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NANO MEDICINE: Towards Development of Patient Friendly Drug Delivery Systems Oncological Applications

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Abstract: *The interest in nanotechnology in cancer treatment and diagnosis is intensified due to the serious side effects caused by anticancer agents due to their cytotoxic actions on normal cells. This non-specific action of chemotherapy has awakened a need for formulations capable of the ultimate goal of improving tumor killing. Nano-oncology, the application of nanobiotechnology in cancer management, is currently the most important area of nanomedicine. Currently, several nanomaterial-based drug delivery systems are in vogue and several others are in various stages of development. Tumor drug delivery systems are expected to be silver bullets for cancer treatment, and several groups are working worldwide to develop powerful systems.*

Nanoparticles (NPs) have emerged as a versatile platform for biomedical applications, particularly in targeted drug delivery and cancer therapy. This study reports the design, synthesis, and characterization of engineered NPs for enhanced therapeutic efficacy. We fabricated [insert type/material] NPs and functionalized them with [insert targeting ligand/ drug]. The NPs exhibited [insert size/shape] and demonstrated [insert property, e.g., pH-responsive release]. In vitro and in vivo studies revealed [insert results, e.g., enhanced cellular uptake, improved bioavailability, and reduced toxicity]. Our findings suggest that these engineered NPs hold great promise for targeted drug delivery and cancer therapy, offering a potential breakthrough in nanomedicine..

Keywords: Patient-Friendly, Drug-Delivery Systems, Cancer, Nanomedicine

I. INTRODUCTION

Nanotechnology is the latest trend in modern technology and has applications in some problems related to human diseases. Nanotechnology refers to understanding and control of matter in the dimensions between around 1 and 100 nanometers, where unique phenomena allow new applications. Dimensions between about 1 and 100 nanometers is known as nanoscale. Unusual physical, chemical and biological properties can appear in materials .
This scale and these properties can differ significantly from the properties of bulk materials and individual atoms or molecules. Nanotechnology has been applied various fields such as electronics, energy, space, medicine, food and chemical sensors and in molecular manufacturing. Nanomedicine is a branch that focuses on the application of nanotechnology for faster diagnosis, improved therapies, improved imaging and prevention of various clinical conditions. It is mainly used in drug delivery, diagnostics, imaging and therapy. Many nanomaterial-based agents are in various stages of development and have medical applications, and some are in clinical use. With the changing incidence of diseases, mortality and response to treatment of chronic diseases such as cancer, neurodegenerative disorders or metabolic syndrome, there is a need to develop new technologies for early and rapid diagnosis and new safe drugs for treatment. Nanotechnology based agents have provided many promising directions in these areas. Among many fields, cancer nanotechnology or nano-oncology has generated considerable interest for many groups. Currently there are many agents based on nanomaterials for the treatment of cancer in clinics and many others.
Manipulation of matter on an atomic or molecular scale, known as nanotechnology, has evolved rapidly across the many stages of its development and has revolutionized many fields, including medicine. Its most promising

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applications lie in cancer therapy-whether it involves diagnosis, treatment, or monitoring-and so this review aims to show the many applications of nanotechnology in cancer therapy, with the latest innovations and possible future directions. From nanoparticle-based drug delivery systems to nanoscale imaging agents and cancer-specific targeting, we'll explore the state-ofthe-art research and technologies that are reshaping the treatment of cancer.

II. NANOTECHNOLOGY IN MEDICINE:

A nanoparticle (NP) is defined as the smallest unit (10−9 meters) that can still behave as a whole entity in terms of properties and transport. NPs are dispersions of particulates or solid particles that range in size from 10 to 100 nm (in one dimension) and are developed to: improve drug delivery, abrogate treatment-induced drug resistance, and reduce nonspecific toxicity of drugs. Several recent studies have shown that nanomaterials are able to cross biological membranes and enter cells, tissues, and organs, something that larger particles cannot normally do. Depending on the chemical nature of the preparations, there are several types of nanoparticles that have been synthesized and evaluated. Nanomaterial-based agents used for drug delivery include carbon nanoparticles, dendrimers, ceramic nanoparticles, chitosan nanoparticles, liposomes, low-density lipoproteins, nanoemulsions, and nanospheres, etc. [1] In all these types, the drug can be absorbed on the surface, entrapped or dissolved in the NP matrix.Recent advances in medicine and healthcare have significantly improved the life expectancy of the people. This increase in life expectancy is also associated with an increased risk of some types of cancer, because cancer is considered a disease of old age. It is also true that during aging individuals present with several comorbidities in addition to their cancerdiagnosis. Therefore, there is a growing need to develop new cancer treatment agents that are effective and address the associated risks. Currently, Chemotherapy with cytotoxic agents is the mainstay of treatment for many malignant people. In addition, cytotoxic chemotherapy, antihormonal therapy, and molecularly targeted therapies are also being used, either as monotherapy or in combination with conventional therapies. However, several issues, including cost and off-target toxicity, limit these combination treatments. There is therefore a need to develop new agents for the treatment of cancers that are less toxic, affordable, and provide a better quality of life.

III. LIMITATION OF CURRENT CANCER TREATMENT MODALITIES

Currently available chemotherapy agents are time-tested, and confer good disease-free survival for a limited period of time. Nevertheless, nontarget tissue toxicity and drug resistance curtails the utility of these agents. Thus there is scope to develop newer agents or site-specific delivery systems to transfer these chemotherapeutic agents, which can annul the important obstacles of toxicity and drug resistance.

IV. NANOPARTICLE AS DELIVERY VEHICLE

Nanoparticle-based drug delivery systems have made a significant difference in the on-site delivery of chemotherapeutic agents, due to their physical and chemical characteristics and biological attributes. Research in this exciting field has continued for more than two decades, but only in the last decade have some of these formulations been commercialized and are now commonly used in clinics. This type of research is very promising and the combined skills of a multidisciplinary team of polymer chemists, cancer biologists and pharmacologists have made some innovative agents available.

A great approach with nanoparticle-based delivery vehicles is to achieve targeted therapy and drug delivery. Among these examples are:

- Liposomes: artificial vesicles made of lipids, used to deliver drugs, genes, or proteins.
- Polymeric nanoparticles: composed of biodegradable polymers that are used for drug delivery, proteins, or nucleic acids.
- Solid lipid nanoparticles (SLNs): composed of solid lipids for drug or other therapeutic agent delivery.
- Gold nanoparticles: drug delivery, imaging, and photothermal therapy.
- Magnetic nanoparticles: drug delivery, imaging, and magnetic hyperthermia.
- Dendrimers: A tree-like nanoparticle drug, gene, or protein delivery.

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- Carbon nanotubes: Drug, protein, and nucleic acid delivery.
- Nanoporous silica nanoparticles: Delivery of drugs or other therapeutic agents.
- Quantum dots: Small crystals for use in imaging and targeted drug delivery.
- Nanocrystals: Used for drug and/or other therapeutic agents.

These delivery devices have several advantages based on nanoparticle delivery vehicles, such as
Targeted delivery
Improved bioavailability
Lower toxicity
Increased efficacy
Controlled release
They are being developed for a variety of applications, including cancer therapy, gene therapy, vaccine delivery, and treatment of neurodegenerative diseases.

V. CONTRIBUTION BASIC CANCER BIOLOGY FOR DRUG DELIVERY

1. Research in the field of molecular oncology, which deals with basic disease mechanisms, has shown six important characteristics of tumor cells, referred as the "hallmarks of cancer".
2. Sustained angiogenesis is one characteristic, which indicates that tumors develop their own blood supply from the existing host vessels for nourishment. Several studies on tumor vasculature have shown them to possess structural anomalies that impede drug delivery. The tumor vasculature is known to possess poor architecture with an abnormal basement membrane and fissures between the endothelial cells due to an absent pericyte lining. This state of leaky vasculature accompanied by a poor lymphatic drainage system causes a differential interstitial pressure at the center of tumors than at the periphery. Due to this pressure difference, molecules ranging from approximately 10 nm to 100 nm, preferentially accumulate in the tumors and are retained longer, unlike the uncoated drugs, which are of much smaller size and cleared by the kidneys.
3. This phenomenon is called the enhanced permeability and retention effect (EPR). A schematic representation of leaky vasculature and EPR is shown in Figure 1. Studies have shown that the retention time of drugs packed in NPs is ten times higher than that of unpacked drugs, which eventually return to the vascular system.[4]

Hence, this EPR effect attributed to the leaky vasculature is considered as a boon for drug-delivery systems within the nanosize range. A schematic representation for passive targeting of NPs owing to EPR effect in tumors is shown in Figure 2.

