LexInnova

Nanoparticles Smart Drug Delivery System for Cancer

Technology Landscape

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1. Introduction

Nanotechnology is a rapidly expanding field, encompassing the development of man-made materials in the 5–200 nanometer size range. This dimension vastly exceeds that of standard organic molecules, but its lower range approaches that of many proteins and biological macromolecules. In the scientific world, the term “nano” is, however, somewhat ambiguous since it does not designate the same reality for physicists, chemists and biologists. Conceptually, nanotechnologies in general and nanoparticles in particular have revolutionized the administration of medicines. There is, nevertheless, a wide consensus that nanotechnology represents not simply a miniaturization of larger objects but the preparation of nanomaterials with physical and chemical properties which dramatically differ from those of bulk materials, because they are on a nanometric scale.

Nanotechnology involves the engineering of functional systems at the molecular scale. Such systems are characterized by unique physical, optical and electronic features that are attractive for disciplines ranging from materials science to biomedicine. One of the most active research areas of nanotechnology is Nano-medicine, which applies nanotechnology to highly specific medical interventions for the prevention, diagnosis and treatment of diseases. By virtue of their unique physicochemical properties, nanoparticles have shown promise in delivering a range of molecules to desired sites in the body. To develop safer and more effective therapeutic nanoparticles, researchers have designed novel multifunctional nanoparticle platforms for cell/tissue-specific targeting, sustained or triggered drug delivery, co-delivery of synergistic drug combinations, etc.

Advances in biocompatible nanoscale drug carriers such as liposomes and polymeric nanoparticles have enabled more efficient and safer delivery of a myriad of drugs. Advantages in

HIGHLIGHTS

Global market analysis representing trends in patent filings and investments in this technology in recent years

Count based feature-wise patent protection analysis in different jurisdictions also indicating white spaces.

Identifying feature-wise earliest expiring/expired patents in different jurisdictions

Assignee based analysis representing their focus on different technological areas of nanoparticle based targeted drug delivery systems for cancer treatment

Detailed technical analysis of a patent set consisting 1349 patents filed till date.

nanoparticle drug delivery, particularly at the systemic level, include longer circulation half-lives, improved pharmacokinetics and reduced side effects. In cancer treatments, nanoparticles can further rely on the enhanced permeability and retention effect caused by leaky tumor for better drug accumulation at the tumor sites. These benefits have made therapeutic nanoparticles a promising candidate to replace traditional chemotherapy, where intravenous injection of toxic agents poses a serious threat to healthy tissues and results in dose-limiting side effects.

Late 1970's	Current Era	Future
First Nanoscale drug delivery system was lipid vesicles.	Nowadays, liposomes, cream, capsule, tablets, gel, aqueous solution, aerosols/spray are used as forms of delivery.	Nano enabled technology will take the maximum share of the market making up nearly 90% of drug delivery market
Considered impossible to administer the pharmaceuticals suspensions by intravenous means, due to obvious risks of embolism.	15% of market uses nanoparticle for drug delivery systems.	Safe, Effective and without side effects. No wastage and increased bioavailability are going to be the basis of future drug delivery.
First paper was published in 1976; it focused on development of nanoparticle for vaccine purposes.	More specific for treatment.	More-energetic and more-targeted methods, in which medications ride passively on the circulating bloodstream, where they may or may not arrive at micro cracks in a high-enough dosage to initiate healing.

Table 1: Technology evolution of targeted drug delivery using nanoparticles for Cancer treatment

In this review, we mainly focus on the type of nanoparticle, its response to stimuli, route of administration, form of delivery, its purpose, drug target and application that is used in targeted drug delivery of cancer. It highlights several areas of opportunity where current and emerging nanotechnologies could enable novel classes of therapeutics. These major heads completely define how cancer can be treated by using nanoparticles on its affected site.

2. Background

The emergence of nanotechnology has made a significant impact on clinical therapeutics in the last two decades. Advances in biocompatible Nano scale drug carriers such as liposomes and polymeric nanoparticles have enabled more efficient and safer delivery of a myriad of drugs. Advantages in nanoparticle drug delivery, particularly at the systemic level, include longer circulation half-lives, improved pharmacokinetics and reduced side effects. In cancer treatments, nanoparticles can further rely on the enhanced permeability and retention effect caused by leaky tumor vasculatures for better drug accumulation at the tumor sites.

Nanoparticles have the advantage of targeting cancer by simply being accumulated and entrapped in tumors (passive targeting). The phenomenon is called the enhanced permeation and retention effect, caused by leaky angiogenetic vessels and poor lymphatic drainage and has been used to explain why macromolecules and nanoparticles are found at higher ratios in tumors compared to normal tissues.

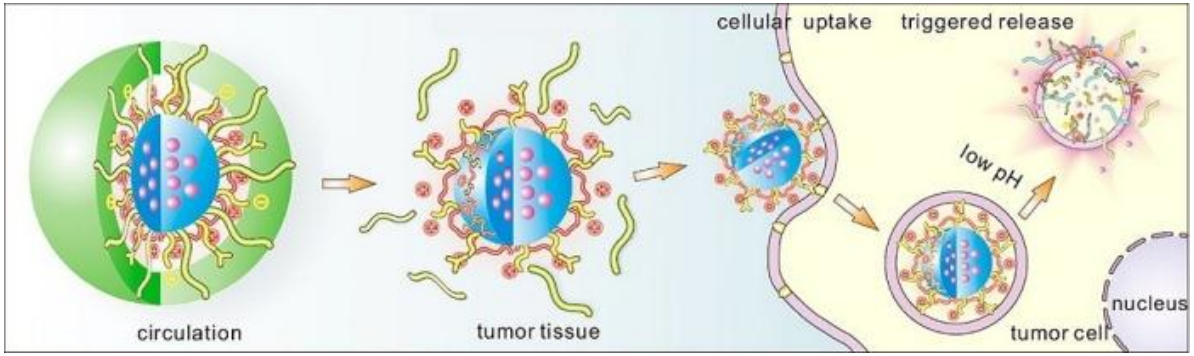


Figure 1: Multi block Polymer Nanoparticles Attacks Tumors (LINK)

Figure 1 shows the step by step process of drug delivery. When nanoparticles circulating in the bloodstream reach tumor tissue, lower pH cleaves off the polyethylene glycol molecules, exposing a shell of tumor-targeting antibodies (yellow Y's) and Gemini quaternary ammonium groups (red strands). These two groups help the particles penetrate cancer cells (right), where the even lower pH breaks up the particles and releases the drug payload trapped in the particles' cores (pink dots).

3. Need and Importance

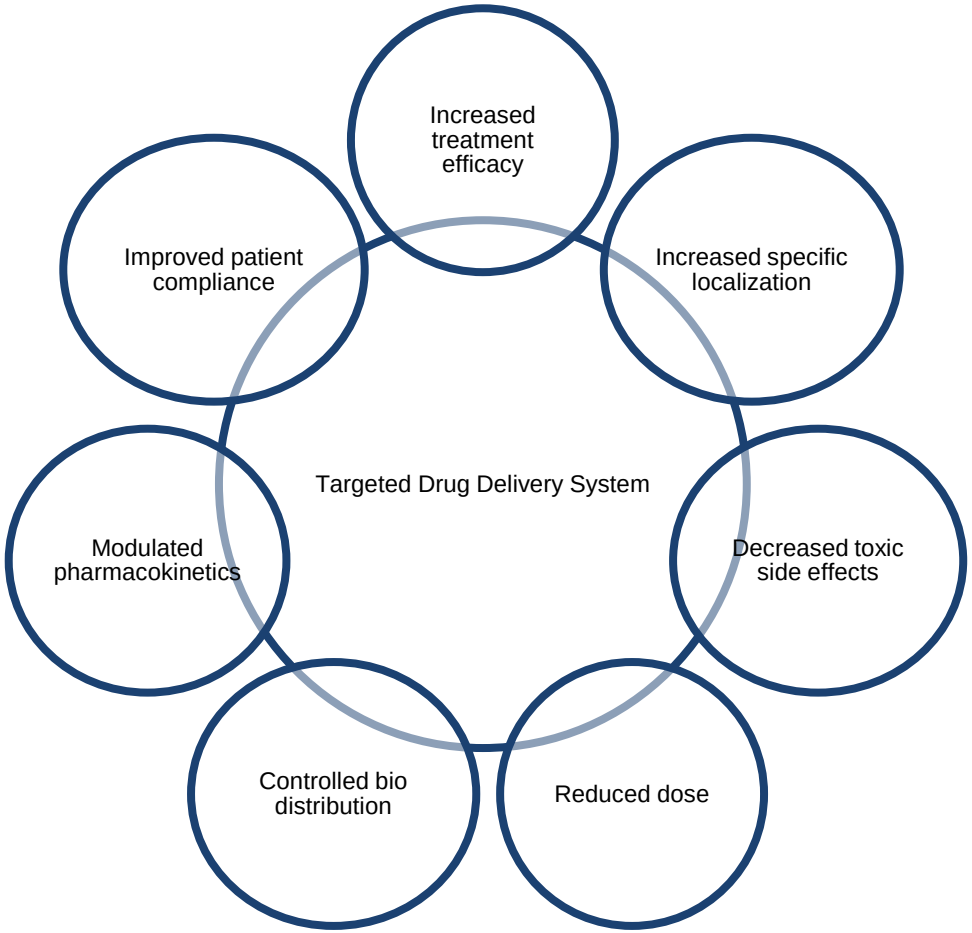


Figure 2: Advantages of targeted drug delivery system

The continuing improvements in the pharmacological and therapeutic properties of drugs are driving the revolution in novel drug delivery systems. In fact, a wide spectrum of therapeutic nanocarriers has been extensively investigated to address this emerging need. Accordingly with the recent developments in the use of nanoparticles as drug delivery systems for many diseases, finally we will introduce how nanoparticles can be used in the treatment of cancer using targeted drug delivery. Nanoparticles are designed to safely reach their target and specifically release their cargo at the site of the disease, this way increasing the drug's tissue bioavailability.

