within their polymer network. By optimizing bond type, density, and network architecture, hydrogels can be tailored for enhanced reparative efficiency while maintaining essential properties such as biocompatibility and mechanical strength.[209] This self-repairing capability not only improves material durability but also reduces the need for replacements, positioning self-healing hydrogels as a transformative solution for long-term biomedical applications.

3.1.6. Tuning Mechanical Properties of Hydrogels Guided by Materials Chemistry.

Stiffness and strength in hydrogels are primarily governed by the density and type of cross-linking within the polymer network. Shorter polymer chains and higher cross-link densities create rigid networks, enhancing both stiffness and strength by restricting molecular mobility.[210] Covalent cross-linkers further reinforce these mechanical properties by establishing stable, permanent connections within the network.[211] However, excessive cross-linking reduces energy dissipation, leading to brittleness and diminished toughness.[212] This trade-off underscores the importance of optimizing cross-link density to achieve a balance between mechanical rigidity and flexibility, ensuring that hydrogels maintain both durability and functional performance in biomedical applications.

Conversely, toughness and elasticity in hydrogels are primarily enhanced by longer polymer chains and moderate cross-link densities, which facilitate molecular flexibility and

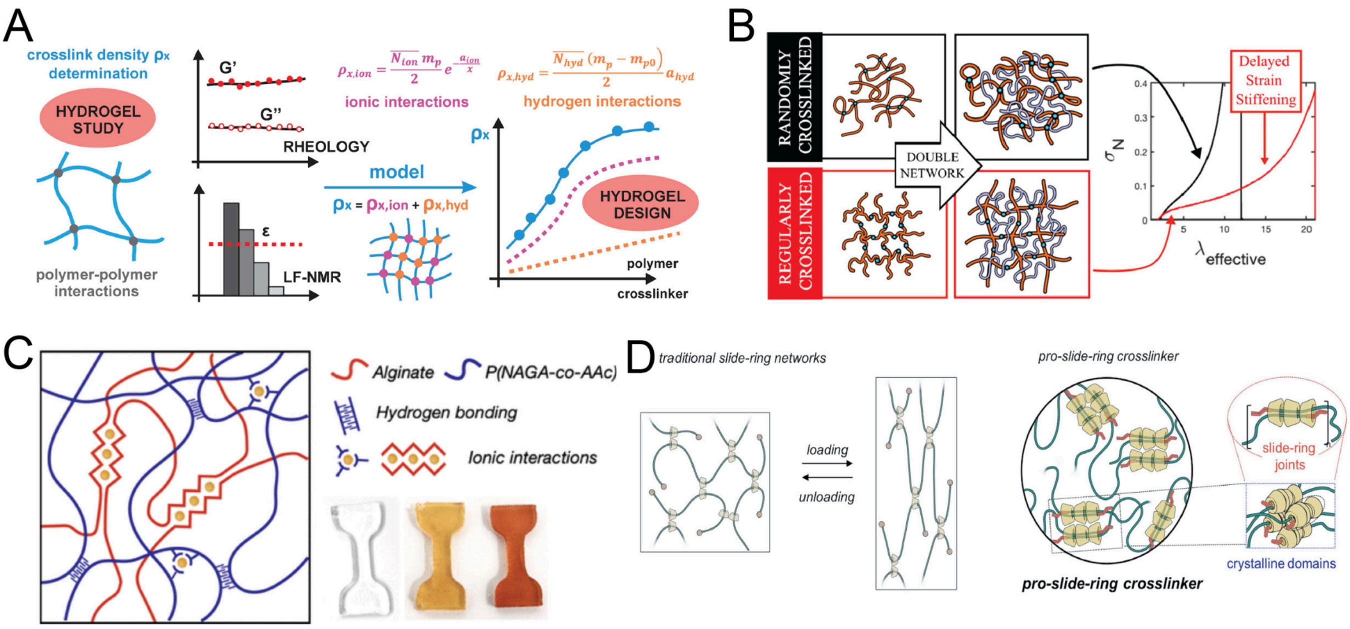

Figure 7. Representative approaches to adjust hydrogel mechanical properties include: (A) incorporating ionic and hydrogen-bonding interactions into the network[202] (Reproduced with permission from ref 202. Copyright 2022 Elsevier), (B) modulating cross-link homogeneity to influence high-strain elasticity in polymer networks[203] (Reproduced with permission from ref 203. Copyright 2024 American Chemical Society under [CC BY 4.0]), (C) designing hybrid hydrogels with orthogonal transient cross-links for enhanced tunability[204] (Reproduced with permission from ref 204. Copyright 2023 American Chemical Society), and (D) employing reinforced double-threaded slide-ring networks to expedite hydrogel development and enable 3D printing[205] (Reproduced with permission from ref 205. Copyright 2023 Elsevier).

energy dissipation.[213] Hydrogen bonds and ionic interactions, as dynamic cross-links, are essential for reversible bonding under deformation, which dissipates energy and helps prevent structural failure[202] (Figure 7A). Longer polymer chains contribute to elasticity by allowing greater deformation and recovery, while moderate cross-link densities maintain chain mobility, enhancing both toughness and elasticity.[214]

Self-healing hydrogels leverage reversible cross-linking interactions, including host−guest chemistry, ionic bonds, and hydrophobic associations.[215] These dynamic bonds enable network reformation after damage, restoring structural integrity.[216] Longer polymer chains and lower cross-link densities facilitate this process by promoting chain mobility and rearrangement. In contrast, rigid covalent cross-links hinder self-healing due to their inability to dynamically reorganize.[217]

Innovative design can simultaneously optimize stiffness, strength, toughness, elasticity, and self-healing in hydrogels. Double-network (DN) hydrogels exemplify this approach by combining a brittle, rigid network that enhances stiffness and strength with a soft, ductile network that improves toughness and elasticity[203] (Figure 7B). Sacrificial bonds in the brittle network dissipate energy under stress, while the ductile network maintains integrity. Adding reversible interactions, such as ionic or hydrogen bonding, further enables self-healing.[218] For instance, DN hydrogels cross-linked with calcium ions exhibit enhanced stiffness, strength, toughness, and self-healing.[219]

Hybrid hydrogels, combining covalent and dynamic cross-links, also achieve multifunctionality.[220] Alginate-polyacrylamide dual-network hydrogels balance stiffness and toughness while utilizing ionic cross-links for self-healing[204] (Figure 7C). Additionally, nanocomposite hydrogels incorporating nanoparticles such as graphene oxide or silica further enhance mechanical properties.[221] These nanoparticles act as physical cross-linking agents, improving stiffness and strength while maintaining toughness and self-healing capabilities.

Advanced designs, such as slide-ring and triple-network hydrogels, further illustrate the potential of tailored architectures[205] (Figure 7D). Slide-ring hydrogels utilize "pulley-like" cross-links that allow polymer chains to slide under stress, improving energy dissipation and elasticity while maintaining strength. Triple-network hydrogels, integrating rigid, soft, and dynamically cross-linked networks, enhance stiffness, toughness, and self-healing.[222] For example, alginate-polyacrylamide hydrogels with Schiff base cross-links exhibit superior mechanical performance and reparative efficiency.[222]

Fine-tuning polymer chain length, cross-linking density, and interaction mechanisms enables hydrogels to achieve an ideal mechanical balance, addressing the specific needs of applications like cartilage repair, wound healing, and tissue scaffolding.[223] These strategies underscore the critical role of materials chemistry in advancing multifunctional hydrogel design.

3.2. Adhesive Ability and Antiadhesive Ability

3.2.1. Adhesive Ability. The adhesive ability of hydrogels, defined as their capacity to bond with diverse surfaces such as biological tissues, synthetic materials, or other hydrogels, is critical for applications in tissue adhesives, wound dressings, and wearable devices.[224] This property arises from a combination of physical interactions (e.g., hydrogen bonding, hydrophobic associations, and electrostatic forces) and chemical interactions (e.g., covalent bonding and ionic interactions)[225] (Figure 8).

The adhesive ability of hydrogels is commonly assessed through mechanical tests such as lap shear, pull-off, and tack tests, which quantify the hydrogel's ability to bond with substrates under various loading conditions.[226] In a lap shear

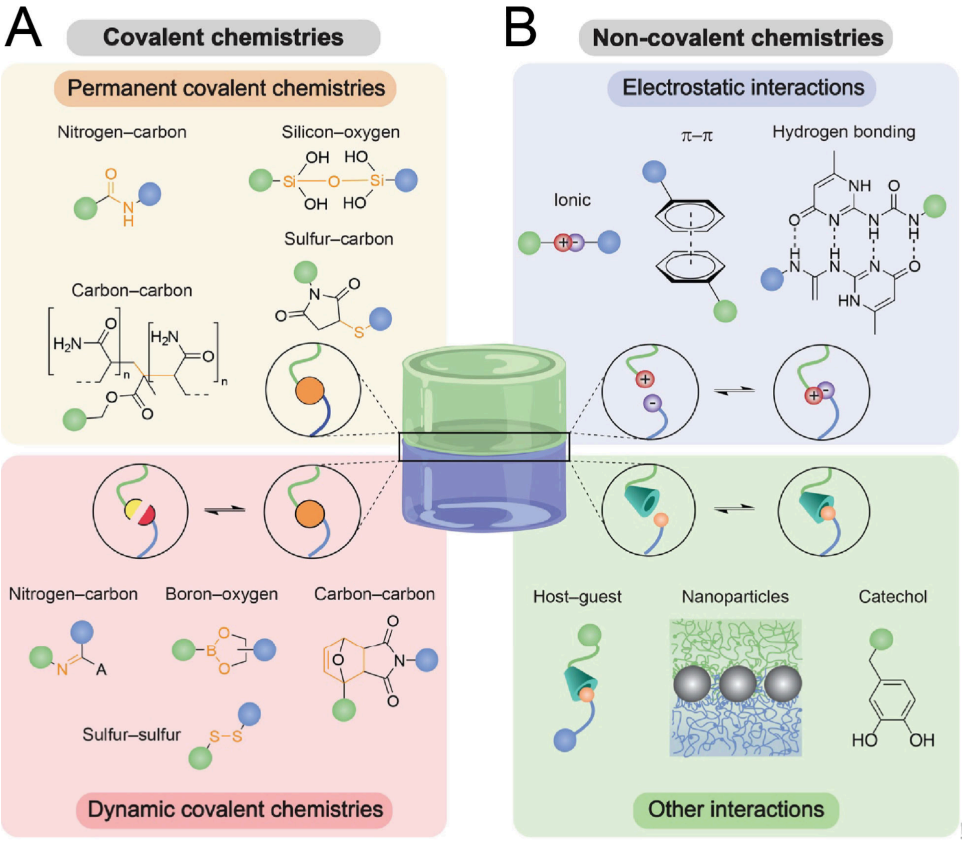

Figure 8. Illustration showcasing how covalent and noncovalent interactions contribute to dynamic material design. Covalent bonding strategies are categorized into permanent and dynamic types. (A) Permanent covalent bonds, such as N–C, C–C, Si–O, and S–C, form irreversible linkages, whereas dynamic covalent bonds, including N–C, B–O, C–C, and S–S, are reversible and impart adaptivity to the material. (B) In the realm of noncovalent interactions, electrostatic interactions encompass ionic bonding, $\pi-\pi$ stacking, and hydrogen bonding, enabling adjustable and reversible connections. Additional mechanisms, such as host–guest interactions, nanoparticle incorporation, and catechol-based chemistry, enhance molecular recognition and facilitate materials assembly. The central graphic underscores the synergy between these chemical modalities, illustrating how their integration imparts dynamic and functional behavior to advanced materials.[225] Reproduced with permission from ref 225. Copyright 2021 American Chemical Society under [CC BY-NC-ND 4.0].

test, a hydrogel is placed between two substrates, and a shear force is applied until failure, providing shear strength data.[227] The pull-off test measures the tensile force required to detach the hydrogel perpendicularly from a substrate, yielding pull-off strength.[228] The tack test evaluates the hydrogel's initial adhesion by measuring the peak force required to separate a probe pressed onto its surface.[229] These methods are widely used due to their simplicity and relevance for applications such as tissue adhesives, wound dressings, and wearable devices.[230]

Physical adhesion mechanisms enable dynamic and reversible bonding, making them ideal for adaptable applications. Hydrogen-bonding hydrogels, such as poly(vinyl alcohol) (PVA), exhibit robust underwater adhesion due to their hydroxyl-rich networks.[231] Host–guest complexes, such as cyclodextrin-adamantane interactions, allow rapid adhesion.[232] Additionally, hydrophobic modifications, such as stearyl methacrylate coatings, enhance adhesion in saline environments by displacing interfacial water, improving bonding strength.[233]

Chemical strategies improve hydrogel durability through covalent interactions. Strategies such as Schiff's base reactions, Michael additions, and enzymatic cross-linking establish stable bonds with biological tissues. Mussel-inspired catechol chemistries, exemplified by dopamine-functionalized hydrogels, achieve strong adhesion in wet and dry environments via hydrogen and covalent bonding.[234] Additionally, tunicate-inspired pyrogallol chemistries have emerged as a powerful alternative for achieving superior adhesion in saline environments by forming multiple covalent and noncovalent interactions.[235] Coacervation-based adhesion, inspired by sandcastle worms, leverages oppositely charged polyelectrolytes to form cohesive and robust networks.

Nature-inspired strategies further enhance hydrogel adhesion by mimicking biological systems. For instance, octopus- and gecko-inspired micropatterns utilize capillary forces and suction to ensure strong adhesion on wet and uneven surfaces.[236] Structural modifications, such as microneedle arrays and surface microstructures, enhance mechanical interlocking and energy dissipation, enabling robust adhesion under dynamic conditions.[237] These strategies are particularly valuable for applications like tissue patches and biosensors, which require stable adhesion in fluidic environments.

Integrating multiple adhesion mechanisms have been developed to address challenges such as interfacial water competition and long-term stability.[238] Hybrid systems combining covalent and noncovalent interactions, zwitterionic polymers, or hydrophobic domains achieve an optimal balance of adhesion strength and mechanical resilience.[239] For example, double-network hydrogels incorporating sacrificial

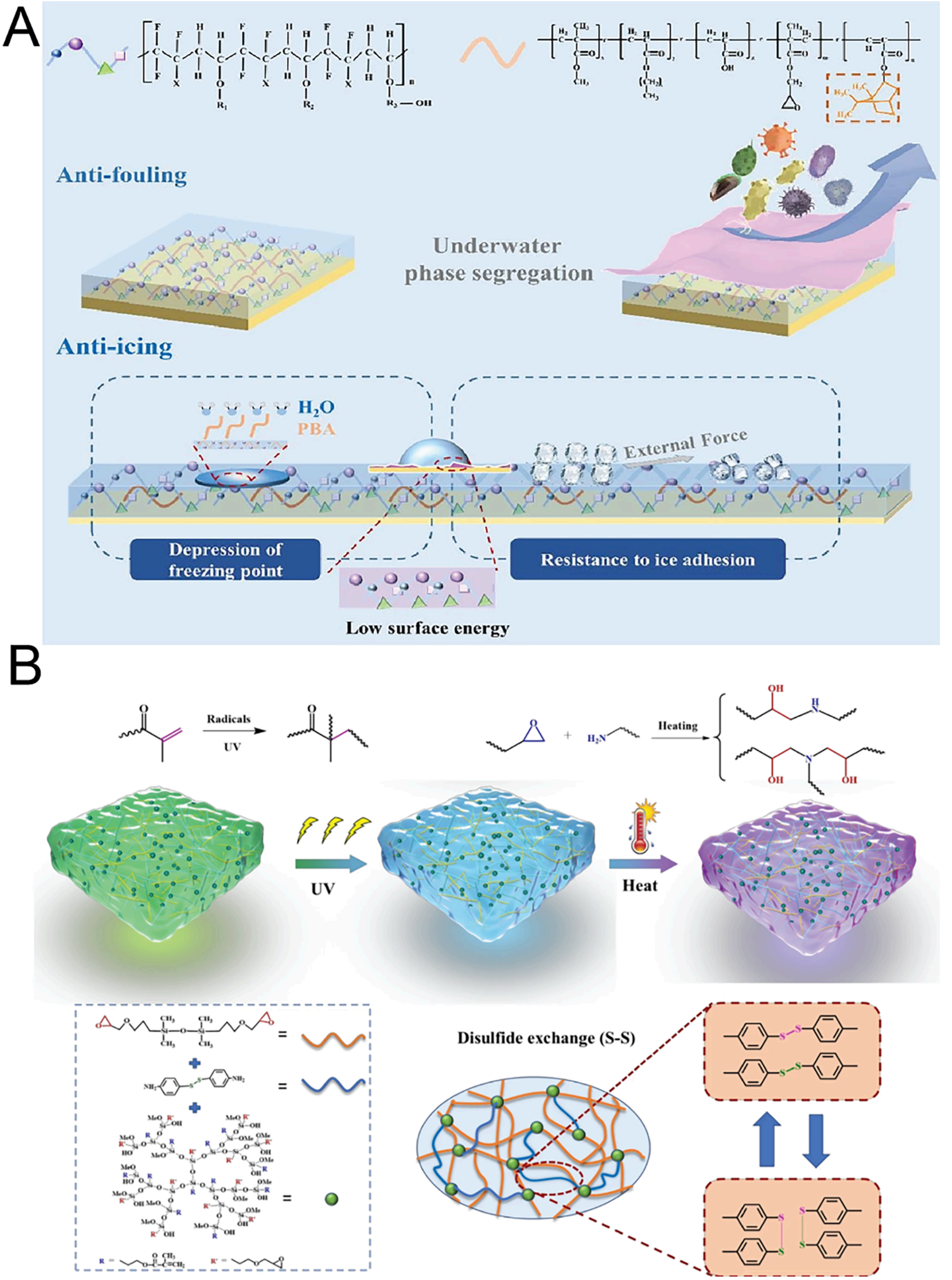

Figure 9. Antiadhesive properties of hydrogels. (A) Coatings based on fluorocarbon self-layering interpenetrating polymer networks, engineered to improve antifouling and anti-icing performance.[252] Reproduced with permission from ref 252. Copyright 2023 Elsevier. (B) Self-healing siloxane elastomers featuring hierarchical covalent cross-linking and reversible dynamic bonds, tailored for use in flexible electronics.[251] Reproduced with permission from ref 251. Copyright 2022 Springer Nature.

bonds further enhance both adhesion durability and toughness under mechanical stress.[239]

Adhesive hydrogels are increasingly utilized in therapeutic delivery, bioelectronics, and regenerative medicine, underscoring the importance of tailoring adhesion strategies to specific needs.[240] Conductive hydrogel patches for myocardial infarction treatments, for instance, incorporate bioionic liquids to enhance tissue integration while maintaining electrical conductivity.[241] Injectable hydrogels with in situ cross-linking chemistries offer minimally invasive localized drug delivery, leveraging both physical and chemical interactions for stable adhesion.[242]

3.2.2. Antiadhesive Ability. The antiadhesive ability of hydrogels, defined as their capacity to resist adhesion or bonding with surfaces such as biological tissues, synthetic materials, or other hydrogels, is crucial for applications in antifouling coatings, medical implants, and drug delivery systems.[243] This property arises from a combination of physical factors (e.g., low surface energy or hydrophilicity) and chemical features (e.g., zwitterionic groups or highly hydrated polymer networks).

Antiadhesive performance is commonly evaluated through mechanical and surface-based tests, including adhesion force measurements, protein adsorption assays, and bacterial adhesion studies.[243] Adhesion force measurements assess the detachment force required to separate a probe or substrate from the hydrogel surface, where lower forces indicate stronger antiadhesive properties.[244] Protein adsorption assays quantify the amount of protein bound to the hydrogel surface, with lower adsorption correlating to better antifouling ability.[245] Similarly, bacterial adhesion studies evaluate the extent of microbial attachment on hydrogel-coated surfaces, providing insights into antibiofouling effectiveness.[246]

Physical mechanisms for achieving antiadhesion rely on minimizing interfacial interactions between the hydrogel and external surfaces. Hydrophilic polymers, such as poly(ethylene glycol) (PEG), polyacrylamide (PAM), and zwitterionic polymers (e.g., poly(sulfobetaine methacrylate) and poly(carboxybetaine methacrylate)) form hydration layers that create steric repulsion, effectively resisting adhesion of proteins or cells. Moreover, the molecular weight and length of polymeric chains significantly influence antiadhesive performance. Longer chains, such as PEG with molecular weights exceeding 10 kDa, provide thicker hydration barriers compared to shorter chains (e.g., 2 kDa), enhancing fouling resistance.[247] However, excessively long chains may entangle, reducing chain mobility and dynamic adaptability.[248] The structural architecture also plays a crucial role: flexible chains, such as linear PEG, can dynamically rearrange under mechanical stress to optimize hydration, while rigid polymers like poly(2-methyl-2-oxazoline) (PMOXA) offer dense, stable hydration layers, ensuring long-term resistance to fouling.[248] Additionally, zwitterionic polymers, such as poly(carboxybetaine) or poly(sulfobetaine), generate highly hydrated shells through electrostatic interactions, further reducing protein or microbial attachment.[249] For example, zwitterionic hydrogels have shown remarkable resistance to bacterial adhesion in marine and medical environments.[250]

Chemical strategies to enhance antiadhesive properties primarily involve the incorporation of low-surface-energy groups, such as fluorocarbon and siloxane-based moieties, which effectively reduce adhesive forces.[251] Fluorocarbon-modified hydrogels demonstrate pronounced antiadhesive properties, attributed to their low polarizability and minimal van der Waals forces, leading to ultralow adhesion[252] (Figure 9A). Similarly, siloxane-based hydrogels achieve remarkable antifouling performance by forming stable, low-surface-energy layers, making them particularly suitable for long-term medical implants and marine applications[251] (Figure 9B). These strategies provide durable antiadhesive surfaces capable of resisting biofouling and maintaining performance in dynamic environments.

Bioinspired designs further enhance antiadhesive properties by mimicking natural systems. For instance, the lotus leaf effect, characterized by micro/nanostructured hydrophobic surfaces, has been replicated in hydrogels to create superhydrophobic coatings with self-cleaning and antiadhesive capabilities.[253] Similarly, marine organisms, such as fish and whales, inspire the development of ultrasmooth hydrogel coatings that resist biofouling in underwater applications.[254] These bioinspired designs combine structural features with antiadhesive chemistry, providing robust solutions for diverse environments.

Emerging strategies for enhancing antiadhesive properties include the integration of self-cleaning mechanisms, such as hydrogels with responsive swelling behaviors that detach adhered particles through expansion or contraction.[255] Additionally, multifunctional hydrogels that combine antiadhesive properties with drug release capabilities have been developed for preventing postsurgical adhesions.[256] For instance, hydrogels incorporating anti-inflammatory agents, along with zwitterionic or PEG-based networks, simultaneously reduce adhesion and provide therapeutic benefits.[256]

Overall, the antiadhesive ability of hydrogels can be precisely tailored by optimizing polymer composition, network architecture, and surface properties. These advancements position hydrogels as versatile materials for addressing adhesion-related challenges in biomedical, industrial, and environmental applications, paving the way for innovations in nonstick coatings, antibiofouling technologies, and implantable medical devices.

3.2.3. Tuning the Adhesive and Antiadhesive Ability of Hydrogel. Adhesiveness is a key interfacial property of hydrogels that requires careful optimization for specific therapeutic needs. Strong adhesion to biological tissues is essential in wound healing, tissue engineering, and surgical sealing, as it secures hydrogel placement, facilitates tissue integration, and minimizes the need for sutures or external supports. Conversely, in antiadhesion barriers or bioinert coatings, minimal tissue adhesion is essential to prevent postoperative fibrosis, undesired tissue contact, or organ tethering. Achieving either adhesive or antiadhesive behavior requires careful modulation of the hydrogel's interfacial chemistry, hydration state, and network dynamics.

To enhance adhesive performance, chemical strategies typically focus on introducing functional groups capable of forming strong bonds with tissue substrates. Catechol groups, inspired by mussel adhesive proteins, establish both covalent and noncovalent interactions with nucleophilic residues on wet tissue surfaces (e.g., $-NH_2$, $-SH$), thereby enabling effective adhesion under physiological conditions.[257] Similarly, aldehyde and NHS-ester moieties can form Schiff base or amide linkages with amine-rich proteins at the wound interface. These chemical handles are widely employed in hydrogels developed for surgical sealants, tissue glues, or regenerative implants requiring mechanical anchorage.

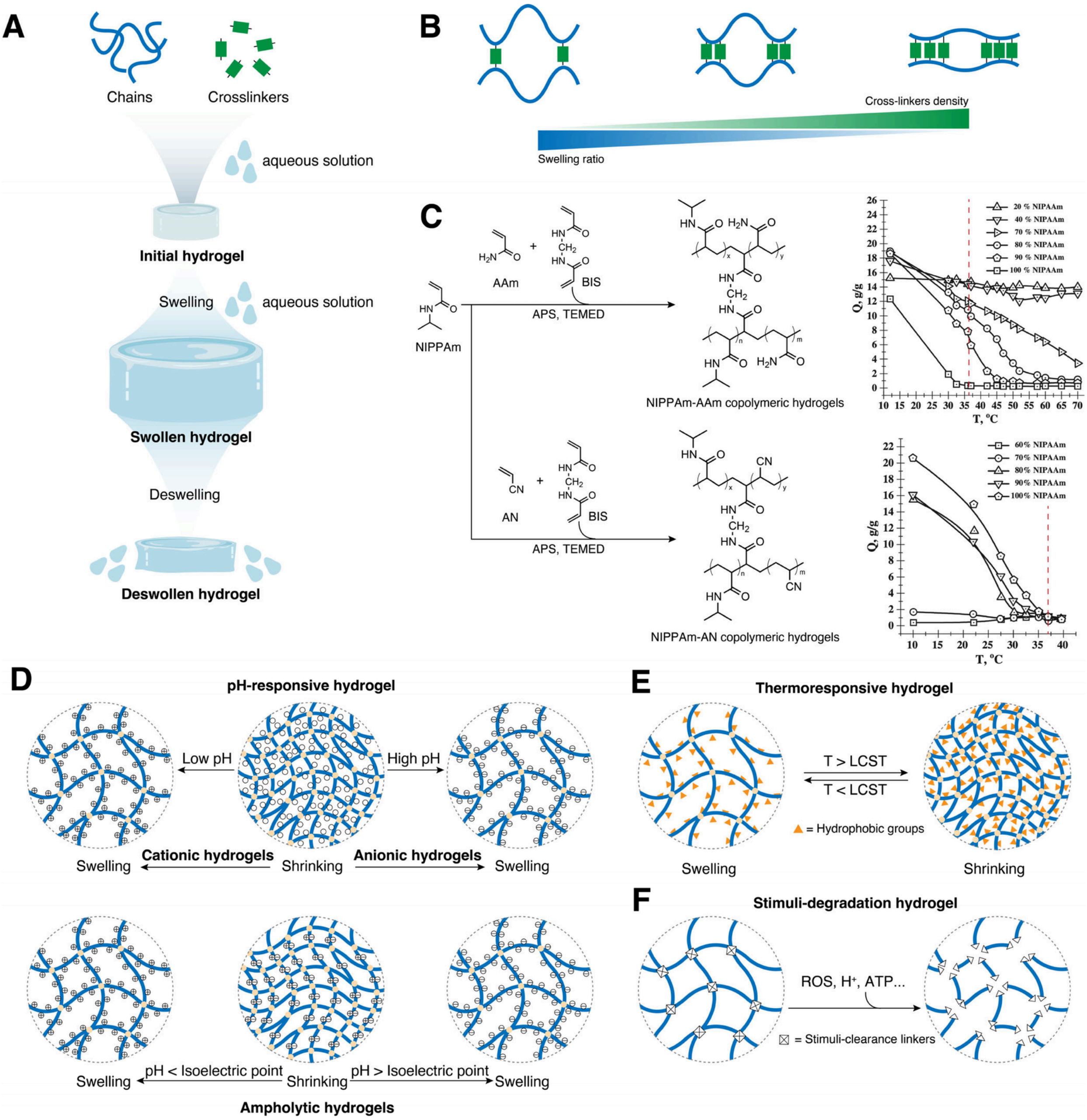

Figure 10. Stimuli-responsive hydrogels. (A) Schematic depicting the swelling and shrinking behavior of hydrogels. (B) Swelling ratio as a function of cross-linker density. (C) Swelling ratio comparison between NIPPAM-AAm and NIPPAm-AN copolymer hydrogels. (D) and (E) illustrate the "shrink–swell" response of pH- and thermoresponsive hydrogels, respectively. In (D), pH-responsive hydrogels alter their volume through functional group ionization, swelling or shrinking with pH changes. (E) Thermoresponsive hydrogels contract at elevated temperatures and expand when cooled due to polymer chain dynamics. (F) Stimuli-triggered degradation of cross-linked hydrogels designed for stimuli-responsive clearance.

In contrast, antiadhesive hydrogels are designed to resist cell and protein adsorption by controlling surface hydration, electrostatic charge, and steric repulsion.[258−260] Common approaches include the incorporation of zwitterionic polymers (e.g., carboxybetaine, sulfobetaine) or polyethylene glycol (PEG) chains, both of which establish dense hydration shells that effectively prevent nonspecific biofouling.[261,262] Such materials are particularly well-suited for postoperative anti-adhesion membranes, where reducing interorgan fibrosis is paramount. Notably, emerging hydrogel designs feature spatially asymmetric or patterned surfaces, combining adhesive and nonadhesive regions within the same construct to achieve directionally selective interactions with surrounding tissues.

The ability to precisely regulate tissue adhesion enables the rational design of multifunctional hydrogels tailored for site-specific therapeutic requirements. For instance, injectable hydrogels for spinal applications may be engineered to adhere selectively to dura mater while presenting an antiadhesive surface on the opposing side to mitigate epidural scarring.[263] Such spatially encoded interfacial architectures exemplify the next generation of adaptive hydrogel systems. Realizing these functions requires not only targeted chemical modification but also spatial control over network topology, cross-linker distribution, and surface presentation at the mesoscale.

3.3. Swelling and Shrinking

3.3.1. Swelling Property. The swelling property of hydrogels, defined as their ability to absorb and retain water, is a critical parameter in determining their functionality across various biomedical and industrial applications[264] (Figure 10A). Swelling behavior directly impacts drug delivery, tissue engineering, and wound healing, where precise control of water uptake ensures optimal performance and compatibility with the surrounding environment.[265]

The swelling behavior of hydrogels is commonly expressed by the swelling ratio (SR), defined as SR = (Ws − Wd)/Wd, where Ws and Wd represent the swollen and dry weights, respectively. The equilibrium swelling ratio, achieved when osmotic pressure balances network elasticity, provides a measure of the hydrogel's hydration capacity.[263] Complementary techniques, such as rheological analysis, can evaluate changes in mechanical properties induced by swelling, offering a comprehensive understanding of hydrogel behavior under hydrated conditions.[266]

Cross-linking density is a key determinant of hydrogel swelling (Figure 10B). Higher cross-linking densities create tightly packed networks, limiting water uptake and reducing the swelling ratio.[267] Conversely, lower cross-linking densities result in looser networks with larger pore sizes, enhancing water absorption. Dynamic cross-linkers, such as boronic acid-diol complexes or reversible imine bonds, further enable tunable swelling by allowing hydrogels to adapt to environmental stimuli, such as pH or glucose concentration.[268] This adaptability is particularly valuable for hydrogels used in responsive drug delivery or biosensing applications.

Stimuli-responsive hydrogels exhibit swelling behavior that changes in response to external triggers, such as pH, temperature, or ionic strength[269] (Figure 10C−F). pH-sensitive hydrogels, incorporating functional groups like carboxylic acids or amines, swell under acidic or basic conditions due to protonation or deprotonation.[270] Temperature-responsive hydrogels, such as those based on PNIPAM, undergo phase transitions around their lower critical solution temperature (LCST), enabling precise control over swelling and deswelling.[271] These hydrogels are particularly advantageous for drug delivery systems, where controlled swelling facilitates the release of therapeutic agents in response to local temperature.[3]

Swelling behavior is critical to the performance of hydrogels in biomedical applications. In drug delivery, it regulates drug diffusion, enabling controlled and targeted release.[272] In tissue engineering, optimal swelling enhances the hydrogel's ability to absorb extracellular fluids, transport nutrients, and support cell adhesion and proliferation.[273] For wound healing, hydrogels with controlled swelling maintain a moist environment while absorbing wound exudates, accelerating the healing process and reducing the risk of infection.[26]

Optimizing swelling properties involves balancing high water absorption with mechanical stability. Excessive swelling can compromise structural integrity, while insufficient swelling may limit the material's functionality.[274] Strategies to address these challenges include hybrid hydrogels that integrate covalent and physical cross-linking, offering enhanced mechanical strength without sacrificing swelling performance.[258] Tailoring polymer architectures, such as comb-like or star-shaped configurations, further refine swelling behavior, ensuring compatibility with specific application requirements.

3.3.2. Shrinking Property. The shrinking behavior of hydrogels, characterized by their ability to lose water and reduce in size under certain conditions, is a key feature in the design of stimuli-responsive and dynamic materials.[275] Shrinkage significantly influences hydrogel performance in biomedical and industrial fields, such as drug delivery, biosensing, and tissue engineering, where precise volumetric control is critical.[276]

Shrinking is typically measured as the shrinking ratio (*SR*), defined as $SR = (W_S - W_C)/W_S$ where W_S is the swollen weight of the hydrogel and W_C is its weight after shrinking.[277] This ratio reflects the degree of volume or mass loss during shrinking, providing insights into the hydrogel's response to environmental stimuli.[278] Complementary analytical techniques, such as optical microscopy and volumetric analysis, are often employed to monitor hydrogel size and shape changes during shrinking, enabling real-time characterization of this dynamic behavior.[279]

Cross-linking density significantly influences the shrinking capacity of hydrogels. Highly cross-linked networks exhibit restricted chain mobility, limiting water expulsion and reducing the extent of shrinking.[280] Conversely, loosely cross-linked hydrogels allow greater chain relaxation and water release, leading to more pronounced shrinking.[280] Dynamic cross-linking systems, such as reversible covalent bonds or ionic interactions, enable adaptive shrinking behavior in response to environmental changes, such as pH, temperature, or ionic strength.[281]

Polymer architecture also plays a crucial role. Hydrogels with flexible polymeric chains can readily collapse and expel water under external stimuli, while rigid chains provide structural resistance, mitigating excessive shrinking.[282] Tailored architectures, such as star-shaped or branched polymers, allow fine-tuning of shrinking behavior to meet specific application requirements, balancing water release with structural stability.

3.3.3. Tuning Swelling and Shrinking Property. Hydrogels' capacity to reversibly swell or shrink in response to environmental stimuli is key to their applications in drug delivery, biosensing, and tissue engineering. However, selecting or designing swelling behavior is not merely a material property—it must be critically matched to the intended therapeutic context. Hydrogels that swell dramatically in aqueous environments, such as poly(acrylic acid)-based systems, can generate expansion forces useful for wound plugging or pressure-driven drug release.[283] Yet these same properties may limit their use in confined anatomical sites, where volumetric changes can cause tissue compression or inflammatory responses.

