





Review

# Peptide-Hydrogel Nanocomposites for Anti-Cancer Drug Delivery

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**Abstract:** Cancer is the second leading cause of death globally, but conventional anticancer drugs have side effects, mainly due to their non-specific distribution in the body in both cancerous and healthy cells. To address this relevant issue and improve the efficiency of anticancer drugs, increasing attention is being devoted to hydrogel drug-delivery systems for different kinds of cancer treatment due to their high biocompatibility and stability, low side effects, and ease of modifications. To improve the therapeutic efficiency and provide multi-functionality, different types of nanoparticles (NPs) can be incorporated within the hydrogels to form smart hydrogel nanocomposites, benefiting the advantages of both counterparts and suitable for advanced anticancer applications. Despite many papers on non-peptide hydrogel nanocomposites, there is limited knowledge about peptide-based nanocomposites, specifically in anti-cancer drug delivery. The aim of this short but comprehensive review is, therefore, to focus attention on the synergies resulting from the combination of NPs with peptide-based hydrogels. This review, which includes a survey of recent advances in this kind of material, does not aim to be an exhaustive review of hydrogel technology, but it instead highlights recent noteworthy publications and discusses novel perspectives to provide valuable insights into the promising synergic combination of peptide hydrogels and NPs for the design of novel anticancer drug delivery systems.

**Keywords:** peptide; peptide-based hydrogels; nanoparticles; nanocomposite; cancer; drug delivery



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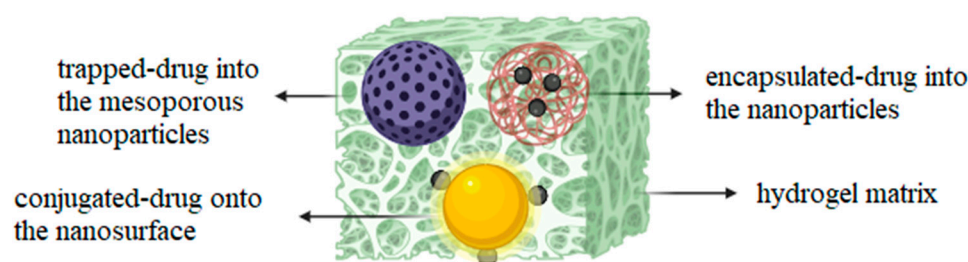
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## 1. Introduction

Traditional chemotherapy is limited by the unselective distribution of drugs in both cancerous and healthy tissues, resulting in adverse and long-term side effects for the patients [1,2]. In recent years, there have been admirable efforts to develop nano-based drug delivery systems (DDSs) benefiting various controlled-release properties, including pH- and thermo-sensitive, photo-induced, enzyme-responsive, and target-specific properties, which result in an enhanced selectivity of the drugs towards cancer cells with lower dosages required to achieve the pharmacological effects [3–10]. To date, more than 30 types of different inorganic and organic nanoparticles (NPs) have been approved in the clinic. [11] With the COVID-19 pandemic, FDA-approved lipid nano-carriers for mRNA vaccines have shown the key role of nanomedicine in managing new global challenges [12]. In fact, these lipid nano-carriers are considered the largest fraction of clinically approved NPs parenterally administered. Inorganic NPs are the second biggest group of medical nanomaterials due to their unique electronic structures. Inorganic NPs include several important and unique materials such as porous silica [13], iron oxides [14–16], titania [17,18], and silver and gold NPs [19–29]. These have been the subject of many studies, such as

anticancer and antibacterial, thanks to the success of therapies that accurately combine pharmaceuticals with NPs to achieve a synergic effect [30]. In drug delivery applications, nanocarriers allow gradual and controlled drug release, extend drug circulation time, and protect drugs against oxidation/degradation. Furthermore, nanocarriers can modify the physicochemical properties of drugs (hydrophilicity/hydrophobicity) in order to enhance their therapeutic index [6,31].

Hydrogels are three-dimensional (3D) polymeric networks that can adsorb and retain large amounts of water inside their matrices; they can be used as stabilizers/scaffolds for NPs to enhance their stability against aggregation and oxidation [32]. Three-dimensional hydrogel matrices can be designed in order to contain suitable functional groups for loading a variety of biomolecules and drugs. Of course, NPs may affect the mechanical and swelling features of hydrogels. [33–35]. Hydrogel nanocomposites are a developed class of inorganic–organic gel-type materials that may be used as drug delivery systems (DDSs), combining the benefits of both nanomaterials and hydrogels in a single platform with reinforced structures and multifunctional capabilities [36–40] (Figure 1). Hydrogel nanocomposites should have some basic properties for being used as DDS with maximum efficacy: (1) exhibit excellent mechanical strength and injectability to enhance in vivo drug stability as well as in situ protection/retention of drugs [41–44]; (2) have strong drug-carrier interactions to guarantee controlled and sustained drug release; (3) be structurally tunable for providing different release profiles based on the type of drug; and (4) have the capacity/ability to load several therapeutic components inside the hydrogel matrix to imply a synergic efficacy and multifunctionality.



**Figure 1.** Scheme of the inclusion/incorporation of NPs in three-dimensional polymeric structures.

The incorporation of NPs within hydrogels creates multifunctional systems to achieve tunable delivery systems. Besides improving the mechanical properties of the hydrogels, the presence of NPs modulates the response of the nanocomposites to different stimuli (e.g., electric, magnetic, and light-responsive hydrogels), as shown in Table 1.

**Table 1.** Examples of nanocomposite hydrogels with properties that are triggered or enhanced by nanoparticles for DDS applications. Reprinted with permission from [38]. Copyright 2015 American Chemical Society.

Benefits	Nanoparticles	Ref.
Controlled drug release under electrical stimuli	Carbon NPs	[38,45]
Controlled drug release under magnetic stimuli	Iron oxide magnetic NPs	[38,46]
Controlled drug release under light stimuli	Carbon NPs	[38,47]

Based on the source and origin of the hydrogels, the obtained nanocomposites may be classified as natural or synthetic systems. Peptide hydrogels are an interesting class of materials made from amino acid precursors. They are generally biocompatible and suitable for biological applications, including anticancer drug delivery [48,49]. Over the past decades, considerable developments in the synthesis and technology of non-peptide hydrogel nanocomposites have qualified them as promising candidates for designing controlled-release drug delivery systems. Comparatively, there is little knowledge of

peptide-based hydrogel nanocomposites [50], so this review aims to highlight recent advances in the use of peptide-based nanocomposites as anticancer drug delivery vehicles. The inclusion/incorporation of nanoparticles in three-dimensional (3D) peptide hydrogels is an innovative strategy for obtaining multifunctionality, adding synergistic benefits to the new 3D structures, which are the main focus of this short but comprehensive review.

