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Recent Advances and Future Directions in Nanoparticulate Drug Delivery for Gastrointestinal Cancer Therapy

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Abstract : The gastrointestinal (GI) cancers, including colorectal, stomach, pancreatic, and hepatic malignancies, do so, and their group is a major cause of cancer morbidity and mortality on the World scale, faced to a great extent by non-selective biodistribution, dose limitations and resistance to drugs currently being studied. Nanoparticulate drug delivery systems have become one of the most promising platforms, able to overcome these limitations based on their distinct physicochemical characteristics, such as exploiting particle dimension, high surface-area to volume ratio, versatile surface chemistry, and controlling and stimuli-responsive drug delivery methods. The present review provides a comprehensive overview of the current state of affairs and recent developments in nanoparticulate drug delivery to treat GI cancer, discussing in detail the main types of nanocarriers, such as polymeric nanoparticles, lipid-based systems, inorganic nanoparticles, natural polymer-based carriers, and carbon nanomaterials, and their characteristics, limitations, and uses in the treatment of GI cancer. Mechanistic foundations and passive targeting methods through the use of the enhanced permeability and retention effect and active targeting with receptor-specific ligands such as folic acid, hyaluronic acid, transferrin, and antibody conjugates are heavily scrutinized. A special focus is put on the surface functionalization methods, especially amino functionalization of mesoporous silica nanoparticles, and stimuli-triggered drug release systems applied to the GI tumor microenvironment. Recent preclinical and clinical developments in nanoparticulate systems against colon cancer, gastric cancer, pancreatic cancer, and cancer of the liver are presented systematically with important in vivo and in vitro evaluation systems. The obstacles to clinical translation that are currently present such as EPR variability, protein corona formation, scaling of manufacturing, and the complexity of regulation are under discussion, and the future is directed to emerging prospects of theranostic nanoparticles, AI-guided formulation design, personalized nanomedicine, biomimetic platforms, and nanoparticle-immunotherapy combinations.

IndexTerms **– Nanoparticulate drug delivery, Gastrointestinal cancer, Mesoporous silica nanoparticles, Targeted cancer therapy, Tumor microenvironment, Stimuli-responsive drug release**

INTRODUCTION

Gastrointestinal (GI) tract cancer is one of the most catastrophic and widespread categories of cancer that pose threats to the global population health in the twenty-first century [1]. It is the gastrointestinal system, the part of the human body that includes the esophagus, stomach, small intestine, colon, rectum, liver, gallbladder, and pancreas, which collectively is the origin of some of the deadliest as well as most commonly diagnosed cancers in the world [2]. Based on GLOBOCAN 2022, colorectal cancer is the third most frequently diagnosed cancer and the second-topraking cancer-related fatalities worldwide with about 1.9 million incidences annually and 900,000 deaths per year [3]. With a growing burden among East Asian, Eastern European, and Latin American populations, gastric cancer, although decreasing in incidence in a few parts of the world with better eradication of Helicobacter pylori and dietary changes, kills more than 760,000 people annually [4]. Though comparatively lower in absolute incidence, pancreatic ductal adenocarcinoma has an appalling prognosis with a five-year survival rate that remains significantly less than 12%, mostly due to its late manifestation, aggressive biological behaviour, and complete resistance to currently available treatment. The most common primary malignancy in the liver is hepatocellular carcinoma, which is associated with about 830,000 deaths per year and is directly related to the global disease burden of chronic viral hepatitis, cirrhosis, and metabolism liver disease [5].

Surgery, radiation therapy and systemic cytotoxic chemotherapy have been the three pillars of therapeutic management of GI cancers [6]. Although surgical resection is the only potentially curative measure of localized disease, most GI cancer patients arrive at an advanced disease stage, where the curative surgery option is no longer possible. Systemic chemotherapy using 5-fluorouracil, oxaliplatin, irinotecan, gemcitabine, cisplatin, has shown only modest increases in survival in metastatic and locally advanced GI cancers, although the clinical utility of the treatment is often undermined by severe dose-limiting toxicity, including myelosuppression, peripheral neuropathy, nephrotoxicity and gastrointestinal side effects [7]. The non-selective biodistribution of standard chemotherapeutic agents leads to high drug exposures in normal tissues and is frequently observed to attain subtherapeutic levels at the tumor site, an inherent result of the pharmacokinetic characteristics of small molecule drugs delivered using conventional formulations. Moreover, the mechanisms of intrinsic and acquired drug resistance such as multidrug resistance transporter overexpression, deregulated apoptotic signatory processes, and epigenetic reprogramming also play a significant role in mitigating the therapeutic advantages of cytotoxic chemotherapy in the GI cancers over the long term [8].

The development of specific molecular therapies and immune checkpoint products have brought new levels of treatment of GI cancer. Bevacizumab, cetuximab, trastuzumab, as well as pembrolizumab, have shown clinical benefit on particular molecular subsets of GI cancers [9]. Nonetheless, the biologics are only effective in molecularly-defined patient groups, have their own adverse effects spectrum, and are frequently constrained by the emergence of acquired resistance. The necessity to develop new drug delivery modalities that have the capacity to surmount the pharmacokinetic and pharmacodynamic constraints imposed by the current therapies and allow the delivery of drugs to the cancer in a localized and targeted manner has thus emerged as an emergency requirement in the study of GI oncology. Over the last twenty years, nanotechnology has become a paradigm shift in the therapeutic use of nanoparticulate drug delivery systems in cancer treatment [10]. Nanoparticulate carriers A nanoscale, 1 to 1000 nanometers in diameter, nanoparticles consist of unique physicochemical properties that challenge the conceptual basis of conventional drug formulations allowing them to overcome complex barrier systems in the body, preferentially target tumor areas and deliver therapeutic payloads with greater specificity and efficacy than any other formulation [11]. Rational design of nanoparticle composition, size, surface chemistry, and drug release pathways have created novel opportunities to deal with the unmet clinical requirements of nanoparticles in the treatment of GI cancer [12].

The current review is a thorough exploration of the current paradigm of nanoparticulate drug delivery systems in the context of GI cancer therapy, and it outlines the major types of nanocarriers, their surface functionalization and targeting properties, recent findings in particular types of GI cancer, notable assessment methodologies, and the obstacles and opportunities that are destined to shape the future of this high-growth field.

2. Overview of Gastrointestinal Cancers

Gastrointestinal cancers are a heterogeneous set of malignancies originating in the epithelium of the digestive tract and related tissues and have unique molecular drivers, tumor microenvironment, clinical presentation, and treatment issues [13]. The rational design of nanoparticulate drug delivery systems to address the unique biological context of each of the major types of GI cancers requires comprehensive knowledge about the pathophysiology, molecular landscape, and microenvironmental features of each cancer type. Colorectal cancer (CRC) is the most widespread GI malignancy regarding worldwide incidence and has been the one most investigated in relation to nanoparticulate drug delivery [14]. CRC develops in a highly characterised multistage carcinogenic mechanism characterized by the progressive accumulation of genetic and epigenetic changes in the colonic epithelium, passing through hyperplastic polyps, adenomatous polyps, and then invasive carcinoma [15]. The major molecular changes that contribute to the pathogenesis of CRC comprise activating mutations in the KRAS and NRAS oncogenes, loss-of-function mutations in tumor suppressor genes like APC, TP53, and SMAD4, and Wnt/ -catenin and PI3K/Akt signaling pathway dysregulation. The molecular subtype of CRC that is clinically relevant as it leads to a different response to immunotherapy is called microsatellite instability (MSI), caused by the failure to repair mismatches in DNA [16]. Immunological inflammation, re-modeling of the colonic tumor microenvironment, and overexpression of surface receptors such as folate receptor, EGFR and CD44 typify the colonic tumor microenvironment of CRC and are major targets of nanoparticle-mediated active targeting therapeutics [17].