Chemically cross-linked hydrogels typically exhibit lower swelling ratios but higher mechanical integrity, making them suitable for applications requiring dimensional stability, such as intra-articular delivery or scaffold prepatterning. By contrast, physically cross-linked or supramolecular gels are often more sensitive to ionic strength, pH, or temperature, and are better suited for stimuli-responsive drug delivery or biosensor platforms. For example, poly(*N*-isopropylacrylamide) (PNIPAAm) shrinks at temperatures above its lower critical solution temperature (~32 °C), enabling thermally triggered drug release or reversible tissue interaction.[284]

Crucially, the swelling−shrinking dynamics must be aligned with drug release kinetics, tissue pressure constraints, and biodegradation profiles. In inflammatory microenvironments, pH-responsive swelling may enhance cargo diffusion but also

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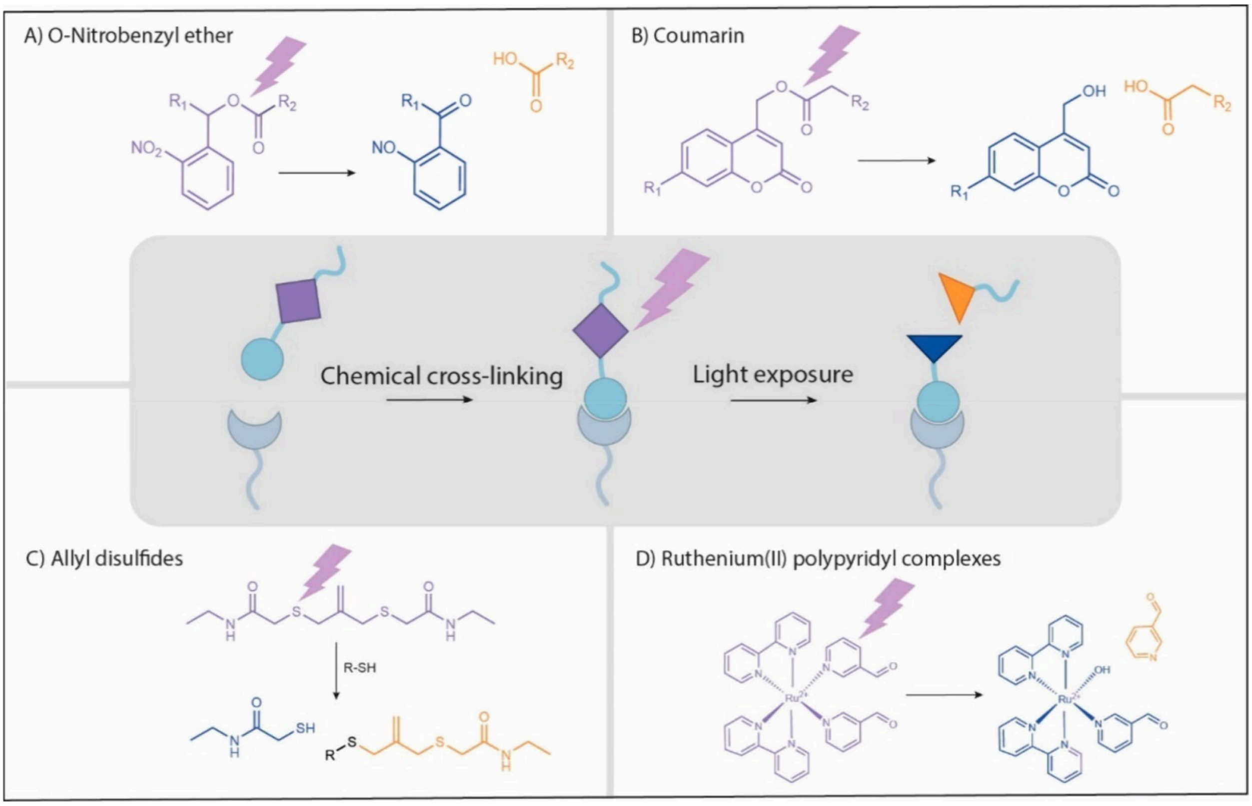

Figure 11. Representative types of photolabile groups commonly employed in light-responsive hydrogels for photodegradation or photoconjugation applications in tissue engineering, along with their associated single-photon activation wavelengths. (A) O-Nitrobenzyl ether; 365 nm and derivatives up to 480 nm, (B) coumarin derivatives; 320−500 nm, (C) allyl disulfides; 365 nm, and (D) ruthenium(II) polypyridyl complexes; 400−500 nm.[286] Reproduced with permission from ref 286. Copyright 2023 American Chemical Society under [CC BY 4.0].

accelerate hydrogel breakdown. Conversely, dense cross-linking may limit swelling but prolong material persistence, which is advantageous in chronic implantation scenarios. Therefore, swelling behavior should be evaluated not only by its magnitude but by its compatibility with therapeutic timeframes, route of administration, and local biological conditions. Rational hydrogel design thus requires integrated consideration of cross-linking type, network density, and environmental responsiveness to achieve context-specific functional performance.

3.4. Stimulus Responsiveness

3.4.1. Light Responsiveness. The light-responsive behavior of hydrogels is deeply influenced by the characteristics of their polymeric chains and cross-linking strategies, which govern the incorporation, distribution, and efficiency of photoactive moieties.[285] Adjustments to these structural parameters enable precise control of photoresponsive properties, enhancing the adaptability and functionality of hydrogels across various applications.[286]

The choice of polymeric chains plays a pivotal role in determining the efficiency of light responsiveness. Hydrophilic polymers such as poly(ethylene glycol) (PEG) and polyacrylamide (PAM) facilitate the uniform incorporation of photoactive moieties like azobenzene, spiropyran, or o-nitrobenzyl derivatives.[287] Their water-absorbing properties improve light penetration into the hydrogel matrix, which is particularly advantageous for applications requiring deep-tissue light delivery. Additionally, the molecular weight and chain length significantly influence the mobility of photoactive groups;[288] longer chains provide flexibility but may hinder light-induced conformational changes due to steric effects, whereas shorter chains allow faster responses but may compromise mechanical strength.[289] Thus, balancing chain length and molecular weight is essential for optimizing light responsiveness without detracting from structural integrity.

Polymer chain rigidity and functionalization further refine light-responsive properties. Flexible chains like PEG allow dynamic structural adjustments under light stimulation, whereas rigid chains, such as polystyrene derivatives, stabilize the network and prevent undesired deformations.[290] Functionalizing polymeric chains with photoactive groups or antifouling moieties enhances their responsiveness while maintaining structural durability.[291] These tailored designs ensure that hydrogels meet the demands of both dynamic applications, such as drug delivery, and those requiring mechanical stability, like tissue scaffolds.

Cross-linking strategies significantly influence light responsiveness by determining the network architecture and adaptability of hydrogels. Photoactive cross-linkers, such as azobenzene dimers and o-nitrobenzyl derivatives, introduce direct light-triggered control over the hydrogel's properties[286] (Figure 11). Azobenzene-based hydrogels undergo reversible changes between the cis and trans form of azobenzene molecules within the network structure under UV or visible light, enabling tunable swelling and stiffness. Moreover, o-nitrobenzyl-derived cross-linkers facilitate light-induced cleavage, allowing for controlled degradation or molecular release.[292]

Dynamic cross-linkers and hybrid systems offer enhanced adaptability and resilience. Reversible cross-linkers, such as boronic acid-diol complexes or host−guest interactions involving cyclodextrin, enable hydrogels to repeatedly adjust their structure in response to light without compromising integrity.[293] Hybrid cross-linking strategies, integrating both covalent and physical interactions, combine stability with responsiveness, allowing hydrogels to perform in complex environments requiring multifunctionality.[293]

Cross-linking density further modulates light-responsive behavior by balancing responsiveness and structural strength. High cross-linking densities create stable networks with limited chain mobility, resulting in controlled but less pronounced light-induced changes.[294] Conversely, lower densities allow greater responsiveness at the expense of mechanical robustness.[295] Carefully optimizing cross-linking density ensures that hydrogels achieve the desired balance between adaptability and stability, tailored to specific application needs.[296]

By meticulously designing polymeric chains and cross-linking systems, light-responsive hydrogels can achieve precise, efficient, and tunable behaviors. These strategies advance the development of smart materials for applications ranging from controlled drug delivery to adaptive soft robotics, ensuring both functionality and versatility in complex environments.

3.4.2. Thermal Responsiveness. Thermoresponsive hydrogels undergo dynamic and reversible phase transitions, volume changes, and network restructuring in response to temperature variations, making them highly valuable for applications in drug delivery, tissue engineering, and soft robotics.[297] These properties arise from the interplay of polymeric chain characteristics and cross-linking strategies, which together define the hydrogel's thermal behavior and mechanical performance. Through deliberate selection and design of components, hydrogels can be customized for targeted functions and environmental conditions.[298]

The polymeric backbone plays a pivotal role in determining the thermal responsiveness of hydrogels[299] (Figure 12A). Polymers like poly(*N*-isopropylacrylamide) (PNIPAM) exhibit a well-defined lower critical solution temperature (LCST), transitioning from a hydrophilic, swollen state below the LCST to a hydrophobic, collapsed state above it.[300] This behavior can be finely tuned through copolymerization with hydrophilic or hydrophobic monomers, allowing for the adjustment of the LCST for specific applications.[300] Chain architecture, including length and molecular weight, also modulates thermal responsiveness; longer chains enhance hydration and swelling, while shorter chains result in sharper transitions.[302] Flexible chain systems, such as PEG-based polymers, facilitate dynamic structural changes, whereas rigid chains provide stability, enabling versatile adaptation to thermal stimuli.[303]

Cross-linking is equally critical in shaping the hydrogel's network structure and thermal response[301] (Figure 12B). Covalent cross-links provide robust frameworks that withstand repeated swelling and deswelling cycles, while dynamic covalent cross-links, such as Schiff bases or disulfide bonds, introduce adaptability through reversible bonding.[304] Physical cross-linking mechanisms, such as hydrophobic interactions and hydrogen bonding, contribute to temperature-sensitive behavior, with hydrophobic domains driving sharp phase transitions and hydrogen bonds modulating swelling and mechanics.[305] Hybrid cross-linking strategies that combine both covalent and physical interactions balance mechanical stability with enhanced responsiveness, enabling hydrogels to perform effectively in demanding conditions.[305] The density of cross-linking further influences thermal behavior, with lower densities amplifying swelling and deswelling dynamics.

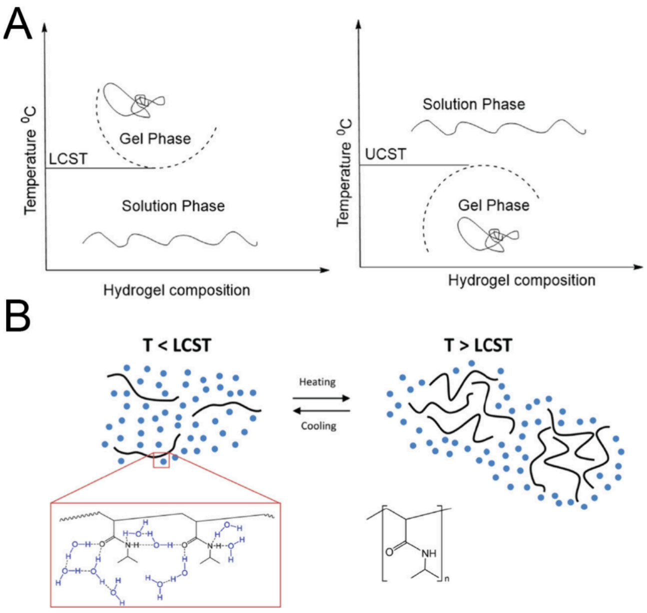

Figure 12. Thermoresponsive hydrogels. (A) Diagram depicting phase transitions: LCST-type hydrogels collapse when heated above their critical temperature, while UCST-type hydrogels swell upon cooling below their threshold.[299] Reproduced with permission from ref 299. Copyright 2022 MDPI under [CC BY 4.0]. (B) Schematic showing PNIPAAm polymer chains (black) interacting with water molecules (blue) across varying temperatures.[301] Reproduced with permission from ref 301. Copyright 2019 Elsevier.

3.4.3. pH Responsiveness. pH-responsive hydrogels undergo swelling and structural changes in response to variations in environmental pH, driven by the ionization or protonation of functional groups within their polymer networks[306] (Figure 13). This property, crucial for applications

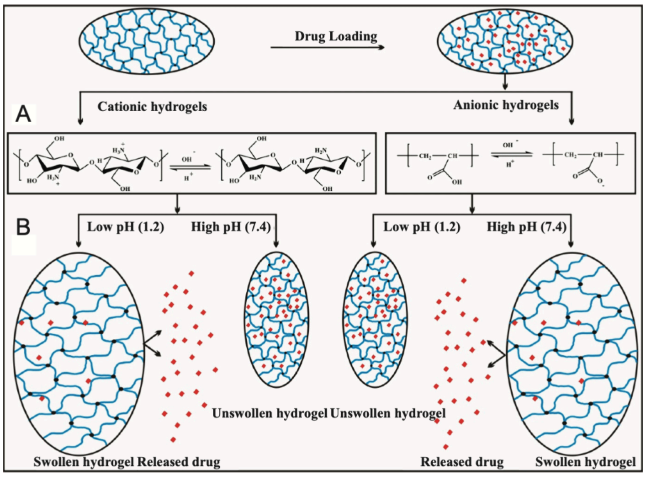

Figure 13. pH-responsive hydrogel drug release mechanism. (A) Schematic representation of cationic and anionic hydrogels used for drug loading, showing the molecular structures of representative hydrogel polymers. (B) Drug release behavior under different pH conditions. At low pH (1.2), the hydrogel remains unswollen, leading to limited drug release. At high pH (7.4), the hydrogel swells, promoting enhanced drug diffusion and release.[306] Reproduced with permission from ref 306. Copyright 2017 MDPI under [CC BY 4.0].

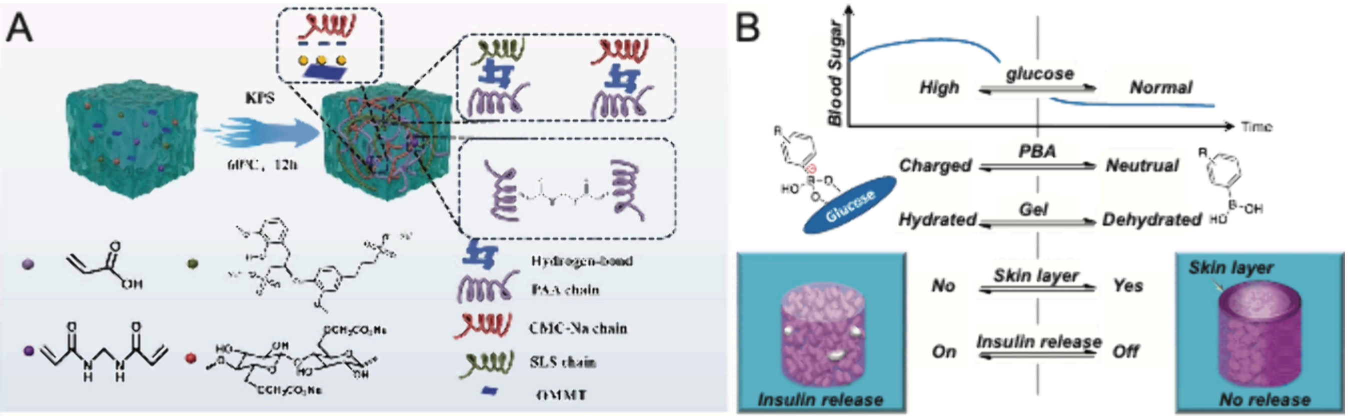

Figure 14. Smart hydrogel system for glucose-responsive insulin delivery. (A) Schematic of a hydrogel incorporating multiple functional polymers designed for controlled drug release, with each polymeric component enhancing stability and responsiveness.[325] Reproduced with permission from ref 325. Copyright 2024 Elsevier. (B) Mechanism of glucose-triggered insulin release. At elevated glucose levels, the hydrogel transitions from a gel to a hydrated state, enabling insulin diffusion and release. At normal glucose concentrations, it remains dehydrated, effectively preventing insulin leakage. The lower panels depict insulin release (left) and retention (right) depending on glucose concentration.[328] Reproduced with permission from ref 328. Copyright 2017 American Association for the Advancement of Science under [CC BY-NC 4.0].

in drug delivery, biosensing, and tissue engineering, is primarily determined by the choice of polymeric chains and cross-linking strategies. Polymers containing ionizable groups, such as carboxylic acids, amines, or sulfonic acids, are commonly used to achieve pH sensitivity.[307] Anionic polymers, like poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA), swell at higher pH due to the deprotonation of carboxylic acid groups, which creates electrostatic repulsion. Conversely, cationic polymers, such as poly(2-dimethylaminoethyl methacrylate) (PDMAEMA) and chitosan, swell under acidic conditions when amine groups are protonated.[308] Copolymerization with neutral or hydrophilic monomers, such as poly(ethylene glycol) (PEG) or polyacrylamide (PAM), is often employed to fine-tune responsiveness while ensuring mechanical stability.[309]

The architecture and molecular weight of polymeric chains further influence the hydrogel's pH sensitivity. Longer chains enhance swelling capacity by increasing flexibility, while branched or comb-like structures combine responsiveness with mechanical strength.[310] Functionalization with zwitterionic groups or other stabilizing moieties improves performance in complex biological environments, ensuring consistent behavior despite fluctuating conditions.[311] These features make polymeric chain design a cornerstone for achieving tailored pH responsiveness in hydrogels.

Cross-linking strategies play an equally crucial role in defining the adaptability and durability of pH-responsive hydrogels. Covalent cross-linkers, such as N,N′-methylenebis(acrylamide) (MBA), provide a stable framework capable of withstanding pH-induced swelling or deswelling cycles. Meanwhile, dynamic covalent bonds, such as Schiff-base linkages, offer reversible cross-linking that responds flexibly to pH changes.[312] Physical cross-linking mechanisms, including ionic interactions and hydrogen bonding, introduce reversible noncovalent interactions that enhance pH sensitivity.[313] For example, hydrogels cross-linked via multivalent ions, such as calcium-alginate networks, respond to pH variations by modulating ionic interactions, while hydrogen-bonded networks exhibit reversible structural adjustments.[314] Hybrid cross-linking approaches, combining covalent and physical interactions, ensure a balance of durability and responsiveness, allowing hydrogels to maintain structural integrity while adapting to environmental changes.

The mechanisms underlying pH-responsive behavior are rooted in osmotic pressure changes resulting from the ionization or protonation of functional groups.[315] At low pH, acidic groups remain protonated, minimizing electrostatic repulsion and reducing swelling, while at high pH, deprotonation increases repulsion, leading to network expansion. For example, chitosan-based cationic hydrogels, which contain protonated amine groups, swell at low pH and collapse at high pH due to pH-dependent electrostatic repulsion.[316] This controlled swelling behavior has enabled diverse applications, including drug delivery systems that exploit pH differences between tissues, like the acidic microenvironment of tumors or the gastric tract, for site-specific therapeutic release.[317] In biosensing, poly(acrylic acid)-based or poly(*N*-isopropylacrylamide-*co*-acrylic acid) hydrogels have been engineered to detect pH fluctuations in real time, as their swelling behavior and mechanical modulus change measurably in response to acidic or alkaline environments.[318] In tissue engineering, pH-responsive scaffolds adapt to local biological conditions, promoting cell adhesion, proliferation, and nutrient transport.[319]

Despite their potential, pH-responsive hydrogels face challenges in balancing sensitivity with mechanical integrity, as excessive swelling or deswelling can lead to structural instability.[267] Strategies to address these issues include designing hierarchical polymer architectures, employing hybrid cross-linking systems, and incorporating stabilizing elements like zwitterionic or hydrophobic groups to regulate hydration.[320] Future advancements lie in the development of multiresponsive hydrogels that integrate pH sensitivity with other stimuli, such as temperature or light, enabling precise control over material behavior in complex applications.[321] By refining polymeric chains and cross-linking strategies, pH-responsive hydrogels can evolve as versatile tools for next-generation smart materials, meeting the demands of biomedical, industrial, and environmental technologies.

3.4.4. Chemical Responsiveness. Chemically responsive hydrogels exhibit structural and functional alterations when exposed to specific stimuli, including ions, redox agents, and small molecules like glucose.[322] Such responsiveness is critical for drug delivery, biosensing, and tissue engineering, where fine-tuned environmental adaptation is essential.[323] These hydrogels operate through dynamic interactions or chemical processes, such as ionic binding, redox reactions, glucose sensing, and enzymatic degradation, allowing them to execute complex functions in both biomedical and industrial applications.[323]

Ion-responsive hydrogels are typically containing polyelectrolytes that swell or shrink based on ionic strength or specific ion concentrations.[324] For example, poly(acrylic acid)-based hydrogels exhibit swelling behavior modulated by changes in ionic strength, while hydrogels containing crown ethers demonstrate selective binding to target ions[325] (Figure 14A). Additionally, redox-responsive hydrogels utilize functional groups like disulfide bonds or ferrocene moieties to undergo reversible structural changes under oxidative or reductive conditions.[326] These hydrogels are particularly advantageous for applications such as tumor-targeted drug delivery, where elevated levels of intracellular glutathione can trigger hydrogel disassembly, facilitating localized drug release.

Glucose-responsive hydrogels, as part of chemically sensitive materials, exhibit remarkable potential in biomedical applications, especially in diabetes management and drug delivery.[327] By incorporating boronic acids, these hydrogels form reversible covalent bonds with glucose, leading to swelling or deswelling based on glucose concentrations[328] (Figure 14B). This responsiveness allows for controlled drug release, such as insulin delivery, in accordance with blood glucose levels. Additionally, enzymatic systems using glucose oxidase catalyze the conversion of glucose to gluconic acid, lowering the pH and inducing pH-sensitive behavior.[329] These hydrogels are widely utilized in glucose sensors and insulin delivery systems, offering precise control over material behavior in diabetic applications.

The polymeric chains used in chemically responsive hydrogels play a pivotal role in determining their sensitivity and specificity. Polymers with ionizable groups, such as poly(acrylic acid) or poly(sulfobetaine methacrylate), demonstrate high responsiveness to ions and glucose, due to their high reactivity and strong hydration properties.[330] Redox-active polymers, such as polythiols or poly(ferrocenylsilane), enable hydrogels to adapt reversibly to oxidative or reductive environments.[331] Functional polymers with enzyme-cleavable or glucose-binding groups further enhance the specificity of chemical responsiveness, enabling precise control over hydrogel behavior.[332]

Cross-linking strategies also significantly influence the chemical responsiveness of these hydrogels by controlling network architecture and adaptability.[333] Dynamic covalent cross-linkers, such as boronic acid-diol complexes and disulfide bonds, enable reversible network formation and degradation in response to chemical stimuli, allowing hydrogels to adapt and degrade based on environmental conditions.[333] Hydrogels cross-linked with cleavable bonds, such as esters or hydrazones, enable controlled disassembly under defined conditions, including pH shifts or oxidative stress.[334] Additionally, ionic cross-linkers, such as multivalent ions in alginate-based hydrogels, permit rapid adjustment to changes in ionic strength, rendering them suitable for applications in biosensing and marine environments.[314]

Chemically responsive hydrogels are increasingly employed in advanced biomedical applications. For instance, they enable targeted and controlled drug delivery by responding to environmental cues, such as glucose levels or oxidative states, to release therapeutics at the desired site. In tissue engineering, chemically degradable hydrogels promote scaffold degradation, enhance cell migration, and promote tissue regeneration. In biosensing, these hydrogels provide precise and sensitive detection of biological or environmental analytes. The strategic combination of tailored polymeric chains and cross-linking strategies ensures that chemically responsive hydrogels can meet the demands of dynamic biological applications, ensuring adaptability and precision.

3.4.5. Tuning the Stimuli Responsiveness of Therapeutic Hydrogel.

The incorporation of stimuli-responsive behavior into hydrogels offers a powerful strategy for enhancing their functional precision in biomedical applications. Hydrogels that respond to environmental triggers, such as pH, temperature, redox potential, enzymatic activity, or small-molecule analytes, can dynamically regulate drug release, network remodeling, or degradation in a controlled spatiotemporal manner. However, their effectiveness relies heavily on the nature of the chemical modifications that mediate these transitions, and their suitability must be critically evaluated within the context of specific therapeutic objectives.

pH-responsive hydrogels typically incorporate ionizable moieties such as carboxylic acids (e.g., in poly(acrylic acid), alginate, or hyaluronic acid) or primary amines (e.g., in chitosan or poly(L-lysine)), which undergo protonation or deprotonation in response to changes in local pH. These reversible ionic transitions affect osmotic swelling pressure and chain conformation, leading to controllable volumetric or permeability changes. In acidic tumor microenvironments or inflamed tissues, carboxyl-rich hydrogels can swell and facilitate drug release. However, overly acidic or basic pK_a shifts can compromise responsiveness in physiologically buffered regions, underscoring the need to tune group pK_a and substitution density.

Thermoresponsive hydrogels often exploit lower critical solution temperature (LCST) behavior, as exemplified by poly(*N*-isopropylacrylamide) (PNIPAAm), whose thermosensitivity arises from hydrophobic isopropyl groups that undergo temperature-induced phase separation.[335] Above ∼ 32 °C, PNIPAAm transitions from hydrophilic to hydrophobic, driving hydrogel collapse. Copolymerization with hydrophilic (e.g., PEG) or hydrophobic monomers allows precise adjustment of the LCST for specific tissue environments. Other systems incorporate poly(ethylene glycol)-*b*-poly(propylene glycol) (PEG−PPG) or elastin-like polypeptides, enabling reversible sol−gel behavior suitable for injectable formulations or temperature-controlled delivery.[336]

Redox-responsive hydrogels are engineered with cleavable disulfide bonds (−S−S−), thioketal linkages, or ferrocene−ferrocenium pairs, which respond to intracellular glutathione levels or oxidative bursts. Disulfide-based cross-linkers degrade in reductive cytosolic environments, facilitating cargo release inside cells, whereas thioketal moieties undergo oxidative cleavage in inflammatory sites. These groups are typically incorporated as dynamic covalent cross-linkers or pendant side chains. While offering high selectivity, their stability under ambient storage conditions or during sterilization must be carefully managed.

Enzyme-responsive hydrogels rely on the incorporation of cleavable peptide sequences that serve as substrates for specific proteases. For instance, MMP-sensitive motifs (e.g.,

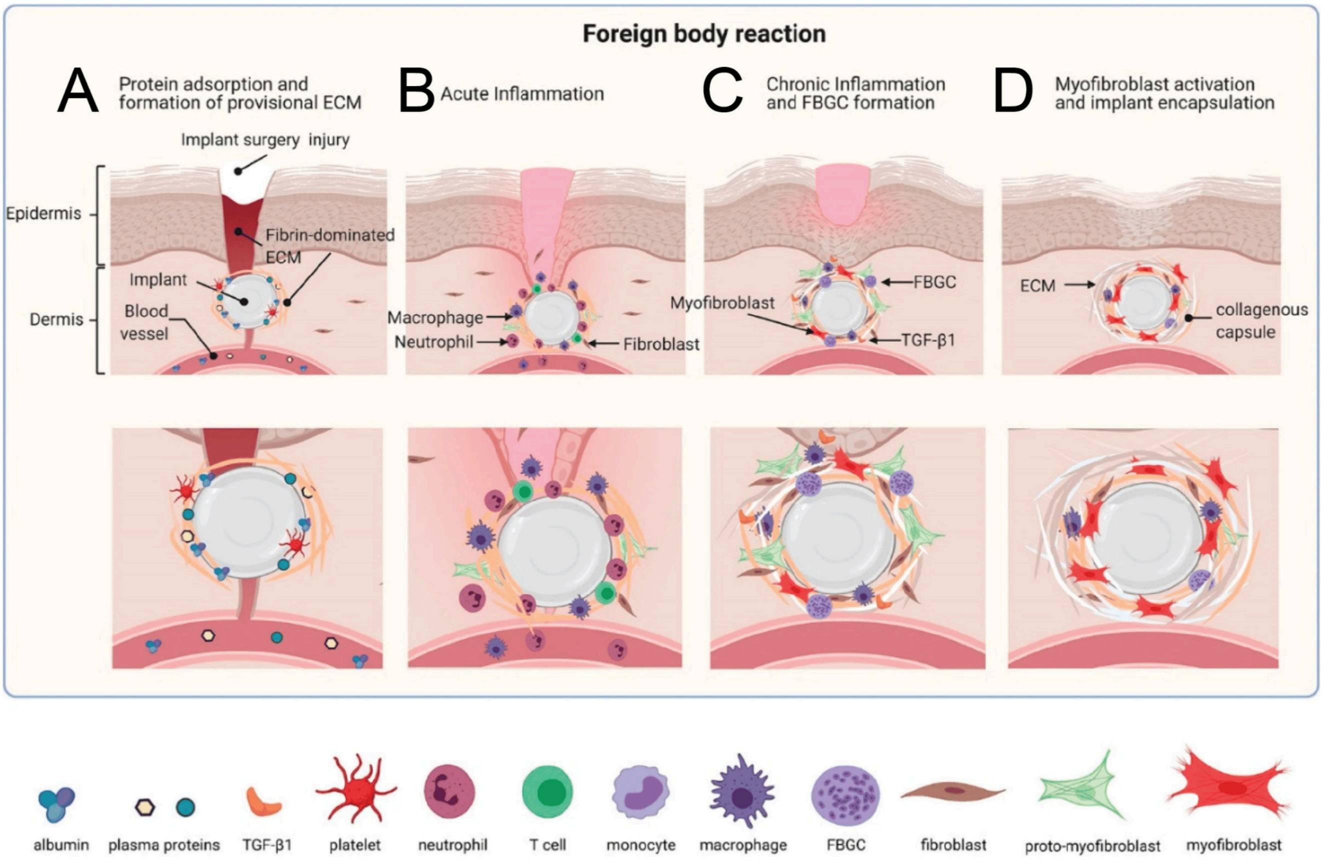

Figure 15. Foreign body response to implantable biomaterials. Implantation initiates a multiphase foreign body response comprising four stages. (A) Initially, plasma proteins such as albumin and fibrin adsorb onto the implant surface, forming a provisional extracellular matrix (ECM). (B) Subsequently, acute inflammation occurs, marked by neutrophil and macrophage recruitment to the injury site and release of inflammatory mediators. (C) Persistent inflammation transitions to a chronic phase, featuring foreign body giant cell (FBGC) formation through macrophage fusion, fibroblast infiltration, and ECM accumulation, with TGF-β1 driving fibrotic remodeling. (D) Finally, myofibroblasts activate, promoting collagen deposition and encapsulation of the implant within a dense fibrotic capsule, potentially compromising long-term biocompatibility and performance. This cascade underscores the intricate immune response to biomaterials and highlights the need for implant designs that mitigate chronic inflammation and fibrosis.[340] Reproduced with permission from ref 340. Copyright 2021 MDPI under [CC BY 4.0].

GPQGIWGQ) can be embedded into PEG-based networks, enabling selective degradation in tumors or chronic wounds.[337] The sequences can be engineered into cross-linkers or grafted onto backbone chains. Other common enzymatic targets include elastase, thrombin, and hyaluronidase. Success depends not only on cleavage kinetics but also on enzyme accessibility and retention in vivo, which are influenced by hydrogel mesh size and tissue penetration.

Chemical-analyte-responsive hydrogels are designed to respond to small molecules such as glucose, urea, lactate, or ROS. These systems often integrate molecular recognition elements such as phenylboronic acid (for glucose binding via reversible diol complexation), ROS-cleavable thioketals, or imine/hydrazone bonds for reversible covalent sensing. For example, in glucose-sensitive insulin depots, phenylboronic acid-modified hydrogels respond to hyperglycemia by altering their swelling or degradation rates.[338] Such functionalities must be optimized to prevent nonspecific reactivity, ensure long-term recognition fidelity, and maintain functional sensitivity under fluctuating physiological conditions.

Ultimately, the responsiveness of a hydrogel depends not only on the selected trigger and chemical motif, but also on the density, accessibility, and dynamic reversibility of these functional groups within the 3D network. Multistimuli-responsive hydrogels that integrate multiple chemistries, e.g., pH/redox dual-responsive designs, offer enhanced specificity but can suffer from synthetic complexity, reduced reproducibility, and more stringent regulatory challenges.[339] As with swelling behavior, the responsiveness profile must be matched to the therapeutic time frame, delivery route, and disease pathology. A rational design strategy thus requires not only a deep understanding of stimuli chemistry but also of the hierarchical structure−function relationships that govern hydrogel performance in vivo.

4. REGULATION OF BIOLOGICAL PROPERTIES OF HYDROGELS

4.1. Biocompatibility

4.1.1. Foreign-Body Reaction of Implanted Hydrogels. The foreign-body reaction (FBR) represents a critical immunological response to implanted hydrogels, significantly influencing their functionality and long-term compatibility in biomedical applications[340] (Figure 15A-D). Upon implantation, hydrogels often trigger a cascade of immune responses, starting with protein adsorption and immune cell recruitment, followed by the formation of a fibrous capsule.[341] This encapsulation can isolate the hydrogel from surrounding tissues, impairing its intended functions, such as drug delivery or tissue integration.

The intensity of the FBR is influenced by the hydrogel's physicochemical properties, including material composition, surface chemistry, mechanical properties, and degradation behavior.[342] Hydrogels composed of inert or biocompatible materials, such as PEG or zwitterionic polymers, exhibit reduced immune activation due to their ability to resist protein adsorption and mitigate immune cell adhesion.[343] The hydration layers formed by these hydrophilic polymers minimize fouling and immune activation, effectively dampening the FBR.[344]

Surface chemical properties also play a pivotal role in modulating the immune response. Functionalization with bioactive molecules, such as anti-inflammatory agents or immunomodulatory peptides, can suppress macrophage activation and fibrous capsule formation.[345] For instance, zwitterionic coatings on hydrogel surfaces not only prevent nonspecific protein adsorption but also reduce macrophage adhesion, thereby minimizing chronic inflammation.[250] Conversely, hydrogels with reactive or nonbiodegradable components can exacerbate the FBR by triggering oxidative stress or prolonged immune activation.[250]

The mechanical and geometrical properties of hydrogels further influence the FBR. For example, hydrogels with mechanical stiffness that matches surrounding tissues are less likely to provoke immune responses, as they avoid creating abnormal mechanical environments that can stimulate macrophage polarization toward a pro-inflammatory phenotype.[346] Additionally, hydrogels with smooth or porous surfaces are often better tolerated, as irregular geometries can trap immune cells and enhance inflammatory signaling.

Cross-linking density and network architecture also determine hydrogel biocompatibility. Highly cross-linked networks provide mechanical stability and resistance to degradation but may lead to chronic immune responses due to their persistence in tissues.[347] In contrast, hydrogels with biodegradable cross-linkers, such as enzymatically cleavable peptides or hydrolytically labile bonds, degrade over time, reducing the duration of immune exposure and facilitating natural tissue integration.[348] Dynamic covalent cross-linkers, such as imine or disulfide bonds, offer additional benefits by enabling hydrogels to adapt to the surrounding tissue environment, mitigating prolonged immune responses.[349]

Emerging strategies to reduce the FBR include incorporating immunomodulatory agents into the hydrogel matrix and designing smart, stimuli-responsive hydrogels that release anti-inflammatory drugs in response to heightened immune activity.[350] By tailoring polymeric chain properties, surface chemistry, and cross-linking architecture, hydrogels can be engineered to minimize FBR, ensuring their efficacy and compatibility in long-term biomedical applications.[351] These advances underscore the importance of understanding and addressing the complex interplay between hydrogels and the immune system to optimize their performance in vivo.

4.1.2. Cross-Linking Network Choice. The cross-linking network architecture of hydrogels plays a pivotal role in determining their biocompatibility by influencing their mechanical properties, degradation behavior, and interactions with biological tissues.[173] An optimally designed cross-linking network minimizes adverse immune responses, enhances integration with host tissues, and maintains functionality for specific biomedical applications, such as drug delivery, tissue engineering, and regenerative medicine.[352]

Hydrogels with chemically inert and stable cross-linkers, such as poly(ethylene glycol) diacrylate (PEGDA), often exhibit enhanced biocompatibility due to their resistance to protein adsorption and immune cell adhesion.[353] These cross-linkers create a neutral and hydrophilic surface that reduces nonspecific interactions with biological molecules, mitigating the risk of inflammation and fibrous encapsulation.[354] Additionally, hydrogels cross-linked using bioinspired or naturally derived agents, such as enzymatically cleavable peptides or polysaccharides, leverage their inherent biocompatibility to promote cellular attachment, proliferation, and tissue integration.[329] For instance, alginate or hyaluronic acid–based cross-linkers facilitate cell adhesion and matrix remodeling while minimizing chronic immune responses.[355]

The use of dynamic and stimuli-responsive cross-linkers, such as boronic acid-diol complexes or reversible disulfide bonds, further enhances biocompatibility by allowing the hydrogel to adapt to its biological environment.[268] Such networks facilitate controlled degradation or remodeling in response to physiological cues—including variations in pH, redox state, and enzymatic activity—promoting seamless integration of the hydrogel with surrounding tissues.[356] Hydrogels cross-linked with such dynamic systems are particularly advantageous for applications where biodegradability and controlled material clearance are critical, such as temporary scaffolds in wound healing or drug-eluting implants.[357]

Biodegradable cross-linkers, including ester or hydrazone bonds, provide an additional layer of biocompatibility by enabling controlled hydrogel degradation.[358] The breakdown products of these cross-linkers are often nontoxic and can be metabolized or cleared by the body, minimizing the risk of long-term inflammation or tissue damage.[359] Enzymatically cleavable cross-linkers, designed to respond to specific biological signals, offer precise control over degradation rates, allowing hydrogels to align with the dynamic needs of tissue regeneration or drug release.[360]

Hybrid cross-linking systems that combine covalent and physical interactions provide a promising approach to balancing mechanical stability and biocompatibility.[361] For instance, ionic cross-linkers, such as calcium-alginate bonds, can enhance hydrogel stability while maintaining a degree of flexibility and adaptability to biological environments.[362] Similarly, double-network hydrogels, composed of a rigid covalent network and a soft physical network, exhibit superior mechanical properties without compromising biocompatibility.[363]

However, the choice of cross-linking network must carefully balance structural integrity and biological compatibility. Overly rigid or nondegradable cross-linkers can provoke foreign-body reactions by creating persistent and nonresorbable materials in vivo.[364] Conversely, excessively soft or rapidly degrading networks may fail to provide sufficient mechanical support or controlled functionality.[364] Future developments in cross-linking strategies focus on integrating immunomodulatory agents, such as anti-inflammatory drugs or peptides, within the hydrogel network to further minimize immune activation and enhance biocompatibility.[345] Through careful design of cross-linking networks, hydrogels can be tailored to meet the specific demands of biomedical applications, ensuring both functional performance and long-term safety.