## 2. Drug Delivery Using Hydrogel Nanocomposites

### 2.1. Formulation Methods of Peptide-Hydrogel Nanocomposites

To fabricate advanced hydrogel nanocomposites and obtain the desired properties, there are four main methods, including blending, grafting, in situ precipitation, and swelling [49]. Among these methods, the swelling strategy is an in situ methodology in which the hydrogel nanocomposites are synthesized in one step. On the other hand, blending and grafting methods are considered ex situ strategies, and the nanocomposites are prepared in multiple steps [51].

In the blending method, the nanoparticles are first synthesized and then mixed with hydrogel precursors, followed by gel formation. Despite its simplicity, this method sometimes suffers from the interference of nanoparticles with gel formation, which negatively affects the final structure of the nanocomposite. Also, the lack of uniform distribution of the nanoparticles might result in their diffusion outside the hydrogel matrix upon swelling.

The grafting methods (grafting-through, grafting-from, and grafting-onto) consist of the use of grafted/grafting nanoparticles having suitable functional groups to allow the covalent bonding of nanoparticles with the peptide monomers during gel formation. Despite this advantage, the long, high-cost, and complicated fabrication process limits its use in nanocomposite preparation [51].

In the in situ precipitation method, nanoparticles are prepared in situ inside the hydrogel network during gel formation. This strategy should be performed in mild conditions (neutral pH, room temperature) and is, therefore, suitable for nanoparticles having mild condition synthesis processes. In the swelling method, after hydrogel synthesis, the nanocolloids are incubated with the gel network, which is useful for the development of microgels [51].

The intermolecular interactions among peptides in hydrogel nanocomposites are usually non-covalent (e.g., hydrogen bonds, electrostatic interactions, van der Waals,  $\pi$ - $\pi$  stacking) and different secondary structures ( $\alpha$ -helix,  $\beta$ -sheet,  $\beta$ -hairpin) can be formed [32].

Considering the number of hydrophobic drugs used in the clinic and those currently under development, hydrogels-DDSs for hydrophobic drugs could offer multiple advantages to patients and clinicians.

To deliver hydrophobic drugs, these could be covalently incorporated within a hydrogel network. A similar effect can be obtained using hydrophobic crosslinkers, resulting in amphiphilic hydrogels [52].

Regarding drug release from the nanocomposites, there are three main mechanisms:

1. Passively controlled drug release: Drug molecules in the hydrogel matrix are passively released through swelling and diffusion.
2. Stimuli-responsive drug delivery: Smart hydrogels drastically change their volume in response to environmental stimuli (e.g., pH, temperature, magnetic field, light, and chemical signals), triggering the release of the loaded drug.
3. Site-specific drug delivery: Drug delivery primarily relies on the properties of the hydrogel network comprising targeting components (e.g., antibodies, aptamer, folate, peptides), which allow nanoparticle design to be only focused on tuning the drug release. Such a hybrid strategy provides an opportunity to design highly specific DDSs [53].

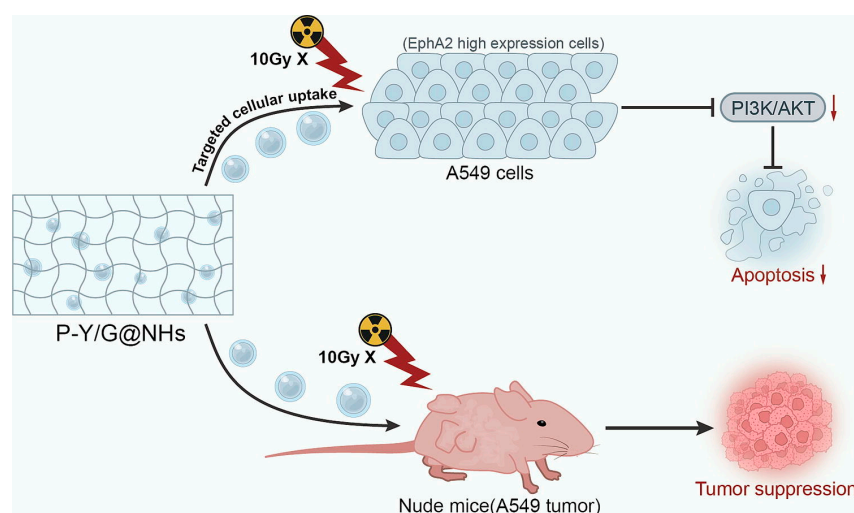
### 2.2. Peptide-Based Hydrogel Nanocomposites Containing Inorganic NPs

As a prevalent malignancy, lung cancer has been a leading cause of cancer-related deaths in males globally [54], and non-small cell lung cancer (NSCLC) is the most com-

mon type (85% of all lung cancers [55]). For NSCLC treatment, there have been different strategies, such as targeted therapy, chemotherapy, surgical resection, radiotherapy, and immunotherapy. However, the overall survival rates of NSCLC are low. Therefore, it is vital to improve current methods [56,57], for instance, by the advancement of novel drugs and combined methods to extend them to a broader range of patients and improve overall outcomes in NSCLC.

