ABDALLAH RAFI SHTAIYAT BIOMIMETIC ANALYSIS OF THERANOSTIC NANOPARTICLES FOR CANCER APPLICATIONS NEU 2021

BIOMIMETIC ANALYSIS OF THERANOSTIC NANOPARTICLES FOR CANCER APPLICATIONS

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES

OF

NEAR EAST UNIVERSITY

By

ABDALLAH RAFI SHTAIYAT

In Partial Fulfillment of the Requirements for the Degree of Master of Science

in

Biomedical Engineering

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Approval of Director of Institute of Graduate Studies

Prof. Dr. K Hüsnü Can BAŞER

We certify this thesis is satisfactory for the award of the degree of Master of Science in Biomedical Engineering

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are original to this work.

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Date: **24/12/2020**

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To my Family…

ABSTRACT

There have been great forwards for biomedical applications of nanoparticles in recent past years because of their distinctiveness, physical, chemical, and biological properties. Nanoparticles have different types (polymers, lipids, peptides, metals) and have additional shape structures (pyramids, rods, spheres). In medicine, the main concentration is on biocompatibility and biodegradability of nanoparticles and their ability to be a targeted therapy to the specific biological barrier. The growing interest in medical imaging has opened up prospects for nanoparticle use in most interactive areas: therapy and diagnostic. Besides, the design of nanoparticles represents a nano-molecules that can provide both detection and delivery system Simultaneously. Consequently, giving theranostic applications. Cancer affects a large number of people worldwide per year. It is estimated that 18 million people have cancer annually, and about seven million deaths annually. Surgery, radiotherapy, and chemotherapy are considered the most treatment used for cancer. However, these methods are not very useful because they affect not only the cancer cells but they affect healthy cells as well. The problem is also that cancer, in most cases, develop a treatment resistance strategy.

Keywords: Nanoparticles (NPs), Theranostic agents, Nanomedicine, Breast Cancer, Targeted therapy

ÖZET

Son yıllarda, ayırt edici fiziksel, kimyasal ve biyolojik özelliklerinden dolayı nanoparçacıkların ileriye dönük biyomedikal uygulamaalrı çok çalışılmaktadır. Nanoparçacıklar farklı tipte (polimerler, lipidler, peptipler ve metaller) ve ilave şekil (piramidler, çubuklar ve küreler) yapılarındadırlar.

Tıp alanında nanoparçacıkların, biyouyumluluk ve biyobozunabilme özellikleri ile özgül biyolojik engelleri hedefleyebilen tedavi yetenekleri konularına yoğunlaşılmıştır. Biyomedikal görüntüleme alanına büyüyen ilgi, nanoteknoloji ile teşhis ve tedavi alanlarında yeni bakış açısı gelişmesine neden olmuştur. Bununla birlikte, teşhis ve tedavi amaçlı tasarlanan nanomolekül ve parçacıklar hedefe yönelik çoklu fonksiyonlu ilaç sistemleri geliştirilmesine olanak sağlamaktadırlar.

Sonuç olarak teranostik mikro ve nanoparçacıklar, biyomedikal görüntüleme yardımı ile teşhis edilen hasta bölgeye tedavi amaçlı ilaç salınımı yapabilecek yeteneğe sahip araçlar olarak tasarlanabilmektedirler.

Her yıl, Dünya çapında kanser hastalığından pek çok kişi zarar görmektedir. Yılda yaklaşık 18 milyon kanser hastasının olduğu ve ortalama yedi milyonunun yaşamını yitirdiği varsayılmaktadır. Tedavi yöntemlerinden, cerrahi, radyoterapi ve kemoterapi en yaygın olarak kullanılan yöntemlerdir. Bu yöntemlerin yan etkilerinden dolayı ne yazık ki sağlıklı hücrelerde zarar görmektedirler. Ayrıca, bağışıklık sisteminin, kanser tedavilerinin çoğuna karşı direnç stratejisi geliştirdiği de çözülmesi gereken önemli bir problemdir. Çözüm olarak geliştirilen teranostik ajanlar bu tezde biyometrik yöntemlerle analiz edilmiştir.

Anahtar Kelimeler: Nanoparçacıklar, Teranöstik ajanlar, Nanotıp, Göğüs kanseri, hedefe yönelik ilaç tedavisi.

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CNTs: Carbon Nanotubes

ADC: Antibody Drug Conjugate

Au: Gold

NIR: Near Infrared Spectroscopy

LSPR: Localized Surface Plasmon Resonance

MRI: Magnetic Resonance Imaging

CT: Computed Tomography Imaging

MNPs: Magnetic Nanoparticles

EPR: Enhanced Permeability and Retention

SPIONS: Superparamagnetic Ion Oxide Nanoparticles

AgNPs: Silver Nanoparticles

AuNPs: Gold Nanoparticles

ROS: Reactive Oxygen Species

RT: Radio Sensitization.

UCNPs: Up conversion Nanoparticles.

FA: Folic Acid

PEG: Polyethylene Glycol

DOX: Doxorubicin

QDs: Quantum Dots

CNPs: Carbon-Based Nanoparticles

DSPE-HA: Distearoylphos-Phatidylethanolamine-Hyaluronic Acid

PLGA: Poly(d,l-lactic-co-glycolic) Acid

PEG: Polyethylene Glycol

PEDOT: Poly(3,4-ethylenedioxythiophene)

TNPs: Theranostic Nanoparticles

DENPs: Dendrimer-entrapped nanoparticles

DSNPs: Dendrimer-stabilized nanoparticles

NSCLC: Nonsmall-cell lung carcinoma

POM: Polarized optical microscopy

SEM: Scanning electron microscope

TEM: Transmission electron microscopy

SERS: Surface-enhanced Raman scattering

CHAPTER 1

INTRODUCTION

1.1 Background on Theranostic Approach

Theranostic means a combination of therapeutics and diagnostics words. Theranostic presents and creates a multi medical procedure in one single agent that combines both diagnostic and therapeutic applications, leading to a promising medical platform, including diagnosis, drug delivery, and monitoring drugs and treatment response. Theranostic present a whole new vision in predictive, preventive, and personalized medicine by using biological pathways to obtain images for diagnostic purposes and delivering specific restorative material to a specific site in the human body. Targeting therapy based on an interaction between target on tumor cells and a specific target molecule that have binding action on specific receptors on tumor cells; this treatment procedure presents a significant improvement by offering right treatment, right patient and right time with right dose thus, leading to targeted, efficient therapy as theranostic approach (Shrivastava et al., 2019). The theranostic approach relies on exploiting biological pathways to obtain proper diagnostic images.

In 1938 hertz and Robert present the first pure theranostic platform (Hertz et al., 1938) by using radioiodine in thyroid disorder; after that, they present another example using radioiodine for Graves' disease (Hertz et al., 1942).

A theranostic approach started by Seidlin et al. in 1946 by using radioiodine therapy for thyroid cancer. Iodine was the first theranostic agent and used in thyrotoxicosis treatment. Iodine does both identify the tumor condition and assist in tumor therapy at the same time. Iodine emitting radioactive beta signals that can destroy tumor cells and detect agents for gamma rays imaging technique. At the beginning of the 2000s, theranostic term starting to grow up in the medical field between scientists and clinicians, and it means choosing optimal care level to treat patients medically. In modern life, the medical sector focuses on improving treatment platforms by applying personalized medicine and theranostic approaches in different medical branches.

Theranostic is now mainly based on imaging and therapy principles and applying them to a complex molecule, nanotechnology, and nanomedicine (Chen et al., 2013). theranostic in medicine approach applied directly before 80 years ago in nuclear medicine procedures and targeted therapy applications in nuclear medicine. It started in 1935 by Chiewitz and Hevesy (Chiewitz et al., 1935). they used 23P in bones; after that, Erf and Lawrence (Erf et al., 1941) applied the same procedure on leukemia and polycythemia, and it replaced the chemotherapy radioactive used at that time. In 1942 Pecher (Pecher et al., 1942) used 89Sr in the bone tumor, and after five decades, it was used as a therapeutic drug. These two examples are presented as theranostic and targeted therapy backbone for the world. First, the theranostic application is made by using sodium iodine symporter with targeting therapy.

In 2002 Funkhouser used the theranostic term directly to point to multiple subjects that can carry together diagnosis and therapeutic function consequently. Theranostic Term is Started as a personalized treatment for a specific patient and specific pathological sites. In general, theranostic approach is used in persistent disease management like cancer the theranostic approach's main objective is to improve various medical fields: pharmacokinetics, pharmacodynamics, and biodistribution in drug delivery strategies at the right time, right place, and the right dose to the right patient (Funkhouser, 2002).

Nano theranostic is a sub approach of the theranostic approach; it mainly focuses on developing nanomedicine strategies for theranostic approaches. The main characteristics of nano theranostic are dimensions, therapeutic profile, and diagnosis agents. Nano theranostic include nanocarriers such as dendrimers, liposomes, micelles, and other and engineered nano theranostic like bacteria and viruses. These biological particles have the power to design a novel theranostic system because of their unique properties. Nano theranostic can be used as imaging agents for imaging modalities like MRI, PET, SPECT, and other modalities. Nano theranostic can also be used to sense biomarkers in different diseases and monitor various biological processes like the accumulation of specific drugs or molecules in a specific site in the human body; besides, it can treatment evaluation for specific drugs. Theranostic agents could also be used in aging diseases.

1.2 Theranostic Definition

Theranostic is a word that combines two words therapeutics and diagnosis. It is a trending term in the medical field. It is used simultaneously and sequentially in diagnosis and treatment procedures. It is like to get a supreme medical package that contains diagnosis and therapy together. It is a time and money saver in various medical procedures; besides, it helps avoid unwanted biological effects in different medical strategies.

Theranostic presents targeted efficient and safe pharmacotherapy that attracts around centered care for a patient. Mainly it has combined diagnosis and therapeutic applications and present a phenomenal new vision for using personalized medicine instead of traditional medicine, "the conventional ones." the idea behind personalized medicine or precision medicine is to present a modern platform which gives the right patient the right medicine at the right time even a right dose. Theranostic have three cornerstone pharmacogenetics, proteomics, and biomarker (Figure 1.1).

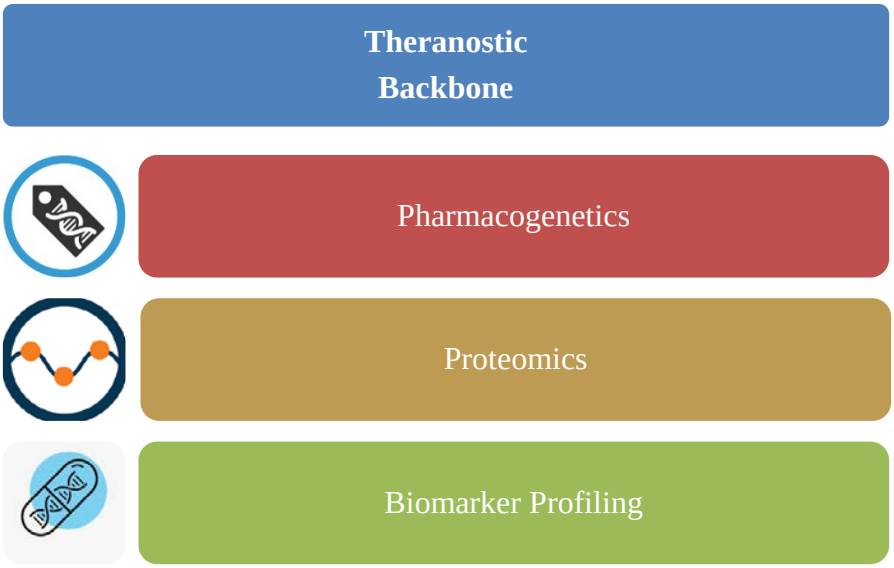

Figure 1.1: Theranostic Backbone.

Pharmacogenetics

The science that studies human response for specific drugs, overall health based on their DNA sequencing using biomarker; it is playing an essential role in drug delivery applications, and it includes RNA and protein applications in therapy decisions.

Proteomics

The science which studies characteristics, applications, functions, isoforms for all proteins in the human body using the genome map analysis. Proteins have crucial vital keys in the body; they also have therapeutic capabilities that make them essential in analysis and their functions.

Biomarker

Biomarkers profiling is crucial for drug delivery applications in addition to diagnostics and nanomedicine. Biomarkers act as an interface between genes, proteins, and identification diseases. It opens a real opportunity to develop new drugs or redesign protein replaced by the damaged one by binding proteins and a particular disease. Every person has his/her particular profile; thus, theranostic can design a specific therapy for every individual based on his/her biomarker profile by avoiding side effects for medications, improving drug response properties, and increase bioavailability. Today's biomarker is tomorrow, theranostic (Kim et al., 2013).

Theranostic based on new technologies and advances in genetics, molecular-scale elements and particular diagnosis and therapy platforms; thus can successfully make a real transition from universal medicine "one medicine for all" to personalized medicine "specific drug for a specific individual." by studying the personal drug response and variations we have the theranostic approach strategy besides theranostic could be improve the prognosis and this lead to create better diagnosis and therapy map. Theranostic is a union between therapeutic and diagnosis to create a specific treatment plan for an individual's pathology (Jeelani et al., 2014).

Theranostic means a single-agent ability to build a complete therapeutic model, which includes diagnosis, drug delivery, and monitor drug response (Figure 1.2). The theranostic approach studies the patient-drug interaction; after that, designing a customized medication based on

previous interaction. the theranostic approach in medicine providing such magnificent improvements as the following:

1- Cost-effective treatment platforms.

2- Specific medicine strategies and protocols

3- Providing pre-clinical development strategies.

4- Increase clinical trial efficiency.

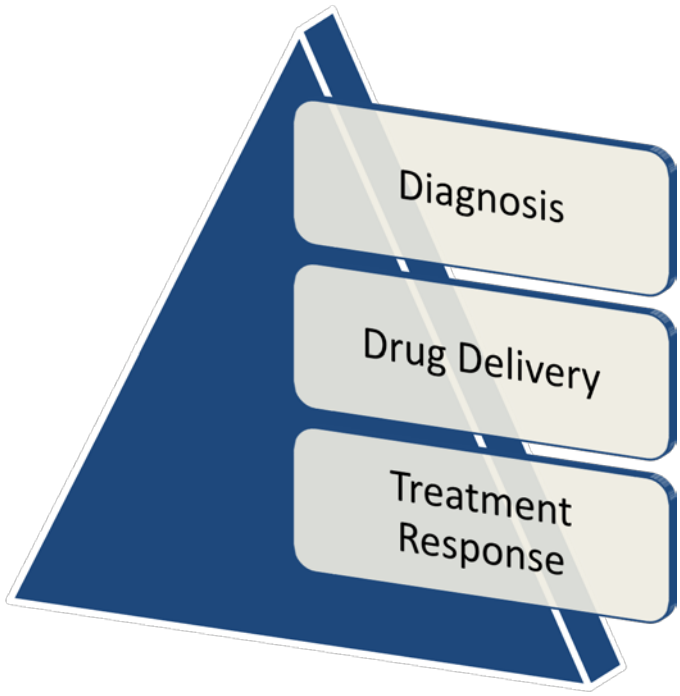

Figure 1.2: Therapeutic Model in Theranostic Approach

1.3 Theranostic Concept

Personalized medicine and nanotechnology focus on diagnosis and therapeutic applications in one hybrid system called theranostic. With help in nanomaterial and nanostructures, proper diagnosis and therapeutic targeting disease and evading the Immune-response sites can be achieved. Figure 1.3 shows most of the materials that can be used in various Theranostic applications.

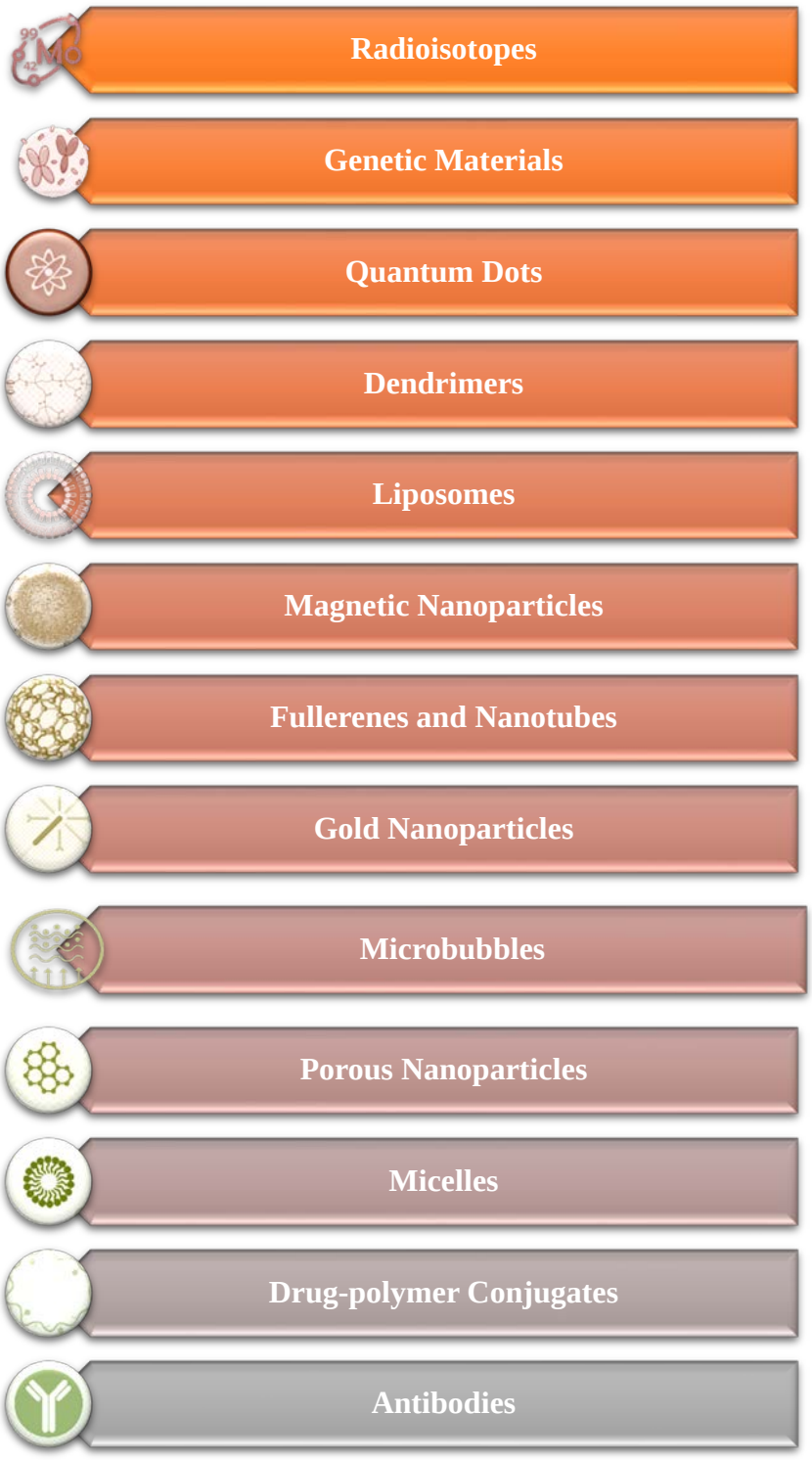

Figure 1.3: Theranostic Materials Platforms

1.4 Theranostic in Personalized Medicine

Personalized medicine is the modern aspect and rich field in healthcare research. It can be used after and before a treatment plan. It is engineered to be a specific treatment for the specific patient instead of a global medicine vision that all treatments fit all patients. It is based on metabolic, protein, genes, and molecular analysis for a specific patient, although Predicting a specific disease's occurrence in the future. PM can be advanced pharmaceutical development by monitoring the drug response result for a specific disease (Scannell et al., 2012). biomarkers' discoveries and theranostic approach have been forwarding the PM to be the next care of the future. Providing imaging diagnostic systems and therapy sequentially makes the perfect theranostic approach widely used in PM strategy. Theranostic plays an essential role in Personalized medicine by presenting early disease detection, staging, therapy selections, identified early side effects and improving the follow-up therapies (Kim et al., 2013). for example, in cancer theranostic system identifies the cancer class, obtain a diagnostic image after that apply a tailored therapy, and finally monitoring the treatment response. Nanotechnology is crucial for theranostic improvement by utilizing nanostructured materials with diagnostic and therapeutic functions based on their distinctive properties.

Personalized medicine exploits nanotheranostic ability to acquire imaging diagnosis systems and screen for specific diseases such as cancer and improving therapeutics and diagnostic and delivering strategies. In particular, the nanothersnostic system improves personalized medicine quality. Theranostic have some challenging issues due to lacking biomarkers for early-stage detections. Biomarkers are molecules such as proteins, genes, and other biological molecules; biomarkers have been used to improve disease prognosis, an essential process in personalized medicine. Prognosis can help in choosing the perfect drug and dose in treatment protocols. Biomarkers help to obtain more understanding of distribution and correlations, thus developing of personalized medicine platform. The theranostic system can help personalized medicine by utilizing nano-drug carriers and imaging agents to improve personalized medicine theranostic systems. Theranostic personalized medicine system relies on the targeting moiety, imaging, and therapy techniques used; besides, all the previous objects should be balanced and well understood. The future of personalized medicine is highly based on pharmacokinetics, toxicity

studies, and quality control on a pre-clinical scale. Personalized is not limited to biomarkers, but it relies on developing detections of diseases and therapeutic response predictions.

