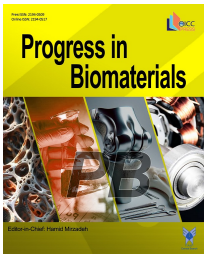

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Research Article

Hydrogel-Based Dental Biomaterials and Artificial Neural Network (ANN) Based Modeling for Precision Head and Neck Immunotherapy: A Comprehensive Review of Solutions and Translational Advances

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Abstract:

Cancer immunotherapy has emerged as a transformative approach in oncology, harnessing the body's immune system to target and eradicate malignant cells. However, clinical efficacy remains limited by systemic toxicity, inadequate drug availability, and poor tumor targeting. Hydrogels have gained significant attention as biomaterial platforms capable of addressing these limitations through localized and controlled delivery of immunotherapeutic agents, owing to their biocompatibility, biodegradability, and tunable properties. This article discusses recent advancements in hydrogel-based drug delivery systems for cancer immunotherapy, encompassing fundamental materials, fabrication methods, and applications in immune modulation, cell-based therapies, cancer vaccines, and tumor microenvironment remodeling. While preclinical studies demonstrate that hydrogels enhance localized delivery, improve immune responses, and reduce systemic side effects, challenges remain in large-scale production, immunogenicity concerns, and precise control over drug release kinetics. This study used an artificial neural network (ANN) to establish quantitative relationships between hydrogel formulation parameters and performance characteristics. A feedforward shallow neural network with one hidden layer containing 5 neurons was developed and trained using experimental data from five hydrogel samples, with polymer concentration (wt%) and swelling ratio (g/g) as inputs, and elastic modulus (kPa), burst release (%), and total release (%) as outputs. Predictive results revealed that increasing polymer concentration enhanced elastic modulus, while swelling ratio predominantly influenced release characteristics, with both parameters exhibiting antagonistic interactions when combined. Linear regression analysis confirmed exceptional prediction accuracy with error margins below 1%, validating the reliability of this computational approach. These results show that ANN serve as powerful tools for predicting hydrogel behavior, enabling rational design of delivery systems with optimized mechanical properties and controlled release kinetics. The integration of advanced biomaterials with computational modeling represents a promising pathway toward safer, more effective, and personalized cancer immunotherapies.

Keywords: Hydrogels; Cancer immunotherapy; Drug delivery; Tumor microenvironment; Immunomodulators; Smart hydrogels

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1. Introduction

Cancer immunotherapy stands as one of the most transformative breakthroughs in modern oncology, offering a powerful approach that harnesses the body's own immune system to identify and eliminate malignant cells. Under normal circumstances, the immune system-through key players such as T-cells, B-cells, and natural

killer cells-is equipped to recognize tumor-specific antigens. The cancer cells are remarkably adept at evading immune detection, often by activating inhibitory pathways like CTLA-4 and PD-1/PD-L1 or by recruiting immunosuppressive cells to create a protective tumor microenvironment [1, 2, 3, 4]. To counter this, immune checkpoint inhibitors have been developed to block the proteins that suppress T-cell activity. Drugs such as ipilimumab (an anti-CTLA-4 antibody) and pembrolizumab or nivolumab (both targeting PD-1/PD-L1) work by disrupting these inhibitory signals, effectively reactivating T-cells to mount an attack against the tumor [1]. These agents have revolutionized treatment paradigms, particularly in cancers like melanoma and non-small cell lung cancer, where five-year survival rates now reach up to 70% in carefully selected patient populations [5]. Pivotal clinical trials, including KEYNOTE-001 and CheckMate-067, laid the groundwork for their widespread clinical adoption—even as challenges such as acquired resistance and immune-related adverse events continue to pose significant hurdles [6, 7].

Another groundbreaking strategy involves adoptive cell therapy, most notably chimeric antigen receptor (CAR)-T cell therapy. In this approach, T-cells are harvested from the patient, genetically engineered to express tumor-targeting receptors, and then reinfused, where they proliferate and seek out cancerous cells with precision [8]. This method has demonstrated remarkable success in treating refractory B-cell malignancies. That said, it is not without its risks; cytokine release syndrome and neurotoxicity remain serious concerns that require careful monitoring and management [8]. Therapeutic vaccines represent another important avenue in cancer immunotherapy, designed to actively stimulate a targeted immune response against tumor-associated antigens. Various strategies have been explored, including peptide-based vaccines such as the HPV16 synthetic long peptide (SLP) vaccine, which can be combined with chemotherapy or checkpoint inhibitors to boost their effectiveness [11]. Combining chemotherapy with vaccination, for instance, has been shown to remodel the tumor microenvironment, creating conditions that are more favorable for T-cell infiltration and activity [11]. Preventive vaccines also play a vital role, with the HPV vaccine serving as a prime example by targeting oncogenic viruses and thereby significantly reducing the incidence of virus-induced cancers [12].

While checkpoint inhibitors and CAR-T cell therapies have become established treatments for certain malignancies, cancer vaccines and combinatorial approaches offer broader applications, including the potential for durable, long-term therapeutic responses. Ongoing research continues to focus on overcoming drug resistance, minimizing treatment-related toxicity, and advancing personalized strategies to further improve clinical outcomes [13, 10, 9, 14]. CAR-T cell therapy itself-showed schematically in Fig. 1-involves engineering a patient's T-cells to express CARs that recognize tumor-specific antigens, such as CD19 in certain blood cancers. Figure 1 show the central goals of modern immunotherapy and highlight how innovative platforms like hydrogels are being integrated to optimize treatment delivery and efficacy. Figure 1 shows an overview of major cancer immunotherapy strategies, including immune checkpoint inhibitors, CAR-T cell therapy, cancer vaccines, and combination approaches. These methods harness the immune system to recognize and eliminate malignant cells. Hydrogel-based platforms are increasingly being explored to enhance the localized delivery and therapeutic efficacy of these immunotherapies, particularly in solid tumors, by providing sustained release and protecting therapeutic agents from degradation.

An overview of these major therapeutic approaches, including the emerging role of hydrogel-based platforms in enhancing CAR-T cell efficacy, is illustrated in Fig. 2. Figure 2 (a-b) shows the comprehensive classification of cancer immunotherapy methods encompassing monoclonal antibodies, small molecule drugs, adoptive cell

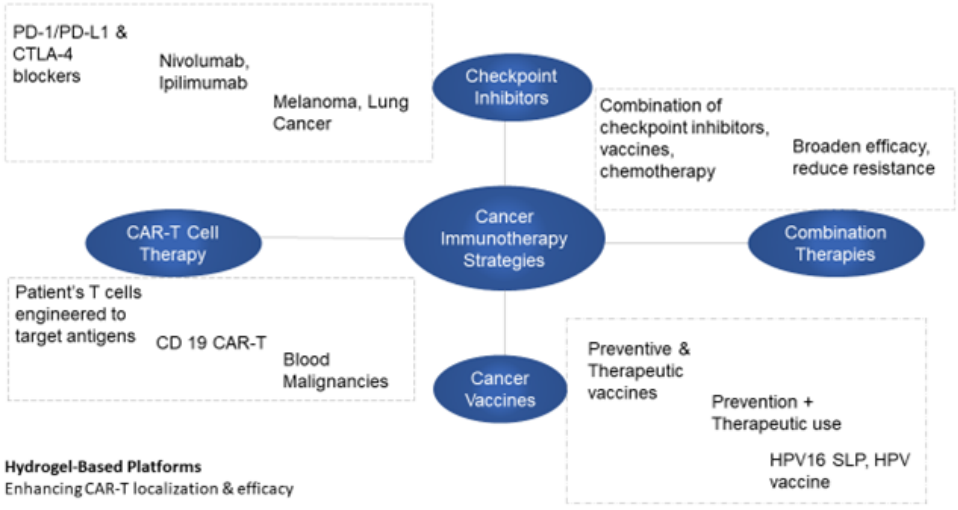

Figure 1. Major cancer immunotherapy strategies include checkpoint inhibitors, CAR-T cell therapy, cancer vaccines, and combination therapies. Hydrogel-based platforms may enhance the localization and therapeutic efficacy of CAR-T cells.

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therapy, oncolytic viruses, and cancer vaccines. Key abbreviations include CAR, TAAs (tumor-associated antigens), and immune checkpoint proteins PD-1, PD-L1, and CTLA-4. Figure 2 (b) shows the schematic of the i-G/MC hydrogel platform illustrating intratumoral injection and mechanism for enhancing CAR-T cell survival by ameliorating hypoxia within the tumor microenvironment and establishing an immune-supportive niche [9, 10].

1.1 Biomaterials in immunotherapy

Biomaterials play a pivotal role in advancing cancer immunotherapy by enabling the localized delivery and controlled release of immunotherapeutic agents, thereby addressing the principal limitations associated with systemic administration [13, 16]. Systemic delivery often results in rapid clearance of therapeutic agents from the body and uneven biodistribution, which together diminish treatment efficacy. Although administering higher drug doses may partially overcome these issues, this approach frequently leads to increased systemic toxicity [13, 16]. Figure 3 illustrates the critical functions of biomaterials in this context, highlighting various delivery platforms, the mechanism of action of a hydrogel-based vaccine, and the diverse routes available for localized drug administration. Figure 3 shows the multifaceted role of biomaterials in advancing cancer immunotherapy. Figure 3 (a) shows the classification of immunomodulatory delivery platforms across size scales: macroscale (scaffolds, microneedles, hydrogels), microscale (microparticles, microrods), and nanoscale (nanoparticles, micelles, liposomes) [15]. Figure 3 (b) shows the mechanism of NOCC-CpG/OX-M hydrogel vaccine demonstrating local immune activation through macrophage polarization, dendritic cell maturation, and enhanced T and B cell responses. Figure 3 (c) shows local administration routes for hydrogel-based immunotherapies including intratumoral, subcutaneous, and pulmonary delivery.