Paclitaxel (PTX) is a well-known clinical anticancer agent [58], widely employed as a radiosensitizer [59], capable of overcoming hypoxia-inducible factor-1 $\alpha$ -induced radioresistance of human lung adenocarcinoma cells [60]. For PTX-targeted delivery, YSAYPDSVPMMS (YSA) peptide was successfully tested to selectively target Ephrin type-A receptor 2 (EphA2) activation when anchored with liposomal docetaxel (a common clinical formulation of PTX) in A549 lung cancer cell line [61]. Moreover, succinic anhydride (SA)-modified NPs were previously evaluated as biodegradable and biocompatible DDSs (with no anticoagulant activity) to deliver cisplatin to lung cancer cells in nude mice [62]. Regarding the inorganic radiosensitizers for radiotherapy, gold NPs are well researched in this field owing to their high X-ray absorption and unique physicochemical properties, inertness, easy synthetic method, well-known chemistry, and more importantly, their potent anticancer effects in lung cancer due to their ability to generate reactive oxygen species (ROS) in A549 cells and subsequent cell apoptosis [63]. It has been shown that a combination of such therapeutic NPs and hydrogel technology results in advanced and multifunctional nanocomposites for achieving highly effective local drug delivery [53]. In such applications, the surface of NPs should be precisely modified by suitable stabilizers. In this sense, dextran was recently employed as both a stabilizing and reducing reagent for preparing biocompatible gold NPs with high monodispersity [64]. In general, dextran-based radioconjugates can enhance the therapeutic effect of radiotherapy, and dextran uptake further accompanies the activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway upon entry of viruses into cells [65,66], which can enhance the sensitivity of NSCLC radiotherapy [67]. Based on the above considerations, in 2023, Zhang et al. evaluated the effects of a nano-DDS composed of YSAYPDSVPMMS (YSA) peptide-modified gold NPs-dextran-hydrogel loaded with paclitaxel-succinic anhydride (P-Y/G@NHs) on NSCLC cell radiosensitivity. P-Y/G@NHs hydrogel nanocomposite was prepared using the following three-step method: (1) combining SA and PTX to obtain PTX-SA; (2) chemical conjugation of YSA-peptide to the PTX-SA by *N*-hydroxysuccinimide (NHS) and dicyclohexylcarbodiimide (DCC) coupling reagents to prepare the drug (PTX-SA-YSA); (3) self-assembly of polyethylene glycol-modified gold NPs, dextran, and PTX-SA-YSA to form the resultant hydrogel drug delivery system. The therapeutic properties of the P-Y/G@NHs in NSCLC cells were studied by monitoring the PI3K/AKT signaling pathway and evaluating apoptosis, colony formation, and reactive oxygen species (ROS) generation of A549 cells under 10Gy X-ray irradiation. The authors also successfully tested the *in vivo* therapeutic effect of this nanocomposite on A549 tumor-bearing mice. The results showed that P-Y/G@NHs can reduce the number of colonies of A549 cells by inducing both ROS production and cell apoptosis under 10Gy X-ray irradiation. In fact, the radiosensitivity of A549 cells was enhanced using P-Y/G@NHs by inhibiting the PI3K/AKT signaling pathway. The *in vivo* fluorescence results confirmed effective targeting and accumulating of P-Y/G@NHs at the tumor site in nude mice to enhance the radiosensitivity of target tumors without significant side effects or immune toxicity, which highlighted the potential application of P-Y/G@NHs in radiotherapy of NSCLC cells by repressing the PI3K/AKT signaling pathway (Figure 2) [68].

Other reports on peptide-based hydrogels loaded with inorganic nanoparticles for anticancer drug delivery, alongside their main advantages and disadvantages, are reported in Table 2.



**Figure 2.** Schematic representation of in vivo and in vitro studies of YSAYPDSVPMMS (YSA) peptide-modified gold NPs-dextran-hydrogel. Reprinted with permission from [68]. Copyright 2023, Elsevier.

**Table 2.** Summary of the DDS applications, advantages, and disadvantages associated with the peptide-based hydrogels loaded with inorganic nanoparticles. The disadvantages can be transversal to other composites [50].

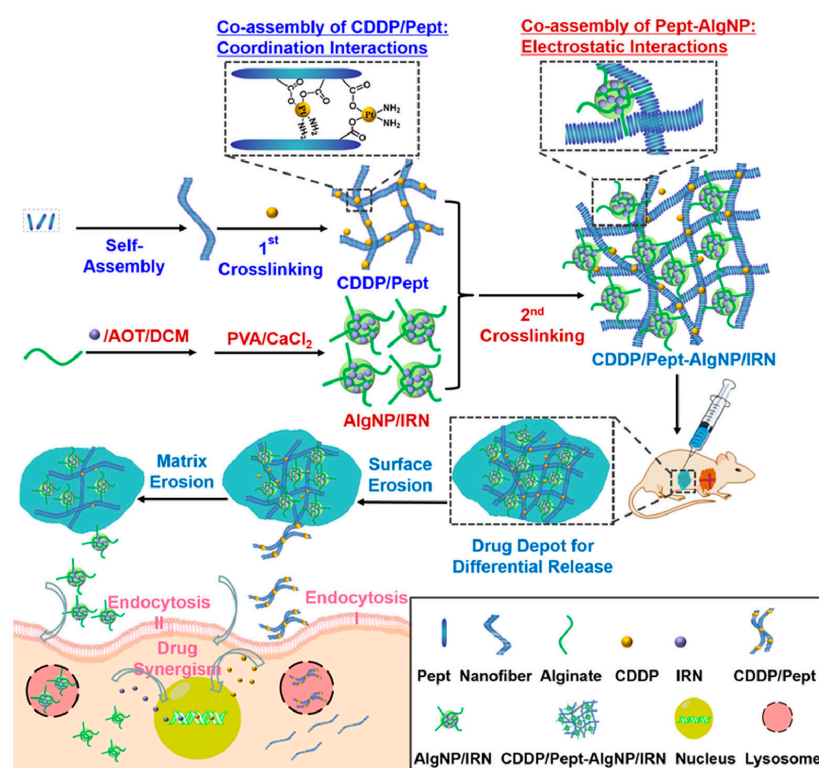
Hydrogel-Inorganic Nanoparticle Composite	Advantages	Disadvantages
Iron oxide magnetic NPs [69–71]	Synergy with magnetic hyperthermia Magnetoresponse MRI contrast	Requires screening functionalization to achieve co-assembly
Gold/silver NPs [72]	Low-cost sensors Synthesis in situ Facile synthesis and tunability Synergy with photothermia /photodynamic therapy	Heterogeneous dispersion Uncontrolled release Challenging reproducibility of in situ synthesis

### 2.3. Peptide-Based Hydrogel Nanocomposites Containing Organic NPs

One of the main drawbacks of conventional chemotherapy is the acquisition of multiple drug resistance (MDR) and systematic toxicity towards currently used small therapeutic molecules [73–79]. Combination cancer therapy, combining two or more drugs, enhances the treatment efficacy compared to the mono-therapy approach because it provides synergistic or additional mechanisms to damage cancer cells. This approach also potentially reduces drug resistance [80–82] because (1) different drugs exhibit varying pharmacokinetics and tissue distribution patterns; (2) each drug can have its own function through varying downstream/upstream mechanisms intracellularly, thus demanding drug delivery in chronological order. In fact, clinical studies on this controlled multi-drug delivery have shown an improved response rate and extended survival of patients [83–85], so it is highly desirable to develop DDSs that have the ability to differentially release multiple drugs.