In recent years, scientists and engineers have been exploring different approaches to delivering multiple therapeutic agents with single drug nanocarriers. Such efforts have been motivated by the fact that applying multiple drugs can suppress the notorious phenomenon known as cancer chemo resistance, which is accountable for most of the failed cases in cancer therapy. On the one hand, applying multiple drugs with different molecular targets can raise the genetic barriers that need to be overcome for cancer cell mutations, thereby delaying the cancer adaptation process. On the other hand, it has also been demonstrated that multiple drugs targeting the same cellular pathways could function synergistically for higher therapeutic efficacy and higher target selectivity.

The use of such nanoparticles as delivery vehicles ensures that their cargo exerts its effect only inside the targeted cells. The compounds used in cancer chemotherapy are often highly toxic to many cell types, so targeting is crucial to minimizing collateral damage to healthy bystander cells. Efficient targeting thus significantly lowers the risk of serious side-effects, while allowing the dose required for a meaningful clinical response to be reduced.

The primary goals for research of nano-bio-technologies in drug delivery include:

- ✓ More specific drug targeting and delivery,
- ✓ Reduction in toxicity while maintaining therapeutic effects,
- ✓ Greater safety and biocompatibility, and
- ✓ Faster development of new safe medicines.

With the advancement in technology, intelligent nanoparticles are developed which must have a high capacity for cargo, and an envelope that is compatible with biological membranes and can present ligands that bind to specific receptors on target cells. Once the particles have entered the cell, they must be stimulated by some sort of signal to release their chemical cargo. “It is extremely difficult to design a particle that meets all these criteria at once. But now a system has been developed which achieves this goal, and provides a generally applicable platform that is compatible with different cargos and target cells.

4. Current Market Scenario

At present there are 30 main drug delivery products on the market. The total annual income for all of these is approximately US$33 billion with an annual growth of 15 %(based on global product revenue).

Two major drivers are primarily responsible for this increase in the market. First, present advances in diagnostic technology appear to be outpacing advances in new therapeutic agents. Highly detailed information from patients is becoming available, thus promoting much more specific use of pharmaceuticals. Second, the acceptance of new drug formulations is expensive and slow, taking up to 15 years to obtain accreditation of new drug formulas.

A new study by Macmillan Cancer Support shows a dramatic increase in the median cancer survival times over the past 40 years. Although nanotechnology is revolutionizing the diagnosis and treatment of a number of cancers, it is only six years since the first Nano particulate drug delivery product for the treatment of breast cancer, Abraxane, was launched by Abraxis Oncology, a division of American Pharmaceutical Partners, Inc. (now Abraxis Biosciences) the initial announcement saw the company’s share prices rise by 50% and required the Food and Drug Administration (FDA) to create a new class of therapeutic products. But this was only the opening shot in the war against cancer.

Market Trend: ***Source:*** *Report*

The global market trend that was observed for nanoparticles used in targeted drug delivery is as follows:

- The global market for nanoparticles in biotechnology, drug development and drug delivery was valued at $17.5 billion in 2011 and should reach nearly $21.6 billion in 2012. Total market value is expected to reach $53.5 billion in 2017 after increasing at a five-year compound annual growth rate (CAGR) of 19.9%.
- Drug delivery systems are expected to increase from $11.3 billion in 2012 to $30.9 billion in 2017, a CAGR of 22.2%.
- Drug development and formulation should total nearly $9.4 billion in 2012 and nearly $20.5 billion in 2017, a CAGR of 16.9%.

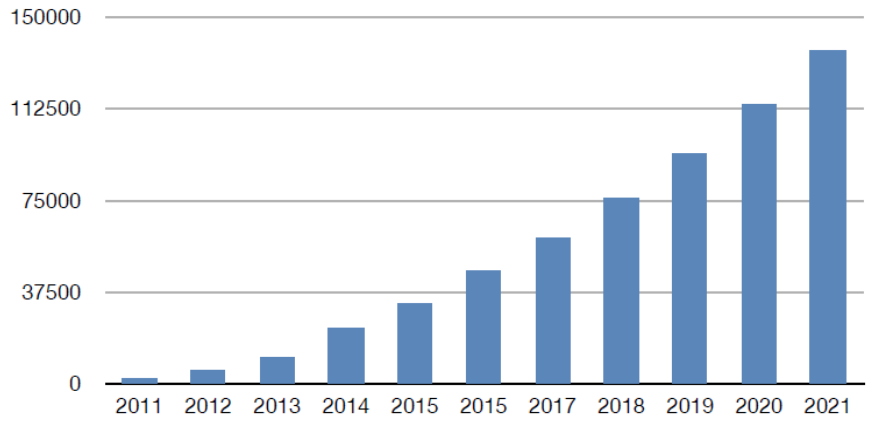


Figure 3: Global Market trends for Nanotechnology in Drug delivery 2011-21

The total market size, in 2021, is forecasted to be US$ 136 billion with a 60/40 ratio in favor of drug nanocrystals, although developing new delivery mechanisms may allow more value to be created for companies and entrepreneurs.

There are many companies that are emerging in the field of using nanoparticles for drug delivery systems. Some of the companies are: Access Pharmaceuticals is an emerging biopharmaceutical company specializing in products for cancer and supportive care. The company's lead development candidate for the treatment of cancer is ProLindac™, a nanopolymer DACH platinum prodrug.

ProLindac has successfully completed a European Phase II trial in patients with ovarian cancer, and Cobalamin™ is Access proprietary nanopolymer oral drug delivery technology. Leonardo Bio systems, is the exclusive provider of a revolutionary multistage drug delivery platform (MSV™) focused on the treatment of metastatic cancers. The first stage consists of a silicon nanoparticle that is rationally designed to circumvent the multiple biological barriers in the bloodstream, and concentrate near cancer cells. Leonardo plans to generate revenue through the development of a series of breakthrough oncology products, and through partnerships with pharmaceutical companies where improvement in safety and/or efficacy of their drugs is desired. Some of the major players that played an important role are: Abraxis Biosciences (Celgene Corp.), Immunolight LLC, Abbott Cardiovascular System and Brigham.

5. Trends in Cancer targeting nanoparticles Technology

The aim of this section is to study overall environment of the intellectual property concerning the development of cancer targeting nanoparticle technology. This analysis also gives a country wise patent filing trend over the recent years indicating an estimated technological growth that has taken place in a geographical region over the years.

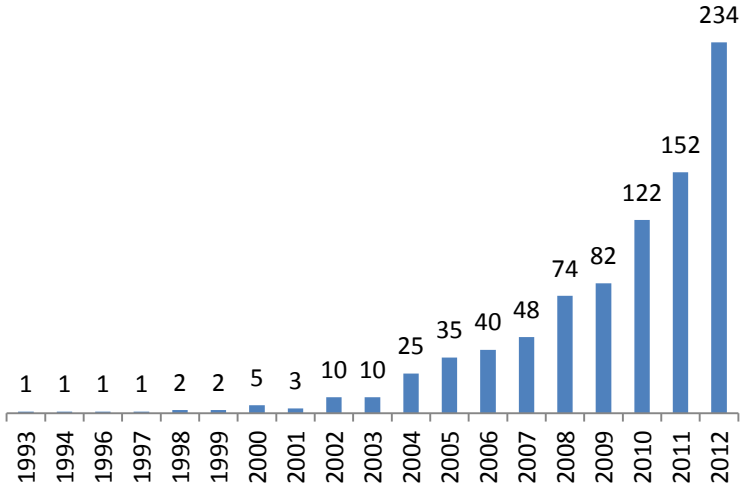


Figure 4: Year wise patent filing trend

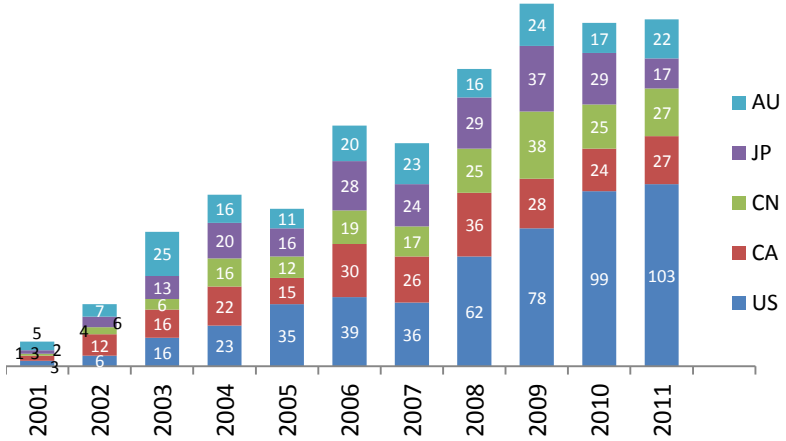


Figure 5: Country wise patent distribution on the basis of filings in recent year

Figure 4 shows the patent filing trend in the field of cancer targeting nanoparticle technology. A steep increase in the trend suggests the increasing research that is happening on in this field at a global level with a major share in patent filings being held by US. It also depicts the cumulative % growth rate over 2009-2012 to be approximately 185% while it was just 111% for 2005-2008. Figure 5 shows the country wise distribution based on recent patent filings. While clearly an exponential growth is observed in patent filings in US, other countries like Japan, China and Canada show moderate increase in patent filings over the years. Also despite being a major player in 2001, the filing trend in Australia remains more or less constant.