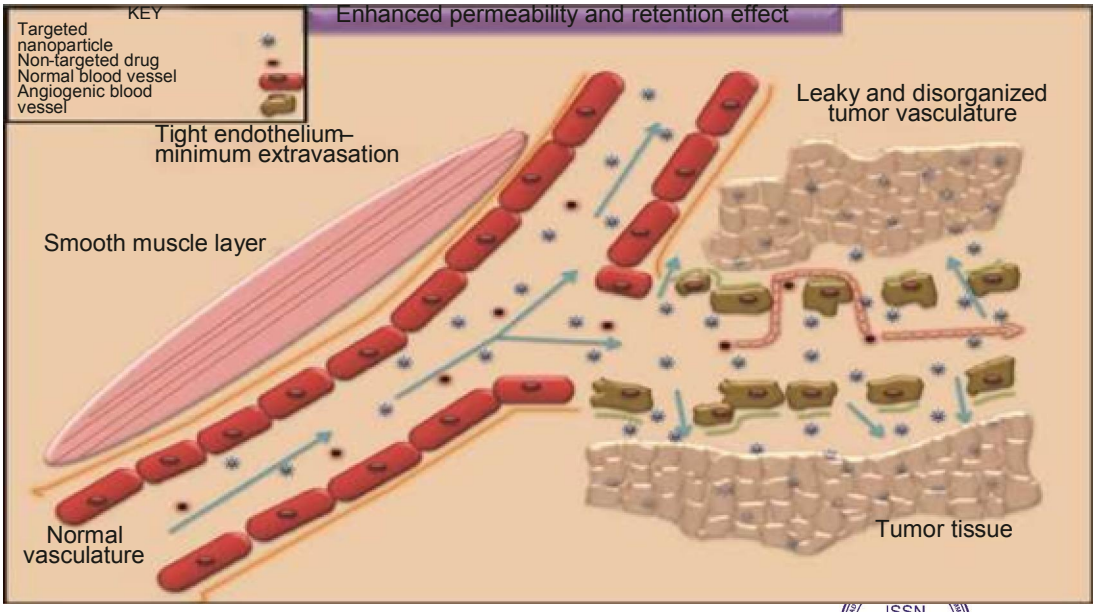

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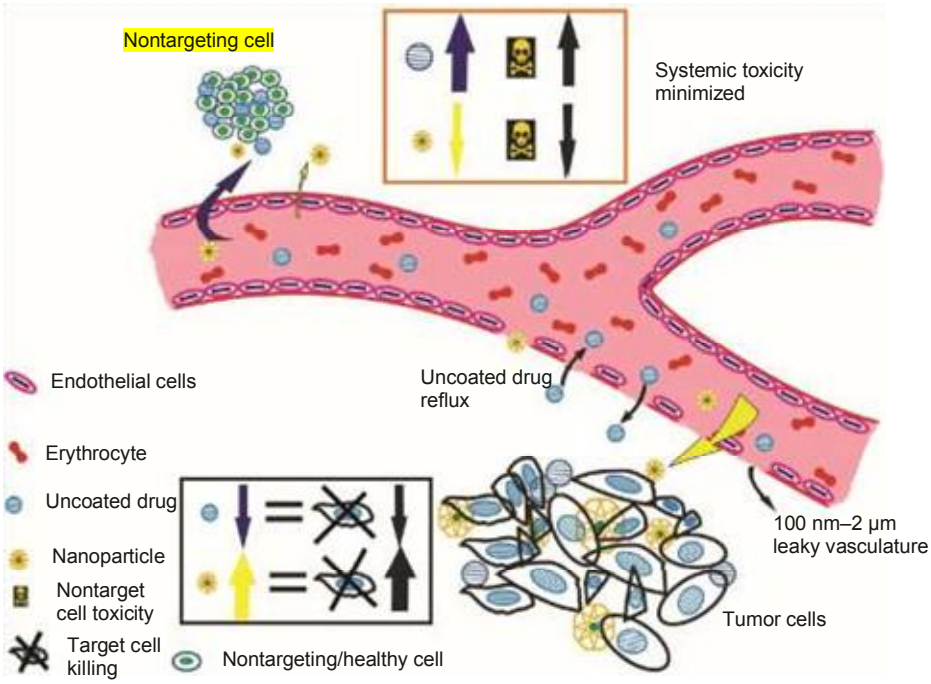
Figure 1 The enhanced permeability and retention effect operating in tumor milieu permitting accumulation of nanometer-sized particles in cancer cells. Blood vessels in tumor tissue have defective architecture with gaps as large as 200–1000 nm allowing nanoparticles to extravasate and accumulate inside the tumor tissue. The retention time of drugs packed in nanoparticles is ten times higher than that of unpacked drugs, which eventually return to the vascular system. This phenomenon of permeability of molecules due to their size is a boon to cancer therapy and is known as the enhanced permeability and retention effect

Passive targeting



(fig no. 2)

Figure 2 Passive targeting of nanoparticles to tumor cells according to tumor vasculature and size characteristics. Passive targeting of nanoparticles: nanoparticles (in yellow) concentrate to tumor sites taking advantage of leaky vasculature and diminished lymphatics. Tumor angiogenesis is torturous and aberrant with gap sizes of 100 nm–2 µm. Nanocarriers because of their small size can thus accumulate in tumorinterstitium minimizing systemic toxicity and enhancing tumor cell killing. Free or uncoated anticancer drugs (blue) lack this advantage accounting for serious side effects due to extravasation to healthy cells and reflux at target sites. Yellow arrows indicate the extravasation of nanocarriers to the tumor site (indicated with thickened arrows, in addition, to represent higher biodistribution). Blue arrows indicate the extravasation of the uncoated drug to the nontargeting site rendering systemic toxicity, which is further thickened to symbolize higher concentration of the uncoated drug.

EXAMPLES OF NANO MATERIALS USED IN DRUG DELIVERY

There is great flexibility in the choice of starting materials and synthesis methods that can be used to fabricate nanoscale drug delivery systems depending on their application. In this review, we will discuss different types of nanomaterial-based drug delivery systems, focusing on their components, applications, advantages, and limitations of the preparations.

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• LIPOSOMES

Liposomes are self-assembled phospholipid membranes with an inner core where the drug can be entrapped. Liposomes are relatively stable, biodegradable and do not cause any immune response. They are effective vehicles for the targeted delivery of hydrophobic drugs. Liposomes are vesicular formulations of synthetically prepared lipid bilayers. Water-soluble drugs are present in the aqueous compartments while fat-soluble and amphiphilic drugs are inserted into the phospholipid bilayer. Liposomes are widely used for various applications, such as DNA delivery in gene therapy and genetic engineering, drug delivery in food and nutritional supplements, or cosmetics.

Liposomes can be synthesized in various sizes and shapes, but nanoscale liposomes, called nanosomes, are of particular interest in cancer. These nanosomes are several nanometers in size and most often contain anticancer drugs. [5],[6] Because nanosomes are soluble in aqueous solvents (such as blood), they can carry both hydrophilic and hydrophobic molecules, allowing the delivery of anticancer drugs that have shown low efficacy. due to their limited solubility. A nanosome is essentially a vesicular lipid bilayer with the polar heads facing the solvent and the tail regions facing each other. Cancer medication, if it is hydrophobic, so it can be contained in the tail region, and if hydrophilic, soluble in the liposomal core. Surface modification of liposomes with polyethylene glycol (PEG) gives liposomes the property of stealth, which

prevents them from being destroyed by the reticuloendothelial system. PEGylated liposomal doxorubicin (STEALTH) (Doxil®, Caelyx; Schering-Plough Pharmaceuticals, Kenilworth, NJ) was the first liposomal anticancer drug for the treatment of ovarian cancer to be approved by the US Food and Drug Administration. Several lipid-based formulations, such as liposomes, have been synthesized and characterized. We will review important types for their novelty in terms of composition, synthesis, size, shape, and application. New generations of liposomes that contain two anticancer agents in a single liposome are under development. Lipid-based nanocapsules offer a new approach for low-cost drug encapsulation. soluble drugs such as cisplatin or paclitaxel. Burger and colleagues developed a new method for the efficient encapsulation of cisplatin in a lipid formulation based on the repeated freezing and thawing of a concentrated solution of cisplatin in the presence of negatively charged phospholipids, namely dioleoylphosphatidylserine and dioleoylphospha=tidylcholine.

