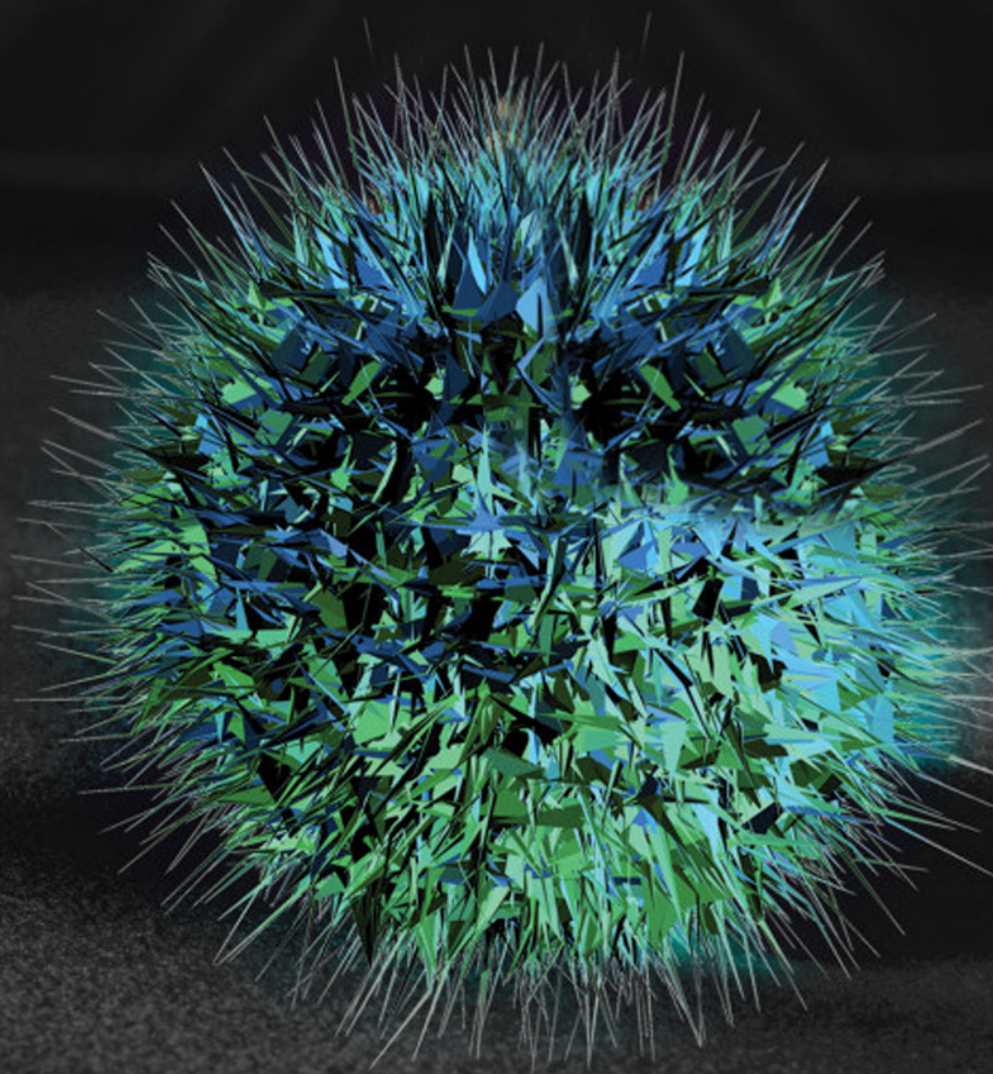# NANOPARTICLE DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT
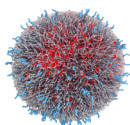
By **Anup Patwa**
Associate, Technology and Patent Research

