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REVIEW

Nanomedicine-Based Therapeutic Approaches in Colorectal Cancer Using Patient-Derived Xenograft Models: Prospects and Challenges

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Abstract: Colorectal cancer is leading cause of morbidity and mortality worldwide. Advances in surgery, chemotherapy, and targeted therapies have improved treatment options, effective clinical management remains limited by tumor heterogeneity, resistance to therapy, and metastatic spread. In recent years, nanomedicine has gained attention as an effective strategy to address these challenges by improving drug delivery to tumor sites, enhancing bioavailability, and reducing systemic toxicity. Patient-derived xenograft models have become an important tool in preclinical cancer research because they preserve the histological and genetic characteristics of original human tumors and more closely reflect clinical disease behavior. This review summarizes recent advances in nanomedicine-based approaches for colorectal cancer treatment, with a particular focus on their evaluation using patient-derived xenograft models. A range of nanocarrier systems, including nanoparticles, liposomes, and dendrimers, have been explored for delivery of chemotherapeutic agents, biologics, and small-molecule inhibitors, demonstrating improved tumor targeting and therapeutic potential. Despite these encouraging developments, several challenges remain, including the complexity of tumor microenvironment, variability between patients, and concerns related to safety, scalability, and clinical translation. This review highlights current progress to enable the successful application of nanomedicine-based therapies for colorectal cancer in clinical practice.

Keywords: nanomedicine, colorectal cancer treatment, patient-derived xenograft models, drug delivery systems, tumor heterogeneity, chemotherapy resistance

Introduction

Colorectal cancer (CRC) represents a multifactorial and complex disease, ranking as the third most diagnosed malignancy and the second most prevalent cause of cancer-related death worldwide. The risk factors contributing to CRC are shown in Figure 1. The onset of CRC is characterized by the transformation of the epithelial cells within the colorectal mucosa, progressing through distinct stages such as hyperplasia, varying degrees of atypical hyperplasia (mild, moderate, or severe), and the formation of adenomas, eventually culminating in carcinoma. The underlying carcinogenic mechanisms are frequently initiated by factors that cause genetic alterations, leading to the conversion of normal cells into malignant ones. This progression is marked by key morphological stages, including epithelial hyperplasia, atypical hyperplasia, adenoma formation, carcinoma in situ, and invasive carcinoma. In 1990, Fearon and Vogelstein introduced a molecular model to describe the initiation and progression of CRC.[1] Subsequent studies have identified three central molecular mechanisms that contribute to CRC development: (i) chromosomal instability, a hallmark of familial adenomatous polyposis (FAP);[2] (ii) genetic mutations, particularly those linked to Lynch syndrome and other forms of sporadic mismatch repair (MMR) deficiencies;[3] and (iii) hypermethylation of CpG islands in gene promoters.[4] These genetic and epigenetic changes are commonly associated with mutations in key tumor suppressors and oncogenes, such as APC (Adenomatous Polyposis Coli), DCC (Deleted in Colorectal Carcinoma), TP53 (Tumor Protein p53), KRAS (Kirsten Rat Sarcoma Viral

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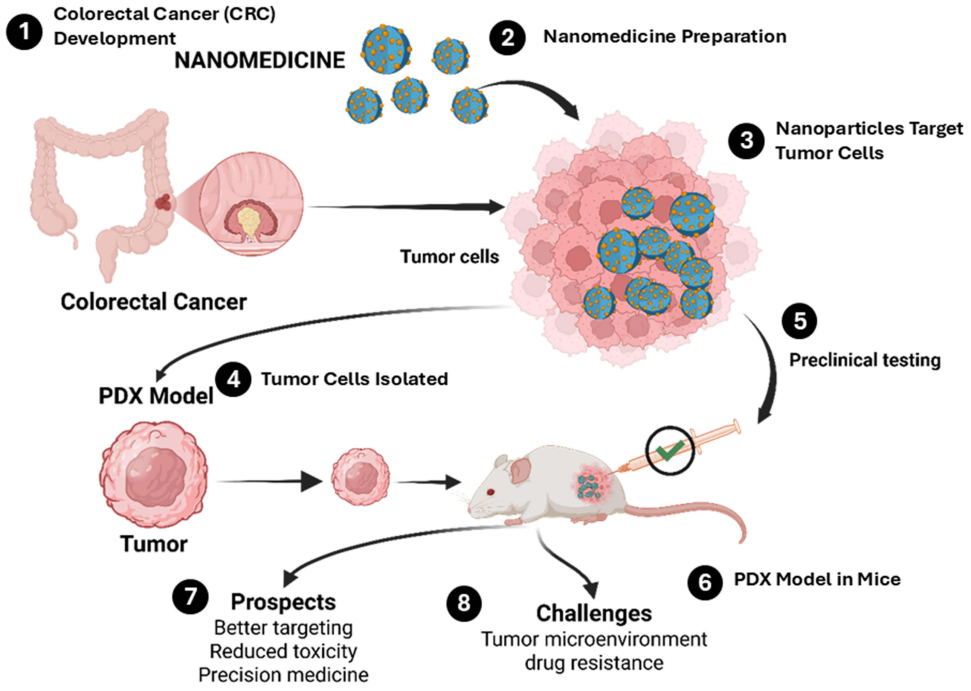
Graphical Abstract



Oncogene Homolog), c-MYC (cellular MYelocytomatosis oncogene), MCC (Mutated in Colorectal Cancer), and mismatch repair (MMR)-related genes including hMLH1 (human MutL Homolog 1), hMLH3 (human MutL Homolog 3), hMSH2 (human MutS Homolog 2), hMSH3 (human MutS Homolog 3), hMSH6 (human MutS Homolog 6), hPMS1 (human Postmeiotic Segregation Increased 1), and hPMS2 (human Postmeiotic Segregation Increased 2).[5–7]

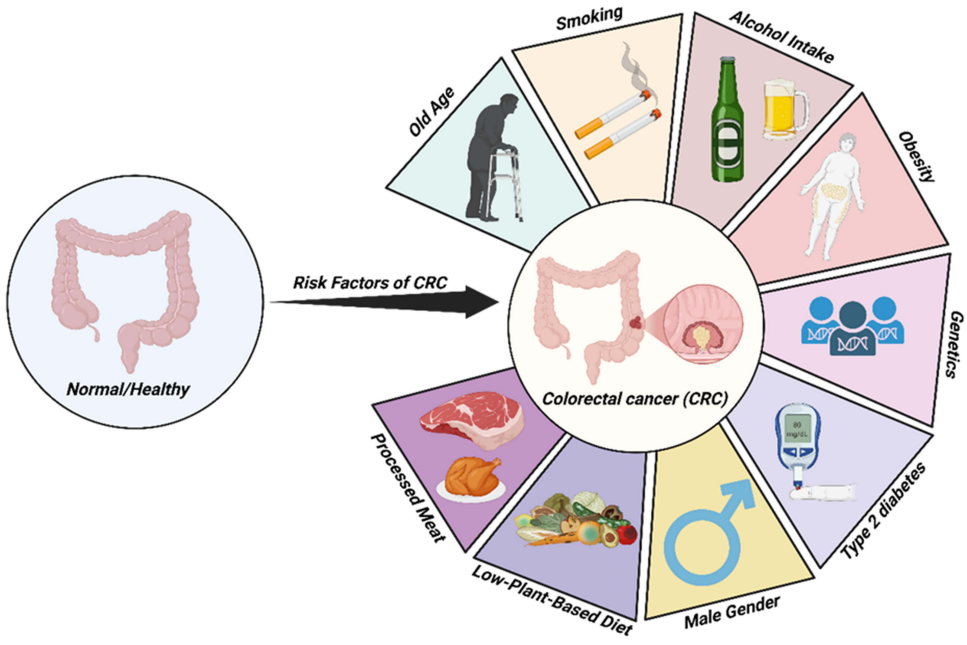


Figure 1 This figure summarizes the risk factors in the development of colorectal cancer (CRC), including some of the most important lifestyle, genetic, and health-related factors.