This method generated nano-capsules, composed of small aggregates of cisplatin coated with a single monolayer of lipids. These lipid preparations demonstrated an exceptional drug-to-lipid ratio and, when tested in ovarian cancer cells, demonstrated cytotoxicity 1000-fold higher than that of the free herb. Although cisplatin is the drug of choice especially for the treatment of ovarian neoplasms, its use is limited in the clinical setting due to its dose-limiting toxicity and acquired resistance. It is therefore imperative to develop administration vectors capable of circumventing these problems. Several groups have attempted lipidbasednano formulations for cisplatin delivery, but their application is limited due to the low solubility of cisplatin in water and lipids. This study by Burger et al is unique in that it addressed these issues using a basic freeze-thaw method for nanoformulation, using simple phospholipids.[7]

Several research groups have used various lipid combinations to generate liposomes of ideal quality. In one such effort, researchers have made hyperbranched carboxylated polymeric liposomes that act upon a pH-dependent stimulus.

Hyperbranched 3-methyl-glutarylated poly(glycidol) polymers (HPG) were constructed with varying degrees of polymerization and a pH-responsive stimulus that showed enhanced uptake of NPs due to the presence of active fusogenic membranes. Such liposomes were built on the idea that the presence of active membrane proteins Fusogens conjugated to polymers would be stable prior to lipid membrane fusion, but would release their contents upon contact with endosomal compartments or lysosomal proteins into the cytosol. HPG polymers are similar to PEG chains, except that these polymers carry carboxyl side groups and are complex and convoluted to give a three-dimensional (3D) spherical appearance rather than a linear appearance.

This 3D structure generates a necessary steric hindrance during membrane fusion. Many of these polymers are surface conjugated with viral fusogenic peptides that enhance their endocytic uptake by the target cell. This new approach works as a potent substitute for poly(ethylene glycol) providing 3D rendering of liposomes highlighting cell membrane attachment. Addition of fusogenic peptides, such as viral proteins, further promotes efficient

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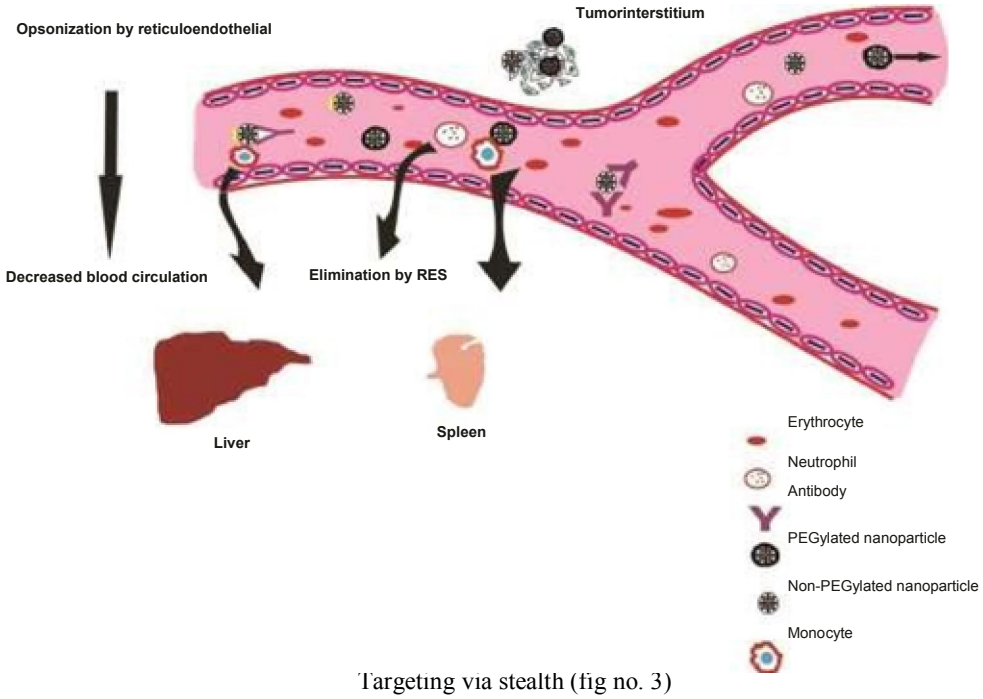
fusion of the target cell membrane and ultimately ensures endocytosis by target cells. Figure 3. illustrates the performance and selective advantages of a stealth NP in in vivo systems. Torchilinet al. reported enhanced efficacy of a tumor-specific monoclonal antibody with limited specificity by nucleosome-conjugated PEGylated doxorubicin-loaded liposomes.[9] Actively targeted liposomes carry monoclonal antinuclear autoantibodies 2C5 that mediate cytotoxicity via antibody-dependent cellular cytotoxicity (ADCC) and bind to intact tumor-specific surface nucleosomes from nearby apoptotic tumor cells.

An innovation in these targeted liposomes is that the tumor recognition antibody, 2C5, is derived from PEG and then inserted into the liposomal corona. Liposome modification using this method resulted in a stoichiometry of approximately 70 antibody molecules on the liposome surface, providing strong antigen-antibody interaction, promoting delivery of the therapeutic payload to tumor cells. Nanosized liposomes are also enriched to address issues such as multidrug resistance commonly observed during free drug delivery. This is due to the action of adenosine triphosphate (ATP)-activated adenosine triphosphate (ATP) efflux pumps. A study reported the successful reduction of cellular resistance and efficient cell death by constructing a cationic liposome incorporated with doxorubicin and small interfering RNA (siRNA) targeting MRP1 and . BCL2 mRNA. In this study, a multifunctional cationic liposome containing doxorubicin and siRNA for the multidrug resistance protein MRP1 and the antiapoptotic protein BCL2 was fabricated. Although it was innovative in the synthesis of a system that consists of a therapeutic payload and siRNA, and was subjected to cell biology and in vitro studies, it did not show data that would justify in vivo performance. Active targeting through novel secretory liposomes conjugated to the surface with fibronectin mimetics to specifically target tumor endothelial cells that overexpress the alpha(5) integrin family. beta(1) has also been tested.[10] Nanosomes have also diversified for diagnostics and imaging outside of tumor therapy. A recent study reported the development of actively targeted paramagnetic and fluorescent liposomes for tumor angiogenesis by conjugating alpha(5) integrin inhibitors. beta(1).[11]

System (RES) Enhanced blood circulationleading to hightened tumor biodistribution



Targeting via stealth (fig no. 3)

There are several dietary chemopreventive agents which shows potent bioactivity. Among these agents, turmeric (Curcuma longa) is a crystalline compound commonly used in cooking and medicinal purposes in India. Curcumin

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(diferulomethane), a yellow pigment substance, is the active ingredient in turmeric. The effectiveness of curcumin has been documented as a chemotherapeutic agent against several cancers of the stomach, prostate, breast and lung.[12-14] The limitation of the clinical application of this agent is its own low bioavailability and hydrophobic. Few research groups started manufacturing delivery systems based on nanomaterials to throw off these restrictions. A recent study reported the development of liposomal curcumin that incorporates anticancer curcumin into liposomal formulations. [15]

The efficacy of liposomal curcumin was examined in prostate cancer cell lines, LNCaP and C42B, in vitro. Treatment of cells with liposomal curcumin for 24–48 h resulted in 70–80% suppression of cell proliferation at a concentration of 5–10 μM compared with free or uncoated curcumin, which resulted in equal suppression at a concentration greater than 50 μM. In another study, liposomal curcumin preparations showed superior antiproliferative and apoptotic effects on six pancreatic cancer cell lines and also inhibited pancreatic tumor growth in mouse models. vehicle controls, but this study did not include a group of animals treated with curcumin. uncoated curcumin. The above-mentioned studies on curcumin show that nanomaterial preparations such as liposomes are very useful for effectively delivering such dietary compounds with low solubility and hydrophobicity to tumors. Although liposomes are associated with significant advantages over free drugs, they exhibit serious toxicities such as keratopathy, mucositis, and myelosuppression, which are not observed when free anti-cancer drugs are administered. They have circulation time issues and have been shown to induce immune responses. Han and colleagues suggested to incorporate a comb-shaped polymer consisting of a poly(methyl methacrylate) side chain to further improve circulation time.[18] Previous studies have also reported that the immune response is caused by polymers grafted onto the liposomal membrane and lipid dosage.[19],[20] PEGylated liposomes induce anti-PEG IgM response in a T-cell-independent manner while B cells may play an essential role in evoking an immune response against empty PEGylated liposomes.21 This in vitro lymphocyte proliferation study published by Ishida showed that PEGylated liposomes induce a T-cell-independent manner. ELISA performed on the blood of nude mice pretreated with PEGylated liposomes showed a strong antiimmunoglobulin M (anti-IgM) response after 5 days and a weak IgG response. Although the description of liposomes as drug-loaded biosimilar phospholipid bilayers seemed innocuous during development, their performance in in vivo models demonstrated their limitations, which could not have been anticipated otherwise. In addition to liposomes, micelles are nanosized lipid-based preparations that have proven useful for drug delivery applications. Micelles are colloidal aggregates of surfactants when dispersed in an aqueous solution.

