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Review

Advanced Biopolymer Hydrogels for Targeted Cancer Therapy: From Molecular Design to Controlled Drug Transport and Clinical Translation

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Abstract

Biopolymer-based hydrogels offer adaptable platforms for localized cancer therapy by regulating administration, tissue retention, payload protection, and therapeutic release. This review critically examines polysaccharide-, protein-, peptide-, and polynucleotide-based hydrogels, relating polymer composition, crosslinking, network architecture, swelling, degradation, and payload interactions to pharmaceutical and biological performance. Physical, chemical, enzymatic, and ionic gelation strategies are evaluated alongside diffusion-, swelling-, affinity-, and degradation-controlled release and their mathematical interpretation. Macrogels, microgels, nanogels, and hybrid systems are compared according to administration route, disposition, and oncology-relevant function. The review further distinguishes local placement, passive accumulation, ligand-mediated cellular interactions, and endogenous or externally triggered release. Applications in chemotherapy, radiotherapy, immunotherapy, hyperthermia, and phototherapy are assessed across colorectal, gastric, liver, pancreatic, and breast cancers. Marketed devices, patented technologies, clinically evaluated systems, and regulatory considerations are also examined. Despite extensive preclinical development, translation remains constrained by polymer variability, incomplete pharmaceutical characterization, sterilization and scale-up challenges, uncertain degradation and clearance, and limited clinically representative evidence. Progress will depend on clinically defined product design, reproducible manufacturing, quantitative disposition and safety assessment, and demonstration of meaningful benefit over existing therapeutic or procedural alternatives.

Keywords: biopolymer hydrogels; localized cancer therapy; controlled drug release; stimuli-responsive delivery; hydrogel characterization; clinical translation; precision

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oncology

1. Introduction

Cancer remains a major global health burden, with treatment outcomes limited by disease heterogeneity, metastatic progression, recurrence, therapy resistance, and treatment-associated toxicity [1–4]. Surgery, systemic chemotherapy, radiotherapy, immunotherapy, targeted therapy, and externally activated treatments have improved disease management, but their effectiveness can be constrained by inadequate exposure at the tumor site, nonspecific distribution, poor penetration into dense or poorly perfused lesions, dose-limiting toxicity, and biological differences among patients and between regions of the same tumor. These limitations have driven the development of delivery systems capable of controlling where, when, and for how long a therapeutic agent is available.

Research activity in hydrogel-based cancer treatment has expanded substantially, with contributions from an increasingly international research community. The geographical distribution and publication trends from 2015 to 2026 are summarized in Figure 1. This growth reflects increasing interest in localized drug delivery, responsive materials, combination treatment, postoperative therapy, and image-guided intervention. Publication growth, however, should not be interpreted as evidence of equivalent clinical progress because most therapeutic hydrogel systems remain at the preclinical stage.

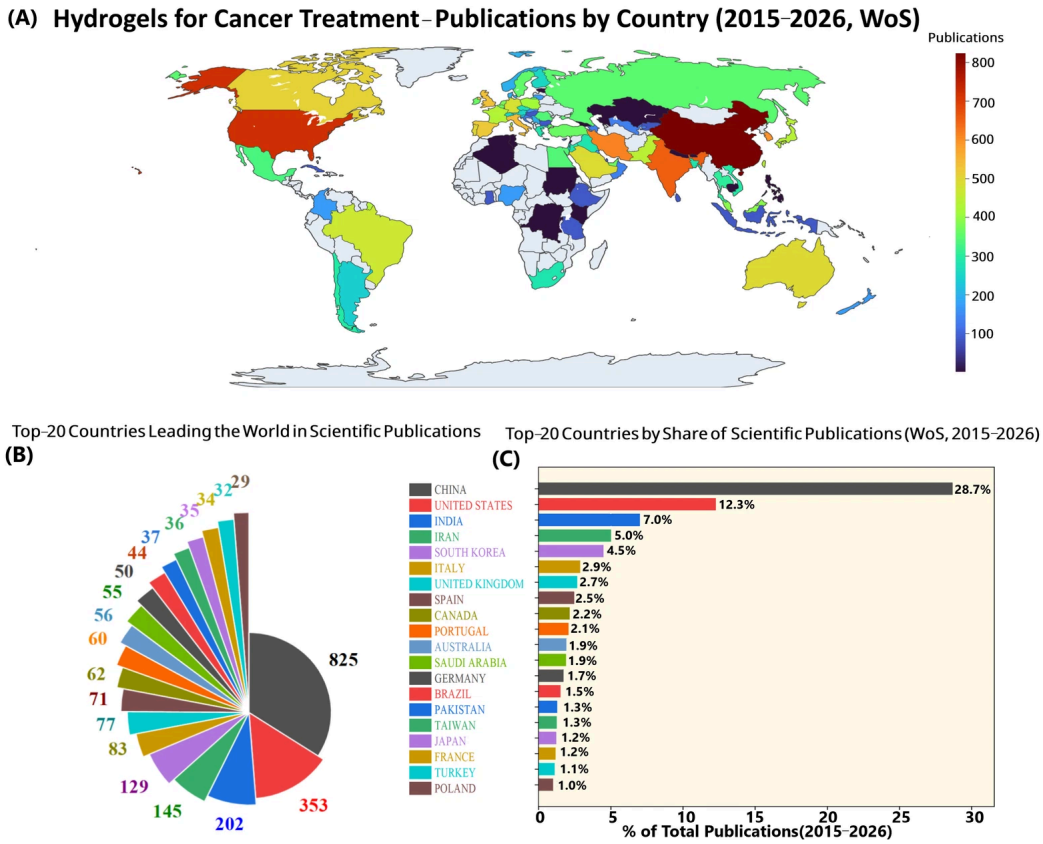


Figure 1. Global publication trends in hydrogel-based cancer therapy from 2015 to 2026 based on Web of Science records [5]. (**A**) Geographical distribution of publications, with color intensity representing publication output. (**B**) Ranking of the 20 countries with the highest publication counts. (**C**) Percentage contribution of the leading countries to the retrieved global publication output.

Search strategy, database coverage, and access date should be reported because the results may change with database updates.

Hydrogels are three-dimensional, water-swollen polymer networks whose composition, crosslinking, mesh structure, swelling, degradation, and payload interactions can be adjusted to regulate administration, mechanical behavior, tissue retention, and therapeutic release [6–10]. Biopolymer systems formed from polysaccharides, proteins, peptides, and polynucleotides are particularly attractive because their diverse functional groups support physical, ionic, enzymatic, dynamic covalent, and permanent covalent network formation. These materials can incorporate small-molecule drugs, proteins, antibodies, nucleic acids, cells, radionuclides, photoactive agents, and particulate carriers. Nevertheless, natural origin does not guarantee uniform composition, mechanical suitability, non-immunogenicity, complete biodegradation, or biological safety. Molecular-weight distribution, biological source, purity, chemical modification, residual reagents, sterilization, crosslink density, degradation products, and administration route can substantially alter final-product performance [9–12].

Hydrogel architecture includes macroscopic injectable or implantable depots, films and patches, microgels, nanogels, and multicomponent hybrid systems [10,13–17]. These formats are not sequential stages of a single technology. Each produces a different balance of payload capacity, administration feasibility, anatomical retention, tissue transport, cellular uptake, degradation, manufacturing complexity, and clearance. Macrogels are generally suited to accessible tumors, resection cavities, and locoregional treatment; microgels can support particulate, mucosal, oral, pulmonary, or transarterial delivery; nanogels may enable nanoscale transport or cellular delivery; and hybrid hydrogels combine a continuous matrix with nanoparticles, liposomes, micelles, fibers, cells, or inorganic components [9,13,14,18]. Platform selection should therefore be guided by the clinical function, tumor anatomy, payload properties, administration route, required exposure period, and acceptable degradation and clearance rather than by size or polymer origin alone.

Targeting and stimulus-responsive release are related but distinct functions. Direct intratumoral, peritumoral, intraperitoneal, postoperative, endoscopic, or transarterial placement can increase exposure at an anatomically defined site, but local retention does not establish molecular targeting, homogeneous payload distribution, or reduced systemic toxicity. For systemically administered nanoscale carriers, passive accumulation associated with abnormal tumor vasculature and impaired lymphatic drainage is variable and depends on tumor type, perfusion, stromal organization, interstitial pressure, particle properties, protein adsorption, and systemic clearance [19–28]. Ligand functionalization with antibodies, peptides, aptamers, hyaluronic acid, or folate derivatives may improve receptor-associated binding or cellular uptake after a carrier reaches an accessible target, but it does not independently overcome poor vascular access, dense extracellular matrix, or heterogeneous receptor expression [29–38].

Similarly, tumor-associated acidity, intracellular reducing conditions, reactive oxygen species, hypoxia, and altered enzyme activity can modify hydrogel swelling, payload affinity, crosslink stability, or degradation [39–45]. These conditions are spatially and temporally heterogeneous and are not exclusive to tumors; inflammation, infection, ischemia, and wound healing may reproduce several of the same stimuli. Responsiveness demonstrated only at an extreme pH, glutathione concentration, enzyme level, temperature, or irradiation condition should therefore not be interpreted as evidence of tumor-selective release. Physiological baseline leakage, activation threshold, stimulus range, response kinetics, reversibility, and performance under relevant nonmalignant pathological conditions must also be considered.

Hydrogels can support chemotherapy, radiotherapy, immunotherapy, hyperthermia, photothermal therapy, photodynamic therapy, and multimodal treatment by providing local retention, controlled or triggered release, protection of labile agents, or spatial coordination of therapeutic components [10,15–17,46–48]. Their role differs among modalities. Chemotherapy primarily relies on payload loading, release, local pharmacokinetics, and adequate tissue exposure; radiotherapy-related systems require radionuclide or radiosensitizer retention, dosimetry, or function-specific spacer and marker performance; immunotherapy requires preservation of biological potency and demonstration of functional immune activation; and externally activated treatments require clinically relevant energy penetration, spatial dose distribution, and adjacent-tissue safety. Material activation, prolonged release, tumor-associated fluorescence, or increased immune-cell abundance should not be used as substitutes for evidence of therapeutic benefit.

The anatomical and biological barriers to translation also differ among cancer types. Colorectal and gastric cancers may permit oral, rectal, endoscopic, intraperitoneal, or postoperative administration but are affected by gastrointestinal transit, mucus turnover, digestive conditions, motility, microbiota variability, and peritoneal dissemination. Liver tumors may be approached through image-guided intratumoral or transarterial procedures, although cirrhosis, vascular shunting, impaired hepatic function, and heterogeneous perfusion can alter distribution and safety. Pancreatic tumors present dense desmoplasia, poor perfusion, elevated interstitial pressure, and proximity to critical organs, whereas breast tumors and postoperative cavities are comparatively accessible but remain heterogeneous in subtype, stromal organization, immune status, and residual-disease distribution. These differences require cancer-specific evaluation of administration, anatomical coverage, payload distribution, systemic leakage, therapeutic outcome, degradation, and clearance.

Although numerous hydrogel formulations produce favorable results in release studies and small-animal models, clinical translation remains limited by source-dependent polymer variability, incomplete pharmaceutical characterization, sterilization incompatibility, scale-dependent manufacturing, batch inconsistency, payload instability, uncertain degradation-product safety, and insufficient long-term biodistribution and clearance data [9–12]. Subcutaneous tumor models and simplified release media frequently fail to reproduce human anatomy, stromal barriers, clinical administration procedures, and treatment-associated tissue changes. Moreover, marketed oncology-relevant hydrogel products are predominantly spacers, tissue markers, embolic materials, sealants, and adhesion barriers rather than therapeutic anticancer depots. These supportive devices and drug-, biologic-, radionuclide-, or cell-containing combination products differ substantially in primary mode of action, quality requirements, clinical endpoints, and regulatory pathway.

This review critically evaluates biopolymer-based hydrogel systems across the complete development pathway from molecular design to clinical translation. Section 2 compares polysaccharide-, protein-, peptide-, and polynucleotide-based materials, including their network-forming mechanisms, payload interactions, advantages, and limitations. Section 3 examines crosslinking, structure–release relationships, mechanistic and mathematical interpretation of payload release, and pharmaceutical characterization encompassing rheology, injectability, swelling, degradation, payload integrity, sterilization, stability, and interbatch reproducibility. Section 4 compares macrogels, microgels, nanogels, and hybrid hydrogels according to architecture, administration route, disposition, and oncology-relevant function. Section 5 distinguishes local placement, passive accumulation, ligand-mediated cellular interactions, and endogenous or externally triggered re-

lease. Section 6 critically compares chemotherapy, radiotherapy, immunotherapy, hyperthermia, and photothermal or photodynamic treatment using formulation, release, disposition, efficacy, and safety outcomes. Cancer-specific applications in colorectal, gastric, liver, pancreatic, and breast cancers are then examined in relation to anatomical accessibility and disease-specific barriers. Sections 7 and 8 distinguish marketed devices, patented technologies, clinically evaluated systems, and product-specific regulatory requirements. Section 9 integrates material variability, biological safety, manufacturing, preclinical relevance, standardization, and a staged translational roadmap. By connecting hydrogel chemistry and architecture with clinically representative administration, quantitative disposition, manufacturing readiness, regulatory classification, and function-specific evidence, this review aims to identify which design features are most likely to support meaningful oncology translation.

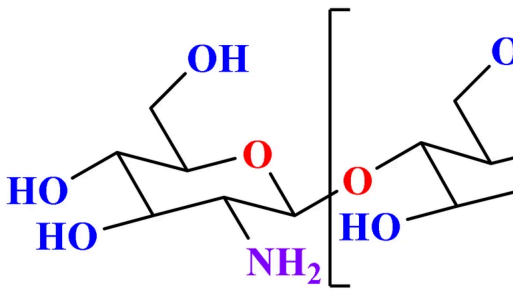
2. Biopolymer-Based Hydrogels for Targeted Cancer Therapy

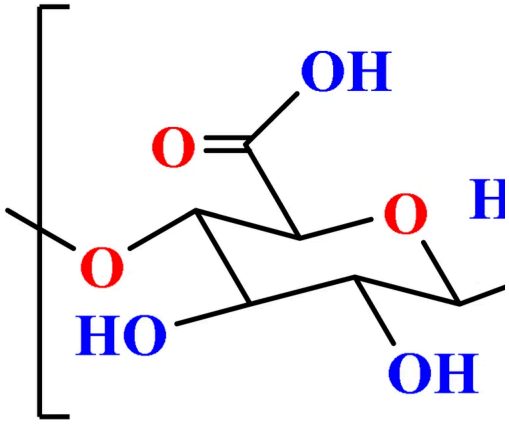
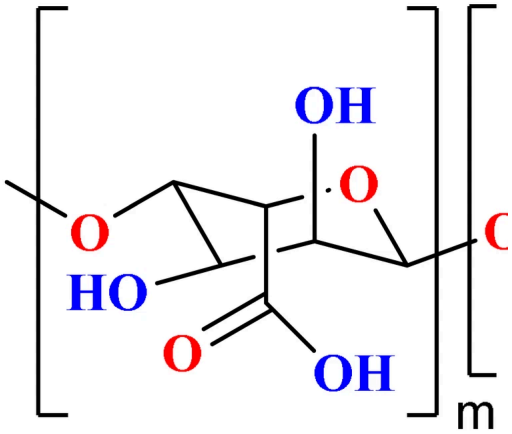
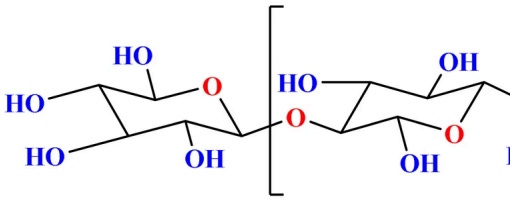
Biopolymer-based hydrogels are hydrated three-dimensional networks formed from naturally occurring macromolecules, biologically derived polymers, or their chemically modified derivatives. Their functional groups support physical or chemical crosslinking and enable the incorporation of small-molecule drugs, proteins, nucleic acids, cells, and nanoscale carriers. In cancer treatment, these materials are primarily used to form injectable or implantable depots, protect labile therapeutics, regulate local release, and coordinate chemotherapy, radiotherapy, immunotherapy, hyperthermia, and phototherapy [10,15–17].

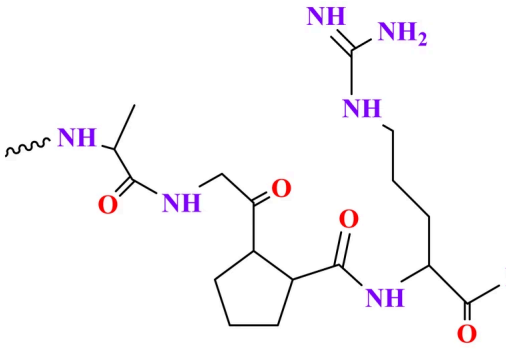
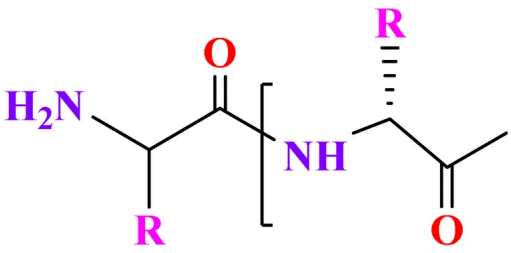
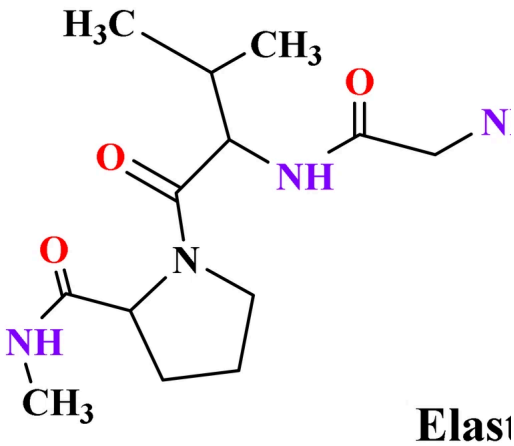
Hydrogel performance depends on polymer composition, molecular weight, crosslinking chemistry, network architecture, swelling, degradation, and interactions with the therapeutic payload. These properties influence injectability, gelation, mechanical stability, drug loading, release kinetics, tissue retention, and biological response [9–12]. Naturally derived polymers generally provide favorable aqueous processability and biological interactions but may exhibit source-dependent variability, weak mechanical properties, rapid degradation, or limited batch reproducibility. Chemical modification and hybridization can improve network stability and release control, although each additional component increases manufacturing, characterization, degradation, and regulatory complexity [10–12].

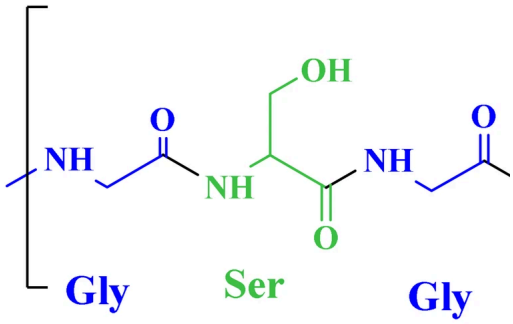
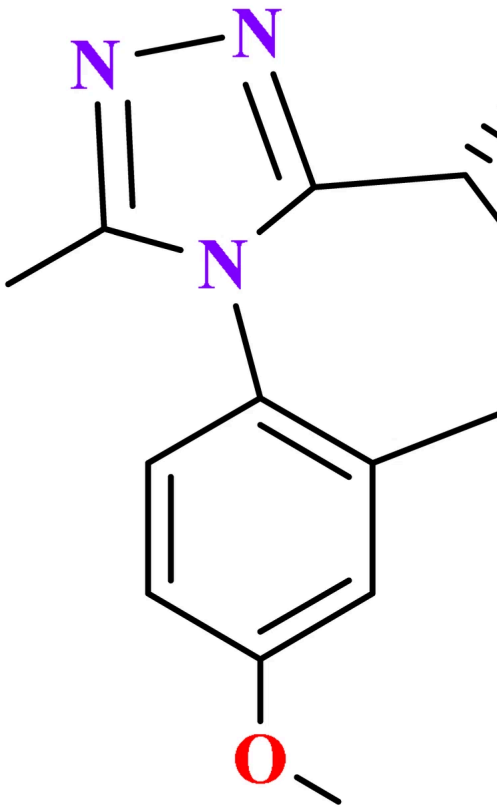
Table 1 shows representative structural motifs of the principal polysaccharide-, protein-, peptide-, and polynucleotide-based materials discussed in this review. These structures illustrate characteristic chemical features rather than complete or unique molecular structures, particularly for heterogeneous or sequence-variable biopolymers.

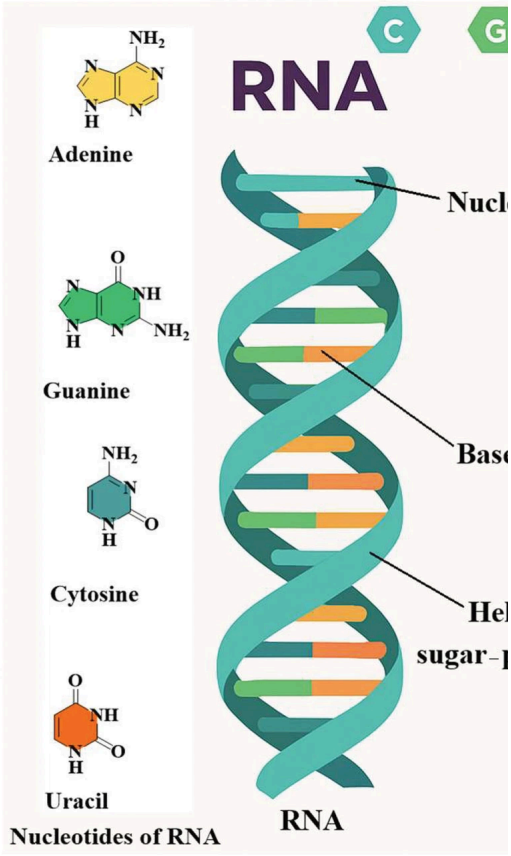
Table 1. Chemical structures of representative biopolymers.

Category	Examples
Polysaccharide-based Biopolymers	 Chit

Category	Examples
	
	Hyaluron
	
	Algin
	
	Cellulo

Category	Examples
Protein-based Biopolymers	 **Gelatin**
	 **Coll**
	 **Elast**

Category	Examples
	
	Silk F
	
	Sc

Category	Examples
Polynucleotide-based Biopolymers	
	DNA & RNA (Polynucleotides)

2.1. Polysaccharide-Based Hydrogels

Polysaccharides contain hydroxyl, carboxyl, amino, aldehyde, or sulfate groups that support hydrogen bonding, ionic association, covalent crosslinking, and chemical functionalization. Hyaluronic acid, chitosan, alginate, cellulose derivatives, dextran, starch, carrageenan, and related modified polysaccharides are among the most widely investigated materials for cancer-related hydrogel systems [15–17].

These polymers can incorporate hydrophilic therapeutics directly or carry poorly soluble payloads through embedded liposomes, micelles, nanoparticles, and microparticles. Their chemical diversity enables modulation of swelling, mucoadhesion, degradation, injectability, and stimulus-dependent release, supporting intratumoral, postoperative, oral, intraperitoneal, and transarterial administration [9,16,17,49]. Some polysaccharides also participate in biologically relevant interactions. Hyaluronic acid can facilitate CD44-associated cellular uptake in receptor-expressing tumors [29,30], whereas selected polysaccharides can undergo enzyme- or microbiota-mediated degradation in the gastrointestinal tract or tumor microenvironment [40,42].

The main limitations of polysaccharide hydrogels include source and batch variability, heterogeneous molecular weight or substitution, insufficient mechanical stability, and variable degradation under physiological conditions. Chemical oxidation, methacrylation, grafting, or incorporation of synthetic crosslinkers can improve performance but may alter biological recognition, generate heterogeneous reaction products, or introduce residual reagents. Polysaccharide systems therefore require formulation-specific characterization of composition, crosslinking, rheology, payload distribution, degradation, and biological safety [9–12].

2.1.1. Chitosan

Chitosan is a cationic polysaccharide produced through partial deacetylation of chitin. Protonation of its primary amino groups confers pH-dependent solubility and supports ionic interactions, mucoadhesion, and chemical crosslinking. Chitosan/β-glycerophosphate formulations remain liquid at lower temperatures and undergo thermally induced gelation near physiological temperature through changes in electrostatic, hydrogen-bonding, and hydrophobic interactions [50,51]. Chemical modification, grafting, and incorporation of additional crosslinkers can further regulate gelation, mechanical stability, degradation, and payload release [52].

In cancer treatment, thiolated chitosan hydrogels have been investigated for localized co-delivery of doxorubicin and liposome-encapsulated curcumin. The reported formulation gelled near 37 °C and released both agents more rapidly under acidic conditions, producing sustained cytotoxic activity in the evaluated cell models [53]. Chitosan has also been co-formulated with interleukin-12 for intratumoral immunotherapy. Local administration increased cytokine retention, induced complete regression in a high proportion of treated murine tumors, and generated tumor-specific protection against rechallenge [54]. The principal limitations of chitosan hydrogels include pH-dependent solubility, batch variation in molecular weight and deacetylation, weak mechanical properties, rapid or heterogeneous degradation, and potential inflammatory effects. Their performance therefore depends on careful control of polymer characteristics, gelation, crosslinking, payload stability, degradation, and local tissue compatibility.

2.1.2. Hyaluronic Acid

Hyaluronic acid (HA) is an anionic polysaccharide composed of repeating *N*-acetyl-D-glucosamine and D-glucuronic acid units. Its hydroxyl and carboxyl groups permit chemical modification and physical or covalent crosslinking, enabling the formation of injectable hydrogels, microgels, nanogels, and composite delivery systems [55–57]. HA can also promote CD44-associated binding and cellular uptake in receptor-expressing cancer cells [29,30,55–57]. However, CD44 expression is heterogeneous and is not restricted to malignant cells; HA functionalization should therefore not be interpreted as evidence of uniform tumor targeting or increased whole-tumor accumulation.

A sprayable HA-based composite hydrogel containing polydopamine-coated oxaliplatin–Mn^{2+}–curcumin coordination-polymer nanoparticles was developed for postoperative colorectal-cancer treatment [58]. The formulation exhibited tissue adhesion, sustained release for more than 20 days, and staged pH-responsive payload release. In the evaluated mouse models, treatment eliminated residual tumors, prevented recurrence during the 80-day observation period, and inhibited peritoneal dissemination [58]. HA-based composite hydrogels incorporating polydopamine and doxorubicin have also been investigated for localized, environment-responsive treatment [59]. The principal limitations of HA hydrogels include rapid enzymatic degradation, weak standalone mechanical properties, heterogeneous molecular weight, and source- or modification-dependent variability. Photopolymerization, enzymatic crosslinking, and integration with synthetic polymers or nanoparticles can improve stability and release control but may increase formulation, manufacturing, and regulatory complexity [60,61].

2.1.3. Alginate

Alginate is a linear anionic polysaccharide composed of β-D-mannuronic acid and α-L-guluronic acid residues arranged in M-, G-, and alternating MG-blocks. G-rich regions exhibit strong affinity for divalent cations, particularly Ca^{2+}, enabling rapid ionic crosslinking through the egg-box mechanism [62,63]. Alginate hydrogels can be pre-

pared by external ion diffusion or internal gelation using calcium sources such as $CaCO_3$, with polymer composition, molecular weight, ion concentration, and gelation conditions governing network stiffness, porosity, degradation, and payload release [64].

In cancer treatment, alginates have been formulated as injectable hydrogels, beads, microgels, and nanoparticle-containing composites for localized or oral delivery of chemotherapeutics and biological agents [61,65]. Alginate matrices can sustain doxorubicin release, although local retention and prolonged release should not be interpreted as evidence of tumor-specific accumulation without biodistribution data [66,67]. Combining alginate with chitosan can increase mucoadhesion and modify mechanical and release properties; such composite systems have been investigated for breast-cancer drug delivery, immunotherapy, and diagnostic applications [68]. The principal limitations of alginate hydrogels include weak cell adhesion, limited mechanical stability, uncontrolled ion exchange, heterogeneous gelation, and variable degradation. Oxidation, covalent modification, and integration with other polymers or nanocarriers can improve performance but increase manufacturing and analytical complexity [61,64,65].

2.1.4. Cellulose

Cellulose is a linear β-(1→4)-linked D-glucose polysaccharide whose extensive hydrogen bonding provides structural stability but limits the aqueous solubility of the native polymer. Hydrogel formulations therefore commonly use carboxymethyl cellulose, methylcellulose, hydroxypropyl cellulose, oxidized cellulose, cellulose nanocrystals, or cellulose nanofibrils. These derivatives support hydrogen bonding, physical association, grafting, Schiff-base formation, and other covalent crosslinking strategies and can provide pH-responsive swelling, thermogelation, mucoadhesion, or mechanical reinforcement [8,69]. Cellulose-based hydrogels have been investigated for sustained drug delivery, and carboxymethyl-cellulose systems are particularly established as modifiable hydrogel carriers. Beyond conventional cellulose hydrogels, crystallization-induced molecular assembly combined with dual-ion complexation has recently been used to create cellulose ionogels with improved mechanical strength, ionic conductivity, and thermal stability. Although developed primarily for flexible electronic and sensing applications rather than drug delivery, this strategy illustrates how control of cellulose chain assembly and noncovalent interactions can mitigate trade-offs among network strength, environmental stability, and functional performance [70].

Oncology-related examples include oxidized-cellulose/chitosan hydrogels for pH-responsive release, methylcellulose-based injectable depots, cellulose-containing systems for local chemotherapy, and cellulose-nanocrystal hydrogels incorporating photoactive components [71–74]. Their limitations include poor solubility of native cellulose, heterogeneous chemical substitution, residual derivatization or crosslinking reagents, variable swelling, and potentially slow or incomplete degradation. Characterization should therefore address substitution, crystallinity, rheology, mechanical stability, payload release, degradation, and clearance.

2.2. Protein-Based Hydrogels

Protein- and peptide-based hydrogels are formed from natural proteins, recombinant polypeptides, self-assembling peptides, or chemically modified derivatives. Their peptide backbones and amino-acid side chains provide sites for hydrogen bonding, hydrophobic association, β-sheet formation, enzymatic reactions, and covalent crosslinking. Gelatin, collagen, elastin-like polypeptides, silk fibroin, soy protein, and self-assembling peptide sequences are among the principal materials investigated for cancer-related delivery [75–78].

Protein and peptide hydrogels can accommodate small-molecule drugs, enzymes, antibodies, nucleic acids, and particulate carriers under comparatively mild preparation conditions. Their amino-acid sequence, secondary structure, molecular weight, and intermolecular interactions influence gelation, mechanical properties, degradation, and payload release. Recombinant or synthetically designed polypeptides can additionally be engineered for temperature responsiveness, receptor interaction, protease sensitivity, or controlled self-assembly [79–83].

Representative applications include elastin-like polypeptide hydrogels for co-delivery of gemcitabine and anti-PD-L1 antibodies [79], silk-fibroin hydrogels for local chemotherapy and cancer-stem-cell treatment [84,85], and self-assembling peptide hydrogels for pH-responsive chemotherapy and localized immune modulation [86–89]. Their principal limitations include source-dependent composition, immunogenicity, proteolytic instability, aggregation, weak or variable mechanical properties, and incomplete control over degradation. Chemical crosslinking can improve stability but may reduce payload activity or introduce residual reagents. Protein- and peptide-based hydrogels therefore require formulation-specific assessment of purity, structural integrity, gelation reproducibility, payload bioactivity, degradation products, immunogenicity, and clearance [9–12].

2.2.1. Gelatin

Gelatin is obtained through the partial hydrolysis of collagen and contains amino, carboxyl, and hydroxyl groups that facilitate chemical modification and therapeutic-payload incorporation. Native gelatin forms thermoreversible physical networks, whereas methacrylation, enzymatic crosslinking, Schiff-base formation, and natural crosslinkers can improve stability under physiological conditions [75–77]. In cancer treatment, gelatin-based hydrogels and nanogels have been investigated for localized delivery of chemotherapeutics, nucleic acids, and immunomodulators. Redox-sensitive gelatin/silica nanogels functionalized with the AS1411 aptamer have been investigated for siRNA protection and glutathione-responsive intracellular release in nucleolin-expressing cancer cells [90]. Gelatin has also been incorporated into oxidized-starch-based composite hydrogels for localized postoperative treatment and reinforcement of adoptive natural-killer-cell therapy [91]. Principal limitations include weak mechanical stability, rapid enzymatic degradation, source-dependent variability, and potential toxicity from residual crosslinkers [75–77].

2.2.2. Collagen

Collagen is an extracellular-matrix protein composed of three polypeptide chains arranged in a triple-helical structure. Under physiological conditions, type I collagen self-assembles into fibrillar networks, while chemical crosslinking, methacrylation, or combination with other polymers can improve mechanical stability and regulate degradation [78,92]. Collagen hydrogels can incorporate small molecules, proteins, nucleic acids, and particulate carriers and are particularly useful when extracellular-matrix interactions influence tumor-cell behavior or therapeutic transport. Injectable collagen-containing hydrogels have been investigated for localized drug delivery and combined treatment of primary and metastatic tumors [93,94]. However, collagen-network stiffness and organization can also affect tumor-cell migration, invasion, and drug penetration. Additional limitations include network contraction, rapid collagenase-mediated degradation, weak standalone mechanical properties, animal-source variability, and potential immunogenic or pathogen-related concerns [78,92–94].

2.2.3. Elastin and Elastin-like Polypeptides

Elastin-like polypeptides are engineered proteins derived from repetitive motifs in tropoelastin. Their hydrophobic domains undergo reversible, sequence- and concentration-dependent thermal phase transitions, enabling self-assembly into nanoparticles, injectable depots, and crosslinked hydrogels [80,82,83]. Molecular weight, guest-residue composition, polymer concentration, and crosslinking can be adjusted to regulate transition temperature, mechanical properties, swelling, degradation, and payload release [80–83].

In cancer treatment, elastin-like polypeptide hydrogels have been investigated for sustained local delivery of small-molecule drugs and biologics. An in situ-forming elastin-like polypeptide hydrogel co-delivering gemcitabine and an anti-PD-L1 antibody provided sustained release, increased intratumoral CD8-positive T-cell infiltration approximately threefold, reduced regulatory T-cell abundance by approximately 60% relative to the phosphate-buffered saline control, and improved tumor control in a preclinical melanoma model [79]. Elastin-like polypeptide–collagen hydrogels have also enabled composition-dependent control of doxorubicin release and reduced glioblastoma-cell survival and proliferation in vitro [81]. Principal limitations include sequence- and molecular-weight-dependent phase behavior, aggregation, recombinant-production consistency, potential immunogenicity, and incomplete characterization of long-term degradation and clearance [80,82,83].

2.2.4. Silk Fibroin

Silk fibroin is a structural protein containing glycine- and alanine-rich sequences that form ordered β-sheet domains. These domains provide mechanical stability and support hydrogel formation through physical self-assembly induced by changes in protein concentration, temperature, pH, ionic strength, enzymatic treatment, sonication, or irradiation [95]. Silk-fibroin hydrogels can incorporate hydrophobic drugs and nanoparticle formulations while providing sustained local release.

An injectable silk-fibroin hydrogel containing an SN-38–cholesterol nano-prodrug reduced the nano-prodrug release rate relative to nanoparticles alone and demonstrated cytotoxic activity in an in vitro HepG2 model [84]. However, this study did not establish antitumor efficacy in an animal model. In a separate system, salinomycin- and paclitaxel-loaded silk-fibroin nanoparticles were dispersed within an injectable silk-fibroin hydrogel to target cancer-stem-cell and non-stem-cell populations. The composite formulation reduced CD44-positive/CD133-positive tumor cells and inhibited tumor growth more effectively than the evaluated single-drug hydrogels and systemic dual-drug treatment in an H22 subcutaneous hepatic-tumor model [85]. Principal limitations include processing-dependent β-sheet formation, residual sericin, variable mechanical properties, slow or heterogeneous degradation, and insufficient long-term biodistribution and clearance data [95].

2.2.5. Soy Protein

Soy protein is an amphiphilic plant-derived material containing amino, carboxyl, and hydrophobic groups that support therapeutic-payload binding and chemical functionalization. Soy-protein nanoparticles, nanogels, and macroscopic hydrogels can be formed through thermal denaturation, hydrophobic association, grafting, or covalent and enzymatic crosslinking [96–100]. However, these architectures should be distinguished because evidence obtained with nanoscale soy-protein carriers does not directly establish the performance of injectable bulk hydrogels.

For cancer-drug delivery, TPGS-grafted soy protein was crosslinked with an acid-la-

bile ortho-ester crosslinker to produce pH-responsive nanogels containing cisplatin [101] . The approximately 200-nm nanogels remained comparatively stable under neutral conditions but degraded and released cisplatin more rapidly under acidic conditions. TPGS functionalization increased cellular internalization and cisplatin accumulation in resistant A549/DDP cells by inhibiting MRP2- and ATP7A/7B-associated drug efflux and improved penetration into three-dimensional tumor spheroids [101]. The evidence, however, was derived primarily from cellular and spheroid models and does not establish the performance of a macroscopic injectable hydrogel or in vivo tumor-selective delivery. Principal limitations of soy-protein systems include compositional variability, aggregation, potential allergenicity, heterogeneous degradation, and limited evidence concerning parenteral safety, immunogenicity, biodistribution, and long-term clearance [96–100].

2.3. Polynucleotide-Based Hydrogels for Cancer Therapy

Polynucleotide hydrogels are formed from DNA, RNA, or synthetic oligonucleotides through complementary base pairing, strand entanglement, enzymatic ligation, rolling-circle amplification, or chemical crosslinking. Their sequence programmability enables the incorporation of aptamers, CpG oligodeoxynucleotides, siRNA, antisense agents, proteins, and intercalating chemotherapeutics [102,103]. A programmable DNA hydrogel containing ATP-responsive aptamers and polymerized CpG sequences provided staged delivery of doxorubicin and an anti-PD-L1 antibody, coordinating immunogenic tumor-cell death, dendritic-cell activation, and checkpoint inhibition [104].

Polynucleotide-containing hydrogels have also been investigated for localized siRNA and gene-regulatory delivery in breast, pancreatic, and other tumor models [105–107]. These hydrogels can protect nucleic-acid payloads and prolong local exposure, but depot retention should be distinguished from intact intracellular delivery and functional gene regulation. Principal limitations include nuclease susceptibility, weak mechanical properties, production cost, innate immune activation, off-target gene regulation, and difficulty verifying intracellular trafficking [102–108]. Chemical backbone modification and reinforcement with polymers or nanoparticles can improve stability but increase manufacturing, analytical, degradation, and regulatory complexity.

Table 2 systematically compares these hydrogel classes across critical parameters—composition, natural sources, drug-loading mechanisms, stimulus responsiveness, cancer-specific applications, mechanical properties, and recent advances—highlighting their potential for combination therapy and personalized medicine.

Table 2. Comparative Overview of Natural Biopolymer-Based Hydrogels for Cancer Drug Delivery and Combination Therapy.

Feature	Polysaccharide-Based Hydrogels	Protein- and Peptide-Based Hydrogels	Polynucleotide Hydrogels
Representative components	Chitosan, alginate, hyaluronic acid, cellulose derivatives, dextran, starch, and carrageenan [109]	Collagen, gelatin, elastin-like polypeptides, silk fibroin, soy protein, and self-assembling peptides [110,111]	DNA-, RNA-, and synthetic-oligonucleotide-based networks in which nucleic acids mediate crosslinking, assembly, or molecular recognition [102,112]
Sources and production	Obtained from animal, marine, plant,	Isolated from animal, insect, or plant	Isolated nucleic acids are possible, but most

Feature	Polysaccharide-Based Hydrogels	Protein- and Peptide-Based Hydrogels	Polynucleotide Hydrogels
	or microbial sources, or produced as chemically modified derivatives [109]	sources; recombinant and synthetic peptide variants are also used [110,111]	therapeutic systems use chemically or enzymatically synthesized oligonucleotides [102,112]
Principal network formation	Ionic crosslinking, hydrogen bonding, hydrophobic association, Schiff-base reactions, enzymatic crosslinking, or covalent modification [109]	Physical self-assembly, β-sheet or triple-helix formation, enzymatic crosslinking, photocrosslinking, and other covalent reactions [110,111]	Complementary base pairing, strand entanglement, hybridization-chain reaction, rolling-circle amplification, enzymatic ligation, or chemical crosslinking [102,112]
Payload incorporation	Physical entrapment, electrostatic association, affinity interactions, covalent conjugation, or incorporation of drug-loaded particles [109]	Physical entrapment, hydrophobic and electrostatic interactions, affinity binding, covalent attachment, or carrier-in-hydrogel loading [110,111]	Sequence-specific hybridization, aptamer binding, electrostatic association, intercalation, physical entrapment, or covalent conjugation [102,112]
Responsive behavior	May display pH-, enzyme-, redox-, temperature-, ROS-, or microbiota-responsive behavior after appropriate polymer modification or network design [40,42,113]	May exhibit temperature-, pH-, enzyme-, redox-, or light-responsive behavior depending on amino-acid sequence, formulation, and crosslinking chemistry [79–83,114]	Nuclease-, pH-, ATP-, strand-displacement-, aptamer-, enzyme-, or complementary-sequence-responsive behavior [102,112,115]
Representative cancer applications	Postoperative HA-based composite hydrogel for colorectal-cancer treatment [58]; chitosan/IL-12 formulation for localized immunotherapy [54]	Alginate–collagen hydrogel for combined photothermal therapy and immunotherapy [93]; elastin-like polypeptide hydrogel for gemcitabine and anti-PD-L1 delivery [79]; peptide hydrogels for localized chemoimmunotherapy [87–89]	Programmable DNA hydrogels for staged chemotherapy and immunotherapy [104] ; nucleic-acid-containing hydrogels for local siRNA or gene-regulatory delivery [105–107]

Feature	Polysaccharide-Based Hydrogels	Protein- and Peptide-Based Hydrogels	Polynucleotide Hydrogels
Multimodal-delivery capability	Compatible with co-delivery of drugs, immunomodulators, nucleic acids, and nanoparticle formulations [49,54]	Compatible with chemotherapy, proteins, antibodies, immune agonists, and photoactive agents [79,85,87–89,93]	Sequence programmability allows staged or stimulus-dependent delivery of chemotherapeutics, oligonucleotides, antigens, and immune modulators [102,104,112]
Mechanical characteristics	Mechanical properties vary widely with molecular weight, polymer concentration, ionic environment, substitution, and crosslink density [109]	Mechanical behavior ranges from weak reversible gels to reinforced fibrillar, β-sheet-rich, or covalently crosslinked networks [110,111]	Unreinforced networks commonly have limited mechanical strength, although polymer, particle, or secondary-network incorporation can substantially increase stability [102,112]
Principal advantages	Diverse chemistry, mild gelation, mucoadhesion, injectable or oral processing, and compatibility with composite delivery systems [109]	Bioactive peptide sequences, extracellular-matrix-like interactions, tunable self-assembly, and compatibility with proteins and cells [110,111]	Sequence programmability, molecular recognition, modular therapeutic incorporation, and controlled strand-mediated responses [102,112]
Principal limitations	Source and batch variability, heterogeneous substitution, weak mechanical stability, uncontrolled ion exchange, and variable degradation [109]	Proteolytic instability, aggregation, source-related variability, possible immunogenicity, and batch-dependent gelation [110,111]	Nuclease susceptibility, weak mechanics, synthesis cost, innate immune activation, off-target hybridization, and limited large-scale manufacturing experience [102,112,115]
Representative advances	Sprayable HA composite hydrogels for postoperative colorectal-cancer treatment [58]	Engineered elastin-like polypeptide and self-assembling peptide hydrogels for localized chemoimmunotherapy [79,87–89]	Programmable DNA hydrogels for sequential chemotherapy, immune activation, and checkpoint inhibition [104]

Abbreviations: ATP, adenosine triphosphate; HA, hyaluronic acid; IL-12, interleukin-12; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; siRNA, small interfering RNA. Note:

The listed characteristics are formulation-dependent. Polynucleotide hydrogels are defined as networks in which nucleic acids contribute to crosslinking, assembly, or molecular recognition; systems that only encapsulate nucleic-acid cargo are classified according to the network-forming matrix.