Inherited mutations in genes like APC, those involved in DNA mismatch repair, K-ras, and p53 are responsible for unchecked cell proliferation, facilitating the progression of CRC. These genetic alterations are often associated with specific stages of the disease's development.[8,9] The mutated genes lead to the production of defective proteins that fail to function properly, allowing damaged DNA to persist, which in turn drives further mutations and promotes the development of a malignant phenotype (Figure 2).[10] At the early stages of CRC, these genetic changes are not readily detectable, which complicates early diagnosis. This challenge in early detection is a major factor contributing to the high mortality rate associated with CRC. In addition to challenges in early detection, CRC diagnosis is hindered by several other challenges. Among the primary diagnostic obstacles are accurate pre-operative staging and imaging techniques, which are essential for detecting lymph node involvement and micro-metastatic disease. These factors play a pivotal role in optimizing patient care and management. Surgical treatment continues to be the primary approach for CRC, particularly in the early stages (0 to II).[11] In more advanced stages, surgery is frequently combined with adjuvant therapies, such as chemotherapy and targeted therapies. A key challenge in surgical management arises in determining the role of laparoscopic resection for individuals diagnosed with low rectal cancer. Given the high prevalence of CRC, there is a critical need for the development of surgical strategies that are universally applicable, impacting both the techniques used and the associated training. The postoperative care and overall prognosis of CRC patients are largely dependent on the pathological assessment of tumor resection specimens. However, challenges arise in the examination and reporting of these specimens, either due to challenges in applying existing criteria or the introduction of new concepts in pathology.[12] High-quality pathology reports are crucial for providing accurate prognoses and guiding patient management decisions. Furthermore, drug resistance to chemotherapeutic agents presents a major challenge for the increasing number of CRC patients. Over the past few decades, advancements in chemotherapy regimens have led to improved overall survival in individuals with advanced colon cancer. While modern systemic therapies can yield response rates as high as 50%, nearly all CRC patients eventually develop resistance to chemotherapy, diminishing the efficacy of treatment and ultimately contributing to chemotherapy failure.[13,14]

A range of nanomaterials, including lipid-based, polymeric, and inorganic nanoparticles (NPs), has been developed for the targeted delivery of therapeutic nucleic acids, chemotherapeutic agents, and immunotherapeutic agents to tumors. Currently,

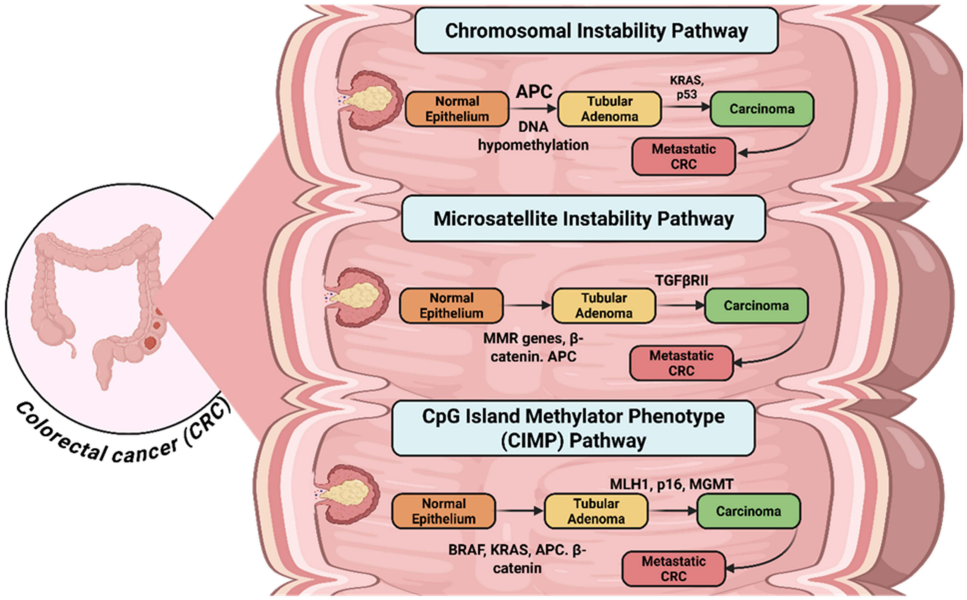


Figure 2 This figure shows the three significant pathways of colorectal cancer (CRC) development. The Pathway of Chromosomal Instability commences with the development of tubular adenomas (resulting in DNA hypomethylation) caused by mutations in the APC gene in normal epithelium. Further development of KRAS and p53 mutations leads to carcinoma and metastatic CRC. Microsatellite Instability Pathway can be described by the mutation in MMR genes, catenin, and APC that lead to the development of tubular adenoma. TGF beta II gene mutation then results in carcinoma and metastatic CRC. CpG Island Methylator Phenotype (CIMP) Pathway entails a mutation of BRAF, KRAS, APC, and 2-catenin in normal epithelium leading to development of tubular adenomas. MLH1, p16 and MGMT mutations subsequently lead to carcinoma and metastatic CRC. The figure shows the progression of normal epithelium into tubular adenomas to carcinoma and finally into metastatic CRC.

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over 15 cancer nanomedicines have received global regulatory approval, and more than 80 novel nanomedicines are undergoing investigation in over 200 clinical trials. Despite this progress, none of the actively targeted cancer nanomedicines have yet been approved, with only 10 candidates currently being tested in clinical trials. Advances in nanotechnology, along with a deeper understanding of cancer biology and the interactions between nanoparticles and biological systems, have driven the creation of diverse nanocarriers aimed at enhancing therapeutic outcomes while minimizing off-target toxicity. These nanocarriers are designed to selectively target tumor tissue, cells, and organelles.[15,16] Tumor-specific targeting is typically achieved by functionalizing nanoparticles with targeting ligands, such as antibodies, antibody fragments, aptamers, peptides, proteins, carbohydrates, and small molecules. These ligands bind to tumor-specific or overexpressed antigens or receptors on the surface of tumor cells, which not only increases the retention of the nanocarriers in the tumor tissue but also facilitates their internalization by the tumor cells.[17] Alternatively, a biomimetic targeting approach has gained significant attention in recent years. This approach involves coating nanocarriers with plasma membranes sourced from cancer cells, blood cells, or stem cells, which impart adhesive properties to the nanocarriers. These properties can be either homotypic or heterotypic, enhancing their ability to specifically target tumor cells.[18,19] The development of nanomedicines aimed at targeting organelles has recently gained considerable attention, marking the emergence of a third generation of nanomedicines that extends beyond conventional targeting of tumor tissue and cells.[20,21] Increasing preclinical and clinical evidence underscores the distinct advantages of organelle-targeted nanomedicines over traditional-free drugs and conventional nanomedicines. These advanced nanomedicines can deliver therapeutic agents directly to their intended intracellular sites of action, which not only enhances efficacy at lower drug doses but also holds the potential to overcome or even reverse multidrug resistance (MDR).[22] Various approaches have been developed to improve the ability of nanocarriers to bypass endosomal entrapment and effectively target-specific organelles, including the nucleus, mitochondria, lysosomes, endoplasmic reticulum, and Golgi apparatus.[23]

The development of PDX models is driven by the belief that these models could serve as more effective preclinical tools, providing better predictions of human cancer biology and treatment responses. Patient-derived xenograft (PDX) models offer a promising approach for personalizing cancer treatment for individual patients. Validating PDX models can be conducted from various perspectives, one of which involves comparing the histopathological, biological, and genetic characteristics of the PDX model with those of the original tumor. This approach assumes that PDX models retain critical features of the donor tumor, and these characteristics are preserved through successive in vivo passages in mice.[24] Around the world, numerous PDX biobanks collect cancer samples that represent diverse genomic and transcriptomic profiles. These resources are invaluable for preclinical screening in the development of novel therapies, as they help identify potential biomarkers and signatures that predict which patients are most likely to benefit from specific treatments. For instance, the Novartis Institutes for BioMedical Research established a PDX-based platform with a "one animal per model per treatment" design, which was used to evaluate responses to 62 distinct treatment strategies.[25] Additionally, Schütte et al developed a preclinical platform that assesses the drug sensitivity of clinical treatments, utilizing multi-omics data to uncover new biomarkers for predicting drug responses.[26] Furthermore, Lindner et al performed protein analysis on CRC PDX models and identified fourteen biomarkers that distinguish cetuximab-sensitive tumors from cetuximab-resistant ones.[27]

The aim of this review article is to thoroughly review the latest developments in nanomedicine and the application of nanomedicine in the treatment of colorectal carcinoma with a specific focus on the benefits exclusive to PDX models in preclinical research. It aims to emphasize the role of nanomedicines in enhancing targeted drug delivery, improving therapeutic efficacy, and reducing systemic toxicity, particularly in CRC. Additionally, the review aims to present perspectives of these nanotechnologies besides recapping the great challenges and constraints that might be faced in their evolution, clinical translation, growth and expansion, and future research avenues to surmount the current challenges in order to bring the advanced methods of nanomedicine successfully into the treatment models of CRC.