Micelles differ from liposomes in that they are unilamellar and therefore smaller. Micelles have recently been used to deliver foreign gene drugs in gene therapy trials for cancer and genetic disorders. Micelle formation is due to dissolution at a threshold called the critical micelle concentration (CMC),[22] which is the surfactant concentration above which micelles form. Micelles have recently been applied in oncology to create nanoscale formulations capable of transporting anticancer agents and/or delivering tumor suppressor genes. Micelle formation is affected by several factors, such as surfactant concentration, temperature, pH, and ionic strength. Micelles show increased efficacy in cancer compared to free or encapsulated drugs due to their EPR effect and reduced opsonization by surface conjugation with polymers. Since micelles are formed by monolayer binding of surfactants, these molecules cannot contain only one type of anti-cancer drug at a time, being hydrophobic. Therefore, micelles can be an advantage in cases of administration of only one type of hydrophobic antitumor drug. such as the taxol family. So micelles are a different type nanosomal preparation formed with a single layer of a surfactant (usually a phospholipid) useful in gene therapy and delivery of hydrophobic drugs for cancer therapies.

In one of the first studies to report the synthesis of PEG-phosphatidylethanolamine (PE), which contains the micelles the hydrophobic drug paclitaxel. Immunomicelles are engineered with PEG-PE and have both stealth and tumor targeting properties. While PEG confers stealth, the mAb incorporated into the micellar crown confers its tumor targeting properties. In addition, the constructed immunomicelle was radiolabeled with 111In to quantify uptake and image the target site. These novelimmunomicelles developed by Torchilin's group had a unique antibody that

specifically recognizes tumor cell nucleosomes.to tumor cells.[23]

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The lipid content of the micelle has allowed the incorporation of poorly soluble anticancer drugs, such as taxol. Immunomicelles, when tested in a mouse model of Lewis lung carcinoma, have shown improved tumor inhibition compared with free taxol. Immunomicelles carrying ligands against tumor-specific antigens that incorporate the hydrophobic drug into their lipid bilayer can enhance drug biodistribution. Due to their low solubility, drugs such as taxol have a very low therapeutic index, but when administered with such nanosystems, they demonstrate improved efficacy and off-target toxicity.[23],[24] Micelles have also shown advantages over liposomes in several ways. First, micelles are smaller than liposomes, providing better absorption at tumor sites.[23]

Liposomes require optimal orientation for their successful localization in the tumorinterstitium and benefit from the permeable vasculature and reduced number of lymphatics, whereas micelles exhibit softness and easy accumulation at the target site and do not show such limitations. Liposomes and micelles are synthesized from simple lipids and have their advantages and limitations among alternative preparations for polymer formulations for drug delivery explored by several groups around the world.

Table 1 Clinically approved nanoparticle systems and their indication

Compound	Nature	Trade name	Indication	Status	Yearof approval
Liposomal daunorubicin drug conjugate	Liposome-Dauno	Xome	Kaposi's sarcoma	Approved	1996
Rapamycin	Antibiotic	Rapamune	Antiproliferative agent in colorectal cancer	Approved	1999
Liposomal vincristine	Liposome-drug conjugate	OncoTCS	Non-Hodgkin's lymphoma	Approved	2004
Liposomal doxorubicin	Liposome-drug conjugate	Myocet	Metastatic breast cancer in combination with cyclophosphamide	Approved (europe)	2005
Stealth liposomal doxorubicin	Liposome-drug conjugate	Doxil/Caelyx	Kaposi's sarcoma, refractory ovarian and breast cancer	Approved	2005
Albumin-paclitaxel	Albumin-drug conjugate	Abraxane/ABI-007	Metastatic breast cancer	Approved	2005
Megesterol acetate	Hormone	Megace	Breast and endometrial cancer	Approved	2005
Fenofibrate	Hypolipidemic agents	TriCor	Reduction of cholesterol	Approved	2005
PeG-L-asparaginase	PeG-enzyme conjugate	Oncaspar	Leukemia	Approved	2006
Nanopaclitaxel	Mitotic inhibitor	Nanoxel	Breast cancer	Approved	2007
Aprepitant	NK1receptor antagonist	emend	Suppression of chemotherapy-induced nausea and vomiting	Approved	2008

Abbreviation: PeG, poly(ethylene glycol)

SYNTHETIC COPOLYMERS FOR DRUG AND siRNA NANOFORMULATIONS

Polymer formulations for drug delivery have been in vogue for a long time, but their potential in this field has been hampered by stability and biocompatibility. However, several groups have developed unique polymer formulations to address these issues. Polymer formulations of chemotherapeutic drugs have several advantages, such as

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increased solubility, prolonged exposure time, selective drug delivery to the site of action, improved therapeutic index, and potential to overcome drug-associated parental resistance. Among the long list of polymer formulations, poly(cyanoacrylate) and poly(lactic acid)-based preparations have been extensively explored by several research groups due to their biocompatibility and biodegradability. We will briefly discuss relevant approaches using these formulations. Amphiphilic copolymers consist of hydrophilicand lipophilic moieties. Poly(alkyl cyanoacrylate) (PACA)are amphiphilic copolymers that were first developed 25 years ago by the anionic polymerization of alkyl cyanoacrylate in the presence of dextran. PACA NPs are composed of polymers that undergo degradation in vivo and exhibit good biocompatibility.

Several types of PACA NPs have been designed, including nanospheres and nanocapsules containing oil and water. These NPs have enabled the in vivo delivery of many types of drugs, including those with serious delivery problems.[25] Ambruosi and colleagues studied the distribution in the brain and body of tumor-bearing mice of 14C-labeled poly(butyl2-cyanoacrylate) NPs loaded with doxorubicin and poly(butyl-2-cyanoacrylate) coated with polysorbate-80 (P-80). .[26]

The study showed that the polysorbate coating of NPs prevented their uptake by reticuloendothelial cells and that the drug-loaded particles also showed uptake intracranially implanted glioblastoma cells, crossing the blood-brain barrier. Another study by the same group determined the influence of surfactants, polymer loading and doxorubicin on the antitumor effect of poly(butyl cyanoacrylate) NPs. in a mouse glioma model.[27] The NPs were coated with various surfactants and injected intravenously on days 2, 5 and 8 after intracranial implantation of glioblastoma in mice. Thirty-five percent of tumor-bearing animals treated with P-80-coated poly(N-butyl cyanoacrylate) nanoparticles loaded with doxorubicin survived for more than 180 days, whereas animals treated with other nanoparticle preparations had shorter survival times. The authors concluded that the difference in antitumor efficacy can be attributed to the variable behavior of the nanoparticle formulations,
their surface charge, and their interaction with blood and the EPR effect.[27]

Brigger and colleagues evaluated the preclinical efficacy of PEG-coated poly(hexadecyl)cyanoacrylate (PEG-PHDCA) nanospheres loaded with doxorubicin, which, as an unencapsulated drug, has poor distribution in the central nervous system. in intracranially implanted brain tumor cells. These nanospheres overcame multidrug resistance and outperformedCaelyx (Janssen-Cilag Ltd, Buckinghamshire, UK), a commercially available liposomal preparation of doxorubicin. A subsequent study by the same group, using the same polyacrylate nanoparticle preparations, questioned the preclinical efficacy of free and nanosphere-encapsulated doxorubicin in gliosarcomatumor models, showing that doxorubicin-loaded nanospheres accumulated more in the lungs and spleen. binding of plasma proteins to the surfaces of loaded nanospheres. Despite this nonspecific accumulation of doxorubicin-loaded nanospheres, tumor-bearing 9L animals demonstrated a higher maximum tolerated dose for nanospheres compared with free drug.

In a recent study, curcumin- and chitosan-loaded poly(butyl cyanoacrylate) nanoparticles were prepared by emulsion polymerization.[30] The particles thus prepared had a spherical morphology and showed cytotoxicity similar to native curcumin against three human carcinoma cell lines. The authors also demonstrated that the loaded cyanoacrylate nanoparticles did not show any toxicity to the cell lines. The study also showed that curcumin-loaded cyanoacrylate particles decreased the levels of angiogenic stimulators, namely vascular endothelial growth factor and cyclooxygenase-2. Furthermore, curcumin-loaded particles could inhibit hepatocellular xenografts in mice. An important aspect of this study is that the encapsulation of curcumin in poly(butyl cyanoacrylate) nanoparticles showed an altered pharmacokinetic profile compared to native curcumin. This study is important because it is well known that native, unpackaged curcumin has good anticancer potency when tested under in vitro conditions, while it has reduced bioavailability under in vivo conditions. Thus, the NP preparation was effective in delivering the drug to the target site without any compromise. In a recent study, a natural apolipoprotein was used as a targeting ligand for curcumin-loaded poly(butyl cyanoacrylate) NPs. . These studies are important as natural products with proven anticancer activity packaged in NP formulation have a better bioavailability profile and potential as useful agents for further research. This is because natural products like curcumin have very low or very low cellular toxicity. Poly(MePEG-).