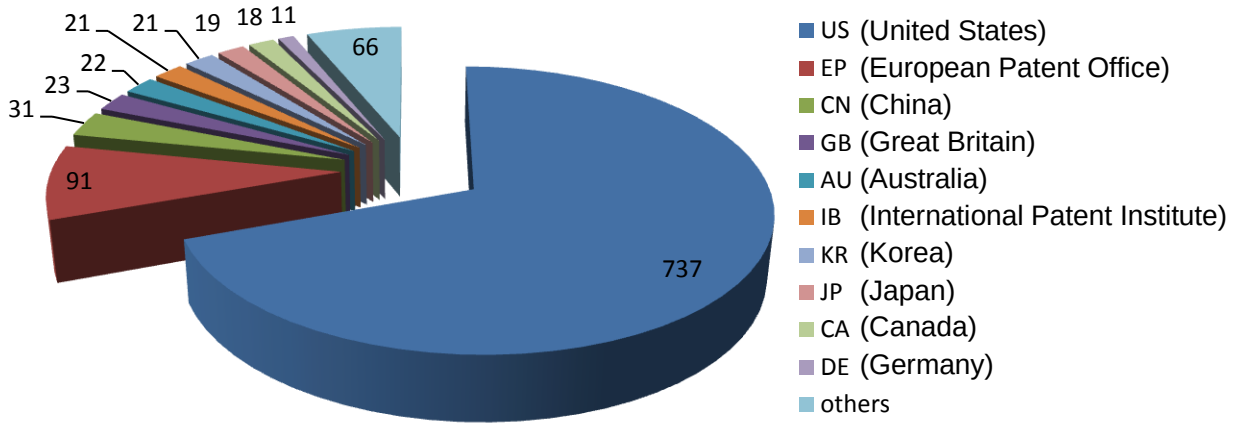


Figure 6: Priority country distribution

Figure 6 shows an analysis of the filings of priority patent applications in various geographical locations. The pie chart gives an overview of all countries where the research activities is prevalent. It can be observed that about 75% of priority patent applications are from US as most of our major assignees (including top universities) belong to this geographical region. EP patent filings are in second lead with 91 priority patent applications.

6. Taxonomy

6.1 Nano-particles

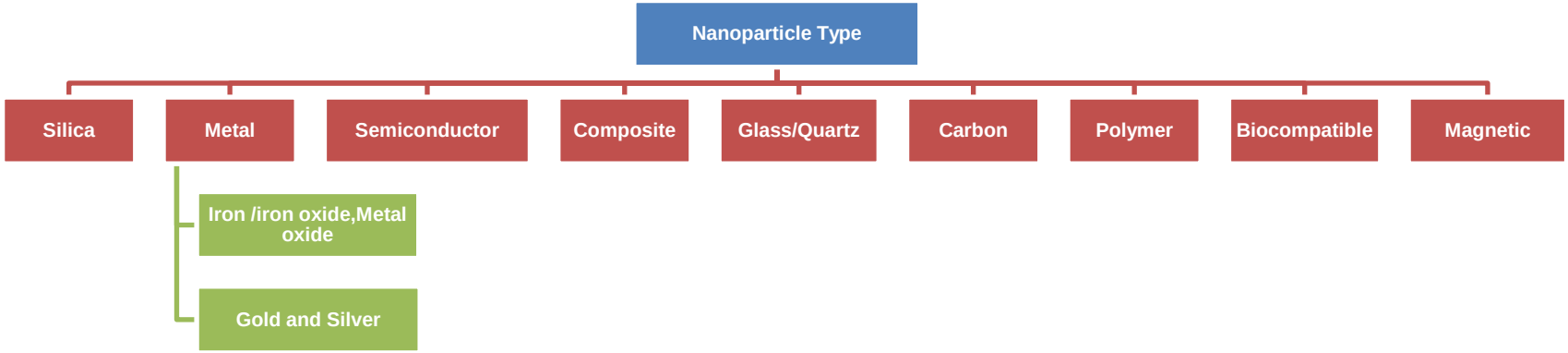


Figure 7: Different Nanoparticle types

Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. For the drug to stay longer in the tumor, and to increase the therapeutic efficacy, the nanoparticles comprising gold, metal, iron oxides, polymers, silica, silver, composite and carbon types are used as shown in Figure 7. Researchers have also developed strategies to render nanostructures biocompatible and capable of being coated with biological properties. The composite magnetic and fluorescent chitosan nanoparticles are potential candidates as a smart drug delivery system. Properties like cross-linking the composite particles with glutaraldehyde tailored the size, morphology, surface properties and drug release behaviors of the different nanoparticle forms.

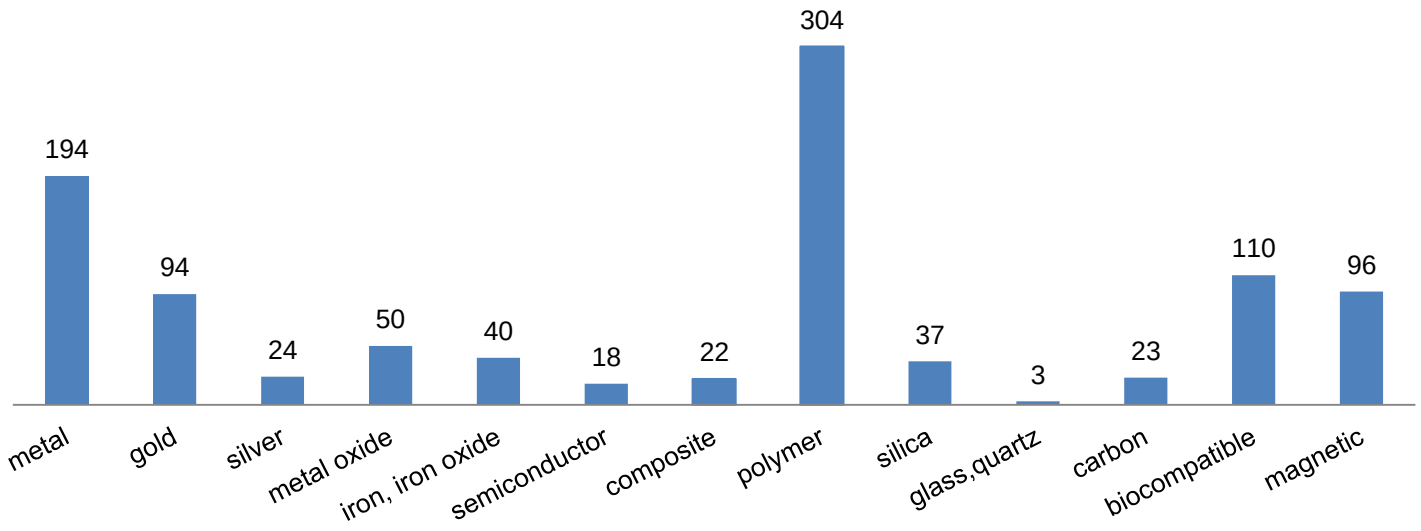


Figure 8: Patent distribution on the basis of Nanoparticle types

Figure 8 represents the patent distribution according to the different types of nanoparticles used. As evident from the graph, the use of polymeric drug nanoparticles is the highest as it increases the therapeutic performance of poorly soluble drugs in any route of administration. The unique characteristics of noble metal nanoparticles, such as high surface-to-volume ratio, broad optical properties, ease of synthesis, and facile surface chemistry and functionalization hold pledge in the clinical field for cancer therapeutics, thus, ranking them as second most widely used material form. Moreover, metals like gold and silver can efficiently convert light or radiofrequencies into heat, thus enabling thermal ablation of targeted cancer cells. Example: patent **US20100029544A1** talks about the new heteroalkyl polymer based nanoparticles used for treating cardiovascular diseases and cancer. The graph also very clearly depicts a significant number of patents involving the use of gold nanoparticles because of their basic tendency to stick to the site of action i.e. tumor. Example: patent **US20070031337A1** discloses the use of gold nanoparticles using proton therapy to treat the tumor cells.

6.2 Stimulus

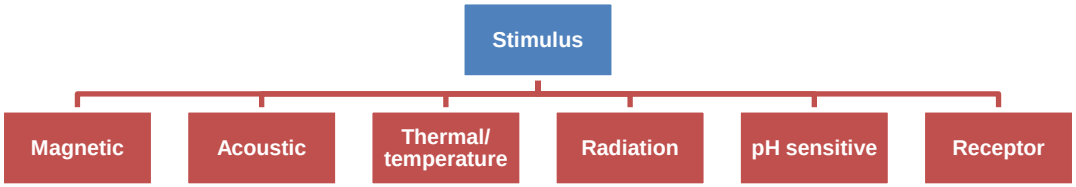


Figure 9: Various stimuli

Nanoparticles when used in drug delivery systems respond to certain types of stimuli and thus function accordingly as shown in Figure 9. The analysis indicated that nanoparticles generally respond to factors like light, ultrasound, thermal conditions, magnetic field, pH, temperature, radiation and receptors or aptamers. In case of nanoparticles that respond to the magnetic stimulus, the drug directs its action towards the site of a detected magnetic field.

