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Recent advances in long-acting drug delivery systems for anticancer drug

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ABSTRACT

The use of systemic anticancer chemotherapy is intrinsically limited by its toxicity. Whether dealing with small molecules or biopharmaceuticals, after systemic administration, small doses fail to reach effective intratumoral concentrations, while high doses with significant tumor inhibition effects may also drive the death of healthy cells, endangering the patients. Therefore, strategies based on drug delivery systems (DDSs) for avoiding the systemic toxicity have been designed. Due to their ability to protect drugs from early elimination and control drug release, DDSs can foster tumor exposure to anticancer therapeutics by extending their circulation time or steadily releasing drugs into the tumor sites. However, approval of tailored DDSs systems for clinical use is minimal as the safety and the *in vivo* activity still need to be ameliorated by manipulating their physicochemical characteristics. During the last few years, several strategies have been described to improve their safety, stability, and fine-tune pharmaceuticals release kinetics. Herein, we reviewed the main DDSs, namely polymeric conjugates, nano or microparticles, hydrogels, and microneedles, explored for long-acting anticancer treatments, highlighting recently proposed modifications and their potential advantages for different anticancer therapies. Additionally, important limitations of long-acting anticancer therapies and future technology directions were also covered.

Contents

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1. Introduction

Cancer includes a range of diseases, with millions of new cases arising each year, and these numbers are expected to increase yearly [1]. Therefore, despite all efforts, it remains a leading health problem worldwide and a significant cause of mortality.

Current cancer treatment options include surgical intervention, radiotherapy, and systemic therapies, such as chemotherapy, targeted therapy, hormonal therapy, and immunotherapy [2]. Chemotherapy is an essential line of defense against cancer. However, these drugs do not act selectively on the tumor sites and can also act on healthy tissues, and whether for chemo or other systemic therapy, low intratumoral accumulation leads to the administration of higher doses. Above two shortcomings could both generate systemic toxicity, which is associated with severe side effects [3–5]. The scenario is even worse for some small molecules, peptides, or proteins, which in addition to the non-specific biodistribution and toxicity, have a short half-life, limiting the long-term anticancer effects [6]. In sum, due to their limited tumor-targeting ability or rapid elimination, the safety and effectiveness of chemotherapy can be lower than expected and needed. Hence, the development of drug delivery systems (DDSs) may possess a potential to benefit cancer patients.

DDSs, such as polymeric conjugates, nanoparticles (NPs), microparticles, liposomes, hydrogels, microneedles, and many others, have been developed and suggested to address current anticancer treatment shortcomings [7]. Following implantation or systemic administration, DDSs can protect anticancer molecules from premature elimination and drive intratumoral accumulation [8]. Therefore, improving therapies efficacy without taking the risk of administering too high doses [9].

For systemically administered DDSs, therapeutic delivery is often guided by tumors' anatomical and physiological features and tumor microenvironment (TME) [8]. The enhanced permeability and retention (EPR) effect, first reported in 1986, is the basis for most tumor-targeting DDSs [10]. In the EPR effect, the systems circulating in the bloodstream escape into tumor tissues, due to increased blood vessels permeability, and are retained due to dysfunctional lymphatic drainage, two general features of tumors [1]. To take advantage of the EPR effect, systems should circulate for an extended period. In this way, they can reach tumor site and accumulate more than the free drug. However, despite their remarkable features, one significant obstacle to their long-term circulation is clearance by the mononuclear phagocyte system (MPS) [11]. MPS is part of the innate immune system composed of dendritic cells, monocytes, and macrophages, whose primary role is to protect our body through phagocytosis of foreign substances, including DDSs [12]. Thus, different strategies and methods have been recently described to address this difficulty and construct innovative long-acting anticancer DDSs. Long-acting DDSs are systems capable of extending systemic or local exposure to a given drug over a period of time, after a single administration [13,14]. Even though they have a long history of use for contraception purposes, they have been quite explored for anticancer drug delivery, extending therapies length and, potentially, their efficacy.

In addition to extending therapies circulation, long-acting DDSs can also control and sustain drugs release over time [15]. DDSs release kinetics depends on several factors, including molecules diffusion within the system matrix, system biodegradation, or molecules-system affinity [16–19]. Thus, by modulating these factors, one can design DDSs with specific release kinetics, avoiding fluctuating drug concentrations. From a pharmacokinetic point of view, injectable long-acting DDSs present several benefits, including increased anticancer molecules bioavailability, since they do not face absorption barriers or hepatic metabolism, and improved patient compliance due to a decrease in injection frequency [13,20]. Moreover, if implantable DDSs are used and directly placed on the tumor bed, it is possible to save healthy tissues from treatment exposure. Therefore, compared to systemic administration, local administration can further increase anticancer molecules' tumor bioavailability and limit their multi-organ biodistribution [13]. In short, through multiple processes, DDSs can keep anticancer therapeutics concentration within the therapeutic window over longer periods and increase tumor exposure to therapeutics while reducing systemic exposure. Due to the described potential advantages, they can bring to patients, long-acting DDSs for anticancer treatment have been extensively explored. As we will discuss, the more recently reported alternatives seek to improve the biosafety, the drug release kinetics control over time, improving overall long-acting anticancer performance of DDSs.

Herein, we aim to overview the recent advances in long-acting DDSs with enhanced anticancer efficacy. We divide long-acting anticancer DDSs into four major categories: polymeric-conjugates, stealth-coated nanosystems, hydrogels, and microneedles. For each category, we present both the main advantages and challenges. More importantly, recently reported innovations as well as the rationale behind their development are described, followed by examples of their applications for multiple types of anticancer therapies. Finally, we also address the future directions of long-acting anticancer DDSs, including their clinical translation potential.

2. Recently proposed long-acting drug delivery systems for cancer treatment

2.1. Polymeric conjugates-based long-acting drug delivery systems

Despite the current efforts in oncological drug discovery, newly proposed molecules often fail to be approved for clinical use [21]. This is partly a result of pharmacokinetic problems, such as low aqueous solubility, low *in vivo* stability, or quick renal filtration, which limit tumor exposure and reduce their effectiveness [22].

Since the 1970s, covalent conjugation between polymers and therapeutic molecules has been suggested as an alternative to improve the latter pharmacokinetic profile: polymers can protect therapeutics from renal clearance, hydrolytic enzymes, and phagocytosis while increasing their aqueous solubility, extending circulation time [23–30]. Therefore, polymer conjugates-assisted long-acting anticancer therapies are used and in continuous development.

The most frequently used polymer in conjugates construction is poly(ethylene glycol) PEG. PEG is neutral, flexible, biocompatible, and water-soluble, as each ethylene glycol molecule can interact with two or three water molecules [31]. Also, the molecule weight increased, PEG prevents renal filtration of therapeutics with molecular weights lower than 50KDa and increases their half-life [32]. For instance, this was reported for interleukin (IL)-10 and irinotecan [24,25]. Moreover, due to PEGylated irinotecan - Etirinotecan Pegol, currently in clinical trials (NCT05158491) - constructed via a biodegradable ester linkage, irinotecan release is sustained, ergo its half-live increases from 2 to 50 days [25]. PEGylation also increases proteins' half-life, as for L-asparaginase – Oncaspar® approved for acute lymphoblastic leukemia treatment and currently in multiple clinical trials to treat other cancer diseases [33]. In this case, it went from less than one day to almost 15 days, allowing for a long-acting anticancer treatment and decreasing patient administration frequency [26]. Furthermore, as mentioned, through steric hindrance, PEG acts as a shield, protecting biopharmaceutics from proteases and MPS [34]. Despite the first

successfully approved polymer-anticancer drug conjugates, there are still several concerns and challenges to be addressed.

