



Applications Of Nanomaterials In Improving The Traditional Diagnostic Approach

Jaya Chaudhary¹, Anushka Tyagi², Shubham Bhatt³, Anuj Pathak⁴, N.G. Raghavendra Rao^{5*}, Sonal Mittal⁶

ABSTRACT

The broad art of uses of nanomaterials or nanoparticles and nanodevices that are used in medical healthcare to diagnose and cure a variety of diseases has recently developed as a result of recent advancements in pharmaceutical research. So, in this review article, we will discuss the various art of nanomaterials that are used in various forms to develop various nano-devices and nano technologies that are widely used in medical applications, such as cantilevers, which are highly stable devices that are integrated into highly sensitive disease markers in diagnostic detectors and display reliable performance for a long time. These nanoparticles are also employed in the creation of various dosage forms that are used to either cure or diagnose diseases. These nanotechnologies are frequently used as sophisticated tools or gadgets in the early identification of cancer and atherosclerosis in the human body, where subsequent therapy such as nano-surgery may be used to cure them. These are well-known superior materials that are necessary for many fields due to their nano size.

Keywords:-Atherosclerosis, Medical applications, Nanomaterials, Nanotechnologies, Nanodevices

^{1,2,3,4,5,*6}KIET School of Pharmacy, KIET Group of Institutions, Delhi-NCR, Ghaziabad, UttarPradesh, 201206, India

*Correspondence Address:- Dr.N.G.Raghavendra Rao, Professor,

*KSOP, KIET Group of Institutions, NCR-Delhi, Meerut Road, Muradnagar, Ghaziabad - 201206, U.P, India.
Email Address: raghavendra.rao@kiet.edu, drnraghu@gmail.com, Contact No: +91 9966794479.

1.0 INTRODUCTION OF NANOMATERIALS

The recent development in pharmaceutical science develops the different art of applications of nanomaterials or nanoparticles and nano-devices that are applied in medical healthcare to diagnose varieties of diseases and treat them very well. So this review article going to describe the different art of nanomaterials that are used in different forms to develop varieties of nano-devices and nano technologies that are widely applied in the medical applications such as cantilevers which is a highly stable device that is integrated into highly sensitive disease marker in the diagnostic detectors and display reliable performance for a long period of time.

Bioaffinity developments have made it possible to develop personalised NP medications for tumor therapy, integrated nanodevices for early cancer diagnosis and treatment, and NP probes for molecular and cellular imaging. With the help of these developments, it may be possible to identify and treat patients' molecular profiles of genetic and protein biomarkers and give them with customised medicines. These nanomaterials are also used in the development of different dosage forms that are either used to treat the disease or mark them or detection. These nanotechnologies are widely preferred to use as sophisticated tool or devices in detection of cancer and atherosclerosis at their early stage in human body and further treatment such as nanosurgery can be performed to cure them. Due to their nano size these are well known superior materials and indispensable in many areas.

NANOTECHNOLOGY BASED APPROACH USED IN THE TREATMENT OF DISEASES

Nanotechnology used for Cardiovascular Disease (CVDs)

Cardiovascular diseases (CVDs) are the leading cause of death. In 2019, 18.6 million people worldwide passed away from cardiovascular disease (S. S. Virani, A. Alonso, 2021). Changes in the normal functioning of the heart and its supporting structures frequently cause heart disease and its accompanying conditions, such as atherosclerosis, arrhythmia, coronary heart

disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism.

The main cause of this reported distress is an inactive lifestyle with little to no physical workout, which has been shown as the key contributor to CVD in humans (J. W. Rhee and J. C. Wu, 2013). Designer nanoparticles with targeting ligands have been developed for plaque and heart-targeted medication delivery as a means of preventing CVD. These nanocarriers transport drugs to a specific therapeutic spot without harming normal tissue. Instability, poor bioavailability, poor solubility, poor absorption, and negative side effects are barriers to conventional, systemic medication administration that are intended to be removed using nanotechnology-based methods (W. Jiang and H. Liu, 2016).

Understanding and utilising modern technologies will create a secure and reliable platform for the controlled, targeted distribution of actives that will reduce the incidence of lipid disorders and other diseases (H. Liu and T. J. Webster, 2007). The limitations associated with employing conventional biomaterials were overcome using nanomaterials (O. Pagliarosi, V. Picchio, 2020). Need for a Nano-cardiovascular Targeting Approach. Additionally, combining new technologies with nanotechnology will alter the way CVDs are treated. Numerous researchers had created nanomaterials that resembled the extracellular matrix and sped up the healing process (N. Kapil, Y. H. Datta, 2017).

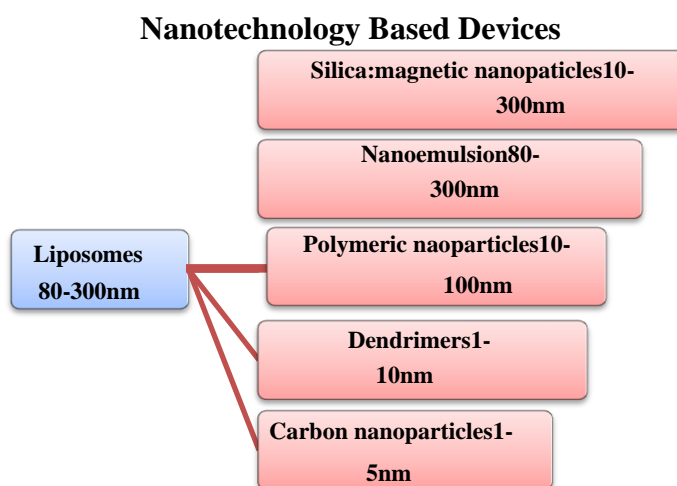
The main goals of contemporary CVD therapy are to restore regular blood flow and to prevent recurrent cardiovascular shocks. Treatment with statins lowers atherosclerotic plaque growth and thickness, as well as its effects on exterior elastic membranes, fibrous and dense calcium volumes (S. C. Johnston, J. D. Easton, 2018). First-line antiplatelet drugs for the prevention of cardiovascular disease include aspirin and clopidogrel, which work to reduce clot formation and platelet aggregation (S. C. Johnston, J. D. Easton, 2018).

According to reports, people who received both clopidogrel and aspirin after having a small ischemic stroke saw a lower risk of significant ischemic events than those who only received aspirin (K. Raj and S. Malini,

2018). Additionally, it has been discovered that ethidium bromide is displaced from its DNA binding site when it binds to the calf thymus DNA signal that indicated clopidogrel bisulfate (D. A. Tonetti, B. T. Jankowitz, 2020). Additionally, aspirin reduces the availability of clopidogrel bisulfate in basic medium due to its reduced acidity (P. Stano, S. Bufali, 2004).

Antiplatelet therapy has to be improved because of its numerous unfavourable side effects and limited patient compliance (B.

Alotaibi, E. Tousson, 2021). Additionally; some patients' antiplatelet medication reactions are subpar, which negatively affects their long-term prognosis. People who respond poorly to clopidogrel after an acute myocardial infarction are more likely to experience subsequent cardiovascular events. This result is in line with earlier research (N. K. Egilmez, Y. Iwanuma, 1996). This shows the promise for nano-medicine and the necessity for technological advancements.