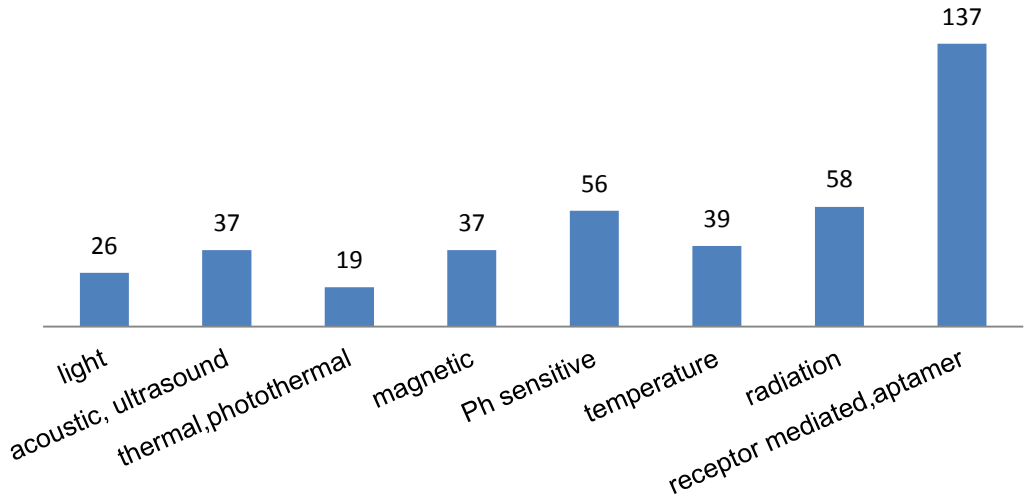


Figure 10: Patent distribution on the basis of various stimuli

Figure 10 represents the patent distribution according to the responses to different stimuli. As visible from the graph, the highest responses tend to fall under the receptor/aptamer mediated category. Receptors/aptamers are used as an attractive strategy to enhance the therapeutic index of drugs and to specifically deliver these agents to the defined target cells, thus keeping them away from healthy cells, which are sensitive to the toxic effects of the drugs. Ultrasound field coupled with low pH factors and polymer nanoparticles are widely used as vesicles for treating carcinoma group of cancers. These dually responsive vesicles show no cytotoxicity below 250 µg/ml, and can encapsulate anticancer drugs; exhibiting retarded release profile and controllable release rate when subjected to ultrasound radiation or varying pH in tris buffer at 37°C. However, the evolution of stimuli-responsive vesicles from bench to bedside still seems far away for the limitations of current stimuli forms such as ultrasound, light, photo thermal, etc. For example, patent **US20080131366A1** discloses diagnosing and treating a patient with solid tumor (lymphoma) comprising of nanoparticles which respond to the steroid receptor. Likewise in patent **US20120259152A1**, radiation, as a stimulus, is used for treating hypoxic tumors with nanoparticles used with photosensitizing agent.

6.3 Delivery systems

6.3.1 Route of administration

A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body. In this analysis, as shown in Figure 11, the drug delivery systems have been classified into six routes on the basis of their location and site of action. Parenteral route involves all administration via three basic forms –IM, IV AND SC (intra muscular, intravenous and subcutaneous). Topical route includes: the application of drug preparations to the surfaces of the body, especially the skin (administration, cutaneous) or mucous membranes. Buccal /sublingual route refers the mode of administration of drug under the tongue.

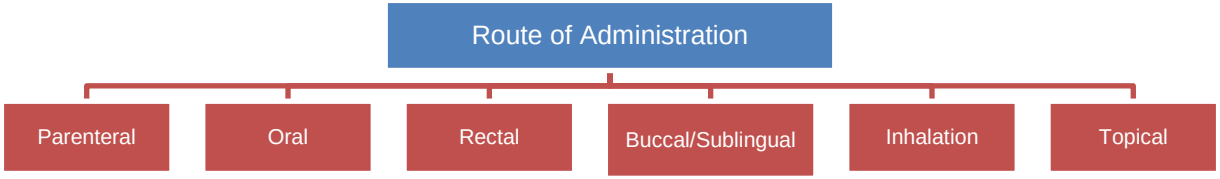


Figure 11: Different routes of administration

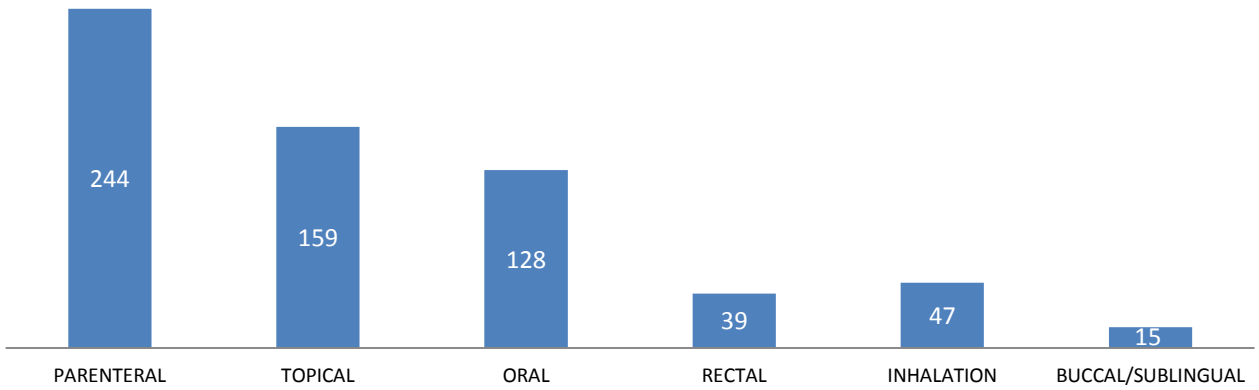


Figure 12: Patent distribution on the basis of routes of administration

Figure 12 represents the patent distribution according to the routes of administration of the drug particle. According to the represented analysis, the most commonly used route is parenteral, owing to the fact that the effects of the medication are much rapid and that it can be administered directly to the site. Following this trend, topical route is the second most important as this method of treatment is used to avoid systemic side effects when high doses are required at a localized area, or as an alternative systemic administration route to avoid hepatic processing. Example: **US20130195983A1** talks about treating carcinoma and sarcoma classes of cancer by using the parenteral routes of action, more specifically the intravenous route.

6.3.2 Form of delivery

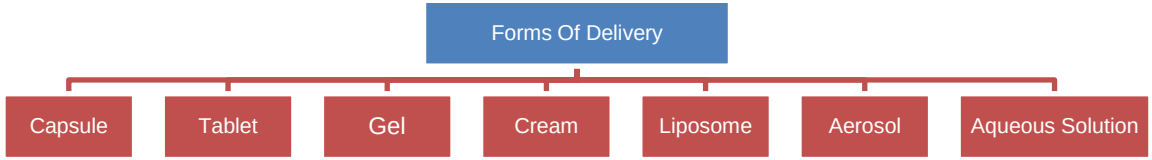


Figure 13: Different forms of drug delivery

Linked with the routes of administration, the form of delivery of drugs can be divided into classes as cream, capsule, gel /hydrogel, tablet, liposome, aerosol, spray and aqueous solutions as shown in the Figure 13. A liposome is an artificially-prepared vesicle composed of a lipid bilayer in which the drug is entrapped. Another form of delivery, aerosol, used basically for inhalation and topical routes, is defined as a colloidal system of solid or liquid particles in a gas.

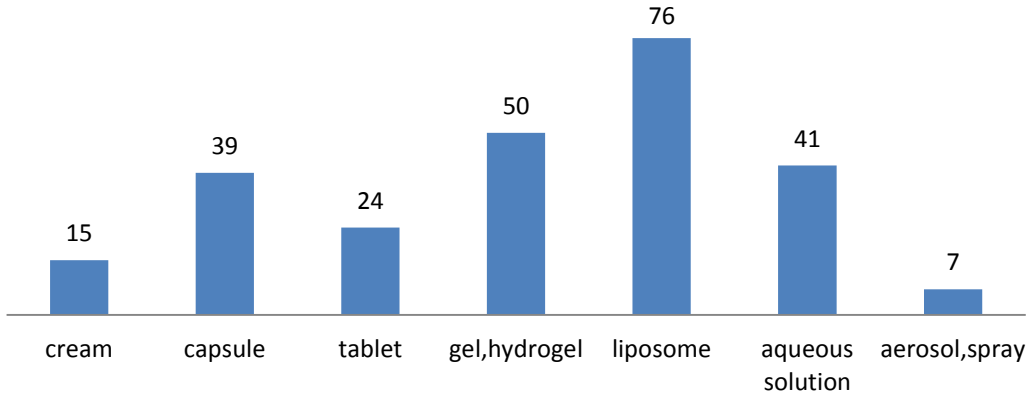


Figure 14: Patent distribution on the basis of forms of delivery

Figure 14 depicts the patent distribution on the basis of form of delivery. Earlier known as lipid vesicles, the recent most popular form of delivery of the drugs are liposomes, as is evident from the graph. The exceptionally high use of liposomes accounts to the fact

that, they have high retention rates and excellent targeted sustained release. Following closely is the use of gels, mainly in rectal and oral formulations, as it is easy to administer over the affected area. Example – the patent **CN100515497C** talks about liposomal drug delivery using nanoparticles to treat ovarian cancer conditions. Table 2 represents the different features of the mentioned routes of administration .The first pass effect(mentioned in the table) is defined as phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation.

S. No.	Delivery route	Preferred forms of delivery	Type of effect	Bioavailability	Absorption
1	Oral	Tablets, Capsules, gels	Systemic	5-100%	First pass effect
2	Parenteral	Aqueous solutions, aerosols	Systemic	75-100%	Rapid effect
3	Buccal/sublingual	Tablets	Systemic	5-100%	First pass effect
4	Rectal	Aqueous solutions., Cream, Gel	Local	30-100%	50% first pass effect
5	Topical	Creams, Gel, Aerosol, Aqueous solution	Local	80-100%	Sustained effect
6	Inhalation	Aerosol sprays	Systemic, local	5-100%	Rapid effect

Table 2: Delivery routes and their properties

6.3.3 Purpose

Two major heads are made on the basis of the purpose of drug delivery systems, namely – treatment and diagnostics.