Current Diagnostic Strategies for Colorectal Cancer

Optical colonoscopy (OC) remains the gold standard for early detection of CRC due to its high diagnostic performance. OC allows for biopsy sampling, which provides a definitive diagnosis, and enables simultaneous therapeutic polypectomy, ultimately reducing CRC-related deaths in the long term.[28] However, OC can be a challenge or incomplete in certain patient populations, such as those with tumor-related stenosis, older individuals, or those with other health

conditions.[29,30] In recent years, computed tomography colonography (CTC) has been extensively studied as a potential alternative to endoscopy.[31,32] CTC generates images based on the X-ray attenuation of low-density objects, such as the air in the colonic lumen, compared to the denser bowel walls. This difference creates an interface that allows for clear imaging. CTC uses low radiation doses to obtain diagnostic images, and low-dose CT protocols are recommended for CRC screening.[33] Studies, including one by Pickhardt et al, have shown that CTC is comparable to colonoscopy in detecting larger colorectal polyps.[31] Two meta-analyses reported a high sensitivity of 100% for detecting colon cancer and 87.9% for detecting adenomas smaller than 10 mm.[34] Another alternative is Magnetic Resonance Imaging (MRI) colonoscopy, which does not involve radiation exposure.[35] For assessing the extent of CRC, MRI is the preferred modality due to its high accuracy in determining tumor location, stage, and its relationship to surrounding structures, such as the mesorectal fascia. MRI also provides important details on the relationship between the tumor and the peritoneal reflection, which helps define the treatment approach.[36] MRI is a valuable tool for measuring the distance between the anorectal junction and the distal edge of the tumor, as well as for evaluating tumor length. Endorectal ultrasound (ERUS) has become an essential technique for assessing the integrity of the rectal wall. With an accuracy ranging from 69% to 97%, ERUS is currently considered the most precise imaging modality for evaluating T1 tumors. While ERUS and endorectal MRI demonstrate similar accuracy in differentiating superficial (T1 and T2) tumors from advanced (T3) tumors,[37] endorectal MRI is more expensive, less widely accessible, and generally less comfortable for patients. Consequently, it is not recommended by the European Society for Medical Oncology Guidelines as the preferred imaging method for clinical T staging in CRC.[36] At diagnosis, metastases are present in approximately 25% of patients with colon cancer and 18% of patients with rectal cancer. The most used imaging modalities for detecting CRC metastases include ultrasound (US), computed tomography (CT), MRI, and positron emission tomography (PET)/CT.[38] According to the National Comprehensive Cancer Network guidelines, CT or MRI of the chest, abdomen, and pelvis is recommended for initial staging, while fluorodeoxyglucose (FDG) FDG-PET/CT is typically employed for surveillance or problem-solving purposes. ERUS, CT, and MRI are primarily used to assess lymph node involvement based on size, though lymph node size alone is not a reliable marker for metastasis and does not provide sufficient accuracy for making clinical decisions.[39] While FDG-PET offers superior insights into tumor biology, its limited spatial resolution can compromise the reliable detection of small lymph node metastases. However, FDG-PET/CT has shown improved performance in detecting lymph node metastases, with sensitivity and specificity of 51% and 85% for local lymph nodes, and 62% and 92% for distant lymph nodes, respectively.[40] Detecting hepatic and pulmonary metastases can be challenges due to the challenges of distinguishing them from benign lesions in these organs. CT outperforms US in diagnosing CRC liver metastases, with a sensitivity of 74%–84% and specificity of 95%–96%.[41]

Advances in Nanomedicine for the Treatment of Colorectal Cancer

Nanotechnology, as defined by the National Nanotechnology Initiative (NNI), a U.S. government program established in 2001, involves the science and engineering of designing, synthesizing, characterizing, and applying materials and devices that have at least one dimension in the nanoscale (usually between 1 and 100 nanometers).[42] Since its introduction several decades ago, nanotechnology has gained significant attention from both academic researchers and industries. Its applications extend beyond materials science and engineering, such as in light-emitting devices and solar cells, to areas like biotechnology and medicine, including disease diagnostics, prevention, and treatment. As a result, the growing interest in nanotechnology has led to the development of new nanotechnology platforms for medical use, a surge in government funding, and increased investment from venture capitalists.[43] The term “nanomedicine” refers to the use of engineered nanomaterials in the medical field.

Myocet: Non-PEGylated Liposomal Doxorubicin Formulation

Myocet is a liposomal doxorubicin nanomedicine, the key distinction is the lack of PEG functionalization on the surface. This lack of PEGylation leads to a shorter circulation time (approximately 2.5 hours), and the liposomes are not invisible to the reticuloendothelial system (RES). Consequently, Myocet does not cause the pegylated liposomal doxorubicin toxicity, the dose limiting side effect of Doxil, and has a lower rate of mucositis than Doxil.[44] Nevertheless, Myocet still persists in its circulation long enough to be successful in tumor targeting by passive targeting. Although the circulation time of Myocet is

much shorter than that of Doxil, the effectiveness of Myocet is similar in most clinical studies.[45] One Phase III study comparing doxorubicin and Myocet in metastatic breast cancer showed that both treatment options had the same response and progression-free survival.[46] Myocet, however, was not linked to a higher rate of cardiac toxicity. Leukopenia or neutropenia is confirmed as the main dose limiting toxicity (DLT).[47] Myocet liposome is comprised of bilayer membrane composed of egg phosphatidylcholine and cholesterol in the proportion of 55:45 mole. The loading of Doxorubicin into the internal aqueous core of the liposome occurs by an active loading process under pH gradient. Doxorubicin molecules once inside liposome form noncovalently cross-linked citrate cross-linked fibers. Unlike Doxil, Myocet exudes its dose of doxorubicin faster. In vivo, 90% of the doxorubicin is released within 24 hours.[44] This accelerated release rate is related to the fact that there is no PEG coating which in Doxil serves to stabilize the liposome membrane and prevent the leakage of drugs. Although Myocet is not currently being used in the USA, where Phase III clinical trials are ongoing to approve its use as first-line therapy in metastatic breast cancer in the HER2 positive setting, it is being sold in Canada and Europe in combination with cyclophosphamide as first-line therapy in metastatic breast cancer.[47]

DaunoXome: Liposomal Daunorubicin for Anticancer Therapy

DaunoXome is a lipid-encapsulated form of the anthracycline daunorubicin. Daunorubicin does not have a hydroxyl group at the 14-position.[48] The preferred choice of daunorubicin over doxorubicin to make DaunoXome was because daunorubicin had a better aqueous stability and an improved cytotoxic activity against selected solid tumors.[44] The DaunoXome liposome is a bilayer membrane of distearoyl phosphatidylcholine and cholesterol in 2:1 molar proportion with the citrate salt of daunorubicin located in the inner aqueous core of the vesicle. The particles measure about 50 nm in diameter and show a high level of stability with little leakage of the encapsulated daunorubicin.[49,50] In the US, DaunoXome has been authorized as a first-line drug in patients with advanced HIV-related Kaposi's sarcoma. Moreover, its possible clinical effectiveness in several types of leukemia is the subject of many ongoing clinical trials.[51]

Rexin-G: Targeted Gene-Based Nanomedicine Platform

The cancer collagen matrix-targeting nanomedicine platform consists of liposome system with a high-affinity collagen-binding motif based on von Willebrand factor (vWF), which is genetically engineered into the liposomes surface proteins. The model product in this platform is Rexin-G, which is a tumor-targeting replication-incompetent retroviral virus that expresses an N-terminal deletion mutant of the cyclin G1 gene that exhibits some antineoplastic effects.[52] MicroRNA is also encapsulated in the platform. The NPs (~100 nm), when given intravenously, accumulate selectively in cancerous regions where the collagen matrix of a tumor is revealed by tumor invasion, neoangiogenesis, and extracellular matrix remodeling. This build-up in the microenvironment around the cancer cells maximizes the effectiveness of gene transfer via natural viral cell receptor mechanisms. In preclinical and clinical trials conducted by Epeius, Rexin-G demonstrated considerable antitumor activity against a wide spectrum of solid tumors.[53,54] Despite ongoing clinical trials of Rexin-G being carried out in both the USA and elsewhere, it has already been made available in the Philippines to treat all solid tumors due to convincing evidence of single-agent effectiveness in a wide range of chemoresistant malignancies. In 2003, Rexin-G received an Orphan Drug Designation in pancreatic cancer, such as safety and efficacy reports of studies conducted in the Philippines, and in 2008, in osteosarcoma and soft tissue sarcoma.[52] As of 2009, Epeius finished its Phase II/ Advanced Phase I trials in pancreatic cancer, sarcoma, and osteosarcoma, meeting all its primary and secondary endpoints. Rexin-G is now granted a Status and Priority by the US FDA and an accelerated approval of these clinical indications is being pursued.[55]