First, regardless of improving the pharmacokinetic profile, conjugation often reduces therapeutic conjugates activity, particularly protein activity, which can be interesting anticancer molecules [35]. For instance, considering the extracellular matrix remodeling role in cancer development, metalloprotease inhibitor proteins hold promise for its treatment [36,37]. However, due to their low molecular weight and serum stability, these proteins are eliminated within a few minutes following animal injection and never accumulate in tumors [38]. Owing to the high prevalence of cysteine or lysine residues, metalloprotease inhibitor proteins PEGylation by polymer binding to either via maleimide or N-hydroxysuccinide chemistry would most likely generate multiple heterogeneous polymer-protein conjugates [34]. These would be more stable but less functional and difficult to isolate. As an alternative, Hyarun *et al.* used recombinant gene technologies to introduce a non-canonical amino acid, propargyl lysine, into a naturally occurring metalloprotease inhibitor protein (Fig. 1) [27]. Through propargyl lysine and PEG-azide binding, they induced site-specific PEGylation. Compared with the free protein, the site-specific PEGylated protein proved to resist serum proteases better, being stable for up to 18 days in human serum at 37 °C while maintaining the affinity and metalloproteases inhibitory potency. In intravenously injected mice, PEGylation increased protein half-time about 8-fold, confirming that site-specific PEGylation can delay bloodstream elimination, prolonging the treatment period and system exposure to the therapeutic without compromising its bioactivity.

Another challenge relates to the polymeric conjugate's molecular architecture [32,34,39]. This factor is critical in conjugates *in vivo* fate, and studies show that branched or circular structures boost therapeutics' half-time and anticancer efficacy more than linear structures [40]. This way, non-linear polymeric conjugates have been studied as potential strategies for long-acting anticancer treatments. Recently, Jia *et al.* conjugated a lytic peptide, with possible anticancer activity, to a PEG bottlebrush [28]. This bottlebrush consists of multiple PEG chains covalently linked to a central chain, creating a stronger peptide protective shield than linear monoPEGylation. In this case, the PEG bottlebrush increased peptide half-life after intravenous administration to immunocompetent mice since it prevented its elimination by the MPS and renal filtration. Furthermore, in mice bearing NCI-H358 xenografts, lytic peptide-PEG bottlebrush conjugates significantly reduced tumor growth, probably due to increased tumor exposure to treatment. Although this is not yet a recognized long-acting treatment, this study's promising results shed light on the possibility of exploring conjugate structures to develop polymeric conjugated-assisted long-acting anticancer therapies.

There are also concerns about the safety of long-acting polymer-conjugate anticancer treatments [41]. This is mainly due to *in vivo* bioresistant PEG accumulation and the possible side effects of its chronic use [31]. Thus, there is a growing interest in biodegradable polymers, such as proteins or polysaccharides, as PEG substitutes [42]. For instance, designed ankyrin repeat proteins (DARPs), which target epithelial cell adhesion molecules, have been successfully conjugated to cytotoxic molecules and proposed as an alternative [43]. Interestingly, DARPs have also been

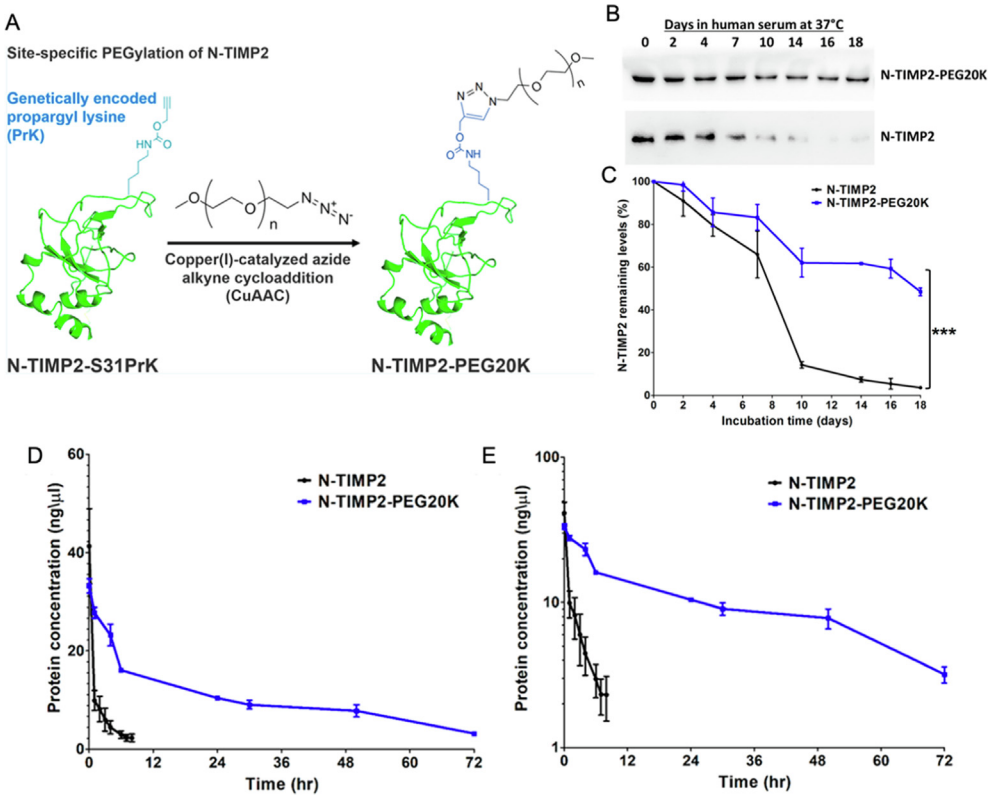

Fig. 1. PEGylation improves matrix metalloproteases protein inhibitor (N-TIMP2) stability in human serum, extend their half-time and, consequently, systemic exposure. (A) Site-specific conjugation between genetically encoded propargyl lysine (PrK) amino acid and PEG, via Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). (B) Free protein, N-TIMP2, and PEGylated-protein, N-TIMP2-PEG20K, stability in human serum at 37 °C, for 18 days, analyzed by western blot. (C) N-TIMP2 and N-TIMP2-PEG20K degradation curves in human serum at 37 °C, for 18 days. (D) Linear and (E) logarithmic graphics of free and PEGylated protein serum concentration after injection in mice. Reprinted with permission from Bioconjugate Chemistry, Vol 33 (5), Hayun *et al.*, Bioorthogonal PEGylation Prolongs the Elimination Half-Life of N-TIMP2 While Retaining MMP Inhibition, 795–806. Copyright 2022 American Chemical Society.

used to assess the conjugate size impact on its anticancer efficacy [29]. Equimolar conjugates ranging from very short, short, intermediate, and long were injected in nude mice bearing EpCAM-positive T29 tumor xenografts. Results showed that both very short and long conjugates were not effective because the short conjugates with low half-time and long conjugates with low tumor penetration and distribution limited their anticancer potential. Accordingly, intermediate conjugates had the best anticancer performance, which alerts researchers to the need to find a balance between treatment extension with molecule size and weight increases and intratumoral diffusion.

