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RESEARCH ARTICLE

Nanotechnology in Medicine-Nanomedicine

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ABSTRACT

Nanotechnology for drug delivery involves the approaches of nanoparticles to deliver drugs, other therapeutic substances to specific types of cells. Nano-sized devices are a lot smaller than human cells but similar size to biomolecules such as proteins and enzymes. They have the ability to penetrate even the blood brain barrier which is impervious to most therapeutic agents; this is due to their small size. This review focuses on types of nanocarriers for drug delivery and their respective drugs which include Lipid-Based Nanoparticles – Doxil, Inflexal V, ImmTher, DaunoXome, CPX-1, LE-SN38, MCC465, anti-HER2; Polymeric Micelles - Genexol-PM, NK911, SP1049C, NK105, NC6004; Polymer-Based Nanoparticles – Zoladex, Lupron Depot, Oncaspar, PEG intron, Zinostatin (Stimamler), PK1; Protein-Based Nanoparticles – Abraxane, Ontak, Zevalin, Bexxar, ABI-008 (nab-docetaxel), ABI-009 (nab-rapamycin); Microparticles and Nanoparticles - AI-850, IL-2 XL; Nanoemulsions - NB-001, MagForce Nanotechnologies AB. This paper also discusses some nanotechnology-based drugs that are commercially available or in human clinical trials which include Abraxane, Doxorubicin Liposomal (Doxil), Onivyde, C-dots (Cornell dots), Loteprednol etabonate, KPI-121 and nanotechnology in medicine application in various area such as drug delivery, therapy techniques, diagnostic techniques, anti-microbial techniques, cell repair.

Keywords: Lipid-Based Nanoparticles, Polymeric Micelles, Polymer-Based Nanoparticles, Protein-Based Nanoparticles, Microparticles, Nanoparticles, Nanoemulsions, Abraxane, Doxil, Onivyde, C-dots, Loteprednol etabonate, KPI-121

INTRODUCTION

Nanomedicine is the medical application of nanotechnology [96]. Nanomedicine ranges from the medical applications of nanomaterials and biological devices, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology such as biological machines. Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future [96,3]. The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry that may include advanced drug delivery systems, new therapies, and in vivo imaging [4]. Nanomedicine research is receiving funding from the US National Institutes of Health, including the funding in 2005 of a five-year plan to set up four nanomedicine centers. Nanomedicine is a large industry, with nanomedicine sales reaching $6.8 billion in 2004, and with over 200 companies and 38 products worldwide, a minimum of $3.8 billion in nanotechnology R&D is being invested every year [5]. In April 2006, the journal Nature Materials estimated that 130 nanotech-based drugs and delivery systems were being developed worldwide [6]. As the nanomedicine industry continues to grow, it is expected to have a significant impact on the economy.

The most notable nanomedicine advancements have been in the field of oncology. With the discovery of the enhanced permeation and retention (EPR) effect, passive targeting of chemotherapeutics to solid tumor tissues is an achievable objective given specific particle sizes and chemical characteristics [7]. As its name implies, the EPR effect is the selective accumulation of macromolecules in solid tumor tissue and the retention of those macromolecules within the tissue for a prolonged time due to increased leakage of tumor blood vessels and decreased effective lymphatic drainage. Figure 1 summarizes the characteristics of tumor tissues, which permit the passage and retention of nanoparticles.

While small molecules can diffuse freely into normal tissues as well as tumor tissues, nanoparticles within a specific size range will not diffuse freely into normal tissues and will diffuse through the gaps in the endothelium of tumor tissues. Furthermore, the nanoparticles are retained within the tumor tissue for a prolonged time period because of the lack of adequate lymphatic clearance to remove the nanoparticles from the tumor. The size of the defects in the tumor vasculature is dependent on the cancer type, tumor site, and the stage of the disease, but the upper cutoff size is generally around 300 to 400 nm [8]. Furthermore, therapeutics must be larger than 10 nm to avoid first-pass elimination in the kidney and smaller than 150 to 200 nm to avoid clearance in the liver and spleen [9]. Thus, having nanoparticles with tunable size properties on the nanoscale (e.g., in the 20-100 nm range) is essential to taking advantage of the EPR effect and is one of the reasons that nanomedicine has become essential in the development and improvement of cancer therapeutics.

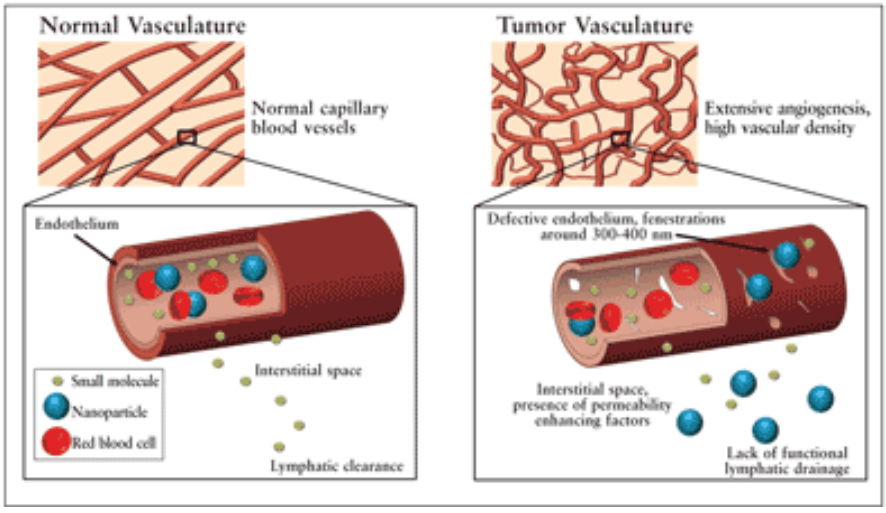


Figure 1. Illustration of the physiological factors that contribute to the enhanced permeation and retention (EPR) effect.