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BACKGROUND OF THE DOMAIN

Nanotechnology is a rapidly evolving domain, as it solves various issues associated with conventional drug therapeutics, including poor water solubility, lack of targeting capability, non-specific distribution, systemic toxicity and low therapeutic index. Nanoparticles are 1–100 nanometres in size. These particles can be used in a targeted drug delivery approach, as they can specifically target a drug or drug carrier to minimise drug-originated systemic toxic effects. In addition, nanoparticles are designed to assist therapeutic agents to pass through biologic barriers, mediate molecular interactions and identify molecular changes. After nanoparticles bind with the receptors, they rapidly undergo receptor-mediated endocytosis or phagocytosis by cells, releasing the encapsulated drug inside the cell cytoplasm. Nanoparticles were developed in the late 1960s. During the 1970s, the first nanoparticle drug delivery system, lipid vesicle, was developed. In 1983, the US FDA approved the first micellar drug, Sandimmune®, for systemic administration of nanoparticles in humans. In 1990, the first polymer–drug nanoconjugate Adagen® was clinically approved for human use.
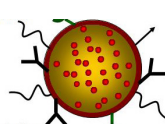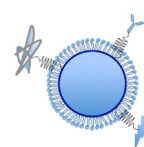
Types of Nanoparticles
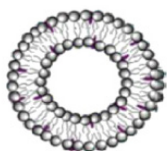
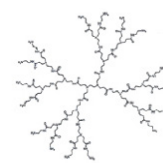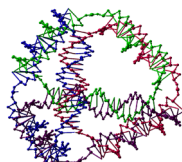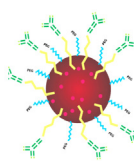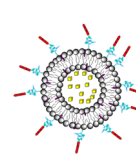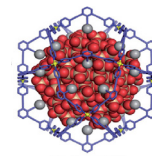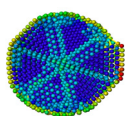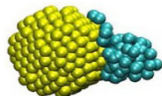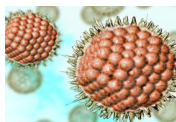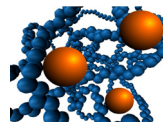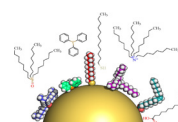|				
Polymeric micelles	Liposomes	Biodegradable/ biocompatible nanoparticles	Nanoparticle drug carriers	Dendrimers
Nanospheres, nanocapsules, nanotubes	Artificial DNA nanostructures	Drug nanoparticle conjugates	Stimuli-based drug releasing nanoparticles	Silica nanoparticles
Metal nanoparticles	Carbon nanoparticles	Magnetic nanoparticles	Nanocomposites	Targeting ligand -modified nanoparticles	Protein–drug nanoconjugates
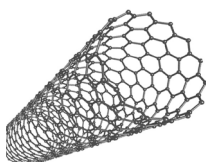
Nanoparticles have promising applications in diagnostic, therapeutic and drug delivery systems for cancer, as they can enter the tissues at the molecular level; these particles have given platforms for cancer therapy and diagnostics. Nanoparticles provide a new mode for cancer drug delivery as a carrier for entry through fenestrations in tumour vasculature, allowing direct cell access. The modified nanoparticles allow binding to cancer cell membranes, microenvironment, or cytoplasmic or nuclear receptor sites. This initiates the delivery of high drug concentrations to the targeted cancer cell with reduced toxicity of normal tissues. Over the past several decades, the development and application of engineered nanoparticles to more effectively treat cancer have witnessed significant advancement.
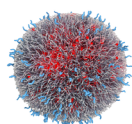
MECHANISM OF TARGETING

Nanoparticles target tumour cells in two ways: active and passive.

- **Passive targeting:** This term refers to the accumulation of the drug in areas around the tumour with leaky vasculature; it also known as the enhanced permeation and retention (EPR) effect.

- **Active targeting:** This term refers to specific interactions between the drug/drug carrier and target cells, usually through specific ligand receptor interactions or antibody-antigen recognition, for intracellular localisation of the drug.