The gastric mucosa develops into gastric cancer, which is mainly adenocarcinoma but can be squamous cell carcinoma [18]. Gastric cancer progresses through sequential carcinogenic cascade that advances through chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and invasive carcinoma as proposed in the Correa pathway. The Cancer Genome Atlas (TCGA)-based molecular classification of gastric adenocarcinoma has defined four molecular subtypes, including EBV-positive tumors, microsatellite unstable tumors, genomically stable tumors, and chromosomally unstable tumors each possessing unique therapy susceptibilities. The most validated therapeutic target in gastric cancer, which is clinically validated, is HER2 amplification that occurs in about 15-20% of the cancers. The mucous secretes of the stomach tumor pose special problems with regard to drug administration such as highly acidic gastric environment, thick mucous lining, fast gastric emptying, and extensive stromal activities that cumulatively hinder drug penetration and bioavailability [19].

Pancreatic ductal adenocarcinoma (PDAC) is unique to the rest of GI cancers by its extremely thick desmoplastic stroma that forms up to 90 percent of the overall tumor mass and forms an almost impenetrable physical and biological barrier to drug delivery [20]. This desmoplastic microenvironment comprises cancer-associated fibroblasts, stellate cells, immune cells as well as high level of extra-cellular matrix proteins such as collagen, fibronectin and hyaluronic acid that together induce high interstitial fluid pressure, compress tumor vessels, and inhibit drug-delivery. Treatment resistance and aggressive biology of this malignancy are heterogeneously mandated by near-universal activating mutations in KRAS (present in more than 95% of PDAC). The hypoxia and immunosuppressive character of the microenvironment of the PDAC solid further undermine the effectiveness of traditional chemotherapy and future immunotherapeutic options, showing an urgent necessity to create nanoparticulate systems that can overcome the barriers of the stroma and demonstrate effective intratumor delivery of medications [21].

Hepatocellular carcinoma (HCC) has a special place in the list of GI cancers owing to its occurrence almost solely within the framework of preexisting chronic liver disease, such as cirrhosis caused by chronic hepatitis B or C viral infection, alcoholic liver disease, and non-alcoholic steatohepatitis [22]. The impaired liver hepatic clearance of the underlying liver disease limits the systemic therapeutic choice of HCC patients greatly because many cytotoxic compounds pose unacceptable hepatotoxicity in this cohort. HCC is typified by elevated vascularization and expression of certain surface receptors such as the asialoglycoprotein receptor (ASGPR) which is highly expressed on hepatocytes and HCC cells, and glypican-3, a proteoglycan that is largely overexpressed on the surface of HCC cells, offering crucial molecular targets to facilitate nanoparticulate drug delivery at the liver. The dual blood flow through the hepatic artery and portal vein such that the tumor vasculature depends mainly on the hepatic artery

because it is the main hepatic blood flow allows the use of loco-regional therapeutic approaches that can be integrated with the delivery of nanoparticulate drugs to control local tumors [23].

3. Nanoparticulate Drug Delivery Systems: An Overview

Nanoparticulate drug delivery systems refer to a structurally diverse and broad family of carriers built at the nanoscale, which is generally characterized by at least one dimension of 1 to 1000 nanometers in size, and which is engineered to deliver therapeutic molecules to their biological target location with greater precision, efficiency and reduced toxicity [24]. These carriers are nanoscale in nature and have a unique range of physicochemical properties not seen in bulk materials such as quantum effects, very high surface-area-to-volume ratio, high surface reactivity, and altered biodistribution and pharmacokinetic behavior in biological systems. All these properties together allow nanoparticulate systems to engage with biological structures at the molecular and cellular scale in a fundamentally different manner than conventional drug formulations, and biomedical researchers have yet to make the most of this ability in targeting and controlled drug delivery. One of the most important determinants of how nanoparticles behave in vivo is particle size [25]. Nanoparticles that have less than 8 nanometers diameter are normally subject to rapid excretion in the kidneys, whereas those that are more than 200 nanometers are effectively cleared by the mononuclear phagocyte system, especially by Kupffer cells in the liver and splenic macrophages. The best size range of the systemic circulation and tumor built-up with the EPR effect is always agreeable to be in the range of 50 to 200 nanometers, yet the optimal size can differ according to the tumor type, vascularization and the desired pathway. Particle size additionally is a key determinant of cellular uptake processes with particles of the size range 100-200nm normally undergoing clathrin-mediated endocytosis where larger size particles may undergo endocytosis by macropinocytosis or phagocytosis [26].

Polydispersivity index (PDI) is a valuable parameter of homogeneity of the size distribution of the nanoparticles, where a PDI of less than 0.2 is generally regarded as a sign of monodisperse population that can be used in pharmaceutical applications. Colloidal stability and protein adsorption behaviour as well as cellular interactions are controlled by surface charge, which is measured in terms of the zeta potential [27]. When the zeta potential value of nanoparticles exceeds ±30 m V, the nanoparticles are normally well-stabilized with regard to aggregation. The positively charged nanoparticles tend to exhibit improved cellular uptake based on electrostatic interaction with the negatively charged phospholipid bilayer of the cell apparent as well as increased non-specific tissue interactions and non-specific cytotoxicity over negatively charged or neutral particles [28]. The encapsulation efficiency of drugs, which is the ratio of the total drugs taken into the nanocarrier, and drug loading capacity, which is the ratio of the mass of drugs per unit mass of nanoparticle is of vital importance in defining the therapeutic payload and dosing requirements of nanoparticulate formulations [29].

The increased permeability and retention (EPR) effect, which was initially proposed by Matsumura and Maeda in 1986, offers the mechanistic explanation of passive tumor targeting with nanoparticles and is one of the most significant ideas in nanomedicine [30]. Dysfunctional vasculature occurs in rapid angiogenesis in solid tumors, such as GI cancers, i.e., irregular architecture, wide fenestrations of 100-800 nanometers and impaired pericyte coverage. These vascular defects, in combination with the defective lymphatic drainage of most solid tumors, allows nanoparticles of the correct size range to leech out of the tumor vasculature and accumulate in the tumor interstitium over time [31]. PEGylation, or the covalent modification of the nanoparticle surface by polyethylene glycol chain, is the most commonly used method to extend systemic circulation by creating a steric hydrophilic shell that decreases opsonization, reduces phagocytic recognition and increases blood residence time, which maximizes passive tumor accumulation through the EPR effect. Besides passive targeting, nanoparticulate systems may be active targeted by surface decoration to receptors overexpressed on cancer cells or tumor vasculature allowing receptor-dependent endocytosis and intracellular drug delivery. The introduction of stimuli-responsive moieties into the nanoparticle architecture allows localization of the drug release in response to certain physiological or pathological cues in the tumor microenvironment, such as acidic pH (around 5.0-6.5 in lysosomes and tumor interstitium), high glutathione concentration in the intracellular cytoplasm, hypoxia, overexpressed enzymes, including matrix metalloproteinases, and external stimuli, such as heat, light, and magnetic fields. All such multi-functional properties, in turn, permit nanoparticulate drug delivery systems to demonstrate superior therapeutic selectivity and efficacy over traditional formulations [32].