Table 1. Selected FDA-Aproved Agents Utilizing Nanomedicine

PORDUCT	COMPOSITION	INDICATOR	APPROVED
Lipid- Base Nanoparticles			
Abelcet	Lipid Complex formulation of amphotericin B	Invasive fungal infections	1995
AmBisome	Liposomal preparation of amphotericin B	Fungal and protozoal infection	1997
DaunoXome	Liposomal preparation of daunorubicin	HIV-related Kaposi's sarcoma	1996
DepoCyt	Liposomal formulation of cytarabine	Lymphomatous meningitis	1999
DepoDur	Liposomal formulation of morphine sulfate	Relief of postsurgical pain	2004
Doxil/Caelyx	PEGylated liposomal formulation of doxorubicin	Various cancers	1995
Inflexal V	Liposomal influenza vaccine	Influenza	1997
Visudyne	Liposomal formulation of verteporfin	Wet age related macular degeneration	2000
Polymer- Based Nanoparticles			
Adagen	PEGylated adenosine deaminase enzame	Severe combined Immunodeficiency disease	1990
Cimzia	PEGylated Fab' fragment of a humanized anti TNF-alfa antibody	Crohn's disease, rheumatoid arthritis	2008
Copaxone	Polymer composed of L-glutamic acid, L-alanine, L-lysine, and L-tyrosine	Multiple sclerosis	1996
Eligard	Leuprolide acetate and PLGH polymer formulation	Advanced prostate cancer	2002
Macugen	PEG-anti-VEGF aptamer	Neovascular age-related macular degeneration	2004
Mircera	Chemically synthesized ESA, methoxy PEG and Filgrastim	Symptomatic anemia associated with chronic kidney disease	2007
Neulasta	Conjugate of PEG and filgrastim	Chemotherapy-induced neutropenia	2002
Oncaspar	PEGylated formulation of L-asparaginase	Acute lymphoblastic leukemia	1994
Pegasys	PEGylated interferon alfa-2a	Hepatitis C	2002
Peglntron	PEGylated interferon alfa-2b	Hepatitis C	2001
Renagel	Polyamine (plymer loaded with amine groups)	Chronic kidney disease	2000
Somavert	PEGylated human growth Hormone receptor antagonist	Acromegaly	2003
Protein-Based Nanoparticles			
Abraxane	Albumin-bound paclitaxel (nab-paclitaxel)	Breast cancer	2005

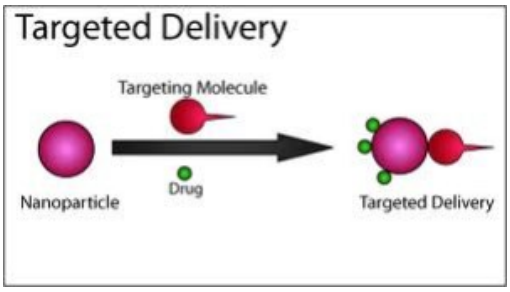
ESA: erythropoiesis-stimulating agents; PEG: polyethylene-glycol; PLGH: Poly (DL-lactide-co-glycolide); TNF-alpha: recombinant human tumor necrosis factor-alpha.

In addition to oncologic applications, nanomedicine research has stretched across the spectrum of medical specialties. Likewise, the array of nanotechnology products being applied to medicine is equally as varied: magnetic nanoparticles, quantum dots, liposomes, nanocrystals, nanosuspensions, gold nanoparticles, microspheres, carbon nanotubes, and other polymeric nanoparticle designs. While most of these technologies are still in preclinical development, there is a growing list of nanomedicine-enabled products already on the market and in clinical trials. Table 1 lists some of the FDA-approved drugs that have been developed or improved by nanomedicine techniques [10].

The application of nanotechnology to the drug development process allows scientists to design and develop nanoscale pharmaceuticals that meet the size requirements necessary to achieve passive targeting. By virtue of their size and unique surface properties, nanoparticles are also capable of active targeting to diseased cells in order to deliver drugs at a higher concentration while reducing drug-related side effects by preventing or reducing the interaction with normal cells. Administration of drugs via nanoparticles allows manipulation of the absorption, distribution, metabolism, and elimination (ADME) of drugs and increases the overall therapeutic effect.

Nanoencapsulation of drugs in a minuscule polymer or lipid matrix will allow them to easily pass through the gastrointestinal lining and reach the bloodstream where their payload will be released. Additionally, nanoparticles, which can be as small as a virus, can efficiently enter into diseased cells and facilitate more effective diagnosis and treatment. In whichever application, nanomedicine will drastically improve a patient's quality of life by early detection and/or more efficient treatment with less drug-related side effects. Over all, expansion of these nanopharmaceuticals will improve the practice of medicine and clinical outcomes in the coming years.

Nanotechnology for drug delivery



Nanotechnology for drug delivery involves the approaches of nanoparticles to deliver drugs, other therapeutic substances to specific types of cells. Nano-sized devices are a lot smaller than human cells but similar size to biomolecules such as proteins and enzymes. They have the ability to penetrate even the blood brain barrier which is impervious to most therapeutic agents; this is due to their small size.

For the nanoparticle to be a suitable drug carrier, it should be small enough to avoid elimination from the body by mononuclear phagocytic system which is part of the immune system that consists of primarily monocytes and macrophages. They should also be big enough to avoid rapid renal filtration. Their small size also allows them to interact readily with biomolecules on the cell surface and within the cell.

Nanoscale drug delivery systems have the abilities to cross cell membranes, thus allowing the drug to be able to be delivered to specific organelles inside the cell. Nanoparticles have greater surface area to volume ratio, thus faster dissolution of nanoparticles in solution, resulting in greater bioavailability, smaller drug dosage and less toxicity [11].