4.1.3. Mechanical and Geometrical Property. The mechanical and geometrical properties of hydrogels are critical determinants of their biocompatibility, influencing their interaction with surrounding tissues, cellular behavior, and functional performance in biomedical applications.[365] The mechanical properties, including stiffness, elasticity, and toughness, dictate the hydrogel's ability to mimic native tissue environments, while the geometrical features, such as shape and porosity, regulate cell infiltration, nutrient diffusion, and tissue integration.[173]

The stiffness of hydrogels is a key determinant of cellular behavior, influencing processes such as adhesion, proliferation, and differentiation. Hydrogels with low stiffness (<1 kPa) are particularly advantageous for neural and adipose tissue applications, as they mimic the softness of native tissues and minimize mechanical irritation and foreign body responses.[366] Conversely, hydrogels with moderate to high stiffness (1−100 kPa) are essential for applications involving load-bearing tissues, such as cartilage or bone, where they provide structural support and resistance to mechanical deformation.[367] However, excessively stiff hydrogels may induce fibrous encapsulation or chronic inflammation, necessitating careful tuning of mechanical properties to balance functionality with biocompatibility.[368]

Elasticity and toughness also influence the hydrogel's long-term performance and compatibility. Highly elastic hydrogels can withstand repetitive deformations without mechanical failure, making them suitable for dynamic environments such as cardiovascular or musculoskeletal tissues.[369] Tough hydrogels, designed with double-network architectures or sacrificial bonds, combine mechanical resilience with damage resistance, ensuring sustained functionality under physiological stresses.[370]

The geometrical properties of hydrogels, including porosity and shape, are equally vital for their biocompatibility. Highly porous hydrogels facilitate cell infiltration, nutrient transport, and waste removal, promoting tissue integration and reducing the risk of necrosis.[371] The pore size and connectivity must be optimized for specific applications; for instance, microporous hydrogels with pore sizes of 10−50 μm are ideal for facilitating angiogenesis, while larger pores (>100 μm) are optimal for osteogenesis and bone regeneration, allowing for cell migration and mineral deposition.[372] Injectable hydrogels, capable of conforming to irregular tissue geometries, improve biocompatibility by minimizing mechanical mismatch and reducing the risk of irritation or rejection.

Surface topography and patterning further enhance hydrogel biocompatibility by influencing cell behavior and tissue integration. Micropatterned or nanopatterned surfaces can guide cell alignment, proliferation, and differentiation, mimicking the ECM structure and promoting functional tissue regeneration.[373] Additionally, smooth hydrogel surfaces minimize protein adsorption and immune cell adhesion, reducing inflammatory responses and improving long-term biocompatibility.[273]

Tailoring the mechanical and geometrical properties of hydrogels requires a comprehensive understanding of the target application and tissue environment.[349] Strategies to achieve this include tuning polymer concentration, cross-linking density, and the incorporation of dynamic cross-linkers.[374] Hybrid hydrogels, integrating physical and covalent networks, offer enhanced mechanical adaptability while maintaining biocompatibility.[375] Advanced fabrication techniques, such as 3D bioprinting or microfluidic templating, enable precise control over hydrogel geometry, ensuring compatibility with specific biological contexts.[351]

Designing hydrogels with finely tuned mechanical and geometrical characteristics enables the development of materials that integrate harmoniously with host tissues, promote cellular activity, and sustain long-term stability.[376] Such progress continues to broaden the applications of hydrogels in tissue engineering, regenerative therapies, and implantable devices, ensuring high functional efficacy alongside biocompatibility.[350]

4.1.4. Surface Chemical Property.

The surface chemical properties of hydrogels play a pivotal role in determining their biocompatibility, as they directly influence interactions with biological tissues, proteins, and cells.[377] The composition, charge, hydrophilicity, and functionalization of the hydrogel surface govern protein adsorption, immune response, and cellular behavior, making surface chemistry a critical design parameter for biomedical applications.[225]

Surface hydrophilicity is a key factor affecting hydrogel biocompatibility. Hydrophilic surfaces, achieved through polymers such as PEG or poly(vinyl alcohol) (PVA), resist protein adsorption and cell adhesion by forming a dense hydration layer.[378] This antifouling property minimizes undesired immune responses and inflammation, ensuring compatibility with surrounding tissues.[379] Conversely, hydrophobic surfaces tend to adsorb proteins nonspecifically, potentially leading to immune activation and fibrous encapsulation.[380] Balancing hydrophilicity and hydrophobicity is essential for applications requiring controlled cell adhesion, such as tissue engineering, where selective cell attachment and growth are desired.[381]

Surface charge also significantly impacts the biocompatibility of hydrogels. Neutral or zwitterionic surfaces, such as those containing sulfobetaine or carboxybetaine moieties, exhibit excellent antifouling properties by maintaining a dense hydration shell even in high-salinity environments.[221] These zwitterionic surfaces effectively reduce protein adsorption and immune cell activation, enhancing long-term biocompatibility. Positively charged surfaces, while promoting initial cell adhesion, may lead to excessive protein adsorption and inflammatory responses.[382] Conversely, negatively charged surfaces, such as those incorporating carboxylic acid groups, facilitate interactions with specific cell types, such as osteoblasts, while resisting nonspecific protein binding.[383]

Functionalizing hydrogel surfaces with bioactive molecules enhances their biocompatibility by mimicking the ECMECM and promoting cellular interactions. For instance, specific functional groups such as RGD peptides, laminin, or fibronectin, promote specific cell adhesion, proliferation, and differentiation, enabling hydrogels to support tissue regeneration.[384] Additionally, the incorporation of anti-inflammatory or immunomodulatory molecules, such as heparin or corticosteroids, can mitigate immune responses and improve the integration of implanted hydrogels with host tissues.[385]

Dynamic surface modifications further enhance hydrogel biocompatibility by enabling adaptation to physiological conditions.[350] For example, hydrogels functionalized with pH- or temperature-responsive groups can alter their surface properties in response to local environmental changes, promoting favorable interactions with surrounding tissues.[386] Similarly, hydrogels with reversible chemical groups, such as boronic acid-diol complexes or disulfide bonds, allow for self-healing and adaptive behavior, ensuring long-term compatibility in dynamic biological environments.[246]

Surface roughness and topography also contribute to hydrogel biocompatibility. Smooth surfaces reduce protein adsorption and immune activation, thereby reducing inflammatory responses. Moreover, micro- or nanotextured surfaces can promote specific cellular interactions by mimicking natural ECM structures.[387] For example, nanostructured hydrogel surfaces have been shown to enhance endothelial cell adhesion and proliferation, promoting vascularization in tissue engineering applications.[358]

Selecting appropriate cross-linkers and polymer compositions is essential for tuning the surface chemistry of hydrogels. Incorporation of hydrophilic or zwitterionic polymers enhances antifouling performance, whereas covalent attachment of bioactive molecules imparts specific cell-adhesive characteristics.[227] Moreover, advanced surface modification approaches, including plasma treatment and click chemistry, enable precise control over surface functionalities, facilitating tailored interactions with target tissues.[358]

By optimizing surface chemical properties, hydrogels can achieve a delicate balance between antifouling behavior and targeted cell adhesion, ensuring biocompatibility in diverse biomedical applications.[228] Progress in surface chemistry design continues to advance hydrogels as versatile materials for applications in tissue engineering, drug delivery, and implantable devices, promoting better integration with biological environments and reducing undesired immune reactions.

4.1.5. Immune Response and Immunomodulatory Design Considerations.

While biocompatibility is a foundational criterion for hydrogel use in vivo, immunological interactions, particularly those linked to cross-linking chemistry, degradation byproducts, and material stiffness, play an equally pivotal role in dictating clinical success or failure. Hydrogels implanted *in vivo* may elicit a foreign body reaction (FBR) characterized by macrophage activation, fibrous capsule formation, and persistent inflammation. The severity of this response is often influenced by the nature of the cross-linking chemistry. For instance, permanent covalent bonds formed via radical polymerization (e.g., acrylate-based PEGDA) have been associated with residual monomer toxicity and oxidative stress. In contrast, dynamic covalent networks (e.g., imine, hydrazone) and physically assembled gels tend to generate milder immune profiles due to their reversibility and reduced cross-linker burden. Furthermore, degradation products such as aldehydes or acidic monomers (e.g., from PLA, PLGA) can exacerbate inflammation by lowering local pH or disrupting membrane integrity. Surface functional groups, especially reactive aldehydes or charged residues, may also trigger protein adsorption and immune recognition.[388−390]

Beyond chemistry, mechanical and microstructural parameters such as stiffness, pore size, and mesh density modulate immune cell infiltration and polarization. Softer hydrogels (<10 kPa) generally favor M2-like macrophage polarization, associated with tissue repair, while stiffer materials (>50−100 kPa) may induce M1 polarization and pro-inflammatory cytokine release.[391,392] Similarly, hydrogels with larger pore sizes (>50 μm) allow for macrophage and T cell infiltration, whereas nanoporous structures tend to sequester immune cells at the periphery. This suggests that architectural tuning can be a viable route for modulating the host immune response.[393]

Recent advances have enabled the engineering of immuno-informed hydrogel systems capable of actively regulating inflammation and tissue repair. Strategies include controlled release of anti-inflammatory cytokines (e.g., IL-10, TGF-β1), incorporation of ECM-mimetic motifs (e.g., RGD, collagen peptides), zwitterionic or PEGylated surface modifications to reduce protein adsorption and immune cell adhesion, micropatterned or topographically structured hydrogels to influence macrophage phenotype via mechano-transduction, and enzyme-responsive degradability tailored to resolve with inflammatory cycles.[394] These approaches represent a promising frontier in hydrogel research aimed at minimizing immunotoxicity while enhancing therapeutic efficacy.

4.1.6. Mechanism-Informed Hydrogel Design: Synchronizing Material Performance with Biological Programs.

While the preceding sections describe general biocompatibility and immunological considerations, optimal therapeutic hydrogel design requires a mechanistically integrated approach—one that aligns material behavior with the cellular and molecular programs governing specific disease states. Increasing evidence demonstrates that hydrogels are not passive scaffolds but active participants in modulating cell fate, immune responses, and tissue remodeling through well-defined signaling axes.[395] Understanding these mechanisms is essential for engineering hydrogels that interact with and direct biological outcomes, rather than merely coexisting within tissue environments.

A prominent example of such interaction lies in mechanotransduction pathways, where matrix stiffness and viscoelasticity regulate stem cell lineage commitment. The YAP/TAZ (Yes-associated protein/transcriptional coactivator with PDZ-binding motif) pathway is one such mechanosensitive axis. Hydrogels with elastic moduli exceeding ∼ 30 kPa induce nuclear translocation of YAP/TAZ in mesenchymal stem cells (MSCs), triggering osteogenic differentiation through Runx2 and osteocalcin transcription.[396,397] Softer hydrogels (<1 kPa) restrict this activation, instead supporting adipogenic or neurogenic fates. Viscoelastic properties and integrin clustering further modulate these effects via the FAK−PI3K−AKT/mTOR pathway, reinforcing the importance of designing matrix stiffness in concert with cytoskeletal signaling requirements.[398]

Beyond differentiation, hydrogel mechanics and architecture also influence immune cell behavior. Stiff or nanoporous hydrogels tend to promote M1-like macrophage polarization and chronic inflammation, while soft and porous matrices support M2-like phenotypes associated with tissue repair and IL-10 production.[399] These immunological outcomes are often regulated through the IL-4/STAT6 and NF-κB pathways, the latter being especially sensitive to surface chemistry, degradation byproducts, and reactive moieties such as aldehydes or acrylates.[399,400] Functionalization with PEG or zwitterionic polymers can attenuate protein adsorption and reduce TLR-mediated immune activation, illustrating the immune-modulatory potential of surface and network-level chemical tuning.

Hydrogel degradation and therapeutic release kinetics must also be rationally designed to match the temporal dynamics of disease progression. In acute conditions such as traumatic injuries or surgical inflammation, rapid-onset drug release within the first 1−3 days is crucial to control edema, bacterial colonization, and immune activation. Ionically cross-linked alginate gels, poloxamer-based thermo-gels, or low-MW PEG-esters offer short-term residence and burst release, clearing naturally with wound closure. In contrast, chronic pathologies such as osteoarthritis, fibrosis, or tumor recurrence require sustained drug or cytokine delivery over weeks to months. Hydrogels with hydrolytically cleavable ester bonds (e.g., PLGA−PEG−PLGA), enzymatically cleavable linkers (e.g., MMP-sensitive GelMA), or dynamic covalent bonds (e.g., disulfides or imines) enable programmable matrix erosion aligned with longer therapeutic timelines.[399,401]

Moreover, degradation-triggered drug release can be made conditional upon disease-specific stimuli. Inflammatory microenvironments rich in ROS or low pH can cleave thioketal, arylboronic ester, or acid-labile cross-linkers, ensuring spatial and temporal specificity in drug activation. Such stimulus-matched delivery has been validated in inflamed joints, tumor tissues, and infected wounds, where material responsiveness becomes integral to therapeutic precision. In immunotherapy and vaccination, hydrogel systems capable of staggered release, through compartmentalization or affinity binding, can replicate infection dynamics, enhance antigen processing, and extend immune memory.[402]

Additionally, hydrogel degradation products may themselves influence biological programs. PEG-based networks yield bioinert fragments, while polyesters (e.g., PLA, PCL) or oxidized polysaccharides may release acidic or immunogenic byproducts that affect local pH or immune cell recruitment.[346] In contrast, some hydrogel fragments, such as hyaluronic acid oligomers or self-assembling peptides, have demonstrated pro-regenerative roles, stimulating angiogenesis or stem cell migration, particularly in ischemic or fibrotic tissues.[403]

Altogether, these examples highlight the need for disease-contextual material design, where the hydrogel's mechanical properties, degradation trajectory, biochemical presentation, and immunological footprint are engineered in harmony with the cellular and temporal logic of pathology.[404] Future hydrogel platforms will likely combine mechanosensitive scaffolds, immune-informed chemistries, and chronotherapeutic delivery strategies to synergize with endogenous repair programs and maximize therapeutic impact.

4.2. Therapeutic Cargo Loading and Release

4.2.1. Loading Strategy. *4.2.1.1. Small-Molecule Cargo.* The loading of therapeutic small molecules into hydrogels is fundamental to advanced drug delivery systems, providing controlled release and enhanced therapeutic outcomes.[388] The high-water content and tunable properties of hydrogels make them ideal matrices for small-molecule encapsulation, offering biocompatibility and environmental responsiveness.[389] The choice of loading strategy profoundly influences the release kinetics, drug stability, and overall functionality of the hydrogel system.[391]

Physical entrapment, one of the simplest methods, involves mixing therapeutic agents with the prepolymer solution before gelation.[366] As the hydrogel network forms, the small molecules become physically trapped within the hydrogel matrix.[366] While straightforward and compatible with diverse hydrogel systems, this method often leads to diffusion-driven release, which may cause burst release or uneven drug distribution.[393]

Chemical conjugation provides a controlled method by covalently linking small molecules to hydrogel matrices through reactive functional groups.[394] For example, amine-containing drugs can form stable Schiff bases or Michael adducts within the hydrogel network.[395] Incorporating degradable linkers, such as disulfide or ester bonds, enables stimulus-responsive drug release under conditions like oxidative stress or pH variation.[396] This approach offers precise and sustained release profiles, making it particularly suitable for highly specific applications, including targeted cancer therapies.[398] Alternatively, host−guest chemistry, as demonstrated by cyclodextrin-based hydrogels,[399] employs reversible inclusion complexes with hydrophobic drugs, allowing dynamic loading and release triggered by pH or ionic strength shifts.[405]

Hydrogels designed with ionic or hydrophobic domains expand the range of drug loading capabilities.[406] Ionic hydrogels, constructed from polyelectrolyte polymers, enable electrostatic binding of charged therapeutic molecules.[407] The release from these systems is highly dependent on environmental ionic strength and pH, providing tunable control over drug diffusion.[408] Similarly, hydrophobic modifications within hydrogels, such as the incorporation of stearyl methacrylate, create microdomains that stabilize hydrophobic drugs, reducing burst release and enhancing therapeutic stability.[409]

Beyond conventional approaches, more complex strategies integrate nanoparticles loaded with small molecules into the hydrogel matrix, enabling dual-release mechanisms. In these systems, nanoparticles control diffusion, while the hydrogel regulates transport, achieving sequential or sustained drug release. Additionally, the precipitation of drug crystals within the hydrogel during gelation offers another means of achieving sustained release by limiting drug solubility.[410] By limiting drug solubility, this approach ensures gradual dissolution and extended release, maintaining therapeutic efficacy over prolonged periods.[410] However, challenges remain in achieving uniform drug distribution and preventing premature release.[411] Innovations in hybrid hydrogels, combining dynamic and covalent cross-linking, or the application of advanced technologies like 3D printing, hold promise for addressing these limitations.[412] With ongoing advancements and innovations, hydrogel-based drug delivery systems are evolving to provide unprecedented precision and adaptability, meeting the complex demands of modern medicine.[413]

4.2.1.2. Biological Cargo. Embedding therapeutic biological agents—including proteins, peptides, nucleic acids, and cells—within hydrogels marks a significant breakthrough in drug delivery, regenerative medicine, and tissue engineering.[45] Hydrogels offer an ideal matrix for preserving the bioactivity of these biomolecules while enabling controlled and localized release.[376] The high-water content mimics the extracellular matrix, maintaining a favorable environment for biological cargo stability and activity.[413] The design of hydrogel systems for biological cargo loading requires meticulous consideration of network architecture, encapsulation strategies, and release mechanisms to ensure optimized therapeutic outcomes.[414]

Physical entrapment is a widely used approach for incorporating biological cargo into hydrogels.[415] This approach involves embedding proteins, peptides, or nucleic acids within the hydrogel matrix during gelation.[416] Mild gelation techniques, such as ionotropic gelation in alginate or enzymatic cross-linking in fibrin, are particularly advantageous for preserving the structural integrity and activity of bioactive molecules.[417] However, physical entrapment often leads to diffusion-controlled release, which may result in burst release or uneven distribution, especially for small biomolecules.[418]

To address these limitations, covalent conjugation strategies have been developed, wherein therapeutic biomolecules are

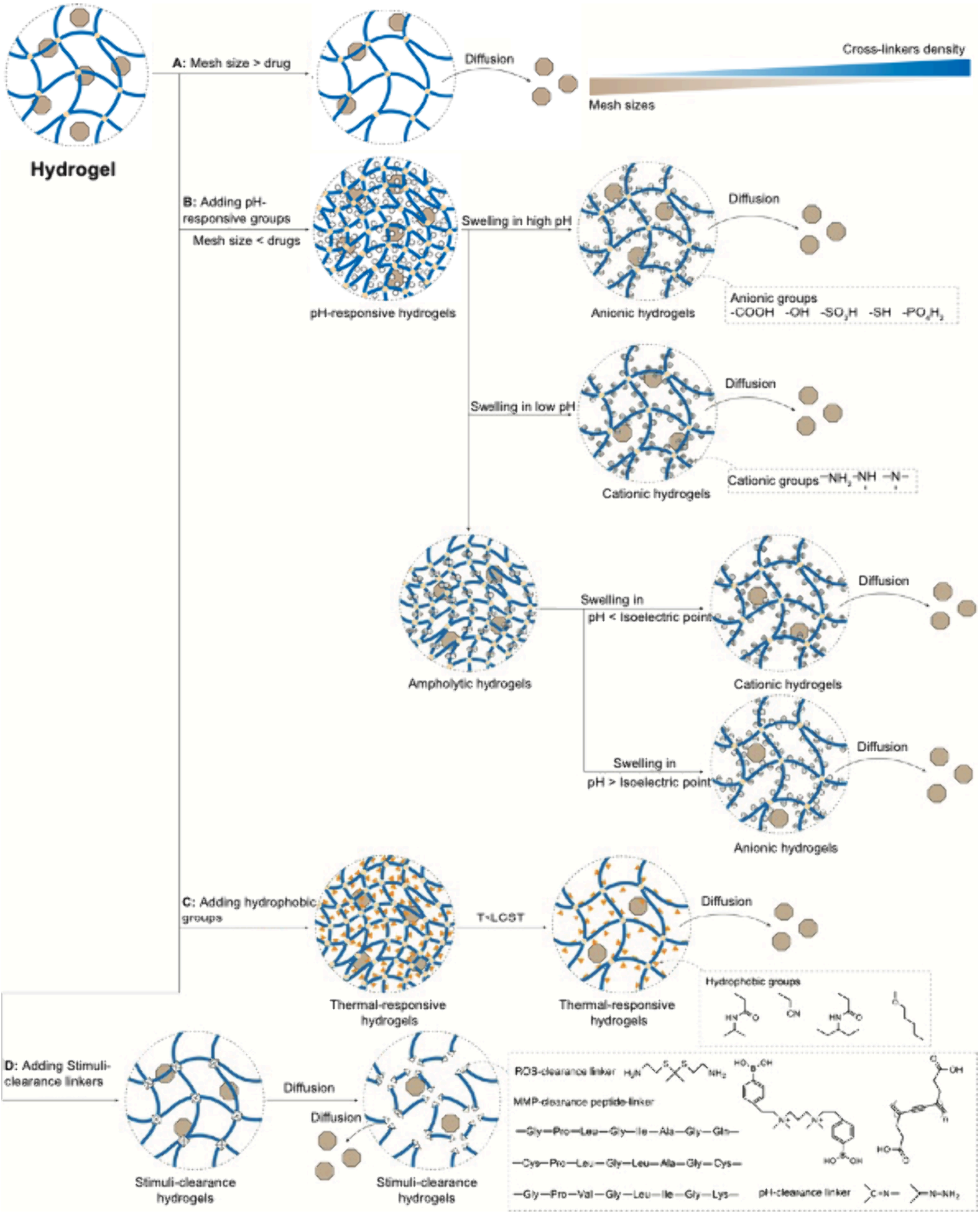

Figure 16. Mesh size modulation for controlled drug release. (A) Diffusion-mediated release occurs when drug molecules, smaller than the hydrogel mesh, diffuse unimpeded. (B) pH-responsive hydrogels are engineered by integrating pH-sensitive moieties into the cross-linked network, enabling drug release triggered by pH fluctuations. (C) Thermoresponsive hydrogels incorporate hydrophobic domains within the network, facilitating temperature-dependent drug release. (D) Stimuli-degradable hydrogels utilize cleavable linkers responsive to biological cues (e.g., ROS, MMPs, or pH), promoting hydrogel degradation and regulated drug delivery.

chemically bonded to the hydrogel network through reactive functional groups.[332] For instance, amine groups on proteins can react with aldehydes or maleimide-functionalized hydrogels via Schiff base formation or Michael addition reactions.[419] Incorporating degradable linkers, such as disulfide or ester bonds, enables stimuli-responsive release in environments with specific redox conditions or enzymatic conditions.[420] These strategies offer sustained release profiles and prevent premature degradation of sensitive biomolecules, making them well-suited for long-term therapeutic applications.[421]

Hydrogels designed with affinity-based systems further enhance the stability and controlled release of biological cargo, such as therapeutic proteins, nucleic acids, and peptides, by leveraging specific interactions like heparin-binding, oligonucleotide hybridization, or host−guest inclusion.[422] Affinity-based hydrogels employ specific interactions, such as heparin-protein binding or nucleic acid hybridization, to immobilize biomolecules within the network.[423] For instance, heparin-mimetic hydrogels leverage the natural affinity of growth factors for heparin to achieve controlled release over extended periods.[424] Similarly, DNA-based hydrogels utilize complementary base pairing to encapsulate and protect therapeutic nucleic acids, such as siRNA or CRISPR/Cas9 systems, enabling precise and tunable delivery.[425]

Stimuli-responsive hydrogels provide additional control by dynamically adjusting cargo release in response to environmental cues, such as pH, temperature, or enzymatic activity.[426] For example, hydrogels containing enzyme-cleavable cross-linkers release proteins or peptides in response to specific enzymes, such as matrix metalloproteinases in wound healing applications.[427] Temperature-sensitive hydrogels, such as poly(*N*-isopropylacrylamide)-based systems, undergo phase transitions near physiological temperatures, enabling on-demand biomolecule release.[428] These stimuli-responsive properties allow hydrogels to tailor the release of biological cargo to specific pathological conditions, enhancing treatment precision and efficacy.[429]

In cell-based therapies, hydrogels function as both protective matrices and delivery vehicles, maintaining cell viability and function while enabling localized therapeutic effects.[429] Cell encapsulation within hydrogels is facilitated through mild gelation processes, such as ionic cross-linking in alginate or enzymatic polymerization in fibrin.[388] These hydrogels act as artificial extracellular matrices, supporting cell proliferation, differentiation, and migration.[430] Functionalizing hydrogels with bioactive peptides, such as RGD motifs, further enhances cell adhesion and interaction with the matrix, promoting therapeutic efficacy in tissue engineering and regenerative medicine.[431]

Although significant progress has been made, several challenges persist, such as preserving bioactivity, preventing premature release, and ensuring uniform distribution of biological cargo within the hydrogel matrix.[432] Emerging approaches, including hybrid hydrogels that integrate dynamic and covalent cross-linking or incorporate nanocarriers for dual-delivery, show great potential in addressing these limitations.[432] As these innovations advance, hydrogel-based systems are poised to transform therapeutic biomolecule delivery, providing unparalleled control, biocompatibility, and versatility across a wide range of biomedical applications.[376]

4.2.2. Release Strategy. *4.2.2.1. Adjusting Mesh Sizes for Cargo-Controlled Release.* Adjusting the mesh size of hydrogels is a critical strategy for achieving controlled release of therapeutic cargo, particularly in drug delivery and tissue engineering applications[433] (Figure 16). The mesh size, which refers to the pore dimensions within the hydrogel network, directly influences the diffusion of encapsulated molecules, determining the release kinetics and overall therapeutic efficacy.[434] By tailoring the cross-linking density, polymer architecture, and dynamic interactions within the hydrogel matrix, researchers can precisely regulate mesh size to accommodate cargo of varying molecular weights and functional requirements.[385]

Cross-linking density is a key factor governing the mesh size of hydrogels. Increased cross-linking results in compact networks with reduced mesh sizes, limiting the diffusion of large biomolecules and supporting prolonged release,[435] which is beneficial for sustained drug delivery systems requiring extended therapeutic effects. In contrast, lower cross-linking densities enlarge mesh size, facilitating the rapid diffusion of small molecules and enabling burst release for immediate therapeutic needs.[436] Incorporating dynamic cross-linkers, such as reversible covalent bonds or ionic interactions, further enhances control by enabling mesh size adjustment in response to environmental stimuli like pH, temperature, or ionic strength, making them well-suited for stimuli-responsive drug delivery.[437]

Polymer architecture also plays a significant role in mesh size modulation. Hydrogels composed of flexible, linear polymers typically exhibit larger mesh sizes due to increased chain mobility, while rigid or branched polymers result in smaller, more stable pores.[438] For example, comb-like or star-shaped polymers introduce architectural complexity, enabling fine-tuning of mesh size without compromising mechanical stability.[439] Additionally, block copolymer-based hydrogels, such as those incorporating hydrophobic segments, can form microphase-separated domains, providing dual mesh sizes within a single hydrogel matrix.[440] These hierarchical structures facilitate the simultaneous release of multiple cargo types with distinct molecular weights, broadening the functional scope of hydrogel-based delivery systems.[261]

Incorporating stimuli-responsive elements into hydrogels further enhances the dynamic control of mesh size.[323] For instance, temperature-responsive polymers like poly(*N*-isopropylacrylamide) (PNIPAM) undergo phase transitions at their lower critical solution temperature (LCST), leading to network shrinkage and reduced mesh size.[441] Similarly, pH-responsive hydrogels containing ionizable groups, such as carboxylic acids or amines, adjust their mesh size through protonation or deprotonation in response to environmental pH changes.[284] These properties enable the on-demand release of encapsulated cargo, making such hydrogels highly effective in targeted drug delivery and biosensing applications.

Dynamic hydrogel networks also leverage reversible interactions to modulate mesh size in real-time.[442] Hydrogels incorporating host−guest chemistries, such as cyclodextrin-adamantane complexes, or bioinspired motifs like catechol-metal coordination, provide tunable porosity that adjusts to external stimuli. These features offer significant advantages for precision medicine, where controlled release profiles must align with the fluctuating needs of the patient's condition.[443]

Despite these advancements, achieving the optimal balance between mesh size and mechanical integrity remains a challenge.[444] Excessively large mesh sizes may compromise structural stability, while overly small pores can hinder diffusion and cargo release.[445] Hybrid hydrogel systems that integrate covalent and dynamic cross-linking networks provide a promising solution, enabling robust mechanical properties while maintaining adaptable mesh size.[158] By leveraging these strategies, hydrogels with tunable mesh sizes continue to advance the field of controlled release, offering tailored solutions for diverse biomedical applications.[446]

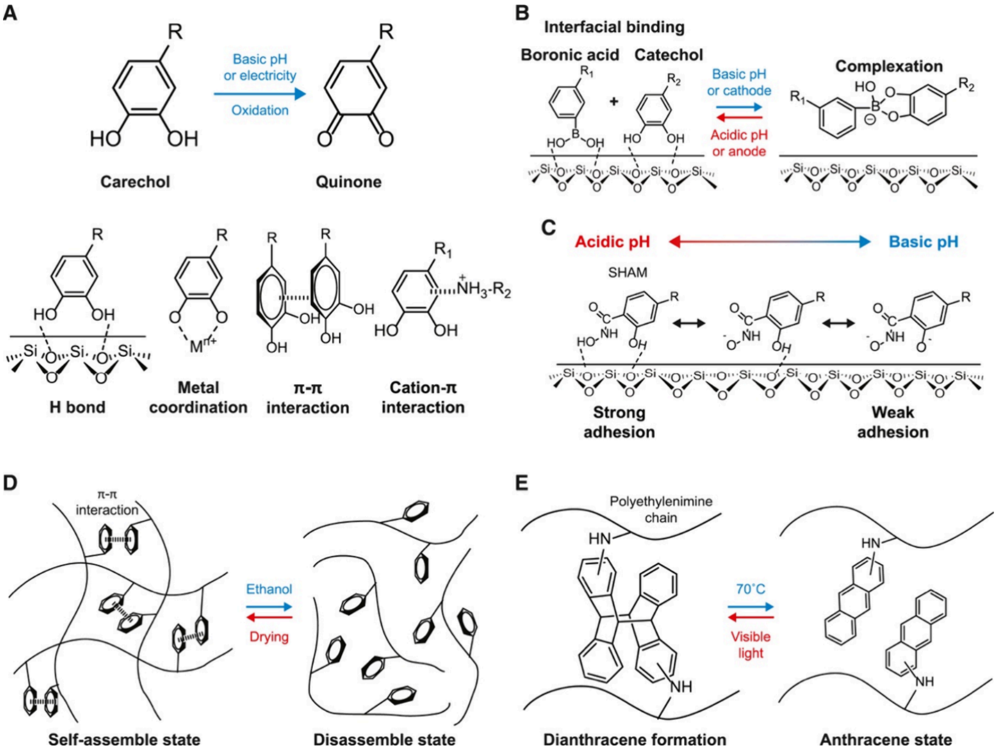

Figure 17. Chemistry of adhesive materials. (A) Structures of catechol and its oxidized form quinone. (B) Reversible adhesion mediated by catechol−boronate complexation. (C) Switchable adhesion mechanism of SHAM. (D) Reversible transition between assembled (high adhesion) and disassembled (low adhesion) states. (E) Anth-PEI functioning as a reversible underwater adhesive, alternating between dianthracene (strong adhesion) and anthracene (weak adhesion) configurations.[462]. Reproduced with permission from ref 462. Copyright 2023 Elsevier under [CC BY 4.0].

4.2.2.2. Regulating Interactions between Cargo and Hydrogel Structure. Modulating the interactions between therapeutic cargo and the hydrogel network is a key strategy to optimize loading efficiency, retention, and release profiles of bioactive agents.[446] These interactions—encompassing physical, chemical, and dynamic bonds—critically determine the hydrogel's ability to deliver therapeutics in a controlled and targeted fashion.[398] By adjusting hydrogel composition, functional groups, and cross-linking chemistry, these interactions can be finely tuned to meet the diverse requirements of biomedical applications, including drug delivery, biosensing, and tissue engineering.[447]

Hydrophobic interactions are particularly important in enhancing cargo retention. Incorporation of hydrophobic segments, such as poly(lactide) or poly(caprolactone) blocks, generates microdomains within the hydrogel that preferentially sequester hydrophobic drugs.[406] This mechanism prolongs the release of lipophilic agents, supporting sustained delivery. By varying the content and spatial distribution of hydrophobic components, the release kinetics can be precisely controlled.[448] Moreover, amphiphilic hydrogels with phase-separated hydrophobic regions enable the coencapsulation and controlled release of both hydrophilic and hydrophobic drugs, adding multifunctionality to drug delivery systems.[449]

Electrostatic interactions are another versatile tool for modulating cargo-hydrogel dynamics. Polyelectrolyte hydrogels, such as those containing cationic chitosan or anionic alginate, interact strongly with oppositely charged biomolecules, enhancing cargo retention.[450] This approach is particularly effective for nucleic acids, proteins, and charged small molecules.[451] By fine-tuning the charge density and ionic strength of the hydrogel, researchers can optimize these interactions to achieve desired release profiles.[452] Additionally, the incorporation of zwitterionic polymers or charged functional groups offers enhanced binding specificity, further improving the efficiency of cargo delivery.[453]

Dynamic covalent interactions provide a reversible mechanism for cargo retention and release. Hydrogels functionalized with boronic acid groups form reversible covalent bonds with diol-containing molecules, such as glucose or catechol derivatives, allowing for responsive release under changing pH or glucose levels.[454] Similarly, Schiff-base chemistry enables the formation of imine bonds with aldehyde- or amine-containing cargo, providing pH-sensitive release profiles suitable for applications in tumor-targeted drug delivery or wound healing.[455] These dynamic interactions allow hydrogels to adapt to environmental cues, ensuring controlled and responsive cargo release.