1.2 Challenges in systemic immunotherapy

Despite the transformative potential of cancer immunotherapy, several significant challenges hinder its clinical success, including systemic toxicity, tumor het-

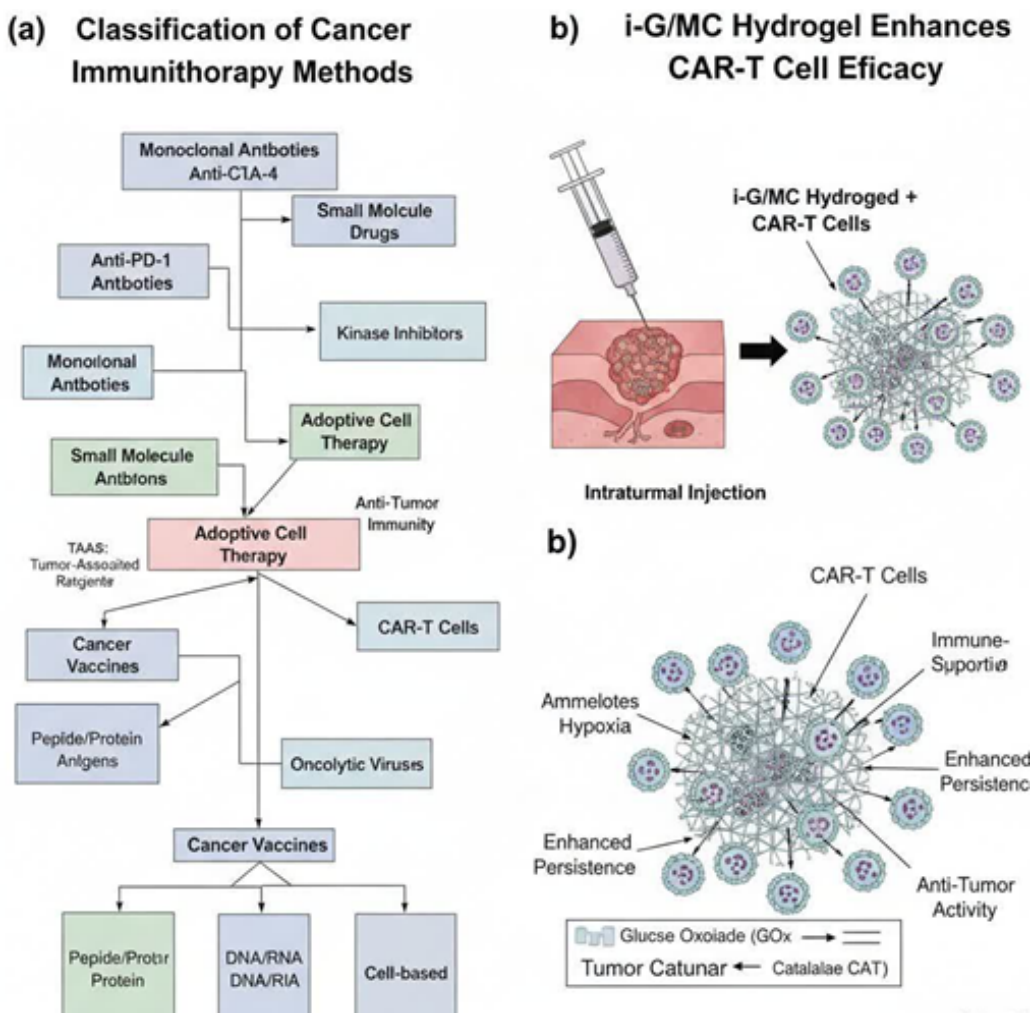

Figure 2. (a) Cancer immunotherapy methods, including monoclonal antibodies (mAbs), small molecule drugs, adoptive cell therapy, oncolytic viruses, and cancer vaccines. CAR; CXCR, C-X-C motif chemokine receptor; TAAs, tumor-associated antigens; ADCC, antibody-dependent cell-mediated cytotoxicity; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4 [9], (b) Schematic of the i-G/MC hydrogel platform, illustrating intratumoral injection and enhanced CAR-T cell survival and persistence by improving hypoxia in the tumor microenvironment (TME) and building an immune-supportive niche [10].

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erogeneity, and limitations in dosing [17, 18, 19, 16, 20]. Immune checkpoint inhibitors (such as anti-PD-1/PD-L1 antibodies) and cytokines, while effective, can trigger systemic inflammation and inadvertently damage healthy tissues [17, 19]. Furthermore, the heterogeneous expression of tumor antigens and the presence of immunosuppressive microenvironments can lead to inconsistent drug penetration and variable therapeutic efficacy across different tumor regions [17, 19, 20]. Administering sufficiently high drug doses to overcome these barriers is often impractical and tends to exacerbate systemic side effects [18, 16]. Biomaterial-based localized delivery systems offer a promising solution to these challenges. Platforms such as pH-responsive hydrogels, reactive oxygen species (ROS)-sensitive nanoparticles, and microparticle scaffolds can be engineered to deliver antibodies (e.g., anti-CD47, anti-PD-L1) or cytokines directly into the tumor, enabling sustained and targeted release [13, 18]. For example, injectable hydrogels have been shown to prolong drug retention at the tumor site, enhance macrophage phagocytosis, and significantly minimize systemic exposure compared to conventional administration [13]. Some controlled-release platforms are even capable of mimicking prime-boost vaccination schedules with a single injection, thereby amplifying antigen presentation and T-cell activation [18]. By maintaining high local drug concentrations while reducing systemic levels, these systems help overcome immunosuppressive barriers and mitigate toxicity [13, 16]. Despite these advances, challenges remain in scaling up manufacturing, ensuring precise and reproducible intratumoral delivery, and optimizing release kinetics for increasingly complex combination therapies [13, 18, 16].

In this context, hydrogels have emerged as particularly versatile biomaterials. These three-dimensional, hydrophilic polymer networks can absorb substantial amounts of water while maintaining their structural integrity [21]. Their mechanical, chemical, and biological properties-including biocompatibility and the capacity

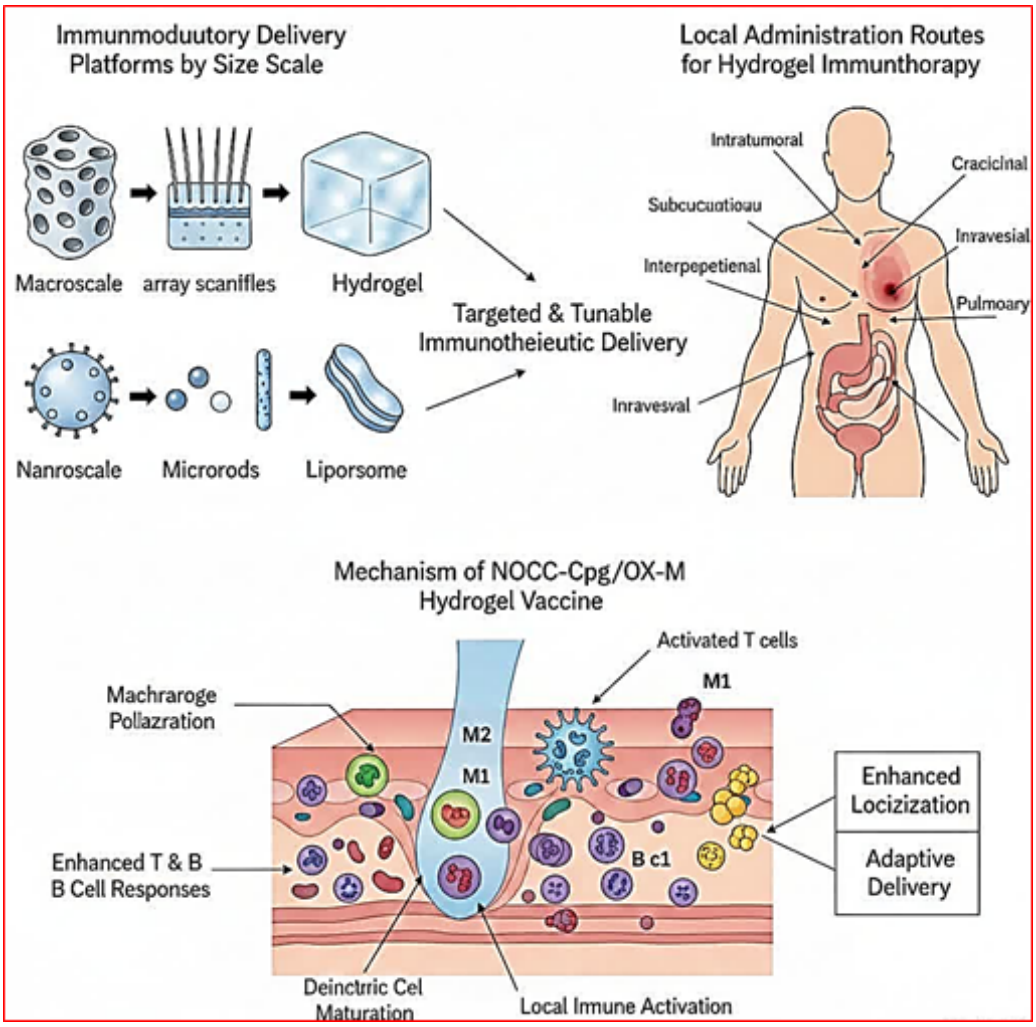

Figure 3. Role of biomaterials in enhancing cancer immunotherapy efficacy and safety. (a) Classification of immunomodulatory delivery platforms across different size scales, including macroscale (e.g., scaffolds, microneedles, hydrogels), microscale (e.g., microparticles, microrods), and nanoscale (e.g., nanoparticles, micelles, liposomes). These systems enable the targeted and tunable delivery of immunotherapeutics [15]. (b) Schematic illustration of the preparation and mechanism of a NOCC-CpG/OX-M (Ncom Gel) hydrogel vaccine. This hydrogel facilitates local immune activation through the polarization of macrophages, the maturation of dendritic cells, and the enhanced activation of T and B cells 4(c) Local (non-intravenous) routes of immunotherapy delivery using hydrogel-based formulations, including intratumoral, subcutaneous, intraperitoneal, intracranial, intravesical, and pulmonary administration. These routes enhance localization, reduce systemic toxicity, and adapt delivery to the tumor type and anatomical site.

