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Nanoparticles for Lung Cancer Therapy: Recent Evolution and Challenges

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HUMAN

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ABSTRACT

Prompt development in nanotechnology toward the expansion of nanomedicine agents grips immense potential to improve therapeutic methods against cancer. Nanomedicine products characterize a prospect to attain cultured targeting strategies and multifunctionality. The initiation of nanotechnology has transformed the arena of cancer diagnosis and treatment. Nanoparticles (1–100 nm) can be used to treat cancer due to their specific benefits such as biocompatibility, reduced toxicity, more exceptional constancy, improved penetrability, maintenance outcome, and particular targeting. Investigation of nanotechnology cancer therapy extends outside drug transport into the conception of new therapeutics accessible only through the use of nanomaterial properties. Although small associated with cells, nanoparticles are large sufficient to encapsulate many small molecule compounds, which can be of multiple types. At the same time, the comparatively large surface area of a nanoparticle can be functionalized with ligands, including small molecules, DNA or RNA strands, peptides, aptamers, or antibodies. These ligands can be used for healing effects or to direct nanoparticle fate in vivo. These stuffs support mixture drug delivery, multi-modality treatment, and combined therapeutic and diagnostic, known as “theranostic,” action.

INTRODUCTION

The term cancer denotes the abnormal growth of the cells, which takes in oxygen and nutrients from other living cells. The cancer cells lose its cell adhesion with other living cells and spread to other parts of the body through the bloodstream and initiate the development of the secondary tumour growth. The tumour can be removed from its early stage of growth from the body[1]. Most of the cancer death patients under go metastasis of various cancers like lungs, liver and bone. The malignancy has a hyper capacity of replication of cells in the rapid formation of the bloodstream. In contrast to malignancy, the metastasis cancer can be cured to some extent. Closely 200 types of cancers are existing on various symptoms. This is due to various life factors like lifestyle, age, and genetic causes. Tumours may be benign or malignant. The term "cancer" refers to those tumours that are malignant. Benign tumours can be eradicated from the body without affecting the normal tissues. They have slow rate of proliferation, are encapsulated, and do not infiltrate surrounding tissues. Death does not occur due to such benign tumours. On the contrary, malignant tissues grow irregularly, have a high rate of cell proliferation, invade healthy tissues [lack differentiation], are resistant to apoptosis, and then migrate to the bloodstream, lymphatic system, or other parts of the body. This process of spread is known as "metastasis" [2].

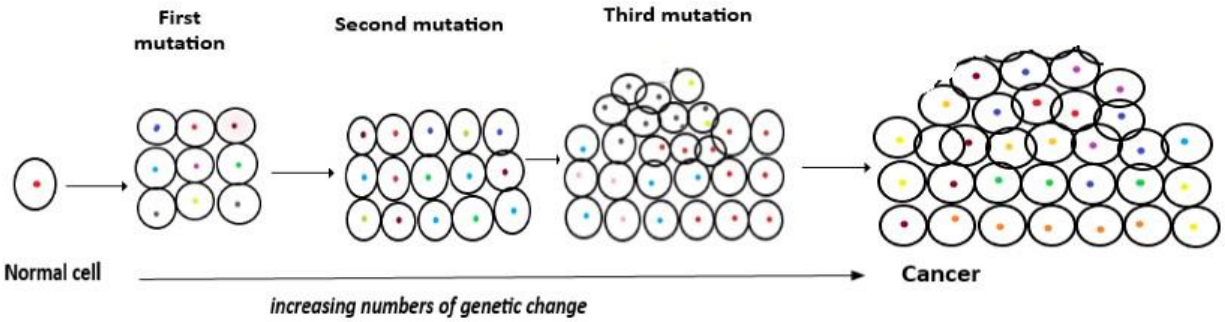

Figure No. 1: Different stages of mutation of normal cell

Cancers are a group of diseases characterized by uncontrolled growth and the spread of abnormal cells. If the spread of cancer cells this stage is known as metastasis is not controlled, it can result in death[3]. Cancer remains a leading cause of death worldwide with an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths in 2012, compared with 12.7 million infections, in 2008 [4].

CANCER SCENARIO IN INDIA

Data from cancer patients was compiled from 2004 to 2010 in India and shown in figure no. 2. Based on the increasing trends of cancer patients during the last few decades, the numbers of cancer patients have been predicted by the end of 2015 and 2020 in India. These compiled data show that the number of males, female and the total cancer patients in 2004 were 390809, 428545 and 819354 respectively. The number of male and female cancer patients increased continuously up to 2009, with 454842, 507990 and 962832 cases for male, female and total cancer patients, respectively. Similarly, 462408 male cancer patients and 517378 female cancer patients were recorded, with a total number of 979786 patients in 2010. Thus, it is clear from figure no.2 that the number of cancer cases has increased gradually with time. Moreover, a prediction of cancer patients in 2015 and 2020, respectively, has also been made.

The different types of cancers observed in India are discussed in the following sub-sections briefly [5].

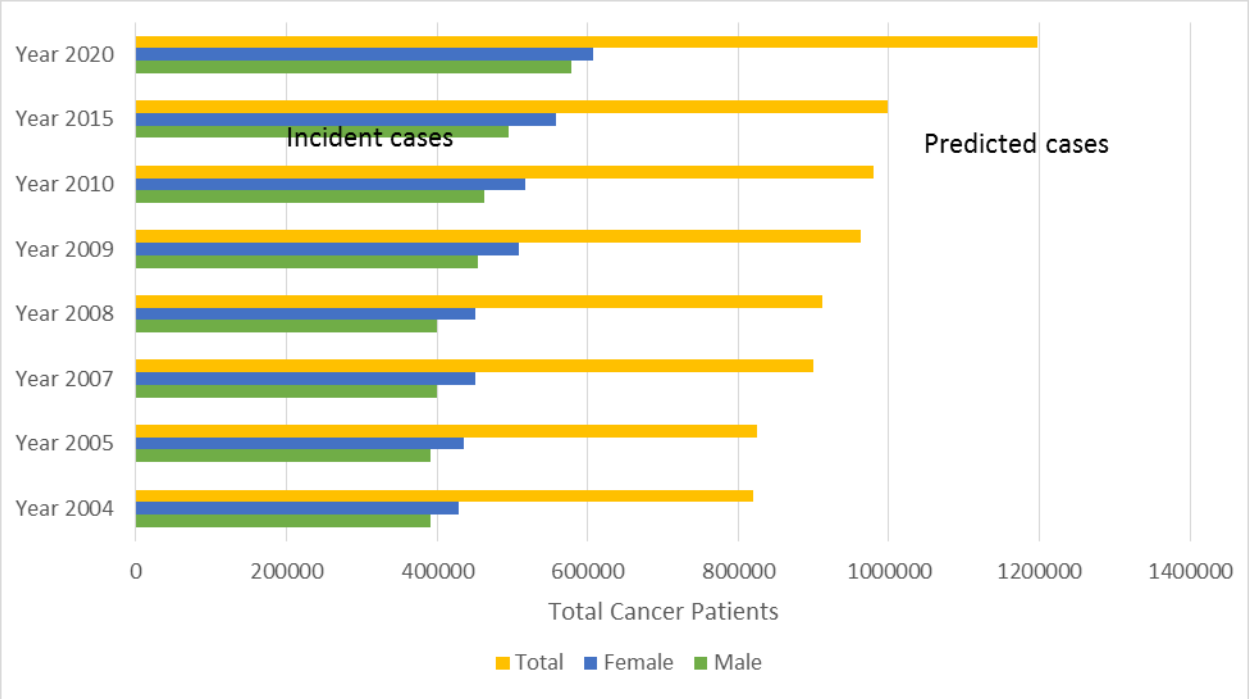

Figure No. 2: Year-wise total cancer prevalence in India [ICMR,2006; ICMR,2009]

CANCER CASES IN CHHATTISGARH

Chhattisgarh, a tribal-dominated state in central India, has a population of 25.6 million with 30.62% of them being coming under scheduled tribes [Census 2011]. It consists of 27 districts divided into 5 divisions [i.e. Raipur, Durg, Bastar, Sarguja, Bilaspur][6]. Regional

Cancer Centre [RCC], Dr.B.R.Ambedkar Memorial Hospital, Raipur, is the only tertiary care Government cancer Hospital & referral centre for cancer patients in the state of Chhattisgarh. A total of 16,395 patients were registered at the RCC during the 5 year period i.e. 2011 to 2015. We observed that number of incident cases is showing increasing trend i.e. from 3028[2011] to 3315[2015].