Mechanism of Nanomedicines in Cancer Therapy

Active Targeting

Active targeting involves the functionalization of NPs with specific ligands such as antibodies, peptides, aptamers, or nucleic acids that bind selectively to overexpressed receptors or antigens on cancer cells. This ligand–receptor interaction promotes the recognition and binding of NPs to tumor cells, followed by receptor-mediated endocytosis, facilitating internalization. Active targeting can also extend to targeting tumor vasculature or specific subcellular organelles, improving precision delivery

of therapeutic payloads. This method enhances specificity, limits off-target effects, and improves intracellular drug delivery by exploiting molecular recognition, receptor-mediated transport, or engineered responsiveness. For example, NPs may be designed to target receptors like vascular endothelial growth factor receptor 2 (VEGFR2) or integrins on tumor cells or tumor blood vessels, even overcoming heterogeneous tumor environments and poor passive targeting effects. Additionally, biomimetic strategies coating NPs with cell membranes impart them with homotypic or heterotypic adhesive properties for enhanced targeting. The internalization and controlled release within subcellular compartments like mitochondria or lysosomes further augment therapeutic efficacy,[56] the process is illustrated in Figure 3.

Passive Targeting

Passive targeting primarily exploits the EPR effect inherent in solid tumors. Rapidly growing tumors induce abnormal angiogenesis, resulting in leaky vasculatures with large fenestrations and inefficient lymphatic drainage. These characteristics permit NPs within the optimal size range (typically 10–100 nm) to extravasate through tumor blood vessels and accumulate selectively in the tumor interstitial space while being retained longer due to poor lymphatic clearance. This phenomenon enhances drug concentration at the tumor site without requiring specific ligand targeting. However, passive targeting efficacy is limited by tumor heterogeneity in vascular permeability, extracellular matrix density, and hypoxia, which may affect

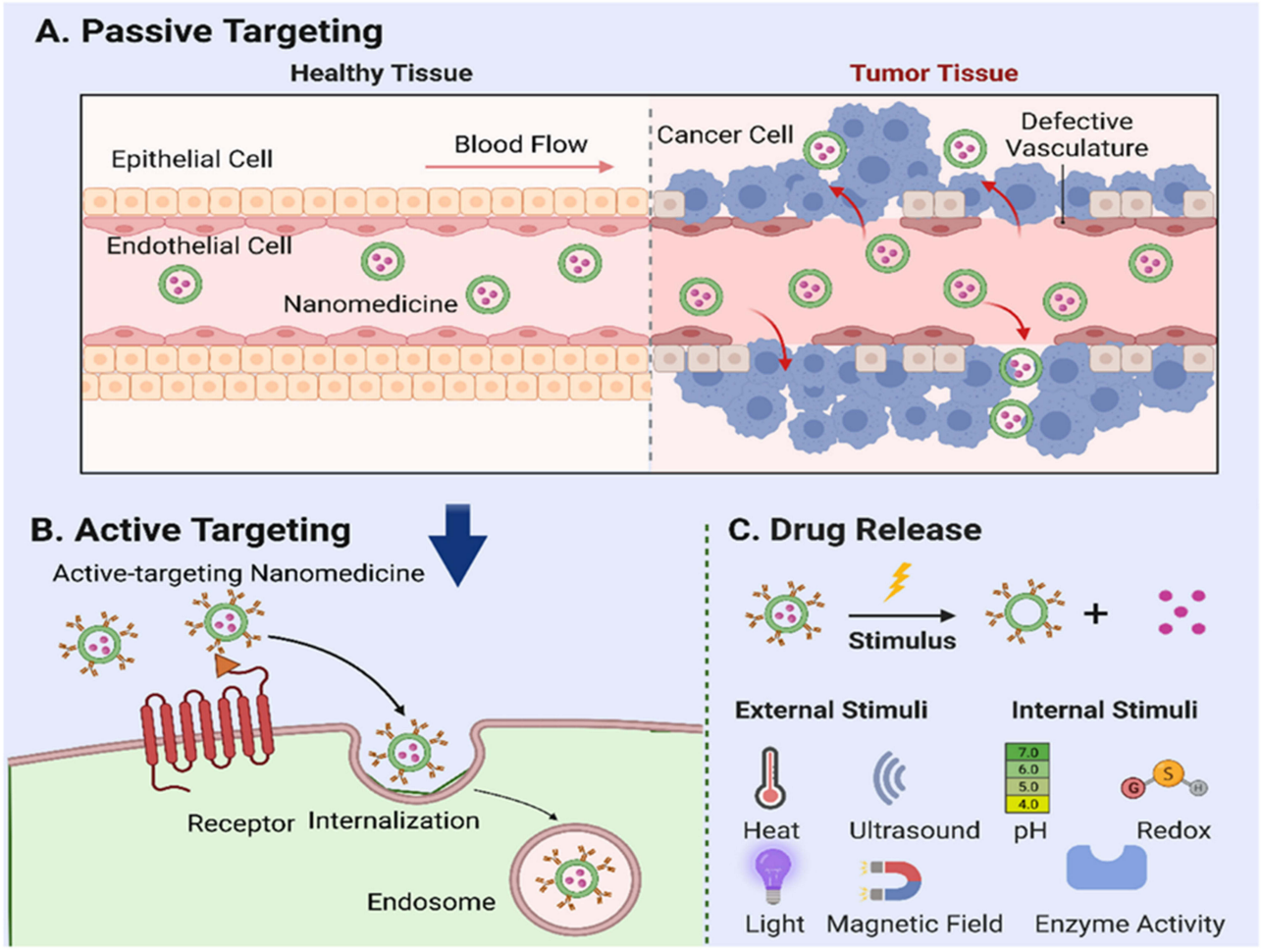

Figure 3 Drug delivery through nanoparticles. (**A**) Passive targeting: building up nanomedicine onto tumor tissues by taking advantage of their physical and chemical characteristics, which is called the enhanced permeation and retention (EPR) effect. (**B**) Active targeting: using ligands or antibodies to bind to tumor cells receptors on their surfaces. After the internalization stage, they undergo processing through the nuclear endosome, where more processing and release of the drugs can take place. (**C**) External factors, which may be used to cause the release of drugs loaded in nanoparticles and include temperature, ultrasound, light, and magnetic fields, as well as internal factors, such as pH, redox reactions, and enzyme activation.

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nanoparticle penetration and retention. The EPR effect underpins many clinically approved nanomedicines but tends to show variable outcomes, necessitating complementary strategies like active targeting,[57] the process is illustrated in Figure 3.