Liposomes

For the targeted delivery of medications to distant organs, liposomes are the unilamellar or multilamellar lipid membrane carries both hydrophilic and lipophilic medicines. The vesicle's spherical form closely matches the cell membrane in structure. Liposomes reduce the toxicity that results from entrapment and are biocompatible and biodegradable (Jabir NR, Tabrez S, 2004). Thin-film hydration was used to create the liposomes utilising DSPC (di-stearoylphosphatidylcholine), DSPG (di-stearoylphosphatidylglycerol), and cholesterol (Gao XH, Cui YY, 2004). In mice, the liposome formulation demonstrated a 50% reduces cytotoxicity and death rate. Additionally, the liposomes reduced the number of inflammatory neutrophils and inflammatory monocyte infiltration in the heart while increasing angiogenesis (Soutschek J, Akinc A, 2004).

Nanoparticles

Smaller sizes and the ability to surface functionalize with new side chains define NP. Their reduced size provides a significant surface area for binding and interaction (Morrissey DV, Lockridge JA, 2005). Since, the NPs may be made both hydrophilic and hydrophobic, they can easily pass through tight junctions. The cardiac magnetic resonance that aids in the diagnosis of atherosclerosis can be improved by targeting macrophage scavenger receptors with NPs conjugated with d-block and f-block components (Matsumura Y, 2004). The Ehrlich ascites carcinoma cardiac toxicity can also be treated by entrapping natural medicines like curcumin inside the NPs (Flynn MA, Casey DG, 2004). The amount of tumor cells decreased and the amount of ascites fluid's apoptotic cells significantly increased after the administration of NPs. The cardiac indicators were also reduced by the therapy (Flynn MA, Casey DG, 2004).

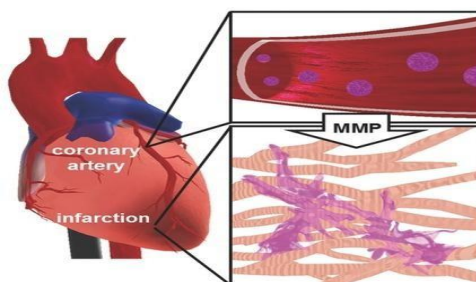


Figure.1.0. Application of nanoparticles intravenously at the site of acute myocardial infarction using targeting method

In a rat model of an acute myocardial infarction, it is explained how to retain intravenously delivered nanoparticles at the location of the infarction. By acting on enzyme-responsive peptide-polymer amphiphiles, matrix metalloproteinase (MMP-2 and MMP-9), which are up-regulated in heart tissue after myocardial infarction, induce them to morphological shift from spherical discrete materials to network-like assemblies (Verma UN, Surabhi RM, 2008).

Nanofibers

The term "nanofibers" refers to fibres with a diameter between 1 and 1000. The nanofibers are used for regenerating and engineering heart tissue. For the purpose of regenerative engineering and the therapy of dilated cardiomyopathy, many researchers combined nanofibers with drug elution and implanted cells (De Jonge J, Holtrop M, 2006). Using PLGA-based nano-fiber scaffolds, the human inducible pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were cultivated on the cardiac patch (Wilson DS, Dalmaso G, 2010).

Another study that was resistant to arrhythmogenesis and supported the use of PLGA in seeding ventricular cardiomyocytes produced from embryonic stem cells did so as well (Fonseca C, Simoes S, 2002). Wu et al. developed an anisotropic 3D cellular cardiac structure for tissue regeneration. Polycaprolactone, silk fibroin, and carbon nanotubes are the primary components of nanofiber yarn (Koziara JM, Whisman TR, 2006). The yarn assisted in the maturation of the cardiomyocyte. The three dimensions of the hydrogel provided a context (Koziara JM, Whisman TR, 2000).

Dendrimers

The word "dendrimer," which appropriately describes the structure of these frequently branching molecules, comes from the Greek word "Dendron," which means "tree" (Crampton and Simanek 2007). Dendrimers are special because of their multibranched, three-dimensional design, low polydispersity, and excellent functioning (Sherje et al. 2018). Dendrimers provide a number of obvious advantages over other nanotechnologies when used as non-viral vectors for medicinal purposes due to their great solubility, enhanced stability, lower immunogenicity, and capacity to assist the actual transport of therapeutic molecules, DNA, and RNAs, they are supercilious to other viral and non-viral analogues. (Mendes et al 2017).

Due to the large number of branches at their surface, dendrimers frequently have highly charged exteriors; this can frequently result in either a highly cationic or highly anionic nature and, if not properly addressed, can cause toxicity difficulties (Jain et al. 2010). In order to tackle CVD, researchers have turned to gene therapy.

As a result, researchers have researched methods to employ cationic liposomes and other nanocarriers to control the up regulation of inflammatory genes as well as techniques to deliver genetic material to the targeted areas more efficiently. Polyanionic DNA is transported to cells by both dendrimers and cationic liposomes (Bhadra D, Bhadra S, 2003) A G5 dendrimer with an ethylenediamine core was used to study gene shift in mouse cardiac grafts. G5 dendrimer expression increased 1000-fold in myocytes and graft filtering cells after seven to 28 days of X-Gal labelling. Dendrimers have been shown to improve plasmid survival (Bhardwaj

A, Misuriya A, 2014).

Nanotechnology in diagnostic and therapeutic for Gastrointestinal Disorders
Nano-tools for Diagnostics Applications
Nanowires applications

Biological and chemical species can be detected directly electrically using devices based on nanowires (Ramalho, et al.2016). As a particle flow through microfluidic channels, nanowires sensors detect molecular structures, relaying the information to a signal analyser (Wei, H et al.2017). Researchers can use such systems to detect altered genes associated with the disease and pinpoint the location of these changes (Dulińska-Litewka et al.2019). A silicon nanowire (SiNW) biosensor array was developed by Zheng et al. for the simultaneous detection of many cancer markers on a single flexible detection substrate. Using SiNW biosensors functionalized with three matching antibodies, three cancer indicators were identified in real time: prostate-specific antigen, carcinoembryonic antigen, and mucin-1. Several distinct biomarkers may be examined simultaneously with excellent sensitivity, which could make cancer early detection even simpler. This study described how aligned ZnO nanowire arrays were made using the vapour-solid method.

Cantilevers applications

The quantitative analysis of specific molecules at low concentrations is made possible by a nano-cantilever. Fast and sensitive detection is provided by cantilever arrays, which are made of microscopic flexible beams that resemble diving boards. Real-time analysis of the cantilevers' physical characteristics reveals

changes brought on by binding events (Kim S.J, Lewis 2016). By fusing an affinity reagent with a surface-immobilized on it to a biomarker protein or nucleic acid (through hybridization), the deflection and resonance frequency of a Nano-cantilever may be finely modulated (Iyer S.R, S Stain, 2016).

For instance, a cancer cell's released molecular products can be selectively bound to by an antibody-coated cantilever. Modern communication tools can be used in conjunction with this detection. (E.g. smart phones) It offers a personalised, real-time diagnosis based on blood indicators for an illness. Patients will therefore have the unique capacity to access their own amount of inflammation in real time.