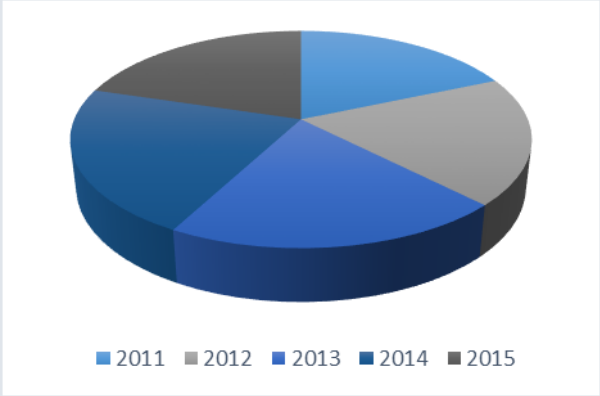

Figure No. 3: Total patients registered during 2011-2015 RCC, Raipur

LUNG CANCER

Lung cancer is among the deadliest cancers for both men and women[7]. Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related death worldwide[8]. Lung cancer is a deadly disease and has a mortality rate higher than that of prostate cancer, breast cancer and colon cancer combined. It is mainly of two types, non-small cell lung cancer and small cell lung cancer. Non-small cell lung cancer accounts for about 85% of all lung cancers with a mean survival rate of 15% and is mainly divided into three subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma out of which adenocarcinoma [30–50% of non-small cell lung cancer] and squamous cell carcinoma [30% of non-small cell lung cancer] are most common[9]. Small cell lung cancer is classified into small cell carcinoma and combined small cell carcinoma a combination of small cell lung cancer with neoplastic squamous and/or glandular components. Small cell lung cancer is more aggressive than non-small cell lung cancer, fast-growing and spreads rapidly while non-small cell lung cancer grows slower. Nonsmall cell lung cancer has a high recurrence rate of 35%-50% among early-stage non-small cell lung cancer patients.

Lung cancer is the most common cancer in men and women in developed countries. It is also the leading cause of cancer death worldwide, causing 18.4% of all cancer deaths. Approximately 70% of patients have advanced disease at the time of diagnosis, and only 15%

of lung cancer patients are still alive 5 years after diagnosis. There are several procedures for lung cancer diagnosis: Including physical exam, medical history, and imaging techniques such as X-ray, computed tomography [CT], bone scan, magnetic resonance imaging [MRI], positron emission tomography [PET], and combined PET-CT scan[10]. On the row of various cancers in the world, the lung cancer falls to number two in both females and male. The primary function of the lungs is the exchange of the gases between the air and blood. Moreover, the purification of the blood expelling carbon-dioxide and in spelled oxygen takes place nearly 95%. Bronchogenic cancer exactly occurs in epithelial cells and it is also called as lung cancer. Its death rate exceeds that of the three most common cancers [colon, breast, and pancreatic] combined. Over half of patients diagnosed with lung cancer die within one year of diagnosis and the 5-year survival is around 17.8% [7].

It was observed that lung cancer was rare in the beginning of the last century but later on it was diagnosed in various patients reported about 9210 consecutive autopsies of lung cancer patients in 1970, which were 14.4% of all cancer types. But, nowadays, it has become almost epidemic resulting in greater number of deaths than those caused by colorectal, breast and prostate cancers. The data collected by the National Cancer Registry Program of the Indian Council of Medical Research; from six different parts of the country including both rural and urban areas; showed varying degrees of incidence in different areas [ICMR, 1988-89]. The most common forms of malignancies in males during 1989 in Bombay, Delhi, and Bhopal were cancers of the trachea, bronchi and lungs. These cancers were also reported in other cities in the order of Madras > Bangalore >Barshi. These sorts of cancers were rare in females except in Bombay and Bhopal, where they ranked at sixth and seventh positions of malignancies, respectively[5]. Efforts have also been made to find out the total number of cancer cases in five metro cities of India [New Delhi, Bombay, Chennai, Bhopal and Bangalore] during 2008. These data have been plotted in figure no. 4.

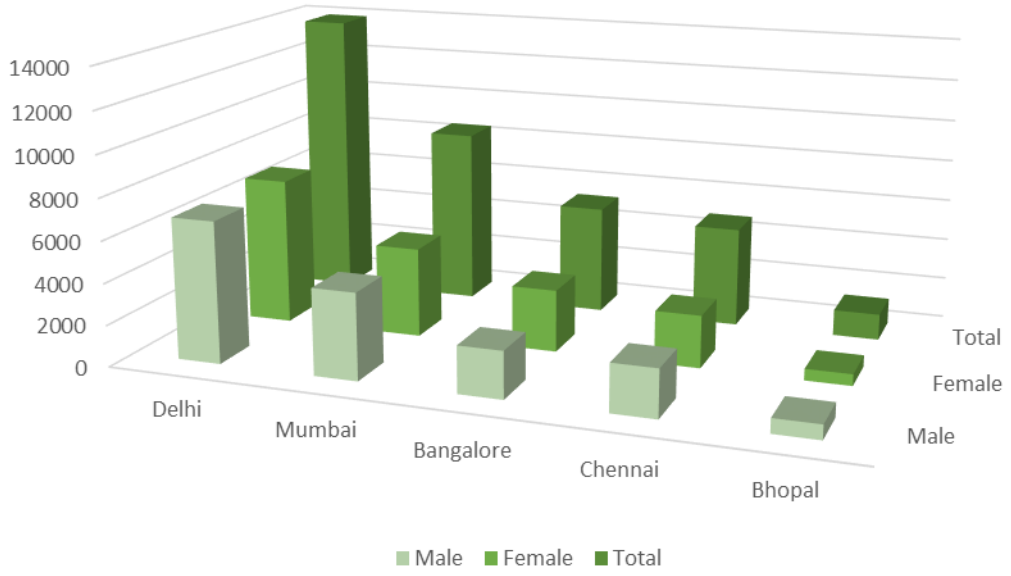

Figure No. 4: Cancer prevalence in five metropolitan cities of India

It is clear from figure no. 4 that Delhi has the highest number of total cancer cases among the five metropolitan cities studied. The total number of cancer patients reported in Delhi was 13920 having 6815 and 7105 males and females, respectively. Mumbai showed the second-highest number of cancer patients with 8505 total cases including 4170 and 4335 males and females, respectively. Bangalore occupied the third position with 2262 and 2998 male and female patients, respectively [total patients; 5250]. Chennai stood at the fourth position having 2296 and 2528 male and female cases; with a total number of 4824 cancer patients. Total cancer patients were low in Bhopal [1255] with 701 and 554 males and females, respectively. These trends of cancer patient distribution among discussed metropolitan cities may be due to different levels of environmental pollution, food habits, living style etc. Besides, the population density in these cities may also be a contributing factor towards the increasing number of cancer patients.

PATHOLOGY OF LUNG CANCER

The lung is a fragile complex organ compared to many cells types with different functions that favour gaseous exchange. 2,000 km of the airway and more than 50 cm^2 of the extremely thin alveolar membrane which enhances the efficient passage of O_2 and CO_2[1]. The efficient passage of oxygen and carbon dioxide between the blood and the environment occurs against a backdrop of exposure to toxic gases and fine particulate contaminants as well as infectious agents. Large inhaled particulates are cleared by ciliary action in the larger airways, whereas

infectious agents are eliminated by immune and phagocytic cells. Mucus-producing cells and neuroendocrine cells also have roles in maintaining the gas exchange function [8]. Due to smoking, morphological changes of bronchial epithelium progress from basal cell hyperplasia to metaplasia, severe dysplasia to carcinoma [in-situ] and finally carcinoma. Adenocarcinoma, heavy lung damage and its dominant subtypes in never smokers with low carcinogen exposure. The progress of adenocarcinomas is associated with less well characterized pre-malignant lesions called atypical adenomatous hyperplasia. Pathological classification of lung cancer is continually changing, with a need for specific terminology and criteria to distinguish squamous cell carcinoma from adenocarcinoma, particularly poor differentiated tumours[1].

CLASSIFICATION OF LUNG CANCER

Lung cancer is a disease of multiple aetiologies that arises as a result of neoplastic metamorphosis of epithelial cells in the lung. A plethora of epigenetic, genetic and molecular aberrations underlie the progression of the disease and also influence disease heterogeneity, and ultimately the diagnostic, therapeutic and prognostic outcomes [11]. To be able to devise a comprehensive, personalized treatment strategy for lung cancer, one must consider not only genetic and molecular information but also histopathological and clinical characteristics.

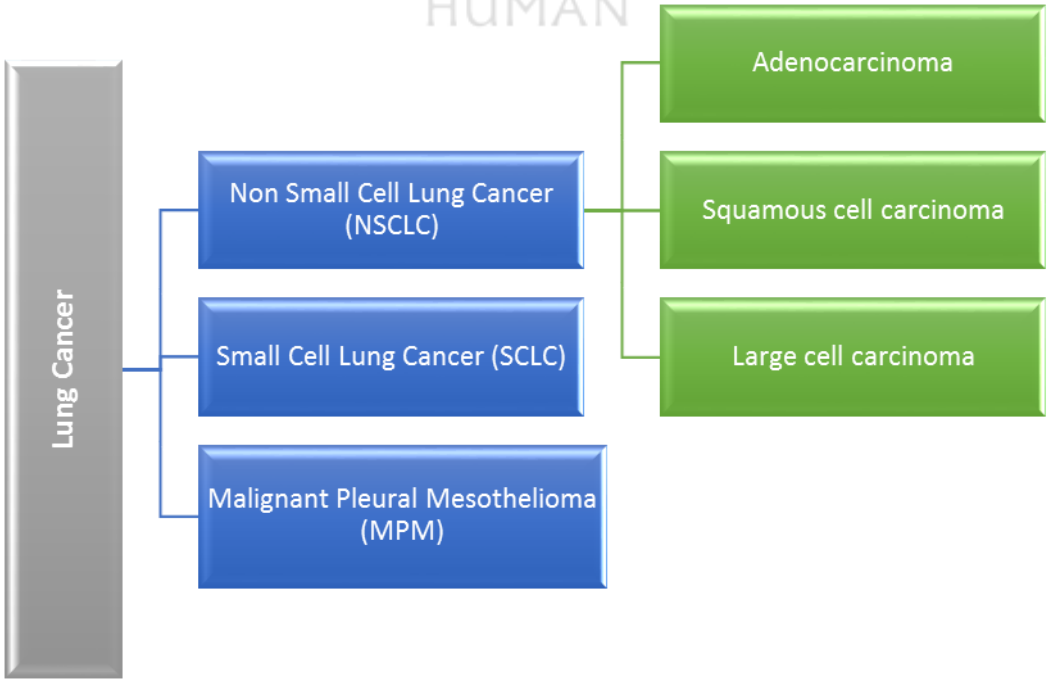

Figure No. 5: Types of Lung Cancer.

NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer [NSCLC] is the predominant form of lung cancer with approximately 85% of total lung cancer cases falling into the diagnostic remit of NSCLC. Of these cases, approximately 65% present with either metastatic or locally advanced disease[11]. Non-small cell lung cancer [NSCLC] represents a very heterogeneous disease in terms of patient and tumour characteristics [12]. The term NSCLC is a clinical umbrella term used to designate a wide variety of malignancies, including squamous-cell carcinoma [SCC], adenocarcinoma [ADC], large-cell carcinoma [LCC] and other less differentiated variants that each possess different cellular, genetic and epigenetic heterogeneity that gives rise to unique tumour microenvironments in patients, significantly contributing to the difficulty of treating NSCLC. NSCLC accounts for 75% to 80% of all lung cancer cases [13].

Adenocarcinoma

The most common type of lung cancer is adenocarcinoma. It arises from small airway epithelial, type II alveolar cells, which secrete mucus and other substances[7]. Adenocarcinoma of the lung usually evolves from the mucosal glands and represents about 40% of all lung cancers. It is the most common subtype to be diagnosed in people who have never smoked. Lung adenocarcinoma usually occurs in the lung periphery, and in many cases, may be found in scars or areas of chronic inflammation [14].

Squamous-cell carcinoma

Squamous cell carcinoma is characterized by the presence of intercellular bridges and keratinization. These NSCLCs are associated with smoking and occur predominantly in men. Squamous cell cancers can present as Pancoast tumour and hypercalcemia. A Pancoast tumour is the tumour in the superior sulcus of the lung. The brain is the most common site of recurrence post-surgery in cases of Pancoast tumour [15].

Large-cell carcinoma

Large cell carcinoma [LCC] is the third most common NSCLC subtype and accounts for approximately 3-9% of NSCLC cases. Large cell carcinoma can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat[10]. Large-cell carcinoma [LCC] morphologically is an undifferentiated lung carcinoma lacking features of

adenocarcinoma [ADC], squamous cell, or small-cell carcinoma. As a result, LCC has evolved into a clinicopathologically heterogeneous entity [16].

SMALL CELL LUNG CANCER

Small cell lung cancer [SCLC]is a malignant epithelial tumour consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round, oval, or spindle-shaped; nuclear molding is prominent. The mitotic count is high. Up to 30% of autopsies in patients with SCLC reveal areas of non–small cell carcinoma differentiation[17]. Small cell lung cancer [SCLC] is a high-grade neuroendocrine tumour characterized by rapid growth, early metastatic spread, and initial responsiveness to therapy[18]. Small cell lung cancer is a recalcitrant malignancy with 5-year survival rates of less than 20% [19]. SCLC is a heterogeneous disease including extremely chemosensitive and chemoresistant clones. SCLC is generally divided into two stages, limited and extensive [20].

MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma [MPM] is a rare and highly aggressive disease, whose incidence is increasing. Asbestos is the primary causal agent [21]. It is associated with previous asbestos exposure, with a latency period of ~40 years between fiber exposure and disease presentation[22]. MPM has a poor prognosis, with a median survival of 4-12 months due to a lack of successful curative treatments and its diagnosis at an advanced stage. MPM is categorized histologically as epithelioid, sarcomatoid or biphasic[23].

NANOPARTICLES

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm[24]. Nanoparticles used as drug delivery vehicles are generally < 100 nm in at least one dimension and consist of different biodegradable materials such as natural or synthetic polymers, lipids, or metals[25]. Nanoparticles may be engineered as the drug delivery carrier, or the drug itself can be engineered at the nanoscale, in which case the drug serves as its own “carrier”. Nanomaterials used in cancer nanotherapeutics include lipids, polymers, dendrimers, organometallic and carbon-based materials[26]. Nanoparticles can be classified into various types, according to their size, shape, and material properties[27]. A nanoparticle can be either a zero-dimensional where the length, breadth and height are fixed at a single point for example nanodots, one dimensional where it can possess only one parameter for example

graphene, two dimensional where it has length and breadth, for example, carbon nanotubes or three dimensional where it has all the parameters such as length, breadth and height for example gold nanoparticles[28]. Nanoparticleshave wide range of applications in areas such as health care, cosmetics, food and feed, environmental health, mechanics, optics, biomedical sciences, chemical industries, electronics, space industries, drug-gene delivery, energy science, optoelectronics, catalysis, single electron transistors, light emitters, nonlinear optical devices, and photoelectrochemical applications[29].

Nanotechnology can be defined as the science and engineering involved in the design, synthesis, characterization and application of materials and devices whose smallest functional organization in at least one dimension is on the nanometer scale [one-billionth of a meter][30]. Nanomedicine is a subset of nanotechnology, which uses tiny particles that are more than 10 million times smaller than the human body. In nanomedicine, these particles are much smaller than the living cell[31].

Types of Nanoparticles

The nanoparticles used in medical treatment usually have specific sizes, shapes, and surface characteristics as these three aspects have a major influence on the efficiency of the nano-drug delivery and thus control therapeutic efficacy. Nanoparticles with a diameter range of 10 to 100 nm are generally considered suitable for cancer therapy, as they can effectively deliver drugs and achieve enhanced permeability and retention [EPR] effect[22].

ORGANIC NANOPARTICLES

Organic nanoparticles can be explained as solid particles composed of organic compounds [mainly lipids or polymeric] ranging in diameter from 10 nm to 1 μm[32]. Because of their excellent properties, such as biological compatibility and degradability, natural or synthetic polymer-formed organic-based nanomaterials have been extensively used in the field of cancer therapies. They can roughly be divided into five types, i.e., polymeric micelles, polymeric nanoparticles, liposomes, dendrimers and polymer-drug conjugates[33].

Polymeric Nanoparticles

Polymeric nanoparticles are colloidal structures composed of synthetic or semi-synthetic polymers. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix[34].

Dendrimers

Dendrimers are nano-sized, radially symmetric molecules with a well-defined, homogeneous, and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell[35].Dendrimers are well-defined, multivalent molecules having branched structure of nanometer size. Dendrimers possess a distinct molecular architecture that consists of three different domains: [i] a central core [ii] branches [iii] terminal functional groups, present at the outer surface of the macromolecule[36].

Nanospheres

Nanospheres or matrix-type nanodevices are nanoparticles where the entire mass is solid and consists of spherical polymeric matrices which have been widely studied as carriers of therapeutic molecules[37].

Nanocapsules

Nanocapsules are composed of polymeric membranes and core of oil, which encompasses drugs that can diffuse out under appropriate conditions, by responding to environmental, chemical, thermal, or biological triggers[38]. A nanocapsule consists of a shell and a space in which desired substances may be placed. Drug-filled nanocapsules can be covered with antibodies or cell surface receptors that bind to cancer or various cells and release their biological compound on contact with that specific tissue[39].

Hydrogel

Hydrogel nanoparticles are three-dimensional polymer structures used for encapsulating and delivering drugs. These structures swell in water or biological environments. Therefore, they absorb more liquids. Responsive polymers release the drugs in response to temperature and pH changes. These systems are used for DNA and protein delivery, wound healing, tissue engineering, and biosensors[40].

Polymeric Micelles

Polymeric micelles are nanosized molecules of coreshell structure that are formed by the self-association of amphiphilic block copolymers when they are added to an aqueous solvent[41]. Polymeric micelles are self-assembled nanoscopic coreshell structures formed by amphiphilic

copolymer inside water, which are able to hold hydrophobic drugs inside the core of micelles and hydrophilic bioactive molecules such as DNA or siRNA in outer shell[42].

Polymersomes

Polymersomes are hollow shell nanoparticles that can be used for the delivery of drugs. Polymersomes[artificial vesicles] represent a promising pharmaceutical vehicle for the delivery of hydrophilic therapeutic agents[43].

Solid Lipid Nanoparticles

Solid lipid nanoparticles [SLNs], also known as lipid carriers, have been under intensive research over the past decade. SLNs are extensively studied worldwide and have emerged as versatile nano-sized drug carriers[44].