Personalized medicine faces significant limitations, such as the viability of drugs, real-time monitoring in pharmacokinetic applications. However, the recent advancement in imaging and therapy modalities and nanomedicine applications approaches like image-guided therapeutic systems (nanothernostic) are promising to avoid Personalized medicine.

1.5 Theranostic Micro and Nano Particles

1.5.1 Microparticles

Microparticles ranged in size from 1 to 100 nanometer it has unique structures. MPs have various structures such as mononuclear, multi-wall, matrix, microspheres, and microcapsules. MPs function directly based on the particles' morphology and structures—MPs characteristics based on manufacturing processes methods.

MPs are used widely in various medical applications such as drug delivery systems due to their size and shape (Bale et al., 2016). Also, MPs are used in pharmaceutical applications due to their formulation features (solids, liquids, semisolids).

In terms of bio carrying, MPs superiority over NPs by not infiltrate through interstitium fluid space between cells means it can be used locally (Wang et al., 2016). MPs are advantageous in bio carrying and encapsulation applications.

Microspheres and Microcapsules

Microspheres are biodegradable polymers microparticles; it can be used in medical applications like drug carrier systems. The biocompatibility features make microspheres suitable for drug-carrying. Microspheres have two main types: natural (chitosan, starch, alginate, albumin, gelatin) and synthetic ones (polylactic acid). In the drug delivery system, microspheres are used in targeting and drug release applications; furthermore, they can be used as a protector for various drugs (Joshi and Joshi, 2019).

Bioadhesive microspheres are used in targeted therapy. They present a suitable coating environment for drugs on specific surfaces, thus prolonging the therapeutic agent's prolonged

delivery time to the site of interest. Magnetic microparticles are also used in targeting therapy applications. It is used for both drug carrier and diagnostic purposes by controlling these particles using an external magnetic field. Besides, they are used in hyperthermia therapy procedures (Joshi et al., 2011). The floating microsphere is used in drug-releasing applications depending on their low-density compared to the gastric juice to be extended drug release. Radioactive microsphere ranged from 10-30 micro. These microparticles in targeting applications can be directly linked to specific tissues (Joshi and Joshi, 2019).

Microcapsules are a particular size of the microsphere with heterogenous complex particles. A microcapsule is a reservoir of particles encapsulated inside a closed wall. Most microcapsules applications are in the carrying and encapsulation process.

Microbubbles

Microbubbles are colloidal structures filled with gas. It ranged from 0.5 micrometers to 10 micrometers in diameter. Microbubbles are extensively used in different medical applications such as drug delivery systems and bioimaging. They are used as an imaging contrast agent and as a bio carrier. Microbubbles are consisting of two main parts the core and the shell. The core is typically filled with gas, and the shell is combined with different molecules such as polymers, proteins, lipids, and other.

The main advantages for microbubbles that it is safer than the other imaging contrast agents such as MNPs. Microbubbles were developed to improve the ultrasound (US) imaging technique performance. Ultrasound waves vibrate them as pressure changes, they showed better resonating features than the tissues themselves, and due to their sizes, they are used in measurement applications like blood flow inside the cancerous cells (Robertson, 2019).

Microbubble used in drug delivery system and cancer applications; they are used to get rid of traditional chemotherapy side effects. Microbubbles can be used effectively in drug-releasing applications by controlling the dose required; thus, reducing the side effects. Several studies showed that microbubbles have significant results in reducing side effects and providing better care to cancer patients (Robertson, 2019).

In general, microbubbles act like a carrier for both antibodies and anti-cancer drugs, and these bubbles are controlled and tracked inside the body using ultrasound waves till they targeted the tumor cell sites. When these bubbles reach the targeted cells, a high frequency of ultrasound wave is applied.

Hybrid Janus Microparticles

Janus microparticles is an asymmetric functionalized polymeric material with two different surface properties; each face has specific physicochemical properties that differ from the other surface. The characteristics of this particle depend on the material which is used through manufacturing or different functional group, due to these features. Janus microparticles can carry two opposite properties consequently, like hydrophilic/hydrophobic and magnetic/fluorescence (Li et al., 2011; Lattuada and Hatton, 2011; Granick et al., 2009).

Janus microparticles focus on scientists' attention to medical applications, especially for theranostic approach as a therapeutic molecule and imaging agents for different imaging techniques. Janus microparticles can carry different properties (mechanical, physical, chemical) in one single particle.

Janus microparticles are used in various medical applications such as bioimaging, therapeutics, bioimaging, diagnosis, and drug delivery (DDS). The asymmetry of these microparticles makes them suitable for drug release applications. Janus microparticles are coated by calcium carbonate (CaCO3) with platinum, moving to tumor acidic environments (Guix et al., 2016).

1.5.2 Nanoparticles

Quantum Dots

Quantum dots (QDs) nanoparticles are made of crystals, and they have significant mechanical and electrical properties with sizes ranged from 1-10 nm. Quantum dots have several properties, such as vigorous lighting properties, nor affected by photobleaching with a high photostability profile, and they are used in vivo approaches.

Liposomes

Liposomes are lipid molecules with a spherical shape and have multiple amphophilic membrane layers ranging from 50 to 500 nm. (Bozzuto and Molinari, 2015). Two prominent characteristics for liposome structures, multiple phospholipid an aqueous core.

Dendrimers

Dendrimers, polymeric tree-shaped structures have various shapes with nanoscale dimensions. Dendrimers composite of three main parts core, branches, and surface (Klajnert and Bryszewska, 2001). mainly, it conjugates with different molecules and is used in various medical applications such as bioimaging as a contrast agent, especially for MRI, drug delivery system (DDS), and gene delivery (Dufe's et al., 2005; Oliveira et al., 2010).

Polymeric Nanoparticles

Polymeric nanoparticles contain specific particles and nanofillers distributed in the matrix. They have different shapes like spherical, capsules, fibers, and other shapes. Polymeric NPs ranged from 1-50 nm in diameter. Polymeric NPs are used widely in drug carrier applications due to their properties in release controlling, drug protection, and bioavailability (Soppimath et al., 2001; OwensIII and Peppas, 2006). The drug dissolved and released in nanocapsules and shells, respectively.

Gold Nanoparticles

Gold Nanoparticles (AuNPs) have shown significant results in the theranostic application and is considered a promising agent for various applications. AuNPs have several advantages, such as easy to produce, bioconjugation properties with good biocompatibility and toxicity properties (Boisselier and Astruc, 2009).

Carbon Nanoparticles

Carbon-based nanoparticles (CNPs) have significant characteristics that make them promising theranostic NPs like thermal, optical, structural diversity, and chemical. Most Carbon nanostructures used in medical applications are carbon nanotubes, graphene quantum dots, and

graphene oxide. CNPs are used in drug delivery systems (DDS) and cancer theranostic applications (Maiti et al., 2018).

Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) are used widely in medical applications, especially in hyperthermia therapy procedures and Magnetic Resonance Imaging (MRI) techniques. MNPs can be used in cancer treatment applications by controlling NPs using an external magnetic field. MNPs sometimes could harm the healthy tissue because they are nonspecific accumulation, especially in the liver and spleen. MNPs are also used in drug delivery systems (DDS), especially those containing iron oxide bases. MNPs are widely used due to their high compatibility and biodegradability features.

Up-Conversion Nanoparticles

Up-conversion nanoparticles (UCNPs) are composed of fluorophore molecules that have remarkable optical properties. UCNPs can convert wavelengths from long to short. UCNPs are used in various medical applications like Photodynamic therapy and bioimaging techniques. UCNPs have a wide range of emission (UV to v-NIR). UCNPs are carried by antibodies and leading to destroying tumor cells.

The two tables below, Table 1.1, illustrate comparing theranostic nanoparticles and microparticles in different applications, and Table 1.2 shows the difference between theranostic nanoparticles (NPs) and microparticles (MNPs) as ultrasound (US) agents.

Table 1.1: Different Theranostic Nano and Micro Particles Applications

Imaging agent	Size	Applications	Ref.
Magnetic NPs	20-200 nm	MRI contrast enhancement	Sun et al., 2008
		Cancer imaging	
		Prolonged delineation of tumor cells	Enochs et al., 1999
		Enhance cellular internalization	
		Slower clearance from tumor sites	Varallyayet al., 2002
		Cardiovascular disease imaging	
		Enhance contrast of MRI in early lesion detection	Sosnovik et al., 2007
		Molecular imaging	
		Cell migration imaging	
		Apoptosis detection	Nahrendorf et al., 2006
		Enzyme activities imaging	
			Bulte and Kraitchman, 2004
			Shellenberger et al., 2004
			Tung et al., 2000

Table 1.1 Continued

SPIONs	10-100 nm	Liver tumor imaging Metastasis imaging	Corot et al., 2006 Semelka and Helmberger, 2001
USPIONs	3 nm	Identification lymph nodes metastases with MRI Treatment of prostate, breast and colon cancers Improving delineation of brain tumor boundaries Quantify tumor volumes Distinguishing neoplastic tissue from necrosis Evaluating risks of acute ischaemic	Harisinghani et al., 2003 Harisinghani et al., 2003 Harisinghani and Weissleder et al., 2004 Enochs et al., 1999 Neuwelt et al., 2014 Teschner et al., 2005 Kooi et al., 2003
CTX-targeted IONPs	10-100 nm	Enhance tumor contrast	Sun et al., 2008
MNPs-annexin V	20-200 nm	Non-invasive quantification of apoptosis response	Schellenberger et al., 2004

Table 1.1 Continued

AuNPs	5-400 nm	Fluorescence modulator Promote SERS dye adsorption PAT imaging improvement	Vinhas et al., 2015 Xia et al., 2008 Wang et al., 2011
Au nanobeacons (Au-ssDNA)	15.1+/- 1.1 nm	Quenching (fluorescence observation) Tracking silence effect in cells	Vinhas et al., 2015
Au-DENPs	2-4 nm	In vivo and in vitro imaging for lung adenocarcinoma	Wang et al., 2011
Gd-loaded Au-DENPs	2-4 nm	Hybrid imaging (CT/MRI)	Wen et al., 2013
AuNPs-DTPA	2-2.5 nm	Increasing stability for X-Ray CT and MRI Radiotherapy sensitizer	Alric et al., 2008
AuNR-SiO2-FA	5-400 nm	Increase sensitivity in X-Ray Tumor targeting in CT Photothermal therapy	Peng et al., 2011
Co@pt-AuNPs	5-400 nm	Monitoring progression of Aβ protofibrils in Alzheimer	Boisselier and Astruc, 2009
Au nanorods	38, 28, 17 nm	Improve spatial resolution in PAT Deep penetration depth in PAT	Webb and Bardhan et al., 2014

Table 1.1 Continued

		Image contrast improvement in PAT	
Liposome-AuNR hybrid	100-120 nm	Real-Time imaging of siRNA	Taruttis et al., 2013
Microbubbles	0.5-10 µm	MR guided US in therapy MRI, PET, DEI X-Ray PET/CT	Kogan et al., 2010
Hyperpolarized-gas microbubbles		Blood vessel imaging Safer in renal imaging	Mosbah et al., 2008
18F-lipid-labeled microbubbles		Biodistribution monitoring Kidney function improvement	Tartis et al., 2008 Williams et al., 2008
Lipid-coated perfluoro carbon microbubbles		Optimize DEI scattering	Kogan et al., 2010
Microspheres	1-1000 µm	CT liver cancer imaging MR liver cancer imaging	John et al., 2012
Protein-shell microspheres		MRI, US Imaging-guided drug delivery Image resolution improvement Providing Real-Time imaging	John et al., 2012
RGD-NR-SPIO protein microsphere		MM-OCT imaging Hybrid imaging	John et al., 2012

Table 1.1 Continued

Janus microparticles	50-90 µm	Real-Time and visualization for optical imaging	Le et al., 2019
Drug carrier			
Fibroblast IONPs	10-20 nm	In vivo coronary arteries	White et al., 2006
Magnesium NPs	10 nm	Radiation therapy for cancer	KumarCSSR and Mohammad, 2011
Iron oxide-PEG	10-20 nm	Targeting	Zhang et al., 2004
Mesoporous silica NPs	2-50 nm	Tumor cells suppression	Liu et al., 2016
AgNPs-polymer	2-20 nm	Antimicrobial applications	Pozdnyakov et al., 2016
Graphene oxide (GO)	1.1 nm	For pH-sensitive drugs	Ma et al., 2015
Quantum dots composites	2-10 nm	Hypoxia RNA Molecular Imaging Targeting Drug delivery	Zhu et al., 2015 Bwatanglang et al., 2016 Wang et al., 2016
Carbon Dots	1-10 nm	Imaging drug delivery	Feng et al., 2016
DNA NPs	2 nm	Newcastle disease	Firouzamandi et al., 2016
Folate liposome	100-122 nm	Melanoma	Chen et al., 2016

Table 1.1 Continued

Lipid nanotubes	10-1000 µm	Anti-cancer drug delivery	Ilbasmis-Tamer et al., 2016
Lipoprotein NPs	7-13 nm	Drug delivery	Czapar et al., 2016
Polymer NPs	1-1000 µm	Gene delivery Drug releasing Stem cells Drug delivery Passive targeting Lung cancer Breast cancer	Zhao et al., 2016 El-Meliegy et al., 2016 Das et al., 2016 Tamai et al., 2000 Bolu et al., 2016 Van et al., 2010 Obayemi et al., 2016
Micelles	100 nm	Delivery vehicle in cancer	Unger et al., 2014
Liposomes	100 nm	Delivery vehicle	Schroeder et al., 2019
Microspheres	1-8 µm	Delivery vehicle	Reich, 1998
Microbubbles	1-8 µm	Delivery vehicle	Lentacker et al., 2009

Abbreviations**:** NPs, nanoparticles; MRI, magnetic resonance imaging; SPIONs, superparamagnetic iron oxide nanoparticles; USPIONs, ultrasmall superparamagnetic iron oxide nanoparticles; CTX, chlorotoxin; IONPs, iron oxide nanoparticles; MNPs, magnetic nanoparticles; AuNPs, gold nanoparticles; SERS, surface enhanced Raman scattering; PAT, photoacoustic imaging; Au-ssDNA, gold-single stranded DNA; Au-DENPs, dendrimers entrapped gold nanoparticles; CT, computed tomography; AuNPs-DTPA, gold nanoparticles coated with dithiolated diethylenetriamine pentaacetic acid; AuNR-SiO2-FA, silica layer-coated gold nanoparticles with folic acid; Co, cobalt; pt, platinum; siRNA, small interfering

Table 1.1 Continued

RNA; US, ultrasound; MR, magnetic resonance; PET, positron emission tomography; CT, computed tomography; DEI, diffraction-enhanced imaging; RGD-NR-SPIO, arginine-glycine-asparagine-Nile Red-superparamagnetic iron oxide; MM-OCT, magnetomotive optical coherence tomography; AgNPs, silver nanoparticles; PEG, polyethylene glycol

Table 1.2: Difference Between NPs Ultrasound Agents and MNPs Ultrasound Agents

	Nanoparticles (NPs)	**Microparticles (MNPs)**
Size	Less than 500 nm	More than 500 nm
Material needed	High	Cheap Widely used (availability)
Stability	Aggregation High surface energy	No aggregation Strong oscillation
Loading efficiency	Low loading	High loading
Cell uptake	Easy	Very difficult
Image effect	Very weak Difficult in clinical applications	Strong Commercial for clinical applications

1.6 Theranostic Applications

1.6.1 Diagnosis

Recently, the emergence needing for non-invasive medical imaging is required for improving the nanomedicine therapeutic strategies. Most nanomedicine applications are designed to be a diagnostic manner. In pre-clinical procedures, labeling nanotheranostic particles with imaging contrast agents have significant contributions. Different non-invasive imaging techniques can obtain more biological information at a molecular scale-like circulation time, targeting accumulation and localization in both theranostic and therapeutic medicine. nanodiagnostic

NPs proved their roles in different medical applications, such as providing better information and understanding for physiological properties in normal and abnormal tissues, treatment procedures, and imaging labeling applications (Rizzo et al., 2013).

Diagnostic agents are used widely in vivo procedures on small animals; also, they have limitations in pharmacokinetics applications. Diagnostic agents with MR used in blood vessels tumor, circular system abnormalities (Fink et al., 2003; Chiribiri et al., 2008; Wagner et al., 2002), stem cells, and liver legion visualization (Politi et al., 2007). for example, Resovist IONPs used in stem cell monitoring (Zhu et al., 2006), lymph nodes (Harisinghani et al., 2003), cancer vaccination, and in macrophages activities (Tang et al., 2009).

Lately, diagnostic agents are used widely in tumor visualization and detecting receptor overexpression in abnormal cells. Three factors are essential for using cancer application diagnostic agents: quickly discharged outside blood vessels, high penetrate property, and fine distribution features.

Imaging of infection diseases

It is not easy to acquire images for infections because it depends on many factors. It needs a well-sophisticated design and specific radiopharmaceuticals. Different infections factor, needing advanced techniques is required. Labeling leukocytes is used in infection and inflammation imaging applications (Kumar, 2005); also, it is used in visualization in clinical procedures (Palestro et al., 2007).

Diagnostic agents like radiopharmaceutical must provide an early diagnosis with low radiation and dose intake besides providing a clear difference between inflammation and infections through different types of tissues such as soft and muscle tissues. These agents should provide safe imaging (nontoxic), cost-effective, rapidly discharge from the bloodstream, not aggregation on the specific part inside the body like organs (Gemmel et al., 2009).

Leukocyte Targeting

Leukocytes activate specific infections and expressing receptors and leaving for interstitial and accompanying inflammation. Proteins and peptides can cross through the endothelium with labeled signaling molecules like chemokines, cytokines, and somatostatin, targeting

capabilities. These small signaling molecules targeting neutrophils, lymphocytes, and mononuclear cells (Peters, 1998) are also used in inflammatory disease targeting. Besides, it is promising for seeking radiotracers. This process faces limitations due to toxicity, high immunogenic, and low doses in signaling molecules (cytokines and chemokines) (Kumar, 2005; Tulchinsky and Peters, 2005). the promising radiochemistry agent is cytokine interleukin-8.

Micro-Organisms Targeting

Radiolabeled ciprofloxacin and antimicrobial agents are used in these applications. There is no need for leukocytes in micro-organism targeting (Kumar, 2005). many studies from the 1980s nominated using antibiotic radiolabel molecules as imaging tracer for Single Photon Emission Computed Tomography (SPECT) and Positron emission tomography (PET) like 18C, 3H labeled, 18F-fluconazole, 99mTc-erythromycin.

1.6.2 Therapy

Biomarkers

Theranostic is an identifier of biomarkers that can be used in personalized medicine by providing a better bioavailability and avoiding unnecessary effects during the treatment plan. In general, theranostic methods improve drug development processes (Table 1.1).

Table 1.3: Recent Theranostic Research in Biomarkers

Biomarker	Disease	Drug	Ref.
UGT1A1	Colorectal cancer	Camptosaw TM	Vogenberg et al., 2010
DPYD	Breakdown chemotherapeutics		Vogenberg et al., 2010
DLBCL	Patients with activated B-like DLBCL	Cytarabine daunorubicin	Golub et al., 1999
ERBB2	Breast Cancer	Herceptin TM	Harari et al., 2000

Table 1.3 Continued

KRAS	Metastatic colorectal cancer	Erbitux TM	Van Cutsem et al., 2009

Abbreviations: UGT1A1, bilirubin uridine diphosphate glucuronosyl transferase (bilirubin-UGT) enzyme; DPYD, Dihydropyrimidine dehydrogenase; DLBCL, Diffuse large B-cell lymphoma; ERBB2, Receptor tyrosine-protein kinase; KRAS, Kirsten rat sarcoma viral oncogene

Chemotherapy

Theranostic' role in chemotherapy summarizes by improving the drug distribution inside interest cells. nanotheranostic methods are applied to control and deliver a proper function due to their characteristics like permeability, biocompatibility, drug carriers, prolonged circulation time (Avendaño and Menéndez, 2015). for example, using a hydrophilic shell layer to prolong the circulation time and stimulate the tumor cell site's accumulation process.

Biotherapy

Gene therapy is used in disease treatment by transform specific genetic materials into the area of interest. It provides therapeutic processes include controlling protein amount that reaches the disease cells, control gene expression, and stimulate a cytotoxic protein in featured sites; also, it has monitoring capabilities. Most modern drugs and medications are biotherapies, thus needing to calculate the treatment response for patients precisely. Theranostic approaches have constituted a new monitoring method for biotherapies.

Immune Response

Nanotheranostic particles have cross-linking abilities that are used in different immune cells like T-cells. It helps in releasing these cells with drugs. For example, MNPs can be used to prevent early tumor cell's constitution.

Cancer Therapy

By improving target therapy, nanotheranostic can acquire specific images that help in diagnostic at a molecular level. For example, antibodies incorporate nanomedicine and help in

a synergistic effect, and reduce the toxicity of the tumor cells. nanotheranostic particles with significant light characteristics can be used in the identification and detection of cancer cells.