The EPR effect, a unique characteristic of tumour cells, enables targeted delivery of anticancer agents. Passive targeting is based primarily on size; the nanoparticle surface may be modified with several ligands that would interact with specific receptors over-expressed on the surface of the tumour cells, thus imparting specificity for active targeting.
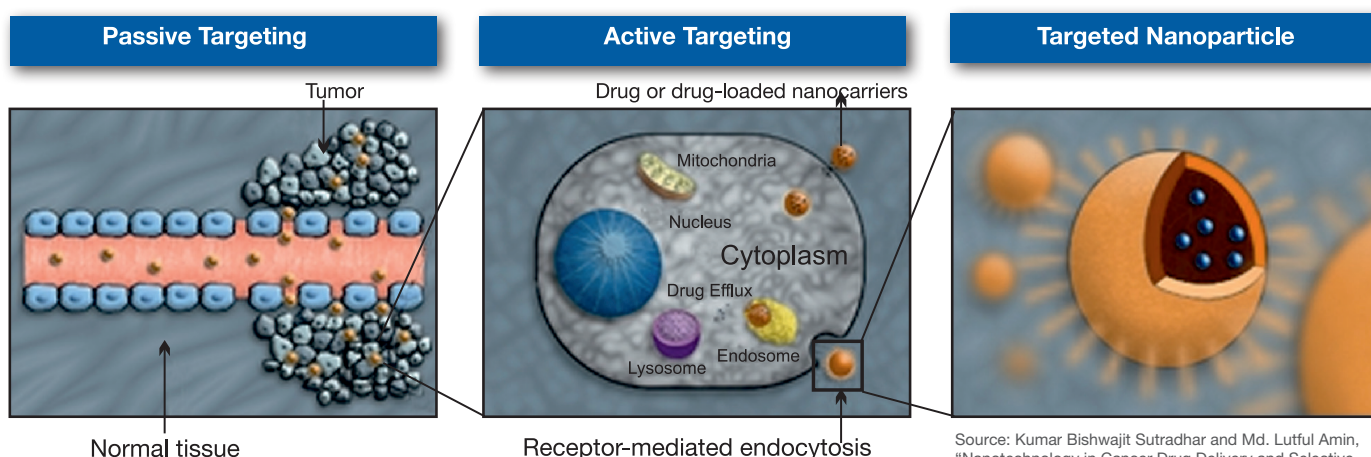
Fig.1. Active and passive targeting by nanoparticles
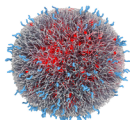
UNMET NEEDS OF CONVENTIONAL DOSAGE

THE CONVENTIONAL DRUG DELIVERY SYSTEM HAS THE FOLLOWING DISADVANTAGES:

1. Drug resistance

2. Lack of selectivity

3. Lack of drug solubility

4. Dynamic changes of cancer cells

5. Serious side effects of chemotherapy

6. Poor targeting of heterogenic tumours

7. Small amount of drug reaches the cancer cells

8. Nonspecific targeting of conventional delivery

9. Inability of the drug to enter the core of tumours, resulting in impaired treatment with reduced dose and low survival rate

ADVANTAGES OF NANOPARTICLES:

1. Entry into tissues at the molecular level

2. Increased drug localisation and cellular uptake

3. Cancer diagnosis and treatment applications

4. Feasibility to programme nanoparticles for recognising cancerous cells

5. Selective and accurate drug delivery, and avoiding interaction with healthy cells

6. Direct and selective targeting of the drug to cancerous cells (both active and passive targeting)

7. Larger surface area with modifiable optical, electronic, magnetic and biologic properties vis-à vis macroparticles

8. Assisting therapeutic agents to pass through biologic barriers, mediate molecular interactions and identify molecular changes
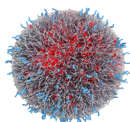
FACTORS DRIVING NANOPARTICLE-BASED CANCER DRUG DELIVERY SYSTEMS

Ability to locate and specifically target deep-seated tissues and organs

Encapsulation or conjugation of small biomolecules such as proteins, enzymes, carboxylic acid, DNA and amino acids

Successful delivery of the drug to the targeted region of the body

Prevents tissue damage through regulated drug release

Efficient encapsulation of drugs

Biocompatibility

Reduces the effect on non-target tissues

Exhibits the EPR effect, a unique property of nanoparticles to accumulate and interact with tumour cells

Improves pharmacokinetics and biodistribution of the drug

Reduces drug clearance rates

Lowers volume of distribution of the drug

Successful release of the drug

Likely to overcome drug resistance

Delivers drugs with serious side effects (such as anticancer agents)

Delivers unstable molecules (proteins, siRNA and DNA) using liposomes and polymeric nanoparticles

Delivers to difficult sites (brain, retina, tumours and intracellular organelles)