Types of Nanocarriers (Drug Delivery Vehicles) for drug delivery:

1. Lipid-Based Nanoparticles

Liposomal drug carriers may be the most prolific nanomedicine technology currently on the market. Liposomes are composed of one or more concentric lipid bilayers encapsulating an inner aqueous core (Figure 2A**).** Their ubiquitous use in pharmaceutical formulations is because the outer lipid layer of liposomes protects the encapsulated drug from the external environment and because the outer surface can be functionalized to improve targeting.

Indicated for recurrent ovarian cancer, relapsed/refractory multiple myeloma, and AIDS-related Kaposi's Sarcoma, **Doxil** highlights some of the benefits of liposomal technology to improve drug delivery [12]. Doxil's liposomal shell surrounding the doxorubicin molecules is coated with polyethylene glycol (PEG). The liposomal carrier increases the blood

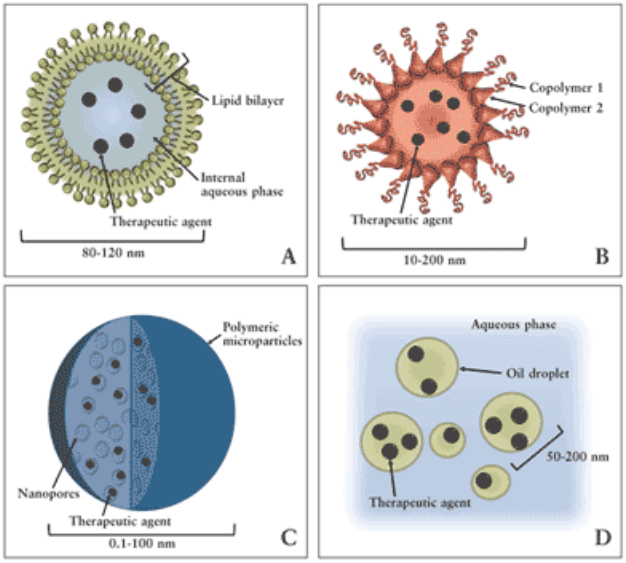


Figure 2. Examples of nano-sized drug carriers, including A) liposomal carriers that have one or more lipid bilayers to surround and protect the active ingredient within the liposome; B) polymeric micelles that have hydrophilic shell (copolymer I) and hydrophobic core (copolymer 2); C) microparticles that encompass a diverse group of particles with different porosities, materials, and sizes and that are tailored to the delivery route, drug release profile, and active ingredients; and D) nanoemulsions that are usually made with surfactants that stabilize nano-sized oil droplets (oil-in-water nanoemulsions).

circulation time of the drug, and the polymer PEG lends the liposome "stealth" qualities, largely avoiding the immune system. The prolonged blood circulation time of Doxil results in the passive accumulation of the drug at the tumor site by the EPR effect. Most importantly, the liposomal encapsulation limits the cardiotoxicity of doxorubicin [13]. Numerous clinical trials confirmed the improved pharmacokinetics of doxorubicin when it is released from Doxil compared with the free drug. Crucell's virosome product, **Inflexal V**, utilizes 150-nm-diameter liposomes as the base of its vaccine formulation. The liposomes mimic the native virus structure, thus allowing cellular entry and membrane-fusion properties to the formulations [14].

Liposomal nanotechnology also extends to cancer vaccines such as **ImmTher**, a liposome-encapsulated disaccharide tripeptide. ImmTher has been shown to have activity against liver and lung colorectal metastases in a phase I trial, and a phase II trial is ongoing assessing the 2-year disease-free survival of patients with high-risk Ewing's sarcoma who are given vincristine, doxorubicin, cyclophosphamide, and dexrazoxane (VACdxr) with and without ImmTher [15, 16].

While **DaunoXome** and **Doxil** are currently clinically approved, **CPX-1** and **LE-SN38** are examples of liposomal-based drugs that encapsulate a topoisomerase I inhibitor and are currently in Phase-II clinical trials for the treatment of colorectal cancer or colon cancer [17, 18]. However, all of these formulations are based on a passive form of delivery, and future work seeks to actively target tumor cells. In fact, **MCC465** is a targeted liposomal-based drug currently in Phase-I clinical trials [19], and numerous other targeted liposomal-based formulations have recently been reported. For example, **anti-HER2** immunoliposomes have been shown to be far more cytotoxic in HER2-overexpressing breast cancer cells than non-targeted liposomes [20].

All of the FDA-approved liposomal drug formulations and those still in the development pipeline represent a wide range of delivery routes, indications, and compounds, which attests to the flexibility and versatility of liposomal formulations.

2. Polymeric Micelles

Similar to the spheroidal structure of liposomes, micelles are aggregates of surfactant or polymer dispersed in an aqueous solution but do not have an internal aqueous phase like that of liposomes **(**Figure 2B**)**. Polymeric micelles have the same advantages as other polymeric formulations and liposomal formulations: namely, the protection of the therapeutic agent from degradation and increased circulation time of the drug. Generally, polymeric micelles are made with two different polymers: a hydrophilic shell that is responsible for colloidal stability and protects the active ingredient, and a hydrophobic core polymer that either physically and/or chemically protects the active ingredient [21].

Genexol-PM, developed by the South Korean company Samyang Corporation, is a PEG-poly (lactic acid) micelle formulation of paclitaxel. These micelles are 20 to 50 nm in size. The two main objectives of Genexol-PM are to reduce Cremophor EL-related toxicities and to increase therapeutic efficacy [22]. Cremophor EL is a synthetic surfactant excipient used to dissolve paclitaxel in Taxol (paclitaxel, Bristol-Myers Squibb) and requires premedication to negate its side effects. Encasing the paclitaxel within the micelle negates the use of Cremophor EL by protecting the paclitaxel molecules within the hydrophobic core of the micelle and by maintaining high aqueous solubility because of the micelle's hydrophilic PEG shell.

