Published in the Slovak Republic
European Journal of Molecular Biotechnology
Has been issued since 2013.
E-ISSN: 2409-1332
2019, 7(2): 49-62

DOI: 10.13187/ejmb.2019.2.49
www.ejournal8.com


**Articles**

# Modern Nanomaterials and Nanotechnology in Diagnosis and Treatment of Malignant Tumors of Gastrointestinal Tract

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**Abstract**

This review aims to systematize current achievements in the use of nanotechnology for the detection, diagnosis, treatment and prognosis of gastrointestinal (GI) malignant tumors. Information about the use of nanovesicles isolated from the body (exosomes) and synthesized (liposomes) for targeted delivery of drugs and imaging agents to cancer cells for this purpose is presented. A separate section of the review deals with revealing the laws of transport and interaction of nanoparticles with tumor cells to diagnose and treat GI malignant tumors. Here we present modern research to determine the effectiveness of micelles, liposomes, solid lipid nanoparticles, mesoporous silica nanoparticles and particles containing perfluorocarbon. The problems and achievements in the use of nanoparticles for targeted delivery of chemotherapy drugs to cancer cells using ultrasound are considered. The authors conclude the review with a list of the most promising areas of development in this field of molecular medicine and biotechnology, including combinations of direct cytotoxic action, immunomodulation, impact on tumor vessels (1), and combination of diagnostic component with facilitating the detection of tumor cells well-known as teranostics.

**Keywords:** nanotechnologies, nanoparticles, nanovesicles, gastrointestinal tract, malignant tumors, teranostics, target therapy, target drug delivery.

## 1. Introduction

Nanomaterials, literally, meaning materials with a dimension of $10^{-9}$, in fact include all natural, modified or completely artificial objects that have their own dimensions, or surface profile, or pores smaller than 100 nm. They have now revolutionized materials science and became one of the main drivers of technological progress. Complexes of processes based on these materials, defined as nanotechnologies, have led to the rapid development of energy, electronics, computer technologies, and many other branches of human activity (Breding et al., 2014; Lapčík et al., 2019; Madamsetty et al., 2019; Shi, Lammers, 2019).

Applied to biology and medicine, nanotechnology proved to be a great tool for understanding life at the molecular level, and immediately after their first application for this purpose, scientists began to develop technologies for active intervention in biological systems. As a result, we have genetic engineering, molecular diagnostics, and high-precision (targeted, personified drug delivery to target cells) technologies for treating diseases. Moreover, at a certain stage, it turned out to be

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very effective to combine these two directions. As a result, a new modern direction appeared in medicine, named as teranostics, like the combination of treatment and diagnosis in one technology (Ai et al., 2016; Deyev, Lebedenko, 2017; Sokolov et al., 2017).

Modern nanotechnologies have significantly improved the diagnostics and treatment of cardiovascular, autoimmune, endocrine diseases (primarily diabetes and thyroid diseases), infections, injuries and disorders of the musculoskeletal system, dental pathology, etc. (Sharma et al., 2015; Melerzanov et al., 2016; Kalita et al., 2016; Novochadov et al., 2016; Mukherjee et al., 2019).

Teranostic agents can be obtained using the following strategies: screening plant extracts for nanomaterial synthesis (1); standardization of various physical and chemical parameters for biosynthesis (2); addition of therapeutic and imaging agents (3); and characterization of nanocarriers using analytical methods (4) (Duan et al., 2015; Madamsetty et al., 2019).

Of particular interest is the progress caused by the introduction of theranostics of nanotechnology in experimental and clinical oncology. The vector of development in antitumor therapy is aimed at an approach called precision personified medicine with the most integrated and versatile effect on the tumor (Arnedos et al., 2015; Lloyd et al., 2015). The acquired knowledge and technologies are actively used to create new methods and tools for cancer diagnosis and therapy based on compounds selectively acting on specific molecular targets, as well as new systems for delivering these agents to cancer cells that do not affect healthy organs and tissues.