3. Design, Gelation, Release, and Characterization

Hydrogel composition and crosslinking determine gelation, injectability, mechanical stability, degradation, payload retention, and release. Physical, chemical, enzymatic, and ionic crosslinking strategies provide different balances among administration, depot stability, biological compatibility, and therapeutic availability [116]. Scheme 1 summarizes the relationships among hydrogel network formation, drug-release mechanisms, thermoresponsive behavior, and oncology-relevant properties.

3.1. Hydrogel-Based Gelation Mechanisms

3.1.1. Physical Crosslinking

Physical crosslinking arises from reversible noncovalent interactions, including hydrogen bonding, hydrophobic association, electrostatic interactions, host–guest complexation, crystallization, and polymer-chain entanglement. The absence of reactive crosslinkers can benefit injectable formulations containing labile drugs or biologics. However, physically crosslinked networks are often sensitive to dilution, temperature, pH, ionic composition, and mechanical stress, which can compromise depot stability and accelerate payload leakage [117,118].

Alginate forms ionically crosslinked networks through coordination between guluronate-rich chain regions and divalent cations, most commonly Ca^{2+} [119]. Chitosan/β-glycerophosphate formulations undergo temperature-dependent gelation through coordinated changes in electrostatic, hydrogen-bonding, and hydrophobic interactions [120,121]. Gelatin forms thermoreversible physical networks through partial reformation of collagen-like helical junctions during cooling; these interactions weaken upon heating, limiting stability near physiological temperature unless the network is further reinforced [122]. Supramolecular host–guest and self-assembling peptide hydrogels provide additional reversible platforms with shear-thinning, self-healing, and stimulus-responsive properties [117,118]. Their major limitations remain variable mechanical strength, environmental sensitivity, and premature payload leakage.

3.1.2. Chemical Crosslinking

Chemical crosslinking generates covalent bonds between polymer chains and generally produces more stable networks than reversible physical association. Photocrosslinking of methacrylated polymers, including gelatin methacryloyl (GelMA) and methacrylated hyaluronic acid (HAMA), enables spatial and temporal control over gel formation and permits adjustment of network stiffness, swelling, and molecular transport. Click-type reactions, including thiol–ene, azide–alkyne cycloaddition, Diels–Alder cycloaddition, and thiol–Michael addition, can support hydrogel formation under relatively mild and selective conditions. Dynamic covalent reactions, particularly Schiff-base formation between aldehyde and primary amine groups, facilitate rapid in situ gelation and are widely used in injectable polysaccharide hydrogels [123–126].

Covalent crosslinking can improve depot persistence and regulate swelling, degradation, and payload release. However, a high crosslink density may reduce mesh size, restrict payload diffusion, delay degradation, and compromise tissue compatibility. Unreacted monomers, crosslinkers, catalysts, and photoinitiators may also impair therapeutic-cargo activity or cause local cytotoxicity. Crosslinking kinetics and precursor concentrations must therefore be optimized to prevent premature gelation during adminis-

tration while ensuring adequate network formation after placement [123–126].

3.1.3. Enzymatic and Ionic Gelation

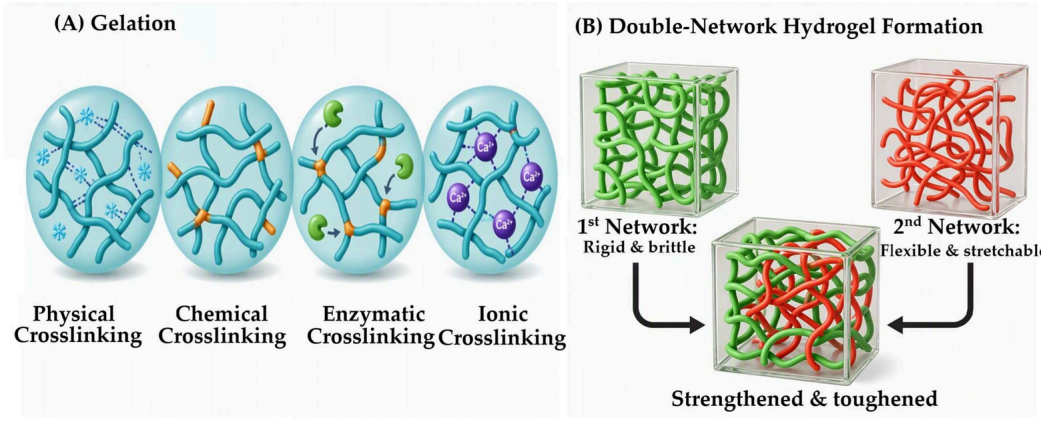
Enzymatic crosslinking uses catalysts such as horseradish peroxidase, transglutaminase, tyrosinase, or laccase to generate covalent junctions under aqueous and near-physiological conditions. Horseradish-peroxidase-mediated coupling of phenol- or tyramine-functionalized polymers is frequently used in injectable hydrogels because crosslinking can proceed near physiological pH and temperature. Enzyme–substrate specificity may limit nonspecific reactions and facilitate the encapsulation of labile therapeutic cargo. However, gelation kinetics and the resulting network properties depend on enzyme concentration and activity, the degree of polymer functionalization, substrate accessibility, oxidant availability, and local pH and temperature [127,128].

Ionic gelation arises from electrostatic association or coordination between charged polymers and multivalent counterions, as illustrated by alginate–Ca^{2+} and chitosan–tripolyphosphate networks. These systems provide rapid gelation without organic solvents or reactive covalent crosslinkers, but ion exchange and counterion diffusion in physiological media can alter swelling, mesh structure, and mechanical stability [129,130]. Dual-crosslinked networks combine ionic or enzymatic gelation with a secondary physical or covalent mechanism to improve mechanical strength, water retention, and structural persistence [130,131]. Nevertheless, their design requires control of gelation kinetics, spatial network homogeneity, payload stability, degradation behavior, and any residual reactive components.

Physical, chemical, enzymatic, and ionic crosslinking provide different balances among injectability, network stability, reversibility, and biological compatibility. Networks with complementary structural and mechanical characteristics can also be combined to improve resistance to deformation, as summarized in Scheme 1.

3.2. Structure–Crosslinking–Release Relationships

Hydrogel performance reflects the combined effects of polymer composition and molecular weight, crosslinking mechanism and density, mesh size, swelling, degradation, and payload–matrix interactions. Increasing crosslink density generally reduces mesh size and equilibrium swelling while increasing network modulus and structural stability. These changes can slow molecular diffusion and prolong local retention, but excessive crosslinking may restrict payload availability, delay network degradation, and prevent complete release [132–134]. Experimental studies confirm that polymer concentration and crosslink density jointly regulate small-molecule release, although this relationship can reach a saturation point beyond which additional crosslinking provides little further control [133]. More broadly, recent analysis of biomass-derived functional gels indicates that macroscopic performance can be improved through multiscale topology reconstruction, including dual-network formation, polymer entanglement, nanocomposite reinforcement, dynamic molecular interactions, and medium engineering [135]. For drug-delivery applications, however, increased mechanical robustness and environmental stability must be balanced against injectability, mesh-dependent payload transport, biodegradation, and the safety of reinforcing or crosslinking components.



Scheme 1. Crosslinking and network-formation strategies for hydrogel systems. (**A**) Physical, chemical, enzymatic, and ionic crosslinking mechanisms. (**B**) Conceptual formation of a double-network hydrogel by combining a relatively rigid first network with a more flexible second network. The resulting mechanical properties depend on polymer composition, crosslink density, network connectivity, and interactions between the constituent networks.

The effect of network structure depends on the hydrodynamic dimensions and physicochemical properties of the payload. Small hydrophilic molecules can diffuse through water-filled meshes unless retained through electrostatic, hydrogen-bonding, hydrophobic, host–guest, or covalent interactions. By contrast, proteins, antibodies, nucleic acids, liposomes, and nanoparticles experience greater steric restriction and may require network swelling, crosslink cleavage, or polymer degradation for release. Protein transport becomes increasingly hindered when the payload dimensions approach the hydrogel mesh size [132,136]. Affinity interactions can reduce initial burst release and extend protein retention, but excessively strong binding may reduce the fraction available for release and biological activity [137].

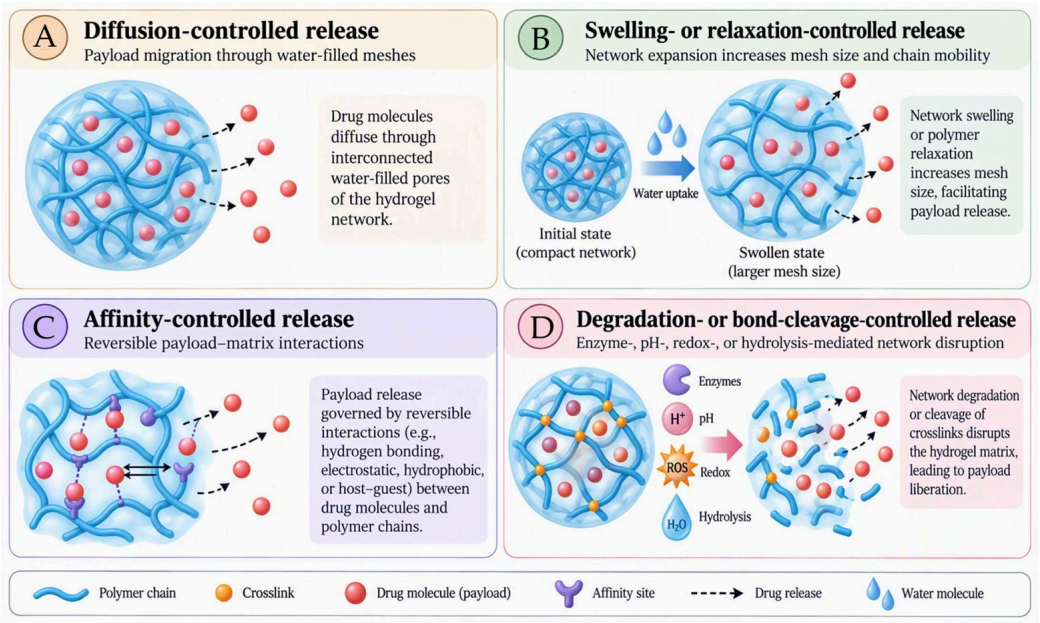
Physically crosslinked networks can provide reversible gelation, shear-thinning behavior, and self-healing, but may be destabilized by dilution, competing ions, temperature changes, or mechanical deformation. Covalently crosslinked networks generally provide greater persistence but may introduce residual reactive components and slower clearance. Dynamic covalent bonds, including imine, hydrazone, boronate-ester, and disulfide linkages, bridge these categories by maintaining network integrity while permitting bond exchange or stimulus-induced cleavage. Their effective responsiveness depends not only on bond chemistry but also on the magnitude, duration, and spatial heterogeneity of the biological trigger.

Diffusion, swelling, polymer relaxation, bond cleavage, and matrix degradation often contribute simultaneously to release, and their relative contributions may change over time. Early release may be dominated by surface-associated payload and rapid diffusion, whereas later release may depend on network relaxation, crosslink cleavage, or matrix erosion [9,132]. Crosslinking should therefore be optimized according to payload dimensions and affinity, therapeutic window, administration route, tumor anatomy, required depot residence, and acceptable degradation and clearance profiles.

3.3. Drug-Release Mechanisms and Mathematical Models

Drug release from biopolymer hydrogels is governed by the relationship among payload dimensions and chemistry, hydrogel mesh size, swelling, polymer relaxation, degradation, and payload–matrix affinity. Small molecules may diffuse through water-filled network meshes, whereas macromolecules and particulate carriers may require

network expansion, crosslink cleavage, or matrix degradation. Electrostatic, hydrophobic, hydrogen-bonding, host–guest, and covalent interactions can further delay release by retaining the payload within the network. Hydrogel-mediated release typically reflects overlapping contributions from molecular diffusion, network swelling and relaxation, reversible payload–matrix interactions, and matrix degradation or crosslink cleavage, as Scheme 2 illustrates.



Scheme 2. Principal mechanisms governing payload release from hydrogels. Payload release may occur through (**A**) diffusion across water-filled network meshes, (**B**) network swelling or polymer relaxation that increases mesh size, (**C**) reversible payload–matrix interactions, and (**D**) matrix degradation or crosslink cleavage triggered by enzymes, pH, redox conditions, or hydrolysis. These mechanisms frequently overlap, and their relative contributions may evolve during release.

The individual mechanisms illustrated in Scheme 2 are discussed below. Although they are presented separately for clarity, more than one process may govern release from a single formulation, and the dominant mechanism may change over time.

3.3.1. Diffusion-Controlled Release

Diffusion-controlled release occurs when dissolved payload molecules migrate through the water-filled meshes of a hydrogel in response to a concentration gradient. The release rate depends on the effective diffusion coefficient of the payload, network mesh size and tortuosity, hydrogel swelling, payload solubility, and interactions between the payload and polymer chains [9,132,136]. Small hydrophilic molecules generally diffuse more readily than proteins, nucleic acids, nanoparticles, or drug-loaded vesicles. Proteins with dimensions approaching the hydrogel mesh size can exhibit hindered diffusion, whereas larger cargo may remain trapped until the network swells or degrades [134].

Electrostatic attraction, hydrogen bonding, hydrophobic association, or host–guest complexation may substantially decrease molecular mobility even when the network mesh size would otherwise permit diffusion [132,137]. Diffusional release should therefore not be predicted from payload size and mesh dimensions alone.

A rapid initial release may arise from payload adsorbed near the hydrogel surface, retained in large pores, or located within weakly crosslinked regions. This burst release

can provide an initial therapeutic dose, but excessive release may increase local or systemic toxicity and shorten the effective treatment duration. Increasing polymer concentration or crosslink density can reduce diffusion and burst release by decreasing effective mesh size, although excessive network densification may restrict payload availability and prevent complete release [133,134,136].

3.3.2. Swelling- and Relaxation-Controlled Release

Swelling- and relaxation-controlled release becomes important when water uptake and polymer-chain rearrangement occur at rates comparable to or slower than payload diffusion. Following contact with physiological fluid, solvent penetrates the network, hydrates hydrophilic groups, and increases the distance between polymer chains. The resulting expansion enlarges the effective mesh size and facilitates payload transport [132,138].

The rate and extent of swelling depend on polymer hydrophilicity, charge density, concentration, molecular weight, crosslink density, pH, ionic strength, and the presence of degradable or dynamic linkages [132–134,138]. Ionizable hydrogels based on chitosan, alginate, hyaluronic acid, or carboxymethyl cellulose may therefore exhibit different swelling and release profiles under physiological and acidic conditions. Swelling should be evaluated kinetically rather than reported only as an equilibrium value because the timing of network expansion determines when transport pathways become accessible.

Excessive swelling is not necessarily advantageous. It may weaken an injectable depot, promote premature leakage, alter local tissue pressure, accelerate erosion, or reduce retention at the administration site. For localized cancer therapy, the hydrogel should permit sufficient network expansion for therapeutic transport without losing structural integrity or undergoing uncontrolled volumetric change [132,138].

3.3.3. Affinity- and Interaction-Controlled Release

Payload release may also be regulated through reversible interactions with the hydrogel matrix, including electrostatic attraction, hydrogen bonding, hydrophobic association, host–guest complexation, ligand binding, and nucleic-acid hybridization. These interactions can reduce burst release and prolong local retention even when the payload is smaller than the hydrogel mesh [132,137]. Affinity hydrogels, for example, regulate protein transport through diffusion coupled with reversible binding rather than through diffusion alone [137].

The release rate depends on the concentration and accessibility of binding sites, binding and dissociation kinetics, payload diffusivity, and competition from ions, proteins, metabolites, or other molecules in the surrounding biological medium. Weak interactions may provide insufficient retention, whereas excessively strong binding may reduce the pharmacologically available fraction or prevent complete release. Payload–matrix affinity should therefore be optimized together with mesh size, swelling, and degradation rather than treated as an independent design variable [132,137].

Changes in pH, ionic strength, temperature, enzyme activity, or concentrations of competing molecules may alter affinity and trigger payload dissociation. However, selective release requires that these changes be sufficiently different between the target tissue and surrounding physiological environment.

3.3.4. Degradation- and Erosion-Controlled Release

Degradation-controlled release occurs when cleavage of the polymer backbone or crosslinks gradually enlarges the network and enables payload escape. Degradation may proceed through hydrolysis, enzymatic cleavage, oxidation, reduction, ion exchange, or

dissociation of reversible crosslinks. Cleavage may occur throughout the matrix as bulk degradation or predominantly at the material–fluid interface as surface erosion [9,132,138].

Biopolymer hydrogels are particularly sensitive to the surrounding biological environment. Hyaluronidase, collagenase, matrix metalloproteinases, nucleases, and other enzymes can degrade hyaluronic acid-, collagen-, gelatin-, peptide-, and polynucleotide-based networks. Acid-labile imine or hydrazone bonds, reduction-sensitive disulfide linkages, and oxidation-sensitive groups may additionally accelerate network disassembly under selected conditions.

Degradation-controlled release should be distinguished from simple diffusion by measuring mass loss together with molecular-weight changes, bond cleavage, swelling, mechanical deterioration, degradation-product formation, and cumulative payload release [9,138]. Polymer content, gelation conditions, crosslink density, erosion, and drug–polymer reactions may interact to produce the observed release profile; therefore, mass loss alone does not establish the governing mechanism [138].

3.3.5. Time-Dependent Contributions and Mathematical Interpretation

Diffusion, swelling, polymer relaxation, bond cleavage, and matrix degradation frequently contribute concurrently to payload release, although their relative importance may change over time. Early release may be dominated by surface-associated payload and rapid diffusion, whereas later release may increasingly depend on network relaxation, crosslink cleavage, or matrix erosion [9,132,138]. Release profiles should therefore be interpreted according to the physicochemical behavior of the formulation rather than assigned to a single mechanism solely from mathematical curve fitting.

Mathematical models provide useful tools for comparing release profiles and identifying probable rate-controlling processes. However, model selection should be guided by the expected physical behavior of the formulation rather than solely by the highest coefficient of determination. Model comparison should include residual distribution, parameter uncertainty, and information criteria where appropriate. The principal mathematical models used to interpret hydrogel-mediated release are summarized in Table 3.

Table 3. Mathematical models of drug release from hydrogels.

Model	General Equation	Main Interpretation	Appropriate Use	Important Limitation
Zero order	$M_t = M_0 + k_0 t$	Approximately constant release rate	Designed depots with sustained input	Rarely maintained throughout swelling and degradation
First order	$\ln(M_\infty - M_t) = \ln M_\infty - k_1 t$	Release depends on drug remaining	Depletion-dependent release	Does not identify the underlying transport process
Higuchi	$M_t = k_H t^{1/2}$	Diffusion-dominated matrix release	Early diffusion from relatively stable matrices	Assumptions may fail during substantial swelling or erosion

Model	General Equation	Main Interpretation	Appropriate Use	Important Limitation
Korsmeyer–Peppas	$M_t/M_\infty = kt^n$	Empirical distinction between diffusion and mixed transport	When the mechanism is uncertain	n depends on geometry and fitted data range
Peppas–Sahlin	$M_t/M_\infty = k_1 t^m + k_2 t^{2m}$	Apparent diffusion and relaxation contributions	Swelling and relaxing polymer networks	Parameter correlation can complicate interpretation
Hixson–Crowell	$M_0^{1/3} - M_t^{1/3} = k_{HC} t$	Release associated with changing dimensions or surface area	Eroding or dissolving matrices	Unsuitable for dimensionally stable diffusion systems
Hopfenberg	$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a_0}\right)^n$	Surface-erosion-controlled release	Surface-eroding depots or implants	Not suitable for dominant bulk degradation
Weibull	$M_t/M_\infty = 1 - \exp[-(t/\alpha)^\beta]$	Empirical release-curve description	Comparing complex profiles	Strong fit does not reveal a unique mechanism

3.4. Mathematical Description of Drug Release

Mathematical models provide a quantitative means of comparing formulations and identifying release behavior consistent with diffusion, swelling, relaxation, dissolution, or erosion. However, model fitting alone does not conclusively establish a molecular mechanism. Similar release profiles may be described by more than one model, particularly when diffusion, swelling, and degradation occur simultaneously. Reviews of polysaccharide-based delivery systems emphasize that multiple mechanisms may operate in parallel and that sustained-release studies should therefore combine kinetic modelling with structural and physicochemical characterization [139].

3.4.1. Zero-Order Model

The zero-order model describes release at an approximately constant rate:

$$M_t = M_0 + k_0 t \quad (1)$$

where M_t is the cumulative amount released at time t, M_0 is the initial amount released, and k_0 is the zero-order release constant. Zero-order behavior is desirable when a nearly constant therapeutic input is required, but it is difficult to maintain in conventional hydrogels because concentration gradients, swelling, and degradation change over time. Zero-order kinetics are associated with systems designed to provide approximately constant release rather than a release rate controlled by the amount of drug remaining [140].

3.4.2. First-Order Model

The first-order model assumes that the release rate is proportional to the amount of drug remaining in the formulation:

$$\ln(M_\infty - M_t) = \ln M_\infty - k_1 t \quad (2)$$

where M_∞ represents the amount released at infinite time and k_1 is the first-order rate constant. This model commonly produces a relatively rapid initial release followed by a progressively decreasing release rate.

3.4.3. Higuchi Model

The Higuchi model describes diffusion-dominated release from a matrix:

$$M_t = k_H t^{1/2} \quad (3)$$

where k_H is the Higuchi release constant. A linear relationship between cumulative release and the square root of time is consistent with diffusion-controlled transport under the assumptions of the model. However, substantial swelling, degradation, changing geometry, or strong drug–polymer interactions can violate these assumptions. A recent hydrogel study reported that its release profiles followed the Higuchi model and interpreted this as Fickian diffusion, illustrating its continued application to sustained-release hydrogel systems [141].

3.4.4. Korsmeyer–Peppas Model

The Korsmeyer–Peppas power-law model is useful when the release mechanism is uncertain or involves more than one transport process:

$$\frac{M_t}{M_\infty} = k t^n \quad (4)$$

The Korsmeyer–Peppas model is generally fitted to the initial portion of the release profile, commonly $M_t/M_\infty \leq 0.60$, when appropriate. k is a kinetic constant incorporating structural and geometric characteristics, and n is the release exponent. The value of n is commonly used to assess whether the observed behavior is consistent with Fickian diffusion, combined diffusion and polymer relaxation, or relaxation- and erosion-dominated transport. Interpretation of n depends on sample geometry and model assumptions; therefore, threshold values should not be transferred uncritically among films, cylinders, spheres, macrogels, microgels, and nanogels.

3.4.5. Peppas–Sahlin Model

When both Fickian diffusion and polymer relaxation contribute substantially, the Peppas–Sahlin model can separate their apparent contributions:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \quad (5)$$

where the first term represents the apparent Fickian contribution and the second term represents polymer relaxation. This model may be particularly useful for highly swelling hydrogels, provided that sufficient experimental time points are available for robust parameter estimation.

3.4.6. Hixson–Crowell Model

The Hixson–Crowell model evaluates release associated with changes in the dimensions or surface area of an eroding or dissolving system:

$$M_0^{1/3} - M_t^{1/3} = k_{HC} t \quad (6)$$

where M_0 is the initial amount of drug in the formulation and k_{HC} is the Hixson–Crowell constant. This model is more relevant when matrix dimensions and surface area change appreciably during release than when transport occurs through a stable hydrogel network. The Hixson–Crowell law describes release associated with changes in particle diameter and surface area [140].

3.4.7. Hopfenberg Model

The Hopfenberg model is used for systems in which surface erosion controls payload release. It may be considered for hydrogels or implantable matrices that maintain their approximate shape while progressively eroding from the external surface. It is less appropriate for networks dominated by bulk degradation or rapid equilibrium swelling.

The Hopfenberg model describes drug release from polymeric systems in which surface erosion is the predominant release mechanism:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_0 a_0}\right)^n \quad (7)$$

where M_t is the cumulative amount of drug released at time t, M_∞ is the total releasable amount, k_0 is the surface-erosion rate constant, C_0 is the initial drug concentration in the matrix, and a_0 is the initial half-thickness or radius of the system. The geometry-dependent exponent n is 1 for a slab, 2 for a cylinder, and 3 for a sphere. This model is applicable to hydrogel depots or implantable matrices that retain their approximate geometry while progressively eroding from the external surface. It is less appropriate for systems dominated by bulk degradation, rapid equilibrium swelling, or diffusion through a stable swollen network. The Hopfenberg model describes geometry-dependent drug release from surface-eroding polymer matrices [142].

3.4.8. Weibull Model

The Weibull model is an empirical function capable of describing different release-curve shapes:

$$\frac{M_t}{M_\infty} = 1 - \exp\left[-\left(\frac{t}{\alpha}\right)^\beta\right] \quad (8)$$

where α is a scale parameter related to the release timescale and β describes curve shape. Although the Weibull model can provide a strong statistical fit, its parameters do not independently prove a specific molecular mechanism [140].

3.5. Model Selection and Reporting Requirements

Release models should be selected according to the expected physical behavior of the formulation rather than solely according to the highest coefficient of determination. Model comparison should include adjusted R^2, residual distribution, information criteria where appropriate, parameter uncertainty, and physical plausibility. Zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models are commonly compared when analyzing pharmaceutical release profiles [143].

For hydrogel-based anticancer formulations, release studies should report:

- Hydrogel geometry and dimensions.

- Polymer and crosslinker concentrations.
- Initial drug loading and encapsulation efficiency.
- Release-medium composition, volume, pH, ionic strength, and temperature.
- Sink-condition justification.
- Sampling and medium-replacement procedures.
- Analytical drug-quantification method.
- Cumulative release and mass-balance calculations.
- Swelling, mass loss, and degradation measured under the same conditions.
- The range of experimental data fitted to each model.
- Fitted parameters, residuals, and measures of model uncertainty.
- Biological relevance of the selected release medium.

Standardization is important because differences in release media, analytical methods, sample geometry, and mathematical treatment can prevent meaningful comparison among hydrogel studies. Current characterization guidance highlights the need to harmonize drug quantification, release-assay conditions, diffusion evaluation, and interpretation of release kinetics [9].

The preferred interpretation is therefore mechanistically integrated: kinetic fitting should be evaluated alongside mesh size, swelling kinetics, rheology, mass loss, degradation products, and drug–polymer interactions. A Higuchi fit may support diffusion-dominated release, whereas simultaneous increases in swelling and mass loss may indicate that diffusion is coupled with network relaxation or degradation. Mathematical models should consequently be treated as tools for hypothesis testing and formulation comparison rather than as standalone proof of release mechanism.

The principal mathematical models used to analyze drug release from hydrogels are compared in Table 3. Model selection should consider the underlying network behavior and experimental conditions rather than relying solely on statistical goodness of fit.

3.6. Pharmaceutical Characterization of Hydrogel Formulations

Reliable pharmaceutical characterization is required to connect hydrogel composition and manufacturing conditions with injectability, depot stability, payload loading and release, degradation, safety, and therapeutic performance. Comparisons among formulations remain difficult because studies often use different test conditions and analytical methods. Characterization should therefore integrate rheological, mechanical, swelling, degradation, payload-quality, stability, and manufacturing assessments under conditions relevant to the intended route of administration and clinical application [9,144,145].

3.6.1. Rheology, Gelation, and Injectability

Rheological analysis should quantify viscosity, storage modulus (G′), loss modulus (*G*″), gelation kinetics, yield behavior, shear thinning, thixotropy, and structural recovery. The *G*′–*G*″ crossover or another predefined rheological criterion may be used to estimate gelation time, but the selected endpoint and measurement conditions must be reported. Time, frequency, and amplitude sweeps provide complementary information on network formation, viscoelastic stability, and the linear viscoelastic range, whereas step-strain testing can determine recovery after shear-induced network disruption [144,145].

Rheological measurements alone do not establish injectability. Direct testing should use the intended syringe and needle or catheter at the relevant temperature, injection rate, and formulation volume. Injection force, blockage risk, dose delivery, and post-extrusion recovery should be evaluated. For intratumoral or postoperative administration, gelation must be sufficiently rapid to limit leakage but sufficiently slow to permit accu-

rate placement and conformity to irregular tissue spaces. Payload integrity should also be confirmed after injection when shear-sensitive proteins, nucleic acids, cells, viral vectors, liposomes, or nanoparticles are incorporated.

3.6.2. Mechanical Properties, Swelling, and Degradation

Mechanical testing should reflect hydrogel geometry, implantation site, and clinical function. Compression is appropriate for bulk depots, tensile testing for films and patches, and oscillatory rheology for soft injectable networks. Adhesive formulations additionally require measurement of interfacial adhesion, cohesive failure, and performance on wet tissue. Initial stiffness should not be interpreted independently of swelling and degradation because water uptake, bond exchange, polymer erosion, and physiological loading can substantially alter mechanical performance after administration.

Swelling should be measured as a function of time under relevant temperature, pH, ionic strength, protein concentration, and enzymatic conditions. Percentage swelling may be calculated as:

$$\text{Swelling ratio} = \frac{W_s - W_d}{W_d} \quad (9)$$

where W_d is the initial dry mass and W_s is the swollen mass at time t. If swelling is reported as a dimensionless ratio rather than a percentage, multiplication by 100 should be omitted. The calculation convention and dry- or wet-mass basis should be stated explicitly. Equilibrium swelling alone is insufficient for responsive systems because transient expansion or contraction can modify mesh size, payload diffusion, mechanical stability, and pressure on surrounding tissues. Both the rate and extent of swelling should therefore be reported.

Hydrogel degradation should be evaluated by combining mass loss with changes in molecular weight, network chemistry, mechanical properties, and morphology. Percentage mass loss may be calculated as:

$$\text{Mass loss}\,(\%) = \frac{W_0 - W_t}{W_0} \times 100 \quad (10)$$

where W_0 is the initial dry mass and W_t is the remaining dry mass after degradation for time t. Samples should be dried to constant mass before comparison. Mass loss alone may underestimate degradation when polymer-chain cleavage occurs before soluble fragments leave the network. Conversely, apparent mass changes may reflect incomplete drying, dissolution, or sample loss rather than controlled degradation.

For natural polymers, degradation testing should account for biologically relevant enzymes, source-dependent composition, and batch variability. Degradation products should be identified where possible and evaluated for local toxicity, inflammatory potential, clearance, and interference with payload activity or analytical measurements.

3.6.3. Payload Loading, Distribution, Release, and Integrity

Drug-loading capacity and encapsulation efficiency should be reported separately because they describe different formulation attributes. Drug loading may be expressed as:

$$\text{Drug loading}\,(\%) = \frac{\text{Mass of encapsulated drug}}{\text{Total mass of drug} - \text{loaded formulation}} \times 100 \quad (11)$$

where $M_{\text{encapsulated}}$ is the mass of payload retained in the hydrogel and $M_{\text{loaded formulation}}$

is the total mass of the payload-loaded formulation. Encapsulation efficiency may be calculated as:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Mass of encapsulated drug}}{\text{Initial mass of drug used}} \times 100 \quad (12)$$

where $M_{initial}$ is the payload mass initially introduced during formulation. Because alternative definitions are used, particularly for drug loading, the denominator and dry- or wet-mass basis should be reported explicitly.

Payload distribution should be assessed where technically feasible because surface-associated or spatially heterogeneous loading can cause an initial burst and inconsistent local exposure. Analytical methods used for payload quantification and release testing should be validated in the presence of the hydrogel matrix. Accuracy, precision, selectivity, sensitivity, extraction recovery, and matrix interference require particular attention because polymers, degradation products, and incorporated nanomaterials can interfere with chromatographic, spectroscopic, fluorescence, and bioassay measurements [9].

For small-molecule therapeutics, chemical identity, concentration, impurities, and degradation should be monitored during fabrication, storage, injection, and release. For proteins, antibodies, enzymes, nucleic acids, cells, and viral vectors, quantitative recovery must be complemented by assays of structural integrity and biological potency. Total payload content does not demonstrate that the released cargo remains pharmacologically active. Complex formulations containing liposomes or nanoparticles should additionally be assessed for aggregation, leakage, carrier disruption, and changes in size or surface properties.

Release testing should use sink conditions and sampling intervals appropriate to the expected release duration. The test medium should reproduce relevant physiological variables where practicable, while accelerated conditions should be clearly distinguished from clinically representative testing. Interpretation should consider diffusion, swelling, payload–matrix interactions, bond cleavage, and hydrogel erosion rather than assigning release to a single mechanism solely from mathematical curve fitting. Detailed kinetic models are summarized separately in Table 3.

3.6.4. Stability, Sterilization, and Reproducibility

Stability studies should determine whether the formulation retains its predefined physicochemical, mechanical, pharmaceutical, and biological attributes during storage and clinically relevant handling. Testing should reflect the proposed packaging, storage temperature, light exposure, freeze–thaw conditions, transport, reconstitution, and precursor-hold time. Relevant endpoints include appearance, pH, osmolality, gelation time, rheology, swelling, degradation, payload recovery, release behavior, sterility, and biological potency.

Sterilization should be evaluated using the complete formulation rather than the unloaded polymer alone. Heat, irradiation, filtration, or chemical treatment may alter polymer molecular weight, crosslink formation, gelation kinetics, mechanical properties, degradation, release, or payload activity. Sterility and endotoxin control should therefore be verified together with post-sterilization product performance [9–12].

Batch reproducibility must be demonstrated across independently manufactured batches rather than inferred from repeated measurements of a single batch. Critical material attributes and process parameters should be linked to predefined product-quality attributes and acceptance criteria. This is particularly important for natural polymers, for which molecular-weight distribution, degree of substitution or deacetylation, purity, moisture, residual biological material, and endotoxin burden can vary with source and

purification.

Manufacturing variables such as component ratios, mixing sequence, temperature, pH, ionic strength, curing time, sterilization, and filling conditions should likewise be controlled. For hydrogels containing complex biological or particulate payloads, inter-batch assessment should include payload distribution, aggregation, leakage, structural integrity, and biological potency [9–12,49].

The principal characterization parameters and their pharmaceutical relevance are summarized in Table 4. No single measurement is sufficient to establish hydrogel performance. Rheology cannot replace direct injection testing, equilibrium swelling cannot define release behavior, and mass loss alone cannot establish degradation, clearance, or safety. Characterization should therefore use an integrated, formulation-specific test strategy aligned with the administration route, payload, tumor location, depot function, and intended clinical use.

Table 4. Pharmaceutical characterization of hydrogel formulations for cancer therapy.

Characterization Domain	Principal Measurements	Pharmaceutical Relevance
Gelation and rheology	Gelation time; viscosity; G', G'', and tanΔ; yield stress; shear thinning; structural recovery	Defines the administration window, network formation, flow behavior, and post-injection depot stability.
Injectability	Injection force; blockage; delivered volume; leakage; post-extrusion recovery	Confirms administration through the intended needle, catheter, or endoscopic device and reproducible dose delivery.
Mechanical and adhesive properties	Compression or tensile properties; toughness; cyclic stability; tissue adhesion and cohesion	Assesses structural integrity, tissue conformity, and retention at the application site.
Swelling	Time-dependent mass or volume change in physiologically relevant media	Indicates dimensional stability and changes in mesh size, payload diffusion, and mechanical properties.
Degradation and clearance	Mass loss; molecular-weight change; bond cleavage; mechanical deterioration; degradation-product analysis	Defines depot persistence and erosion-mediated release and supports assessment of degradation-product safety and clearance.
Payload loading and distribution	Loading capacity; encapsulation efficiency; content uniformity; spatial distribution	Establishes dose and identifies heterogeneous or surface-associated payload that may contribute to burst release.
Release performance	Cumulative release; burst fraction; release duration; mass balance; mechanism-based kinetic analysis	Determines whether local exposure is compatible with the therapeutic window and identifies contributions from diffusion, swelling, bond cleavage, and erosion.

Payload integrity and potency	Chemical stability; binding or enzymatic activity; transfection, infectivity, or other cargo-specific functional assays	Confirms that the encapsulated and released payload remains structurally intact and biologically active.
Analytical-method suitability	Accuracy; precision; recovery; sensitivity; selectivity; matrix interference	Ensures reliable quantification in the presence of polymers, nanomaterials, release media, and degradation products.
Sterilization and microbiological quality	Sterility; endotoxin burden; pre- and post-sterilization comparison of critical formulation attributes	Confirms microbiological quality without unacceptable changes in network properties, release, or payload activity.
Storage stability	Appearance; pH; rheology; gelation; payload recovery; impurities; aggregation; release; potency	Supports specification of packaging, storage conditions, shelf life, and in-use stability.
Batch reproducibility	Interbatch comparison of critical material, process, and product-quality attributes	Supports manufacturing control, scale-up, and consistent performance, particularly for source-variable natural polymers.

Abbreviations: G′, storage modulus; G″, loss modulus; tanΔ=G″/G′, loss tangent. Note: The characterization strategy should be selected according to hydrogel architecture, payload type, administration route, tumor location, and intended clinical function. Measurements should be performed under application-relevant conditions using independently manufactured batches where applicable [9–12,49,144,145].

No single parameter is sufficient to establish hydrogel performance. Rheology without injection testing may not predict administration, equilibrium swelling without kinetic measurements may not predict release, and mass loss without degradation-product analysis may not establish clearance or safety. Pharmaceutical characterization should therefore use an integrated test battery aligned with the intended route of administration, payload, tumor location, and clinical function.

4. Oncology-Relevant Hydrogel Platforms and Functional Properties

Hydrogel platforms used in cancer treatment range from bulk injectable depots and postoperative films to microgels, nanogels, and multicomponent hybrid systems. Their dimensions and architecture influence administration route, anatomical retention, tissue penetration, payload distribution, degradation, and clearance. Platform selection should therefore be guided by tumor accessibility, anatomical location, treatment objective, payload properties, and intended administration route rather than by polymer origin alone. The relationships among network structure, crosslinking, swelling, degradation, and release are discussed in Sections 3.2–3.4; the present section focuses on their functional implications for cancer treatment [10,13,14,16,17].

The principal hydrogel architectures investigated in oncology are compared in Figure 2.

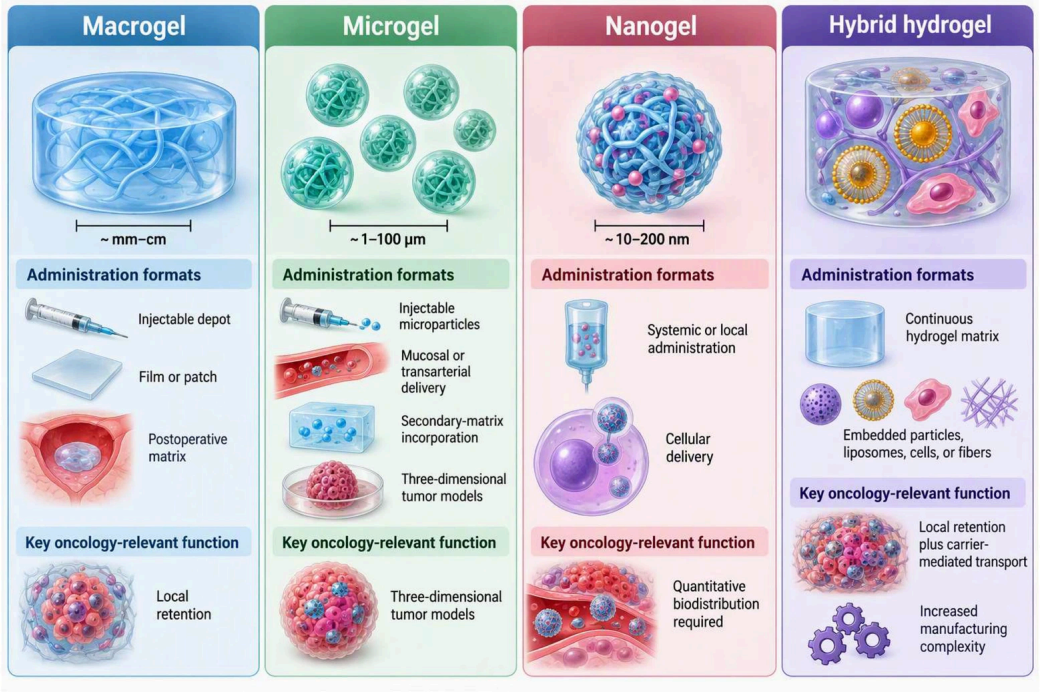


Figure 2. Comparative architectures and oncology-relevant applications of hydrogel systems. Macrogels, microgels, nanogels, and hybrid hydrogels differ in scale, administration format, and function, supporting local retention, particulate or cellular delivery, tumor modeling, and carrier-mediated transport. Scale ranges are approximate.

4.1. Oncology-Relevant Functional Requirements

Biopolymer hydrogels can support minimally invasive administration, conformity to irregular tumor margins or postoperative cavities, local retention of therapeutic agents, and incorporation of chemotherapeutics, proteins, antibodies, cytokines, nucleic acids, radionuclides, photosensitizers, immune cells, and nanoparticle formulations [11,12,45,47,146,147]. However, these advantages are formulation- and route-specific. Intratumoral depots must resist backflow, leakage, and rapid dispersion; postoperative systems must conform to resection surfaces without excessive swelling or compression of adjacent tissues; intraperitoneal formulations must remain localized under continuous fluid movement; and transarterial systems must retain catheter compatibility and undergo controlled localization after administration.

Biological interactions may provide additional functionality. Hyaluronic acid can facilitate CD44-associated interactions in tumors expressing this receptor, whereas antibodies, peptides, aptamers, and folate derivatives may support receptor-mediated binding or cellular uptake [29,30]. Cyclodextrin-mediated host–guest interactions can improve the incorporation and retention of hydrophobic payloads [148]. Nevertheless, ligand-mediated targeting should be distinguished from local placement, passive accumulation, and prolonged retention. Ligand functionalization may improve cellular interactions after a carrier reaches the tumor but does not necessarily overcome poor vascular access, a dense extracellular matrix, elevated interstitial pressure, heterogeneous receptor expression, or uneven intratumoral penetration. Claims of tumor targeting should therefore be supported by receptor-specific uptake or quantitative tumor-to-normal-tissue distribution data rather than by local retention or tumor-associated imaging signals alone.