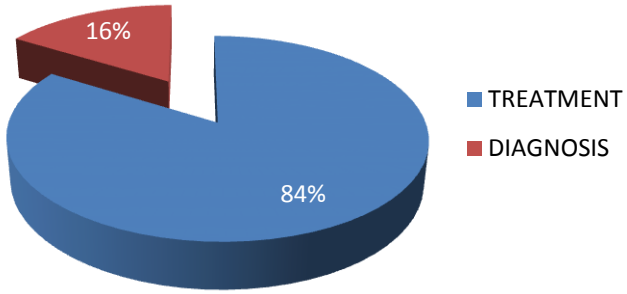


Figure 15: Purpose of drug delivery

Nanoparticles as drug delivery systems enable unique approaches for cancer treatment. Nanoparticles are often used to deliver drugs, especially those that are highly toxic, directly to cancer cells. Example: the patent **CN100515497C** uses liposomal drug delivery systems to treat ovarian cancer. More recently developed nanoparticles are demonstrating the potential sophistication of these delivery systems by incorporating multifunctional capabilities and targeting strategies, in an effort to increase the efficacy of these systems against the most difficult challenges in cancer treatment, including drug resistance and metastatic disease. Another example is **WO2010003232A1**, which discloses the therapeutic action of drugs using nanoparticles to typically treat breast cancer forms. For diagnosing the cancer types and to detect the disease, different types of diagnostic methods are used, which include MRI, tomography, imaging and CAT scan. Microbeam radiation therapy (MRT) can be enhanced by the prior administration of gadolinium-based nanoparticles to the patient. The nanoparticles also improve contrast in magnetic resonance imaging (MRI) permitting localization of the tumor. For example, patent **WO2005021501A1** directly refers the therapeutic and the diagnostic methods for the renal function monitoring analysis.

6.3.4 Drug target

Under this head, mainly five major classes of cancer are mentioned and analyzed as shown in the figure 16.The classes are divided on the basis of location and action of cancer in the human body.

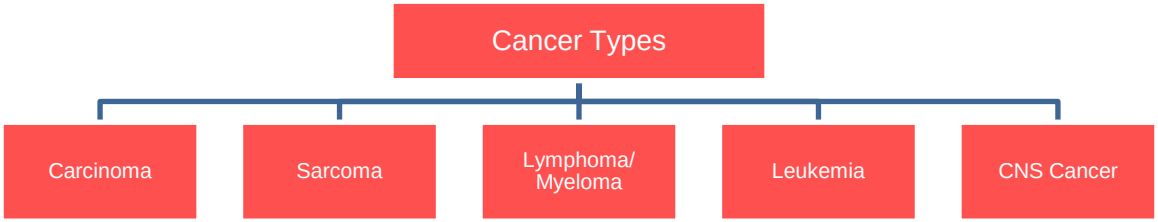


Figure 16: Various cancer types

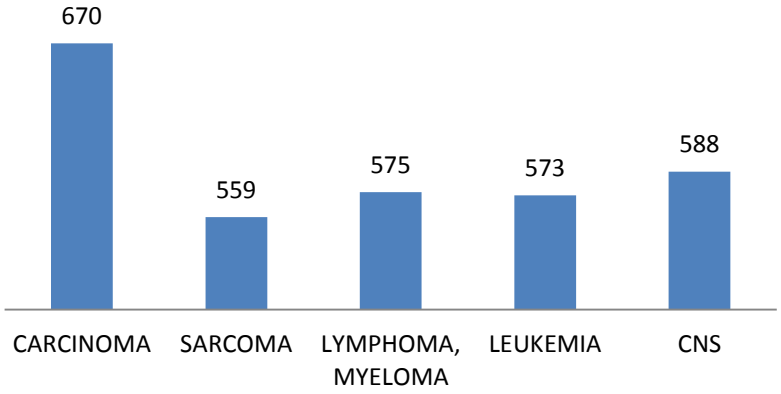


Figure 17: Patent distribution on the basis of various cancer types

Figure 17 comprises of the patent distribution trends relating the five broad classifications of cancer types. Most widely treated cancer is carcinoma, which contributes the highest ratio of patents as analyzed from the above graph. Carcinoma class includes the most common type of cancers occurring in humans and can be cured using the technology implying nanoparticles, while Sarcoma cancers, related to bone and the connective tissues, is a very complex category and is difficult to treat using any technique .Hence, sarcoma class of cancers are least curable using nanoparticles as drug delivery methods. Table 3 classifies the different types of cancers and explains those giving relevant examples from the patent analysis.

S.no.	Cancer types	Definition	Example
1	Carcinoma	Cancer that begins in the skin or in tissues that line or cover internal organs fall under this class	**EP1796683A1** depicts the method, compositions and administration of calcium chelators to treat carcinoma.

2	Lymphoma & myeloma	Cancers that begin in the cells of the immune system are referred in this category	Patent **US20120195961A1** has its claims based upon the use of spinosyn compositions for treating solid tumors, a lymphoma type of blood cancer, in humans.
3	Leukemia	Leukemia refers to the cancer that starts in blood-forming tissue such as the bone marrow and causes a large number of abnormal blood cells to be produced and enter the blood.	In patent **US20120039995A1** an arsenic compound is being used for treating the leukemia type of blood cancer.
4	Sarcoma	Cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue come under this category of cancer.	Patent **WO2013082535A2** with an oligo receptor binding ability is useful for treating the sarcoma group of cancer.
5	Central nervous system(CNS) Cancer	Cancers that begin in the tissues of the brain and spinal cord, nervous disorders and childhood disorder and thus the subsequent occurrence of brain cancer are called CNS class of cancer.	Nanoparticles using oral and parenteral routes of drug administration are used as claimed by patent **EP1682152A2** to treat the brain cancer forms.

6.3.5 Application

Table 3: Various cancer types with relevant patent examples

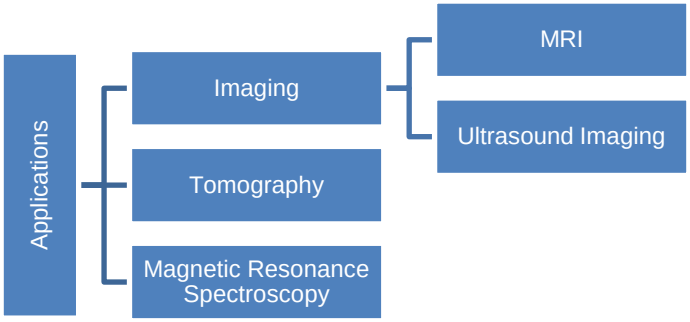


Figure 18: Various diagnostic applications

Imaging

An MRI (or magnetic resonance imaging) scan is a radiology technique that uses magnetism, radio waves, and a computer to produce images of body structures. Example – patent **US20100183504A1** reveals a method that detects diseased cancer cell types using MRI imaging techniques.

Ultrasonic imaging - Ultrasonic imaging is a mature medical technology. It accounts for one in four imaging studies and this proportion is increasing.

Computed Tomography

A CT scan may be used to make sure a procedure is done correctly. For example, the doctor may use CT to guide a needle during a tissue biopsy, or to guide the proper placement of a needle to drain an abscess. Example: **US20070031337A1** shows the use of gold nanoparticles, which bind to a specific receptor site and thus are used for tomography purposes.

Magnetic Resonance Spectroscopy (MRS)

MR spectroscopy is conducted on the same machine as conventional MRI (see Magnetic Resonance Imaging). The MRI scan uses a powerful magnet, radio waves, and a computer to create detailed images. Spectroscopy is a series of tests that are added to the MRI scan of your brain or spine to measure the chemical metabolism of a suspected tumor.

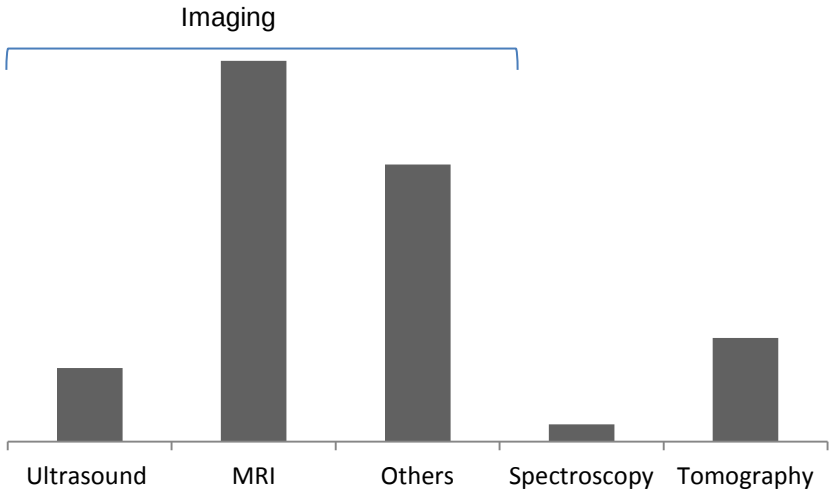


Figure 19: Patent distribution on the basis of applications

Figure 19 depicts the patent distribution trends according to their diagnostics applications. The most widely used applications include primarily imaging techniques. Nanoparticle types like manganese oxide particles are used as contrasting agent in MRI scan thus, accounting to its wide application. Apart from MRI scanning, the nanoparticles, especially gold, are used as optical resonance factor for tomography.

7. Some important trends in technology heads

This section includes trends in relation to the nanoparticle type and various other technology heads. Here, trends have been shown to signify the growing demand of a particular type of nanoparticle, and what is the percentage focus with respect to other technology heads.