Quantum Dots applications

Quantum dots (QDs) are semiconductor Nanocrystals that are easily manufactured and have unique features that fall in between those of discrete molecules and those of bulk semiconductors (Kumar, s et al.2016) QDs have size between 2 and 10 nm. They exhibit size dependent fluorescence characteristics and quantized energy levels (Hobson, N.J et al.2019) Quantum dots fluorescent characteristics make them excellent for imaging and cancer targeted applications. Due to their increased permeability and retention at the site of a tumor, semiconductor nanoparticle can build up at a target site (Shari, S et al.2015). In axenograft model using a human prostate cancer cell line in naked mice, the target accumulation of quantum dots was experimentally proven in- vivo (Wang, Z.J et al.2019)

Table.1.0 Examples of application of nanotechnology in gastroenterology

Sr.No.	Characteristics and Potentialities	Example of Application in GI (Target, Aim of Study)
1.	Loaded molecule control release	Apo B siRNA that has been chemically modified is Administered intravenously and is reduced in the liver and jejunum to lower total cholesterol (Vigneron and Bankson 2019).
2.	Gene delivery applications	Hepatitis B virus Si RNA administered intravenously reduces the amount of HBVDNA in the liver. (Geraghty and keshari 2017)
3.	Low toxicity and antigenicity	Micelles containing paclitaxel and poly aspartate (block polyethylene glycol) are being developed to treat colon cancer (Cho and keshari 2017).
4.	Loaded molecule control release	Targeting the peritoneal cavity to prevent tumor Development and inflammation (Malik and pundir 2019)
5.	Gene delivery applications	Hepatocyte growth factor (Zhang and Salameh 2017) is encapsulated and administered intravenously to treat liver cirrhosis.
6.	Low toxicity and antigenicity	Intravascular infusion of bcl2siRNA-loaded RNAi to suppress the development of liver metastases. (Cho and Keshari 2017)

7.	No control release	Hemagglutinin-presenting virosomes bind to and Fuse with cells that are being targeted in order to deliver iRNA. (Kostarelos and bianco 2009)
8.	Gene delivery applications	Reduction of DSS-induced colitis with intra-rectal Injection of DNA that inhibits colon inflammation. (Keren and zedra 2020)
9.	Loadedmolecule control release	Oraladmini stration of TNF-siRNA-loaded Thioketal NPs in the colonic tissue of mice with colitis caused by DSS. (welsher and sherlock2009)
10.	Gene delivery applications	Oral administration of insulin-loaded zirconium phosphate nanoparticles. (Garg and sung 2009)

Nanoparticles role in detection & treatment of Lung Cancer

Lung cancer is catch all phrase for a group of diverse diseases that account for 18.4%of all cancer diagnoses are cancer, and approximately 70% of patients had advanced disease at the time of diagnosis: include a physical examination, a medical history

review, and imaging procedures such as x-rays, computed tomography (CT), bone scans, MRIs PET Scans and combination PET- CT Scans.(Kurhanewicz J et al.2019) We shall talk about the possible applications of nanoparticles for the treatment of lung cancer throughout the review.(Garg, B, Sung, C.H,2015)

Table.2.0. finalize lung cancer clinical trials using nanoparticles. In August 2020, a thorough search on ClinicalTrials.gov was conducted “for & nanoparticles and lung cancer” These were examined and chosen in accordance with the state of the research.

Clinical trials gov Identifier (NCT no.)	Study Type	Description	Primary outcome	Planned enrollment (n)	Recruitment Status
NCT01792479	Phase-II	A phase II investigation to ascertain the security and effectiveness of BIND 014 (docetaxel nanoparticles for injectable suspension) as second-line treatment for Patients with NSCLC.	Objective response rate	64	Completed
CT02283320	Phase-II	In patients with NSCLC or v-Ki- ras 2 Kirsten rat sarcoma viral oncogene homolog mutation who have progressed following treatment with one prior platinum-containing chemotherapy regimen, BIND014(docetaxel nanoparticles for injectable solution) is being evaluated.	Disease control rate	69	Completed
CT0055346 2*	PhaseII	In this Phase II trial, the effectiveness of radiation treatment, erlotinib, and a carboplatin and paclitaxel albumin-stabilized nanoparticle formulation is being investigated in patients with Stage III NSCLC who are not candidates for surgical resection.	Overall survival at12 months	78	Completed
CT0072961	Phase-II	This Phase II trial is evaluating the efficacy of co-administration of carboplatin and paclitaxel albumin-stabilized nanoparticle formulation for the treatment of patients with Stage IIIB, Stage IV, or recurrent NSCLC.	Overall response rate	63	Completed
CT00077246	PhaseI-II	ABI-007 is being tested in a Phase I/II trial to determine its side effects, optimal dosage, and effectiveness in treating stage IV NSCLC patients.	Maximum tolerated dose and dose-limiting toxicity of ABI-007 Objective target lesion response	64	Completed
CT0138076 9*	PhaseII	This research compares patients with advanced NSCLC who received CRLX101 to those who received the best supportive care to determine whether group of patients had a higher median overall	Overall survival	157	Completed



APPLICATIONS OF NANOMATERIALS AND DEVICES

Drug Delivery System

Nano materials are colloidal particles composed of environment-friendly polymer and their dimensions ranges between 10-1,000 nm. Pharmacologically active substance can be immersed on the surface of colloidal particles, embedded in polymer or liquefy in the polymer matrix (Nurunnabi et al.2014). Liposomes are an example of dds (Cai, X, Zhu, 2019). DDs improve physicochemical properties of the drug such as partition coefficient, solubility, pharmacokinetics, biodistribution, and efficacy of drug

(Kwiatkowski G et al, 2017). Nanomaterials as it may be utilized for target specific drug delivery at the site of disorder to increase absorption of insoluble drugs (Dong, Y.C,2019),drug target to a particular site and bioavailability of drug also enhance.Several anticancer drugs have been successfully formulated using nanotechnology paclitaxel, doxorubicin, dexamethasone, 5-fluorouracil (Yousaf, T,2018).Dexamethasone bind to receptors and the drug receptors complexes are subsequently transport to cell nucleus, which leads to the appearance of specific genes so that easily control cell multiplication (Hemond, C.C,2018).

Nanomaterials in Drug Delivery System obtain FDA approval

Table.3.0. Nanomaterials in drug delivery system obtain FDA approved

Drug or therapeutic agent (tradename)	Indication	Reference
Liposomal amphotericin B (Ambisome, Ablecet, Amphoteric)	Fungal infections, Leishmaniasis	Alder-Moore (1994)
PEG-adenosine deaminase (Pegademase)	Severe combined immunodeficiency disease	Bory et al. (1991)
PEG-stabilized liposomal doxorubicin(Doxil, Evacet)	Kaposi's sarcoma, refractory ovarian cancer	Muggia and Hamilton (2001),Northfelt et al.(1996)
liposomal cytosine arabinoside(DepoCyt)	Lymphomatous meningitis, neoplastic meningitis	Glantz et al. (1999a), Glantz et al. (1999b)
Interleukin 2-diphtheria toxin fusion protein (Denileikin Diffitox)	Cutaneous T -cell lymphoma	Olsen et al. (2001)
Liposomal verteporfin (Visudyne)	Wet macular degeneration	Bressler (2001)
PEG-interferon α -b(Pegasys)	Hepatitis c	Gule et al.(2000)
PEG-granulocyte colony-stimulating factor(Neulasta)	Chemotherapy associated neutropenia	Siena et al.(2003)
Protein bound paclitaxel (Abraxane)	Metastatic breast cancer	Nyman et al.(2005)
PEG L- asparaginase (Oncaspar)	Acute lymphocytic leukemia	Rosen et al.(2003)
PEG aptanib (Macugen)	Wet macular Degeneration	Lee et al.(2005a,b)
Pemetrexed (Alimta)	Malignant pleural mesothelioma	Ceresoli et al.(2006)