Nanomedicine Optimization in Colorectal Cancer Using Patient-Derived Xenograft Models

Nanomedicine as targeted drug delivery in CRC because of its unique characteristics, in that their size, surface charge, and functional surface chemistry, can be used to improve the accumulation of nanoparticles to tumor and efficacy of nanoparticles compared to conventional chemotherapy. To enhance tumor uptake and reduce systemic toxicity, nanoparticles (liposomes, polymeric micelles, solid lipid nanoparticles, etc.) are intended to enhance pharmacokinetic profiles, stability, and controlled release of drugs; in a variety of nanoparticle platforms investigated in vivo that feature CRC models that assess biodistribution and sustained release properties.[58] The key pathway of passive targeting, the Enhanced EPR effect, increases stickiness of nanoparticles in tumor tissue owing to aberrant vascular structure and inefficient lymphatic drainage characteristic of solid tumors, which can be heterogeneous across tumors with different PDX types hence influencing the consistency of passive targeting.[59] PDX models of CRC retain the genetic, histological, and microenvironmental properties of human tumours and, therefore, act as very predictive in vivo models to assess the performance of nanomedicine and overcome the limitations of conventional models.[60,61]

These models maintain patient-specific tumour markers, allowing comparative efficacy measurements of nanomedicine designs, including surface functionalization with targeting ligands, and a more representative translational bridge between preclinical and clinical results, which reflects patient heterogeneity when compared to xenografts of immortalized cell lines.[62] CRC PDX models have been used to study nanoparticle targeting mechanisms, such as theranostic agents that combine therapy and diagnostics, and optimize formulations to achieve better tumor uptake and therapeutic response which in certain cases have performed better than non-targeted controls.[63] The combination of PDX-derived pharmacokinetic (PK) and tumor response data can be used to optimize dosing regimens and nanoparticle design parameters, so the models are essential to the development of precision nanomedicine in CRC and to the personalization of treatment to tumor subtypes and individual patient characteristics.[64]

Potential and Limitations of Nanomedicine-Based Cancer Therapies

Nanocarriers enhance the stability, solubility, and bioavailability of poorly soluble drugs, providing regulated release which improves the therapeutic efficacy, and minimizes systematic toxicity. Moreover, nanomedicines penetrate biological barriers like the blood–brain barrier, providing the treatment of tumors in complicated regions. They provide multifunctional methods by employing imaging and therapy (theranostics), thereby providing personalized medication engineered to tumor features. Various types of nanomaterials including carbon nanotubes provide mechanical strength to destroy drug-resistant cancer cells. These benefits offer the capability to address multidrug resistance mechanisms, enhanced pharmacokinetics, and improved drug delivery.[65] However, the design and clinical translation of nanomedicines offer various obstacles including limitations in mass production with reproducibility, poor diffusion into solid tumors, inconsistency in tumor targeting because of heterogeneous tumor microenvironments, significant toxicity, and immunogenicity of nanoparticles. Further, the NP circulation duration can be decreased by biological barriers like opsonization and clearance by the reticuloendothelial system. The complex nature of tumors also limits the efficient targeting, which necessitates complicated architecture and surface modification of nanocarriers. Moreover, clinical acceptance may be impeded due to cost and scalability problems. Notwithstanding development, further research is required to optimize design, enhance specificity, and minimize side effects, thereby ensuring safe and effective application of nanomedicines in cancer treatment.[65]

Role of Patient-Derived Xenograft Models in Colorectal Cancer Research

Overview and Development of Patient-Derived Xenograft Models

PDX models are advanced cancer research models created by implanting tumor tissue or cells directly from a cancer patient into immunodeficient or humanized mice. This allows the tumor to grow in a living organism while maintaining the genetic, histological, and molecular characteristics of the original patient tumor. Unlike traditional cancer cell lines

which often lose heterogeneity and undergo genetic changes in culture, PDX models preserve the tumor's complexity, including its microenvironment, which is critical for studying tumor behavior and drug response. These models provide a physiologically relevant system that mimics human tumor growth, allowing more accurate evaluation of anti-cancer therapies and personalized treatment strategies. PDX models are widely used for preclinical testing of drugs, identification of biomarkers, studying tumor biology, and exploring mechanisms of drug resistance. Their high fidelity to patient tumors makes them predictive of clinical outcomes and valuable tools for precision oncology.[66]

Significance of Patient-Derived Xenograft Models in Colorectal Cancer Research

It is widely recognized that a major challenge in the development of oncology drugs is the low success rate of new treatments.[67] Chemotherapy is the most established form of anticancer treatment, repeatedly validated in clinical practice for various cancers. However, chemotherapy resistance is the primary cause of cancer-related deaths worldwide. Additionally, there is a lack of reliable methods to assess chemosensitivity for guiding first-line chemotherapy. The PDX model plays a crucial role in improving chemotherapy selection, identifying sensitivity, exploring resistance mechanisms, and providing a suitable platform for testing new drugs and drug delivery methods. Various studies have demonstrated that PDX models preserve the heterogeneity of CRC primary tumors.[68] The outcomes of drug evaluations in these models are the most like clinical scenarios. The engraftment rate depends on the strain of immunodeficient mice and the method of delivery. Typically, tumor tissue is transplanted heterotopically into subcutaneous or sub-renal sites.[69] However, some studies have used enzymatic digestion to isolate tumor cells for model development.[70] Other research has developed CRC PDX models orthotopically, which allows for the formation of endogenous metastases that can spread to the lungs and liver, mimicking the behavior of a patient's primary tumor. In contrast, subcutaneous engraftment does not lead to metastasis to other organs.[71] The highest engraftment rate in CRC is observed with PDX models using NOD/SCID mice.[72] These models maintain crucial gene mutations, including KRAS, BRAF (v-Raf murine sarcoma viral oncogene homolog B), PIK3CA (Phosphatidylinositol-4, 5-bisphosphate 3-kinase), gene expression, copy number variations, and microsatellite instability from the primary tumor.[73] Most studies agree that PDX models preserve the stromal structure, histological differentiation, and histopathological subtypes. The applications of CRC PDX models are extensive, including the evaluation of drug response rates for agents like cetuximab and other chemotherapies, as well as in cell line production, drug and biomarker discovery, further understanding tumor biology, and colosphere production.[74]

Comparison of Patient-Derived Xenograft Models with Conventional Cell Line Models

PDX models retain the original tumor's histopathological architecture, genetic profile, molecular signatures, and intratumor heterogeneity much more faithfully than cell line models. This includes maintaining distinct tumor subpopulations and tumor microenvironment components that are often lost or altered in cell culture.[66] PDX tumors remain biologically like the patient's tumor through multiple passages, they provide more predictive and translational insights into drug responses and resistance mechanisms. Their drug response patterns correlate better with clinical outcomes compared to traditional models.[75] PDX models maintain the interactions between cancer cells and the surrounding stromal and immune cells (although human stroma is gradually replaced by murine components), enabling study of tumor behavior in a more physiologically relevant context. Traditional cell lines adapt to in vitro culture conditions, which can cause genetic drift and loss of heterogeneity. PDX models minimize such artifacts by growing tumors in vivo, preserving the native characteristics. PDX models serve as "avatars" for individual patients, allowing screening of therapeutic agents to predict personalized treatment efficacy before clinical application. PDX provides a robust system for biomarker discovery, understanding mechanisms of drug resistance, evaluating novel drug combinations, and developing new therapies, especially when integrated with modern technologies such as multi-omics and deep learning.[66] Many studies have shown that PDX can maintain the histopathology and genetic characteristics of the original tumor.[76]

Applications of Patient-Derived Xenograft Models

Numerous PDX biobanks globally collect cancer samples from various genomic and transcriptomic backgrounds. These platforms serve as valuable tools for preclinical screening when developing novel therapies, allowing for the identification of signatures and biomarkers that can help determine which patients are likely to benefit from specific treatments.[77,78] Various PDX models have been utilized to assess the efficacy of different treatment strategies across a range of cancer types, providing valuable insights into their therapeutic potential. In breast cancer, orthotopic PDX models treated with docetaxel, 5-fluorouracil, and trastuzumab demonstrated a response rate (RR) of 71%.[79] Furthermore, another study showed a 100% response rate in a breast cancer orthotopic model treated with docetaxel, doxorubicin, and trastuzumab combined with lapatinib (Lap).[80] In colorectal cancer, heterotopic PDX models treated with cetuximab and panitumumab achieved good response rate.[81] Similarly, a study of heterotopic PDX models responses to cetuximab recapitulated the clinical data in patients, with complete or partial response, and the response strictly restricted to KRAS wild-type models.[82] The treatment of colorectal cancer using oxaliplatin in heterotopic PDX models led to a 92% RR.[73] In case of ovarian cancer, heterotopic models preserved with cisplatin showed 81% RR,[83] while treatment with 5-fluorouracil, cyclophosphamide, and doxorubicin produced a reduced RR (0%–27%).[84] In case of gastric cancer, regorafenib treatment of heterotopic PDX models demonstrated 96% RR.[85] In non-small cell lung cancer (NSCLC), heterotopic PDX models with EGFR mutations demonstrated a small reaction, with only 10% of tumors reacting to gefitinib treatment.[86] The pancreatic ductal adenocarcinoma (PDAC) models preserved with gemcitabine revealed a comparatively reduced RR of 17%.[87] These results reveal the significance of PDX models in preclinical drug analysis as well as the variation in treatment response among various cancer types. These reports demonstrate a correlation between clinical findings in people with colorectal cancer and how well PDX models react to drugs.[88] PDX clinical trials are essential to evaluate anti-cancer treatments before performing human clinical trials. Therefore, the distinctive features of these models have advanced research institutions and pharmaceutical companies to produce PDX repositories. Novartis has produced more than 1000 Avatar mice from different malignant tissues because of this initiative. Avatar models are principally employed in personalized medicine, where they estimate how certain patients will react to treatment, even if there is not a considerable technical difference between them and PDX models.[89] More than 1500 PDX samples are currently in the possession of the EurOPDX consortium, which was formed in Europe to keep PDXs.[24,90] PDX models are part of a nationwide collection of Patient-Derived Models (PDMs) that the National Cancer Institute (NCI) has been building since 2017. To offer researchers a broad variety of biological and clinical samples for their research, the NCI plans to establish a long-term storage facility for at least 1000 PDX models.[91]