Biodegradation can facilitate carrier removal and contribute to payload release, but it does not independently establish biosafety or complete biological clearance.

Premature degradation may cause depot collapse, burst release, and increased systemic payload exposure, whereas prolonged persistence may increase the risk of fibrosis, chronic inflammation, or foreign-body responses [9,10,16,17,138].

Biological performance should therefore be evaluated across the complete disposition pathway of the final formulation:

Administration → local retention → spatial payload distribution → systemic leakage → hydrogel degradation → biodistribution of the payload and degradation products → organ clearance → immune response.

Local depot persistence does not establish homogeneous intratumoral or cavity-wide distribution, and hydrogel degradation does not establish complete elimination from the body. Studies should quantify depot residence, spatial payload distribution, systemic exposure, tissue and organ biodistribution, degradation-product identity, renal or hepatic elimination, local inflammation, foreign-body responses, and payload-specific immunogenicity. Evaluation periods should be sufficient to capture both the intended therapeutic exposure and the subsequent clearance of the hydrogel, payload, and degradation products [9,10,16,17,138].

Accordingly, the oncology-specific value of a hydrogel depends on coordinated control of administration, anatomical conformity, retention, spatial distribution, payload release, systemic leakage, degradation, and clearance. Evidence of sustained release or local retention should not be interpreted independently as proof of homogeneous tumor exposure, molecular targeting, reduced systemic toxicity, or therapeutic superiority.

4.2. Size- and Architecture-Defined Hydrogel Platforms

4.2.1. Macrogels

Macrogels include injectable bulk depots, films, patches, and surface-conforming formulations intended principally for intratumoral, peritumoral, intraperitoneal, or postoperative administration. Their major advantages are high local payload capacity, prolonged residence, and conformity to accessible tumors or resection cavities. Surface-filling hydrogels can cover irregular anatomical regions, whereas injectable and thermosensitive formulations can form localized depots after administration [149–151].

Bulk retention, however, does not guarantee uniform release, complete coverage of tumor margins, or deep penetration of released agents. Crosslink density, mesh size, payload affinity, swelling, degradation, and depot geometry may produce heterogeneous exposure. Clinically relevant evaluation should therefore address gelation time, injection force, backflow, anatomical conformity, positional stability, swelling, spatial payload distribution, systemic leakage, and degradation.

For postoperative formulations, antitumor performance should also be distinguished from hemostasis, wound healing, tissue sealing, and adhesion prevention because these are separate clinical functions requiring different endpoints.

4.2.2. Microgels

Microgels are crosslinked hydrogel particles that provide high surface area and may be administered as suspensions or incorporated into secondary matrices [152]. Oral microgels have been investigated for protection of therapeutic agents during gastrointestinal transit and preferential delivery to the colon, including polysaccharide-based systems carrying 5-fluorouracil [153]. Pulmonary microgels may support localized respiratory delivery, whereas microgel-like and hydrogel-forming embolic systems can combine vascular occlusion with local therapeutic delivery.

In transarterial applications, embolization and payload delivery should be evaluated as distinct functions. Silk–elastin-like systems, for example, have demonstrated

catheter-compatible gelation and potential as localized chemoembolic carriers [154,155]. Relevant parameters include particle or precursor dimensions, deformability, catheter passage, vascular distribution, durability of occlusion, non-target embolization, payload release, degradation, and local tissue response.

Routine intravenous use of microgels remains challenging because microscale carriers may undergo rapid phagocytic uptake or capillary entrapment. Route selection should consequently be based on particle dimensions, deformability, biodistribution, and clearance rather than on the assumption that all microgels are suitable for systemic delivery.

4.2.3. Nanogels

Nanogels are nanoscale crosslinked networks capable of incorporating small molecules, proteins, nucleic acids, photosensitizers, and imaging agents [7,152]. Their dimensions and hydrated structure may support circulation, tissue transport, and cellular uptake, but these outcomes depend on hydrodynamic size, surface charge, deformability, aggregation, protein adsorption, and colloidal stability.

Functionalized nanogels have demonstrated therapeutic activity in glioblastoma models, including miR-34a delivery and near-infrared-activated biomimetic systems [156,157]. These formulation-specific observations should not be generalized to all nanogels. Nanoscale dimensions do not independently establish blood–brain barrier penetration, tumor targeting, cellular uptake, or homogeneous intratumoral distribution. Likewise, increased tumor-associated imaging signal may represent vascular retention, extracellular accumulation, or released label rather than delivery of an intact nanogel.

Nanogel studies should therefore quantify blood pharmacokinetics, intact-carrier distribution, tumor-to-organ ratios, intratumoral localization, cellular uptake, systemic toxicity, degradation, and renal or hepatobiliary clearance. Where blood–brain barrier transport is claimed, the distribution of the intact nanogel should be distinguished from that of released payloads or imaging labels.

4.2.4. Hybrid Hydrogels

Hybrid systems incorporate nanoparticles, nanogels, liposomes, micelles, proteins, synthetic polymer segments, or inorganic components within a hydrogel matrix [18,49,158–160]. The bulk network may provide anatomical retention, whereas the incorporated carrier controls payload solubilization, cellular uptake, imaging, energy conversion, or sequential release. Representative systems include hydrogels containing drug-loaded liposomes, polymeric micelles, magnetic particles, photothermal agents, and membrane-coated nanocarriers [48,49,159,160].

This added functionality increases analytical and manufacturing complexity. A sustained bulk-release profile does not establish that intact nanoparticles are released, retain their original dimensions and potency, or reach the intended cellular compartment. Moreover, the hydrogel matrix, incorporated carrier, payload, and degradation products may follow different biodistribution and clearance pathways.

Hybrid formulations should therefore be evaluated at three levels: the hydrogel matrix, the incorporated carrier, and the integrated final product. Critical attributes include component ratios, spatial homogeneity, particle aggregation, payload leakage, sequential-release behavior, sterilization compatibility, and storage stability. Biological studies should distinguish the distribution and safety profiles of the matrix, carrier, payload, and degradation products. Additional components should be included only when they address a defined clinical or pharmaceutical limitation, because increasing multifunctionality can compromise manufacturing reproducibility, analytical control, sterilization,

and regulatory development.

4.3. Route-Specific Design and Platform Selection

Administration route is a primary design constraint. Intratumoral formulations require predictable injection, limited backflow, and reliable gelation; postoperative systems require anatomical conformity, positional stability, and controlled swelling; intraperitoneal depots require retention despite fluid movement; and transarterial systems require catheter compatibility and controlled embolization. Oral formulations must tolerate gastrointestinal transit before releasing their payload at the intended site, whereas systemically administered nanogels require acceptable circulation, quantitative biodistribution, and organ-clearance assessment [9–12,16,17].

These requirements frequently compete. Rapid gelation may improve local retention but increase the risk of premature gelation within a needle or catheter. Greater crosslink density may stabilize a depot but restrict payload diffusion, tissue integration, immune-cell migration, or degradation. Strong payload affinity may reduce initial burst release but also reduce therapeutic availability. Clinically representative administration conditions, including needle or catheter dimensions, injection force, preparation time, component-mixing accuracy, formulation temperature, placement accuracy, imaging compatibility, and operator dependence, should therefore be incorporated early in preclinical development.

No platform architecture is intrinsically superior. Macrogels are generally suited to accessible tumors, postoperative cavities, and sustained local treatment; microgels to mucosal, pulmonary, particulate, or transarterial delivery; nanogels to systemic or cellular delivery; and hybrid systems to applications requiring coordinated retention and carrier-mediated transport. Platform selection should integrate tumor accessibility, treatment objective, payload properties, administration route, required exposure period, and acceptable degradation and clearance profiles.

Comparative interpretation should distinguish local retention, spatial distribution, systemic leakage, release, tumor-volume change, tumor-growth inhibition, recurrence control, survival, degradation, and clearance as separate outcomes. The strongest evidence arises when hydrogel architecture and administration route are explicitly connected to clinically relevant delivery, disposition, safety, and therapeutic endpoints.

Whereas Section 4 classifies hydrogel platforms according to architecture, administration route, disposition, and oncology-relevant function, Section 5 examines the targeting and stimulus-responsive mechanisms used to control cellular interactions and payload release.

5. Targeting Strategies and Stimuli-Responsive Release

Targeting and stimulus-responsive release are related but distinct functions. Targeting governs where a formulation or released carrier accumulates and which cells it interacts with, whereas stimulus responsiveness governs when and under which conditions the hydrogel changes its network structure, payload affinity, or release behavior. Neither function is intrinsic to all hydrogels, and neither should be inferred solely from local administration, prolonged retention, or release under an experimentally selected condition. The diffusion-, swelling-, degradation-, and affinity-controlled mechanisms underlying release are discussed in Section 3.3; the present section focuses on their implications for localization and tumor-associated activation [16,17,45].

5.1. Local Placement and Passive Accumulation

Direct intratumoral, peritumoral, intraperitoneal, postoperative, or transarterial ad-

ministration can increase exposure at an anatomically defined treatment site. However, local placement is not equivalent to molecular targeting. A hydrogel may remain near the administration site while releasing its payload unevenly, failing to penetrate the tumor, or allowing substantial systemic leakage. Local targeting claims should therefore be supported by quantitative depot retention, spatial payload distribution, systemic exposure, and tumor-to-normal-tissue data.

For systemically administered nanogels and hydrogel-derived nanocarriers, passive accumulation may be influenced by abnormal tumor vasculature and impaired lymphatic drainage, commonly described as the enhanced permeability and retention effect [19–22,25–27]. Its magnitude, however, varies among tumor types, patients, lesions, and regions within the same tumor. Perfusion, vascular permeability, elevated interstitial pressure, stromal density, particle dimensions, surface chemistry, protein adsorption, and clearance by the mononuclear phagocyte system can all restrict accumulation and penetration [23,24,28,161].

The enhanced permeability and retention effect should therefore be treated as a variable transport phenomenon rather than a universal mechanism of tumor targeting. Particle accumulation should be distinguished from intact-carrier delivery, cellular uptake, and therapeutic-payload availability. Increased tumor-associated fluorescence alone is insufficient because the signal may arise from circulating material, vascular retention, released dye, or extracellular accumulation.

5.2. Ligand-Mediated Targeting and Cellular Uptake

Active targeting introduces ligands that recognize tumor-associated receptors or extracellular components. Antibodies, peptides, aptamers, hyaluronic acid, folate derivatives, and related ligands have been used to facilitate receptor-associated binding or cellular uptake [29–37]. Representative targets include CD44, HER2, epidermal growth factor receptor, integrins, transferrin receptors, and tumor-associated vascular markers.

Ligand functionalization acts mainly after the carrier has reached an accessible target. It does not independently overcome poor perfusion, dense extracellular matrix, elevated interstitial pressure, or limited tissue penetration. Moreover, receptor abundance may differ across patients, tumor regions, disease stages, and treatment histories. Receptor expression should therefore be quantitatively verified in the intended indication rather than assumed from cell-line data.

Evidence for active targeting should include appropriate non-targeted or ligand-blocking controls, receptor-specific uptake, intact-carrier tracking, and tumor-to-normal-tissue distribution. Greater cytotoxicity in receptor-positive cells may support receptor-associated uptake but does not establish in vivo tumor targeting or reduced systemic toxicity. Dual- or multiligand strategies may broaden cellular interactions, but they also increase manufacturing, analytical, immunogenicity, and regulatory complexity [36,38].

Passive accumulation and ligand-mediated interactions operate at different stages of delivery. Passive accumulation is influenced by circulation, vascular permeability, interstitial transport, particle properties, and systemic clearance, whereas active targeting primarily affects receptor-associated binding and cellular uptake after the carrier reaches an accessible target. Tumor-associated acidity, oxidative stress, hypoxia, intracellular reducing conditions, and altered enzyme activity may subsequently modify hydrogel swelling, payload affinity, crosslink stability, or degradation, as summarized in Figure 3.

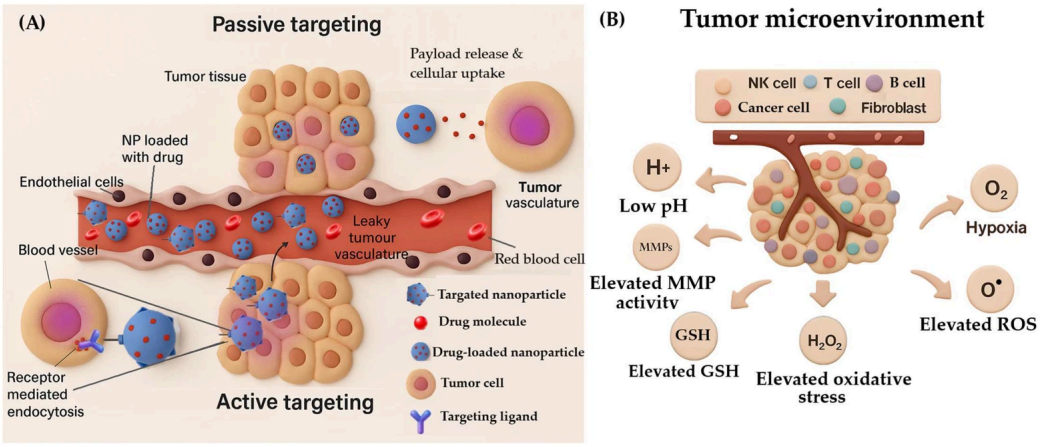


Figure 3. Targeting mechanisms and endogenous tumor-associated conditions relevant to hydrogel-based drug delivery. (**A**) Passive accumulation is influenced by abnormal tumor vasculature, extravasation, interstitial transport, particle properties, and systemic clearance, whereas ligand-mediated targeting promotes receptor-associated binding or cellular uptake after the carrier reaches an accessible target. (**B**) Tumor-associated conditions that may be exploited for responsive release include extracellular acidity, hypoxia, oxidative stress, altered protease or enzyme activity, and intracellular reducing conditions. These features are spatially and temporally heterogeneous and are not exclusive to malignant tissues. Panels were adapted and redrawn from Refs. [45,162].

5.3. Endogenous Stimuli-Responsive Release

Endogenous stimuli-responsive hydrogels exploit biochemical differences associated with tumors, including extracellular acidity, intracellular reducing conditions, elevated reactive oxygen species, hypoxia, and altered enzyme activity. These conditions can change polymer ionization, swelling, payload–matrix affinity, crosslink stability, or network degradation. However, tumor-associated stimuli vary spatially and temporally and are not exclusive to malignant tissues. Inflammation, infection, ischemia, and wound healing can reproduce several of the same biochemical conditions.

A measurable response under an extreme experimental condition does not establish selectivity under physiological conditions. Evaluation should therefore compare healthy physiological conditions, tumor-relevant stimulus ranges, intracellular conditions where applicable, and relevant nonmalignant pathological controls. Baseline release in the absence of the intended trigger, activation thresholds, response kinetics, reversibility, and performance after repeated stimulation should also be reported.

5.3.1. pH-Responsive Hydrogels

pH-responsive hydrogels use ionizable polymer groups or acid-labile bonds to modify swelling, network stability, or payload release. Protonation of chitosan and related cationic polymers can increase hydration and chain repulsion, whereas imine, hydrazone, acetal, and related linkages may undergo accelerated cleavage under acidic conditions [69,86,87,163–169].

The extracellular pH of solid tumors is generally only moderately lower than that of healthy tissues and may vary substantially within a lesion. More acidic conditions occur in endosomal and lysosomal compartments, meaning that some systems require cellular uptake before substantial activation. Release studies should therefore compare physiological, tumor-relevant extracellular, and intracellular-compartment conditions rather than relying on a single extreme acidic medium.

5.3.2. Redox-Responsive Hydrogels

Redox-responsive hydrogels commonly contain disulfide or related reduction-sensitive linkages that undergo cleavage under glutathione-rich intracellular conditions [39,170,171]. An alginate-derived porous hydrogel crosslinked using a disulfide-containing PEG linker released more than 90% of its encapsulated doxorubicin in 10 mM glutathione [172]. This formulation differs from the pH- and glutathione-responsive dendrimer–alginate hydrogel summarized in Table 5, which released approximately 76% of its doxorubicin under combined 10 mM glutathione and pH 5.5 conditions [173]. Redox responsiveness has also been combined with folate- or hyaluronic-acid-mediated cellular interactions, fluorescence tracking, magnetic hyperthermia, and light-responsive treatment [44,171,174].

Because millimolar glutathione concentrations principally represent intracellular reducing conditions, redox-triggered release usually requires cellular internalization or close intracellular access. Evaluation should therefore distinguish extracellular depot release from intracellular carrier disassembly and should test physiologically relevant glutathione ranges.

5.3.3. ROS-, Enzyme-, and Hypoxia-Responsive Hydrogels

Reactive-oxygen-species-responsive hydrogels use oxidation-sensitive groups, including thioketal and phenylboronic-ester moieties, or incorporate components that generate or amplify oxidative stress [175–178]. Enzyme-responsive systems may contain peptide or polysaccharide segments cleavable by matrix metalloproteinases, cathepsins, hyaluronidase, esterases, or other disease-associated enzymes [40,42]. Hypoxia-responsive platforms can release payloads under low-oxygen conditions or incorporate oxygen-generating or oxygen-consumption-modulating components to improve oxygen-dependent treatment [40,42,179–181].

These strategies remain susceptible to biological heterogeneity. Reactive oxygen species, enzyme activity, and oxygenation vary among patients and across tumor regions and may change during treatment. Responses observed at a single, highly elevated stimulus concentration should not be interpreted as evidence of tumor selectivity. Testing should include stimulus gradients, relevant pathological controls, temporal changes, and combined conditions representative of the intended tumor microenvironment.

5.4. Externally Triggered Release

External stimuli, including light, magnetic fields, ultrasound, ionizing radiation, and controlled heating, can provide greater temporal control than endogenous triggers. Their effectiveness nevertheless depends on energy penetration, spatial distribution, treatment geometry, exposure duration, and the position of the hydrogel relative to the energy source. External activation should therefore be evaluated using clinically relevant equipment and tissue depths rather than only through superficial or small-animal models.

5.4.1. Light-Responsive Hydrogels

Light-responsive hydrogels can support photothermal heating, photosensitizer activation, bond cleavage, or stimulus-dependent payload release. Near-infrared irradiation is generally favored over ultraviolet or visible light because of greater tissue penetration, although attenuation and nonuniform energy deposition remain important limitations [182,183].

For example, a methylcellulose-based hybrid hydrogel containing IR820 and doxorubicin-loaded silica nanoparticles generated local heat and enhanced drug release under near-infrared irradiation [184]. Other platforms have combined photosensitizers, im-

mune modulators, inorganic particles, or responsive prodrugs to integrate photothermal, photodynamic, chemotherapeutic, and immunotherapeutic effects [185]. Such systems should be evaluated through wavelength, power density, irradiation duration, penetration depth, intratumoral energy distribution, thermal or reactive-oxygen dose, treatment repeatability, and injury to adjacent tissues.

5.4.2. Magnetic-, Ultrasound-, and Radiation-Responsive Systems

Magnetic hydrogels incorporate magnetic particles that can be retained within a hydrogel matrix and activated by an applied magnetic field. Under an alternating magnetic field, the particles may generate heat for magnetic hyperthermia, while field-induced particle movement can also produce mechanical deformation or alter payload transport [186–188]. Ultrasound-responsive hydrogels use acoustic energy to promote drug release through mechanisms including acoustic cavitation, localized heating, pressure-induced network deformation, erosion, or disruption of acoustically active components embedded within the matrix [189,190]. Hydrogels used with radiotherapy can localize radionuclides, radiosensitizers, chemotherapeutics, or immune modulators at the treatment site, thereby coordinating local delivery with external-beam radiotherapy or brachytherapy [191–194].

These externally activated systems introduce modality-specific safety and equipment requirements. Magnetic studies should report magnetic-particle concentration, field strength, frequency, specific absorption rate or heating efficiency, exposure duration, and spatial temperature distribution. Ultrasound studies should report frequency, acoustic pressure, intensity, duty cycle, pulse duration, treatment time, cavitation conditions, and tissue depth. Radiation-associated systems should specify radiation type, dose, dose rate, fractionation, treatment geometry, and dosimetry. Across all systems, evaluation should include carrier stability, baseline and stimulus-triggered release, spatial energy distribution, adjacent-tissue exposure, systemic leakage, degradation, biodistribution, and long-term clearance. Material activation, including heating, cavitation, network disruption, or increased release, should be distinguished from improved tumor control.

5.5. Thermoresponsive Hydrogels and Hyperthermia

Thermoresponsive hydrogels undergo temperature-dependent changes in swelling, network organization, solubility, or physical state. Many injectable thermogels are liquids during preparation or administration and form localized depots near physiological temperature [195–198]. Their performance depends on the sol–gel transition range, precursor viscosity, gelation time, dilution resistance, post-gelation mechanical stability, and reproducibility under clinically relevant handling conditions.

Thermoresponsive behavior should be distinguished from therapeutic hyperthermia. A temperature-induced sol–gel transition does not itself generate a therapeutic thermal dose. Hyperthermia requires an external or internally activated heat source, such as light-absorbing materials, magnetic particles exposed to an alternating magnetic field, radiofrequency or microwave energy, or focused ultrasound [188,197–200]. A thermoresponsive hydrogel may carry a heat-generating component or release a payload during heating, but temperature responsiveness alone should not be described as hyperthermia.

Hydrogel-assisted thermal systems should report both material behavior and treatment-specific parameters. Material evaluation should include gelation temperature, gelation time, rheology, injectability, and temperature-dependent release. Thermal evaluation should include the energy source, power density or field strength, exposure time, heating rate, intratumoral and adjacent-tissue temperatures, thermal dose, spatial heat

distribution, repeated-exposure effects, and clearance of the heat-generating component. Hyperthermia should not be described as inherently tumor-selective because selectivity depends on hydrogel placement, energy distribution, tissue perfusion, tumor depth, and the thermal sensitivity of surrounding tissues.

5.6. Selectivity, Validation, and Translational Limitations

Stimulus responsiveness should be regarded as a mechanism for modifying the probability, rate, or timing of payload release rather than as definitive evidence of tumor-specific delivery. A formulation may respond more strongly under tumor-associated conditions while still releasing a substantial payload in circulation or healthy tissues. Similarly, ligand-mediated targeting may increase receptor-specific binding or cellular uptake without necessarily increasing total tumor accumulation or producing homogeneous intratumoral distribution [23,28,32,34,45].

Responsive systems should therefore be evaluated across the complete sequence:

Administration → localization → stimulus exposure → network response → payload release → tissue distribution → cellular uptake → therapeutic effect → degradation and clearance.

Release studies should compare physiological conditions, tumor-relevant conditions, and relevant nonmalignant pathological controls, including inflammation, infection, ischemia, and wound healing where appropriate. Baseline leakage in the absence of the intended stimulus should also be quantified. The stimulus concentration, exposure duration, reversibility, activation threshold, response kinetics, and performance after repeated activation should be reported [9,10,45].

Multi-stimulus systems may increase activation stringency by requiring sequential or simultaneous triggers. However, additional materials, ligands, responsive bonds, nanocarriers, and reaction mechanisms may reduce manufacturing reproducibility and complicate sterilization, storage stability, analytical control, degradation assessment, scale-up, and regulatory classification [10–12,36,38].

Validation should connect hydrogel structure, mechanical properties, degradation, and application-relevant release kinetics with clinically representative administration and biological performance [9,10,16,17]. Where tumor targeting or systemic transport is claimed, evidence should include intact-carrier tracking, quantitative tumor-to-organ distribution, spatial payload mapping, pharmacokinetics, and appropriate non-targeted or receptor-blocking controls. Tumor-associated accumulation should be distinguished from vascular retention, extravasation, tissue penetration, cellular uptake, and release of the imaging label or payload [23,28]. Likewise, ligand functionalization may increase receptor-specific binding or endocytosis after a carrier reaches an accessible target but does not necessarily increase total tumor accumulation or overcome poor perfusion, stromal barriers, and heterogeneous receptor expression [32,34].

Section 6 examines how these localization and release-control strategies are applied to chemotherapy, radiotherapy, immunotherapy, hyperthermia, and phototherapy.

6. Hydrogel-Based Therapeutic Modalities in Cancer

Hydrogels can support cancer treatment by localizing therapeutic agents, modifying their release kinetics, protecting labile payloads, and coordinating complementary treatment modalities at anatomically defined sites. Their value nevertheless depends on the complete sequence from administration and depot formation to payload release, tissue distribution, therapeutic response, degradation, and clearance. Local retention, sustained release, or stimulus-dependent activation should not independently be interpreted as evidence of homogeneous tumor exposure, reduced systemic toxicity, or supe-

rior efficacy [9,10,16,17]. Representative quantitative formulation, release, retention, and therapeutic outcomes are compared in Table 5.

The principal roles of hydrogel platforms in chemotherapy, radiotherapy, immunotherapy, hyperthermia, and photothermal or photodynamic therapy are summarized in Figure 4.

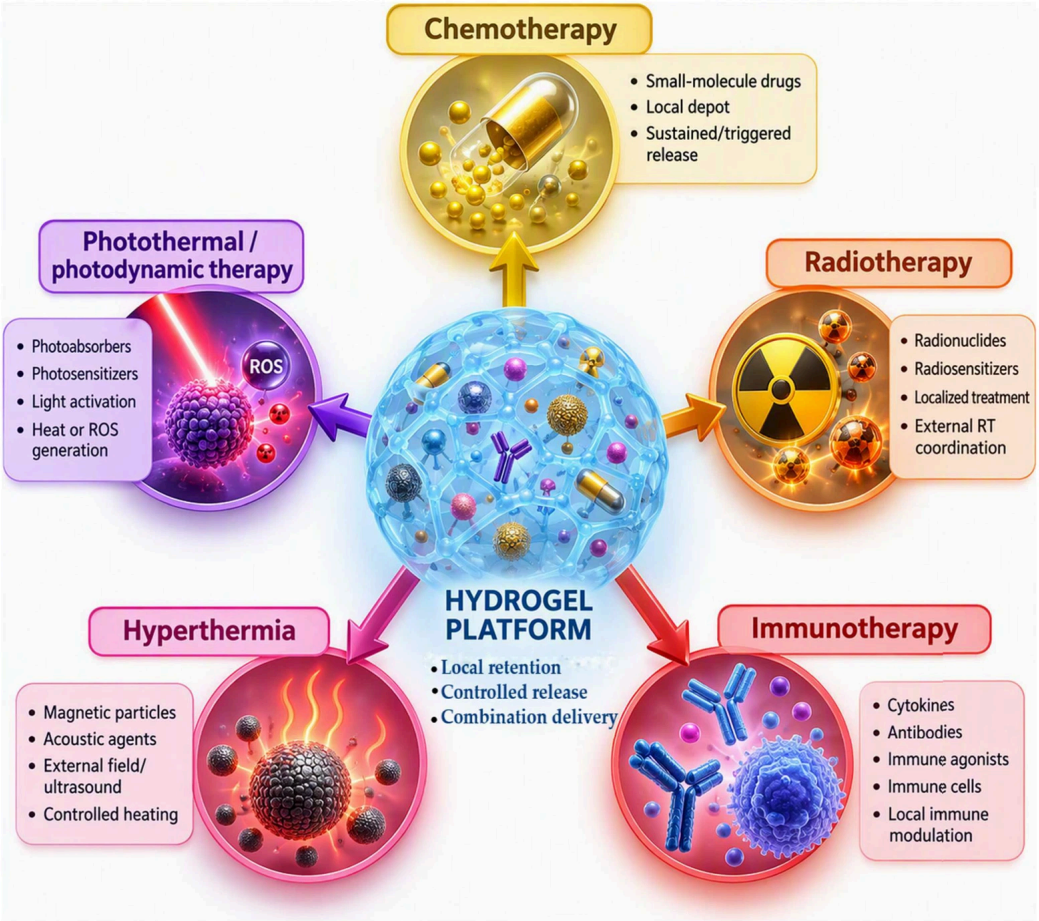


Figure 4. Hydrogel-based platforms for localized cancer therapy. Hydrogels enable local retention, controlled release, and combination delivery of therapeutic agents for chemotherapy, radiotherapy, immunotherapy, hyperthermia, and photothermal/photodynamic therapy.

The contribution of the hydrogel should be evaluated using modality-appropriate controls, including the free payload, unloaded hydrogel, nonactivated formulation where applicable, individual therapeutic components, and an appropriate standard-of-care comparator. For externally activated treatments, material activation, such as heating, reactive-oxygen-species generation, or accelerated release, should be distinguished from therapeutic benefit. The following subsections examine the formulation requirements, therapeutic evidence, and principal limitations associated with each modality.

6.1. Hydrogel-Based Chemotherapy

Systemic chemotherapy is frequently limited by nonspecific biodistribution, rapid clearance, dose-limiting toxicity, poor intratumoral penetration, and drug resistance. Injectable, implantable, and in situ-forming hydrogels can retain chemotherapeutic agents at intratumoral, peritumoral, intraperitoneal, transarterial, or postoperative sites and regulate their release through diffusion, swelling, degradation, or drug–matrix interactions [9,15–17].

Chemotherapeutic agents may be incorporated directly into a hydrogel or first loaded into liposomes, micelles, nanoparticles, or other carriers embedded within the matrix. Carrier-in-hydrogel systems can improve payload solubilization, protection, and sequential release but introduce additional variables related to carrier size, aggregation, distribution, leakage, stability, and manufacturing reproducibility [10–12,16,17,49]. A sustained bulk-release profile does not establish that an intact carrier is released, retains its original properties, or reaches the intended cellular compartment.

Evaluation should therefore include drug loading, content uniformity, burst and cumulative release, mass balance, residual drug within the depot, systemic exposure, spatial payload distribution, hydrogel degradation, and clearance. Appropriate controls should include the free drug, unloaded hydrogel, and, where relevant, nonresponsive or carrier-only formulations. Therapeutic benefit should be demonstrated through tumor response, recurrence, survival, and local and systemic safety rather than inferred from prolonged release alone [9,10,15–17].

Hydrogel-based chemotherapy is particularly relevant when local administration addresses a defined clinical limitation, such as postoperative residual disease, peritoneal dissemination, restricted vascular delivery, or dose-limiting systemic toxicity. Detailed formulation-specific outcomes are presented in Table 5 and the cancer-specific subsections.

6.2. Hydrogel-Assisted Radiotherapy

Hydrogels may complement radiotherapy by localizing radionuclides, radiosensitizers, chemotherapeutics, antiangiogenic agents, oxygen-modulating materials, or immune modulators at the treatment site. These strategies have been investigated in external-beam radiotherapy, brachytherapy, postoperative irradiation, and combined chemoradiotherapy.

An injectable hyaluronic acid–tyramine hydrogel containing endostatin was combined with radiotherapy to modulate tumor vasculature, reduce hypoxia, and improve the radiation response in a preclinical lung-cancer model [201]. Because vascular normalization is dose- and time-dependent, the resulting changes in perfusion and oxygenation should not be generalized beyond the evaluated formulation and treatment schedule.

Thermosensitive hydrogels containing gold nanoparticles and doxorubicin have also been developed for localized chemoradiotherapy, with the nanoparticles acting as radiosensitizers and doxorubicin providing complementary cytotoxicity [191]. Hydrogels can additionally localize therapeutic radionuclides. In a preclinical hepatocellular-carcinoma model, a PCL–PEG–PCL hydrogel co-delivering ^{188}Re sulfur colloid and paclitaxel-loaded micelles prolonged intratumoral radionuclide retention and improved tumor-growth control relative to the corresponding single-modality comparators [192].

Radiotherapy-associated hydrogels should be evaluated using radiation type, dose, dose rate, fractionation, treatment timing, irradiation geometry, radionuclide or radiosensitizer retention, absorbed-dose distribution, systemic leakage, organ exposure, and adjacent-tissue toxicity. A hydrogel that delivers a radionuclide or radiosensitizer should not automatically be described as radiation-responsive. Such terminology requires evidence of radiation-induced structural change, degradation, crosslinking, or payload release under treatment-relevant conditions.

6.3. Hydrogel-Based Immunotherapy

Cancer immunotherapy is often restricted by inadequate immune-cell infiltration, limited tumor immunogenicity, macromolecular transport barriers, and an immunosuppressive tumor microenvironment. Hydrogels can provide localized delivery of check-

point inhibitors, immune agonists, cytokines, antigens, enzymes, nucleic acids, immune-modulating small molecules, or therapeutic cells [16,17,47].

Localized immunotherapy may promote antigen presentation, dendritic-cell maturation, tumor-associated macrophage repolarization, cytotoxic-lymphocyte recruitment, checkpoint inhibition, or immunogenic cell death. These outcomes should be evaluated individually because immune-cell recruitment does not necessarily establish activation, and primary-tumor control does not establish systemic immunity or durable immune memory.

A melittin–RADA32 peptide hydrogel containing doxorubicin inhibited primary melanoma growth and was associated with natural-killer-cell recruitment, dendritic-cell activation, cytotoxic T-cell responses, and a reduction in M2-like macrophages [88]. A compositionally distinct melittin–(RADA)6 hydrogel containing the Ca^{2+}/calmodulin-dependent protein kinase II inhibitor KN93 induced immunogenic tumor-cell death and enhanced the response to anti-PD-1 treatment in a hepatoma-ascites model [89]. These systems illustrate the potential to coordinate local tumor-cell killing with immune activation, but melittin-containing formulations require rigorous evaluation of hemolysis, systemic leakage, peptide degradation, immunogenicity, and repeated-dose toxicity [202].

Hydrogel-immunotherapy studies should assess immune-cell phenotypes and functional activation, cytokine profiles, antigen presentation, distant-tumor responses, recurrence, rechallenge protection, survival, and systemic immune-related toxicity. Claims of systemic immunity or immune memory require direct evidence and should not be inferred solely from local tumor suppression.

6.4. Hydrogel-Assisted Hyperthermia

Hyperthermia uses controlled heating, generally at approximately 39–45 °C, to sensitize tumors to chemotherapy, radiotherapy, or immunotherapy. It should be distinguished from thermal ablation, which uses higher temperatures to produce direct coagulative tissue destruction. Hyperthermia can impair protein homeostasis, mitochondrial function, membrane integrity, and DNA-damage repair while modifying perfusion, oxygenation, antigen release, and immune activity [199].

Thermoresponsive hydrogels and hyperthermia-generating systems are also distinct. Thermoresponsive hydrogels undergo temperature-dependent swelling, network reorganization, or sol–gel transition and can form local depots near physiological temperature [197,198,200]. These changes do not themselves generate a therapeutic thermal dose. Hyperthermia requires an external or internally activated energy-conversion mechanism, such as light absorption, magnetic particles exposed to an alternating magnetic field, radiofrequency or microwave energy, or focused ultrasound.

Hydrogels can support magnetic hyperthermia by retaining magnetic particles at the treatment site. For example, an injectable mPEG-*b*-PLV hydrogel containing Fe_3O_4 nanoparticles generated local heating under an alternating magnetic field and induced ROS accumulation, lipid peroxidation, mitochondrial damage, ferroptosis, autophagy, and apoptosis in preclinical hepatocellular carcinoma models [188].

Thermal studies should report the energy source, field strength or power density, frequency, exposure duration, heating rate, minimum and maximum intratumoral temperatures, spatial temperature distribution, cumulative thermal dose, treatment depth, repeated-exposure effects, and adjacent-tissue heating. Heating or temperature-triggered release demonstrates material activation but does not independently establish improved tumor control. Efficacy must be assessed using tumor response, recurrence, survival, systemic exposure, and normal-tissue injury.

6.5. Photothermal and Photodynamic Therapy

Photothermal therapy converts absorbed light into heat, whereas photodynamic therapy activates a photosensitizer to generate reactive oxygen species, particularly singlet oxygen [182,203,204]. Hydrogels can retain photoactive agents at intratumoral or postoperative sites and coordinate their activity with chemotherapy or immunotherapy.

Photothermal systems may incorporate organic dyes, carbon-based materials, metallic particles, semiconductor materials, or conjugated polymers. Local hydrogel retention can reduce immediate dispersion, but it does not eliminate absorber-specific toxicity, systemic leakage, uneven heating, or off-target tissue injury. Photodynamic therapy is additionally limited by light attenuation, photobleaching, variable photosensitizer distribution, and tumor hypoxia.

An ROS-responsive and Raman-traceable hydrogel was developed to co-deliver a photosensitizer and an immune-checkpoint-blockade antibody. During photodynamic treatment, the hydrogel protected the antibody from excessive ROS exposure and underwent ROS-mediated degradation to release its payloads. The formulation inhibited postoperative recurrence, metastasis, and rechallenged-tumor growth in the evaluated model [177]. This system illustrates the dual role of ROS as both a therapeutic mediator and a trigger for hydrogel degradation.

Photothermal and photodynamic activities can also be integrated within one material. An injectable hydrogel formed from amino-modified carbon dots and aldehyde-functionalized cellulose nanocrystals used the carbon dots as both crosslinking and photoactive components. The carbon dots exhibited a photothermal-conversion efficiency of 77.6% and a singlet-oxygen quantum yield of 0.37 under 660 nm irradiation [71]. Because 660 nm light has limited penetration in deep tissues, these photophysical properties should not be interpreted independently as evidence of broad clinical applicability.

Phototherapy studies should report wavelength, irradiance, fluence, exposure duration, treatment geometry, tissue depth, intratumoral light and temperature distributions, photobleaching, oxygen availability, ROS production, systemic leakage, adjacent-tissue injury, hydrogel degradation, and clearance. Heating, fluorescence, singlet-oxygen generation, or increased release represents activation of the formulation rather than proof of therapeutic superiority.

6.6. Comparative Evaluation of Therapeutic Modalities

Direct comparison among hydrogel-based therapeutic modalities is difficult because studies differ in polymer composition, payload definition, administration route, tumor model, release conditions, treatment schedule, observation period, and clinical endpoint. Loading capacity, encapsulation efficiency, release, local retention, tumor-associated fluorescence, tumor-growth inhibition, regression, recurrence control, and survival are distinct outcomes and should not be used interchangeably.

Tumor-associated fluorescence may reflect vascular retention, extracellular accumulation, carrier degradation, or release of an imaging label rather than delivery of an intact hydrogel-associated carrier [23,28]. Similarly, ligand functionalization may increase receptor-mediated binding or uptake after the carrier reaches an accessible target but does not necessarily increase total tumor accumulation or overcome inadequate perfusion, stromal barriers, elevated interstitial pressure, or heterogeneous receptor expression [32,34].

Evaluation should therefore connect the following:

Administration → localization → treatment or stimulus exposure → network response → payload release → tissue distribution → cellular or biological interaction → therapeutic effect → hydrogel degradation → systemic clearance.

The strongest evidence combines:

- Hydrogel composition, crosslinking, rheology, and mechanical properties;
- Payload loading, content uniformity, release kinetics, and mass balance;
- Payload stability and retained biological activity;
- Clinically representative administration;
- Intact-carrier and payload tracking;
- Quantitative tumor-to-organ distribution and pharmacokinetics;
- Spatial mapping of the payload, radiation dose, temperature, light, or other applied energy;
- Appropriate targeted versus nontargeted, responsive versus nonresponsive, and stimulated versus unstimulated controls;
- Tumor response, recurrence, survival, and modality-specific biological outcomes;
- Local and systemic toxicity; and;
- Degradation-product identification, biodistribution, and clearance [9,10,16,17].

Multimodal formulations should also be compared with the relevant monotherapies and component controls to determine whether a combination provides additive or synergistic benefit. Additional components may increase functional capability but also increase the number of critical quality attributes, manufacturing variables, analytical requirements, degradation products, and potential failure modes [10–12]. Multifunctionality should therefore be justified by clinically meaningful improvement rather than technological complexity alone [36,38].

Representative formulation, release, retention, biodistribution, and therapeutic results are compared in Table 5.

Loading capacity, encapsulation efficiency, cumulative release, local retention, tumor-associated signal, tumor-growth inhibition, tumor-volume change, tumor regression, recurrence control, and survival represent distinct formulation or biological outcomes and should not be treated as interchangeable. Tumor-growth inhibition refers to a calculated comparative percentage, whereas a lower increase in relative tumor volume should not be classified as tumor regression unless tumor size decreases below its pretreatment value. Similarly, increased local retention or higher tumor-associated signal does not establish tumor targeting without quantitative tumor-to-normal-tissue distribution data. Reduced postoperative recurrence should not be described as complete recurrence prevention unless all treated subjects remain recurrence-free throughout the predefined observation period, and survival improvement should be stated only when survival was formally evaluated. Accordingly, prolonged release or local retention alone should not be interpreted as evidence of therapeutic superiority.

6.7. Cancer-Specific Applications of Biopolymer Hydrogels

The clinical requirements of hydrogel-based treatment vary substantially with tumor anatomy, disease dissemination, accessibility, treatment stage, and standard clinical workflow. Colorectal and gastric cancers may permit oral, endoscopic, intraperitoneal, or postoperative delivery; hepatocellular carcinoma can be approached through intratumoral or transarterial administration; pancreatic cancer requires strategies compatible with a dense stroma and anatomically constrained delivery; and breast cancer provides opportunities for intratumoral, neoadjuvant, and postoperative-cavity treatment. Hydrogel selection should therefore be based on a defined disease-specific barrier rather than on material novelty alone. Representative quantitative formulation, release, retention, biodistribution, and therapeutic results are summarized in Table 5.

Table 5. Critical comparison of representative hydrogel systems for cancer therapy.