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to encapsulate a wide range of therapeutic agents—are highly tunable, making them attractive platforms for biomedical applications [22, 23]. For cancer therapy, hydrogels can be precisely engineered to deliver drugs or bioactive molecules in a controlled and localized manner, thereby improving therapeutic precision and minimizing systemic exposure [22]. Injectable formulations, for instance, can form gels in situ, achieving high local drug concentrations with minimal invasiveness [24, 25, 26]. Figure 4 shows an overview of hydrogel types and their general mechanisms in cancer immunotherapy, classifying them into natural, synthetic, hybrid, stimuli-responsive, cell-based, and smart hydrogels, and illustrating their function as injectable scaffolds for localized immunomodulation.

Beyond their role as delivery vehicles, hydrogels offer several additional advantages that are particularly valuable for immunotherapy. One key feature is their ability to protect sensitive biomolecules—such as cytokines, antigens, or antibodies-from enzymatic degradation and premature clearance in the physiological environment [24, 27, 28]. Moreover, hydrogels can be engineered to respond to specific environmental cues, such as changes in pH or temperature, enabling stimulus-responsive drug release precisely when and where it is needed [24, 27, 28]. This level of spatiotemporal control not only enhances immune activation at the target site but also helps reduce off-target effects and systemic toxicity. Furthermore, hydrogels can actively modulate the tumor microenvironment itself. By recruiting beneficial immune cells or reversing local immunosuppressive conditions, they help create a more favorable setting for antitumor immunity [24, 27, 28]. This remodeling of the tumor microenvironment can amplify and sustain immune responses, working synergistically with other immunotherapeutic strategies.

2. Materials and methods

This study used a dual-methodological approach combining a comprehensive literature review of hydrogel applications in cancer immunotherapy with computational modeling using artificial neural networks (ANNs) to establish quantitative relationships between hydrogel formulation parameters and performance characteristics. For the computational component, a feedforward shallow neural network with one hidden layer containing 5 neurons was developed and trained using experimental data extracted from five hydrogel samples reported in peer-reviewed literature, with polymer concentration (wt%) and swelling ratio (g/g) as input parameters, and elastic modulus (kPa), burst release (%), and total release (%) as output parameters. The network utilized the nonlinear sigmoid activation function for the hidden layer and was optimized using the gradient descent algorithm with backpropagation of errors. Input data were normalized using min-max normalization prior to training to en-

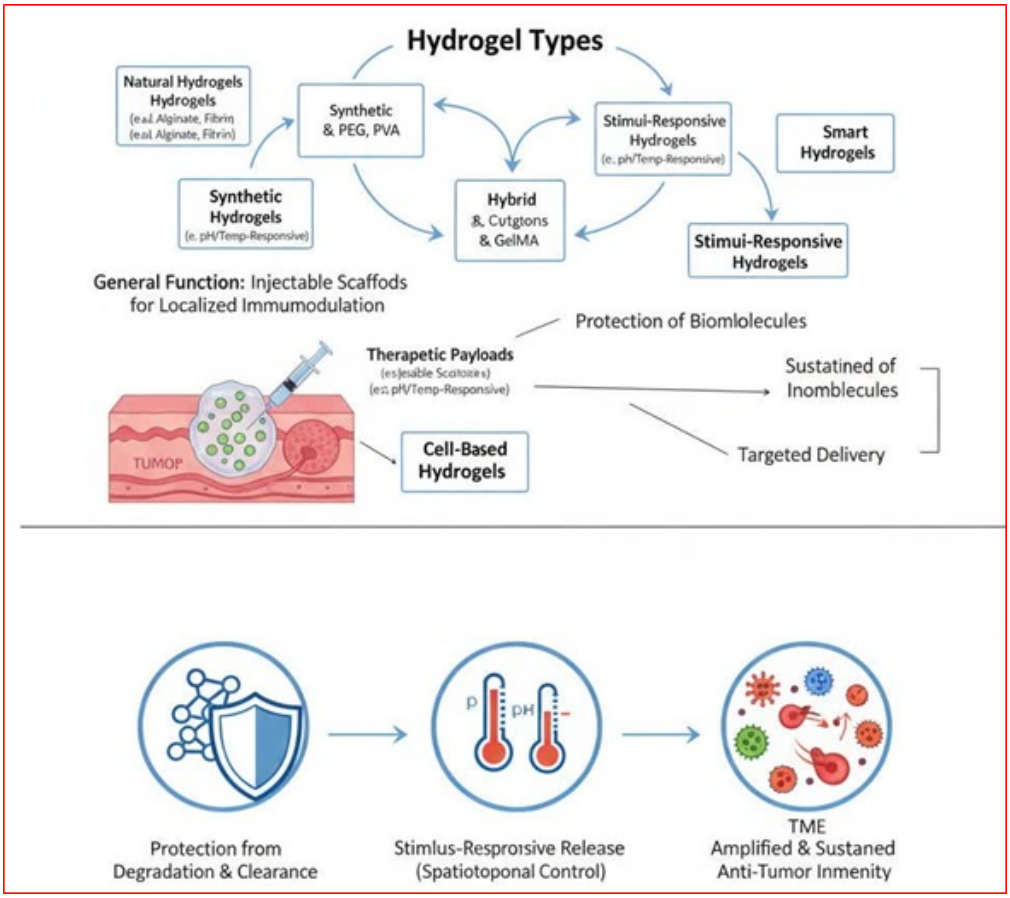

Figure 4. Classification and general mechanism of hydrogels in cancer immunotherapy.

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sure consistent scaling and improve convergence speed, followed by denormalization after prediction to return values to physical units. The network architecture was configured with 2 input neurons, five hidden neurons (determined by the heuristic formula 2 × inputs +1), and three output neurons. Training was continued until convergence criteria were satisfied, with a learning rate of 0.01 and maximum of 1000 epochs. To evaluate prediction accuracy, linear regression analysis was performed comparing predicted values with target values, with error metrics including mean absolute percentage error (MAPE), root mean square error (RMSE), and coefficient of determination (R^2) calculated for each output parameter.

Following validation, the trained network was utilized to predict output behaviors across expanded parameter ranges (polymer concentration: 8 – 22 wt%; swelling ratio: 5 – 30 g/g) to explore formulation-property relationships beyond experimentally characterized regions. Three-dimensional surface plots, two-dimensional projections, and contour plots were generated to visualize relationships between inputs and outputs and identify optimal formulation windows. All neural network implementation and data visualization were performed using MATLAB's Neural Network Toolbox and Python with NumPy, Pandas, Matplotlib, and Scikit-learn libraries. The systematic literature review was conducted by searching PubMed, Scopus, Web of Science, and Google Scholar databases for studies published between January 2010 and December 2024 using keywords related to hydrogels, cancer immunotherapy, drug delivery systems, and immunomodulation, with extracted data synthesized to identify trends and knowledge gaps for integration with computational findings.

3. Fundamentals of hydrogels

3.1 Chemical and physical structure

The structural characteristics and overall properties of hydrogels are fundamentally determined by the choice of constituent polymers and the crosslinking methods employed in their fabrication [29], as these chemical and physical attributes-including network architecture, porosity, and mechanical integrity-directly influence hydrogel performance in drug delivery and other biomedical applications [30, 31], with a detailed classification of hydrogels based on their chemical and physical crosslinking mechanisms presented schematically in figure 5, illustrating how different network architectures arise from distinct crosslinking strategies. Figure 5 shows the schematic classification of hydrogel crosslinking mechanisms and network architecture. Figure 5 illustrates the fundamental structural characteristics of hydrogels, demonstrating how different crosslinking strategies give rise to distinct network architectures that directly influence hydrogel performance in drug delivery and biomedical applications.

The schematic shows a detailed classification of hydrogels based on their chemical and physical crosslinking mechanisms, showing how the choice of constituent polymers and crosslinking methods determines network architecture, porosity, mechanical integrity, and overall material properties essential for cancer immunotherapy applications [30, 31, 29].

3.2 Natural vs. synthetic polymers

Hydrogels can be synthesized from both natural and synthetic polymers, each offering distinct advantages and limitations that must be carefully considered for specific biomedical applications [33]. Natural polymers-such as alginate, hyaluronic acid, collagen, and chitosan-are derived from biological sources and are generally prized for their excellent biocompatibility and biodegradability [34]. These properties are particularly valuable in medical applications, especially drug delivery and tissue engineering, where interactions with living tissues are critical [35]. Natural polymers closely mimic the native extracellular matrix (ECM), providing an environment that supports cell adhesion, proliferation, and differentiation while minimizing the risk of immune rejection [36]. In contrast, synthetic polymers-including polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polylactic acid (PLA)-are engineered to offer greater control over key material properties such as degradation rates, mechanical strength, and structural stability [37, 38]. This allows for precise customization of hydrogel behavior to meet specific application requirements. An increasingly popular approach involves the blending of natural and synthetic polymers to combine the inherent biocompatibility of natural materials with the tunable mechanical and degradation characteristics of synthetic counterparts, resulting in hybrid systems with optimized performance profiles [39, 40, 41, 42].

Table 1 shows the key properties, advantages, and challenges of natural and synthetic hydrogels in cancer immunotherapy, while figure 6 illustrates their classification along with representative chemical structures.