A single-arm, multicenter phase II clinical trial was conducted to evaluate the safety and efficacy of Genexol-PM in metastatic breast cancer patients [22]. Currently, Genexol-PM has ongoing phase II trials for pancreatic cancer, ovarian cancer, and non-small-cell lung cancer, and phase III and phase IV trials in patients with recurrent breast cancer, studying the toxicity, progression-free survival, and tumor control rate [23].

NK911 and **SP1049C** are both examples of micellar-based drugs currently in Phase-I and Phase- III stages of clinical trials respectively [24-27]. **NK105** and **NC6004** are also both micellar-based drugs currently in either Phase- II or Phase-I/II stages of clinical trials [28, 29]. While encouraging, all of these formulations passively deliver chemotherapeutics to cancer cells, and future work involves targeting ligand addition within these constructs. These ligands include proteins (including antibodies), vitamins, as well as various carbohydrates [30-32]. For example, immunomicelles containing a photosensitizing agent and tumor-specific monoclonal antibody have been successfully used in photodynamic therapy against murine lewis lung carcinoma [33].

Micelles containing a folate moiety have been shown to be significantly more cytotoxic to ovarian carcinoma cells than non-targeted micelles [34]. In fact, folate has also been successfully used recently as a targeting ligand in micelles to deliver poorly water-soluble chemotherapeutics (either tamoxifen or paclitaxol) to colon carcinoma cells [32]. In addition, hyaluronic acid (HA)-paclitaxel conjugate micelles have recently been shown to be far more cytotoxic toward HA receptor overexpressing cancer cells than for HA receptor deficient cells [35].

3. Polymer-Based Nanoparticles

While the use of both liposomes and micelles as drug delivery systems for chemotherapeutics have received much attention in cancer therapy, there are numerous other polymer-based nanocarriers that have experienced similar clinical success. Polymeric nanoparticles provide the solution to some of the most persistent challenges in drug delivery: drug solubility and stability, circulation half-life, and reduction of toxicity to non-target tissues. Polymeric nanoparticles are defined by their structure and polymer composition, with the therapeutic agent conjugated to the surface or interior of the nanoparticle [9]. Some of the general advantages of polymeric nanoparticles are the ability to alter the release profile of the drug, the ability to control the targeting of the therapeutic through active or passive targeting, and the ability to minimize its degradation within the bloodstream [36].

For example, **Zoladex** and **Lupron Depot** are composed of either small polymer rods or polymer microparticles respectively, and both entrap Luteinizing hormone-releasing hormone (LHRH) analogues in order to treat prostate cancer [37, 38]. Both **Oncaspar** and **PEG intron** are PEGylated drugs used to treat acute lymphoblastic leukemia and various types of cancers respectively [39, 40]. **Zinostatin (Stimamler)** is a polymer-protein conjugate, which is composed of the anti-tumor protein neocarzinostatin covalently linked to two styrene maleic anhydride polymer chains, and is used to treat hepatocellular carcinoma [41]. As far as promising new polymerdrug conjugates, **PK1** is a nanocarrier-based system composed of N-(2-hydroxypropyl) meth-acrylamide (HPMA) copolymer which is in Phase-II/III stages of clinical trials for the treatment of breast cancer [37, 42].

Polymeric nanoparticle products approved by the FDA are listed in Table 1 [10]. From this list, nine of the drugs incorporate PEGylation technology, the covalent attachment of the polymer PEG to the drug or to the drug carrier. By controlling the number of PEG chains, the molecular weight and the structure of the PEG chains, and the attachment chemistry, PEGylation can shield active ingredients from recognition and degradation by the immune system, can reduce renal filtration, and can alter the biodistribution of the drug by increasing the circulation half-life [43]. An increase in the circulation half-life reduces the overall dosage of the drug by reducing the frequency of its administration. PEGylation technology has most impacted the delivery of therapeutic proteins, such as enzymes, hormones, and antibodies, which are naturally unstable and have very short circulating half-lives. The drug candidate Aurimune (CYT-6091) conjugates PEG to the surface of 27 nanometer-size colloidal gold particles to avoid immune detection within the bloodstream, thereby allowing its active ingredient, recombinant human tumor necrosis factor-alpha (TNF-alpha), to reach the tumor tissues. Phase I trials for Aurimune demonstrated that considerably higher doses of TNF are possible with Aurimune's carrier system, and accumulation of the drug was observed in and around tumor sites [44].

4. Protein-Based Nanoparticles

Similar to the polymeric nanoparticles, natural proteins which act as the nanocarrier are also used to improve the pharmacokinetics and toxicity of current drug formulations. **Abraxane** which is paclitaxel protein-bound particles of approximately 130 nanometers, was first approved by the FDA in 2005 for metastatic breast cancer [45]. By stabilizing the paclitaxel particles with serum albumin, no solvent, such as Cremophor-EL, is needed in the formulations, thereby improving the infusion time and eliminating the need for premedications [46].

A distinctive additional advantage associated with the use of some proteindrug conjugates is the ability to actively bind cancer cells, as is the case with the drug **Ontak**. It is a protein-drug conjugate in which a fusion protein is generated by combining sequences from IL-2 (specific for the CD25 component of the IL-2 receptor) with sequences from diphtheria, and is currently used to treat cutaneous T-cell lymphoma [47, 48]. Also, both **Zevalin** and **Bexxar** function in a similar manner, and

are used to treat patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma [49]. It should be noted however, that while Ontak undergoes cellular internalization, both Zevalin and Bexxar do not as their target is the non-internalizing receptor CD20 antigen.

