Narrative Review Article

The Implications and Applications of CAR-T Cells and Nanoparticles

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ABSTRACT

The management and treatment of colorectal cancer (CRC) has recently focused on two new and upcoming therapies: Chimeric Antigen Receptor T-cells(CAR-T cells) and nanoparticles. CAR-T Cells are T cells that have been genetically modified to detect and target cancer cells in the body by delivering medication into the body in the area where the cancer cells are present. Nanoparticles are microscopic particles engineered to detect and target cancer cells in the body by delivering medication or staining lymph nodes in a combined therapy approach. This paper addresses the question of how CAR-T cell therapies and nanoparticles can be used as a treatment for CRC, acknowledging the limitations and consequences present. Analysis of CAR-T cells has shown promising results in terms of medication administration and the prevention of metastases. Analysis of nanoparticles has shown promising results in the detection of sentinel lymph nodes(SLN) and the administration of medication. Both treatments show measurable effects, but this is not without the presence of different adverse effects that highlight the need for further analysis and additional supportive measures through combination therapies.

Keywords: CRC therapies; CAR-T cell therapy; Nanoparticle-based therapy; Therapies for metastatic CRC; biomarkers for CRC treatment

INTRODUCTION

CRC (Colorectal Cancer) is among the most diagnosed cancers worldwide. CRC is particularly prevalent in areas like Europe, Asia, Oceania, North America, and South America, which report high mortality rates (1). CRC remains a pressing global health issue, with 1.9 million cases reported in 2020. CRC is caused not only by genetic factors and medical conditions, but also by lifestyle choices, such as a sedentary lifestyle, smoking, and stress, which have been linked to its development and progression. Current standard treatments for CRC include surgery, chemotherapy, and radiation. As CRC incidence continues to rise, particularly in developed nations like the U.S., there is growing urgency to explore more effective treatments. Emerging therapeutic approaches include CAR-T cell therapy and nanoparticles. This raises the central question of how emerging therapies and tools like CAR-T cells and nanoparticles can be leveraged to improve CRC treatment outcomes (2).

These two therapies are commonly administered via intravenous injection. Specifically, CAR-T cell therapy is a new type of cancer immunotherapy currently being studied. CAR-T cells are T cells that have antigen receptors that have been engineered to detect certain

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Accepted December 22, 2025
https://doi.org/10.70251/HYJR2348.417789

antigens in cancer cells in the body. CAR-T cells can be given through allogeneic cell therapy (cells harvested from a donor) or autologous cell therapy (cells harvested from the patient themselves). CAR-T cells are typically generated by collecting T cells from the patient or a donor and then genetically modifying them to express chimeric antigen receptors. Next, the CARs are attached to the T-cells. CARs are engineered to recognize tumor-specific antigens, enabling targeted immune responses. These genetically modified T cells are transported into the body using either viral or non-viral methods (3). The extracellular target antigen-binding domain on CAR-T cells helps detect antigens, the hinge region gives the cell flexibility, the transmembrane domain helps with signaling and attachment to the T cell, and the intracellular signaling domain of the CAR-T cell assists in T cell activation. Domains for signaling have been expanded over time to include more domains for increased efficacy. Nanoparticles in cancer treatments are microscopic particles that are usually loaded with therapeutic drugs. Specifically, targeted nanoparticles target proteins on a cell's surface to treat cancers such as CRC. To ensure specificity, ligands such as antibodies, aptamers, or peptides are attached to the surface of targeted nanoparticles, enhancing their ability to bind to specific markers. Nanoparticles are crucial when it comes to efficient drug delivery to cancerous cells, as they recognize specific antigens on the cells to provide specialized treatment.

This review paper focuses on the mechanisms of CAR-T cells and nanoparticles, current and past clinical trials that highlight the clinical progress of these therapies, and the limitations of these therapies, to evaluate the current uses of CAR-T cells and nanoparticles, and how they can be improved.

CAR-T CELL THERAPIES

CAR-T cell therapy has revolutionized hematological malignancies; its translation to solid tumors like CRC faces hurdles. CAR-T cells have recently been looked at as an avenue for utilizing a patient's immune system and amplifying the immune response it has to malignancies. This is done through the engineering of an individual's own T-cells to produce CAR-T cells that are then infused into the body and result in cell death, as explained in Figure 1, which shows the engineering of T-cells and how they work in the body. Nevertheless, its application in CRC remains challenging. Solid tumors like CRC pose hurdles such as the lack of tumor-exclusive