## 2. Discussion

### Nanotechnology teranostics of GI malignant tumors: The common principles

In this review, we focused on the systematization of recent successes in this direction on the example of malignant GI tumors. These tumors are among the most common and deadly malignancies worldwide, mainly due to late diagnosis and lack of effective treatment methods. The most typical tumors of this localization are esophageal squamous cell carcinoma (ESCC), gastric cancer (GC), colorectal cancer (CRC), and peritoneal carcinomatosis (PC) (Bray et al., 2018). It is these models are the base to develop new technologies for influencing GI tumors (Huang et al., 2019).

Special attention should be paid to CRC, because due to its relatively slow and hidden progression, as well as its high prevalence, the early detection and effective treatment of this tumor constitute not only a medical but also a social problem in the modern world.

Thus, the problem is to accurately identify, diagnose, and prescribe therapy at the earliest possible stages of tumor progression. The appearance of precancerous lesions that result from abnormal cell growth indicates a precancerous condition with high risk to develop into tumors. These conditions include atrophic gastritis, chronic ulcerative colitis, various variants of epithelial metaplasia and dysplasia (Li et al., 2018b; Rentien et al., 2018; Huang et al., 2019).

A serious point in the treatment of tumors is the situation when cancer cells develop drug resistance and stop responding to chemotherapy. It resulted in necessity to increase the dose (and toxicity) or provide targeted delivery of the drug to the tumor cell (Lian et al., 2017; Li et al., 2019).

There are four critical aspects to consider when developing an effective teranostic nanoplatform: choosing an effective therapeutic agent (1), choosing a stable carrier (2); implementing a targeted and sustainable approach to drug release (3); choosing a imaging agent carefully (4) (Muthuraj et al., 2016; Chi et al., 2017).

Special attention is paid to NPs obtained from plant viruses. They are attractive because they are both biocompatible and biodegradable, and their antigenicity can be weakened by a polymer coating (Pitek et al., 2016; Czapar, Steinmetz, 2017). Viral NPs can be designed and constructed using genetic and chemical protocols. Plant viruses (as opposed to animal or human viruses) are a safe platform because they do not cause diseases in humans. Their size is in the nanometer range, which helps to increase tissue permeability and retention in tumors. Multivalent nature of these NPs allows the incorporation of several molecules with different functions, which allows, for example, combining a cell targeting ligand and an imaging agent on the same nanoparticle (Gamper et al., 2019).

Nanovesicles (NVs), which will be discussed first, may have different origins. One group includes natural NVs (exosomes), which have a diameter from 25 to 1000 nm, and therefore the largest of them, strictly speaking, no longer belong to nanoobjects. Exosomes can be found in body

fluids, where they are involved in antigen presentation, immune response, intercellular signaling, and RNA and protein transport (Sun et al., 2018; Zhu et al., 2018). Second group unites synthetic vesicles, which can be exclusively synthetic biomimetic materials or combined into hybrids with natural NVs (Atay et al., 2018; Danaei et al., 2018; Li et al., 2018a).

Of particular note are the so-called tumor exosomes containing proteins and RNA (including microRNAs and messenger RNAS), which are malignant vesicles that are found in the blood serum and other biological fluids of cancer patients. These exosomes have great promise in diagnosing and predicting diseases, as they can protect labile cancer biomarkers from degradation (Boyiadzis et al., 2017; Arenaccio et al., 2019).

**Success in using NVs for precancerous and malignant GI diseases**

Both body-derived NPs and synthesized NVs are widely used in the detection, diagnosis, treatment and prognosis of different GI tumors, especially in primary focal lesions. Figure 1 demonstrates the working classification of NVs (Huang et al., 2019) and variants with achieved success in GI malignant diseases using NVs.