In 2020, Wu et al. reported the synthesis of a new hydrogel nanocomposite as a DDS (abbreviated as cisplatin/Pept-AlgNP/irinotecan) composed of alginate NPs (AlgNP) and peptide-based hydrogels for delivering two clinically used anticancer drugs (irinotecan and cisplatin), which were loaded separately in the two different domains of the nanocomposite matrix. The authors specifically selected these two drugs based on previous clinical studies demonstrating a low probability of side effects with a higher response rate when irinotecan was administered after cisplatin [86] because the topoisomerase I inhibitory activity of irinotecan can be improved by cisplatin [87,88]. The designed peptide hydrogel exhibited biocompatibility and injectability thanks to its tunable amino acid sequence and peptide

composition [89–94], in which the carboxyl residues of peptides form covalent bonds with cisplatin and reinforce the supramolecular self-assembly of peptide conjugates [95–97]. Afterward, AlgNPs were incorporated into the hydrogel matrix to act as the inner domain, to further enhance the mechanical strength of hydrogel by electrostatic interactions and significantly facilitate the encapsulation of the second drug, irinotecan, to achieve differential release profiles (Figure 3). These covalent and non-covalent interactions increased the storage capacity of the hydrogel nanocomposite up to 42-fold, compared with the native peptide gel. This drug formulation guaranteed a fast release of cisplatin before a controlled release of irinotecan, resulting in excellent synergism of the drugs in cell inhibition studies (compared to the simple mixture of the drugs), with efficacious antitumor potency confirmed by the *in vivo* study against A549-xenografted tumor in mouse. These studies pave the way towards the development of mechanically stable hydrogel nanocomposites as DDSs for loading individual drugs in co-assembled structures/domains to temporally control drug release and address clinical demands for combination therapy [98].



**Figure 3.** Schematic illustration of double-crosslinked cisplatin/Pept-AlgNP/irinotecan nanocomposite hydrogel for differential release of cisplatin (CDDP) and irinotecan (IRN) in combination therapy. Reprinted with permission from [98]. Copyright 2020, Elsevier.

Diphenylalanine (FF) is an aromatic dipeptide extracted from Alzheimer’s  $\beta$ -amyloid polypeptide as a core recognition motif for molecular self-assembly [99]. Reches and Gazit first reported the synthesis of diphenylalanine nanotubes hydrogels (FNTs), and ever since, different advanced nanostructures, e.g., nanofibrils and spherical vesicles, have been prepared from FNTs building blocks [100], by the self-assembly of FFs via  $\pi$ - $\pi$  interactions of the aromatic rings and backbone-backbone hydrogen bonds [101–104]. For drug delivery purposes, these biocompatible peptide-based FNTs are superior to carbon nanotubes (CNT) due to the potential toxicity of CNT in clinical studies [105].

To prepare smart DDSs, FF self-assembled structures can be conjugated with targeting ligands to become highly selective to specific cancer cells [103,106,107], with potential applications in theranostics, e.g., combined active-drug delivery with imaging tools [108]. As a well-studied targeting molecule, folic acid (FA) has a key role in the targeted delivery of various pharmaceuticals because of the overexpression of folate receptors (FR) by most

advanced tumors [109,110], such as brain, lung, and breast cancers. Besides folate-based drug delivery, this technology has been successfully used for other therapeutic applications, e.g., selective fluorescence, MRI, and radio imaging of cancer cells [111,112].

Among the inorganic NPs mentioned in the introduction section, magnetic NPs (MNPs) are considered a special class with high application potential in clinical studies due to their unique superparamagnetism, biocompatibility, well-known chemistry, and low cost. MNPs are being extensively investigated as the next generation of MRI contrast agents, magnetic-based DDSs, and hyperthermia agents [113–116].

FA conjugation to nanotubes and NPs has been investigated through both covalent and non-covalent strategies. Covalent bonding is superior and preferable due to its several advantages such as colloidal stability at different physiological conditions [117–119].

Surface coating/modification is one of the main strategies used to decrease the risks of NPs and design safer nanotechnological devices. In fact, the coating material, if chosen correctly, provides biocompatibility and affects the fate (e.g., accumulation, degradation, excretion) and the behavior (e.g., colloidal stability) of NPs following their administration in the complex environment of biological fluids. Since bioavailability and potential toxicological effects of NPs are dependent on their dispersion state, an ideal coating material provides high colloidal stability for the resultant NPs in salt- and protein-containing media, such as buffer solutions or cell culture media, for their *in vitro* testing in biological cells and *in vivo* testing in animal models [120].

Regarding iron oxide NPs, numerous formulations have been studied in both preclinical and clinical settings, and some of them have already been introduced into the market. Besides, there are several FDA (Food and Drug Administration)-approved iron oxide NPs for clinical use, such as Feraheme<sup>®</sup> (for iron deficiency, Combidex<sup>®</sup> (U.S.), and Sinerem<sup>®</sup> (Europe) as magnetic resonance imaging (MRI) agents, Nanotherm<sup>®</sup> (MagForce) for cancer treatment and Lumirem<sup>®</sup> as an oral gastrointestinal tract imaging agent.

Feraheme<sup>®</sup> (ferumoxytol injectable solution) was also approved in Canada (2011) and Europe (2012) and has been clinically used for treating iron-deficiency anemia (IDA). In addition, ferumoxytol has shown great promise for many other biomedical applications, including MRI, drug delivery, oral biofilm treatment, and anti-cancer and anti-inflammatory therapies. For instance, ferumoxytol is being used as an MRI contrast agent in ongoing clinical trials [121].

In 2017, Emtiazi et al. synthesized micro and nanotubes from the self-assembly of FNTs conjugated with FA/MNPs and studied their potential applications for the delivery of the well-known anticancer therapeutic 5-fluorouracil (5-FU). The conjugation was performed by covalent linkage of the carboxylic groups on FA/MNPs with the amine groups on FNTs (using the *N*-hydroxysuccinimide/carbodiimide (NHS/EDC) chemistry). 5-FU was loaded in FNT hydrogels, exhibiting a controlled and slow release, specifically within the first 2 h. This nanocomposite combined biocompatibility and biofunctionality in a single platform with a high selectivity towards MCF-7 cancer cells [122].