Two further albumin-bound drug formulations utilizing the same technology as Abraxane, **ABI-008 (nab-docetaxel)** and **ABI-009 (nab-rapamycin)** from Abraxis BioSciences, which is now a subsidiary of Celgene Corporation, are currently in active clinical trials. Abraxis' nab technology stands for nanoparticle albumin -bound, whose nanoparticles exploit the natural carrier properties of albumin as well as taking advantage of the EPR effect. ABI-008 is in phase I/II clinical trials for hormone-refractory prostate cancer, and ABI-009 is in phase I trials for patients with advanced nonhematologic malignancies [50].

5. Microparticles and Nanoparticles

Microspheres and microcapsules, collectively referred to as microparticles, have been widely used in pharmacy for drug delivery. These drug delivery systems contain a variety of polymers, including both biodegradable and nonbiodegradable. Microparticles are used in drug formulations to control the release of the drug, to protect sensitive therapeutics from degradation, and to allow for surface functionality of the microparticle for targeting and delivery (Figure 2C). The degradation rate and drug release rate of microparticles are controlled by the material choice, porosity, surface properties, and the size of the microparticles. Admittedly larger than traditional nanomedicine products, microparticles are usually on the scale of microns rather than nanometers but have similar properties and functions as those particles that fit within the rigid definition of nanotechnology.

Yet another paclitaxel formulation, **AI-850**, is a polymeric formulation utilizing sponge-like sugar microspheres (<2 mcm diameter) to increase the solubility of the paclitaxel nanoparticles, to reduce the IV infusion time, and to eliminate the need for premedication with the elimination of Cremophor EL. While the phase I studies did not show evidence that AI-850 is superior to published data on other paclitaxel formulations, the study did show that the microsphere delivery system could be a potential alternative for paclitaxel delivery and warrants further research, especially since the infusion time was reduced in this study and no premedication was administered [51]. Developed by Acusphere, Inc., the worldwide rights to AI-850 were licensed to Cephalon in 2008.

Another oncological candidate comes from Flamel Technologies, Inc. **IL-2 XL** is a complex of interleukin-2 (IL-2) with Flamel's Medusa controlled-release delivery system that is targeted at renal cell carcinoma. Their Medusa nanoparticle delivery system contains a polymer that spontaneously forms a stable nanogel in water. The nanogel is made of 20 to 50 nm nanoparticles containing the captured active ingredient for the extended release of the protein or peptide [52]. Some advantages of the Medusa system are the reduction of burst release of the drug, the ability to incorporate a wide range of proteins and peptides, and the system's biocompatibility and biodegradable properties. The phase I/II trial for IL-2 XL demonstrated that Flamel's formulation could compete with the approved IL-2 treatments and has the potential for better efficacy through an increased immunologic cellular response and sustained pharmacodynamic response [52].

6. Nanoemulsions

Another field of research under the umbrella of nanomedicine is the utilization of nanoemulsions in drug delivery (Figure 2D). Nanoemulsions are stabilized nano-sized oil droplets emulsified in water. The oil droplets can range in size from 10 to 500 nm in diameter and act as carriers for water-insoluble drug compounds. NanoBio Corporation's **NB-001** is a nanoemulsion formulation, consisting of 180-nm oil droplets emulsified in water [53]. NB-001 is indicated for herpes labialis infection and has demonstrated its safety, efficacy, and tolerability in phase II trials involving over 800 patients. The nano-sized oil droplets purportedly cross the skin through pores and hair follicles and accumulate in the epidermis and dermis, directly acting at the site of infection. In 2009, NanoBio and GlaxoSmithKline (GSK) announced an exclusive licensing agreement for the OTC use of NB-001, building on GSK's Abreva brand [54].

Nano-Cancer therapy, from **MagForce Nanotechnologies AB**, is yet another nanomedicine therapy for cancer but is distinctive in its mode of action. Coated iron oxide nanoparticles approximately 20 nm in diameter (Nano-Therm therapy) are locally delivered to tumor tissues, followed by the application of a magnetic field to cause

the nanoparticles to vibrate. The vibration of the iron oxide nanoparticles generates heat, killing the surrounding tumor cells. Both phase I and phase II trials have been completed in various tumor types, including glioblastoma multiforme and prostate, cervical, esophageal, pancreatic, and breast cancers [55, 56].

Nanotechnology-based drugs

Some nanotechnology-based drugs that are commercially available or in human clinical trials include:

1. **Abraxane**, approved by the U.S. Food and Drug Administration (FDA) to treat breast cancer [57], non-small- cell lung cancer (NSCLC) [58] and pancreatic cancer [59], is the nanoparticle albumin bound paclitaxel.

Paclitaxel: Paclitaxel is a drug used to treat ovarian, breast, lung, pancreatic and other cancers [60]. Common side effects include: hair loss, muscle and joint pains, and diarrhea, among others [60]. It results in a greater risk of infections which can be potentially serious [60]. Use during pregnancy often results in problems in the infant [60]. Paclitaxel was discovered beginning in 1962 [61] as a result of a U.S. National Cancer Institute-funded screening program; being isolated from the bark of the Pacific yew, Taxus brevifolia, thus its name "taxol". Developed commercially by Bristol-Myers Squibb, the generic name has changed to "paclitaxel" with trademark becoming Taxol. Other trademarks include Abraxane. Paclitaxel is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system [62]. Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. The chemical name for paclitaxel is 5β,20-Epoxy- 1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. It is highly lipophilic, insoluble in water, and melts at approximately 216°C to 217°C. Paclitaxel has the structural formula as shown in figure 3.