Analyzing the general problems of targeted use of NVs, it is necessary to point out the need to comply with the basic principles of biofunctionality, biomimetics and biocompatibility. Only in this case, a specific delivery system will be able to transport microRNA, mRNA, siRNA, lncRNA, peptides and synthetic drugs to the target cells (Barile, Vassalli, 2017; Zhang et al., 2018b).

NVs should ideally not exhibit significant cytotoxicity or activate the body's defense systems (Tagalakis et al., 2017). Implantation of NVs carrying targeted molecules can be performed indirectly (penetration through a concentration gradient) (Roma-Rodrigues et al., 2017) or using direct methods (electroporation) (Ye et al., 2018). This method involves direct NVs injection into the cytoplasm, bypassing the endocytosis pathway. For example, the 3DNEP chip was designed to deliver extremely small biological elements to huge plasmids with almost zero negative effects on target cells (Ye et al., 2018).

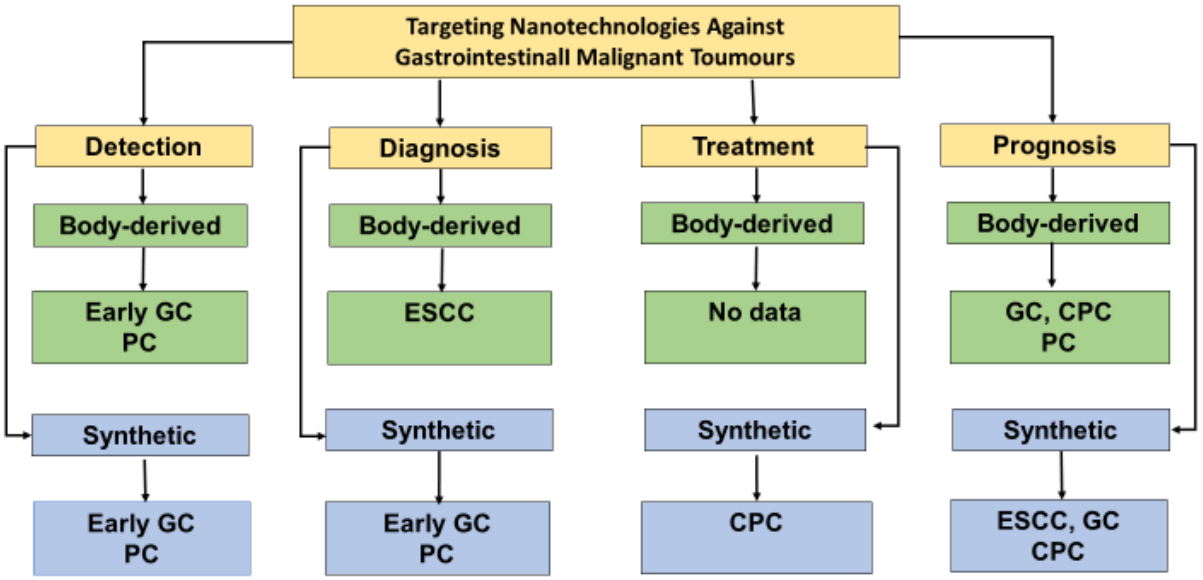


**Fig. 1.** Targeted using NVs of various origins in the most common malignant GI tumors

For primary detection of GI tumors, both NVs isolated from the body and synthetic ones are used. Thus, Lin et al. (2018) described that the tumor factor lncU EGC1, encapsulated in exosomes, can be the basis for highly sensitive, stable, and non-invasive diagnosis of precancerous chronic atrophic gastritis. MicroRNAs, lncRNAs, and multiple proteins in tumor exosomes can be used as non-invasive disease biomarkers for early GC diagnosis (Wang et al., 2018). Exosomes released into the serum by cancer cells protect their contents from degradation and can be used to detect PC at the earliest, most treatable stage (McMullen et al., 2017). Among the synthetic NVs used for the detection of GI tumors, it should be noted that they are used in the composition of liposomes as contrast agents for screening and detecting the early GC stage (Zhang et al., 2018a) and effective