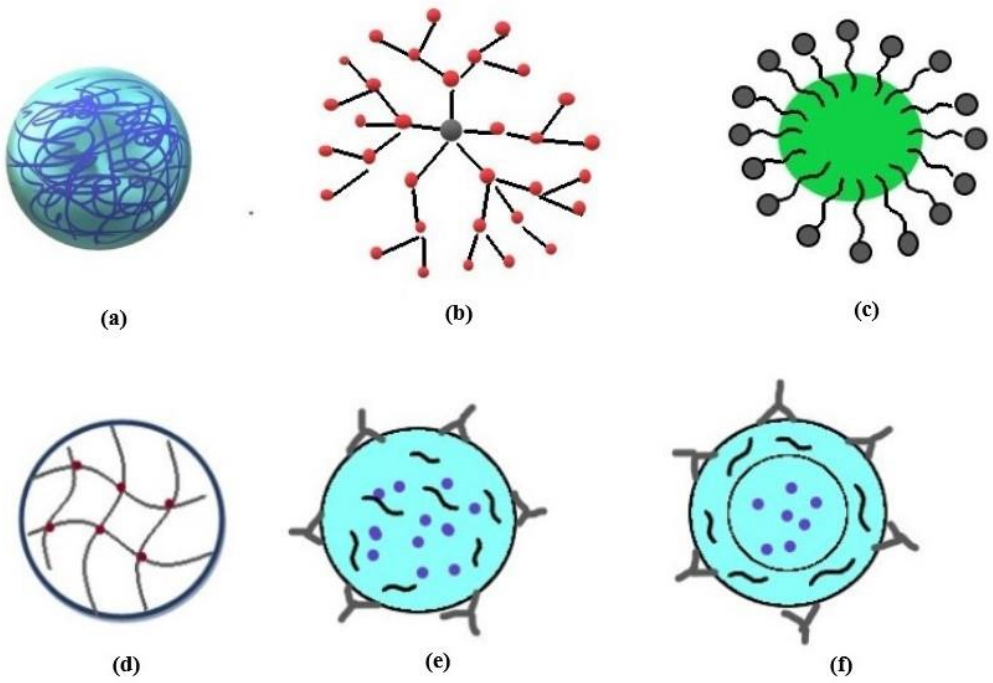

Figure No. 6: Structure of Organic Nanoparticles [a] Polymeric nanoparticles [b] Dendrimers [c] Polymeric Micelles [d] Hydrogels [e] Nanosphere [f]Nanocapsule

INORGANIC NANOPARTICLES

Inorganic nanoparticles have the advantage of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation, although this usually occurs at the expense of poorer biocompatibility and biodegradability[45].

Gold Nanoparticles

Gold nanoparticles occur in various size ranges from 2-100 nm; however, 20-50 nm particle size ranges showed the most efficient cellular uptake. Specific cell toxicity has been shown by 40-50 nm particles[46]. Gold nanoparticles are the clustered particles in the range of a few to several hundreds of nanometers which consist of a gold core and a surface coating[47].

Magnetic Nanoparticles

Magnetic nanoparticles [MNPs] are a very interesting class of metal oxides, which can be magnetized by an external field. Magnetic nanoparticles can be served as contrast agents for magnetic resonance imaging in cancer screening and diagnosis[48].

Silica Nanoparticles

Silica nanoparticle [SiO_2] is the combination of silicon [46.83%] and oxygen [53.33%][49]. Silica nanoparticles have great potential for medicinal use due to their biocompatibility, lack of toxicity, and biodegradability[50].

Quantum Dots

Quantum dots are also known as zero-dimensional semiconductor nanocrystals, with a size in the range of 1–10 nm. Quantum dots have different optical and electrical properties compared to macroscopic materials of the same composition due to their quantum confinement effect, size effect, dielectric confinement effect, macroscopic quantum effect, and surface effect[51]. The main advantage of using quantum dots is that because of controlled size, it is possible to have very precise control over the conductive properties of the material. Quantum dots are particularly significant for optical applications due to their high extinction coefficient[52].

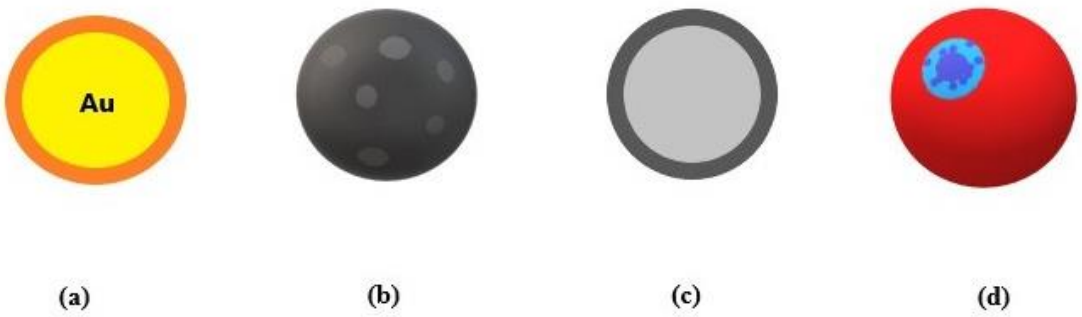

Figure No. 7: Structure of Inorganic Nanoparticles [a] Gold NPs [b] Silica NPs [c] Magnetic NPs [d] Quantum dots

OTHER NANOPARTICLES

Carbon-based Nanoparticles

Fullerenes and carbon nanotubes [CNTs] represent two major classes of carbon-based nanoparticles. Fullerenes contain nanomaterial that is made of the globular hollow cage such as allotropic forms of carbon. They have created noteworthy commercial interest due to their electrical conductivity, high strength, structure, electron affinity, and versatility[53].

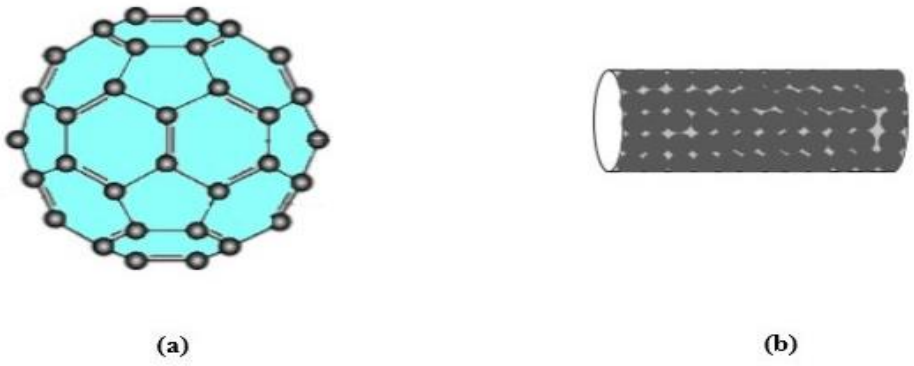

Figure No. 8: Carbon Based Nanoparticles [a] Fullerenes [b] Carbon nanotube

Metal Nanoparticles

Metal nanoparticles [MNPs] have a metal core composed of inorganic metal or metal oxide that is usually covered with a shell made up of organic or inorganic material or metal oxide[54].

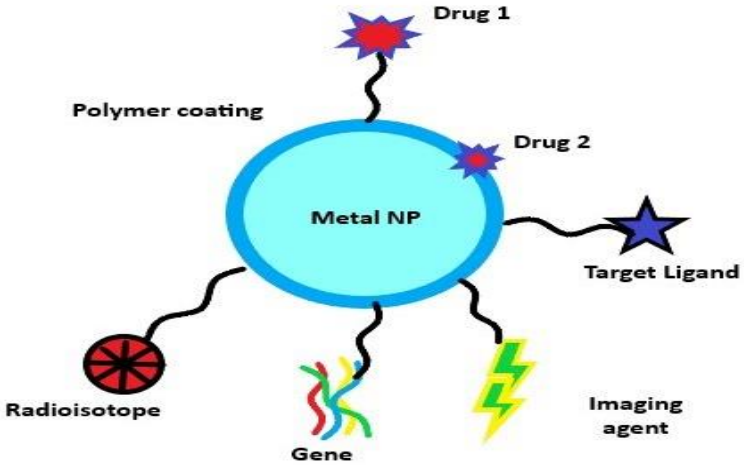

Figure No. 9: Metal Nanoparticles

Silver Nanoparticles

Silver nanoparticles are particles of silver, with particle sizes between 1 and 100 nm in size. While frequently described as being "silver" some are composed of a large percentage of silver oxide due to their large ratio of surface to bulk silver atoms[55].

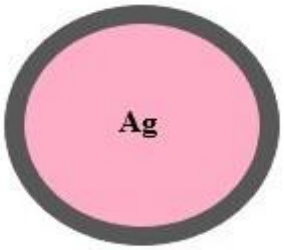

Figure No. 10: Silver Nanoparticles

Ceramic Nanoparticles

Ceramic nanoparticles are inorganic solids made up of oxides, carbides, carbonates, and phosphates. These nanoparticles have high heat resistance and chemical inertness. They have applications in photocatalysis, photodegradation of dyes, drug delivery, and imaging[56].