Host−guest interactions offer an additional layer of specificity and adaptability. Hydrogels incorporating macrocyclic hosts, such as cyclodextrins, cucurbiturils, can encapsulate guest molecules through noncovalent inclusion complexes.[432] These interactions provide high selectivity and tunable binding strength, enabling the controlled release of small molecules or peptides.[394] By adjusting the type of host molecule or modifying the hydrogel network to include multiple host motifs, researchers can design hydrogels capable of simultaneously delivering a range of cargo with diverse physicochemical properties.[414]

Nonspecific interactions, such as van der Waals forces and hydrogen bonding, also contribute to cargo retention but must be carefully regulated to prevent premature release or excessive binding.[456] Hydrogels designed with balanced hydrogen-bonding capacity or optimized polymer-chain mobility can retain cargo effectively while allowing for predictable and sustained release.[457] For example, hydrogels incorporating PEG-based matrices achieve moderate hydrogen-bonding interactions, providing effective loading and controlled diffusion of therapeutic agents.[458]

Despite these advancements, a key challenge lies in balancing the strength of cargo-hydrogel interactions with the desired release kinetics.[459] Excessively strong interactions may hinder cargo release, while weak interactions risk premature diffusion.[460] To address this, hybrid hydrogels combining multiple interaction types, such as hydrophobic, electrostatic, and dynamic covalent bonds, have emerged as effective platforms.[428] These systems enable precise control over drug binding and release, ensuring targeted delivery of therapeutic agents at the right time and location.[461] By leveraging the interplay of multiple interaction mechanisms, hydrogels with regulated cargo-hydrogel dynamics hold great promise for advancing drug delivery and other biomedical applications.

4.3. Tunable Adhesive Abilities to Tissue Surface

4.3.1. Adhesive Abilities to Skin Surface.

4.3.1.1. Chemical Groups of Skin Surface. The skin's surface chemistry is a key determinant of its interaction with external materials, including hydrogels[462] (Figure 17A-E). The stratum corneum, the outermost skin layer, comprises keratinized cells within a lipid matrix[462] and contains abundant chemical groups that modulate adhesion. Hydrophilic functionalities, such as hydroxyl (−OH) and carboxyl (−COOH) groups present in keratin and natural moisturizing factors, facilitate strong hydrogen bonding with adhesive materials.[463] Furthermore, amino groups ($-NH_2$) in proteins and free amino acids enable covalent or electrostatic binding to functionalized hydrogel networks.[464] These hydrophilic constituents render the skin a dynamic interface for hydrogels employing polar or ionic adhesion mechanisms.

In contrast, the lipid matrix of the stratum corneum contributes a significant hydrophobic characteristic to the skin surface.[465] This lipid layer, composed of ceramides, free fatty acids, and cholesterol, introduces hydrocarbon chains that mediate van der Waals interactions.[466] These hydrophobic components pose challenges for hydrogels with predominantly hydrophilic backbones but also provide opportunities for materials designed with hydrophobic domains to achieve enhanced adhesion through balanced polar and nonpolar interactions.[467]

Electrostatic forces further influence skin adhesion due to the presence of charged groups on its surface.[468] Anionic residues, such as sulfates and carboxylates in glycosaminoglycans and proteoglycans, dominate the charge profile of the skin, offering sites for interaction with cationic hydrogels.[469] While cationic groups are less prevalent, they may still contribute to localized electrostatic interactions. These charged interactions are further influenced by the skin's acidic pH, typically ranging from 4.5 to 5.5, which impacts the ionization states of these functional groups and the behavior of interacting hydrogels.[470]

The skin's dynamic nature adds complexity to its adhesive profile. A thin aqueous film composed of sweat, natural moisturizing factors, and extracellular water covers the surface, forming a hydration layer that supports hydrogen bonding and electrostatic interactions.[471] However, this layer can also act as a barrier, necessitating hydrogel designs that displace interfacial water to establish strong adhesion. Additionally, skin hydration, enzymatic activity, and pH variability create a constantly shifting substrate that demands adaptive adhesive strategies.[472] Understanding the chemical complexity of the skin surface enables the rational design of hydrogels tailored for precise and reliable adhesion, particularly in applications such as drug delivery patches, wound dressings, and wearable biosensors.

4.3.1.2. Interaction of Residual Chemical Groups of Hydrogels. Effective and tunable adhesion between hydrogels and skin relies on the interactions between their respective chemical groups, which are critical for biomedical applications such as wound care, drug delivery, and wearable devices.[473] These interactions—including hydrogen bonding, electrostatic attraction, hydrophobic association, and covalent linkage—jointly determine adhesion strength, durability, and reversibility.[474] Achieving optimal performance requires fine-tuning hydrogel composition, surface functionalization, and cross-linking design to align with the skin's dynamic and heterogeneous properties.[245]

Hydrophilic moieties in hydrogels, including −OH, −COOH, and $-NH_2$ groups, enable strong hydrogen bonding with corresponding functional groups present in skin components like keratin, proteins, and natural moisturizing factors.[475] For instance, hydroxyl-rich hydrogels, such as those made from poly(vinyl alcohol) (PVA), can form extensive hydrogen bonds with keratin, enhancing adhesion in moist environments.[476] Similarly, carboxylic groups in hydrogels interact with amine-rich skin proteins, facilitating both hydrogen and ionic bonds that improve adhesive strength even under dynamic conditions.[297] These interactions are modulated by the local hydration level and chemical microenvironment, which influence the bonding dynamics and the strength of interfacial adhesion.

Electrostatic interactions further enhance the adhesion of hydrogels to the skin by leveraging charged functional groups. Hydrogels with anionic residues, such as carboxylates in poly(acrylic acid) (PAA) or sulfates in sulfobetaine polymers, interact with positively charged groups on skin proteins, such as lysine and arginine residues.[221] Conversely, cationic hydrogels, such as those containing chitosan or polyethylenimine (PEI), form electrostatic bonds with negatively charged sulfate and carboxylate groups on skin glycoproteins and lipids.[477] These interactions are highly sensitive to the local pH, which governs the ionization states of both the hydrogel and the skin surface, allowing for pH-responsive adhesive behavior that can be tailored for specific applications.[478]

Hydrophobic interactions complement these mechanisms by targeting the lipid-rich regions of the stratum corneum. Hydrogels incorporating hydrophobic moieties, such as stearyl methacrylate or alkyl-modified polymers, establish van der Waals forces with lipid components like ceramides, fatty acids, and cholesterol.[479] These interactions are particularly effective at displacing interfacial water, which often acts as a barrier to adhesion.[480] By creating microdomains that foster close contact with skin lipids, hydrophobic interactions enhance adhesion in environments where aqueous interference is a challenge.

For long-term and robust adhesion, covalent bonding strategies have been widely explored. Hydrogels functionalized with reactive groups, such as aldehydes (−CHO) or catechols

($-C_6H_4(OH)_2$), can form covalent bonds with amine groups on the skin surface through Schiff base reactions or Michael addition. Catechol-functionalized hydrogels, inspired by mussel adhesion, form strong covalent and hydrogen bonds with both dry and wet surfaces, providing stable and durable adhesion.[481] These hydrogels are particularly promising for applications that require sustained adhesion under mechanical stress or exposure to fluids.

The combined effects of physical and chemical interactions highlight the need to customize hydrogel chemistry to complement the skin's surface characteristics.[482] Fine-tuning the density, spatial arrangement, and functionalization of residual chemical groups allows hydrogels to balance adhesion strength with reversibility, ensuring precise, application-oriented performance. Hybrid approaches that synergistically integrate mechanisms such as hydrogen bonding, covalent linkage, and hydrophobic interactions provide a flexible strategy for designing advanced hydrogels with adjustable adhesion, suited to a wide range of biomedical and wearable technologies.[483]

4.3.2. Adhesive Abilities to Major Organ Surface.

4.3.2.1. Surface Properties of Major Organs. The adhesion of hydrogels is strongly influenced by the surface properties of major organs, which exhibit distinct chemical compositions, structural features, and biomechanical attributes.[152] These properties can vary significantly across different organs, influenced by factors such as tissue composition, hydration level, mechanical behavior, and the presence of biological fluids, posing distinct challenges and opportunities for hydrogel-based adhesion.[222]

The lung surface is lined with a thin layer of surfactant and is primarily composed of hydrophilic and hydrophobic lipid molecules, along with proteins such as pulmonary surfactant-associated proteins.[484] This surface exhibits low surface tension to facilitate alveolar expansion and contraction during respiration. Hydrogels designed to adhere to lung tissue must account for the dynamic mechanical stresses and high fluid content of the pulmonary environment.[485] Hydrophilic functional groups and mild adhesion mechanisms, such as hydrogen bonding and electrostatic interactions, are commonly employed to ensure compatibility and performance under these conditions.[486]

The heart's surface is covered by the pericardium, a fibrous sac that secretes a lubricating fluid to reduce friction during cardiac motion.[487] The surface is rich in glycosaminoglycans, collagens, and proteins, providing sites for potential adhesion.[488] However, its constant mechanical motion and lubrication pose significant challenges for hydrogel adhesion. Effective adhesion strategies for the heart involve incorporating dynamic covalent bonding (e.g., catechol chemistry) or mechanical interlocking mechanisms are often employed to ensure stability under continuous motion and shear stress.[489]

The liver and kidneys feature smooth, hydrophilic surfaces primarily composed of extracellular matrix components such as collagen, elastin, and proteoglycans.[490] The liver, with its high vascularization, has a glycocalyx-rich surface on endothelial cells, which contains a mixture of hydrophilic and charged groups.[491] Similarly, the kidney's glomerular and tubular surfaces involve a complex interplay of hydrophilic and hydrophobic regions. Hydrogels targeting these organs often employ ionic or hydrogen bonding for adhesion, leveraging the presence of charged groups to ensure compatibility without disrupting tissue function.[492]

The gastrointestinal (GI) tract, including the stomach and intestines, features a mucosal layer composed of glycoproteins, lipids, and polysaccharides, such as mucin. This mucosal surface is hydrophilic and negatively charged, providing a slippery, dynamic environment with high turnover rates.[493] Adhesion to the GI tract typically relies on mucoadhesive mechanisms, such as ionic or hydrogen bonding with mucin, or on hydrogels functionalized with bioadhesive polymers like chitosan or thiolated derivatives, which form covalent disulfide bonds with the thiol groups in mucin.[494]

The skin, a major external organ, is characterized by a stratified structure with a lipid-rich stratum corneum and a hydrophilic epidermal layer beneath. The skin's surface presents a combination of hydrophilic and hydrophobic chemical groups, influenced by its lipid and protein content. Adhesion to the skin requires hydrogels with dual hydrophilic−hydrophobic functionalities, capable of interacting with both lipid components and hydrophilic proteins like keratin.[495]

The brain and spinal cord are surrounded by the cerebrospinal fluid (CSF) and meningeal layers, which provide a hydrophilic, lubricated environment.[496] These surfaces are dominated by glycoproteins, polysaccharides, and collagen. Hydrogels intended for neural adhesion must balance soft mechanical properties to match tissue compliance with bioactive functional groups that promote adhesion without eliciting inflammatory responses.[497]

Overall, the surface properties of major organs underscore the importance of designing hydrogels tailored to specific chemical, mechanical, and structural characteristics.[498] By carefully considering the unique attributes of each organ's surface, hydrogels can achieve robust, stable, and biocompatible adhesion for a range of biomedical applications.

4.3.2.2. Adhesive Abilities to Major Organ Surface. Effective adhesion to major organ surfaces is essential for the successful use of hydrogels in tissue engineering, drug delivery, and surgical repair.[252] This adhesion is governed by the hydrogel's compatibility with the organ's unique chemical composition, structure, and mechanical characteristics.[499] By tuning the properties of polymeric chains, cross-linkers, and surface chemical groups in hydrogels, it is possible to optimize their adhesion to diverse organ surfaces, addressing the challenges posed by varying biological environments.[500]

The design of polymeric chains in hydrogels plays a pivotal role in modulating adhesion to organ surfaces. For hydrogels targeting hydrophilic surfaces, such as those of the lungs, liver, or gastrointestinal tract, incorporating hydrophilic polymers like PEG, polyacrylamide (PAM), or poly(carboxybetaine methacrylate) enhances hydrogen bonding and hydration.[501] Moreover, zwitterionic polymers are particularly effective in maintaining hydration and promoting adhesion under dynamic and fluid-rich conditions, such as in the gastrointestinal tract or kidneys.[502] Conversely, hydrogels intended for lipid-rich surfaces, like the stratum corneum of the skin or the pulmonary surfactant in the lungs, benefit from hydrophobic modifications.[503] Polymers with alkyl or stearyl groups can form hydrophobic interactions with lipid components, enabling stronger adhesion in these environments. Additionally, the length and flexibility of polymeric chains influence adhesion. Flexible chains provide dynamic adaptation to tissue movements, while rigid chains can create dense and stable hydration layers for prolonged adhesion.[504]

Cross-linking strategies significantly influence the adhesive performance of hydrogels on organ surfaces by controlling

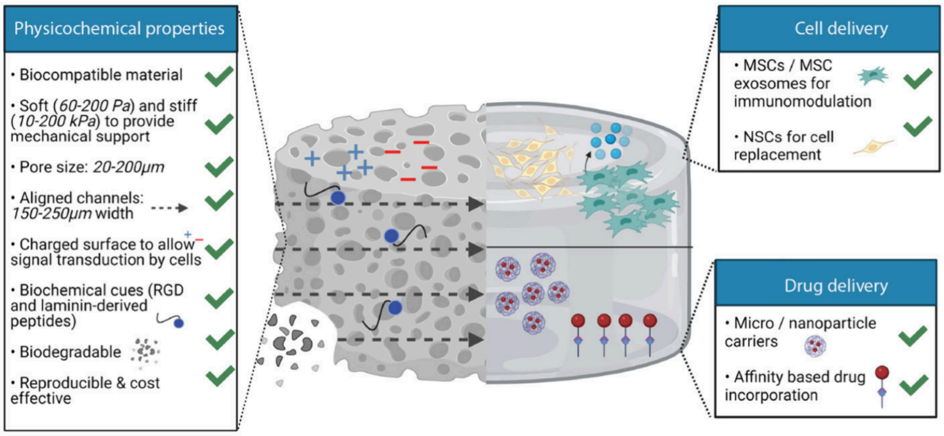

Figure 18. Factors illustrated in the diagram can be applied individually or synergistically to develop functional hydrogel scaffolds, with careful consideration of their physicochemical characteristics to enhance performance in diverse cell and drug delivery applications.[520] Reproduced with permission from ref 520. Copyright 2022 Elsevier under [CC BY 4.0].

network architecture, adaptability, and chemical reactivity.[505] Hydrogels incorporating dynamic covalent cross-linkers, such as disulfide bonds, boronic acid−diol complexes, and Schiff-base linkages, can establish reversible interactions with biological tissues, thereby improving adhesion in physiological environments.[246] These cross-linkers are particularly effective for surfaces experiencing mechanical motion, such as the heart or lungs, as they can reform bonds after stress-induced disruption.[506] For organs with smooth and hydrated surfaces, like the liver or kidney, ionic cross-linkers enable robust adhesion by interacting with charged surface components such as glycoproteins and proteoglycans.[507] Hybrid cross-linking systems combining covalent and physical interactions, such as calcium-alginate networks with catechol modifications, provide a balance between stability and adaptability, making them suitable for applications involving dynamic organ environments.[508]

The surface chemical groups of hydrogels are another key factor in modulating organ-specific adhesion. Functionalization with chemical groups that mimic the native ligands of organ surfaces enhances binding specificity and strength. For example, catechol groups inspired by mussel adhesive proteins enable strong covalent and hydrogen bonding to amine- or thiol-containing groups on the skin or gastrointestinal mucosa.[509] Similarly, aldehyde-functionalized hydrogels form Schiff-base linkages with the amines in skin keratin or glycoproteins on organ surfaces, achieving durable adhesion even under wet conditions. Incorporating sulfobetaine or phosphorylcholine groups enhances compatibility with negatively charged surfaces, such as the glycocalyx of the liver or kidney. For hydrogels designed to adhere to the brain or spinal cord, incorporating bioactive peptides or glycosaminoglycan-mimicking groups improves adhesion while minimizing immune response and inflammation.

By carefully tailoring the polymeric chain composition, cross-linking chemistry, and surface functionalization of hydrogels, it is possible to optimize their adhesion to the unique surfaces of major organs. These strategies ensure compatibility, stability, and adaptability, enabling hydrogels to perform effectively in diverse biomedical applications, from surgical adhesives to drug delivery systems. Such advancements continue to expand the potential of hydrogel technology, providing solutions for complex challenges in organ-specific therapies.

4.3.2.3. Antiadhesive Abilities to Major Organ Surface.

Antiadhesive hydrogels play a critical role in preventing unwanted interactions with organ surfaces, addressing challenges such as biofouling, immune response activation, and fibrosis in biomedical applications. Designing hydrogels with antiadhesive properties tailored to major organ surfaces requires careful consideration of polymeric chain composition, cross-linking strategies, and surface modifications, ensuring that these materials remain functional and biocompatible in complex biological environments.

Choosing appropriate polymeric chains is essential for imparting antiadhesive properties to hydrogels on organ surfaces. Hydrogels made from highly hydrophilic polymers, such asPEG, polyacrylamide (PAM), or zwitterionic polymers like poly(carboxybetaine methacrylate) (PCBMA), form dense hydration layers that effectively repel proteins, cells, and other fouling agents.[510] These layers emulate the natural antiadhesive glycocalyx present on organ surfaces like the kidney and liver.[511] Notably, zwitterionic polymers retain their hydration and antifouling capabilities even under high ionic strength or protein-rich conditions, as encountered in blood or the gastrointestinal tract.[512] Adjusting the molecular weight and flexibility of polymer chains further improves hydration dynamics, with longer, more flexible chains offering adaptability to changing environments while sustaining robust antiadhesive performance.[513]

Cross-linking strategies significantly influence the antiadhesive behavior of hydrogels by dictating network structure and adaptability.[514] Dynamic cross-linkers, such as boronic acid-diol complexes or reversible imine bonds, allow hydrogels to adjust their surface properties in response to changes in pH, ionic strength, or glucose concentration, enabling sustained antiadhesion in varying organ environments.[515] For example, dynamic cross-linking can be particularly effective in the gastrointestinal tract, where changing pH and enzyme activity necessitate adaptive surface properties.[516] High cross-linking density further enhances antiadhesive performance by reducing pore sizes and preventing penetration by fouling agents such as proteins or immune cells.[517] However, excessive cross-linking can limit surface mobility and hydration dynamics, underscoring the need for balance when designing antiadhesive hydrogels for organ-specific applications.

Surface chemical modifications enhance the antiadhesive abilities of hydrogels by introducing functional groups that actively resist interactions with organ surfaces.[518] Incorporating sulfobetaine or phosphorylcholine groups into the hydrogel matrix mimics the natural antiadhesive properties of cell membranes, ensuring compatibility with negatively charged surfaces like the glycocalyx of the liver or vascular endothelium.[518] Additionally, functional groups such as carboxylic acids or saccharides can stabilize hydration layers, further reducing fouling and adhesion.[519] For applications in blood-contacting devices, hydrogels modified with zwitterionic or PEG-based groups effectively resist protein adsorption and platelet adhesion, minimizing thrombotic risk.[519]

4.4. Cell Scaffolds

4.4.1. Physicochemical Properties of Hydrogels Affecting Cellular Response. The physicochemical properties of hydrogels are critical in shaping cellular responses, influencing adhesion, proliferation, differentiation, and migration[520] (Figure 18). These properties enable hydrogels to mimic the ECM, creating microenvironments that support and guide cellular behavior. Among these properties, stiffness is particularly important, as it determines the mechanical cues transmitted to cells.[521] Softer hydrogels with low elastic moduli (0.1−1 kPa) resemble the mechanical environment of soft tissues like the brain, promoting neural differentiation, while stiffer hydrogels (10−100 kPa) replicate bone tissue rigidity, driving osteogenic differentiation.[522] Adjusting polymer composition and cross-linking density enables precise tuning of hydrogel stiffness to suit targeted cellular applications.

Porosity and hydration are equally pivotal, as they govern the transport of nutrients, oxygen, and waste, as well as the degree of cellular infiltration. Larger pores (50−300 μm) facilitate cell migration and proliferation, making them suitable for applications like vascular or musculoskeletal tissue engineering, while smaller pores support applications requiring restricted cell movement.[523] The high-water content inherent to hydrogels ensures a hydrated environment that supports cell viability and reduces mechanical stress. Hydrogels composed of highly hydrophilic polymers, such as PEG, are particularly effective in creating soft, hydrated scaffolds suitable for delicate cell types or soft tissue engineering.[345]

Surface chemistry is another decisive factor influencing cellular interactions. Functionalizing hydrogels with bioactive molecules, such as RGD peptides or growth factors, enhances cell adhesion and specific signaling pathways.[360] These modifications mimic ECM components, promoting processes like angiogenesis or chondrogenesis. In contrast, hydrogels designed with nonfouling surfaces using zwitterionic or hydrophilic polymers minimize nonspecific interactions, offering precise control over cell attachment and behavior.[221] Surface topography further modulates cell responses by providing physical cues. Aligned fibers, grooves, or nanoscale patterns can guide cell migration, polarization, and organization, proving valuable for neural and vascular tissue scaffolds.

Degradability is another essential attribute, allowing hydrogels to adapt to tissue remodeling processes. Hydrogels composed of biodegradable polymers, such as poly(lactic-*co*-glycolic acid) (PLGA) or gelatin, degrade gradually under enzymatic or hydrolytic conditions.[524] This feature supports the release of bioactive molecules and enables the scaffold to be replaced by native tissue over time. Fine-tuning the degradation rate through polymer composition or cross-linking chemistry ensures synchronization with tissue regeneration, making these hydrogels particularly effective in dynamic biological environments.[525]

In sum, the combined effects of hydrogel stiffness, porosity, hydration, surface chemistry, degradability, and topography govern their ability to modulate cellular behavior.[526−529] By carefully designing these properties, hydrogels can be engineered to meet the specific requirements of diverse tissue engineering applications, offering a versatile platform for advancing regenerative medicine.

4.4.2. Functional Groups of Cross-Linking Networks Affecting Cellular Response. *4.4.2.1. Chemical Functional Groups.* The chemical functional groups embedded in the cross-linking networks of hydrogels profoundly influence cellular responses, serving as key determinants of cell adhesion, proliferation, migration, and differentiation. By modulating the biochemical milieu, these functional groups facilitate targeted interactions with cells and their receptors, which are essential for directing cellular behavior in tissue engineering and regenerative medicine.

Functional groups such as −OH, −COOH, $-NH_2$, and -SH provide distinct biochemical cues that interact with cell surface receptors and ECM components. Carboxyl and amino groups, for instance, play an integral role in ionic and hydrogen bonding with integrins, which mediate cell adhesion and signaling pathways.[530] These interactions influence cytoskeletal organization and focal adhesion formation, promoting cell attachment and spreading on hydrogel surfaces.[531] Similarly, sulfhydryl groups enable covalent linkages with thiol-containing cellular proteins, enhancing the stability of cell-hydrogel interactions and promoting specific signaling cascades essential for cell survival and function.[532]

Hydrogels functionalized with bioactive chemical groups also enable controlled delivery of molecular cues to regulate cellular response. For example, hydrogels incorporating boronic acid groups can respond to glucose concentrations, releasing encapsulated biomolecules in a manner that aligns with cellular metabolic needs.[311] Such functionalization not only supports dynamic cellular environments but also facilitates tissue remodeling by providing timely biochemical stimuli.

In bioinspired hydrogel systems, functional groups like catechols, derived from mussel adhesion proteins, enhance cellular responses in wet environments. Catechol-functionalized hydrogels support robust cell adhesion through both covalent and hydrogen bonding, even under dynamic and aqueous conditions.[216] Similarly, phosphorylcholine-functionalized hydrogels mimic cell membrane zwitterionic properties, reducing immunogenicity and promoting a biocompatible environment that supports cell attachment and proliferation.

Dynamic functional groups within cross-linking networks add additional layer of cellular responsiveness. Reversible bonds such as Schiff bases or disulfide bonds allow the hydrogel to adjust its biochemical environment in response to cellular activity or external stimuli, creating a feedback mechanism that aligns with tissue regeneration processes.[533] These dynamic interactions enable hydrogel remodeling, supporting long-term cellular integration and functionality.

Precisely adjusting the type, density, and spatial arrangement of functional groups within hydrogel matrices enables researchers to modulate cellular responses to suit specific application needs. Hydrogels incorporating appropriately selected functional groups not only emulate the native ECM but also deliver active biochemical cues that support cell viability, drive tissue-specific differentiation, and enhance regenerative outcomes. These advances highlight the critical importance of functional group engineering in the development of next-generation hydrogels for advanced biomedical applications.

4.4.2.2. Physical Functional Groups. Physical functional groups within hydrogel cross-linking networks play an essential role in modulating cellular responses through their influence on the hydrogel's mechanical, structural, and topographical properties. Unlike chemical functional groups, which engage directly in biochemical signaling, physical groups primarily interact with cells through structural and mechanical cues, creating an environment that mimics the ECM and supports tissue-specific cellular behavior.[533]

Physical functional groups play a pivotal role in modulating hydrogel stiffness by altering cross-linking density and matrix elasticity, thereby influencing cellular perception of mechanical cues. Stiffer hydrogels, reinforced by strong physical cross-links such as ionic interactions or hydrophobic associations, emulate the rigidity of bone tissue and drive osteogenic differentiation of mesenchymal stem cells.[534] In contrast, softer hydrogels with lower cross-linking rigidity foster neuronal growth and are better suited for neural tissue engineering, where compliance and flexibility are essential to replicate the native tissue environment.[535]

Physical functional groups also affect the porosity and mesh size of hydrogels, which are crucial for cell infiltration, nutrient diffusion, and waste removal.[536] Hydrogels with tunable porosity, enabled by cross-linkers such as alginate-calcium interactions or self-assembling peptides, allow cells to migrate and proliferate within the matrix.[537] By tuning pore size and network architecture via physical functional groups, hydrogels can be optimized to support diverse cell types and applications, ranging from vascularized tissue scaffolds to compact cartilage constructs.

Topographical cues imparted by physical functional groups further enhance cellular response by providing structural guidance for cell alignment, spreading, and migration.[538] For example, hydrogels with anisotropic cross-linking or aligned fibers, created through dynamic physical interactions, direct fibroblast migration and endothelial cell orientation, which are critical for wound healing and angiogenesis.[539] The spatial arrangement of physical groups within the hydrogel matrix can also replicate tissue-specific features, such as the aligned collagen fibers in tendons or the porous trabecular structure of bone, offering additional control over cellular behavior.[540]

Dynamic physical interactions, such as reversible ionic cross-links or hydrophobic domains, contribute to the adaptability of hydrogels in dynamic biological environments. These interactions allow the hydrogel matrix to adjust its physical properties in response to external forces or cellular activity, creating a responsive scaffold that evolves with the tissue regeneration process.[541] For instance, hydrogels with reversible ionic bonds can soften or stiffen under changing ionic strengths, providing a dynamic niche that adapts to the needs of proliferating or differentiating cells.[542]

Physical functional groups within hydrogel cross-linking networks thus play a pivotal role in shaping the cellular microenvironment by controlling mechanical properties, structural features, and topographical cues. By designing hydrogels with well-tuned physical functional groups, researchers can create versatile platforms that not only support cellular viability and proliferation but also guide complex processes such as tissue morphogenesis, wound healing, and organ regeneration.[543] This highlights the importance of engineering physical functionality alongside biochemical cues for developing advanced hydrogels tailored to specific biomedical applications.

4.4.2.3. Biological Functional Groups. Biological functional groups embedded within hydrogel cross-linking networks play a critical role in modulating cellular behavior by facilitating biochemical signaling, replicating ECM functions, and strengthening cell−material interactions.[344] These groups directly influence cell adhesion, migration, proliferation, and differentiation, making them indispensable for the development of bioactive hydrogels in tissue engineering and regenerative medicine.[544]

Incorporating cell-adhesive ligands, such as the arginine−glycine−aspartic acid (RGD) peptide, is a widely used approach to enhance cell attachment to hydrogels.[545] By binding to integrin receptors on cell membranes, these ligands promote focal adhesion assembly and activate downstream pathways that regulate cytoskeletal dynamics, proliferation, and differentiation.[546] Hydrogels functionalized with RGD peptides, for instance, have demonstrated the ability to support strong mesenchymal stem cell adhesion and drive osteogenic and chondrogenic differentiation, highlighting their utility in bone and cartilage engineering.[547]

Growth factor-binding domains represent another category of biological functional groups that influence cellular response. These domains mimic natural ECM components like heparan sulfate, providing a scaffold for the sequestration and presentation of growth factors. For example, hydrogels functionalized with heparin-mimicking groups improve the retention and bioavailability of vascular endothelial growth factor (VEGF), thereby promoting angiogenesis and endothelial cell proliferation.[548] Likewise, incorporating insulin-like growth factor (IGF)-binding domains into hydrogels enhances skeletal muscle cell proliferation and differentiation, facilitating accelerated tissue regeneration in muscle repair models.[549]

Incorporating proteolytically degradable functional groups allows hydrogels to interact dynamically with cells by responding to enzymatic cues. Specifically, peptide sequences sensitive to matrix metalloproteinases (MMPs), such as those cleaved by MMP-2 or MMP-9, enable cells to actively remodel their surrounding microenvironment.[550] This degradability not only facilitates cell migration and invasion but also supports the integration of hydrogels into surrounding tissues, making them ideal for applications such as wound healing and tumor microenvironment modeling.

Hydrogels can also be functionalized with bioactive moieties that mimic ECM proteins, such as laminin or fibronectin, providing additional biochemical cues for cell behavior. For example, laminin-derived peptide sequences, such as IKVAV, have been shown to promote neuronal adhesion and differentiation, making them valuable in neural tissue engineering.[551] Similarly, fibronectin-derived peptides, like PHSRN, enhance fibroblast migration and wound closure, accelerating the healing process.[552]

Incorporating biological functional groups that modulate cell behavior in response to specific stimuli further expands the functionality of hydrogels. For instance, hydrogels functionalized with ligands for mechanosensitive ion channels, such as YIGSR peptides, can stimulate mechano-transduction pathways, enhancing the response of cells to mechanical cues.[553] Additionally, hydrogels containing pH- or redox-sensitive bioactive groups enable controlled cell-material interactions under dynamic physiological conditions, offering unique solutions for complex tissue regeneration scenarios.[554]

The spatial arrangement and density of biological functional groups within hydrogels critically influence cellular behavior. Uniformly high densities of adhesive ligands support consistent cell adhesion and spreading, whereas gradients in functional group distribution can guide cell migration and facilitate tissue patterning.[555] Such precise modulation of the biochemical microenvironment enables the design of hydrogels tailored to specific tissue requirements and regenerative objectives.

Incorporating a variety of biological functional groups into cross-linked networks transforms hydrogels into bioactive scaffolds that effectively replicate extracellular matrix properties. These functionalized hydrogels create a dynamic, supportive niche for cells, advancing the development of next-generation materials for tissue engineering, wound repair, and regenerative medicine.

4.4.3. Nutrient Compound-Added Hydrogel.

4.4.3.1. Basic Nutrient Compounds in Hydrogel-Based Cell Scaffolds. Incorporating basic nutrient compounds into hydrogel-based cell scaffolds is a key approach to improving cell viability, proliferation, and differentiation in tissue engineering and regenerative medicine. By providing essential nutrients, these compounds emulate the ECM, establishing a supportive microenvironment that closely mirrors physiological conditions and promotes tissue regeneration.

Basic nutrient compounds primarily include glucose, amino acids, and vitamins, which are crucial for cellular metabolism and function. Glucose serves as a primary energy source for cellular respiration, supporting the production of adenosine triphosphate (ATP) and promoting metabolic activity. Incorporating glucose into hydrogels enables sustained energy supply for embedded cells, particularly in hypoxic or nutrient-deprived environments such as ischemic tissues. Similarly, amino acids, as fundamental building blocks for protein synthesis, play a critical role in cell proliferation and tissue development. Hydrogels supplemented with essential and nonessential amino acids ensure a continuous supply of substrates for cellular repair and growth, fostering enhanced regenerative outcomes.[556]

Vitamins, particularly those involved in enzymatic cofactor activity, further enhance cellular performance in hydrogel-based scaffolds. For instance, hydrogels enriched with vitamin C (ascorbic acid) promote collagen synthesis and enhance the proliferation of fibroblasts and mesenchymal stem cells, which are essential for connective tissue formation.[557] Similarly, vitamin D3 (cholecalciferol) supports osteogenic differentiation of stem cells, while vitamin E (tocopherol) mitigates oxidative stress, protecting cells from damage in reactive oxygen species-rich environments.

The delivery of these nutrient compounds is often achieved through controlled-release mechanisms embedded within the hydrogel matrix. Hydrogels designed with responsive properties—such as enzymatic degradation, pH sensitivity, or temperature responsiveness—enable the gradual and localized release of nutrients, matching the metabolic demands of cells.[558] For instance, hydrogels incorporating glucose oxidase can modulate glucose availability, preventing hyperglycemic conditions that may disrupt cellular homeostasis.[559] Similarly, hydrogel matrices functionalized with amino acid derivatives or vitamin-encapsulated nanoparticles enable sustained release, ensuring a stable supply over prolonged culture durations.[560]

The spatial distribution and concentration gradients of nutrient compounds within the hydrogel also significantly influence cellular behavior. By engineering nutrient gradients, hydrogels can direct cell migration and differentiation, mimicking the natural morphogen gradients present during tissue development.[561] This spatial regulation is particularly valuable in complex tissue engineering scenarios, such as angiogenesis, where nutrient gradients guide endothelial cell organization and vessel formation.

Despite progress, maintaining a balance between nutrient delivery and hydrogel structural integrity remains challenging. Overloading hydrogels with nutrient compounds may weaken mechanical strength or disrupt the cross-linked network, resulting in premature degradation and diminished functionality.[562] Dual-network designs, combining a nutrient-rich layer with a mechanically resilient matrix, represent a promising solution to these issues.

By providing essential nutrients while closely replicating the natural cellular microenvironment, nutrient-enriched hydrogels offer a versatile platform to support cell viability and function. Such scaffolds advance the development of next-generation materials tailored to meet the metabolic and physiological needs of various tissue engineering and regenerative medicine applications.

4.4.3.2. Solving in Aqueous Phase and Controlled Release. The solubility of nutrient compounds within the aqueous phase of hydrogel scaffolds and their controlled release are key determinants of delivery efficiency and cellular bioavailability. Hydrogels' inherent aqueous environment provides an optimal medium for dissolving and stabilizing hydrophilic nutrients—such as glucose, amino acids, and select vitamins—that are vital for cell metabolism and growth.[563] Nonetheless, precise regulation of release kinetics necessitates sophisticated approaches in hydrogel formulation and design.

Dissolution of nutrient compounds within the hydrogel matrix promotes uniform distribution, ensuring a consistent supply to embedded or surrounding cells. This process largely depends on the hydrophilic nature of both the hydrogel and the nutrient molecules.[564] For example, hydrogels composed of polymers like PEG or polyacrylamide (PAM) exhibit high water retention and enable efficient solubilization of hydrophilic compounds. Likewise, zwitterionic hydrogels, including poly(sulfobetaine) and poly(carboxybetaine), stabilize charged molecules, enhancing their bioavailability and preventing aggregation.[221]

Controlled release of these dissolved compounds is achieved through a combination of hydrogel mesh size, polymeric chain interactions, and cross-linking density. The mesh size of the hydrogel, which is determined by the degree of cross-linking and polymer concentration, dictates the diffusion rates of nutrients.[565] Hydrogels with smaller pore sizes slow the diffusion of nutrients, enabling sustained release over extended periods, while larger mesh sizes permit rapid release, which may be necessary for applications requiring an immediate nutrient supply. For example, dual-network hydrogels with an outer dense network and an inner porous core can provide both initial bursts and sustained release phases, matching the metabolic demands of cells during different growth stages.[440]

Dynamic and stimuli-responsive hydrogels offer additional opportunities for controlled release by enabling the on-demand delivery of nutrients in response to environmental cues.[323] pH-sensitive hydrogels, incorporating ionizable groups such as carboxylic acids or amines, release nutrients at specific pH levels, which can be tailored for applications such as wound healing or tumor microenvironments. Temperature-responsive hydrogels, such as those based on poly(*N*-isopropylacrylamide) (PNIPAM), exhibit phase transitions that regulate nutrient diffusion, providing spatial and temporal control over delivery. Similarly, enzyme-degradable hydrogels enable the targeted release of nutrients in regions with elevated enzymatic activity, aligning delivery with cellular metabolic hotspots.[566]

To enhance the retention and release control of hydrophobic nutrients, such as lipid-soluble vitamins (e.g., vitamin D or vitamin E), hydrogels are often functionalized with amphiphilic components or encapsulation systems.[567] For instance, the incorporation of micelles or liposomes within hydrogels allows for the encapsulation of hydrophobic molecules, providing a reservoir for their gradual release.[568] These systems prevent premature diffusion into the surrounding medium, maintaining localized concentrations at the scaffold-tissue interface.