Multi-drug resistance (MDR) is a critical contributor to over 90% of deaths of patients in traditional cancer chemotherapy [123]. Cancer cells show MDR due to either acquired defense behaviors or inherent mechanisms, including enhanced drug efflux and DNA repair capacity, elevated xenobiotics metabolism, and even genetic factors (e.g., epigenetic alterations and gene mutations) [124]. Based on these diverse modes of MDR development, it is imperative to introduce novel methods to overcome MDR mechanisms and enhance the survival rate.

In the past decade, RNA interference (RNAi) technology has been introduced as a potential alternative to conventional chemotherapy because this kind of gene therapy can inhibit almost every single protein expression of the target cancer cells [125], which can eliminate the MDR phenotype in cancer cells. This unique technology has demonstrated a high specificity towards the target cells, and therefore, it is able to reduce the most common side effects of chemotherapy. For the clinical applications of small interfering RNA (siRNA), however, there are some limitations, including the low transport efficiency of siRNA and

their instability/high degradation rate [126]. Injectable hydrogels have been developed to address these challenges, having minimal adverse effects and highly controlled delivery of different cargos [127], which could also increase patient comfort with a single injection of the drugs.

To achieve this aim, DNA has been commonly applied as a crosslinker in hydrogels, having unique features such as structural rigidity/designability and excellent targeting capability [128]. Moreover, DNA crosslinked hydrogels provide very high injectability and thixotropic abilities due to their hydrogen bond formation with complementary DNA sequences [129].

In 2023, Chen et al. synthesized an injectable hydrogel nanocomposite for the co-delivery of the anticancer drug doxorubicin and MDR-targeted siRNAs for its potential application for combined gene- and chemotherapy. Specifically, tetra-armed PEG served as the backbone of the hydrogel nanostructure. The authors used tetra-armed PEGs to prepare the hydrogel, and complementary DNA sequences were cross-linked into the hydrogel matrix by hydrogen bonds between the DNA–base pairing. To enhance the mechanical properties of this hybrid hydrogel, laponite nanoclay was incorporated into the gel matrix by physical interaction. Moreover, both nanoclay and DNA sequences improved the loading capacity of the nanocomposite for positively charged doxorubicin by intercalating within the interlayer spaces of nanoclay and the DNA structure. Then, MDR-targeted siRNAs, which were previously complexed with the membrane-permeable peptides with stearyl-octaarginine (STR-R8), were incorporated within the hydrogels. To control the degradation of this composite, MMP-2 cleavable peptide sequences were also conjugated to DNA sequences and tetra-armed PEG. By the upregulated expression of the MMP-2 tumor-associated enzyme, this hydrogel nanocomposite was degraded and released dsDNA/doxorubicin, laponite/doxorubicin, TR-R8/siRNA, and complexes. Doxorubicin released from the nanoclay complexes first damaged the target tumor (breast cancer) without the MDR effect. Then, the cancer cells endocytosed STR-R8/siRNA, followed by doxorubicin release from dsDNA/doxorubicin, to eliminate MDR cancer cells. This composite was directly injected into the tumor site thanks to its in situ gelation and degradability properties, which demonstrate its potential capacity in targeted cancer therapy with low side effects. The authors suggested that this DDS nanocomposite can deal with the MDR effect and potentially prevent tumor metastasis [130].

In chemotherapy, potent pharmaceuticals are administrated in specific intervals at high concentrations, which inevitably causes their unselective distribution in the whole body and sometimes brings irreversible damage to healthy tissues [131–133]. Localized drug delivery is an alternative methodology to ensure highly localized drug dosages at the target sites, decreasing the unselective toxicity on non-cancerous organs [134–136]. This aim is perfectly achievable using hydrogel and NP-DDSs [137,138], and poly(lactic-co-glycolic acid) (PLGA) NPs have been extensively studied for this aim due to their high biocompatibility and tunable degradability [139,140]. Their practical applications, however, have been restricted due to their quick diffusion into the surrounding tissues, which can be modified by the fabrication of hydrogel-PLGA nanocomposites.

As mentioned in the introduction section, the combination of NPs with peptide-based hydrogels can reinforce the fragile structure of hydrogels and enhance their in vivo stability, as well as tunable drug release [141–144]. Simultaneously, the peptide hydrogel serves as a fixing scaffold for NPs at a local site to prevent their uncontrolled diffusion. So, these nanocomposites benefit both nano- and gel-type materials by incorporating multiple drugs having different pharmaceutical characters in the various domains of the hydrogel nanocomposites for independent tuning of their release patterns [145,146].

In 2020, Wu et al. reported the synthesis of a novel and injectable peptide-based hydrogel nanocomposite for the controlled co-delivery of cisplatin and irinotecan (cisplatin/Peptide@NP/irinotecan), composed of an inner part of irinotecan-loaded PLGA NPs and an outer section of cisplatin-loaded hydrogel to provide the differential release of irinotecan and cisplatin. Due to the presence of PLGA, this nanocomposite exhib-



ited superior mechanical properties than pristine hydrogel and cisplatin/peptide. As mentioned above, cisplatin and irinotecan have shown synergistic anticancer effects on various cancers, e.g., esophageal adenocarcinoma, glioma, and non-small cell lung cancer (NSCLC) [87,147–149], especially when irinotecan was used after cisplatin [86] which results in higher therapeutic effects and lower side effects. This injectable nanocomposite demonstrated a longer retention time in mice compared to the individual formulations (when subcutaneously administered). The *in vitro* drug release profiles showed a sustained release of irinotecan and a fast release of cisplatin before irinotecan, with a synergic anticancer effect against NSCLC A549. Thus, this study provides a template technology for hydrogel nanocomposites with tunable drug release, enhanced mechanical stability, and improved anticancer efficacy through the synergism of multiple drugs [150].

As mentioned above, combination chemotherapy is generally much more effective than single-drug chemotherapy, which has been well-documented in clinical settings [151–154]. Current combined chemotherapy is based on the sequential injections of different drugs, requiring long-term patient hospitalization and precise monitoring by trained specialists, which is highly uncomfortable for patients and increases medical costs. It is predicted that next-generation chemotherapy will rely on smart DDSs, and in this regard, hydrogels and nanomaterials (e.g., metal and metal oxide NPs, micelles, liposomes, nanofibers, and polymeric NPs) are promising candidates possessing unique advantages, such as drug capacity and control of release [155–161].

