REVIEW PAPER

Cetuximab antibody and fragment-engineered nanoplatforms in targeted cancer therapy and diagnosis

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ABSTRACT

Background: Nanotechnology serves as a promising platform in modern cancer therapy, enabling targeted drug delivery, improved bioavailability, and multifunctional treatment approaches. There are numerous molecular targets implicated in the progression of several malignancies, among which epidermal growth factor receptor (EGFR) has been pivotal role. Cetuximab is a monoclonal antibody for EGFR inhibition has demonstrated clinical benefits; however, its therapeutic impact remains constrained by tumor penetration of targeted city, and resistance development.

Objective(s): This review summarizes recent progress in cetuximab-based nanoplatforms for cancer diagnosis and therapy, highlighting their mechanisms, therapeutic performance and strategies to overcome resistance.

Materials and Methods: Relevant studies were searched from credible databases (Google Scholar, PubMed, Science Direct, Cochrane Library,…) and analyzed to evaluate the design and biomedical applications of cetuximab-conjugated nanocarriers, including polymeric nanoparticles, liposomes, mesoporous silica nanoparticles, gold and iron oxide nanoparticles, dendrimers, and DNA-based nanostructures. Antibody fragment-based systems such as Fab and scFv were also considered.

Results: Cetuximab functionalized nanoparticles enhanced tumor targeting, improved cellular uptake, and increased cytotoxicity compared with free drug formulations. Many systems demonstrated reduced off-target toxicity and improved pharmacokinetics. Multifunctional nanoplatforms integrating chemotherapy, gene silencing, phototherapy or imaging agents showed promising therapeutic potential. Antibody fragment-modified carriers further improved tumor penetration and targeting specificity. Several studies reported effective inhibition of tumor growth and partial reversal of multidrug resistance in preclinical models.

Conclusion: Cetuximab based nanoplatforms represent a promising approach for enhancing EGFR-targeted cancer therapy. Continued optimization, standardized safety assessment, and clinical validation are required to turn these systems into clinical oncology practice.

Keywords: *Cetuximab; ErbB receptors; Nanoparticles; Drug delivery systems; Neoplasms*

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GRAPHICAL ABSTRACT

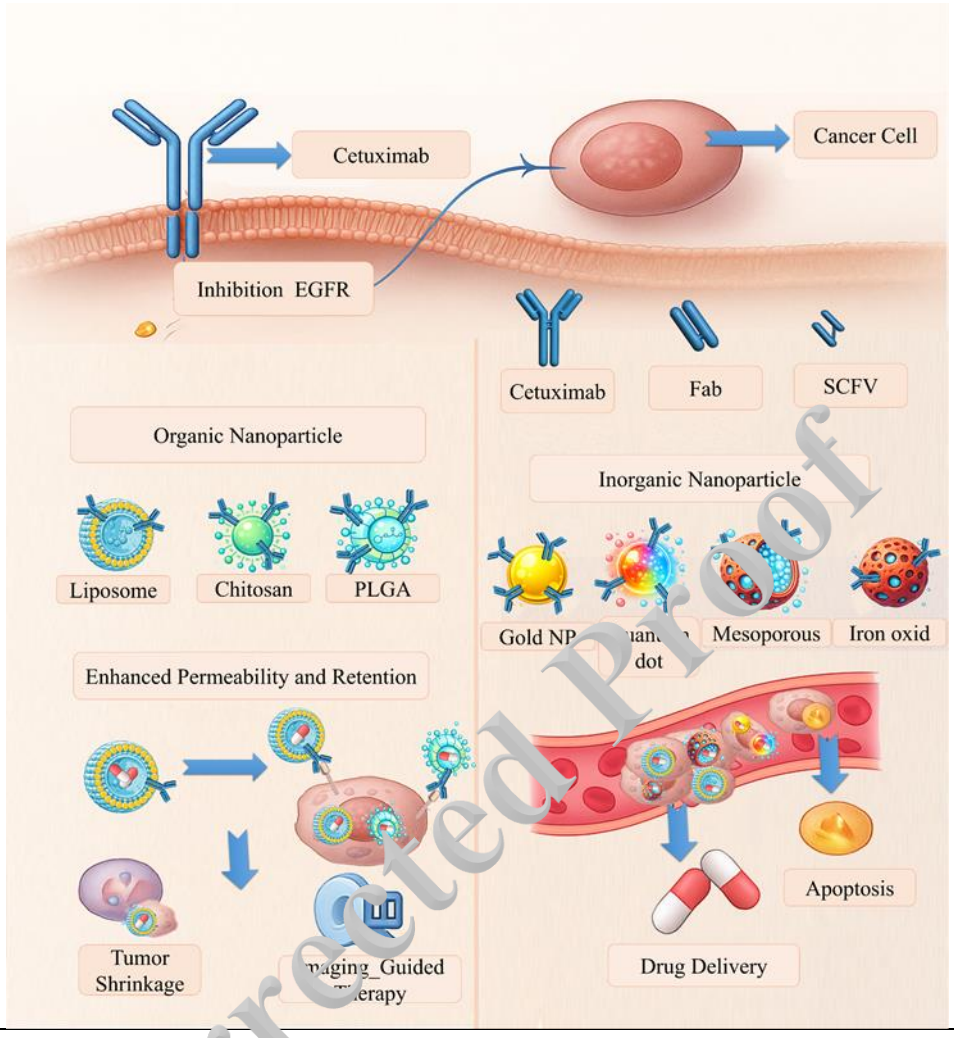

Fig. 1. Schematic view of the targeting mechanism of EGFR-expressing cancer cells by cetuximab-based nanoparticles

INTRODUCTION

Despite extensive research efforts devoted to cancer diagnosis and treatment, it remains most significant challenges in medical science. This highlights the urgent need for effective treatment strategies and accurate diagnostic tools to improve patient outcomes[1]. Although considerable advances have been achieved in surgery, chemotherapy, and radiotherapy, a definitive cure for cancer has yet to be achieved [2]. Chemotherapy, one of the most widely used treatments, is frequently associated with serious side effects such as drug resistance and bone marrow suppression [۳], mainly due to rapid drug clearance, inadequate drug accumulation at the tumor site, and systemic toxicity [4]. To overcome these challenges, targeted therapeutic strategies have been developed to enhance efficacy and reduce systemic toxicity.