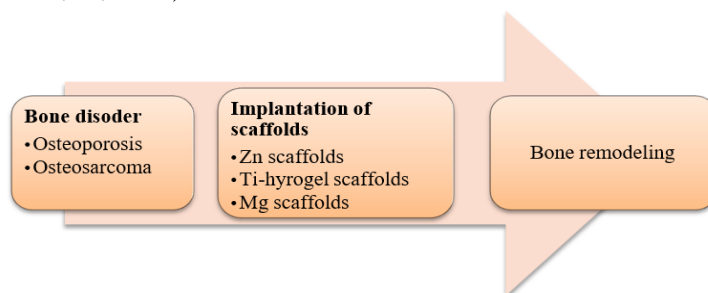


Application in Surgery
Maxillofacial Surgery using Nanomaterials
 Nanomaterials have the potential to

revolutionise the fields of oral surgery and dentistry through the use of nanorobots, nanomaterials, and biotechnology. (Behzadi, A.H, 2019) Nanorobots have a diameter of 0.5-3m and are made up of components ranging in size from 1-100 nm. They can perform precise procedures at the cellular and molecular level(Dong, Y.C,2019). To enable oral and maxillofacial surgeons keep up with the cutting-edge field of nanotechnology and nanosurgery, maxillofacial surgeons need to put in more effort, and supportive groups or societies need to provide more resources in the field of research.(Silvestri, A,2016).

Bone Regeneration Therapy

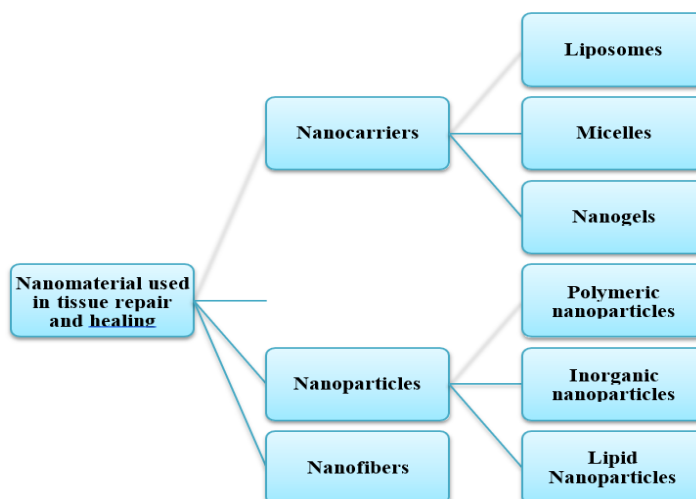
Biomaterials are widely involved in regenerative therapy and tissue engineering in bone. Bone diseases such as osteoporosis, osteosarcoma and bone loss require bone regeneration therapy. Nanotechnology are utilised for bone regeneration and detection of bone disorders. Nanomaterials (nanoliposomes, gold nanoparticles) loaded in scaffold and subsequently implant into the defected site. Drug released from the nanomaterials. Inorganic nanomaterials silica and metal-based materials, calcium phosphorus having great mechanical properties for bone defect repairing.(Nakagawa, T,2016)



Soft Tissue Repair & Healing

Wound and burn care are two sector of health care that are benefited by advances in nanotechnology. (Santos, B.S,2019) Wound dressing made using nanotechnology can be able to significantly improve tissue repair. Nanoparticles can be made from various materials using methods. Nanoparticles are a

promising tool in the field of tissue engineering. Nanomaterial have potential to promote cell homeostasis. Nanomaterial properties involve in soft tissue repair and regeneration cell adhesion, ability to respond to external stimuli, promote cell proliferation.(Siegel R,2017)





Application in Pro Imaging

Proimaging has stepped forward significantly in current decades and allows us to exactly acquire anatomical data through unique modalities (Siegel R,2014). Nanomaterials play a enormous element in proimaging,as mentioned below :

Magnetic Resonance Imaging (MRI)

MRI is a non-invasive imaging approach that can offer comprehensive and multiparametric information (Duncan R,2005). The introduction of magnetic resonance imaging in the revolutionized modern clinical imaging technology. It is rapidly becoming one of the most useful tools for diagnosis and monitoring of disease (Jabir NR, Anwar K,2017). Approximately 17 million MRIs were performed in the US in 2015. Contrast agent improves visualization and performs a crucial role in MRI. Ideally contrast agent administered and excreted from the body without causing any side effects. However, most of the contrast agent currently exhibit adverse effects such as liver toxicity, gado liniumde position. Technical advance- ment in the field of nanomaterials has shown the possibility of using them as contrast agents in MRI and decreasing number of side effects.

Currently SPIO are used as MRI contrast agent .Targeting ligands that binds to particular cancer biomarkers such as proteins, peptides, antibodies attach with nanoparticle for site specific targeting for example MG ,CK19 (Breast cancer biomarker) if bind to SPIO provide targeted retention of SPIO in cancer cells results in detection of cancer by MRI.(Nguyen KT,2011)

Computed Tomography (CT) Scan

CT uses an x-ray source and set of detectors to create an image .It has been extensively utilized in medical imaging and produce image with high resolution Nanoparticles having more advantages in comparison to CT contrast agent like prolonged blood-pool residence periods, the potential for cell tracking and ability to be used for targeted imaging (Shim MS, Lee HT,2002)It can find out internal bleeding, blood clots, tumor cells, spinal and brain injury without using any kind of invasive approach .Gold nanoparticles widely used as contrast agent for computed tomography. (Patri AK et al.2002)

Positron Emission Tomography (PET)

Positron emission tomography (PET) used for clinical diagnosis of various diseases.(Cloninger MJ,2002)It contains positron-emitting isotopes which administered into the body and the gamma radiation produced by that isotope is recorded to determine the exact location of a physiological process.(Choi Y, Thomas T, 2005) Silicon nanoparticles, gold nanoparticles used as contrast agent for positron emission tomography (PET).Given that it combines high-resolution anatomic data produced from CT with quantitative PET imaging, PET- computed tomography (CT) is the ideal modality choice for this application.(Chen C, Cheng YC,2005) Fluorochromes were added to the nanoparticles utilised in this work to make it easier to validate the placement of the agent using optical imaging methods.(Shim MS, Lee HT,2002)

Table.4.0. Application of nanomaterials in the proimaging techniques

Proimaging Technique	Type of nanoparticles
Magnetic resonanceimaging (MRI)	Magnetic nanoparticles
Computer tomography	Inorganic nanoparticles(gold nanoparticles, quantum dots, superparamagnetic iron oxide nanoparticles,)
Positron emission tomography	Silicon nanoparticles, gold nanoparticles

4.0. CONCLUSION

Nanotechnologies are being actively developed to create diagnostic and therapeutic devices. nanoparticle range in size

from 1-100nm and can be used to exhibit certain properties at the cellular atomic and molecular level. Nanoparticle-based drugs have limitless potential as new application

continue to be developed for the detection, imaging and treatment of cardiovascular disease, gastrointestinal disorder, lung cancer. Many nanomaterials are still in the pre-clinical stages, it is important to study bio-distribution of nanomaterial. By using nanomaterials as a contrast agent in different diagnosis technique such as gold nanoparticles used as contrast agent in positron emission tomography reduced side effects caused by traditional contrast agent for example side effects of gadolinium are nephrogenic systemic fibrosis. Nanoparticles can attach to biomolecules allow detection of disease biomarkers in lab sample at very early stage. Nanoparticles increasingly used in diagnosis of various cardiovascular diseases like atherosclerosis, arrhythmia, coronary heart disease, gastrointestinal disorder nanowires used for detection of altered genes associated with disorder cancer, brain disorders (biosensors used in diagnosis of Parkinson disease).