Considering cancer complexity, molecular heterogeneity, and combination therapy potential, long-acting polymer-anticancer molecule combinations can enhance drugs' efficacy compared to monotherapy [44]. Arroyo-Crespo *et al.* conjugated polyglutamic acid with a chemotherapeutic, doxorubicin (DOX), and an estrogen-modulating agent, aminoglutethimide [30]. DOX and aminoglutethimide were directly conjugated via a Gly, a Gly-Gly, or a Gly-Phe-Leu-Gly linker. Authors verified in *in vitro* assays that the therapeutics release profile depends on the binding chemistry, with direct binding inducing a simultaneous and slow release of 10% of both drugs in 72 h. In the orthotopic 4 T1 breast tumor mouse model, animals treated with the DOX and aminoglutethimide conjugates survived longer than those treated with single conjugates. The DOX half-life increased by about 9-fold. Therefore, this is an example of replacing PEG with a degradable polymer and of polymeric conjugates application in long-acting combined anticancer therapy. Furthermore, this highlights the importance of the chemical link choice to control drug release kinetics. If the binding is not stable enough, drugs may be prematurely released, whereas if the release is insufficient, molecules' full therapeutic potential might not be achieved [32].

It is also essential to mention recent advances in long-acting immunotherapy based on polymeric conjugates, this is, systems capable of releasing immune drugs through a long-term sustained manner. Often, immunotherapy is based on programmed cell death ligand-1 (PD-L1) antibody blockers usage to incite cytotoxic T cells activity and tumor cell elimination [45]. However, PD-L1 is actively recycled, maintaining its expression on the tumor cell surface [46]. Following these therapy specificities, strategies under development are not only aiming for drug half-life extension. For example, it was recently reported that a strategy based on polymeric conjugates prevents receptor recycling and leads to their degradation [47]. Briefly, multiple PD-L1 antagonist peptides were conjugated to N-(2-hydroxypropyl)methacrylamide (HPMA) (Fig. 2). Regardless of changes in this peptide half-life, within 24 h after injection into syngeneic BALB/c mice bearing 4T1 tumors, the conjugate induces receptors cross-linking and consequent elimination, unlike antibodies or unconjugated antagonist peptides, that only offer a transient block. Indeed, after polymeric conjugated-assisted chemotherapy, HPMA-PD-L1 antagonist peptide eradicated all tumors and allowed animals to resist tumor development after re-injection of 4T1 cells. Thus, it is also possible to establish long-acting polymer conjugates-based immunotherapies, which appear to be highly innovative and effective.

Recent advances in long-acting polymeric conjugate construction maintain molecules' bioactivity, decrease conjugate immunogenicity, and present physical and chemical characteristics that guarantee a balance between treatment extension and effectiveness. However, in the future, more rigorous and systematic strategies must be designed to guarantee reproducibility, scalability, and acceptable costs during conjugates production, promoting the clinical translation.

Based on other non-covalent bonds, such as hydrophobic interactions, van der Walls, or hydrogen bonds, different strategies can also drive polymers and therapeutic molecules interaction and give rise to other long-acting anticancer DDSs [48]. Polymers modification strategies employed in other long-acting anticancer drug delivery systems will be explored in the following sections.

2.2. Polymer-coated nanoparticles-based long-acting drug delivery systems

The coating of DDSs for systemic application has been used to overcome their premature clearance by MPS, extending blood circulation half-life of the systems [49]. For this, a stealth-coating layer is grafted onto the surfaces of the nanosystems, such as nanoparticles (NPs), with an electrically neutral hydrophilic surface layer [49,50]. The most used materials are nonionic polymers and surfactants, which restrict the interactions between NPs and opsonin proteins that mediate phagocytic clearance [51].

Over the years, most studies on the surface stabilization of NPs have been performed with PEG [52]. The first nanosystem for cancer treatment approved by Food and Drug Administration (FDA) was Doxil®, a liposome encapsulating DOX with PEG [53]. Since then, numerous PEGylated products have emerged in the market for various biomedical applications, including systems for cancer treatment that significantly extend the circulation time and tumor tissue accumulation [54].

Coating NPs surface with PEG blocks electrostatic and hydrophobic interactions, increasing their blood circulation half-time and therefore increasing specific binding and internalization of NPs into the desired tumor cells or organs [55]. Incorporating PEG in nanosystems can prolong the circulation time in blood 1.5–5-fold, and consequently, the plasma half-lime increases [56]. Characteristics of PEGylated NPs for long-acting delivery include dose independence, saturation, and first-order kinetics under therapeutic dose regimens.

Nevertheless, coating nanosystems with PEG may impair DDSs performance. Some studies reported that PEGylated systems can generate immunogenic responses, such as anti-PEG antibodies [57]. Moreover, there is a commonly reported immunogenic response after administering PEGylated nanosystems, known as the "Accelerated Blood Clearance" (ABC) phenomenon [58]. The ABC effect is correlated with the rapid clearance of the PEGylated NPs after multiple administrations.

To overcome PEGylation limitations, alternative surface modification strategies have arisen, including substitute polymers [59], conditional removal of PEG [51], and biomimetic coatings [60].

The substitute polymers can include polyoxazolines (POZ or POx) [61], poly(amino acids) such as poly(hydroxyethyl l-glutamine) or poly(hydroxyethyl-l-asparagine) (PHEA) [62], HPMA [63], polyglycerols [64], polysaccharides, and betaines such as sulfobetaine and carboxybetaine [65].

Polysaccharides used in the stealth coating of nanosystems' surfaces are mainly derivatives of chitosan, dextran, hyaluronic acid, and heparin [51]. They are advantageous because of their biodegradability, low immunogenicity, and reduced toxicity. Most importantly, DDSs based on polysaccharides coating have prolonged circulation times of the loaded drugs, enhancing their accumulation in tumors [52].

An example is chitosan, which improves NPs-cells interactions at weakly acidic pH, due to its positive charge [66]. Coating nanosystems with chitosan improved the blood retention level, increasing the length of activity of the drug [67]. Additionally, chitosan coating of polymeric systems enhanced tumor-targeting selectivity as their accumulation in the cancer tumor site [68]. Another polysaccharide widely used in DDS is albumin, the most abundant plasma protein across the mammalian species [69]. A significant advantage of using albumin in DDSs is its more than 15-days plasma half-life, which improves the circulation time and allows the tailoring of long-acting systems. Different human