The inclusion of binding motifs within the hydrogel network further refines nutrient release profiles. Covalent interactions, such as Schiff base linkages or dynamic boronic acid-diol bonds, enable the formation of reversible complexes with nutrient compounds, such as amino acids and vitamins, ensuring their retention under physiological conditions and controlled dissociation in response to specific triggers, like an acid environment.[569] Noncovalent interactions, including hydrogen bonding and host−guest chemistries (e.g., cyclodextrin inclusion complexes), offer an additional means of regulation, enabling hydrogels to dynamically modulate release rates in response to the biological environment.[570]

By integrating these strategies, hydrogels can achieve precise control over the dissolution and release of nutrient compounds, ensuring their bioavailability aligns with cellular metabolic demands. These advances not only improve the efficacy of hydrogel-based cell scaffolds but also expand their potential for use in complex tissue engineering applications, where dynamic nutrient delivery is essential for successful regeneration and integration.

4.4.3.3. Tethering on the Cross-Linking Networks. Tethering nutrient compounds onto the cross-linking networks of hydrogels represents a sophisticated strategy to achieve sustained and localized delivery, particularly in tissue engineering and cell scaffolding applications. This approach ensures the prolonged availability of bioactive molecules while minimizing premature diffusion or degradation. By chemically or physically attaching nutrients to the hydrogel matrix, the release dynamics can be fine-tuned to align with cellular demands and the requirements of the surrounding tissue microenvironment.[571]

Chemical tethering involves covalent bonding of nutrient compounds to functional groups within the hydrogel network. Functionalized cross-linkers, such as those containing carboxylic acids, amines, or thiols, provide reactive sites for covalent attachment. For example, amino acid derivatives or peptides can be tethered via amide or thiol−ene chemistry, creating a reservoir of bioactive molecules that are gradually cleaved through hydrolysis or enzymatic activity.[572] This approach is particularly advantageous for delivering growth factors, such as vascular endothelial growth factor (VEGF) or bone morphogenetic proteins (BMPs), which require precise spatial and temporal release to guide tissue regeneration and cellular differentiation.[573]

Dynamic covalent bonds offer an additional level of control, enabling nutrient release in response to environmental stimuli. For instance, boronic acid-diol linkages provide reversible bonding for sugar-based nutrients, releasing them under varying glucose concentrations. Similarly, hydrogels incorporating Schiff base or hydrazone linkages allow for pH-sensitive tethering and release, ensuring that nutrients are available in acidic or alkaline microenvironments.[574] These systems are particularly effective in wound healing applications, where metabolic activity often induces localized pH changes.

Physical tethering, on the other hand, utilizes noncovalent interactions such as hydrogen bonding, electrostatic forces, or host−guest inclusion complexes. Nutrient compounds with charged functional groups, such as amino acids or nucleotides, can be electrostatically bound to polyelectrolyte hydrogels like chitosan or alginate.[575] These interactions are reversible, allowing for gradual release as the ionic strength or pH of the surrounding environment changes. Host−guest interactions, such as those involving cyclodextrins or cucurbiturils, enable the encapsulation and tethering of hydrophobic nutrients or vitamins within the hydrogel matrix, enhancing their stability and bioavailability.[576]

The spatial arrangement of tethered nutrients within the hydrogel network significantly impacts cellular response and tissue regeneration. The uniform distribution of tethered molecules ensures consistent exposure across the scaffold, promoting homogeneous cell growth and differentiation. However, gradient tethering—where nutrient concentrations vary spatially within the hydrogel—can guide directional cell migration or tissue formation, mimicking the natural gradients found in developing or regenerating tissues.

Tethering nutrients to cross-linking networks also enhances their protection from degradation or inactivation, particularly in environments with high enzymatic activity or oxidative stress. For example, antioxidant molecules such as ascorbic acid or glutathione can be tethered to hydrogels to neutralize ROS while maintaining their activity over prolonged periods.[577]

Despite its advantages, tethering strategies must balance the strength of nutrient-hydrogel interactions with the desired release profile. Overly strong bonds may hinder nutrient availability, while weak interactions risk premature diffusion. Advances in hybrid tethering approaches, combining covalent and noncovalent interactions, offer a promising solution by enabling dual-phase release: an initial burst followed by sustained delivery.[578] These systems provide the flexibility needed to cater to diverse biomedical applications, ensuring that nutrient compounds are delivered precisely and effectively to support cellular activity and tissue regeneration.

5. TAILORING THERAPEUTIC HYDROGELS FOR BIOMEDICAL APPLICATIONS

5.1. Drug Depots for Local Treatment

5.1.1. Solid Malignant Tumor Treatment. Solid malignant tumors are among the most complex and challenging local diseases to treat worldwide. Current treatment strategies include surgery, radiotherapy, chemotherapy, and immunotherapy, such as immune checkpoint blockade (ICB) therapy, tumor vaccines, and adoptive cell therapy.[579]

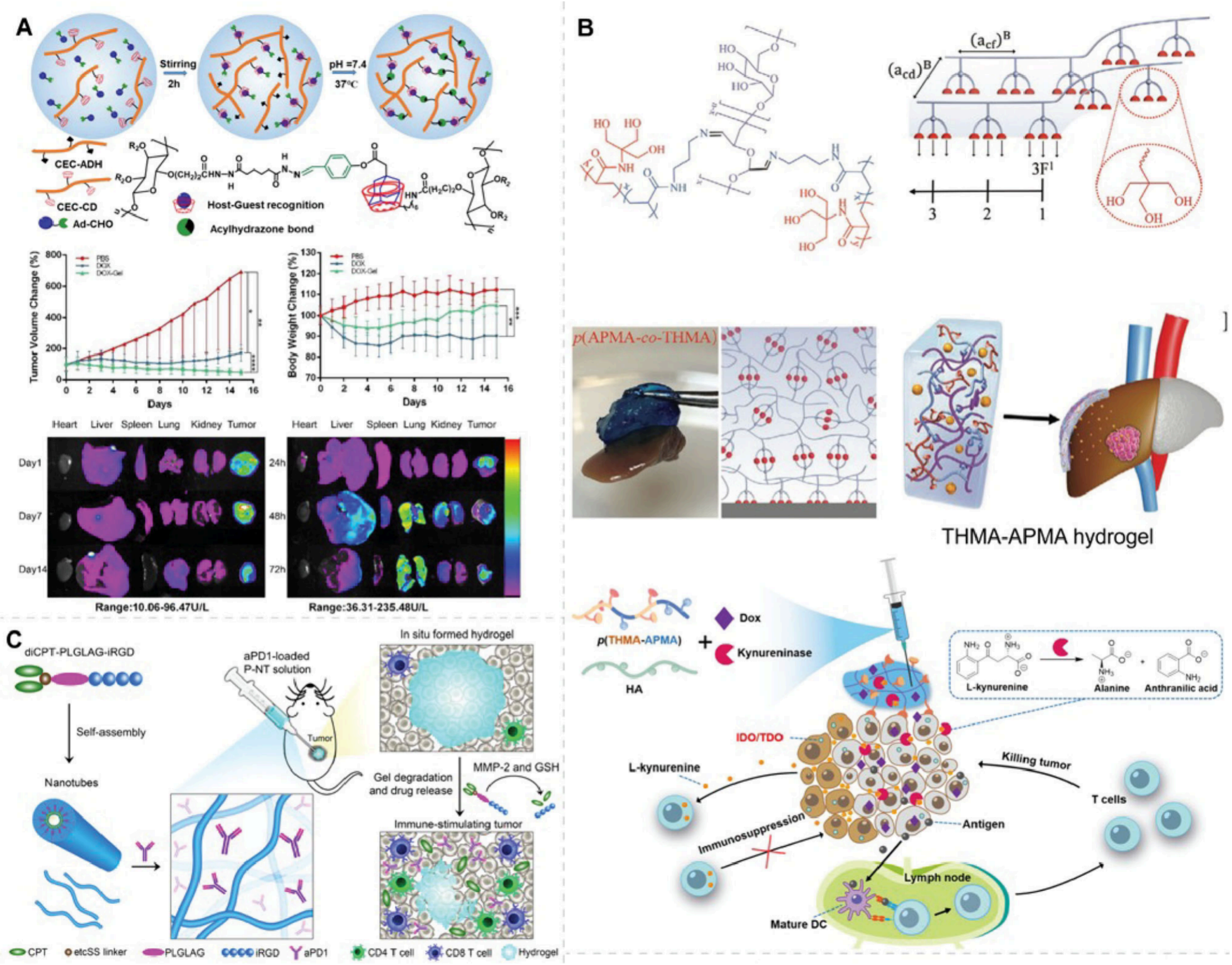

Figure 19. Hydrogel-based local chemotherapy platforms for cancer treatment. (A) Schematic of an injectable DOX-loaded hydrogel demonstrating in vivo antitumor efficacy.[580] Reproduced with permission from ref 580. Copyright 2022 Elsevier. (B) Schematic of a biodegradable adhesive hydrogel formed by cross-linking p(APMA-*co*-THMA) with Dex-CHO, where load-sharing properties inhibit interfacial crack propagation and enhance mechanical stability. An additional schematic illustrates an injectable hydrogel enabling localized chemo-immunometabolic therapy, boosting antitumor immunity and inhibiting tumor growth.[581] Reproduced with permission from ref 581. Copyright 2022 Springer Nature under [CC BY 4.0] (C) Schematic of an in situ-formed supramolecular hydrogel delivering capecitabine (CPT) and anti-PD1 (aPD1), providing bioresponsive drug release and modulating the tumor microenvironment to improve therapeutic efficacy.[585] Reproduced with permission from ref 585. Copyright 2020 American Association for the Advancement of Science under [CC BY-NC 4.0].

Apart from surgery and radiotherapy, both chemotherapy and immunotherapy require the targeted delivery of therapeutic agents to tumor sites. Nevertheless, the cytotoxic nature of many antitumor drugs often results in significant adverse effects upon systemic administration, including immune cell damage and immunosuppression. Therefore, localized drug delivery is a more suitable approach for solid tumor treatment. Hydrogel-based drug depots offer distinct advantages over conventional drug solutions for local antitumor drug delivery, including prolonged retention rate at the tumor site. In addition, tumor microenvironment factors such as low pH (H^+), ROS, and MMP can be utilized to design stimuli-responsive hydrogels for controlled drug release.

5.1.1.1. Local Chemotherapy. Hydrogel-based local chemotherapy not only prolongs the retention of antitumor drugs at tumor sites and minimizes their side effects but also enables the combination of multiple antitumor drugs to achieve synergistic effects. Doxorubicin (DOX), a commonly used hydrophilic antitumor drug, can be efficiently loaded into hydrogels. For instance, Jiang et al. developed injectable hydrogels featuring acyl hydrazone linkages in place of ester bonds, enhancing resistance to esterase-mediated degradation within the tumor microenvironment.[580] This modification extended the release of DOX from 3 days to over 14 days (Figure 19A), while also localizing the drug within the tumor site to minimize systemic toxicity.[580] Enhancing the adhesive properties of hydrogels can further improve antitumor efficacy. For example, Wang et al. developed "triple hydrogen bonding clusters" (THBCs) in hydrogels, which strengthened adhesion to tumor tissues through enhanced hydrogen bonding interactions[581] (Figure 19B). They coencapsulate DOX and Kynureninase (an enzyme that catalyzes L-kynurenine into alanine and anthranilic acid, reversing tumor immunosuppression) within these hydrogels. The strong adhesive properties of THBCs ensured prolonged retention of the hydrogel at the tumor site, leading to chemo-immunometabolic therapeutic

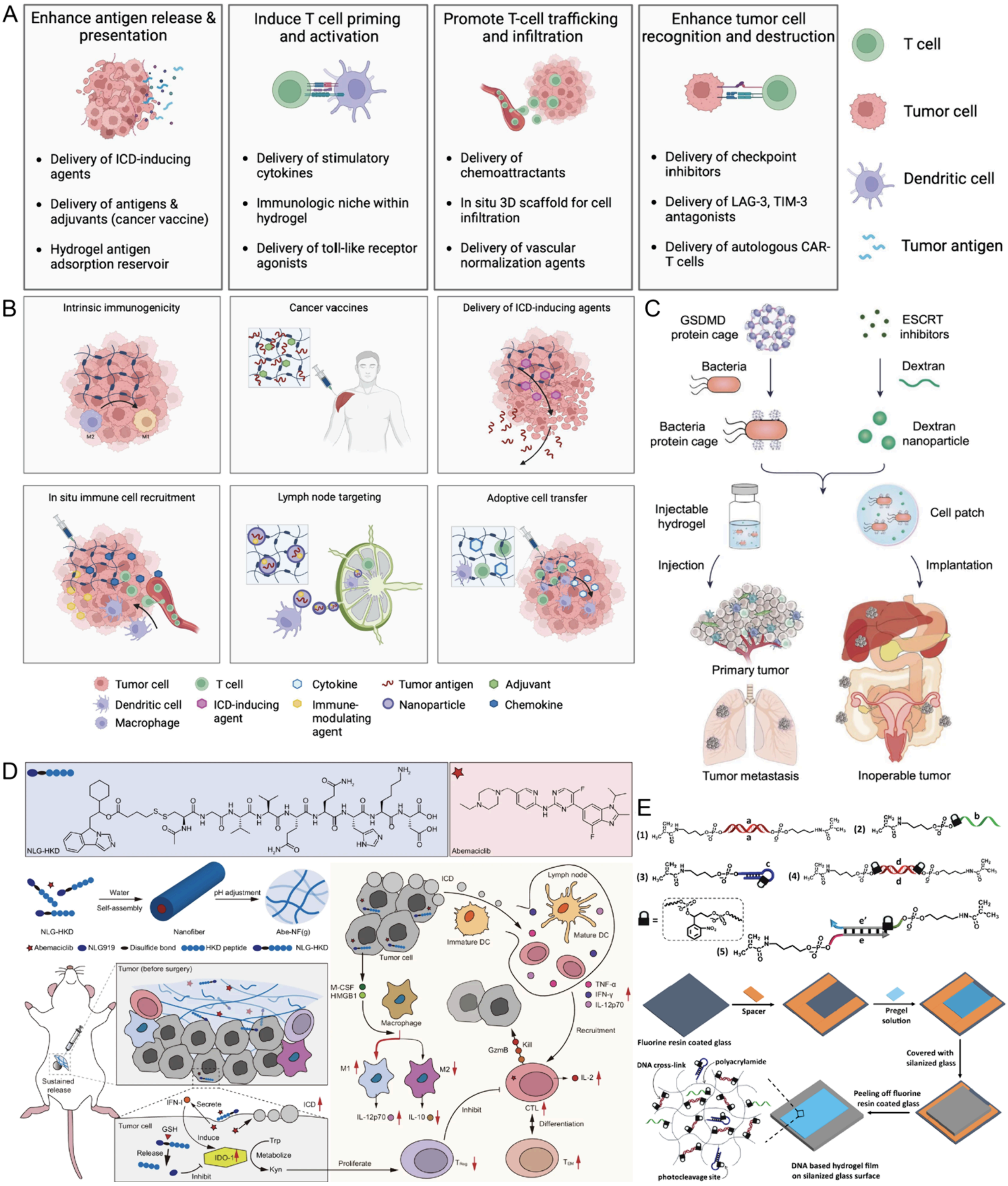

Figure 20. Hydrogel-based approaches for cancer immunotherapy. (A) Schematic depicting the roles of in situ-forming hydrogels in augmenting various phases of the cancer immunity cycle.[587] Reproduced with permission from ref 587. Copyright 2023 Elsevier. (B) Examples of hydrogel applications in localized immunotherapy.[587] Reproduced with permission from ref 587. Copyright 2023 Elsevier. (C) Illustration of an advanced hydrogel platform integrating gasdermin D (GSDMD) proteins cross-linked into protein cages and conjugated to attenuated *Salmonella typhimurium* (VNP-GD), with an ESCRT inhibitor encapsulated in dextran nanoparticles (EI-NP). Two delivery formats—an injectable hydrogel and a cell patch—were developed to codeliver VNP-GD and EI-NP for local treatment of primary tumors or implantation in inoperable cancers.[593] Reproduced with permission from ref 593. Copyright 2022 Springer Nature under [CC BY 4.0]. (D) Design of the Abe-NF(g) supramolecular hydrogel, highlighting its potential in immunotherapy.[596] Reproduced with permission from ref 596. Copyright 2025 Springer Nature under [CC BY-NC-ND 4.0]. (E) Composition of a photoresponsive hydrogel based on o-nitrobenzyl phosphate esters, forming light-sensitive polyacrylamide networks. The schematic outlines the stepwise synthesis of hydrogel films incorporating acrydite-modified units (1)−(5) as functional building blocks.[597] Reproduced with permission from ref 597. Copyright 2021 Springer Nature under [CC BY 4.0].

effects. This hydrogel system was also applied to cisplatin-based local chemotherapy, achieving significant antitumor activity.[582] For example, Jin et al. introduced a self-assembled hydrogel strategy to further extend the release of DOX and enhance its anticancer activity.[583] They synthesized a hybrid peptide (RADA32)-linked DOX and melittin amphiphilic self-

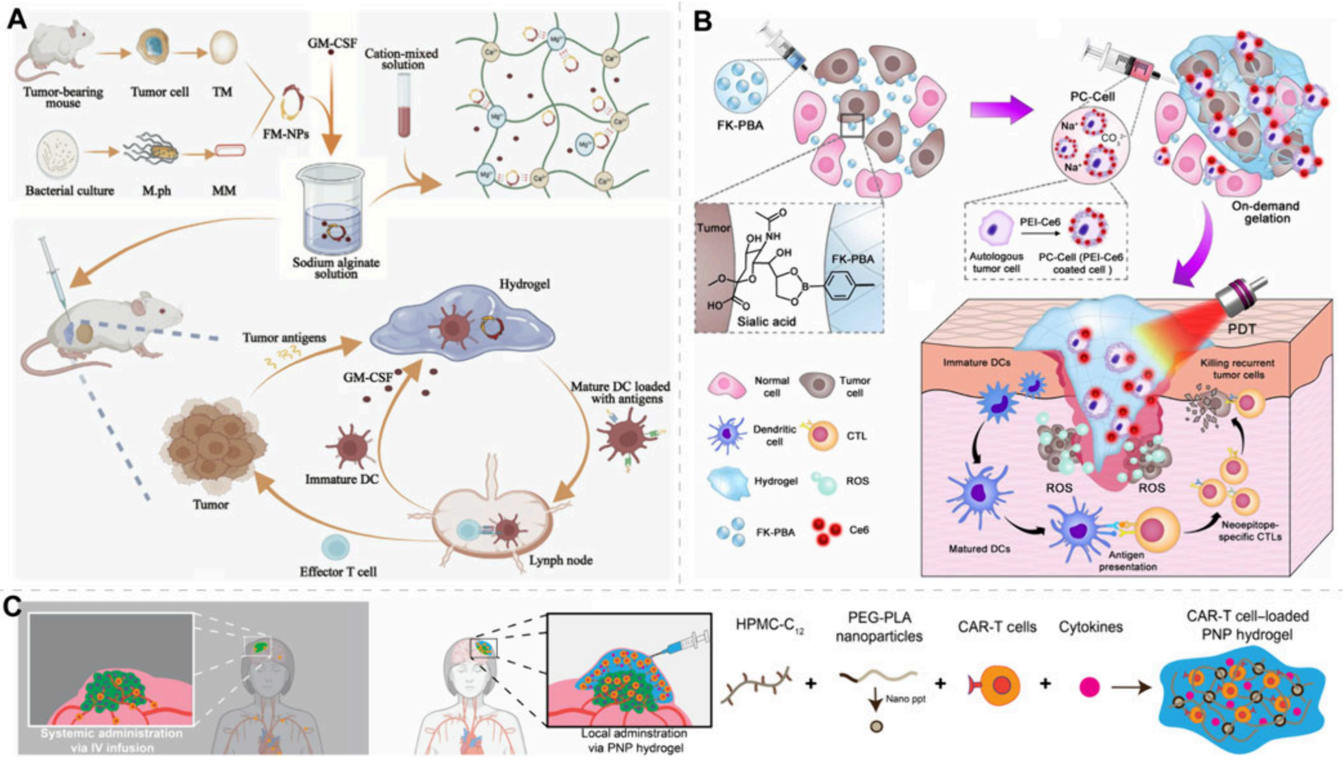

Figure 21. Injectable hydrogels for cancer immunotherapy. (A) Schematic of a bifunctional fusion membrane-based hydrogel designed to enhance tumor immunotherapy by activating dendritic cells, thereby eliciting a stronger antitumor immune response.[598] Reproduced with permission from ref 598. Copyright 2022 John Wiley & Sons. (B) Illustration of PC-Cell@gel, a hydrogel-based tumor vaccine that combines oxidized autologous tumor cells with PEI-Ce6 to induce immune activation through photodynamic therapy (PDT).[601] Reproduced with permission from ref 601. Copyright 2020 American Association for the Advancement of Science under [CC BY-NC 4.0]. (C) Injectable hydrogel system for localized CAR-T cell delivery in glioma treatment, establishing an inflammatory microenvironment to improve CAR-T cell retention and therapeutic efficacy.[609] Reproduced with permission from ref 609. Copyright 2022 American Association for the Advancement of Science under [CC BY 4.0].

assembling elements to create stable hydrogels, which prolonged the release of DOX and melittin for up to 20 days in PBS. A single hydrogel injection combining DOX and melittin achieved over 95% inhibition of primary melanoma tumor growth by exploiting their synergistic effects.

Cytosine nucleoside drugs, such as gemcitabine and capecitabine, represent another class of hydrophilic anticancer agents suitable for hydrogel-based local chemotherapy. Given the toxicity of gemcitabine and ICB antibodies, Wang et al. designed a ROS-responsive linker, N1-(4-boronobenzyl)-N3-(4-boronophenyl)-N1, N1, N3, N3-tetramethylpropane-1,3-diaminium (TSPBA), to cross-link diols on PVA chains.[584] The in situ injectable hydrogel enabled controlled release of gemcitabine and anti-PD-L1 antibodies, triggered by elevated ROS levels in the tumor microenvironment. The TSPBA-PVA hydrogels improved the local release of gemcitabine and antibodies by approximately 30% and 50%, respectively, compared to control groups. Moreover, Wang and co-workers developed MMP-2-responsive prodrug self-assembling hydrogels for local delivery of aPD1 antibodies and CPT, achieving sustained drug release for over 30 days[585] (Figure 19C). In addition, they incorporated a STING agonist (c-di-AMP (CDA)) into the hydrogel system.[586] The positively charged surface of CPT prodrug self-assembled nanofibers facilitated electrostatic complexation with negatively charged CDA, resulting in stable coloading and prolonged drug release.

5.1.1.2. Local Immunotherapy. In recent decades, immunotherapy has gained significant attention as a promising cancer treatment, leveraging the patient's immune system to target and eliminate malignant cells[587] (Figure 20A). Despite its potential, the clinical application of immunotherapy continues to face substantial challenges, primarily due to limitations in overall efficacy and safety, which remain critical barriers to its broader adoption.[588]

Local immunotherapy has emerged as an effective strategy to reduce systemic toxicity and improve therapeutic outcomes.[587] Among the delivery platforms developed for targeted cancer treatment, hydrogels have attracted significant interest for their capacity to achieve controlled in situ release of immune agents, effectively addressing the limitations of traditional immunotherapy.[589]

Immunotherapy aims to sustain antitumor immunity by enhancing the cancer immunity cycle[587] (Figure 20B). Hydrogels support this process by locally delivering antigens, cytotoxic agents, or immunomodulators such as cytokines and adjuvants. They enable controlled release, promote antigen-presenting cell (APC) activation, and create an immune-friendly microenvironment.

Hydrogels with intrinsic immunomodulatory properties can directly influence immune responses through their structural and chemical characteristics, without requiring additional drugs.[368] For example, cationic hydrogels, like polyethylenimine (PEI) or cationic dextran cross-linked hydrogel, can reprogram tumor-associated macrophages (TAMs) and MDSCs into antitumor phenotypes via TLR-4 pathways, thereby enhancing pro-inflammatory cytokine production and boosting antitumor immunity in murine models.[590] PEI-based hydrogels have also been shown to upregulate CD86 and

MHC II expression on dendritic cells (DCs) while increasing TNF-α and IL-6 secretion.[591] Moreover, hydrogel composition influences DC activation, costimulatory molecule expression, and T-cell polarization, while their degradation kinetics affect immunogenicity through variations in particle size and shape.[592]

Cancer vaccines, composed of tumor antigens and adjuvants, elicit tumor-specific immune responses and promote long-term immunological memory. Hydrogels enable prolonged and simultaneous delivery of various antigen types, including proteins,[593] peptides,[594] nucleic acids,[595] and whole-tumor cell lysates. For example, Li et al. developed an injectable hydrogel system codelivering antitumor bacteria and GSDMD protein cage, which enhanced tumor pyroptosis and functioned as a cancer vaccine[593] (Figure 20C). Similarly, Zhu et al. designed an abemaciclib-loaded supramolecular peptide hydrogel, formed by conjugating a β-sheet-forming peptide with NLG919, an indoleamine 2,3-dioxygenase 1 inhibitor, for neoadjuvant immunotherapy in triple-negative breast cancer[596] (Figure 20D). This injectable hydrogel enables sustained release of abemaciclib, which induces immunogenic cell death and increases IL-2 secretion by cytotoxic T lymphocytes, while NLG919 suppresses kynurenine production. The combined therapy significantly reduces tumor recurrence and pulmonary metastasis, prolonging survival in animal models. In addition, Huang et al. developed a photolithographic and two-photon laser patterning strategy to fabricate nucleic acid−based polyacrylamide hydrogel films with tunable stiffness and spatially selective functionalization, enabling stress-mediated shape transformations that guided the patterned organization of HeLa cell aggregates[597] (Figure 20E).

Recent advances in hydrogel-based cancer vaccines have leveraged controlled antigen release and immune modulation to enhance antitumor responses. For instance, Ke et al. utilized the differential release kinetics of small-molecular compounds, granulocyte-macrophage colony-stimulating factor (GM-CSF), and nanoparticle-based fusion membranes (FM-NPs) composed of autologous tumor cell membranes and *Mycobacterium phlei* membranes to enhance the immune responses in an injectable Ca^{2+}/Mg^{2+} cross-linked alginate hydrogel-based cancer vaccines[598] (Figure 21A). The rapid release of GM-CSF recruited native DCs into the hydrogels, where they processed autologous tumor antigens and subsequently migrated to the tumor site to activate T cells for cancer cell elimination. Similarly, Li et al. designed a trauma-inflammation-responsive TPSBA-PVA hydrogel-based autologous cancer cell vaccine to suppress postoperative metastasis.[599] The hydrogel facilitated sustained immune activation by leveraging the high ROS content within postsurgical inflammatory environments to trigger antigen release at the surgical resection site, thereby enhancing the vaccine's antitumor efficacy. Wang et al. designed a personalized cancer vaccine by encapsulating JQ1 (a BRQ4 inhibitor) and indocyanine green (ICG) within tumor cells embedded in Fomc-based peptides self-assembling hydrogels. The tumor-penetrable peptides facilitated deep tumor antigen delivery, enhancing immunogenic responses.[600] Fang et al. developed a similar tumor cell-based vaccine using oxidized autologous tumor cells loaded with polyethylenimine-conjugated chlorin e6 (PEI-Ce6) in Fmoc self-assembled hydrogels (PC-Cell@gel) (Figure 21B).[601] PEI-Ce6 effectively coats tumor cell surfaces through electrostatic interactions and enables photodynamic therapy (PDT) upon near-infrared (NIR) laser irradiation. Inorganic ions have also been investigated for their immunomodulatory effects. For instance, Cao et al. achieved both burst and sustained calcium ion release by incorporating $CaCl_2$ and $CaCO_3$ into hydrogels, inducing immunogenic cell death (ICD) of residual tumor cells via calcium overload.[602] Additionally, $CaCO_3$ acted as a pH modulator, allowing controlled release of R837 to sustain immune activation.

Immunotherapy strategies that harness chemotherapy-induced ICD represent a promising approach to boost antitumor immunity. Certain chemotherapeutics, such as doxorubicin (DOX), trigger ICD by releasing tumor antigens and damage-associated molecular patterns (DAMPs), thereby stimulating immune responses. Hydrogels can prolong these ICD effects and enhance dendritic cell (DC) recruitment. Qin et al. developed a heat-responsive α-cyclodextrin (CD)-based hydrogel (DOX/ICG/CpG-P-ss-M/CD) that codelivers DOX, the photothermal agent ICG, and vaccine-mimicking nanoparticles (CpG-P-ss-M) upon irradiation.[603] This system facilitates antigen transport to lymph nodes, promotes DC maturation, and activates immune responses. When combined with PD-L1 blockade therapy, it effectively suppresses tumor growth while preventing recurrence and metastasis.

Tumor-draining lymph nodes are critical for DC-mediated antigen presentation and T cell activation,[604] though tertiary lymphoid structures near tumors can also serve as functional immune niches. Gao et al. designed an injectable, thermosensitive chitosan hydrogel loaded with lipid-encapsulated IRF5 mRNA and CCL5 siRNA (LPR) nanoparticle complexes (LPR@CHG) to reprogram the tumor immune microenvironment.[605] This hydrogel upregulates IRF5 and downregulates CCL5, promoting M1 macrophage polarization, which in turn initiates T cell-mediated immunity. By alleviating immunosuppression, the LPR@CHG hydrogel enhances pancreatic cancer immunotherapy efficacy with reduced systemic toxicity.

Macroporous hydrogels incorporating chemokines or cytokines can create localized microenvironments that modulate DC activity in situ.[606] Such "cell-homing" hydrogels release factors like GM-CSF, TNF-α, and CCL21 to recruit immature DCs, which infiltrate the scaffold, process antigens, and mature to enhance antigen presentation and T cell priming.[607] For example, Wang et al. demonstrated that peritumorally injected macroporous alginate gels loaded with GM-CSF, CpG oligonucleotides, and a DOX-iRGD conjugate enhance tumor cell ICD, increase systemic tumor-specific $CD8^+$ T cells, repolarize tumor-associated macrophages toward a pro-inflammatory M1 phenotype, and significantly improve antitumor responses in poorly immunogenic triple-negative breast cancers (TNBCs). This strategy also prevents postsurgical recurrence and achieves complete metastasis-free survival following tumor rechallenge.[608]

Hydrogels can also improve cell-based immunotherapy. Grosskopf et al. engineered self-assembled and injectable polymer−nanoparticle (PNP) hydrogels for CAR-T cell delivery[609] (Figure 21C). Subsequently, they developed a self-assembled peptide-based hydrogel for the locoregionally immobilization of therapeutics in tumor resection cavities. Chen et al. also reported the use of Fmoc-peptide self-assembling hydrogels to encapsulate CAR-macrophages for glioblastoma multiforme treatment.[610]

5.1.1.3. Physical Stimuli (Light, Heat, Microwave)-Assisted Therapy. Hydrogels can also be engineered to complement physical antitumor therapies, including photodynamic therapy (PDT), radiotherapy, and photothermal therapy (PTT). PDT

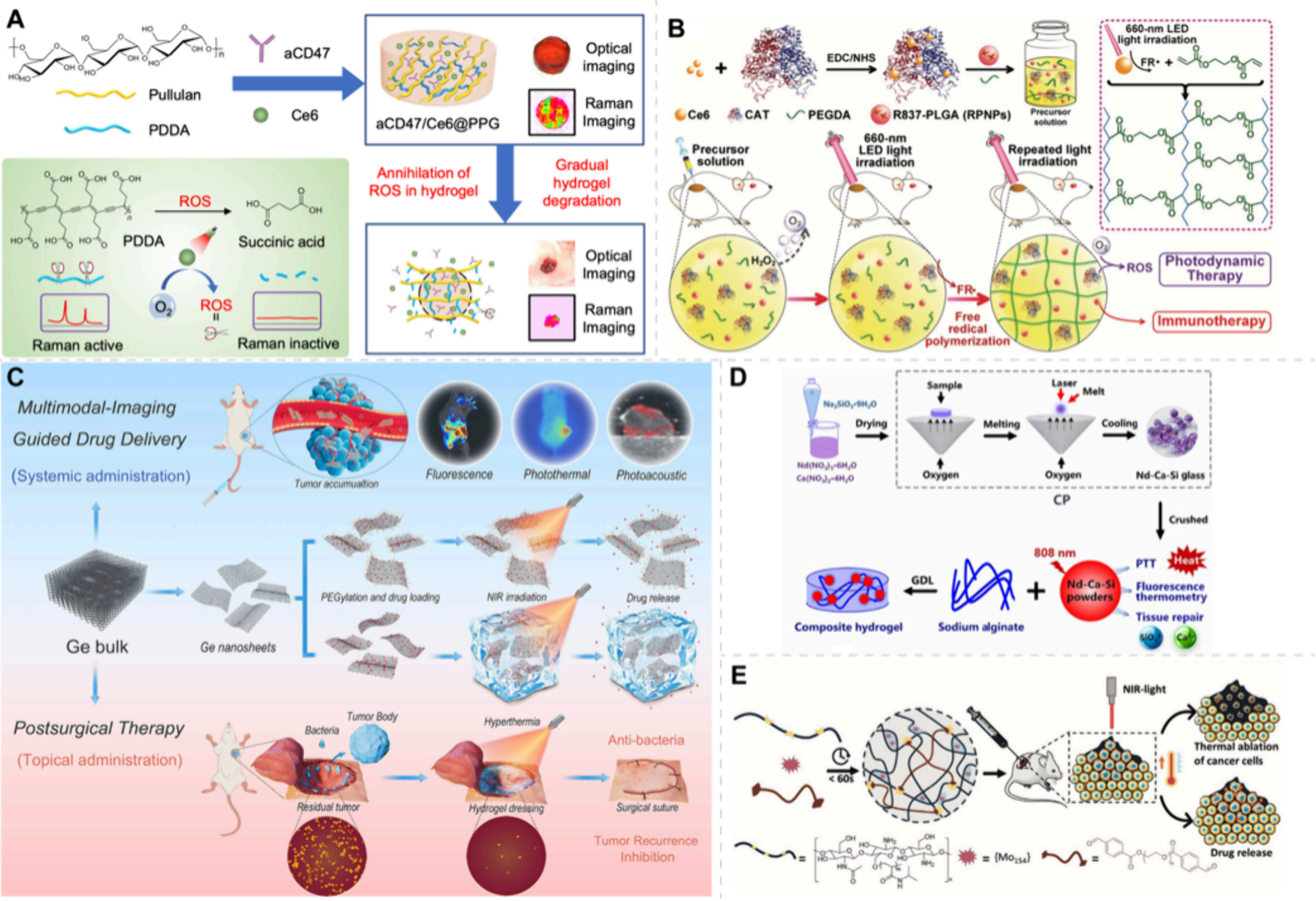

Figure 22. Hydrogel-based strategies for photodynamic and photothermal cancer therapy. (A) Schematic of the aCD47/Ce6@PPG hydrogel design, highlighting its ROS-responsive degradation and applicability in photodynamic therapy.[611] Reproduced with permission from ref 611. Copyright 2022 Springer Nature under [CC BY 4.0]. (B) Light-triggered formation of Ce6-CAT/PEGDA hydrogel in tumors, showcasing its ability to enhance photodynamic therapy *in vivo*.[612] Reproduced with permission from ref 612. Copyright 2019 John Wiley & Sons. (C) Two-dimensional germanene (Ge) incorporated into a hydrogel platform has been developed as a tumor surgery adjuvant therapy, designed to prevent wound infections and inhibit tumor recurrence.[23] Reproduced with permission from ref 23. Copyright 2020 Elsevier. (D) Preparation of multifunctional Nd–Ca–Si bioglasses, where coprecipitation and container-less processing techniques are used to develop materials with photothermal, fluorescence, and bioactive properties for therapeutic applications.[614] Reproduced with permission from ref 614. Copyright 2020 American Association for the Advancement of Science under [CC BY-NC 4.0]. (E) General schematic of photothermal therapy and NIR-triggered DOX release, highlighting the design, preparation, and synergistic effects of Mo_{154}Gel for enhanced cancer treatment.[615] Reproduced with permission from ref 615. Copyright 2021 John Wiley & Sons under [CC BY 4.0].