CURRENT RESEARCH

Nanoparticles have been modified and enhanced to enable the delivery of drugs across the blood–brain barrier (BBB) as well as improved upon to create polyethylene glycol (PEG) modified (PEGylated) nanoparticles with a prolonged blood circulation time. Targeting ligands (such as small organic molecules, peptides, antibodies and nucleic acids) have been added to the surface of nanoparticles to specifically target cancerous cells by selectively binding to the receptors over-expressed on their surface. Furthermore, site-specific release of a drug contained in a nanoparticulate system by applying an external stimulus, such as hyperthermia, to a thermosensitive device is another innovative strategy to achieve targeted delivery. Moreover, multiple types of therapeutic drugs and/or diagnostic agents (such as contrast agents) could be delivered using the same carrier to enable combination therapy to overcome multidrug resistance and achieve real-time determination of treatment efficacy.
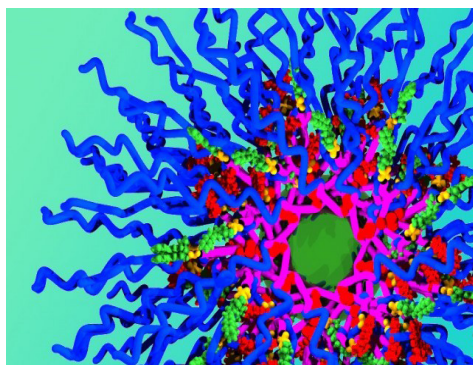
Polymer Nanoparticles

Polymer nanoparticles are prepared using biodegradable polymers such as poly(D,L-lactic acid) (PLA) and poly(D,L-lactic-co-glycolic acid) (PLGA). Such nanoparticles can be used to encapsulate the drug in a polymer coating.
In addition, targeted polymer nanoparticles can be used to deliver drugs to tumour cells with greater efficacy and reduced cytotoxicity on healthy tissues. Various drug-encapsulated polymer nanoparticles are formulated using biocompatible and biodegradable polymers.

New MIT nanoparticles consist of polymer chains (blue) and three different drug molecules: doxorubicin (red), camptothecin (small green particles) and cisplatin (larger green core).
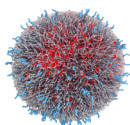
Source: Jeremiah A. Johnson et.al, A Convergent Synthetic Platform for Single-Nanoparticle Combination Cancer Therapy: Ratiometric Loading and Controlled Release of Cisplatin, Doxorubicin, and Camptothecin, J. Am. Chem. Soc. 2014, 136 (16), pp 5896–5899, DOI: 10.1021/ja502011g

Jeremiah A. Johnson and co-workers of Massachusetts Institute of Technology, US, developed a novel polymer nanoparticle drug delivery system (J. Am. Chem. Soc. 2014, DOI: 10.1021/ja502011g). They developed the first polymer nanoparticles that carry a precise ratio of three cancer drugs (doxorubicin, camptothecin and cisplatin) and release them with three independent release mechanisms. These triple-threat nanoparticles get rid of ovarian cancer cells better than nanoparticles that utilise either one or two medications. The design of nanoparticles allows modification to add more drugs. This approach could lead to new methods of delivering specific amounts of multiple drugs to patients and could help researchers optimise doses of such combination therapies. Currently, studies are being conducted on mice for triple-threat nanoparticles. In addition, Johnson and his co-workers are testing four-drug combinations as well as co-administering nanoparticles and therapeutic small-interfering RNAs.

The new technique of drug-polymer blending allows attaching drug molecules to the polymer's individual units like pendants before these units assemble into a polymer nanoparticle (for instance, nanoparticles with hydrophobic docetaxel and hydrophilic cisplatin). After loading the drugs on the nanoparticle, a ligand is added that binds to a molecule present on the surfaces of most prostate cancer cells. This ligand allows these nanoparticles to bypass healthy tissues and reduce the side effects caused by most chemotherapy drugs. Thus, the drugs are directly delivered to the target region.