Table 1: Classification of Nanoparticulate Systems Used in GI Cancer Therapy [33–36]

Category	Type	Size Range	Key Features	Advantages	Limitations	GI Cancer Application
Polymeric NPs	PLGA, PLA, Chitosan, PEG-based	100–500 nm	Biodegradable, tunable release, surface modifiable	FDA-approved polymers, controlled release, scalable	Batch variability, burst release	Colorectal, gastric cancer
Lipid-Based Systems	Liposomes, SLNs, NLCs	50–300 nm	Biocompatible, dual drug loading,	High biocompatibility, clinical precedent	Poor stability, drug leakage	HCC, CRC, pancreatic cancer

			membrane mimicking			
Inorganic NPs	Mesoporous Silica, Gold, Iron Oxide	50–200 nm	High surface area, porous, multifunctional	High drug loading, stimuli-responsive	Non-biodegradable concerns	Colon, pancreatic, liver cancer
Natural Polymer NPs	Alginate, Hyaluronic acid, Gelatin, Pectin	100–400 nm	Mucoadhesive, receptor-targetable, biocompatible	Natural origin, low toxicity	Variable quality, low mechanical strength	Colorectal, gastric cancer
Carbon Nanomaterials	CNTs, Graphene oxide, Fullerenes	10–100 nm	Ultra-high surface area, photothermal properties	High drug loading, PTT capability	Toxicity concerns, poor biodegradability	GI cancers (experimental)
Dendrimers	PAMAM, PPI dendrimers	1–10 nm	Monodisperse, multivalent surface, precise architecture	Controlled structure, multifunctionality	Complex synthesis, cytotoxicity at higher generations	Colon cancer
Protein-Based NPs	Albumin, Ferritin, Gelatin	100–200 nm	Naturally derived, biodegradable, low immunogenicity	Biocompatible, SPARC-mediated targeting	Limited drug loading, costly	Pancreatic, gastric cancer
Hybrid NPs	Lipid-polymer, Organic-inorganic	100–300 nm	Combined properties of constituent materials	Enhanced stability and functionality	Complex fabrication	CRC, HCC, pancreatic cancer

4. Types of Nanoparticles in GI Cancer Therapy

4.1 Polymeric Nanoparticles

Polymeric nanoparticles are the most studied type of nanocarrier in cancer drug delivery, which is supported by decades of research revealing that polymeric nanoparticles are versatile, biocompatible, and can be readily surface engineered. Out of the broad range of possible polymers used in the production of nanoparticles, poly(lactic-co-glycolicacid) (PLGA) has a particularly special place because it is approved to be used in humans by the FDA, it can be fully bio-degraded by hydrolysis into non-toxic lactic acid and glycolic acid metabolites, and can have patterns of drug release that can be highly tailored both by adjusting the polymer molecular weight and lactide-to-glycolide ratio and by controlling end-group chemistry. PLGA nanoparticles have also shown promising preclinical outcomes in colorectal cancer models, with reports that suggest PLGA nanoparticles that are loaded with 5-fluorouracil have shown a great deal of improvement in cytotoxicity rates in the analysis of file colorectal cancer models over several additional hours compared with the free drug solution, namely, 24-72 hours. PEGylation of surfaces of PLGA nanoparticles to form PEG-PLGA core-shell structures has been extensively studied to achieve simultaneous long systemic circulation, active tumor targeting, and regulated drug delivery in GI cancer models [37].

Chitosan, a naturally derived polysaccharide derived by deacetylation of chitin, has become an extremely appealing polymer in the delivery of GI cancer drugs because of its intriguing biocompatibility, biodegradability, mucoadhesive properties and intrinsic cationic charge. The mucoadhesive properties of chitosan are due to the ability to form electrostatic interactions between the protonated amino-lines of chitosan and negatively charged mucin glycoproteins of the gastrointestinal mucosa to lengthen the residence time and increase drug permeation across mucosal barriers. Thiolated chitosan derivatives, resulting as a result of covalent bonding between thiol groups to the chitosan backbone, show even higher mucoadhesion due to the formation of disulfide bonds with puccinic cysteine residues, and have proven better retention of drugs in the colon than chitosan nanoparticles. The pH-sensitive swelling property of chitosan nanoparticles due to protonation and deprotonation of amino groups when moved through the GI pH gradient is useful to release select drugs in the colonic microenvironment and chitosan-based systems can be especially useful in colon-specific drug delivery in colorectal cancer therapy [38].

4.2 Lipid-Based Nanoparticles

Nanoparticulate systems based on lipids are the most developed type of nanocarriers and a number of such formulations have found regulatory approval and multiple clinical applications in oncology. Liposomes, spherical vesicles made of a single or multiple phospholipid bi-layers that surround a body of aqueous core, were among the earliest nanomedicines to have shown clinical efficacy, and continue to be one of the best-characterized drug delivery platforms. This amphiphilic character of phospholipids allows liposomes to initially deliver hydrophilic drugs stored in their water-containing lumen and lipophilic drugs stored in their lipid bilayer, giving it outstanding versatility as carriers of a broad lower lipid profile of chemotherapeutic agents pertinent to the treatment of GI cancer. PEGylated liposomal doxorubicin (Doxil/Caelyx), the first FDA-approved nanomedicine, showed considerably lower cardiotoxicity and different pharmacokinetics than free doxorubicin, the initial clinical demonstration of nanoparticulate drug delivery [39].

Solid lipid nanoparticles (SLNs), a response to liposomes and polymeric nanoparticles, are prepared using a solid lipid matrix that is held in the solid state at both room and body temperature. SLNs have a number of benefits such as high physical stability over liposomes, preservation of drug molecules encased within the vesicle by an organic layer, site-specific release of the drug due to the presence of a solid lipid core and absence of organic solvents during their production which can be replaced by high-pressure homogenization. A second generation lipid nanoparticle system that addresses the inherent drawback of SLNs such as the expulsion of drugs as the lipids recrystallize, nanostructured lipid carriers (NLCs) uses a mix of solid and liquid lipids to entrap a drug in less ordered lipid matrix with better pharmacokinetic and physical stability under long-term storage conditions. Both SLNs and NLCs have been widely investigated in delivering hydrophobic chemotherapeutic agents such as docetaxel, paclitaxel and curcumin in models of GI cancers, which show high encapsulation processes, controlled release mechanisms, and in vitro cytotoxicity [40].