generates reactive oxygen species (ROS) at laser-irradiated sites, which can additionally trigger drug release from ROS-responsive hydrogels. For example, Zhang et al. designed a biocompatible ROS-sensitive hydrogel formed by cross-linking the conjugated polymer poly(deca-4,6-diynedioic acid) (PDDA) with the natural polysaccharide pullulan, enabling codelivery of anti-CD47 (aCD47) antibodies and Ce6[611] (Figure 22A). During PDT, the PDDA backbone protected aCD47 antibodies from oxidative damage while simultaneously undergoing gradual degradation, thereby enabling controlled Ce6 release. Moreover, Meng et al.[612] designed an *in situ* photo-cross-linked hydrogel system to retain chlorin-(Ce6) linked catalase protein and the immunosensitizer imiquimod (R387) at the tumor sites[612] (Figure 22B). During PDT, ROS generated at tumor sites were converted into O_2 by catalase, improving the hypoxic tumor microenvironment (TME) and enhancing the immunostimulatory effects of R837. Similar to PDT, radiotherapy also induces ROS production at target sites, which can promote the release of therapeutics from ROS-responsive hydrogels. For example, Sun et al. utilized radiotherapy to enhance the controlled release of anti-PD-1 (aPD-1) antibodies and STING agonists within TSPBA-PVA hydrogels. This combined approach improved the sustained infiltration of T cells and restored their effector function. As a result, a robust antitumor immune response was triggered, leading to significant tumor growth inhibition.[613]

PTT is a physical tumor ablation method that generates localized hyperthermia upon light irradiation at tumor sites. The efficacy of PTT mainly depends on the presence of inorganic materials within therapeutic hydrogels. For example, our group developed agarose-chitosan cross-linked hydrogels coloaded with 2D Germanene (Ge) nanosheets and DOX for antitumor PTT[23] (Figure 22C). PEGylated Ge nanosheets were incorporated into the hydrogel matrix, ensuring stability. Upon NIR irradiation, localized hyperthermia was generated, triggering NIR-mediated drug release. This approach effectively eliminated residual tumor cells and exhibited potent antibacterial effects. Moreover, Ma et al. reported multifunctional Nd–Ca–Si silicate glass-encapsulated alginate hydrogels with dual photothermal and fluorescence-emitting properties

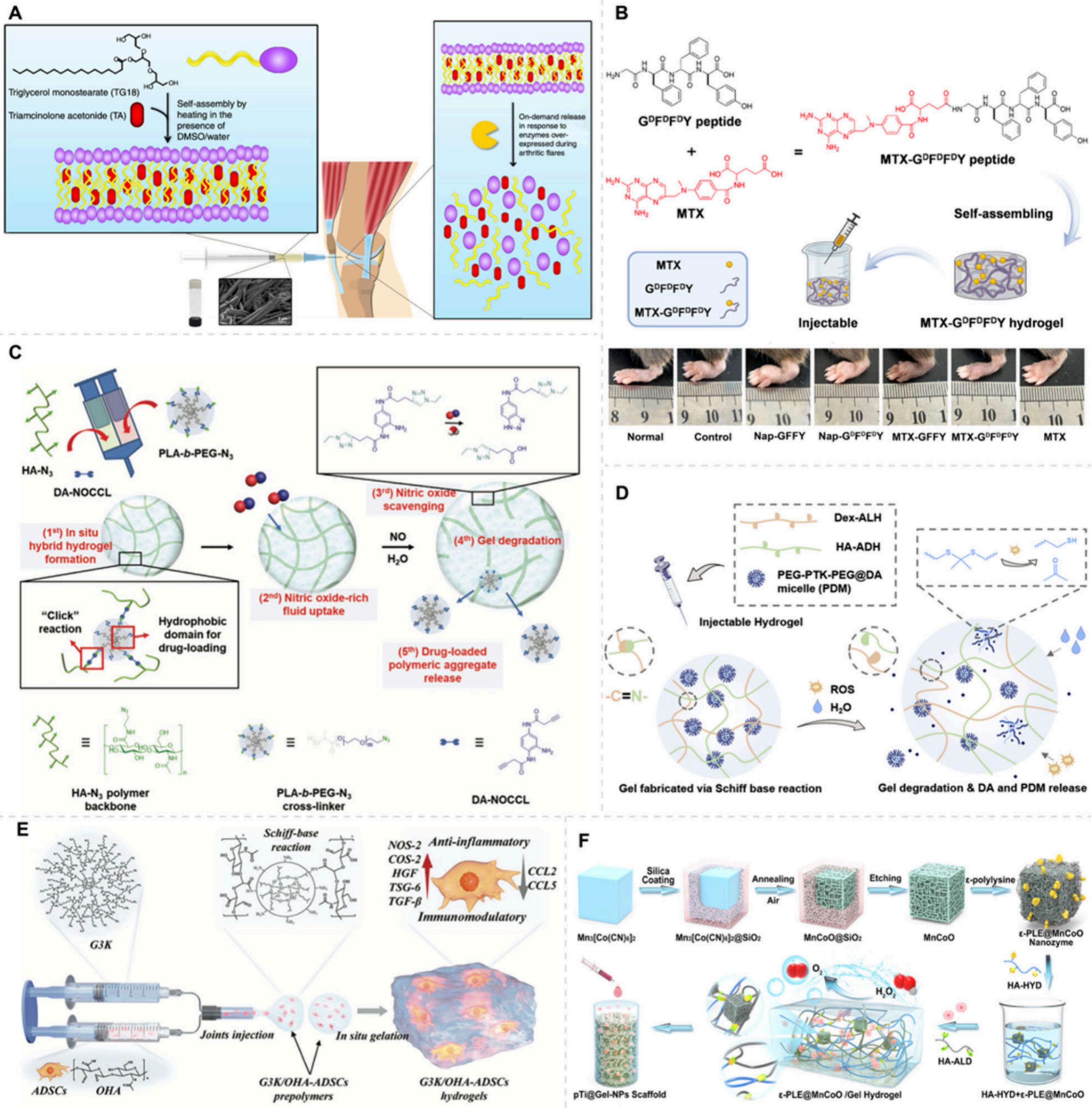

Figure 23. Hydrogel-based strategies for treating articular inflammation leverage diverse designs to achieve targeted and effective therapies. (A) A self-assembled triglycerol monostearate (TG-18) hydrogel was developed to respond to arthritis flare inflammation, enabling localized drug delivery.[618] Reproduced with permission from ref 618. Copyright 2018 Springer Nature. (B) Methotrexate (MTX) was conjugated to GDFDFDY peptides through carboxyl−deaminated glycine chemistry, forming injectable hydrogels via $\pi-\pi$ stacking interactions for targeted arthritis therapy.[620] Reproduced with permission from ref 620. Copyright 2022 Elsevier. (C) A hybrid nitric oxide (NO)-scavenging "click" hydrogel, incorporating self-healable cross-links and DA-NOCCL, reacts with NO to release drug-loaded aggregates for combinatorial osteoarthritis treatment.[621] Reproduced with permission from ref 621. Copyright 2021 John Wiley & Sons. (D) Another system combined hyaluronic acid (HA) and dextran (Dex) through Schiff base chemistry to create a hydrogel loaded with dexamethasone acetate-encapsulated PEG-PTK-PEG micelles (PDM) for in vivo osteoarthritis therapy.[622] Reproduced with permission from ref 622. Copyright 2021 Elsevier. (E) Additionally, a G3K/oxidized hyaluronic acid (OHA) hydrogel with immunomodulatory properties was prepared via Schiff base cross-linking to enhance osteoarthritis outcomes.[623] Reproduced with permission from ref 623. Copyright 2023 John Wiley & Sons under [CC BY 4.0]. (F) Finally, enzyme-reinforced hydrogels functioning as H_2O_2-driven oxygenators were designed to regulate stem cell behavior and promote cartilage regeneration.[624] Reproduced with permission from ref 624. Copyright 2022 Springer Nature under [CC BY 4.0].

under 808 nm laser irradiation (Figure 22D).[614] This system achieved precise PTT with minimal damage to surrounding healthy tissue by optimizing the treatment temperature. Thermal energy can also enhance the release of therapeutics

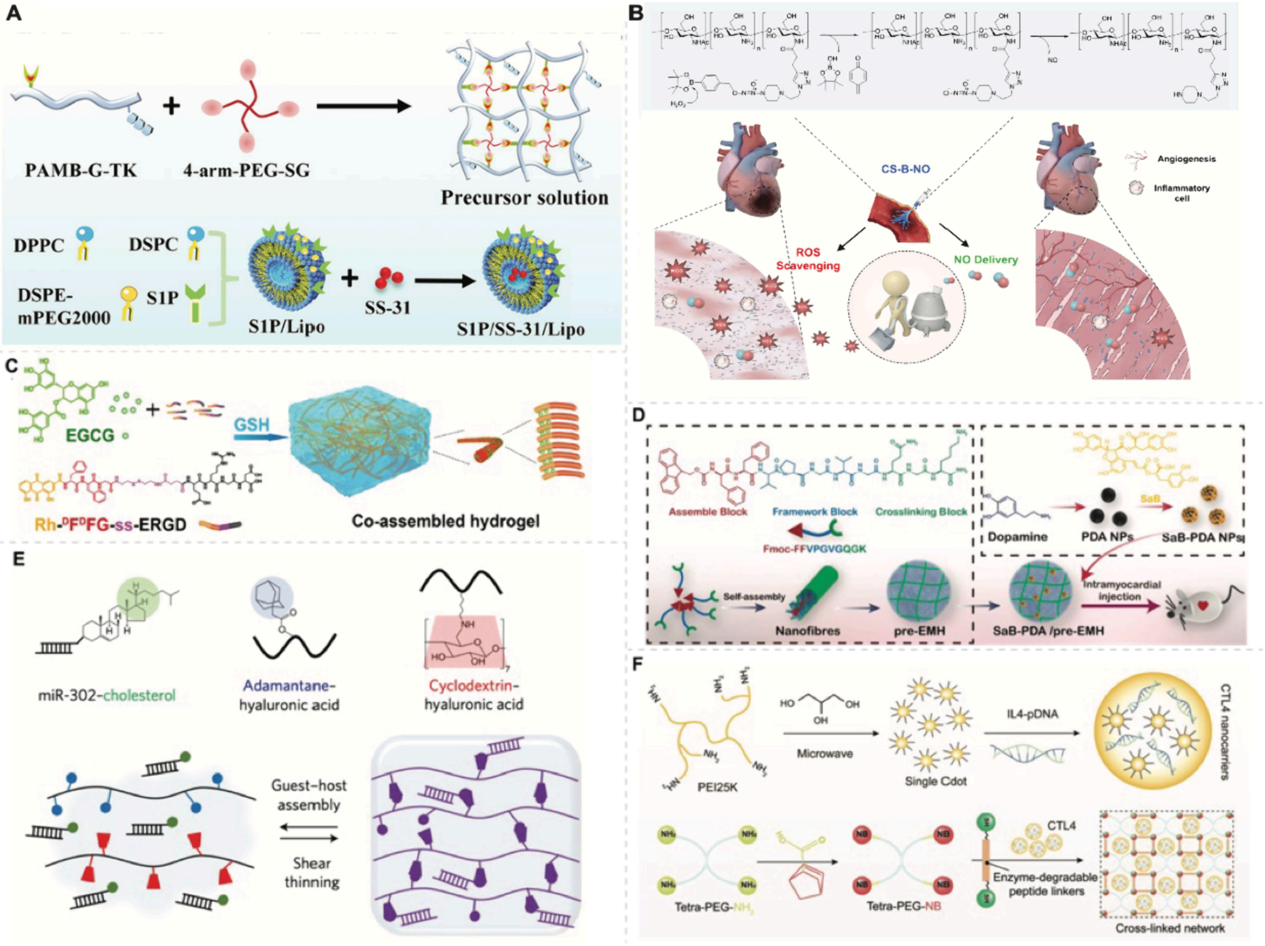

Figure 24. Hydrogel-based treatment for cardiovascular diseases. (A) Schematic illustration of the formation and mechanism of an S1P/SS-31/Lipo-encapsulated ROS-responsive composite hydrogel for the efficient treatment of MI.[627] Reproduced with permission from ref 627. Copyright 2022 John Wiley & Sons. (B) Schematic illustration of the treatment of I/R heart injury by CS-B-NO.[628] Reproduced with permission from ref 628. Copyright 2022 John Wiley & Sons under [CC BY 4.0]. (C) Synthetic scheme of EGCG@Rh coassembled hydrogel.[629] Reproduced with permission from ref 629. Copyright 2022 Elsevier. (D) Schematic illustration showing the preparation of peptide-constructed pre-EMH and SaB-PDA NPs hydrogel. Intramyocardial injection of SaB-PDA/pre-EMH undergoes an in situ TGase-responsive cross-link progress, promoting angiogenesis and inhibiting ventricular remodeling.[630] Reproduced with permission from ref 630. Copyright 2021 Elsevier. (E) Hyaluronic acid (HA) modified with adamantane (AD) or cyclodextrin (CD) self-assembled into shear-thinning and self-healing hydrogels. The system enables sustained release of miR-302, facilitated through cholesterol-CD interactions for cardiac regeneration.[631] Reproduced with permission from ref 631. Copyright 2017 Springer Nature. (F) MMP-2/9-responsive PEG cross-linked hydrogel, designed for plasmid DNA delivery using carbon dot encapsulation.[632] Reproduced with permission from ref 632. Copyright 2023 John Wiley & Sons.

from thermo-responsive hydrogels. For example, Guedes et al. reported a dual-responsive hydrogel incorporating Mo_{154} NPs for PTT (Figure 22E).[615] In response to the acidic tumor microenvironment and NIR-triggered heating of Mo_{154} NPs, DOX was rapidly and controllably released at the tumor site. In addition, Fan et al. developed an injectable adhesive hydrogel based on copolymeric NIPAAM (N-isopropylacrylamide) and dopamine methacrylamide (DMA) chains, with a sol–gel transition temperature of 32 °C, aligning with body temperature.[616] Catechol groups within DMA facilitated the encapsulation of MnO_2 NPs in the hydrogel. Upon NIR irradiation, MnO_2-mediated PTT induced immunogenic cell death, releasing autologous tumor-derived protein antigens. The catechol groups within the hydrogel further captured and sustained the release of these tumor antigens, enhancing cancer immunotherapy. Our group also developed a hydrogel (CM@Gel) coencapsulating MnO_2 nanosheets and the vascular-disrupting agent combretastatin A-4 phosphate (CA4P) to enhance the efficacy of cancer immunotherapy.[20]

5.1.2. Articular Inflammation Treatment.

Articular inflammation is a chronic and challenging condition caused by complex physiological factors. One of the major limitations in its treatment is the short intra-articular half-life of anti-inflammatory agents. Therefore, prolonging drug retention within the joint is a critical aspect of effective therapy. Hydrogel-based drug depots have played a significant role in addressing this challenge. For example, Yu et al. developed a thermosensitive hydrogel by cross-linking Pluronic F127 with hyaluronic acid (HA) to encapsulate chondroitin sulfate (CS)-E disaccharide.[617] This hydrogel rapidly underwent a "sol–gel" transition as the temperature increased from 4 to 37 °C, enabling a sustained release of CS-E for nearly 11 days. Moreover, Joshi et al. designed an arthritis flare-responsive hydrogel by self-assembling the small-molecule amphiphile triglycerol monostearate (TG-18) for the delivery of the corticosteroid triamcinolone acetonide (TA) (Figure 23A).[618] The hydrogel was engineered to reassemble in response to matrix metalloproteinases (MMPs), which are overexpressed during inflammatory flares. The hydrogel loaded with 40 mg/mL TA exhibited a cumulative release of 45% over 30 days and significantly reduced paw thickness compared to TA solution injections. A similar approach was employed to deliver calcium peroxide, facilitating the controlled release of psoralen and oxygen (O_2) over 30 days.[619] Additionally, Ma et al. developed a peptide-based hydrogel that self-assembles from Gly-Phe-Phe-Tyr-Asp peptides conjugated to methotrexate (MTX) for the treatment of rheumatoid arthritis (Figure 23B).[620] The Gly-Phe-Phe-Tyr-Asp-MTX hydrogel extended the release of MTX for nearly 15 days, demonstrating exceptional anti-inflammatory outcomes.

Selective depletion of excess nitric oxide (NO) or ROS has emerged as a novel strategy for treating articular inflammatory diseases by reducing oxidative stress and inflammation. For example, Kim et al. developed a NO-cleavable cross-linker, *N*, *N*-(2-amino-1, 4-phenylene) depentyn-4-amide, which was incorporated into an azide-functionalized hyaluronic acid backbone (Figure 23C).[621] Additionally, they synthesized an azide-functionalized PEG−PLA block copolymer, which self-assembled into nanoparticles for dexamethasone loading, a widely used anti-inflammatory agent. The hydrogel, cross-linked via Schiff-base chemistry, exhibited both injectability and self-healing properties. This dual-functional hydrogel effectively cleared excess NO within the joints while simultaneously releasing dexamethasone for sustained therapeutic effects. For ROS clearance, Zhou et al. developed an injectable hydrogel encapsulating drug-loaded ROS-scavenging micelles for efficient OA therapy[622] (Figure 23D). This hydrogel system effectively reduced oxidative stress, leading to improved inflammatory control and joint protection.

Adipose-derived stem cell (ADSC) therapy holds promise as a cell-based treatment for arthritis, but the inflammatory microenvironment often compromises ADSC survival and function. To overcome these limitations, hydrogel-based delivery systems have been developed to improve ADSC viability and therapeutic outcomes. Zhu et al. created an injectable ECM-mimicking hydrogel for ADSC encapsulation, incorporating dendritic polylysine or polysaccharide peptides through Schiff base cross-linking to provide a biomimetic niche that enhances cell retention and functionality (Figure 23E).[623] To further shield stem cells from ROS damage, Zhao et al. developed a nanozyme-enhanced hydrogel that acts as an H_2O_2-responsive oxygenator for delivering bone marrow-derived mesenchymal stem cells (BMSCs)[624] (Figure 23F). This hydrogel, synthesized by cross-linking MnCoO nanozymes with polylysine via Schiff base chemistry, effectively mitigated local inflammation and promoted osseointegration. Similarly, Zhu et al. utilized RAD-based self-assembling hydrogels to deliver mRNA-29b-5p into inflamed joints, successfully recruiting stem cells to the injury sites.[625] This strategy promoted cartilage repair and chondrocyte rejuvenation, demonstrating its potential in regenerative arthritis therapy.

5.1.3. Cardiovascular Disease Treatment.

Cardiac diseases remain one of the global leading causes of mortality. The advent of endoscope-assisted pericardial injections has enabled direct drug delivery to the heart, making injectable hydrogels a promising therapeutic platform for cardiac disease treatment.[626]

One major contributor to cardiac dysfunction is the overproduction of ROS, which induces oxidative stress and promotes the progression of various cardiac diseases. ROS-scavenging hydrogels offer a dual benefit by simultaneously eliminating ROS and delivering therapeutic agents. For example, Li et al. developed a TPSBA-PVA hydrogel loaded with acidic fibroblast growth factor (aFGF) into the pericardial cavity injection.[627] The hydrogel spread over the pericardial cavity, forming a therapeutic patch, allowing sustained aFGF release, which penetrated the myocardium, preserved cardiac function, and reduced fibrosis in an ischemia-reperfusion (I/R) injury rat model. Additionally, Zheng et al. developed an injectable ROS-responsive PAMB-G-TK/4-arm-PEG-SG hydrogel encapsulating liposomes loaded with elamipretide and sphingosine-1-phosphate.[627] The thioketal linkages in the hydrogel actively scavenged ROS while triggering the controlled release of liposomal therapeutics, thus achieving both ROS clearance and targeted drug delivery (Figure 24A).

Nitric oxide (NO) plays a crucial role in angiogenesis and cardioprotection. Based on this, Hao et al. developed an injectable hydrogel using boronate-protected diazeniumdiolate (CS-B-NO) linked chitosan, which simultaneously scavenged ROS and released NO[628] (Figure 24B). The oxidative stress can also be inhibited by antioxidative agents. For example, Liao et al. designed an injectable hydrogel system by coassembling antioxidative agents, epigallocatechin-3-gallate (EGCG) and a rhein-peptide (Rh-gel) to provide sustained antioxidative effects[629] (Figure 24C). This hydrogel effectively cleared ROS, reduced inflammation and improved cardiac function.

The hydrogels facilitated the sustained release of antioxidative agents while effectively scavenging ROS, thereby mitigating inflammation-associated oxidative stress. This dual action contributed to improved cardiac function and reduced scar formation. Additionally, an Fmoc-based self-assembled hydrogel was engineered for the delivery of salvianolic acid B, a potent antioxidative compound[630] (Figure 24D). The hydrogel's self-healing and adhesive properties enhanced its retention on cardiac tissue, enabling prolonged and controlled drug release.

Genetic therapies have emerged as promising strategies for the treatment of cardiac diseases. In a recent study, Li et al. developed a genetically engineered hydrogel incorporating mesoporous silica nanoparticles (MSNs) loaded with mRNA-21−5p for myocardial infarction therapy.[631] This ROS-responsive hydrogel was designed with Schiff base linkers that degrade in the acidic microenvironment of infarcted cardiac tissue, enabling the controlled release of mRNA-21−5p for targeted therapeutic effects. Moreover, Wang et al. introduced a supramolecular hydrogel system based on host−guest interactions for the delivery of cholesterol-functionalized miR-302 mimics. The cholesterol modification served a dual function: anchoring miR-302 to the cross-linked hydrogel network while enhancing its cellular uptake by cardiomyocytes. The hydrogel facilitated a sustained miR-302 release over 1 week, leading to a significant reduction in end-diastolic (39%) and end-systolic (50%) volumes, along with improvements in ejection fraction (32%) and fractional shortening (64%) compared to control groups (Figure 24E).[631]

Chen et al. designed a matrix metalloproteinase (MMP-2/9)-responsive polyethylene glycol (PEG)-based hydrogel for the controlled delivery of IL-4 plasmid DNA encapsulated in carbon dots.[632] Upon exposure to MMP-2/9 in the infarcted myocardium, the hydrogel underwent enzymatic degradation, facilitating the sustained release of plasmid DNA to enhance blood supply and mitigate extracellular matrix[632] (Figure 24F).

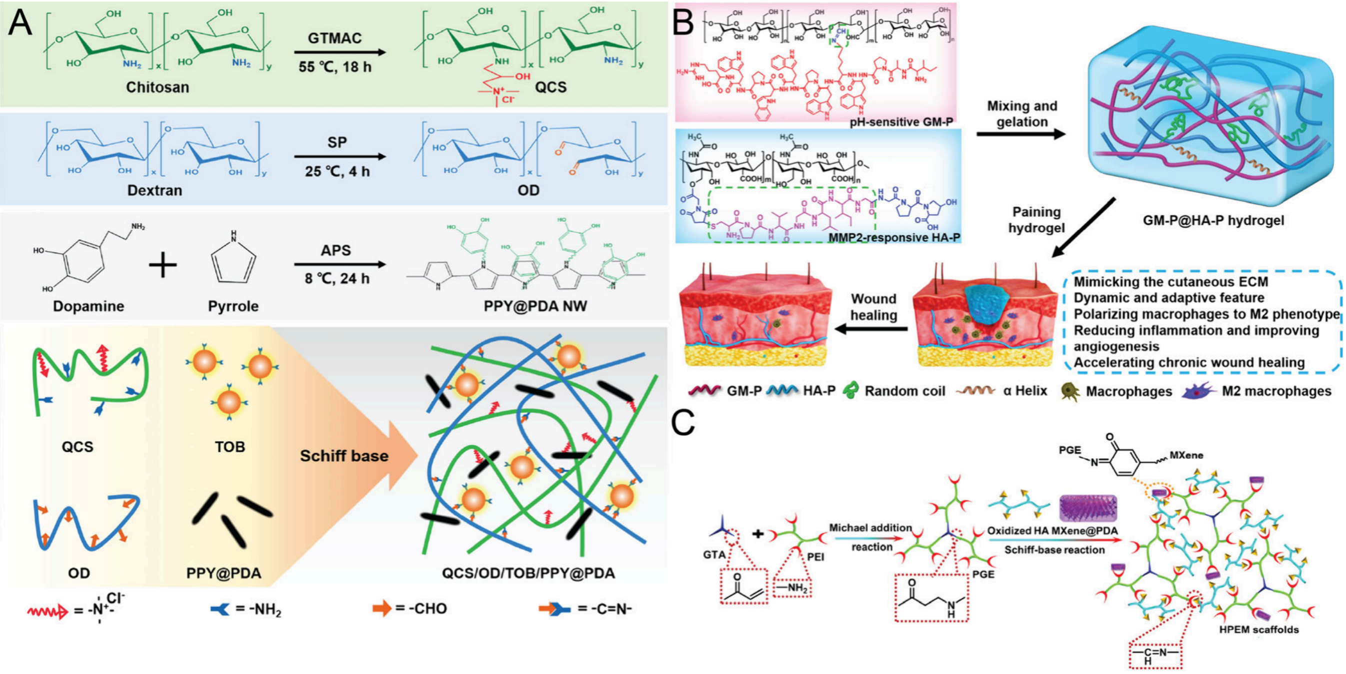

Figure 25. Adhesive hydrogel for skin wound healing. (A) Schematic illustration of the synthesis of QCS, OD, TOB, and PPY@PDA hydrogels.[633] Reproduced with permission from ref 633. Copyright 2022 American Chemical Society. (B) Schematic diagram showing the formation and application of a biomimetic GM-P@HA-P glycopeptide hydrogel as a multifunctional dressing for MRSA-infected chronic skin wound healing.[634] Reproduced with permission from ref 634. Copyright 2022 American Association for the Advancement of Science under [CC BY-NC 4.0]. (C) Fabrication and application of HPEM scaffolds for wound healing in multidrug-resistant bacteria infection.[635] Reproduced with permission from ref 635. Copyright 2021 American Chemical Society.

Hydrogel-based vehicles have been widely explored for mesenchymal stromal cell (MSC) therapy, which is gaining traction as a regenerative approach for myocardial infarction. Hydrogels provide a supportive microenvironment that preserves MSC viability and enhances their therapeutic potential. For example, You et al. developed poly(2-alkyl-2-oxazoline) (POx) cross-linked hydrogels functionalized with cell-adhesive peptides to improve MSC retention and activity.[636] These hydrogels exhibited strong tissue adhesive properties, prolonging MSC survival and maintaining their regenerative functions, which collectively promoted cardiac function recovery and enhanced neovascularization.[636]

5.1.4. Diabetes Mellitus Treatment.

Glucose-sensitive hydrogels have emerged as an advanced platform for diabetes management, enabling insulin delivery that dynamically responds to real-time fluctuations in blood glucose levels.[637] These hydrogels are typically functionalized with glucose-responsive moieties, such as phenylboronic acid, which forms reversible covalent bonds with glucose,[638] or glucose oxidase, an enzyme that catalyzes glucose oxidation to gluconic acid, thereby modulating hydrogel swelling and insulin release.[308] The resultant structural or pH-responsive changes trigger insulin release in a controlled manner, offering a self-regulating system for glycemic control. Injectable glucose-sensitive hydrogels, upon subcutaneous administration, establish localized insulin reservoirs, thereby improving pharmacokinetics while reducing the frequency of injections and enhancing patient adherence.

Mucoadhesive hydrogels are engineered to adhere to mucosal surfaces, providing an alternative route for insulin delivery via nasal or pulmonary administration. These formulations incorporate bioadhesive polymers, including chitosan and Carbopol, to prolong hydrogel residence time at mucosal interfaces, thereby enhancing insulin absorption and bioavailability. By circumventing gastrointestinal degradation and hepatic first-pass metabolism, these hydrogels enable rapid and efficient insulin uptake. Their mechanical properties and surface chemistry are meticulously tuned to optimize adhesion while minimizing mucosal irritation. Additionally, embedded controlled-release mechanisms ensure precise dosing, making these hydrogels particularly suited for managing acute glycemic fluctuations. Ongoing advancements in polymer architectures and mucoadhesive functionalization continue to expand the potential of these systems as noninvasive alternatives to traditional insulin administration.

5.2. Adhesive and Antiadhesive Hydrogels Serve as Medical Bandages

5.2.1. Adhesive Hydrogels for Skin Wound Healing.

Hydrogels have gained much attention in skin wound healing due to their high-water content, which provides a biocompatible, moist, and protective barrier against external environmental factors. Their inherent versatility allows for the incorporation of therapeutic functionalities such as antibacterial, anti-inflammatory, and antioxidant properties through rational chemical modification. Additionally, hydrogel-based wound dressings require a certain level of adhesion to ensure prolonged retention on wound surfaces, thereby enhancing their therapeutic efficacy.

Aldehyde-functionalized polymers are widely used in adhesive hydrogels for their ability to form Schiff base linkages with amino groups on the skin. These dynamic bonds not only provide strong adhesion but also enable controlled therapeutic release in the acidic wound microenvironment.[641] For instance, Huang et al. designed a Schiff base hydrogel from oxidized dextran and quaternized chitosan, achieving pH-responsive

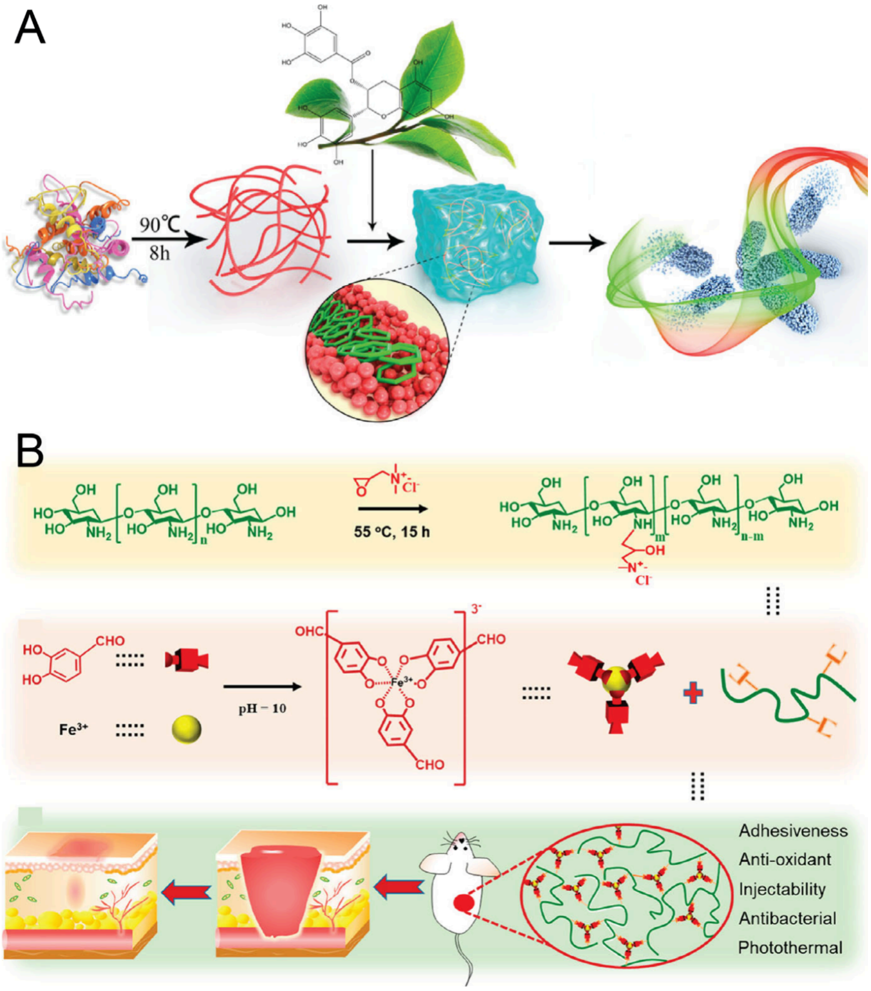

Figure 26. Catechol-based adhesive hydrogel for skin disease treatment. (A) Schematic representation of polyphenol-binding amyloid fibrils self-assembling into reversible hydrogels with antibacterial activity.[639] Reproduced with permission from ref 639. Copyright 2018 American Chemical Society. (B) Schematic illustration of the preparation and application of an adhesive hydrogel for the treatment of bacteria-infected wounds.[640] Reproduced with permission from ref 640. Copyright 2021 American Chemical Society.

tobramycin (TOB) release.[633] This hydrogel maintained antibacterial efficacy against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* for up to 11 days (Figure 25A). Similarly, Liu et al. designed a pH- and MMP-2-responsive hydrogel incorporating endogenous antibiotic peptides and cell-adhesive motifs, which supported fibroblast adhesion and promoted chronic wound healing in *Staphylococcus aureus*-infected wounds[634] (Figure 25B).

Hydrogel-based wound dressings have also been explored for their synergistic antibacterial effects when combined with near-infrared (NIR) irradiation. For instance, Zhou et al. incorporated two-dimensional Ti_3C_2Tx MXene nanosheets into Schiff base hydrogels, achieving a photothermal effect under NIR irradiation that eradicated MRSA with 99.03% efficiency[635] (Figure 25C). These hydrogels also exhibited rapid hemostatic capability, making them promising candidates for treating infected wounds.

The catechol group is another common adhesive group for hydrogel-based wound dressing. For example, Hu et al. reported amyloid fibrils self-assembled hydrogels by adding epigallocatechin gallate (EGCG). The hydrophobicity of the polyphenols locked EGCG on the amyloid fibrils, while the trihydroxyl groups maintained the hydrophilicity of the EGCG-binding amyloid fibril nanofibers. The simple hydrogelation also kept the antibacterial functions of amyloid fibrils, which was desirable for the healing of Gram-positive and Gram-negative bacteria-infected wounds[639] (Figure 26A). Moreover, Liang et al. developed quaternized chitosan cross-linked hydrogels to load Fe^{3+} and protocatechualdehyde (PA) through Schiff base linkers; the catechol groups within PA enhanced the adhesive ability of hydrogels and promoted methicillin-resistant *Staphylococcus aureus* (MRSA)-infected wound healing[640] (Figure 26B).