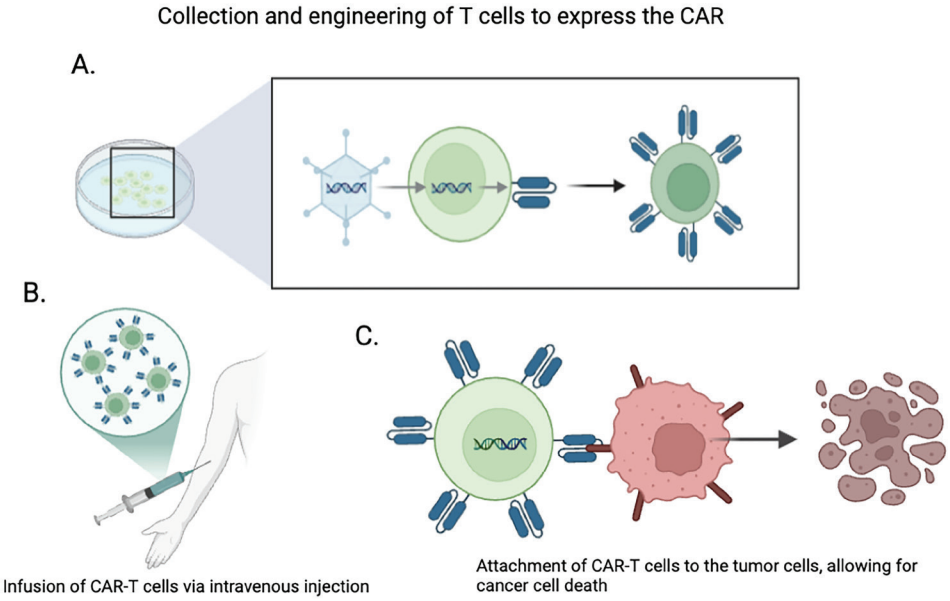

Figure 1. ***Mechanism of CAR-T Cell Therapy in Colorectal Cancer. A.*** *Samples would be collected from individuals and engineered to express the CAR and would be loaded with therapeutic drugs to target a certain antigen or expression on the cancer cells' surface B. The CAR-T cells would be infused back into the individual via intravenous injection C. These infused CAR-T cells would travel through the bloodstream and attach to the ligands present on the surface of cancer cells, releasing the drug and inducing apoptosis.*

antigens, treatment-related toxicities like cytokine release syndrome (CRS), and barriers imposed by the tumor microenvironment that suppress T cell activity. In this section, we examine recent CRC-specific CAR-T trials through four key challenges: antigen selection, T-cell persistence, toxicity management, and delivery in the tumor microenvironment to highlight the potential of this treatment.

Tumor Antigen Selection & Specificity

A critical requirement for effective CAR-T therapy in CRC is selecting antigens that are expressed on tumor cells but absent or minimally present in healthy tissues. Several CRC trials have targeted tumor-associated antigens like *CEA*, *GUCY2C*, and *EpCAM*. *CEA*+-specific CAR-T cells can be used as an effective treatment for metastatic CRC. In this study, ten patients received *CEA*+-specific CAR-T cells, which were created through viral transduction, cell culturing, and the combination of different immune cell subsets with memory T cells. Lymphodepletion was also used in this study, although it is usually not applied to solid tumors; however, it showed effectiveness even with an initial decrease in lymphocyte levels. Patients who received a high dose showed short-term CAR-T expansion, and minor CRS was observed. Two patients experienced fever, but no severe adverse effects occurred. Additionally, immune function was enhanced, and 70% of patients had stable disease progression, with two experiencing tumor shrinkage (4).

In another study, patients underwent leukapheresis and lymphodepletion three days before infusion with *GCC19* CART-cells. This treatment is promising because it targets two proteins that are highly expressed in CRC patients. Two patients had a partial response, and one had a partial metabolic response with stable disease progression (5). One study also showed an overall remission rate(ORR) of 40%, with the second dosage type having a higher ORR than the first, with a 57% (6).

IM96, a *GUCY2C*-specific CAR-T therapy, can also be an efficient option for patients with pMMR metastatic CRC due to its high objective response rate(ORR) and ability to control disease 6 months post-infusion. Twenty patients received lymphodepletion with fludarabine and cyclophosphamide, followed by IM96. Of those on dosage levels 2–4, 11 had grade 3 diarrhea, 7 had grade 1–3 oral mucositis, 14 had grade 1–3 rash, and 16 experienced grade 1–2 CRS. The disease control rate was 73.7%, and ORR was 26.3%, especially high in the highest dosage group (7). The treatment IMC001, a CAR-T therapy targeting *EpCAM*, is useful in CRC. Four CRC patients underwent lymphodepletion followed by infusion with one of three dose levels. Circulating tumor cells (CTCs) were eliminated in all patients, and 4 out of 5 patients (with CRC or gastric cancer) had stable disease progression (8). Together, these studies highlight both the opportunities and risks of antigen selection in CRC. While *GUCY2C* and *EpCAM* offer promise due to their tumor-restricted expression, antigens like *CEA* may pose off-tumor toxicity risks due to expression in healthy gastrointestinal tissues.

These studies all utilize heterogeneous antigen-based CAR-T cells to target CRC. Although the efficacy of targeting a single antigen is potent, this still raises a concern across many studies when it comes to addressing tumor antigen heterogeneity when developing treatments. Although many studies have not explored combating this phenomenon yet, the use of multi-antigen-based CAR-T cells can address concerns with metastasis and proliferation. Multi-antigen-based CAR-T cells work exactly like CAR-T cells, except they are engineered to target multiple antigens on a cell's surface. Considering this, all these studies do show how CAR-T cells are currently used with other treatments, which also could be used to help address tumor antigen heterogeneity by providing a multi-modal approach to CRC.

T Cell Exhaustion and Persistence

Another limitation of CAR-T therapy in solid tumors is poor persistence and T cell exhaustion. A study monitoring exhaustion markers and memory cell expansion has shown signs of improved immune function. Low levels of TIM-3 and LAG-3 suggested a reduction in T-cell exhaustion. Increases in CD45RA+ naïve T cells and CD45RO+ memory T cells further supported improved immune function. However, sustained persistence over time remains inconsistent, and more work is needed to engineer CAR-T products that maintain functionality in hostile tumor environments. One example of this could include gene editing to reduce exhaustion markers. The usage of *CEA*+-specific CAR-T cells in this study allowed for a low expression of exhaustion markers TIM-3 and LAG-3, suggesting low levels of T cell exhaustion (4). One example of such could be the use of inhibitory cytokines to overcome and regulate suppression by the body of T-cells.