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cyanoacrylate-co-hexadecylcyanoacrylate) nanospheres loaded with tamoxifen were synthesized and characterized by Brigger and colleagues.[32]

Tamoxifen encapsulated in nanospheres demonstrated transcriptional inhibitory activity in ex vivo experiments. Gemcitabine is a rapidly metabolized anticancer drug. To protect the drug, Stella and colleagues covalently attached an acyl chain and this lipophilic derivative was encapsulated using nanospheres and poly(H(2)NPEGCA-co-HDCA) nanocapsules.[33]

Their cytotoxicity was tested in two human cancer cell lines and compared with the cytotoxicity of gemcitabine and free 4-(N)-stearoylgemcitabine. Several research groups are actively working on NP-based delivery systems for chemotherapeutic drugs to induce effective tumor regression. Some groups are involved in the development of cancer biotherapies that involve the activation of the cell's own machinery to achieve regression. Among these biotherapeutic efforts, RNA interference (RNAi) is one such strategy. siRNAs are biomolecules that effectively utilize the cell's enzymatic machinery to knock down or regulate mRNA levels of key proteins. Effective tumorregression can be achieved by sequencing siRNAs to silence genes or proteins involved in tumorigenesis. Although RNAi technology is only about ten years old, few clinical trials have been developed to evaluate its therapeutic potential. SUCCESS of this technology is limited by several factors, most notably siRNA stability, inability to cross biological membranes, and off-target effects. Therefore, concerted efforts are being made to develop a suitable support for efficient and specific siRNA delivery.

In an interesting study by Toub and colleagues, siRNA against the EWS-Fli1 oncogenic transcription factor fusion gene was encapsulated in a core poly(isobutyl cyanoacrylate) nanocapsule and delivered to ectopically expressing NIH/3T3 cells. Ewing sarcoma fusion. Intracellular penetration by confocal microscopy showed that the nanocapsules improve the intracellular penetration of siRNA with a predominantly cytoplasmic localization. These siRNA-loaded biodegradable nanocapsules were then tested in vivo in a mouse tumor xenograft expressing EWSFli1 and found to induce a dose-dependent inhibition of tumor growth after intratumoral injection. Specific inhibition of EWS-Fli1 was also observed. This study demonstrated that alkylcyanoacrylate nanoparticles can serve as versatile carriers for various therapeutic regimens, including drugs and therapeutic biomolecules such as siRNA. An obvious drawback of this study is the intratumoral administration of the nanoformulation. This approach does not allow these nanomaterials to be evaluated with therapeutic biomolecules in the systemic circulation.

CURRUNT STATUS OF NANOMATERIALS-BASED DRUG-DELIVERY SYSTEMS

Nanotherapies are rapidly advancing and are being applied to address several limitations of conventional drug delivery systems, such as non-specific delivery and targeting, lack of aqueous solubility, low oral bioavailability, and low therapeutic index. Several studies on the stability and loading of NP formulations have shown that they are highly stable with high transport capacity, are capable of incorporating hydrophilic and hydrophobic substances, and can be delivered by various routes, including oral application and inhalation. [35][,36]

NPs are designed for optimal size and surface characteristics to increase their circulation time in the blood and biodistribution. They are also capable of delivering their loaded active drugs into cancer cells by selectively exploiting the unique pathophysiology of tumors, such as their enhanced permeability and retention effect, and the tumor microenvironment. A number of NP-based drugs have been approved for the treatment of a variety of chronic diseases, including cancer. Table 1 provides a list of these clinically approved NP systems and their indications. NP-based drugs such as Emend® (Merck Sharp and Dohme Ltd, Herts, UK) and TriCor® (Abbott Laboratories, North Chicago, IL) are approved to suppress nausea and vomiting caused by chemotherapy and to lower cholesterol. In 1996, the first NP-based drug, DaunoXome® (Gilead Sciences, Cambridge, UK), was approved by the US Food and Drug Administration for treatment of Kaposi's sarcoma. Multifunctional and multiplex NPs are now the subject of active research and are on the horizon as the next generation of NPs for personalized and tailored cancer treatment. Drug delivery systems based on nanomaterials synthesized from raw materials, such as lipid-based liposomal formulations or cyanoacrylate-based formulations, have been tested in several models and found useful for drug delivery. A limited number of these preparations are also used clinically for the treatment of

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malignant diseases. However, despite their acceptable ability to deliver a therapeutic payload, these systems suffer from disadvantages such as biocompatibility and lack of target specificity. The need for the development of targeted drug delivery using nanoformulations has gained importance and now plays a leading role. Many targets are discovered through the application of genomic and proteomic technologies. So there is much room for improving these systems to meet the problems mentioned above and some groups, including ours, are working to improve the targeting properties of NPs and for this development of targeted therapies. IN the next section will discuss current research on the development of targeted drug delivery systems.

VI. INTRODUCTION TO TARGETED DRUG DELIVERY

A promising strategy to achieve direct drug delivery is the development of active targeting of cancer cells through ligand-mediated interactions such as antibodies, lectins, aptamers, folates, and peptides, such as indicated NPs. Active tumor targeting of NPs can be achieved by direct targeting or a multi-step pretargeting method. In the case of direct targeting, the NPs can be covalently linked to the ligand and the resulting drug carrier can be administered immediately. In thepretargeting approach, the therapeutic molecule is not bound to the ligand and is administered after an appropriate delay after the target ligand. This delay gives the antibody time to localize and concentrate in the tumor. Typically, the pretreatment protocol includes an avidin-biotin system or bispecific antibodies.

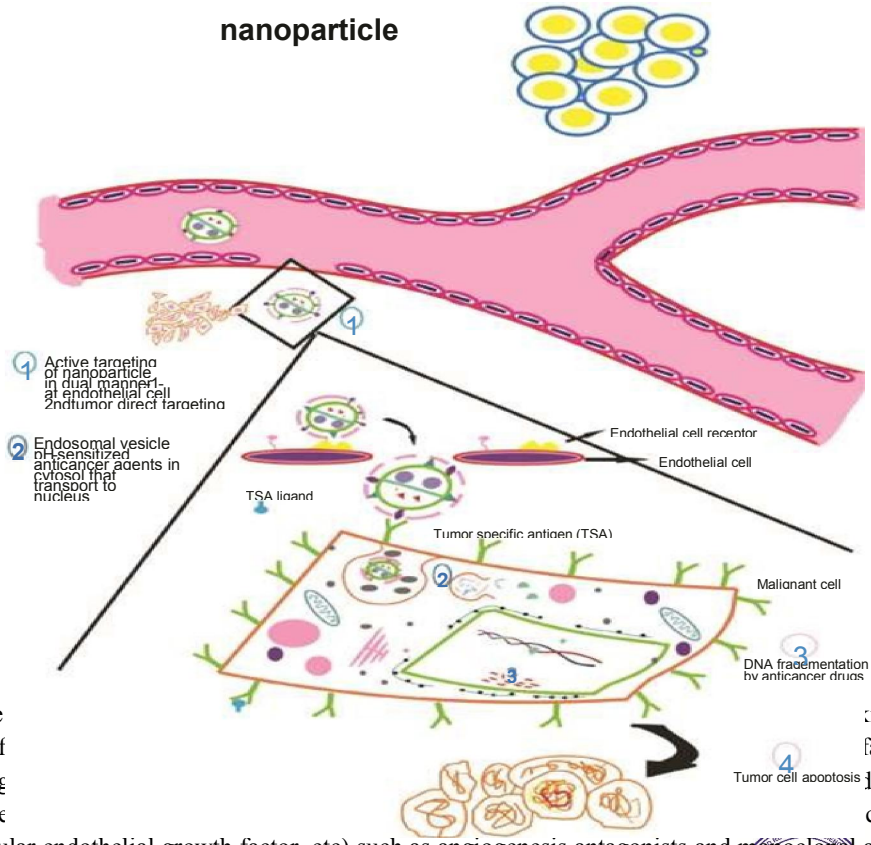

Figure 4 Active ing addresses on nanoparticle surf face tagged with a certain ligand ag del here discusses dual targeting e cellular adhesion molecules, vascular endothelial growth factor, etc) such as angiogenesis antagonists and monoclonal antibodies against

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typical tumor signatures such as endothelial growth factor receptors, HeR2, which result in tumor cell apoptosis. endothelial cell targeting curbs angiogenesis of tumorinterstitium preventing oxygen supply and nutrients while tumor targeting causes direct cell killing as the nanoparticle encapsulating the anticancer drug is taken up by the cell. (1) The nanoparticle is targeted against endothelial cell receptor and against a tumor antigen. (2) The nanoparticle is taken up by the tumor cell via endocytosis wherein nanocarrier vesicles formed release the contents in a pH-dependent manner. The anticancer drug(s) embedded in the nanovector is(are) released and translocated to the nucleus. (3) Action of anticancer drug results in DNA fragmentation that finally leads to (4) programmed cell death.