Graphene oxide (GO) nanocarriers have been introduced as suitable DDSs because of their high specific surface area (up to  $500 \text{ m}^2 \text{ g}^{-1}$ ) [162], suitable for loading large amounts of poorly bioavailable drugs, e.g., anthracyclines, taxanes, and camptothecin analogs [163–169]. GO surfaces have numerous hydroxyl groups, epoxides, and carboxylic acids that are suitable functional groups for conjugating other targeting and stabilizing molecules to enhance therapeutic efficiency and prolong drug circulation time [170,171].

Regarding peptide-based hydrogels, “designer” peptides have been used to synthesize hydrogel-based DDSs because of their inherent biocompatibility, tenability, biodegradability, and fast gelation via hierarchical self-assembly [172]. As a commonly used designer peptide, Max8 sequence (VKVKVKVKVDPPTKVEVKVKV-NH<sub>2</sub>, DP: d-proline) is a stimuli-responsive peptide which shows stability at low ionic strength and self-assembles into 3.2 nm diameter  $\beta$ -hairpin nanofibers in physiological conditions [173]. Branco et al. showed that Max8-hydrogel has little resistance to the transport of both large and small molecules (e.g., fluorescein–dextran conjugates) at low gel fractions (0.5–2 *w/w*) [174]. In combination chemotherapy, the limited control over the relative flux of multiple diffusing drugs restricts their practical *in vivo* applications. Hydrogel nanocomposite systems containing nanocarriers embedded in the peptide hydrogel have shown great promise for precise delivery of multiple cargos [175–178].

In 2020, Schneible et al. developed a new nanocomposite comprising doxorubicin-loaded modified-GO NPs embedded in a gemcitabine-loaded Max8 hydrogel. The synergistic effect of doxorubicin and gemcitabine was extensively studied in terms of pharmacokinetic and molar ratio (gemcitabine/doxorubicin > 1) [179–182] with the optimal synergic effect at 10:1 ratio when doxorubicin was being administered after gemcitabine [183]. The authors studied the surface modification of GO NPs at different conditions to tune their hydrophobicity and surface charge; then, doxorubicin loading and release at different ionic strengths and pHs were investigated. Interestingly, surface modification with tris(2-aminoethyl) amine (TREN) resulted in high drug loading (0.2–0.6 mg doxorubicin/mg GO) and showed an initially fast release of 18.9% of the drug (within 72 h), followed by a sustained release (31.4% over 4 weeks). Using molecular dynamics simulations, the doxorubicin/TREN-GO interaction at different conditions to gain molecular-level insight into the release/adsorption behavior of the drug in the TREN-GO system was also studied. Afterward, DOX–TREN-GO NPs were embedded in a gemcitabine/Max8 hydrogel and successfully tested on a triple-negative breast cancer cell line (MDA-MB-231). The composite DDS demonstrated a high synergic index of  $0.093 \pm 0.001$ , significantly lower than the

free doxorubicin-gemcitabine combination ( $CI = 0.396 \pm 0.034$ ) at the same 1:10 molar ratio and concentration [184].

In vivo studies of NPs have shown their rapid clearance via the reticuloendothelial system (RES) and accumulation at the tumor site [185] due to the enhanced permeability and retention (EPR) effect because of the leakiness of tumor blood vessels [186,187]. Nano-DDSs show different mechanisms to enter cells, such as endocytosis, which can be divided into five distinct subgroups (micropinocytosis and phagocytosis, clathrin- and caveolin-independent endocytosis, clathrin-dependent endocytosis, and caveolin-dependent endocytosis). Alternatively, nano-carriers can cross the plasma membrane of cells via physical or biochemical ways to directly enter the cytoplasm by lipid fusion, electroporation, microinjection, or translocation [188]. NP features (e.g., surface chemistry, morphology, size, chemical nature, charge) affect their interaction and mechanism of cell uptake [189]. Another advantage of nano-DDSs is that they can simultaneously carry multiple biologically relevant molecules (nucleic acids, organic/metallic drugs, and contrast agents) [190–192]. Nano-DDSs can safeguard the loaded bioactive molecules from potential degradation/inactivation in the bloodstream and guarantee the safe reaching of these nano-carriers to their targets, together with the controlled release of drugs to enhance in vivo therapeutic efficacy [193]. Moreover, some poorly hydrophilic drugs (e.g., danazol, paclitaxel, and naproxen) can be formulated using nanocarriers without requiring non-biocompatible organic solvents for their solubilization [194], which provides improved in vivo pharmacodynamic and pharmacokinetic properties of the drug and reduced toxicity. Regarding doxorubicin, for instance, in 1995, the Food and Drug Administration (FDA) introduced a liposomal formulation (commercially known as Doxil<sup>®</sup>/Caelyx<sup>®</sup>) for several tumors such as metastatic breast cancer with cardiac risk [195]. This liposomal formulation can significantly reduce cardiotoxicity and myelosuppression of doxorubicin and enhance its pharmaceutical efficiency due to the different biodistribution of the formulated drug [196,197]. There are currently a few other commercialized drug nano-carriers [198], such as Eligard<sup>®</sup> (based on polymeric PLGA (poly(lactic-co-glycolic acid), for prostate cancer therapy), Abraxane<sup>®</sup> and Genexol PM<sup>®</sup> (for paclitaxel delivery, metastatic breast cancer), and one for Irinotecan vehiculation (Onivyde<sup>®</sup>, for pancreatic cancer) [199].

Nanogels (NGs) have been studied as novel biocompatible DDSs, specifically for the in vivo delivery of contrast agents and therapeutics [200,201]. Nanogels are nano-sized supramolecular assemblies, having an internal hydrogel-like core which is stabilized by an exterior surfactant shell, obtained from the submicronization of macroscopic hydrogels or peptide sequences. Because of their biodegradability, biocompatibility, and easy synthesis method (mild pH and temperature values), peptide-based nanogels are attractive platforms for developing DDSs. Similarly to micelles and liposomes, NGs are injectable and compatible with accumulation and prolonged bloodstream circulation, and different targeting molecules (e.g., peptides, antibodies, or small organic molecules) can be attached to their surface to recognize the site of action. Unlike micelles and liposomes, NGs resemble hydrogels (due to their inner matrix) with their entangled fibrillary and porous network, which can accommodate a large quantity of water and establish non-covalent interactions between their peptide moieties (aromatic and aliphatic groups of amino acid segments), which is probably the most important feature of peptide-NGs because they can be easily tuned for modifying their loading and release properties by simply changing their primary peptide sequence.