The development of cancer therapies with high specificity and low toxicity remains a major challenge in pharmaceutical and oncology research, requiring further investigation. Antibodies, which have high specificity, are widely used in targeted cancer therapy and molecular imaging. Produced by the immune system in response to foreign antigens, they are classified into five types and consist of two main regions: FAB and FC. In antibodies, the initial recognition of the target is carried out by the Fab part. Monoclonal antibodies (mAbs) are structurally Y-shaped glycoproteins composed of two heavy chains and two light chains, and they constitute more than 30% of the recombinant drugs currently in clinical use and have a special place in terms of therapeutic value for the treatment of solid and hematological cancers. By specifically binding to tumor-associated antigens, these mAbs can increase the accuracy and improve the efficacy of chemotherapy and radiotherapy in these cancers

[5-8]. Despite all the progress in the clinical success of antibody-drug combinations, there are still limitations, such as high production costs and poor penetration into solid tumors, in the way of using these compounds. Among the approaches proposed to partially overcome these problems today are the use of smaller and more versatile antibody formats such as antigen-binding fragments (Fab), single-chain variable fragments (scFv), and heavy-chain-only antibodies (HcAb), which can be used as promising alternatives for improved therapeutic targeting and delivery [9].

With advances in cell chemistry and genomics, new methods are being designed that reduce off-target effects and minimize toxicity. These modern targeted therapies are increasingly designed to affect specific molecular targets that are overexpressed in cancer cells [10]. One of these targets is the epidermal growth factor receptor (EGFR), which is frequently dysregulated in various malignancies. To address this problem, monoclonal antibodies have been designed and engineered to target EGFR and induce tumor regression, including the chimeric monoclonal antibody cetuximab (CTX), which binds to EGFR with high affinity, blocking ligand interaction and downstream signaling [11]. This mechanism inhibits receptor dimerization, phosphorylation, and signal transduction, ultimately leading to suppression of cancer cell proliferation and metastasis.

On the other hand, cetuximab enhances the apoptotic pathway using modulating key regulators such as Bcl2 and Bax [12-14]. This drug has shown remarkable clinical efficacy in the treatment of various cancers, including head and neck squamous cell carcinoma (HNSCC) and metastatic colorectal cancer (CRC) [15]. This review focuses on the application of cetuximab and its derivatives in nanotechnology-based cancer diagnosis and therapy, highlighting recent advances, current challenges, and future prospects with the aim of increasing the effectiveness of antibody- based targeted therapies in oncology.

MATERIALS AND METHODS

A comprehensive search of literature was conducted in major credible databases, including PubMed, Scopus, Web of Science, ScienceDirect, Google Scholar, and the Cochrane Library. Studies were retrieved using combinations of the following keywords: “cetuximab”, “EGFR-targeted therapy”, “nanoparticles”, “nanocarriers”, “drug delivery”, “antibody fragments”, “Fab”, “scFv”, “polymeric nanoparticles”, “liposomes”, “mesoporous silica nanoparticles”, “gold nanoparticles”, “iron oxide nanoparticles”, “dendrimers”, and “DNA nanostructures”.Articles were screened based on relevance to the design, functionalization, and biomedical applications of cetuximab-conjugated nanocarriers in cancer diagnosis and therapy. Both experimental (in vitro and in vivo) studies and relevant clinical investigations were included. Original articles were primarily used to support background information. Studies not directly related to cetuximab-based nanosystems, non-English publications, conference abstracts without full text, and duplicate records were excluded. The retrieved articles were critically analyzed to evaluate nanoparticle design strategies, targeting efficiency, therapeutic outcomes, imaging capabilities, and translational potential.

Cetuximab: structure and mechanism of action

As previously mentioned, cetuximab is a chimeric monoclonal antibody of the IgG1 class, like other members of this antibody class, is composed of four polypeptide chains, including two heavy chains (approximately 449 amino acids) and two light chains (approximately 214 amino acids). These chains are held together by covalent disulfide bonds and non-covalent interactions, creating two antigen-binding fragments (Fab) and one crystallizable fragment (Fc) [16]. Each Fab fragment is composed of both constant domains (CH1 and CL) and variable domains of the heavy (VH) and light (VL) chains. The VH and VL domains together form the Fv region, which contains three complementarity-determining regions (CDRs). These CDRs are responsible for recognizing and specifically binding to the extracellular domain of the epidermal growth factor receptor (EGFR). The Fc fragment, comprising CH_2 and CH_3 domains of the heavy chains, mediates immune effector mechanisms including antibody-dependent cellular cytotoxicity. CTX exhibits high affinity to EGFR and thereby blocking ligand binding, receptor dimerization, and phosphorylation, which consequently affects downstream signaling pathways, receptor internalization and degradation, reduces cancer cell proliferation, and enhances apoptotic responses [16, 17] .By binding with high affinity to the EGFR, CTX thereby prevents the interaction of natural ligands such as EGF; this inhibition blocks EGFR dimerization and disrupts downstream signaling pathways that increase cancer cell proliferation, survival, and metastasis, which is one of the key therapeutic mechanisms of CTX.

CTX interferes with ligand binding and receptor activation, effectively blocking essential growth signals in malignant cells. [11, 16]. In addition to directly inhibiting the receptor, CTX engages the

immune system through its Fc region, stimulating antibody-dependent cellular cytotoxicity by natural killer cells [7, 8]. By inducing receptor endocytosis and lysosomal degradation, cetuximab reduces EGFR surface expression and attenuates oncogenic pathways [17]. Together, these mechanisms contribute to the therapeutic effects of CTX, contributing to its efficacy in reducing tumor growth, enhancing apoptosis, and suppressing metastasis in EGFR-expressing cancers [12, 14, 18].

Role of Cetuximab in Cancer Treatment

Colorectal cancer (CRC) is a significant global health issue, ranking as the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths[19].

In patients with metastatic CRC with high expression EGFR and wild-type *RAS* gene, CTX has been approved as a first-line treatment for patients as monotherapy and sometimes in combination with chemotherapy. Several clinical trials have confirmed the therapeutic efficacy of cetuximab; notably, the *FIRE-3* trial demonstrated that CTX-based treatments significantly improved overall survival in patients with wild-type *KRAS* and *NRAS* compared to alternative therapies. Early tumor shrinkage has been shown is associated with favorable outcomes in metastatic colorectal cancer patients receiving CTX combined with chemotherapy. Evidence from pooled analyses of the CRYSTAL and OPUS trials confirms that incorporating CTX into first-line therapy significantly enhances clinical efficacy in patients with wild-type KRAS [20, 21]. CTX has gained clinical approval for CRC and SCCHN, where EGFR is overexpressed in more than 90% of SCCHN cases [22]. It has demonstrated both safety and efficacy as a monotherapy in patients with unresectable SCCHN who are refractory to chemotherapy, thus supporting further assessment in larger clinical trials [23]. Non-small cell lung cancer (NSCLC) represents the third major cancer type investigated for CTX, after colorectal and head and neck cancers. Phase II and III clinical trials have evaluated CTX in EGFR-expressing NSCLC, mainly in combination with chemotherapy or radiotherapy [24, 25]. Despite these considerable advances, CTX-based treatment remains limited by a major challenge. The most critical challenge in clinical practice is the development of primary or acquired resistance to CTX. Resistance to CTX arises through multiple mechanisms, including the activation of compensatory signaling pathways that bypass EGFR inhibition, as well as the occurrence of mutations in downstream effectors such as *KRAS*, *NRAS*, and *BRAF* [3, 4]. Furthermore, CTX administration is associated with multiple adverse effects. Hypomagnesemia, infusion-related reactions, and acneiform rash represent the most frequently encountered toxicities [3]. These adverse side effects may undermine treatment adherence and negatively impact patient quality of life, highlighting the necessity of ongoing efforts to identify predictive biomarkers and develop refined therapeutic strategies to overcome toxicity and resistance.