use of NVs loaded with superparamagnetic iron oxide as new contrast agents for human CRC imaging (Feng et al., 2016).Diagnostic use of NVs is to specify the location, stage, and degree of tumor malignancy. Yan et al. (2018) described the possibility of diagnosing and predicting further human ESCC progress by analysis of oncogenic exosomes expressing Stathmin-1. Similarly, increased expression of MicroRNA 296-5p in exosomes may be a promising diagnostic biomarker for early GC (Huang et al., 2017). A synthetic pegylated liposome modified with the Arg-Gly-Asp peptide and containing Indocyanine Green can accumulate in tumor tissues for the diagnosis of early GC (Ding et al., 2015). The near-infrared fluorescent liposomal probes effectively targeting peritoneal disseminated tumors for accurate GC diagnosis may be another example of effective NVs application (Hoshino et al., 2015).

We have met few successful examples of NVs using for treatment of malignant GI tumors. Pegylated melanin-like liposomes were able to carry enough doxorubimicin (DOX) for targeted delivery to human CRC cells. As the size of the particles that were synthesized at a pH of approximately 7.5-8 increased, the loading efficiency of the drug also increased due to the expanded internal volume for the drugs. However, in contrast to the loading efficiency, the release of the drug occurred much faster from smaller particles that were synthesized at pH 9. The developed NVs are able to overcome drug resistance during long-term chemotherapy (Wang et al., 2016; Li et al., 2017).

Studying the possibilities of NVs using for tumor prognosis Sun et al. (2017) found that microRNA in exosomes secreted by both cancer stem cells and differentiated cells may reflect the stage of GC progression and metastasis, as well as indirectly act like an indicator for measuring the likelihood of GC recurrence after therapy. Exosomal microRNAs from lavage peritoneal fluid are potential predictive biomarkers for peritoneal metastasis in GC (Tokuhisa et al., 2015).

Exosomal microRNA 19a in serum is an early predictive biomarker of relapses in human CRC (Matsumura et al., 2015). There are examples of successful use of synthetic NVs for predicting the course of GC. Thus, liposomes transfected with the PEGfp-N1 Kangai 1 plasmid can inhibit migration and invasion of GC cells and improve tumor prognosis (Guo et al., 2015). Nanoliposomal quercetin in combination with CD133 antiserum may be a prognostic marker in human ESCC cases (Zheng et al., 2014). NVs obtained by "green chemistry" methods using grapefruit juice can improve the prognosis of colitis caused by dextran sulfate sodium in mice, which is a model of precancerous colitis in humans (Wang et al., 2014).

Nanocapsulation of chemotherapeutic agents in biocompatible polymer or lipid matrices has great potential for improving the pharmacokinetics and effectiveness of traditional chemotherapy while reducing the systemic toxicity of anti-cancer drugs. Labeling the surface of nanoparticles with specific ligands for cancer cells, namely monoclonal antibodies or antibody fragments, provides a means to target more aggressive clones. This increases the effectiveness of nanopreparations, while reducing their side effects. Other ligands, such as peptides/small proteins and antibodies/antibody fragments that have an affinity for either the tumor cells or its vascular system, are also widely and successfully used for targeting GI carcinomas. To date, two nanocomplexes have advanced beyond the preclinical stages for advanced solid tumor metastases: MCC-465, an anti-myosin heavy chain(a) as an immunoliposome (1); and MBP-426, a transferrin-liposome-oxaliplatin conjugate (2). However, none of them have yet been approved for clinical use (Fernandes et al., 2015).