ACKNOWLEDGMENT

We are highly grateful to the Director Dr. (Col.) A. Garg and Joint Director, Dr. Manoj Goel, KIET Group of Institutions, and Dr. K. Nagarajan, Principal, KIET School of Pharmacy, Ghaziabad for their motivation, and all-around support.

ABBREVIATIONS

CardiovascularDisease(CVDs), Nanoparticles (NPs), Positron emission tomography (PET), Computed tomography (CT Scan), Drug delivery system(DDs), Quantum dots (QDs), Magnetic resonance imaging (MRI), human inducible pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), Silicon nanowire (SiNW), Superparamagnetic iron oxide nanoparticles (SPIO), Deoxyribose nucleic acid (DNA), di-stearoyl phosphatidylcholine (DSPC), di-stearoyl phosphatidylglycerol (DSPG) Metalloproteinase (MMP), Polylactic-co-glycolic (PLGA), Small interfering ribonucleic acid (siRNA), Zinc oxide(ZnO), Tumor necrosis factor-alpha small interfering RNA(TNF- α siRNA), Non-small cell lung cancer(NSCLC), Polyethylene glycol (PEG), Cytokeratin 19(CK-19), Myasthenia gravis(MG), Dextran sodium sulphate (DSS-induced colitis), Hepatitis B virus(HBV),

Gastrointestinal (GI).

REFERENCES

1. Allen, T. M., Cullis, P. R. Drug Delivery Systems: Entering the Mainstream. *Science* 2004, 303, 1818–1822.
2. B. Alotaibi, E. Tousson, T. A. El-Masry, N. Altwaijry, and A. Saleh, “Ehrlich ascites carcinoma as model for studying the cardiac protective effects of curcumin nanoparticles against cardiac damage in female mice,” *Environmental Toxicology*, vol. 36, pp. 105–113, 2021.
3. Bhardwaj Bhadra D, Bhadra S, Jain S, Jain NK: A PEGylated dendritic nanoparticulate carrier of fluorouracil. *Int J Pharm* 2003, 257(1–2):111-124.
4. A, Bhardwaj A, Misuriya A, Maroli S, Manjula S, Singh AK. Nanotechnology in dentistry: present and future. *J Int Oral Health* 2014;6:121-6.
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2018;68:394-424.
6. Behzadi, A.H, Farooq, Z, Newhouse, J.H, Prince, M.R. MRI and CT contrast media extravasation. *Medicine* 2018, 97.
7. C. M. Kelleher and J. P. Vacanti, “Engineering extracellular matrix through nanotechnology,” *Journal of the Royal Society Interface*, vol. 7, suppl_6, pp. S717–S729, 2010.
8. Cai, X, Zhu, Q, Zeng, Y, Zeng, Q, Chen, X, Zhan, Y. Manganese oxide nanoparticles as mri contrast agents in tumor multimodal imaging and therapy. *Int. J. Nanomed.* 2019, 14, 8321–8344.
9. Cho, A, Lau, J.Y.C, Geraghty, B.J, Cunningham, C.H, Keshari, K.R. Noninvasive interrogation of cancer metabolism with hyperpolarized ^{13}C MRI. *J. Nucl. Med.* 2017, 58, 1201–1206.
10. Cloninger MJ. Biological applications of dendrimers. *Curr Opin ChemBiol* 2002; 6: 742-8.
11. Choi Y, Thomas T, Kotlyar A, Islam MT, Baker JR Jr. Synthesis and functional evaluation of DNA-assembled polyamidoamine dendrimer clusters for cancer cell-specific targeting. *Chem Biol*

- 2005; 12: 35-43.
12. Chen C, Yu CH, Cheng YC, Yu PH, Cheung MK. Micelle formation and sol-gel transition behavior of comb-like amphiphilic poly ((PLGA-b-PEG) MA) copolymers. *J PolymSci Part A: Polym Chem* 2008; 46: 1954-63
 13. Cho, A, Lau, J.Y.C, Geraghty, B.J, Cunningham, C.H.; Keshari, K.R. Noninvasive interrogation of cancer metabolism with hyperpolarized ¹³C MRI. *J. Nucl. Med.* 2017, 58, 1201–1206.
 14. Cho, A, Lau, J.Y.C, Geraghty, B.J, Cunningham, C.H, Keshari, K.R. Noninvasive interrogation of cancer metabolism with hyperpolarized ¹³C MRI. *J. Nucl. Med.* 2017, 58, 1201–1206.
 15. Cai, X, Zhu, Q, Zeng, Y, Zeng, Q, Chen, X, Zhan, Y. Manganese oxide nanoparticles as mri contrast agents in tumor multimodal imaging and therapy. *Int. J. Nanomed.* 2019, 14, 8321–8344.
 16. D. A. Tonetti, B. T. Jankowitz, and B. A. Gross, "Antiplatelet therapy in flow diversion," *Neurosurgery*, p. 86, 2020.
 17. De Jonge J, Holtrop M, Wilschut J, Huckriede A. Reconstituted influenza virus envelopes as an efficient carrier system for cellular delivery of small-interfering RNAs. *Gene Ther* 13: 400 – 411, 2006
 18. De La Zerda, A, Zavaleta, C, Keren, S, Vaithilingam, S, Bodapati, S, Liu, Z, Levi, J, Smith, B.R. Ma, T.J, Oralkan, O. et al. Carbon nanotubes as photoacoustic molecular imaging agents in living mice. *Nat. Nanotechnol.* 2008, 3, 557–562.
 19. Dulińska-Litewka, J.; Łazarczyk, A.; Hałubiec, P.; Szafranski, O.; Karnas, K.; Karczewicz, A. Superparamagnetic iron oxide nanoparticles-current and prospective medical applications. *Materials* 2019.
 20. Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. *Advanced Drug Delivery Reviews* 2005; 57: 2215-37.
 21. De Jonge J, Holtrop M, Wilschut J, Huckriede A. Reconstituted influenza virus envelopes as an efficient carrier system for cellular delivery of small-interfering RNAs. *Gene Ther* 13: 400 – 411, 2006.
 22. Diaz A, David A, Perez R, Gonzalez ML, Baez A, Wark SE, Zhang P, Clearfield A, Colon JL. Nanoencapsulation of insulin into zirconium phosphate for oral delivery applications. *Biomacromolecules* 11: 2465– 2470, 2010
 23. Dulińska-Litewka, J.; Łazarczyk, A.; Hałubiec, P.; Szafranski, O.; Karnas, K.; Karczewicz, A. Superparamagnetic iron oxide nanoparticles-current and prospective medical applications. *Materials* 2019.
 24. Dong, Y.C, Hajfathalian, M, Maidment, P.S.N, Hsu, J.C, Naha, P.C, Si-Mohamed, S, Breuilly, M, Kim, J, Chhour, P, Douek, P, et al. Effect of gold nanoparticle size on their properties as contrast agents for computed tomography. *Sci. Rep.* 2019, 9, 1–13.
 25. Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. *Advanced Drug Delivery Reviews* 2005; 57: 2215-37.
 26. De La Zerda, A, Zavaleta, C, Keren, S, Vaithilingam, S, Bodapati, S, Liu, Z, Levi, J, Smith, B.R. Ma, T.J, Oralkan, O, et al. Carbon nanotubes as photoacoustic molecular imaging agents in living mice. *Nat. Nanotechnol.* 2008, 3, 557–562.
 27. E. G. Nabel, G. Plautz, and G. J. Nabel, "Site-specific gene expression in vivo by direct gene transfer into the arterial wall," *Science*, vol. 249, no. 4974, pp. 1285–1288, 1990.
 28. Flynn MA, Casey DG, Todryk SM, Mahon BP. Efficient delivery of small interfering RNA for inhibition of IL-12p40 expression in vivo. *J Inflamm* 1: 4, 2004.
 29. Fonseca C, Simoes S, Gaspar R: Paclitaxel-loaded PLGA nanoparticles: preparation, physicochemical characterization and in vitro anti-tumoral activity. *J Control Release* 2002, 83(2):273-286.
 30. Gao XH, Cui YY, Levenson RM, Chung LWK, et al. In vivo cancer targeting and