Gold Nanoparticles

Various metal nanoparticles have been tested for selective delivery of drugs to cancer cells. Of all metallic nanoparticles, gold proved to be the safest and least toxic agent for drug delivery. Gold nanoparticles (AuNPs) possess several properties such as inert nature, well-developed synthesis strategies, tunable size, and flexible and easy surface modification with various chemical and biological molecules that enhance performance as drug delivery vectors.
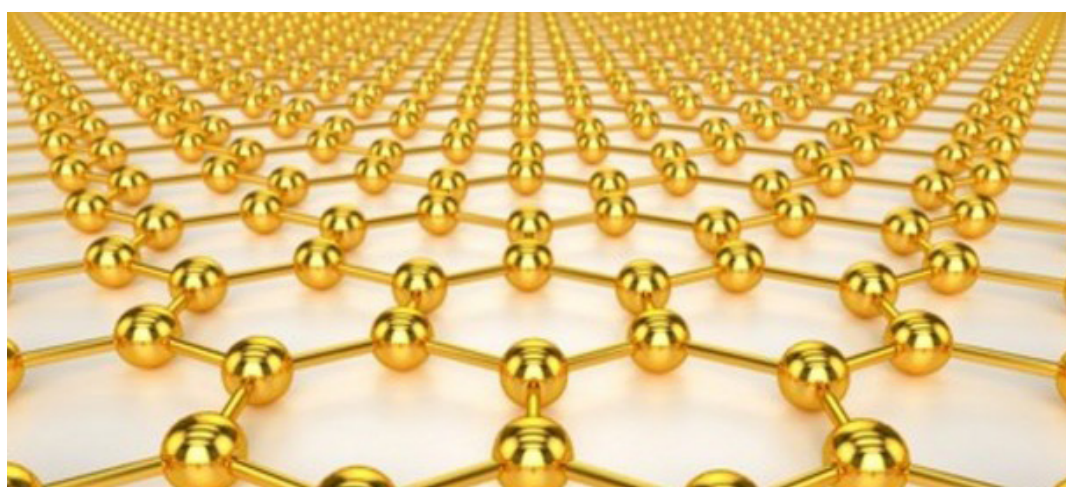

AuNPs exhibit a combination of physical, chemical, optical and electronic properties unique from other biomedical nanoparticles. These properties enable multifunctional applications such as imaging and diagnosing diseases, selectively delivering therapeutic agents, sensitising cells and tissues to treatment regimens, monitoring and guiding surgical procedures, and preferentially administering electromagnetic radiation to disease sites. AuNPs show size-dependent optical properties. In general, the intrinsic colour of nanoparticles changes with size due to surface plasmon resonance. Such nanoparticles are useful for molecular sensing, diagnostic and imaging applications. For instance, AuNPs can exhibit different colours based on size. The drugs coupled to AuNPs help to improve their solubility and uptake into cancerous tissues. AuNPs can be used to deliver low solubility and poor pharmacokinetic drugs and imaging agents. Moreover, they can deliver compounds that are inherently susceptible to enzymatic degradation as well as those that exhibit poor intracellular penetration (such as siRNA). Gold nanostructures can simultaneously engage multiple and adjacent receptor sites, achieving increased selectivity in their uptake. Furthermore, AuNPs are readily synthesised and modified with chemical and biological molecules, enhancing their effectiveness for drug delivery and molecular diagnostics.

The current research on AuNPs focuses on AuNPs surface functionalised with active ligands, allowing optimisation of their binding affinity for a particular disease type, stage or patient. One of the best methods to deliver a DNA vaccine is a gene gun using AuNPs, which have been extensively used for epidermal delivery of DNA vaccines. AuNPs provide the nano-prodrug system

with reduced size, high loading efficiency, three-dimensional structure and enhanced cellular uptake capability. Human pilot studies exploring the use of intravenously administered PEGylated silica–Au core–shell nanoparticles for NIR laser photothermal ablation of recurrent and/or refractory head and neck tumours are completed in the US (NCT00848042; Nanospectra Biosciences, Inc.), with ongoing human pilot studies investigating the use of this technology for the treatment of primary prostate cancer in Mexico.
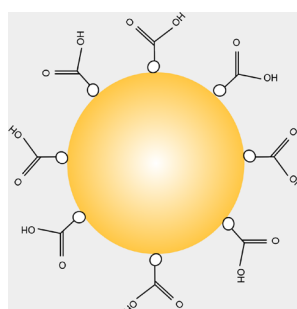