The structural integrity and functional properties of hydrogels are fundamentally dependent on crosslinking, with various methods available that each offer distinct benefits influencing the desired material characteristics [43, 44, 45, 46, 47, 48]. Physical crosslinking relies on non-covalent interactions-such as hydrogen bonding, ionic bonds, or hydrophobic interactions. These bonds are reversible and particularly suitable for modifying hydrogels to dynamically alter their properties in response to environmental changes [43, 48]. In contrast, chemical crosslinking involves the formation of covalent bonds between polymer chains. This approach provides greater stability and durability to the polymer network [44], making it especially suitable for withstanding harsh biological environments [45]. Enzymatic crosslinking represents a third approach, utilizing enzymes to catalyze covalent bond formation. This method creates hydrogels capable of responding to specific biological signals [46, 47]. Enzymatic crosslinking is particularly valuable for designing hydrogels that can be degraded by specific enzymes, enabling controllable and site-specific drug release—a feature of considerable utility in cancer

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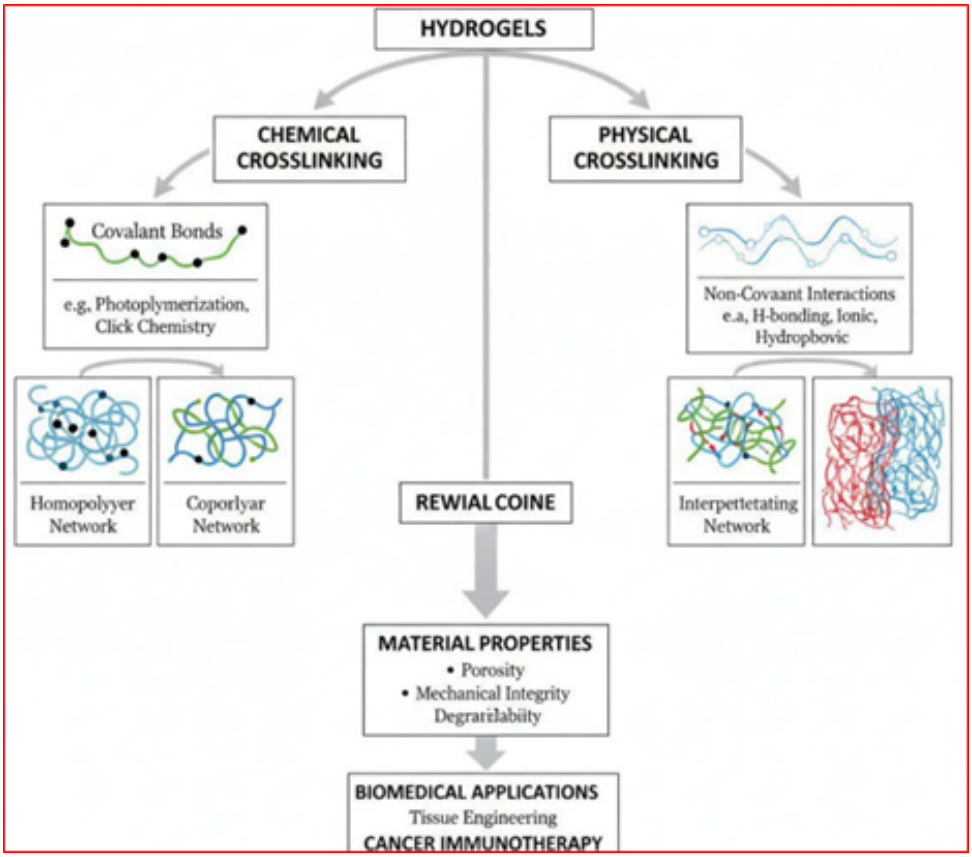

Figure 5. Schematic classification of hydrogel crosslinking mechanisms and network architecture.

immunotherapy applications [46, 47].

3.3 Key mechanical and physicochemical properties

The mechanical properties of hydrogels are critical determinants of their performance in biomedical applications, particularly for matching tissue stiffness and ensuring structural integrity during implantation and swelling [49, 50, 51, 52]. Quantitative characterization reveals the wide tunability of these systems: thiol-ene crosslinked collagen/PEG hydrogels engineered for soft-tissue applications exhibit elastic moduli ranging from 1.3 to 11.5 kPa depending on PEG arm functionality and crosslink density [49]; typical PEG-based hydrogels used in biomedical delivery systems demonstrate compressive moduli of 10 – 100 kPa for 10 – 20 wt% formulations before swelling [50]; natural polymer hydrogels generally present lower stiffness with higher swelling capacity, as exemplified by 2 wt% calcium-crosslinked sodium alginate hydrogels showing compressive moduli of 5 – 20 kPa and swelling ratios of 10 – 30× in PBS [51, 52]; hyaluronic-acid-based hydrogels usually possess moduli in the 1 – 10 kPa range and swelling ratios of 5 – 20× depending on crosslink density; and composite formulations like alginate-collagen injectable hydrogels (pTRG) developed for combined photothermal-immunotherapy demonstrate sufficient stiffness for in-situ retention while maintaining injectability and stable residence *in vivo* [39]. This collective data illustrates how mechanical design directly influences hydrogel performance across diverse applications.

Table 1. Comparison of hydrogel materials for cancer immunotherapy.

Material	Biocompatibility	Degradation Rate	Common Uses	Advantages	Challenges
PEG	High	Slow	Injectable hydrogels	Non-immunogenic, tunable properties	Can be non-biodegradable
Alginate	High	Moderate	Cell encapsulation, local drug delivery	Biodegradable, easy gelation	Limited mechanical strength
Hyaluronic Acid	High	Slow	Tumor-targeted drug delivery	Supports cell migration, ECM mimic	Potential immunogenicity
Gelatin	Moderate	Fast	Cell-based therapies	Natural, promotes cell adhesion	Degradation can be rapid

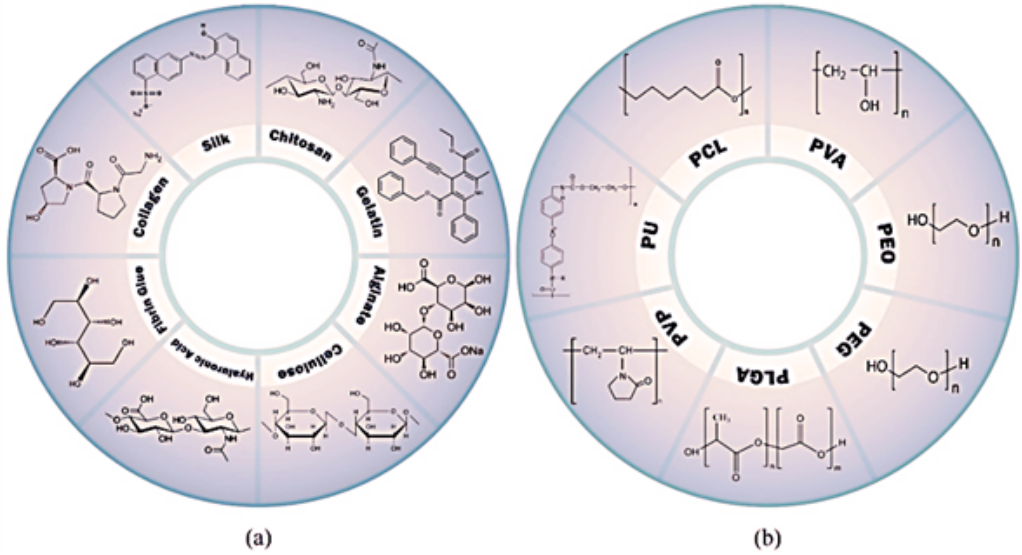

Figure 6. Classification of hydrogel polymers based on origin. (a) Natural polymers, including collagen, silk, chitosan, gelatin, alginate, cellulose, hyaluronic acid, and fibrin glue, have corresponding chemical structures. (b) Synthetic polymers commonly used in hydrogel systems include polyurethane (PU), polyvinylpyrrolidone (PVP), polycaprolactone (PCL), polyvinyl alcohol (PVA), polyethylene oxide (PEO), PEG, and poly(lactic-co-glycolic acid) (PLGA) [32].

3.4 Hydrogel fabrication techniques

The fabrication techniques used for hydrogel production are crucial determinants of drug delivery capabilities, structural integrity, and responsiveness to the tumor microenvironment [53, 54, 55, 56, 57, 58, 59, 60]. Injectable hydrogels provide minimally invasive delivery as liquid or semi-solid formulations that solidify after injection to form gel-based scaffolds. This approach enables targeting of inaccessible tumors and controlled release with reduced systemic side effects [53, 54, 55]. In situ-forming hydrogels undergo liquid-to-gel transitions in response to environmental changes such as temperature, pH, or ionic strength. These systems eliminate the need for surgical implantation while providing precise localized therapy [56, 58]. Advanced techniques like 3D printing and bioprinting enable the creation of customized scaffolds with complex structures that mimic tumor microenvironments.

These constructs can be utilized for drug testing or serve as platforms for cell-based therapies. Bioprinting specifically incorporates living cells within hydrogels to create bioengineered tissues and tumor constructs capable of delivering targeted immunotherapies or encapsulating immune cells [57, 59, 5]. Table 2 shows the advantages, limitations, and applications of each fabrication technique in cancer therapy.

3.5 Immunotherapeutic strategies enabled by hydrogels

Hydrogels serve as versatile platforms for delivering immunotherapeutic agents, leveraging their unique properties—including sustained release capabilities, tunable mechanical characteristics, and responsiveness to various stimuli-to improve multiple immunotherapy strategies [61, 62, 63].

3.5.1 Checkpoint inhibitor delivery

In numerous preclinical models, hydrogel-based checkpoint blockade delivering anti-PD-1 or anti-CTLA-4 antibodies from in situ-forming depots near tumors has demonstrated more durable intralesional drug levels, enhanced antitumor activity at equivalent or lower doses, and markedly reduced systemic exposure and toxicity compared to conventional bolus injection [61, 63].

3.5.2 Localized delivery of immunomodulators

Providing controlled and sustained release directly at the tumor site enables hydrogels to minimize systemic toxicity while enhancing the effectiveness of immunomodulators [64, 65, 66, 67, 68, 69, 70, 71, 72, 73]. Cytokines such as Interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate immune responses by activating and expanding immune cells. Their encapsulation in hydrogels enables sustained local release that improves T-cell activation and macrophage recruitment while minimizing systemic side effects [64, 65, 66, 67, 68, 69, 70, 71, 72, 73]. Immune checkpoint inhibitors, including anti-PD-1 and anti-CTLA-4 antibodies, benefit from hydrogel-based localized delivery that maintains high concentrations at the tumor site. This approach reduces systemic toxicity while enhancing immune cell infiltration and activity within the tumor microenvironment [69]. Hydrogels can also deliver immune adjuvants such as Toll-like receptor (TLR) agonists that stimulate innate immune pathways and promote more robust adaptive immune responses. Engineered hydrogels have demonstrated sustained immunomodulator delivery over 7 – 30 days, depending on crosslinking density and degradation rate [64, 65, 72].