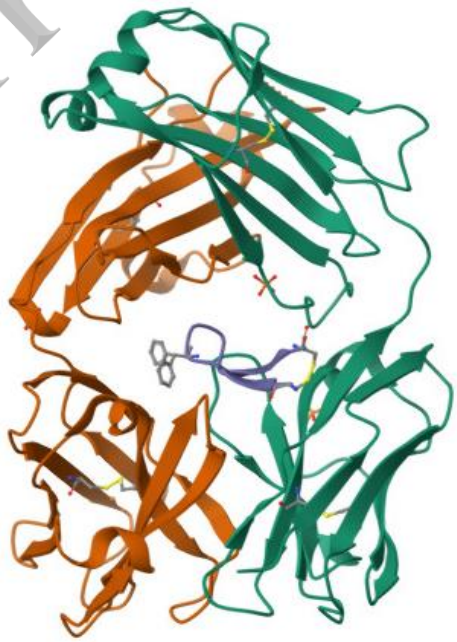

Fig. 2. cetuximab 3D structure
Cetuximab Fab in complex with CQFDA(Ph)2STRRLKC. Mus musculus, Homo sapiens, synthetic construct.
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Nanoparticles and their application in targeting

The development of highly selective anticancer therapies that combine minimal toxicity with favorable pharmacokinetic properties continues to represent a major challenge in pharmaceutical sciences. Nanoparticles (NPs), whether inorganic (e.g., gold, silica, iron oxide) or organic (e.g., liposomes, polymeric NPs, dendrimers), provide a versatile platform for therapeutic innovation. Their tunable size, shape, surface chemistry, and physicochemical stability enable them to overcome many of the intrinsic limitations of conventional therapies [26-30]. The large surface-area-to-volume ratio of nanoparticles facilitates efficient drug loading, sustained release, and site-specific delivery. This mechanism is accomplished through passive targeting (via the enhanced permeability and retention [EPR] effect) and active targeting through ligand-receptor interactions. [7, 31-36].

Functionalization of NP surfaces with chemical groups (e.g., $–NH_2$, –COOH, –SH) or polyethylene glycol (PEG) enhances biocompatibility, increases biocompatibility, reduces clearance by the reticuloendothelial system, and improves systemic circulation, thereby reducing particle aggregation.[27, 37, 38]. By enabling receptor-mediated internalization, active targeting increases drug concentration in tumor cells intracellular while reducing off-target effects [39]. In the development of antibody-nanoparticle conjugates (Ab–NPs), it is crucial to maintain the structural integrity of the nanoparticles while maintaining antibody binding activity, especially in the Fab region, as noted by Mittelheisser et al. while antibody conjugation significantly improves tumor targeting, the NPs size and composition predominantly govern in vivo bio-distribution and systemic animal-life [26].

Modern nanoplatforms function as versatile carriers for the delivery and transport of small molecules, peptides, nucleic acids, and proteins, and serve both preclinical and clinical applications, protecting these molecules from enzymatic degradation and environmental instability [40]. On the other hand, in tumor tissues, due to the presence of abnormal vessels and impaired lymphatic drainage, the retention of nanoparticles is facilitated, and this action leads to increased local drug delivery at the tumor site and reduced systemic toxicity [40, 41]. Despite significant advances in targeted nanoparticle-based therapies to date, the clinical application of these therapies still faces major obstacles, including immunogenicity, tumor vascular heterogeneity, resistance mechanisms, and long-term safety concerns [42, 43].

Cetuximab-based nanocarriers for targeted therapy

Among the promising strategies that are currently being used to increase the accuracy and effectiveness of cancer treatment, including for tumors with EGFR overexpression, is the use of CTX-conjugated nanoparticles. In this strategy, by using the specific properties of nanoparticles, the delivery of pharmaceutical and therapeutic agents to the target cell is increased while off-target effects are significantly reduced. Due to these factors, the accumulation of the drug in the target cell is increased, and at the same time, it is possible to use lower doses of the desired drug, which naturally reduces the side effects of common chemotherapy drugs (ref). Today, achieving full optimization of the clinical potential of these nanoplatforms has received much attention. There are two key areas in this direction: investigating the tumor targeting performance of these nanoplatforms both in vitro and in vivo; and designing and engineering CTX-derived fragments, particularly scFv and Fab, to enhance tumor penetration and drug delivery accuracy.

Tumor Targeting with Cetuximab-Conjugated Nanoparticles

Targeted drug delivery systems based on chitosan have been extensively investigated [44-46]. Chitosan is well-known to be biodegradable, biocompatible, comparatively low-cost, easily chemically altered, and to possess natural hydrophilic properties that enable its injection and mucoadhesive properties [47-49] .

In this comparative study, cetuximab-conjugated modified citrus pectinate–chitosan nanoparticles (Cet-MCPCNPs) encapsulating curcumin were evaluated against their non-conjugated equivalents (MCPCNPs) to assess targeted efficacy in EGFR-overexpressing cancer cells. The conjugation slightly increased the zeta potential but did not affect drug encapsulation efficiency or mucoadhesiveness. When compared to non-targeted formulations, Cet-MCPCNPs demonstrated superior cytotoxic and pro-apoptotic effects in Caco-2 cells and minimal activity in HCT-116 cells, indicating target-specific action. The enhanced therapeutic result was attributed to increased cellular uptake enabled by cetuximab-mediated active targeting. Cet-MCPCNPs also showed promise as an effective EGFR-targeted delivery system, as a higher proportion of Caco-2 cells were arrested in the G2 phase after treatment [50] .

In another study, Mayaa and Lekshmi G developed a targeted drug delivery system that delivered paclitaxel (PTXL) to cancer cells that overexpress EGFR using O-carboxymethyl chitosan (O-CMC) nanoparticles conjugated with cetuximab. The nanocarriers exhibited favorable characteristics, including a mean particle size of 180 ± 35 nm and an encapsulation efficiency of 75 ± 4%. The pH-dependent release of PTXL persisted for ten days. The safety of the nanoparticles for systemic administration was validated by hemocompatibility tests. Studies on cellular uptake backed by flow cytometry and fluorescence microscopy revealed that internalization took place via receptor-mediated endocytosis. Crucially, in comparison to non-targeted formulations, cetuximab-conjugated nanoparticles showed reduced IC_{50} values and increased cytotoxicity in EGFR-positive cell lines (A549, A431, and SKBR3) [51].