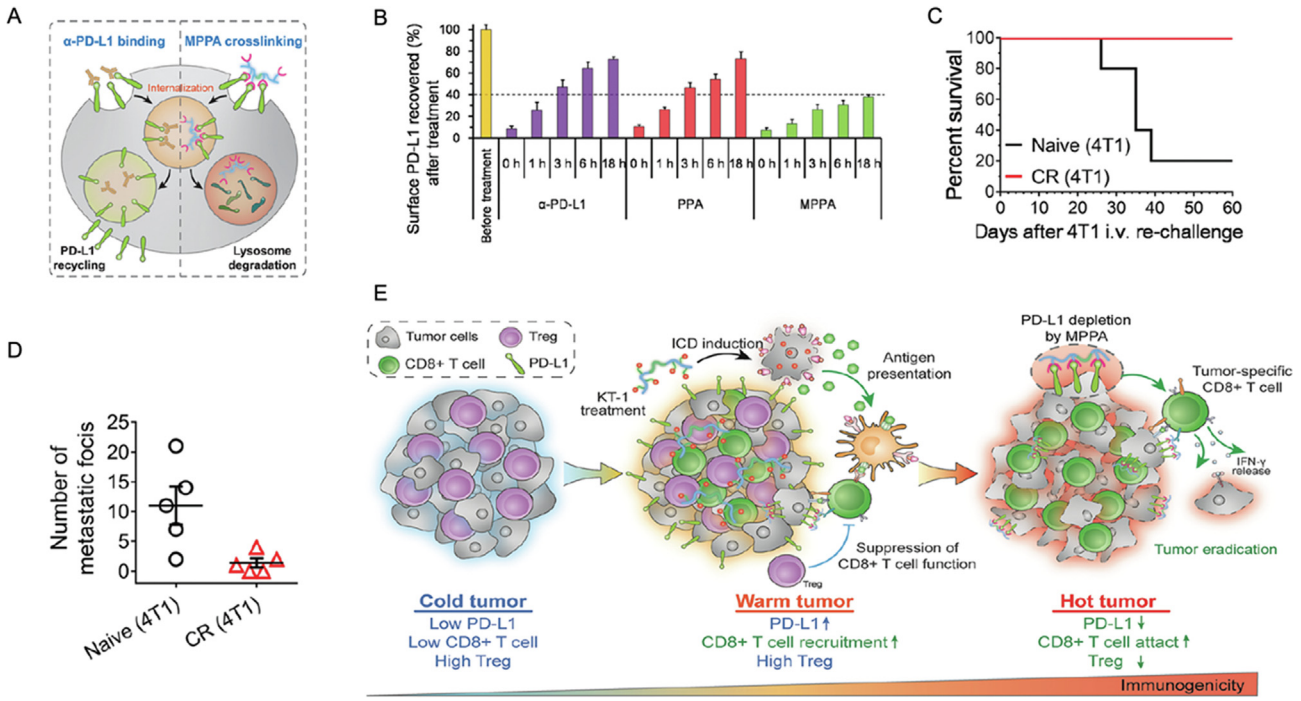

Fig. 2. PD-L1 antagonist peptides conjugated with HPMA (MPPA) drive PD-L1 crosslinking and elimination, fostering long-acting anticancer immunity. (A) Schematic illustration of single anti-PD-L1 antibody's transient PD-L1 blocking, followed by PD-L1 recycling, versus MPPA-induced PD-L1 elimination via lysosome degradation. (B) Surface PD-L1 recovery, for 18 h, after treatment with PD-L1 antibodies (a-PD-L1), single PD-L1 antagonist peptides (PPA), and MPPA. (C) Survival curves of naïve mice (Naïve) and mice pre-treated with MPPA (CR) after re-injection of 4T1 tumor cells. (D) Number of lung metastatic focis of Naïve and CR mice after re-injection of 4T1 tumor cells. (E) Schematic illustration of MPPA-triggered antitumor activity following chemotherapy induced immunogenic cell death. Reprinted with permission from Advanced Functional Materials, Vol 30, Li *et al.*, Inhibition of Immunosuppressive Tumors by Polymer-Assisted Inductions of Immunogenic Cell Death and Multivalent PD-L1 Crosslinking, 1908961. Copyright 2022.

serum albumin-coated nanosystems loaded with docetaxel [70] and paclitaxel [71] have demonstrated a sustained drug release over multiple weeks for anticancer therapy.

Another exciting alternative to PEG is poly-zwitterions such as poly(sulfobetaine) (PSB) and poly(carboxybetaine) (PCB) [72]. Zwitterion molecules have tunable surface charge properties since they contain positively and negatively charged groups with an overall neutral charge [73]. Like other hydrophilic stealth polymers, they can escape immune surveillance and increase the blood circulation half-life [74]. Studies have shown that NPs with zwitterionic moieties can reduce non-specific protein adsorption and prolong blood circulation under physiological conditions [73]. Specifically, systems are retained in tumor tissues by EPR effect, which results in an enhanced cellular uptake *in vivo* and tumor growth inhibition. Due to their advantages, zwitterionic polymer-coated NPs have great potential to achieve cancer therapeutic efficacy.

In recent years, most attention on DDS coating is toward using live cells and cell derivates to mimic a cell-like behavior due to the intrinsic biological functions and immunological properties [49]. DDSs decorated through bio-stealth have several associated advantages. Examples are improving specific interactions with the environment, enhancing particular targeting, biocompatibility, prolonged circulation time, and preferential accumulation in the TME [75,76].

Immune cells, such as macrophages, T cells, and red blood cells (RBC), have been exploited as membrane sources to develop biohybrid stealth systems with versatile functions [77]. In addition, their application in nanosystems has enhanced their targeting ability and circulation time.

RBCs half-life is about 120 days, providing prolonged circulation [78]. Furthermore, the advantages of using RBCs are extended to good biocompatibility, immune recognition evasion, and low immunogenicity. Antigens such as CD47 or CD59 present in RBCs surface act as a "do not eat me" signal, inhibiting MPS uptake and allowing these cells to remain in circulation [79,80]. For these reasons, RBCs have been explored for drug delivery purposes. Studies with NPs loaded with anticancer therapies that include components of RBCs have shown circulation times of up to 50 days in experiments carried out in mice [81–84]. These findings indicate that RBC membrane-camouflaged NPs exhibit a prolonged blood circulation time.

2.3. Hydrogel-based long-acting drug delivery systems

Tumor surgical resection is the most frequently used treatment for solid tumors [85]. Post-surgery patients end up with the so-called tumor resection cavity, a space with the potential to house local anticancer therapeutics that can help prevent disease recurrence [86].

Hydrogels have been extensively proposed and explored for local anticancer treatment, as these water-retaining polymeric networks can serve as drug reservoirs [87]. Compared with systemic drug administration, hydrogel-based pools accommodated in tumor resection cavities increase intratumoral drug concentration and limit the off-target distribution [88], contributing to therapy success and reducing toxicity or adverse reactions, huge issues resulting from aggressive anticancer therapeutics short of specificity [88].

Several polymers, such as chitosan, or co-polymers, such as poly (lactide-*co*-glycolide)-block-poly(ethylene glycol) (PLGA-PEG) or poly(caprolactone)–poly(ethylene glycol) (PCL-PEG), can be applied to anticancer hydrogels development [19]. In the last decade, many proposed systems have been "smart" [89]. For instance, they turn into gels *in situ*, in response to body temperature, pH, or biomolecules' concentration, while they are liquid and easily

Table 1
Summary of recently reported hydrogel-based long-acting DDS for anticancer therapy.