7.1 Polymer based Nanoparticle

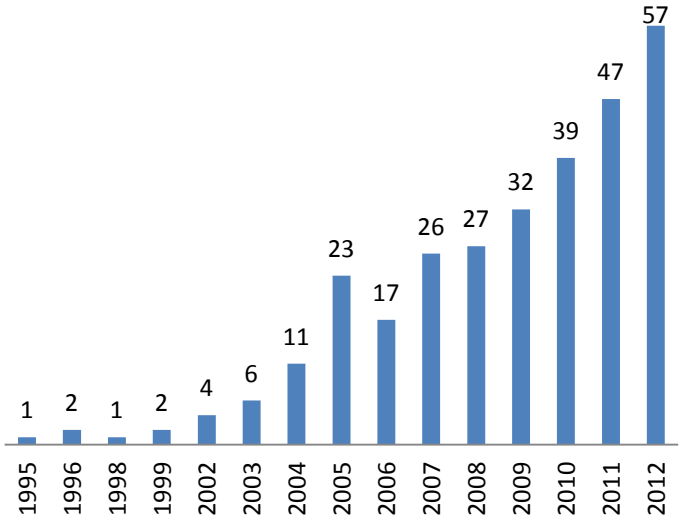


Figure 20: Patent distribution trend of polymer based nanoparticle type

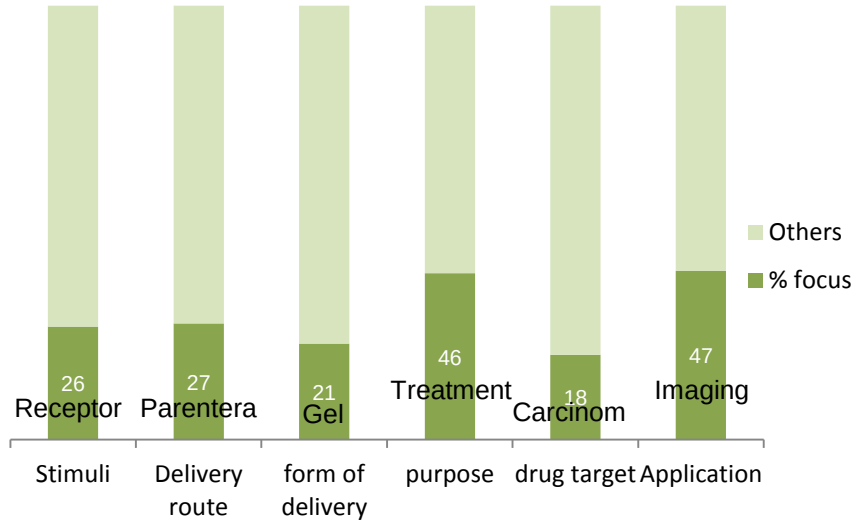


Figure 21: Percentage focus on the basis of various technology heads

Figure 20 shows the exponentially increase in use of polymer based nanoparticle for the targeted drug delivery to cancerous cells and as seen in Figure 21, there are certain combinations of polymer based nanoparticles with other technology heads that are generally preferred. For example, the analysis shows that a more preferred form of delivery for polymer based nanoparticle is gel due to its high absorption and high gel strength.

7.2 Gold Nanoparticle

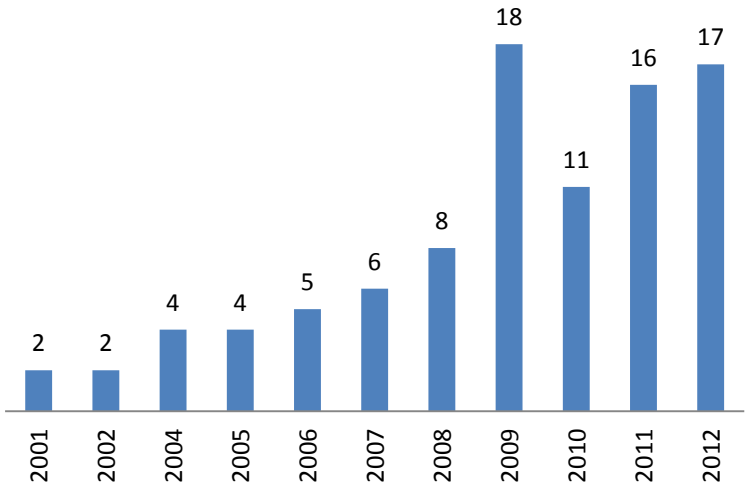


Figure 22: Patent distribution trend of Gold nanoparticle type

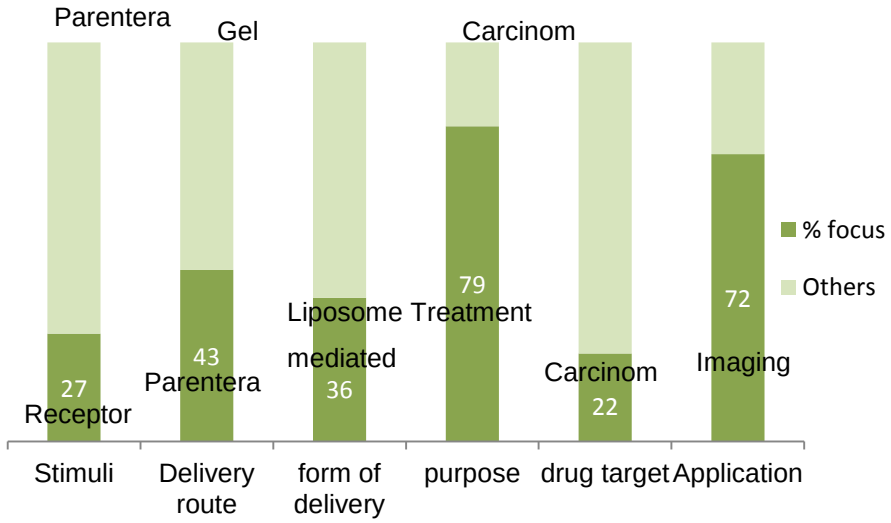


Figure 23: Percentage focus on the basis of various technology heads

Figure 22 shows the exponential increase in use of gold nanoparticles over the recent years, for the targeted drug delivery to cancerous cells. Figure 23 shows the combinations of gold nanoparticles with other technology heads that are generally preferred. For example, the analysis shows that a more preferred form of delivery for gold nanoparticle is liposome mediated, as liposomes increase stability via encapsulation and moreover they are non-toxic and biocompatible. A sudden increase in patent filings in the year 2009 may be accounted due to the fact that many ground breaking studies into the use of gold nanoparticles in cancer treatment, by universities like MIT; Stanford etc., surfaced around that time (source).

8. Assignee analysis

8.1 Major assignees geographical presence

Figure 24 represents the top ten assignees in the field of targeted drug delivery using nanoparticles, for the treatment of cancer. This analysis is performed by considering one member per family. Pharmaceutical giants like Abbott, Abraxis Bioscience (CELGENE Corp.) & Immunolight and leading universities including MIT, University of California & University of Texas play an important role in research worldwide.

Figure 22:

According to our analysis, all the major assignees are based in the US. The top assignee (company) Abraxis Bioscience, a wholly-owned subsidiary of Celgene Corporation, has done a significant amount of research in the technology and has disclosed the use of albumin stabilized nanoparticles in targeted drug delivery system. Major share of the patents in the technology is held by leading universities.

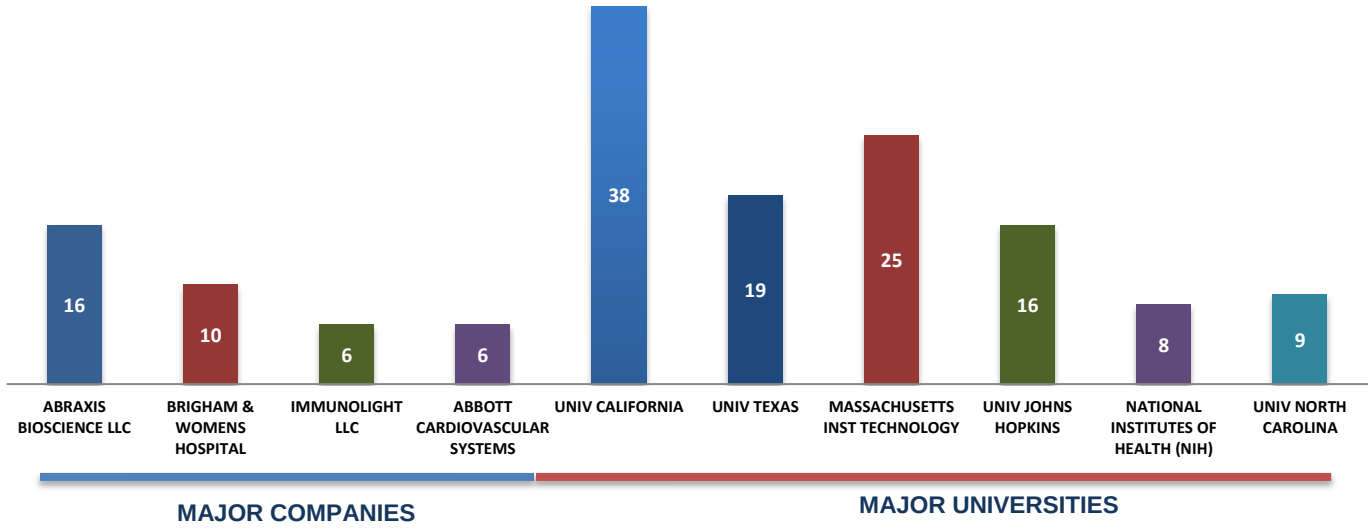


Figure 24: Patent portfolio of dominant assignees in the field of targeted drug delivery system using nanoparticles for Cancer treatment.