**Success in using NPs for precancerous and malignant GI diseases**

Chemotherapy drugs such as doxorubicin (DOX) are usual approach to first-line therapy against CRC and lung cancer, but the effectiveness of these drugs is limited by the development of drug resistance. One way to overcome this disadvantage is to synthesize new compounds suitable for targeted selective delivery of the drug to cancer cells (Martins et al., 2016; Ma et al., 2016; Lenis-Rojas et al., 2017).

In the last 10 years, nanoscale drug delivery systems such as liposomes, solid lipid nanoparticles, polymer micelles, mesoporous silica, carbon nanomaterial, and gold NPs have emerged that have increased the selectivity of anti-cancer therapy and reduced the toxicity of drugs (Qu et al., 2014; Hou et al., 2016; Tang et al., 2017; Millard et al., 2017). For example, Huo et al. (2014a) presented platform on gold NPs with different sizes, and they found that small gold NPs can effectively enter the cell nucleus. Similarly, DNA nanotechnology is widely studied in various

biomedical fields, including as a promising drug delivery system for cancer treatment (Miao et al., 2015; Xia et al., 2016; Wang et al., 2017).

Although ultrasound is most widely known for its use in diagnostic imaging, its energy can be used to influence cell function and drug delivery. In recent years, increasing attention has been paid to drug delivery using ultrasound, as it allows spatially limited delivery of the therapeutic compound to target areas such as tumors (Xhu et al., 2013). The combination of ultrasound and nanocomposition drug delivery systems eliminates the main limitations of traditional drug delivery systems, including: insufficient absorption and accumulation of nanoparticles by cells (1); limited amount of drug delivered or released from nanoparticles (2); specific targeted drug-delivery carriers nanoparticles (3) (Tharkar et al., 2019).

In addition, the NPs combination with ultrasound has significant potential to improve drug delivery efficiency and reduce drug side effects by better overcoming physiological barriers such as endothelial lining of blood vessels, endothelium of target tissues, dense epithelial cell layers, tissue interstitial, plasma cell membrane, diffusion through the cytoplasm, and penetration into the nucleus through the nuclear membrane (Barua, Mitragotri, 2014; Rosenblum et al., 2018; Thakkar et al., 2019).

Figure 2 summarized more interesting information about the properties of different NPs used in ultrasound techniques to facilitate the delivery of anti-cancer drugs to target cells based on open sources (You et al., 2016; Horise et al., 2019; Özdemir et al., 2019; Sadegh Malvajerd et al., 2019; Tharkar et al., 2019).