4.3 Inorganic Nanoparticles

Inorganic nanoparticles, including mesoporous silica nanoparticles (MSNs), gold nanoparticles, iron oxide nanoparticles, and calcium phosphate nanoparticles, have received much and increasing attention in the area of GI cancer drug delivery due to their rigidity in structure, chemical stability, and multifunctional surface chemistry enabling complex drug loading and release regimens, which are not available with purely organic nanocarriers. The most promising inorganic nanocarrier platform in the delivery of GI cancer drugs would be mesoporous silica nanoparticles with highly ordered hexagonal or cubic porous architecture, 2-50 nm pore diameters, large surface areas of up to 1000 m^2/g, and large pore volumes. The exceptionally large interior surface area of MSNs means that they can adsorb and entrap much larger quantities of drug molecules than solid nanoparticles of similar size, overcoming one of the limiting factors of most other nanocarrier systems. Additionally, silanol groups (-SiOH) widely available on the MSN surface offer highly versatile anchoring sites to covalently conjugate a very broad array of functional groups and targeting ligands using well-developed organosilane chemistry [41].

Amino-functionalized MSNs (NH_2-MSNs) obtained by surface modification of the MSNs with amino groups (-NH_2) reacted with aminopropyltriethoxysilane (APTES) or aminopropyltrimethoxysilane (APTMS) possess various desirable qualities in the delivery of anti-cancer drugs. Primary amine functional groups greatly enhance loading of negatively charged drug molecules by electrostatic interaction, allow conjugation of targeting ligands, antibodies, and polymers through the action of amine-reactive crosslinkers and end with pH-responsive drug delivery behavior due to protonation of amine functional groups in the acidic tumor microenvironment and lysosomal compartment after endocytosis. Amino functionalization gives the positive charge to the surface further enabling the interaction with the negatively charged cancer cell membrane, promoting cellular uptake by electrostatic forces. Research has shown that, amino-functionalized MSNs have greatly improved loading efficiencies of alkaloid and phytochemical drugs than unmodified MSNs, and the profile of pH-triggered drug release is observed to have a selective release at pH 5.0 and 6.5 representing lysosomal and tumor microenvironmental representations, and reduced superfluous release at physiological pH 7.4 [42].

Gold nanoparticles have tunable localized surface plasmon resonance characteristics that make them ideal in photothermal cancer therapy, where near-infrared light irradiation of gold nanoparticles accumulated in tumor tissue produce localized heating to the extent of killing cancer cells but leaving normal tissues intact. Iron oxide nanoparticles, specifically superparamagnetic iron oxide nanoparticles (SPIONs) offer dual functionality as both imaging contrast agents in magnetic resonance imaging and as magnetically guided drug delivery vehicles, which allows them to be used in theranostics in the management of GI cancer. External magnetic field can be used to target SPION-loaded nanoparticles to tumors, which may increase intratumor drug concentrations at lower systemic exposures [43].

4.4 Natural Polymer-Based Nanoparticles

Nanoparticles made of natural polymers and derived via the biotechnology of plants, animals, or microbes have received growing interest in GI cancer drug delivery, due to their common biocompatibility, biodegradability, and capacity to engage with biological processes via biologically relevant molecular interaction. The hyaluronic acid (HA), a naturally occurring glycosaminoglycan, which is found in the extracellular matrix, has been identified as one of the most commonly studied natural polymers in the targeted delivery of drugs to cancer cells because of its selective and high-affinity binding to CD44, a cell surface glycoprotein which is both a hyaluronic acid receptor and a broadly expression of cancer stem cells in cancers of the colorectum, gastric, and pancreas. HA-functionalized nanoparticles take advantage of this cellular recognition to have the ability to selectively target cancer cells or cancer stem cells expressing the CD44 receptor via receptor-mediated endocytosis into cells, allowing the tumor-initiating cell population that causes tumor recurrence, metastasis, and drug resistance to be targeted [44].

Alginate is a natural anionic polysaccharide generated by brown seaweed and it is an ionic crosslinked divalent cation hydrogel nanoparticles, which shows pH-sensitive swelling properties, which can be used to deliver drugs specifically to the colon. Alginate nanoparticles keep their gel structure fine and intact in the acidic stomach and small intestinal environment but swell and release their drug payload in the colon in the neutral to slightly alkaline pH. Another plant-derived polysaccharide, pectin, also is subject to enzyme degradation by pectinase-producing colonic microbiota, thus allowing bacteria to promote release of drugs targeted to the colon, which makes pectin-based nanoparticles an especially attractive platform in colorectal cancer drug delivery. Nanoparticles made of denatured collagen, gelatin nanoparticles, have been examined in delivering chemotherapeutic agents by intravenous delivery into pancreatic cancer models, proving biocompatible, biodegradable, and readily surface modified to with targeting ligands [45].

4.5 Carbon-Based Nanomaterials

Carbon-based nanomaterials constitute an array of structurally and functionally heterogeneous nanocarrier systems that have been studied in cancer drug delivery and photothermal therapy and include carbon nanotubes (CNTs), graphene oxide (GO), fullerenes, and carbon quantum dots. The carbon nanotubes are single-walled and multi-walled, and they offer extraordinary aspect ratio and mechanical strength, as well as electrical conductivity, and near-infrared absorption characteristics that facilitate photothermal tumor ablation. The external surface of CNTs is large and facilitates large drug loading by non-covalent interaction between π-π stacks with aromatic drug molecules and increases aqueous dispersibility, reduces non-specific adsorption to proteins and allows conjugation of targeting ligands [46].

The attention especially on graphene oxide as a nanocarrier platform is due to its remarkable surface area, the presence of numerous oxygen-containing functional groups to enable covalent and non-covalent loading of drugs, and a photothermal response in the near-infrared. Graphene oxide sheets functionalized have also been explored as the co-delivery of chemotherapeutic agents including doxorubicin with small interfering RNA (siRNA) targeting drug resistance genes in colorectal cancer models, with synergistic effects found in anticancer with combined chemotherapy and gene silencing via RNA interference. Carbon-based nanomaterials, in spite of their exceptionally promising in vitro and in vivo performance, are subject to very prominent concerns regarding long-term biocompatibility, biodegradability, and possible pulmonary and systemic toxicity, which pose important scientific and regulatory issues that are currently tightly regulated before clinical translation can even be contemplated [47].