VII. MODELS FOR TARGETED DRUG DELIVERY ANTI-HER2 ANTIBODY-LABELED NPS

Antibody-labeled NPs are one of the most promising ways of targeting active NPs. MAB is currently the only therapeutic option in the clinic as a form of cancer immunotherapy, targeting aberrantly regulated cell surface receptors essential for tumor cell proliferation, motility and metastasis. Thus blocking the activity of the upregulated receptor in Binding to a ligand (such as the monoclonal antibody presented in the nanovector) will block the signaling pathways. Therefore, monoclonal antibodies are useful for recognizing cell surface antigens that are commonly dysregulated in cancers, for example RTKs such as EGFR/HER2. HER2 is an oncogene and its upregulation is manifested in several malignancies such as breast, ovarian, endometrial and gastric cancer and therefore constitutes a widely studied model for cancer therapy. Figure 4 explains the concept of antibody drug delivery as a model for active targeting. In a study by Nobs and colleagues, two approaches were tested for targeted delivery of biodegradable polylactic acid nanoparticles to tumor cells.[37]

Anti-HER2 monoclonal antibodies (trastuzumab; Herceptin® [Roche Products Ltd, Herts, United Kingdom]) and anti-CD20 monoclonal antibodies (rituximab; Mabthera® [Roche Products Ltd]) were used as targeting ligands. Two cell lines were used, SKOV-3 human ovarian cancer cells expressing the HER2 antigen and Daudi lymphoma cells expressing the CD20 antigen. In each cell line, the antibody directed against the unexpressed antigen served as an irrelevant Ig control isotype-matched. In the direct approach, NPs displayingmAbs on their surface were incubated with both tumor cell lines. In the pretreatment protocol, tumor cells were pretreated with biotinylated mAbs prior to administration of avidin-labeled NPs. Cellular interactions of fluorescently labeled NPs were measured by flow cytometry. The analysis showed that targeted NPs accumulated in antigen-positive cells compared to non-targeted NPs. Park and colleagues studied the pharmacokinetics and therapeutic efficacy of anti-HER2 immunoliposomes containing doxorubicin in animal models and demonstrated that anti-HER2-doxorubicin immunoliposomes exhibited greater therapeutic benefit compared to combinations of free Herceptin monoclonal antibody plus free doxorubicin or free monoclonal antibody plus liposomal doxorubicin.38 This study concluded that anti-HER2 immunoliposomes produced enhanced antitumor efficacy upon targeted administration. Sun and co-workers synthesized poly(d,l-lactide-co-glycolide)/montmorillonite (PLGA/MMT), which was decorated with the HER2 antibody trastuzumab for targeted chemotherapy of breast cancer using paclitaxel as a model anticancer drug. with surface decoration can be 12.74 times higher than that of bare nanoparticles and 13.11 times higher than that of taxol. Gold and gold sulfide nanoparticles exposed to a near-infrared resonant pulsed laser exhibit photoluminescence that can be used to visualize cancer cells in vitro. When these nanoparticles are conjugated to anti-HER2 antibodies, there is specific binding to SK-B3 breast cancer cells where the HER2 receptor is overexpressed, allowing precise imaging of the cancer cells. When higher excitation power is used, thermal damage leading to cancer cell death is also observed.[40]

APOPLIPOPROTEIN-LABELED NPs

Apolipoproteins are carrier proteins that combine with lipids to form lipoprotein particles, which have hydrophobic ligands in the heart and hydrophilic side chains composed of amino acids.

These lipoproteins are metabolized in the liver and muscles by receptor-mediated endocytosis, recognized by the apoproteins of the complex. Thus, the apoproteins provide an address to the lipoprotein so that it is absorbed by specific receptors. The fact that apoproteins act as localization ligands has prompted researchers to use

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them as a targeting marker for NP. Recently, lipoproteins have caught the attention of oncologists with the observation that high-density lipoproteins (HDL) show increased uptake by tumor cells and, in turn, affect cell proliferation. This is possible due to overexpression of the HDL receptor, the B1 receptor (SR-B1).[40] The receptor has been shown to be expressed in normal cells, such as liver cells, but reports have shown a significant increase in SR-B1 in tumor cells. HDLconcentrated cells are required for active cell proliferation involving the STAT3 and FAK pathways. Thus, efforts have been made to synthesize targeted HDL NPs that can trick a tumor cell into taking up HDL, thereby loading the anticancer agent that carries the tumor mass to directly kill the cells. A group of scientists reported a detailed and unprecedented study on the administration of siRNAlabeled siRNA with reconstituted synthetic HDL (rHDL) NPs.[41]

The study was initiated by the synthesis of surface-labeled siRNA with HDL molecules and their characterization by transmission electron microscopy, followed by in vitro studies on human cancer cell lines. In vitro studies on cell lines demonstrated effective silencing of target mRNA. siRNA-loaded rHDL was also tested and found effective in nude mice bearing ovarian xenografts.

PEPTIDE LABELED NPs

Peptide labeling of NPs is gaining importance in cancer research. It can be used to target drug-conjugated NPs to specific cancer cells, as they can be based on ligands that bind to receptors on specific tumor cells/organs/cells or tumor-supporting structures, such as stroma or neovascularization. Peptides can also be used as building blocks of the NPs themselves. Peptide-labeledNPs can be used in imaging tumor cells and tumor tissues.

Molecularly linked fluorescent silica NPs (FSiNPs) The recognition element enables efficient in vitro and ex vivo imaging of tumor cells and tissues. A study reported the targeting and imaging of human breast cancer cells MDA-MB-231 using FSiNPslabeled with arginine-glycineaspartic acid (RGD) peptides; FSiNPs showed high binding to alpha(5)beta(3) integrin receptor (ABIR)-positive MDA-MB-231 breast cells in vitro. MB-231 tumors were clearly visible due to the special targeting effects of RGD-labeledFSiNPs.Peptide-labeled NPs can also be used for target gene silencing. The study shows that RGD-CH-NP is a novel and highly selective delivery system for siRNA with potential for broad applications in human diseases. [43]

The RGD peptide conjugated to chitosan by the thiolation reaction was confirmed by proton nuclear magnetic resonance (H-NMR). . The binding of RGD-CH-NP to alpha(5)beta(3) integrin was examined by flow cytometry and fluorescence microscopy. The antitumor efficacy was examined in orthotopic models of ovarian carcinoma. This approach resulted in significant inhibition oftumor growth compared to controls.

APTAMER-LABELED NPS

Aptamers are DNA or RNA oligonucleotides that, through intramolecular interactions, fold into unique tertiary conformations capable of binding target proteins with high affinity and specificity. This property makes them an attractive class of targeting molecules because they are also non-immunogenic and exhibit remarkable stability and are often referred to as chemical antibodies. Docetaxel (Dtxl) NPs encapsulated with PLGA-b-PEG copolymer and surface-bound fluoropyrimidine RNA aptamers have been reported to recognize the extracellular domain of prostate-specific antigen (PSMA), a well-known antigen on the surface of prostate cancer cells. . . They bind and are taken up by cells, resulting in significantly increased cellular toxicity in vitro compared to non-targeted NPs lacking PSMA, demonstrating their therapeutic potential.[44] FOLATE-LINKED NPs Folic acid, a member of the B complex group of vitamins, is an important cofactor in one-carbon transfer reactions for nucleotide biosynthesis and plays a key role in DNA and RNA synthesis, epigenetic processes, cell proliferation, and survival. Three different transporters mediate cellular uptake of folate. Among them, the folate transporter called folate receptor (FR), often referred to as high-affinity folate binding protein, is a glycosylanchored glycopeptide. phosphatidylinositol (GPI) on the cell surface, which characteristically binds folic acid and transports it by a non-classical endocytic mechanism.[45]-[47] A wide range of chemical conjugates of folic acid, drugs, and antifolate agents. Immunoassays have been used to develop therapeutic and imaging methods. agents for various diseases. Studies showed a significant correlation between FR alpha expression and the grade and

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differentiation status of tumors, and even poorly differentiated and aggressive tumors express high levels of FR alpha.[48]