Abraxane: Albumin-bound paclitaxel (trade name Abraxane, also called nab-paclitaxel Figure 3) is an alternative formulation where paclitaxel is bound to albumin nano-particles. Much of the clinical toxicity of paclitaxel is associated with the solvent Cremophor EL in which it is dissolved for delivery [63]. Abraxis BioScience developed Abraxane, in which paclitaxel is bonded to albumin as an alternative delivery agent to the often toxic solvent delivery method. This was approved by the U.S. Food and Drug Administration in January 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy [64].

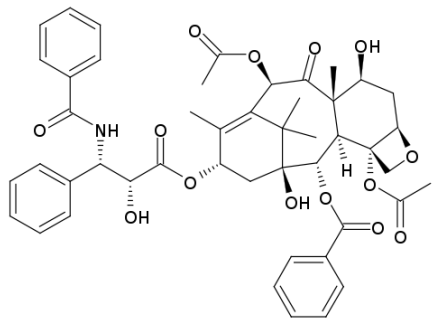


Figure 3. Paclitaxel

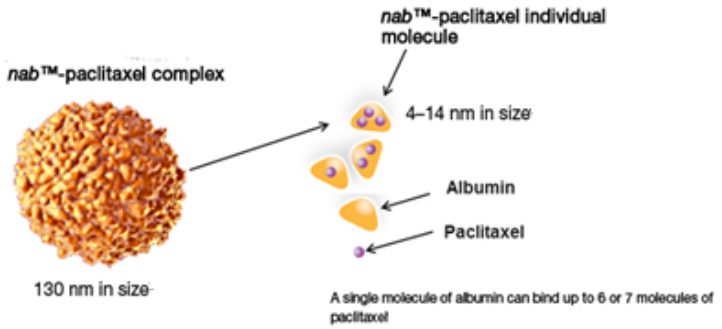


Figure 4 Nab-Paclitaxel [65-67]

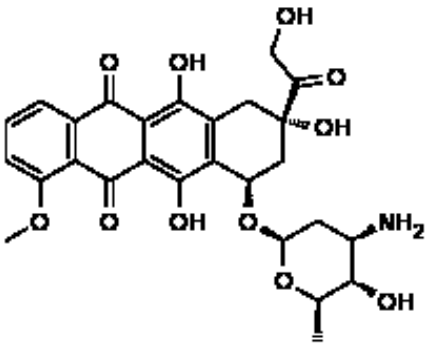


Figure 5. Doxorubicin

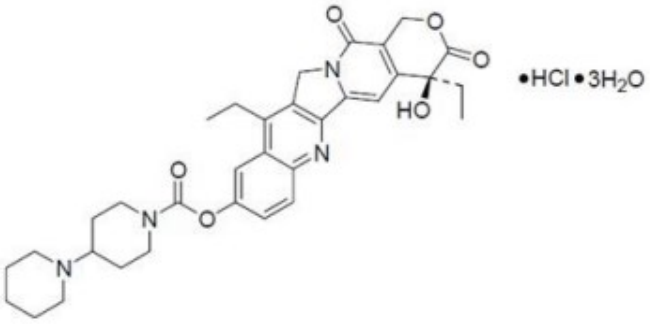


Figure 6. Irinotecan Hydrochloride Trihydrate

Docetaxel: Synthetic approaches to paclitaxel production led to the development of docetaxel. Docetaxel has a similar set of clinical uses to paclitaxel and is marketed under the name of Taxotere.

Recently the presence of taxanes including paclitaxel, 10-deacetylbaccatin III, baccatin III, paclitaxel C, and 7-epipaclitaxel in the shells and leaves of hazel plants has been reported [68]. The finding of these compounds in shells, which are considered discarded material and are mass-produced by many food industries, is of interest for the future availability of paclitaxel.

2. Doxorubicin Liposomal (Doxil): Doxil is the trade name for doxorubicin liposomal. Doxorubicin (liposomal) is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. The drug doxorubicin is encapsulated in a closed lipid sphere (liposome) which helps to extend the life of the drug that is being distributed. Liposomes are self-assembling, spherical, closed colloidal structures that are composed of lipid bilayers that surround an aqueous space. The liposomes also help to increase the functionality and it helps to decrease the damage that the drug does to the heart muscles specifically [69]. This medication is classified as an "anthracycline antibiotic. Doxorubicin (liposomal) is used to treat AIDS-related Kaposi's sarcoma, breast cancer, ovarian cancer, and other solid tumors. The empirical formula of Doxorubicin is $C_{27}H_{29}NO_{11}$and the molecular weight is 543.52 g/mole. The molecular structure is shown in figure 5.

3. **Onivyde:** Onivyde, liposome encapsulated irinotecan to treat metastatic pancreatic cancer, was approved by FDA in October 2015 [70]. Onivyde is formulated with irinotecan hydrochloride trihydrate, a topoisomerase inhibitor, into a liposomal dispersion for intravenous use. The chemical name of irinotecan hydrochloride trihydrate is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy -3,14-dioxo1H-pyrano [3′,4′:6,7] indolizino [1,2-b]quinolin-9-yl-[1,4′bipiperid-ine]-1′-carboxylate, mono-hydrochloride, trihydrate. The empirical formula is C33H38N4O6·HCl·3H2O and the molecular weight is 677.19 g/mole. The molecular structure is shown in Figure 6.

4. **C-dots (Cornell dots)** are the smallest silica-based nanoparticles with the size <10 nm. The particles are infused with organic dye which will light up with fluorescence. Clinical trial is underway since 2011 to use the C-dots as diagnostic tool to assist surgeons to identify the location of tumor cells [71].

Brightly glowing nanoparticles known as "Cornell dots" are a safe, effective way to "light up" cancerous tumors so surgeons can find and remove them. According to research at Memorial Sloan-Kettering Cancer Center (MSKCC), Cornell dots, also known as C dots, are biologically safe and stable and small enough to be easily transported across the body's structures and efficiently passed through the kidneys and out in urine.