In the next chapter, we will discuss theranostic applications in cancer therapy in detail.

Cardiovascular Diseases

CVD is a leading disease worldwide. It involves heart, blood vessel diseases such as coronary artery diseases (CAD). nanotheranostic applications obtained several successes in the preclinical stage, and it is the promised future in this field. Nanotheransotic provides real-time explorations, noninvasive and translation approaches. Till now, there is no standard to evaluate the nanotheranostic in these types of diseases (CVD) (Fitzgerald et al., 2011). In atherosclerosis, ultrasmall particles of iron oxide (IOPs) are the first theranostic agent used as a noninvasive imaging approach besides being used as an evaluator for drug therapy in atherosclerosis (Kooi et al., 2003; Tang et al., 2009). microbubbles are also used as a theranostic agent in targeting applications in CVD. They can bind with platelets, thus enhancing imaging for thrombi using ultrasound imaging; besides, they could help in clot localization and prevent them from the constitution in blood vessels (Wang et al., 2016). nanotheranostic can obtain a development in therapeutic and monitoring strategies to anticipate drug response in fibrinolytic applications.

Central Nervous System

Traditional medical methods in the central and peripheral nervous systems still not sufficient to prevent the disease from progression; furthermore, it cannot even reduce the symptoms' effects or brain injury or related neurodegenerative diseases. Theranostic approaches present a suitable and well-engineered system involving transport imaging contrast probe or therapeutic one through the blood-brain barrier (BBB) to the entire nervous system in the human body. Theranostic techniques afford improvements in the central nervous system, thus understanding the disease state and for surgical purposes. MRI modality is the most used in brain disorders. PET is also used in monitoring various types of disease and pathophysiology of Alzheimer's disease and obtain a better understanding. Understanding the mechanism of pathophysiology and neurodegenerative state radiolabeled amyloid ligands are used.

1.7 Theranostic Nanomedicine (Nanotheranostic)

Nanotechnology is one of the main cornerstones in the medical research field. Physicochemical properties for nanomaterials such as surface area, loading capacity, and easy functionalization make them leading in modern research applications. Nanotheranostic directly related to the personalized medicine approach. Personalized medicine or, in another way, we can say P4, which means Predictive, Personalized, Preventive, and participatory (Hood et al., 2013) Approach. Personalized medicine builds on different individual data like drug response, health conditions, disease history, and environmental factors.

Nanotechnology is the study that deals with designing atoms and nanomolecules (1-100 nm) and their characteristics. Different size in nanosystems mean different applications, and production is based on three main properties biological, physical, and chemical. one of the most promising field in nanotechnology is nanomedicine technology, where nanomaterials are using for diagnosis, treatment, controlling, and monitoring all biological systems in human body (Thomas et al., 2015). nanotechnology rely on three disciplines delivering therapeutic and diagnostic agents, targeting therapy and treatment platform for diseases. Nanomedicine achieved tremendous advances in medicine such as early detection, improved treatment plans, reduced side effects in different medical procedures, and cancer therapy innovations. Nowadays, some technologies can imagine the area of interest or infectious sites with nanodevice assist. Nanoparticles are essential due to their magnetic properties, improving the imaging models, and imaging-guided therapy techniques. For after monitoring applications, the drug nanocarriers imaging is essential to detect drug response, drug distribution, drug effects, and monitor the pharmacokinetics in the delivery system (Thomas et al., 2015).

CHAPTER 2

THERANOSTIC IN CANCER

2.1 Nanotheranostic System

Nanotheranostic system is a hybrid medical system that combines Nanotechnology, diagnostic, and therapy (Figure 2.1).

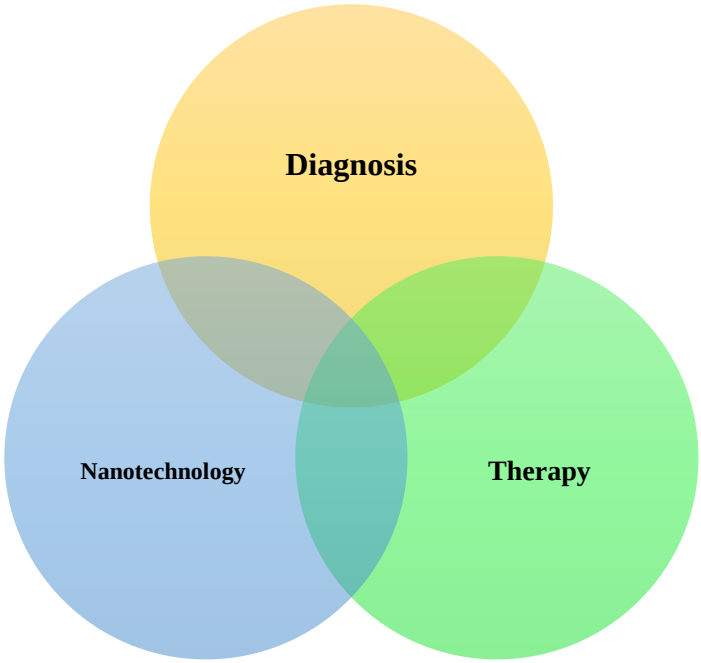

Figure 2.1: Schematics Nanotheranostic System Component

Nanotheranostic system is a promising and trending advanced in the medical research field, and it provides crucial functional nanomaterials for different medical protocols. It includes diagnosis, therapy, and drug response monitoring from the moment enter the body till it outside the body. These systems' advantages lie in real-time monitoring and the noninvasive manner; it also showed a significant improvement in treatment performances. Theranostic agents must be include imaging agents, therapeutic agents, and carriers to be applied in imaging and various

therapeutic applications. Targeting ligands are required for targeting therapy strategies in theranostic systems (Figure 2.2).

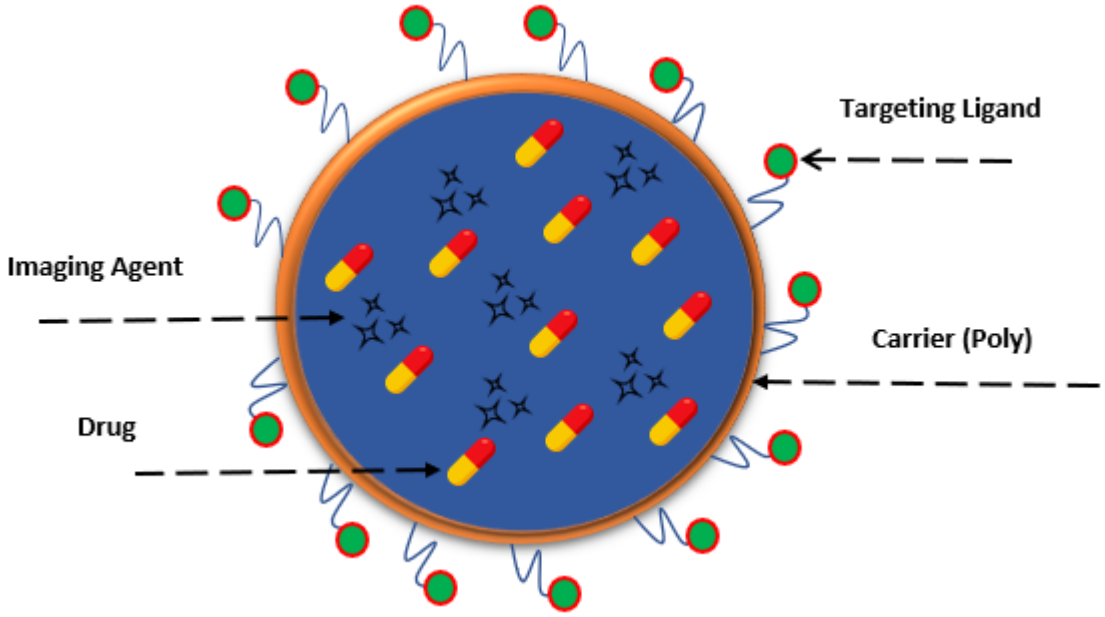

Figure 2.2: Targeting Ligands in Theranostic Agent

2.2 Nanotechnology Progress in Cancer Research

Nanomedicine is widely used in most medical procedures, such as monitoring, diagnosis, treatment, and control. To meet the medical requirements, the work should be done on the molecular scale. One of the leading medical procedures is diagnostic; it can be in vivo or in vitro. In vitro used nanoparticles or nanodevices to capture, concentrate, and recognize molecules, and in vivo using a synthetic molecule that can be a promising contrast agent for medical imaging technique. X-ray, nuclear imaging, MRI, Spectroscopy, and ultrasound are the classical medical imaging modalities used widely in different applications in medicine. (Boisseau and Loubaton, 2011; Toy et al.,2014).

Medical imaging is an excellent tool for diagnostic and image-guided therapy, and it is beneficial for monitoring diseases. Contrast agents are beneficial in detecting and identification

for diseases with different shapes and morphological forms also it can be used in targeting treatment applications. Contrast agents have also been used in drugs and other molecules accumulation activities inside the cells, inflammation monitoring purposes, and tumor detection and localization. (De Souza et al., 2015).

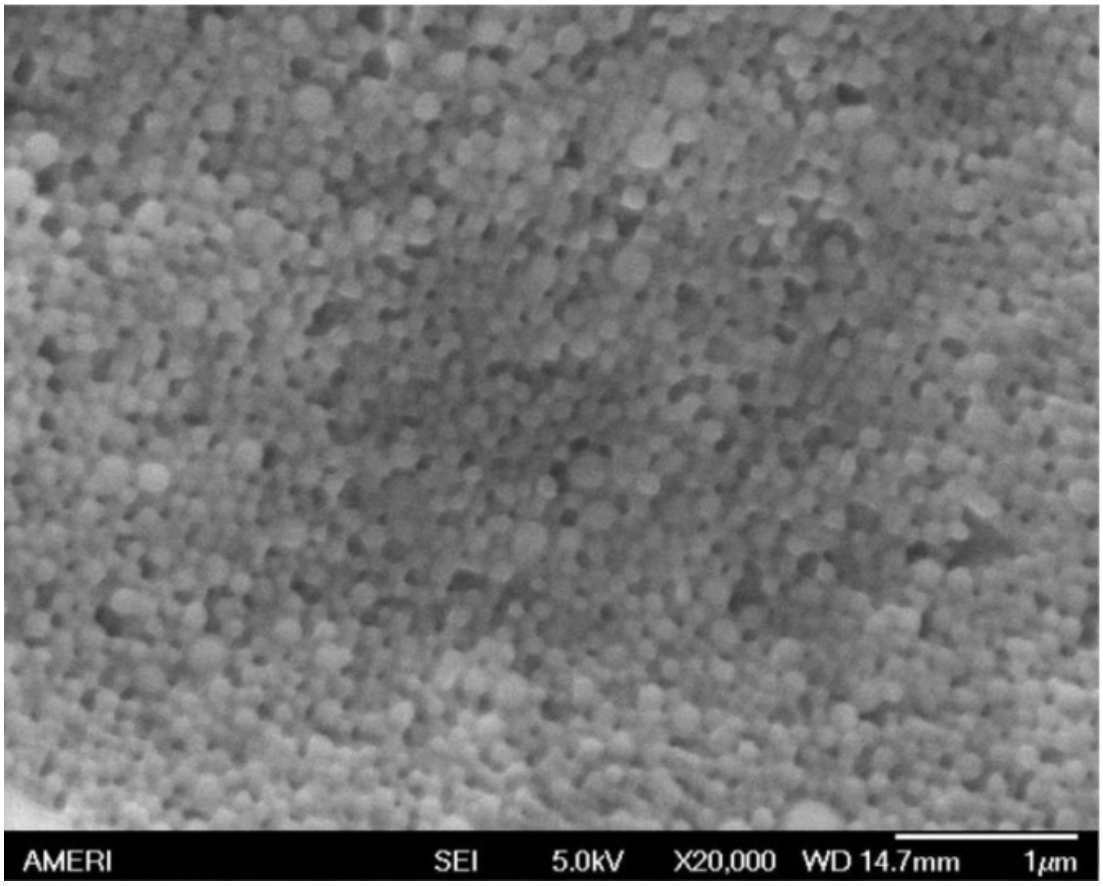

Figure 2.3: NPs Loaded with Indocyanine Green and DOX.

After cancer cells metastasized, it can be detected by imaging, and this is not enough because it is essential to know the nature of cancer cell (malignant or benign) and for developing a better responsive action for the treatment, and this is why we need to take a biopsy to identify cancer and make it visible too. Nanoparticles accomplished this mission and made it easy to reach. For

example, metal oxide nanoparticles loaded with antibiotics can be used as a contrast agent for MRI or CT to recognize specific tumor cells (Boissea and Loubaton, 2011).

Imaging is not limited to theranostic applications. It may be used in the drug delivery system by acting as a stimulus for drug release activation. There are many types of stimuli, such as temperature, ultrasound, and even laser light. An enzyme can be response existence for specific biomolecular.

Table 2.1: Medical Imaging Modalities

Computed Tomography (CT)	**Magnetic Resonance Imaging (MRI)**	**Positron Emission Tomography (PET)**	**Ultrasound (US)**	**X-Ray**	**Hybrid Modalities**
Abdomen	Neuro-Imaging	Oncology	Transrectal	Radiography	PET-CT
Appendix	Cardiovascular	Neuro-Imaging	Breast	Mammography	PET-MRI
Bladder	Musculosketel	Cardiology	Abdominal	Fluoroscopy	SPECT-CT
Brain	Liver	Infected Tissues	Gallbladder	Contrast	MRI-SPECT
Breast	Gastrio-intestinal	Pharmacokinetics	Spleen	Arthrography	MRI-CT
Chest	Functional	Small Animal	Doppler	Discography	US-MRI
Cervix	Oncology	musculoskeletal		Dexa Scan	US-CT
Kidney	Phase Contrast			Upper GI	
Lungs					
Pancreas					
Esophegous					

Because it is dangerous to take the brain's biopsy, it is hard to detect brain tumors. Still, scientists have developed a nanostructure strategy based on an endoscopic nano-patterned pen that can be used to take protein and cells from the brain's surface adhesion region with no harm.

The application of nanoparticles structures in medicine summarized but not limited to the following: controlling drug delivery for theranostic systems, providing target delivery for biological substances, cancer diagnosis and therapy by identify tumor cells and destroy the abnormal cells, and restoration of human tissues with higher biocompatibility (Logothetidis, 2011; Stylios et al., 2005).

Nanoparticles have such unique properties, such as nanometric size, remarkable physicochemical properties, and high surface volume ratio. They can also improve drugs' stability in various biological environments, expand blood circulating time, and control drugs (Wicki et al., 2015).

Nanostructures are smaller than human cells; they are similar to enzymes and receptors in humans. After the penetration started, nanoparticles can detect the abnormalities(diseases) and cure it by delivering specific biological molecules for the zone of interest (Stylios et al., 2015).

2.3 Personalized Medicine in Cancer

Personalized oncology based on personalized medicine approach used in cancer treatment plans considering the heterogenic nature in cancerous cells. The problem with tumor cells is that it can be tricky to identify it, especially when they respond to a specific therapy type. Clinically they seem similar, but at the molecular level, they are different, and this is the challenge. The tumor contains different stem cells with different properties like metastatic and therapeutic responsive and can be identified in the breast, colon, and lung. Because of cancer heterogeneity, it is unrealistic to develop a drug for all patients. to solve this and break this barrier, treatment development should be based on individual disease profiles to meet the patient's particular characteristics (Liu, 2012).

As we mentioned before, cancer should be identified at a molecular level to obtain a perfect or a promising personalized medicine platform treatment for cancer; thus, initiation and innovation for tumor cells are obtained effectively. Nanotheranostic materials like peptides, antibodies, and others play a crucial role in this development process due to their functions in targeting cell ligands and drug delivery to the area of interest; besides, they have a diagnosis therapeutics and monitoring capabilities for different cancer therapy treatment plans.

Deliverance is not limited to a drug, but these particles can deliver specific cells and gene materials "from the patient" to improve different medical procedurals' performance in diagnosis and therapy (Liu, 2012; Toy et al., 2014).

In chapter one, we talked about biomarkers profile in personalized medicine. Biomarkers can be used in cancer personalized medicine by identifying the tumor cells' nature and used in the therapeutic protocol. It is hard to identify the cancer markers, and this is why biomarkers are essential. Theranostic particles can diagnose, prognosis, and treatment monitoring for tumors cells in a non-invasive way. MNPs can be used to catch cancers in the bloodstream, QDs can provide early detection for any cancer constitution, and finally, biosensors can identify the biomarkers in tumor cells (Liu, 2012).

Cancer treatment platforms mainly rely on the targeting therapy approach, but targeting therapy faces some limitations due to the heterogeneity of tumors cells even if a specimen take because it does not tell the whole story; thus, it leads to failure to present the right treatment and cause drug resistance. By using molecular-scale characteristics, perfect classification is obtained. Better classification means better specific therapy for patients and cost-effective.

2.4 Theranostic Applications in Cancer

Nanotheranostic have various types of applications in the medical research field. Nanostructures agents can provide diagnosis and therapeutic applications because of their magnificent properties. In clinical cancer management applications, nanotheransotic offers several advances in cancer applications like increasing patient satisfaction, imaging-guided therapy, focal therapies, and post-treatment monitoring.

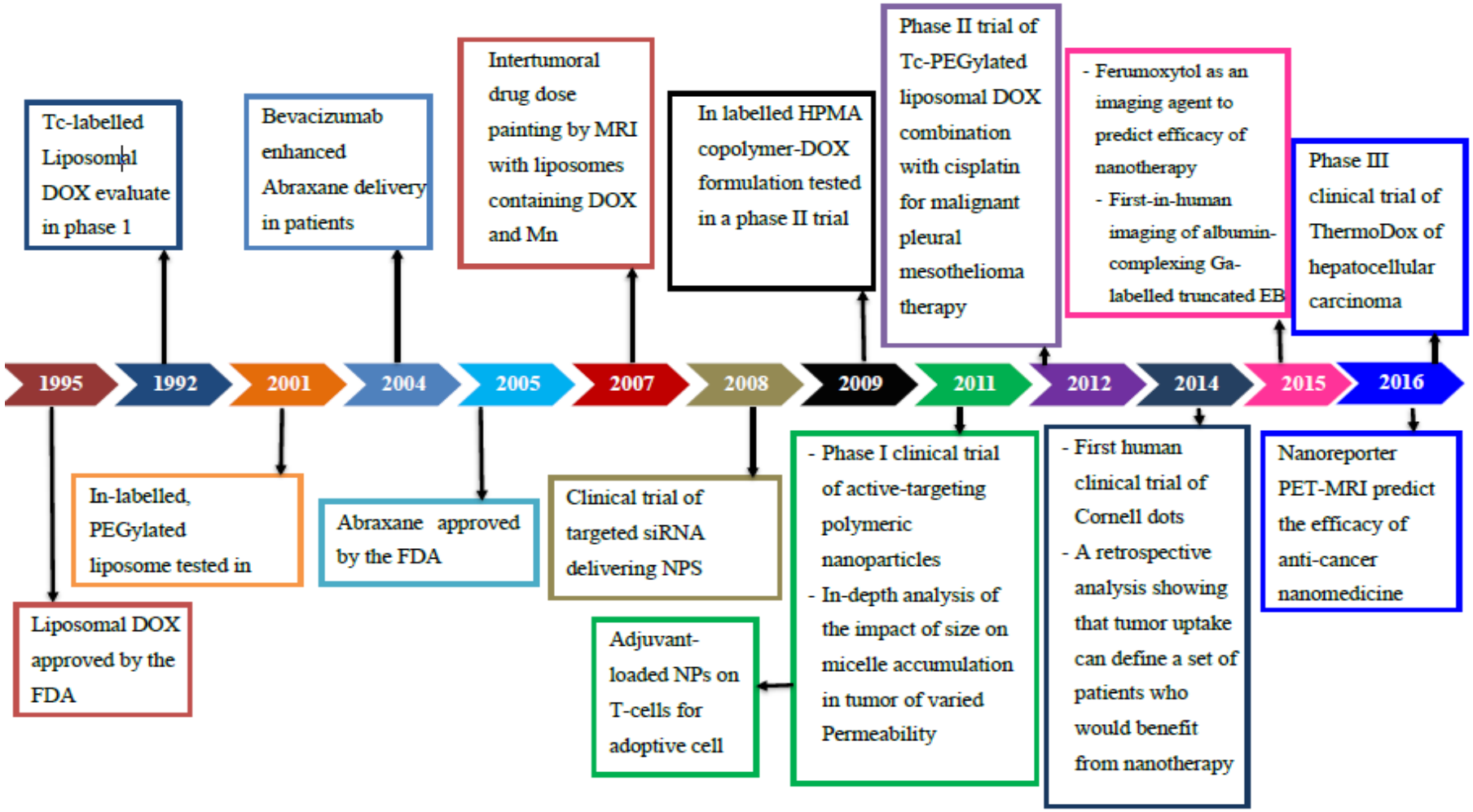

Figure 2.4: Theranostic Advances in Cancer Applications

2.4.1 Molecular Imaging and Photothermal Therapy

Molecular imaging providing visualization and process measurement at cellular and subcellular scales in living organisms. Standard imaging modalities such as PET and SPECT are high insensitivity, but on the other hand, they have limitations and disadvantages like high cost, resolution, short life tracers. Optical imaging can provide highly sensitive, low-cost, high-resolution imaging; besides, they are invasively comparing to traditional nuclear imaging modalities. In clinical application, penetrations issues are essential, and this makes drawbacks in tumor cells imaging terms. For better imaging performance, NIR is used to improve optical imaging applications' penetration issues due to their light absorption properties (Simpson et al., 1999; Wagenaar et al., 2008). fluorescent agents are used in optical imaging for cancer cell detection. Fluorescent agents can easily detect the boundaries between healthy tissues and tumor ones; also, they can be used in surgical guiding procedures.