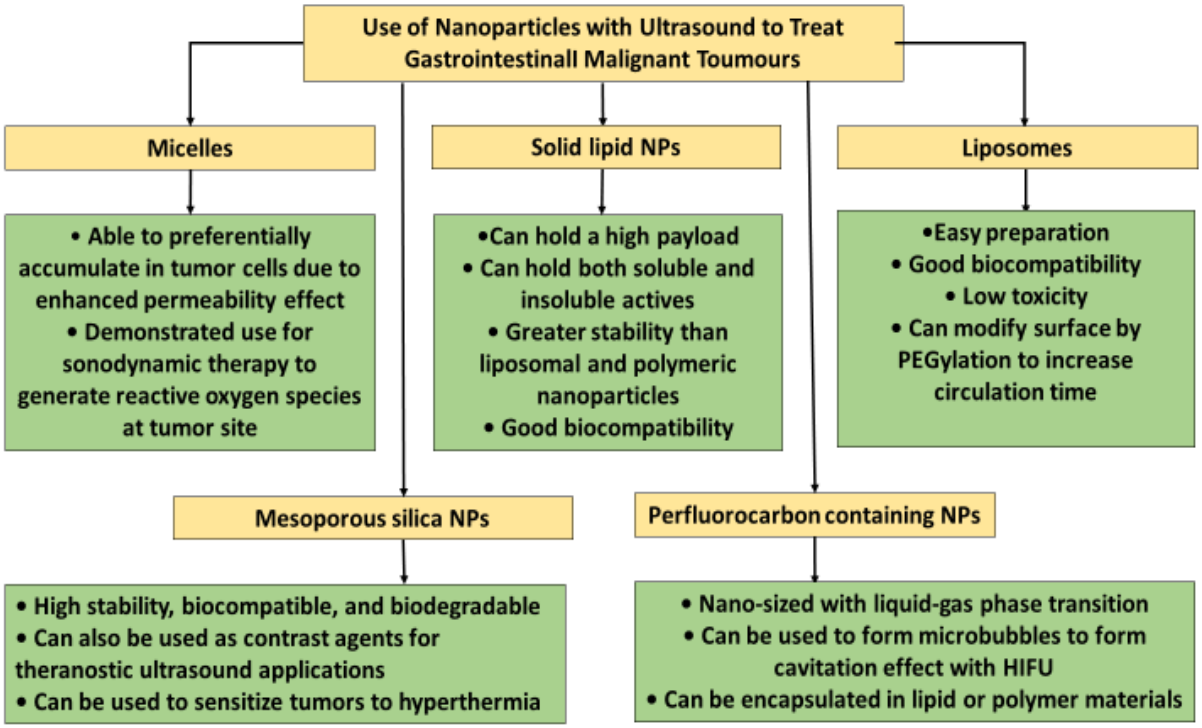


**Fig. 2.** Joint use of nanoparticles and ultrasound in the treatment of GI tumors: properties of different variants of nanoparticles

The most used tumor-specific fragments for targeting are abnormally overexpressed tumor receptors. These substances include endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR integrin receptor vascular), folate receptor (FR), and human epidermal growth factor receptor 2 (HER2) (Ko et al., 2019).

Encapsulation of therapeutic drug molecules in nanoparticles can improve their bioavailability, bio-distribution, and can also improve internalization in the target cell. However, despite recent advances in nanotechnology, only ~1 % of nanoparticles accumulate in tumors (Wilhelm et al., 2016).

The effective extravasation of NPs through the tumor microenvironment is a serious barrier. Tumor tissue usually have abnormal vascularization, exhibit excessive extracellular matrix density, which resists the diffusion of therapeutic NPs to cancer cells. In addition, increased interstitial fluid pressure, which is the result of rapid cell proliferation, leads to ineffective anti-cancer treatment activity (Sriraman et al., 2014; Zhang et al., 2019a). Mucus becom another barrier to drug/nanoparticle delivery to GI tumors (Chen et al., 2017).

Ultrasound delivery of drug-loaded NPs eliminates the above limitations by increasing the accumulation and uptake of NPs by cells, as well as stimulating the release of the drug only at the target cells. We can achieve these effects through various processes, such as sonoporosis, cavitation, or hyperthermia (Mullick Chowdhury et al., 2017).

Khaled et al. (2019) developed a new type of composite of silver nanoparticles, including pegylated graphene quantum dots and decorated silver nanoprisms (pGAgNPs), which demonstrated good intracellular absorption and radiosensitization *in vitro* in radiation-sensitive HCT116 cells and relatively radiation-resistant HT29 cells of human CRCr.

To improve the treatment of CRC Zhong et al. (2019) prepared paclitaxel-loaded NPs from PLGA (PLGA-PTX) and evaluated their anti-cancer activity in co-administered protocol with the iRGD peptide. Compared to free PTX, encapsulated ones retained preferential cytotoxicity in relation to various CRC cells, effectively sparing healthy cells. Treatment with PLGA-PTX resulted in stopping the cell cycle in the G2/M phase and apoptosis, which led to inhibition of migration and invasion of cancer cells. The proposed co-administration system, devoid of covalent conjugation, provided more convenient means to combine various therapeutic agents with iRGD achieving personalized nanotherapy (Zhong et al., 2019).