8. 1.1 Major Inventors

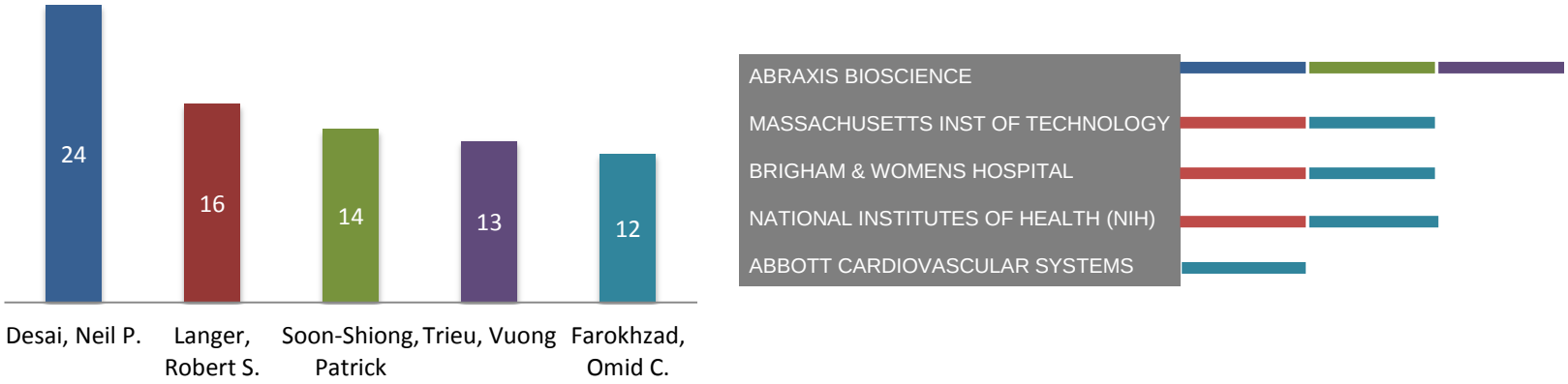


Figure 25: Patent portfolio of dominant inventors in the field of targeted drug delivery system using nanoparticles for Cancer treatment.

Figure 25 represents top ten assignees in the field of targeted drug delivery using nanoparticles for the treatment of cancer. This analysis is performed by considering one member per family. Most of the inventors listed above can be related to the major assignees in the field. Abraxis Biosciences is the standardized assignee for the patent filings by 3 out of 5 major inventors. Inventor Farokhzad, Omid C. has patent portfolio distributed among top assignees such as Abbott cardiovascular Systems, NIH, MIT and Brigham& Women hospital.

8.2 Major assignees: Technology focus

8.2.1 Nanoparticle type

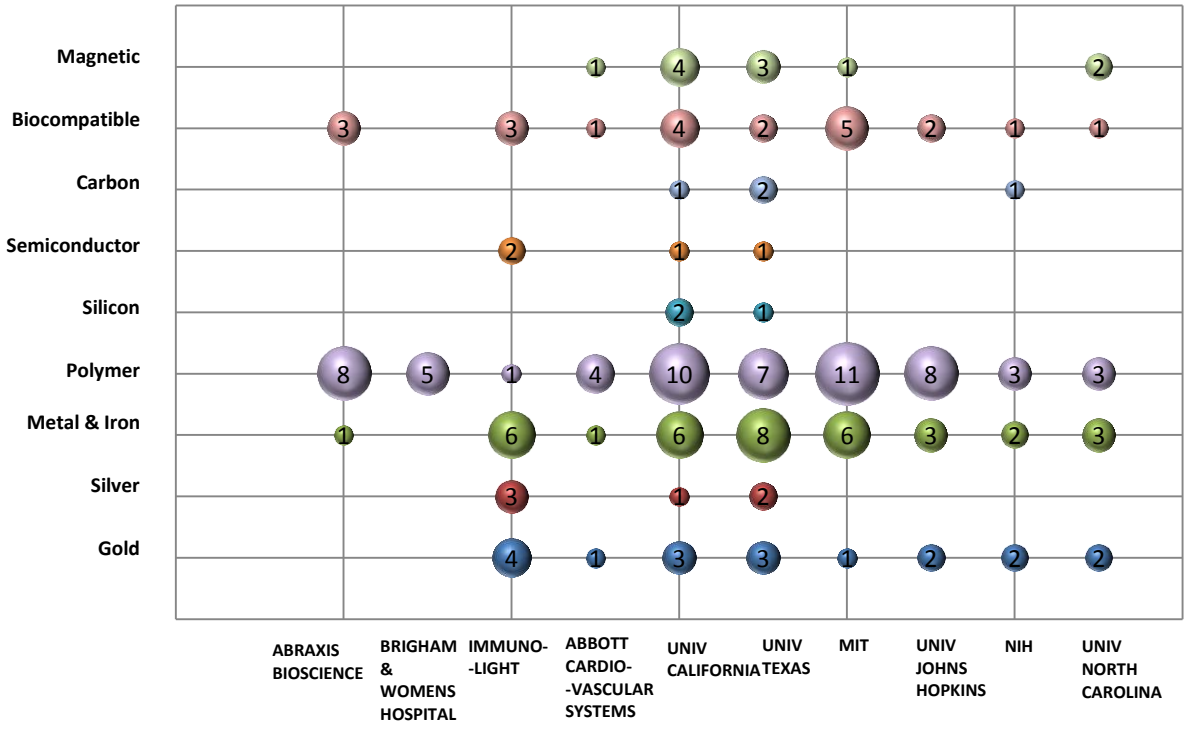


Figure 26: Patent distribution by assignee on the basis of nanoparticle type

Figure 26 reveals the number of patents filed by an assignee in the technology relating to the various types of nanoparticles used for targeted drug delivery to cancerous cells. The count given above is mutually inclusive as one patent can reveal multiple types of nanoparticles. We can also conclude that all the major assignees primarily use polymer-based nanoparticles as drug carriers. E.g. Abraxis biosciences majorly use polymer

based nanoparticles. University of California and University of Texas show research work done on almost all nanoparticle types. A Significant focus can be seen on the use of gold based and biocompatible material based nanoparticles. Also a white space can be observed for carbon based and semiconductor based nanoparticles.

8.2.2 Route of Administration

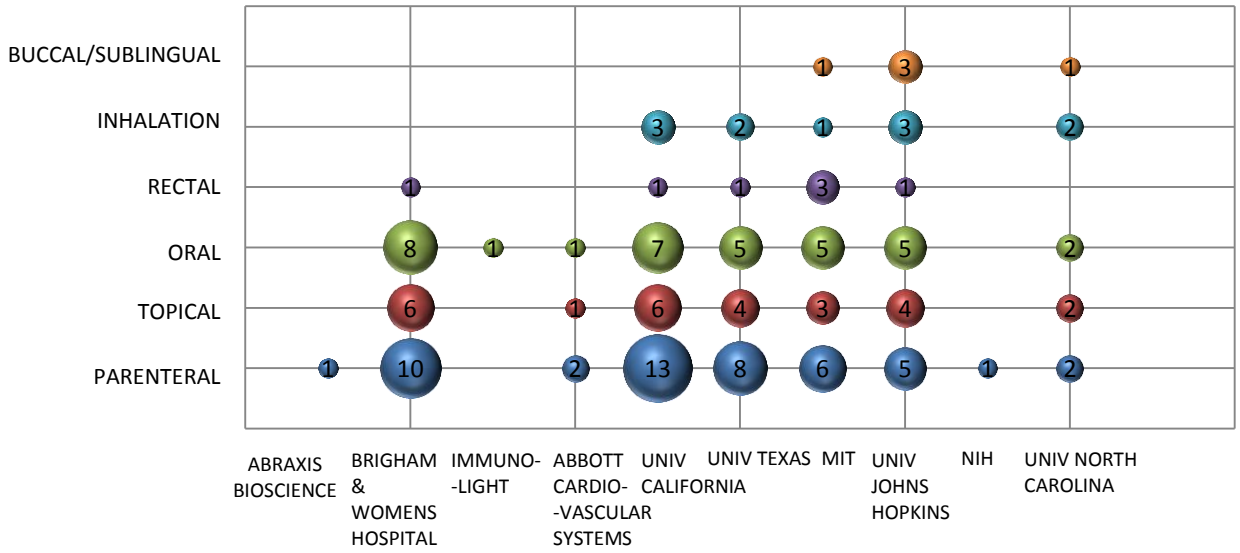


Figure 27: Patent distribution of assignees on the basis of Route of administration

Figure 27 reveals a number of patents filed by an assignee in the technology relating to the various routes of administration of drug carrying nanoparticles. The count given above is mutually inclusive as one patent can reveal multiple routes of administration. We can also conclude that all the major assignees mainly focus on parenteral drug delivery route. MIT and Johns Hopkins University have researched all routes of administration as can be seen from the figure. A significant focus can also be seen on oral and topical route of drug administration. It is also

observed that route of administration is co-related to the form of drug delivery e.g. for nanoparticles in the form of sprays/aerosols, the preferred route of administration is inhalation. Also, a white space can be observed for rectal route of drug delivery.

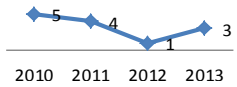
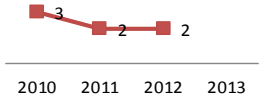
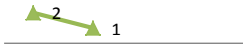
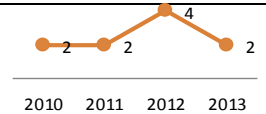
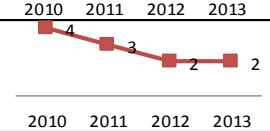
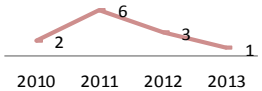
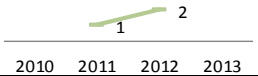
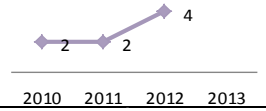
	Assignee name	Number of patents /applications	Filing trend by application year(2010 onwards)	% portfolio filed since 2010	Material type	Delivery route	Stimulus	Diagnosis
MAJOR COMPANIES	Abraxis BioScience	16		81%	5	10	1	2
	BRIGHAM AND WOMEN'S HOSPITAL A Teaching Affiliate of Harvard Medical School	10		70%	9	1	6	1
	IMMUNOLIGHT LLC	6		50%	6	1	5	-
	Abbott A Promise for Life ABBOTT CARDIOVASCULAR SYSTEMS	6		66%	5	1	2	-
MAJOR UNIVERSITIES	UNIVERSITY OF CALIFORNIA	38		71%	21	15	15	5
	UNIVERSITY OF TEXAS	19		52%	13	8	12	5
	MASSACHUSETTS INST TECHNOLOGY	25		44%	16	6	14	6
	JOHNS HOPKINS UNIVERSITY	16		75%	10	5	6	3
	NIH National Institutes of Health Turning Discovery Into Health	8		37%	6	1	1	2
	UNIV NORTH CAROLINA	9		88%	6	2	4	3

Table 4: Scorecard of top assignees

9. Scorecard

Table 4 discloses the year wise filing trend of the top assignees in the field of targeted drug delivery using nanoparticles for cancer treatment. It is observed that the major patent filing activity in last three years is seen in universities, with the maximum patents being filed by University of California. With other top assignees, the trend is more or less constant.