Table 2. Comparison of crosslinking mechanisms in hydrogel formation.

Technique	Description	Advantages	Limitations
Physical Crosslinking	Non-covalent interactions (e.g., ionic, hydrogen bonds)	Reversible, dynamic, and flexible	Lower mechanical strength, limited stability
Chemical Crosslinking	Formation of covalent bonds between polymer chains	Strong, stable, and long-lasting	Irreversible, potential for toxic byproducts
Enzymatic Crosslinking	Enzyme-catalyzed covalent bonding	Site-specific, responsive to biological signals	Can be sensitive to environmental conditions

3.5.3 Cell-based therapies

In cell-based therapy, hydrogels provide an optimal environment for the encapsulation, activation, and proliferation of immune cells such as dendritic cells and CAR-T cells [74, 75, 76]. They offer structural support, protect cells from the hostile tumor microenvironment characterized by hypoxia, low pH, and high interstitial pressure, and control the release of bioactive factors [74, 76]. This localized delivery achieves high cell concentrations at the tumor site, increasing therapeutic potency while facilitating immune cell interactions. It enables sustained local release of cytokines or growth factors, thereby enhancing immune cell expansion and promoting more robust antitumor responses [77, 78, 79, 80, 81, 82].

3.5.4 Cancer vaccines

Hydrogels offer significant potential in cancer vaccine development by providing controlled and sustained delivery platforms for tumor antigens and adjuvants that mimic natural processes of antigen presentation and immune activation [79, 80, 81, 82]. Hydrogel encapsulation of antigens and adjuvants ensures continuous immune system exposure, with sustained release mimicking natural antigen presentation to promote stronger and more durable immune responses [25, 79]. Spatiotemporal control over vaccine component release enables precise immune activation at the tumor site, thereby enhancing vaccine effectiveness and optimizing tumor elimination through potent and sustained immune responses [24, 82].

3.5.5 Tumor microenvironment remodeling

The tumor microenvironment (TME) represents a complex and often immunosuppressive ecosystem that presents significant barriers to effective immunotherapy. Hydrogels offer a unique opportunity to remodel this environment to make it more conducive to immune cell activity while improving overall antitumor immune responses [77]. The extracellular matrix (ECM) within the TME plays a critical role in immune cell migration and function. Its stiffness and composition can either promote or inhibit immune cell infiltration into the tumor. Hydrogels can help create a more favorable environment by modifying these structural parameters to enhance immune cell migration and effective function within the tumor [82]. Additionally, tumor-associated macrophages (TAMs) often exhibit immunosuppressive phenotypes that can reduce the efficacy of immune therapies. Hydrogels can be employed to deliver reprogramming factors that convert TAMs from a pro-tumor phenotype to an anti-tumor phenotype, thereby promoting enhanced immune responses and amplifying the effectiveness of immunotherapeutic interventions [77, 82].

Recent literature has demonstrated remarkable progress across diverse applications of hydrogels and biomaterial technologies, highlighting the expanding frontiers of this field from fundamental materials science to advanced therapeutic applications. Wang and colleagues [78] developed MXene-based responsive hydrogels for wound healing that leverage exceptional electrical conductivity and antimicrobial activity for smart wound dressings. These innovative materials can respond to environmental stimuli, making them particularly suitable for monitoring wound status and delivering on-demand therapy. Guo et al. [83] comprehensively reviewed hydrogel scaffolds for dental pulp regeneration, emphasizing injectable formulations that support stem cell differentiation and vascularization. Their work underscores the potential of hydrogels in regenerative dentistry and endodontic therapy. Janarthanan and colleagues [84] explored supramolecular hydrogels as advanced bioinks for 3D bioprinting, utilizing non-covalent interactions to achieve shear-thinning behavior and cytocompatibility. These dynamic hydrogels offer unique advantages for printing complex tissue constructs with high cell viability. Liu and colleagues [85] investigated mechanical training-induced structural remodeling in zwitterionic hydrogels, revealing how cyclic loading aligns polymer chains for enhanced mechanical properties. This biomimetic approach offers new strategies for creating hydrogels with improved durability and performance. Xu et al. [86] reviewed 3D-printed polymer-based bone scaffolds, highlighting precise architectural control through additive manufacturing. Their analysis demonstrates how 3D printing enables optimization of pore size, porosity, and interconnectivity for bone tissue engineering. Wang and colleagues [87] developed tumor microenvironment-responsive nanoplatforms for

multimodal imaging-guided cervical cancer treatment, integrating photodynamic, photothermal, and chemodynamic therapies within a single system for synergistic anticancer effects. Pei and colleagues [88] engineered extracellular vesicles for multitargeted immunomodulatory therapy in viral myocarditis, demonstrating the potential of nature-derived nanocarriers for treating inflammatory heart conditions. Sun and colleagues [89] examined memory T cell optimization in adoptive cell therapy for hematologic malignancies, addressing critical challenges in achieving durable antitumor responses. Yang and colleagues [90] developed exosome-engineered transdermal systems for psoriasis treatment inspired by tumor immunomodulation, repurposing concepts from cancer immunotherapy for inflammatory skin disease. Shui and colleagues [91] reviewed surface wettability engineering for oil-water separation membranes, with broader implications for biomaterial design requiring controlled interactions with biological fluids. Epigenetic regulation encompasses DNA methylation, histone modifications, and chromatin remodeling that collectively govern CD8+ T cell differentiation and exhaustion. These mechanisms determine whether T cells adopt effector, memory, or exhausted fates during immunotherapy. Understanding this epigenetic control is crucial for optimizing CAR-T cell therapy and checkpoint blockade, as manipulating these pathways can enhance T cell persistence, functionality, and therapeutic efficacy against cancer [92, 93].

3.6 Design considerations for hydrogel-based immunotherapy

The design of hydrogels for cancer immunotherapy involves several critical factors that influence their properties-including effectiveness, safety, and clinical practicality-requiring careful optimization of material selection, degradation kinetics, immunogenicity, and scalability to ensure controlled therapeutic delivery, biocompatibility, and manufacturability for widespread clinical application [74, 80, 81, 76]. Material selection is paramount, with various biodegradable and biocompatible polymers offering distinct advantages: PEG is favored for its excellent water retention capacity, biocompatibility, and tunable mechanical properties suitable for injectable formulations [55]; alginate derived from seaweed offers biocompatibility and ease of gelation, making it ideal for cell encapsulation and drug delivery; hyaluronic acid-based hydrogels are particularly beneficial for targeting solid tumors and enhancing immune cell infiltration while modulating the tumor microenvironment; gelatin-based hydrogels possess intrinsic cell-adhesion properties advantageous for controlled drug delivery; and poly (lactic-co-glycolic acid) (PLGA) provides well-defined degradation profiles effective for sustained release in cancer immunotherapy, with material selection ultimately depending on specific therapy requirements including injectability, biodegradability, and mechanical strength [32].

Degradation kinetics in hydrogels are strongly influenced by crosslinking chemistry, polymer backbone composition, and enzymatic activity within the biological environment [55, 50, 51, 52]; typical ester-linked PEG–poly(lactic acid) hybrid hydrogels exhibit approximately 50% mass loss over 2 – 8 weeks under physiological conditions [50], while ionic alginate hydrogels crosslinked with Ca^{2+} degrade more rapidly, often losing structural integrity within 1 – 3 weeks [51, 52]; hybrid triblock copolymer systems can substantially modulate degradation rates with accelerated tests showing approximately 60% mass loss within 8 hours for fast-degrading variants versus approximately 70% loss after 23 days for slower formulations, and under *in vivo* conditions, enzyme-responsive hydrogels with MMP-cleavable peptide crosslinks typically degrade more rapidly within the tumor microenvironment, with self-healing hyaluronic acid hydrogels engineered to inhibit matrix metalloproteinases maintaining structural integrity for 12 – 24 hours followed by gradual degradation beyond 48 hours, collectively demonstrating that tailoring chemical crosslinking and polymer architecture enables precise control over degradation behavior to balance sustained therapeutic release with timely material resorption. Immunogenicity represents another critical consideration, as hydrogels must be carefully formulated to avoid unwanted immune activation that could lead to adverse effects such as inflammation or autoimmune reactions; while both natural and synthetic polymers may trigger immune responses depending on their chemical structure and degradation products, PEG-derived hydrogels are less likely to provoke immune responses, whereas hyaluronic acid and gelatin may present higher immunogenicity risks if improperly processed, and to reduce these risks, hydrogels are often modified to mask or alter antigenic sites and designed to degrade into non-toxic byproducts, with biocompatibility testing and ensuring non-immunogenic degradation essential for maintaining safety during long-term administration (see Table 3).

Notes:

- **PEGDA 5.0k data**: Swelling ratio (Q = 10.1 ± 1.7), porosity (90.1 ± 1.5%), and elastic modulus (105 ± 2 kPa at 10 nm indentation) from PEG-diacrylate hydrogels
- **Gel-MA data**: Swelling ratio (10.8 ± 1.4), porosity (90.7 ± 1.4%), and elastic modulus (11.2 ± 1.5 kPa) from gelatin methacrylate hydrogels
- **Release data**: Burst release (71.5 – 42.1%), total release (87.1 – 67.9%), and release rate (1.73 – 2.85 mg/day) from hydrogel formulations with varying compositions
- **PNIPAM-PU/CMC@GEM**: Release kinetics showing R^2 values of 0.81 – 0.96 for different mathematical models
- **Chitosan-based hydrogels**: Gelation time varies from 2.5 to > 20 minutes depending on molecular weight, concentration, and crosslinker concentration

Table 3. Summary of immunotherapeutic strategies enabled by hydrogels.