In 2020, Smaldone et al. introduced a highly stable peptide-NG formulation [202], which was synthesized using  $N\alpha$ -9-fluorenylmethoxycarbonyl-diphenylalanine and Fmoc-FF (Fmoc-Phe-Phe-OH, a well-studied low molecular weight hydrogelator), forming self-assembling hydrogels under physiological conditions [203] with the capability of doxorubicin encapsulation [204,205]. The authors evaluated the cytotoxicity of the unloaded NGs on a panel of breast cancer cell lines. By the treatment with unloaded NGs, one of the tested cell lines was more affected than the others, so it was found that this cargo-independent cell-specific cytotoxicity is due to the specificity of the machinery used by Fmoc-FF NGs,

which shows a selectivity towards the cancer cell lines overexpressing the protein caveolin1 and efficiently performing caveolae-mediated endocytosis.

Anticancer immunotherapy is based on helping the immune system (using synthetic or natural reagents) to specifically damage cancer cells, a promising anticancer treatment with huge potential. As a type of immunotherapy, checkpoint inhibitor therapy (ICT) blocks proteins that prevent the immune system from attacking cancer cells. The programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) have exhibited a potent response in various tumors such as triple-negative breast cancer (TNBC); however, only a small portion of TNBC patients respond to ICT because of the immunosuppressive tumor microenvironment (TME) and immunologically “cold” tumors, which later show low mutational load, lack of T-cell infiltration, deficient PD-L1, and low MHC I expressions. To improve the antitumor efficacy, complementary therapies are necessary to remold TME. For enhancing PD-1/L1 effectiveness, the modulation of T cells is desirable (to make an inflamed “hot tumor”) [206–208].

Immunogenic cell death (ICD) mechanism triggers the antitumor immune response, which is well known to improve/modify the low immunogenicity of “cold” tumors by releasing damage-associated molecular patterns (DAMPs) [209], such as adenosine triphosphate (ATP) secretion, calreticulin (CRT) surface exposure, and high mobility group box 1 protein (HMGB1), followed by the maturation of antigen-presenting dendritic cells (DCs) and inducing a cascade process leading to antigen-specific T-cell infiltration [210]. Also, the binding of TLR4 to HMGB1 triggers inflammatory responses as well [211]. These in situ vaccine-like phenomena can induce immune responses to ease the transformation of “cold tumors” into “hot tumors” and eventually reshape the immunosuppressive microenvironment and remove cancer cells [212].

Previous research has shown that some therapeutics (e.g., radio-/photodynamic therapy, hyperthermia, and some types of chemotherapy [213]) can initiate ICD, which makes the tumor accessible to the immune system. Chemotherapy-induced ICD plays a key role in improving immunotherapy, and doxorubicin chemo-drug has been frequently used for various malignancies, stimulating ICD-induced immunity [214]. However, this doxorubicin immunogenicity is weak by itself, and tumor relapse can often be detected in clinical cases [215].

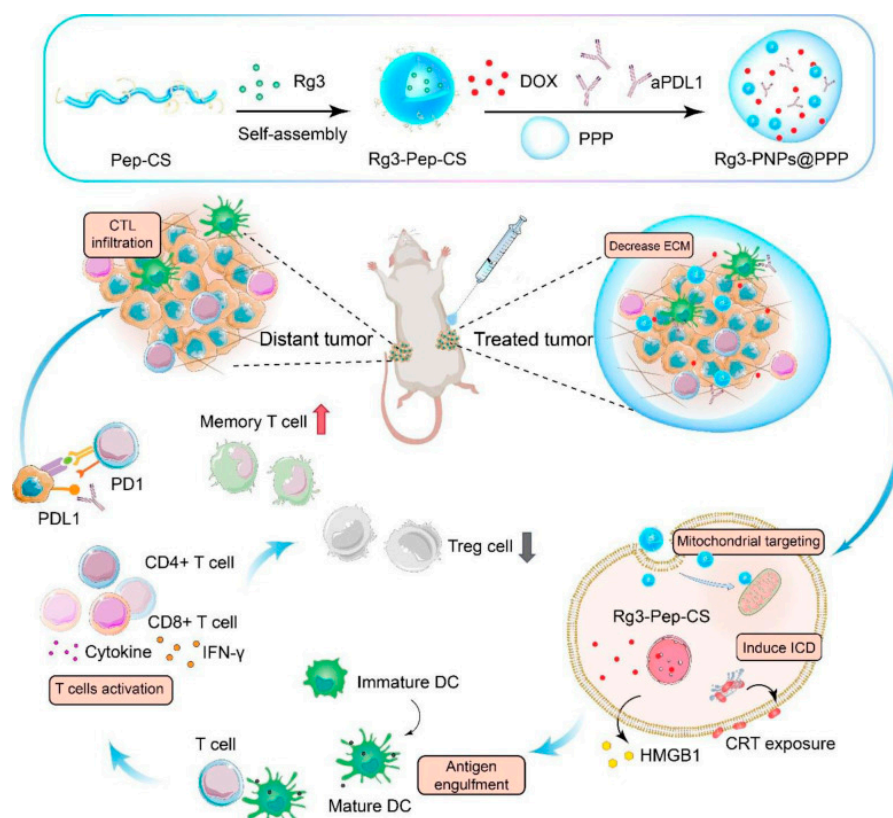
Traditional Chinese medicine has exhibited great potential for introducing biocompatible cancer adjuvants. Ginsenoside Rg3 is a steroidal saponin obtained from *Panax ginseng*, which has shown various antitumor effects and immune-modulatory activities. More importantly, the combination of well-known chemotherapeutics (e.g., doxorubicin, docetaxel, and paclitaxel) with Rg3 has received great attention for significant antitumor activities in different kinds of malignant tumors [216]. Rg3 can also improve the ICD effect stimulated by doxorubicin and activated by the immunity system in acute myeloid leukemia (AML) mice [217]. However, its poor solubility and lack of targeting ability restrict Rg3 penetration into tumors, thus decreasing the outcome of combination doxorubicin-Rg3 therapy.