Fluorescent nanodiamonds (NDs) with nitrogen-vacancy (NV) centers have emerged as highly promising tools in biotechnology and nanomedicine due to their exceptional optical properties, low cytotoxicity, and biocompatibility. Their intrinsic fluorescence and nanoscale resolution make them great choices for biosensing and targeted drug delivery. To improve therapeutic specificity, NDs have recently been functionalized with anticancer drugs and targeting ligands like cetuximab and cisplatin. In order to confirm surface modification, one such nanoconjugate system showed efficient loading of both agents, increasing particle size from 110 nm to 263 nm and slightly shifting the zeta potential. FTIR analysis confirmed the cetuximab-ND interaction. The CCK-8 assay results showed that these nanoconjugates increased the cytotoxicity of HepG2 liver cancer cells by 40% compared to non-targeted controls. 3D Raman imaging showed that cetuximab-modified nanoparticles performed better in entering cells, further confirming their enhanced cellular uptake and specificity. The potential utility of ND-based conjugates as a dual platform for EGFR-overexpressing cancer imaging and treatment is indicated by all of these findings [52]. Albumin nanoparticles represent a versatile and biocompatible platform for targeted drug delivery, especially for EGFR-overexpressing tumors, due to their desirable physicochemical properties and ability to reduce systematic toxicity. Albumin, the most abundant plasma protein with a molecular weight of 66.5 kDa, is stable in pH 4–9, soluble in 40% ethanol, and can be heated at 60°C for 10 hours without loss of stability [53]. Its characteristics, such as preferential accumulation in tumors, biodegradability, lack of toxicity, and low immunogenicity, make it an ideal candidate for drug delivery [54]. Albumin nanoparticles have been used as carriers for conjugation with monoclonal antibodies due to their unique properties. For example, in a study, researchers designed and synthesized a novel drug delivery platform by conjugating anti-CD19 monoclonal antibody to human serum albumin nanoparticles, showing a strong antiproliferative effect on KOPN-8 cells [55]. In a recent study, bovine serum albumin (BSA) nanoparticles were used to co-deliver cetuximab and valine-citrulline-linked doxorubicin (vc-DOX) as a targeted treatment for tumors that overexpress EGFR. Mass spectrometry and ^{1}H-NMR structural validation verified that the conjugates were successfully synthesized. In comparison to non-targeted controls, cetuximab-functionalized nanoparticles demonstrated noticeably higher cytotoxicity in EGFR-positive RKO and LS174T cell lines. Cetuximab-vc-DOX-Cy7-BSA nanoparticles were shown to accumulate preferentially in tumors in in vivo biodistribution studies, confirming receptor-mediated targeting. Additionally, the targeted formulation outperformed free doxorubicin in RKO xenograft mouse models in terms of tumor inhibition, systemic toxicity, and survival outcomes. These findings highlight cetuximab-vc-DOX BSA nanoparticles' therapeutic potential as a safer and more efficient substitute for EGFR-targeted cancer therapy [56].

Because of their high surface area, chemical versatility, and adjustable porosity, mesoporous silica nanoparticles (MSNs) have demonstrated great promise as platforms for biomedical applications. Effective loading of therapeutic agents and imaging probes is made possible by their biocompatible structure. Antibody-conjugated MSNs for targeted delivery, such as abciximab-functionalized MSNs, are one recent advancement that has shown enhanced antithrombotic efficacy in vitro [57-59]. Similarly, Mesoporous SiO_2 nanoparticles functionalized with cetuximab were created in order to deliver doxorubicin and gefitinib in a way that is EGFR-targeted and GSH-responsive. These nanoparticles spared EGFR-low cells while selectively releasing their payload in EGFR-high cancer cells through intracellular disulfide bond cleavage. Gefitinib-loaded CET-capped NPs showed promise in overcoming resistance through targeted nanotherapy by efficiently inhibiting tumor growth in TKI-resistant models in vivo without causing systemic toxicity [60].

In a related study, cetuximab-conjugated MSNs loaded with 5-fluorouracil were evaluated against colorectal cancer both in vitro and in vivo. In addition to enhancing cytotoxicity, tumor targeting,

apoptosis, and cell cycle arrest, this nanoconjugate successfully reduced cancer cell migration and metastasis [61].

Another investigation involved cetuximab-conjugated MSNs loaded with siRNA targeting polo-like kinase 1 (PLK1), a mitotic regulator overexpressed in lung cancer. This nanoconjugate efficiently targeted non-small cell lung cancer (NSCLC) cells, silenced PLK1 expression, and caused mitotic arrest at the G2/M phase. In an orthotopic lung tumor model, treatment led to reduced tumor growth and extended survival [62].

Gold nanoparticles possess important criteria such as chemical stability, broad working potential range, high surface area to volume ratio, catalytic activity, and excellent biological compatibility. As a result, they have become very attractive for tumor targeting [63]. Recent studies have demonstrated that drugs conjugated with AuNPs are used for cancer treatment; for example, folate-conjugated and doxorubicin-loaded polymeric gold nanoparticles (GNPs) have been developed for the targeted treatment of folate receptor-overexpressing breast cancers [64] .

According to recent research, cetuximab and gold nanoparticles increase their capacity to eradicate cancer cells that overexpress EGFR. Better cellular uptake and EGFR degradation are the sources of this synergy. While EpCAM essentially stays the same, the treatment also reduces MCAM and HER3 levels [٦٥] . Gemcitabine-loaded gold nanoparticles conjugated with cetuximab efficiently targeted pancreatic cancer cell lines that overexpress EGFR (PANC-1, AsPC-1 and MIA PaCa-2), preventing cell division. Compared to controls, these targeted nanoconjugates in vivo decreased tumor growth in mice by roughly 80% [66].

Poly(lactic-co-glycolic) acid (PLGA), a biodegradable copolymer that has FDA approval, is frequently employed as an effective nanocarrier in clinical drug delivery applications. In a targeted drug delivery study, magnetic iron oxide nanoparticles were added to PLGA carriers with CPT-11 to dual target EGFR-positive glioma cells, and then surface-modified with cetuximab. The final nanoparticles demonstrated a moderate level of encapsulation efficiency (33.5%) and drug loading (22.1%). In U87 cells, fluorescence imaging verified specific EGFR binding, and cytotoxicity tests demonstrated that encapsulated CPT-11 was more effective than its free form at killing cells. Hemolysis and fibroblast assays confirmed the biocompatibility, showing low toxicity. Site-specific delivery and cytotoxicity were further improved in vitro by the use of a magnetic field. The combination of ligand-mediated and magnetically guided targeting strategies proved effective, as evidenced by the highest tumor suppression observed in orthotopic glioma models treated with cetuximab-conjugated magnetic nanoparticles under magnetic guidance in vivo [67].