Cancer/Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
Ovarian cancer model	Chemotherapy	Diels–Alder-crosslinked oxaliplatin hydrogel, hydrogel–OxPt	Oxaliplatin	NR	78.8% released over 7 days; release fitted the Higuchi model, R^2 = 0.9179, and Korsmeyer–Peppas model, R^2 = 0.8924	Sustained oxaliplatin exposure and cytotoxic activity in ovarian-cancer cells	Evidence was principally in vitro; loading, in vivo efficacy, biodistribution, degradation, and clearance require evaluation	[205]
Gastric cancer with peritoneal dissemination	Intraperitoneal chemotherapy	In situ-crosslinkable HA–adipic dihydrazide/HA–aldehyde hydrogel	Cisplatin	NR	Local cisplatin release was maintained for approximately 4 days	Reduced peritoneal tumor burden relative to the comparator groups in a preclinical model	Short release period; loading was not quantified, and pharmacokinetics, survival, systemic exposure, and long-term clearance were not assessed	[206]
Gastric cancer with peritoneal dissemination	Intraperitoneal chemotherapy	Cisplatin-loaded HA nanogel incorporated into an injectable HA hydrogel	Cisplatin	Cisplatin loading efficiency: 17 wt%; administered dose: 20 µg per treatment	87% release within 72 h from the 1 wt% HA formulation; 81%	Significantly fewer total peritoneal nodules than with free cisplatin, p =	Limited activity against nodules > 1.0 mm; the 2 wt% formulation increased blood	[207]

Cancer/ Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
					release over 7 days from the 2 wt% formulation	0.032; mean number of nodules < 1.0 mm: 1.9 versus 14.4 with free cisplatin	urea nitrogen; survival and long-term clearance were not assessed	
Gastric cancer; MKN45 subcutaneous xenograft and peritoneal-dissemination models	Nanoparticle-assisted local chemotherapy	Thermosensitive PEG-modified BSA hydrogel containing paclitaxel-loaded red-blood-cell-membrane nanoparticles, PRNP-gel	Paclitaxel	Loading efficiency: 85.45 ± 1.32%; loading content: 22.10 ± 0.25%	23% paclitaxel release at 10 h and 36% at 144 h; gelation within 11.75 min at 37 °C; tumor-site retention detected through day 7	Tumor-growth inhibition was 64.53% in the subcutaneous model; peritoneal nodule count was 19.0 ± 8.0 versus 34.25 ± 11.67 following free paclitaxel	Incomplete cumulative release, animal-derived components, and limited long-term and clinically representative safety data	[208]
Colorectal cancer; orthotopic CT26-Luc and subcutaneous CT26 mouse models	Oral chemo-immunomodulatory therapy	Oxa@HMI inulin hydrogel containing hollow MnO_2 nanocarriers	Oxaliplatin	Encapsulation efficiency: 64.5 wt%; drug-loading capacity: 45.0 wt%	pH- and inulinase-responsive release; approximately threefold higher tumor-associated fluorescence than with	Lower orthotopic tumor burden than in the control groups and marked inhibition of subcutaneous	Performance may depend on intestinal transit and microbiota composition; long-term MnO_2 clearance,	[209]

Cancer/ Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
					nanoparticle only treatment at 24 h	CT26 tumor growth after oral administration at 20 mg/kg/day for 14 days	pharmacokinetics, and repeated-dose safety remain unresolved	
Colorectal cancer with peritoneal metastasis; CT26 mouse model	Local chemotherapy	Thermosensitive methylcellulose-based injectable hydrogel	Oxaliplatin	NR	Complete oxaliplatin release at approximately 48 h versus 6 h for free oxaliplatin; gelation within 90 s at 37 °C; fluorescence-based local retention detected through day 7	Reduced tumor-nodule number versus saline, $p < 0.01$, and reduced nodule weight versus saline, $p < 0.001$, and free oxaliplatin, $p < 0.01$	Loading was not quantified; retention was measured using a fluorescent surrogate; pharmacokinetics, survival, and long-term clearance were not assessed	[72]
HepG2 hepatocellular carcinoma cells	Redox- and pH-responsive chemotherapy	Alginate hydrogel containing a glutamic acid–cysteine dendrimer with internal disulfide bonds and physically	Doxorubicin	NR	Cumulative doxorubicin release was 35% at pH 7.4, 56% at pH 5.5, 62% with 10 mM GSH at pH 7.4, and	Time- and concentration-dependent cytotoxicity against HepG2 cells; activity was weaker than that of free	Loading was not quantified; in vitro evidence was limited to in vitro testing, and 10 mM GSH primarily represents	[173]

Cancer/ Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
		crosslinked with PEG			76% with 10 mM GSH at pH 5.5	doxorubicin at 24 h but comparable after 72 h	an intracellular rather than extracellular tumor condition	
Pancreatic cancer; Panc-1 xenograft model	Local chemotherapy	Injectable PCLA–PEG–PCLA nanobiohybrid thermogel containing montmorillonite–gemcitabine complexes	Gemcitabine	Initial gemcitabine content: 10 mg/g hydrogel, approximately 1 wt%; loading efficiency: NR	At 12 h, gemcitabine release was 12% from the nanobiohybrid hydrogel versus approximately 40% from the hydrogel without montmorillonite; the depot retained 31 wt% of its initial dry mass after 8 weeks in vivo	Tumor-growth inhibition was 81% after 8 weeks versus 65% with free gemcitabine; tumor volume increased approximately fivefold from baseline versus approximately tenfold with free gemcitabine	Small exploratory cohort, subcutaneous rather than orthotopic model, and no pharmacokinetic, biodistribution, or long-term montmorillonite-clearance data	[210]
Pancreatic cancer; PANC-1 xenograft model	NIR-II-triggered chemo-photothermal therapy	Thermosensitive 15 wt% PDLLA–PEG–PDLLA Lip-Gel containing DG@Lips	Gemcitabine and DPP–BTz	NR	62% gemcitabine release after 120 min of intermittent 1064 nm irradiation;	The reported tumor-growth-inhibition rate was 91.73% after one intratumoral	Encapsulation was not quantified; the study used a subcutaneous model, and thermal	[211]

Cancer/ Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
					87% DG@Lips release from the hydrogel over 96 h; gel formation within approximately 1 min at 37 °C	injection combined with 1064 nm irradiation	dosimetry, pharmacokinetics, systemic leakage, adjacent-tissue injury, and long-term safety require evaluation	
Triple-negative breast cancer; postoperative orthotopic mouse model	Postoperative NK-cell immunotherapy	Injectable oxidized starch/gelatin GOSAM hydrogel containing drug-loaded mesoporous bioactive-glass nanoparticles	SAHA and 3-methyladenine, combined with UCB-NK cells	NR	At day 21, SAHA release was 91.6% at pH 6.5 versus 29.6% at pH 7.4; 3-methyladenine release was 92.3% versus 28.1%, respectively; fluorescent drug signals persisted at the resection site for at least 14 days	Enhanced UCB-NK-cell-mediated antitumor activity and reduced postoperative TNBC recurrence during the reported observation period; the hydrogel also supported hemostasis and wound healing	Loading was not quantified; retention was measured using fluorescently labelled drugs, and long-term degradation, biodistribution, systemic leakage, and manufacturing reproducibility require evaluation	[91]
TNBC and melanoma; 4T1 and B16F10	Chemo-immunomodulatory therapy	Injectable supramolecular p(THMA-APMA)/HA hydrogel	Doxorubicin and kynureninase	NR	A single low-dose peritumoral administration	Inhibited primary-tumor growth, prolonged	Loading and release were not	[212]

Cancer/ Model	Modality	Hydrogel Formulation	Payload or Therapeutic Component	Loading or Encapsulation	Quantitative Release or Retention Outcome	Biological or Therapeutic Outcome	Principal Limitation	Ref.
mouse models					provided concurrent local delivery; a directly comparable cumulative-release percentage was not reported	survival relative to the control groups, produced a distant-tumor response, and reduced postoperative recurrence in the evaluated models	standardized; enzyme stability, activity, immunogenicity, biodistribution, batch reproducibility, and feasibility of peritumoral administration require evaluation	
Hepatocellular carcinoma; subcutaneous BNL hepatoma mouse model	Local chemo-radionuclide therapy	Injectable 25% PCL–PEG–PCL thermosensitive hydrogel containing ^{188}Re sulfur colloid and paclitaxel-loaded micelles	^{188}Re sulfur colloid and paclitaxel	^{188}Re radiolabelling efficiency > 95%; paclitaxel concentration 2 mg/mL; paclitaxel encapsulation efficiency NR	Paclitaxel release remained <10%; tumor-associated radioactivity was 49.2 ± 11.9%, 36.6 ± 12.4%, and 36.3 ± 11.5% of the injected dose at 1, 8, and 48 h, respectively	On day 10, relative tumor volume was 291.54 ± 79.09% in the combination group versus 642.81 ± 113.99% with paclitaxel-micelle hydrogel; survival was significantly prolonged relative to the corresponding monotherapy groups	Small cohorts, subcutaneous model, absence of a hydrogel-embedded ^{188}Re-only control, limited dosimetry, and insufficient long-term hepatic-safety data	[192]

Note: Values were extracted under the experimental conditions reported in the original studies

and should not be interpreted as a direct ranking of formulation performance. Differences in hydrogel composition, geometry, release conditions, administration route, tumor model, comparator, dosing schedule, observation period, and endpoint definition limit cross-study comparability. NR, not reported or not reliably comparable.

6.7.1. Hydrogels in the Treatment of Colorectal Cancer

Colorectal cancer (CRC) is a major gastrointestinal malignancy with substantial metastatic potential [213,214]. Surgery, chemotherapy, and radiotherapy remain central treatment modalities, but systemic toxicity, insufficient local drug exposure, recurrence, and peritoneal dissemination continue to limit therapeutic outcomes [215]. Hydrogel-based formulations offer several routes for localized treatment, including oral colon-targeted delivery, rectal administration, intraperitoneal depots, and postoperative placement. The structure-dependent release mechanisms and mathematical models applicable to these systems are discussed in Sections 3.2 and 3.3; this subsection therefore focuses on their anatomical suitability and therapeutic performance in CRC. Representative quantitative formulation, release, retention, and therapeutic outcomes are compared in Table 5.

For postoperative intraperitoneal chemotherapy, oxaliplatin-loaded PLGA microparticles have been incorporated into crosslinked hyaluronic acid/sodium carboxymethyl cellulose (HA/CMCNa) hydrogels. The composite formulation prolonged oxaliplatin release, increased intraperitoneal bioavailability and residence time, and reduced postoperative peritoneal adhesion in rats [216]. This platform illustrates the potential to combine localized chemotherapy with a physical antiadhesion barrier. However, improved peritoneal pharmacokinetics should not be equated with uniform exposure of all metastatic nodules, and future studies should quantify spatial drug distribution, systemic leakage, bowel adhesion, local inflammation, and hydrogel clearance.

Oral polysaccharide hydrogels have been investigated to protect therapeutic agents during upper gastrointestinal transit and promote release in the colon. Alginate/CMC hydrogels carrying methotrexate and aspirin provided payload protection followed by preferential release under colonic conditions [73]. Other oral systems included folic acid-functionalized alginate nanoparticles incorporated into a hydrogel matrix for pH-dependent delivery of curcumin (diferuloylmethane) [217]. These formulations exploit gastrointestinal transit, pH variation, polymer degradation, and mucosal accessibility, but their performance may be affected by food intake, transit time, mucus turnover, inflammation, and interpatient variability in the intestinal microbiota.

Hydrogel mechanics and interfacial properties may additionally affect tumor behavior and local retention. Type I collagen hydrogels demonstrated stiffness-dependent regulation of CRC-cell migration [218], whereas vitamin D-functionalized ABA triblock hydrogels improved the local delivery and therapeutic activity of bevacizumab in an animal model of metastatic CRC [219]. Poly(acrylic acid)-grafted cellulose nanocrystal hydrogels exhibited mucin-responsive rheology and prolonged local cisplatin delivery [74]. Chitosan–chondroitin sulfate hydrogels containing curcumin and silver nanoparticles have also been combined with photodynamic treatment to enhance singlet-oxygen-mediated cytotoxicity [220]. Collectively, these studies indicate that stiffness, mucoadhesion, rheology, payload organization, and administration route can be as consequential as polymer identity.

A multifunctional oral platform was developed using an inulin-based hydrogel containing oxaliplatin-loaded hollow MnO_2 nanocarriers, designated Oxa@HMI (Figure 5 A,B) [209]. The preparation sequence is illustrated in Figure 5A: hollow MnO_2 nanocarriers were fabricated using a silica template, loaded with oxaliplatin, coated with inulin, and incorporated into the hydrogel matrix. Following oral administration, the formula-

tion remained stable during upper gastrointestinal transit and underwent inulinase-mediated degradation in the colon (Figure 5B). Fermentation of the inulin matrix generated short-chain fatty acids, including butyrate, while microbiota modulation contributed to regulation of the tumor immune microenvironment. Degradation of the matrix also exposed the oxaliplatin-loaded hollow MnO_2 nanocarriers, enabling local oxaliplatin release and MnO_2-associated modulation of oxidative stress and oxygen availability [209].

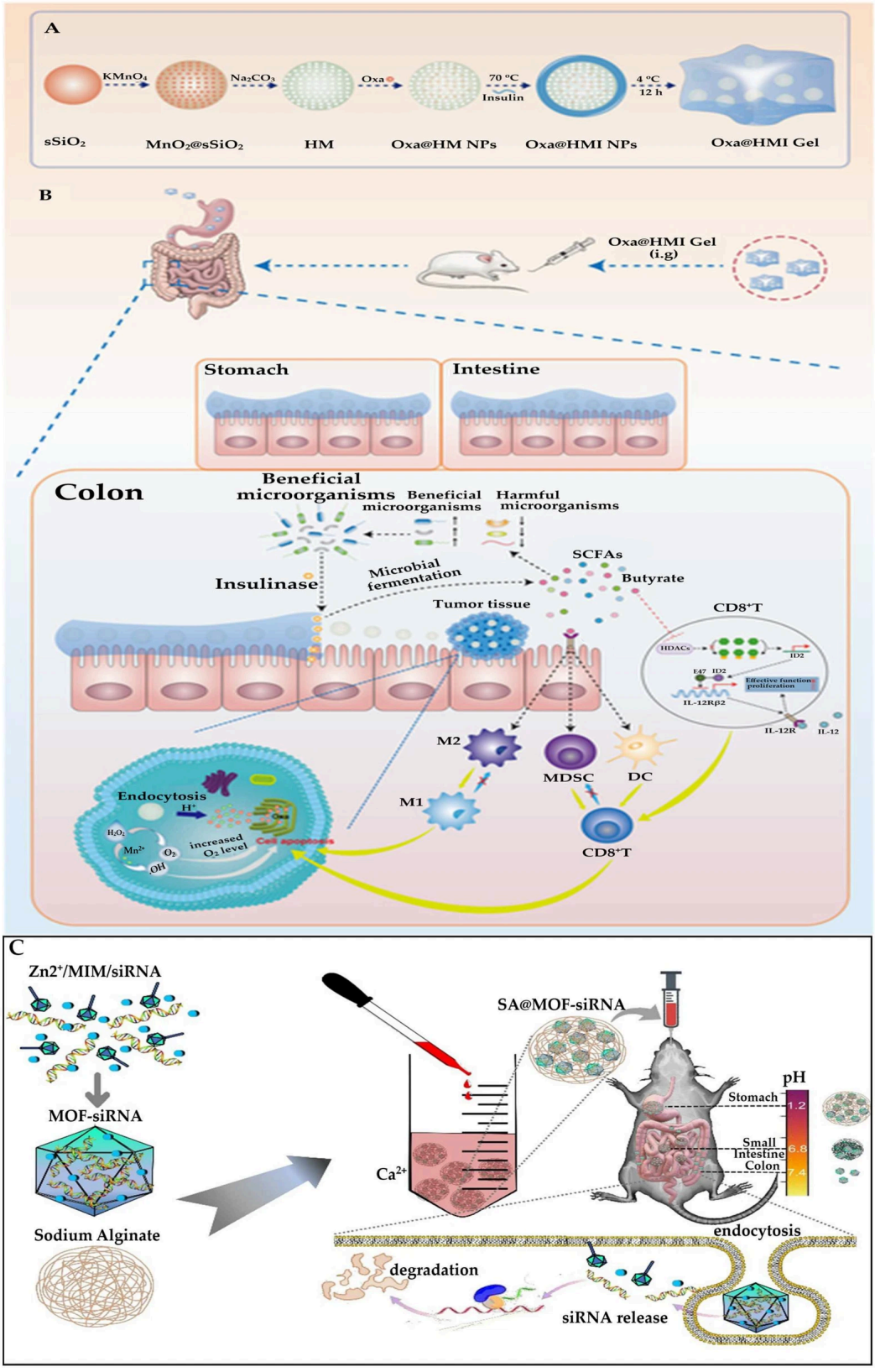


Figure 5. Representative biopolymer-based hydrogel systems for colon-targeted therapeutic applications. (**A**) Preparation of the inulin-based Oxa@HMI hydrogel incorporating oxaliplatin-loaded hollow MnO_2 nanoparticles. (**B**) Proposed mechanism of Oxa@HMI hydrogel-mediated colorectal cancer therapy through microbiota modulation, short-chain fatty acid (SCFA) production, immune microenvironment regulation, and enhanced antitumor activity [209]. (**C**) Sodium alginate–metal–organic framework hybrid hydrogel (SA@MOF-siRNA) for pH-responsive oral delivery of TNF-α-

targeting siRNA in an inflammation-associated colorectal disease model [221].

The Oxa@HMI strategy is particularly relevant to CRC because it combines colon-oriented delivery with the prebiotic and immunomodulatory properties of inulin. Its performance, however, may vary with gastrointestinal transit, diet, antibiotic exposure, microbiota composition, inulinase activity, and disease-associated dysbiosis. Evidence of stability in simulated gastric and intestinal fluids should therefore be supplemented by quantitative measurement of colonic retention, intact-nanocarrier distribution, oxaliplatin exposure, systemic leakage, microbiota changes, degradation products, and therapeutic outcomes. The corresponding quantitative results are summarized in Table 5.

Chitosan-based microbead hydrogels have similarly been evaluated for oral bevacizumab delivery. Their mucoadhesive and pH-responsive properties protected the payload during gastrointestinal transit and facilitated release in the colonic region, producing antitumor activity in cellular and murine CRC models [222]. For local rectal or colonic administration, poloxamer P407/P188–alginate hydrogels underwent gelation near physiological temperature and exhibited shear-thinning behavior, potentially facilitating administration and retention at the treatment site [223]. Drug release from these formulations was predominantly diffusion-controlled under the reported experimental conditions [223]. Clinical translation will require assessment under dynamic conditions that reproduce intestinal fluid flow, mucus renewal, motility, fecal contact, and repeated mechanical deformation.

Hydrogels have also been investigated for multimodal CRC treatment. Injectable PDLLA–PEG–PDLLA hydrogels co-delivering oxaliplatin and the TLR7/8 agonist R848 promoted immunogenic tumor-cell death, dendritic-cell maturation, and T-cell activation in preclinical models of advanced CRC with peritoneal metastasis [224]. Other systems combined copper-dependent cell death, immune regulation, and radiotherapy through localized delivery of copper-associated therapeutic components [225,226]. Supramolecular hydrogels containing indocyanine green and bortezomib supported combined chemotherapy, photothermal therapy, and photodynamic therapy [227]. Although such multifunctional systems may enhance treatment activity, the contribution of each component should be established using relevant monotherapy and component-control groups. Added complexity also increases the requirements for sterilization, payload-stability testing, sequential-release analysis, batch reproducibility, degradation assessment, and quality control.

Sodium alginate–metal–organic framework composites have been investigated for oral delivery of TNF-α-targeting siRNA (SA@MOF-siRNA; Figure 5C) [221]. As illustrated in Figure 5C, siRNA-loaded MOF particles were encapsulated within a Ca^{2+}-crosslinked sodium alginate matrix to protect the nucleic-acid payload during gastrointestinal transit and facilitate release in the colon. The formulation increased colonic delivery, reduced TNF-α expression, and alleviated disease severity in a murine ulcerative colitis model [221]. However, the system was not evaluated in an established CRC model. This panel should therefore be interpreted as demonstrating an inflammation-associated colorectal delivery strategy with possible relevance to CRC prevention or inflammation-driven carcinogenesis, not as direct evidence of antitumor efficacy.

Overall, polysaccharide-based hydrogels are particularly suited to colorectal cancer because the gastrointestinal tract permits oral, rectal, endoscopic, intraperitoneal, and postoperative administration. Oral and rectal systems can exploit regional pH changes, colonic microbiota or enzyme-mediated degradation, mucoadhesion, and prolonged mucosal residence, whereas intraperitoneal and postoperative depots are more appropriate for residual disease and peritoneal dissemination. These advantages do not necessarily produce tumor-selective exposure, because gastrointestinal transit, mucus re-

newal, motility, fecal contact, microbiota variability, and lesion depth can alter hydrogel retention and release. Future studies should therefore use clinically representative gastrointestinal, postoperative, and metastatic models and quantify spatial payload distribution, local toxicity, systemic exposure, microbiota-dependent variability, recurrence, degradation, and long-term clearance.

6.7.2. Hydrogels in the Treatment of Gastric Cancer

Gastric cancer (GC) remains a major cause of cancer-related morbidity and mortality, particularly in East Asia. Surgery, chemotherapy, and radiotherapy remain the principal treatment modalities, but drug resistance, systemic toxicity, postoperative recurrence, and peritoneal dissemination continue to limit treatment outcomes [228]. Hydrogel formulations are therefore being investigated as intraoperative and intraperitoneal depots that can maintain therapeutic agents near primary tumors, disseminated peritoneal lesions, or postoperative residual disease. The structure-dependent release mechanisms and mathematical models applicable to these formulations are discussed in Sections 3.2 and 3.3; this subsection focuses on their anatomical suitability, biological interactions, and therapeutic relevance in GC. Representative quantitative loading, release, retention, and therapeutic outcomes are compared in Table 5.

Biodegradable PDLLA–PEG–PDLLA thermogels have been developed for the intraoperative co-delivery of cisplatin and 5-fluorouracil. Following administration, these formulations form localized depots that prolong drug exposure within the surgical region. In preclinical GC models, the combination hydrogel induced tumor-cell apoptosis, reduced residual and metastatic tumor growth, and improved survival relative to the corresponding free-drug treatment (Figure 6A) [229]. This approach is relevant to postoperative GC because direct placement can expose residual disease and peritoneal tumor deposits that may receive insufficient drug concentrations after systemic administration. Its clinical feasibility will nevertheless depend on depot distribution across irregular surgical surfaces, gelation under diluted physiological conditions, burst release, interference with wound healing, and systemic leakage.

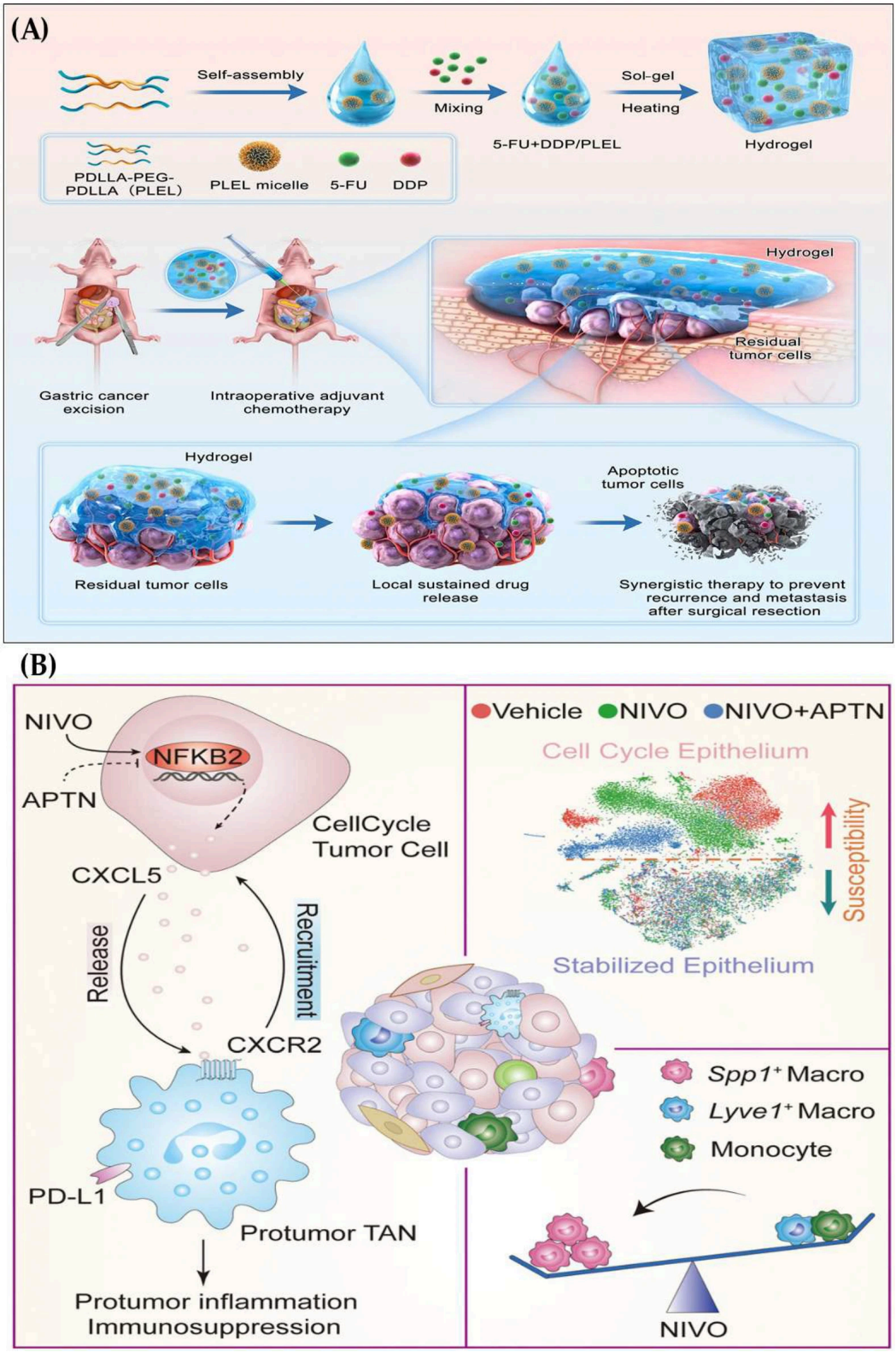


Figure 6. Representative hydrogel-related strategies for gastric cancer therapy. (**A**) Thermosensitive PDLLA–PEG–PDLLA hydrogel for intraoperative co-delivery of 5-fluorouracil and cisplatin in gastric cancer [229]. (**B**) Immunosuppressive characteristics of the gastric cancer microenvironment that limit anti-PD-1 therapy and provide a rationale for locally delivered immunomodulatory treatments [230].

Hyaluronic acid (HA)-based hydrogels have also been investigated as intraperitoneal cisplatin depots. An in situ-crosslinkable matrix formed from HA–adipic dihy-

drazide and HA–aldehyde sustained cisplatin release for more than four days and reduced the weight of disseminated peritoneal tumor nodules in a murine GC model, whereas free cisplatin showed no significant antitumor effect under the reported conditions [206]. A subsequent hybrid system incorporated cisplatin-loaded HA nanogels within an injectable HA hydrogel, thereby introducing an additional barrier to payload diffusion and extending nanogel release [207]. The hybrid formulation showed substantial activity against small disseminated nodules but lower activity against larger lesions [207]. This size-dependent outcome indicates that prolonged peritoneal residence does not necessarily provide deep or homogeneous drug penetration into established tumor nodules.

A PEG-modified bovine serum albumin hydrogel containing paclitaxel-loaded red-blood-cell-membrane nanoparticles provided another localized chemotherapeutic strategy [208]. The nanoparticle component increased paclitaxel incorporation and retention, whereas temperature-induced gel formation limited rapid dispersion from the administration site. The composite system inhibited tumor growth in subcutaneous-xenograft and peritoneal-dissemination models [208]. However, translation would require standardized red-blood-cell-membrane sourcing, control of bovine-serum-albumin variability, assessment of immunogenicity, complete accounting of released and retained paclitaxel, and evaluation of long-term intraperitoneal degradation and safety. The principal quantitative results are summarized in Table 5.

Other polymeric systems have been explored for gastric retention and local chemotherapy. Gelatin microsphere–alginate networks have been investigated for prolonged 5-fluorouracil delivery [231]. However, gastric retention alone should not be interpreted as evidence of anticancer efficacy unless the formulation is evaluated in an appropriate GC model. Poly(organophosphazene)-based hydrogels provide an alternative platform in which thermogelation and matrix erosion can be adjusted to support local docetaxel delivery [232]. These systems demonstrate that therapeutic performance depends not only on release duration but also on depot distribution, payload availability, degradation, and contact with tumor deposits.

Thermosensitive formulations have shown particular relevance to GC with peritoneal dissemination. A docetaxel-loaded poly(organophosphazene) hydrogel reduced tumor burden and peritoneal metastasis and improved survival in a preclinical GC model [233]. A docetaxel-loaded Pluronic–conjugated linoleic acid hydrogel similarly induced tumor-cell apoptosis and reduced peritoneal metastatic nodules [234]. Another thermosensitive hydrogel containing gambogic acid-loaded nanoparticles functionalized with the tumor-penetrating peptide iRGD further combined local depot formation with integrin-associated cellular uptake [235]. These systems illustrate that thermogelation can improve intraperitoneal residence, while nanoparticle incorporation and ligand functionalization may influence tumor-cell interactions. However, ligand-mediated uptake should not be treated as evidence that the hydrogel overcomes heterogeneous integrin expression, stromal barriers, or uneven peritoneal distribution.

Injectable hydrogels have also been developed for localized GC immunotherapy. A shear-thinning PEG/polylysine hydrogel co-delivering polyphyllin II and the Toll-like receptor 7/8 agonist resiquimod promoted repolarization of tumor-associated macrophages toward an M1-like phenotype, dendritic-cell activation, and CD8-positive T-cell infiltration [236]. The resulting immune remodeling improved tumor-growth control relative to the evaluated free-drug treatment [236]. Nevertheless, changes in immune-cell abundance or marker expression should be distinguished from sustained functional antitumor immunity, which requires evaluation of cytokine activity, distant-tumor responses, recurrence, rechallenge protection, and systemic immune-related

toxicity.

The immunosuppressive gastric-cancer microenvironment can limit the response to immune-checkpoint blockade. Single-cell analysis of humanized gastric-cancer patient-derived xenografts showed that nivolumab induced CXCL5 expression in proliferating malignant epithelial cells, promoting recruitment of CXCR2-positive protumor tumor-associated neutrophils and reinforcing inflammation-associated immunosuppression. Anti-PD-1 treatment also increased the relative abundance of immunosuppressive SPP1-positive tumor-associated macrophages. Combination treatment with apatinib suppressed epithelial CXCL5 upregulation, reduced protumor neutrophil recruitment, remodeled the myeloid-cell ecosystem, and enhanced sensitivity to anti-PD-1 therapy. These findings provide a mechanistic rationale for hydrogel-based local co-delivery of checkpoint inhibitors and microenvironment-modulating agents to sustain tumor-site exposure while limiting systemic dispersion (Figure 6B) [230].

Local nucleic-acid delivery has likewise been investigated using in situ-forming hydrogels containing siRNA/polyethylenimine complexes. These formulations prolonged local siRNA availability, enhanced intracellular delivery, and suppressed inhibitor-of-DNA-binding-1 expression in preclinical GC models [237]. Because polyethylenimine can produce molecular-weight- and dose-dependent cytotoxicity, clinical development would require evaluation of uncomplexed polymer, siRNA-complex stability, local inflammation, systemic leakage, degradation, and repeated-dose safety.

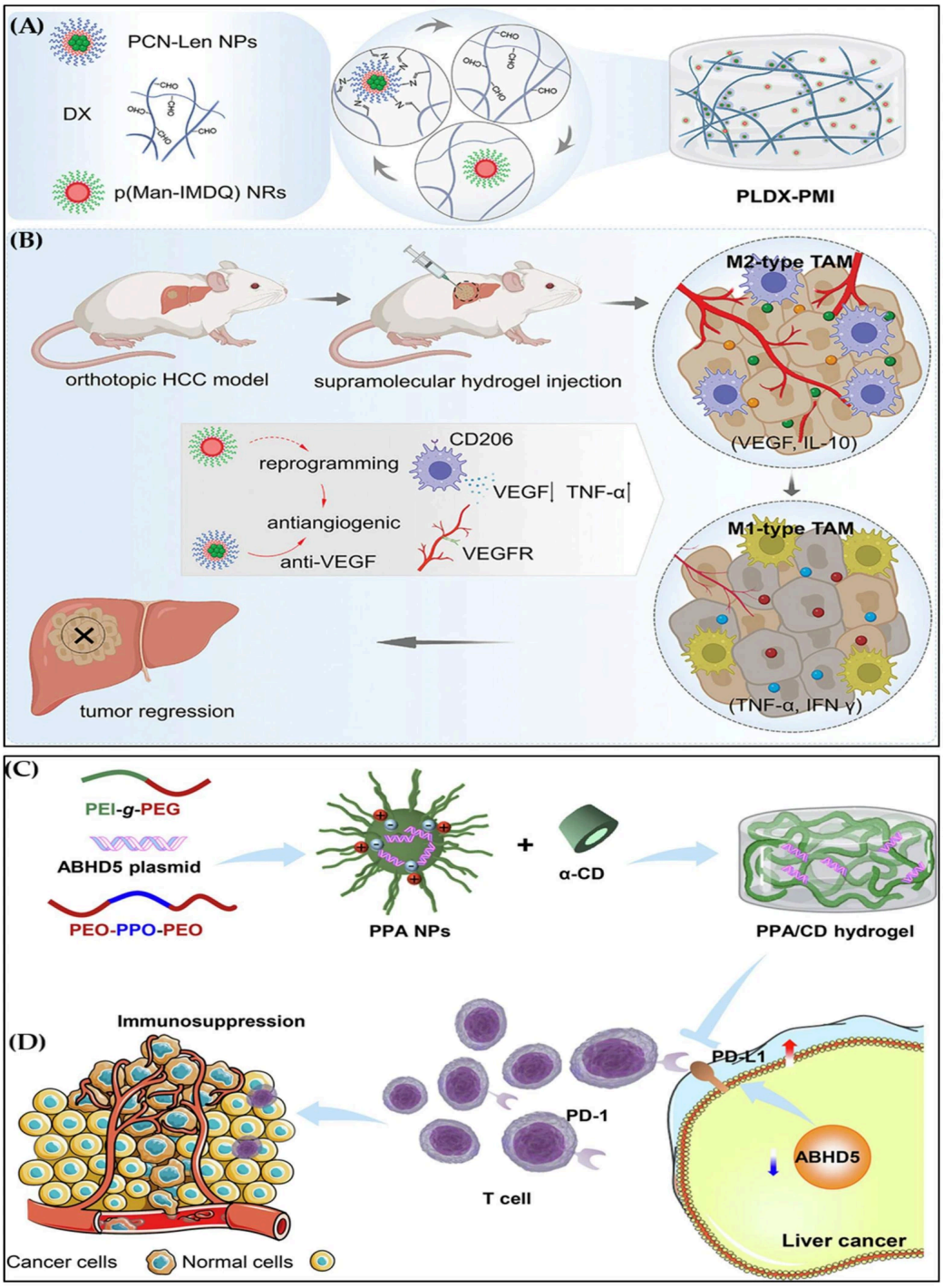
Overall, gastric cancer is accessible to endoscopic injection or placement, while intraperitoneal and in situ-forming hydrogels may support treatment of postoperative residual disease and peritoneal dissemination. Mucoadhesive and thermosensitive systems can improve local retention, but gastric acidity, digestive enzymes, mucus turnover, peristalsis, food-dependent changes, and rapid luminal dilution may destabilize the formulation or alter payload release. Intraperitoneal residence likewise does not establish uniform exposure of disseminated nodules or penetration into larger lesions. Future studies should reproduce clinically relevant gastric and peritoneal conditions and quantify retention, peritoneal pharmacokinetics, lesion-size-dependent penetration, spatial payload distribution, systemic leakage, postoperative adhesion, local inflammation, degradation, clearance, recurrence, and survival.

6.7.3. Hydrogels in the Treatment of Liver Cancer

Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, remains difficult to treat because of frequent recurrence, therapeutic resistance, and underlying hepatic dysfunction [238]. These limitations have encouraged the development of injectable, postoperative, intraperitoneal, and transarterial hydrogels for locoregional treatment [239]. Because hydrogel release mechanisms are discussed in Sections 3.2 and 3.3, this subsection focuses on HCC-specific applications. Representative formulations and therapeutic outcomes are compared in Table 5.

Hydrogels based on hyaluronic acid, poloxamers, PEG-containing copolymers, gelatin, cellulose derivatives, κ-carrageenan, and PNIPAm derivatives have been investigated for HCC treatment [240–244]. A PDLLA–PEG–PDLLA thermogel containing paclitaxel-loaded nanoparticles prolonged local drug exposure and suppressed liver metastatic tumors [245]. For postoperative treatment, PEG–poly(glutamic acid) micelles embedded within a fibrinogen–thrombin hydrogel coordinated hemostasis with local immunotherapy, reducing postoperative recurrence while promoting dendritic-cell maturation and T-cell activation [246]. Such systems require separate evaluation of hemostatic performance, therapeutic release, immune activation, degradation, and hepatic safety.

Hydrogels have also been designed to remodel the HCC microenvironment. The supramolecular PLDX-PMI hydrogel combined lenvatinib-containing nanoparticles with mannose-functionalized polyTLR7/8a nanoregulators (Figure 7A) [247]. Lenvatinib inhibited VEGFR-associated angiogenic signaling, whereas the nanoregulators promoted repolarization of proangiogenic M2-like macrophages toward an M1-like phenotype (Figure 7B). In an orthotopic HCC model, the formulation reduced microvessel density and M2-like macrophage abundance, promoted vascular maturation, and inhibited tumor progression [247]. Glycyrrhetinic-acid-modified curcumin hydrogels have similarly been investigated for receptor-associated uptake and stimulus-dependent release [248]. However, ligand functionalization alone does not establish uniform tumor accumulation or tissue penetration.



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Figure 7. Representative hydrogel-based strategies for hepatocellular carcinoma therapy. (**A**) Composition of the PLDX-PMI supramolecular hydrogel containing PCN-Len nanoparticles, an oxidized-dextran hydrogel network, and macrophage-targeting polyTLR7/8a nanoregulators. (**B**) Proposed antiangiogenic and immunomodulatory mechanism involving VEGFR inhibition and M2-to-M1 tumor-associated macrophage repolarization [247]. (**C**) Construction of the PPA/CD host–guest hydrogel. (**D**) Local ABHD5 gene delivery for modulation of PD-L1-associated signaling and enhancement of T-cell-mediated antitumor immunity [249].

Thermosensitive PCL–PEG–PCL hydrogels have been used to co-localize ^{188}Re sulfur colloid and paclitaxel-loaded micelles within hepatoma tumors [192]. Intratumoral administration prolonged local radioactivity retention, reduced systemic dispersion, and improved tumor control relative to the evaluated comparator groups. Nevertheless, the limited cumulative paclitaxel release may indicate either prolonged confinement or insufficient payload availability. Because the study used a subcutaneous BNL hepatoma model, confirmation in orthotopic HCC models with radiation dosimetry, normal-liver toxicity, and long-term clearance remains necessary.

Responsive hydrogels have also been evaluated for local chemotherapy. PNIPAm-*co*-PAAm hydrogels provided pH- and temperature-dependent curcumin release [250], while self-healing *N*-carboxyethyl chitosan/PEGDA hydrogels showed acid-accelerated doxorubicin release [164]. Porous PNIPAm-based particles enabled co-delivery of 5-fluorouracil and metformin [251], and TPGS-modified Pluronic F127 hydrogels reduced P-glycoprotein-associated drug efflux in resistant HCC cells [252]. These findings demonstrate responsive release and pharmacological activity but do not independently establish tumor-selective delivery.

Immune-evasive mechanisms have been addressed using gene-, virus-, and ferroptosis-based hydrogel systems. The PPA/CD host–guest hydrogel provided sustained local ABHD5 gene delivery, increased transfection, reduced PD-L1-associated immunosuppression, and promoted tumor-cell apoptosis and immune-mediated killing (Figure 7 C,D) [249]. Because the formulation contained branched polyethylenimine, its development requires careful evaluation of cationic-polymer toxicity, inflammation, off-target transfection, and hepatic clearance.

V-Navo@gel co-delivered the IDO1 inhibitor navoximod and herpes simplex virus type 1, creating a local reservoir that enhanced viral replication, oncolysis, and antitumor immunity [253]. The formulation prolonged disease-free survival and reduced postoperative recurrence in HCC-bearing mice and was also evaluated in an orthotopic rabbit liver-tumor model. Translation will require assessment of viral shedding, extra-tumoral replication, antiviral immunity, and environmental biosafety.

For malignant ascites associated with advanced HCC, a chitosan-hydrochloride/oxidized-dextran hydrogel containing sulfasalazine induced immunogenic ferroptosis, M1-like macrophage repolarization, and dendritic-cell activation [254]. Combined with anti-PD-1 treatment, the system produced more than 50% ascites regression and treatment-associated immune memory in the evaluated model. These findings apply specifically to peritoneal dissemination and malignant ascites and should not be generalized to established intrahepatic tumors.

Hydrogel depots may additionally protect nucleic-acid therapeutics and prolong local exposure. GalNAc-conjugated siRNA/DP7-C nanoparticles embedded within a thermosensitive hydrogel improved siRNA stability and suppressed the oncogenic regulator Pin1 [255]. An alginate/polyethylenimine nanohydrogel delivering miR-192 inhibited WNT10B-associated Wnt/β-catenin signaling, reduced CD90, EpCAM, and CD133 expression, and suppressed tumor growth and metastasis [256]. These systems require quantitative assessment of intact nucleic-acid delivery, off-target gene regulation, innate

immune activation, and carrier clearance.

Overall, liver tumors are amenable to image-guided intratumoral, transarterial, and intraoperative hydrogel delivery because of established interventional access and the need to concentrate treatment within diseased tissue while limiting systemic exposure. Hydrogel systems can support chemotherapy, radionuclide delivery, antiangiogenic therapy, ferroptosis, gene delivery, oncolytic virotherapy, and immunomodulation. Their performance may nevertheless be compromised by cirrhosis, impaired liver function, heterogeneous arterial perfusion, portal hypertension, vascular shunting, and proximity to major vessels, which can affect placement, retention, distribution, and clearance. Future studies should quantify intratumoral coverage, tumor-to-normal-liver exposure, hepatic and extrahepatic biodistribution, treatment-specific dosimetry, liver-function changes, non-target delivery, degradation, and clearance using orthotopic and clinically representative models [257].

6.7.4. Hydrogels in the Treatment of Pancreatic Cancer

Pancreatic cancer, particularly pancreatic ductal adenocarcinoma, remains highly lethal because of late diagnosis, early metastasis, treatment resistance, and limited eligibility for surgical resection [238,258–260]. Its dense desmoplastic stroma, poor perfusion, elevated interstitial pressure, and immunosuppressive microenvironment restrict drug penetration [261,262]. Injectable and implantable hydrogels are therefore being investigated as local depots that can partially bypass vascular barriers and sustain therapeutic exposure within or adjacent to pancreatic tumors. Because hydrogel release mechanisms are discussed in Sections 3.2 and 3.3, this subsection focuses on pancreatic-cancer-specific applications. Representative quantitative outcomes are compared in Table 5.

Protein-containing hydrogels have been developed to prolong the local activity of apoptosis-inducing agents. An injectable hydrogel formed through thiol–maleimide crosslinking between thiolated human serum albumin and four-arm PEG-maleimide provided sustained delivery of TNF-related apoptosis-inducing ligand. In a Mia PaCa-2 xenograft model, the TRAIL-loaded hydrogel reduced tumor growth relative to the comparator hydrogel and untreated control [263]. Translation requires confirmation of retained TRAIL activity, reproducible gelation, storage stability, immunogenicity, and degradation-product safety.

Localized radionuclide therapy has been investigated using thermoresponsive elastin-like polypeptides conjugated with iodine-131. Following intratumoral injection, the biopolymer formed a depot through temperature-induced phase separation and radiation-associated stabilization. Combined with systemically administered nanoparticle albumin-bound paclitaxel, ^{131}I–ELP brachytherapy produced marked tumor regression in subcutaneous and orthotopic pancreatic-tumor models and altered stromal collagen and junctional proteins in association with increased paclitaxel accumulation [264]. Clinical development will require radiochemical-stability testing, individualized dosimetry, assessment of radionuclide leakage, and measurement of radiation exposure to adjacent organs.