Toxicity Management (CRS, ICANS, etc.)

Despite promising responses, CAR-T therapies frequently induce toxicities such as CRS, immune effector cell-associated neurotoxicity syndrome (ICANS),

and organ inflammation. One study assessed the safety profiles of different CAR-T constructs used in CRC. A phase 1 trial infused 4 patients with *GCC19* CART-cells after leukapheresis and lymphdepletion. All four patients in the study utilizing *GCC19* CART-cells experienced CRS, 75% experienced diarrhea, and some experienced ICANS. Although adverse effects were common, the second dosing group had a 50% remission rate (5). In another trial that utilized different dosages of the IMC001 treatment, 11 patients experienced grade 3 diarrhea, 7 patients had grade 1 to 3 oral mucositis, 14 developed rash, and 16 developed CRS of grade 1 to 2. The highest dose group had the strongest objective response rate (7). Another study reported that all patients expressed hematologic toxicity that was grade 3 or less; no patients showed signs of ICANS. Although most adverse events were grade 1–2 and manageable, the frequent occurrence of CRS—even with CRC-targeted CAR-T cells—emphasizes the importance of safety optimization in ongoing trials (8). When looking at Table 1, it highlights how across multiple studies, similar outcomes have been reported regarding adverse effects. One reason for this could be due to there being a lack of sufficient research on CAR-T cells, when comparing them to other therapies that have fewer adverse effects. Furthermore, many trials highlight how adverse effects, such as a fever, which two patients experienced in this trial, seem to be similar across multiple studies (4). These frequent occurrences of CRS, even with CRC-targeted CAR-T cells, underscore the critical challenge of toxicity management and emphasize the ongoing need for safety optimization in clinical trials. Even with these challenges, trials have shown improvements in the adverse effects that appear. One study with *GCC19* CART cell-based treatment in patients with metastatic CRC has shown potential to be a safe and effective treatment due to its partial response of 40%, and its metabolic response in 11/15 patients. The study utilized platforms such as coupledCAR to engineer CAR-T cells that targeted *CD19* and *GCC*, administering them after lymphodepletion. They found that 93% of patients had adverse effects of grade 3 or higher; however, these adverse effects were all able to be treated quickly (9).

The toxicity present in all these studies stems from responses of the immune system, such as cytokine release, that result in inflammation, neurological toxicities, or organ failure. Studies can look into the use of specifically engineered CAR-T cells that prevent toxicity from occurring when detected or utilize CAR-T cells that target a variety of antigens.

Tumor Microenvironment & Delivery

The solid tumor microenvironment in CRC presents physical and immunologic barriers to CAR-T efficacy,

Table 1. *Summary of CAR-T Cell Clinical Trials in CRC*

Study	Target Antigen/ Receptor	Delivery Type	Patient Population	ORR	DCR	Grade ≥3 AEs
Zhang et al. (2017)	CEA+	Autologous	Metastatic CRC (n=10)	N/A	70%	Mild CRS, fever (2 pts)
Keenan et al. (2024)	GCC19	Autologous	Metastatic CRC (n=4)	15.4–50%	Not reported	CRS, ICANS, diarrhea
Qi et al. (2024)	GUCY2C	Autologous	pMMR mCRC (n=20)	26.30%	73.70%	CRS, mucositis, rash
Fang et al. (2022)	EpCAM	Autologous	CRC/Gastric (n=4 CRC)	Not reported	100% CTC clearance	Hematologic toxicity ≤ Grade 3, no ICANS
Prenen et al. (2021)	NKG2D	Allogeneic	Relapsed/refractory CRC (n=15)	Partial response in 2 pts	60% stable disease	None > Grade 3, no GvHD

A. Many CAR-T cells undergo autologous delivery, as it can prevent immune compromise. B. Many adverse effects of CAR-T cells are also common, such as CRS and ICANS.

including poor infiltration, immune suppression, and tumor heterogeneity. Some studies, such as Prenen *et al*., have begun exploring delivery methods and engineered cells that may overcome these obstacles. One study revealed how the CAR-T cell-based treatment CYAD-101, which targets the *NKG2D* receptor, can be effective at treating patients with relapsed or refractory metastatic CRC. A FOLFOX cycle was given to 15 patients before three infusions of the treatment. No patients experienced adverse effects higher than grade 3, dose-limiting toxicities, or GvHD. GvHD was a main concern, as the therapy was allogeneic, which could pose immune complications. However, 2 patients experienced a partial response, and 7 of the 9 patients with stable disease had a stable progression lasting for 3 months. This trial also suggests that allogeneic CAR-T products could reduce manufacturing time and expand accessibility, though further evaluation of durability and tumor targeting is needed (10). Elevated MDSC and PD-1 levels also can indicate persistent tumor-mediated immunosuppression regardless of an increase in memory and naive T-cells (4). This all underscores the pertinent issue of immune suppression when it comes to improving the efficacy of CAR-T cells.