Folic acid is known to promote intracellular uptake of NPs.[49] Folic acid is conjugated to human serum albumin (HSA) NPs. by a reaction with carbodiimide leading to the formation of HSA-NP spheres. Cell attachment and uptake were studied in normal foreskin fibroblasts (HFF), human neuroblastoma UKF-NB3 cells, and mouse glioblastoma cell lines. Increased NP uptake was observed in cancer cells, but not in normal HFF. This suggests their application in targeted delivery of antitumor drugs. Folate-linked NPs can also be used in tumor imaging and radiotherapy. In a recent study, folate-conjugated shell (SCK) cross-linked NPs were functionalized with folate, fluorescein thiosemicarbazide (FTSC) and TETA. [50] SCK were obtained by cross-linking the shell of micelles obtained from amphiphilic diblock copolymers. It was studied in KB cells and evaluated in athymic mice bearing KB cell xenografts. The specific interaction of FTSC-SCK-folate with FR in vitro was confirmed. The Cu-labeled SCKs64 evaluated showed long circulation in the blood and were able to passively accumulate in tumors. In the case of cancers such as colorectal carcinoma, where early detection can significantly improve mortality, folate chitosan NPs complexed with alginate have been described for photodynamic detection. These NPs are easily ingested by cancer cells via folate receptor-mediated endocytosis. When loaded with 5aminolevulinic acid (5-ALA), an increased release was observed in the cellular lysosome, suggesting an excellent vector for the specific delivery of 5-ALA to colorectal cancer for fluorescent endoscopic detection. [51]

Folate-conjugated liposomes show minimal nonspecific binding to serum proteins. Folate-PEG loaded liposomes of doxorubicin showed 45-fold higher uptake in FRenriched KB cells compared to untargeted doxorubicin-liposomes and cytotoxicity 86 times higher. In mice bearing KB cell tumor xenografts, treatment with folatetargeted liposomal doxorubicin produced a 31% inhibition of tumor growth.[52] Another study using a multidrug-resistant M109R cell line overexpressing FR demonstrated that liposomal doxorubicin was taken up independently of a functional drug efflux pump operating within the cells. This preparation had cytotoxicity 10fold higher than untargeted liposome controls. Magnetic resonance imaging of mice bearing subcutaneous KB tumors demonstrated that superparamagnetic iron oxide (SPIO) nanoparticles were rapidly taken up by tumorcells in vivo only when conjugated with folate.[53],[54] Tumor-targeted drug delivery systems are currently considered silver bullets for cancer treatment, and several groups are working worldwide to develop robust systems that address specificity issues. A summary of some important nanovector prototypes against typical tumor signatures is presented in Table #2 below

Table 2 Important nanovector paradigms against typical tumor signature **(table no. 2)**

Target	Animal model	Nanoparticle used	Hallmark targeted	Target ligand	Reference
veGFR-2	BALB/c (4T1 xenografts)	Boronated dendrimers	Angiogenesis	veGF analogue	Backer et al[55]
veGF	Nude mice (K1735-M2 melanoma and CT-26 xenografts)	Dextran magnetic Nanoparticles conjugated with 90Y-anti-veGF mAb	Angiogenesis	anti-veGFmAb	Li et al[56]
αvβ3	Nude mice (M-21 L melanoma xenografts)	Cationic nanoparticles conjugated to integrin αvβ3– targeting ligand	Angiogenesis	RGD mimetics	Hood et al[57]
vCAM-1	Nude mice (CoLo 677 xenografts)	vCAM-1 targeted immunoliposomes	Angiogenesis	anti-vCAMmAb	Gosk et al[58]
HeR-2	Nude mice (BT-474, MCF-7 xenografts)	Anti-HeR-2 Fab' conjugated PeGylated immunoliposomes	Uncontrolled cell proliferation	Trastuzumab mAb, anti-HeR-2 Fab'	Kirpotin et al[59]

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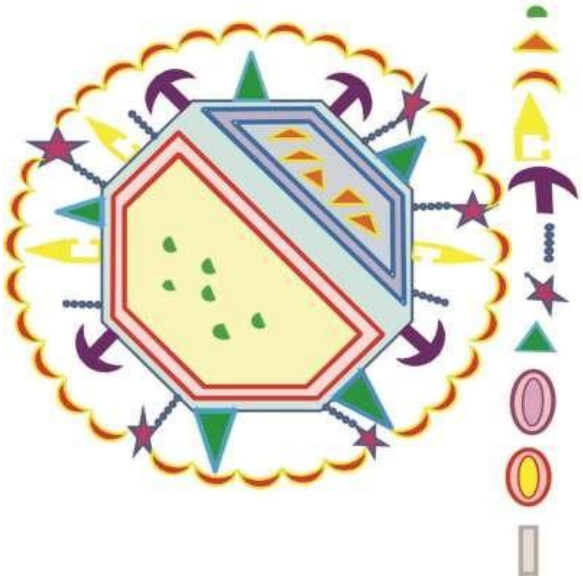
Transferrin receptors	NMRI Mice xenografts)	(HT-29	Transferrin-modified nanoparticles containingDNAzymes	Uncontrolled proliferation	cell	Transferrin Analog	Pun et al[60]
Folate receptor	BALB/c mice xenografts	J6456-FR	Folate-targeted liposomes	Uncontrolled proliferation	cell	Folate	Shmeeda et al[61]

Abbreviations: veGFR-2, vascular endothelial growth factor receptor-2; veGF, vascular endothelial growth factor; $\alpha_v\beta_3$, alpha5 beta 3 integrin; vCAM-1, vascular cell adhesion molecule 1; HeR-2, human epidermal growth factor receptor-2; mAb, monoclonal antibody; RGD, arginine, glycine, aspartate; Fab, fragment antigen-binding



Anticancer drug 1
Anticancer drug 2
Poly(ethylene glycol)
Cell penetrating agent
Fab to tumor specific antigen
Biopolymer
Image contrast agent
Endothelial cell receptor ligand
Hydrophilic matrix for stimulus-dependent release
Lipophilic matrix for stimulus sensitive release
Gel matrix for compartmentalisation

VII. CONCEPT OF MULTIFUNCTIONAL NPs

Nanoscale formulations for oncology have overcome the challenges deficiencies related to chemotherapeutic drugs such as specificity, toxicity, biodistribution at the target site, elimination and excretion. NPs are therefore biodegradable materials containing anticancer agents inside. Their nanometric dimensions allow for efficient uptake at the tumor site thanks to their improved permeability and retention effect. We suggest a model for multifunctional NPs (Figure 5) that act as a drug delivery system as well as a diagnostic agent. with the concept of combined chemotherapy in practice is useful for the administration of two different drugs with different mechanisms of action in a single delivery vehicle. For this purpose, the system can be designed to incorporate two anticancer drugs, drug 1 and drug 2, which are separated from each other by an emulsion column. Specifically,

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the anticancer agents are dissolved in specific matrices based on their solubility, either lipophilic or hydrophilic. Furthermore, the model illustrates a stimulus-dependent release of drugs. This is based on the concept that chemotherapeutic agents administered as prodrugs are only metabolized to the active form under suitable conditions, ideally present in the tumorinterstitium. Thus, stimuli (such as oxygen pressure or pH) act as a catalyst to trigger the release of the anticancer agents, particularly at the target site. Externally, the presence of a cellpenetrating peptide facilitates cellular entry of the nanomaterial. When a nanomaterial has the above-mentioned components, targeting to the tumor site is passive, whereas engineered ligands to tumor-specific antigens will provide more specific uptake to the tumor site, a phenomenon known as active targeting. In our model, we suggest dual targeting: one against the endothelial cell receptor and a second against the tumor marker. Endothelial cell targeting is a novel strategy to inhibit angiogenesis by sequestering receptors, such as vascular cell adhesion molecules, selectins, and vascular endothelial growth factor receptors that have been documented to be associated with tumor angiogenesis. In addition, tumor destruction by antiangiogenic therapy has been engineered through several pharmacological means. In this sense, the development of agents Antagonizing the angiogenic properties of endothelial cells would reduce tumor growth, strategically reducing the supply of oxygen and nutrients to the tumorinterstitium.[62]

A study led by Jain said that herceptin, the monoclonal antibody against the cell surface receptor HER2, has antiangiogenic properties to normalize tumor vascularization in a mouse model.[63]

Malignant tumorsare known to arise due to large mutations attributed to the positive regulation of certain proteins that are made signatures of various cancers (especially HER2, PSA, EGFR). Monoclonal antibodies that target these

Tumor markers allow direct targeting of the tumor to the tumor site, leaving normal cells unharmed, thereby shrinking them significant cytotoxicity. The strategy involves the reduction of oxygen and nutrients to the tumor cells. A polymer like PEG is included to secure it secretion of the reticuloendothelial system to improve the bioavailability of the NP. For diagnostic purposes, an imaging contrast agent can be added to facilitate magnetic resonance imaging. NPs designed for diagnosis would allow early tumor detection. This would also facilitate rapidtumor treatment before metastasis.