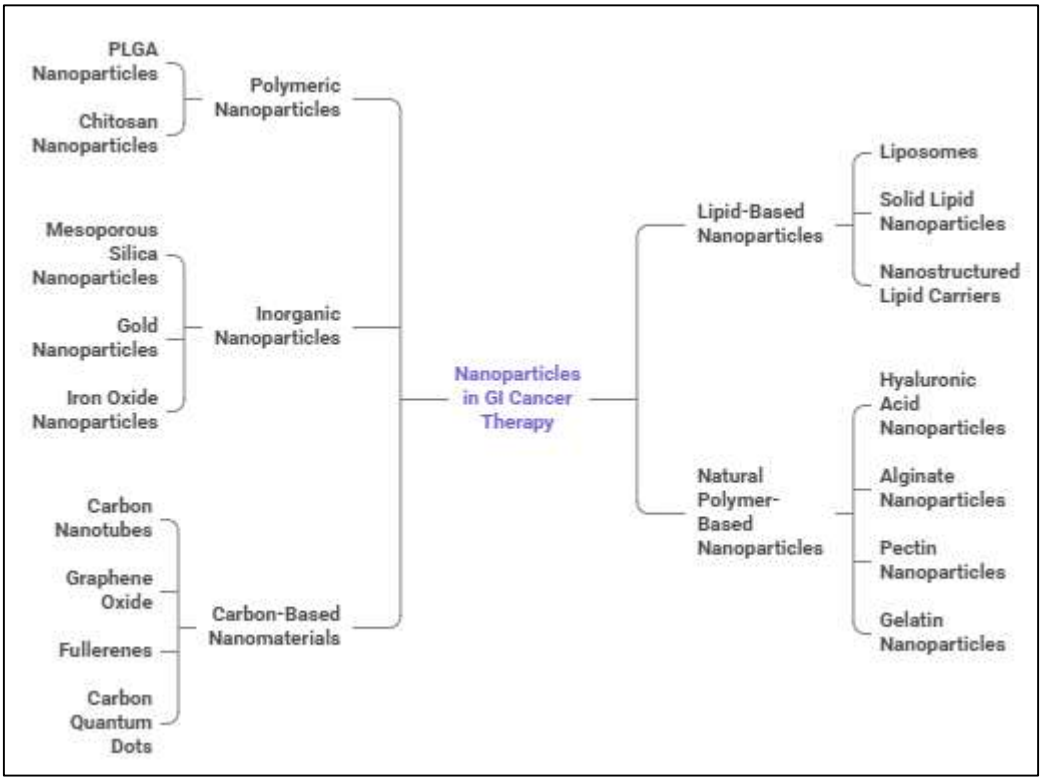

Figure 1: Types of Nanoparticles in GI Cancer Therapy

5. Surface Functionalization and Targeted Delivery Strategies

Surface functionalization of nanoparticles forms the basis of rational nanocarrier design in targeted cancer drug delivery because the basic physicochemical properties of the nanoparticle surface fundamentally define the relationship between it and biological fluids, cell membranes, immune surveillance systems and ultimately its designed therapeutic behavior in vivo. Precisely by engineering the surface of nanoparticles by reflecting important functional groups, polymeric coatings, targeting ligands and stimuli-sensitive components, nanoparticles can be programmed to follow a predetermined path through the intricate biological environment surrounding the administration site to the tumor, and reduce off-target interactions that cause systemic toxicity [48].

The most basic type of targeting widely used in nanoparticulate delivery of drugs to solid tumors such as GI cancers is passive targeting that takes advantage of the EPR effect. The physiological mechanism of the EPR effect in GI tumors lies in their rapid and deregulated angiogenesis, caused by the overexpression of pro-angiogenic factors such as vascular endothelial growth factor

(VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), leading to tumor blood vessels with a characteristically abnormal architecture, with wide inter-endothelial distances of 100-800 nanometers, and with inadequate pericyte coverage [49]. These pathologic changes allow leaking out of the circulating nanoparticles out of the tumor vasculature into the tumor interstitium and the complementary lack of functional lymphatic removal in the tumor leads to persistent accumulation over time. The EPR effect is extremely variable between tumor types, and well-vascularized tumors such as HCC normally have stronger nanoparticle accumulation mediated by EPR than poorly vesselized, hypovascular tumors like pancreatic cancer with dense desmoplastic stroma. PEGylation of nanoparticle surfaces with chains of polyethylene glycol of optimal molecular weight (2-10 kDa) and surface density is the most universally utilized approach to maximize EPR-mediated passive targeting by forming a hydrophilic brush-like protective corona that reduces adsorption of serum opsonins, minimizes recognition by phagocytic cells, and enhances blood circulation half-life to minutes to hours [50].

Active targeting is a supplementary and more significant strategy aimed at attaining specific if receptor-based recognition and uptake of nanoparticles on cancer cells with a higher expression of a target receptor relative to normal tissues. Various targeting moieties repertoire has been examined with regard to the GI cancer-directed nanoparticle targeting. One of the most studied targeting ligands used in GI cancer targeting is folic acid, which is a small vitamin molecule with a strong affinity to the folate receptor (FR), as these receptors are highly expressed in colorectal, gastric, and pancreatic cancers in contrast to most normal tissues [51]. Nanoparticles conjugated to folate have shown increased cellular uptake and cytotoxicity of FR-positive GI cancer cell lines in endocytosis via folate receptors. Another valuable active targeting opportunity is transferrin receptor (TfR) which is overexpressed in fast-growing cancer cells to meet their increased iron need. Many other nanoparticles have been conjugated to the surfaces of the insects using anti-EGFR antibodies and antibody fragments to target EGFR-overexpressed cells in the cancer types of CRC and gastric cancer over their clinical validation of EGFR as a therapeutic target [52].

Aptamers, short single-stranded oligonucleotides of DNA or RNA found using systematic evolution of ligands by exponential enrichment (SELEX) have come into the limelight as more promising against nanoparticle surface decoration on the basis of their various unique benefits over antibodies, such as smaller molecular size, reduced immunogenicity, facile chemical synthesis, thermal stability, and reversible folding. EpCAM-targeting aptamers, nucleolin-targeting aptamers, and AS1411 aptamer have been loaded onto different nanoparticle systems to deliver drugs to GI cancer in Targeted Therapy: Preclinical Assets show selective binding and uptake in cancer cells expressing EpCAM in preclinical models. Amino functionalization, which can be performed by covalent attachment of primary amine (-NH2) groups onto surfaces of nanoparticles through silane coupling reagents in silica-based particles or polymer grafting in organic nanoparticles, has multifunctional uses in nanoparticle design in the case of GI cancer drug delivery [53]. In addition to improving the efficiency of electrostatic loading of drugs and facilitating covalent conjugation of targeting ligands via amine-reactive chemistry, the presence of amino functional groups is also a key determinant of pH-responsive drug release behavior. The local pH environment is very sensitive to the protonation state of amino groups, which switches between neutral free base state at physiological pH 7.4 and protonated ammonium form at low acidic pH values similar to the tumor interstitium (6.5-6.8), endosomes (pH 6.0-6.5) and lysosomes (pH 4.5-5.0). The pH-dependent protonation adjusts the electrostatic interactions between the functionalized nanoparticle surface and the adsorbed drug molecules, which allows drug release (pH-adjusted) in the acidic tumor microenvironment and intracellular compartments experienced upon endocytosis and reduces premature drug leakage (pH-neutral) in the neutral pH of the bloodstream [54].