Figure No. 11: Ceramic Nanoparticle

COMPONENTS USED IN NANOPARTICLES

Polymers used in the preparation

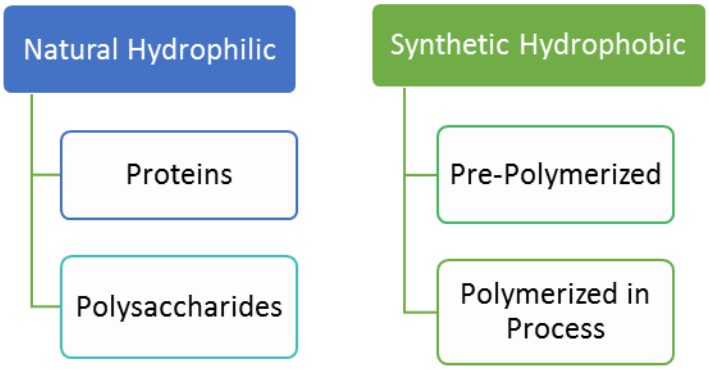

Figure No.12: Natural& Synthetic Hydrophilic Polymers

Natural Hydrophilic Polymers

Natural polymers are a class of polymeric materials that have natural [animal, plant, and algal] origins, consisting primarily of the glycosidic linkage. Natural polymeric raw materials hold a special importance to both industry and our daily life. A global revival concerning the utilization and interdisciplinary research of natural polymers has been spurred on due to the importance of renewable resources, the development of innovative products for science and technology through functional modifications, and abundant availability of natural polymers. The excellent biological and chemical properties of natural polymers make them potentially useful in areas including chemical engineering, environmental engineering, agriculture, nutrition, pharmaceuticals, biomedical, membranes, coatings, food, and horticulture[57].

Natural polymers usually have the advantage of biocompatibility and biodegradability, but because of the distress of purification, their most common limitation is batch to batch variation which causes differences in final formulation[58].

Table No. 1: Different Types of Natural Hydrophilic Polymers and their uses

S.No.		Particulars	Examples	Uses
1.	Natural Hydrophilic Polymers	Proteins	Gelatin	Drug and Gene Carrier
2.			Lectin	Specific Targeting
3.			Albumin	Nanocarriers
4.		Polysaccharides	Alginates	Drug delivery
5.			Dextran	Nanodrug carrier/ Nano biosensors
6.			Chitosan	Gene delivery and carrier for protein release and drugs

Synthetic Hydrophobic Polymers

Synthetic polymers have the advantage of sustained-release over days to several weeks compared to the relatively shorter duration of drug release of natural polymers. Their benefits include the use of organic solvents and the requirement of typical conditions during encapsulation. Polymeric nanoparticles have therefore been widely investigated as drug delivery systems over the past few decades[59].

a. Pre-polymerized

These polymers are pre-polymerized from their monomers and thereafter used for nanocarrier preparation.

b. Polymerized-in-process

These polymers are synthesized from monomers during the preparation of nanoparticles.

Table No. 2: Different types of Synthetic Hydrophobic Polymers and their uses

S.No.		Particulars	Examples	Uses
1.	Synthetic Hydrophobic Polymers	Pre-Polymerized	Poly [e-caprolactone][PECL]	Drug delivery
2.			Poly [lactic acid][PLA]	Sustained release and target delivery
3.			Poly[lactide-co-glycolide] [PLGA]	Drug delivery
4.			Polysterene	Biosensors
5.		Polymerized in process	Poly[butylcyanoakrylates][PBCA]	Nanocarriers
6.			Polyhexylcyanoacrylate[PHCA]	Drug delivery
7.			Poly methyl [methylacrylate][PMMA]	Drug delivery

PREPARATION OF NANOPARTICLES

The selection of the appropriate method for the preparation of nanoparticles depends on the physicochemical character of the polymer and the drug to be loaded[60]. The primary manufacturing methods of nanoparticles from preformed polymer include:

1. Solvent Evaporation Method

2. Salting Out / Emulsion Diffusion Method

3. Emulsion Polymerization Method

4. Spray Drying Method

Solvent Evaporation Method

In this method the preformed polymers such as polylactic acid or poly[D, L-lactic co-glycolic acid] are dissolved in an organic solvent such as chloroform, acetone, or ethyl acetate. The payload drug is generally dissolved in the polymer solution, which is transferred to an aqueous phase that contains a surfactant such as polyvinyl alcohol to form an oil-in-water emulsion[61]. The evaporation of organic solvent can be aided by continuing the homogenization process for a sufficient period. At the end of the homogenization period, the

nanoparticles are collected by ultracentrifugation. A schematic of this method is presented in figure no. 13. Process variables such as polymer-to-organic solvent ratio, type of organic solvent, and homogenization speed and time can be modified to achieve the desired particle size and other properties.

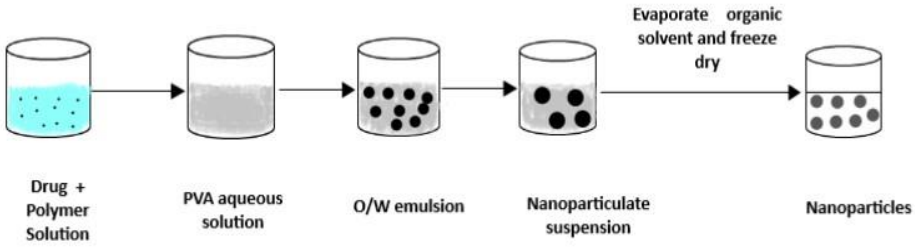

Figure No. 13: Nanoparticle preparation by Solvent Evaporation Method

Salting Out / Emulsion Diffusion Method

In this method, water-soluble polymers are dissolved in a highly concentrated solution of electrolytes or nonelectrolytes to obtain a viscous gel [aqueous phase]. This aqueous gel is added to an organic phase such as acetone to obtain an oil-in-water emulsion under vigorous stirring. The formation of nanoparticles is facilitated by adding an excess amount of water, which diffuses the acetone out. The residual organic solvent is removed by continuous stirring or high-speed homogenization[61]. A schematic of this method is presented in figure no. 14.

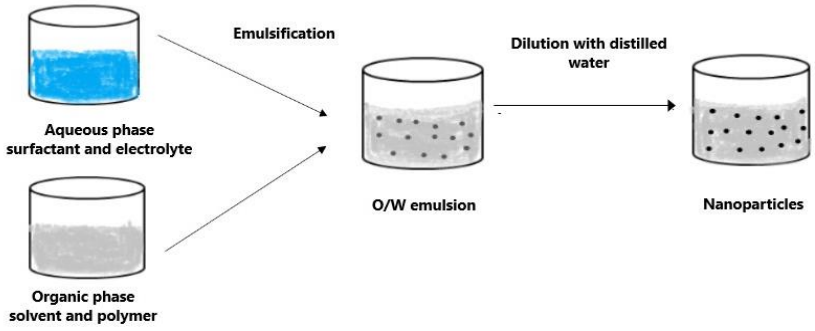

Figure No. 14: Nanoparticle preparation by Salting out Method

Emulsion Polymerization Method

Emulsion polymerization is among the fastest methods available for nanoparticle preparation and is classified into two categories, based on the use of an organic or aqueous continuous phase. The continuous organic phase process adepts the dispersion of monomer into an emulsion or inverse microemulsion, or any nonsolvent as represented in figure no.15. Alternatively, the monomer can be converted to an initiating radical by applying high energy, the chain propagates when this radical monomer collides with another monomer, and before or after termination occurs, phase separation and formation of solid particles can take place. Initially, surfactants and other protective soluble polymers were used to prevent the clogging of the particles in the early stages of polymerization[62].

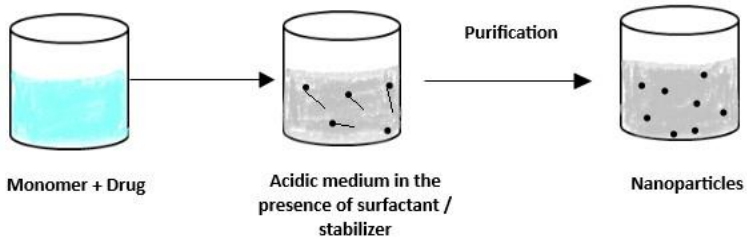

Figure No. 15: Nanoparticle preparation by Polymerization Method

Spray Drying

Spray drying technology produces nanoparticles of relatively low and uniform size, and it is easy to scale up. In this method, the polymer and drugs are dissolved in an organic solvent and sprayed through a nozzle, whereby the droplets are dried simultaneously to obtain the nanoparticles. The size of the nanoparticles can be controlled by modifying the process variables such as spray flow and inlet and outlet temperatures. Spray drying technology can also be combined with freeze-drying figure no. 16. In this modified method, the drug and polymer solution is sprayed through a nozzle into a chamber containing liquid nitrogen and ethanol. The droplets from the nozzle precipitate and collect in the ethanol[61]. The liquid nitrogen evaporates and the organic solvent is extracted by the ethanol, which hardens the nanoparticles. Finally, the nanoparticles are filtered and dried under a vacuum.