In vivo approaches, nanotheranostic structures are used in various imaging modalities such as CT, MRI, nuclear and optical applications; also, they are used as imaging agents and in drug delivery systems (Kim et al., 2010). theranostic approach obtained by using these nanostructures in imaging agents in hyperthermia, radiation, and photodynamic applications in cancer treatment procedures. Imaging guided therapy is one of the approaches in theranostic systems in cancer. Usually, MNPs and Iron oxide NPs are used with MRI for hyperthermia applications in cancer. Yang et al. used hydrophobic magnetic nanocrystals and DOX to inhibit tumor cell growth. Magnetic polymeric is conjugated in HER2 for various cancer applications, like targeting and therapy (Yang et al., 2007).

The multifunctional hybrid approach is essential in cancer early detection, real-time monitoring, customized therapies for cancer, treatment progression, cancer diagnosis, and clinical prognosis applications (Park et al.., 2007). in optical imaging, all AuNPs structures are used because of their optical characteristics. They have strong absorption, visibility, and they are in the NIR region. They are using in optical, CT, and photothermal therapy, sensing, drug delivery, and in hybrid imaging modalities (Huang et al., 2008; Huff et al., 2007; Oyelere et al., 2007).

NIR dyes can also be used as a theranostic agent. NIR dyes include cyanine, rhodamine, phthalocyanine, and nepthlocyanine. They are used as imaging agents and photothermal agents. Using multiple NIR dyes is beneficial and effective in enhancing the contrast performance in imaging applications. NIR dyes are used in cardiac measurement applications, assessing kidney and liver functions, photothermal therapy, photodynamic therapy, and imaging (Dorshow et al.., 2007; Johansen al., 1990). localizing hyperthermia is based on the energy extracting from NIR dye after a laser source exposes it, and it shows better results than AuNPs because it extracted less energy (Temperature) than AuNPs. The challenge in hyperthermia application that delivering the proper amount of dye to target tissues without degradation. Due to their low stability properties, a hybrid method is used to overcome this issue by combining two different dye to produce a dye with better stability properties (IR820) (Fernandez-Fernandez et al., 2011).

Nanocarrier is used to improve the deliverance of NIR dyes to the target tissues.

Nanoformulation of ICG (ICG loaded with PLGA) has better performance than the free or the ordinary ICG NIR dyes, and it showed a promising result in vivo application. Nano formulations enhanced uptake properties and prolonged plasma circulation time (Saxena et al., 2006). ICG can be entrapped inside a theranostic agent and still can kill cells; in this system multifunctional theranostic approach obtained by loaded ICG and DOX into PLGA NPS as a carrier to apply it in image-guided chemotherapy and hyperthermia applications in cancer therapy (Fernandez-Fernandez et al., 2011). Like chemotherapy combined with hyperthermia, multifunctional approaches showed a better result than chemotherapy and hyperthermia alone (Tang et al., 2010).

2.4.2 Ultrasound Image-guided Therapy

Nanobubbles are used as a theranostic imaging agent in ultrasound imaging for tumor cells. It has various functions like leaking in tumor cells through EPR, activated through the tumor-cells in ultrasound imaging, and can be used in deliverance strategies. Nanobubbles play an essential role in cell permeability and cytotoxicity functions (Wang et al., 2010). perfluorocarbon NPs stabilized by copolymer micelles to formulate a DOX drug encapsulated to enhance the release properties in the tumor cell sites (Gao et al., 2008); this theranostic system also, enhancing the

tumor-specific uptake with real-time imaging using ultrasonography imaging modality. After that, another study used perfluoro-15-crown-5-ether (PFCE) loaded with an anticancer drug called paclitaxel; this theranostic system showed promising results in enhancing monitoring delivery drugs, improve biodistribution properties using in MRI and Ultrasonography (Rapoport et al., 2011). non-uniform vascularization is one of the challenges in cancer therapy and imaging due to heterogeneity in the previous approach's distribution; it can also lead to the development of resistance in tumor cells for other types of cancer drugs (Rapoport et al., 2010).

hybrid models may be used with ultrasound in image-guided therapy for diagnosis and therapeutic applications. ultrasound-PET with nanobubbles in gene delivery applications, PET is used to monitor function (Watanabe et al.., 2010). ultrasound-OI can be used with PLGA encapsulated with dye as a contrast agent for this hybrid modality even though high-intensity ultrasound is used in various applications such as thermal ablation, hyperthermia, and chemotherapy (Paparel et al., 2015; Prat et al., 2013).

2.4.3 Therapy Response Monitoring

After therapy, the response is essential in tumor cell studies, and it improves the prognosis after treatment is applied. Theranostic agents can be used in sensing applications inside the tumor environment, which have a big effect on therapeutic progression. There are significant biological differences between the tumor environment and health cells environment like PH, hypoxia, and existing some biomarkers or not. Effective therapy will ease the previous tissue microenvironment parameters, thus helping in monitoring therapy, evaluating the previous therapy function, and guiding for a better therapy in the future (Chen et al., 2017). this application is still in progress because it is realistic to use a particular diagnosis method to follow the therapy; it presents that a theranostic approach is not limited to carrying both prognosis and therapy functions in these applications still unfavorable to use a single particle for both imaging and therapeutics because the theranostic particle is targeted different components. Limitations still exist in pharmacokinetics, dosage quantity for diagnosis, and therapeutic use when using one particle for both applications. Some studies achieved promising results in this field and obtained better prognosis predictions.

2.4.4 Focal Therapy

The theranostic agent used in photodynamic and photothermal therapies. Photodynamic and photothermal therapy have some advantages over chemotherapy in cancer treatment platforms; PDT and PTT have low toxicity, high tumor selectivity, and no induced resistance. PDT and PTT rely on photoirradiation phenomena instead of particles and molecule distribution in tumor cells. Distribution still essential to monitor the tumor accumulation process. in most PTT and PDT applications, they are still using separated protocols in diagnosis and therapy. The theranostic approach still in vivo approach, and it is used on animals. PTT and PDT are still promising because they are closer to the skin, internal lining, and accessible using endoscopy, and can be exposed to their surfaces through surgery. The problem is issued because of compatibility issues in light delivery and collateral damage for healthy cells surrounding the tumor ones (Chen et al., 2017).

Porphyrin lipoprotein (PLP-NPs) theranostic system is used for imaging and surgery for focal therapy (PDT and PTT). PLP showed selectivity and accumulations properties in tumor metastatic. PET and fluorescence imaging are used to visualize the tumor cell sites to obtain irradiation and eradicate targeted cells. Another study used porphysome for its high density, heat, and light efficiency. As a result, these types of theranostic systems can lead to a better focal therapy by enhancing selectivity profile, matching the tumor boundaries, and improve damaging tumor cells with minimal effects on the normal cells (Jen et al., 2016).

PTT imaging agents could be good candidates for photoacoustic imaging agents due to their light and heat conversion properties. Photoacoustic imaging is used in tracking PTT NPs, thus saving the need for an extra imaging probe. AuNPs and Iron-oxide NPs are used widely in these types of applications (Lin et al., 2016).

Theranostic particles are less studied in radiation therapy than PDT and PTT. Radiation therapy has no any problem with tissue-light penetration issues. X-rays can be used to obtain images of tumor cells in depth. The main problem in cancer radiotherapy is that tumor cells are resistant to the treatment. Chemoradiation therapy is a therapeutic hybrid platform that includes using both chemotherapy and radiation therapy. Chemotherapy is used to enhance sensitization

characteristics (Strom HH et al., 2013; Lukianova et al., 2014; Begg et al., 2011; Adams et al., 2016). nanotechnology is used to reduce side-effects and improve bioavailability properties. Many studies are conducted using liposomal and DOX as radiosensitizing for lung cancer, breast cancer, bladder cancer (Koukourakis et al., 1999; Elban et al., 2013). theses nanoparticle not used in clinical studies and slowly translated in nanomedicine also not designed to adjunct to radiotherapy either their radiosensitizing is not optimal enough to be used. Genexol-PM is a micelle formulation used in the chemoradiation nanotheransotic system. It showed promising results in increased paclitaxel accumulation in non-small cell lung cancer (Werner et al., 2013). Genexol-PM improving radiation therapy by reducing the toxicity in healthy cells; histone deacetylase inhibitors and wortmannin are promising radiosensitizers to be used if focal therapy and hybrid modalities.

Gold, iodine, and gadolinium can be used in chemotherapeutic applications as radiosensitizer agents. They enhance radiation therapy by increasing absorption in cross-sections, improving energy deposition, and reducing the dose (Baumann et al., 2016). nanotheranostic particles are incorporated in different phases in clinical trials to improve the radiotherapy efficacy in different types of sarcomas; they are also used in phase one and two for head, neck, liver, prostate, and rectal cancer for radiation therapy.

Focal treatment could be coupled with radiation therapy. Using PDT with radiation therapy is used in tumor cell destruction. Nevertheless, it can still not be applicable in clinic applications. The hybrid model between PDT and radiotherapy shows a significant advance in PDT penetration (Chen et al., 2017). theranostic agents' nanoparticles are used in guiding surgical procedures; this is an essential procedure because tumor cells are different in shape, and boundaries between harmful cells and healthy cells are hard to identify during the surgery. Removal of healthy cells could induce excessive tumor distributions. Gd and MRI are used in a guided surgical procedure in cancer. This system still has some limitations and restrictions like low specificity and high dose injections; for this problem developing an optical probe with better sensitivity and specificity with better boundaries detection are required. one of the promising techniques is plasmonic nanobubbles with acoustic probe (Lukianova et al., 2016). in brain tumor, MRI-PAI-Raman nanoprobe is studied for use in guided surgical procedures in

cancer. MRI is used to detect and plan the tumor cells, Raman is used to improving the removal accuracy for tumor bulk, and PAI is used to guide resection during operation (Kircher, 2012).

2.5 Nanotheranostic Role of Nanomedicine in Cancer

Nanotheranostic can produce and engineer nanoparticles-based drugs with the capability to diagnose and treat diseases. Theranostic nanomedicine aims to improve disease detection, increase treatment efficiency in cancer, and reduce the toxicity in the healthy environment due to the treatment for tumor cells; besides, it improves therapeutic targeting therapy by ensuring an increase in the concentration of drugs or molecules in the target sites. Theranostic can offer a post-treatment evaluation so scientists can prepare for the next therapy and know the response for the previous one outcome; thus, this reinforces the idea of "Personalized Medicine in Cancer" beside it can guide if repeating drug is necessary or not. MRI is used to evaluate the effect of theranostic therapy.

2.6 Nanotheranostic Challenges in Oncology

2.6.1 Lung-Target Therapy

Drug targeting cell-specific biomarkers are developed to be used in nonsmall-cell lung cancer (NSCLC). From 2002 to 2005, EGFR-targeted inhibitors tested clinically as a treatment for NSCLC. in 2009, PEGylated pH-sensitive liposome conjugated to the EGFR antibody as a drug delivery system for a chemotherapy anti-cancer drug "gemcitabine" to cure NSCLC (Kim et al., 2009).

Gemcitabine is a chemotherapy agent for NSCLC; hematological toxicity profile and harmful side-effects make it not perfect or not an ultimate treatment solution. The nontarget liposome is affected by 40% inhibition; on the other hand, targeted gemcitabine-encapsulating liposome inhibition reaches 80% (Nehal Salahuddin et al., 2017). The drug delivery system of gemcitabine liposome conjugated with anti-EGFR antibody critically improved the treatment of NSCLC due to enhancing the circulation time and stimulate the apoptosis process in tumor cells.

2.6.2 Brain-Target Therapy

In all nanotheranostic particles, none of them are used in targeted brain applications. In a clinical trial in nanomedicine, just one is available for glioblastoma and three for neck and head cancers (Nehal Salahuddin et al., 2017). the main challenge in the brain the drug journey to the area of interest in passing through two biological barriers: first is the blood-brain barrier (BBB) then from blood circulation in the brain through the brain tissue itself, after this the theranostic or drugs should be crossed the tumor cell membrane for internalization process inside brain tumor cells. A normal braincase of nanomedicine will pass through between cerebral cells and BBB (Begley et al., 2014). in brain tumor cases like glioblastoma, BBB is disrupted; thus, this allows cross of molecules up to 12 nm as measured in vivo method (Lampson, 2009).

Some barriers limit diffusion through the extracellular. On the way to tumor cells in the brain, drug or nanotheranostic material could release in different target cells, thus high cerebrospinal fluid change in rate and efflux, which result in eliminating this part from the brain (Huyng et al., 2016; Throne and Nicholson, 2006). glioblastoma is hard to deal with in all matter because it diffused in surrounding brain healthy tumor, thus making it hard to be removed in conventional surgery and mostly it a recurrence of tumor cell even Glioblastoma chemotherapy is not perfect and has a limitation in low BBB tissue penetration and low targeting threshold for tumor cells (Pardridge, 2007).

2.6.3 Drug Resistance

If the patient responds well at the beginning of the drug course, it will eventually get resistant to the drug with time (Hurvitz et al., 2013). silent cancer nature and its resistance to the first drug session has, on its own, a resistance approach for this specific drug session. It is not clear in all drug sessions what resistance has occurred in the first place due to multiple pathways for resistance. The target tumor sometimes cells subjectively to change with time and this open ability for using multiple treatment procedures.

In chronic cancer patients' cases, it hard to obtain precise, personalized medicine. Temporal changes like cancer cells could lead to changes in cell sensitivity, thus changing the therapeutic and mechanism in the cell environment and this cause the early discharging for specific agents,

resulting in low efficiency for the whole treatment plan. Adjuvant and neoadjuvant strategies are used to minimize drug resistance issues in cancer (Pliarchopoulou and Pectasides, 2009). drug resistance issues in cancer make real boundaries and barriers to the personalized medicine approach in cancer.

The main idea behind therapy for chronic cancer cases is to stimulate the immune system and incorporate it as a theranostic tool. Targeting therapy is used in cancer treatment to reach this approach. They are improving deliverance capabilities in chemotherapy agents and other formulations. Long term drug delivery is ranged from months to years. In such cases where long drug delivery is not suitable, using self-administered formulations as home therapy. nanotheranostic vehicles and strategies can significantly improve anti-cancer drugs and immune system response to provide longer life to patients with no disease and increase the overall survival rate.

2.7 Breast-Target Therapy

In breast cancer, estrogen and estrogen receptors are essential. Targeting estrogen and estrogen receptors have been used in estrogen-positive cancer. They are used to suppress the signaling pathways for estrogen. Tamoxifen anti-cancer drug, was used for reducing recurrences by half (den Hollander et al., 2013).

Another alternative therapy is to reduce estrogen synthesis in breast cancer cells using aromatase inhibitors (den Hollander et al., 2013). HER2 proteins are considered the most important biomarker for breast cancer therapy; Herceptin was the first anti-breast cancer drug based on targeting therapy targeting the HER2 proteins by trastuzumab antibodies (Pegram et al., 1998). Two other agents were used after trastuzumab and showed significant results by not develop any resistance, but the problem is that they have side effects on patients.

The unique formulation in development and remodeling with time and related to hormones changes in the body. Changing to full epithelial only after a full-term pregnancy, lactation, and involution (Croshaw et al., 2007). the continuous changing and repair of the progenitor cell cause heterogeneity of breast cancer cells (Prat and Perou, 2009). heterogeneity in breast cancer cells makes intra-tumoral cells inside and independent tumor spot, different between metastatic

and primary and molecular type subtypes. Classification for various types of subtypes in breast cancer based on growth factor receptors such as estrogen receptor (ER), human epidermal growth factor receptors (HER2), and progesterone receptor (PR); furthermore, every subtype has a unique response to therapy and survival factors.

Cell surface receptors like EGFR, FGF-R2, IGFR, GLUT1, and androgen receptor are used in classifications for breast cancer subtypes (Koda et al., 2010; Macdonald and Byrd, 2013; Subik et al., 2010). breast cancer heterogeneity required a sophisticated nanomedicine and powerful nanotheranostic system to beat the targeting therapy issues. PEGylated liposomal DOX is a promising candidate to reduce breast cancer mortality.

CHAPTER 3

THERANOSTIC NANOPARTICLES IN CANCER

3.1 Nanotheranostic Particles

NPs are used extensively in medical applications due to their super small sizes (1-100 nm). Nanoparticles can be made from various types of materials such as polymers, metals, silica, carbons, and biomolecules. NPs form unique types of morphological shapes like tubes, spheres, and cylindrical; due to their surface modification features, they can be used in therapeutic agents, and they can transport through blood circularity to the area of interest (Figure 3.1).

In general, nanoparticles are compounded from three main layers include a surface layer, a shell layer, and a core. Different types of molecules can easily functionalize the surface layer.

The shell layer contains various chemical materials. The core is the center of these particles (Khan et al., 2017) Table below illustrates the different between metabolic particles and nanoparticles.

NPs have significant features (chemical, biological, and physical) that make them perfect for medical applications. They widely used various cancer therapy applications, protein detection, targeting therapy, tissue engineering, biosensing, etc. Quantum size and area to volume ratio make them suitable for most biomedical applications. Also, NPs are editable in size, shape, and morphological matters.

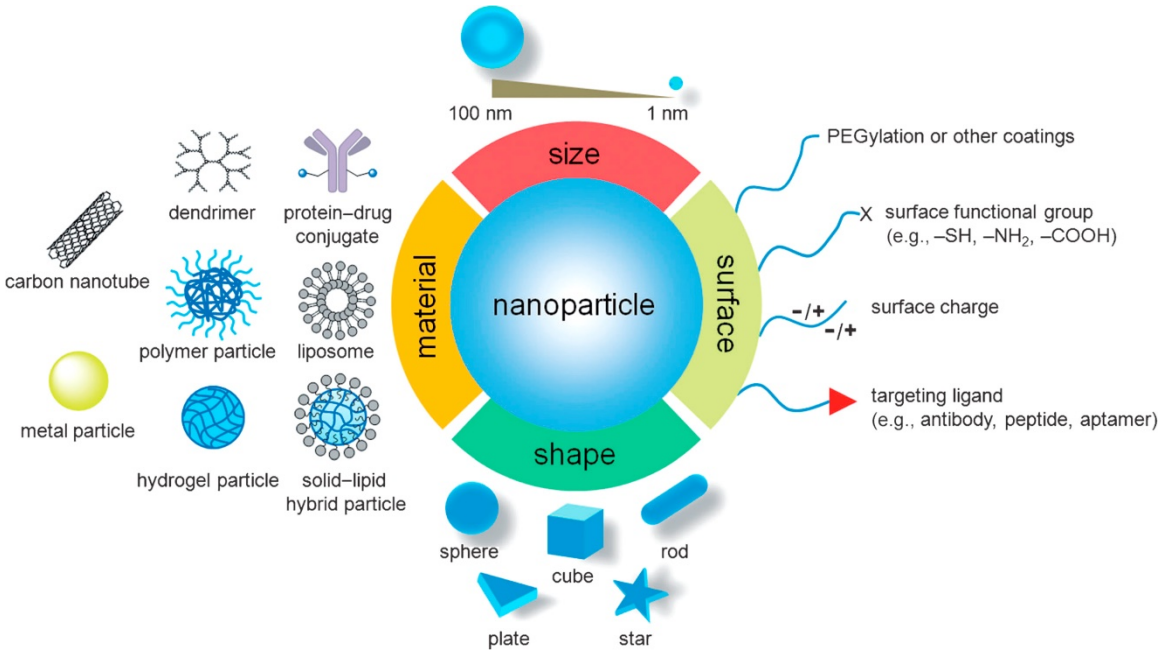

Figure 3.1: NPs in Drug Delivery Systems in Cancer Applications with Physiochemical Properties and other Characteristics

(Sun et al., 2014)

Nowadays, theranostic get much concentration in the biomedical research field, and they represent nanoparticles with biocompatibility and biodegradable properties, which qualify them to do both diagnosis and therapeutic applications. Theranostic nanoparticles are created to be applied in most imaging modules such as Positron Emission Tomography (PET), Single Photon Computed Tomography (SPECT), Ultrasound (US), Magnetic Resonance Imaging (MRI), and Optical Imaging.

The primary task for TNPs is to provide better accumulation for molecules in the area of interest, increase the therapeutic effects, drug delivery properties, and reducing toxicity levels in normal and healthy cells. Also, TNPs should be discharged after considerable time from the body without any harm (nontoxic) Table below illustrates the main difference between metabolite molecules and nanoparticles.