- imaging with semiconductor quantum dots. *Nat Biotechnol.* 2004; 22:969–76.
31. Garg, B, Sung, C.H, Ling, Y.C. Graphene-based nanomaterials as molecular imaging agents. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 2015, 7, 737–758.
 32. H. San, Z. Y. Yang, V. J. Pompili et al., “Safety and short-term toxicity of a novel cationic lipid formulation for human gene therapy,” *Human Gene Therapy*, vol. 4, no. 6, pp. 781–788, 1993.
 33. H. Liu and T. J. Webster, “Nanomedicine for implants: a review of studies and necessary experimental tools,” *Biomaterials*, vol. 28, no. 2, pp. 354–369, 2007.
 34. H. San, Z. Y. Yang, V. J. Pompili et al., “Safety and short-term toxicity of a novel cationic lipid formulation for human gene therapy,” *Human Gene Therapy*, vol. 4, no. 6, pp. 781–788, 1993.
 35. H. Lin, M. S. Parmacek, G. Morle, S. Bolling, and J. M. Leiden, “Expression of recombinant genes in myocardium in vivo after direct injection of DNA,” *Circulation*, vol. 82, no. 6, pp. 2217–2221, 1990
 36. Hobson, N.J, Weng, X, Siow, B, Veiga, C, Ashford, M, Thanh, N.T.K, Schätzlein, A.G, Uchegbu, I.F. Clustering superparamagnetic iron oxide nanoparticles produces organ-Targeted high-contrast magnetic resonance images. *Nanomedicine* 2019, 14, 1135–1152
 37. Hromadka M, Collins JB, Reed C, Han L, Kolappa KK, Cairns BA, Andrady T, van Aalst JA. Nanofiber applications for burn care. *J Burn Care Res* 2008;29:695-703.
 38. Hemond, C.C, Bakshi, R. Magnetic resonance imaging in multiple sclerosis. *Cold SpringHarb. Perspect. Med.* 2018, 8, 1–21.
 39. Iyer, S.R, Xu, S, Stains, J.P, Bennett, C.H, Lovering, R.M. Superparamagnetic iron oxide nanoparticles in musculoskeletal biology. *Tissue Eng. Part. B Rev.* 2017, 23, 373–385
 40. J. W. Rhee and J. C. Wu, “Advances in nanotechnology for the management of coronary artery disease,” *Trends in Cardiovascular Medicine*, vol. 23, no. 2, pp. 39–45, 2013.
 41. Jabir NR, Tabrez S, Ashraf GM, Shakil S, et al. Nanotechnology-based approaches in anticancer research. *Int J Nanomed.* 2012; 7:4391–408. Ishiyama K, Ohgi T, Irimura T. Antitumor activity of small interfering RNA/cationic liposome complex in mouse models of cancer. *Clin Cancer Res* 10: 7721–7726, 2004
 42. Jabir NR, Anwar K, Firoz CK, Oves M, Kamal MA, Tabrez S. An overview on the current status of cancer nanomedicines. *Current Medical Research and Opinion.* 2017; 1-22.
 43. M. Banach, C. Serban, A. Sahebkar et al., “Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies,” *BMC Medicine*, vol. 13, 2015.
 44. M. J. Lipinski, J. C. Frias, V. Amirbekian et al., “Macrophage specific lipid-based nanoparticles improve cardiac magnetic resonance detection and characterization of human atherosclerosis,” *JACC: Cardiovascular Imaging*, vol. 2, pp. 637–647, 2009.
 45. M. Khan, Y. Xu, S. Hua et al., “Correction: Evaluation of changes in morphology and function of human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) cultured on an aligned- nanofiber cardiac patch,” *PLoS One*, Vol. 10, no. 10, p. e0141176, 2015.
 46. Morrissey DV, Lockridge JA, Shaw L, Blanchard K, Jensen K, Breen W, Hartsough K, Machemer L, Radka S, Jadhav V, Vaish N, Zinnen S, Vargeese C, Bowman K, Shaffer CS, Jeffs LB, Judge A, MacLachlan I, Polisky B. Potent and persistent in vivo anti-HBV activity of chemically modified siRNAs. *Nat Biotechnol* 23: 1002–1007, 2005.
 47. Matsumura Y. Polymeric micellar delivery systems in oncology. *Jpn J Clin Oncol* 38: 793–802, 2008. Yano J, Hirabayashi K, Nakagawa S, Yamaguchi T, Nogawa M, Kashimori, Naito H, Kitagawa H, Ishiyama K, Ohgi T, Irimura T. Antitumor activity of small interfering RNA/cationic liposome complex in mouse models of cancer. *Clin Cancer Res*