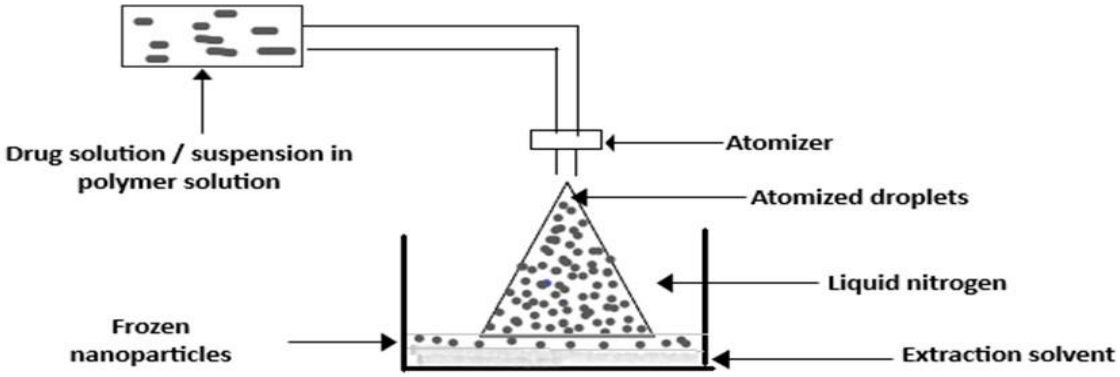

Figure No. 16: Nanoparticle preparation by Spray drying

ROLE OF NANOPARTICLES IN CANCER

Nanotechnology contributes in the management of lung, blood disease and also it counters multiple drug resistance in leukemia by blocking drug efflux from cancer cells and induce efficient delivery of siRNA into lymphocytes to block apoptosis in sepsis[63]. Nanoparticles play an important role in increasing drug concentration in cancer cells by enhancing drug accumulation by passive and active targeting mechanisms as well as by decreasing drug efflux from cancer cells. The passive targeting nanoparticle is the mechanism by which the drugs leak from blood vessels supplying cancer cells and accumulate in the cells by enhanced permeability and retention [EPR] effect. The active targeting nanoparticles, on the other hand, target ligands conjugated on the surface of nanoparticles, resulting in increased cellular uptake by receptor-mediated endocytosis and therefore increased drug accumulation in cancer cells[64].

Types of Targeting by Nanoparticles

Passive Targeting

Passive targeting takes the benefit of permeability of tumour tissues. Leaky and defective vasculature of fast-growing cancerous tissues can be taken into advantage to achieve passive targeting of chemotherapeutic drugs [figure no.17]. This is called as enhanced permeation and retention effect or EPR effect[17]. Example: Passive targeting of Genoxol-PM, paclitaxel loaded poly[lactic acid]- blockpoly[ethylene glycol] polymeric micelle-formulation.

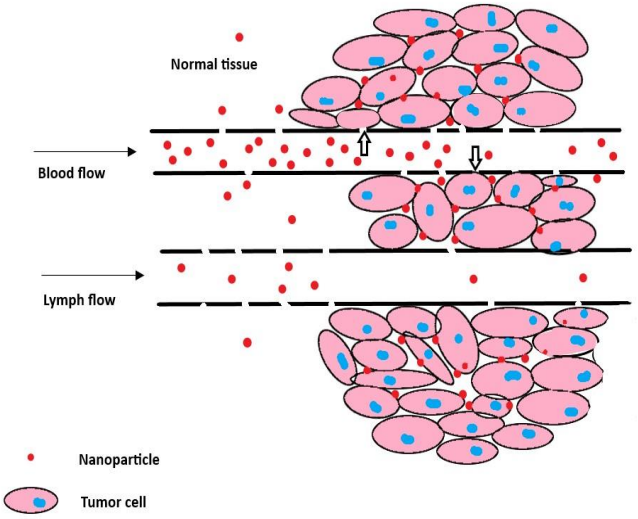

Figure No. 17: Schematic diagram showing EPR effect of nanoparticles in tumours

Active Targeting

Active targeting is usually achieved by conjugating the nanoparticle to a targeting moiety, thereby allowing the preferential accumulation of chemotherapeutic drugs in the tumour tissue, within individual cancer cells, or even within intracellular organelles. The targeting moiety/ligand can be antibodies [mAbs], aptamers, small molecules [Folate molecules] and proteins [Transferrin] [figure no. 18][17].

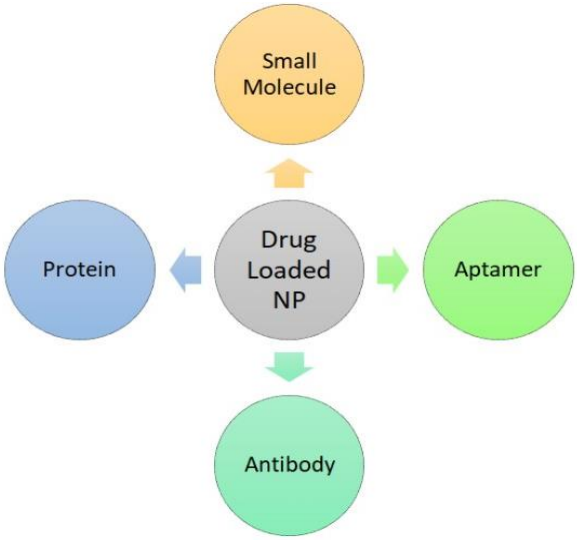

Figure No.18: Four different strategies for active targeting of nanoparticle based drug delivery systems

Table No. 3: Reported Patents in Nanoparticles

S.No.	Patent No.	Nanoparticles	Patent Title	Inventors	Outcome	Ref.
1.	US 9,993,437 B2 US9993437B2	Silica nanoparticles	Mesoporous silica nanoparticles for biomedical applications	Monty Liong, Jie Lu, FuyuhikoTamanoi, Jeffrey I. Zink, Andre E. Nel	A submicron structure for delivering anticancer drugs into cancer cells, comprising: a silica body defining a plurality of pores, where said plurality of pores are suitable to receive anticancer molecules therein and to subsequently release said anticancer molecules therefrom, said silica body further defining an outer surface between pore openings of said plurality of pores.	65
2.	US 9,574,136 B2	Nanosponges	Nanoparticles, Nanosponges, Methods of Synthesis, and Methods of Uses	Kun Lian	A method for making metallic-core carbon-shell nanoparticles said method comprises the steps: [a] impregnating biological fibers with a solution of metal ions in an aqueous or non-aqueous solvent; [b] removing the solvent, while leaving at least some of the metal ions impregnated in the fibers.	66
3.	US 8,679,539 B2	Poly [alkyl-cyanoacrylate]	Drug-loaded poly [alkyl-	Yu-Der Lee Chi-Yu Huang	The present invention provides a process for preparing drug-loaded poly[alkyl-cyanoacrylate] nanoparticles with high loading and	67

		nanoparticles	cyanoacrylate] nanoparticles and process for the preparation thereof	Chih-Ming Chen	encapsulation efficiencies. Particularly for the highly hydrophobic agents, the solubility of encapsulants in polymerization medium critically determines the drug-loading efficiency of carriers. To increase the loading and encapsulation efficiencies of PACA nanoparticles, the miniemulsion polymerization process is utilized consequently.	
4.	US 9.234,078 B2	Gold nanoparticles	Conjugated gold nanoparticles	Duxin Sun, Hongwei Chen, Wei Qian, Yong Che, Masayuki Ito, Hayley Paholak, Kanokwan Sansanaphongpricha	The present invention provides methods of generating unsaturated conjugated gold nanoparticles by mixing naked gold nanoparticles with the first type of attachment molecules at a molar ratio such that the attachment molecules attach to the naked gold particles at a density level below the saturation level of the naked gold particles [e.g., at a saturation level of 1-99%]	68

5.	US 7.625,637 B2	Metal nanoparticles	Production of metal nanoparticles from precursors having low reduction potentials	Hyungrak Kim	The present invention provides an improved process for forming metallic nanoparticles from metal pre cursors having a reduction potential less than about 0.6 V. In one embodiment, the invention is to a nanoparticle, comprising: a core having a largest dimension less than about 10 nm, and a metal layer substantially surrounding the core and having a largest dimension less than about 200 nm.	69
6.	US 10,662,060 B2	Lipid-based nanoparticles	Manufacture of lipid-based nanoparticles using a dual asymmetric centrifuge	Ulrich Massing	A process for forming a lipid-based nanoparticle, the process comprising homogenizing a lipid component with an aqueous component in a dual asymmetric centrifuge [DAC] for a centrifugation time, wherein the lipid component is not performed as a lipid-based nanoparticle before homogenization.	70
7.	US 8,314,078 B2	Silver nanoparticles	Silver nanoparticles as anti-microb	Shaker A. Mousa, Robert J. Linhardt	The present invention provides a method for forming a silver nanocomposite, comprising: chemically reacting silver nitrate with a reducing agent to form a silver nanoparticle conjugated to the	71

			ial		reducing agent, wherein the reducing agent is selected from the group consisting of a glycosaminoglycan [GAG] or glucose.	
8.	US 9.211,250 B2	Polymeric micelles	Heterogeneous polymeric micelles for intracellular delivery	Paul Johnson, Patrick S. Stayton, Allan S. Hoffman, Robert Overell, Anna Gall, Mary Prieve, Amber Paschal, Charbel Diab, Priyadarsi De	The present inventions provide, in various aspects more fully enumerated below, heterogeneous polymeric micelles, compositions comprising heterogeneous polymeric micelles, methods for preparing such micelles and such compositions, and various methods for using such micelles and such compositions. More particularly, preferred aspects of the inventions are directed to compositions comprising a heterogeneous polymeric micelle and an agent associated with the micelle.	72
9.	US 8,093.474 B2	Nanospheres	Metallic nanospheres embedded in nanowires initiated on nanost	Saleem Zaidi, Joseph W. Tringe, Ganesh Vanamu, Rajiv Prinja	A nanostructure according to one embodiment comprises a substrate having an area with a nanofeature; and a nanowire extending from the nanofeature, the nanowire having metallic spheres formed therein, the spheres being characterized as having at least one of about a uniform diameter and about a uniform spacing therebetween.	73

			ructure s and metho ds for synthe sis			
10.	US 2011/0 251547 A1	Magnet ic nanopar ticles	Transf ection with magne tic nanop article s and ultraso und	James XING, Wiebing Lu	This invention comprises a method to deliver biomolecules or other molecules of interest into cells using a molecular delivery vehicle, which is magnetically drivable and capable of binding to at least one bio-molecule. This molecular delivery vehicle can pass through the cell wall with the aid of an external magnetic force.	74