The first AuNP therapy that has reached early phase clinical trials is CYT-6091, 27-nm citrate-coated AuNPs bound with thiolated PEG and tumour necrosis factor-α (TNF-α) (Aurimmune; CytImmune Sciences); this nanoparticle has the dual effect of increasing tumour targeting and tumour toxicity. TNF-α is a multifunctional cytokine that is both cytotoxic and immunomodulatory. The previous clinical trials of TNF-α demonstrated dose-limiting toxicities of hypotension and nausea at concentrations of 225 μg m–2, which limited wide clinical use. Recent preclinical studies compared TNF alone with citrate AuNP–TNF complexes. The results showed a drastic improvement in tumour specificity when PEG-thiol was added, with active tumour uptake and a gradual reduction in liver and spleen concentrations over six hours. Intracellular AuNPs were detectable in post-treatment tumour biopsies, but not in normal tissue. A phase I trial of TNF-bound colloidal gold (CYT-6091) was conducted by intravenously administering these particles in subjects with advanced solid organ malignancies. This phase I trial (NCT00356980; CytImmune Sciences, Inc.) was performed to determine the side effects and best dose of TNF-bound colloidal gold in treating patients with advanced solid tumours. The results of these phase I clinical trials indicated that PEGylated AuNPs are well tolerated in humans at therapeutically relevant dosages for TNF-α.

Preclinical studies of CYT-6091 bound with paclitaxel (known to synergise with TNF) have demonstrated 10 times more paclitaxel uptake in solid tumours than paclitaxel alone. AuNPs conjugated to chemotherapeutic drugs can overcome multidrug resistance through increased particle uptake by endocytosis and subsequent drug release. Cheng and co-workers coupled doxorubicin (DOX) to 5-nm PEGylated gold nanospheres via an intracellular enzyme-cleavable disulfide linkage. The results showed that DOX-functionalised nanoparticles had an increased cellular uptake relative to nanoparticles without DOX, as well as an increased cytotoxicity towards the multidrug resistance cell line. Polymer-functionalised (PEGylated) AuNPs can exhibit long circulation times (nearly 51 hour of blood half life) and can avoid off-target uptake and blood clearance associated with recognition by the immune system.

Some polymer and ligand-functionalised AuNPs are used for controlled drug delivery of cancer therapeutics. AuNPs can allow increasingly specific and accelerated drug delivery that minimises unintended side effects, increases tolerable dosages and overcomes insensitivity in several treatment-resistant cell lines.
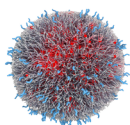
Liposomes

Liposomes are self-assembling, spherical, closed colloidal structures that are composed of lipid bilayers surrounding an aqueous space. Certain anticancer drugs, such as doxorubicin (Doxil) and daunorubicin, are provided via liposomes. Liposomal cisplatin has received an orphan drug designation for pancreatic cancer from the European Medicines Agency (EMA).

CPX-351 (cytarabine:daunorubicin) liposome injection represents a new approach to develop combinations of drugs, in which drug molar ratios with synergistic anti-tumour activity are encapsulated in a drug delivery vehicle to maintain the desired ratio after administration. The US FDA granted an orphan drug status to CPX-351 to treat acute myeloid leukaemia (AML). Currently, CPX-351 is in phase III clinical development for the treatment of AML.
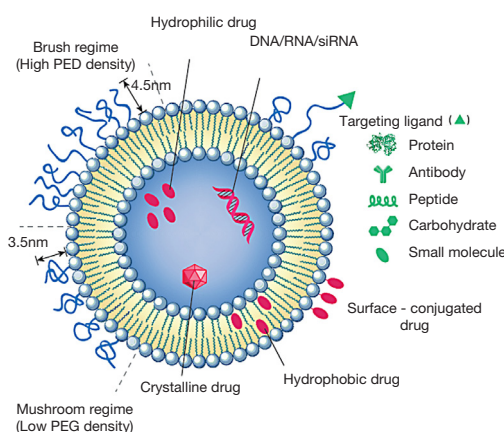
On 20 January 2015, Celator Pharmaceuticals received the FDA Fast Track designation for CPX-351 to treat elderly patients with secondary AML. The FDA established the Fast Track designation process to facilitate the development and expedite the review of drugs intended to treat serious or life-threatening conditions, and address an unmet medical need. On 19 November 2014, Merrimack Pharmaceuticals announced the FDA granted nanoliposomal irinotecan injection (MM-398), also known as nal-IRI, the Fast Track designation to treat patients with metastatic pancreatic adenocarcinoma, who have been previously treated using the gemcitabine-based therapy. Currently, Merrimack Pharmaceuticals is preparing a New Drug Application (NDA) for MM-398 in the US to treat pancreatic cancer.