Table 3.1: Difference Between Metabolite Molecules and Nanoparticles

Modality	**Small Molecules (Metabolite)**	**Nanoparticles**
Sensor of disease Biomarker for diagnosis	Particular ligand for receptor Enzyme sensor Antibody	Specific ligand for receptor Enzyme sensor Aptamer EPR effect
Therapeutic / diagnosis output	Release of drug Fluorophore activation Photosensitizer activation	Release of content (drug, imaging agent) Photosensitizer siRNA
Regulation mechanism	Molecular structure conversion	NPs collapsing Linker cleavage between molecules and NPs
Current applications	Cancer	Cancer Vascular diseases Grafts protection
Advantages	Easy to maintain Accessibility of effector Fast actuation	Multi range of output

Abbreviations: EPR, enhanced permeability and retention; NPs, nanoparticles; siRNA, small interfering

3.2 Nanotheranostic Particles Classification

In general, Nanosystems are essential for drug delivery, diagnosis, monitoring, and therapy applications. For clinical applications, they enhance theranostic principles by providing multifunctional nanoparticles (Diagnosis and therapeutic) for improving the whole imaging abilities in both diagnosis and therapy procedures for diseases. Theranostic includes polymers, metals, carbons, ceramics, and others. Lipids nanoparticles are used in theranostic applications due to their unique properties such as biocompatibility, low toxicity, biodegradability, and loading features for hydrophilic and hydrophobic materials liposome NPs have an essential role in pharmacodynamics and kinetics platform improvement for drug profile and target therapy strategies. See the table below.

Table 3.2: Nanoparticles Main Classifications

Nanoparticles Classifications			
Dimension	**Morphology**	**Properties**	**Characteristics**
Zero-Dimension	Flatness	Biological	Size
1-Dimension	Aspect Ratio	Physical	Surface Change
2-Dimension	Sphericity	Chemical	Hydrophobicity
3-Dimention			Drug release

Lipids nanoparticles are used because of their ability to be functionalized with various types of molecules such as peptides, antibodies, and aptamers (Huwyler et al., 2008; Puri et al., 2009). polymeric nanoparticles are biocompatible, biodegradable, and not toxic at all. Biocompatibility features make it perfect for different biomedical applications such as tissue engineering and drug delivery systems; they are organic natural material within 1 nm. Polymeric NPs have two main structures nanospheres and nanocapsules. also, these nanostructures used in drug delivery. The main feature of these two structures is enhancing stability and bioavailability for hydrophobic molecules.

Metallic nanoparticles are used in different medical applications, whether diagnostic or therapeutics. Quantum dots (QDs), gold nanoparticles (AuNPs), and magnetic nanoparticles (MNPs) are an example of this type of nanoparticles; besides, they are mainly used as bioimaging agents and in drug delivery applications. Cu, Ag, and Au are the Nobel metal group (Chaniotakis et al., 2015).

Metallic nanoparticles have impressive electronic and optical, and chemical features besides surface modification properties, making them useful in bioimaging, biosensing, and thermal therapy. AgNPs have enormous properties and features: conductivity, stability, and antibacterial, making them beneficial for various medical applications like drug delivery, thermal therapy, disinfection, and cellular imaging techniques applications (Plackal et al., 2018). Semiconductor crystals are a metallic nanoparticles family, and it is known as quantum dots (QDs). QDs have unique chemical and optical characteristics. QDs are used in theranostic and bioimaging applications.

Iron oxides nanomaterial has several properties like chemical and biological properties includes nontoxicity, stability, biocompatibility, and other magnetics features. oxidation is considered one of the main drawbacks for using iron oxide nanoparticles; thus, avoiding the oxidation issue, iron oxide is coated with biocompatible molecules like polymers or ceramic to inhibit any accumulation activities. For hyperthermia therapy, target therapy, and bioimaging, nanoparticles are encapsulated in different types of molecules like protein, antibodies, or drugs (Vats et al., 2010).

Fullerenes and carbon nanotubes are carbon-based nanoparticles used in various health procedures. Fullerenes have a complex structure, and it is an allotrope of carbons. Besides, it has some features like insoluble in water and a less tendency for accumulation processes. Fullerenes are used in antiviral, antioxidant, drug delivery, photodynamic, imaging, and photothermal therapy. Ceramic nanoparticles are extensively used in catalysis, photodegradation, and imaging agents. Ceramics are nonmetallic inorganic material.

Hybrid nanoparticles are designed specially to beat the common challenges in nanomedicine systems. Hybrid nanoparticles are based on using two different molecules to develop a new,

enhanced, and better molecule. for example, AuNPs capsulated with silica NPs to produce an effective cancer therapy platform (Kim et al., 2018). DNA nanorobots, combined with DNA aptamers, represent a target therapy molecule, especially for tumor cells with super-efficient results (Li et al., 2018).

3.3 Nanotheranostic Particles Synthesis

There are two main approaches for NPs synthesis, which are bottom-up (chemical) and Top-down (Mechanic) (Figure 3.2). A chemical approach is based on designing macromolecules from atoms and molecules. The mechanical approach is based on the that large molecule disintegrated into smaller molecules then designed into new proper nanoparticles (Iravani et al., 2014).

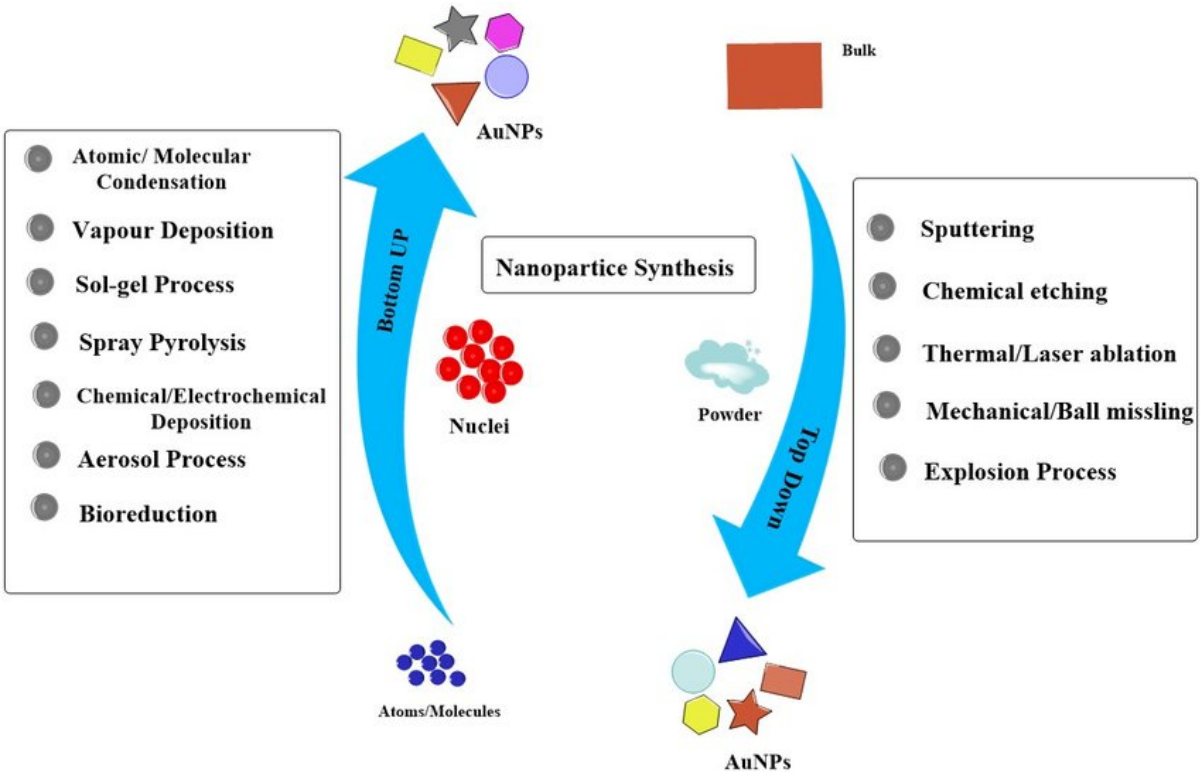

Figure 3.2: Top-Down and Bottom-Up Synthesis Approaches.

The classical synthetic methods have drawbacks like reducing and stability issues, which increase the danger of toxicity inside the cells. Nowadays, green chemistry synthesis-based methods have been used to replace the MNPs with microorganisms and plant molecules. Figure 3.3 shows the three main approaches in NPs synthesis.

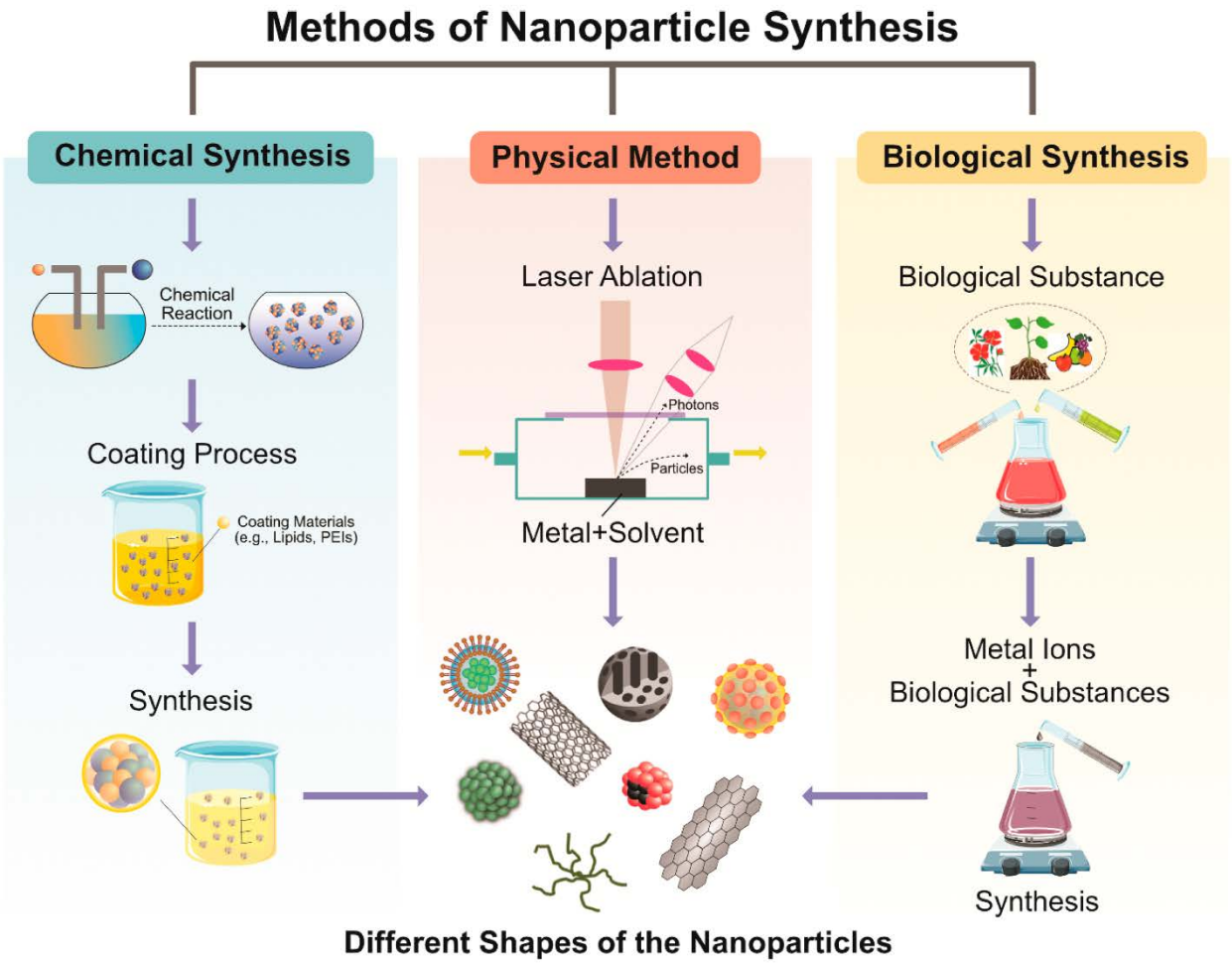

Figure 3.3: Nanoparticles Synthesis Main Methods

Bacteria and fungi are used in the purifying process of toxic material by getting rid of metal ions. Fe, Cu, Au, and Ag derivatives are examples of green synthesis approaches. To eliminate

the oxidative state, bio complexes like alkaloids, enzymes, proteins, sugar, and others are used to achieve zero oxidative levels, especially in metal salts (Roy et al., 2019).

Green synthesis has impressive advantages over physicochemical synthesis, like no need for using toxic material in the production process, safer and using one hundred natural agents. Scientists succussed in producing mesoporous crystals oxide, mesoporous TiO2-SiO2, anatase crystals, and Ag nanoparticles. in a result, green synthesis is safer and more trustworthy than the traditional methods. DNA nanotechnology method was used to design and produce customized shaped nanoparticles; moreover, it produced 2D and 3D precise sized forms of nanostructures. These precise structures are providing a better understanding of interactions at the molecular scale regarding tumor detection prospects.

Theranostic are engineered by several methods such as conjugating therapeutic with imaging nanoparticles agents like iron oxide, Au nanocages, and QDs) besides, they are encapsulated in imaging and therapeutic Nanosystems. Porphycenes (CuS), Au nanoshells, or nanocages are unique theranostic agents with imaging and therapeutic capabilities (Chen et al., 2014).

3.4 Nanotheranostic Particles Characteristics

Shape, size, optics, and structure are physicochemical properties for NPs, and so many methods can characterize them. For morphological characterization, different microscopic techniques are used, such as optical (POM) and electronic (SEM and TEM). SEM is providing a nanoscale level for nanoparticles. TEM controlled the size of the material used in nanoparticle synthesis for various magnifications (Khan et al., 2017).

Structured properties include composition and type of bonding between materials most used methods for analyzing bulk properties are X-ray diffraction (XPR), Infrared Spectroscopy (IR), Zeta Sized Analyzer, X-ray Photoelectron Spectroscopy (XPS), and Braunauer-Emmett-Teller (BET). For example, the crystallization phase in nanoparticles classified using XRD technology. The most used technology is XRD because it is directly linked to the exact amount ratio needed in the production process and identification bonding type between materials (Khan et al., 2017).

Reflectance, phosphorescence, absorption, and luminescence are the optical properties of nanoparticles. We can characterize these particles by applying fundamental light principles and Beer-Lambart law. Most techniques used are UV, UV-Vis, and Diffuse Reflectance Spectroscopy (DRS), which anticipate the light process and better understand light's natural properties (Khan et al., 2017).

3.5 Nanotheranostic Particles in Cancer

Nanoparticles are an essential and promised approach to cancer treatment plans that can beat the drawbacks of classical and conventional therapies. The basic idea of Theranostic is to offer both diagnostic and therapeutic properties for image-guided treatment and early detection of early-stage diseases. Nanoparticles seek to apply and develop strategies to introduce advanced nanostructures by creating some nucleic carriers such as gold-based nanomaterials, dendrimers, metal, and inorganic nanoparticles, CNTs biodegradable polymers. These nanocarriers should be targeted, controlled, and sustained to theranostic agents to get better theranostic effects and fewer side effects.

The theranostic word comes from two words therapeutic and diagnostic. Nano-theranostic is considered one of the main classifications for nanomedicine in addition to nano-drug delivery and nano-regenerative therapy. Nano theranostic classified into two primary category diagnoses and imaging tools and treatment (Sabu et al., 2015). The figure below shows different applications for nanoparticles as theranostic agents.

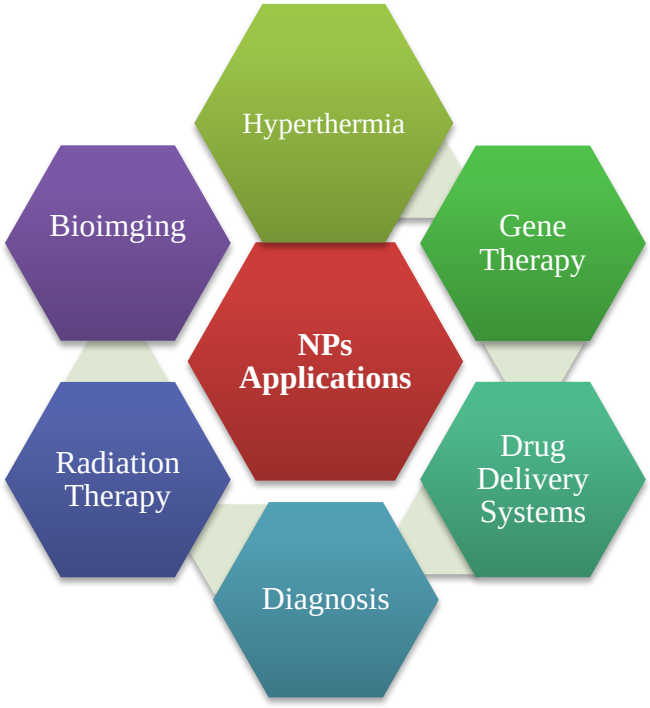

Figure 3.4: Nanoparticles Applications as Theranostic Agent

In recent years, nanotechnology has provided scientists with many potentials to develop imaging technology and medical diagnostics of cancers, thus creating a multi-characteristic theranostic (diagnosis and therapy) Nanomedicine model. To be an integrated model for diagnosing and treating cancers (Vijay et al., 2019). In 2018 the total number of deaths reached 10 million, which makes cancer the second cause of death all around the world. for six of the number of deaths globally, one of them is due to cancer. In developed countries, the number of deaths caused by cancer decreases; in contrast, in developing countries, the number of deaths increases. One-third of cancer deaths are caused by poor dietary habits and inappropriate lifestyle, including smoking, obesity, lack of vegetables and fruits in the diet, lack of physical activity, and excessive alcohol use (Ferlay et al., 2015; Bray et al., 2018). There is some limitation in current strategies for conventional curing cancer methods Now. Researchers focus on improving nanoparticle agents such as lipids, metal nanoparticles, liposomal nanoparticles, viral nanoparticles, and protein nanoparticles (Mukherjee and Patra, 2016; Yue and Dai, 2018).

Nanoparticles have unique characteristics that allow them to develop therapeutic and diagnostic properties for various types of cancers; This is due to their small size, ease of functionalization, drug loading, penetration abilities, and enhanced retention inside target cells. The need for theranostic nanoparticles is increasing due to their essential roles in complete biomedical applications like bio-imaging, bio-sensing, diagnostic and therapeutic applications, and their outstanding biocompatibility and biodegradability (Vijay et al., 2019). Nowadays, the number of theranostic particle agents is still less than to be used widely in clinical trials. In the future, the number of these nanoparticles are going to increase.

For every biomedical application, specific nanoparticles are needed for capsulation and different medical procedures. Nanoparticles should meet specific characteristics. Firstly, nanoparticles should not oppose any of the pharmacological elements, and it should keep molecules safe from early degradable and be biocompatible in the area of interest, which makes a significant decrease in toxicity. Secondly, it should provide specific chemical, physical, and catalytical properties; they should also have impressive optical properties for diagnostic imaging applications. Three critical factors that are essential for selecting NPs are biocompatibility, stability, and suitable circulation time. In the oncology field, scientists focus on developing new theranostic elements to achieve a particular result in targeting therapy.

Theranostic word carry both meanings together therapeutic and diagnostic. Diagnosis is accompanied by therapy to meet patient needs. To monitoring the early response of treatment efficiency, the treatment is followed by a diagnosis. Diagnostics and therapeutic is also capable of codeveloping between each other. Platforms of nanoparticles are engineered to deliver imaging and therapy elements and components and label the antibodies used and conjugated with the drug load as an antibody-drug conjugate (ADC) for treatment. Cancer theranostic represents both diagnosis and therapeutic pathway for cancer disease and aims to reduce the time to get treatment and offer more relaxation care. It is necessary for cancer personalized medicine.

Sometimes theragnostic used instead of theranostic term or expression. In recent years there has been a trend toward theranostic in medicine. Theranostic directly related to molecular and

nanomedicine. The scientists are putting potential efforts into integrating molecular imaging and molecular therapy using theranostic agents. This multidisciplinary field has provided the needs that are insufficient in the medical world.

For every biomedical application, specific nanoparticles are needed for encapsulation and different mechanical procedures. Nanoparticles should meet some requirements and characteristics. Firstly, nanoparticles should not oppose any pharmacological molecules, and it should keep a molecule safe as possible from early degradation processes, and after that, be biodegradable in the area of interest; thus, this leads to decreasing toxicity levels. Secondly, it should provide specific chemical, electrical and catalytical properties. Also, NPs should have impressive optical properties for various imaging applications. Three critical factors for selecting nanoparticles these factors are biocompatibility, stability, and long circulation time.

Chemotherapy, radiotherapy, and surgery are the traditional and classic cancer treatment, but at the same time, these methods are not perfect enough because it involves side effects on patients. the main problem lies on that these methods are not affected only the damaged cells but also the healthy ones. Target therapy is a promising treatment strategy procedure for these types of diseases with no harm to the surrounding healthy tissues.