Synthesis and Future Directions

Altogether, CAR-T cell therapy in colorectal cancer has entered an exciting yet complex era. CAR-T cells exhibit extraordinary adaptability, which allows this treatment to be versatile and unique for each patient. This adaptability has been demonstrated in studies where allogeneic methods have been used to derive T cells and produce positive results. Not only that, the methodology behind CAR-T cells allows them to be implemented alongside other treatments that would be less effective by themselves. This is because CAR-T cells introduce a far more efficient and time-saving approach to CRC treatment.

Although many of these trials have shown promising results, CAR-T cell therapies overall have limitations and barriers. Some common and unmentioned limitations of this therapy include low remission rates in patients after infusion and treatment. Furthermore, low sample sizes in studies continue to be a constraint, as they decrease the reliability of results and the detection of accurate outcomes. A pivotal example of this would be that although the *GCCI9* CAR-T cell treatment poses beneficial findings, the low sample size of 4 individuals makes it difficult to distinguish the rigor, reproducibility, and advantages of CAR-T cell therapy from the disadvantages present (5). This is further highlighted by the usage of scRNA-Seq to show severe ICANS in patients given the anti-CD19 CAR T cell infusions. This led researchers to explain how, although there are toxicities present, further development of scRNA-Seq can prove to be an effective method for predicting the expression of cells and their toxicity (11).

Nevertheless, future directions require integrated approaches that combine improved antigen selection, enhanced cell engineering, safer methods of implementation, and possibly the use of supporting tools like nanoparticles or immune modulators to enhance CAR-T functionality in solid tumors like CRC. Strategies such as this and the use of other currently used treatments, as mentioned above, can improve the functionality of CAR-T cells and promote the adoption of this treatment across clinics. This could be done through the combination of nanoformulations that could be used with Phytochemicals such as curcumin (12), or bioactive compounds such as allicin. Allicing specifically has been shown to inhibit signaling between cancer cells, preventing their proliferation and the deactivation of tumor suppressors in the body, suggesting a unique avenue for exploration in this field of treatment (13). Considering this, it is important to keep in mind that advances also need to be made regarding the administration of targeted therapy only if receptors are expressed. This can be done through Bone marrow blasts to show certain receptors or antigens present, an example being bone marrow blasts being used to detect the *CD19* protein in patients to administer them CAR-T cells (14). This remains an issue in certain trials and, when overcome, can show sought-after results. A type of CAR-T cell treatment called GRm13Z40-2 was able to discover issues with their treatment due to their treatment planning, which included tests to ensure individuals being treated expressed the antigens being targeted (15).

NANOPARTICLE-BASED THERAPIES

Nanoparticles are a revolutionary and upcoming treatment for CRC that utilizes microscopic particles that effectively travel through the body to administer medication. This treatment has already demonstrated therapeutic benefits in initial CRC trials where nanoparticles have been used in targeting small tumors in CRC. Nanoparticle therapies differ in structures/compositions, functions, and applications. Specifically, nanoparticle composition is largely dependent on the arrangement and size of the nanoparticle. Examples of

nanoparticle compositions currently being investigated include carbon nanoparticles, metal nanoparticles (such as gold nanoparticles or copper nanoparticles), and lipid-based nanoparticles. Different compositions have their own benefits, including better toxicity management and biocompatibility with the tumor microenvironment, as highlighted in Table 2. Table 2 further highlights how different mechanistic abilities and parts of nanoparticles are paired with certain delivery methods. This is to ensure efficient and controlled circulation and delivery of certain drugs. Examples of nanoparticle functions and applications include drug delivery and particles used for cancer detection. Most targeted nanoparticle treatments fall into the three categories of passive tumor targeting, active targeting, or stimuli-responsive gatekeeper tumor targeting. Passive targeting utilizes the EPR effect, as it is present in many solid tumor cancers. This effect is crucial when treating nanoparticles, as it ensures simpler nanoparticle administration and targeting. Active targeting also utilizes the EPR effect, which can have an uncertain extent in human tumors, as it varies from patient to patient. The surface of nanoparticles is modified using ligands that bind to receptors that are heavily expressed. RNA interference is a method in which genes that support cancer development are silenced. Small interfering RNAs (siRNAs) can block proteins from being produced by cancer cells. Furthermore, stimuli-responsive gatekeepers targeting is where nanoparticles can utilize gatekeepers that essentially prevent the nanoparticle from releasing the therapeutic agent until there is a tumor microenvironment(TME) stimulus. This can be done through pH-responsive gatekeepers, redox-responsive gatekeepers, and enzyme-responsive gatekeepers (16). This section focuses on the benefits of nanoparticles for tumor management and lymph node detection in different types of colorectal cancers, while also examining the complications that arise with nanoparticle therapy, such as toxicity and a lack of efficiency when introduced to the tumor.