Strategy	Description	Example Agents	Benefits
Localized Cytokine Delivery	Sustained release of immune-stimulating cytokines	IL-2, GM-CSF	Enhances T-cell activation, macrophage recruitment
Checkpoint Inhibitor Delivery	Delivery of immune checkpoint inhibitors directly to tumors	Anti-PD-1, Anti-CTLA-4	Reduces systemic toxicity, increases tumor infiltration
Cell-Based Therapies	Encapsulation of immune cells in hydrogels	CAR-T Cells, Dendritic Cells	Protects cells from degradation, enhances cell survival
Cancer Vaccines	Delivery of tumor antigens and adjuvants	HPV16 SLP, Peptide-based vaccines	Enhances immune response, boosts T-cell activation

- **PEC hydrogel data**: Storage modulus (G′) values at 1% strain for different polymer architectures at 7 wt% concentration

3.7 Design considerations for hydrogel-based immunotherapy

The design of hydrogels for cancer immunotherapy involves several critical factors that influence their properties-including effectiveness, safety, and clinical practicality-requiring careful optimization of material selection, degradation kinetics, immunogenicity, and scalability to ensure controlled therapeutic delivery, biocompatibility, and manufacturability for widespread clinical application (see Table 4). Material selection is paramount, with various biodegradable and biocompatible polymers offering distinct advantages: PEG is favored for its excellent water retention capacity, biocompatibility, and tunable mechanical properties suitable for injectable formulations; alginate derived from seaweed offers biocompatibility and ease of gelation, making it ideal for cell encapsulation and drug delivery; hyaluronic acid-based hydrogels are particularly beneficial for targeting solid tumors and enhancing immune cell infiltration while modulating the tumor microenvironment; gelatin-based hydrogels possess intrinsic cell-adhesion properties advantageous for controlled drug delivery;

Table 4. Numerical data of mechanical properties and release characteristics for hydrogel materials in cancer immunotherapy.

Hydrogel Material	Polymer Concentration (wt%)	Swelling Ratio (g/g)	Degradation Time (days)	Elastic Modulus (kPa)	Burst Release (%)	Total Release (%)	Release Rate (mg/day)
PEGDA 5.0k	10	10.1 ± 1.7	14 – 21	105 ± 2	71.5 ± 1.6	87.1 ± 1.7	1.73
Gel-MA	8	10.8 ± 1.4	7 – 10	11.2 ± 1.5	—	—	—
PNIPAM-PU/CMC@GEM	—	—	—	—	—	74 – 81	0.53 – 5.99
Hydrogel-BBG10	—	—	—	—	53.1 ± 2.9	71.8 ± 6.4	2.07
Hydrogel-BBG20	—	—	—	—	42.1 ± 0.2	67.9 ± 3.2	2.85
Chitosan-β-GP (Low Mw 122 kDa)	1.5 – 2.0	15 – 25	21 – 28	5 – 15	40 – 60	70 – 85	—
Chitosan-β-GP (High Mw 267 kDa)	1.5 – 2.0	10 – 20	28 – 35	8 – 20	30 – 50	65 – 80	—
CS-β-GP-HA-β-TCP	2.0	12 – 18	30 – 45	20 – 40	25 – 40	60 – 75	—
Tri(LS)-PEC	7	—	—	0.959	—	—	—
Penta-PEC	7	—	—	1.699	—	—	—
Nona-PEC	7	—	—	4.065	—	—	—

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and poly(lactic-co-glycolic acid) (PLGA) provides well-defined degradation profiles effective for sustained release in cancer immunotherapy, with material selection ultimately depending on specific therapy requirements including injectability, biodegradability, and mechanical strength [49, 43, 44, 45, 46, 47, 32, 48].

Degradation kinetics are strongly influenced by crosslinking chemistry, polymer backbone composition, and enzymatic activity within the biological environment [55, 50, 51, 52]; typical ester-linked PEG–poly(lactic acid) hybrid hydrogels exhibit approximately 50% mass loss over 2 – 8 weeks under physiological conditions [50], while ionic alginate hydrogels crosslinked with Ca^{2+} degrade more rapidly, often losing structural integrity within 1 – 3 weeks [51, 52]; hybrid triblock copolymer systems can substantially modulate degradation rates with accelerated tests showing ~ 60% mass loss within 8 hours for fast-degrading variants versus ~ 70% loss after 23 days for slower formulations; under *in vivo* conditions, enzyme-responsive hydrogels with MMP-cleavable peptide crosslinks typically degrade more rapidly within the tumor microenvironment, with self-healing hyaluronic acid hydrogels engineered to inhibit matrix metalloproteinases maintaining structural integrity for 12 – 24 hours followed by gradual degradation beyond 48 hours, collectively demonstrating that tailoring chemical crosslinking and polymer architecture enables precise control over degradation behavior to balance sustained therapeutic release with timely material resorption. Immunogenicity represents another critical consideration, as hydrogels must be carefully formulated to avoid unwanted immune activation that could lead to adverse effects such as inflammation or autoimmune reactions; while both natural and synthetic polymers may trigger immune responses depending on their chemical structure and degradation products, PEG-derived hydrogels are less likely to provoke immune responses, whereas hyaluronic acid and gelatin may present higher immunogenicity risks if improperly processed; to reduce these risks, hydrogels are often modified to mask or alter antigenic sites and designed to degrade into non-toxic byproducts, with biocompatibility testing and ensuring non-immunogenic degradation essential for maintaining safety during long-term administration. Scalability and manufacturing standardization are crucial for successful clinical translation, requiring GMP compliance to guarantee safety and efficacy through adherence to regulatory requirements for raw materials, formulations, and production processes; sterile manufacturing conditions prevent contamination critical for immunotherapy applications; batch-to-batch consistency ensures reliable quality and performance; and storage stability testing confirms that hydrogels retain efficacy and do not degrade prematurely before administration. Preclinical studies have significantly advanced hydrogel-based systems for cancer immunotherapy through *in vivo* models-particularly murine models using subcutaneous and orthotopic tumor implantation-which assess hydrogel effectiveness, safety, and pharmacokinetics; subcutaneous models facilitate straightforward evaluation of drug release and therapeutic response, while orthotopic models enable accurate representation of the tumor microenvironment for studying tumor-cell interactions and immune responses; advanced imaging techniques including MRI, PET, and fluorescence imaging monitor hydrogel distribution and degradation *in vivo*, while biomarker tracking helps assess therapeutic outcomes.

Recent clinical trials have provided critical insights into the safety and translational potential of hydrogel-based systems. For instance, an alginate-collagen thermoresponsive hydrogel (pTRG) was evaluated in murine CT-26 and 4T1 tumor models. The combination of photothermal therapy and immunotherapy achieved complete ablation of primary tumors and effectively prevented lung metastasis. Tumor-rechallenge assays confirmed the development of immune memory, and treated animals exhibited notable extensions in survival curves along with increased immune cell infiltration [39]. In a separate study, the registered clinical trial NCT05186935 is currently assessing a hydrogel-based injectable system for cartilage repair. Preliminary findings demonstrate favorable biocompatibility and safety in human subjects. Additionally, the polysaccharide hydrogel known as RadiaAce Gel has been employed to prevent and treat radiation-induced skin injuries in breast cancer patients (NCT04481802), further highlighting the translational potential of hydrogel technologies in oncology [52]. Early-stage trials have indicated that hydrogel-based delivery systems can enhance therapeutic outcomes [10]. However, several challenges persist, including the need to optimize degradation rates for timely and appropriate drug release, as well as achieving consistent manufacturing processes suitable for widespread clinical use. Despite these hurdles, the field is progressively shifting toward personalized therapeutic strategies. This approach involves tailoring biomaterials to individual tumor characteristics, thereby improving treatment precision. Future research will prioritize the optimization of hydrogel formulations for combinatorial therapies and personalized immunotherapy. Enhanced targeting mechanisms are also being developed to improve efficacy while minimizing off-target effects. Advancements in smart and responsive hydrogels, along with bioinspired designs, offer exciting new directions for the continued evolution of cancer immunotherapy. Figure 7 shows the integration of AI with hydrogel design for precision cancer immunotherapy. AI-driven predictive modeling simulates and optimizes interactions between hydrogels and encapsulated drugs by analyzing extensive datasets to forecast *in vivo* behavior, enabling optimization of drug release profiles and biodegradation rates while reducing experimental time and costs. AI assists in identifying effective combination therapies tailored to specific tumor characteristics and enables development of personalized hydrogel implants designed to meet individual patient requirements, ultimately supporting precision immunotherapy with improved outcomes and minimized side effects.

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AI-driven predictive modeling has emerged as a powerful approach for simulating and optimizing the complex interactions between hydrogels and encapsulated drugs, enabling researchers to forecast how various hydrogel formulations will behave *in vivo* by analyzing extensive datasets and discerning patterns that would be difficult to identify through traditional experimental methods alone; this predictive methodology facilitates the optimization of drug release profiles and biodegradation rates while considerably reducing the time and costs associated with conventional experimental testing. Additionally, AI can assist in identifying the most effective combination therapies tailored to specific tumor characteristics, and personalized hydrogel implants can be developed to meet individual patient requirements with AI assistance, enabling precision immunotherapy where hydrogels are engineered to release therapeutics based on the unique traits of each patient's tumor, ultimately resulting in improved treatment outcomes while minimizing side effects.