A single dot consists of several dye molecules encased in a silica shell that can be as small as 5 nanometers in diameter (a nanometer is one-billionth of a meter, about three times the diameter of a silicon atom). The silica shell, essentially glass, is chemically inert. Coating the dots with polyethylene glycol, a process called PEGylation, further protects them from being recognized by the body as foreign substances, giving them more time to find targeted tumors.

The outside of the shell can be coated with organic molecules that will attach to such desired targets as tumor surfaces or even locations within tumors. The cluster of dye molecules in a single dot fluoresces under near-infrared light much more brightly than single dye molecules, and the fluorescence will identify malignant cells, showing a surgeon exactly what needs to be cut out and helping ensure that all malignant cells are found.
According to MSKCC researchers, the technology also can show the extent of a tumor's blood vessels, cell death, treatment response and invasive or metastatic spread to lymph nodes and distant organs.

5. **Loteprednol etabonate:** In 2014, a Phase 3 clinical trial for treating inflammation and pain after cataract surgery, and a Phase 2 trial for treating dry eye disease were initiated using nanoparticle loteprednol etabonate [72]. Loteprednol (as the ester loteprednol etabonate) is a corticosteroid used in ophthalmology. Marketed by Bausch and Lomb as Lotemax in the U.S., ocular applications for this drug include the treatment of inflammation of the eye due to allergies, as well as chronic forms of keratitis, vernal keratoconjunctivitis, pingueculitis, and episcleritis. The empirical formula is $C_{24}H_{31}ClO_7$ and the molecular weight is 466.951 g/mole. The molecular structure is shown in figure 7.

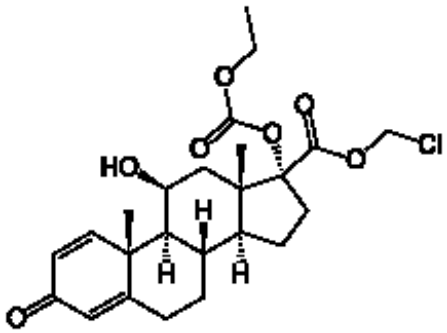
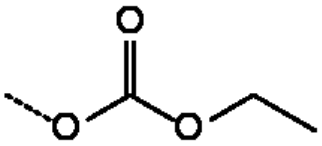


Figure 7. (A) Loteprednol etabonate



(B) The etabonate group

Etabonate is the name for ethyl carbonate esters in International Nonproprietary Names (INNs) and United States Adopted Names (USANs) for pharmaceutical substances [73]. Examples include: Loteprednol etabonate, a corticosteroid; Remogliflozin etabonate, an antidiabetic drug; Sergliflozin etabonate, another antidiabetic drug

6. **KPI-121:** In 2015, the product, KPI-121 was found to produce statistically significant positive results for the post-surgery treatment [74]. KPI-121 is a novel nanoparticle formulation of loteprednol etabonate utilizing Kala's proprietary mucus-penetrating particle (MPP) technology to enhance penetration into target tissues of the eye. KPI-121 has been studied in multiple clinical trials, including 1% and 0.25% formulations for the treatment of post-surgical ocular inflammation and pain and a 0.25% formulation for dry eye and meibomian gland disease.

Kala is a clinical stage pharmaceutical company focused on innovative nanoparticle-based treatments for ocular diseases affecting both front and back of the eye. Kala leverages its proprietary mucus-penetrating particle (MPP) technology to develop topical ophthalmic formulations with enhanced delivery into ocular tissue by facilitating penetration through the tear film mucus. Beyond ophthalmology, Kala's MPP technology has potential applications in women's reproductive health, respiratory and gastrointestinal diseases, and other indications.

Nanotechnology in Medicine Application

The use of nanotechnology in medicine offers some exciting possibilities. Some techniques are only imagined, while others are at various stages of testing, or actually being used today. Nanotechnology in medicine involves applications of nanoparticles currently under development, as well as longer range research that involves the use of manufactured nano-robots to make repairs at the cellular level (sometimes referred to as nanomedicine). The use of nanotechnology in the field of medicine could revolutionize the way we detect and treat damage to the human body and disease in the future, and many techniques only imagined a few years ago are making remarkable progress towards becoming realities [75].

1. Drug Delivery

One application of nanotechnology in medicine currently being developed involves employing nanoparticles to deliver drugs, heat, light or other substances to specific types of cells (such as cancer cells). Particles are engineered so that they are attracted to diseased cells, which allows direct treatment of those cells. This technique reduces damage to healthy cells in the body and allows for earlier detection of disease. Researchers at the Wyss Institue are testing nanoparticles that release drugs when subjected to sheer force, such as occurs when passing through a section of artery that is mostly blocked by a clot. Lab tests on animals have shown that this method is effective in delivering drugs used to dissolve clots. Researchers at the University of Illinois have demonstated that gelatin nanoparticles can be used to deliver drugs to damaged brain tissue more efficently than standard methos. Researchers at MIT are investigating the use of nanoparticles to deliver vaccine.The nanoparticles protect the vaccine, allowing the vaccine time to trigger a stronger immune response as shown in lab tests with mice. Additional work needs to be done to adapt the technique to human patients.

Reserchers are developing a method to release insulin that uses a sponge-like matrix that contains insulin as well as nanocapsules containing an enzyme. When the glucose level rises the nanocapsules release hydrogen ions, which bind to the fibers making up the matrix. The hydrogen ions make the fibers positively charged, repelling each other and creating openings in the matrix through which insulin is released. So far this has been shown to be effective in tests with lab mice.