Beyond covalent bonding, hydrogen bonding interactions have been leveraged to enhance the adhesive capabilities of hydrogels. For example, Huang et al. introduced carboxymethyl groups on agarose hydrogels, which could load Ag^+ on the dissociative carboxymethyl groups[642] (Figure 27A). The loaded Ag^+ could be released under the acidic microenvironments within the wounds to kill bacteria. Moreover, Wang et al. designed a peptide-based hydrogel loaded with an antimicrobial octapeptide (IKFQHFD) that transitions into its antimicrobial form under acidic conditions[643] (Figure 27B). The hydroxy groups on the cross-linked networks facilitate hydrogel localization on wounds through hydrogen bonding, enhancing its effectiveness in wound healing. Furthermore, Cai et al. developed thermo-responsive adhesive hydrogels incorporating *N*-isopropylacrylamide (NIPAM) and tetrahy-

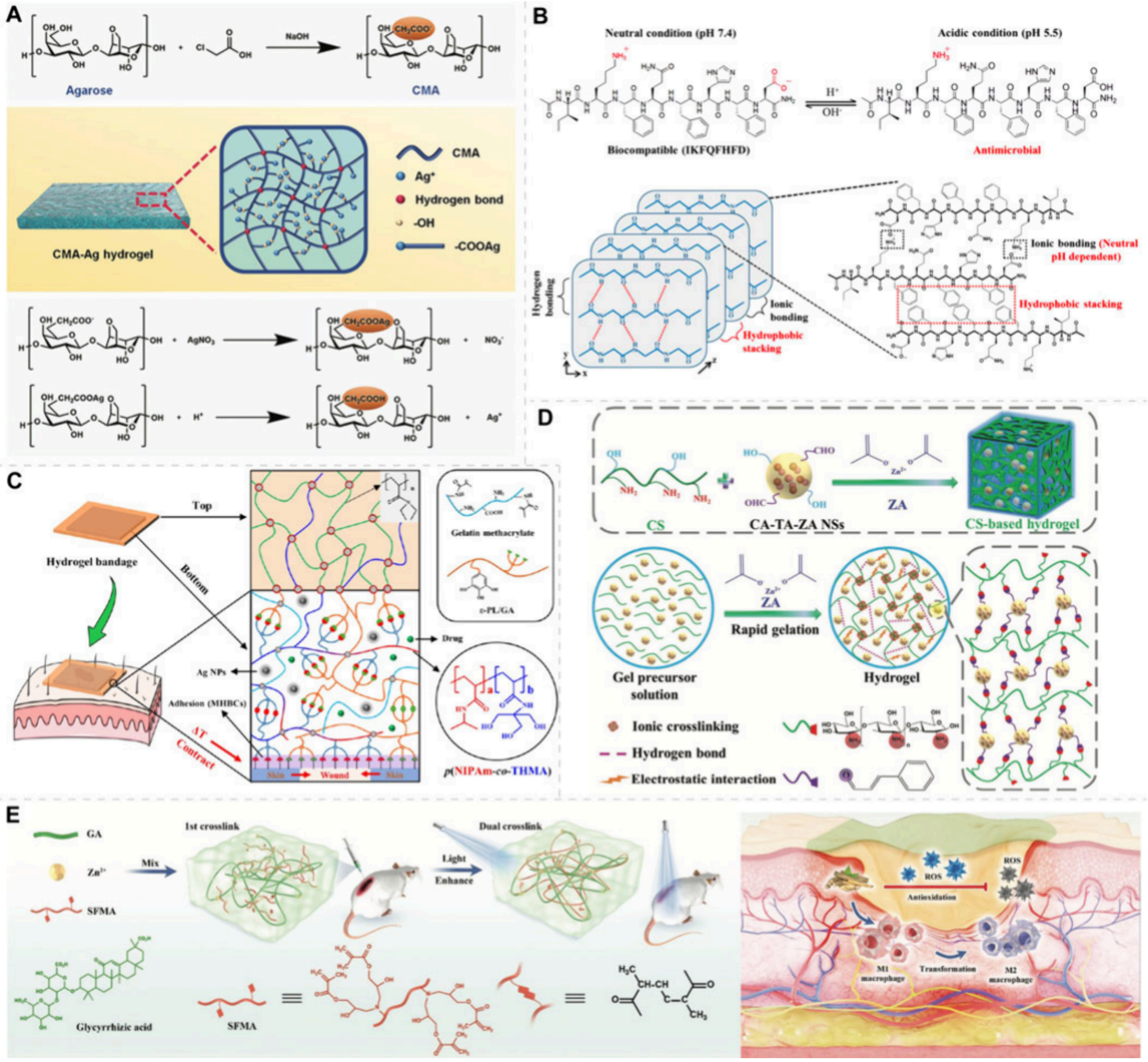

Figure 27. Hydrogel-based strategies for wound healing and skin repair. (A) Schematic representation and architecture of the CMA molecule and CMA−Ag hydrogel architecture, with pH-responsive release of Ag^+ from the CMA−Ag hydrogel.[642] Reproduced with permission from ref 642. Copyright 2020 John Wiley & Sons. (B) Chemical structure of IKFQFHFD under neutral and acidic conditions. The proposed molecular arrangement of IKFQFHFD forming self-assembled supramolecular nanofiber networks of the hydrogel at neutral pH.[643] Reproduced with permission from ref 643. Copyright 2019 American Chemical Society. (C) Schematic diagram illustrating the composition of the top and bottom sides of the hydrogel.[644] Reproduced with permission from ref 644. Copyright 2022 American Chemical Society. (D) Illustration of the synthesis process and potential gelation mechanisms involved in the formation of chitosan (CS)-based hydrogels.[645] Reproduced with permission from ref 645. Copyright 2022 John Wiley & Sons. (E) A photoenhanced glycyrrhizic acid hybrid hydrogel as an immunoregulatory scaffold for diabetic wound repair. (Left) Schematic illustration of the preparation of the SF/GA/Zn hybrid hydrogel. (Right) Immunoregulation of the SF/GA/Zn hybrid hydrogel dressing in diabetic wound healing.[646] Reproduced with permission from ref 646. Copyright 2022 John Wiley & Sons.

droxy methacrylate (THMA), utilizing a physical healing mechanism for wound closure (Figure 27C).[644] The presence of THMA enhances hydrogen bond interactions between the hydrogel and the skin, while temperature changes induce hydrogel contraction, thereby maintaining wound closure. Sun et al. constructed injectable chitosan-based hydrogels capable of delivering cinnamaldehyde-tannic acid-zinc acetate nanospheres, which exhibit antibacterial, antioxidant, and anti-inflammatory properties[645] (Figure 27D). These multifunctional hydrogels form in situ, effectively modulating the wound microenvironment and promoting skin tissue regeneration. Additionally, Qian et al. reported interpenetrating polymer networks (IPNs) incorporating Zn^{2+} ions and glycyrrhizic acids, designed to maintain structural integrity in diabetic wound cavities[646] (Figure 27E). The Zn^{2+} ions and glycyrrhizic acids contribute to the hydrogel's antioxidative effects and facilitate macrophage polarization from the pro-inflammatory M1 phenotype to the pro-regenerative M2 phenotype, thus accelerating wound healing.

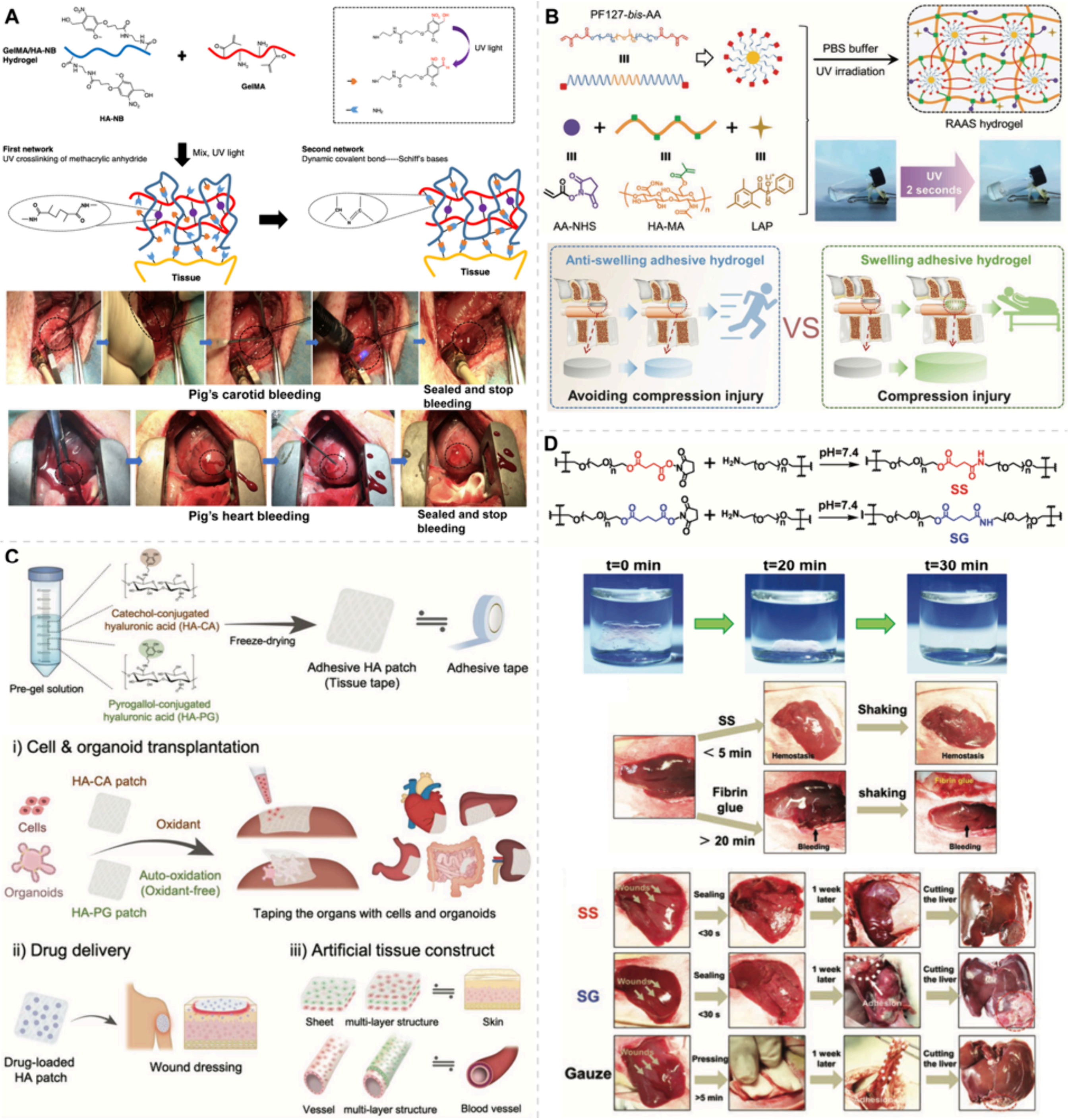

Figure 28. Adhesive hydrogels for organ injury healing. (A) Constituent chemical structures and a schematic diagram illustrating the formation of the phototriggered imine-cross-linked matrix hydrogel.[647] Reproduced with permission from ref 647. Copyright 2019 Springer Nature under [CC BY 4.0]. (B) Schematic illustration of the fabrication of RAAS hydrogel through photo-cross-linking for bone injuries.[648] Reproduced with permission from ref 648. Copyright 2022 John Wiley & Sons. (C) Adhesive HA-based patch platform for versatile biomedical applications, including (i) cell and organoid transplantation, (ii) drug delivery, and (iii) artificial tissue construct.[649] Reproduced with permission from ref 649. Copyright 2019 John Wiley & Sons. (D) Schematic illustration of the fabrication, degradation, and hemostasis function of tetra-PEG-SS-based hydrogels for organ bleeding.[650] Reproduced with permission from ref 650. Copyright 2019 John Wiley & Sons.

Collectively, hydrogel-based wound dressings function as bioactive platforms that provide a protective barrier, facilitate the absorption of wound exudates, and promote cell migration and proliferation. The incorporation of biofunctional agents, including antimicrobial compounds, growth factors (e.g., EGF, VEGF), and anti-inflammatory molecules, further accelerates the wound healing process by modulating inflammation, enhancing tissue regeneration and preventing infections. Advances in bioinspired polymer chemistry have significantly improved the functionality of these hydrogels, optimizing their adhesion, mechanical properties, and controlled-release capabilities for more effective therapeutic outcomes.

5.2.2. Adhesive Hydrogels for Major Organ Injury Healing.

Unlike skin wounds, injuries to internal organs such

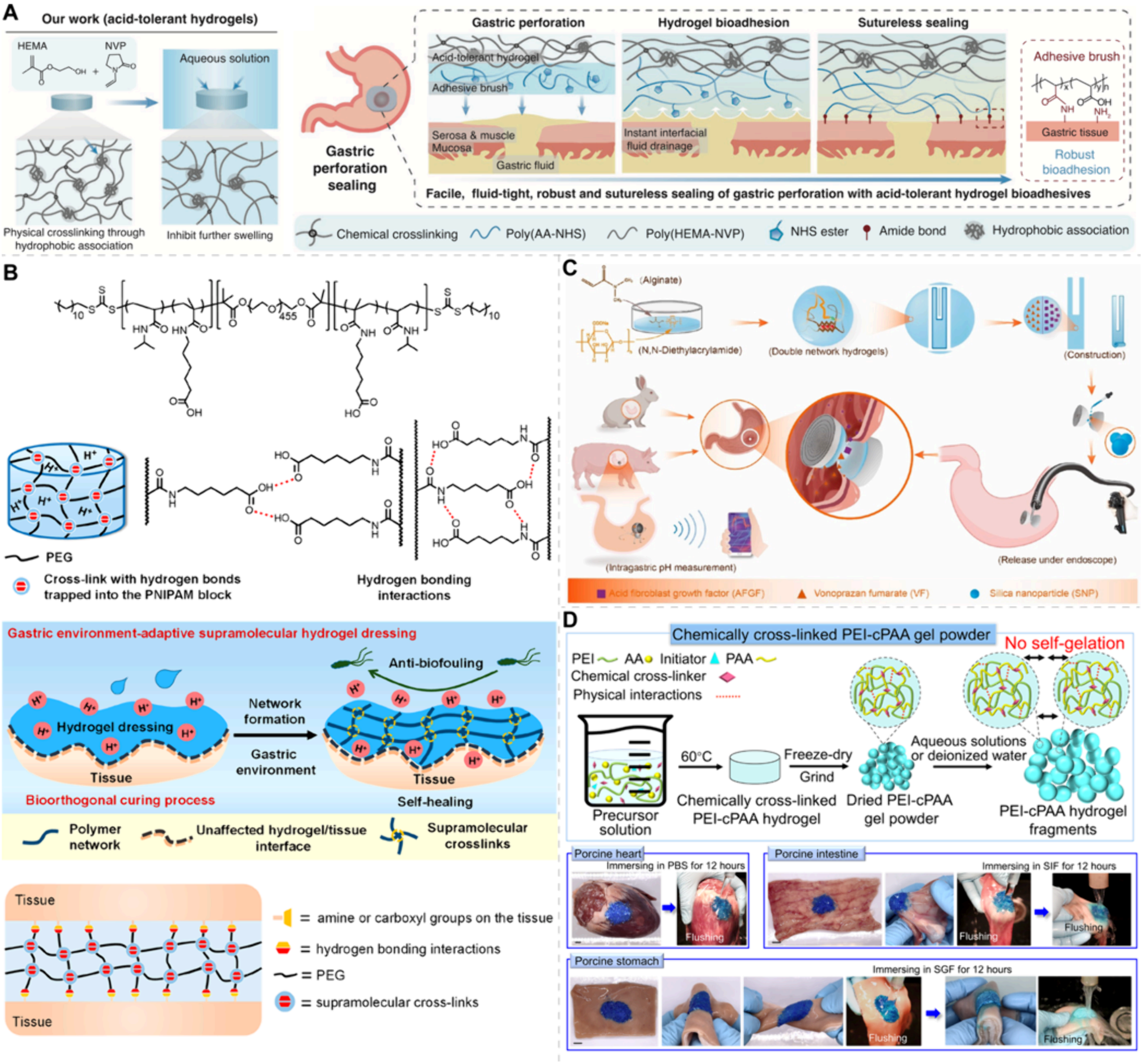

Figure 29. Adhesive hydrogel for gastric tissue repair. (A) Conventional chemically cross-linked hydrogel networks tend to swell significantly when immersed in water or under extreme conditions (e.g., low pH). In contrast, the proposed hydrogel adhesives—physically cross-linked through hydrophobic associations—exhibit limited swelling, as the broadly distributed hydrophobic domains effectively restrain further water uptake in such environments.[651] Reproduced with permission from ref 651. Copyright 2022 John Wiley & Sons. (B) Schematic illustration of an acid nonresistant injectable hydrogel dressing formed through the nonbioorthogonal curing process and the gastric environment-adaptive supramolecular hydrogel as an internal wound dressing. Chemical structure of the ABA triblock copolymer and supramolecular hydrogel network structure.[652] Reproduced with permission from ref 652. Copyright 2021 American Chemical Society. (C) Schematic representation of a mushroom-cap-inspired compressible device for sealing and healing gastric perforations, designed with a hyperboloid shape for enhanced adhesion.[653] Reproduced with permission from ref 653. Copyright 2023 American Chemical Society. (D) Preparation and characterization of PEI/PAA hydrogels, demonstrating excellent adhesive properties on various biological surfaces.[654] Reproduced with permission from ref 654. Copyright 2021 American Association for the Advancement of Science under [CC BY-NC 4.0].

as arteries, the heart, and the liver present additional challenges due to their wet surfaces and continuous bleeding. Hydrogel adhesion in such environments requires rapid gelation, strong tissue adhesion, and mechanical robustness to withstand physiological blood pressure.

Rapid adhesion, short gelation time, and adequate mechanical strength are critical factors of hydrogels for achieving hemostasis in organ injuries. Hong et al. reported UV-triggered hydrogels capable of forming within seconds and establishing strong adhesion to wet biological tissues[647] (Figure 28A). These dual-cross-linked hydrogels exhibited exceptional toughness, enabling them to withstand high blood pressure (up to about 130 mmHg), while the rapid formation of Schiff base bonds ensured firm adhesion to wet surfaces. In addition, the incorporation of nanomaterials enhanced the antiswelling properties of the hydrogels by increasing cross-

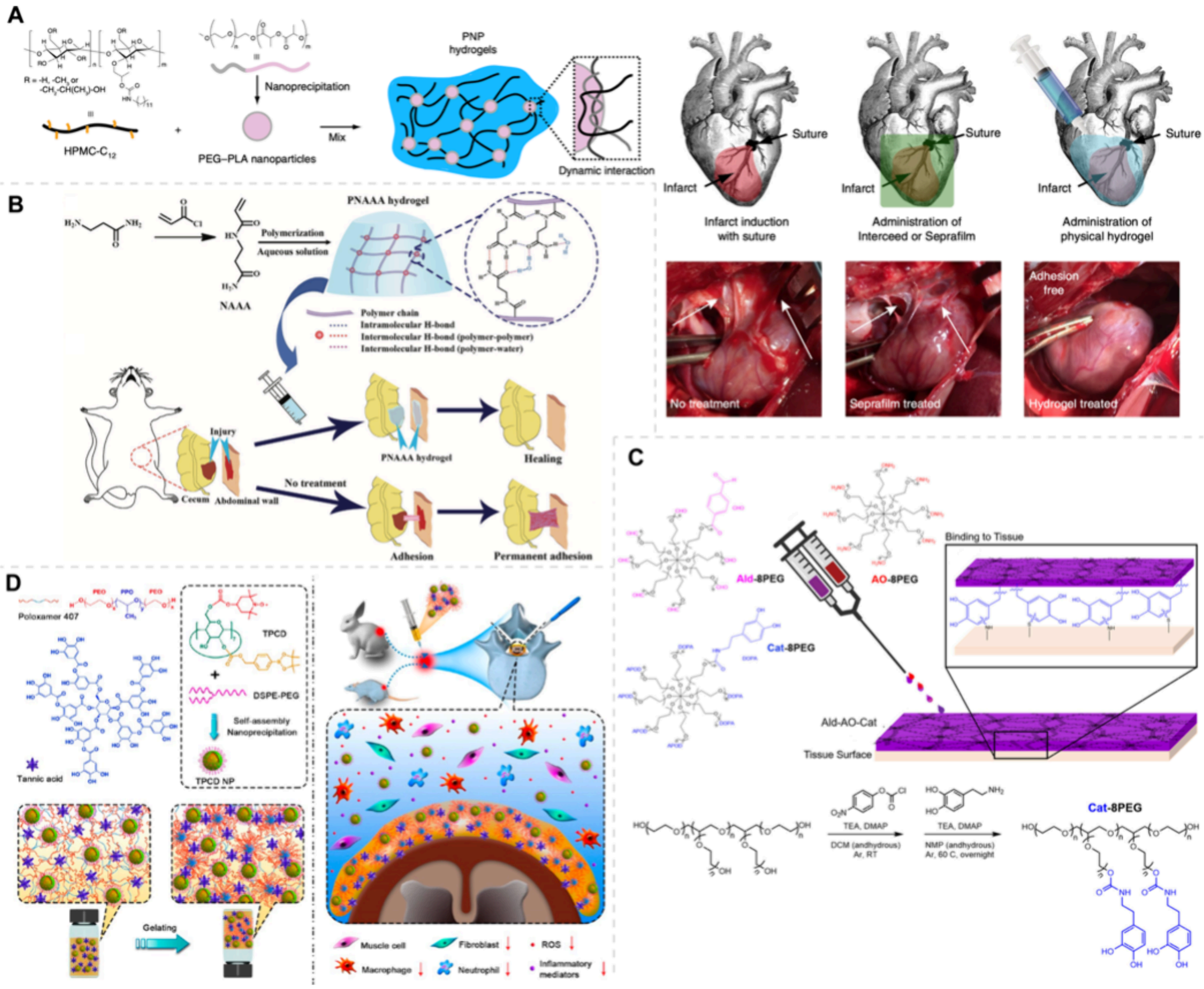

Figure 30. Therapeutic hydrogels as antiadhesive biobarriers. (A) Hydrogels formed through multivalent and dynamic noncovalent interactions between hydrophobically modified HPMC-C12 and PEG-PLA can be easily applied using standard spray equipment. The HPMC-C12 component imparts tissue adhesiveness, creating a viscoelastic barrier that prevents postoperative adhesion formation between organs and tissues.[655] Reproduced with permission from ref 655. Copyright 2019 Springer Nature. (B) Schematic illustrations of a supramolecular PNAAA hydrogel with an H-bonding cross-linked network. The hydrogel is applied in a rat cecum-abdominal wall adhesion model, either with or without treatment using the PNAAA hydrogel.[656] Reproduced with permission from ref 656. Copyright 2021 John Wiley & Sons. (C) An oxime-based hydrogel is formed using three distinct 8-arm star PEG polymers. The Ald-8PEG/Cat-8PEG solution is mixed with the AO-8PEG solution in a 1:1 ratio and applied to tissue surfaces using a FibriJet gas-assisted applicator. Rapid formation of oxime bonds occurs between Ald-8PEG and AO-8PEG, while the catechol groups in Cat-8PEG covalently bond with primary amines on the tissue surface, promoting strong hydrogel−tissue adhesion.[657] Reproduced with permission from ref 657. Copyright 2021 Springer Nature under [CC BY 4.0]. (D) Schematic illustration of a multifunctional injectable hydrogel designed to prevent postoperative epidural fibrosis following lumbar laminectomy.[658] Reproduced with permission from ref 658. Copyright 2020 American Chemical Society.

linking density, thereby reducing volumetric expansion and minimizing patient discomfort[648] (Figure 28B). Moreover, Shin et al. developed a hydrogel-based adhesive tape incorporating phenolic adhesive moieties (e.g., catechol and pyrogallol) conjugated with hyaluronic acids, which enabled strong adhesion to wet tissues[649] (Figure 28C). This system was particularly suitable for stem cell therapy and drug delivery, as therapeutic agents could be preloaded onto the adhesive surface. Moreover, Yuk et al. proposed a dry hydrogel-based double-sided adhesive tape designed for organ injuries. This adhesive layer, composed of poly(acrylic acid) functionalized with *N*-hydroxysuccinimide ester, formed covalent amide bonds with tissue-resident amine groups, while a biodegradable polymeric layer cross-linked with chitosan provided additional support.[659] This dry tape exhibited rapid adhesion within five seconds, offering a promising approach for surgical applications. Additionally, Bu et al. developed fast-degradable hydrogels via cross-linking Tetra-PEG-NH_2 and Tetra-PEG-SS[650] (Figure 28D). The residual succinimidyl-active esters within the cross-linked network reacted with amino groups in tissue proteins, forming robust covalent bonds with wet organ surfaces. This innovative strategy ensures strong yet biodegradable adhesion, making it a potential candidate for clinical hemostatic applications.

Gastric injury is particularly challenging due to the highly acidic microenvironment, necessitating acid-resistant hydrogel

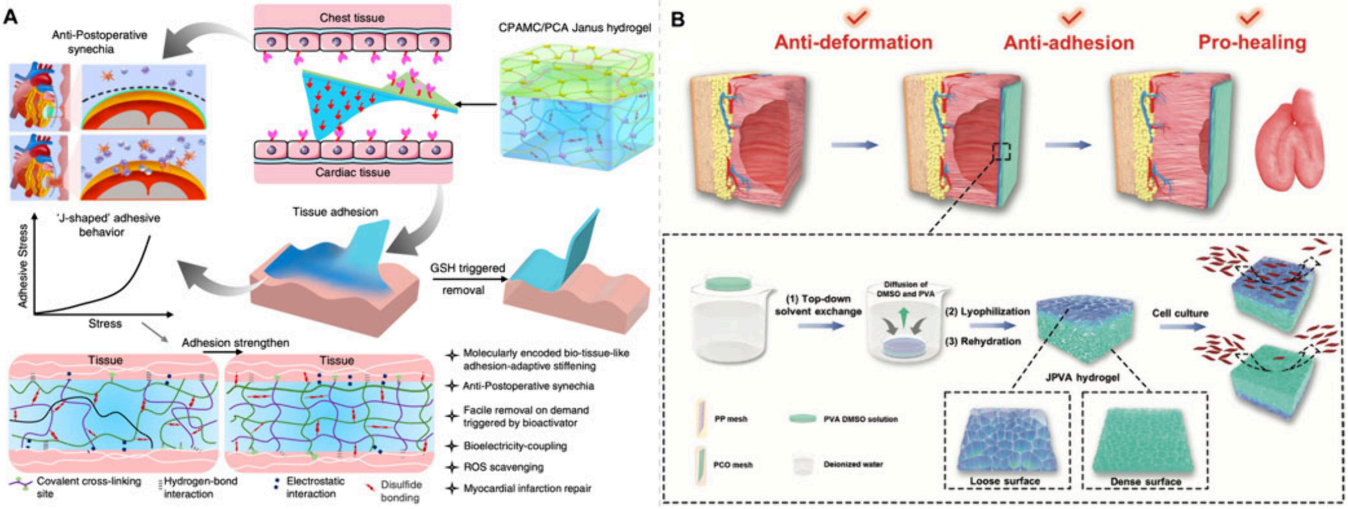

Figure 31. Biomimetic hydrogel system for antiadhesion and pro-healing applications. (A) Schematic illustration of a smart Janus adhesive and an on-demand removable CPAMC/PCA hydrogel, designed as a multifunctional engineered cardiac tissue patch (ECP) for myocardial infarction (MI) repair in a rat model.[255] Reproduced with permission from ref 255. Copyright 2022 Springer Nature under [CC BY 4.0]. (B) The JPVA hydrogel has unique asymmetric cell-adhesion behavior, along with excellent mechanical and antiswelling properties. These characteristics enable simultaneous antiadhesion, pro-healing, and antideformation effects, contributing to enhanced repair of abdominal wall defects.[660] Reproduced with permission from ref 660. Copyright 2022 John Wiley & Sons.

formulations. To address this, Chen et al. developed a dual-layer acid-tolerant hydrogel for gastric perforation[651] (Figure 29A). The hydrogel consisted of an NHS-ester-modified adhesive layer that enabled firm localization on gastric walls, while a hydrophobic poly(HEMA-NVP) cross-linked layer provided resistance against the acidic environment. Furthermore, Wang et al. reported an injectable, self-healing supramolecular hydrogel based on an ABA triblock copolymer, which incorporated a central polyethylene glycol (PEG) block and poly(*N*-isopropylacrylamide) (PNIPAM) side chains[652] (Figure 29B). To enhance tissue adhesion in acidic conditions, they functionalized the PNIPAM chains with pH-sensitive acryloyl-6-aminocaproic acid (A6ACA) groups, which reinforced hydrogen bonding between the hydrogel and gastric tissues. For total gastric perforation repair, Liu et al. designed a mushroom-shaped adhesive hydrogel-based device capable of sealing perforations[653] (Figure 29C). This device was composed of two layers: an inner dimethylacetamide (DMA) matrix cross-linked with biodegradable N,N-cystaminebis-(acrylamide) (CBA) and an outer sodium alginate (SA) network cross-linked with Ca^{2+} ions. To further enhance adhesion, silica nanoparticles were coated onto the device's surface, while the DMA and Ca^{2+} cross-linkers improved resistance to deformation in acidic conditions. In addition, Peng et al. developed an alternative approach by developing in situ gelling hydrogel-based powders for gastric injury treatment[654] (Figure 29D). Upon absorbing water, these powders rapidly gelled within two seconds, forming a continuous hydrogel layer over the injured gastric wall. Strong hydrogen bonding ensured firm adhesion to the stomach lining, effectively preventing gastric juice infiltration and promoting healing. This powder-based hydrogel system offers a convenient and minimally invasive solution for gastric injury repair.

5.2.3. Therapeutic Hydrogels as Antiadhesive Biobarriers for Postsurgical Adhesions. Postsurgical adhesions pose significant complications in procedures such as abdominal, pelvic, cardiac, and epidural surgeries, potentially leading to chronic pain, bowel obstruction, and other severe outcomes. Bioinspired hydrogel-based barriers have been developed to prevent adhesions by physically separating tissue surfaces while minimizing inflammatory responses.

Stapleton et al. designed a sprayable hydrogel composed of hydroxypropylmethylcellulose (HPMC) polymers cross-linked with poly(ethylene glycol)-*b*-poly(lactic acid) (PEG-PLA) nanoparticle) nanoparticles[655] (Figure 30A) This sprayable formulation was particularly suitable for cardiac antiadhesion applications, as it could uniformly cover surgical sites and remain in place for up to 2 weeks, effectively reducing pericardial adhesion formation. Additionally, Yu et al. developed an ultrasoft and highly swollen hydrogel-based biobarrier by incorporating methylene groups into the two amides of *N*-acryloyl glycinamide (NAGA), thereby reducing intermolecular hydrogen bond density[656] (Figure 30B). This modification resulted in an ultrasoft hydrogel that resisted adhesion formation while simultaneously protecting the postsurgical area.

Injectable hydrogels have also been explored as biobarriers. Fujita et al. reported an injectable hydrogel formed through cross-linking aldehyde (Ald), aminooxy (AO), and catechol-functionalized PEG chains[657] (Figure 30C). The incorporation of catechol groups improved the hydrogel's adhesion to tissue, while the cross-linked PEG network inhibited protein and cell attachment, thereby reducing postoperative adhesion formation. To prevent epidural adhesions after surgery, Wang et al. designed a hydrogel-based biobarrier composed of poloxamer 407, tannic acid as an adhesive component, and anti-inflammatory nanoparticles[658] (Figure 30D). Poloxamer 407 conferred antiadhesive properties, while tannic acid enhanced tissue adhesion. Additionally, the presence of anti-inflammatory nanoparticles helped mitigate local oxidative stress and suppress inflammatory responses, further reducing adhesion formation. Collectively, these hydrogel-based strategies represent promising approaches for preventing postsurgical adhesions by combining physical separation with biofunctional properties that modulate inflammatory responses.

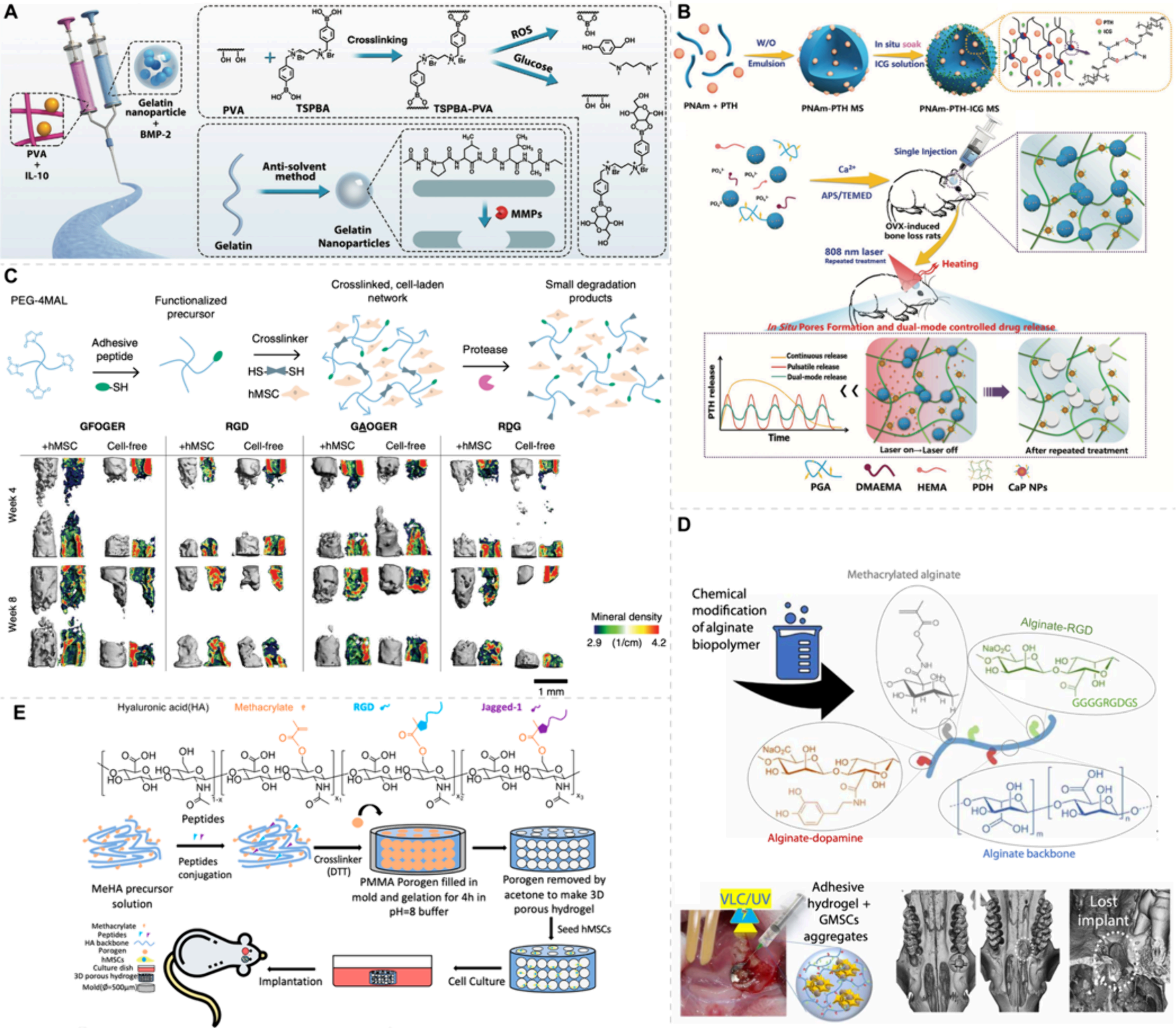

Figure 32. Multifunctional hydrogel systems for bone regeneration. (A) Schematic diagram showing the design principle of a logic-based hydrogel with both diagnostic and therapeutic functions. The hydrogel facilitates HIB-induced diabetic bone regeneration by reprogramming the immune-osteo cascade.[671] Reproduced with permission from ref 671. Copyright 2022 John Wiley & Sons. (B) Injectable NIR-light responsive DHCP-PIP hydrogel enhances cranial defect repair in osteoporosis rats.[672] Reproduced with permission from ref 672. Copyright 2021 John Wiley & Sons. (C) Integrin-specific peptide-functionalized hydrogels modulate cell adhesion and enhance mineralization. The hydrogel network incorporates bioactive peptides (e.g., GFQGER, RGD) to support mesenchymal stem cell (MSC) differentiation and promote osteogenesis, as demonstrated by in vivo mineral density analysis at various time points).[673] Reproduced with permission from ref 673. Copyright 2020 Springer Nature under [CC BY 4.0]. (D) Chemically modified alginate hydrogels exhibit enhanced adhesion and mechanical properties, making them suitable for tissue engineering applications. Methacrylated alginate (MeHA) hydrogels are functionalized with bioactive motifs (e.g., RGD, dopamine) to improve cell adhesion and osteogenic potential.[674] Reproduced with permission from ref 674. Copyright 2020 American Association for the Advancement of Science. (E) Schematic illustration of the fabrication process for peptide-functionalized hydrogels. The porous MeHA hydrogel is synthesized using a porogen-leaching method and loaded with MSCs for bone tissue engineering applications.[675] Reproduced with permission from ref 675. Copyright 2022 American Chemical Society.

Janus hydrogel-based barriers have garnered significant attention for postsurgical adhesion prevention due to their unique asymmetric design, where one side possesses adhesive properties while the other side remains antiadhesive. This dual functionality allows for effective tissue integration while simultaneously preventing unwanted adhesions. He et al. developed Janus hydrogels for myocardial infarction repair[255] (Figure 31A). The bottom layer featured a loosely porous structure that promoted cardiac cell proliferation, while catechol group modification enhanced its adhesive properties, ensuring strong tissue attachment. In contrast, the top layer was constructed with densely cross-linked acrylic acid, effectively resisting cell adhesion and thereby preventing postsurgical adhesions. Similarly, Liang et al. reported poly(vinyl alcohol) Janus hydrogels synthesized via a top-down solvent exchange method for abdominal postsurgical adhesion prevention[660] (Figure 31B). By adjusting the ratio of dimethyl sulfoxide (DMSO) to water, a gradient in PVA solubility was achieved, resulting in a densely porous and smooth top layer that inhibited fibroblast adhesion, while the bottom layer remained loosely porous and rough to facilitate tissue integration and healing. These innovative Janus hydrogel designs provide a promising approach for postsurgical adhesion prevention by balancing tissue adhesion and antiadhesive properties within a single material.