Limitations of Patient-Derived Xenograft Models in Colorectal Cancer Research

PDXs have turned into important tools in colorectal cancer research, in which they are effective in reflecting patient tumor heterogeneity and drug responses. However, using them is limited by several serious concerns including high financial and time-constraints, low-assay engraftment efficiency, loss of human immune and stromal factors due to aging, ethical concerns of using animals and source of patient tissue, and scaling constraints per high-throughput usage.

High Cost and Time Requirements

Production and distribution of the PDX models is also rather expensive in vivo due to the need to use special strains of mice that are immunodeficient, the utilization of surgical implantation techniques, and the long-term breeding of the animals. The timescales of engraftment typically fall within a range of 2–6 months until tumours are large enough to be palpated (150–200 mm^3), which is far longer than the scale of rapid expansion possible using cell lines or organoids. Primary tumor engraftment in the instance of colorectal cancer would entail fresh surgical tissues passaged directly into mice, thereby raising costs because of veterinary care and growth surveillance imaging. The latter constrains the applicability of PDX to resource-constrained settings and slows down iterative drug testing cycles that are required to obtain accuracy in the oncology pipeline.[72,92,93]

Variability in Engraftment Efficiency

Engraftment efficiency, or take rate, is highly variable with regard to tumor aggressiveness, site of implantation (subcutaneous or orthotopic), recipient mouse strain and passage number. The overall take rates in colorectal cancer cohort studies are generally 40–70% more successful (up to 78 in NOD/SCID but not in nude mice) with NOD/SCID than with nude mice (63%) but there are also some chemorefractory or low-grade tumors that do not fail. This stochasticity introduces selection bias towards aggressive clones, decreasing model diversity, and decreasing the statistical power of preclinical studies. The rates are increased to 60–80 with optimization techniques such as orthotopic implantation into the cecum that makes the process more challenges.[72,94]

Loss of Human Immune Components

This is also a major limitation of classical PDX because after 2–3 passages, the human stroma and leukocytes are substituted by mouse ones in the tumor microenvironment (TME). Replacement of human fibroblasts and tumor-related macrophages occurs, altering the patterns of cytokines and composition of the extracellular matrix that is critical in colorectal cancer development. This compromises the testing of immunotherapeutics including anti-PD-1 agonists since murine immune cells are poor models of human T-cell interactions and checkpoint-response. This is surmounted in the developing humanized mice, which possess CD34+ hematopoietic stem cells through conserving the functional human immunity, albeit currently only colorectal-specific panels are available.[66,95–97]

Ethical Considerations

Ethical concerns regarding PDX modeling are multi-dimensional and largely explained by the fact that extensive animal studies are performed that permit serial passaging and endpoint tumor burden studies of hundreds of mice. It is determined by the regulations of such organizations as the AVMA that need the presence of humane endpoints and the tumor ulceration and cachexia that necessitate frequent culling that strain the welfare requirements. In addition, institutional review board approved consent is required to get viable patient tumors and the dilemma of weighing risk to donor versus scientific benefit and humanized chimeras creates bioethical considerations on bans of partial embryogenesis. These issues ensure that the principles of 3Rs (replacement, reduction, refinement) must be implemented to be able to justify PDX as a more appropriate choice when compared to in silico or organoid.[98,99]

Scalability Challenges for High-Throughput Screening

PDX models have failed because they are slow to form (months per model), expensive per-animal, tedious to passage (manual) which cannot be compatible with screening thousands of compounds. PDX panels of colorectal cancer are genetically stable but poor throughput (10–50 scale panels possible per year) relative to organoid systems which can be expanded in a 96-well format. This renders PDX confirmatory and co-clinical trials offer an intermediate solution.[93,100]

Advanced Nanomedicines in CRC

Targeted Nanoparticle-Based Strategies in CRC

In CRC, the use of targeted nanoparticle therapy has significantly improved overall survival for patients. The development of checkpoint inhibitors is progressing rapidly, driven by the increased effectiveness of treatments like the anti-EGFR agent (cetuximab) and the anti-angiogenesis agent (bevacizumab), which target several immune pathways.[101] Targeted delivery can be achieved through passive or active targeting, which aims to precisely focus on cancer cells. Compared to free drugs, targeted drug delivery helps reduce toxicity to normal cells, protects drugs from degradation, extends their half-life, increases the loading capacity, and improves solubility.[102] Nanoparticulate drug delivery systems have been widely explored for their potential to improve the targeted delivery and efficacy of various drugs. Several types of NPs have been developed, each incorporating specific active agents, ligands, and receptors to enhance the therapeutic effects. For instance, PEGylated hollow mesoporous ruthenium NPs loaded with [Ru(bpy)2(tip)]2+ and RBT as the active agents utilize SS-Fc as a ligand targeting the carcinoembryonic antigen receptor, with a particle size of approximately 110 nm.[103] Hyaluronic acid–Doxorubicin NPs, with doxorubicin as the drug, use hyaluronic acid to target the RHAMM and CD44 receptors, with a size range of 175 nm.[101] Cyclodextrin-based host–guest complexes, which encapsulate regorafenib, employ mannose to bind the mannose receptor, and have a size of about 100 nm.[102] Cationic liposomes carrying ESC8 and anti-Hsp90 plasmid as active agents utilize

dexamethasone to target the glucocorticoid receptor, with a size of 251 nm.[104] Polymersomes containing doxorubicin utilize transferrin as the ligand to target the transferrin receptor, with a particle size of 72 nm.[15] PLGA NPs, delivering 5-fluorouracil, employs wheat germ agglutinin to target N-acetyl-D-glucosamine and sialic acid receptors, with a size of 156 nm.[105] Nanoscale metal-organic frameworks, which carry talazoparib and temozolomide, use fucoidan as a ligand to target the P-selectin receptor, with a size of 84 nm.[106]

Some formulations of nanocarriers that are used to deliver drugs to treat CRC have demonstrated potential in clinical practices in recent studies. Yet even though they promise improvement, most of these trials remain in the infancy, and the critical examination of the results, the success rate, and obstacles faced might help to have a clearer picture of their potential clinical application.

Immune Checkpoint Inhibitor-Based Nanomedicine Approaches

FDA approved Tregs that contain antibodies used to attack cytotoxic antibodies on the surface of Tregs to enhance the immune response of the body against CRC cells. This method has demonstrated potential in preclinical models and was approved to be used by the FDA in clinical settings. Nevertheless, the therapeutic benefit must be confirmed by detailed efficacy information and long-time follow-up in patients with CRC. Initial findings show improvement in immune response and lack a clear data of patient survival and clinical response. Future concerns on immune-related adverse effects and long-term effectiveness in various groups of patients are still a major challenge. Immune checkpoint blockade mechanism that has already shown efficacy in other types of cancers is a primary factor that contributed to progression although no comprehensive data on CRC is available.[107,108]

Antibody-Targeted Polymeric Nanoparticle Systems

Phase I trial of metastatic CRC is ongoing, whose preliminary results indicate promise in tumor-targeting capabilities, but clinical response rates are not available yet. The use of NPs, cetuximab, and somatostatin analogues has proven to be effective in destroying targeting killing of CRC cells when compared to conventional medicines. Due to the complexity of the combination of multiple agents (NPs, cetuximab, and somatostatin analogues), stability, bioavailability, and systemic toxicity might be challenging. It is critical that biology and nanoparticles be fine-tuned to provide the best therapeutic results. Potential of combination therapies can be synergistic and thus the current issues should not stop future research.[109]