To provide spatiotemporally controlled tumor-microenvironment drug release, stimuli- Some nanoparticles have been engineered to include pH- sensors, redox-, enzyme-, or thermoresponsive- based stimuli- responsive drug release systems. Redox-responsive nanoparticles take advantage of the significantly higher concentration of the intracellular cytoplasm (glutathione) of the cellular cytosol (2-10 mM) relative to the extracellular environment (2-20 muM), and utilizes disulfide bonds to cleave and release drug cargo following intracellular internalization. Enzyme-responsive systems exploit the high levels of the activity of tumor-associated enzymes such as matrix metalloproteinases (MMPs), hyaluronidase and cathepsins to activate nanoparticle degradation or surface modification at the tumor locations, allowing local activation of drugs. These multi-stimuli-responsive systems have a future of very selective intratumoral drug delivery with low systemic exposures [55].

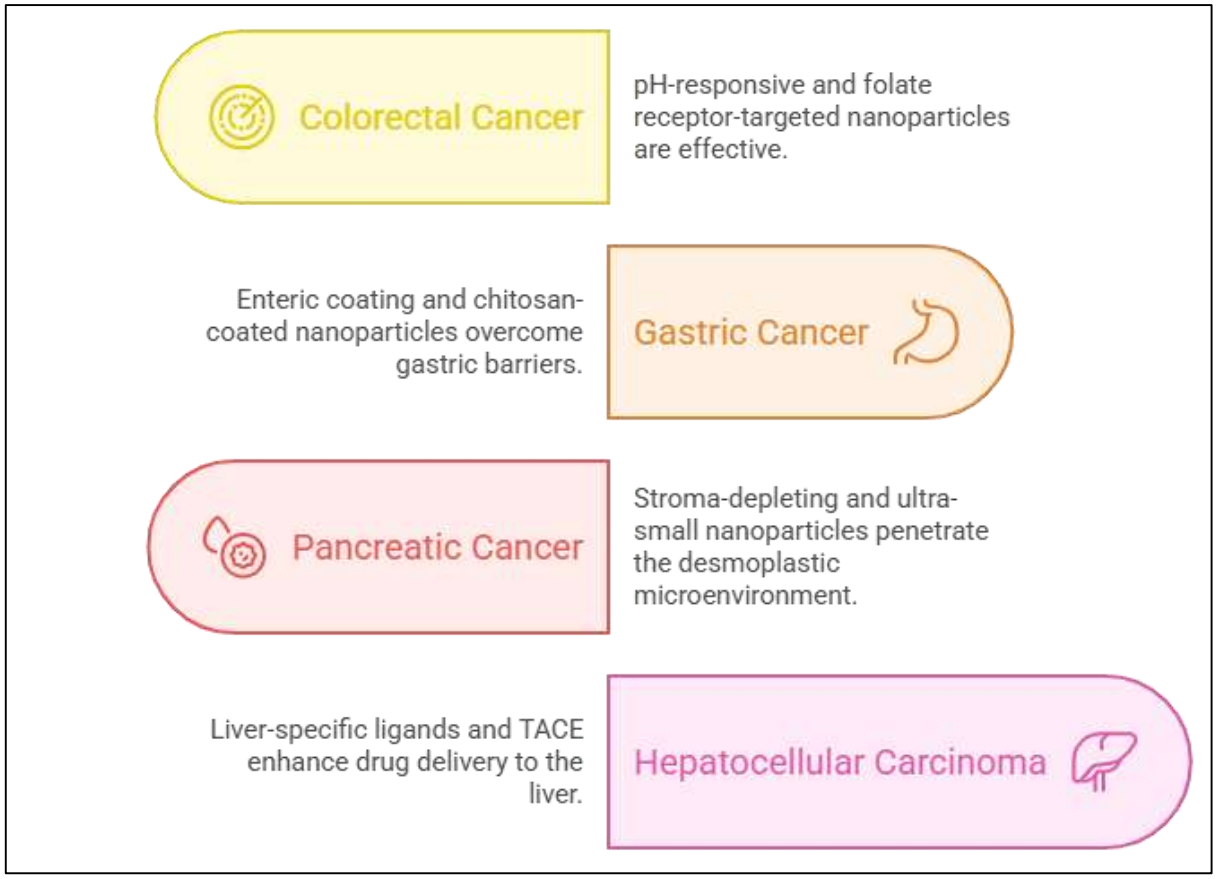

Figure 2: Targeted Nanoparticulate Systems for GI Cancers

6. Recent Advances in Nanoparticulate Systems for Specific GI Cancers

6.1 Colorectal Cancer

Nanoparticulate drug delivery inflammations have found a first testing ground in colorectal cancer in the GI oncology domain owing to the accessibility of well-characterized cell line types, established animal models, and the accessibility of the colon to oral and systemic drug delivery approaches. Peculiar physiological features of the colorectal cancer environment such as the alkaline colonic luminal pH of 6.8-7.4, enriched colonic microbiota with its diverse enzymatic repertoire, and overexpression of various surface receptors on CRC cells all offer multiple biological handles to the development of colon-targeted and tumor-selective nanoparticulate systems. pH-responsive PLGA and Eudragit S100-based nanoparticles have been explored extensively as an oral delivery system [56].

Nanoparticulate systems that selectively target the follate receptor have been one of the most fruitful active methods of targeting in CRC, and have been successfully used in a variety of studies, showing much improved cellular internalisation and cytotoxicity in fares receptor-overexpressing HT-29, HCT-116 and SW480 colorectal cancerous cell lines when compared to non-targeted formulations. Amino-functionalized, phytochemical-loaded MSNs have garnered an increased number of studies in the treatment of CRC, utilizing both the pH sensitivity of drug delivery with amino-MSNs and the naturally occurring raft of plant-based alkaloid or amino-produced alkaloid cascades themselves with anti-cancer properties. These systems have shown good in vitro release profiles with accelerated release during acidic conditions that mimic the lysosomal environment, and potent cytotoxic response against CRC cell lines with the induction of apoptosis, cell cycle arrest, and alterations in the expression of the common signaling pathways. Synergetic anticancer effects have been observed in CRC models when chemotherapeutic agents are co-delivered with siRNA or microRNA using cationic nanoparticulate delivery systems that enabled simultaneous cytotoxic death of cancer cells and silencing of drug resistance genes, indicating that this represents a multi-mechanistic method to surmount the treatment resistance problem posed by advanced CRC [57].

6.2 Gastric Cancer

Gastric cancer is an especially difficult target of nanoparticulate drug delivery because of a very hostile physicochemical environment of the gastric lumen, which place severe restrictions on the stability and functionality of nanoparticulate formulations delivered orally. The high acidity of the stomach (pH 1.2-2.0), the presence of numerous proteolytic enzymes, thick gastric mucous membrane, and high rate of gastric emptying are all formidable obstacle to effective nanoparticle-mediated drug delivery. Enteric coating with acid-resistant acid polymers like Eudragit L100-55 and cellulose acetate phthalate, pH-responsive nanoparticles that are designed to preserve structural integrity at gastric pH and release payload at the higher gastric mucosa pH in pathological conditions, and formation of injectable nanoparticulate systems to achieve systemic delivery avoiding the excessive gastric environment are all strategies that have been used to overcome such gastric barriers [58].