5.3. Hydrogel-Based Cell Scaffolds for Tissue Regeneration

5.3.1. Bone Regeneration. Regenerative medicine, particularly in the context of bone repair, represents a critical application area for hydrogel-based biomaterials. The highly tunable properties of hydrogels allow them to adapt to varying bone stiffness, while their diverse drug-loading capabilities enable the sustained delivery of bioactive molecules essential for bone regeneration.

The bone healing process involves inflammation, bone formation, and remodeling, requiring bioactive molecule delivery platforms for sustained release and enhanced efficacy.[661] Growth factors (GFs) like BMP-2, VEGF, and SDF-1α promote osteogenesis, angiogenesis, and cell recruitment but face limitations such as poor stability and high cost, necessitating controlled release systems.[662] Drugs like PTH,[663] ADA,[664] and DFO[665] target bone defects and underlying diseases but require localized delivery to avoid systemic side effects and improve therapeutic outcomes.

Bioactive ions (e.g., Ca^{2+},[664] Zn^{2+},[665] Mg^{2+},[666] Cu^{2+}[667]), as well as silicate ions, modulate bone regeneration by influencing osteoblast differentiation, angiogenesis, and gene expression. However, precise concentration control is essential to prevent cytotoxicity. Stem cell-based therapies, including mesenchymal stem cells (MSCs) and adipose-derived stem cells (ADSCs),[666] demonstrating potential in bone repair through osteogenic differentiation and intercellular communication. Additionally, extracellular vehicles (EVs) have emerged as a promising alternative, offering advantages such as reduced immunogenicity and ease of administration.[667] Gene therapies, such as miRNA,[668] siRNA,[669] and CRISPR-Cas9,[670] enable precise regulation of bone regeneration pathways. However, their effectiveness relies on delivery systems that can efficiently bypass biological barriers. In this context, hydrogel-based platforms have emerged as versatile and promising carriers, providing sustained and localized release of these agents and enhancing the efficacy of bone regeneration therapies.

To address the challenges of diabetic bone regeneration, Li et al. developed a triple-stimuli-responsive poly(vinyl alcohol) (PVA)-TPSBA hydrogel for controlled delivery of interleukin-10 (IL-10) and bone morphogenetic protein-2 (BMP-2)[671] (Figure 32A). In this system, IL-10 was dispersed within the PVA matrix, while BMP-2 was encapsulated in matrix metalloproteinase (MMP)-responsive nanoparticles. The hydrogel was engineered to release both cytokines in response to ROS, elevated glucose, and MMP activity in the bone microenvironment, offering a targeted, adaptive therapeutic strategy for diabetic bone repair. Similarly, recognizing the role of parathyroid hormone (PTH) in osteoclast activation and bone remodeling, PTH-loaded calcium phosphate nanoparticles were embedded in a poly(dimethylaminoethyl methacrylate-*co*-2-hydroxyethyl methacrylate) (DHCP) hydrogel[672] (Figure 32B). This hybrid system responds to near-infrared (NIR) irradiation, where localized heating triggers PTH release, promoting osteoblast and osteoclast activity at the injury site. These approaches demonstrate the promise of NIR-responsive hydrogels for spatiotemporally controlled bone regeneration.

In addition to biochemical delivery, hydrogels have been extensively explored as platforms for mesenchymal stem cell (MSC) therapy due to their biocompatibility, tunable properties, and ability to support cell survival and differentiation. Polyethylene glycol (PEG)-based hydrogels, in particular, are widely utilized for MSC delivery because of their cytocompatibility and low inflammatory response. For example, Clark et al. developed a 4-arm PEG-4MAL hydrogel system for the delivery of human marrow-derived mesenchymal stem cells (hMSCs)[673] (Figure 32C). To enhance cellular adhesion, the hydrogel network was functionalized with cysteine-terminated adhesive peptides, which recruit integrins, thereby promoting hMSC survival, proliferation, and osteogenic differentiation. Moreover, alginate-based hydrogels have been developed as biofriendly carriers for gingival mesenchymal stem cells (GMSCs) therapy[674] (Figure 32D). For example, RGD peptide-modified alginate hydrogels enhanced osteogenesis and ossification by promoting cell adhesion, while dopamine-modified groups improved the adhesive strength of the hydrogel. Similarly, hyaluronic acids (HA)-based hydrogels were engineered to enhance MSC-mediated bone regeneration. These hydrogels were functionalized with both RGD peptides and Jagged-1 peptides to activate the Notch signaling pathway, thereby promoting mechano-transduction and osteogenesis[675] (Figure 32E). Additionally, a porous architecture was introduced using a PMMA porogen, which dissolved within the alginate hydrogel matrix, creating microsized meshes. This structural modification provided sufficient space for hMSC infiltration, proliferation, and differentiation, further supporting bone tissue regeneration.

5.3.2. Muscle Regeneration. *5.3.2.1. Mechanical Properties of Muscle-Guided Muscle-Like Hydrogels.* Muscle regeneration requires hydrogel-based scaffolds that closely mimic the elasticity, flexibility, and dynamic mechanical behavior of native muscle tissue. Given that muscle tissue undergoes continuous cycles of contraction and relaxation, hydrogels designed for muscle repair must exhibit high resilience, tunable viscoelasticity, and the ability to withstand mechanical deformation while providing structural support for cellular attachment, proliferation, and alignment.[676]

To achieve these mechanical properties, hydrogels are typically fabricated from biomaterials such as PEG, poly(vinyl alcohol) (PVA), and elastin-like polypeptides (ELPs), which confer elasticity and resilience to mimic the biomechanical functionality of muscle. Hydrogels incorporating natural biopolymers such as gelatin and fibrin further enhance bioactivity by providing an ECM-like microenvironment conducive to cell adhesion and differentiation.

Given the electrical excitability of muscle tissue, conductive hydrogels have been increasingly explored for muscle regeneration applications. Materials such as polypyrrole, polyaniline, and graphene oxide have been integrated into hydrogel matrices to facilitate the transmission of bioelectric signals that regulate myoblast alignment, fusion, and differentiation.[677] Notably, graphene oxide-enhanced hydrogels have demonstrated improved conductivity and mechanical performance, leading to enhanced functional outcomes in muscle repair.[678]

Beyond electrical conductivity, stress-relaxation behavior and viscoelastic properties are crucial considerations for hydrogels used in dynamic muscle environments. To confer these properties, hydrogels have been engineered with dynamic covalent bonds (e.g., imine or disulfide linkages) and noncovalent interactions (e.g., hydrogen bonding, ionic interactions), enabling the scaffold to undergo reversible deformation while maintaining structural integrity. Such dynamic cross-linking mechanisms enhance hydrogel durability and extend its functional lifespan under cyclic loading conditions.[679]

Another critical design consideration is the hierarchical alignment of muscle fibers.[680] The anisotropic mechanical properties of native muscle tissue necessitate hydrogel scaffolds with aligned micro- or nanofiber structures that guide myoblast orientation and facilitate the formation of functional muscle fibers.[681] Fabrication techniques such as electrospinning and 3D bioprinting have been employed to create fiber-aligned hydrogels that provide topographical cues for myoblast alignment, significantly enhancing muscle regeneration outcomes.[682]

5.3.2.2. Proliferation and Differentiation-Promoting Components for Muscle Cells. The regeneration of muscle tissue relies on the proliferation and differentiation of muscle cells, processes that can be supported by hydrogels engineered to replicate the biochemical and mechanical features of the native ECM. These bioengineered hydrogels create a supportive microenvironment that facilitates myogenic activity by providing structural support for muscle cell attachment and organization, while also delivering bioactive molecules to enhance regeneration.

Growth factors are central to regulating muscle cell functions. Insulin-like growth factor-1 (IGF-1) is widely applied for its ability to stimulate myoblast proliferation and differentiation into mature muscle fibers.[683] To further enhance regeneration, vascular endothelial growth factor (VEGF) is often codelivered to promote angiogenesis, improving nutrient and oxygen delivery to the repairing tissue.[684] To achieve localized and sustained release while minimizing systemic side effects, hydrogels employ controlled-release strategies, including nanoparticle carriers and covalent tethering of growth factors.[685]

In addition to growth factors, hydrogels have incorporated bioactive peptides derived from ECM proteins to influence muscle cell adhesion, migration, and differentiation.[686] Laminin-derived sequences, such as IKVAV and YIGSR, provide specific ECM-mimicking cues that direct myoblast alignment and foster the formation of multinucleated myotubes. Similarly, RGD motifs are widely used for their ability to interact with integrins on muscle cell surfaces, enhancing cell attachment and spreading within the hydrogel scaffold.

Hydrogels incorporating exosomes derived from myogenic progenitor cells have emerged as an innovative approach to muscle regeneration. Exosomes serve as carriers of proteins, lipids, and RNA molecules that regulate cellular behavior and facilitate tissue repair. When incorporated into hydrogels, these exosomes provide sustained paracrine signaling that enhances myoblast proliferation, differentiation, and fusion.[687] Notably, exosome-loaded hydrogels have demonstrated improved muscle regeneration in volumetric muscle loss models by accelerating tissue repair and mitigating inflammation.[688]

In addition to biochemical signaling, conductive hydrogels have been explored as bioelectronic platforms for muscle regeneration. Given the importance of electrical signaling in myogenesis, the integration of conductive materials, such as polypyrrole, polyaniline, and gold nanowires, within hydrogel matrices enables the transmission of bioelectric cues necessary for myoblast differentiation and contractile function.[688] For instance, hydrogels incorporating graphene oxide have shown superior myoblast alignment and myotube formation under electrical stimulation, mimicking the physiological conditions of functional muscle tissue.[689]

Mechanical properties play a vital role in guiding myogenic differentiation. Hydrogels with tunable stiffness and viscoelasticity can mimic the biomechanical characteristics of native muscle tissue, providing essential mechano-transduction signals to stem cells. For example, soft hydrogels with an elastic modulus comparable to that of muscle tissue (∼10−12 kPa) have been shown to enhance stem cell differentiation into myogenic lineages, promoting the formation of functional muscle fibers.[690]

Preclinical studies have further demonstrated the effectiveness of these hydrogels in enhancing muscle regeneration. For example, IGF-1 and VEGF-loaded hydrogels have been shown to accelerate muscle repair and vascularization in animal models of volumetric muscle loss.[691] Additionally, laminin-mimetic peptide-functionalized hydrogels have been demonstrated to improve the alignment and fusion of myoblasts, resulting in the formation of robust and functional muscle tissue.

5.3.3. Tendon Regeneration.

5.3.3.1. Mechanical Properties of Tendon-Guided Tendon-Like Hydrogels. The mechanical properties of tendon-guided hydrogels are pivotal in replicating the unique tensile strength and elasticity of native tendons, which endure repetitive mechanical loads and facilitate force transfer between muscles and bones. Designing hydrogels with mechanical properties tailored for tendon regeneration requires meticulous material selection, structural engineering, and reinforcement strategies to achieve the necessary robustness and flexibility.

Native tendons are characterized by high tensile strength and low compressive resistance, largely attributed to their hierarchical collagen fiber organization. To replicate these structural features, hydrogels are often reinforced with nanofibers or microparticles that provide mechanical support while directing cell orientation and ECM deposition. Among the most commonly used biomaterials for hydrogel reinforcement are silk fibroin and collagen, both of which exhibit excellent biocompatibility and mechanical properties.[692] These fibers not only provide mechanical strength but also create an aligned structure that guides cell orientation and matrix deposition. Synthetic materials, such as polycaprolactone (PCL) or polyethylene glycol diacrylate (PEGDA), are frequently combined with natural polymers to achieve enhanced durability and tunable mechanical properties.[693]

Aligned nanofiber-reinforced hydrogels have demonstrated superior mechanical performance, closely mimicking the anisotropic properties of native tendons.[694] Electrospinning is a widely used technique to fabricate aligned nanofibers within hydrogels. These hydrogels exhibit enhanced tensile strength and modulus, enabling them to withstand the cyclic tensile loading typical of tendon function.[695] Beyond mechanical reinforcement, the aligned nanostructure provides essential topographical cues that promote fibroblast orientation, leading to the organized deposition of collagen type I, a key ECM component essential for tendon repair.

Table 3. Representative Hydrogels and Their Properties for Biomedical and Therapeutic Applications

Hydrogel System	Composition	Therapeutic Application	Primary Function	Mechanical Properties	Biocompatibility	Regulatory Status	Degradation Rate	Ref
ReGel®	PLGA–PEG–PLGA	Local paclitaxel delivery for bladder cancer	Tumor-localized chemotherapy (temperature-triggered depot)	Low–moderate (soft depot, injectable)	Good (cell viability >80%, transient inflammation)	FDA IND/Investigational	Weeks–months (hydrolytic degradation of PLGA)	701
Oxiplex®	Carboxymethylcellulose + Poly(ethylene oxide)	Antiadhesion barrier (neurosurgery/gynecology)	Postoperative antiadhesion barrier	Low (nonadhesive, resorbable)	Excellent (minimal tissue reaction in vivo)	FDA approved	Days–weeks (enzymatic and hydrolytic degradation)	702
Photo-cross-linked PEGDA	PEG diacrylate	Intraoperative sealing, tissue scaffolds	Surgical sealing and scaffold fabrication	High (photo-cross-linked, tunable)	Good (cell viability >75–90%)	Approved (ReSure® variant)	Tunable (hours to weeks depending on cross-linking density and PEG MW)	703
GelMA + MMP-cleavable peptide	Gelatin methacryloyl, MMP-sensitive linkers	Tissue regeneration, muscle repair	3D tumor modeling and stem cell support	Moderate, cell-compatible, enzyme-degradable	Excellent (cell viability >90%, low cytokine level)	Preclinical/widely studied	Days–weeks (MMP-dependent enzymatic degradation)	704
Boronic acid–functionalized hydrogel	Phenylboronic acid modified polymers	Glucose-responsive insulin delivery	Cartilage repair matrix	Moderate (reversible covalent)	Moderate–Good (biocompatibility depends on pK_a, dose)	Preclinical research	Hours–days (reversible dynamic covalent bonds, dose and pH dependent)	705
Self-assembled peptide hydrogel (e.g., RAD-based)	Short amphiphilic peptides (RAD, FEFK, etc.)	Nucleic acid/cytokine delivery, immunotherapy	Cranial and spinal dura sealing	Soft (self-assembled, tunable)	Excellent (high viability, low IL-6/TNF-α response)	Preclinical (e.g., arthritis, cancer)	Hours–days (noncovalent, shear- or dilution-sensitive)	706
Matrigel®	Basement membrane extract	3D tumor model, stem cell culture	Injectable wound filler or depot (ionic fast-gelling)	Very soft, ECM-like	Excellent (widely used for stem cells)	In vitro use only (research)	Hours–days (enzyme-sensitive ECM proteins)	707
HYAFF®-11	Benzyl ester of hyaluronic acid	Cartilage repair scaffold	Wet-tissue adhesive hydrogel (sealant)	Moderate (HA ester network)	Good–Excellent (used clinically in cartilage repair)	EU approved (Orthovisc)	Weeks–months (ester hydrolysis of HA backbone)	708
DuraSeal®	PEG-based synthetic sealant	Cranial and spinal dura sealing	Thermoresponsive drug depot (injectable)	High (synthetic sealant)	Good (mild acute response resolved within 1 week)	FDA approved	Weeks–months (hydrolytic degradation of PEG-based network)	709
Alginate–Ca^{2+}gel	Sodium alginate + Ca^{2+} ions	Injectable depot, wound filler	Growth factor modulation and controlled delivery	Low–moderate, ionic and reversible	Good–Excellent (low TNF-α/IL-1β in vivo)	Research/component of CE products	Hours–days (ionically cross-linked, reversible in physiological conditions)	710
Catechol–modified PEG	PEG–catechol conjugate	Wet adhesion, tissue sealant	Glucose-responsive insulin delivery	Moderate (catechol-linked)	Good (cell viability 80–90%, mild inflammation)	Preclinical adhesive platform	Days–weeks (oxidation and hydrolysis sensitive)	711
PNIPAAm hydrogel	Poly(*N*-isopropylacrylamide)	Injectable drug depot, thermosensitive	mRNA or cytokine delivery for cancer or arthritis immunotherapy	Low below LCST, gels above 32 °C	Moderate (nondegradable, bioaccumulation risk)	Preclinical	Nondegradable (physiological condition stable)	712
Heparin-mimetic hydrogel	Sulfated polysaccharides or PEG mimics	Growth factor stabilization and release	Muscle/tissue regeneration via cell-adhesive matrix	Tunable (charged interactions)	Good (low cytokine, cell-safe in 2D/3D models)	Research use	Days–weeks (hydrolysis or enzymatic cleavage depending on backbone)	713
DNA–hydrogel hybrid	PEG/alginate + DNA strands	Nucleic acid delivery (Cas9, siRNA)	Gene/siRNA delivery via bioresponsive hybrid systems	Soft, programmable (DNA-dependent)	Good–Excellent (no detectable toxicity in murine models)	Preclinical (siRNA, CRISPR tools)	Hours–days (nuclease-sensitive DNA domain)	714

Interpenetrating polymer networks (IPNs) have also emerged as a promising strategy for tendon-mimicking hydrogels. By combining two or more polymer networks with complementary properties, IPNs achieve a synergistic enhancement in toughness, resilience, and elasticity. For instance, hydrogels composed of a rigid primary network and soft, ductile secondary network for both high mechanical strength and flexibility, essential for load-bearing applications.[367]

Dynamic cross-linking further contributes to the mechanical adaptability of tendon-like hydrogels. Incorporating reversible bonds, such as Schiff base linkages or disulfide bonds, allows hydrogels to recover from mechanical deformations and self-heal after damage.[13] These properties extend the lifespan of the scaffold and maintain its structural integrity under repetitive loading. Additionally, sacrificial bonds and hidden length mechanisms within the hydrogel matrix dissipate energy during tensile loading, preventing mechanical failure and improving toughness.

The porosity and hierarchical structure of tendon-like hydrogels also play a critical role in their mechanical performance. Hydrogels with interconnected pore networks facilitate nutrient diffusion and cellular infiltration while maintaining mechanical stability. Gradients in pore size and density can be engineered to replicate the transition zones between tendons and bones, ensuring seamless integration and load transfer across these interfaces.

5.3.3.2. Proliferation and Differentiation-Promoting Components for Fibroblasts. Fibroblasts are essential for tendon repair as they are responsible for producing and organizing ECM components, particularly collagen, essential for restoring the structural integrity and functionality of tendons. Hydrogels designed to support fibroblast proliferation and differentiation incorporate various biochemical, mechanical, and bioactive components to create an optimal regenerative environment.

Growth factors regulate fibroblast activity and are commonly incorporated into hydrogels for tendon regeneration. Transforming growth factor-beta (TGF-β) is a potent inducer of fibroblast proliferation and ECM synthesis, particularly collagen production.[696] Hydrogels engineered for controlled TGF-β release promote fibroblast differentiation into tenogenic phenotypes, enhancing the deposition of tendon-specific matrix components. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) further stimulate fibroblast migration and proliferation during early tendon healing.[697]

Bioactive peptides derived from ECM proteins enhance fibroblast functionality. RGD motifs, mimicking cell-adhesion sites in fibronectin and other ECM proteins, are commonly incorporated into hydrogels to facilitate fibroblast attachment and spreading.[534] Peptides from collagen or tenascin-C provide additional cues, promoting fibroblast differentiation and matrix organization. These peptides engage integrin receptors on fibroblasts, triggering intracellular signaling pathways that regulate cytoskeletal dynamics and ECM synthesis.[698]

Hydrogels designed for fibroblast support often incorporate topographical and mechanical cues to mimic the native tendon microenvironment. Aligned nanofibers or microgrooves within the hydrogel structure provide guidance for fibroblast orientation, promoting the deposition of aligned collagen fibrils characteristic of healthy tendons.[699] Matrix stiffness is also critical; tendon-like stiffness (50–100 kPa) promotes tenogenic differentiation and the formation of aligned ECM fibers.

Mechanical stimulation is another important factor in promoting fibroblast activity. Hydrogels designed for tendon regeneration often incorporate dynamic and responsive elements, such as strain-responsive cross-linking or piezoelectric materials, to deliver mechanical cues that mimic the loading conditions of tendons.[700] These mechanical stimuli activate mechano-transduction pathways in fibroblasts, enhancing their ability to produce and organize collagen fibrils.

6. CONCLUSION: CHALLENGES AND PERSPECTIVES

Therapeutic hydrogels have emerged as a versatile class of biomaterials with broad-ranging applications in drug delivery, wound healing, antiadhesion barriers, and tissue regeneration.[715,716] Their biomedical success hinges on precise chemical engineering, which governs essential physicochemical attributes such as mechanical robustness, bioadhesion, and responsiveness to physiological stimuli. This review has highlighted the intricate interplay between hydrogel design strategies and their functional outcomes, emphasizing how rational molecular engineering enables the development of clinically optimized hydrogel systems (Table 3).

To further illustrate successful clinical translation, we highlight three representative hydrogel systems that exemplify how rational chemical design enables functional performance in real-world applications. ReGel is a thermoresponsive and biocompatible hydrogel composed of a triblock copolymer of PLGA–PEG–PLGA.[717] It remains in a sol state at room temperature but undergoes sol–gel transition at physiological temperature, allowing for minimally invasive injection followed by *in situ* gelation. This property has been leveraged in sustained intravesical delivery of paclitaxel for bladder cancer, enabling prolonged drug residence and reducing systemic toxicity. In addition, ReSure is a light-activated, PEG-based synthetic hydrogel approved for sealing corneal incisions. Its design relies on cross-linking four-arm PEG precursors via photoinitiated polymerization, forming a robust yet biocompatible barrier that withstands ocular dynamics.[718] The system meets key clinical needs, including transparency, rapid curing, and noninflammatory degradation. Matrigel, while not a synthetic hydrogel, has served as a foundational ECM-derived scaffold for 3D cell culture and tissue engineering.[719,720] Derived from Engelbreth–Holm–Swarm (EHS) mouse sarcoma, it contains laminin, collagen IV, and entactin, providing native-like biochemical cues that support cell adhesion, differentiation, and morphogenesis. Despite its utility, its undefined composition and batch-to-batch variability limit its direct regulatory approval for therapeutic use, highlighting the trade-offs between biological complexity and clinical scalability.[721] These examples collectively underscore how different design paradigms, thermoresponsive polymers, photo-cross-linkable networks, and ECM mimetics can be aligned with specific therapeutic contexts and regulatory requirements to achieve clinical translation.

At the core of hydrogel functionality lies a set of shared design principles that dictate structural integrity and therapeutic effectiveness. The choice of cross-linking mechanism profoundly influences network stability, drug retention, and release kinetics.[714] Distinct bonding strategies impart unique mechanical characteristics: supramolecular interactions confer self-healing ability, hybrid covalent–supramolecular systems enhance toughness, and dynamic covalent bonds

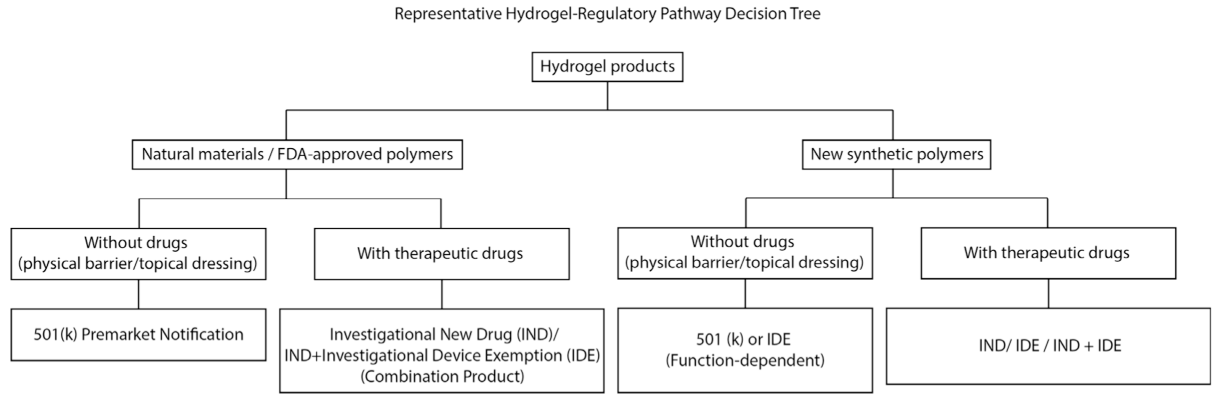

Figure 33. Regulatory decision tree for hydrogel-based products. A representative decision tree outlining the regulatory pathways for hydrogel-based medical products in the United States. Pathways are determined by material type (natural vs synthetic), presence of therapeutic agents, and intended function. Products composed of natural or FDA-approved polymers and used as physical barriers or dressings without drugs typically follow the 501(k) Premarket Notification route. In contrast, hydrogels incorporating therapeutic agents (e.g., drug-loaded systems) may require Investigational New Drug (IND), Investigational Device Exemption (IDE), or a combination pathway, particularly for combination products. The pathway for new synthetic polymers is function- and risk-dependent, requiring additional regulatory scrutiny.

support shear-thinning behavior conducive to injectability.[715] Similarly, adhesive interactions rely on covalent or supramolecular motifs to ensure firm biointerface attachment, while functional moieties such as carboxyl, amino, and hydroxyl groups mediate both tissue adhesion and stimuli-responsive behavior.[716] These interdependencies underscore the centrality of fine-tuned chemical modification in achieving multifunctional therapeutic performance.

Despite these advances, hydrogel development continues to face the challenge of reconciling therapeutic goals with material constraints. For example, in wound healing, hydrogels must adhere effectively to moist tissue, yet excessive cross-linking may hinder drug diffusion.[718] Incorporating degradable or stimuli-responsive linkers can decouple mechanical integrity from release profiles. Likewise, loading hydrophobic nanoparticles often results in over-rigid matrices that may trigger immune responses. Introducing supramolecular elements can restore flexibility and biocompatibility, preserving delivery functionality without compromising safety.[719]

However, only a fraction of hydrogel platforms achieves clinical approval. Successful translation hinges on four convergent parameters: biocompatibility, tunable degradation kinetics, mechanical compatibility, and scalable manufacturing. Products like DuraSeal, ReSure, and Juvederm share traits such as chemically well-defined architectures, predictable *in vivo* performance, and use of generally recognized as safe (GRAS) components (e.g., PEG, HA, fibrin).[707] Conversely, many advanced designs fail due to formulation complexity, poorly characterized degradation products, or regulatory ambiguities—especially for systems at the drug–device interface.[721] In particular, hydrogel platforms that incorporate multiple functional components, such as drug payloads, genetic elements, or live cells, often fall into the category of combination products, requiring parallel evaluation under both drug and device frameworks (e.g., Investigational New Drug (IND) and Investigational Device Exemption (IDE) filings). This dual-path regulatory burden introduces delays and uncertainty, especially when the mechanism of action involves dynamic responsiveness or bioactive degradation fragments. Moreover, Chemistry, Manufacturing, and Controls (CMC) requirements become more stringent for such complex systems, where batch-to-batch consistency, sterilization compatibility, and scalable formulation protocols are difficult to standardize. These regulatory bottlenecks highlight the need for early engagement with approval agencies and strategic design choices that balance functionality with regulatory tractability.

To further clarify the pathway from bench to bedside, we summarize the general timeline for therapeutic hydrogel development. This multiphase process typically spans 7–12 years, beginning with material synthesis and *in vitro* validation, followed by small and large animal testing to assess biocompatibility, degradation, and functional performance. Hydrogel systems intended solely for structural support or as inert barriers may follow a Class II device pathway (e.g., FDA's 510(k) route), whereas those delivering drugs, harboring engineered cells, or exhibiting responsive behavior may be classified as combination products, requiring both IND and IDE approvals.[33] Material composition and cross-linking chemistry play pivotal roles in this regulatory designation. Hydrogels based on natural polymers with GRAS status, such as HA or gelatin, may expedite toxicology assessment, while synthetic or bioresponsive chemistries may demand more stringent safety evaluation.[722] Critical CMC factors, such as sterilizability, batch consistency, and scalable production, must also be addressed early in development. To guide readers through this complexity, we have provided a decision-tree schematic (Figure 33) mapping hydrogel types and functionalities to their likely regulatory pathways.[723]

Stimuli-responsive and multifunctional hydrogels face additional hurdles in quality control and validation. Many are incompatible with conventional sterilization techniques (e.g., gamma irradiation), necessitating aseptic manufacturing. Moreover, the lack of standardized benchmarks for gelation kinetics, degradation profiles, and immunogenicity complicates platform comparison.[724]

A significant number of hydrogel systems remain in the preclinical stage due to misalignment with biological demands. For example, natural polymers may degrade too rapidly to support tissue regeneration, while highly cross-linked synthetic matrices may inhibit integration. Other designs lack a defined clinical indication or economically viable synthesis route. In regenerative medicine, poorly defined end points further impede trial design and regulatory approval.[725]

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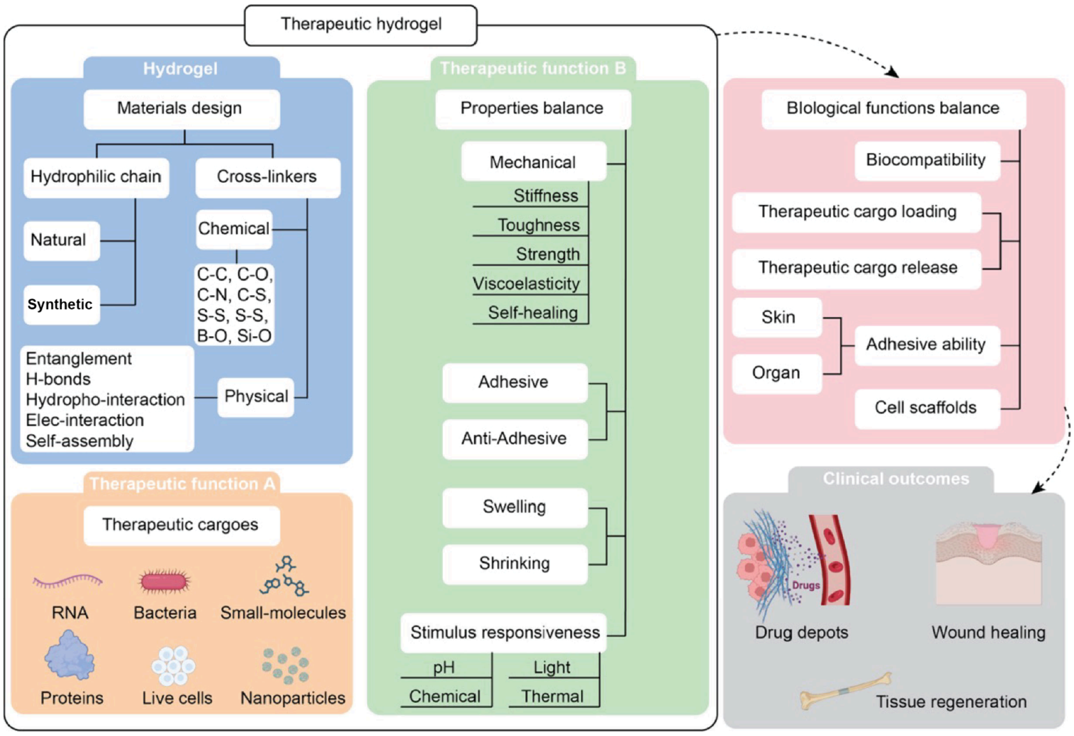

Figure 34. A systems-level schematic linking hydrogel material design to clinical outcomes. This integrative framework maps the rational design of hydrogels—from polymer chain selection and cross-linking strategies to functional and biological tuning—toward specific therapeutic applications and outcomes. The schematic incorporates hydrogel–cargo interactions (e.g., RNA, proteins, cells), mechanical and responsive properties (e.g., stiffness, swelling, self-healing), and biological integration (e.g., tissue adhesion, biocompatibility), ultimately guiding hydrogel selection for applications such as drug delivery, wound healing, and tissue regeneration. This figure combines elements of both a decision matrix and a design-to-clinic translation model.

Addressing these translational gaps requires emphasis on simplicity, modularity, and regulatory alignment. Future hydrogel platforms should adopt chemically validated building blocks, utilize immunocompetent animal models, and implement scalable synthesis protocols. Strategic design that anticipates downstream challenges, such as classification, sterilization, and end point validation, will improve the likelihood of clinical success.

To further broaden biomedical utility, therapeutic hydrogels are increasingly converging with frontier technologies.[173] For example, bioelectronic hydrogels offer a unique combination of electrical conductivity and tissue-like mechanics, enabling neural interfacing, biosignal recording, and responsive stimulation in wearable or implantable formats.[726] Self-reporting or feedback-responsive hydrogels, which embed biosensors or optical reporters, allow real-time tracking of pH, enzymatic activity, or drug concentration, facilitating closed-loop therapeutic systems.

Hydrogels are also being harnessed in synthetic biology, acting as scaffolds for engineered living cells or genetic circuits. These enable programmable secretion of therapeutic molecules in response to environmental cues.[727] Meanwhile, organoid and organ-on-chip systems increasingly rely on ECM-mimetic hydrogels to replicate tissue microenvironments for disease modeling, drug screening, and regenerative research.[728]

These developments emphasize the role of hydrogels as dynamic interfaces between biology and engineering. To ensure that hydrogel research remains strategically impactful, future directions should focus on three interconnected priorities. First, the integration of emerging technologies, such as AI-driven molecular modeling, generative design, and immuno-informed hydrogel platforms, will accelerate discovery and tailor hydrogel behavior to disease-specific biology.[729] These tools can predict degradation profiles, simulate immune compatibility, and streamline material optimization. Second, cross-platform integration is needed to align hydrogels with cutting-edge biomedical domains. Hydrogels can function as cohesive interfaces for synthetic biology, spatial omics, and multimodal therapeutics, demanding designs that are mechanically adaptable, biochemically orthogonal, and spatially resolved.[27] Third, at the platform level, critical needs include scalable synthesis routes that preserve chemical modularity, clinically relevant mechanical tuning (e.g., elasticity, burst pressure), and intelligent, self-reporting behavior. Bridging material chemistry with device engineering, clinical logistics, and regulatory foresight will be vital to future success (Figure 34).

Looking ahead, next-generation hydrogels will be shaped by advances in smart materials, 3D bioprinting, and machine learning-assisted design.[730] Spatially patterned constructs will unlock new opportunities in tissue regeneration, while hydrogels facilitating cell and gene delivery will propel personalized therapies.[731] The convergence of biodegradable conductive hydrogels and bioelectronics may inaugurate a new era of implantable diagnostics, neural modulation, and adaptive drug release systems.

Despite these exciting prospects, widespread clinical translation will require overcoming regulatory and ethical challenges. Disparate approval standards across agencies (e.g., FDA, EMA, NMPA) must be harmonized, particularly regarding biocompatibility, degradation testing, and batch reproducibility.[3] Ethical issues, including data privacy in biosensor-enabled medicine and organ-on-a-chip governance, must also be addressed to ensure responsible innovation.

In summary, therapeutic hydrogels offer a uniquely modular and chemically tunable platform for addressing complex medical needs. Advancing this field demands an integrated approach combining molecular design, biological insight, engineering functionality, and translational foresight. Through such multidimensional innovation, hydrogel-based therapies are well-positioned to transform clinical practice across a spectrum of diseases.

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Notes

The authors declare the following competing financial interest(s): W.T. receives consults (or is on scientific advisory boards) for, lectured (and received a fee), or conducts sponsored research at Harvard Medical School/Brigham and Womens Hospital for the following entities: Novo Nordisk A/S, Henlius USA Inc. The other authors declare no competing interests.

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Qian Chen received her Ph.D. degree under the supervision of Prof. Shan Mou in Internal Medicine from Shanghai Jiao Tong University in 2025. She joined Prof. Wei Tao's lab in 2023 as a joint Ph.D. candidate at the Center for Nanomedicine, Brigham and Women's Hospital, Harvard Medical School. Her current research focuses on the development of RNA-based therapeutics for kidney diseases and the targeted delivery of nanoparticles to renal tissues.

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