Hydrogel–nanocarrier composites have also been designed for local chemotherapy. PR_b-functionalized liposomes containing gemcitabine and paclitaxel were incorporated into a biodegradable PVLA–PEG–PVLA thermogel [265]. The hydrogel prolonged drug release, while the PR_b-peptide promoted integrin α5β1-associated cellular interactions. The formulation inhibited PANC-1 tumor spheroids more effectively than the corresponding nontargeted systems, although these findings do not establish deep tumor penetration or in vivo targeting [265]. Similarly, a PCLA–PEG–PCLA hydrogel containing montmorillonite–gemcitabine complexes reduced initial drug diffusion, prolonged

depot persistence, and improved tumor-growth inhibition in a subcutaneous pancreatic-cancer model [210]. Long-term montmorillonite biodistribution and clearance remain to be established.

Hydrogels have further been combined with ablation and immunotherapy. An interventional hydrogel microsphere vaccine was administered after irreversible electroporation and released Fms-like tyrosine kinase 3 ligand and CD40 ligand within the relatively acidic post-ablation tumor bed (Figure 8A,B) [266]. The formulation promoted migration of tumor-resident type 1 conventional dendritic cells to tumor-draining lymph nodes, enhanced antigen cross-presentation and endogenous CD8-positive T-cell responses, inhibited distant lesions, and prolonged survival in an orthotopic pancreatic-cancer model (Figure 8C,D) [266]. This approach demonstrates the potential to reinforce ablation-induced antigen release with localized immune stimulation, although device–hydrogel compatibility and efficacy in larger models remain to be established.

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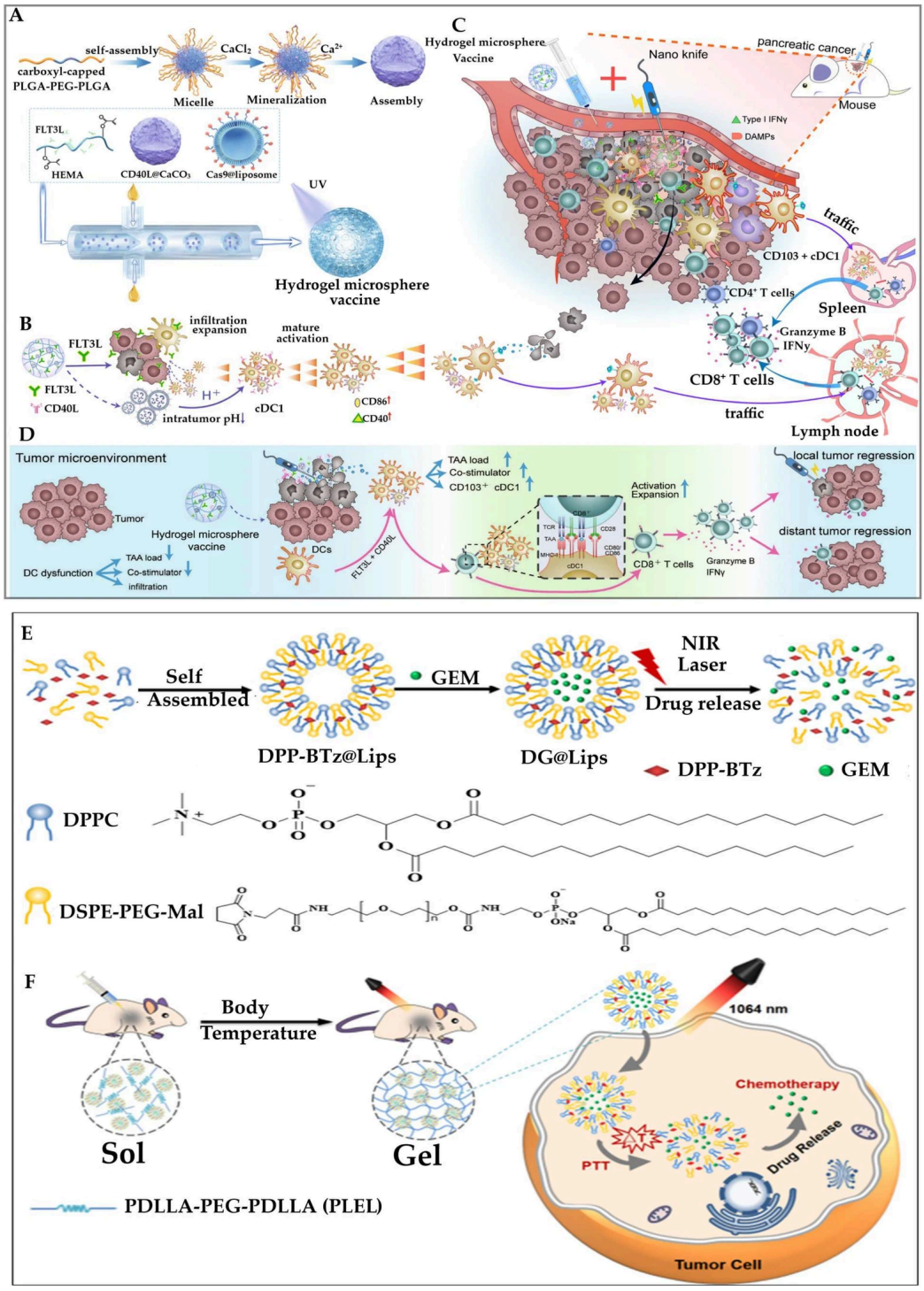


Figure 8. Representative hydrogel-based strategies for pancreatic-cancer therapy. (**A**) Preparation of an interventional hydrogel microsphere vaccine for administration after irreversible electroporation. (**B**) pH-responsive release of Fms-like tyrosine kinase 3 ligand and CD40 ligand within the post-ablation tumor bed. (**C**) Amplification of type 1 conventional dendritic-cell-mediated antigen cross-presentation and endogenous $CD8^+$ T-cell activation. (**D**) Suppression of local and distant pancreatic tumors [266]. (**E**) Construction of an injectable thermosensitive Lip-Gel containing gemcitabine and DPP–BTz within thermosensitive liposomes. (**F**) NIR-II-triggered photothermal heating, liposomal disruption, gemcitabine release, and combined chemo-photothermal treatment [211]. Panels (**A**–**D**) reproduced from Ref. [266] under its respective Open Access Creative Commons license, and Panels (**E**,**F**) reproduced/adapted from Ref. [211] with permission; Copyright © 2021 American Chemical Society.

Postoperative hydrogels have been designed to combine surgical-site sealing with local immunotherapy. A dual-crosslinked adhesive hydrogel comprising methacrylated and sulfhydryl-modified hyaluronic acid–dopamine contained polydopamine-coated interleukin-15 and anti-TIGIT-conjugated platelets [267]. The formulation sealed the pancreatic stump and limited postoperative increases in amylase and lipase in rodent fistula models. In pancreatic-cancer models, the hydrogel activated CD8-positive T cells and natural-killer cells and reduced residual-tumor regrowth and distant metastasis [267]. Fistula prevention, wound healing, immune activation, recurrence control, and metastatic suppression should nevertheless be evaluated as distinct outcomes.

Thermosensitive liposomal hydrogels provide another combination strategy. An injectable 15 wt% PDLLA–PEG–PDLLA Lip-Gel contained thermosensitive liposomes coencapsulating gemcitabine and the NIR-II photothermal agent DPP–BTz [211]. Physiological temperature induced depot formation, whereas 1064 nm irradiation generated heat, disrupted the liposomes, and promoted gemcitabine release (Figure 8E,F). The resulting chemo-photothermal treatment suppressed tumor growth in a PANC-1 xenograft model [211]. Translation requires clinically feasible light delivery, spatial thermal dosimetry, pharmacokinetic analysis, and evaluation of injury to adjacent pancreatic and gastrointestinal tissues.

Overall, localized hydrogels are relevant to pancreatic cancer because they can sustain chemotherapy, radionuclide therapy, photothermal treatment, immune stimulation, or postoperative treatment despite poor perfusion and rapid systemic clearance of many therapeutic agents. However, the dense desmoplastic stroma, high interstitial pressure, heterogeneous vascularization, immunosuppressive microenvironment, and proximity to the duodenum, stomach, bile duct, and major vessels can restrict hydrogel placement and payload penetration. Local retention should therefore not be interpreted as homogeneous intratumoral exposure. Future studies should assess endoscopic-ultrasound-guided, intraoperative, and image-guided percutaneous delivery and quantify injection coverage, stromal penetration, spatial payload distribution, systemic leakage, degradation, clearance, and adjacent-organ toxicity in orthotopic and clinically representative models.

6.7.5. Hydrogels in the Treatment of Breast Cancer

Breast cancer remains a major therapeutic challenge, particularly triple-negative breast cancer (TNBC), which lacks established hormone or HER2-directed targets and is associated with therapeutic resistance, metastatic progression, and postoperative recurrence. Injectable, peritumoral, and postoperative-cavity hydrogels are attractive because breast tumors and resection beds are comparatively accessible for local treatment. Such systems can coordinate chemotherapy with metabolic regulation, epigenetic remodeling, immune-cell activation, and tissue repair. Because hydrogel release mechanisms are discussed in Sections 3.2 and 3.3, this subsection focuses on breast-cancer-specific applications. Representative quantitative outcomes are compared in Table 5.

A hybrid supramolecular hydrogel composed of p(THMA-APMA) and hyaluronic acid was developed for concurrent delivery of doxorubicin and kynureninase (Figure 9 A) [212]. Doxorubicin induced immunogenic tumor-cell death, whereas kynureninase degraded the immunosuppressive metabolite kynurenine. A single low-dose peritumoral administration remodeled the tumor immune microenvironment, suppressed primary-tumor growth, prolonged survival, produced an abscopal response, and reduced postoperative recurrence in preclinical TNBC and melanoma models [212]. The original study described this strategy as a locally administered chemo-immunometabolic therapy. Translation will require confirmation of enzyme activity during manufacture, steril-

ization, storage, residence, and release, together with evaluation of immunogenicity, biodistribution, degradation, and batch reproducibility.

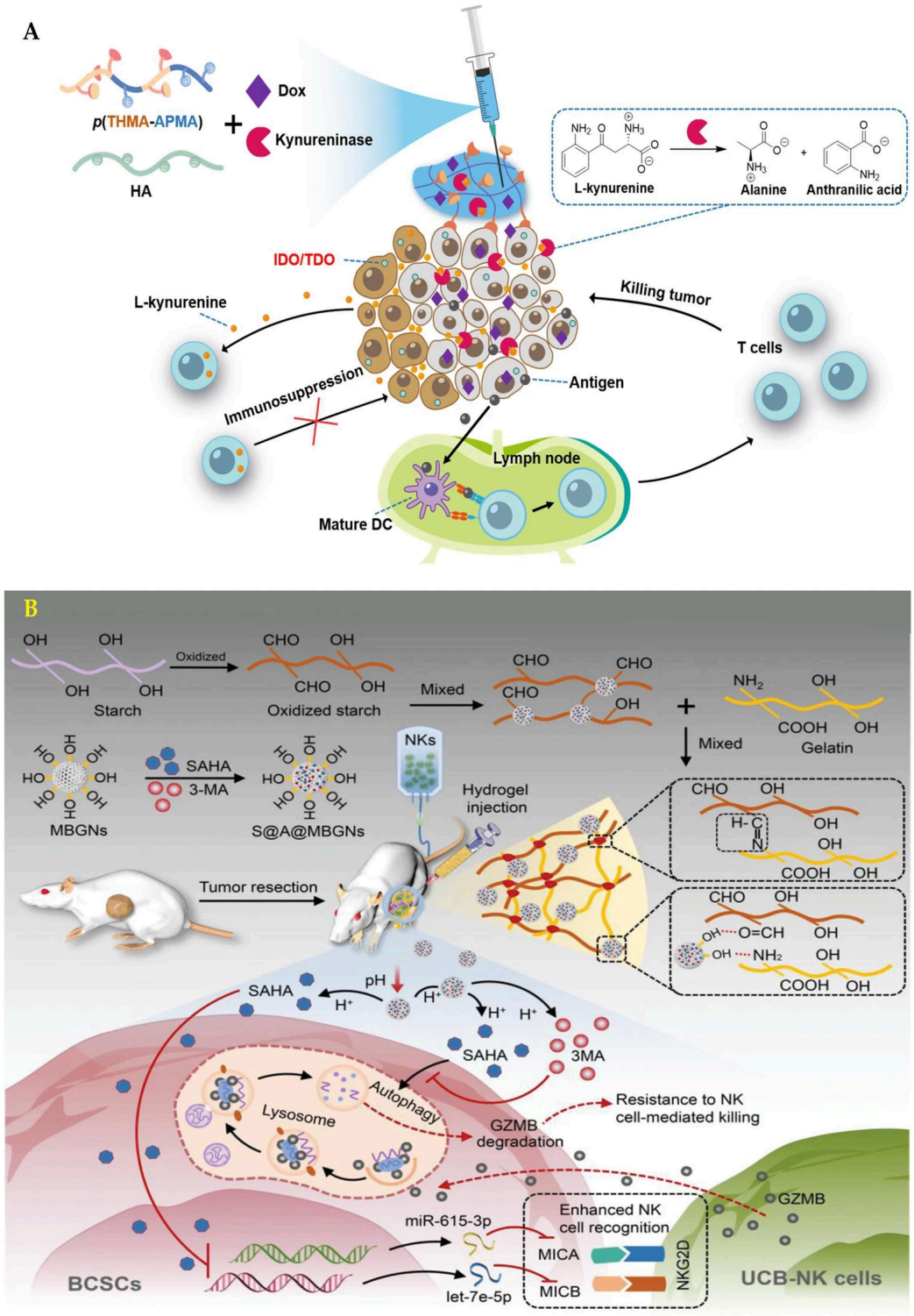


Figure 9. Representative injectable hydrogel platforms for localized treatment of triple-negative breast cancer. (**A**) Hybrid p(THMA-APMA)/hyaluronic acid supramolecular hydrogel for concurrent delivery of doxorubicin and kynureninase, combining immunogenic tumor-cell death with kynurenine depletion and metabolic remodeling of the tumor immune microenvironment [212]. (**B**) Oxidized starch/gelatin-based GOSAM hydrogel containing SAHA- and 3-MA-loaded mesoporous bioactive-glass nanoparticles, used in combination with UCB-NK-cell infusion to enhance tumor-cell killing and reduce postoperative TNBC relapse [91].

A complementary neoadjuvant strategy used a supramolecular hydrogel formed from abemaciclib-loaded peptide–NLG919 prodrug nanofibers [268]. Following local administration, the hydrogel remained at the tumor site for at least seven days and provided sustained release of abemaciclib and the indoleamine 2,3-dioxygenase 1 inhibitor NLG919. The treatment promoted immunogenic tumor-cell death, dendritic-cell maturation, macrophage activation, cytotoxic T-cell infiltration, and effector-memory T-cell generation. A single administration reduced postoperative TNBC recurrence and pulmonary metastasis while limiting systemic lymphopenia and hepatic toxicity [268]. This formulation should be classified as a peptide–drug supramolecular hydrogel rather than a conventional natural-biopolymer network.

Natural-polymer composite hydrogels have also been developed for postoperative immunotherapy. The injectable GOSAM hydrogel consisted of oxidized starch and gelatin crosslinked through Schiff-base reactions and reinforced with mesoporous bioactive-glass nanoparticles carrying suberoylanilide hydroxamic acid (SAHA) and 3-methyladenine (3-MA) (Figure 9B) [91]. SAHA increased expression of the natural-killer-cell activation ligands MICA/B, whereas 3-MA limited autophagy-mediated degradation of natural-killer-cell-derived granzyme B. In combination with umbilical-cord-blood-derived natural-killer-cell infusion, the hydrogel reduced postoperative TNBC relapse and provided hemostatic and wound-healing functions [91]. Long-term degradation, systemic drug leakage, immune responses to the composite components, and manufacturing reproducibility remain important translational considerations.

The three systems represent distinct material and therapeutic strategies. The p(THMA-APMA)/hyaluronic acid formulation is a hybrid synthetic–natural supramolecular hydrogel, the abemaciclib/NLG919 formulation is a peptide–prodrug supramolecular hydrogel, and GOSAM is a natural-polymer composite hydrogel. These classifications should remain explicit because composition affects degradation, manufacturing, analytical control, and regulatory assessment.

Hydrogel patches have also been developed to address tumor-cell plasticity and multidrug resistance. A tumor-microenvironment-responsive patch released an LSD1 inhibitor and a chemotherapeutic agent following ROS-mediated linker cleavage [269]. Inhibition of LSD1 shifted tumor-initiating cells from self-renewal toward differentiation, restored chemosensitivity, enhanced tumor immunogenicity, and reduced postoperative recurrence and metastasis in chemoresistant TNBC models [269]. Because epigenetic modulation may produce prolonged or off-target effects, payload leakage, treatment duration, reversibility, and gene-expression changes in normal tissues require evaluation.

Chitosan-, alginate-, gelatin-, and related natural-polymer systems have additionally been investigated for pH-responsive breast-cancer drug delivery [270]. Chitosan-coated nanocarriers containing curcumin, for example, inhibited MCF-7-cell proliferation in vitro [271]. Such findings support the use of chitosan to disperse and deliver hydrophobic compounds but do not establish tumor-selective accumulation or in vivo efficacy. Nanoparticles and liposomes should also not be classified as hydrogels unless a continuous hydrated polymer network is present.

Overall, breast cancer is well suited to localized hydrogel treatment because primary tumors and postoperative resection cavities are comparatively accessible through intratumoral or peritumoral injection and intraoperative placement. Hydrogels can conform to irregular surgical cavities and combine local chemotherapy with metabolic regulation, epigenetic remodeling, immunotherapy, hemostasis, and wound support. Performance may nevertheless vary with molecular subtype, stromal organization, immune status, vascularization, cavity geometry, and the spatial distribution of residual tu-

mor cells. Future studies should use clinically representative postoperative models and quantify cavity-wide payload distribution, systemic leakage, local tissue compatibility, degradation, immunogenicity, recurrence, and distant metastasis.

7. Marketed and Clinically Evaluated Hydrogel Products Relevant to Oncology

The clinical maturity of hydrogel technologies relevant to oncology varies markedly according to product function. Marketed products are predominantly radiotherapy spacers, tissue markers, embolic materials, adhesion barriers, and surgical sealants. Their principal functions are physical or procedural rather than pharmacological; accordingly, they should not be presented as marketed anticancer drug-delivery systems. Therapeutic hydrogels carrying chemotherapeutics, biologics, immune modulators, nucleic acids, cells, or radionuclides remain primarily at the preclinical, patent, or clinical-investigation stage.

This distinction is important because supportive hydrogel devices and therapeutic combination products differ in primary mode of action, critical quality attributes, manufacturing controls, nonclinical evidence, clinical endpoints, and regulatory pathway. The following subsections therefore separately examine marketed hydrogel-related products, the patent landscape, and clinically evaluated systems.

7.1. Marketed Hydrogel Products Relevant to Oncology

Representative marketed hydrogel and hydrogel-related products are summarized in Table 6. These products are used principally for adhesion prevention, tissue marking, radiotherapy spacing, embolization, or surgical sealing. Their oncology relevance arises from their use during cancer surgery, radiotherapy, image-guided intervention, or supportive care rather than from direct delivery of anticancer agents.

Table 6. Marketed hydrogel and hydrogel-related devices relevant to oncology.

Product Name	Company	Composition/Material Form	Primary Clinical Application	Product Category/Regulatory Function	Relevance to Oncology	Refs.
Seprafilm® Adhesion Barrier	Baxter Healthcare Corporation (Deerfield, IL, USA)	Chemically modified sodium hyaluronate and carboxymethylcellulose, bioresorbable membrane	Reduction in postoperative adhesions following abdominal or pelvic laparotomy	Non-medicated, bioresorbable surgical adhesion-barrier device	May support abdominal or pelvic oncological surgery; it does not deliver an anticancer agent	[272]
GYNECARE INTERCEED® Absorbable Adhesion Barrier	Ethicon, Johnson & Johnson MedTech (Raritan, NJ, USA)	Oxidized regenerated cellulose; absorbable knitted fabric	Reduction in postoperative pelvic adhesions following open gynecological surgery	Absorbable surgical adhesion-barrier device	May support open pelvic oncological surgery when used within its labeled	[273]

Product Name	Company	Composition/Material Form	Primary Clinical Application	Product Category/Regulatory Function	Relevance to Oncology	Refs.
					indication; it is not an anticancer drug-delivery system	
Oxiplex®	FzioMed, Inc. (San Luis Obispo, CA, USA)	Polyethylene oxide and sodium carboxymethylcellulose dual-polymer absorbable gel	Protection of neural structures and reduction in postoperative symptoms following lumbar spinal surgery	Synthetic, absorbable spinal-surgery barrier device	Limited indirect oncology relevance; it may support applicable spinal procedures but has no therapeutic anticancer function	[274]
Oxiplex/AP®	FzioMed, Inc. (San Luis Obispo, CA, USA)	Polyethylene oxide and carboxymethylcellulose-based absorbable gel	Temporary separation of traumatized tissue surfaces during abdominal and pelvic surgery	Bioresorbable abdominopelvic anti-adhesion device	May support applicable abdominal or pelvic oncological procedures; it does not deliver an anticancer agent	[274,275]
Oxiplex/SP®	FzioMed, Inc. (San Luis Obispo, CA, USA)	Polyethylene oxide and sodium carboxymethylcellulose-based absorbable gel	Reduction in epidural fibrosis and postoperative symptoms following spinal surgery	Bioresorbable spinal anti-adhesion device	Limited indirect relevance to spinal oncological procedures; it should not be assigned specifically to pancreatic or liver resection	[274]
Hyalobarrier® Gel and Hyalobarrier®	Anika Therapeutics, Inc.	Autocrosslinked hyaluronic acid gel	Prevention or reduction	Bioresorbable abdominopelvic adhesion-	May support abdominal,	[276]

Product Name	Company	Composition/Material Form	Primary Clinical Application	Product Category/Regulatory Function	Relevance to Oncology	Refs.
Gel Endo	(Bedford, MA, USA)		in adhesions after open, laparoscopic, or hysteroscopic abdominopelvic surgery, depending on product version	barrier device	pelvic, or gynecological oncological surgery when consistent with the labeled indication	
Adcon® Gel	Leader Biomedical (Groningen, The Netherlands)	Polydextran sulfate or polyglycan ester combined with absorbable porcine-derived gelatin in phosphate-buffered saline	Reduction in postoperative peridural fibrosis after laminotomy, laminectomy, or spinal decompression surgery	Resorbable spinal anti-adhesion device	Limited indirect oncology relevance; it is not indicated generally for gastrointestinal or abdominal oncological surgery	[277]
TraceIT® Tissue Marker	Augmenix, Inc. / Boston Scientific Corporation (Marlborough, MA, USA)	Crosslinked, polymerized polyethylene glycol hydrogel	Radiographic marking of soft tissue for treatment localization and subsequent imaging	Implantable Class II radiopaque tissue-marker device	Supports image-guided radiotherapy and treatment localization; it contains no therapeutic drug payload	[278]
Barrigel® Rectal Spacer	Palette Life Sciences (Santa Barbara, CA, USA), now part of Teleflex (Wayne, PA, USA)	Non-animal stabilized hyaluronic acid gel	Temporary separation of the rectal wall from the prostate during prostate radiotherapy	Absorbable perirectal spacer device	Reduces rectal radiation exposure during prostate-cancer radiotherapy; it is not a colorectal-cancer	[279]

Product Name	Company	Composition/Material Form	Primary Clinical Application	Product Category/Regulatory Function	Relevance to Oncology	Refs.
					treatment	
DuraSeal® Dural Sealant System	Integra LifeSciences (Princeton, NJ, USA)	Crosslinked hydrogel formed from polyethylene glycol ester and trilysine amine precursors	Adjunct to sutured dural repair for watertight closure during cranial surgery	Synthetic, absorbable cranial dural-sealant device	May support applicable cranial neuro-oncology procedures; it is not indicated for breast reconstruction or anticancer-drug delivery	[280]

Note: Inclusion indicates relevance to an oncology-related procedure or treatment pathway and does not imply that the product delivers an anticancer agent or possesses direct antitumor activity. Indications and regulatory status may vary by jurisdiction; product descriptions should be interpreted according to the cited labeling and access date.

The experience gained from these products demonstrates that hydrogel-based devices can be manufactured, sterilized, packaged, stored, and administered under controlled conditions. However, such experience cannot be directly extrapolated to drug-loaded or biologic-loaded hydrogels. Incorporation of an active therapeutic component changes the product's analytical requirements, release behavior, systemic-exposure profile, biological risks, clinical endpoints, and regulatory status. Therefore, commercial use of a polymer as a spacer, marker, or barrier supports the feasibility of that material class but does not establish the safety or efficacy of a new therapeutic formulation.

7.2. Patent Landscape

Recent patent publications describe injectable depots, postoperative matrices, image-guided systems, stimuli-responsive networks, cell-capturing materials, and hydrogels designed for localized combination therapy. Representative examples are summarized in Table 7.

Table 7. Representative patents for hydrogel-based technologies relevant to localized cancer treatment.

Patent Publication	Title	Applicant or Assignee	Priority; Filing; Publication Dates	Hydrogel System	Intended Therapeutic Function	Claimed or Described Cancer Application	Developmental Significance	Ref.
US20230094016A1 (2023)	Injectable shear-thinning hydrogel	Mayo Foundation (Rochester, MN,	Priority: 29–30 September 2021;	Shear-thinning gelatin-based	Catheter-assisted local delivery	Local treatment of solid tumors;	Combines catheter deliverability with	[281]

	containing a polypeptide therapeutic agent for enhanced tumor therapy	USA); Boston Scientific Scimed, Inc. (Maple Grove, MN, USA); University of California, San Diego (La Jolla, CA, USA); Obsidio, Inc. (Columbia, MD, USA)	filed: 29 September 2022; published: 30 March 2023	polymer–silica nanoparticle biomaterial containing a polypeptide therapeutic agent	of biologics, including anti-PD-1 agents, as an intratumoral depot	no cancer-specific clinical indication established	rapid recovery of a cohesive local depot after injection	
WO2019092049A1 (2019)	A thermo-responsive hydrogel for intratumoral administration as a treatment in solid tumor cancers	Royal College of Surgeons in Ireland (Dublin, Ireland)	Priority: 7 November 2017; filed: 7 November 2018; published: 16 May 2019	Poloxamer P407, chitosan, genipin, and 2-hydroxypropyl-β-cyclodextrin; injectable at room temperature with in situ gelation	Intratumoral retention and local release of one or more chemotherapeutic agents	Solid tumors; individual cancer indications should be reported only when explicitly identified in the patent	Integrates thermogelation with a genipin-crosslinked chitosan scaffold intended to prolong local drug delivery	[282]
WO2022040612A1 (2022)	Injectable hydrogels and methods for capturing cells using the same	Virginia Tech (Blacksburg, VA, USA)	Priority: 21 August 2020; filed: 21 August 2021; published: 24 February 2022	Stimuli-responsive injectable hydrogel designed to attract or capture target cells	Postoperative-cavity placement followed by externally triggered manipulation or ablation of captured cells	Post-resection cancer applications; specific indications depend on the patent claims and embodiments	Proposes cell capture as an alternative to payload-release-driven postoperative treatment	[283]

US20220177708A1 (2022)	"Smart" hydrogel for the radiosensitization and controlled delivery of therapeutics triggered by irradiation	Trustees of the University of Pennsylvania (Philadelphia, PA, USA)	Priority: 31 March 2019; filed: 30 March 2020; published: 9 June 2022	Biodegradable polyphosphazene hydrogel containing radiation-responsive diselenide components	Radiation-responsive release and radiosensitization during radiotherapy	Tumors treated with radiotherapy; colorectal applicability should not be claimed unless explicitly stated in the patent	Couples therapeutic release to the radiation-treatment event; the application was subsequently granted as US12486401B2	[284]
US20250032676A1 (2025)	3D hydrogel composite with cancer-cell apoptotic effect and preparation method thereof	Dongguk University Industry–Academic Cooperation Foundation (Seoul, Republic of Korea)	Priority: 20 April 2022; filed: 14 October 2024; published: 30 January 2025	Three-dimensional hydrogel composite containing photothermally active liquid-metal particles and chemically immobilized anticancer agents	Combination photothermal therapy and chemotherapy	Multiple cancer-cell types; no specific gastrointestinal cancer indication should be inferred without explicit patent support	Integrates near-infrared-responsive liquid-metal particles with immobilized anticancer agents in one composite	[285]
US11938186B2 (2024)	Thermosensitive hydrogel for cancer therapeutics and methods of preparation thereof	Indian Institute of Technology Hyderabad (Hyderabad, India)	Priority: 20 May 2021; filed: 23 December 2021; granted: 26 March 2024	Thermosensitive polymer–protein hydrogel containing polyvinyl alcohol, poloxamer 407, and bovine serum albumin, with optional therapeutic components	Temperature-triggered local drug delivery, with potential combination photothermal treatment	Solid tumors; a gastric-cancer indication should be retained only if explicitly claimed or exemplified	Uses a polymer–protein matrix to support thermoresponsive gelation and local combination treatment	[286]
US20250082787A1 (2025)	Alginic acid-based	National Cancer Center,	Priority: 21 November	Injectable alginic-acid-	Lesion localization and	Disease-lesion localization,	Combines lesion marking,	[287]

	injectable hydrogel system	Korea (Goyang-si, Gyeonggi-do, Republic of Korea)	2024; filed: 21 November 2024; published: 13 March 2025	based hydrogel capable of lesion marking, local payload delivery, and imaging detection	localized delivery of drugs or contrast agents	including potential minimally invasive oncologic procedures; gastric specificity should be confirmed from the claims	image visibility, and local delivery within an injectable formulation	
US20250177532A1 (2025)	Temperature-sensitive hydrogel for cancer treatment capable of photothermal therapy and preparation method therefor	Korea National University of Transportation Industry–Chungju-si, Republic of Korea))	Priority: 2 March 2022; filed: 1 April 2022; published: 5 June 2025	Thermosensitive hydrogel containing gold nanostars, S-nitrosocysteine, and an immunotherapeutic agent	Photothermal heating, temperature-induced nitric-oxide release, improved intratumoral penetration, and immunotherapy	Cancer treatment broadly; gastric- or liver-specific claims should be reported only when explicitly stated	Integrates photothermal therapy, nitric-oxide-mediated effects, and immunotherapy in one temperature-responsive platform	[288]
US20130022545A1 (2013)	Drug-delivery system for the treatment of liver cancer based on intervention injection of temperature- and pH-sensitive hydrogel	Research & Business Foundation, Sungkyunkwan University (Suwon-si, Republic of Korea)	Priority: 18 July 2011; filed: 18 July 2012; published: 24 January 2013	Temperature- and pH-sensitive block-copolymer hydrogel designed to gel after arterial administration	Hepatic arterial administration, local embolic action, and sustained drug release	Liver cancer	One of the table's most disease-specific systems, designed for catheter-based locoregional treatment of liver tumors	[289]
US20240139304A1 (2024)	Nitric oxide-releasing thermosensitive hydrogels as a	Georgia Tech Research Corporation (Atlanta,	Priority: 5 March 2021 and 19 January	Thermosensitive polymer–polypeptide hydrogel capable	Sustained and controlled delivery of	Broad therapeutic and diagnostic applications; with	Combines a thermosensitive depot	[290]

	therapeutic delivery system	GA, USA)	2022; filed: 4 March 2022; published: 2 May 2024	of releasing micellar assemblies	therapeutic or diagnostic agents to specified tissues	hepatic-tumor use should not be inferred unless claimed or exemplified	controlled release of micelle-associated agents	
WO2024013354A1 (2024)	Hydrogels for drug delivery	Adocia SAS ((Lyon, France))	Priorities: 13 July, 19 September, and 28 December 2022; filed: 13 July 2023; published: 18 January 2024	Crosslinked anionic dextran hydrogel containing an active pharmaceutical ingredient	Implantable depot for sustained drug delivery	Broad drug-delivery applications; liver- and pancreatic-cancer indications should not be assigned without explicit patent support	Provides a chemically defined dextran-based implant platform for sustained release of active pharmaceutical ingredients	[291]
US20240165071A1 (2024)	Methods of treating pancreatic cancer	PanTher Therapeutics, Inc. (Cambridge, MA, USA)	Priority: 17 November 2022; filed: 26 October 2023; published: 23 May 2024	Implantable biodegradable, multilayer local drug-delivery device with an active-pharmaceutical-ingredient layer positioned in direct contact with tumor tissue	Sustained, direct local drug delivery to pancreatic tumor tissue	Pancreatic cancer	Disease-specific implant intended to address poor drug penetration and systemic toxicity; subsequently granted as US12605356B2 in April 2026	[292]
WO2025139283A1 (2025)	Zebrafish hydrogel for radiosensitization after breast-	Hangzhou Biotech Biomedical Technology Co Ltd. (China)	Priority: 25 December 2023; filed: 24 October	Injectable modified chitosan–hyaluronic-acid hydrogel	Postoperative sustained therapeutic-delivery, immunotherapy, and	Residual disease following breast-conserving surgery	Explicitly designed for postoperative placement at the	[293]

	conserving surgery for breast cancer and preparation method therefor		2024; published: 3 July 2025	containing mesoporous gold nanoparticles	enhancement of local radiation-energy deposition		breast tumor bed to combine radiosensitization with sustained local therapy	
US20230172851A1 (2023)	Deformable hydrogel particles and pharmaceutical composition for cancer treatment comprising the same	Korea University Research and Business Foundation; Scholar Foxtrot Co., Ltd. (Seoul, Republic of Korea)	Priority: 16 March 2020; filed: 12 March 2021; published: 8 June 2023	Deformable polymeric hydrogel particles containing polycaprolactone-related components and capable of carrying proteins or antibodies	Delivery of antibody- or biologic therapeutics using deformable hydrogel particles	Cancer treatment broadly; breast-cancer specificity should not be inferred without explicit claims or examples	Particle deformation may support transport through confined biological environments and delivery of macromolecular therapeutics	[294]

Note: Patent publication or grant does not establish experimental validation, clinical efficacy, regulatory approval, commercial availability, or freedom to operate. Applications and granted patents were interpreted according to their published claims and embodiments. Product-development status should be independently verified.

Patent publications should be interpreted cautiously. A published or granted patent defines intellectual-property claims and does not establish technical reproducibility, peer-reviewed validation, regulatory approval, clinical efficacy, commercial availability, or freedom to operate. The table therefore reports claimed or described functions without treating them as confirmed therapeutic outcomes.

The patent landscape indicates substantial interest in integrating hydrogel formation with catheter delivery, postoperative treatment, immunotherapy, radiotherapy, cell capture, or stimulus-triggered release. Nevertheless, increased formulation complexity may also expand the requirements for component characterization, manufacture, sterilization, stability, biological evaluation, and regulatory control. Patent activity should therefore be viewed as evidence of technological exploration rather than clinical maturity.

7.3. Clinically Evaluated Hydrogel Systems

Hydrogel systems entering clinical evaluation encompass distinct product types, including radiotherapy spacers and markers, radionuclide-containing depots, topical or endoscopically administered drug-delivery gels, and embolic formulations. These products should not be grouped under a single maturity category because a completed feasibility study of a spacer or marker is not equivalent to evidence of therapeutic efficacy from a drug-loaded hydrogel.

Representative clinically evaluated systems are summarized in Table 8. Registered or authorized studies should be described according to their stated objective, enrollment

status, and reported results. Trial registration, regulatory authorization, or Investigational Device Exemption approval confirms permission to investigate a product but does not establish safety or efficacy.

Table 8. Representative clinical and regulatory-stage hydrogel technologies for therapeutic and supportive applications in oncology.

Hydrogel System	Clinical Condition	Intended Function and Administration	Study Objective or Reported Outcome	Development Status	Trial or Regulatory Identifier	Refs.
RadioGel® yttrium-90 hydrogel	Non-resectable papillary thyroid carcinoma	Intratumoral radionuclide delivery	First-in-human safety and feasibility evaluation authorized; clinical outcomes not yet reported	FDA feasibility IDE approved, 6 July 2026	FDA IDE; trial ID NR	[295]
TraceIT® radiopaque PEG hydrogel spacer	Localized pancreatic cancer	EUS-guided placement between the pancreas and duodenum before radiotherapy	Feasibility, anatomical separation, dosimetric performance, and procedural safety evaluated	Completed	NCT03998566	[296]
TraceIT® radiopaque hydrogel marker	Borderline-resectable or locally advanced pancreatic adenocarcinoma	Injection at the pancreas–duodenum interface for radiotherapy localization	Marker visibility and image-guided localization evaluated	Completed	NCT03307564	[297]
Poloxamer thermogel containing 5-fluorouracil	Colorectal cancer	Transendoscopic colonic delivery for enhanced local drug adhesion	Phase 2 evaluation of feasibility, safety, and preliminary efficacy	Recruiting	NCT06385418	[298]
DC Bead™ doxorubicin-loadable hydrogel	Hepatocellular carcinoma	Transarterial chemoembolization for arterial embolization	Randomized comparison of doxorubicin-	Completed randomized clinical trial,	NCT00261378	[299]

Hydrogel System	Clinical Condition	Intended Function and Administration	Study Objective or Reported Outcome	Development Status	Trial or Regulatory Identifier	Refs.
microspheres		and localized doxorubicin delivery	loaded DC Bead TACE with conventional TACE, evaluating tumor response and treatment safety	PRECISION V		
Embrace™/Instylla HES	Hypervascular tumors	Catheter-directed arterial embolization using an in situ-forming PEG hydrogel	Prospective randomized multicenter pivotal trial versus standard-of-care transarterial embolization (TAE) or conventional transarterial chemoembolization (cTACE)	Pivotal study completed; FDA-approved for embolization of hypervascular tumors	NCT04523350; IDE G200149	[300]
AceGel alginate–calcium lactate hydrogel	Esophageal, gastric, and colorectal neoplasms	Submucosal injection during EMR or ESD	Adequate mucosal elevation and wound healing, with no serious adverse events reported in a 12-patient feasibility study	Completed	NCT03321396	[301]

Note**:** The table distinguishes study objectives from reported clinical outcomes. Status reflects the cited registry or regulatory information and may change over time. , drug-eluting bead irinotecan; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasonography; FDA, U.S. Food and Drug Administration; HES, Hydrogel Embolic System; IDE, Investigational Device Exemption; NR, not reported; PEG, polyethylene glycol; TACE, transarterial chemoembolization.

7.4. Current Clinical Landscape and Translational Interpretation

The available evidence shows a clear difference between supportive hydrogel devices and therapeutic drug-delivery systems. Clinically established or comparatively advanced products are predominantly radiotherapy spacers, tissue markers, embolic materials, sealants, and adhesion barriers. Their performance can be assessed using defined procedural endpoints, including placement accuracy, geometric stability, imaging visibility, dosimetric improvement, vascular occlusion, sealing, or prevention of postoperative adhesion. By contrast, therapeutic hydrogel depots must demonstrate payload identity and potency, local and systemic pharmacokinetics, controlled release, therapeutic benefit, degradation, clearance, and formulation-specific safety [9–12,302].

Marketed use of a hydrogel-forming polymer does not establish the safety or effectiveness of a new therapeutic formulation. Chemical modification, crosslinking, therapeutic loading, administration route, tissue exposure, and degradation can substantially alter material performance and biological response. Marketed products should therefore be interpreted as evidence that hydrogel technologies can satisfy defined manufacturing and clinical requirements, not as direct validation of experimental anticancer depots.

Patent activity is greater than clinical validation. Many patented systems introduce multiple responsive linkages, targeting ligands, nanoparticles, imaging functions, or therapeutic components, but relatively few have advanced to clinical testing. This gap reflects the added difficulty of establishing component identity, payload integrity, release reproducibility, sterilization compatibility, degradation, biodistribution, clinical administration, and manufacturing consistency for multicomponent formulations [10–12].

The most credible translational opportunities are applications that address a specific local-treatment limitation and can be delivered through an established clinical workflow. These include postoperative treatment of accessible resection beds, image-guided intratumoral delivery, catheter-based embolization or local therapy, endoscopic administration, and temporary protection of adjacent tissues during radiotherapy. Advancement should depend on measurable benefit relative to the free payload, conventional systemic administration, existing local-delivery approaches, or current procedural alternatives. Product classification, manufacturing controls, biological evaluation, clinical-evidence requirements, and lifecycle oversight are discussed in Section 8.

8. Regulatory Considerations for Biopolymer-Based Hydrogel Products

The physicochemical, pharmaceutical, stability, sterilization, and reproducibility assessments described in Section 3.4 provide the analytical basis for regulatory development. These measurements must be translated into product-specific critical quality attributes, acceptance criteria, manufacturing controls, and clinical-performance requirements. Regulatory expectations depend on the final formulation, intended use, administration route, duration of exposure, primary mode of action, therapeutic payload, and delivery device rather than on the hydrogel-forming polymer alone [9–12].

8.1. Product Classification and Regulatory Pathways

Biopolymer hydrogels may be regulated as medicinal products, biological products, medical devices, or combination products. Classification depends principally on the product's intended use and primary mode of action. Hydrogels used predominantly as radiotherapy spacers, tissue markers, sealants, adhesion barriers, or embolic matrices may follow medical-device pathways, whereas formulations whose principal therapeutic action is mediated by an incorporated drug or biologic may be regulated as medicinal or biological products. Systems in which the hydrogel matrix, therapeutic payload, and administration device make distinct contributions may fall within combination-product

frameworks [303–306].

In the United States, single-entity or co-packaged combination products are subject to the applicable requirements for their constituent parts and to the current good manufacturing practice provisions of 21 CFR Part 4. Device-led products are also subject to the Quality Management System Regulation in 21 CFR Part 820, whereas drug or biologic constituents remain subject to the applicable pharmaceutical or biological-product requirements. The responsible lead center and development pathway depend on the primary mode of action and the relative contribution of the constituent parts [303,304,307].

In the European Union, the applicable pathway depends on whether the hydrogel is regulated as a medical device, a medicinal product incorporating a device component, or a device containing an ancillary medicinal substance. Regulation (EU) 2017/745 establishes the requirements for medical devices, while Directive 2001/83/EC applies to medicinal products. For integral drug–device products regulated as medicines, Article 117 may require evidence of conformity of the device component with the applicable general safety and performance requirements, including a notified-body opinion where relevant [305,306,308].

Classification should be resolved before pivotal development because it influences the quality-management system, nonclinical evidence, clinical endpoints, submission route, manufacturing controls, and post-market obligations. Early engagement with the relevant regulatory authority is particularly important for stimuli-responsive, biologic-loaded, cell-containing, radionuclide-containing, and multimodal hydrogels whose therapeutic performance cannot be attributed to a single constituent [303–306].

8.2. Quality, Manufacturing, and Risk Management

Regulatory development should convert the characterization parameters described in Section 3.4 into formulation-specific critical material attributes, critical process parameters, and critical quality attributes. Depending on the product, these may include polymer identity, molecular-weight distribution, purity, degree of substitution or deacetylation, crosslinker content, gelation time, viscosity, injection force, rheological recovery, mechanical performance, payload content and uniformity, release, degradation, sterility, endotoxin burden, packaging integrity, and storage stability [9–12].