Another treatment for cancer includes the following: epigenetic therapy, endo-radiotherapy, immunotherapy, nuclear therapy, and nanotechnological drug delivery strategies (Delia et al., 2017)

Nanoparticles drug delivery systems guarantee that drugs will reach only for the tissue of interest specifically. There are two critical terms in this field: active and passive targeting; active targeting means a unique ligand for the receptors on the target tissue like peptides or protein; passive targeting acts like specific actions like diffusion and accumulations through the tumor cells.

Stimulating the Apoptosis process is an effective way to destroy tumor cells in a particular way. We can even treat cancer by killing the tumor cells by using nanoparticles; for example, nanoshells can absorb light and emit heat to destroy the surrounding tumor cell. Nanoshells can

absorb NIR light and releasing heat that can kill the tumor cells without affecting the healthy ones (Aly, 2012).

They are exploiting the physical and chemical properties of cancer cells for passive targeting therapy. EPR (Permeability and Retention Effect) directly related to the aggregation of nanoparticles in drugs on the cancer cells; those types of targeting therapy obtained with no direct functionalization for nanoparticles in specific (Duhem et al., 2014; Kanapathipillai et al., 2014 Nichols and Bae, 2012).

In the oncology field, scientists pay attention to developing new theranostic molecules to achieve a particular result in targeting therapy. However, nanoparticles should have physical and chemical characteristics for affecting one specific area of cells (tumor cells) for imaging and therapeutic applications.

3.6 Nanotheranostic Particles Based Agents in Cancer

3.6.1 Quantum Dots

Quantum dots are massive metallic crystals with the ability to emit light, and it is up to 10 nanometers in size. They have a super photostability and long-term intensity. The main application for these nanoparticles is tracking the RT dynamics process inside cells, and most importantly, they do not affect the natural process inside the cells, such as viability, proliferation, morphology, and differentiation. See the figure below.

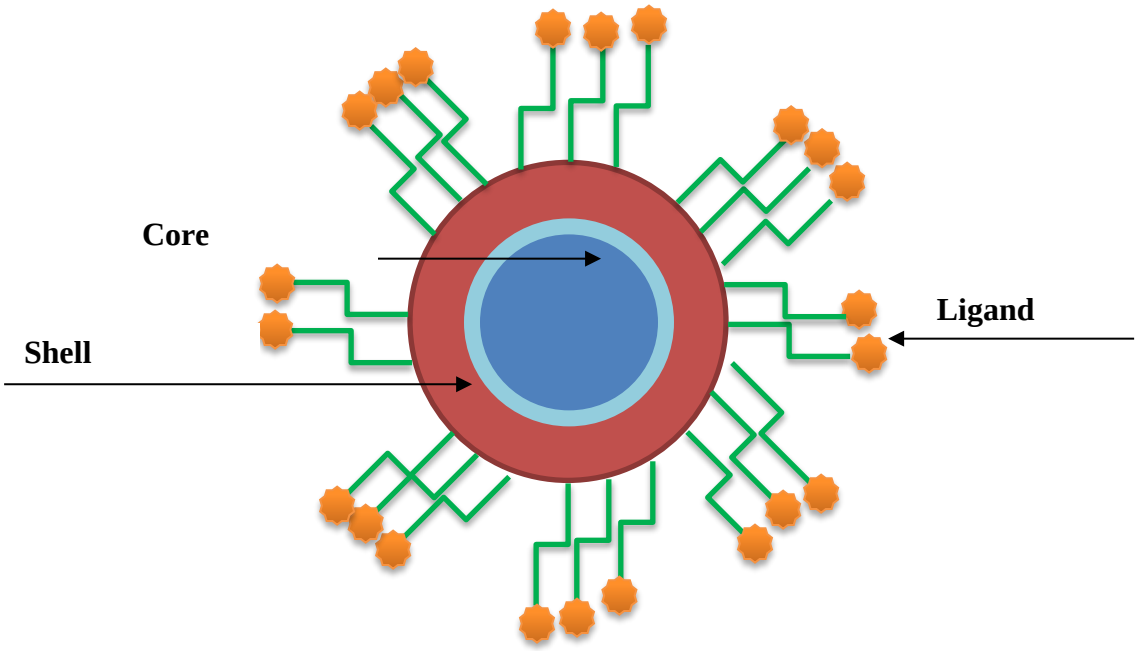

Figure 3.5: Quantum Dots Basic Structure

QDs are used in medical applications like bioimaging and various diagnostic applications. At a particular wavelength, the QDs nanoparticles emit an exceptionally light color depends on their sizes. Comparing to traditional fluorescent molecules, QDs have better photostability, and they are brighter in intensity matter. QDs can be covered by targeting molecules for accumulation detection after a probe is injected directly into the vein. PEG can coat QDs for increasing the biocompatibility properties and secure from degradation; also, this complex can be functionalized by the antibodies for the detection of prostate cancer. QDs used in many applications like drug delivery and like a theranostic agent showed promising cancer identification and therapy (Kawasaki and Player, 2005).

Synthesis

In quantum dots synthesis, two main approaches used Top-Down and Bottom-Up. The top-down approach includes beam epitaxy, X-ray lithography, and ion implantation; on the other hand, aqueous chemical reaction methods for Bottom-up processing in quantum dots synthesis (Biswas and Torchilin, 2014; Yue and Ma, 2015).

To make a super-thin material diameter for semiconductor materials, Top-down methods are used. for previous methods, three techniques could be used: itching chemical method, beam lithography, and reactive etching methods; besides they are used in shape and size controlling throw the production processes, these methods are not perfecting they have drawbacks in QDs design such as impurities and imperfect patterns

Wet-chemical and vapor-phase are used in material synthesis. The wet-chemical method followed the control of parameters for one solution or more (precipitation). This method is limited in NPs synthesis processes. Nucleation occurs after molecules get a specific shape or size, and it subdivides into three groups: secondary nucleation, homogeneous, and heterogeneous.

The wet-chemical method consists of several technologies such as sonic wave, electrochemistry, sol-gel, and others. The synthesis is controlled by cationic precursors and dopant ions with Sulfur.

Applications

Biosensing

Quantum dots are used to detect biomolecules like antigens, sugar, enzymes, and other biomolecules. Detection criteria based on fluorescence and FRET biosensor. The main significant characteristic that makes Quantum dots important in the biomedical application is their narrow emission band feature, which allows detection functions for DNA, antibodies, and other pathological molecules. QDs are used in cancer biomarkers detection, and they are conjugated with anti-cancer and antibodies. QDs conjugated with oligonucleotide acid and improved the sensitivity in FRET detection and die labeled methods with AuNPs assistant.

Gene and Drug Therapy

Quantum dots are widely used as drug and gene carriers after the functionalization of their surfaces. siRNA is encapsulated inside quantum dots then functionalized with amines to transport and delivering siRNA molecules efficiently; also, DNA and RNA can be delivered after conjugated with quantum dots and released by the cytosol (Biju, 2014). Quantum dots are

also used in drug/gene delivering monitoring by making their surfaces functionalized or load them with other molecules such as liposomes with cationic features.

Liposomes, aptamers other hydrophilic structures are used in improving intracellular delivering functions in prostate cancer. The leading role of quantum dots in this process is to observe the moieties of these structures. Choosing the surface-functionalized molecules for quantum dots is very sensitive because it depends on the biomarkers that exist in the target cells. FRET is using quantum dots either to detect the fluorophores or DOX.

Therapy

Quantum dots are used in photodynamic therapy plans with photosensitizers. Photostability is the reason why quantum dots are used in photodynamic therapy, but at the same time, quantum dots have low efficiency as a suitable activator for oxygen singlet species. Quantum dots are used as a photosensitizer. Quantum dots are conjugated with oxygen singlet species and act as a complex sensitizer. The previous complex was used in cancer detection applications when it conjugated with specific antibodies. The main drawback in quantum dots that they still have cytotoxicity issues (Park et al., 2009; Valizadeh et al., 2012).

Bioimaging

Quantum dots are usually used in cellular imaging applications. The cellular imaging mechanism depends on the nature of the molecule located on the outer surface of quantum dots. Quantum dots can be conjugated with various types of molecules and other cellular parts like a membrane. For nucleus and mitochondrial imaging, quantum dots are conjugated with peptides to improve labeling and targeting features. for intracellular improvement, quantum dots surfaces get functionalized by liposomes, although it is used as a carrier for drugs and gene molecules. Quantum dots are superior to nonspecific extracellular and intracellular labeling. For labeling applications, quantum dots are conjugated with transferrin, antibodies, and growth factors.

Quantum dots are used in the bioluminescence resonance energy transfer techniques and molecular imaging. Quantum dots are conjugated with enzymes to act as a light source for

energy transfer features (Frigerio et al., 2012; Wegner and Hildebrandt, 2015). Quantum dots conjugates with specific molecules and are used in various applications like metastasis diagnostic, tumor vascularization, and migration. Besides, these dots are used in leukocyte imaging by conjugate them with D-lactose. Quantum dots are used in SPECT, PET, and MRI imaging modalities as contrast agents (Wang and Hu, 2014). Figure below shows the quantum Dot System in various theranostic applications.

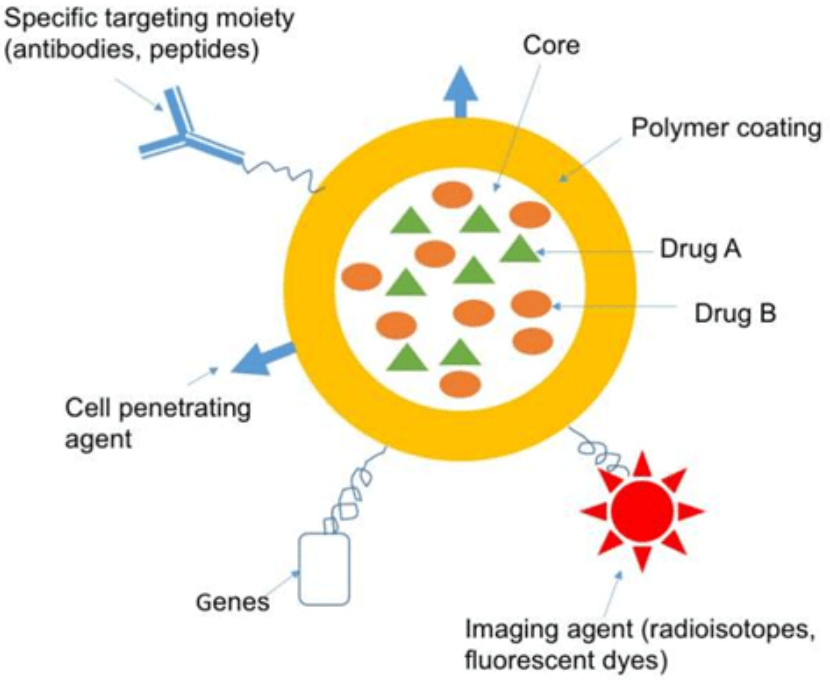

Figure 3.6: Quantum Dots System in Theranostic Applications

3.6.2 Liposomes

Liposomes are composed of phospholipids (Natural or synthetic); for using liposomes in biomedical application, it should be fused with a liquid solution, PH gradient methods, or organic solvent. It can be useful in the area of interest by extravasation from vessel to interstitial

space; it could be passive or active; it also functions with binding molecules to the lipid surface liposome structure. Figure below shows the basic structure of liposome.

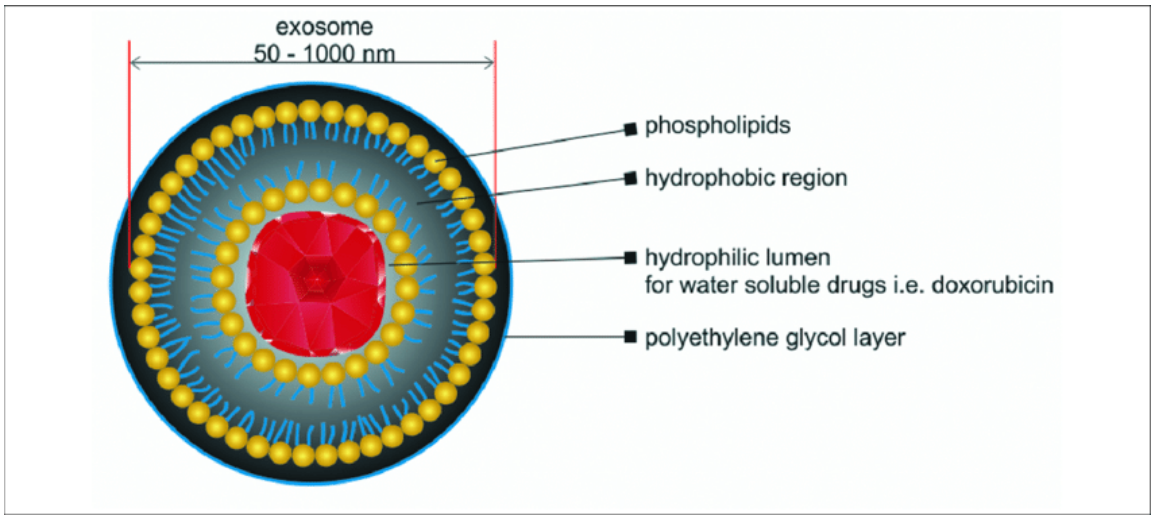

Figure 3.7: Liposome Basic Structure

Liposome nanoparticles are biocompatible and non-toxicity due to their phospholipid membrane; they keep the drug safe from degradation and combined in hydrophilic and hydrophobic molecules. Liposome nanoparticles play an essential role in current anti-cancer drugs using liposomes to repress the toxicity in healthy cells, even the concentration is high inside them. These nanoparticles are used, especially in prostate cancer detection and therapy, by repressing the cell proliferation inside the tumor cells even better than most common drugs.

Liposomes have drawbacks, instability, and short-life properties; these drawbacks can be beaten by functionalization with other molecules (Ouvinha de Oliveira et al., 2014), resulting in a stable PH complex ability to deliver drugs in an acidic environment.

Synthesis

Three main stages to the synthesis of liposomes firstly, extract them from lipids using organic materials. Secondly, breaking the lipids up in an aqueous environment and finally, purifying them get pure liposomes. Liposomes are less than 100 nm. Extrusion and sonications mechanical methods are used to utilize smaller liposomes for controlling applications. The

significant property of liposomes is amphiphilic; this means that they are both hydrophilic (vesicle) and hydrophobic (lipid) simultaneously; thus, liposomes are capable of carrying both types of drugs hydrophobic and hydrophilic. Hydrophilic DOX can be loaded in liposome to product Doxil (Barenholz. 2012), and Ambition hydrophobic drugs loaded on the lipid layer in the liposome structure (Adler-moore, 1993).

In general, liposomes' function is to reduce the toxicity inside the surrounding cellular environment around the injected tumor cells, and it improved the biodistribution feature. liposomes are the first nanomedicine which used in drug delivery applications

Applications

Liposome theranostic applications have been trendy in the biomedical research field, especially as biomolecules carriers like Cu-labeled, amine, prodrugs, and photosensitizer. Liposomes are used in photodynamic therapy after applied to a light-emitting diode (660 nm), and it can also be imaged by Positron Emission Tomography (Fing et al., 2017). liposomes could also be used as imaging probe fluorescence applications and anti-cancer carrier.

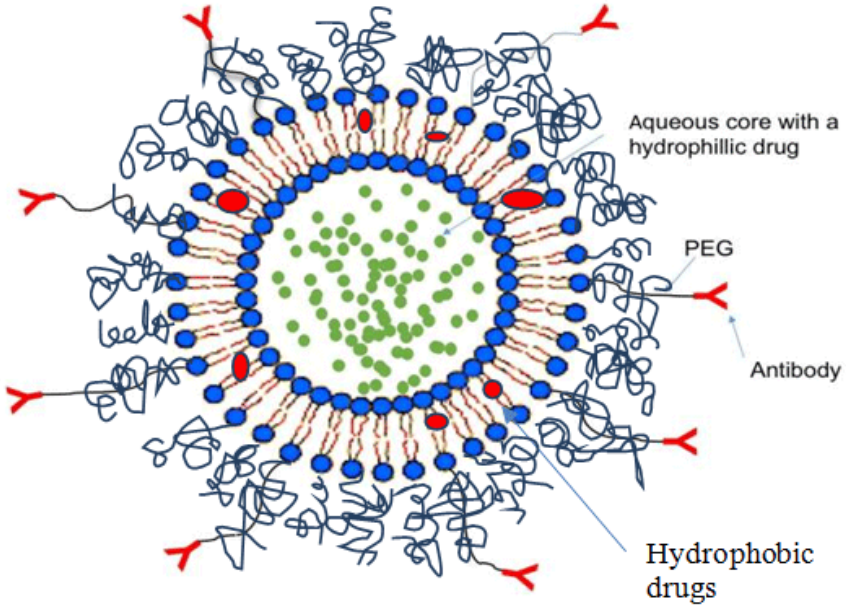

Figure 3.8: Liposome Structure in Drug Delivery Application.

Liposomes have been achieved a significant improvement in cancer imaging and therapeutic application in vivo approaches. Liposomes are used in hybrid photodynamic chemotherapy by loaded them with photosensitizer Ce6, Tirapazamine drug, and gene imaging probe (Zhang et al., 2018); also, liposomes are used in photothermal therapy in cancer by coated with Au nanoparticles (Rengan et al., 2015). in theranostic applications, liposomes Lu-labeled is improving the cellular uptake in tumor cells in vitro approaches by 3% Injected dose per Gram. liposome labeled with Cu has been shown improvements in uptake and biodistribution; hence, they can be used as an efficient imaging agent for lu liposomes (Petersen et al., 2016). Figure Below.

Liposomes used in pH-sensitive drug release application in cancer, specifically modified peptides, are coupled with liposomes used to load anti-cancer drugs such as DOX, and it obtains a significant raise by 80% at 6.5 pH level for DOX drug (Zhao et al., 2016).

3.6.3 Dendrimers

Dendrimers are symmetric, and homogeneous 3D nano-molecules have three primary arms in their structures. Dendrimers are discovered in 1978 by Fritz Vogtle; later on, it developed by Tomalia in the 1980s. It means trees or cascaded molecules. They are changing in shape and size; also, they have significant flexibility features that can be tolerated due to the function needed. Dendrimers have a significant feature, which makes them phenomenal for various applications such as control flexibility, nanosize, different structural groups, and interior cavities structures.

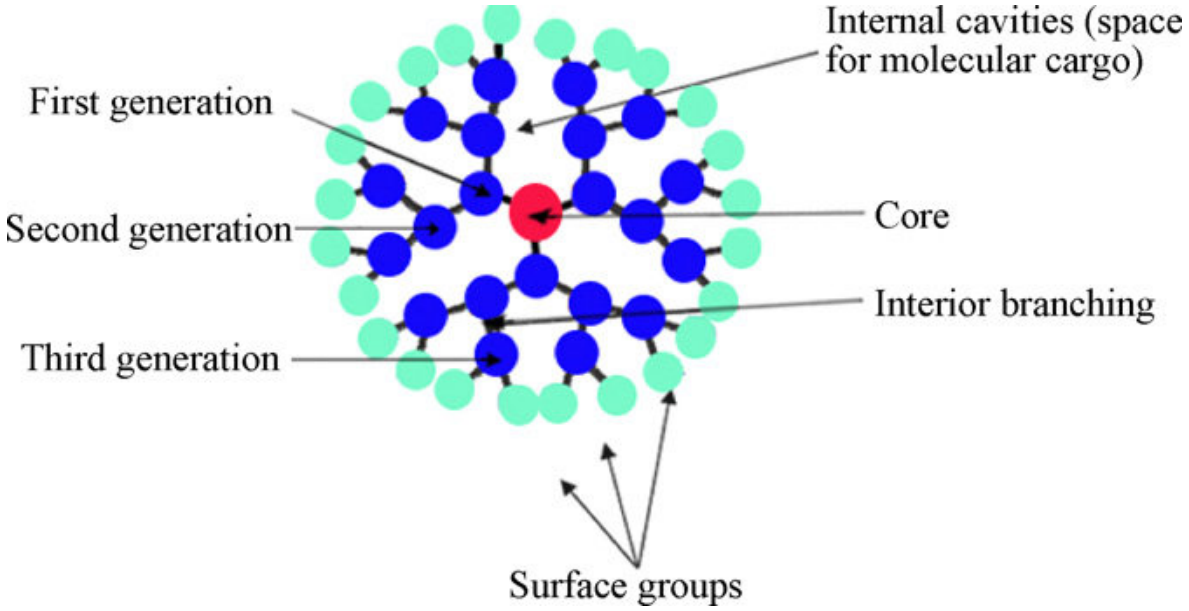

Figure 3.9: Dendrimers Basic Structure

Dendrimers have been used in different applications, but the leading applications are imaging agents; they have peripheral groups, providing excellent targeting and conjunctions for other molecules, thus increasing their versatility.

Dendrimers can be produced in various sizes and shapes; hence, homogeneity properties; they are widely used in ligand function due to their density of different functional groups on their surface structures (Kesharwani et al., 2014). Compared to other polymers, they have advanced properties, making them a perfect solution in the medical applications field; they have better and enhanced physicochemical properties than linear polymers. For example, Polyamidoamine and Polypropylenimine are dendrimers used in ligand function with gene nanomaterials like DNA or siRNA to enhance their uptake properties by producing a new biological complex called dendriplexes (Kesharwani et al., 2012: Michelle et al., 2008; Thakur et al., 2015).