Tumor Management

The most common use of nanoparticles is for assisting in drug delivery at the tumor site. Due to the miniature size of nanoparticles, this proves to be efficient. Usually, this treatment is done with a combination of surgery and other drugs. One study demonstrated the importance of combining drugs, such as gemcitabine, with nanoparticle-based treatments like nab-paclitaxel, to achieve optimal tumor management (17). Another study had also discovered efficacy when using the camptothecin nanoparticle, CRLX101, in inducing downstaging in patients and moderate pathological responses in 58% of individuals. 31 patients with advanced rectal cancer (a type of colorectal cancer) were initially given chemoradiotherapy (CR) after meeting the criteria and then given weekly dosages of the CRLX101 treatment after undergoing surgery. Downstaging from before and after treatment was seen in 50% of patients at the primary treatment site, 69% of patients experienced node downstaging, and 48% of patients showed no cancerous

Table 2. *Types of Nanoparticles Investigated for CRC*

Type	Material	Targeting Mode	Application	Example Study
Carbon NPs	Carbon black dye	Passive (SLN mapping)	Lymph node detection	Sun et al. (2018)
Gold Nanocages	Gold + galunisertib	Stimuli (NIR light, pH)	Tumor ablation + immunotherapy	Wang et al. (2021)
Semiconducting Polymers	PCPDTBSe, PFBTDBT10	Stimuli (NIR)	Photothermal therapy	McCarthy et al. (2021)
Lipid NPs	Liposomes (CPT, 5-FU)	Passive/EPR	Chemotherapy delivery	Ünal et al. (2021)
MG-based NPs	Mastic gum	Controlled release	Colon-specific 5-FU delivery	Hani et al. (2025)
CMPBC	MSNs + BNN6 + CP	NIR & ROS stimuli	Tumor inhibition + survival	Wang et al. (2025)

A. Nanoparticles tend to show more differences in their engineering and mechanistic abilities as they are engineered more specifically towards each patient or group in a study.

lymph nodes after surgery. This highlights the potency of nanoparticles, even in the tumor microenvironment (18). Another study underscored the tumor suppressive ability of Polycationic CD nanoparticles loaded with camptothecin(CPT), especially in rats with early stage development, as the group of rats that were given the CPT-NPs had fewer metastatic foci than the group given the CPT suspension group in the early stage in vivo model (19). One study also found that *cblb* knockouts limited tumor growth in CRC compared to wild-type CAR-T cells. Mice models with MC38 colon cancer and prepared CAR-T cells using CRISPR-Cas9-based editing to investigate the reason behind exhaustion in *CD8*+ T cells were used. The study found that the *cblb* gene was potent in *CD8*+ T cells that were found to be exhausted in the tumor microenvironment. This was further supported by stained cells from the isolated *CD8*+ TILs that showed similar conclusions. Additionally, when this gene was inhibited in CAR-T cells, no adverse effects regarding toxicity were shown in the mouse models (20). Moreover, another study showed how out of 21 mice that were given the AOM injection and then given the IRT-P-HA-NPs, and examined, the group of mice (of the model with 10 mice) that were only treated with saline and the free IRT had a deteriorating condition as their tumor continued to grow. In the HT29 model, the expression of *CD44* was shown and proved to be a useful marker and target for colon cancer (21).

Rapid drug absorption has posed a challenge when it comes to drug administration for patients with CRC, as only minimal amounts of the treatment are reaching the patient's tumor site, especially when administered orally. Moreover, as shown in Table 2, MG-based nanoparticles loaded with the drug 5-FU also have a high efficacy when it comes to targeted drug release and controlled absorption in the body. 12 albino rats were divided into three groups of four, one group being the control group, one group treated with the 5-FU, and one group treated with the MGNPs through a cannula before the rats were sacrificed to study their tissues. Absorption occurred quickly in the rats given the 5-FU, with 41.33% of the medication being absorbed by hour 8. However, the rats treated with the MGNPs saw absorption of 63.52% on day 8 (22). This highlights the promising effects of nanoparticle treatments on increasing the solubility, absorbability, and persistence of drug delivery systems for patients with colon cancer due to their unique properties (such as their encapsulations and ligands) and controlled release systems that make them unique from other treatments.

Beyond direct drug delivery, nanoparticles are also being explored for their ability to enhance other therapeutic modalities, such as photothermal therapy (PTT), by converting light into therapeutic heat at the tumor site to create an effective treatment. In these studies, nanoparticles are designed to absorb near-infrared light(NIR) and convert the light from the irradiation into heat that can be used to destroy the cancerous cells while also delivering therapeutic drugs, as demonstrated by Figure 2. One study also

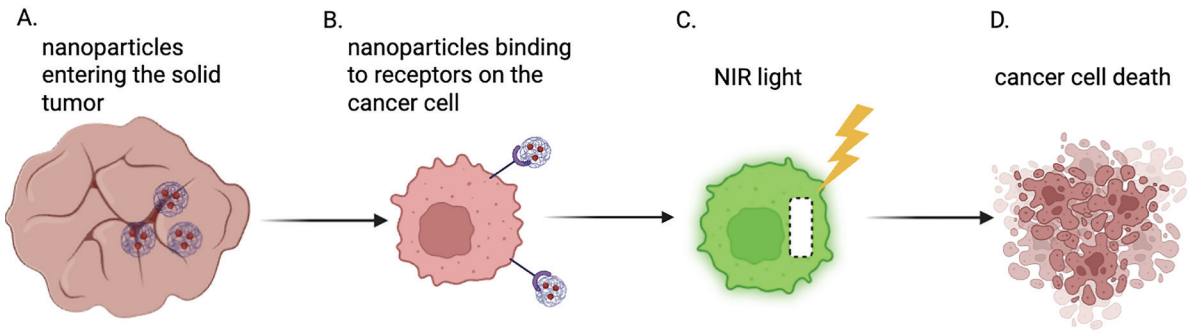

Figure 2. ***Nanoparticle-Based Drug Delivery in CRC. A.*** *Nanoparticles would be infused into an individual and enter the solid tumor.* ***B.*** *Nanoparticles would bind to different ligands that they were programmed to attach to on the cancerous cells' surface. Over time, these nanoparticles would accumulate on the cancer cells' surface. C. The activation of NIR light would be absorbed by the nanoparticles and converted into heat that, in turn, heats the cancer cells and the tumor. D. The heat absorbed by the nanoparticles would result in cancer cell death, as explained further by the PTT(Photothermal Therapy) effect.*