- 10: 7721–7726, 2004
48. McMahon, M.T, Bulte, J.W.M. Two decades of dendrimers as versatile MRI agents: A tale with and without metals. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 2018, 10, e1496.
 49. Moghimi, H, Zohdiaghdam, R, Riahialam, N, Behrouzki, Z. The assessment of toxicity characteristics of cellular uptake of paramagnetic nanoparticles as a new magnetic resonance imaging contrast agent. *Iran. J.Pharm. Res.* 2019, 18, 2083–2092.
 50. Malik, M, Chaudhary, R, Pundir, C.S. An improved enzyme nanoparticles based amperometric pyruvate biosensor for detection of pyruvate in serum. *Enzym. Microb. Technol.* 2019, 123, 30–38.
 51. N. Kapil, Y. H. Datta, N. Alakbarova et al., “Antiplatelet and anticoagulant therapies for prevention of ischemic stroke,” *Clinical and Applied Thrombosis/Hemostasis*, vol. 23, pp. 301–318, 2017.
 52. Nurunnabi, M, Khatun, Z, Reeck, G.R, Lee, D.Y, Lee, Y.K. Photoluminescent graphene nanoparticles for cancer phototherapy and imaging. *ACS Appl. Mat. Interf.* 2014, 6, 12413–12421
 53. Nakagawa, T, Gonda, K, Kamei, T, Cong, L, Hamada, Y, Kitamura, N, Tada, H, Ishida, T, Aimiya, T, Furusawa, N, et al. X-ray computed tomography imaging of a tumor with high sensitivity using gold nanoparticles conjugated to a cancer-specific antibody via polyethylene glycol chains on their surface. *Sci. Technol. Adv. Mater.* 2016, 17, 387–397.
 54. Nguyen KT. Targeted nanoparticles for cancer therapy: promises and challenges. *JNanomedNanotechnol* 2011; 2: 103e.
 55. N. K. Egilmez, Y. Iwanuma, and R. B. Bankert, “Evaluation and optimization of different cationic liposome formulations for in vivo gene transfer,” *Biochemical and Biophysical Research Comm uni cations*, vol. 221, no. 1, pp. 169–173, 1996.
 56. Nakagawa, T, Gonda, K, Kamei, T, Cong, L, Hamada, Y, Kitamura, N, Tada, H, Ishida, T, Aimiya, T, Furusawa, N et al. X-ray computed tomography imaging of a tumor with high sensitivity using gold nanoparticles conjugated to a cancer-specific antibody via polyethylene glycol chains on their surface. *Sci. Technol. Adv. Mater.* 2016, 17, 387–397.
 57. O. Pagliarosi, V. Picchio, I. Chimenti, E. Messina, and R. Gaetani, “Building an artificial cardiac microenvironment: a focus on the extracellular matrix,” *Frontiers in Cell and Development Biology*, vol. 8, p. 8, 2020.
 58. P. Stano, S. Bufali, C. Pisano et al., “Novel camptothecin analogue (gimatecan)-containing liposomes prepared by the ethanol injection method,” *Journal of Liposome Research*, vol. 14, 2004
 59. Patri AK, Majoros I, Baker JRJ. Dendritic polymer macromolecular carriers for drug delivery. *Curr Opin Chem Biol* 2002; 6: 466- 471.
 60. Panyam J, Labhasetwar V: Sustained cytoplasmic delivery of drugs with intracellular receptors using biodegradable nanoparticles. *Mol Pharm* 2004, 1(1):77-84.
 61. O. Pagliarosi, V. Picchio, I. Chimenti, E. Messina, and R. Gaetani, “Building an artificial cardiac microenvironment: a focus on the extracellular matrix,” *Frontiers in Cell and Development Biology*, vol. 8, p. 8, 2020.
 62. Ould-Ouali L, Noppe M, Langlois X, Willems B, TeRiele P, Timmerman P, Brewster ME, Arien A, Preat V: Self-assembling PEGp(CL-co-TMC) copolymers for oral delivery of poorly water-soluble drugs: a case study with risperidone. *J Control Release* 2005, 102(3):657-668.
 63. Oh S, Brammer KS, Li YS, Teng D, Engler AJ, Chien S, Jin S. Stem cell fate dictated solely by altered nanotube dimension. *Proc Natl Acad Sci U S A* 2009;106:2130-5.
 64. Rogosnitzky, M.; Branch, S. Gadolinium-based contrast agent toxicity: A review of known and proposed mechanisms. *BioMetals* 2016, 29, 365–376.
 65. R. Ravichandran, V. Seitz, J. Reddy Venugopal et al., “Mimicking native extracellular matrix with phytic acid crosslinked protein nanofibers for cardiac tissue engineering,” *Macromolecular*

- Bioscience, vol. 13, no. 3, pp. 366–375, 2013.
66. Ramalho, J, Semelka, R.C, Ramalho, M, Nunes, R.H, AlObaidy, M, Castillo, M. Gadolinium- based contrast agent accumulation and toxicity: An update. *Am. J. Neuroradiol.* 2016, 37, 1192–1198
67. S. C. Johnston, J. D. Easton, M. Farrant et al., “Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA,” *The New England Journal of Medicine*, vol. 379, pp. 215–225, 2018
68. S. Malini, K. Raj, and M. Sennappan, “Electrochemical and spectroscopic studies of interaction of clopidogrel bisulphate with calf thymus DNA,” *Asian Journal of Chemistry*, vol. 30, pp. 129–132, 2018.
69. Sun YP, Fu KF, Lin Y, Huang WJ. Functionalized carbon nanotubes: Properties and applications. *Accounts Chem Res.* 2002; 35:1096–104.
70. Shari, S.; Seyednejad, H.; Laurent, S.; Atyabi, F. Superparamagnetic iron oxide nanoparticles for in vivo molecular and cellular imaging. *Contrast Media Mol. Imaging* 2015.
71. S. S. Virani, A. Alonso, H. J. Aparicio et al., “Heart Disease and Stroke Statistics-2021 Update A Report from the American Heart Association,” *Circulation*, vol. 143, no. 8, pp. E254–E743, 2021
72. S. C. Johnston, J. D. Easton, M. Farrant et al., “Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA,” *The New England Journal of Medicine*, vol. 379, pp. 215–225, 2018.
73. S. Malini, K. Raj, and M. Sennappan, “Electrochemical and spectroscopic studies of the interaction of clopidogrel bisulphate with calf thymus DNA,” *Asian Journal of Chemistry*, vol. 30, pp. 129–132, 2018
74. S. Pok, J. D. Myers, S. V. Madihally, and J. G. Jacot, “A multilayered scaffold of a chitosan and gelatin hydrogel supported by a PCL core for cardiac tissue engineering,” *Acta Biomaterialia*, vol. 9, no. 3, pp. 5630–5642, 2013.
75. Sun YP, Fu KF, Lin Y, Huang WJ. Functionalized carbon nanotubes: Properties and applications. *Accounts Chem Res.* 2002; 35:1096–104.
76. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9-29.
77. Soutschek J, Akinc A, Bramlage B, Charisse K, Constien R, Donoghue M, Elbashir S, Geick A, Hadwiger P, Harborth J, John M, Kesavan V, Lavine G, Pandey RK, Racie T, Rajeev KG, Rohll, Toudjarska I, Wang G, Wuschko S, Bumcrot D, Koteliansky V, Limmer S, Manoharan M, Vornlocher HP. Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs. *Nature* 432: 173–178, 2004
78. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9-29.
79. Shim MS, Lee HT, Shim WS, Park I, Lee H, Chang T, Kim SW, Lee DS. Poly (D,L-lactic acid-co-glycolic acid)-b-poly (ethylene glycol)-b-poly (D,L-lactic acid-co-glycolic acid) triblock copolymer and thermos reversible phase transition in water. *J Biomed Mater Res* 2002; 61: 188-96.
80. Silvestri, A, Zambelli, V, Ferretti, A.M, Salerno, D, Bellani, G, Polito, L. Design of functionalized gold nanoparticle probes for computed tomography imaging. *Contrast Media Mol. Imaging* 2016, 11, 405–414
81. Santos, B.S, Ferreira, M.J. Positron emission tomography in ischemic heart disease. *Rev. Port. Cardiol.* 2019, 38, 599–608.
82. Theiss AL, Laroui H, Obertone TS, Chowdhury I, Thompson WE, Merlin D, Sitaraman SV. Nanoparticle-based therapeutic delivery of prohibitin to the colonic epithelial cells ameliorates acute murine colitis. *Inflamm Bowel Dis* 2010.
83. T. Geisler, H. Langer, M. Wydymus et al., “Low response to clopidogrel is associated with cardiovascular outcome after coronary stent implantation,” *European Heart Journal*, vol. 27, 2006.
84. K. Raj and S. Malini, “Cyclic voltammetric studies of invitro interaction of clopidogrel bisulphate and aspirin,” *Materials Today: Proceedings*, vol. 5, pp. 22390–22398, 2018