Natural and biologically derived polymers require particular attention because their composition may vary with biological source, harvesting conditions, purification, molecular-weight distribution, residual proteins or nucleic acids, microbial contamination, endotoxin burden, moisture content, and supplier-specific processing. Material specifications should be linked to final-product performance rather than based solely on general compendial identity or prior use of the unmodified polymer [10–12].

Manufacturing controls should address precursor preparation, component ratios, mixing order and time, temperature, pH, ionic strength, crosslinking conditions, payload incorporation, filling, sterilization, packaging, and storage. These parameters can affect network homogeneity, gelation, injectability, payload distribution, degradation, and release. Rapidly crosslinking, thermoresponsive, enzyme-mediated, particulate, and biologic-loaded formulations may be particularly sensitive to changes in equipment, batch size, heat and mass transfer, pumping, and shear exposure [10–12].

Process validation should demonstrate that the proposed manufacturing process consistently produces material meeting predefined specifications. Reproducibility must be established across independently manufactured batches rather than inferred from repeated measurements of a single preparation. Scale-up studies should evaluate mixing and mass-transfer differences, component homogeneity, filling accuracy, gelation kinetics, payload distribution, sterilization exposure, and packaging performance. The result-

ing data should support batch release, stability commitments, process comparability, change control, and lifecycle management [10–12,309].

Risk management should extend across the complete product lifecycle and consider material variability, administration failure, premature gelation, device blockage, leakage, incomplete depot formation, dose-delivery errors, payload instability, degradation-product toxicity, systemic exposure, and delayed clearance. Risk controls should be linked to design verification, process validation, usability evaluation, clinical evidence, and post-market surveillance [310–312].

8.3. Sterility, Endotoxin Control, and Stability

Injectable and implantable hydrogel products require a formulation-specific sterility-assurance strategy. Terminal sterilization may alter polymer molecular weight, crosslink integrity, gelation kinetics, rheology, mechanical properties, degradation, release, or payload activity. The effects of heat, irradiation, and chemical sterilants should therefore be assessed using the complete formulation rather than the unloaded polymer alone [9–12].

When terminal sterilization is incompatible with the formulation, separately sterilized or filtered components followed by aseptic compounding, filling, and assembly may be required. High-viscosity precursors, particles, cells, viral vectors, liposomes, and preformed networks may not be compatible with sterilizing filtration. The selected manufacturing strategy should therefore address cleanroom controls, environmental monitoring, personnel qualification, container-closure integrity, process simulation, and the maximum allowable precursor-hold and in-use periods [11,313,314].

Sterility and bacterial endotoxin control should be evaluated separately because elimination of viable microorganisms does not necessarily remove or inactivate endotoxins. Polymers, surfactants, salts, nanoparticles, proteins, and degradation products may interfere with endotoxin-detection or microbial-recovery methods. Raw-material controls, method-suitability testing, appropriate dilution or interference controls, and validated product-specific procedures are therefore required [315,316].

Stability studies should reflect the proposed packaging, storage temperature, light exposure, freeze–thaw conditions, transport, preparation, and clinical handling. Relevant endpoints may include appearance, pH, osmolality, polymer molecular weight, gelation time, rheology, mechanical performance, payload recovery and potency, impurities, aggregation, release, sterility, and container-closure integrity. Complex formulations should also be evaluated for interactions among the hydrogel matrix, payload, incorporated carrier, packaging components, and delivery device [9–12].

8.4. Biological Evaluation

Biological safety cannot be inferred solely from the natural origin, biodegradability, or prior use of a polymer. Evaluation should address the final formulation, including chemical modifications, crosslinkers, residual reagents, therapeutic payloads, nanoparticles or other incorporated carriers, degradation products, and processing-related impurities. The biological evaluation plan should reflect the administration route, tissue contact, exposure duration, degradation profile, systemic distribution, and intended clinical function [312,317].

Relevant endpoints may include cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute and repeated-dose systemic toxicity, implantation response, genotoxicity, hemocompatibility, immunotoxicity, inflammatory responses, and degradation-product safety, as applicable to the product. Blood-contacting or intravascular systems may additionally require formulation-specific assessment of hemolysis, coagulation,

platelet interactions, and complement-related responses [317,318].

Degradation should be evaluated as a biological-disposition process rather than only as bulk mass loss. Polymer fragments, residual crosslinkers, payload carriers, and inorganic or nanoscale components may persist locally or redistribute to other organs. Evaluation should therefore integrate degradation-product identification, local tissue response, systemic exposure, biodistribution, and renal or hepatobiliary clearance. Testing should extend beyond the period of therapeutic release when substantial residual material remains [9,10,317].

Animal-derived polymers may require additional controls related to species and tissue source, transmissible agents, viral inactivation or removal, traceability, and immunogenic impurities. Changes in biological source, purification process, or supplier should be assessed through risk-based comparability studies rather than treated as routine material substitutions [317,319].

8.5. Clinical Evidence, Administration, and Lifecycle Oversight

Clinical evidence should correspond to the product's intended function, regulatory classification, administration route, and anticipated risks. Therapeutic depots may require evaluation of local pharmacokinetics, systemic exposure, tumor response, recurrence, progression-free or overall survival where appropriate, and treatment-associated toxicity. Clinical benefit should be demonstrated relative to an appropriate comparator, such as the free payload, conventional administration, another local-delivery approach, or the current standard of care [10,12].

Supportive hydrogel devices require different endpoints. Radiotherapy spacers and markers may require assessment of placement success, geometric persistence, imaging visibility, dosimetric benefit, adjacent-organ protection, and procedural complications. Embolic systems require evidence of catheter deliverability, vascular distribution, durability of occlusion, non-target embolization, and compatibility with interventional workflows. Sealants and adhesion barriers require function-specific evaluation of sealing, leakage, adhesion prevention, tissue compatibility, and procedural safety [10,302].

Usability and human-factors evaluation should reproduce the intended clinical workflow. Relevant variables may include preparation time, mixing accuracy, device assembly, injection force, catheter or needle blockage, premature gelation, leakage, placement accuracy, delivered volume, operator training, and use-related errors. For combination products, the hydrogel formulation and delivery device should be evaluated as an integrated system because each can affect delivered dose and clinical performance [12,304].

Premarket studies should be complemented by lifecycle controls where long-term degradation, migration, repeat administration, or delayed adverse effects cannot be fully characterized before approval. Post-market surveillance and, where applicable, post-market clinical follow-up should address uncommon procedure-related complications, local inflammation, fibrosis, migration, degradation-product accumulation, repeat-administration risks, and long-term clinical performance [303–305].

Material-specific quality controls should reflect the source, chemical modification, and biological variability of each hydrogel-forming polymer. Relevant attributes may include identity, molecular-weight distribution, purity, degree of substitution or deacetylation, residual biological materials, endotoxin burden, gelation, degradation, and interactions with the incorporated payload. However, regulatory classification is determined by the intended use, route and duration of administration, primary mode of action, and composition of the final product rather than by the polymer alone. Biological evaluation, manufacturing controls, and acceptance criteria should therefore be established for the

complete formulation using a risk-based, product-specific strategy [304,312,317,320].

Compliance with regulatory and product-quality requirements does not by itself establish translational readiness. Clinical development also depends on reproducible manufacturing, feasible administration, formulation-specific biological safety, relevant preclinical models, and clinically meaningful endpoints. These unresolved issues are examined in Section 9.

9. Critical Discussion and Translational Priorities

Biopolymer hydrogels provide adaptable platforms for localized cancer treatment, but favorable biocompatibility, biodegradability, or stimulus-responsive release does not establish translational readiness. Clinical development requires a clearly defined therapeutic or procedural function, reproducible manufacturing, clinically feasible administration, formulation-specific safety, and evidence that the hydrogel improves outcomes beyond those achievable with the unencapsulated payload or existing treatment. The pharmaceutical tests supporting these assessments are described in Section 3.4, while product classification and regulatory control strategies are addressed in Section 8. This section focuses on the principal barriers connecting preclinical performance with clinical implementation [9–12].

9.1. Material Variability, Biological Safety, and Clearance

Natural origin should not be treated as evidence of uniform composition or biological safety. Molecular-weight distribution, degree of substitution or deacetylation, residual proteins and nucleic acids, endotoxin burden, moisture content, and source-dependent impurities can change gelation, mechanical stability, degradation, payload release, and tissue response. Chemical modification and incorporation of nanoparticles, synthetic polymer segments, crosslinkers, or biologically active payloads introduce additional variables that may alter cytotoxicity, complement activation, immunogenicity, inflammation, and foreign-body reactions [9–12,310,318,320].

Biological evaluation should therefore be performed on the final formulation rather than inferred from the unmodified polymer or from historical use of the material through another administration route. This distinction is especially important for intratumoral, intraperitoneal, transarterial, and implantable systems, whose local concentration and residence time may substantially exceed those associated with conventional excipient use. The safety of the hydrogel matrix, therapeutic payload, incorporated carrier, residual reagents, and degradation products should be assessed both individually and as an integrated product [9,10,317,320].

Degradation is likewise a dynamic biological process rather than a simple decline in bulk mass. Polymer-chain cleavage may precede measurable mass loss, while soluble fragments or detached nanoparticles may redistribute to the liver, spleen, kidneys, lymphatic system, or other tissues. Premature degradation can destabilize the depot and increase systemic payload exposure, whereas prolonged persistence may promote fibrosis, chronic inflammation, granuloma formation, or foreign-body encapsulation. Evaluation should therefore integrate mass loss, molecular-weight change, mechanical deterioration, degradation-product identity, local tissue response, systemic biodistribution, and renal or hepatobiliary clearance [9,10,317,320].

Tumor-associated acidity, oxidative stress, reducing conditions, enzyme activity, inflammation, and tissue ischemia may further alter degradation and immune responses. Results obtained only in physiological buffer or healthy subcutaneous tissue may consequently fail to predict behavior within tumors, postoperative cavities, or chronically inflamed sites. Claims of complete biodegradation, non-immunogenicity, or long-term

safety require route-specific and duration-appropriate evidence extending beyond the period of therapeutic release to the eventual clearance of the hydrogel, payload, and degradation products.

9.2. Sterility, Manufacturing, Scale-Up, and Clinical Logistics

Sterility assurance should be established early because conventional terminal sterilization may damage the hydrogel network or therapeutic cargo. Heat, irradiation, and chemical sterilants can alter polymer molecular weight, crosslinking, gelation, rheology, degradation, and release, while biologics, nucleic acids, liposomes, cells, and viral vectors may lose structural integrity or potency. If terminal sterilization is incompatible with the complete product, separately sterilized or filtered components followed by aseptic compounding and filling may be required, increasing manufacturing complexity, validation requirements, contamination risk, and cost [9–11,313,314,321].

Sterility and endotoxin control should not be treated as interchangeable. A process that removes viable microorganisms may not eliminate bacterial endotoxins, and hydrogel components can interfere with endotoxin-detection and microbial-recovery assays. Raw-material controls, method-suitability assessment, environmental monitoring, and product-specific acceptance criteria are therefore required. High-viscosity precursors and formulations containing particles, cells, viruses, or preformed networks may also be incompatible with sterilizing filtration, making the sterility-assurance strategy a potential determinant of formulation feasibility rather than a late-stage manufacturing decision [9,11,313–316,321].

Laboratory-scale reproducibility does not guarantee manufacturing-scale consistency. Changes in vessel geometry, mixing efficiency, shear exposure, heat and mass transfer, pumping, filling, and precursor-hold time can alter crosslinking kinetics, component distribution, injectability, payload stability, and final network structure. Rapidly crosslinking, thermoresponsive, enzymatically gelled, and particle-containing systems are particularly sensitive to scale-dependent processing changes [10–12].

Reproducibility must consequently be demonstrated across independently manufactured batches rather than inferred from repeated measurements of one preparation. Critical material attributes and process parameters should be linked to predefined product-quality attributes, including gelation time, injection force, rheological recovery, payload content and distribution, release, degradation, sterility, endotoxin burden, and biological potency. Source-variable natural polymers require tighter incoming-material specifications, supplier qualification, traceability, and formal comparability assessment after changes in supplier, production scale, equipment, or sterilization process [10–12].

Clinical logistics may impose additional constraints. Thermoresponsive precursors, proteins, nucleic acids, cells, viruses, and radionuclides may require controlled-temperature transport, short in-use periods, specialized preparation, radiation handling, or administration at designated treatment centers. A formulation that performs well under tightly controlled laboratory conditions may have limited clinical value if it requires complicated mixing, narrow temperature control, rapid multistep preparation, or highly operator-dependent placement. Packaging, storage, preparation time, delivery-device compatibility, and ease of use should therefore be incorporated into the target product profile from early development.

9.3. Preclinical Relevance and Clinically Meaningful Evidence

A major translational limitation is the frequent reliance on subcutaneous tumor models that do not reproduce the anatomy, stromal organization, perfusion, immune environment, or delivery constraints of human disease. Small tumors in mice can often be

covered by a single injection volume that would be impractical or unsafe in a large, irregular, fibrotic, or poorly perfused human lesion. Subcutaneous models may also underestimate resistance to distribution within pancreatic desmoplasia, cirrhotic liver, disseminated peritoneal disease, postoperative cavities, or heterogeneous breast-tumor margins [9,10,16,17,45].

Experimental design should therefore progress from initial feasibility studies to orthotopic, immunocompetent, postoperative, metastatic, and, where justified, large-animal models. The selected model should reproduce the proposed clinical route, anatomical scale, treatment schedule, and relevant biological barriers. For example, postoperative hydrogels should be applied to realistic resection surfaces, pancreatic formulations should be assessed through clinically feasible image-guided or intraoperative delivery, and transarterial systems should be evaluated for catheter passage, vascular distribution, embolic performance, and non-target delivery.

Hydrogel distribution and therapeutic exposure should also be distinguished. Depot retention does not establish homogeneous payload distribution, tissue penetration, cellular uptake, or reduced systemic exposure. Similarly, tumor-associated fluorescence may reflect vascular retention, extracellular accumulation, carrier degradation, or release of an imaging label rather than delivery of an intact formulation. Studies claiming tumor targeting or barrier penetration should include quantitative pharmacokinetics, intact-carrier tracking, spatial payload mapping, tumor-to-organ distribution, systemic leakage, and appropriate nontargeted or stimulus-independent controls [9,10,16,17,23,28,32,34].

Clinical endpoints must correspond to the product's intended function. Therapeutic depots should be evaluated using payload exposure, tumor response, recurrence, progression-free or overall survival where appropriate, and local and systemic toxicity. Immune-modulating formulations additionally require evidence of functional immune activation, distant-tumor responses, recurrence control, rechallenge protection, and immune-related adverse effects. Apparent improvements in immune-cell abundance or biomarker expression should not substitute for durable therapeutic outcomes.

Supportive hydrogel devices require different endpoints. Radiotherapy spacers and markers should be assessed through placement success, geometric stability, imaging visibility, dosimetric improvement, adjacent-organ protection, and procedural complications. Embolic systems require evaluation of delivery control, durability of occlusion, non-target embolization, local payload release, and compatibility with interventional workflows. Sealants, barriers, and postoperative materials similarly require function-specific evidence of sealing, adhesion prevention, wound compatibility, or hemostatic performance. These outcomes should not be presented as equivalent to anticancer efficacy [10,12,302].

Long-term studies should extend beyond the treatment period to capture delayed inflammation, fibrosis, depot migration, immunogenicity, degradation-product accumulation, organ distribution, and clearance. Repeat administration should also be considered when clinically plausible because immune responses, tissue remodeling, or residual material may alter the safety and performance of subsequent doses.

9.4. Standardization and Translational Roadmap

The diversity of hydrogel compositions and clinical functions makes a universal test battery inappropriate. Standardization should instead establish a common core of material, pharmaceutical, biological, and manufacturing information supplemented by application-specific assessments. Common reporting should include polymer identity and variability, composition, geometry, crosslinking, gelation, injectability, rheology, swelling

kinetics, degradation, payload distribution, release, sterilization, stability, and interbatch reproducibility [9,11,12,310,312,320].

Acceptance criteria should remain product-specific. Injectable depots require administration, gelation, placement, and release testing; radiotherapy spacers require geometric and dosimetric stability; embolic systems require catheter delivery and occlusion testing; and films, barriers, and sealants require mechanical, adhesive, and conformability assessments. Harmonized terminology, physiologically relevant test conditions, common reporting principles, and minimum datasets would improve comparison without imposing identical performance limits on products with different functions [317,318,320, 322–324,].

A staged framework for translating biopolymer-based hydrogel systems from formulation design to clinical and lifecycle evaluation is summarized in Figure 10.

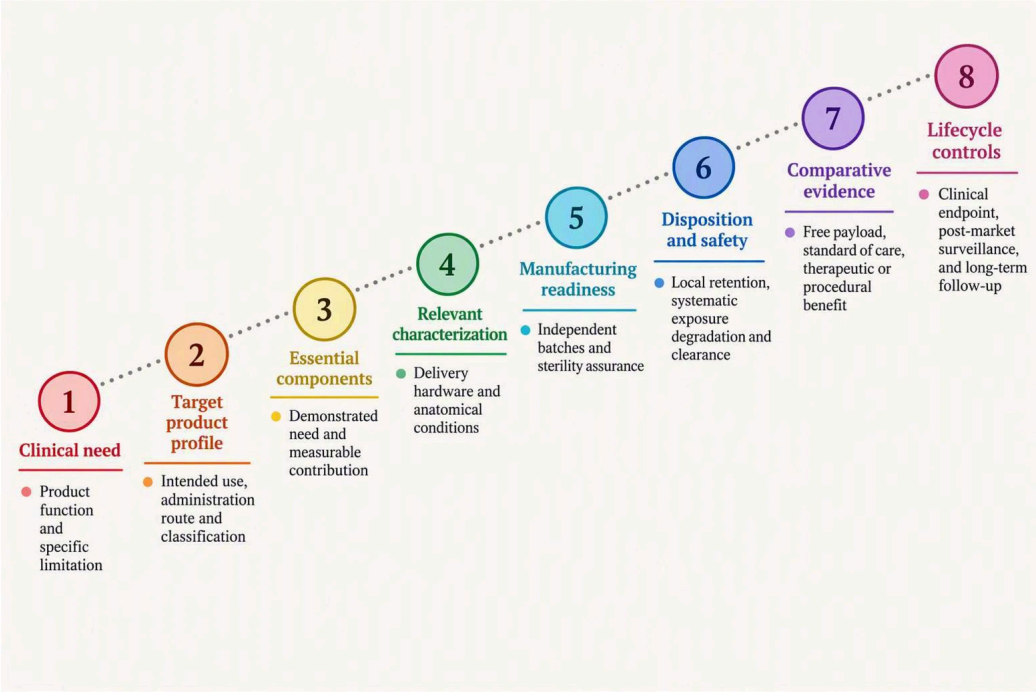


Figure 10. Translational roadmap for biopolymer-based hydrogel products in oncology. Development begins with definition of the clinical need and target product profile, followed by selection of essential formulation components, clinically representative characterization, reproducible manufacturing and sterility assurance, integrated evaluation of disposition and safety, comparative evidence, and function-specific clinical and lifecycle controls.

The translational process should begin with a defined clinical or procedural limitation rather than with material selection alone. The target product profile should specify the intended use, patient population, administration route, delivery device, anticipated exposure duration, and probable regulatory classification. Formulation complexity should then be restricted to components that provide a demonstrated and measurable contribution to administration, payload stability, local exposure, safety, or therapeutic performance. Additional polymers, nanoparticles, targeting ligands, responsive linkages, or imaging agents should not be incorporated solely to increase multifunctionality because every component expands the analytical, manufacturing, toxicological, and regulatory burden [58,62,63].

Characterization should reproduce the intended conditions of clinical use, including formulation temperature, preparation procedure, delivery hardware, administration

rate, anatomical environment, and physiologically relevant stimulus range. Manufacturing readiness requires reproducibility across independently produced batches, control of critical material attributes and process parameters, validated sterilization or aseptic manufacture, and suitable packaging, storage, transportation, and in-use procedures. These requirements should be established before pivotal efficacy studies rather than deferred until late-stage development.

Disposition and safety should be investigated as integrated outcomes. Local retention and spatial payload distribution should be evaluated together with systemic exposure, degradation-product identity, biodistribution, immunogenicity, inflammatory responses, and eventual clearance. Hydrogel retention at the administration site should not be interpreted as evidence of homogeneous drug exposure, effective cellular uptake, or reduced systemic toxicity without direct pharmacokinetic and disposition data. Safety monitoring should extend beyond the therapeutic-release period when residual polymer networks, particulate components, or degradation products remain in the body.

Comparative studies should include the free payload, unloaded hydrogel, relevant component controls, and the current standard of care or established procedural alternative. Added formulation complexity is justified only when it produces a measurable improvement in therapeutic efficacy, safety, administration, or procedural performance. Function-specific clinical endpoints, usability assessment, post-market surveillance, and long-term follow-up should reflect the product's actual therapeutic or procedural claim.

Biopolymer-based hydrogels are most likely to advance when material design is subordinated to a defined clinical need and supported by reproducible manufacturing, clinically feasible administration, complete biological-disposition data, and function-specific evidence. The central translational question is therefore not whether a hydrogel can provide sustained or stimulus-responsive release under laboratory conditions, but whether the final product can be manufactured consistently, administered reliably, preserve payload activity, improve clinically meaningful outcomes, and degrade or clear without unacceptable local or systemic effects.

10. Conclusions

Biopolymer-based hydrogels provide a versatile framework for localized cancer treatment because their composition, crosslinking, degradation, and payload–matrix interactions can be adjusted to regulate administration, tissue retention, and therapeutic release. Polysaccharide-, protein-, peptide-, and nucleic-acid-based hydrogels have been investigated for delivering small-molecule drugs, biologics, nucleic acids, cells, and particulate carriers across chemotherapy, immunotherapy, radiotherapy, phototherapy, and combination treatments. Their principal value lies not in multifunctionality alone, but in the possibility of coordinating the payload, administration route, anatomical site, and required duration of exposure within a single formulation.

Most therapeutic hydrogel systems, however, remain at the preclinical stage. Favorable release profiles in simplified media or tumor suppression in small-animal models do not establish clinical performance. Tumor heterogeneity can limit the selectivity of pH-, redox-, enzyme-, and temperature-responsive systems, while dense stroma, irregular anatomy, necrosis, interstitial pressure, and treatment-induced tissue changes can restrict hydrogel placement, payload distribution, and tissue penetration. Hydrogel retention should therefore not be interpreted as evidence of homogeneous drug exposure, cellular uptake, or reduced systemic toxicity without quantitative pharmacokinetic and biodistribution data.

Translation is further constrained by variability in natural polymers, scale-dependent manufacturing, sterilization incompatibility, payload instability, incomplete charac-

terization of degradation products, and limited evidence of reproducibility across independently manufactured batches. Claims of biocompatibility, biodegradability, targeting, or controlled release should be supported by formulation-specific evidence obtained under clinically representative conditions. Evaluation should extend beyond the therapeutic-release period to address local inflammation, fibrosis, systemic distribution, degradation-product safety, and eventual clearance of the hydrogel and its incorporated components.

Future development should prioritize formulations that address a defined clinical limitation and provide measurable benefit over the free payload, conventional administration, or existing procedural alternatives. Polymer selection and crosslinking should be guided by payload dimensions and affinity, administration hardware, tumor anatomy, required depot residence, and acceptable degradation and clearance profiles. Clinically relevant disease models, realistic administration procedures, quantitative disposition studies, long-term safety, manufacturing reproducibility, and function-specific endpoints should be incorporated before pivotal development. Progress will depend less on adding multiple responsive, targeting, or imaging functions than on demonstrating that the final product can be manufactured consistently, administered reliably, preserve payload activity, improve therapeutic or procedural outcomes, and degrade or clear without unacceptable local or systemic effects.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
ACS	American Cancer Society

ATP	Adenosine Triphosphate
BBB	Blood–Brain Barrier
BSA	Bovine Serum Albumin
CAFs	Cancer-Associated Fibroblasts
CAMKII	Calcium/Calmodulin-Dependent Protein Kinase II
CMC	Carboxymethyl Cellulose
CPT	Camptothecin
CSCs	Cancer Stem Cells
CT	Computed Tomography
cTACE	Conventional Transarterial Chemoembolization
DC	Dendritic Cell
DEBIRIs	Drug-Eluting Beads Loaded with Irinotecan
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DOX	Doxorubicin
ECM	Extracellular Matrix
EPR	Enhanced Permeability and Retention
FDA	U.S. Food and Drug Administration
FITC	Fluorescein Isothiocyanate
GCO	Global Cancer Observatory
GSH	Glutathione
HA	Hyaluronic Acid
HCC	Hepatocellular Carcinoma
HES	Hydrogel Embolic System
HIFU	High-Intensity Focused Ultrasound
ICD	Immunogenic Cell Death
IL	Interleukin
MMP	Matrix Metalloproteinase
MRI	Magnetic Resonance Imaging
NK	Natural Killer
NP	Nanoparticle
PEG	Poly(Ethylene Glycol)
PDT	Photodynamic Therapy
PTT	Photothermal Therapy
PVA	Poly(Vinyl Alcohol)
RGD	Arginine–Glycine–Aspartic Acid
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SCFA	Short-Chain Fatty Acid
SF	Silk Fibroin
siRNA	Small Interfering RNA
TACE	Transarterial Chemoembolization
TAM	Tumor-Associated Macrophage
TDLN	Tumor-Draining Lymph Node

TNBC	Triple-Negative Breast Cancer
TNF-α	Tumor Necrosis Factor-α
Treg	Regulatory T Cell
VEGF	Vascular Endothelial Growth Factor

References

1. Siegel, R.L.; Kratzer, T.B.; Wagle, N.S.; Sung, H.; Jemal, A. Cancer statistics, 2026. *CA Cancer J. Clin.* **2026**, *76*, e70043. [Google Scholar] [CrossRef]
2. Sung, H.; Filho, A.M.; Laversanne, M.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. *CA Cancer J. Clin.* **2026**, *76*, e70090. [Google Scholar] [CrossRef]
3. Pucci, C.; Martinelli, C.; Ciofani, G. Innovative approaches for cancer treatment: Current perspectives and new challenges. *Ecancermedicalscience* **2019**, *13*, 961. [Google Scholar] [CrossRef]
4. Liu, Y.; Zheng, Z. Understanding the global cancer statistics 2022: Growing cancer burden. *Sci. China Life Sci.* **2024**, *67*, 2274–2276. [Google Scholar] [CrossRef]
5. Analytics, C. Web of Science—Analyze Results. Available online: https://www.webofscience.com/wos/woscc/analyze-results/6e178e5d-b3e2-47d3-84ee-f7ef27e1478d-019a7eb30f (accessed on 22 January 2026).
6. Lee, K.Y.; Mooney, D.J. Hydrogels for Tissue Engineering. *Chem. Rev.* **2001**, *101*, 1869–1880. [Google Scholar] [CrossRef]
7. Hamidi, M.; Azadi, A.; Rafiei, P. Hydrogel nanoparticles in drug delivery. *Adv. Drug Deliv. Rev.* **2008**, *60*, 1638–1649. [Google Scholar] [CrossRef]
8. Del Valle, L.J.; Díaz, A.; Puiggalí, J. Hydrogels for Biomedical Applications: Cellulose, Chitosan, and Protein/Peptide Derivatives. *Gels* **2017**, *3*, 27. [Google Scholar] [CrossRef]
9. Vigata, M.; Meinert, C.; Hutmacher, D.W.; Bock, N. Hydrogels as Drug Delivery Systems: A Review of Current Characterization and Evaluation Techniques. *Pharmaceutics* **2020**, *12*, 1188. [Google Scholar] [CrossRef]
10. Correa, S.; Grosskopf, A.K.; Lopez Hernandez, H.; Chan, D.; Yu, A.C.; Stapleton, L.M.; Appel, E.A. Translational Applications of Hydrogels. *Chem. Rev.* **2021**, *121*, 11385–11457. [Google Scholar] [CrossRef]
11. Alonso, J.M.; del Olmo, J.A.; Perez Gonzalez, R.; Saez-Martinez, V. Injectable Hydrogels: From Laboratory to Industrialization. *Polymers* **2021**, *13*, 650. [Google Scholar] [CrossRef]
12. Almawash, S.; Osman, S.K.; Mustafa, G.; El Hamd, M.A. Current and Future Prospective of Injectable Hydrogels—Design Challenges and Limitations. *Pharmaceuticals* **2022**, *15*, 371. [Google Scholar] [CrossRef]
13. Chyzy, A.; Tomczykowa, M.; Plonska-Brzezinska, M.E. Hydrogels as Potential Nano-, Micro- and Macro-Scale Systems for Controlled Drug Delivery. *Materials* **2020**, *13*, 188. [Google Scholar] [CrossRef]
14. Ahmed, M.S.; Yun, S.; Kim, H.-Y.; Ko, S.; Islam, M.; Nam, K.-W. Hydrogels and Microgels: Driving Revolutionary Innovations in Targeted Drug Delivery, Strengthening Infection Management, and Advancing Tissue Repair and Regeneration. *Gels* **2025**, *11*, 179. [Google Scholar] [CrossRef]
15. Li, X.; Xu, X.; Xu, M.; Geng, Z.; Ji, P.; Liu, Y. Hydrogel systems for targeted cancer therapy. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1140436. [Google Scholar] [CrossRef]
16. Cheng, Y.; Zhang, H.; Wei, H.; Yu, C.-Y. Injectable hydrogels as emerging drug-delivery platforms for tumor therapy. *Biomater. Sci.* **2024**, *12*, 1151–1170. [Google Scholar] [CrossRef]
17. Kim, S.; Kim, D.-D.; Karmakar, M.; Cho, H.-J. Injectable hydrogel systems for local cancer therapy. *J. Pharm. Investig.* **2024**, *54*, 555–591. [Google Scholar] [CrossRef]
18. Palmese, L.L.; Thapa, R.K.; Sullivan, M.O.; Kiick, K.L. Hybrid hydrogels for biomedical applications. *Curr. Opin. Chem. Eng.* **2019**, *24*, 143–157. [Google Scholar] [CrossRef]
19. Fan, D.; Cao, Y.; Cao, M.; Wang, Y.; Cao, Y.; Gong, T. Nanomedicine in cancer therapy. *Signal Transduct. Target. Ther.* **2023**, *8*, 293. [Google Scholar] [CrossRef]
20. Sharma, T.; Gorivale, S.; Bhandari, P. Targeted drug delivery in cancer using nanomaterials: Advances and challenges. *J. Nanopart. Res.* **2024**, *26*, 127. [Google Scholar] [CrossRef]
21. Wang, J.; Gong, J.; Wei, Z. Strategies for Liposome Drug Delivery Systems to Improve Tumor Treatment Efficacy. *AAPS PharmSciTech* **2021**, *23*, 27. [Google Scholar] [CrossRef]

22. Quintanar-Guerrero, D.; Allémann, E.; Fessi, H.; Doelker, E. Preparation techniques and mechanisms of formation of biodegradable nanoparticles from preformed polymers. *Drug Dev. Ind. Pharm.* **1998**, *24*, 1113–1128. [Google Scholar] [CrossRef]
23. Wu, J. The Enhanced Permeability and Retention (EPR) Effect: The Significance of the Concept and Methods to Enhance Its Application. *J. Pers. Med.* **2021**, *11*, 771. [Google Scholar] [CrossRef]
24. Sabit, H.; Pawlik, T.M.; Radwan, F.; Abdel-Hakeem, M.; Abdel-Ghany, S.; Wadan, A.-H.S.; Elzawahri, M.; El-Hashash, A.; Arneth, B. Precision nanomedicine: Navigating the tumor microenvironment for enhanced cancer immunotherapy and targeted drug delivery. *Mol. Cancer* **2025**, *24*, 160. [Google Scholar] [CrossRef]
25. Maeda, H.; Bharate, G.Y.; Daruwalla, J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. *Eur. J. Pharm. Biopharm.* **2009**, *71*, 409–419. [Google Scholar] [CrossRef]
26. Huang, D.; Sun, L.; Huang, L.; Chen, Y. Nanodrug Delivery Systems Modulate Tumor Vessels to Increase the Enhanced Permeability and Retention Effect. *J. Pers. Med.* **2021**, *11*, 124. [Google Scholar] [CrossRef]
27. Xiao, X.; Teng, F.; Shi, C.; Chen, J.; Wu, S.; Wang, B.; Meng, X.; Essiet Imeh, A.; Li, W. Polymeric nanoparticles-Promising carriers for cancer therapy. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1024143. [Google Scholar] [CrossRef]
28. Belyaev, I.B.; Griaznova, O.Y.; Yaremenko, A.V.; Deyev, S.M.; Zelepukin, I.V. Beyond the EPR effect: Intravital microscopy analysis of nanoparticle drug delivery to tumors. *Adv. Drug Deliv. Rev.* **2025**, *219*, 115550. [Google Scholar] [CrossRef]
29. Pashkina, E.; Bykova, M.; Berishvili, M.; Lazarev, Y.; Kozlov, V. Hyaluronic Acid-Based Drug Delivery Systems for Cancer Therapy. *Cells* **2025**, *14*, 61. [Google Scholar] [CrossRef]
30. Jia, Y.; Chen, S.; Wang, C.; Sun, T.; Yang, L. Hyaluronic acid-based nano drug delivery systems for breast cancer treatment: Recent advances. *Front. Bioeng. Biotechnol.* **2022**, *10*, 990145. [Google Scholar] [CrossRef]
31. Mahmoudian, F.; Ahmari, A.; Shabani, S.; Sadeghi, B.; Fahimirad, S.; Fattahi, F. Aptamers as an approach to targeted cancer therapy. *Cancer Cell Int.* **2024**, *24*, 108. [Google Scholar] [CrossRef]
32. Spada, A.; Gerber-Lemaire, S. Surface Functionalization of Nanocarriers with Anti-EGFR Ligands for Cancer Active Targeting. *Nanomaterials* **2025**, *15*, 158. [Google Scholar] [CrossRef]
33. Imtiaz, S.; Ferdous, U.T.; Nizela, A.; Hasan, A.; Shakoor, A.; Zia, A.W.; Uddin, S. Mechanistic study of cancer drug delivery: Current techniques, limitations, and future prospects. *Eur. J. Med. Chem.* **2025**, *290*, 117535. [Google Scholar] [CrossRef]
34. Bandyopadhyay, A.; Das, T.; Nandy, S.; Sahib, S.; Preetam, S.; Gopalakrishnan, A.V.; Dey, A. Ligand-based active targeting strategies for cancer theranostics. *Naunyn Schmiedeberg's Arch. Pharmacol.* **2023**, *396*, 3417–3441. [Google Scholar] [CrossRef]
35. Mrsny, R.J. Active targeting strategies in cancer with a focus on potential nanotechnology applications. In *Nanotechnology for Cancer Therapy*; CRC Press: Boca Raton, FL, USA, 2006; pp. 19–42. [Google Scholar]
36. Taghipour, Y.D.; Zarebkohan, A.; Salehi, R.; Rahimi, F.; Torchilin, V.P.; Hamblin, M.R.; Seifalian, A. An update on dual targeting strategy for cancer treatment. *J. Control. Release* **2022**, *349*, 67–96. [Google Scholar] [CrossRef]
37. Nel, J.; Elkhoury, K.; Velot, É.; Bianchi, A.; Acherar, S.; Francius, G.; Tamayol, A.; Grandemange, S.; Arab-Tehrany, E. Functionalized liposomes for targeted breast cancer drug delivery. *Bioact. Mater.* **2023**, *24*, 401–437. [Google Scholar] [CrossRef]
38. Bakshi, A.K.; Haider, T.; Tiwari, R.; Soni, V. Critical parameters for design and development of multivalent nanoconstructs: Recent trends. *J. Pharm. Sci.* **2022**, *12*, 2335–2358. [Google Scholar] [CrossRef]
39. Mollazadeh, S.; Mackiewicz, M.; Yazdimamaghani, M. Recent advances in the redox-responsive drug delivery nanoplatforms: A chemical structure and physical property perspective. *Mater. Sci. Eng. C* **2021**, *118*, 111536. [Google Scholar] [CrossRef]
40. Rivero Berti, I.; Islan, G.A.; Castro, G.R. Enzymes and biopolymers. The opportunity for the smart design of molecular delivery systems. *Bioresour. Technol.* **2021**, *322*, 124546. [Google Scholar] [CrossRef]
41. Lee, S.; Shanti, A. Effect of Exogenous pH on Cell Growth of Breast Cancer Cells. *Int. J. Mol. Sci.* **2021**, *22*, 9910. [Google Scholar] [CrossRef]
42. Sobczak, M. Enzyme-Responsive Hydrogels as Potential Drug Delivery Systems—State of Knowledge and Future Prospects. *Int. J. Mol. Sci.* **2022**, *23*, 4421. [Google Scholar] [CrossRef]
43. Vu, T.T.; Yadav, S.; Reddy, O.S.; Jo, S.-H.; Joo, S.-B.; Kim, B.K.; Park, E.J.; Park, S.-H.; Lim, K.T. Reduction-Responsive Chitosan-Based Injectable Hydrogels for Enhanced Anticancer Therapy. *Pharmaceuticals* **2023**, *16*, 841. [Google Scholar] [CrossRef]
44. Eskandani, M.; Derakhshankhah, H.; Jahanban-Esfahlan, R.; Jaymand, M. Folate-conjugated pH- and redox-responsive magnetic hydrogel based on tragacanth gum for "smart" chemo/hyperthermia treatment of cancerous cells. *J. Drug Deliv. Sci. Technol.* **2023**, *84*, 104449. [Google Scholar] [CrossRef]
45. Solanki, R.; Bhatia, D. Stimulus-Responsive Hydrogels for Targeted Cancer Therapy. *Gels* **2024**, *10*, 440. [Google Scholar] [CrossRef]

46. Lee, K.K.; Go, K.; Lee, E.; Kim, H.; Kim, S.; Kim, J.-H.; Chae, M.S.; Jeong, J.-O. Multifunctional Hydrogels for Advanced Cancer Treatment: Diagnostic Imaging and Therapeutic Modalities. *Gels* **2025**, *11*, 426. [Google Scholar] [CrossRef]
47. Mohammadzadeh, V.; Atapour-Mashhad, H.; Shahvali, S.; Salehi, B.; Shaban, M.; Shirzad, M.; Salahvarzi, A.; Mohammadi, M. Hydrogels as advanced drug delivery platforms for cancer immunotherapy: Promising innovations and future outlook. *J. Nanobiotechnol.* **2025**, *23*, 545. [Google Scholar] [CrossRef]
48. Wang, F.; Chen, J.; Liu, J.; Zeng, H. Cancer theranostic platforms based on injectable polymer hydrogels. *Biomater. Sci.* **2021**, *9*, 3543–3575. [Google Scholar] [CrossRef]
49. Yoon, M.S.; Lee, J.M.; Jo, M.J.; Kang, S.J.; Yoo, M.K.; Park, S.Y.; Bong, S.; Park, C.-S.; Park, C.-W.; Kim, J.-S.; et al. Dual-Drug Delivery Systems Using Hydrogel–Nanoparticle Composites: Recent Advances and Key Applications. *Gels* **2025**, *11*, 520. [Google Scholar] [CrossRef]
50. Chenite, A.; Chaput, C.; Wang, D.; Combes, C.; Buschmann, M.D.; Hoemann, C.D.; Leroux, J.C.; Atkinson, B.L.; Binette, F.; Selmani, A. Novel injectable neutral solutions of chitosan form biodegradable gels in situ. *Biomaterials* **2000**, *21*, 2155–2161. [Google Scholar] [CrossRef]
51. Ruel-Gariépy, E.; Chenite, A.; Chaput, C.; Guirguis, S.; Leroux, J. Characterization of thermosensitive chitosan gels for the sustained delivery of drugs. *Int. J. Pharm.* **2000**, *203*, 89–98. [Google Scholar] [CrossRef]
52. Dang, J.M.; Sun, D.D.N.; Shin-Ya, Y.; Sieber, A.N.; Kostuik, J.P.; Leong, K.W. Temperature-responsive hydroxybutyl chitosan for the culture of mesenchymal stem cells and intervertebral disk cells. *Biomaterials* **2006**, *27*, 406–418. [Google Scholar] [CrossRef]
53. Li, N.; Lin, J.; Liu, C.; Zhang, Q.; Li, R.; Wang, C.; Zhao, C.; Lu, L.; Zhou, C.; Tian, J.; et al. Temperature- and pH-responsive injectable chitosan hydrogels loaded with doxorubicin and curcumin as long-lasting release platforms for the treatment of solid tumors. *Front. Bioeng. Biotechnol.* **2022**, *10*, 1043939. [Google Scholar] [CrossRef]
54. Mantooth, S.M.; Green, J.M.; Green, W.D.; Nguyen, K.G.; Mantooth, K.A.; Meritet, D.M.; Milner, J.J.; Zaharoff, D.A. An injectable hydrogel enhances intratumoral retention and antitumor efficacy of cytokine immunotherapy in murine triple negative breast tumor models. *J. Control. Release* **2025**, *383*, 113761. [Google Scholar] [CrossRef]
55. Ilgin, P.; Avci, G.; Silan, C.; Ekici, S.; Aktas, N.; Ayyala, R.S.; John, V.T.; Sahiner, N. Colloidal drug carries from (sub)micron hyaluronic acid hydrogel particles with tunable properties for biomedical applications. *Carbohydr. Polym.* **2010**, *82*, 997–1003. [Google Scholar] [CrossRef]
56. Ekici, S.; Ilgin, P.; Yilmaz, S.; Aktas, N.; Sahiner, N. Temperature and magnetic field responsive hyaluronic acid particles with tunable physical and chemical properties. *Appl. Surf. Sci.* **2011**, *257*, 2669–2676. [Google Scholar] [CrossRef]
57. Sahiner, N.; Silan, C.; Sagbas, S.; Ilgin, P.; Butun, S.; Erdugan, H.; Ayyala, R.S. Porous and modified HA particles as potential drug delivery systems. *Micropor. Mesopor. Mat.* **2012**, *155*, 124–130. [Google Scholar] [CrossRef]
58. Wang, Y.; Zhang, X.; Zhang, Y.; Shi, F.; Du, S.; Zhang, Z.; Zhao, C.; Luo, S.; Wang, P.; Wu, D.; et al. Sprayed hyaluronic acid based multidrug composite hydrogel for postoperative colorectal cancer ultra-efficient long-lasting multi-stage immunochemo synergistic therapy. *Mater. Horiz.* **2025**, *12*, 4317–4335. [Google Scholar] [CrossRef]
59. Fan, S.; Liu, Q.; Dong, J.; Ai, X.; Li, J.; Huang, W.; Sun, T. In situ forming an injectable hyaluronic acid hydrogel for drug delivery and synergistic tumor therapy. *Heliyon* **2024**, *10*, e32135. [Google Scholar] [CrossRef]
60. Liang, K.; Ng, S.; Lee, F.; Lim, J.; Chung, J.E.; Lee, S.S.; Kurisawa, M. Targeted intracellular protein delivery based on hyaluronic acid-green tea catechin nanogels. *Acta Biomater.* **2016**, *33*, 142–152. [Google Scholar] [CrossRef]
61. Ilić-Stojanović, S.; Nikolić, L.; Cakić, S. A Review of Patents and Innovative Biopolymer-Based Hydrogels. *Gels* **2023**, *9*, 556. [Google Scholar] [CrossRef]
62. Chander, S.; Kulkarni, G.T.; Dhiman, N.; Kharkwal, H. Protein-Based Nanohydrogels for Bioactive Delivery. *Front. Chem.* **2021**, *9*, 573748. [Google Scholar] [CrossRef]
63. Pawar, S.N.; Edgar, K.J. Alginate derivatization: A review of chemistry, properties and applications. *Biomaterials* **2012**, *33*, 3279–3305. [Google Scholar] [CrossRef]
64. Abid, A.I.; Muzammel, H.; Anton, N.; Conzatti, G.; Vandamme, T. Understanding alginate-based hydrogels and their crosstalk with cells. *Carbohyd. Polym. Technol. Appl.* **2026**, *16*, 101252. [Google Scholar] [CrossRef]
65. Valentino, C.; Vigani, B.; Fedeli, I.; Miele, D.; Marrubini, G.; Malavasi, L.; Ferrari, F.; Sandri, G.; Rossi, S. Development of alginate-spermidine micro/nanogels as potential antioxidant and anti-inflammatory tool in peripheral nerve injuries. Formulation studies and physico-chemical characterization. *Int. J. Pharm.* **2022**, *626*, 122168. [Google Scholar] [CrossRef]
66. He, L.; Shang, Z.; Liu, H.; Yuan, Z.-x. Alginate-Based Platforms for Cancer-Targeted Drug Delivery. *Biomed. Res. Int.* **2020**, *2020*, 1487259. [Google Scholar] [CrossRef]