CHALLENGES FOR NANOPARTICLE-BASED DRUG DELIVERY IN LUNG CANCER THERAPY

The past decade has witnessed tremendous growth and development of drug delivery technology utilizing nanoparticle systems. It is expected that the ongoing research efforts in nanomedicine will continue to lead towards safe, efficient, and feasible drug delivery and highly sensitive and improved imaging agents for diagnostic and disease monitoring applications. However, nanomedicine research is facing numerous challenges in bridging rapidly developing novel ideas and translating them into clinical practice. Synthesizing nanoparticle drug delivery systems has always been complicated by designing an appropriate size to carry an effective drug/gene payload and the ability to target the right place. Inappropriate size distribution, undefined structure/shape, poor biocompatibility, and improper surface chemistry are possible risk factors in the biological environment. It has been operose to devise the ideal nanoparticle system for drug delivery to the lungs due to the variability in the physicochemical properties and biological behavior of the particles[75]. Several obstacles including immune reaction, rate of clearance from circulation, efficiency in targeting, and ability to cross biological barriers will follow when these nanoparticle systems

enter the preclinical and clinical testing arenas. Having a solid understanding of the biological behavior of nanoparticles is imperative to achieving the highest drug delivery efficiency.

CONCLUSION

Despite rapidly growing research concerning nanomaterials in cancer treatment, some issues remain unsolved. Toxicity is still one of the main concerns of nanomaterials. Because of the extremely small size, physiological barriers can be penetrated, which may pose potential health hazards. Evidence shows that cellular membranes, organelles, and DNA suffer from free radicals caused by nanoparticles[76]. Nanomaterials delivered intracellularly might stimulate an immune response by reacting with cell surface receptors. As referred to above, nanomaterial toxicity relates to many factors and thus, modification to reduce toxicity is essential in the fabrication process.

REFERENCES

1. Sivarajakumar R, Mallukaraj D, Kadavakollu M, Neelakandan N, Chandran S, Bhojaraj S, Karri VV. Nanoparticles for the treatment of lung cancers. Journal of Young Pharmacists. 2018 Jul 1;10(3):276.
2. Bandyopadhyay A, Das T, Yeasmin S. Nanoparticles in Lung Cancer Therapy-Recent Trends. Springer India; 2015.
3. Mathur G, Nain S, Sharma PK. Cancer: an overview. Acad. J. Cancer Res. 2015;8:1.
4. Sawant S, Shegokar R. Cancer research and therapy: Where are we today. Int J Cancer Ther Oncol. 2014;2(4):02048.
5. Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. Cancer therapy. 2011 Jan 1;8.
6. Sinha AK, Jain RR, Pradhan SK. Epidemiological Trend of Cancer among Patients at Regional Cancer Center, Dr. BR Ambedkar Memoria l Hospital, Raipur: A Tertiary Care Hospital of Central India. International Journal of Health Sciences & Research. 2018;8(2).
7. Zappa C, Mousa SA. Non-small cell lung cancer: current treatment and future advances. Translational lung cancer research. 2016 Jun;5(3):288.
8. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, Petrella F, Spaggiari L, Rosell R. Non-small-cell lung cancer. Nature reviews Disease primers. 2015 May 21;1(1):1-6.
9. Kotiyal S, Bhattacharya S. Lung Cancer Stem Cells and Their Therapeutic Targeting.
10. Carrasco-Esteban E, Domínguez-Rullán JA, Barrionuevo-Castillo P, Pelari-Mici L, Leaman O, Sastre-Gallego S, López-Campos F. Current role of nanoparticles in the treatment of lung cancer. Journal of Clinical and Translational Research. 2021 Apr 22;7(2):140.
11. Cryer AM, Thorley AJ. Nanotechnology in the diagnosis and treatment of lung cancer. Pharmacology & therapeutics. 2019 Jun 1;198:189-205.
12. Käsmann L, Eze C, Taugner J, Roengvoraphoj O, Dantes M, Schmidt-Hegemann NS, Schiopu S, Belka C, Manapov F. Chemoradioimmunotherapy of inoperable stage III non-small cell lung cancer: immunological rationale and current clinical trials establishing a novel multimodal strategy. Radiation Oncology. 2020 Dec;15(1):1-4.
13. Desai C, Mehta A, Mishra D. Usage patterns of biomarkers in non-small-cell lung cancer patients in India: Findings from a systematic review and survey. Lung India: Official Organ of Indian Chest Society. 2014 Jul;31(3):249.
14. Myers DJ, Wallen JM. Cancer, lung adenocarcinoma. StatPearls [Internet]. 2020 Jun 26.
15. Siddiqui F, Siddiqui AH. Cancer, lung. StatPearls [Internet]. 2020 Apr 12.

16. Sholl LM. Large-cell carcinoma of the lung: a diagnostic category redefined by immunohistochemistry and genomics. Current opinion in pulmonary medicine. 2014 Jul 1;20(4):324-31.
17. Sarkar S, Osama K, Mohammad Sajid Jamal Q, Amjad Kamal M, Sayeed U, Khan KA, Siddiqui H, Akhtar S. Advances and implications in nanotechnology for lung cancer management. Current drug metabolism. 2017 Jan 1;18(1):30-8.
18. Kalemkerian GP, Akerley W, Bogner P, Borghaei H, Chow LQ, Downey RJ, Gandhi L, Ganti AK, Govindan R, Grecula JC, Hayman J. Small cell lung cancer. Journal of the National Comprehensive Cancer Network. 2013 Jan 1;11(1):78-98.
19. Abdelhamid K, Kakourou A, Degrauwe N, Nikolopoulou A, Bouchaab H, Peters S, Nguyen-Ngoc T, Mederos N. Small-cell lung cancer: management and novelties. Revue Médicale Suisse. 2020 May 1;16(695):1079-85.
20. Bernhardt EB, Jalal SI. Small cell lung cancer. Lung Cancer. 2016:301-22.
21. Fournel L, Janet-Vendroux A, Canny-Hamelin E, Mansuet-Lupo A, Guinet C, Bobbio A, Damotte D, Alifano M. Malignant pleural mesothelioma: The role of surgery. Revue de pneumologieclinique. 2018 Oct 11;74(5):351-8.
22. Bibby AC, Tsim S, Kanellakis N, Ball H, Talbot DC, Blyth KG, Maskell NA, Psallidas I. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. European Respiratory Review. 2016 Dec 1;25(142):472-86.
23. Hashimoto K, Okuma Y, Hosomi Y, Hishima T. Malignant mesothelioma of the pleura with desmoplastic histology: a case series and literature review. BMC cancer. 2016 Dec;16(1):1-6.
24. Mohanraj VJ, Chen Y. Nanoparticles-a review. Tropical journal of pharmaceutical research. 2006;5(1):561-73.
25. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems. Journal of occupational medicine and toxicology. 2007 Dec;2(1):1-6.
26. Basumallik N, Agarwal M. Small cell lung cancer. InStatPearls [Internet] 2020 Jul 17. StatPearls Publishing.
27. Jadhav SD, Shaikh IA. Synthesis of Nanoparticles an Overflew, a Review Article.
28. Nicolini F, Bocchini M, Bronte G, Delmonte A, Guidoboni M, Crinò L, Mazza M. Malignant pleural mesothelioma: state-of-the-art on current therapies and promises for the future. Frontiers in oncology. 2020 Jan 24;9:1519.
29. Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Research in pharmaceutical sciences. 2014 Nov;9(6):385.
30. Kapil A, Aggarwal G, Harikumar SL. Nanotechnology in novel drug delivery system. Journal of Drug Delivery and Therapeutics. 2014 Sep 14;4(5):21-8.
31. Godwin MA, Shri KM, Balaji M. Nanoparticles and their applications-A mini review. International journal of Research in Engineering and Bioscience. 2015;3(5):11-29.
32. Kumar R, Lal S. Synthesis of organic nanoparticles and their applications in drug delivery and food nanotechnology: a review. J Nanomater Mol Nanotechnol 3: 4. of. 2014;11:2.
33. Zhou Q, Zhang L, Wu H. Nanomaterials for cancer therapies. Nanotechnology Reviews. 2017 Oct 1;6(5):473-96.
34. Ranjit K, Baquee AA. Nanoparticle: An overview of preparation, characterization and application. Int Res J Pharm. 2013;4(4):47-57.
35. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati-Koshki K, Pashaei-Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale research letters. 2014 Dec;9(1):1-0.
36. Nimesh S. Gene therapy: Potential applications of nanotechnology. Elsevier; 2013 Oct 31.
37. García MC. Nano-and microparticles as drug carriers. InEngineering Drug Delivery Systems 2020 Jan 1 (pp. 71-110). Woodhead Publishing.
38. Singh A, Pandey K. Advanced drug delivery systems in kidney cancer. InAdvanced Drug Delivery Systems in the Management of Cancer 2021 Jan 1 (pp. 155-181). Academic Press.
39. Subramani K, Mehta M. Nanodiagnostics in microbiology and dentistry. InEmerging Nanotechnologies in Dentistry 2018 Jan 1 (pp. 391-419). William Andrew Publishing.