Cetuximab-conjugated iron oxide nanoparticles (~19 nm, -21.5 mV) were created by researchers to target glioblastoma cells and perform MRI imaging. In EGFR-amplified GBM neurospheres, these nanoparticles exhibited increased uptake, decreased cell viability, and induced apoptosis. In three rodent GBM models with human EGFR-expressing tumors, cetuximab-IONPs improved survival over free cetuximab and IONPs alone [68].

In another study, silica- and dye-coated iron oxide nanoparticles (MFSN) were conjugated with cetuximab for colon cancer imaging. In vitro and in vivo tests showed enhanced tumor targeting and improved MRI signals in xenograft mice [69]. Early research revealed that heating tumors to 40–43 °C for an hour can harm cancer cells and make them more vulnerable to radiation and chemotherapy [70]. The use of temperature-triggered nanocarrier systems for regulated drug release has been extensively researched. In particular, liposomes are frequently utilized in cancer treatment and other medical conditions [71]. Although liposomes are FDA-approved to treat cancer and reduce toxicity, their protective shell may prevent drugs from releasing at tumors. This problem was addressed with the development of temperature-sensitive liposomes (TSLs) [72]. Magnetic nanoparticles encapsulated in liposomes, known as magnetic liposomes, have shown potential for drug delivery, cancer treatment, and imaging [73]. In a recent study, doxorubicin-loaded citric acid-coated iron oxide nanoparticles were encapsulated in thermosensitive liposomes and coated with cetuximab to target breast cancer cells that express EGFR. When used in conjunction with near-infrared laser phototherapy, these 120 nm nanoparticles decreased the viability of cancer cells. Treatment improved the therapeutic effects in mice by increasing tumor temperatures [74]. In a 2019 study, J. Scott et al. loaded polymeric nanoparticles (~200 nm). The CTX-conjugated NPs showed improved binding, improved CPT delivery, and robust cell cycle arrest and apoptosis via elevated caspase-3/7 activity. In an in vivo PANC-1 xenograft model, they markedly reduced tumor growth in comparison to non-targeted formulations [75].

Fluorescently labeled antibodies are widely used in biological and biomedical studies. These fluorescent antibodies have been used in the medical field, especially in diagnostic imaging and flow cytometry, for cancer cells [76, 77]. In a recent

study, biotinylated cetuximab was linked to bright zwitterionic nanoparticles via streptavidin, enhancing fluorescence imaging of EGFR-expressing cells. The system effectively distinguished cells based on EGFR expression levels [78].

Ag_2S near-infrared quantum dots (NIR QDs) offer deep tissue imaging and good biocompatibility. In 2016, researchers conjugated them with cetuximab to deliver ALA or 5-FU. The nanocarrier showed strong EGFR targeting, enhanced uptake, and increased cytotoxicity in target cells [79, 80] .

Dendrimers are widely studied molecules used in biomedicine, especially as carriers of anticancer drugs. PAMAM dendrimers, in particular, are well-characterized and commercially available [81]. A recent study used a DTPA-CHX chelator to link cetuximab to PAMAM G4 and label it with ^{177}Lu. The survival rate of SW480 colon cancer cells was considerably decreased by the 70 nm nanoconjugates. Tumor targeting was validated by biodistribution, indicating great promise for cancer treatment in the future [82].

Polymersomes, more stable than liposomes, were combined with cetuximab by Sun et al. for targeted EGFR-positive cancer therapy. The nanoconjugate reduced IC50 and enhanced cytotoxicity in breast, liver, and lung cancer cells. In mice, it suppressed both breast and lung tumor growth after IV injection [83, 84].

PLGA-PEG nanoparticles with FDA approval are frequently used for co-delivery. Combining them with cetuximab to administer 2-methoxyestradiol and combretastatin A4 inhibited metastatic liver tumors and extended the duration of drug circulation in one study. Additionally, the nanoconjugate inhibited PRC1, a protein associated with lung cancer. Another study found that using PLGA-docetaxel nanoparticles against NSCLC cell lines led to increased uptake, decreased IC50, induction of G2/M arrest, and promotion of apoptosis, all of which decreased tumor growth and enhanced mouse survival [85-87].

In 2022, cetuximab-linked nanoliposomes were used to deliver siRNA to drug-resistant breast cancer. By stabilizing PEG, employing TAT for uptake, and eliminating PEG that is sensitive to MMP, the system improved siRNA delivery, reduced IC50 fourfold and inhibited resistance-related proteins [88].

Nanoplatforms using Cetuximab scFv and Fab fragments

EGFR is a member of the receptor tyrosine kinase family and is crucial for the development of many types of cancer, such as colorectal cancer (CRC), head and neck squamous cell carcinoma (HNSCC), and breast cancer [89-91]. Cetuximab, a monoclonal antibody targeting EGFR, is clinically approved for metastatic colorectal cancer and small cell squamous cell carcinoma (SCCHN). To improve tumor penetration and reduce off-target toxicity, antibody derivatives, such as Fab and single-chain variable fragments (scFvs), have been developed [92-95].

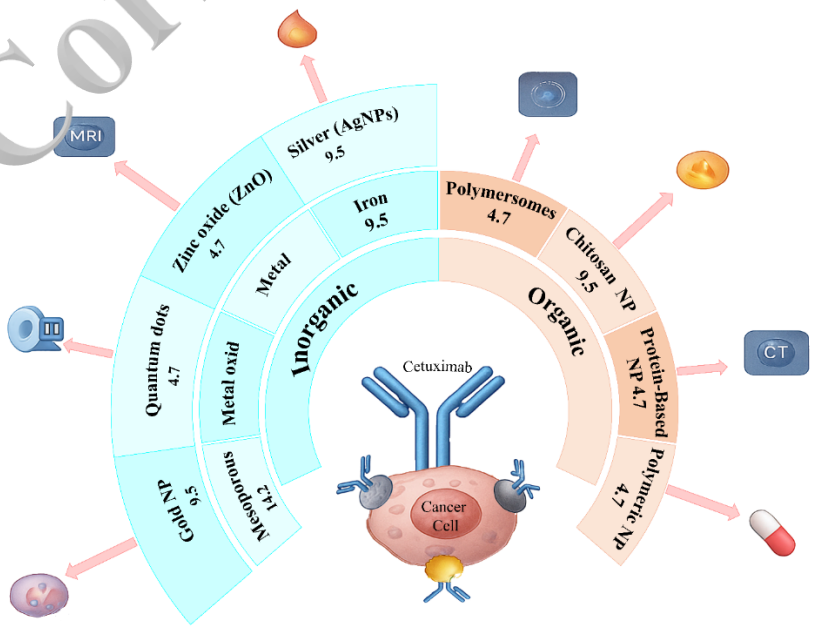

Fig. 3. Schematic view of cetuximab-based nanoparticles in cancer diagnosis and treatment

Recent studies have shown that scFv-functionalized nanocarriers can be useful for targeted drug delivery. Jalalvand et al. (2024) synthesized chitosan nanoparticles containing 5-fluorouracil (5-FU) and modified them with CTX-scFv fragments. Utilizing a fluidic system, the resultant nanoparticles (scFv-CS/5-FU NPs) exhibited regulated drug release, improved EGFR targeting, and markedly increased cytotoxicity, inducing apoptosis in approximately 98% of HCT-116 colorectal cancer cells, surpassing non-targeted formulations [44].