67. Zang, C.; Tian, Y.; Tang, Y.; Tang, M.; Yang, D.; Chen, F.; Ghaffarlou, M.; Tu, Y.; Ashrafizadeh, M.; Li, Y. Hydrogel-based platforms for site-specific doxorubicin release in cancer therapy. *J. Transl. Med.* **2024**, *22*, 879. [Google Scholar] [CrossRef]
68. Patra, P.; Upadhyay, T.K.; Alshammari, N.; Saeed, M.; Kesari, K.K. Alginate-Chitosan Biodegradable and Biocompatible Based Hydrogel for Breast Cancer Immunotherapy and Diagnosis: A Comprehensive Review. *ACS Appl. Bio Mater.* **2024**, *7*, 3515–3534. [Google Scholar] [CrossRef]
69. Zhou, Y.; Zhai, Z.; Yao, Y.; Stant, J.C.; Landrum, S.L.; Bortner, M.J.; Frazier, C.E.; Edgar, K.J. Oxidized hydroxypropyl cellulose/carboxymethyl chitosan hydrogels permit pH-responsive, targeted drug release. *Carbohydr. Polym.* **2023**, *300*, 120213. [Google Scholar] [CrossRef]
70. Li, X.; Tong, Z.; Qiu, Y.; Zheng, Z.; Zeng, S.; Zhao, D.; Yu, H. Balancing mechanical-thermal-electrical properties in cellulose ionogels via crystallization-induced molecular assembly. *Nat. Commun.* **2025**, *16*, 9970. [Google Scholar] [CrossRef]
71. Chen, T.; Yao, T.; Peng, H.; Whittaker, A.K.; Li, Y.; Zhu, S.; Wang, Z. An Injectable Hydrogel for Simultaneous Photothermal Therapy and Photodynamic Therapy with Ultrahigh Efficiency Based on Carbon Dots and Modified Cellulose Nanocrystals. *Adv. Funct. Mater.* **2021**, *31*, 2106079. [Google Scholar] [CrossRef]
72. Yang, J.; Wei, Y.; Gao, L.; Li, Z.; Yang, X. Thermosensitive methyl-cellulose-based injectable hydrogel carrying oxaliplatin for the treatment of peritoneal metastasis in colorectal cancer. *J. Mater. Chem. B* **2024**, *12*, 5171–5180. [Google Scholar] [CrossRef]
73. Sheng, Y.; Gao, J.; Yin, Z.-Z.; Kang, J.; Kong, Y. Dual-drug delivery system based on the hydrogels of alginate and sodium carboxymethyl cellulose for colorectal cancer treatment. *Carbohydr. Polym.* **2021**, *269*, 118325. [Google Scholar] [CrossRef]
74. Vakili, M.R.; Mohammed-Saeid, W.; Aljasser, A.; Hopwood-Raja, J.; Ahvazi, B.; Hrynets, Y.; Betti, M.; Lavasanifar, A. Development of mucoadhesive hydrogels based on polyacrylic acid grafted cellulose nanocrystals for local cisplatin delivery. *Carbohydr. Polym.* **2021**, *255*, 117332. [Google Scholar] [CrossRef]
75. Yue, K.; Trujillo-de Santiago, G.; Alvarez, M.M.; Tamayol, A.; Annabi, N.; Khademhosseini, A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials* **2015**, *73*, 254–271. [Google Scholar] [CrossRef]
76. Sun, M.; Sun, X.; Wang, Z.; Guo, S.; Yu, G.; Yang, H. Synthesis and Properties of Gelatin Methacryloyl (GelMA) Hydrogels and Their Recent Applications in Load-Bearing Tissue. *Polymers* **2018**, *10*, 1290. [Google Scholar] [CrossRef]
77. Zhu, M.; Wang, Y.; Ferracci, G.; Zheng, J.; Cho, N.-J.; Lee, B.H. Gelatin methacryloyl and its hydrogels with an exceptional degree of controllability and batch-to-batch consistency. *Sci. Rep.* **2019**, *9*, 6863. [Google Scholar] [CrossRef]
78. Antoine, E.E.; Vlachos, P.P.; Rylander, M.N. Review of collagen I hydrogels for bioengineered tissue microenvironments: Characterization of mechanics, structure, and transport. *Tissue Eng. Part B Rev.* **2014**, *20*, 683–696. [Google Scholar] [CrossRef]
79. Chen, J.; Cui, M.; He, L.; Mu, Y.; Hu, N.; Guan, X. Engineered elastin-like polypeptide-based hydrogel delivering chemotherapeutics and PD-L1 antibodies for potentiated cancer immunotherapy. *J. Mater. Chem. B* **2023**, *11*, 10355–10361. [Google Scholar] [CrossRef]
80. Zhang, Y.N.; Avery, R.K.; Vallmajo-Martin, Q.; Assmann, A.; Vegh, A.; Memic, A.; Olsen, B.D.; Annabi, N.; Khademhosseini, A. A highly elastic and rapidly crosslinkable elastin-like polypeptide-based hydrogel for biomedical applications. *Adv. Funct. Mater.* **2015**, *25*, 4814–4826. [Google Scholar] [CrossRef]
81. Dragojevic, S.; Turner, L.; Pal, P.; Janorkar, A.V.; Raucher, D. Elastin-like Polypeptide Hydrogels for Tunable, Sustained Local Chemotherapy in Malignant Glioma. *Pharmaceutics* **2022**, *14*, 2072. [Google Scholar] [CrossRef]
82. Jiang, A.; Guan, X.; He, L.; Guan, X. Engineered elastin-like polypeptides: An efficient platform for enhanced cancer treatment. *Front. Pharmacol.* **2023**, *13*, 1113079. [Google Scholar] [CrossRef]
83. Shi, X.; Chen, D.; Liu, G.; Zhang, H.; Wang, X.; Wu, Z.; Wu, Y.; Yu, F.; Xu, Q. Application of elastin-like polypeptide in tumor therapy. *Cancers* **2022**, *14*, 3683. [Google Scholar] [CrossRef]
84. Yang, M.; Dao, A.T.N.; Nakatani, H.; Eguchi, Y.; Suzuki, R.; Koseki, Y.; Oka, K.; Kasai, H. Silk protein-based injectable hydrogel to deliver nano-prodrugs toward localized cancer treatment. *MRS Commun.* **2025**, *15*, 598–605. [Google Scholar] [CrossRef]
85. Wu, P.; Liu, Q.; Wang, Q.; Qian, H.; Yu, L.; Liu, B.; Li, R. Novel silk fibroin nanoparticles incorporated silk fibroin hydrogel for inhibition of cancer stem cells and tumor growth. *Int. J. Nanomed.* **2018**, *13*, 5405–5418. [Google Scholar] [CrossRef]
86. Raza, F.; Zhu, Y.; Chen, L.; You, X.; Zhang, J.; Khan, A.; Khan, M.W.; Hasnat, M.; Zafar, H.; Wu, J.; et al. Paclitaxel-loaded pH responsive hydrogel based on self-assembled peptides for tumor targeting. *Biomater. Sci.* **2019**, *7*, 2023–2036. [Google Scholar] [CrossRef]
87. Liu, Y.; Ran, Y.; Ge, Y.; Raza, F.; Li, S.; Zafar, H.; Wu, Y.; Paiva-Santos, A.C.; Yu, C.; Sun, M.; et al. pH-Sensitive Peptide Hydrogels as a Combination Drug Delivery System for Cancer Treatment. *Pharmaceutics* **2022**, *14*, 652. [Google Scholar] [CrossRef]

88. Jin, H.; Wan, C.; Zou, Z.; Zhao, G.; Zhang, L.; Geng, Y.; Chen, T.; Huang, A.; Jiang, F.; Feng, J.P.; et al. Tumor Ablation and Therapeutic Immunity Induction by an Injectable Peptide Hydrogel. *ACS Nano* **2018**, *12*, 3292–3310. [Google Scholar] [CrossRef]
89. Dai, X.; Meng, J.; Deng, S.; Zhang, L.; Wan, C.; Lu, L.; Huang, J.; Hu, Y.; Zhang, Z.; Li, Y.; et al. Targeting CAMKII to reprogram tumor-associated macrophages and inhibit tumor cells for cancer immunotherapy with an injectable hybrid peptide hydrogel. *Theranostics* **2020**, *10*, 3049–3063. [Google Scholar] [CrossRef]
90. Zhao, X.; Xi, Y.; Zhang, Y.; Wu, Q.; Meng, R.; Zheng, B.; Rei, L. Redox-Sensitive Gelatin/Silica-Aptamer Nanogels for Targeted siRNA Delivery. *Nanoscale Res. Lett.* **2019**, *14*, 273. [Google Scholar] [CrossRef]
91. Gong, Y.; Chen, W.; Chen, X.; He, Y.; Jiang, H.; Zhang, X.; Pan, L.; Ni, B.; Yang, F.; Xu, Y.; et al. An Injectable Epigenetic Autophagic Modulatory Hydrogel for Boosting Umbilical Cord Blood NK Cell Therapy Prevents Postsurgical Relapse of Triple-Negative Breast Cancer. *Adv. Sci.* **2022**, *9*, 2201271. [Google Scholar] [CrossRef]
92. Maher, M.K.; White, J.F.; Glattauer, V.; Yue, Z.; Hughes, T.C.; Ramshaw, J.A.M.; Wallace, G.G. Variation in Hydrogel Formation and Network Structure for Telo-, Atelo- and Methacrylated Collagens. *Polymers* **2022**, *14*, 1775. [Google Scholar] [CrossRef]
93. Hwang, J.; An, E.-K.; Zhang, W.; Kim, H.J.; Eom, Y.; Jin, J.-O. Dual-functional alginate and collagen–based injectable hydrogel for the treatment of cancer and its metastasis. *J. Nanobiotechnol.* **2022**, *20*, 245. [Google Scholar] [CrossRef]
94. Morales, X.; Cortés-Domínguez, I.; Ortiz-de-Solorzano, C. Modeling the Mechanobiology of Cancer Cell Migration Using 3D Biomimetic Hydrogels. *Gels* **2021**, *7*, 17. [Google Scholar] [CrossRef]
95. Madappura, A.P.; Madduri, S. A comprehensive review of silk-fibroin hydrogels for cell and drug delivery applications in tissue engineering and regenerative medicine. *Comput. Struct. Biotechnol. J.* **2023**, *21*, 4868–4886. [Google Scholar] [CrossRef]
96. Tang, C.-H. Assembly of food proteins for nano- encapsulation and delivery of nutraceuticals (a mini-review). *Food Hydrocoll.* **2021**, *117*, 106710. [Google Scholar] [CrossRef]
97. Khatkar, A.B.; Kaur, A.; Khatkar, S.K. Restructuring of soy protein employing ultrasound: Effect on hydration, gelation, thermal, in-vitro protein digestibility and structural attributes. *LWT* **2020**, *132*, 109781. [Google Scholar] [CrossRef]
98. Nesterenko, A.; Alric, I.; Silvestre, F.; Durrieu, V. Influence of soy protein's structural modifications on their microencapsulation properties: α-Tocopherol microparticle preparation. *Food Res. Int.* **2012**, *48*, 387–396. [Google Scholar] [CrossRef]
99. Ding, X.; Yao, P. Soy Protein/Soy Polysaccharide Complex Nanogels: Folic Acid Loading, Protection, and Controlled Delivery. *Langmuir* **2013**, *29*, 8636–8644. [Google Scholar] [CrossRef]
100. Pamfil, D.; Vasile, C. *Nanogels of Natural Polymers BT—Polymer Gels: Perspectives and Applications*; Thakur, V.K., Thakur, M.K., Voicu, S.I., Eds.; Springer: Singapore, 2018; pp. 71–110. [Google Scholar] [CrossRef]
101. Cheng, X.; Zeng, X.; Li, D.; Wang, X.; Sun, M.; He, L.; Tang, R. TPGS-grafted and acid-responsive soy protein nanogels for efficient intracellular drug release, accumulation, penetration in 3D tumor spheroids of drug-resistant cancer cells. *Mater. Sci. Eng. C* **2019**, *102*, 863–875. [Google Scholar] [CrossRef]
102. Zhong, R.; Talebian, S.; Mendes, B.B.; Wallace, G.; Langer, R.; Conde, J.; Shi, J. Hydrogels for RNA delivery. *Nat. Mater.* **2023**, *22*, 818–831. [Google Scholar] [CrossRef]
103. Xu, H.; Fei, Y.; Wang, X.; Jiao, W.; Jin, Y. Advances in Hydrogel-Based Delivery of RNA Drugs for Antitumor Therapy. *Gels* **2025**, *11*, 633. [Google Scholar] [CrossRef]
104. Fan, Y.; Zhan, M.; Liang, J.; Yang, X.; Zhang, B.; Shi, X.; Hu, Y. Programming Injectable DNA Hydrogels Yields Tumor Microenvironment-Activatable and Immune-Instructive Depots for Augmented Chemo-Immunotherapy. *Adv. Sci.* **2023**, *10*, 2302119. [Google Scholar] [CrossRef]
105. Segovia, N.; Pont, M.; Oliva, N.; Ramos, V.; Borrós, S.; Artzi, N. Hydrogel Doped with Nanoparticles for Local Sustained Release of siRNA in Breast Cancer. *Adv. Healthc. Mater.* **2015**, *4*, 271–280. [Google Scholar] [CrossRef]
106. Bakhtiar, A.; Kuan, X.-Y.; Chowdhury, E.H. The potential of nanoparticle-based siRNA delivery in breast cancer treatment. *Nanomedicine* **2025**, *20*, 531–533. [Google Scholar] [CrossRef]
107. Agbaria, M.; Jbara-Agbaria, D.; Golomb, G. Localized delivery of gel-embedded siRNA nanoparticles for pancreatic cancer treatment: Formulation, biodistribution and bioactivity in mice. *Precis. Nanomed.* **2025**, *8*, 1482–1500. [Google Scholar] [CrossRef]
108. Carlesso, A.; Hörberg, J.; Deganutti, G.; Reymer, A.; Matsson, P. Structural dynamics of therapeutic nucleic acids with phosphorothioate backbone modifications. *NAR Genom. Bioinform.* **2024**, *6*, lqae058. [Google Scholar] [CrossRef]
109. Dattilo, M.; Patitucci, F.; Prete, S.; Parisi, O.I.; Puoci, F. Polysaccharide-Based Hydrogels and Their Application as Drug Delivery Systems in Cancer Treatment: A Review. *J. Funct. Biomater.* **2023**, *14*, 55. [Google Scholar] [CrossRef]

110. Katona, G.; Sipos, B.; Csóka, I. Advancements in the Field of Protein-Based Hydrogels: Main Types, Characteristics, and Their Applications. *Gels* **2025**, *11*, 306. [Google Scholar] [CrossRef]
111. Mala, P.H.; D, T.; C, H.R.; G, D.P. Silk based hydrogels in biomedical applications: A review. *Int. J. Adv. Biochem. Res.* **2024**, *8*, 1203–1207. [Google Scholar] [CrossRef]
112. Di, Y.; Wang, P.; Li, C.; Xu, S.; Tian, Q.; Wu, T.; Tian, Y.; Gao, L. Design, Bioanalytical, and Biomedical Applications of Aptamer-Based Hydrogels. *Front. Med.* **2020**, *7*, 456. [Google Scholar] [CrossRef]
113. Rehman, S.; Jamil, Q.A.; Noreen, S.; Ashraf, M.A.; Madni, A.; Mahmood, H.; Shoukat, H.; Raza, M.R. Preparation and Evaluation of pH-Sensitive Chitosan/Alginate Nanohybrid Mucoadhesive Hydrogel Beads: An Effective Approach to a Gastro-Retentive Drug Delivery System. *Pharmaceutics* **2024**, *16*, 1451. [Google Scholar] [CrossRef]
114. Amiryaghoubi, N.; Abdollahiyan, P.; Fathi, M.; Erfan-Niya, H. Injectable chitosan copolymer/gold nanoparticles/gelatin hybrid hydrogels for delivery of doxorubicin for breast cancer treatment. *Polym. Bull.* **2024**, *81*, 14199–14216. [Google Scholar] [CrossRef]
115. Murtaza, G.; Rizvi, A.S.; Qiu, L.; Xue, M.; Meng, Z. Aptamer empowered hydrogels: Fabrication and bio-sensing applications. *J. Appl. Polym. Sci.* **2022**, *139*, e52441. [Google Scholar] [CrossRef]
116. El-Husseiny, H.M.; Mady, E.A.; Hamabe, L.; Abugomaa, A.; Shimada, K.; Yoshida, T.; Tanaka, T.; Yokoi, A.; Elbadawy, M.; Tanaka, R. Smart/stimuli-responsive hydrogels: Cutting-edge platforms for tissue engineering and other biomedical applications. *Mater. Today Bio* **2022**, *13*, 100186. [Google Scholar] [CrossRef]
117. Basu, T.; Goswami, D.; Majumdar, S. Fabrication of crosslinker free hydrogels with diverse properties: An interplay of multi-scale physical forces within polymer matrix. *iScience* **2024**, *27*, 111227. [Google Scholar] [CrossRef]
118. Kumar, A.; Pandey, S.; Kumar, K.; Krishnamoorthi, S.; Tungala, K. Hydrogels: Classification, cross-linking methods, characteristics, and current trends in biomedical applications. *Polym. Bullet.* **2025**, *83*, 49. [Google Scholar] [CrossRef]
119. Kapatsila, S.; Taras, R.; Varchuk, D.; Nosova, N.; Varvarenko, S.; Samaryk, V. Influence of Calcium Crosslinker Form on Alginate Hydrogel Properties. *Gels* **2025**, *11*, 885. [Google Scholar] [CrossRef]
120. Qiu, X.; Yang, Y.; Wang, L.; Lu, S.; Shao, Z.; Chen, X. Synergistic interactions during thermosensitive chitosan-β-glycerophosphate hydrogel formation. *RSC Adv.* **2011**, *1*, 282–289. [Google Scholar] [CrossRef]
121. Rahmanian-Devin, P.; Baradaran Rahimi, V.; Askari, V.R. Thermosensitive chitosan-β-glycerophosphate hydrogels as targeted drug delivery systems: An overview on preparation and their applications. *Adv. Pharmacol. Pharm. Sci.* **2021**, *2021*, 6640893. [Google Scholar] [CrossRef]
122. Zamani Alavijeh, R.; Shokrollahi, P.; Barzin, J. A thermally and water activated shape memory gelatin physical hydrogel, with a gel point above the physiological temperature, for biomedical applications. *J. Mater. Chem. B* **2017**, *5*, 2302–2314. [Google Scholar] [CrossRef]
123. Talaei, A.; O'Connell, C.D.; Sayyar, S.; Maher, M.; Yue, Z.; Choong, P.F.; Wallace, G.G. Optimizing the composition of gelatin methacryloyl and hyaluronic acid methacryloyl hydrogels to maximize mechanical and transport properties using response surface methodology. *J. Biomed. Mater. Res. B Appl. Biomater.* **2023**, *111*, 526–537. [Google Scholar] [CrossRef]
124. Luo, Z.; Wang, Y.; Xu, Y.; Wang, J.; Yu, Y. Modification and crosslinking strategies for hyaluronic acid-based hydrogel biomaterials. *Smart. Med.* **2023**, *2*, e20230029. [Google Scholar] [CrossRef]
125. Li, X.; Xiong, Y. Application of "Click" Chemistry in Biomedical Hydrogels. *ACS Omega* **2022**, *7*, 36918–36928. [Google Scholar] [CrossRef]
126. Wang, S.; Tavakoli, S.; Parvathaneni, R.P.; Nawale, G.N.; Oommen, O.P.; Hilborn, J.; Varghese, O.P. Dynamic covalent crosslinked hyaluronic acid hydrogels and nanomaterials for biomedical applications. *Biomat. Sci.* **2022**, *10*, 6399–6412. [Google Scholar] [CrossRef]
127. Song, W.; Ko, J.; Choi, Y.H.; Hwang, N.S. Recent advancements in enzyme-mediated crosslinkable hydrogels: In vivo-mimicking strategies. *APL Bioeng.* **2021**, *5*, 021502. [Google Scholar] [CrossRef]
128. Naranjo-Alcazar, R.; Bendix, S.; Groth, T.; Gallego Ferrer, G. Research Progress in Enzymatically Cross-Linked Hydrogels as Injectable Systems for Bioprinting and Tissue Engineering. *Gels* **2023**, *9*, 230. [Google Scholar] [CrossRef]
129. Kopplin, G.; Lervik, A.; Draget, K.I.; Aachmann, F.L. Alginate gels crosslinked with chitosan oligomers—A systematic investigation into alginate block structure and chitosan oligomer interaction. *RSC Adv.* **2021**, *11*, 13780–13798. [Google Scholar] [CrossRef]
130. Hidaka, M.; Kojima, M.; Sakai, S.; Delattre, C. Characterization of Chitosan Hydrogels Obtained through Phenol and Tripolyphosphate Anionic Crosslinking. *Polymers* **2024**, *16*, 1274. [Google Scholar] [CrossRef]

131. Feyissa, Z.; Edossa, G.D.; Gupta, N.K.; Negera, D. Development of double crosslinked sodium alginate/chitosan based hydrogels for controlled release of metronidazole and its antibacterial activity. *Heliyon* **2023**, *9*, e20144. [Google Scholar] [CrossRef]
132. Li, J.; Mooney, D.J. Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071. [Google Scholar] [CrossRef]
133. Briggs, F.; Browne, D.; Asuri, P. Role of Polymer Concentration and Crosslinking Density on Release Rates of Small Molecule Drugs. *Int. J. Mol. Sci.* **2022**, *23*, 4118. [Google Scholar] [CrossRef]
134. Zander, Z.K.; Hua, G.; Wiener, C.G.; Vogt, B.D.; Becker, M.L. Control of Mesh Size and Modulus by Kinetically Dependent Cross-Linking in Hydrogels. *Adv. Mater.* **2015**, *27*, 6283–6288. [Google Scholar] [CrossRef]
135. Li, D.; Li, K.; Shen, T.; Zhao, X.; Gu, Z.; Chang, X.; Zhao, D. From Biomass to Functional Gels: Multiscale Topology Reconstruction and High-Performance Applications. *Adv. Funct. Mater.* **2026**, *36*, e77142. [Google Scholar] [CrossRef]
136. Rehmann, M.S.; Skeens, K.M.; Kharkar, P.M.; Ford, E.M.; Maverakis, E.; Lee, K.H.; Kloxin, A.M. Tuning and predicting mesh size and protein release from step growth hydrogels. *Biomacromolecules* **2017**, *18*, 3131. [Google Scholar] [CrossRef]
137. Abune, L.; Wang, Y. Affinity Hydrogels for Protein Delivery. *Trends Pharmacol. Sci.* **2021**, *42*, 300–312. [Google Scholar] [CrossRef]
138. Rockwell, P.N.; Jablonski, E.L.; Vogel, B.M. Degradation, swelling, and drug release behavior of injectable ETTMP/PEGDA hydrogels. *Biomed. Mater.* **2025**, *20*, 035016. [Google Scholar] [CrossRef]
139. Bayer, I.S. Controlled Drug Release from Nanoengineered Polysaccharides. *Pharmaceutics* **2023**, *15*, 1364. [Google Scholar] [CrossRef]
140. Rizwan, M.; Damodharan, N. Mathematical modelling of dissolution kinetics in dosage forms. *Res. J. Pharm. Technol.* **2020**, *13*, 1339–1345. [Google Scholar] [CrossRef]
141. Mohsin, M.E.A.; Siddiqa, A.J.; Mousa, S.; Shrivastava, N.K. Design, Characterization, and Release Kinetics of a Hybrid Hydrogel Drug Delivery System for Sustained Hormone Therapy. *Polymers* **2025**, *17*, 999. [Google Scholar] [CrossRef]
142. Hopfenberg, H. Controlled release from erodible slabs, cylinders, and spheres. In *Controlled Release Polymeric Formulations*; Paul, D.R., Harris, F.W., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, USA, 1976; Volume 33, pp. 26–32. [Google Scholar] [CrossRef]
143. Koduri, S.C.; Napoleon, A.A. Mathematical model application for in vitro release kinetics of ranolazine extended-release tablets. *Appl. Clin. Pharmacol.* **2024**, 182–188. [Google Scholar] [CrossRef]
144. Lee, H.; Jeong, Y.; Lee, N.; Lee, I.; Lee, J.H. Recent Advances in Injectable Hydrogels for Biomedical and Aesthetic Applications: Focus on Rheological Characteristics. *Gels* **2026**, *12*, 11. [Google Scholar] [CrossRef]
145. Liu, B.; Chen, K. Advances in Hydrogel-Based Drug Delivery Systems. *Gels* **2024**, *10*, 262. [Google Scholar] [CrossRef]
146. Hyun, H.; Yoo, Y.B.; Kim, S.Y.; Ko, H.S.; Chun, H.J.; Yang, D.H. Hydrogel-Mediated DOX·HCl/PTX Delivery System for Breast Cancer Therapy. *Int. J. Mol. Sci.* **2019**, *20*, 4671. [Google Scholar] [CrossRef]
147. Mamidi, N.; Poellmann, M.; Javius-Jones, K.; Nam, K.; Hong, S. Innovative hydrogel-based delivery systems for immunotherapy: A review of pre-clinical progress. *Nano Res.* **2024**, *17*, 9031–9043. [Google Scholar] [CrossRef]
148. Zhao, Y.; Zheng, Z.; Yu, C.-Y.; Wei, H. Engineered cyclodextrin-based supramolecular hydrogels for biomedical applications. *J. Mater. Chem. B* **2024**, *12*, 39–63. [Google Scholar] [CrossRef]
149. Majumder, P.; Singh, A.; Wang, Z.; Dutta, K.; Pahwa, R.; Liang, C.; Andrews, C.; Patel, N.L.; Shi, J.; de Val, N.; et al. Surface-fill hydrogel attenuates the oncogenic signature of complex anatomical surface cancer in a single application. *Nat. Nanotechnol.* **2021**, *16*, 1251–1259. [Google Scholar] [CrossRef]
150. Xiong, L.; Luo, Q.; Wang, Y.; Li, X.; Shen, Z.; Zhu, W. An injectable drug-loaded hydrogel based on a supramolecular polymeric prodrug. *Chem. Commun.* **2015**, *51*, 14644–14647. [Google Scholar] [CrossRef]
151. Fan, R.; Sun, W.; Zhang, T.; Wang, R.; Tian, Y.; Zhang, H.; Li, J.; Zheng, A.; Song, S. Paclitaxel-nanocrystals-loaded network thermosensitive hydrogel for localised postsurgical recurrent of breast cancer after surgical resection. *Biomed. Pharmacother.* **2022**, *150*, 113017. [Google Scholar] [CrossRef]
152. de Lima, C.S.A.; Balogh, T.S.; Varca, J.P.R.O.; Varca, G.H.C.; Lugão, A.B.; Camacho-Cruz, L.A.; Bucio, E.; Kadlubowski, S.S. An updated review of macro, micro, and nanostructured hydrogels for biomedical and pharmaceutical applications. *Pharmaceutics* **2020**, *12*, 970. [Google Scholar] [CrossRef]
153. Minhas, M.U.; Ahmad, M.; Anwar, J.; Khan, S. Synthesis and Characterization of Biodegradable Hydrogels for Oral Delivery of 5-Fluorouracil Targeted to Colon: Screening with Preliminary In Vivo Studies. *Adv. Polym. Technol.* **2018**, *37*, 221–229. [Google Scholar] [CrossRef]

154. Poursaid, A.; Price, R.; Tiede, A.; Olson, E.; Huo, E.; McGill, L.; Ghandehari, H.; Cappello, J. In situ gelling silk-elastinlike protein polymer for transarterial chemoembolization. *Biomaterials* **2015**, *57*, 142–152. [Google Scholar] [CrossRef]
155. Poursaid, A.; Jensen, M.M.; Huo, E.; Ghandehari, H. Polymeric materials for embolic and chemoembolic applications. *J. Control. Release* **2016**, *240*, 414–433. [Google Scholar] [CrossRef]
156. Shatsberg, Z.; Zhang, X.; Ofek, P.; Malhotra, S.; Krivitsky, A.; Scomparin, A.; Tiram, G.; Calderón, M.; Haag, R.; Satchi-Fainaro, R. Functionalized nanogels carrying an anticancer microRNA for glioblastoma therapy. *J. Control. Release* **2016**, *239*, 159–168. [Google Scholar] [CrossRef]
157. Zhang, D.; Tian, S.; Liu, Y.; Zheng, M.; Yang, X.; Zou, Y.; Shi, B.; Luo, L. Near infrared-activatable biomimetic nanogels enabling deep tumor drug penetration inhibit orthotopic glioblastoma. *Nat. Commun.* **2022**, *13*, 6835. [Google Scholar] [CrossRef]
158. Gholamali, I.; Yadollahi, M. Bio-nanocomposite Polymer Hydrogels Containing Nanoparticles for Drug Delivery: A Review. *Regen. Eng. Transl. Med.* **2021**, *7*, 129–146. [Google Scholar] [CrossRef]
159. Kim, K. Hybrid Systems of Gels and Nanoparticles for Cancer Therapy: Advances in Multifunctional Therapeutic Platforms. *Gels* **2025**, *11*, 170. [Google Scholar] [CrossRef]
160. Cai, M.-H.; Chen, X.-Y.; Fu, L.-Q.; Du, W.-L.; Yang, X.; Mou, X.-Z.; Hu, P.-Y. Design and Development of Hybrid Hydrogels for Biomedical Applications: Recent Trends in Anticancer Drug Delivery and Tissue Engineering. *Front. Bioeng. Biotechnol.* **2021**, *9*, 630943. [Google Scholar] [CrossRef]
161. Bai, S.; Zhang, Y.; Li, D.; Shi, X.; Lin, G.; Liu, G. Gain an advantage from both sides: Smart size-shrinkable drug delivery nanosystems for high accumulation and deep penetration. *Nano Today* **2021**, *36*, 101038. [Google Scholar] [CrossRef]
162. Holder, J.E.; Ferguson, C.; Oliveira, E.; Lodeiro, C.; Trim, C.M.; Byrne, L.J.; Bertolo, E.; Wilson, C.M. The use of nanoparticles for targeted drug delivery in non-small cell lung cancer. *Front. Oncol.* **2023**, *13*, 1154318. [Google Scholar] [CrossRef]
163. Minchinton, A.I.; Tannock, I.F. Drug penetration in solid tumours. *Nat. Rev. Cancer* **2006**, *6*, 583–592. [Google Scholar] [CrossRef]
164. Qu, J.; Zhao, X.; Ma, P.X.; Guo, B. pH-responsive self-healing injectable hydrogel based on N-carboxyethyl chitosan for hepatocellular carcinoma therapy. *Acta Biomater.* **2017**, *58*, 168–180. [Google Scholar] [CrossRef]
165. Li, L.; Knickelbein, K.; Zhang, L.; Wang, J.; Obrinske, M.; Ma, G.Z.; Zhang, L.-M.; Bitterman, L.; Du, W. Amphiphilic sugar poly (orthoesters) as pH-responsive nanoscopic assemblies for acidity-enhanced drug delivery and cell killing. *Chem. Commun.* **2015**, *51*, 13078–13081. [Google Scholar] [CrossRef]
166. Sonawane, S.J.; Kalhapure, R.S.; Govender, T. Hydrazone linkages in pH responsive drug delivery systems. *Eur. J. Pharm. Sci.* **2017**, *99*, 45–65. [Google Scholar] [CrossRef]
167. Huang, X.; Liao, W.; Xie, Z.; Chen, D.; Zhang, C.Y. A pH-responsive prodrug delivery system self-assembled from acid-labile doxorubicin-conjugated amphiphilic pH-sensitive block copolymers. *Mater. Sci. Eng. C* **2018**, *90*, 27–37. [Google Scholar] [CrossRef]
168. Zhai, Y.; Zhou, X.; Zhang, Z.; Zhang, L.; Wang, D.; Wang, X.; Sun, W. Design, synthesis, and characterization of Schiff base bond-linked pH-responsive doxorubicin prodrug based on functionalized mPEG-PCL for targeted cancer therapy. *Polymers* **2018**, *10*, 1127. [Google Scholar] [CrossRef]
169. Wang, Y.; Huang, D.; Wang, X.; Yang, F.; Shen, H.; Wu, D. Fabrication of zwitterionic and pH-responsive polyacetal dendrimers for anticancer drug delivery. *Biomater. Sci.* **2019**, *7*, 3238–3248. [Google Scholar] [CrossRef]
170. Krisch, E.; Messager, L.; Gyarmati, B.; Ravaine, V.; Szilágyi, A. Redox- and pH-Responsive Nanogels Based on Thiolated Poly(aspartic acid). *Macromol. Mater. Eng.* **2016**, *301*, 260–266. [Google Scholar] [CrossRef]
171. Li, S.; Zhang, J.; Deng, C.; Meng, F.; Yu, L.; Zhong, Z. Redox-Sensitive and Intrinsically Fluorescent Photoclick Hyaluronic Acid Nanogels for Traceable and Targeted Delivery of Cytochrome c to Breast Tumor in Mice. *ACS Appl. Mater. Interfaces* **2016**, *8*, 21155–21162. [Google Scholar] [CrossRef]
172. Vu, T.T.; Gulfam, M.; Jo, S.-H.; Park, S.-H.; Lim, K.T. Injectable and biocompatible alginate-derived porous hydrogels cross-linked by IEDDA click chemistry for reduction-responsive drug release application. *Carbohyd. Polym.* **2022**, *278*, 118964. [Google Scholar] [CrossRef]
173. Li, L.; Lei, D.; Zhang, J.; Xu, L.; Li, J.; Jin, L.; Pan, L. Dual-Responsive Alginate Hydrogel Constructed by Sulfhdryl Dendrimer as an Intelligent System for Drug Delivery. *Molecules* **2022**, *27*, 281. [Google Scholar] [CrossRef]
174. Wang, S.; Zheng, H.; Zhou, L.; Cheng, F.; Liu, Z.; Zhang, H.; Zhang, Q. Injectable redox and light responsive MnO(2) hybrid hydrogel for simultaneous melanoma therapy and multidrug-resistant bacteria-infected wound healing. *Biomaterials* **2020**, *260*, 120314. [Google Scholar] [CrossRef]

175. Zhang, H.; Xu, S.; Zhang, J.; Wang, Z.; Liu, D.; Guo, L.; Cheng, C.; Cheng, Y.; Xu, D.; Kong, M.G.; et al. Plasma-activated thermosensitive biogel as an exogenous ROS carrier for post-surgical treatment of cancer. *Biomaterials* **2021**, *276*, 121057. [Google Scholar] [CrossRef]
176. Jiang, L.; Zhang, M.; Bai, Y.; Cui, F.; Zhang, C.; Wang, Z.; Si, S.; Yang, L.; Wang, Y.; Zhang, Y.; et al. O-carboxymethyl chitosan based pH/hypoxia-responsive micelles relieve hypoxia and induce ROS in tumor microenvironment. *Carbohyd. Polym.* **2022**, *275*, 118611. [Google Scholar] [CrossRef]
177. Zhang, Y.; Tian, S.; Huang, L.; Li, Y.; Lu, Y.; Li, H.; Chen, G.; Meng, F.; Liu, G.L.; Yang, X.; et al. Reactive oxygen species-responsive and Raman-traceable hydrogel combining photodynamic and immune therapy for postsurgical cancer treatment. *Nat. Commun.* **2022**, *13*, 4553. [Google Scholar] [CrossRef]
178. Chen, S.; Qiu, Q.; Wang, D.; She, D.; Yin, B.; Gu, G.; Chai, M.; Heo, D.N.; He, H.; Wang, J. Dual-sensitive drug-loaded hydrogel system for local inhibition of post-surgical glioma recurrence. *J. Control. Release* **2022**, *349*, 565–579. [Google Scholar] [CrossRef]
179. Zou, M.-Z.; Liu, W.-L.; Chen, H.-S.; Bai, X.-F.; Gao, F.; Ye, J.-J.; Cheng, H.; Zhang, X.-Z. Advances in nanomaterials for treatment of hypoxic tumor. *Natl. Sci. Rev.* **2021**, *8*, nwaa160. [Google Scholar] [CrossRef]
180. Zhou, Z.; Zheng, C.; Liu, Y.; Luo, W.; Deng, H.; Shen, J. Chitosan biguanide induced mitochondrial inhibition to amplify the efficacy of oxygen-sensitive tumor therapies. *Carbohyd. Polym.* **2022**, *295*, 119878. [Google Scholar] [CrossRef]
181. Zhou, Z.; Liu, Y.; Jiang, X.; Zheng, C.; Luo, W.; Xiang, X.; Qi, X.; Shen, J. Metformin modified chitosan as a multi-functional adjuvant to enhance cisplatin-based tumor chemotherapy efficacy. *Int. J. Biol. Macromol.* **2023**, *224*, 797–809. [Google Scholar] [CrossRef]
182. Cheng, L.; Wang, C.; Feng, L.; Yang, K.; Liu, Z. Functional nanomaterials for phototherapies of cancer. *Chem. Rev.* **2014**, *114*, 10869–10939. [Google Scholar] [CrossRef]
183. Buwalda, S.J.; Vermonden, T.; Hennink, W.E. Hydrogels for Therapeutic Delivery: Current Developments and Future Directions. *Biomacromolecules* **2017**, *18*, 316–330. [Google Scholar] [CrossRef]
184. Wu, Y.; Chen, F.; Huang, N.; Li, J.; Wu, C.; Tan, B.; Liu, Y.; Li, L.; Yang, C.; Shao, D.; et al. Near-infrared light-responsive hybrid hydrogels for the synergistic chemo-photothermal therapy of oral cancer. *Nanoscale* **2021**, *13*, 17168–17182. [Google Scholar] [CrossRef]
185. Ding, M.; Fan, Y.; Lv, Y.; Liu, J.; Yu, N.; Kong, D.; Sun, H.; Li, J. A prodrug hydrogel with tumor microenvironment and near-infrared light dual-responsive action for synergistic cancer immunotherapy. *Acta Biomater.* **2022**, *149*, 334–346. [Google Scholar] [CrossRef]
186. Carrelo, H.; Escoval, A.R.; Vieira, T.; Jiménez-Rosado, M.; Silva, J.C.; Romero, A.; Soares, P.I.P.; Borges, J.P. Injectable Thermoresponsive Microparticle/Hydrogel System with Superparamagnetic Nanoparticles for Drug Release and Magnetic Hyperthermia Applications. *Gels* **2023**, *9*, 982. [Google Scholar] [CrossRef]
187. Ganguly, S.; Margel, S. Design of Magnetic Hydrogels for Hyperthermia and Drug Delivery. *Polymers* **2021**, *13*, 4259. [Google Scholar] [CrossRef]
188. Zhang, L.; He, X.; Zhu, H.; Sun, Q.; Liu, Y.; Huang, L.; Wen, T.; Li, J.; Lan, Z.; Yu, Z.; et al. Injectable magnetic hydrogel induces multi-programmed cell death and deep tumor regression in magnetic hyperthermia therapy in hepatocellular carcinoma. *Mater. Today Bio.* **2025**, *35*, 102341. [Google Scholar] [CrossRef]
189. Yeingst, T.J.; Arrizabalaga, J.H.; Hayes, D.J. Ultrasound-induced drug release from stimuli-responsive hydrogels. *Gels* **2022**, *8*, 554. [Google Scholar] [CrossRef]
190. Xiao, H.; Aliabouzar, M.; Fabiilli, M.L. Ultrasound-responsive composite hydrogels: Design rules for spatiotemporally controlled drug delivery. *J. Control. Release* **2026**, *395*, 114997. [Google Scholar] [CrossRef]
191. Li, T.; Zhang, M.; Wang, J.; Wang, T.; Yao, Y.; Zhang, X.; Zhang, C.; Zhang, N. Thermosensitive Hydrogel Co-loaded with Gold Nanoparticles and Doxorubicin for Effective Chemoradiotherapy. *AAPS J.* **2016**, *18*, 146–155. [Google Scholar] [CrossRef]
192. Shih, Y.-H.; Peng, C.-L.; Chiang, P.-F.; Chen, C.-T. Antitumor Evaluation of Rhenium-188 and Paclitaxel Co-Delivered via Thermosensitive Hydrogel in a Hepatocellular Carcinoma Animal Model. *Int. J. Mol. Sci.* **2026**, *27*, 775. [Google Scholar] [CrossRef]
193. Xu, N.; Wang, J.; Liu, L.; Gong, C. Injectable hydrogel-based drug delivery systems for enhancing the efficacy of radiation therapy: A review of recent advances. *Chin. Chem. Lett.* **2024**, *35*, 109225. [Google Scholar] [CrossRef]
194. Xie, Y.; Liu, M.; Cai, C.; Ye, C.; Guo, T.; Yang, K.; Xiao, H.; Tang, X.; Liu, H. Recent progress of hydrogel-based local drug delivery systems for postoperative radiotherapy. *Front. Oncol.* **2023**, *13*, 1027254. [Google Scholar] [CrossRef]