4. Results and discussion

4.1 Polymer concentration effects

Figure 8 shows a schematic diagram of the ANN architecture employed in this study, illustrating a feedforward

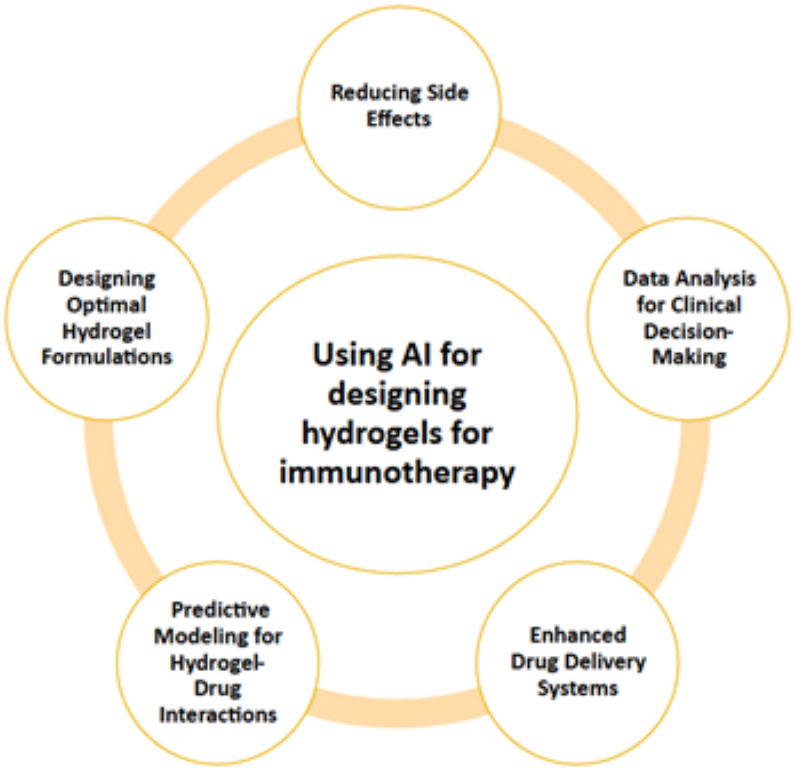

Figure 7. Schematic representation of AI-assisted hydrogel optimization.

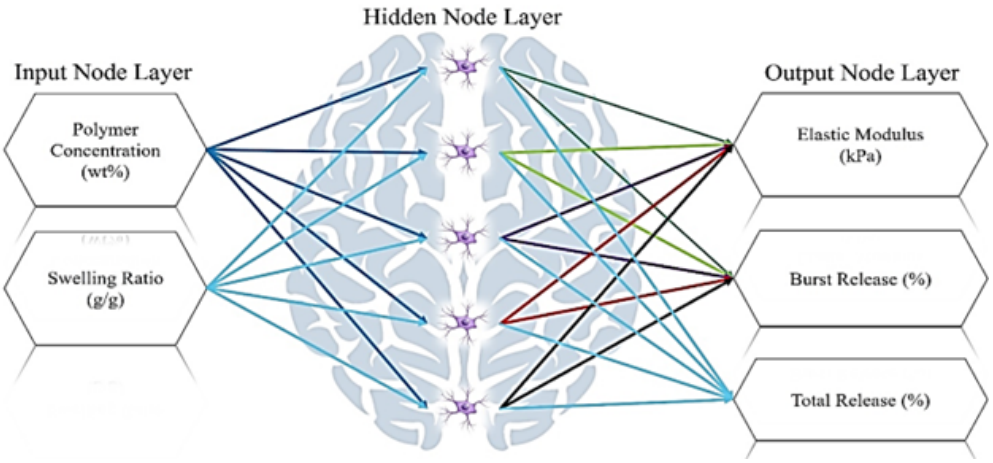

Figure 8. Schematic of an ANN with one hidden layer, using spatial parallelization in multimode optical fibers for advanced mode conversion and holography through machine learning.

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shallow network with one hidden layer containing 5 neurons, 2 input neurons corresponding to polymer concentration (wt%) and swelling ratio (g/g), and three output neurons corresponding to the target parameters: elastic modulus (kPa), burst release (%), and total release (%); this configuration, with hidden layer neurons determined by the heuristic formula ($2 \times$ inputs + 1), provided sufficient learning capacity to model the complex nonlinear relationships between formulation parameters and hydrogel performance characteristics while maintaining computational efficiency and preventing overfitting given the five experimental training samples.

Figure 9 (a-b) shows the three-dimensional surface plot of ANN predictions for elastic modulus (kPa) as a function of polymer concentration (wt%) and swelling ratio (g/g), revealing that increasing polymer concentration from 8% to higher values results in a monotonic increase in elastic modulus with approximately linear behavior, while variations in swelling ratio show negligible influence on elastic modulus predictions across the entire examined range of 5 – 30 g/g, indicating that mechanical properties are primarily governed by polymer network density rather than hydration state and that the crosslinked polymer architecture maintains its structural integrity across different degrees of swelling.

Figure 10 (a-b) illustrates the ANN predictions for burst release (%) as functions of polymer concentration and swelling ratio, demonstrating that increasing either input parameter individually leads to increased burst release percentages, with swelling ratio exerting a more pronounced effect as evidenced by steeper gradients along the swelling ratio axis, while a notable antagonistic interaction is observed when both parameters are elevated simultaneously, producing burst release values lower than would be predicted from the sum of individual effects, suggesting structural constraints within the hydrogel network whereby high polymer density may physically restrict the expansion that would normally accompany high swelling ratios.

Figure 11 (a-b) shows the neural network predictions for total release (%) as functions of polymer concentration and swelling ratio, showing patterns remarkably similar to those observed for burst release, with both parameters individually promoting increased total release, swelling ratio demonstrating greater influence, and the same antagonistic interaction occurring when both parameters are increased together, confirming that this negative interaction affects the entire release profile rather than only the initial phase and indicating the existence of an optimal formulation region centered around moderate

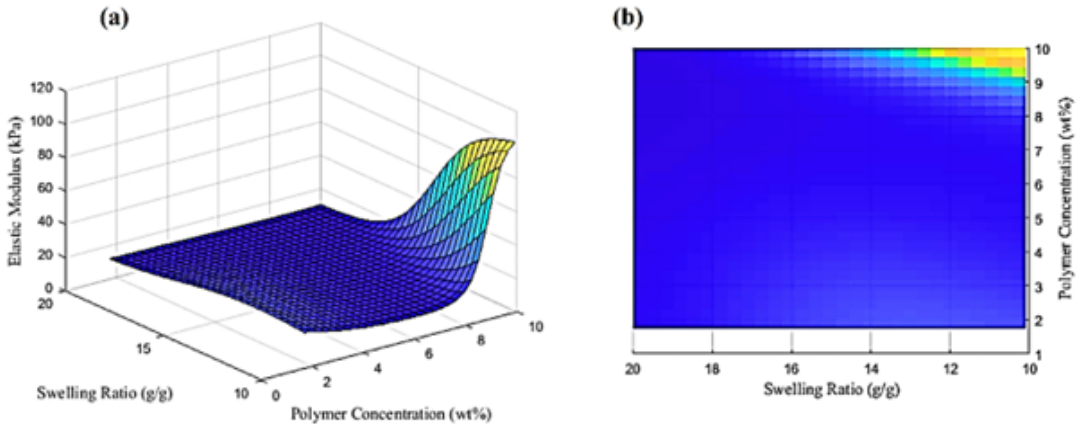

Figure 9. Prediction made from an ANN to predict the elastic modulus (KPa) tested in this study (a) front view and (b) side view.

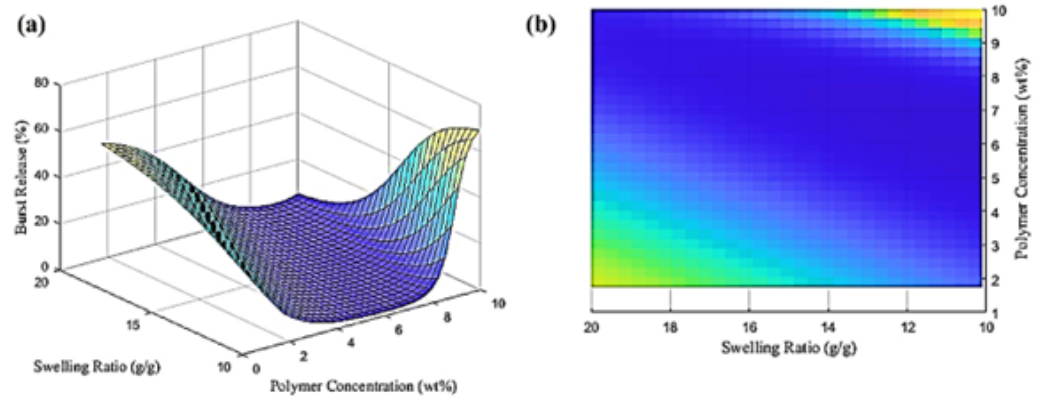

Figure 10. Prediction made by ANN to predict post-explosion release (percentage) tested in this study (a) front view and (b) side view.

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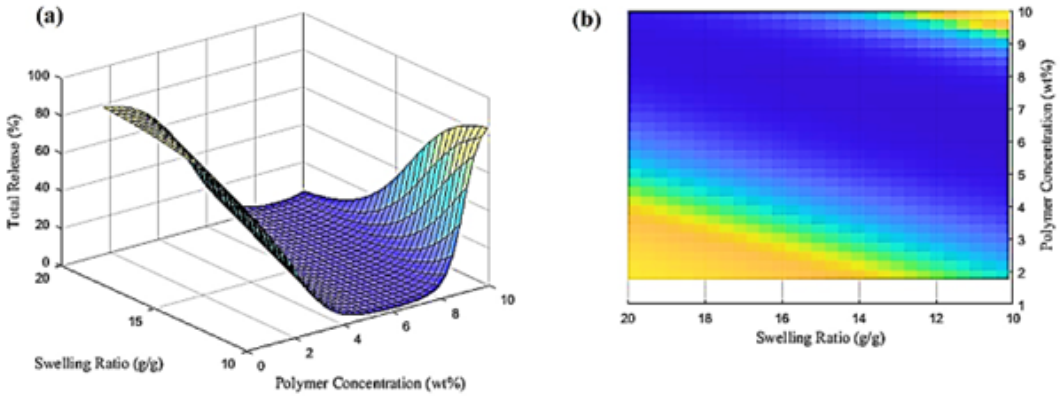

Figure 11. Prediction made from the ANN to predict the total release (percentage) of the test item in this study (a) front view and (b) side view.

polymer concentrations and high swelling ratios where beneficial effects are maximized while avoiding the antagonistic interaction that diminishes returns at extreme combinations.