Nanoparticles coated with chitosan are found to have greater mucoadhesive properties and better gastric retention in experiments of mucin binding in vitro and in living animals, allowing prolonged drug delivery in the gastric mucosa. HER2-targeted

nanoparticulate nanoparticles are a nanoparticle delivery system of special interest to the roughly 15-20% of gastric cancers expressing HER2, where anti-HER2 antibody-conjugated nanoparticles have shown selective accumulation and increased cytotoxicity in HER2-positive cell lines of NCI-N87 and MKN-45 gastric cancers. Recent advances to exosome-inspired nanovesicles and cancer cell membrane-coated nanoparticles have provided new bioinspired biomimetic developmental tools to make homologous targeting of gastric cancer cells through capitalizing on the intrinsic molecular recognition in biological membranes to provide selective targeting of tumors with minimum immune surveillance. These biomimetic vehicles have been shown to possess good tumor-homing potential, and low macrophage uptake in preclinical models of gastric cancer, as opposed to synthetic nanoparticles [59].

6.3 Pancreatic Cancer

The deep desmoplastic microenvironment of pancreatic ductal adenocarcinoma presents arguably the greatest challenge to oncological drug delivery, presenting an almost insurmountable barrier to the intratumoral penetration and efficacy of typical chemotherapy as well as nanoparticulate drug delivery vehicles. There are several new approaches which have been developed to circumvent the pancreatic stromal barrier including utilizing stroma-depleting nanoparticulate systems that deliver cytotoxic drugs and simultaneously stromal-modulating agents, generating ultra-small nanoparticles less than 50 nanometers in diameter which diffusion in the dense extracellular matrix, and the functionalization of nanoparticles with enzymes, typically collagenase or hyaluronidase which degrades the stromal matrix components and enhances tumor penetration [60].

Albumin-bound paclitaxel nanoparticles (nab-paclitaxel, Abraxane) and hap-paclitaxel (safacitibaxin) are the most clinically successful examples of nanoparticulate drug delivery in pancreatic cancer to date, demonstrating an overall survival advantage over traditional gemcitabine monotherapy in the MPACT phase III clinical trial, and resulting in its regulatory approval as first-line during the treatment of metastatic pancreatic cancer in combination with gemcitabine. The increased activity of nab-paclitaxel is explained by several processes such as augmented tumour penetration created by albumin-mediated transportation, SPARC-mediated tumour targeting, and destruction of the desmoplastic stroma that boosts intratumor gemcitabine concentrations. Nanoparticles of hyaluronic acid with CD44-positive pancreatic cancer stem-cell targets have been shown to selectively eliminate the stem cell subpopulation implicated in generating tumors, recurrence, and metastatic spread of in preclinical models of PDAC, fulfilling an urgent unmet goal in the treatment of pancreatic cancer [61].

6.4 Hepatocellular Carcinoma

Hepatocellular carcinoma holds a special niche in the world of nanoparticulate drug delivery because of the hepatic tropism of intravenously delivered nanoparticles, which are naturally collected by the liver via fenestrated sinuously shaped endothelium and through Kupfer cell receptor-mediated nanoparticle uptake. Though it poses a challenge to targeting HCC selectively over normal hepatic parenchyma, it also offers a natural benefit to liver-directed drug delivery that can be enhanced with active targeting using liver-specific ligands. Nanoparticles based on asialoglycoprotein receptor-targeting and conjugated with galactose, lactobionic acid, or N-acetylgalactosamine moieties have been widely developed to deliver drugs specifically to the liver via endocytosis by the clathrin-mediated endogenous route, exploiting the high density of ASGPR expression in hepatocytes and HCC cells (thousand receptor complexes/minute). Transarterial chemoembolization (TACE) with drug-eluting nanoparticle-based embolic beads is a clinically valid loco-regional adjunct capable of achieving ischemic tumor necrosis by embolizing the arteries and delivering high lococal concentrations of chemotherapeutic agents to HCC tumor and reducing systemic drug exposure. Doxorubicin (DEB-DOXO, DC Bead) loaded drug-eluting beads are currently used in clinic practice in TACE in intermediate-stage HCC which is characterized by reduced systemic toxicity of doxorubicin and greater local tumor control than conventional TACE. The application of nanotherapeutics using RNA interference against HCC oncolytic targets such as β-catenin, c-Myc, and VEGF, as siRNA nanoparticles has shown a opportunity to induce substantial tumor growth inhibition in orthotopic HCC mouse models, and opens the door to non-clinical trials on gene therapy in this incurable cancer [62].

7. Challenges and Limitations

Although remarkable strides have been made in preclinical models of GI cancer, clinical implementation of nanoparticulate drug delivery vehicles has lagged far behind these milestones with less than 20 nanoparticulate anticancer platforms worldwide in regulatory approval, so far. A series of biological, physicochemical, manufacturing, and regulatory issues remain as obstacles to the clinical viability of nanomedicine through the translation of promising laboratory findings into practice. Biological complexity and heterogeneity of the issues of the tumor microenvironment have greatly influenced nanoparticle performance that can not be well reproduced in simplified in vitro models. Although the EPR effect is theoretically convincing, it has proven extremely heterogeneous in human tumors, and quantitative PET imaging studies show that only 0.7%- 3% of a given dose of nanoparticles is actually accumulated in tumor tissue, which is significant in questioning its stability in the clinical application as a universal tumor targeting strategy [63].

Another critical challenge is protein corona formation, which is a result of the fast adsorption of serum proteins on nanoparticle surfaces after the administration of such nanoparticles. This protein-coated surface layer essentially changes the circulation time of nanoparticles, the targeting of ligand availability, cellular uptake dynamics, and biodistribution, frequently inducing opsonization and early phagocytic elimination by the mononuclear phagocyte system. Although PEGylation has been widely adopted and alternative antifouling surface coats employed, full resistance to protein adsorption in the complex physiological environment has not been achieved technically. Scalability of manufacturing and batch-to-batch reproducibility are serious practical challenges to commercial production of nanoparticles. Techniques of fabrication used in academics are often hard to scale-up to industrial levels

with the same consistent particle size, drug loading, and surface functionalization. New microfluidic and continuous flow manufacturing technologies are promising, but their large-scale application in pharmaceuticals is not yet a reality. Commercial development is further complicated by long-term stability of the formulation during storage and clinical manipulation, the risks of job aggregation, leaching of drugs, and release of ligands [64].

The issues of regulations are a significant setback to clinical acceptance because detailed harmonized schemes specifically for nanomedicines are still lacking. Regulatory authorities such as the FDA, EMA and CDSCO demand a wide set of preclinical safety package and standardized characterization data and strict manufacturing reproducibility evidence. The largely inadequate predictive accuracy of animal models of human nanoparticle effects coupled with developing complicated quality control standards to multi-component nanoparticulate backgrounds have jointly decelerated regulatory accreditation and raised the development cost in the nanomedicine industry [65].