195. Rafael, D.; Melendres, M.M.R.; Andrade, F.; Montero, S.; Martinez-Trucharte, F.; Vilar-Hernandez, M.; Durán-Lara, E.F.; Schwartz, S., Jr.; Abasolo, I. Thermo-responsive hydrogels for cancer local therapy: Challenges and state-of-art. *Int. J. Pharm.* **2021**, *606*, 120954. [Google Scholar] [CrossRef]
196. Lacroce, E.; Rossi, F. Polymer-based thermoresponsive hydrogels for controlled drug delivery. *Expert Opin. Drug Deliv.* **2022**, *19*, 1203–1215. [Google Scholar] [CrossRef]
197. Xiao, Y.; Gu, Y.; Qin, L.; Chen, L.; Chen, X.; Cui, W.; Li, F.; Xiang, N.; He, X. Injectable thermosensitive hydrogel-based drug delivery system for local cancer therapy. *Colloids Surf. B Biointerfaces* **2021**, *200*, 111581. [Google Scholar] [CrossRef]
198. Zhang, K.; Xue, K.; Loh, X.J. Thermo-Responsive Hydrogels: From Recent Progress to Biomedical Applications. *Gels* **2021**, *7*, 77. [Google Scholar] [CrossRef]
199. Lukácsi, S.; Munkácsy, G.; Győrffy, B. Harnessing Hyperthermia: Molecular, Cellular, and Immunological Insights for Enhanced Anticancer Therapies. *Integr. Cancer Ther.* **2024**, *23*, 15347354241242094. [Google Scholar] [CrossRef]
200. Tanga, S.; Aucamp, M.; Ramburrun, P. Injectable thermoresponsive hydrogels for cancer therapy: Challenges and prospects. *Gels* **2023**, *9*, 418. [Google Scholar] [CrossRef]
201. Wang, N.; Gao, Q.; Tang, J.; Jiang, Y.Q.; Yang, L.S.; Shi, X.X.; Chen, Y.; Zhang, Y.; Fu, S.Z.; Lin, S. Anti-tumor effect of local injectable hydrogel-loaded endostatin alone and in combination with radiotherapy for lung cancer. *Drug Deliv.* **2021**, *28*, 183–194. [Google Scholar] [CrossRef]
202. Wang, A.; Zheng, Y.; Zhu, W.; Yang, L.; Yang, Y.; Peng, J. Melittin-Based Nano-Delivery Systems for Cancer Therapy. *Biomolecules* **2022**, *12*, 118. [Google Scholar] [CrossRef]
203. Yang, D. Recent advances in hydrogels. *Chem. Mater.* **2022**, *34*, 1987–1989. [Google Scholar] [CrossRef]
204. Li, X.; Lovell, J.F.; Yoon, J.; Chen, X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 657–674. [Google Scholar] [CrossRef]
205. Lim, J.V.; Nepacina, M.R.; Hsu, Y.-C. The study of designing a controlled drug release using oxaliplatin-loaded hydrogel for ovarian cancer treatment. *J. Taiwan Inst. Chem. Eng.* **2024**, *163*, 105326. [Google Scholar] [CrossRef]
206. Emoto, S.; Yamaguchi, H.; Kamei, T.; Ishigami, H.; Suhara, T.; Suzuki, Y.; Ito, T.; Kitayama, J.; Watanabe, T. Intraperitoneal administration of cisplatin via an in situ cross-linkable hyaluronic acid-based hydrogel for peritoneal dissemination of gastric cancer. *Surg. Today* **2014**, *44*, 919–926. [Google Scholar] [CrossRef]
207. Ohta, S.; Hiramoto, S.; Amano, Y.; Emoto, S.; Yamaguchi, H.; Ishigami, H.; Kitayama, J.; Ito, T. Intraperitoneal delivery of cisplatin via a hyaluronan-based nanogel/in situ cross-linkable hydrogel hybrid system for peritoneal dissemination of gastric cancer. *Mol. Pharm.* **2017**, *14*, 3105–3113. [Google Scholar] [CrossRef]
208. Qian, H.; Qian, K.; Cai, J.; Yang, Y.; Zhu, L.; Liu, B. Therapy for Gastric Cancer with Peritoneal Metastasis Using Injectable Albumin Hydrogel Hybridized with Paclitaxel-Loaded Red Blood Cell Membrane Nanoparticles. *ACS Biomat. Sci. Eng.* **2019**, *5*, 1100–1112. [Google Scholar] [CrossRef]
209. Li, L.; He, S.; Liao, B.; Wang, M.; Lin, H.; Hu, B.; Lan, X.; Shu, Z.; Zhang, C.; Yu, M. Orally administrated hydrogel harnessing intratumoral microbiome and microbiota-related immune responses for potentiated colorectal cancer treatment. *Research* **2024**, *7*, 364. [Google Scholar] [CrossRef]
210. Phan, V.H.G.; Lee, E.; Maeng, J.H.; Thambi, T.; Kim, B.S.; Lee, D.; Lee, D.S. Pancreatic cancer therapy using an injectable nanobiohybrid hydrogel. *RSC Adv.* **2016**, *6*, 41644–41655. [Google Scholar] [CrossRef]
211. Kong, Y.; Dai, Y.; Qi, D.; Du, W.; Ni, H.; Zhang, F.; Zhao, H.; Shen, Q.; Li, M.; Fan, Q. Injectable and Thermosensitive Liposomal Hydrogels for NIR-II Light-Triggered Photothermal-Chemo Therapy of Pancreatic Cancer. *ACS Appl. Bio. Mater.* **2021**, *4*, 7595–7604. [Google Scholar] [CrossRef]
212. Wang, B.; Chen, J.; Caserto, J.S.; Wang, X.; Ma, M. An in situ hydrogel-mediated chemo-immunometabolic cancer therapy. *Nat. Commun.* **2022**, *13*, 3821. [Google Scholar] [CrossRef]
213. Steele, G.; Ravikumar, T.S. Resection of hepatic metastases from colorectal cancer: Biologic perspectives. *Ann. Surg.* **1989**, *210*, 127. [Google Scholar] [CrossRef]
214. Baize, N.; Gerard, B.; Bleiberg, H.; Caroli-Bosc, F.; Berthier, F.; Legendre, H.; Pector, J.C.; Hendlisz, A. Long-term survival of patients downstaged by oxaliplatin and 5-fluorouracil combination followed by rescue surgery for unresectable colorectal liver metastases. *Gastroentero. Clin. Biol.* **2006**, *30*, 1349–1353. [Google Scholar] [CrossRef]
215. Shitara, K.; Matsuo, K.; Kondo, C.; Takahari, D.; Ura, T.; Inaba, Y.; Yamaura, H.; Sato, Y.; Kato, M.; Kanemitsu, Y.; et al. Prolonged survival of patients with metastatic colorectal cancer following first-line oxaliplatin-based chemotherapy with molecular targeting agents and curative surgery. *Oncology* **2011**, *81*, 167–174. [Google Scholar] [CrossRef]

216. Lee, J.E.; Abuzar, S.M.; Seo, Y.; Han, H.; Jeon, Y.; Park, E.J.; Baik, S.H.; Hwang, S.-J. Oxaliplatin-loaded chemically cross-linked hydrogels for prevention of postoperative abdominal adhesion and colorectal cancer therapy. *Int. J. Pharm.* **2019**, *565*, 50–58. [Google Scholar] [CrossRef]
217. Abbasi, M.; Sohail, M.; Minhas, M.U.; Mahmood, A.; Shah, S.A.; Munir, A.; Kashif, M.U.R. Folic acid-decorated alginate nanoparticles loaded hydrogel for the oral delivery of diferourylmethane in colorectal cancer. *Int. J. Biol. Macromol.* **2023**, *233*, 123585. [Google Scholar] [CrossRef]
218. Castro-Abril, H.; Heras, J.; Del Barrio, J.; Paz, L.; Alcaine, C.; Aliácar, M.P.; Garzón-Alvarado, D.; Doblaré, M.; Ochoa, I. The role of mechanical properties and structure of type I collagen hydrogels on colorectal cancer cell migration. *Macromol. Biosci.* **2023**, *23*, 2300108. [Google Scholar] [CrossRef]
219. Lee, A.L.Z.; Ng, V.W.L.; Gao, S.; Hedrick, J.L.; Yang, Y.Y. Injectable biodegradable hydrogels from vitamin D-functionalized polycarbonates for the delivery of Avastin with enhanced therapeutic efficiency against metastatic colorectal cancer. *Biomacromolecules* **2015**, *16*, 465–475. [Google Scholar] [CrossRef]
220. de Freitas, C.F.; Kimura, E.; Rubira, A.F.; Muniz, E.C. Curcumin and silver nanoparticles carried out from polysaccharide-based hydrogels improved the photodynamic properties of curcumin through metal-enhanced singlet oxygen effect. *Mater. Sci. Eng. C* **2020**, *112*, 110853. [Google Scholar] [CrossRef]
221. Gao, M.; Yang, C.; Wu, C.; Chen, Y.; Zhuang, H.; Wang, J.; Cao, Z. Hydrogel–metal-organic-framework hybrids mediated efficient oral delivery of siRNA for the treatment of ulcerative colitis. *J. Nanobiotechnol.* **2022**, *20*, 404. [Google Scholar] [CrossRef]
222. You, T.; Chen, J.; Zhu, Y.; Shan, N.; Gao, Z.; Shen, Y.; Yu, Y. Novel preparation of pH-responsive hydrogel with chitosan-based microbeads for targeted oral delivery of bevacizumab to enhanced apoptosis in azoxymethane-induced colorectal cancer: Cellular and in vivo mice models. *Drug Deliv. Transl. Res.* **2025**, *16*, 711–724. [Google Scholar] [CrossRef]
223. Al Sabbagh, C.; Seguin, J.; Agapova, E.; Kramerich, D.; Boudy, V.; Mignet, N. Thermosensitive hydrogels for local delivery of 5-fluorouracil as neoadjuvant or adjuvant therapy in colorectal cancer. *Eur. J. Pharm. Biopharm.* **2020**, *157*, 154–164. [Google Scholar] [CrossRef]
224. Wang, M.; Hu, D.; Yang, Y.; Shi, K.; Li, J.; Liu, Q.; Li, Y.; Li, R.; Pan, M.; Mo, D. Enhanced chemo-immunotherapy strategy utilizing injectable thermosensitive hydrogel for the treatment of diffuse peritoneal metastasis in advanced colorectal cancer. *Adv. Sci.* **2023**, *10*, 2303819. [Google Scholar] [CrossRef]
225. Shen, W.; Pei, P.; Zhang, C.; Li, J.; Han, X.; Liu, T.; Shi, X.; Su, Z.; Han, G.; Hu, L. A polymeric hydrogel to eliminate programmed death-ligand 1 for enhanced tumor radio-immunotherapy. *ACS Nano* **2023**, *17*, 23998–24011. [Google Scholar] [CrossRef]
226. Kim, S.; Ahn, J.-H.; Jeong, D.I.; Yang, M.; Jeong, J.-H.; Choi, Y.E.; Kim, H.J.; Han, Y.; Karmakar, M.; Ko, H.-J. Alum-tuned hyaluronic acid-based hydrogel with immune checkpoint inhibition for immunophoto therapy of cancer. *J. Control. Release* **2023**, *362*, 1–18. [Google Scholar] [CrossRef]
227. Qing, W.; Xing, X.; Feng, D.; Chen, R.; Liu, Z. Indocyanine green loaded pH-responsive bortezomib supramolecular hydrogel for synergistic chemo-photothermal/photodynamic colorectal cancer therapy. *Photodiagn. Photodyn. Ther.* **2021**, *36*, 102521. [Google Scholar] [CrossRef]
228. Zhang, Y.; Xu, W.; Ni, P.; Li, A.; Zhou, J.; Xu, S. MiR-99a and MiR-491 regulate cisplatin resistance in human gastric cancer cells by targeting CAPNS1. *Int. J. Bio. Sci.* **2016**, *12*, 1437. [Google Scholar] [CrossRef]
229. Chen, W.; Shi, K.; Liu, J.; Yang, P.; Han, R.; Pan, M.; Yuan, L.; Fang, C.; Yu, Y.; Qian, Z. Sustained co-delivery of 5-fluorouracil and cis-platinum via biodegradable thermo-sensitive hydrogel for intraoperative synergistic combination chemotherapy of gastric cancer. *Bioact. Mater.* **2023**, *23*, 1–15. [Google Scholar] [CrossRef]
230. Luo, Q.; Dong, Z.; Xie, W.; Fu, X.; Lin, L.; Zeng, Q.; Chen, Y.; Ye, G.; Chen, M.; Hu, H. Apatinib remodels the immunosuppressive tumor ecosystem of gastric cancer enhancing anti-PD-1 immunotherapy. *Cell Rep.* **2023**, *42*, 112427. [Google Scholar] [CrossRef]
231. Aycan, D.; Gül, İ.; Yorulmaz, V.; Alemdar, N. Gelatin microsphere-alginate hydrogel combined system for sustained and gastric targeted delivery of 5-fluorouracil. *Int. J. Biol. Macromol.* **2024**, *255*, 128022. [Google Scholar] [CrossRef]
232. Cho, J.-K.; Hong, J.M.; Han, T.; Yang, H.-K.; Song, S.-C. Injectable and biodegradable poly (organophosphazene) hydrogel as a delivery system of docetaxel for cancer treatment. *J. Drug Target.* **2013**, *21*, 564–573. [Google Scholar] [CrossRef]
233. Han, T.-S.; Hur, K.; Choi, B.; Lee, J.-Y.; Byeon, S.-J.; Min, J.; Yu, J.; Cho, J.-K.; Hong, J.; Lee, H.-J. Improvement of anti-cancer drug efficacy via thermosensitive hydrogel in peritoneal carcinomatosis in gastric cancer. *Oncotarget* **2017**, *8*, 108848. [Google Scholar] [CrossRef]

234. Bae, W.K.; Park, M.S.; Lee, J.H.; Hwang, J.E.; Shim, H.J.; Cho, S.H.; Kim, D.-E.; Ko, H.M.; Cho, C.-S.; Park, I.-K. Docetaxel-loaded thermoresponsive conjugated linoleic acid-incorporated poloxamer hydrogel for the suppression of peritoneal metastasis of gastric cancer. *Biomaterials* **2013**, *34*, 1433–1441. [Google Scholar] [CrossRef]
235. Zhang, D.; Chu, Y.; Qian, H.; Qian, L.; Shao, J.; Xu, Q.; Yu, L.; Li, R.; Zhang, Q.; Wu, F. Antitumor activity of thermosensitive hydrogels packaging gambogic acid nanoparticles and tumor-penetrating peptide iRGD against gastric cancer. *Int. J. Nanomed.* **2020**, *15*, 735–747. [Google Scholar] [CrossRef]
236. Yang, Y.; Yang, Y.; Chen, M.; Chen, J.; Wang, J.; Ma, Y.; Qian, H. Injectable shear-thinning polylysine hydrogels for localized immunotherapy of gastric cancer through repolarization of tumor-associated macrophages. *Biomater. Sci.* **2021**, *9*, 6597–6608. [Google Scholar] [CrossRef]
237. Krebs, M.D.; Jeon, O.; Alsberg, E. Localized and sustained delivery of silencing RNA from macroscopic biopolymer hydrogels. *J. Am. Chem. Soc.* **2009**, *131*, 9204–9206. [Google Scholar] [CrossRef]
238. Miller, K.D.; Nogueira, L.; Mariotto, A.B.; Rowland, J.H.; Yabroff, K.R.; Alfano, C.M.; Jemal, A.; Kramer, J.L.; Siegel, R.L. Cancer treatment and survivorship statistics, 2019. *CA Cancer J. Clin.* **2019**, *69*, 363–385. [Google Scholar] [CrossRef]
239. Ma, J.; Wang, B.; Shao, H.; Zhang, S.; Chen, X.; Li, F.; Liang, W. Hydrogels for localized chemotherapy of liver cancer: A possible strategy for improved and safe liver cancer treatment. *Drug Deliv.* **2022**, *29*, 1457–1476. [Google Scholar] [CrossRef]
240. Xu, K.; Lee, F.; Gao, S.J.; Chung, J.E.; Yano, H.; Kurisawa, M. Injectable hyaluronic acid-tyramine hydrogels incorporating interferon-α2a for liver cancer therapy. *J. Control. Release* **2013**, *166*, 203–210. [Google Scholar] [CrossRef]
241. Huang, L.; Shen, M.; Li, R.; Zhang, X.; Sun, Y.; Gao, P.; Fu, H.; Liu, H.; He, Y.; Du, Y. Thermo-sensitive composite hydrogels based on poloxamer 407 and alginate and their therapeutic effect in embolization in rabbit VX2 liver tumors. *Oncotarget* **2016**, *7*, 73280. [Google Scholar] [CrossRef]
242. Guerra, A.D.; Yeung, O.W.H.; Qi, X.; Kao, W.J.; Man, K. The anti-tumor effects of M1 macrophage-loaded poly (ethylene glycol) and gelatin-based hydrogels on hepatocellular carcinoma. *Theranostics* **2017**, *7*, 3732. [Google Scholar] [CrossRef]
243. Ma, F.; Yuan, C.W.; Liu, J.N.; Cao, J.H.; Wu, D.Y. Colorimetric Immunosensor Based on Au@g-C3N4-Doped Spongelike 3D Network Cellulose Hydrogels for Detecting α-Fetoprotein. *ACS Appl. Mater. Interfaces* **2019**, *11*, 19902–19912. [Google Scholar] [CrossRef]
244. Jung, J.M.; Kim, S.H.; Phan, V.H.G.; Thambi, T.; Lee, D.S. Therapeutic effects of boronate ester cross-linked injectable hydrogels for the treatment of hepatocellular carcinoma. *Biomater. Sci.* **2021**, *9*, 7275–7286. [Google Scholar] [CrossRef]
245. Du, C.; Wang, Y.; Shi, K.; Zhao, M.; Tu, L.; Yu, Y.; Li, Z.; Luo, F.; Qian, Z. Efficient suppression of liver metastasis cancers by paclitaxel loaded nanoparticles in PDLLA-PEG-PDLLA thermosensitive hydrogel composites. *J. Biomed. Nanotechnol.* **2017**, *13*, 1545–1556. [Google Scholar] [CrossRef]
246. Zhu, J.Q.; Wu, H.; Li, X.; Li, M.Y.; Li, Z.L.; Xu, X.F.; Gu, L.H.; Yin, D.X.; Shen, F.; Huang, D.S.; et al. Hydrogel Crosslinked with Nanoparticles for Prevention of Surgical Hemorrhage and Recurrence of Hepatocellular Carcinoma. *Adv. Sci.* **2024**, *11*, 2305508. [Google Scholar] [CrossRef]
247. Liu, X.; Huangfu, Y.; Wang, J.; Kong, P.; Tian, W.; Liu, P.; Fang, C.; Li, S.; Nie, Y.; Feng, Z.; et al. Supramolecular Polymer-Nanomedicine Hydrogel Loaded with Tumor Associated Macrophage-Reprogramming polyTLR7/8a Nanoregulator for Enhanced Anti-Angiogenesis Therapy of Orthotopic Hepatocellular Carcinoma. *Adv. Sci.* **2023**, *10*, 2300637. [Google Scholar] [CrossRef]
248. Chen, G.; Li, J.; Cai, Y.; Zhan, J.; Gao, J.; Song, M.; Shi, Y.; Yang, Z. A glycyrrhetinic acid-modified curcumin supramolecular hydrogel for liver tumor targeting therapy. *Sci. Rep.* **2017**, *7*, 44210. [Google Scholar] [CrossRef]
249. Xu, S.; Cai, J.; Cheng, H.; Wang, W. Sustained release of therapeutic gene by injectable hydrogel for hepatocellular carcinoma. *Int. J. Pharm. X* **2023**, *6*, 100195. [Google Scholar] [CrossRef]
250. Santhamoorthy, M.; Vy Phan, T.T.; Ramkumar, V.; Raorane, C.J.; Thirupathi, K.; Kim, S.C. Thermo-Sensitive Poly (N-isopropylacrylamide-co-polyacrylamide) Hydrogel for pH-Responsive Therapeutic Delivery. *Polymers* **2022**, *14*, 4128. [Google Scholar] [CrossRef]
251. Wen, Y.; Liu, Y.; Zhang, H.; Zou, M.; Yan, D.; Chen, D.; Zhao, Y. A responsive porous hydrogel particle-based delivery system for oncotherapy. *Nanoscale* **2019**, *11*, 2687–2693. [Google Scholar] [CrossRef]
252. Gao, L.; Wang, X.; Ma, J.; Hao, D.; Wei, P.; Zhou, L.; Liu, G. Evaluation of TPGS-modified thermo-sensitive Pluronic PF127 hydrogel as a potential carrier to reverse the resistance of P-gp-overexpressing SMMC-7721 cell lines. *Colloids Surf. B Biointerfaces* **2016**, *140*, 307–316. [Google Scholar] [CrossRef]

253. Zhuang, Q.; Zhao, B.; Lin, Z.; Liang, Y.; Zhao, Q.; Wang, Y.; Liao, N.; Tu, H.; Zheng, Y.; Chen, H.; et al. Navoximod modulates local HSV-1 replication to reshape tumor immune microenvironment for enhanced immunotherapy via an injectable hydrogel. *Commun. Biol.* **2023**, *6*, 621. [Google Scholar] [CrossRef]
254. Meng, J.; Yang, X.; Huang, J.; Tuo, Z.; Hu, Y.; Liao, Z.; Tian, Y.; Deng, S.; Deng, Y.; Zhou, Z. Ferroptosis-enhanced immunotherapy with an injectable dextran-chitosan hydrogel for the treatment of malignant ascites in hepatocellular carcinoma. *Adv. Sci.* **2023**, *10*, 2300517. [Google Scholar] [CrossRef]
255. Zhao, B.; Zhou, B.; Shi, K.; Zhang, R.; Dong, C.; Xie, D.; Tang, L.; Tian, Y.; Qian, Z.; Yang, L. Sustained and targeted delivery of siRNA/DP7-C nanoparticles from injectable thermosensitive hydrogel for hepatocellular carcinoma therapy. *Cancer Sci.* **2021**, *112*, 2481–2492. [Google Scholar] [CrossRef]
256. Yang, Q.; Zhuge, X.; Lin, W.; Yu, W.; Zhu, Y.; Shi, C.; Shi, Z. Hydrogel-based miR-192 delivery inhibits the development of hepatocellular carcinoma by suppressing the GSK3β/Wnt/β-catenin pathway. *Neoplasma* **2023**, *70*, 555. [Google Scholar] [CrossRef]
257. Xu, X.; Liu, Y.; Liu, Y.; Yu, Y.; Yang, M.; Lu, L.; Chan, L.; Liu, B. Functional hydrogels for hepatocellular carcinoma: Therapy, imaging, and in vitro model. *J. Nanobiotechnol.* **2024**, *22*, 381. [Google Scholar] [CrossRef]
258. Werner, J.; Combs, S.E.; Springfeld, C.; Hartwig, W.; Hackert, T.; Büchler, M.W. Advanced-stage pancreatic cancer: Therapy options. *Nat. Rev. Clin. Oncol.* **2013**, *10*, 323–333. [Google Scholar] [CrossRef]
259. Orth, M.; Metzger, P.; Gerum, S.; Mayerle, J.; Schneider, G.; Belka, C.; Schnurr, M.; Lauber, K. Pancreatic ductal adenocarcinoma: Biological hallmarks, current status, and future perspectives of combined modality treatment approaches. *Radiat. Oncol.* **2019**, *14*, 141. [Google Scholar] [CrossRef]
260. Nguyen, H.D.; Lin, C.C. Viscoelastic stiffening of gelatin hydrogels for dynamic culture of pancreatic cancer spheroids. *Acta Biomater.* **2024**, *177*, 203–215. [Google Scholar] [CrossRef]
261. Royal, R.E.; Levy, C.; Turner, K.; Mathur, A.; Hughes, M.; Kammula, U.S.; Sherry, R.M.; Topalian, S.L.; Yang, J.C.; Lowy, I.; et al. Phase 2 trial of single agent ipilimumab (Anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J. Immunother.* **2010**, *33*, 828. [Google Scholar] [CrossRef]
262. Brahmer, J.R.; Tykodi, S.S.; Chow, L.Q.M.; Hwu, W.-J.; Topalian, S.L.; Hwu, P.; Drake, C.G.; Camacho, L.H.; Kauh, J.; Odunsi, K.; et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. *N. Engl. J. Med.* **2012**, *366*, 2455–2465. [Google Scholar] [CrossRef]
263. Kim, I.; Choi, J.S.; Lee, S.; Byeon, H.J.; Lee, E.S.; Shin, B.S.; Choi, H.G.; Lee, K.C.; Youn, Y.S. In situ facile-forming PEG crosslinked albumin hydrogels loaded with an apoptotic TRAIL protein. *J. Control. Release* **2015**, *214*, 30–39. [Google Scholar] [CrossRef]
264. Schaal, J.L.; Li, X.; Mastria, E.; Bhattacharyya, J.; Zalutsky, M.R.; Chilkoti, A.; Liu, W. Injectable polypeptide micelles that form radiation crosslinked hydrogels in situ for intratumoral radiotherapy. *J. Control. Release* **2016**, *228*, 58–66. [Google Scholar] [CrossRef]
265. Shabana, A.M.; Kambhampati, S.P.; Hsia, R.-c.; Kannan, R.M.; Kokkoli, E. Thermosensitive and biodegradable hydrogel encapsulating targeted nanoparticles for the sustained co-delivery of gemcitabine and paclitaxel to pancreatic cancer cells. *Int. J. Pharm.* **2021**, *593*, 120139. [Google Scholar] [CrossRef]
266. Liu, X.; Zhuang, Y.; Huang, W.; Wu, Z.; Chen, Y.; Shan, Q.; Zhang, Y.; Wu, Z.; Ding, X.; Qiu, Z.; et al. Interventional hydrogel microsphere vaccine as an immune amplifier for activated antitumour immunity after ablation therapy. *Nat. Commun.* **2023**, *14*, 4106. [Google Scholar] [CrossRef]
267. Zhao, R.; Xiao, Q.; Wu, Y.; Zhang, W.; Liu, J.; Zeng, Y.; Zhan, J.; Cai, Y.; Fang, C. Dual-crosslinking immunostimulatory hydrogel synchronously suppresses pancreatic fistula and pancreatic cancer relapse post-resection. *Biomaterials* **2024**, *305*, 122453. [Google Scholar] [CrossRef]
268. Zhu, B.; Cai, Y.; Zhou, L.; Zhao, L.; Chen, J.; Shan, X.; Sun, X.; You, Q.; Gong, X.; Zhang, W.; et al. Injectable supramolecular hydrogel co-loading abemaciclib/NLG919 for neoadjuvant immunotherapy of triple-negative breast cancer. *Nat. Commun.* **2025**, *16*, 687. [Google Scholar] [CrossRef]
269. Ji, X.; Guo, D.; Ma, J.; Yin, M.; Yu, Y.; Liu, C.; Zhou, Y.; Sun, J.; Li, Q.; Chen, N.; et al. Epigenetic Remodeling Hydrogel Patches for Multidrug-Resistant Triple-Negative Breast Cancer. *Adv. Mater.* **2021**, *33*, e2100949. [Google Scholar] [CrossRef]
270. Nascimento, S.; de Souza, R.R.M.; Sobral, M.V.; Xavier-Junior, F.H.; da Silva, M.V.S.; Viana, M.M.; da Silva, F.F.; Serpe, M.J.; de Souza, A.L. Gelatin-Oxidized Alginate and Chitosan-Coated Zein Nanoparticle Hydrogel Composite to Enhance Breast Cancer Cytotoxicity in Dual-Drug Delivery. *ACS Omega* **2024**, *9*, 45190–45202. [Google Scholar] [CrossRef]

271. Hasan, M.; Elkhoury, K.; Belhaj, N.; Kahn, C.; Tamayol, A.; Barberi-Heyob, M.; Arab-Tehrany, E.; Linder, M. Growth-Inhibitory Effect of Chitosan-Coated Liposomes Encapsulating Curcumin on MCF-7 Breast Cancer Cells. *Mar. Drugs* **2020**, *18*, 217. [Google Scholar] [CrossRef]
272. Surgery, B.A. Seprafilm Adhesion Barrier. Available online: https://www.advancedsurgery.baxter.com/seprafilm (accessed on 24 January 2025).
273. MedTech, J.J. GYNECARE INTERCEED® Absorbable Adhesion Barrier. Available online: https://www.jnjmedtech.com/en-US/product/gynecare-interceed-absorbable-adhesion-barrier (accessed on 8 December 2025).
274. FzioMed, I. Products | FzioMed. Available online: https://www.fziomed.com/usa/products/ (accessed on 8 December 2025).
275. Normedi, AS. Oxiplex/AP—Absorbable Adhesion Barrier Gel. Available online: https://normedi.com/products/laparoscopy/adhesion-prevention/oxiplexap-absorbable-adhesion-barrier-gel/ (accessed on 8 December 2025).
276. Anika, Therapeutics, Inc. Surgical Solutions—Anika Medical Products. Available online: https://anika.com/medical/products/surgical-solutions/ (accessed on 8 December 2025).
277. Leader, Biomedical, B.V. Adcon® Gel—Bio-Resorbable Anti-Adhesion Gel. Available online: https://www.medical-xprt.com/products/adcon-bio-resorbable-anti-adhesion-gel-862408 (accessed on 24 January).
278. Augmenix, Inc. 510(k) Summary—TraceIT Tissue Marker (K121964). Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf12/K121964.pdf (accessed on 8 December 2025).
279. Palette Life Sciences. Barrigel Spacer FAQ—About Barrigel. Available online: https://barrigel.com/about-barrigel/barrigel-spacer-faq (accessed on 8 December 2025).
280. Integra LifeSciences Corporation. DuraSeal®—PEG-Based Hydrogel Surgical Sealant. Available online: https://products.integralife.com/duraseal-dural-sealant-system/product/dural-repair-sealants-duraseal-dural-sealant-system-5-ml (accessed on 8 December 2025).
281. Kim, H.S.; Wujin, S.; Jabbarzadeh, E.; Oklu, R.; Khademhosseini, A. Injectable Shear-Thinning Hydrogel Containing Polypeptide Therapeutic Agent for Enhanced Tumor Therapy. U.S. Patent 20230094016 A1, 2023. Available online: https://patents.google.com/patent/US20230094016A1/en?oq=US20230094016A1+(2023) (accessed on 8 December 2025). [Google Scholar]
282. Kelly, H.; Duffy, G.; Rossi, S.; Hastings, C. A Thermo-Responsive Hydrogel for Intratumoral Administration As a Treatment in Solid Tumor Cancers. U.S. Patent 11,534,401, 27 December 2022. Available online: https://patents.google.com/patent/WO2019092049A1/en (accessed on 8 December 2025). [Google Scholar]
283. Khan, Z.M.; Verbridge, S.S.; Long, T.E.; Vlaisavlijevich, E.; Virginia Tech Intellectual Properties Inc. Injectable hydrogels and methods of capturing cells using the same. U.S. Patent 18/021,637, 5 October 2023. Available online: https://patents.google.com/patent/WO2022040612A1/en. [Google Scholar]
284. Bouché, M.; Cormode, D.; Sheikh, S.; Dorsey, J. 'Smart' Hydrogel for the Radiosensitization and Sustained Delivery of Therapeutics Triggered by Irradiation. U.S. Patent 12,486,401, 2 December 2025. Available online: https://patents.google.com/patent/US12486401B2/en?oq=U.S.+Patent+12%2c486%2c401285. [Google Scholar]
285. Kim, K.B.; Wonjeong, L.E.E.; Kim, S.J.; Industry Academic Cooperation Foundation of Dongguk University. 3d Hydrogel Composite Having Cancer Cell Apoptotic Effect and Preparation Method Thereof. U.S. Patent 20250032676 A1, 2025. Available online: https://patents.google.com/patent/US20250032676A1/en?oq=US%E2%80%AF20250032676A1 (accessed on 8 December 2025). [Google Scholar]
286. Syed, B.A.; Rajalakshmi, P.S.; Rengan, A.K. Thermosensitive Hydrogel for Cancer Therapeutics and Methods of Preparation Thereof. U.S. Patent 11938186 B2, 2024. Available online: https://patents.google.com/patent/US11938186B2/en?oq=US11938186B2 (accessed on 8 December 2025). [Google Scholar]
287. Choi, Y.D.; Lee, S.S.; Kim, H.J.; Sohn, D.K.; Kim, S.K.; Kim, Y.W.; Ryu, K.W.; Yoon, H.M. Alginic Acid-Based Injectable Hydrogel System. U.S. Patent 20250082787 A1, 2025. Available online: https://patents.google.com/patent/US20250082787A1/en?oq=US%E2%80%AF20250082787%E2%80%AFA1 (accessed on 8 December 2025). [Google Scholar]
288. Lee, Y.K.; Park, I.K.; Mohapatra, A.; Mondal, J.; An, J.M. Temperature-Sensitive Hydrogel for Cancer Treatment Capable of Photothermal Therapy and Preparation Method Therefor. U.S. Patent 20250177532 A1. Available online: https://patents.google.com/patent/US20250177532A1/en?oq=US20250177532+A1 (accessed on 8 December 2025).
289. Doo, S.L.; Bong, S.K.; Cong, T.H. Drug Delivery System for Treatment of Liver Cancer Based on Interventional Injection of Temperature and pH-Sensitive Hydrogel. U.S. Patent 20130022545 A1, 2013. Available online: https://patents.google.com/patent/US20130022545A1/en?oq=US20130022545+A1 (accessed on 8 December 2025). [Google Scholar]

290. Susan, N.T.; Kim, S.J. Micelle Releasing Thermosensitive Hydrogels As a Therapeutic Delivery System. U.S. Patent 20240139104 A1. Available online: https://patents.google.com/patent/US20240139104A1/en?oq=US20240139104A1 (accessed on 8 December 2025).
291. Dauty, A.G.; Nicolas, L.; Baptiste, P.; Gerard, S.; Romain, B.; Emmanuel, D. Hydrogels for Drug Delivery. WO 2024013354 A1, 2024. Available online: https://patents.google.com/patent/WO2024013354A1/en?oq=WO2024013354+A1 (accessed on 8 December 2025). [Google Scholar]
292. Indolfi, L.; Sullivan, M.L. Methods of Treating Pancreatic Cancer. U.S. Patent 20240165071 A1, 2024. Available online: https://patents.google.com/patent/US20240165071A1/en?oq=US20240165071+A1 (accessed on 8 December 2025). [Google Scholar]
293. Chen, S.; Liu, W. Nano-Composite Hydrogel for Radiosensitization After Breast-Conserving Surgery for Breast Cancer and Preparation Method Therefor. WO 2025139283, 2025. Available online: https://patents.google.com/patent/WO2025139283A1/en?oq=WO2025139283 (accessed on 8 December 2025). [Google Scholar]
294. Kim, J.; Chae, Y. Deformable Hydrogel Particles and Pharmaceutical Composition for Cancer Treatment Comprising the Same. U.S. Patent 20230172851 A1, 2023. Available online: https://patents.google.com/patent/US20230172851A1/en?oq=US20230172851A1 (accessed on 8 December 2025). [Google Scholar]
295. Vivos Inc. Submits FDA Application for RadioGel Hydrogel-Based Cancer Therapy. Available online: https://trial.medpath.com/news/ee96b163e311f46e/vivos-inc-submits-fda-application-for-radiogel-hydrogel-based-cancer-therapy (accessed on 21 December 2025).
296. Early Feasibility Study For Evaluation Of The TraceIT® Tissue Spacer For Creating Space Between the Duodenum and Pancreas in Patients with Localized Pancreatic Cancer Undergoing Radiation Therapy. 2019. Available online: https://clinicaltrials.gov/study/NCT03998566 (accessed on 8 December 2025).
297. Evaluation of a Novel Absorbable Radiopaque Hydrogel in Patients Undergoing Image-guided Radiotherapy for Pancreatic Adenocarcinoma. 2017. Available online: https://clinicaltrials.gov/study/NCT03307564 (accessed on 8 December 2025).
298. Fluorouracil Treatment via Colon for Colorectal Cancer: An Exploratory Study. 2024. Available online: https://clinicaltrials.gov/study/NCT06385418 (accessed on 8 December 2025).
299. Lammer, J.; Malagari, K.; Vogl, T.; Pilleul, F.; Denys, A.; Watkinson, A.; Pitton, M.; Sergent, G.; Pfammatter, T.; Terraz, S.; et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. *Cardiovasc. Interv. Radiol.* **2010**, *33*, 41–52. [Google Scholar] [CrossRef]
300. Randomized Multi-Center, Subject and Evaluator Blinded, Parallel-Group Study to Evaluate the Safety and Effectiveness of the Instylla Hydrogel Embolic System (HES) Compared with Standard of Care Transcatheter Arterial Embolization (TAE)/Transcatheter Arterial Chemoembolization (cTACE) for Vascular Occlusion of Hypervascular Tumors; A Pivotal Study. 2020. Available online: https://clinicaltrials.gov/study/NCT04523350 (accessed on 8 December 2025).
301. Gut Guarding Gel for Endoscopic Resection to Treat Early Gastroenterological Tumor and Polyps (Evaluation of the Safety of Sodium Alginate Mixed with Calcium Lactate on Endoscopic Mucosal Resection/Endoscopic Submucosal Dissection). 2017. Available online: https://clinicaltrials.gov/study/NCT03321396 (accessed on 8 December 2025).
302. U.S. Food and Drug Administration (FDA); Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry*; FDA: Silver Spring, MD, USA, 2019. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products (accessed on 15 September 2026).
303. U.S. Food and Drug Administration (FDA). Regulation of Combination Products: 21 CFR Part 4. Electronic Code of Federal Regulations. Available online: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-4 (accessed on 21 December 2025).
304. U.S. Food and Drug Administration. Combination Products Guidance Documents. Available online: https://www.fda.gov/combination-products/guidance-regulatory-information/combination-products-guidance-documents (accessed on 24 January 2026).
305. European Parliament and Council of the European Union. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices, Amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and Repealing Council Directives 90/385/EEC and 93/42/EEC. Available online: https://eur-lex.europa.eu/eli/reg/2017/745/oj/eng (accessed on 21 December 2025).

306. European Parliament and Council of the European Union. Directive 2001/83/EC of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use. *Off. J. Eur. Communities* **2001**, *L311*, 67–128. Available online: https://eur-lex.europa.eu/eli/dir/2001/83/oj/eng [Google Scholar]
307. U.S. Food and Drug Administration (FDA). Current Good Manufacturing Practice Requirements for Medical Devices: 21 CFR Part 820. Electronic Code of Federal Regulations. Available online: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820 (accessed on 21 December 2025).
308. European Medicines Agency. *Questions and Answers for Applicants, Marketing Authorisation Holders of Medicinal Products and Notified Bodies Regarding Medicines Used in Combination with Medical Devices and Consultation Procedures for Certain Medical Devices*; EMA/37991/2019, Rev.6; European Medicines Agency: Amsterdam, The Netherlands, 2025. Available online: https://www.ema.europa.eu/system/files/documents/regulatory-procedural-guideline/qa-revision-6_-clean_-mdr-ivd-implementation-dec-2025_en.pdf [Google Scholar]
309. U.S. Food and Drug Administration (FDA). 21 CFR Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General. Available online: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210 (accessed on 16 October 2025).
310. *ISO 10993-1:2025*; Biological Evaluation of Medical Devices—Part 1: Evaluation and Testing Within a Risk Management Process. International Organization for Standardization (ISO): Geneva, Switzerland, 2025. Available online: https://www.iso.org/standard/10993-1 (accessed on 15 September 2026).
311. *ISO 13485:2016*; Medical Devices—Quality Management Systems—Requirements for Regulatory Purposes. International Organization for Standardization (ISO): Geneva, Switzerland, 2016. Available online: https://www.iso.org/standard/59752.html (accessed on 15 September 2026).
312. *ISO 14971:2019*; Medical Devices—Application of Risk Management to Medical Devices. International Organization for Standardization (ISO): Geneva, Switzerland, 2019. Available online: https://www.iso.org/standard/72704.html (accessed on 15 September 2026).
313. European Directorate for the Quality of Medicines & HealthCare (EDQM). Chapter 2.6.1: Sterility. In *European Pharmacopoeia*; Council of Europe: Strasbourg, France, 2008. Available online: http://www.uspbpep.com/ep60/2.6.%201.%20sterility%2020601e.pdf (accessed on 21 December 2025). [Google Scholar]
314. International Organization for Standardization (ISO). ISO/TC 209: Cleanrooms and Associated Controlled Environments. Available online: https://www.iso.org/committee/54874.html (accessed on 15 September 2026).
315. United States Pharmacopeial Convention (USP). United States Pharmacopeia 29-National Formulary 24 (USP 29-NF 24), Chapter <85> Bacterial Endotoxins Test. Available online: http://www.uspbpep.com/usp29/v29240/usp29nf24s0_c85.html (accessed on 21 December 2025).
316. United States Pharmacopeia (USP). Bacterial Endotoxins Test—PDG Harmonization Standard. Available online: https://www.usp.org/harmonization-standards/pdg/general-methods/bacterial-endotoxins (accessed on 21 December 2025).
317. *ASTM F2900-11*; Standard Guide for Characterization of Hydrogels for Regenerative Medicine. ASTM International: West Conshohocken, PA, USA, 2011. Available online: https://www.astm.org/f2900-11.html (accessed on 21 December 2025).
318. Moyo, M.T.G.; Adali, T.; Edebal, O.H. ISO 10993-4 Compliant Hemocompatibility Evaluation of Gellan Gum Hybrid Hydrogels for Biomedical Applications. *Gels* **2024**, *10*, 824. [Google Scholar] [CrossRef]
319. *ISO 22442-3:2020*; Medical Devices Utilizing Animal Tissues and Their Derivatives—Part 3: Validation of the Elimination and/or Inactivation of Viruses and Transmissible Agents. International Organization for Standardization (ISO): Geneva, Switzerland, 2020. Available online: https://www.iso.org/ (accessed on 21 December 2025).
320. *ASTM F2900-25*; Standard Guide for Characterization of Hydrogels for Regenerative Medicine. ASTM International: West Conshohocken, PA, USA, 2025. Available online: https://www.astm.org/f2900-25.html (accessed on 21 December 2025).
321. National Pharmaceutical Regulatory Agency (NPRA); Ministry of Health Malaysia. *Bacterial Endotoxin Test (BET): Training Slides*; NPRA: Putrajaya, Malaysia, 2019. Available online: https://www.npra.gov.my/images/Announcement/Archives/Slides-amv/AMV%20-%20BACTERIAL%20ENDOTOXIN%20TEST%20%28BET%29.pdf (accessed on 21 December 2025).
322. ASTM International. New ASTM Standard Guide Characterizes Hydrogels for Regenerative Medicine; ASTM News Release. 2020. Available online: https://www.astm.org/news/press-releases/new-astm-standard-guide-characterizes-hydrogels-regenerative-medicine (accessed on 04 November 2025). [Google Scholar]
323. BSI Group. The Impact of the EU MDR on Combination Products and Substance-Based Devices. Available online: https://www.bsigroup.com/siteassets/pdf/en/insights-and-media/insights/white-papers/bsi-md-mdr-impact-combination-products-and-s

ubstance-based-devices.pdf (accessed on 21 December 2025).
324. Botta, L. Medical Device Regulation—Harmonised Standards Summary (Regulation (EU) 2017/745). Available online: https://www.medical-device-regulation.eu/?m=pc (accessed on 21 December 2025).

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