Synthesis

First, the synthesis processes begin with building the core of the dendrimer "Polyfunctional core"; monomers are designed in repetitive sequences to obtain the desired dendrimers. The

functional groups are the central part of the core of the dendrimer. Dendrimers, as we mentioned in the previous section, are varied in size. Size depends on the number of repetitive monomers added to the core; thus, adjustable dendrimers size is obtained. Most methods used in dendrimers synthesis are convergent and divergent. In 2014 Kesharwani et al. mentioned other synthesis methods like click and lego chemistry and others.

Divergent and Convergent Methods

In divergent methods, synthesis began with the core and ended with the tree arms step by step and block by block; on the other hand, convergent starts with the outer structure synthesis, and these structures forming the final outer shape for dendrimers (Grayson and Frechet, 2001). divergent consisting of two steps functionalization group on the dendrimers surfaces and expanding the dendrimer's size by adding the monomers gradually on the dendrimer's outer surface. Divergent processes are repetitive to acquire the desired dendrimer size. An example of dendrimer which synthesis by the divergent method is PAMAM dendrimers. These methods easily configure the dendrimers function by adjusting the outer surface functional groups; besides, providing flexibility and selectivity for physicochemical functions configuration (Kesharwani et al., 2014).

The convergent method has many limitations related to the protection manner for the active site, which we need in ligand applications and limitation in reproducibility. in this method, just design one functional group for dendrimers, so it is not flexible as much as a convergent method.

Applications

Imaging contrast agent

Dendrimers are well-shaped, well-functionalized, 3D-molecule, and tree-shaped structure. For these significant properties, it got much attention in the medical research field. In general, dendrimers are coupled with other targeting molecules to improve the cell uptake; thus, improve the molecular image specificity. Dendrimers play a crucial role in various biomolecular applications due to their surface's functional group diversity. Due to dendrimers features, they

are used in pay loading optimization for imaging molecules and passive targeting methods through EPR (Tang et al., 2013).

Dendrimers are superb molecular imaging agents, and they have better properties to make them way too better than classical imaging contrast agents. Dendrimers can be used as a contrast agent for Computed Tomography imaging after coupled with an iodinated contrast image agent; it is also coupled with other molecules such as fluorescent gadolinium for Magnetic Resonance Imaging and Computed Tomography (Michelle et al., 2008).

Dendrimers are used in DENPs and DSNPs applications for Computed Tomography imaging applications (Shen and Shi, 2010); they are also used in MRI applications after functionalized and assembled in other nanoparticle structures. Dendrimers are used in hybrid and multimodal imaging as a contrast agent to improve diagnosis purposes' overall accuracy (Cai et al., 2012; Chen et al., 2013; Wen et al., 2013).

Cell hybrids

Nanostructures are used as a carrier for anti-cancer drugs applications. Tumor cells have a biological barrier, making it harder for drugs to reach peacefully to the area of interest; this could reduce the whole treatment strategy's efficiency. Tumor cells surrounding a biological microenvironment make it harder to let the nanocarriers reach them; they act as a protection medium for tumor cells even if the molecules are specialized. T-Cells and macrophages are used in drug delivery applications for cancer treatment, but they have drawbacks because they interact with tumor cells; thus, leading to tumor cells. Toxicity limited the ability of to carrier to be loaded with drugs directly. Dendrimers are linked with immune cells to form a promising drug delivery system to address the previous issue by improving the viability and mobility features; PAMAM dendrimers are used in hybrid therapy systems (Tang et al., 2013).

3.6.4 Polymeric Nanoparticles

Polymeric nanoparticles have known in cancer therapeutic applications and are used to identify and diagnose tumor cell cancer. Polymers have drug-releasing properties that allow them to

encapsulate for a proper amount of time. The figure below shows the Polymer structures with different Shapes.

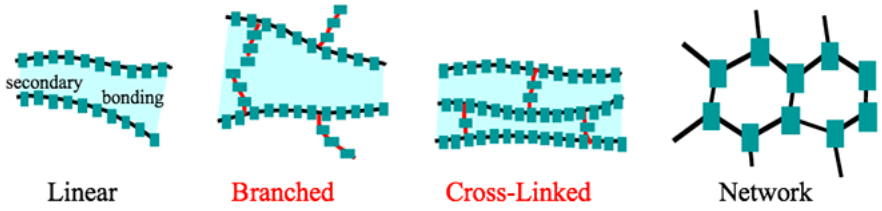

Figure 3.10: Polymer Different Structures

PLGA is one of the preferable polymers used in medical applications because of their biodegradability and biocompatibility properties. PEG can create a specific type of nanoparticles with biocompatibility, easy to modify, and antifouling properties.

PEG and PLGA are used extensively in biomedical studies, especially for those related to drug-delivering ones; PEG and PLGA have several properties as following: biocompatibility, biodegradability, stability, and can be extended the loading time; now they are used as theranostic particles also used to know more about cancer cells.

PEDOT is a new polymer nanoparticle with excellent conductivity and stability; it is used mostly in electrochemistry, biosensing, and bio interface applications. PEDOT coupled with PEG and then immobilized with AuNPs and antibodies or antigen results in a nanostructure complex with impressive sensitivity, selectivity, and low detection limit for cancer detection and therapy (Cui et al., 2016). PEG, PLGA, and PEDOT showed a great result in various biomedical applications for bio interface or biosensor and cancer diagnosis and therapy.

Synthesis

Polymeric Nanoparticles (PNPs) are varied in size; it ranged from 10 to 1000 nm. Methods are used: encapsulation, adsorping, and entrapping. Two primary forms of PNPs can be produced: nanocapsules and nanosphere; the first form of content is core surrounding by the polymeric surface membrane. Carrying abilities in PNPs are coming from the nature of their cores. PNPs

can carry various types of molecules. PNPs nanocapsule's main advantage is that it can be loaded with lipid and aqueous soluble materials. the second form is loaded with therapeutic molecules on the surface or core of NPNs. The synthesis process depends on the desirable and needed physicochemical properties. The copolymers are considered the most stable form of NPNs, specially designed for medical applications (Mohanraj and Chen, 2006; Ghosh, 2000).

PNPs can be produced directly from polymers or by polymerization process for monomers. Several chemical techniques are used, such as solvent diffusion, salting out, solvent evaporation. For polymerization emulsion, interfacial microemulsion can be used for preparation. Chitosan, PLGA, PEG, and gelatin are mostly analyzed polymers (Mohanraj and Chen, 2006; Ghosh, 2000).

Applications

DOX Targeting Delivery

N-acetyl glucosamine is a chemical compound found in the shellfish and can be prepared synthetically. NAG is a form of glucosamine. N-acetyl-D-glucosamine (NAG) derivative significantly used in DDS. NAG acts like a ligand molecule in drug delivery systems. It affects the tumor cells by glucose metabolism action inside them. Glucose carriers have a crucial role in drug delivery systems for various types of cancer like liver, lung, and breast cancer (Tian et al., 2015). glucose is beneficial in targeting anti-cancer drugs, and it prevents the drug from soaking up in the wrong cell sites or the healthy surrounding cells in the tumor area (Dhanikula et al., 2008).

Most anti-cancer drugs have some drawbacks, limitations, and side effects that could negatively reflect the overall efficiency of the treatment plan. Anti-cancer drugs have solubility, stability, and toxicity issues affecting the healthy cells surrounding the tumor ones. Poor targeting abilities in DOX anti-cancer drugs lead to toxicity issues in healthy cells (Hu et al., 2010).

N-acetyl glucosamine can improve the absorption by targeting N-acetyl glucosamine carriers and providing a better delivery for anti-cancer drugs. In 2015 new copolymer was produced to enhancing targeting therapy and drug delivery with less toxicity effect on healthy cells.

Cisplatin Bio-Carrier

Cisplatin is an anti-cancer medication in chemotherapy applications. It is used in various cancer treatment platforms like breast, lung, ovarian cancers, and others. NSCLC is a common type of lung cancer. In general, Cisplatin is considered toxic material. For toxicity effect reduction, PEG-NPs increase circulation time; thus, Cisplatin concentration is down in the bloodstream. If PEG-NPs is large enough, the filtration process will be ignored; thus, toxicity inside the kidney cells down. PEG-NPs are conjugated with Cisplatin molecules to obtain these results (Shi et al., 2015).

3.6.5 Gold Nanoparticles

Gold nanostructures achieved a great forward in biomedical applications. They have unique physicochemical characteristics. They have also been used in cancer cell imaging, thermal therapy, and drug/gene therapy. Building (Au) nanostructures with functional properties for cancer diagnosis and therapeutics includes covalent and non-covalent modification (Wang et al., 2016).

The traditional cancer treatment methods are failed most times due to cancer cells' metastasis and recurrence properties. Generally, these conventional methods can reduce the mortality rate, but it comes with unfortunate side effects like liver damage, kidney malfunction, nausea, hair loss, and toxicity (Daneil et al., 2007; Khuller et al., 2009; Troyan et al., 2009).

These side effects exist because there is no specificity in tumor cells (Petersen et al., 2012). past decade using nanoparticles are extensively used. There are different types of modified and customized (Au) nanoparticles. Figure 2.1 shows us the best candidates for (Au) nanoparticles due to their extraordinary physicochemical properties. The firstly small size of (Au) nanostructures gives them the ability to aggregate on the active site on tumor cells on passive targeting and active targeting by ligands conjugation. Secondly, the near-infrared (650-900 nm) absorption and scattering characteristics for (Au) nanostructures make them promising as contrast image agents for NIR imaging like light scattering imaging, two-photon luminescence, and photoacoustic tomography. Thirdly, high light absorption, and quick heat conversion make (Au) nanoparticles efficient in the thermally conducted agent used in photoablation therapy.

Last, the surface chemistry of (Au) nano-agent makes it easy to simultaneously deliver drug or imaging agents, making it used in designing functional theranostic nanoplatforms.

By interaction between light and gold, we can distinguish the Au from its bulk. The Au nanoparticles are irradiated with scattering and strong light absorption at a specific wavelength, known as LSPR (Localized Surface Plasmon Resonance). Scientists exploit this technique to harnessing the physicochemical characteristics of Au nanostructure applications (Katagiri et al., 2007; Matsui et al., 2006; Yue et al., 2014). Au nanostructures are used widely in biomedical applications like biosensing, imaging, and cancer theranostic due to their optical properties. The size, morphology, shape, and dielectric environment of Au nanostructures are directly linked to the cross-section and frequency of LSPR. Spherical nanoparticles (Au NSs), LSPR absorption, are nearly 520 nm, and wavelength depends on the size and the medium cellular environment (Scherphof, 1985).

Au nanostructures are created as unique imaging probes because of their remarkable optical properties, especially LSPR in the NIR region. Because of their highly efficient light absorption properties, Au nanoparticles have high transitivity inside the biological tissues, which gives it the penetration ability. Au nanoparticles used as imaging contrast agents especially for cancer, and the images tools used are Dark Field Microscope, Two-photon luminescence (TPL), Photoacoustic Tomography (PAT), X-ray Computed Tomography (CT), Optical coherence tomography (OCT), and surface-Enhanced Raman Scattering (SERS) (Wang et al. 2016).

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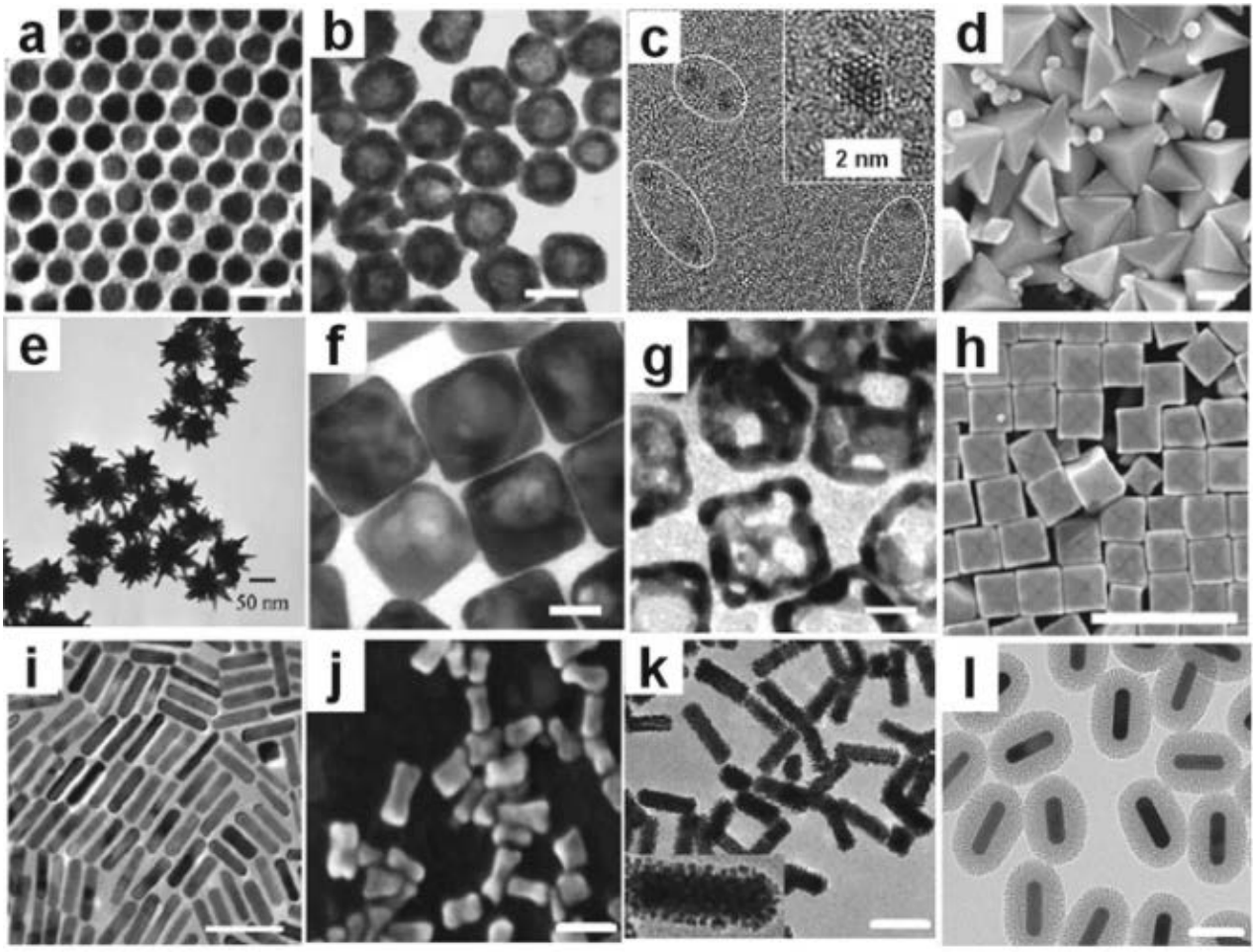

Figure 3.11: Au Nanoparticles Different Morphologies
Au nanosphere. (b) Hollow Au nanosphere. (c) Au nanocluster. (d) Au obtuse triangular bipyramids. (e) Au stars. (f) Au nanoboxes. (g) Au nanocages. (h) Au nanocubes. (i) Au nanorods. (j) Au dog bones. (k) Au Pt nanorods with Pt nanodots. (l) Mesoporous silica-coated Au nanorods.

Synthesis

AuNPs play a key role in several nanomedicine applications due to their significant features. AuNPs are synthesized by three main methods, biological, physical, and chemical. Nevertheless, AuNPs can be reproduced in various shapes and morphological properties. AuNPs are used widely in therapeutic applications for their thermal and optical characteristics;

thus, they have several techniques to produce according to the function needed. AuNPs spheres and rods are manufactured using photochemical methods; on the other hand, for other Au nanostructures like Au cages, Au shells galvanic methods are used (Sauerbeck et al., 2014).

Different synthesis methods to prepare AuNPs to mean different toxicity profile, thickness, Structure, AuNPs wall properties. Using different synthesis methods is related to the desired application needed (Xia and Xia, 2013).

Applications

Spectroscopic Imaging for Cancer

In tumor imaging applications, NIR light is used because of the low absorption in deep tissues. Because of gold nanoparticles' optical properties, they are used as an imaging probe for NIR in cancer diagnosis applications. AuNPs are used as imaging agents after it conjugated with antibodies with EGFR. AuNPs are conjugates used in Surface Plasmon Resonance (SPR) to detect the cells conjugated with AuNPs (Sokolov et al., 2003). in 2005 AuNPs are used with the Dark-field microscopy imaging technique (El-Sayed et al., 2005).

PEGylated-EGFR conjugated with Gold nanorods are used in tumor cell imaging (Choi et al., 2012). PEGylated-EGFR gold nanorods improved the absorption profile in the tumor site. Targeted PEGylated-EGFR showed a better distribution in vivo procedure for AuNPs in tumor cell sites by eight than the nontargeted Au nanorods (Guo et al., 2017).

AuNPs are also used in photoacoustic imaging in cancer diagnosis applications. AuNPs, in general, improved the overall efficiency of photoacoustic imaging techniques due to their significant optical properties. AuNPs have a high heating conversion feature; thus, a robust photoacoustic signal was obtained (Li et al., 2015).

for image-guided phototherapy applications, Au nanorods are coated with PEG and PLGA, showing phenomenal results in a photothermal and photoacoustic profile. (Song et al., 2015). Gold nanoparticles showed better performance as an imaging agent for Computed Tomography than the iodinated contrast agent (Popovtzer et al., 2008; Liu et al., 2012). for cancer imaging improvement purposes, AuNPs surfaces functionalized by PEG to enhance pharmacokinetics

features, and the targeted AuNPs showed a significant improvement in accumulation for AuNPs in the tumor cell sites (Jokerst et al., 2011). for detection purposes, all AuNPs nanostructure is used with the SERS imaging technique (Paul et al., 2015; Huang et al., 2007).

Cancer Detection Imaging Agents

Hybrid imaging modalities are now using in cancer detection and imaging applications like PET/CT, PET/MRI, and US/CT. Using these hybrid systems prevents doses administrations. Choosing hybrid imaging modalities should be careful because every multiple system has advantages and disadvantages so, it depends on what applications are working on needed. Using functionalized gold nanoparticles as imaging agents provides high-efficiency anatomical and molecular images (Huang et al., 2009; Meir et al., 2014; Jin et al., 2014). functionalized AuNPs are providing a real-time non-invasive protocol for post-treatment monitoring application, which improves treatment outcomes. Au nanospheres are used in SPECT/CT imaging for breast cancer; these functionalized nanoparticles have significant stability labeling features. Au-doped gold nanoparticles with PEGylation target breast cancer biomarkers (Zhao et al., 2016). in colorectal cancer, detection using hybrid NPs between Au and Iron oxide NPs in CT imaging modality.

Lectin-PEG-iron oxide-AuNPs complex used in various applications in colorectal cancer as following: prolonged circulation time, improving biodistribution feature in tumor sites, enhancing efficiency for Magnetic Resonance Imaging and Computed Tomography imaging and used as a contrast agent for multi-imaging modality MRI/CT for tumor cells application (He et al., 2014).

3.6.6 Carbon Based Nanoparticles

Carbon nanoparticles like graphene and carbon nanotubes or multilayer are used in cancer therapeutic applications and recently used in drug delivery for anti-cancer treatment. Carbon Nanoparticles are extensively used in biomedical applications. These nanoparticles have excellent morphological and physicochemical properties. Figure below shows different Carbon-based structures.

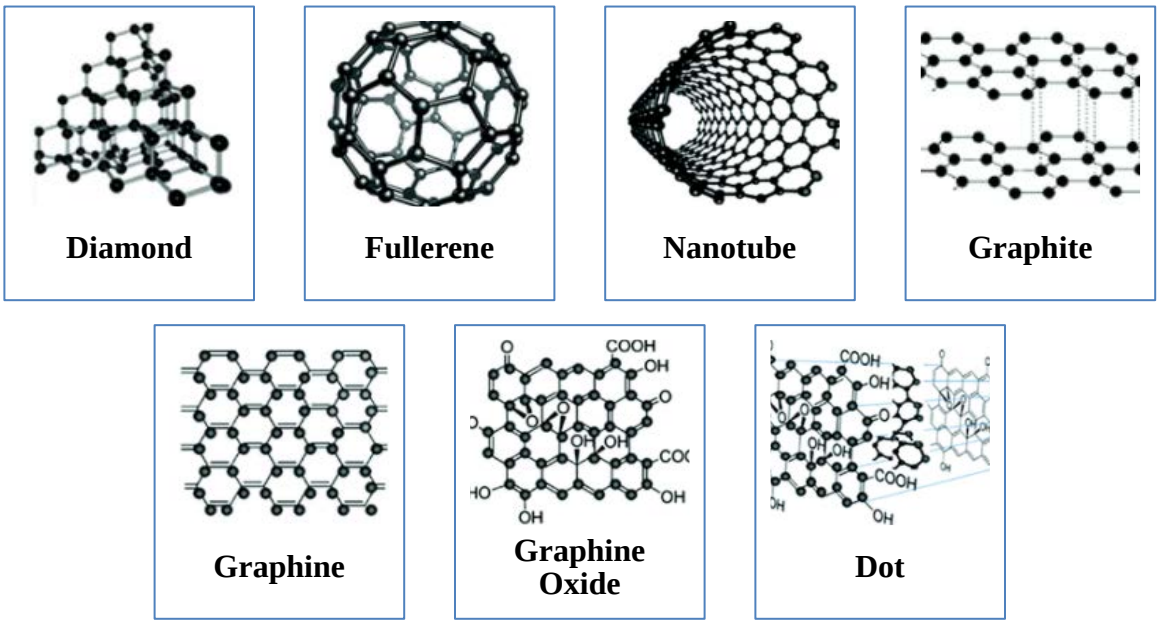

Figure 3.12: Different Carbon-Based Nanoparticle Structures

CNPs combined with MNPs due to their broad surface area allow a better loading for specific drugs and establish an adequate and stable covalent link between molecules (Quyen Chau et al., 2015).