PEGylated Irinotecan Formulations for KRAS-Mutant Colorectal Cancer

Phase II ongoing trial in the treatment of metastatic CRC with KRAS mutations and its Initial findings indicates that NKTR-102 has shown superior pharmacokinetic characteristics and tumor targeting relative to irinotecan, as well as lesser systemic toxicity. The irinotecan released over a long period by the formulation offers prolonged drug exposure, which may improve effectiveness in tumor populations with resistance. Nonetheless, the issue of drug resistance, especially among tumors with advanced Kirsten rat sarcoma viral oncogene homolog KRAS mutations, is also a major issue. Major challenges have been irinotecan resistance, in KRAS mutated CRC. Further molecular profiling is required to determine subgroups of patients that will respond to NKTR-102. Positive early PK results and decreased toxicity indicate a possible benefit in KRAS-mutant CRC patient groups, warranting further research.[110]

Polymeric Micelle-Based Delivery of SN-38

Phase II trial in colorectal, lung, and ovarian cancers and its early data show better solubility and bioavailability of SN-38, although the clinical efficacy of SN-38 in CRC patients is yet to be seen. This design has enhanced the delivery of SN-38, which is a strong chemotherapeutic agent. Patient variability and micelle stability problems during formulation and storage. The problem of preservation of micelles in blood that may influence the delivery of drugs and their concentration in tumors should be resolved. The capability to pass the blood–brain barrier and attack several types of cancers makes the clinical uses more potential, which warrants additional testing.[111]

Liposomal Doxorubicin-Based Therapies

Phase II clinical trial in colon cancer with liver metastasis have demonstrated lower cardiotoxicity than free doxorubicin and better targeting of tumor tissues. Nevertheless, there were some cases of delayed drug release and uneven drug distribution among patients, a limitation to effectiveness. Problems with delayed delivery and skewed medication, which may result in inactive therapeutic effects. Additionally, there is a threat of immunogenicity and clearance by the RES.

Liposomal delivery provides superior targeting and less systemic toxicity which is a compelling argument to proceed with further research despite the challenges.[112]

Combination Liposomal Chemotherapy Platforms

Phase II trials in advanced CRC are underway. CPX-1 showed good response rates in initial trials, especially in patients with metastases to liver and may be a viable treatment option to advanced-stage CRC. The major problem with liposomal formulations is the possibility of immunogenic reactions and poor drug uptake in some types of tumors. Its effectiveness in non-metastatic CRC is still unclear. It is a promising new option due to early efficacy in metastatic CRC populations and has the potential to decrease systemic toxicity.[113]

Cyclodextrin-Based Camptothecin Nanoparticles

Preliminary evidence of Phase I/II trials in solid tumors, including rectal cancer indicates that it has a promising efficacy in rectal cancer, but additional information is required to gauge the effect of this radiation on CRC. Invention of a strong chemotherapeutic named camptothein has enhanced solubility and tumor targeting. Cyclodextrin preparations have problems in drug release kinetics and targeting tumors that may limit their ability to be useful in vivo. The presence of the ability to deliver the chemotherapeutic agents efficiently to the solid tumors is a reason to continue the trial, and the emphasis should be placed on optimizing the formulation.[114]

Carbon Nanoparticles for Diagnostic Applications

Carbon NPs have been tested about their capabilities of improving surgical accuracy and tumor resection in CRC, although clinical outcome data were not yet reported. There are problems with the use of NPs in surgery in tumor targeting and potential complications during surgery. These NPs should be in a position to identify the tumor and spare healthy tissue selectively to improve the result of the surgery. Carbon NPs could give an improved imaging and tumor delineation, which is worth further investigation.[115]

Lipid Nanoparticle-Mediated Kinase Inhibition Strategies

Early data of Phase I in CRC cancer with liver metastases and other cancers are encouraging, especially when it comes to liver metastases, although the entire clinical effectiveness is still being explored. The problems with stability and bioavailability are also issues, as with most lipid-based NP, and there are immune-related side effects that may occur. The encouraging initial results of metastatic CRC create a reason to pursue further research, particularly in liver metastasis.[116,117]

Liposomal Irinotecan-Based Nanomedicine Approaches

Preliminary Results of Phase I/II clinical trials in CRC and advanced gastrointestinal cancers are underway. Nal-IRI has demonstrated enhanced accumulation in tumors and reduced systemic toxicity during first phase trials. Resistance to irinotecan in some of the subtypes of CRC could curtail its efficacy. Further patient stratification and molecular profiling are needed to achieve the best results. This might have an advantage in CRC and gastrointestinal cancers because early pharmacokinetic benefits and decreased toxicity have been encouraged.[118] Table 1 summarizes latest research and prominent literature studies on nanomedicine approaches with patient-derived xenograft (PDX) models.

Table 1 This Table Summarizes Latest Research and Prominent Literature Studies on Nanomedicine Approaches with Patient-Derived Xenograft (PDX) Models

No.	Study/Approach	Model/Focus	Nanomedicine Aspect	Reference
1	LRP-1 targeted theranostic HSA nanoparticles with 5-FU in radio-resistant CRC PDX	CRC PDX (radio-resistant)	Theranostic albumin NP delivering 5-FU with imaging and tumor targeting	[63]
2	Fe_xMo_yS-PEG nanoparticles evaluated in CRC PDX models	CRC PDX (PDX#1 and PDX#2)	PEG-modified metal NPs showing tumor growth inhibition via MAPK pathway modulation	[119]

(*Continued*)

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Table 1 (Continued).

No.	Study/Approach	Model/Focus	Nanomedicine Aspect	Reference
3	CRC PDX platform demonstrating chemosensitivity/resistance mechanisms	CRC PDX (49 models)	Used to test response to conventional and targeted drugs; platform applicable for NP evaluation	[120]
4	PDX used to assess capecitabine efficacy in CRC	CRC PDX established for drug evaluation	Although conventional drug, model validates NP platforms for comparison	[121]
5	Self-assembled nanodrugs enhancing PD-1 blockade in humanized CRC PDX	Humanized CRC-PDX model	Nanostructures combined with immunotherapy to enhance anti-tumor effects	[122,123]
6	MiniPDX as rapid PDX-based assay for drug screening	MiniPDX models with CRC	Platform for rapid in vivo drug testing, useful for NP therapeutic evaluation	[124]
7	Nanoparticle enhanced bevacizumab + paclitaxel in CRC xenograft model	CRC xenograft (albumin NP)	Nanoencapsulated antibody + chemo showing improved intratumoral accumulation	[125]
8	Nanoparticle review highlighting PDX utility for individualized therapy	CRC PDX platforms	PDX model as basis for NP therapy evaluation and personalized screening	[60]
9	Nanoparticle role in CRC treatment modulation (review)	CRC preclinical models	Highlights how NPs improve targeted delivery relevant to PDX studies	[126]
10	Nanoparticle-mediated dual targeting in colorectal cancer (in vitro/in vivo)	EGFR-targeted PDA NPs	Relevant nanoparticle design for potential PDX testing	[127]
11	Broad nanoparticle therapeutic strategies in CRC models	General CRC NP approaches	Includes nanocarrier systems applicable to PDX evaluation	[128]
12	Mesoporous silica nanoparticle (MSN) carriers for CRC	Targeted chemoimmunotherapy with cisplatin (CDDP)-containing nanomedicine.	The results showed strong anti-tumor effects, prolonged survival rate, and low systemic cytotoxicity	[129]

Future Perspectives

The primary problem is the intrinsic complexity and heterogeneity of colorectal tumors, which are effectively maintained in PDX models. However, these cause considerable changes in nanoparticle delivery, distribution, and therapeutic efficiency. The tumor microenvironment (TME) in CRC, featuring hypoxia, dense extracellular matrix, high interstitial fluid pressure, and uneven vascular networks postures physical obstacles that hinder nanoparticle penetration and uniform drug distribution within tumors. This heterogeneity results in varying treatment responses, which make it complicated to forecast therapeutic results precisely. Further, PDX models demonstrate species-specific variations that can influence nanomedicine assessment, while being more therapeutically meaningful in comparison to typical cell line models. The human stromal components in entrenched tumors are progressively substituted by murine stroma, which alter the tumor microenvironment and affect nanoparticle behavior, uptake, and immune interactions in ways not entirely reflective of human biology. This alteration decreases the predictive ability of these models in clinical translation by casting doubt on the extrapolation of PDX study effectiveness and toxicity outcomes to human patients.[130] The biocompatibility and significant toxicity of nanomedicines is further challenging. However, nanocarriers can increase drug solubility, stability, and targeted delivery, their interactions with biological systems may result in unpredicted immunogenic or toxic responses. These negative effects may be species-specific, further obscuring the toxicological evaluation in PDX mouse models. The complex surface functionalization of nanoparticles needed to avoid immune clearance and attain ideal circulation frequently result in problems like off-target accumulation, reticuloendothelial system sequestration, and rapid opsonization, which lower therapeutic efficacy and raise the risk of systemic toxicity.[128]