found that BSeNPs coated with hyaluronic acid were productive at eliminating viable cancer cells in 3D and 2D models. Fluorescent hybrid donor-acceptor polymer particles(HDAPPs) and the BSeNPs were both tested in this study. Both nanoparticles were coated with hyaluronic acid and exposed to NIR light, which led to ablative hyperthermia at doses greater than 1×10^{-10} NP/mL. The coated HDAPPs were only able to penetrate the organoid and had a lower internal concentration compared to the non-coated HDAPPs, even though the coated HDAPPs bound more to the CT26 CRC cells. The utilization of coated BSeNPs with laser exposure eliminated the viable cells in the model, compared to a 26% reduction of viable cells for noncoated BSeNPs. A decrease in viable cells for the coated nanoparticles was also shown without the laser exposure (23). The usage of gold nanocages loaded with galunisertib, referred to as GNC-Gal@CMaP, showed benefits by promoting immune system responses in the tumor environment, preventing metastasis, and limiting adverse effects. Synthesized SNCs were combined with $HAuCl_4$ to synthesize the gold nanocages needed. The treatment of GNC-Gal@CMaP with the NIR showed destruction of primary, inhibition of distant tumor growth, and no pathological alterations to other organs in the body. GNC-Gal@CMaP reduced activity in the signaling pathways between p-SMAD2/3 and pAKT in the CT26 cells, which in turn enhanced the prevention of TGFβ signaling and further tumor growth. GNC-Gal@CMaP accumulated much more persistently and effectively at tumor sites compared to GNCs that were not coated (24). The usage of CMPBC nanoparticles when combined with NIR light also had a promising tumor inhibition rate of 98.6% and a prolonged life expectancy for mice in an in vivo model. CMPBC is a nanoparticle. MSNs are loaded with the drug CP, while PDAs were loaded with BNN6 to make PDA-BNN6 nanoparticles. Ice, given the CMPBC and NIR treatment, showed the smallest tumor burden, with one mouse even showing a complete lack of a tumor. Moreover, the inhibition of tumor growth for this treatment was 98.6%. H&E staining confirmed this further, as this treatment showed the most cancer cell apoptosis. Mice given the CMPBC and the NIR had a prolonged life, with 60% of mice living to the 60-day mark, while the mice in the saline and CP groups had all passed over the 60 days (25).

The EPR effect is a foundation for understanding nanoparticles, as it explains how nanoparticles are able to accumulate specifically in the tumor. All the studies mentioned address the EPR effect; however, an issue when looking at this is the variability and difference in the EPR effect from study to study. This is due to differences in formulation and an individual's own immune system. Integrated approaches of combination therapy can also help decrease the large differences in the EPR effect for each person. The specialization of nanoparticles could also address concerns; however, this would result in a similar time-consuming process of manufacturing as CAR-T cells.

Lymph Node Detection

Nanoparticles are useful when it comes to detecting the origin site of metastatic cancers, allowing surgeons to control the spread of CRC in patients. This is primarily done through sentinel lymph node(SLN) detection, which identifies the area in which the cancer first began to spread. One study has shown how SLN detection in patients with metastatic CRC can be an effective tool for improving cancer treatment overall. They employed carbon nanoparticles to track the cancerous tissues using dye detection and positioning, before undergoing surgery to remove the diseased tissue. 80 patients over 60 years old were admitted, with half of the patients receiving standard surgery to remove cancerous tissue and half of the patients being given the nanoparticle detection protocol. The accuracy rate of the nanoparticles was 94.59% and the specificity of the diagnosis was 87.5% (26). This is important when it comes to nanoparticle therapy, as lymph nodes can carry cancerous cells that could spread to other systems in the body via lymphatic fluid, making accurate detection crucial.

Activated carbon nanoparticles can also be a beneficial tool and therapy for patients with colorectal cancer due to their efficiency when it comes to detecting lymph nodes that are less than 5 mm. Lymph node detection is important when it comes to CRC treatments, as lymph nodes indicate where the cancer first began spreading, where it has continued to spread, and prevent further metastasis of the disease, as lymph nodes can carry cancer cells and spread them through the rest of the body through the lymphatic fluid. In the study mentioned, lymph nodes were harvested through surgery from 40 patients who received the activated carbon nanoparticles (ACNs) and 39 patients who did not receive ACNs, making them a part of the control group. The ACN group had an average number of 11.9 lymph nodes less than 5 mm, while the control group had an average of 4.1 lymph nodes less than 5 mm, highlighting the high efficacy of ACNs when it comes to detecting lymph nodes. Furthermore, the group given the

nanoparticles treatment had an average number of 19.5 lymph nodes greater than 5 mm, while the control group had an average of 17.7 lymph nodes greater than 5 mm (27). This overall exemplifies how nanoparticles are an important avenue for lymph node detection to prevent further metastasis and a higher risk of recurrence.

SLN detection is becoming an increasingly common method of using nanoparticles. The studies mentioned all highlight the efficacy of nanoparticles when it comes to they are used as surgical tools. Although challenges persist regarding improving the potential of nanoparticles for detecting larger amounts of lymph nodes and biocompatibility, this method of using nanoparticles has become a crucial tool for lymph node detection and removal.