40. Aghebati-Maleki A, Dolati S, Ahmadi M, Baghbanzhadeh A, Asadi M, Fotouhi A, Yousefi M, Aghebati-Maleki L. Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. Journal of cellular physiology. 2020 Mar;235(3):1962-72.
41. Yadav HK, Almokdad AA, Sumia IM, Debe MS. Polymer-based nanomaterials for drug-delivery carriers. InNanocarriers for drug delivery 2019 Jan 1 (pp. 531-556). Elsevier.
42. Rana V, Sharma R. Recent advances in development of nano drug delivery. Applications of Targeted Nano Drugs and Delivery Systems. 2019 Jan 1:93-131.
43. Tambe P, Sayed N, Paknikar KM, Gajbhiye V. Poly (Phospho Ester) and Poly (Phosphazene) Nanoparticles as a Promising Tool for Anticancer Therapeutics. InPolymeric Nanoparticles as a Promising Tool for Anti-cancer Therapeutics 2019 Jan 1 (pp. 123-146). Academic Press.
44. Newton AM, Kaur S. Solid lipid nanoparticles for skin and drug delivery: Methods of preparation and characterization techniques and applications. InNanoarchitectonics in Biomedicine 2019 Jan 1 (pp. 295-334). William Andrew Publishing.
45. In GK, Nieva J. Emerging chemotherapy agents in lung cancer: nanoparticles therapeutics for non-small cell lung cancer. Transl Cancer Res. 2015 Aug 26;4(4):340-55.
46. Pandey P, Dahiya M. A brief review on inorganic nanoparticles. J Crit Rev. 2016;3(3):18-26.
47. Lakshmipriya T, Gopinath SC. Introduction to nanoparticles and analytical devices. InNanoparticles in Analytical and Medical Devices 2021 Jan 1 (pp. 1-29). Elsevier.
48. Yazdi MK, Zarrintaj P, Khodadadi A, Ganjali MR, Bagheri B, Habibzadeh S, Saeb MR, Mozafari M. Magnetic nanoparticles in cancer therapy. InMagnetic Nanoparticle-Based Hybrid Materials 2021 Jan 1 (pp. 425-445). Woodhead Publishing.
49. Buyuknalcaci FN, Polat Y, Negawo TA, Döner E, Alam MS, Hamouda T, Kilic A. Carbon nanotube-based nanocomposites for wind turbine applications. InPolymer-based Nanocomposites for Energy and Environmental Applications 2018 Jan 1 (pp. 635-661). Woodhead Publishing.
50. Downing MA, Jain PK. Mesoporous silica nanoparticles: synthesis, properties, and biomedical applications. InNanoparticles for Biomedical Applications 2020 Jan 1 (pp. 267-281). Elsevier.
51. de la Calle I, Romero-Rivas V. The Role of Nanomaterials in Analytical Chemistry: Trace Metal Analysis. InApplications of Nanomaterials 2018 Jan 1 (pp. 251-301). Woodhead Publishing.
52. Ealia SA, Saravanakumar MP. A review on the classification, characterisation, synthesis of nanoparticles and their application. InIOP Conference Series: Materials Science and Engineering 2017 Nov 1 (Vol. 263, No. 3, p. 032019). IOP Publishing.
53. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A. Nanoparticle-based drug delivery in cancer therapy and its role in overcoming drug resistance. Frontiers in Molecular Biosciences. 2020;7.
54. Khan SA. Metal nanoparticles toxicity: Role of physicochemical aspects. InMetal Nanoparticles for Drug Delivery and Diagnostic Applications 2020 Jan 1 (pp. 1-11). Elsevier.
55. Mody VV, Siwale R, Singh A, Mody HR. Introduction to metallic nanoparticles. Journal of Pharmacy and Bioallied Sciences. 2010 Oct;2(4):282.
56. Yetisgin AA, Cetinel S, Zuvin M, Kosar A, Kutlu O. Therapeutic nanoparticles and their targeted delivery applications. Molecules. 2020 Jan;25(9):2193.
57. Halake K, Kim HJ, Birajdar M, Kim BS, Bae H, Lee C, Kim YJ, Kim S, Ahn S, An SY, Jung SH. Recently developed applications for natural hydrophilic polymers. Journal of industrial and engineering chemistry. 2016 Aug 25;40:16-22.
58. Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as drug delivery systems; pros and cons. Trends in Pharmaceutical Sciences. 2019 Mar 1;5(1):7-24.
59. Fatima S, Quadri SN, Parveen S, Beg S, Rahman M, Ahmad FJ, Abdin MZ. Polymeric nanoparticles for potential drug delivery applications in cancer. InNanoformulation Strategies for Cancer Treatment 2021 Jan 1 (pp. 65-88). Elsevier.
60. Pal SL, Jana U, Manna PK, Mohanta GP, Manavalan R. Nanoparticle: An overview of preparation and characterization. Journal of applied pharmaceutical science. 2011 Nov;1(6):228-34.
61. Kammari R, Das NG, Das SK. Nanoparticulate systems for therapeutic and diagnostic applications. Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices. 2017 Jan 1:105-44.

62. George A, Shah PA, Shrivastav PS. Natural biodegradable polymers based nano-formulations for drug delivery: A review. International journal of pharmaceutics. 2019 Apr 20;561:244-64.
63. Vinod P, Siddik U, Viswanathan Mariammal Berlin G, Chandrasekharan G. Nanoparticles in drug delivery and cancer therapy: the giant rats tail. Journal of Cancer Therapy. 2011 Aug 31;2011.
64. Muhamad N, Plengsuriyakarn T, Na-Bangchang K. Application of active targeting nanoparticle delivery system for chemotherapeutic drugs and traditional/herbal medicines in cancer therapy: a systematic review. International journal of nanomedicine. 2018;13:3921.
65. Liong M, Lu J, Tamanoi F, Zink JI, Nel A, inventors. Mesoporous silica nanoparticles for biomedical applications. United States patent US 9,993,437. 2018 Jun 12.
66. Lian K, inventor; Louisiana State University, Mechanical College, assignee. Nanoparticles, nanosponges, methods of synthesis, and methods of use. United States patent US 9,574,136. 2017 Feb 21.
67. Lee YD, Huang CY, Chen CM, inventors; TONG SHEN ENTERPRISE Co Ltd, assignee. Drug-loaded poly (alkyl-cyanoacrylate) nanoparticles and process for the preparation thereof. United States patent US 8,679,539. 2014 Mar 25.
68. Sun D, Chen H, Qian W, Che Y, Ito M, Paholak H, Sansanaphongpricha K, inventors; IMRA America Inc, University of Michigan, assignee. Conjugated gold nanoparticles. United States patent US 9,234,078. 2016 Jan 12.
69. Kim H, inventor; Cabot Corp, assignee. Production of metal nanoparticles from precursors having low reduction potentials. United States patent US 7,625,637. 2009 Dec 1.
70. Massing U, inventor. Manufacture of lipid-based nanoparticles using a dual asymmetric centrifuge. United States patent US 10,662,060. 2020 May 26.
71. Mousa SA, Linhardt RJ, inventors; Vascular Vision Pharmaceutical Co, assignee. Silver nanoparticles as anti-microbial. United States patent US 8,314,078. 2012 Nov 20.
72. Johnson P, Stayton PS, Hoffman AS, Overell R, Gall A, Prieve M, Paschal A, Diab C, De P, inventors; University of Washington, PhaseRx Inc, assignee. Heterogeneous polymeric micelles for intracellular delivery. United States patent US 9,211,250. 2015 Dec 15.
73. Zaidi S, Tringe JW, Vanamu G, Prinja R, inventors; Lawrence Livermore National Security LLC, assignee. Metallic nanospheres embedded in nanowires initiated on nanostructures and methods for synthesis thereof. United States patent US 8,093,474. 2012 Jan 10.
74. James XI, Lu W, inventors; Intelligentnano Inc, assignee. Transfection with magnetic nanoparticles and ultrasound. United States patent application US 13/127,259. 2011 Oct 13.
75. Babu A, Templeton AK, Munshi A, Ramesh R. Nanoparticle-based drug delivery for therapy of lung cancer: progress and challenges. Journal of Nanomaterials. 2013 Oct;2013.
76. Cheng Z, Li M, Dey R, Chen Y. Nanomaterials for cancer therapy: current progress and perspectives. Journal of Hematology& Oncology. 2021 Dec;14(1):1-27.

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