Falahzadeh et al. (2024) also made oxaliplatin-loaded chitosan NPs with CTX-scFv (scFv-OXPT-CS NPs) for CRC cells that have too much EGFR. Their formulation had a high encapsulation efficiency (about 93%), kept good nanoscale properties, and killed more than 99% of the HCT 116 cells that were treated [45].

Both studies underscore the effectiveness of cetuximab scFv fragments in enhancing the specificity, cellular uptake, and cytotoxic impact of nanoparticle-based cancer therapies. These findings support the continued development of antibody fragment-guided nanoplatforms as a promising direction in precision oncology. Figure 1 summarizes and categorizes nanoparticles targeted by cetuximab for use in cancer diagnosis and treatment.

In Vivo and in Vitro Imaging Assays

CTX is a monoclonal antibody of the IgG1 type that has a 100-fold higher affinity for EGFR than its natural ligand [96]. CTX is approved for the treatment of EGFR-positive head and neck squamous cell carcinoma (HNSCC) and metastatic colorectal cancer. The mechanism of action of this drug is to block the interaction between the receptor and the phosphorylation of the ligand, which leads to the inhibition of downstream EGFR signaling. [97-99]. Ultimately, inhibition of this pathway leads to the formation of the apoptosis pathway, G_0/G_1 cell cycle arrest, and suppression of tumor growth, invasion, and metastasis. In addition, the Fc region of CTX leads to the activation of effector immune pathways, including antibody-dependent cytotoxicity (ADCC), which in turn leads to the improvement and enhancement of the antitumor effects of cetuximab [100, 101] [102].

MRI is one of the important imaging techniques that is important in cancer. Despite the ability to image 3D soft tissue, this technique suffers from limitations such as low sensitivity. To overcome this problem, different methods have been used so far. For example, Tseng et al. (2015) used superparamagnetic iron oxide nanoparticles coated with dextran linked to CTX, called CTX-PEG-dex-SPIONs. The use of these agents increased MRI contrast due to their important theranostic properties. Laboratory studies of these researchers demonstrated that the use of this nanoplatform led to increased EGFR degradation and induced apoptosis in cancer cells that expressed EGFR [103].

In addition to the nanoparticles mentioned above, AgSe quantum dots conjugated to CTX have also been used in theranostic imaging, which has shown promising results. These AgSe-CTX nanoprobes released strong near-infrared (NIR) fluorescence signals that selectively accumulated at the tumor site after application to various tumors, including tongue cancer, in mouse models, and remained detectable for more than 24 hours after injection. The use of this nanoplatform led to the induction of apoptosis in EGFR-expressing cells, as well as a reduction in tumor burden, and ultimately, with all these changes, improved and increased survival of the organism [104].

Cetuximab-conjugated nanoplatforms in photherapy and combination therapies

One of the newest approaches to cancer treatment is immunophototherapy. In this method, photosensitizing antibody-conjugates, known as photoimmunoconjugates (PICs), are combined with NIR light (600-900 nm), thereby selectively eliminating and killing cancer cells. The mechanism of this treatment is that it stimulates the death pathway of tumor cells by producing reactive oxygen species (ROS), especially singlet oxygen [105-108]. Also in this strategy, photosensitizers emit fluorescence signals, which during fluorescence-guided surgery improves performance by allowing for real-time visualization and visualization of the tumor [109].

Today, EGFR is recognized as a key target in the treatment of various cancers, including head and neck and ovarian malignancies [110]. Many clinical trials are underway for EGFR-directed PICs such as CTX-IRDye700 and panitumumab-IRDye800 (NCT02422979, NCT0338423), and since CTX has been approved by the FDA to target EGFR, it has been used in many platforms, including benzoporphyrin derivative (BPD) PIC platforms that aim to stimulate more effective photodynamic tumor stimulation [111-115].

Striking a balance between efficient light absorption and specificity is one of the major challenges of PIT at present. To overcome this problem, researchers have used combination therapies, such as combining PIT with chemotherapy. However, efforts are ongoing and evolving to develop nanoplatforms that can

simultaneously deliver both targets. For example, a recent study using multifunctional nanoliposomes (PIC-Nal) that simultaneously encapsulated CTX, BPD, and irinotecan (Nal-IRI) bridged this gap. In ovarian cancer cells, the use of this platform has led to many benefits, including a 30% increase in photoimmunoconjugate uptake, downregulation of EGFR, and mitochondrial dysfunction, which ultimately led to DNA damage and significantly reduced cell survival [107]. In general, it can be said that combination therapies that simultaneously target multiple signaling pathways increase therapeutic potential compared to monotherapy while reducing toxicity.

Many preclinical studies have investigated CTX-based nanoconjugates in various types of cancer, using a variety of imaging tools to track their biodistribution and therapeutic effects. Although molecular imaging using EGFR-targeted contrast agents has made significant progress and has led to improve in tumor detection in vivo, it still faces several challenges such as selecting optimal biomarkers and achieving strong imaging signals, and more extensive research is needed in this area [80]. Table 1 lists studies using cetuximab-conjugated nanoparticles in phototherapy.