Use of nanoscience in cancer is a progressive approach to merge cancer that can eliminate cancer or, at least control it long-term. Nanotechnology is also proving to be a tremendous force in the field of cancer diagnosis and therapeutic treatment; it is a technology that is spearheading enormous changes in these fields. Among the contributions that have been made stands the creation of advanced drug delivery systems that could be used to manipulate the biodistribution, tissue uptake, and pharmacokinetics of therapeutic agents. These developments are of utmost significance in biomedical studies because now more targeted and better therapeutic effects can be achieved. Mechanisms of controlled-release drugs delivery can considerably contribute to the efficacy of pharmacological treatments. The hallmarks that distinguish nanomedicines as a powerful tool in the cancer treatment process include their capacity to deliver drugs into the body in a controlled fashion, to exert site specificity, and their biocompatible nature. The small size of NPs enables effective internalization into cells to form stable nanocompositions that avoid the destruction of the therapeutic agents by nucleases; thus, the molecules will easily reach the sites of the tumors with ease and efficacy. Regardless of the obstacles that currently confine their broad implementation, nanomedicine in the future has considerable potential to be used to detect and treat not only CRC but also enhance other aspects of human physiology. The overall process, goals, and obstacles to clinical translation of PDX models for personalized CRC treatment is summarized in Figure 4.

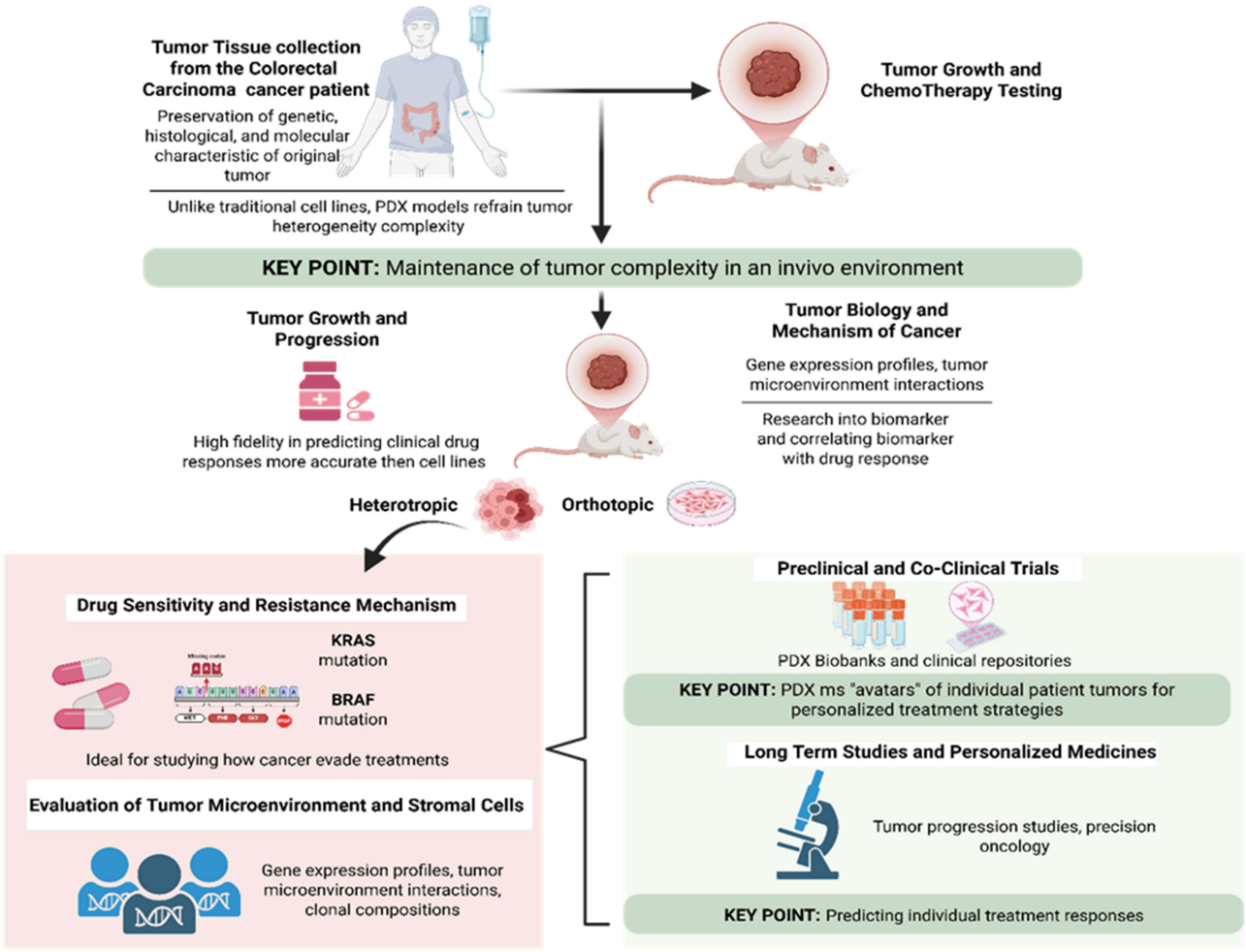

Figure 4 This figure illustrates the procedure and main ideas of personalized cancer treatment research studies focusing on using patient-derived xenografts (PDX) in preclinical and co-clinical trials. The key point is that it is necessary to keep the tumor complex in an in vivo environment to analyze the response to treatment properly. The first step would be to understand the mechanism of drug sensitivity and drug resistance, and this would be by studying mutation in certain genes such as KRAS and BRAF, which play a pivotal role in elucidating how cancerous cells circumvent treatment. The assessment of tumor microenvironment and stromal cells is also mentioned, such as gene expression profile analysis, tumor–stroma interactions, and clonal composition. These are the insights that will lead to personalized medicine and development of therapies. The figure also shows Preclinical and Co-Clinical Trials which employ the PDX models to generate avatars of individual patient tumors which are used to develop individualized approaches to treatment. Lastly, Long-Term Studies and Personalized Medicines will focus on predicting the response to treatment via tumor progression studies and precision oncology, which is more focused on the predictive power of individual patient response to treatment.

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Conclusion

Nanomedicine has become one of the most promising methods to enhance the treatment of CRC, especially in combination with patient-derived xenografts (PDXs) which maintain the molecular, stromal, and vascular heterogeneity of human tumors. PEGylated liposomes, polymeric nanoparticles, lipid-polymer hybrid systems, and ligand-targeted nanocarriers that target all CR-relatable receptors like EGFR and CD44 are the highest potential in the models of CRC PDX since they significantly enhance cumulative concentration, drug stability, and therapeutic effects and reduce systemic toxicity when compared to other platforms reviewed. PDX-guided screening allows rational optimization of the nanoparticle size, surface chemistry, and targeting strategy based on microenvironmental characteristics of a tumor. Nevertheless, there are still serious biological and technical challenges. The disparate heterogeneity of the enhanced permeability and retention effect in various CRC tumors introduces variability in nanoparticle delivery, whereas dense extra-cellular matrix, increased interstitial pressure, and hypoxic regions limit the nanoparticles to penetrate deeper into the tumor. Moreover, the traditional immunodeficient PDX models do not effectively recapitulate immune-nanoparticle interactions, which restricts their predictive capacity of the activity of immunomodulatory or immune-targeted nanomedicines. Scalability of manufacturing, batch-to-batch reproducibility, safety over time, and complicated pharmacokinetics are also key obstacles to clinical translation. Relatively nanomedicines must be highly characterized, have quality control standards and possess solid pharmacokinetic and toxicity profiles to be approved. These hurdles will have to be overcome by using sophisticated PDX models, enhanced nanocarrier engineering, and translational alignment to fully achieve the potential of nanomedicine-based precision therapy of CRC.

Disclosure

The authors report no conflicts of interest in this work.

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