8. Future Directions and Emerging Trends

Nanoparticulate drug delivery in GI cancer treatment is a fast-growing field, with the integration of advanced materials science, artificial intelligence, precision oncology, and immunology with nanoparticle engineering now providing new and heretofore unimaginable therapeutic opportunities. Theranostic nanoparticles (a unified nanoplatform, comprising diagnostic imaging and targeted drug delivery) are one of the most clinically influential emerging areas of GI nanomedicine. Theranostic systems can allow real-time non-invasive imaging of biodistribution and tumor accumulation of nanoparticles, enabling optimization of treatment delivery to individual GI cancer patients with image guidance and personalized therapy, by co-incorporating imaging agents like superparamagnetic iron oxide to MRI, gold nanoclusters to CT or near-infrared fluorescent probes and therapeutic payloads. Artificial intelligence and machine learning are currently being used to speed up the development of nanoformulations by discovering complex multi-parameter correlations between nanoparticle physicochemical characteristics and biological performance. Rational selection of optimal nanoparticle compositions and surface functionalization strategies is facilitated by AI-driven computational models with greatly reduced experimental load of optimizing the formulation, and prioritization of the most promising options to in vitro and in vivo validation [66].

Individual nanomedicine, informed by the personal molecular profile of tumors in individual patients, is a paradigmatic change to traditional drug delivery methods. Personalized screening of nanoparticulate formulations Patient-derived tumor organoids are developing as potent ex vivo models of identifying the most effective therapeutic approach in each patient before administration into the clinic. Combined with the use of computational nanoparticle modeling, integration of multi-omics data will also allow rational selection of targeting ligands based on tumor molecular landscape specifics. Exosome based drug carriers and tumor homing nanoparticles derived via biomimetic nanoparticle platforms are already gaining considerable momentum as next generation delivery vehicles taking advantage of the biological compatibility, tumor-targeting properties of natural cellular membrane and reduced immunogenicity of natural cellular membranes compared to entirely synthetic systems [67]. The most potentially clinically important emerging area is convergence of nanoparticulate drug delivery with cancer immunotherapy, with nanoparticles being developed to co-deliver therapeutic agents with immune checkpoint inhibitors, toll-like receptor agonists and cancer vaccines. This synergistic strategy will concurrently cause immunogenic cancer cell death and re-program the immunosuppressive GI tumor microenvironment and this approach has the potential to overcome the traditionally low immunotherapy response rates in colorectal and pancreatic tumors. Lastly, orally bioavailable nanoparticulate system of systemic GI cancer therapy has great potentials in enhancing patient compliance and quality of life. Growth of knowledge of transcytosis pathways such as FcRn-mediated, vitamin B12-mediated and M cell-mediated cross-membrane transport across intestinal epithelium, and mucus-diffusing PEG-coated nanoparticles, is offering a rational design principles to the next generation of orally deliverable nanomedicines in GI oncology [68].

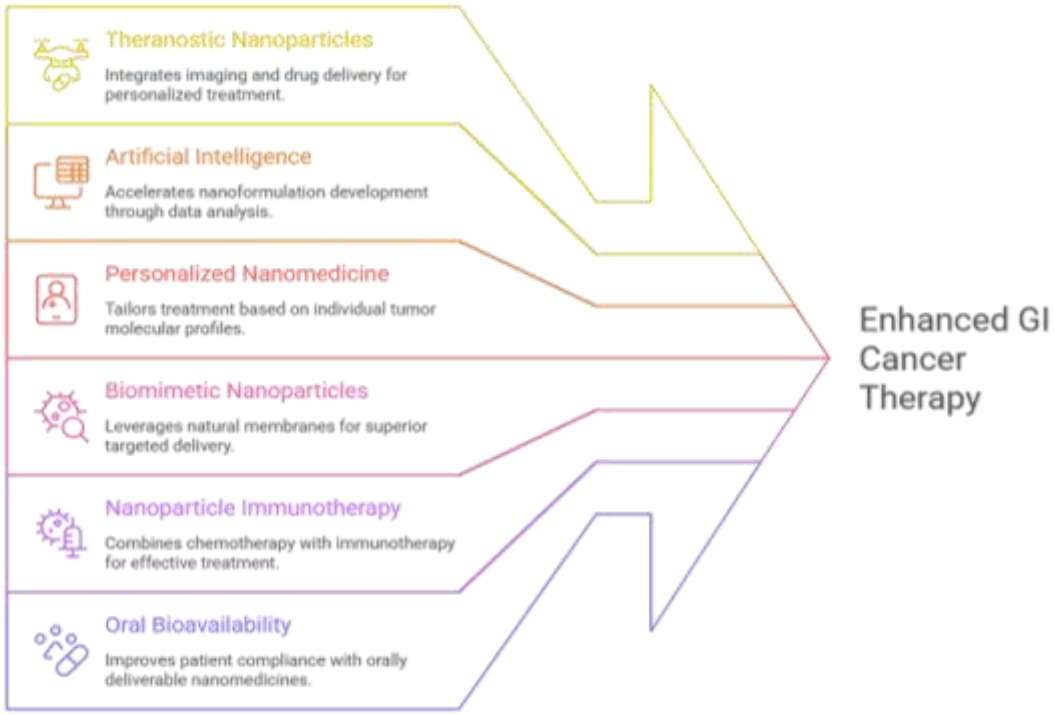

Figure 3: Future Direction of Nanoparticulate Drug Delivery in Gastrointestinal Cancer Therapy

9. Conclusion

The gastrointestinal cancers are collectively viewed as one of the most challenging oncological problems in the twenty first century that can be characterized due to high prevalence, late diagnosis, strong drug resistance, and ineffective treatment with currently available treatment regimens. Nanoparticulate drug delivery systems have proven as revolutionary platforms with true potential to redefine the therapeutic landscape of GI oncology by overcoming the inherent shortcomings of surgery, radiations, and systemic chemotherapy related to pharmacokinetic and pharmacodynamic characteristics. The wide range of nanocarrier platforms discussed in this article, including polymeric nanoparticles, lipid-based systems, amino-functionalized mesoporous silica nanoparticles, natural polymer-based carriers, carbon nanomaterials, etc., present the advantages of complementary value in terms of drug loading capacity, biocompatibility, the state of surface engineering flexibility, and controlled drug release. Combination of passive EPR-mediated targeting with active receptor-directed targeting by use of folate, hyaluronic acid, transferrin, and antibody-based ligands has shown considerable enhancements in tumor selectivity and intracellular drug accumulation in colorectal, gastric, pancreatic, and hepatocellular carcinoma preclinical models. Amino functionalization of surfaces has been especially useful in allowing pH-responsive release of equipped drugs in the acidic tumor microenvironment and in improving drug loading efficiency and receptor-targeted ligand conjugation. Although these are encouraging breakthroughs, such issues as EPR variability in human tumors, the protein corona formation, scalability of manufacturing processes and stability of formulations and lack of harmonized regulatory framework remain the problems that hinder successful clinical translation. The barriers will only be overcome after careful multidisciplinary effort involving materials science, pharmaceutical technology, molecular oncology, and clinical medicine. The integration of nanoparticulate systems with artificial intelligence-guided design and theranostic imaging, biomimetic platforms, personalized organoid-based screening, and cancer immunotherapy all represent a promising future direction of GI cancer nanomedicine that has a real chance to advance patient survival and quality of life.

10. References

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