10. Feature-wise patent protection in different jurisdictions

10.1 By count

		AR	AT	AU	BR	CA	CN	DE	DK	EA	EP	ES	GB	IL	JP	KR	MX	NZ	PT	RU	SG	TW	US	WO
Material Type	Gold	4	1	12	2	18	13	4	1	0	33	2	4	4	18	5	1	1	0	0	1	7	72	68
	Silver	3	1	6	2	7	6	1	1	0	14	1	1	2	7	2	1	1	0	0	0	5	20	20
	Polymer	2	18	74	8	83	60	18	8	4	131	14	7	22	81	26	12	6	6	11	1	10	236	252
	Silicon	0	0	2	1	6	5	0	0	0	13	0	2	1	5	1	1	1	0	0	0	2	25	30
	Semiconductor	2	0	3	1	5	4	1	0	0	10	0	1	0	6	2	1	0	0	0	0	2	16	15
	Metal & Iron	6	7	25	3	34	24	9	4	0	58	5	6	7	36	16	4	0	1	4	0	7	109	116
	Carbon	0	2	10	1	11	6	2	0	0	14	0	1	5	9	4	1	1	0	0	0	0	22	19
	Biocompatible	3	9	29	3	32	22	7	5	4	47	5	2	9	39	9	10	2	3	4	1	7	94	84
	Magnetic	1	1	16	4	15	17	4	1	1	30	4	5	5	16	11	3	1	1	3	1	0	66	75
Delivery Route	Parenteral	3	21	72	13	86	55	15	12	8	114	16	6	23	75	24	23	18	9	7	10	10	187	213
	Oral	4	15	42	11	54	35	12	11	7	63	12	1	16	47	16	17	16	7	7	6	6	103	118
	Topical	2	14	45	11	52	35	10	9	7	76	8	1	15	47	17	13	15	4	6	5	7	124	146
	Rectal	1	6	16	4	16	11	5	3	5	20	5	0	7	13	4	6	6	2	2	2	1	34	36
	Inhalation	1	3	13	3	17	14	1	1	3	24	0	0	5	16	7	3	3	0	3	2	1	38	43
Stimulus	Receptor	1	4	35	5	39	33	6	2	1	62	3	4	11	36	14	12	5	1	3	4	8	110	121
	PH	0	4	11	3	11	13	2	1	1	21	2	2	4	11	6	5	2	1	0	1	1	39	45
	Light	3	1	2	2	7	5	1	1	0	9	0	1	1	6	1	1	0	0	1	1	2	19	22
	Magnetic	1	4	7	2	8	9	4	1	0	13	2	1	2	7	3	3	0	0	1	0	2	34	30

	Thermal	1	4	10	1	13	10	3	2	2	27	0	1	5	14	5	3	2	1	0	0	1	40	46
	Radiation	4	4	10	5	15	13	4	2	0	25	3	2	7	17	4	3	2	1	1	0	6	52	46
	Ultrasound	4	0	8	2	10	10	0	0	0	14	0	3	3	11	2	2	0	0	0	1	4	29	32
	Diagnosis	1	9	48	7	55	35	9	2	1	84	6	8	13	57	18	6	5	1	3	5	4	173	197

Table 5: Feature-wise patent protection in different jurisdictions by count

Table 5 represents the heat map of the number of patents filed under various technical heads in different jurisdictions. This analysis is performed by considering the latest filed country specific member of a specific family i.e. in a particular family, one latest filed patent of each jurisdiction is considered. We can also analyze the major markets for a particular technology head (denoted by red color gradients). This also gives a generalized overview of the markets where the technology is yet to be explored (denoted by green color gradient). This table also represents the share of patents that protect a particular feature in a specific jurisdiction. E.g. Polymer based nanoparticle is highly protected in US & EP regions.

10.2 Earliest expiring/expired patents

		AU		CA		CN		EP		JP		US	
Material Type	Gold	AU200232568	6.5	CA2528460	9.5	CN1960825	10.5	EP1501476	6.5	JP05008977	9.5	US6121425	0.5
	Silver	AU2002365255	7.5	CA2528460	9.5	CN101443048	10.5	EP1631318	9.5	JP05008977	9.5	US7563457	7.5
	Polymer	AU199519473	0.5	CA2184242	0.5	CN1556854	7.5	EP740548	0.5	JP9506109	0.5	US6117454	0.5
	Silicon	AU2005331023	11.5	CA2543923	9.5	CN101443048	10.5	EP1660222	9.5	JP2006528194	9.5	US7563451	9.5
	Semiconductor	AU2004233873	9.5	CA2514968	9.5	CN1812766	9.5	EP1589953	9.5	JP2006516988	9.5	US20060293216	9.5
	Metal & Iron	AU199948545	4.5	CA2409910	7.5	CN1556854	7.5	EP1501476	6.5	JP2005506998	7.5	US6121425	0.5
	Carbon	AU199948545	4.5	CA2452257	7.5	CN101267804	9.5	EP1404372	7.5	JP2004536109	7.5	US6165440	3.5
	Biocompatible	AU199647556	1.5	CA2207961	1.5	CN1556854	7.5	EP805678	1.5	JP10511957	1.5	US5962566	1.5
	Magnetic	AU762893	3.5	CA2311647	3.5	CN1283121	3.5	EP1698347	3.5	JP2001524531	3.5	US20100015087	3.5
Delivery Route	Parenteral	AU199211536	-1.5	CA2099869	-1.5	CN100338086	3.5	EP804153	1.5	JP7500724	-1.5	US20050002860	0.5
	Oral	AU200197249	3.5	CA2270345	3.5	CN100338086	3.5	EP1714969	3.5	JP2010150280	3.5	US20070093547	4.5
	Topical	AU199211536	-1.5	CA2099869	-1.5	CN100338086	3.5	EP804153	1.5	JP7500724	-1.5	US20050002860	0.5
	Rectal	AU199731760	4.5	CA2295177	4.5	CN1283121	4.5	EP986373	4.5	JP03778575	4.5	US7025991	4.5
	Inhalation	AU784356	6.5	CA2395493	6.5	CN1849115	10.5	EP1250152	6.5	JP04215429	6.5	US7125858	6.5
mu	Receptor	AU199211536	-1.5	CA2099869	-1.5	CN1556854	8.5	EP804153	1.5	JP7500724	-1.5	US20050002860	0.5

	pH	AU2002256784	8.5	CA2448303	8.5	CN101928262	8.5	EP1790642	8.5	JP2009280588	8.5	US20080261960	8.5
	Light	AU2003254333	9.5	CA2514968	10.5	CN101479051	13.5	EP1519713	9.5	JP2006516988	10.5	US20060140999	7.5
	Magnetic	AU2003210108	9.5	CA2512206	9.5	CN1556854	8.5	EP1585849	9.5	JP2005537342	9.5	US20060121005	7.5
	Thermal	AU2003237709	9.5	CA2518791	10.5	CN1658902	9.5	EP1509246	9.5	JP2005537342	9.5	US7732404	6.5
	Radiation	AU716364	2.5	CA2209771	2.5	CN1360486	6.5	EP800399	2.5	JP2012036201	2.5	US6121425	1.5
	Ultrasound	AU199948545	5.5	CA2493596	8.5	CN100563718	10.5	EP1551371	9.5	JP2003520210	7.5	US6165440	4.5
Diagnosis		AU755154	4.5	CA2290756	4.5	CN1337886	6.5	EP1019071	4.5	JP04129298	4.5	US6121425	1.5

Table 6: Feature-wise patent protection in different jurisdictions indicating earliest expiring/expired patents

Table 6 represents the heat map of the earliest expiring/expired patents filed under various technical heads in different jurisdictions. This analysis is performed by considering the latest filed, country specific member of a specific family i.e. in a particular family, one latest filed patent of each jurisdiction is considered. It is important to take a note of the markets where the technology has already expired or is about to expire (denoted by green color gradients).

11. Conclusion

Together with the progression of nanoscale drug delivery systems, advances in nanoscale imaging suggest the potential for the development of multifunctional ‘‘smart’’ nanoparticles that may facilitate the realization of individualized and targeted cancer therapy. Almost all types of nanoparticles including polymeric nanoparticles, nanocrystals, polymeric micelles, dendrimers, and carbon nanotubes have been evaluated for their suitability as multifunctional nanoparticles that can be applied for diagnostics imaging and treatment of cancers. Eventually, multiplex nanoparticles may be capable of detecting malignant cells, visualizing their location in the body (real-time in vivo imaging), killing the cancer cells with minimal side effects by sparing normal cells (active targeting and controlled drug release or photo thermal ablation), and monitoring treatment effects in real time.

The alliance of nanotechnology and medicine has yielded an offspring that is set to bring momentous advances in the fight against a range of diseases. Cancer nano therapeutics is rapidly progressing and being implemented to solve several limitations of conventional drug delivery systems such as nonspecific bio distribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. The future

still remains a challenging one, as the creation of complex systems entails an understanding of individual components that make up the delivery vehicle as a whole. Future nanoparticle delivery systems that are able to employ simultaneous delivery of drugs, targeting to specific brain tumor surface markers and/or simultaneous imaging of their delivery will take a great deal of knowledge of how each component works to achieve such goals.

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