PX-351 is a liposomal formulation of a synergistic 5:1 molar ratio of cytarabine and daunorubicin; these two agents are commonly used to treat blood cancers, particularly AML. CPX-1 (irinotecan:floxuridine) is a liposomal formulation of a synergistic 1:1 molar ratio of irinotecan HCI and floxuridine, components of a drug regimen that has proven to be useful in the treatment of cancer, particularly gastrointestinal (GI) tumours. Both drugs are approved for the treatment of colorectal cancer. CPX-1 is undergoing phase II clinical trials.
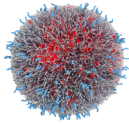
IRON OXIDE NANOPARTICLES

Due to their ultrafine size, magnetic properties and biocompatibility, superparamagnetic iron oxide nanoparticles (SPIONPs) have emerged as promising candidates for various biomedical applications such as:

- Enhanced-resolution contrast agents for MRI

- Targeted drug delivery and imaging

- Hyperthermia

- Gene therapy

- Stem cell tracking

- Molecular/cellular tracking

- Magnetic separation technologies (rapid DNA sequencing)

- Early detection of inflammation, cancer, diabetes and atherosclerosis

To improve cellular uptake, these particles are modified with a peculiar surface coating, so that they can be easily conjugated to drugs, proteins, enzymes, antibodies or nucleotides, and can be directed to an organ, tissue or tumour.
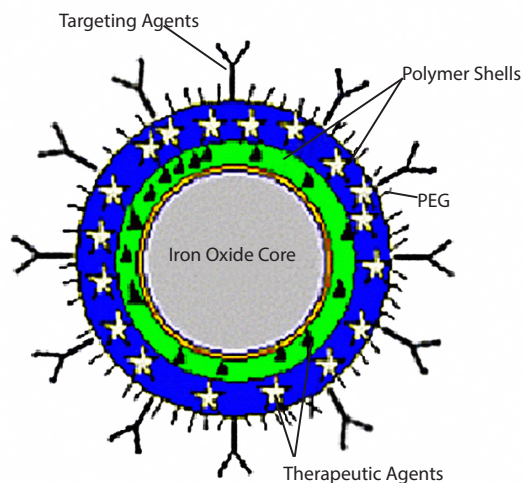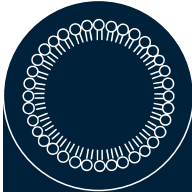

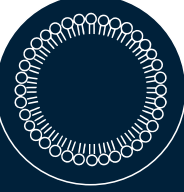Currently, there is not a single clinical trial in progress concerning the use of functionalised IONPs in humans.

REGULATORY AND COMMERCIAL FACTORS

Several nanoparticle-based drugs are being clinically used, including liposomal doxorubicin and albumin conjugate paclitaxel. The carrier-mediated paclitaxel has exhibited significant efficacy in taxane-resistant cancers, an approach highly relevant in prostate cancer where taxanes are the treatment of choice. In addition, studies are focusing on other modifications, including transferrin receptor and folate receptor targeted drug delivery molecules. These innovative therapeutic approaches would enable high-concentration targeted drug delivery to cancer cells with reduced injury of normal cells.