VIII. MULTIFUNCTIONAL MAGNETIC NPs FOR CANCER TREATMENT

Hyperthermia offers an attractive approach to cancer treatment because it is associated with fewer side effects compared to chemotherapy and radiotherapy and can be used concurrently with conventional modalities. Several clinical studies have shown the effectiveness of such combinations.

The first use of magnetic nanoparticles for hyperthermia was reported by Gilchrist in 1957. [64]

Although some potential hyperthermic nanoparticles are available, such as silver, lanthanum and zinc nanoparticles, the thermal activation properties of gold nanoparticles, magnetic nanoparticles and carbon nanotubes are characterized by extremely strong. . at the preclinical level and are the most advanced in terms of possible transposition in biomedical clinical applications.[65]

Thermotherapy is more effective for superficial cancers in the form of three methods: local, regional and whole body hyperthermia. Local and regional application of hyperthermia can be administered using heat delivery systems that can distribute the dose of heat applied to the target area of the cancer.[66]

Radiofrequency ablation is the most commonly used type of local hyperthermia. In this technique, short-duration high-energy radio waves are focused on the tumor site using a thin needle-like probe with an ultrasound guide capable of emitting a high-frequency current that targets the cells malignant heating in a minimally invasive way without harming nearby vitals. structures.[67]

Three-dimensional phantom models were developed to imitate tissue. Merkle and colleagues studied the changes in heat deposition during RF ablation in the presence of SPIO nanoparticles and reported that the temperature along the trajectory of the RF electrode increased significantly due to the iron content of the ghost in polyacrylamide; However, the use of SPIO at physiological concentrations in rabbit models did not produce a significant change in coagulation diameter.[68] and are increasingly used for clinical applications such as drug

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delivery, magnetic resonance imaging, and magnetic fluid hyperthermia. The concept of using magnetic nanoparticles for drug delivery was proposed by Widder and Senyi in 1978.[69]

All magnetic nanoparticles used so far in vivo are composed of iron oxides magnetite (Fe3O4) and maghemite (γ-Fe2 O3) due to their low toxicity and biocompatibility.[70] Ferrite nanoparticles are the most sought after, due to their physical and chemical properties that are best suited for hyperthermic applications. Two key issues dominate the magnetic properties of nanoparticles: finite size effects and surface effects that cause different particular functionalities. Finite-size effects result, for example, from quantum confinement of electrons, while typical surface effects are related to symmetry breaking of the crystal structure at the boundary of each particle. Thus, for hyperthermia treatment, particles smaller than 50 nm in diameter produce the maximum specific absorption rate.[71]

Iron oxide particles smaller than 30–40 nm in diameter are of particular interest because they exhibit superparamagnetic behavior, i.e. once the magnetic field is removed, they do not retain magnetization.Cancer Heating with Magnetic NPs Magnetic NPs can be used as heat-generating systems for therapeutic applications because they generate sufficient thermal energy when exposed to an alternating magnetic field (AMF).

These nanoscale systems act as a single magnetic field and therefore exhibit the properties of a simple magnetic dipole.[64]

Ivkov et al reported the possibility of applying high-amplitude CMA to treat cancer tissue with magnetic NPs embedded in 39 athymic female BALB/c nude mice and observed no adverse effects in mice exposed to CMA amplitudes of #700. However, rats exposed to CMA amplitudes greater than 9500 had disease and injury [72]

Preclinical studies in various types of cancer using magnetic hyperthermia have shown promise in terms of tumor responses in mouse models. These studies were conducted independently by different research teams in breast, prostate, and brain tumor models. The clinical trials were conducted in Germany with 59 patients with glioblastoma multiforme, who underwent a combination of intratumoral thermotherapy and low-dose therapy of 30 Gy, using AMF and SPIO as the transducer. The results of the study reported a median overall survival of 13.4 months in 59 patients, compared with 6.2 months reported in another study using temozolomide as the current standard treatment for primary glioblastoma.[73]

IX. ACTIVE TARGETING OF MAGNETIC NPs

Magnetic targeting can be activated by magnetoliposomes or magnetic polymer particles that can carry active drug molecules that can be focused to a defined target site by local application of an external magnetic field. This could be activated by surface modification of magnetic NPs where the NPs are conjugated with appropriate anti-molecule ligands over expressed in tumors. Occhipinti and colleagues synthesized trastuzumab-functionalized iron oxide nanoparticles as a model to study the interaction between a mAb nanoconjugate and its receptor (HER2) and documented the utility of magnetic nanoparticles in designing and testing novel hybrid targets that deliver random nanovectors. reduces side effects such as nonspecific uptake by normal tissues.[74]

Natarajan and colleagues developed multifunctional radioimmunonanoparticles (RINPs) using recombinant antibody fragments, di-scFv-c, for imaging and therapy of anti-MUC-1 expressing tumors. RINP binding totumor cells was found to be time-dependent and in vivo uptake was confirmed by pharmacokinetics and whole body autoradiography in mouse models of breast cancer.[75] Magnetic nanoparticles have great theranostic applications due to their unique and multifunctional properties. Recent advances in materials science make it possible to control the shape, size, and properties of magnetic nanoparticles with limited toxicity and biodegradability. The challenge is to design it "Perfect" magnetic NPs combining different functionalities for greater specificity towards target tissues and a longer retention time. Such advances may pave the way for effective clinical practice.

X. CONCLUSION

Nanotechnology is the manipulation of materials at the nanoscale. The use of nanotechnology has already flourished in many fields such as information and communication. Nanomedicine is a subdiscipline that focuses on the health

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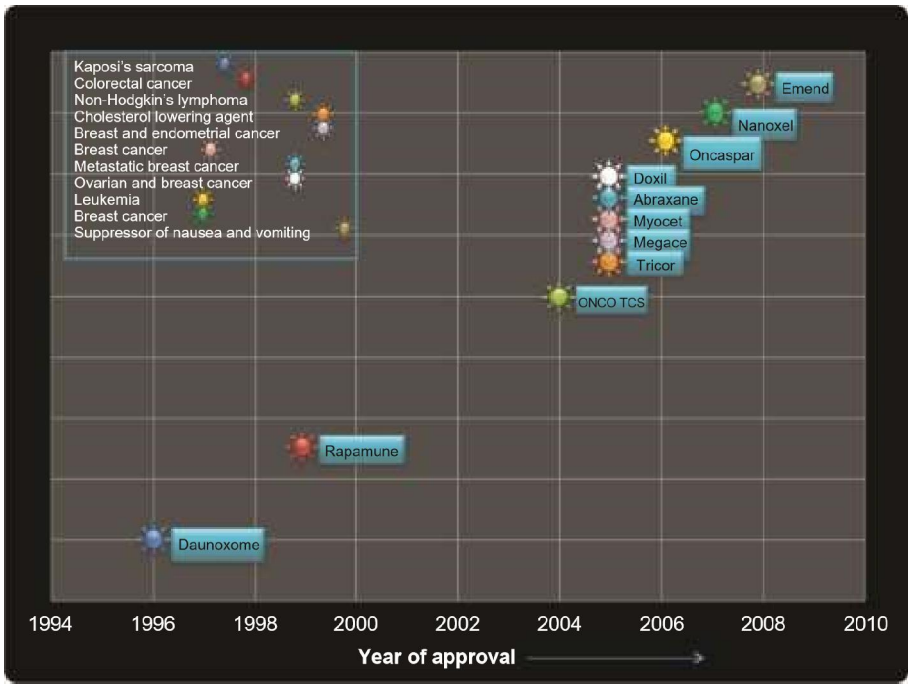
benefits of nanotechnology. Nanoparticle-based drug delivery systems can be synthesized from a wide range of starting materials. There are therefore many opportunities for innovation in chemical synthesis. The chemist involved in such processes should consult a biologist to recognize the application of the materials in medicine and biology, the therapeutic load they can carry, robust laboratory methodology to test efficacy, target specificity and, above all, biological materials. It is necessary for the chemist and biologist to discuss with a pharmacologist the material synthesized for human use, the stability of the systems in biological fluids, and the efficacy compared to conventional methods. Thus, the emerging field of nano-oncology requires an interaction of expertise from many departments of basic and clinical science with the need to test nanomaterial-based drug delivery agents in recognized clinical trials with good ethical practices. A newly developed drug delivery system based on nanomaterials must work at multiple levels; only then can it reach its final application destination to alleviate human diseases. The growing list of medically approved NPs (Figure 6) and new agents in development offer great hope for our future.



(fig no. 6)

Figure 6 Schematic representation of timelines depicting the clinical approval of nanoparticle-based drug vehicles for human diseases.

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