Table 1. Cetuximab-conjugated nanoparticles used in phototherapy

Date	Type of cancer	Nanoparticle type	Image assay technique	Animal/cell line	Result	Ref.
2021	Colorectal cancer	Ag2S quantum dots	NIR optical detection	HT29- HCT116-SW480 cell lines.	Excellent targeting of the high EGFR-expressing cells, A comparative study performed on cell lines with different EGFR expression levels showed a strong intracellular signal for NIR photodetection.	[80]
2010	colon cancer	magneto-fluorescent silica	MRI and confocal laser scanning microscopy (CLSM)	Colon cancer cells (HCT116, HT29, and SW620)/ nude male mice	Nanoconjugates caused significant changes in MRI signal in colon cancer xenograft mouse model compared to untreated control. enable noninvasive imaging and quantification of EGFR-expression *in vivo*	[69]
2018	Breast cancer	CuS NPs	fluorescence imaging	The mouse mammary tumor cell line 4T1 cells/ the human umbilical vein endothelial cells (HUVECs)	Fluorescent evaluation of mouse xenografts showed that the labeled nanoparticles accumulated around the tumor site compared to the control group, which proved the targeting well in this study.	[116]
2018	lung adenocarcinoma	Gold nanoparticle	Computed tomography	C57BL/6 mice and nude mice with A431	Dual-energy CT was used to visualize and quantify gold within the tumors. *In vivo*, Computed tomography in both mice demonstrates that the CTX-targeted group had significantly higher tumor accumulation than the control groups	[117]
2020	thyroid cancer	perfluoro hexane/gold	low-intensity focused ultrasound diagnosis imaging (LIFUS)	human anaplastic thyroid carcinoma line (C643)/ nude mice	Fluorescence intensity in mice xenografts tumors in nanoparticles targeted with CTX compared to nanoparticles without it was shown by fluorescence imaging technique, which confirms the increased specificity in tumor targeting.	[118]
2017	orthotopic tongue cancer	NIR fluorescent and low-biotoxicity Ag2Se	NIR fluorescence images	CAL-27 cells line/nude mice	The target tissue (tongue) was distinguishable from the surrounding tissues, indicating the enrichment of the labeled nanoprobes with CTX at the tumor site. The tumor-to-background ratios (TBRs) of the NIR fluorescence images were analyzed, and Ag2Se–CTX nanoprobes were significantly higher than the control group.	[104]
2018	glioma	iron-oxide	MRI	Dogs with glioma	For the follow-up of dogs treated with nanoparticles conjugated with CTX, MRI was used, and it was found that this intervention caused a 54.9% reduction in the tumor volume of the dogs.	[119]

Cetuximab-Based Nanoplatforms for Multitarget Therapy and Overcoming Drug Resistance

In addition to all the aforementioned properties of CTX-linked nanoparticles, this compound has shown promise in overcoming multidrug resistance (MDR) and as a multitargeted therapy for cancer, especially in refractory malignancies. In this regard, studies have been conducted to investigate CTX-based nanoplatforms in breast cancer, which is one of the leading causes of cancer-related mortality in women. Colombo et al. (2018) developed nanoconjugates that were synthesized by attaching CTX half-chain segments to colloidal nanoparticles. In vitro studies of these researchers on triple-negative breast cancer cell lines characterized by EGFR overexpression and genetic mutations such as KRAS, PTEN, and BRCA1 showed that this nanoplatform has great potential to increase therapeutic efficacy and reduce dosage [120] .

Further advances in this area include smart liposomes functionalized with CTX, TAT peptides, and MMP-sensitive substrates. This smart multifunctional design allows targeting of BCRP, an MDR-associated protein, by a single siRNA. In the design of this platform, CTX plays a role in enhancing targeting specificity, and TAT plays a role in cellular uptake and endogenous evasion, leading to effective gene silencing and thus reversing the multidrug resistance process [88]. In addition, another study in 2021 developed a CTX-HSA/DOX/MDR1 siRNA nanocomplex. This nanoplatform was optimized using a response surface approach and was shown in vitro studies conducted. This nanoplatform, which is a type of non-viral carrier, significantly reduced tumor growth and has a high potential to overcome MDR both in vivo and in vitro [121].

Another study conducted in 2023 used egg serum albumin nanoparticles to bind and deliver CTX to Caco-2 cells, and studies and experiments proved that these nanoplatforms improved drug delivery, reduced toxicity, and increased antitumor activity in these cells [122].

Finally, in another study, CTX-linked solid lipid nanoparticles (Cet-SLN/DOX) were designed and engineered to simultaneously deliver DOX in the treatment of liver cancer, which ranks sixth in global incidence and second in mortality. Studies have shown that these nanoparticles not only have high loading efficiency but also have stimulation-dependent release properties, so this strategy performs much better than single-drug therapy with free drug and antibody. These nanoparticles also increase the induction of cytotoxicity and, on the other hand, cause EGFR-specific synergy [123].

Emerging and novel applications of Cetuximab-based nanoplatforms

Enhancing Cetuximab delivery and efficacy via nanocapsules

In their efforts (2020), Yang and colleagues designed and developed a self-enhancing nanocapsule system that enhances drug delivery and increases the effectiveness of monoclonal antibody (tAbs)-based therapies in cancer treatment. The strategy of this nanoparticle is that by enhancing the permeability and retention (EPR) effect, nanoencapsulated cetuximab is allowed to cross the blood-brain barrier, thereby increasing and improving drug accumulation at the tumor site while preventing rapid elimination by the immune system. After the release of CTX loaded in the nanocomplex, this drug selects tumor-associated endothelial cells and causes increased tumor vascular destruction and increased EPR enhancement, which ultimately leads to increased drug levels at the tumor site. This nanoplatform showed much more significant tumor inhibition within three weeks compared to free CTX, demonstrating the potential of this nanoplatform as a powerful approach in the advancement of antibody-based cancer therapies. It highlighted the blind well [124].

Combination of nano-diamino-tetrac (NDAT) and Cetuximab inhibits cell proliferation

A recent study investigated the combined effects of nano-diaminotetracycline (NDAT) and CTX, focusing on their effects on CRC cell proliferation. A series of gene expression studies and cell proliferation assays demonstrated that thyroxine (T4) induced the expression of proliferative genes such as PCNA, Cyclin D1, and c-Myc in both HT-29 (wild-type K-ras) and HCT 116 (mutant K-ras) cells. However, the simultaneous use of NDAT and CTX resulted in an increased suppression of the expression of these genes. This is while the use of CTX alone did not show such suppressive power. In addition, the use of the combination of (NDAT) and CTX simultaneously increased the expression of pro-apoptotic genes (p53 and RRM2B), which were previously suppressed by T4. From all these findings, it can be concluded that the use of NDAT leads to an increase in the therapeutic effects and effectiveness of CTX, which is one of the important chemotherapy drugs for K-ras mutant colorectal cancer [125].

Cetuximab-conjugated fluorescent magnetic nanohybrids (CET-FMNHs)

Yang and colleagues developed a type of fluorescent magnetic nanohybrid conjugated with

CTX (CET-FMNHs). Their aim in this study was to use these nanoplatforms for dual imaging of tumors through magnetic resonance (MR) and fluorescence techniques. The structure of these nanohybrids is that $MnFe_2O_4$ nanocrystals are encapsulated in PCL-b-PMAA,Edited and pyrene is also used as a surfactant to stabilize these nanoparticles. The structure of these FMNs is spherical and has shown high colloidal stability and biocompatibility. The advantage of using the CET-FMNH nanoplatform is that it enables dual imaging of EGFR-positive cancer cells, highlighting their potential as diagnostic tools for epithelial tumors in the future [126].