Composition	Delivered Drug	Malignancy	Major Advances	Experimental Model	Improvements in Drugs Pharmacokinetic Profile	Reference
Methacryloyl and poly(vinyl alcohol)-methacrylate modified chondroitin sulfate	Dox and sunitinib	NS	Drug release from chondroitin sulfate modified hydrogels depends on the levels of substitution	• In vitro drug release assay	• 20–30% of dox is released in 30 days • 100% of sunitinib is released in 42 days	[92]
Polyacrylamide and alginate-$CaCl_2$	Lomustine	NS	Double network hydrogels can control and sustain drugs release	• In vitro drug release assay	• 50% of lomustine is released in 29 days	[93]
Acetyl, butanoyl or heptanoyl modified chitosan	Dox and gemcitabine	NS	Hydrogels modifications impact on drug release profile can be predicted in silico	• In vitro drug release assay	• 40% of dox is released in 3 days • 30% of gemcitabine is released in 3 days	[94]
PLGA-PEG-PLGA	Gemcitabine modified with a fatty acid	Breast tumor	Gemcitabine sustained release induces a long-acting chemotherapy and radiosensitization	• In vitro drug release assay • 4T1-tumor bearing mice model	• 80% of gemcitabine is released in 37 days • Durable radiosensitization effect during multiple X ray exposures achieves higher tumor growth inhibition in animal models	[103]
CO_2H-PDLLA-PEG-PDLLA-CO_2H/NH_2-PDLLA-PEG-PDLLA-NH_2	Dox and 5,6-dimethylxanthenone-4-acetic acid (DMXAA)	NS	Local and sustained anti-tumor drugs release limits systemic biodistribution and potential toxicity while accomplishes a superior tumor growth inhibition	• In vitro drug release assay • BALB/c nude mice bearing HeLa cells xenografts	• In 40 days, 60% of dox is released at pH 5.5 and 47% is released at pH 7.4 • Superior tumor growth inhibition in animal models in comparison with the free drug	[104]
Alginate and ATP-specific aptamers	CpG oligonucleotide	Colon cancer	It is possible synchronize hydrogel-based drugs release with repeated low doses of chemo or radiotherapy	• BALB/c mice bearing murine • CT26 colon tumors	• CpG oligonucleotide is released in response to chemotherapy or radiotherapy induced released ATP. The hydrogel improves, dramatically, the therapy outcomes, managing to eliminate already established tumors, distant metastases and induce immunological memory.	[105]
Alginate	Pexidartinib and anti-PD1 antibodies	NS	Hydrogels improve anti-PD1 antibodies pharmacokinetics by extending circulation time and tumor accumulation	• C57BL/6 mice surgically implanted with the hydrogel • CT26 colon cancer model	• 60% of anit-PD1 antibody is released in 1 day and 34% of pexidartinib is released in 5 days • Due to improvements in drugs pharmacokinetic profile, hydrogel provides a potent therapeutic effect, protects animals from tumor recurrence, leads to tumor-associated macrophages depletion, and induces tumor T cells infiltration.	[106]
Fibrin	CAR-T cells	Glioblastoma	Hydrogels can accommodate CAR-T cells, sustain their viability and allow their gradual release within the tumor resection cavity	• In vitro release assay • GBM tumor resection model in immunodeficient mice	• Gradual and sustained release of cells (1.5x106) over 5 days • Cells persist at the tumor site for up to 7/8 days after implantation and increase T CD3 + cells infiltration.	[107]

manipulated during production and patient administration [89,90]. However, despite their benefits, the full potential of anticancer therapeutics might not be reached if they are locally applied but rapidly released [91]. Therefore, alternative strategies have been investigated to address this problem, and novel long-acting anticancer hydrogels have been reported (Table 1).

First, it is worth remembering that therapeutics released from hydrogels mainly depend on diffusion processes, which count on their interactions with matrixes [87]. That being the case, polymers' chemical modifications, which modulate their charge or hydrophilicity, can alter those interactions and, consequently, fine-tune the release kinetics [87]. Frequently, hydrophobic groups are introduced into polymers as they could promote polymer-therapeutics hydrophobic interactions delaying the last release [91,92]. Following this strategy, Ornell *et al.* selected methacryloyl groups to covalently modify chondroitin sulfate at different degrees [92]. After polymer crosslinking, chondroitin sulfate with varying substitution levels produces hydrogels with multiple release profiles, faster or slower. Some can sustainably release cationic anticancer therapeutics for more than one month. With the same purpose, using electrostatic interactions between alginate and polyacrylamide, Zeng *et al.* developed a double network hydrogel capable of releasing lomustine for up to approximately one month in a sustained manner [93].

Nonetheless, despite polymers' chemical modifications proving to be an effective strategy to prolong anticancer therapeutics exposure, exploring polymers' chemical modifications to precisely adjust release kinetics based on an educated guess is a difficult, complex, and time-consuming task. Therefore, recently described computational tools that guide chemical modifications and predict release kinetics might be interesting [94]. Initially, the operator introduces parameters as chemical modifications to be carried out, their distribution, and the ratio between therapeutic molecules and polymer chains number in the software, which predicts the therapeutics diffusion coefficient. In the next step, researchers can produce promising anticancer hydrogels and validate in silico anticipated outcomes.

As chemical structure of polymers controls hydrogel payloads release, it can impact release kinetics, as well. Therefore, therapeutics have also been chemically modified and used for long-acting anticancer hydrogel development. For instance, increasing gentamicin lipophilicity via a fatty acid chain incorporation before hydrogel encapsulation allows for zero-order release kinetics, with an 80% cumulative release after 30 days [17]. Furthermore, compared to the same system loaded with the non-modified molecule, long-acting gentamicin hydrogels allowed mice bearing 4T1 mammary tumors radiosensitization for multiple radiotherapy cycles, promoting its anticancer effectiveness.

In the drug delivery field, nano or micro-size systems are frequently used for their ability to sustain the release of loaded therapeutics [95,96]. As so, therapeutics encapsulation, followed by hydrogel incorporation, not only has the potential to increase hydrogels' loading capacity and, therefore, its anticancer potency but can generate long-acting treatments [97]. This was the case reported by Darge *et al.*, who developed DOX-loaded micelles incorporated in a hydrogel [19]. Micelles increased hydrogel DOX loading capacity and prevented its premature release. Moreover, the DOX-loaded micelles hydrogels significantly inhibited tumor growth compared with the free drug in tumor mice.

Even when therapeutics presents a good pharmacokinetic profile, acquired resistance is one of the biggest obstacles to their success. There are limited alternatives to tackle this problem, but, once again, hydrogels can be valuable tools. Hydrogels can prolong anticancer treatments and release two or more molecules simultaneously, and cancer patients seem to benefit from prolonged treatment exposure and combined therapies [44]. However, more recently, one of the innovations catching the field's attention is the design of hydrogels for combined synchronized therapy. Rather than just sustainably releasing therapeutics or in response to tumor microenvironment or external stimulus, hydrogels might respond to other therapies. For instance, Sun *et al.* conjugated alginate with an immunoadjuvant aptamer and produced an ATP-responsive hydrogel [98]. After radiotherapy, free ATP from dead tumor cells triggers aptamer release from the hydrogel, which prolonged CT26 colon tumor-bearing animals' survival.

Since 2018, when discoveries in cancer immunology were awarded a Nobel prize, immunotherapy has represented the "promised land" of anticancer treatment [99]. Tumor-associated macrophage depletion, immune checkpoint inhibitors blockage, or even cancer vaccines are among the hopes to cure cancer patients. Hydrogels can be advantageous, as they may also allow long-acting immunotherapies development [100]. Hydrogel-based strategies recently proposed to prolong the immunotherapeutic effect are like those already described, such as using nano or micro-systems to encapsulate immunomodulators. One of these cases was recently reported by Li *et al.*, who used an alginate hydrogel as a local reservoir of pexidortinib-loaded NPs and PD-L1 antibody functionalized platelets (Fig. 3) [101]. Their results, in a melanoma recurrence mouse model, indicated immunotherapeutic efficacy, as they found tumor-associated macrophage depletion together with T cells infiltration and activation, following NPs and platelets sustained release, in addition to superior animal survival. As hydrogels can transport and deliver viable cells, they have been recently tested for treatments with chimeric antigen receptor (CAR) T cells. In a glioblastoma resection animal model, a fibrin gel loaded with CAR T cells promoted their sustained release and superior anticancer efficacy compared to the same cells intravenously inoculated [102].