The development of multi-functional teranostic NPs presents a number of challenges, including visualization quality, 'load capacity', toxicity of internal ingredients, storage and stability *in vivo*, complexity of synthesis, batch repeatability, production costs, and regulatory barriers. By varying the size, shape, and surface properties of NPs, we can adjust their biocompatibility and specificity with target cells. Current interests are mainly related to noninvasive deep tissue imaging and targeted drug therapy (Yang et al., 2019).

**Selective and complex effects on the tumor: recent findings and directions of development**

NPs can effectively enhance immunomodulatory effects and modulate the immune response by manipulating immune cells to facilitate targeted delivery (Riley et al., 2019; Nam et al., 2019; Sun et al., 2019).

They can act as immunoactive agents to program the tumor cells themselves (Feng et al., 2018; Chen et al., 2019), antigen-presenting cells (Kuai et al., 2016; Zhu et al., 2017), T cells (Tang et al., 2018), or affect tumor-associated macrophages (Zanganeh et al., 2016).

The method of directed radionuclide therapy is based on the selective accumulation of a pharmaceutical containing a radioactive isotope only in the tumorous tissues (Bronte et al., 2015; Vodeneev et al., 2015). Directed radionuclide therapy should only affect tumor cells and not affect normal cells. This condition makes it possible to create a pharmaceutical product with a large, and in the ideal case – with an infinitely large therapeutic index, which will allow you to get high efficiency with minimal side effects (Golden, Apetoh, 2015; Pouget et al., 2015). Creating a pharmaceutical with a prolonged action and a high therapeutic index requires the selection of a radioisotope and a platform for its delivery to the tumor.

Tumor-induced angiogenesis has been one of the focuses of anti-tumor therapy for several decades. The immature and fenestrated vascular network of the tumors contributes to the intravasation of cancer cells and the spread of metastases, while preventing the antitumor effectiveness of immune cells and the effective diffusion of chemotherapy drugs (Mattheolabakis, Mikelis, 2019).

In recent years, starvation therapy has become an effective method of suppressing tumor growth and survival by blocking blood flow or depriving them of essential nutrients or oxygen (Chung et al., 2015; Selwan et al., 2016; Yu et al., 2019). Nutrient transport can be blocked by stopping the blood supply to the tumor through treatment with angiogenesis-inhibiting agents or vascular disrupting agents (Chase et al., 2017) and transarterial chemoembolization (Lin et al., 2016). In addition, agents that can consume intracellular nutrients, oxygen, or mediate the uptake of necessary substances by tumor cells leading to tumor starvation and necrosis (Zhang et al., 2017).

Most in vivo model experiments use mice carrying implanted human tumor cells to develop these platforms. Against GI tumors are the most popular cell line CT26 tumor bearing mice (Song et al., 2016; Liu et al., 2017; Chen et al., 2018). HT-29, C8161 tumor bearing mice and other models are also used to define therapeutic index and possible side effects (Pouget et al., 2015; Sui et al., 2017; Yu et al., 2019). The use of directed radionuclide therapy is convenient for the patient. After the introduction of the drug (within a few minutes), it affects the tumor for several days, the patient should not undergo additional procedures during this time (Golden, Apetoh, 2015). Creating a pharmaceutical with a prolonged action and a high therapeutic index requires the selection of a radioisotope and a platform for its delivery to the tumor.

Various NPs used as materials for starvation therapy can be natural and synthetic polymers (Zhang et al., 2019b; Yang et al., 2019), liposome (Zhang et al., 2018c), organometallic frameworks, or gold nanoparticles (Au-NPs) (Son et al., 2017) and NPs silica (Yang et al., 2018; Yu et al., 2019). All of they were used for co-delivery of carcinogenic agents and other therapeutic agents in order to reduce drug side effects, increase their target effectiveness, increase the stability and half-life of therapeutic agents, and co-delivery of multiple drugs to overcome drug resistance (Jing et al., 2018).