Cetuximab and immunomagnetic albumin nanospheres

Among the new theranostic approaches that have been introduced today for the study of lung cancer is the use of albumin nanoparticles in which superparamagnetic iron oxide is encapsulated and engineered and modified with CTX (anti-EGFR) and gene cargoes. Finally, the resulting C225-IFNG-immunomagnetic albumin nanoplatform (C225-IFNG-IMANS) specifically targets GLC-82 lung cancer cells. To confirm the targeted delivery capability of these nanoplatforms, the Prussian blue immunofluorescence staining technique, TEM and MRI were used. The results of this study showed that this nanoplatform has high synergistic potential in gene therapy, molecular targeting and thermotherapy and can be introduced as a promising multifunctional platform for the treatment of lung cancer [127].

Combining alpha-cyano-4-hydroxycinnamic acid with Cetuximab using nanotechnology

A study presented by Ferreira unveiled a new nanoplatform that combines an alpha-cyano-4-hydroxycinnamic acid (CHC) with an anti-EGFR monoclonal antibody, CTX. These polymeric nanoparticles are synthesized by encapsulating CHC in poly(lactic-co-glycolic acid) (PLGA) and chitosan, which are ultimately attached to the CTX molecule. The encapsulation process leads to an increase in the therapeutic capacity of CHC, and on the other hand, conjugation with CTX leads to targeted cytotoxicity in U251 glioblastoma tumor cells. Confirmatory tests performed on this nanoplatform confirmed favorable physicochemical properties and significant therapeutic potential. All these studies showed that combination therapies using nanoparticles can be considered as promising interventions for aggressive GBM tumors [128].

Cetuximab-conjugated DNA biodots (DNA-BD)

DNA-based biodots (DNA-BDs) are emerging nanostructures that have fluorescent properties, and their main features include high biocompatibility, unique light absorption properties, and very high bioavailability. These nanoparticles can be synthesized under specific conditions, such as high temperature and pressure. In a study conducted by Jha et al., this nanoplatform was used for conjugation with CTX and the final compound was incorporated into etoposide-loaded theranostic liposomes (ETP). These nanoparticles were designed to target NSCLC. The resulting CTX-DNA-BD nanoplatform showed more favorable effects than non-targeted nanoparticles, such as increased tumor selectivity and increased drug delivery to target cells that overexpress the target. Comparison of targeted and non-targeted nanoparticles in vivo showed that the use of targeting nanoparticles leads to more favorable therapeutic outcomes, which can be said in this regard. CTX-DNA-BD liposomes represent a promising theranostic platform for precision lung cancer therapy [129].

PEG-4000 formed polymeric nanoparticles loaded with Cetuximab

In a recent study, Abdullatif and colleagues developed a PEG-4000-based polymeric nanoparticle (PEGNPs) loaded with CTX. In this study, the effect of these nanoparticles was investigated with emphasis on the anticancer effect on A549 (lung) and MCF-7 (breast) cancer cell lines. Molecular cell experiments and investigations conducted in this study confirmed the effect of these targeted nanoparticles on significant changes in the expression of cell cycle regulatory proteins and showed that the use of these nanoplatforms reduced the levels of p21 and stathmin-1. This is because CTX alone has fewer reducing effects. In addition, cells that received CTX-conjugated nanoplatforms were more likely to enter the apoptosis pathway and had a higher risk of DNA fragmentation, all of which indicate increased cytotoxicity in these cells after receiving the drug. Clearly, this study confirmed that the use of these nanoparticles resulted in improved targeting and more favorable outcomes than CTX monotherapy, and introduced PEG-4000-based platforms as a novel approach in cancer treatment [130].

COCLUSION

The development of cetuximab based nanoplatforms represents a significant and promising step toward improving the effectiveness of EGFR targeted cancer therapy. Although cetuximab has already demonstrated remarkable

clinical value in the treatment of colorectal cancer and head and neck squamous cell carcinoma, and other EGFR overexpressing malignancies, its therapeutic performance is still limited by drug resistance, systemic toxicity and suboptimal tumor penetration. The integration of nanotechnology with cetuximab has provided innovative solutions to many of these limitations by enhancing drug delivery, improving tumor-specific accumulation and reducing side effects. Various nanoparticle systems, including liposomes, polymeric nanoparticles, mesoporous silica nanoparticles, gold nanoparticles, iron oxide nanoparticles, dendrimers and DNA-based biodots have shown very good in vitro and in vivo results, particularly in increasing cytotoxicity against cancer cells, inducing apoptosis, overcoming multidrug resistance, and enabling advanced imaging capabilities. In addition, the use of cetuximab derived fragments such as scFv and Fab has further improved tumor penetration and targeting specificity that highlighting the importance of antibody engineering in nanomedicine. Despite these advances, several challenges remain, including tumor heterogeneity, long term biosafety concerns, large scale manufacturing and the need for standardized clinical evaluation.

Future perspectives

Today, nanoplatforms that are engineered and designed as conjugates with CTX are considered one of the promising tools for targeted cancer treatment and diagnosis, which have shown great promise especially in the field of tumors that have high EGFR expression. So far, encouraging and promising progress has been made in this field, but there are still underlying challenges in the use of these nanoplatforms that have limited their use of these nanoplatforms in clinical settings.

The main priority in using these nanoplatforms is to design and synthesize these nanoparticles in such a way that, optimizing the pharmacokinetics of the nanoparticles - blood circulation time, achieving controlled drug release and increasing tumor-specific accumulation. The use of multiple and multifunctional therapies, including combining therapy and imaging (theranostics), activating drug release in response to stimuli (e.g., by pH or temperature), and integrating real-time imaging, is a key strategy for their clinical application.

Among the problems in the process of cancer treatment are tumor heterogeneity and multidrug resistance, which have become the research goals of many scientists. Multiple targeting and gene silencing tools, such as siRNA or miRNA, and combination therapy are often designed to overcome the aforementioned problems. Strategies used in this field should improve the ability to escape the immune system, such as the use of processes such as PEGylation or cell membrane coating that stabilize nanoparticles and increase biodistribution in the treatment.

These strategies include dendrimers, DNA-based biodots, carbon nanostructures, and exosome-inspired carriers, which hold promise for the future expansion of these nanoplatforms. To increase the effectiveness and modify CTX-based therapies and reduce off-target effects of the drug, personalization of therapy based on tumor gene profile and EGFR mutation status was added to the treatment plan, which resulted in increased patient recovery and reduced drug side effects.

To advance in this field, future studies will require the use of standardized preclinical models for long-term safety assessments. The planning for monitoring in this regard should be in accordance with GMP principles, and all systematic clinical evaluation trials should be in place from start to finish. Considering the advances made in the field of biotechnology so far and the emergence of advanced technologies such as CRISPR gene editing, RNA, and AI-based drug discovery, it can be expected that in the future these technologies will be used to integrate with CTX-based nanoplatforms. This convergence of nanotechnology, targeted therapy, and smart diagnostics may bring EGFR-targeted cancer care into a new phase of research and open new doors of advancement in cancer treatment.

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Not applicable. This article is a review article and does not include any studies on humans or animals by the authors.

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We declare no use of AI in the writing of this Article

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