NS = Not Specified.

2.4. Microneedles-based long-acting drug delivery systems

Microneedles are minimally invasive arrays in the range of microns (less than 1000 μm in length) designed to penetrate the primary barrier of the skin, specifically the stratum corneum layer, for intradermal drug delivery [108,109]. The application of microneedles is based on the formation of temporary microchannels in the skin's outer layer that allows the delivery of active molecules through passive diffusion without damaging blood vessels or stimulating nerves.

The use of microneedles for controlled-release drug delivery has been investigated in the last few years [110]. Microneedles offer many advantages, as they can deliver almost any drug in a pain-free manner [111].

Importantly, long-acting drug delivery can be achieved through microneedles [112]. Furthermore, drugs release profile from microneedles is manipulable, using different strategies such as altering drug binding affinity, the type of polymers, and polymer hydration [113,114]. For instance, biodegradable and swellable polymers can be used to promote prolonged drug release from microneedles [115].

In short, there are several gains when using microneedles in transdermal drug delivery, such as safety, convenience, minimal invasiveness, improved drug bioavailability, and efficient drug delivery [116]. Nevertheless, although the use of microneedles is continually increasing, there are some limitations associated with these DDSs, such as the poor loading capacity, production procedures complexity, and the lack of access to deep tissues and organs.

Microneedles can act as long-acting DDSs dependent on their morphology and drug release mechanisms. Regarding these characteristics, microneedles can be divided into five types: solid,

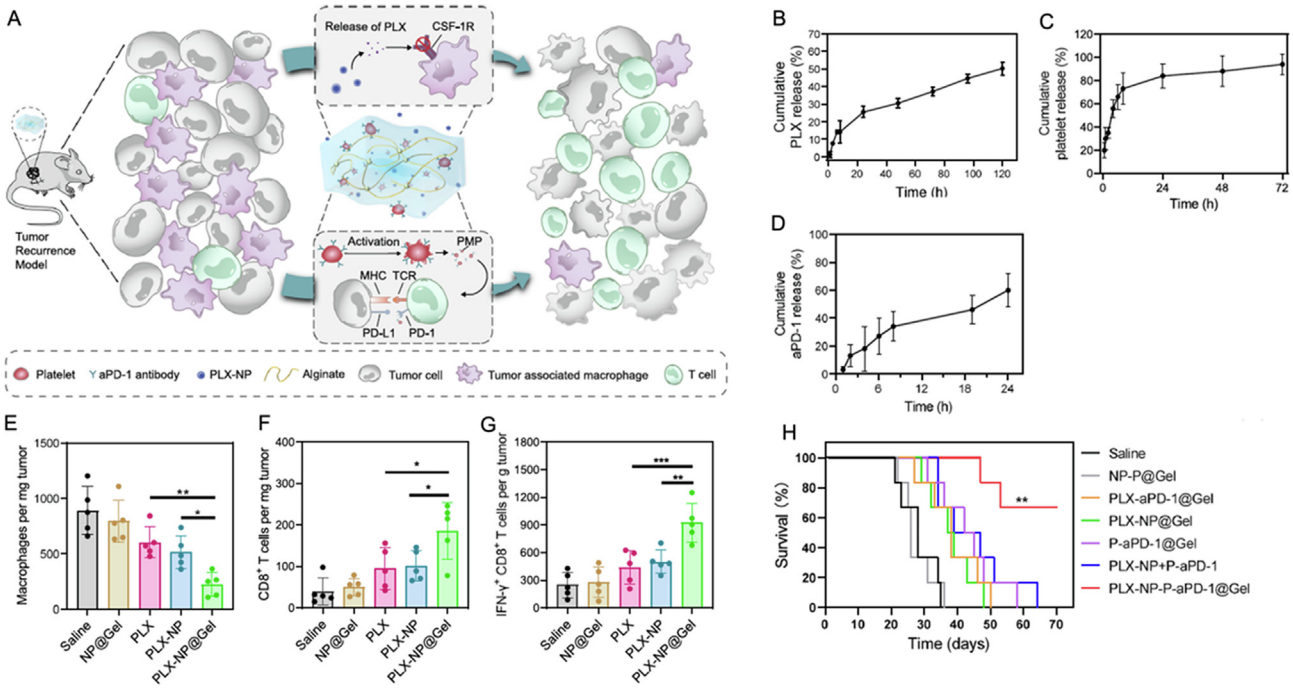

Fig. 3. Alginate hydrogel incorporating pexidortinib-loaded NPs (PLX-NPs) and PD-L1 antibody (aPD-1) functionalized platelets drives extended anticancer immunity. (A) Schematic illustration of pexidortinib-loaded NPs and PD-L1 antibody functionalized platelets alginate hydrogel mechanism of action. (B) PLX-NPs *in vitro* release profile. (C) Platelet *in vitro* release profile. (D) aPD-1 *in vitro* release profile. (E) Macrophages, (F) $CD8^+$ T cells and (G) $INF\text{-}Y^+$ $CD8^+$ T cells per tumor mass following hydrogel treatment and controls implantation on animals' tumor surgical cavities. (H) Survival curves of tumor recurrence mice models after treatment with the hydrogel or controls. Reprinted with permission from Nature Communications, Vol 13, Li *et al*., Depletion of tumor associated macrophages enhances local and systemic platelet-mediated anti-PD-1 delivery for post-surgery tumor recurrence treatment, 1845. Copyright 2022.

coated, hollow, dissolving, and hydrogel-forming microneedles [117].

Microneedles for controlled transdermal delivery are innovative strategies that can overcome the disadvantages related to conventional cancer therapies [118]. Cancer treatment associated with microneedles allows for improved targeted drug delivery, non-invasive controllable administration and release, and a potential therapeutic synergistic effect [119]. Additionally, microneedle systems are being studied to diagnose and prevent cancer and pain management.

In recent years, several review papers have discussed the application of microneedles for controlled transdermal medicine delivery [110,118,119]. Notably, the tunable properties of biodegradable polymers make polymeric microneedles to be explored for sustained delivery to achieve long-acting treatment, as it is possible to manipulate pre-loaded drugs release kinetics. Furthermore, to improve drug delivery for cancer therapy, microneedles have been described to deliver mainly photothermal and photodynamic agents [120], chemotherapeutic drugs [110], therapeutic genes [121], and immunotherapy agents [122], with several potential clinical benefits.

Microneedles for delivering chemotherapeutic agents into tumor tissues are considered a safe treatment, as non-specific interactions with healthy tissues are reduced and, consequently, the side effects [118,119]. In this way, the efficacy of anticancer treatments is improved.

Drugs commonly used in first-line chemotherapeutic regimes include cisplatin and DOX. Lan *et al.* developed a tumor-targeting microneedle technique to mediate the transdermal delivery of lipid-coated cisplatin NPs [123,124]. The NPs presented a sustained release throughout 72 h in dialysis membranes *in vitro*. *In vivo* studies using a xenograft tumor BALB/c murine model demonstrated that the microneedles arrays significantly reduced tumor volume and weight without detecting toxicity. In another study, polymeric NPs loaded with DOX were coated on microneedles for carcinoma treatment and delivered by hypodermic injection to the porcine oral cavity [125]. The system demonstrated a substantial prolonged release of DOX, reducing the concern about the toxicity caused by the burst release. Indeed, DOX-loaded microneedles administered by hypodermic injection can act as long-acting DDSs.