Thus, the epidermal growth factor receptor (EGFR) is often overexpressed in cancer cells and this can be used for selective exposure with the therapeutic monoclonal antibody cetuximab (approved by the FDA for the treatment of CRC). The drug blocks EGFR signaling transduction, leading to cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, metastasis, internalization, and self-regulation (Pabla, 2015; Pedrosa et al., 2019).

Zinc is another such agent. One of these compounds, [Zn (DION)2] Cl2-ZnD (DION-1,10-phenanthroline-5,6-DION), showed high cytotoxic potential against cancer cell lines, with IC50 values 2 times and 70 times lower than doxorubicin (DOX) and cisplatin, respectively. Zn-DION has been described as highly cytotoxic to HCT116 colorectal carcinoma cells, compared to ZnCl2 or only DION. When exposed to IC50 Zn-DION cells, chromatin condensation and core fragmentation were observed for 48 hours, and the number of apoptotic cells increased fourfold during double staining with propidium iodide and V-FITC annexin. Together, these results confirm that Zn-DION induces HCT116 cell death through activation of the internal apoptotic pathway (Pedrosa et al., 2019).Molecular imaging technology is important for detecting tumors and monitoring prognosis as a result of its high accuracy and reliability for elucidating biological processes and monitoring pathological conditions (Zhan et al., 2017). Fortunately, magnetic resonance contrast agents may enhance contrast, thereby increasing the sensitivity of magnetic resonance diagnostics. Approximately 35 % of clinical magnetic resonance imaging devices require CAs (Lei et al., 2017).

Various T1 – or T2-MRI CAS based on NPS gadolinium, manganese, and iron oxide were developed to increase the contrast sensitivity of images. However, conventional drugs based on small-sized complexes usually suffer from short blood circulation times and severe in vivo toxicity, which can lead to nephrogenic systemic fibrosis and cerebral deposition (Xiang et al., 2018). So, researchers turned to superparamagnetic nanoparticles, especially $Fe_3O_4$ NPs. Over the past 20 years, several T2 contrast agents based on these NPs have been clinically tested and approved by the US Food and Drug Administration. Unfortunately, these NPs were somewhat limited in their clinical use due to their own dark signals and susceptibility artifacts in MRI (Neves et al., 2016).

Mn-based contrast agents are considered ideal substitutes because of their bright signals and good biocompatibility. manganese oxide NVs. Variants that have appeared in recent years have shown little toxicity and good contrast effects (Hsu et al., 2016), as well as chemical and magnetic resonance characteristics of reactive contrast agents based on Mn (Garcia-Hevia et al., 2019; Cai, Zhu, Zeng et al., 2019).

Based on previously identified complexes of integrin alpha-6 and E-cadherin on the surface of CRC cells, but not typical for normal colon cells, peptides of the composition CGIYRLRS and CGVYSLRS were created, being able to compete with angiopoietin-like protein 6 in CRC tissues. Modular nanosystems were created to obtain a visualization platform consisting of fluorescent silica-PEG NPs with these peptides on the surface. The NPs contained dye rhodamine A, cyanine 5, or both (two-color). The study silica NPs *in vivo* on model mice with a pseudo-metastatic tumor (human CRC cancer cells were implanted in the spleen of diabetic mice) using three-dimensional

confocal micrography showed that labeled these NPs were located very close to the tumor's blood vessels (Marchio, Bussolino, 2018).

### 3. Conclusion

In modern diagnostics and therapy of GI tumors, NPs of natural, synthetic and hybrid origin are actively used. They can have a solid or composite structure (shell + content), their composition is most often represented by proteins or peptides, DNA or RNA, polysaccharides, lipids, metals, usually in combination with each other. The effects of such NPs are very diverse and include direct cytotoxic action, immunomodulation, impact on tumor vessels, etc. The combination of these different influences and a diagnostic component associated with facilitating the identification of tumor cells is the most promising direction of development in this area being the essence of the new approach, theranostics.

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