85. Koziara JM, Whisman TR, Tseng MT, Mumper RJ: In-vivo efficacy of novel paclitaxel nanoparticles in paclitaxel-resistant human colorectal tumors. *J Control Release* 2006, 112(3):312- 319.
86. Kipp JE: The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. *Int J Pharm* 2004, 284(1-2):109-122
87. Kim, S.J, Lewis, B, Steiner, M.S, Bissa, U.V, Dose, C, Frank, J.A. Superparamagnetic iron oxide nanoparticles for direct labelling of stem cells and in vivo MRI tracking. *Contrast Media Mol.Imaging* 2016, 11, 55–64.
88. Kumar, S.; Kumar, B.S.H.; Khushu, S. Increased transverse relaxivity in ultrasmall superparamagnetic iron oxide nanoparticles used as MRI contrast agent for biomedical imaging. *Contrast Media Mol. Imaging* 2016.
89. Kurhanewicz, J, Vigneron, D.B, Ardenkjaer-Larsen, J.H, Bankson, J.A, Brindle, K, Cunningham, C.H, Gallagher, F.A, Keshari, K.R, Kjaer, A, Laustsen, C et al. Hyperpolarized ¹³C MRI: Path to Clinical Translation in Oncology. *Neoplasia* 2019, 21, 1–16.
90. Kostarelos, K, Bianco, A, Prato, M. Promises, facts and challenges for carbon nanotubes in imaging and therapeutics. *Nat. Nano technol.* 2009, 4, 627–633.
91. Kreuter J (1983) Evaluation of nanoparticles as drug-delivery systems. III. Materials, stability, toxicity, possibilities of targeting, and use. *Pharm Acta Helv* 58:242–250
92. Kwiatkowski, G, Jähnig, F, Steinhauser, J, Wespi, P, Ernst, M, Kozerke, S. Nanometer size silicon particles for hyperpolarized MRI. *Sci. Rep.* 2017, 7, 1–6.
93. P. Stano, S. Bufali, C. Pisano et al., “Novel camptothecin analogue (gimatecan)-containing liposomes prepared by the ethanol injection method,” *Journal of Liposome Research*, vol. 14, 2004.
94. Lux, J, Sherry, A.D. Advances in gadolinium-based MRI contrast agent designs for monitoring biological processes in vivo. *Curr. Opin. Chem. Biol.* 2018, 45, 121–130
95. Larson DR, Zipfel WR, Williams RM, Clark SW, et al. Water-soluble quantum dots for multiphoton fluorescence imaging in vivo. *Science*.2003; 300:1434–6
96. Liu, X, Madhan Kumar, A.B, Miller, P.A, Duck, K.A, Hafenstein, S, Rizk, E, Slagle-Webb, B, Sheehan, J.M, Connor, J.R, Yang, Q.X. MRI contrast agent for targeting glioma: Interleukin-13 labeled liposome encapsulating gadolinium-DTPA. *Neuro.Oncol.* 2016, 18, 691–699
97. Layne, K.A, Dargan, P.I, Archer, J.R.H, Wood, D.M. Gadolinium deposition and the potential for toxicological sequelae – A literature review of issues surrounding gadolinium-based contrast agents. *Br. J. Clin. Pharmacol.* 2018, 84, 2522–2534.
98. Lee, S.B, Lee, S.W, Jeong, S.Y, Yoon, G, Cho, S.J, Kim, S.K, Lee, I.K, Ahn, B.C, Lee, J, Jeon, Y.H. Engineering of radioiodine-labeled gold core-shell nanoparticles as efficient nuclear medicine imaging agents for trafficking of dendritic cells. *ACS Appl. Mater. Interfaces* 2017, 9, 8480–8489.
99. Gao XH, Cui YY, Levenson RM, Chung LWK, et al. In vivo cancer targeting and imaging with semiconductor quantum dots. *Nat Biotechnol.* 2004; 22:969–76.
100. W. Jiang and H. Liu, “Nanocomposites for bone repair and osteointegration with soft tissues,” in *Nanocomposites for Musculoskeletal Tissue Regeneration*, Woodhead Publishing, 2016.
101. Wilson DS, Dalmasso G, Wang L, Sitaraman SV, Merlin D, Murthy N. Orally delivered thioketal nanoparticles loaded with TNF-alpha siRNA target inflammation and inhibit gene expression in the intestines. *Nat Mater* 9: 923–928, 2010.
102. Wei, H, Bruns, O.T, Kaul, M.G, Hansen, E.C, Barch, M, Wiśniowska, A, Chen, O.; Chen, Y, Li, N, Okada, S. et al. Exceedingly small iron oxide nanoparticles as positive MRI contrast agents. *Proc. Natl. Acad.Sci. USA* 2017, 114, 2325–2330.
103. Wang, Z.J, Ohliger, M.A, Larson, P.E.Z, Gordon, J.W, Bok, R.A, Slater, J,

- Villanueva- Meyer, J.E, Hess, C.P, Kurhanewicz, J, Vigneron, D.B. Hyperpolarized ¹³C MRI: State of the art and future directions. *Radiology* 2019, 291, 273–284.
104. Waddington, D.E.J, Sarracanie, M, Zhang, H, Salameh, N, Glenn, D.R, Rej, E, Gaebel, T, Boele, T, Walsworth, R.L, Reilly, D.J, et al. Nanodiamond-enhanced MRI via in situ hyperpolarization. *Nat. Commun.* 2017, 8, 1–8
105. Welsher, K, Liu, Z, Sherlock, S.P, Robinson, J.T, Chen, Z, Daranciang, D, Dai, H. A route to brightly fluorescent carbon nanotubes for near-infrared imaging in mice. *Nat. Nanotechnol.* 2009, 4, 773–780.
106. Yoo HS, Lee KH, Oh JE, Park TG: In vitro and in vivo anti-tumor activities of nanoparticles based on doxorubicin-PLGA conjugates. *J Control Release* 2000, 68(3):419-31.
107. Yoo, S.P, Pineda, F, Barrett, J, Poon, C, Tirrell, M, Chung, E.J. Gadolinium-functionalized peptide amphiphile micelles for multimodal imaging of atherosclerotic lesions. *ACS Omega* 2016, 1,996–1003
108. Yousaf, T, Dervenoulas, G, Politis, M. Advances in MRI Methodology. *Int. Rev. Neurobiol.* 2018, 141, 31–76.
109. Y. Wu, L. Wang, B. Guo, and P. X. Ma, “Interwoven aligned conductive nanofiber yarn/hydrogel composite scaffolds for engineered 3D cardiac anisotropy,” *ACS Nano*, vol. 11, no. 6, pp. 5646–5659, 2017.