Several types of immunotherapies for cancer treatment have been developed in the last years [126]. Nevertheless, immunotherapy has some limitations, including tissue heterogeneity and off-target toxicity.

The transdermal delivery of immune agents loaded in microneedles has been studied as a strategy to overcome the restraints associated with cancer immunotherapy. Skin is a highly active immune organ rich in immune cells containing a large population of dermal dendritic cells (DCs) as resident antigen-presenting cells (APCs) under the stratum corneum, playing an essential role in immunomodulation. Therefore, the transdermal administration of microneedles can incite robust immune responses by activating T-cells [127]. In addition, microneedles have good biocompatibility and can deliver high molecular weight molecules and vaccines across the skin, which makes them excellent candidates for delivering immunological biomolecules to APCs in the skin [128].

Transdermal vaccination mediated with microneedles has been proven to be a practical approach for administering antigens with a prolonged release and an antitumor response. Cancer vaccines can contain proteins, peptides, DCs, tumor lysates, tumor cells, DNA, mRNA, and viral vectors [129]. One of the most studied antigens for microneedles delivery is ovalbumin (OVA), with several reports demonstrating a sustainable release of the macromolecule for days [130]. Specifically, in B16 melanoma tumors, the transdermal delivery of antigen-loaded NPs by the microneedles prolonged skin retention time [131]. Furthermore, the delivery by microneedles efficiently inhibited tumors' proliferation and improved the antigens' stability.

Apart from antigens, the vaccination can be done with synthesized peptides derived from human cells [132] and even the whole tumor lysate [133,134]. Indeed, they all can have a constant plasma concentration for days and improve anticancer effects.

The local delivery of immune checkpoint inhibitors (ICIs) to targeted sites is also possible with microneedles, improving antitumor immunity by inhibiting intrinsic down-regulators of immunity. One of the most studied immune checkpoints is PD-1 and its ligand, PD-L1, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), and indoleamine 2,3-dioxygenase (IDO). As a result, several anticancer immunotherapy strategies, including microneedles, have been developed to target these immune checkpoints [122,135,136]. An example is the microneedles encapsulated with an anti-PD-1 antibody developed for melanoma treatment [122]. The system provided sustained drug delivery in a physiologically controlled manner, with an enhanced retention time of anti-PD-1 in tumor tissues. This strategy had low side effects while improving T-cell immunity. Furthermore, the microneedle-based delivery approach for PD-1 targeting revealed excellent results in treating immunotherapy-unresponsive superficial cancers (Fig. 4).

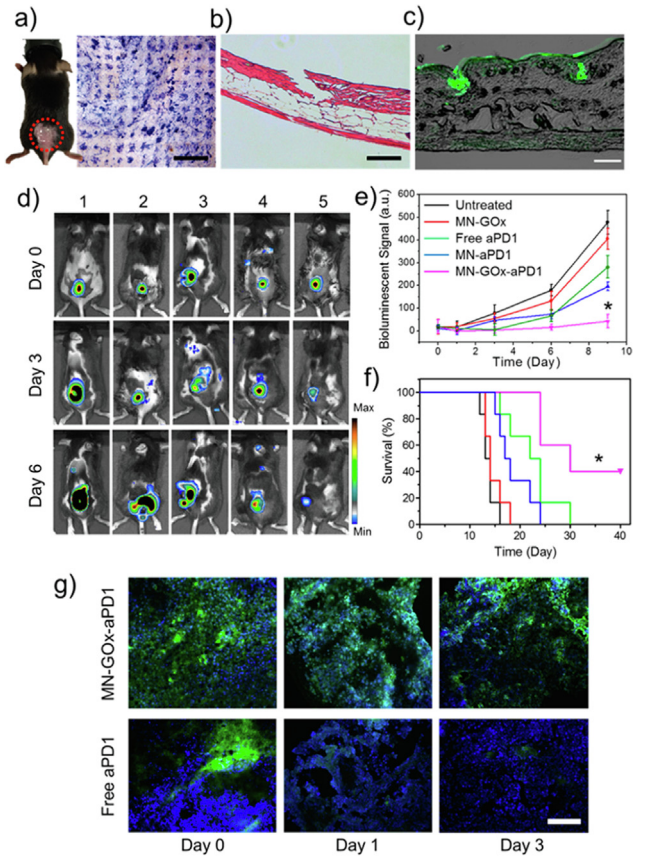

Fig. 4. *In vivo* anti-skin cancer treatment of aPD1 delivered by MNs. (a) Mouse dorsum and relevant skin) was transcutaneously treated with an MN patch (left), with the image of the trypan blue staining showing the penetration of MN patch into the mouse skin (right) (scale bar: 1 mm). (b) H&E-stained section of cross-sectional mouse skin area penetrated by one MN (scale bar: 200 μm). (c) Merged fluorescence and bright field image of the mouse skin penetrated by FITC-antibody loaded MNs (green: aPD1) (scale bar: 200 μm). (d) *In vivo* bioluminescence imaging of the B16F10 tumors of different groups indicated (1, untreated; 2, MN-GOx; 3, free aPD1; 4, MN-aPD1; 5, MN-GOxaPD1). (e) Quantified tumor signals according to d. (f) Kaplan – Meier survival curves for the treated and the control mice. (g) Immunofluorescence staining of tumors treated with MN-GOx-aPD1 or free aPD1 at different time points (green: aPD1, blue: nucleus) (scale bar: 100 μm). Reprinted with permission from Nano Letters, Vol. 16 (4) Wong *et al.*, Enhanced Cancer Immunotherapy by Microneedle Patch-Assisted Delivery of Anti-PD1 Antibody, 2334–2340. Copyright 2022 American Chemical Society.

The combination of anti-PD-1 agents with other immunomodulators for microneedles delivery is a strategy that can enhance the antitumor efficacy [137]. For example, Ye *et al.* developed a dissolving microneedle system for a synergic immunotherapy blockage of IDO and PD-1 in melanoma tumors [136]. The results demonstrated that the synergistic administration reduced local immunosuppression and improved T-cell immunity.

3. The present and the future of long-acting drug delivery systems in cancer treatment – Towards clinical translation

DDSs have been frequently used in long-acting anticancer therapy construction. These can protect therapeutic molecules from renal or MPS elimination or *in vivo* degradation, increasing blood circulation extent. They can also act as reservoirs that control pre-loaded therapeutics release kinetics, providing anticancer molecules with steady and sustained levels throughout extended periods. In any case, by reducing concentration variations, these systems fuel tumor exposure to treatments and, naturally, improve their effectiveness. Regarding loaded and delivered molecules, DDSs can be used to design long-acting chemotherapy, gene therapy, immunotherapy, phototherapy, or thermotherapy, being particularly advantageous for highly unstable molecules or with very narrow therapeutic windows.