Toxicity Management

Although nanoparticles have a lower toxicity and adverse effect rate compared to other CRC treatments, the drugs that nanoparticles are loaded with and the specific structures that nanoparticles are engineered to have can lead to disruptions in the body, leading to negative outcomes. The administration of the nano-camptothecin, CRLX101, resulted in 61% of patients experiencing fatigue, and 45% of patients experiencing lymphopenia. 13 patients who were evaluated specifically showed signs of toxicity at grade 3 or higher, and a case each of grade 3 diarrhea, rectal obstruction, colitis, and radiation dermatitis (18). Adverse effects were also common in the study that used nab-paclitaxel. 80% of patients experienced asthenia, 49% of patients experienced alopecia, 34% of patients experienced diarrhea, and 32% of patients experienced nausea. Neutropenia, asthenia, and peripheral neuropathy were common adverse effects in patients that were experienced at a grade 3 or higher level. The disease control rate was 16%, and no tumor shrinkage or response was observed in patients. Ultimately, 90% of patients stopped treatment due to the disease progressing, and the study could not meet the necessary criteria to move into phase 2 (17). This underscores the need for proper testing to be conducted before the administration of nanoparticle-based treatments.

Synthesis and Future Directions

Nanoparticles are a promising platform for lymph node detection, drug delivery, and tumor inhibition. Nanoparticles still have many obstacles that hinder their progress, such as a lack of studies in general, but especially a lack of studies completed on human patients. This could be due to the shallow depth of literature on nanoparticles and the fact that nanoparticle creation is a time-consuming process. However, this lack of information makes it harder to truly assess the immune responses and clearance of nanoparticles in the human body. Many studies also highlight how nanoparticles need to be paired with other treatments or therapies to be successful. Many of the nanoparticle formulations that did not use NIR light afterwards showed less efficacy compared to nanoparticle formulations that utilized NIR light (28). This is crucial as this shows how not only improvements are needed for nanoparticles themselves, but also the different treatments they are paired with to accommodate the needs and conditions of different patients. The usage of the CRLX101 led the scientists in that study to conclude that further improvements are necessary to be made in the field of nanoparticle technology for drug delivery in chemotherapy, with the researchers suggesting higher radiosensitizing chemotherapy as a tool for patients who do not want to undergo surgery or experience recurring diseases (18).

Keeping that in mind, nanoparticles are overall a versatile tool when it comes to treating CRC. Many new and upcoming studies have begun to utilize prior in vitro studies to test the efficacy of nanoparticles before injection into in vivo models. This new strategy allows for a better understanding of the mechanistic abilities behind nanoparticles when they interact with cancer cells, and it ensures that the treatment is optimized for better yielding results when tested in living organisms. Future directions and improvements in the penetration ability of nanoparticles, the potency of nanoparticles, and the resistance of nanoparticles by themselves will allow nanoparticles to become a more widely implemented therapy.

COMPARATIVE ADVANTAGES AND LIMITATIONS OF CAR-T VS. NANOPARTICLES IN CRC

Both CAR-T cells and nanoparticles show promise as a therapy for CRC, but face distinct challenges. Considering this, both treatments also have many similarities. This discussion explores the similarities and differences between these two favorable therapies and how their unique strengths and weaknesses can be used for the improvement of future applications, as shown in Table 3. Overall, CAR-T cells have demonstrated more promising results due to their adaptability, effectiveness regarding attachment to different proteins and antigens on cancer cells, and effectiveness when it comes to

drug delivery and inducing remission in patients with CRC. Studies have shown that targeting many similar antigens, such as *GUCY2C* and *CEA*+, and giving patient dosages in many stages to examine their effects has yielded promising and beneficial results. Specifically, many studies have shown that lowering T-cell exhaustion levels and, in turn, promoting proper immune system function to prevent metastasis. These results are especially pertinent when CAR-T cells are manufactured utilizing different subsets of T cells, such as naive T cells and memory T cells. Furthermore, nanoparticles have also shown favorable outcomes, as multiple studies have reported efficacy with low amounts of adverse effects. Nanoparticles are fruitful as they not only target cancer cells through drug delivery but also work as a tool for the surgical removal of tumors due to their lymph node detection and staining abilities. Studies have highlighted how nanoparticles lead to remission and lymph node downstaging, while also increasing the absorbability of the chemotherapy drug in the GI tract.

Both targeted therapies have many similarities, as they both offer treatments that help boost a patient's immune system and can even mimic different biological systems in the body. This allows them to be targeted towards specific diseases. A similarity between these two interventions lies in the fact that CAR-T cells and nanoparticles are both primarily used for targeted delivery purposes, specifically to administer certain chemotherapy drugs as they travel through the body and attach to cancer cells. Furthermore, both CAR-T cells and nanoparticles have been shown to have substantial amounts of adverse effects in certain studies. Many of these adverse effects are shared between the two therapies, including toxicity, diarrhea, and low remission and survival rates for patients and/or other in vivo models used. Regarding modality, both CAR-T cells and nanoparticles can be delivered intravenously to an individual, as shown in Table 3. Considering this, nanoparticles can be administered in a larger variety of ways compared to CAR-T cells due to them being particles and not T-cells that require specialized administration due to being "living" cells.