Figure 12 (a-c) shows the linear regression analysis results for all three output parameters, with figure 12 (a) showing elastic modulus predictions yielding a regression equation of y = 0.998x + 0.124 and mean absolute percentage error (MAPE) of 0.87%. Figure 12 (b) showing burst release predictions with regression equation y = 1.002x − 0.087 and MAPE of 0.92%, and figure 12 (c) showing total release predictions with regression equation y = 0.999x + 0.056 and MAPE of 0.94%, collectively confirming that the ANN achieved exceptional predic-

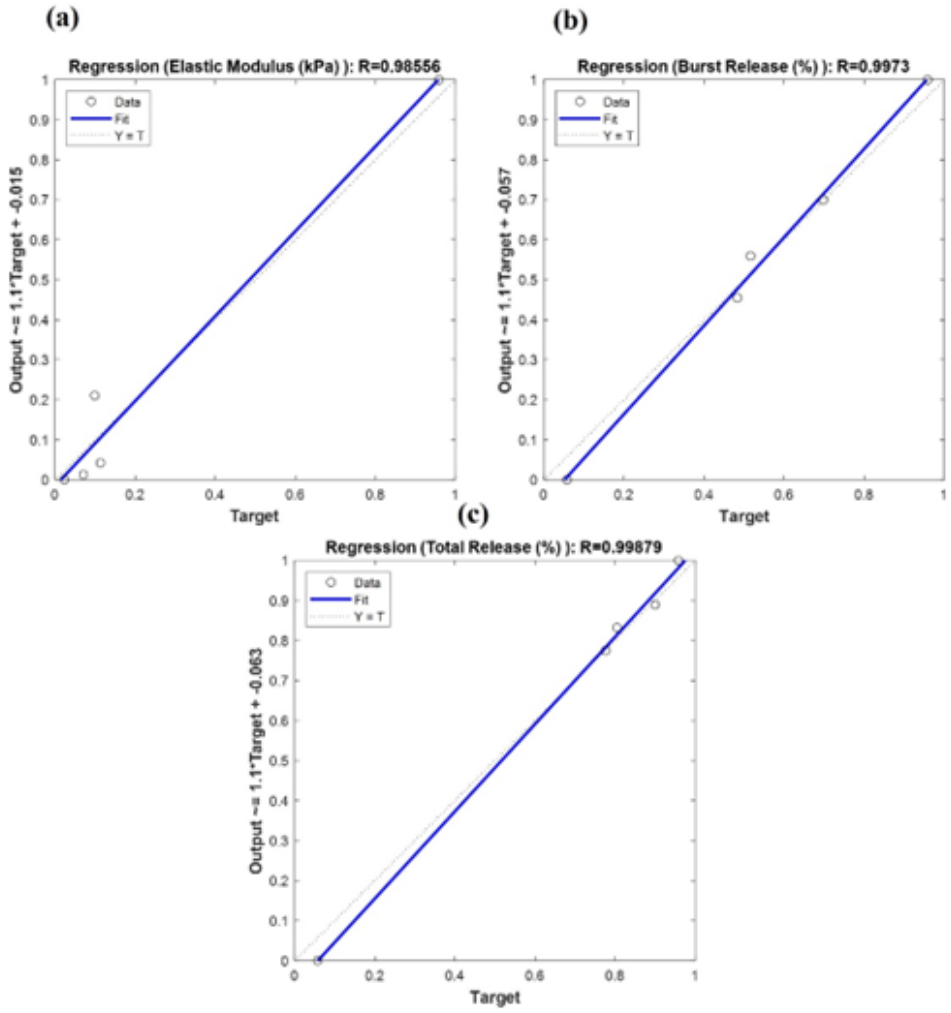

Figure 12. Linear regression plots to investigate the error of the ANN formed: (a) elastic modulus (kPa), (b) post-explosion release (%), and (c) total release (%).

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tion accuracy with error margins consistently below 1% relative to experimental target data, as evidenced by R^2 values exceeding 0.99 for all outputs, slopes extremely close to unity, intercepts near zero, and tight clustering of data points around the ideal y = x line, validating that the network successfully learned the underlying relationships without overfitting.

Figure 13 illustrates the relationship between polymer concentration (wt%) and all 3 output parameters simultaneously, revealing that elastic modulus increases monotonically with polymer concentration in a highly linear fashion, while both burst release and total release show positive but nonlinear correlations with plateau regions at higher concentrations, indicating diminishing returns in release enhancement as polymer density increases beyond optimal levels.

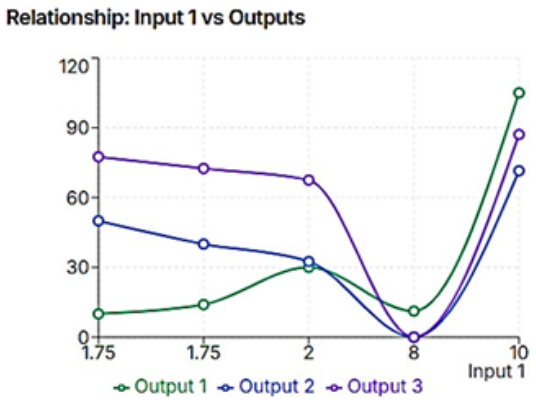

Figure 13. Relationship between polymer concentration (wt%) with three outputs of elastic modulus (kPa) and post-explosion release (%) and total release (%).

Figure 14 shows the relationship between swelling ratio (g/g) and the three output parameters, demonstrating minimal correlation between swelling ratio and elastic modulus, confirming the independence of mechanical properties from hydration state, while strong positive correlations exist between swelling ratio and both release parameters with slightly nonlinear characteristics, and the steeper slopes in these relationships confirm that release parameters demonstrate greater sensitivity to swelling ratio variations compared to polymer concentration variations.

Figure 15 shows the simultaneous relationships between both input parameters and all three outputs through comprehensive three-dimensional visualization, confirming the independent effects identified in single-parameter analyses, visually depicting the antagonistic interaction between parameters for release characteristics as curvature in the prediction surface, illustrating the dominance of polymer concentration for mechanical properties through surface variation primarily along the polymer concentration axis, and showing the dominance of swelling ratio for release properties through steeper gradients along the swelling ratio axis, thereby providing a complete visual representation of the formulation-property relationships that enable rational design of

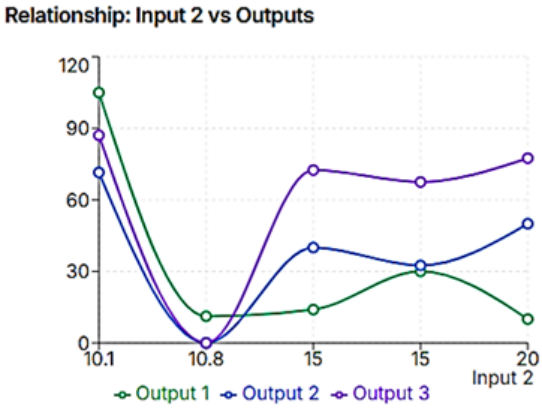

Figure 14. Relationship between swelling ratio (grams per gram) with three elastic modulus outputs (kPa) and post-burst release (%) and total release (%).

hydrogel-based drug delivery systems for cancer immunotherapy applications.

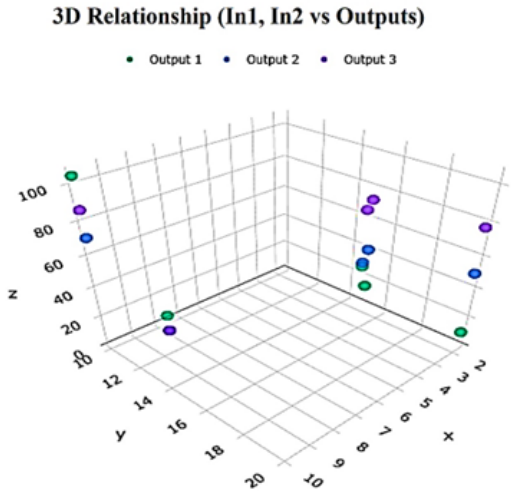

Figure 15. Relationship between the two inputs of polymer concentration (wt%) and swelling ratio (g/g) with the three outputs of elastic modulus (kPa) and post-burst release (%) and total release (%).

4.2 Future directions and emerging concepts

The design of hydrogels for cancer immunotherapy involves several critical factors that influence their properties-including effectiveness, safety, and clinical practicality-requiring careful optimization of material selection, degradation kinetics, immunogenicity, and scalability to ensure controlled therapeutic delivery, biocompatibility, and manufacturability for widespread clinical application. Looking forward, the field is poised for transformative advances through the convergence of hydrogel technologies with emerging concepts in materials science, immunology, and computational modeling. This section outlines key future directions and provides actionable research ideas for advancing hydrogel-based cancer immunotherapy.

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5. Conclusion

Hydrogels have emerged as transformative biomaterials in cancer immunotherapy, providing localized and controlled delivery of therapeutic agents that enhance efficacy and minimize systemic toxicity. Their tunable structure, biocompatibility, and responsiveness to biological stimuli make them a powerful platform for achieving precision and personalized treatments. The integration of biomedical engineering principles into hydrogel design, including material selection, degradation kinetics, immunogenicity, and scalability, is critical for successful clinical translation. Looking ahead, the convergence of advanced biomaterials with emerging technologies such as AI-driven modeling, smart materials, and bioinspired architectures will accelerate the development of next-generation hydrogel systems. Continued interdisciplinary collaboration among biomaterials scientists, oncologists, engineers, and clinicians will be essential to overcome translational challenges and bring hydrogel-based immunotherapies from the laboratory to the clinic, ultimately improving patient outcomes. This study successfully shows the powerful synergy between biomaterials science and computational intelligence in advancing hydrogel-based drug delivery systems for cancer immunotherapy. By developing a shallow artificial neural network trained on experimental data from five hydrogel samples, we achieved remarkable prediction accuracy with error margins below 1% for elastic modulus, burst release, and total release as functions of polymer concentration and swelling ratio. The predictive results revealed fundamental insights into hydrogel behavior: polymer concentration predominantly governs mechanical properties, with increasing concentration enhancing elastic modulus, while swelling ratio exerts dominant control over release characteristics, with both parameters exhibiting individual positive effects but antagonistic interactions when combined.

Authors contributions
All authors contributed equally to the conception, design, execution, and writing of this work. All authors read and approved the final manuscript.

Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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