Exploring long-acting DDSs in cancer treatment is nothing new. Polymers have been studied and used for drug protection and sustained release since the 1960s [138]. However, anticancer molecules release kinetics from recently proposed alternatives is more precisely controlled, for instance, through minor variations in polymers' chemical structure, and systems safety profile has been improved, for example, through PEG substitution. Table 2 lists ongoing clinical trials with long-acting anticancer DDSs. These include, mainly, anticancer molecule-PEG conjugates, PEGylated nanosystems, and a small set of hydrogels and microneedles, not representative of the recently developed and herein reviewed innovative systems. Although these are not yet in clinical trials, we expect newly described long-acting anticancer polymeric conjugates, coated systems, hydrogels, and microneedles to soon begin their journey until clinical approval.

Despite the abundant benefits of innovative systems, there are still a few drawbacks and challenges limiting their therapeutic potential and clinical translation [139–141].

First, little is known about the correlation between systems' physicochemical characteristics, such as charge, size, or stiffness, and *in vivo* fate. Strategies applied in long-acting anticancer treatment development are still very empirical and based on trial-and-error methods. Clarifying and systematizing systems' physicochemical characteristics impact on their activity might drive the design of more rigorous strategies, probably with more predictable results.

Despite appearing advantageous in preclinical settings, most systems fail to improve patient care in clinical trials. Hence, we anticipate the need to establish and use preclinical models better at predicting therapeutic outcomes. On top of that, transparent, robust, and quantifiable criteria to assess long-acting anticancer drug delivery systems' performance still need to be improved.

Ultimately, clinical translation is still hampered by concerns about sterilization, stability, production procedures complexity, scale-up, and shelf-life. These issues must also be addressed to foster long-acting anticancer drug delivery systems approval for patients' treatment. Additionally, there is a lack of guidelines for the production, use, and management of long-acting cancer therapeutics. There are already some guidelines for long-acting therapeutics for other diseases, such as antipsychotics for the treatment of serious mental illness [142], and antiretrovirals for

Table 2
Ongoing clinical trials of drug delivery systems for anticancer treatment (data available at ClinicalTrials.gov).

Polymeric conjugates-based long-acting drug delivery systems			
Name	**Description**	**Indication**	**Stage (Clinical Trial)**
JK-1201I	PEGylated Irinotecan	• Small Cell Lung Cancer	Phase I/II (NCT05158491)
ADI-PEG	PEGylated Asparaginase	• Hepatocelular Carcinoma	Phase II (NCT 04965714)
		• Uveal Melanoma	Phase III (NCT05317819)
		• Acute Myeloid Leukemia	Phase I (NCT03922880)
		• Glioblastoma	Phase I (NCT05001828)
			Phase I (NCT04587830)
ASPARLAS®		• Locally Advanced or Metastatic Pancreatic Cancer	FDA 2018
			Phase I (NCT05034627)
SC-PEG		• Pediatric Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma	Phase II (NCT 01574274)
PEG-ASP		• Lymphoma	Phase II (NCT04414969)
		• Acute Lymphoblastic Leukemia	Phase III (NCT02085655)
			Phase III (NCT02881086)
Oncaspar®		• Lymphoma	FDA 1994
			Phase II (NCT02705508)
			Recruiting (NCT04843150)
Pegilodecakin	PEGylated recombinant human IL-10	• Melanoma, Castrate Resistant Prostate Cancer, Ovarian Cancer, Renal Cell Carcinoma, Colorectal Carcinoma, Pancreatic Carcinoma, Non-Small Cell Lung Carcinoma	Phase I (NCT02009449)
Sylatron™	PEGylated recombinant Interferon alfa-2b	• Chronic Myeloid Leukemia	FDA 2011
		• Hepatocellular Carcinoma	Phase II (NCT03831776)
		• Melanoma	Recruiting (NCT04943679)
			Phase II (NCT00539591)
Stealth coating-based long-acting drug delivery systems			
Name	**Description**	**Indication**	**Stage (Clinical Trial)**
Doxil	PEGylated Liposome with DOX	• Karposi's Sarcoma	FDA 1995/ 2005/2008
		• Ovarian Cancer	
		• Multiple Myeloma	
Onivyde	PEGylated Liposome with irinotecan	• Pancreatic Cancer	FDA, 2015
Genexol-PM	PEGylated Micelle with paclitaxel	• Breast, Pancreatic, NSCL and Ovarian cancers	EMA, 2018
NKTR-102	PEGylated Liposome with irinotecan	• Breast and Colon cancer	Phase III (NCT02915744) (NCT01492101)
Lipoplatin	PEGylated Liposome with cisplatin	• Pancreatic, Head and Neck and Breast Cancer	Phase III (NCT02702700)
Thermodox	PEGylated Liposome with DOX	• Hepatocellular carcinoma	Phase III (NCT02112656)
Nano-QUT	NPs loaded with quercetin, PEG	• Squamous Cell Carcinoma	Phase II (NCT05456022)
GEN-1	PEG-PEI-Cholesterol Lipopolymer, IL-12 plasmid	• Advanced Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer	Phase I/II (NCT03393884)
Hydrogel-based long-acting drug delivery systems			
Name	**Description**	**Indication**	**Stage (Clinical Trial)**
UGN-102	Mitomycin-loaded Hydrogel	• Non-Muscle-Invasive Bladder Cancer	Phase III (NCT05243550)
			Phase III (NCT05136898)
			Phase III (NCT04688931)
LICoRN-01	GMCSF and Mifamurtide-loaded Hydrogel	• Colorectal Liver Metastases	Phase I (NCT04062721)
Microneedles-based long-acting drug delivery systems			
Name	**Description**	**Indication**	**Stage (Clinical Trial)**
	Microneedle array-DOX	• Cutaneous T Cell Lymphoma	Phase I (NCT02192021)
	DOX-containing MNA	• Basal Cell Carcinoma	Phase I/II (NCT04928222)
	Dissolving microneedles arrays with DOX	• Basal Cell Carcinoma	Phase I (NCT03646188)

Human Immunodeficiency Virus (HIV) prevention [143]. Despite being different conditions, challenges and drug management should be comparable in the cancer field. Even so, it is necessary to fill this gap for a successful translation to the clinic.

4. Conclusions

DDSs have been successful in extend anticancer therapeutics activity over time and increase their intratumoral accumulation by prolonging blood circulation. To avoid the premature bioelimination of therapeutics, specific technological approaches, as incorporation of linear PEG chains, have been implemented. These prevent both renal filtration and recognition by immune cells or hydrolytic enzymes by steric hindrance and increases in molecular weight. Concerns about biosafety and the need to further extend therapeutics' half-life have recently led to the use of other strategies, as the use of proteins, polysaccharides, or even cell membranes, instead of linear PEGylation.

On the other hand, anticancer therapeutics activity can also be extended with DDSs that, besides protecting them, drive their systemic or intratumoral long-term release. Release kinetics depends on the type of linkage/interaction between the therapeutic and the system and on biological environment that may or may not pro-

mote drug release. Therefore, novel strategies to refine release kinetics are based on precise and controlled systems' chemical structure modifications.

To foster long-acting anticancer DDSs clinical approval, we still need to face and overcome several challenges. Each anticancer molecule is physiochemically unique, so it will be difficult to design a "one-size-fits-all" strategy. However, it is important to recognize and define the impact of DDSs modifications on *in vivo* fate to hereafter rely on more logical and less empiric alternatives. While a controlled and prolonged drug release can be advantageous, too little release can limit therapeutic efficacy. Also, we need to build and use more accurate pre-clinical models to predict the true clinical potential of currently being developed systems. And finally, there is the need to simplify long-acting anticancer DDSs production and ensure their stability to facilitate large-scale production and storage.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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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