However, this leads to a main difference between these treatments in the ways they are usually engineered to be expressed in the body and the way they are applied in treatment for patients. Usually, CAR-T cells are engineered to release their components when a certain CAR is expressed from an antigen. This antigen-based expression could also be used in nanoparticles, but it is typically not. Instead, nanoparticles are mainly engineered to release their components or act when they recognize a certain stimulus, such as pH level in the body, which is common in areas with cancer cells, as referenced in Table 3. Additionally, a key difference in the construction of both treatments is that CAR-T cells are engineered using T cells that are already present in the body, whereas nanoparticles are synthetically engineered outside the body and then administered. Moreover, unlike nanoparticles, CAR-T cells are not typically used for lymph node detection and dying tissues. Finally, another key difference between nanoparticles and CAR-T cells is the bioavailability and complexity of designing both

Table 3. *Comparative Analysis — CAR-T vs Nanoparticles*

Feature	CAR-T Cells	Nanoparticles
Mechanism	Engineered T cells recognize tumor-specific antigens	Targeted delivery via passive, active, or stimulus-triggered release
Clinical Stage in CRC	Phase I trials are ongoing	Mostly preclinical with some Phase I
Tumor Penetration	Limited in solid tumors due to TME	Excellent (<200 nm size facilitates infiltration)
Administration	Intravenous (often autologous)	Intravenous or oral
Immune Modulation	Immune-enhancing	Often immune-neutral or modulating (e.g., via siRNA or immune ligands)
Toxicity	CRS, ICANS, cytopenias	Fatigue, GI toxicity, cytotoxicity (drug-dependent)
Engineering Source	Patient-derived immune cells (customized)	Synthesized externally (scalable)
Use Cases	Systemic immune attack on tumors	Targeted drug delivery, imaging, and radiosensitization

therapies. CAR-T cells are time-consuming and difficult to engineer and distribute, as they are personalized for each person due to their utilization of an individual's T cells. However, nanoparticles are much more available and easier to implement, and they are not personalized for each patient. This also connects back to an earlier point of how the administration of nanoparticles can be done through many different methods, as they are not restricted to certain administration processes that CAR-T cells are subject to. It is also crucial to mention that although nanoparticles are a more readily available treatment, many trials that have been conducted or that are being conducted are currently in the pre-clinical study stage, which is mentioned further in Table 3 below. This contrasts with CAR-T cell therapy, as many trials are in the clinical trial stage, making CAR-T cells much more developed and easier to implement as of now. Additionally, both therapies are in different stages of implementation and testing. CAR-T cells are mainly in phase 1 trials as of now, while most nanoparticle studies are preclinical, as they are a relatively new treatment.

Nanoparticles and CAR-T cells also show many differences and similarities in translational barriers, as shown in Table 3. CAR-T cell therapy is more developed than nanoparticle therapy, even though both therapies are still in Phase 1 and preclinical trials. The process and mechanistic abilities of nanoparticles allow them to be produced non-specifically, unlike CAR-T cells. This improves the scalability of nanoparticles, especially when looking into future production. When analyzing immune response, CAR-T cells have a better potential for immune clearance as they use T-cells from an individual's own body to prevent adverse effects. The passive delivery of nanoparticles allows them to rely more directly on the EPR effect than CAR-T cells, which are commonly delivered directly or through intravenous injection.

Many of the studies and trials have cited that using multiple different models (in vivo and in vitro) and using different formulations of treatments can allow for a better idea of adjustments and issues with the therapeutic tool. For CAR-T cells specifically, allogeneic methods of deriving T cells and targeting multiple antigens have been mentioned by studies to be beneficial tools and areas for improvement to refine these treatments. When examining nanoparticles, studies have explained how utilizing higher radiosensitizing chemotherapy in conjunction with nanoparticles based on NIR light can improve the biocompatibility of nanoparticle structures when introduced to the body, thereby preventing adverse effects and increasing efficiency when implemented.

CONCLUSION

As technology advances, the pathways towards improving different therapeutic agents and tools, such as the ones mentioned above, have become easier to accomplish. CAR-T cells and nanoparticles have proven to be a promising therapy for CRC due to their ability to target tumors and deliver drugs. This is highlighted by the promising conclusions made by Phase 1 trials, preclinical trials, in vivo models, and in vitro models. CAR-T cells and nanoparticles lack enough evidence and resources to truly demonstrate clinical efficacy at this moment. This is especially pertinent for research regarding CAR-T cells in CRC, specifically as many trials currently investigate CAR-T cells in conditions such as using CAR-T cell therapy and allogeneic stem-cell transplant to treat lymphoblastic leukemia (29) or *CD19* targeted CAR-T cells to treat non-Hodgkin lymphoma (30). it is also crucial that further tests and studies are carried out to improve the efficiency of CAR-T cells and nanoparticles. This is important to further the development of both therapies, but also to normalize their usage as a sole treatment option, instead of them being combined with other treatments as they usually are. Specifically, it is necessary to improve the readiness and availability of CAR-T cells while ensuring that both therapies are still efficient and provide targeted approaches. Looking at this, nanoparticles seem to have a much wider range of adaptability and a more promising manufacturing rate. This would benefit the clinical applicability of nanoparticles.

As the challenges present in lymph node detection, tumor antigen specificity, tumor targeting, and persistence are addressed, future outlooks in the increased use of CAR-T cells and nanoparticles as supportive treatments or multi-targeting treatments will allow CAR-T cells and nanoparticles to become staple cancer therapies.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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