Chitosan (CS) is a natural polysaccharide with high biodegradability and biocompatibility [218], possessing free  $-NH_2$  and  $-OH$  functional groups in its structure, which are amenable to chemical modifications, for its biological applications [219], including lysosomal escape, targeted-drug delivery and TME response [220–222]. It is known that low drug penetration leads to the failure of immunotherapeutic treatments (e.g., TNBC) [223,224], so deep tumor penetration is required in chemotherapy. Cell-penetrating peptides (CPPs) may solve this issue, as they are able to transfer NPs into the cell and improve their curative effectiveness [225].

Cell-penetrating peptides (CPPs) are short peptides (fewer than 30 amino acids) that have been used in preclinical research over the last three decades. Since they facilitate drug or CPP/cargo transport across the plasma membrane (through endocytosis or by perturbation of the lipid bilayer of the cell membrane), they have potential applications in disease diagnosis, including cancer, inflammation, central nervous system disorders, diabetes, otologic and ocular disorders. However, there are no FDA-approved CPPs or

CPP/cargo complexes because many issues still need to be addressed before their clinical translation [226–228].

To minimize the short circulation time and systemic toxicity of doxorubicin, cell-penetrating peptide (R6F3)-modified NPs (PNPs) and chitosan loaded with ginsenoside Rg3 (Rg3) were synthesized using the self-assembly technique, followed by co-encapsulation with doxorubicin-based on thermo-sensitive hydrogel [229]. In a recent work, Wu et al. studied localized chemo-immunotherapy using this thermo-sensitive hydrogel nanocomposite to help the anti-tumor immunotherapeutic efficacy for 4T1 tumor (Figure 4) as a typical TNBC model [230]. The targeted delivery of Rg3 by chitosan and transmembrane peptides can degrade the tumor's extracellular matrix and decrease its solid stress. Moreover, due to the presence of loaded R6F3, Rg3 could dramatically penetrate into tumor cells, followed by targeting mitochondria due to positively charged NPs, thus reinforcing the ICD effect triggered by doxorubicin. Thus, abundant tumor cell debris was detected, with subsequent T cell activation and DC maturation. This methodology decreased the tumor volume in the orthotopic 4T1 model and significantly prolonged its survival time, demonstrating a reliable approach to improve the checkpoint-blocking therapy for 4T1 tumors and converting immune “cold” 4T1 into “hot” tumors.



**Figure 4.** Schematic illustration of a thermo-sensitive hydrogel formation and inhibition of local chemotherapy combined with immunotherapy on abscopal tumors. Reprinted from [230], an open access article distributed under the terms of the Creative Commons CC BY license. Copyright © 2022.

Other publications on peptide-based hydrogel nanocomposites for biological applications are summarized in Table 3.

**Table 3.** Other hydrogel nanocomposites used for biological applications.

Hydrogel Nanocomposite	Application	Ref.
Oxidized carbon nanotubes GO + (Fmoc-Phe-OH/Fmoc-Tyr(Bzl)-OH Fmoc/Tyr-OH/Fmoc-Tyr(Bzl)-OH) hydrogel	drug delivery	[231]
Graphene quantum dots + (Amoc-Phe-OH Amoc-Tyr-OH) hydrogel	drug delivery	[232]
GO + (Py-Gly-Ala-Gly-Ala-Gly-Tyr-OH) hydrogel	drug delivery	[233]
Fmoc-FFpY-hydrogel assembled from enzyme-adsorbed mesoporous silica nanostructures	thermo-responsive doxorubicin release	[234]
Fmoc-FFpY hydrogel nanocomposite containing silica NPs functionalized covalently by alkaline phosphatase	N/A	[235]
graphene oxide as nano-filler for the reinforcement of FEFKFEFK ( $\beta$ -sheet forming self-assembling peptide)	intervertebral disc repair applications	[236]
self-assembling a motif-specific peptide molecule (LLVFGAKMLPHHGA) containing graphene foam	matrices for drug delivery or bone tissue engineering	[237]
RGDAEAKAEAKYWYAFAEAKAEAKRGD- hydrogel-graphene quantum dots	targeting and imaging of tumor cells	[238]
self-assembly of an amphiphilic peptide (APP) into a nanochain with subsequent chemical crosslinking of NIR-II Ag <sub>2</sub> S QDs	ultrasensitive Detection of Peritoneal Metastasis	[239]

### 3. Conclusions

Traditional chemotherapy is still restricted by the low effectiveness and systemic toxicities of drugs. Due to the high recurrence rates of some types of cancers, tumor resection is not the most reliable choice, and therefore, advanced DDSs are required. Hydrogel nanocomposites have shown to be great candidates to enhance the therapeutic efficacy of anticancer drugs. Due to their biodegradability, biocompatibility, and stimuli responsiveness, they are excellent platforms for either passive or targeted drug delivery applications. Combining both peptide-based hydrogels and NPs in a single composite, they have successfully demonstrated the ability to target cancer cells and tumors with high selectivity without compromising healthy tissues. Proof-of-concept studies have shown successful in vivo models. However, for the use of hydrogel nanocomposites in clinical trials, they should have some basic properties: (1) excellent mechanical strength and injectability to enhance in vivo drug stability as well as in situ protection/retention of drugs; (2) strong drug-carrier interactions to guarantee controlled and sustained drug release; (3) tunability of the structure tunable for having different release profiles based on the type of drug; and (4) capacity/ability to load several therapeutic components inside the hydrogel matrix to achieve a synergic efficacy and multifunctionality.

The design of smart hydrogel nanocomposites based on peptide networks and NPs is still a challenging field, with a broad range of physicochemical and therapeutic properties to be controlled and understood. So, more computational and experimental studies are necessary to rationalize their dynamic behavior and relevant interactions with drugs, cells, and tissues to develop more effective formulations that may maximize the selectivity and efficiency of chemotherapy. From a futuristic point of view, we believe that peptide-based hydrogel nanocomposites will be further developed as novel DDSs to maximize the selectivity and efficiency of the chemotherapy.

While significant advances have been recently made in optimizing hydrogel nanocomposites, there are still some challenges for their clinical application in drug delivery. For instance, foreign body reactions frequently cause collagenous capsule formation, which re-

stricts the performance of implantable nanocomposites. To address this challenge, ultra-low-fouling zwitterionic hydrogels have been recently developed to resist capsule formation.

The in vivo safety of hydrogel nanocomposites is another main crucial issue which makes product development challenging; therefore, it is vital to gradually decrease the threshold through multidisciplinary collaborations between chemists, materials scientists, biologists, and clinicians in order to define the future role of peptide-based hydrogel nanocomposites in the field of anti-cancer drug delivery.

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