Researchers are developing a nanoparticle that can be taken orally and pass through the lining of the intestines into the bloodsteam. This should allow drugs that must now be delivered with a shot to be taken in pill form. The researchers have demonstrated the technique with lab mice so far. Researchers are also developing a nanoparticle to defeat viruses. The nanoparticle does not actually destroy viruses molecules, but delivers an enzyme that prevents the reproduction of viruses molecules in the patients bloodstream. The effectiveness of the technique has been demonstrated in lab tests.

2. Therapy Techniques

Researchers have developed "nanosponges" that absorb toxins and remove them from the bloodstream. The nanosponges are polymer nanoparticles coated with a red blood cell membrane. The red blood cell membrane allows the nanosponges to travel freely in the bloodstream and attract the toxins.

Researchers have demonstrated a method to generate sound waves that are powerful, but also tightly focused, that may eventually be used for noninvasive surgery. They use a lens coated with carbon nanotubes to convert light from a laser to focused sound waves. The intent is to develop a method that could blast tumors or other diseased areas without damaging healthy tissue.

Researchers are investigating the use of bismuth nanoparticles to concentrate radiation used in radiation therapy to treat cancer tumors. Initial results indicate that the bismuth nanoparticles would increase the radiation dose to the tumor by 90 percent. Nanoparticles composed of polyethylene glycol-hydrophilic carbon clusters (PEG-HCC) have been shown to absorb free radicals at a much higher rate than the proteins out body uses for this function. This ability to absorb free radicals may reduce the harm that is caused by the release of free radicals after a brain injury.

Targeted heat therapy is being developed to destroy breast cancer tumors. In this method antibodies that are strongly attracted to proteins produced in one type of breast cancer cell are attached to nanotubes, causing the nanotubes to accumulate at the tumor. Infrared light from a laser is absorbed by the nanotubes and produces heat that incinerates the tumor.

3. Diagnostic Techniques

Reseachers at MIT have developed a sensor using carbon nanotubes embedded in a gel; that can be injected under the skin to monitor the level of nitric oxide in the bloodstream. The level of nitric oxide is important because it indicates inflamation, allowing easy monitoring of imflammatory diseases. In tests with laboratory mice the sensor remained functional for over a year.

Researchers at the University of Michigan are developing a sensor that can detect a very low level of cancer cells, as low as 3 to 5 cancer cells in a one milliliter in a blood sample. They grow sheets of graphene oxide, on which they attach molecules containing an antibody that attaches to the cancer cells. They then tag the cancer cells with fluorescent molecules to make the cancer cells stand out in a microscope.

Researchers have demonstrated a way to use nanoparticles for early diagnosis of infectious disease. The nanoparticles attach to molecules in the blood stream indicating the start of an infection. When the sample is scanned for Raman scattering the nanoparticles enhance the Raman signal, allowing detection of the molecules indicating an infectious disease at a very early stage.

A test for early detection of kidney damage is being developed. The method uses gold nanorods functionalized to attach to the type of protein generated by damaged kidneys. When protein accumulates on the nanorod the color of the nanorod shifts. The test is designed to be done quickly and inexpensively for early detection of a problem.

4. Anti-Microbial Techniques

Researchers at the University of New South Wales are investigating the use of polymer coated iron oxide nanoparticles to treat chronic bacterial infections. One of

the earliest nanomedicine applications was the use of nanocrystalline silver which is as an antimicrobial agent for the treatment of wounds.

A nanoparticle cream has been shown to fight staph infections. The nanoparticles contain nitric oxide gas, which is known to kill bacteria. Studies on mice have shown that using the nanoparticle cream to release nitric oxide gas at the site of staph abscesses significantly reduced the infection.

Burn dressing that is coated with nanocapsules containing antibotics. If a infection starts the harmful bacteria in the wound causes the nanocapsules to break open, releasing the antibotics. This allows much quicker treatment of an infection and reduces the number of times a dressing has to be changed.

5. Cell Repair

Nanorobots could actually be programmed to repair specific diseased cells, functioning in a similar way to antibodies in our natural healing processes.

CONCLUSION

Liposomal drug carriers may be the most prolific nanomedicine technology currently on the market. All of the FDA-approved liposomal drug formulations and those still in the development pipeline represent a wide range of delivery routes, indications, and compounds, which attests to the flexibility and versatility of liposomal formulations.

Polymeric micelles have the same advantages as other polymeric formulations and liposomal formulations: namely, the protection of the therapeutic agent from degradation and increased circulation time of the drug. While the use of both liposomes and micelles as drug delivery systems for chemotherapeutics have received much attention in cancer therapy, there are numerous other polymer-based nanocarriers that have experienced similar clinical success. Polymeric nanoparticles provide the solution to some of the most persistent challenges in drug delivery: drug solubility and stability, circulation half-life, and reduction of toxicity to non-target tissues.

Similar to the polymeric nanoparticles, natural proteins which act as the nanocarrier are also used to improve the pharmacokinetics and toxicity of current drug formulations.

Microspheres and microcapsules, collectively referred to as microparticles, have been widely used in pharmacy for drug delivery. The degradation rate and drug release rate of microparticles are controlled by the material choice, porosity, surface properties, and the size of the microparticles. Admittedly larger than traditional nanomedicine products, microparticles are usually on the scale of microns rather than nanometers but have similar properties and functions as those particles that fit within the rigid definition of nanotechnology.

Another field of research under the umbrella of nanomedicine is the utilization of nanoemulsions in drug delivery

Some nanotechnology-based drugs that are commercially available or in human clinical trials are Abraxane, Doxorubicin Liposomal (Doxil), Onivyde, C-dots (Cornell dots), Loteprednol etabonate, KPI-121

Nanotechnology in medicine can be applied over wide range of area such as drug delivery, therapy techniques, diagnostic techniques, anti-microbial techniques, cell repair.

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