Nanoparticle-based Products Under Clinical Trials

NANO-PARTICLE	DRUG PRODUCT	ACTIVE INGREDIENT	CLINICAL TRIAL PHASE	STUDY STATUS	CANCER TYPE	SPONSOR
PEGylated Gold nanoparticles	CYT-6091	TNF-bound gold colloid	Phase II	Ongoing	Advanced solid tumours	National Institutes of Health Clinical Center
PEGylated silica–Gold core–shell nanoparticles	Auroshell	Gold nanoshells	Phase I	Completed	Head and neck tumours	Nanospectra Biosciences
Liposomes	OSI-211	Lurtotecan	Phase II	Completed	Small-cell lung cancer/ recurrent ovarian cancer	Astellas Pharma/ OSI Pharma
Paclitaxel micellar nanoparticle	Nk105	Paclitaxel	Phase III	Ongoing	Breast cancer	Nippon Kayaku Co.,Ltd
Paclitaxel polymeric micelle	Genexol-PM	Paclitaxel	Phase II	Completed	Bladder cancer Ureter cancer	Asan Medical Center/ Samsung Medical Center
PEGylated liposome	NKTR-102	Irinotecan	Phase III	Ongoing	Breast cancer	Nektar Therapeutics
Stealth (PEGylated) liposome	SPI-77	Cisplatin	Phase II	Completed	Ovarian cancer	New York University School of Medicine/ Alza Pharma
Nanoliposome	MM-398	Irinotecan	Phase III	Ongoing	Pancreatic cancer	Merrimack Pharmaceuticals

Commercially Available Nanoparticles

| NANO-PARTICLE	DRUG PRODUCT	ACTIVE INGREDIENT	DOSAGE FORM	APPLICANT	CANCER TYPE	FDA APPROVAL
PEGylated liposomes	Doxil (Caelyx)	Doxorubicin hydrochloride	Injection	Johnson & Johnson, US	Ovarian cancer, AIDS-related Kaposi's sarcoma	17 November 1995
Albumin-bound paclitaxel nanospheres	Abraxane	Paclitaxel	Injectable suspension; IV (Infusion)	Abraxis Bioscience	Breast cancer, non-small-cell lung cancer, pancreatic cancer	7January 2005
Liposome-encapsulated doxorubicin	Myocet	Doxorubicin	Powder, dispersion for infusion	Teva	Breast cancer	13 July 2000, Approved in Europe and Canada
Liposome-encapsulated daunorubicin	DaunoXome	Daunorubicin	Injection	Galen (UK)	AIDS-related Kaposi's sarcoma	8 April 1996
Liposome-encapsulated vincristine	Marquibo	Vincristine	IV injection	Talon Therapeutics	Acute lymphoblastic leukaemia (ALL)	9 August 2012

OUTLOOK

Nanoparticles are currently in an early stage of development. They have the potential and ability to selectively target cancer cells without significantly damaging healthy tissues. Effectively designed nanoparticles have the ability to accumulate in tumours, either by passive or active targeting, and enhance the cytotoxic effects of anti-tumour agents. Several nano formulations of liposomal and PEG-conjugated liposomal, polymeric micelles anticancer drugs have been approved, with some already approved for clinical use and others undergoing phase II and III clinical trials. Moreover, some early phase clinical trials on AuNPs are in progress.

Cancerous tumours can be eradicated by not only targeting a single site but also simultaneously using a multiple-target approach. In addition, we may not have to rely solely on ligand/antibody-modified nanoparticles as a single tumour-specific marker over-expressed on cancer cells for specific tumour-targeted delivery. Several studies are underway on ligand-modified AuNPs; the AuNP-targeting approach can also be used in the future for cancer drug delivery. Stimulus-based drug delivery is another innovative strategy of tumour site-specific release of a drug; it is a form of pH-based hyperthermic therapy. This strategy would require more clinical and commercial research. Nanoparticles offer the opportunity to reformulate drugs that have been discontinued due to poor bioavailability, lack of selectivity to desired target or extreme toxicity. Drug-loaded nanoparticles evade the efflux mechanism and maintain high concentration within tumour cells, thereby avoiding the development of resistance. Nanoparticle-based combination therapy for cancer treatment should focus on the therapeutic chemical and siRNA combination, co-delivery of chemical and siRNA therapeutics within a single nanoparticle, and use of multiple nanoparticles for chemical and siRNA therapeutics.

We expect precisely engineered nanoparticles to emerge as the next-generation platform for site-specific cancer therapy and several other biomedical applications. Of the various nanoparticle cancer drug delivery systems, liposomes, polymer nanoparticles and AuNPs would drive cancer drug delivery. Thus, the development of nanoparticle drug delivery strategies that deliver multiple drugs using both active and passive targeting approaches to multiple cancer cell sites is expected to be extremely beneficial.
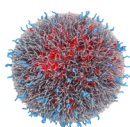
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