Carbon nanotubes compose of tiny cylindrical shells of graphite; shells are composed of hexagonal shape without any sharp edges; they have strong mechanical and electronic properties, and this is providing strength and flexibility at the same time in their structure, besides the ability to customized their functional group, biocompatibility, and biodegradability. Graphene oxide is safer than other carbon nanostructures but with low bio resistance properties. For cancer-targeting applications and improving biocompatibility, nanotubes are coupled with DSPE-HA.

Coupling magnetic nanoparticles with carbon nanotubes, we get a hybrid complex with better performances. It can be used in hypothermia applications by killing the tumor cells after heating the area of interest using an external magnetic field to control the desired heat level. Moreover,

this is mostly used for bone cancer cell therapies. HA hydroxyapatite is essential because of its properties, which are fully compatible with the external bone structure like osteoconductivity, biocompatibility, biodegradability, and the similarity with inorganic structures inside bone tissue (Zhou and Lee, 2011). for supporting HA, walled nanotubes are used for their remarkable thermal, electric, and magnetic properties. Nano complex that is enhanced magnetically by combining HA and carbon nanotubes can be accelerating the Apoptosis process in tumor cells by using a hyperthermia strategy. These nanoparticles showed a significant result in bone cancer therapy.

Synthesis

Carbons nanotubes are used widely in medical applications, especially in nanomedicine applications. Laser ablation, vapor deposition, and arc discharge are the three main methods for synthesizing this type of nanostructure. For laser ablation and arc, discharge carbon is essential for nanotube formation, and carbon is in a solid-state. Carbon nanotubes synthesis produces temperatures around 1000 Celsius, and the vaporization process to build perfect nanotubes structures.

Applications

Several properties and features make these nanostructures perfect in the medical research field, such as smaller in size than different blood cells, biocompatibility, Perfect hollowed structure, and wide surface area suitable for photoluminescence and non-immunogenicity applications, and low toxicity. These nanoparticles are used in various biomedical applications, diagnosis, therapeutics, and biosensing applications (Wang, 2005). Single-walled carbon nanotubes are used as imaging probes in fluorescent and Raman imaging applications (Gong et al., 2013); besides that, these single-walled nanoparticles are used as imaging agents for traditional medical imaging modalities (MRI, SPECT, PAT, PET).

In 2014 single-walled CNTs are used in the drug-delivering system for cancer after studying their functionalization, distribution, toxicity properties (Eatemadi et al., 2014). single-walled CNTs have a sizeable wide surface area; this can affect the toxicity of other molecules. These

nanostructures have a better performance in contact cells due to their large surface, and they can be used to transform various biological molecules through different barriers.

For biocompatibility and solubility improvement purposes for single-walled CNTs, they are functionalized by hydrophilic molecules. Single-Walled CNTs coated by sodium dodecyl sulfate or chitosan to avoid the agglomeration processes (Meng et al., 2012). in 1986 Drug Delivery System has clarified the EPR phenomena critical in tumor cell accumulation for nanoparticles and their physicochemical properties effects on the healthy cells and tumor cells. Tumor cells have several biological defects and changes in biological activities such as high growing activities compared to normal cells, vascularization malfunctions, failing in lymphatic drainage in cell biological system. Drug delivery systems are exploiting the EPR effect on drugs and molecules targeting specific cancerous cells. Single-walled CNTs are used in these applications by loaded them with drugs and molecules after their surface-functionalized properly for a specific function.

In 2011 a new family of Single-Walled CNTs just designed to be used in drug delivery and drug controlling applications. The previous design's main idea is to functionalize the CNTs to act as a drug carrier for DOX and conjugated with two different molecules, chitosan and folic acid. Chitosan provides stability for the system and controls drug-releasing due to the pie interaction abilities on the single-walled CNTs surface (Huang et al., 2011).

Single-Walled CNTs have been used as a drug carrier after it functionalized by DOX anti-cancer drug and PEG; the result showed a significant improvement in increasing the circulation time for the drug (DOX). Instability, poor cellular intake, and nonspecific simulation are limitations for using siRNA in gene expression applications. In 2013 Qiao et al. used single-walled CNTs as a vehicle for siRNA and used it in neuroblastoma cancer (Qiao et al., 2013). Figure below illustrates the Carbon-Based nanoparticles in different medical applications.

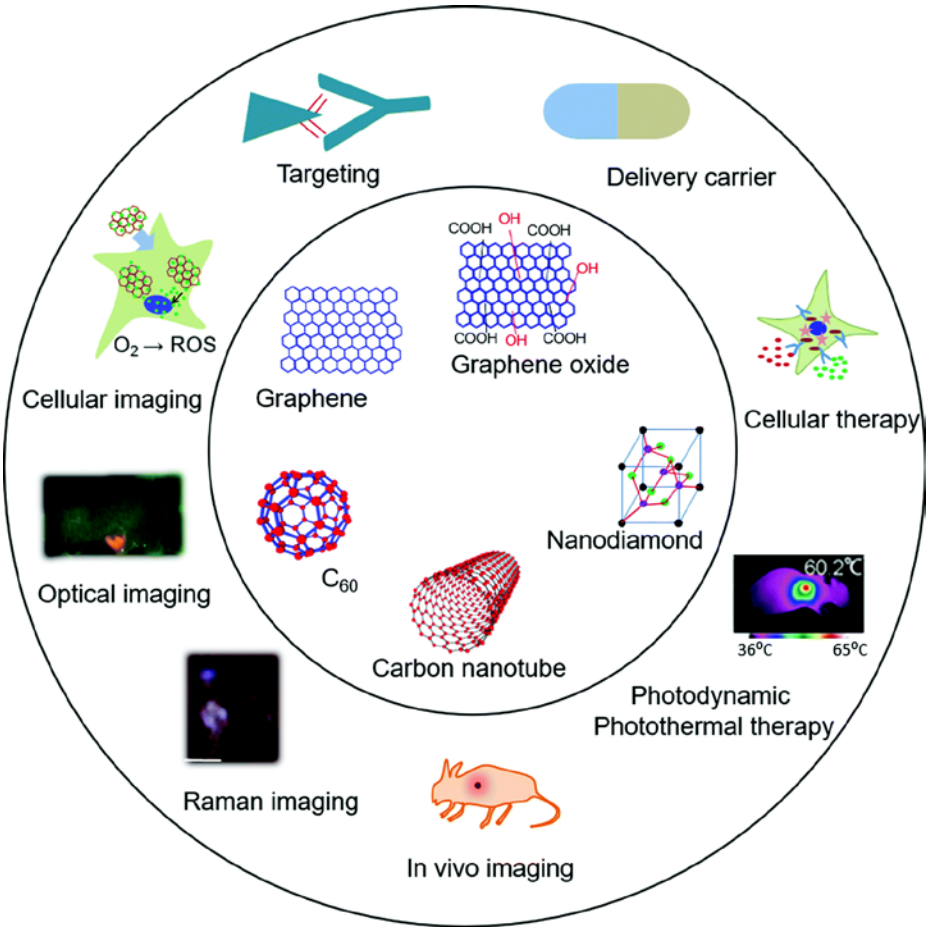

Figure 3.13: Carbon-Based Applications in Medicine

3.6.7 Magnetic Nanoparticles

One of the most used nanoparticles in medicine is its remarkable size, optical properties, easy functionalization, and stability that make it superb for cancer diagnosis and therapy. They are well known in diagnosis, radiotherapy, and drug delivery applications (Ouvinla de Oliveira et al., 2014). MNPs are also used in non-invasive cancer imaging and early cancer detection due to their unique and robust optical properties.

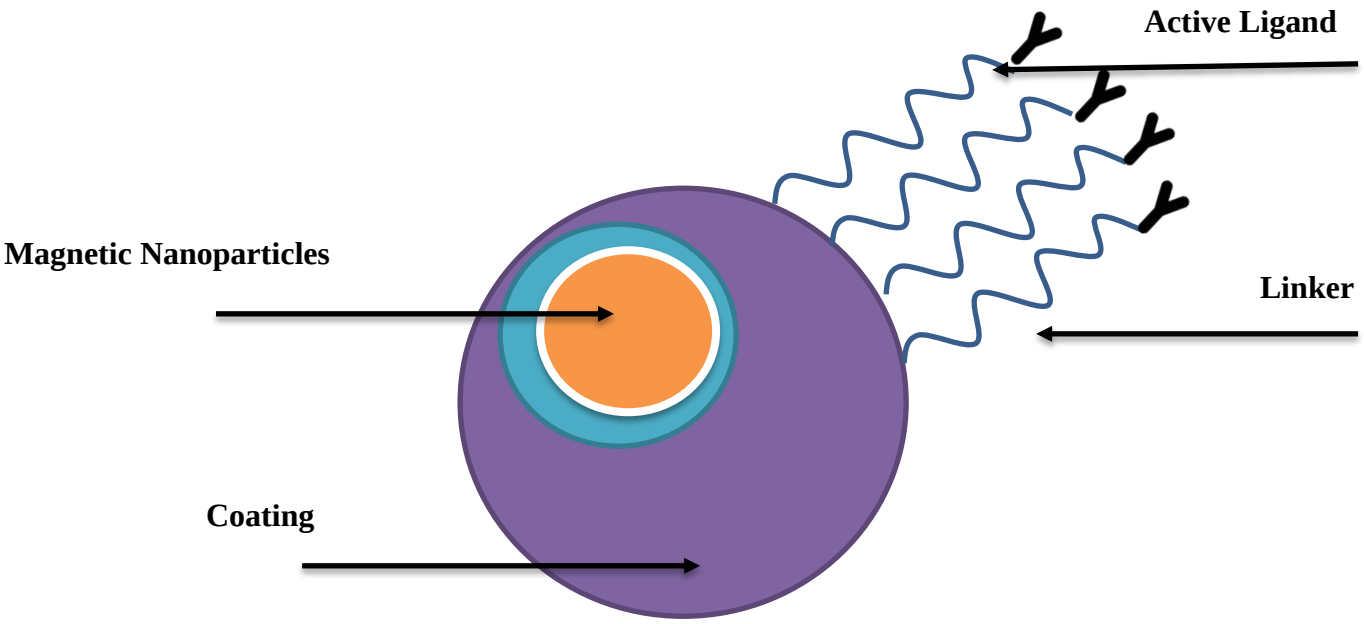

Figure 3.14: MNPs Basic Structure

Magnetic nanoparticles are used in hyperthermia therapy, and they can run a guiding system by applying an external magnetic field to control these particles remotely to a specific area of interest (Tumor cells) even if it is a tissue or organ (Rivas et al., 2013). besides, these MNPs could be combined with other organic and inorganic molecules, by their surface, to allow a particular ligand to be established for specific applications. By combining a non-magnetic molecule with a magnetic molecule and functionalize them together, we get a shielded magnetic molecule. It covers MNPs with non-magnetic molecules, providing better biocompatibility properties and non-toxicity structure for future functionalization (Rivas et al., 2012). hyperthermia is an abnormal increase in human body temperature, and it is clear evidence for the immune response to an infection.

It is possible to destroy cancer cells by applying a high temperature on them, leading to tumor regression. Tumor cells are susceptible to high heat (hyperthermia), and the cell death process happens at a 42-45 Celsius degree. MNPs could be used magnetic fluid hyperthermia (MFH)

to prevent surroundings from being destroyed by high temperatures. Also, MNPs can be injected in tumor areas to accelerate the accumulation process where it is passive or active; active using ligands on MNPs surface that specific for receptors on tumor cells and passive refer for EPR of MNPs.

MNPs can convert electromagnetic energy into heat inside tumor cells using an external magnetic field (Lima-Tenorio et al., 2015). in this strategy, the heat will not affect the surrounding cells, this converts the classic treatment methods for cancer from invasive state to non-invasive state, and this is because MNPs has small size and can easily cross through the biological barriers and this indeed decrease the toxicity inside the cells (Johannsen et al., 2007).

Iron oxide-based nanoparticles are used in hyperthermia applications due to their biocompatibility and non-toxicity properties also; they are used in other medical applications like drug delivery, resonance imaging, and drug targeting therapy (Rivers et al., 2012).

SPIONs (Superparamagnetic Iron Oxide Nanoparticles) is an example of iron oxide-based nanoparticles. SPIONs are used effectively in targeting tumor cells because of their excellent permeability, biocompatibility, and EPR at the base of the damaged cancerous cells y averting the reticuloendothelial system. SPIONs should be hydrophobic to reduce macrophages' endorsement and good circulation time to work efficiently in inactive areas (Brannon-Peppas and Blanchette, 2004). SPIONs can be combined with chitosan, a therapeutic agent for cancer; this combination, the SPIONs, could be delivered to particular cancer cells for theranostic strategies. SPIONs are attached to specific ligands and can be actively targeted and labeled to nanoparticles for theranostic properties enhancement. For the anti-cancer purpose, fe3o4 (magnetite) nanoparticles are used because of their biocompatibility and stability. For tumor targeting, MNPs coated with silica, and surface modification applied then combined with a polymer and finally adjusted with the imidazole group to get the superparamagnetic properties (Yu et al., 2013) Figure below shows the SPION Applications

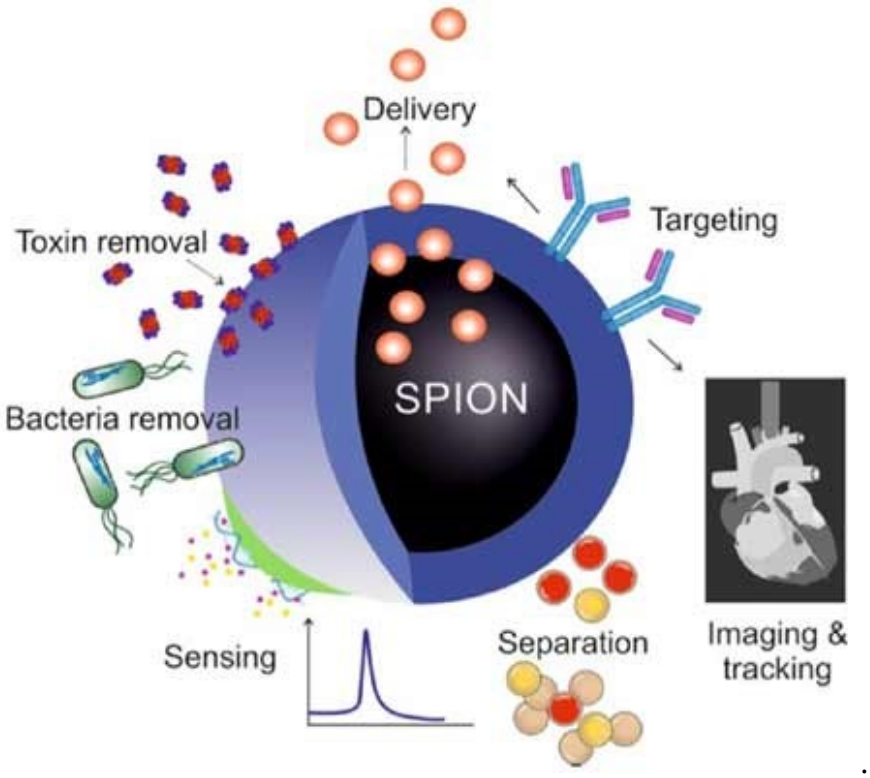

Figure 3.15: Schematic of SPIONs Applications

For large tumors in deep tissue, a therapy is called sonodynamic, and they are used with ultrasound (US), thus providing a penetration activate sensitizers. The advantage of this therapy could be applied directly to tumor cells and can be improving the drug intake at the same time. TiO2 is considered the most recent popular sensitizer with reputable properties such as no cytotoxicity that is biocompatible easy to prepare with stable structure when combined with another biological molecule; it also has the power to produce oxidant radicals with ultraviolet (UV). To get the significant therapeutic effects from these nanoparticles, the titanium dioxide capsulated magnetite nanoparticles were then functionalized with DOX to delivering sonosensitizer with the anti-cancer drug to the area of interest (tumor cells).

In general, MNPs like magnetite and hematite are considered the first choice to be chosen as a cancer theranostic option, and many studies are trying to create a compound with an ultra-superparamagnetic for use in targeting therapy with no harm for normal tissues.

Synthesis

There are several types of synthesis ways to produce MNPs in the desired function and morphology. Magnetic nanoparticle's core is structured from FeO compounds. Both methods are used in MNPs, Bottom-Up, and Top-Down. Green methods are used in MNPs production (Top-Down) method. Several techniques can be used in MNPs manufacturing, such as laser ablation, ultrasonication, and other physical techniques (Merkel et al., 2009; Tsuzuki et al., 2004).

Top-Down methods are commonly used as synthesis methods for MNPs due to their advantages like less expensive, scaling up ability, and complicated. The top-Down method simply relies on breaking down bulk into several parts (nanosize).

Bottom-Up methods rely on building up the NPs from nucleation then gradually forming the desired NP by growth and aggregation processes to obtain specific NPs with the desired shape and size. For quality improvements, microfluidic reactor and biogenic approaches were used. To achieve desired MNPs with perfect specifications in shape and size, wet-chemistry, mechanical, microfluidic, and biogenic methods were used (Mosayebi et al., 2017).

For theranostic applications, MNPs should meet several prerequisites such as shape, structure, and size, depending on the nature of the application for which these NPs are designed for. MNPs are used in therapeutic applications such as hyperthermia, drug targeting applications; thus, all MNPs should be guaranteed to respond to the magnetic field. Factors should be considered, like concentration, temperature, and resident time to guarantee the desired MNPs structure, size, and shape.

Applications

MNPs are used in the diagnosis and therapeutic applications. It is usually used with MRI imaging, hyperthermia applications. Magnetic nanoparticles can do bot therapeutic and

diagnosis functions simultaneously, such as stem cell response; they can also be used in tissue regeneration medicine. MNPs can be used as an imaging contrast agent for MRI imaging techniques which these NPs can be tagged with imaging probes to improve the imaging efficiency (Tudisco et al., 2018).

MNPs are used in hybrid imaging modalities such as OI/MRI, MRI-PET, and MRI-CT. MNPs are used in magnetofluid hyperthermia applications by exploiting the tumor cells' sensitivity for temperature, the whole process depending on the MNPs by acting as a heater when they are exposed to a magnetic field (Tudisco et al., 2018).

MNPs can be used as a bio carrier for drugs and improve cell uptake for a specific molecule. Iron oxide MNPs particles are functionalized with PEG to prolonged circulation time and biocompatibility for different biological and optical applications in cancer therapy applications.

MNPs are also used in coating functions, especially in BBB penetration; these NPs are coated with lactoferrin and transferrin (endogenous ligands) and showed significant results in improving BBB penetration (Yan et al., 2013; Hu et al., 2009). MNPs are used effectively in MRI diagnostic and therapeutic imaging applications. MNPs can be beneficial due to their magnetic properties, which allow them to use in drug release and hyperthermia applications by controlling them by a magnetic field. They can perform diagnostic and therapeutic functions simultaneously by offering diagnosis, drug targeting function, and regenerative medicine application, which makes them perfect for the theranostic platform.

3.6.8 Up-conversion Nanoparticles

UCNPs are a unique type of nanoparticles, like lanthanide-doped crystals. These particles are now used in cancer therapy applications. Due to their flexibility and facile properties, these nanoparticles are the cancer solution besides diagnosis imaging applications.

For targeting imaging for tumor cells, UCNPs combined with fluorescein dye (FITC) and joined with folic acid (FA). UCNPs showed promising results when combined with (FA) in tumor targeting and imaging applications; also, it linked with PEG and loaded with DOX to be used in future research in varying PH values, drug delivery, and controlling tumor cell injections

(Wang et al., 2011). Photodynamic therapy (PDT) is a non-invasive therapy in anti-cancer; PDT is assisted with neat to visible up-conversion technology.

PDT uses NaYF4 (Mesoporous-Silica-Coated) and Yb/Er (Sodium Yttrium Floride, Ytterbium, and Erbium); Vitamin B12 is a biocompatible molecule fused in the mesoporous shells to form a new PDT anti-cancer drug. This type of drug shows a promising result for cancer therapy by accelerating the apoptosis process inside the cancerous cells and create ROS, and the good in this drug that it just kills the abnormal cells just when NIR light is revealed (Xu et al., 2016).

UCNPs are considered unusual nanoparticles for the future of cancer therapy. Sodium yttrium fluoride, yttrium, and erbium are the best for imaging and anti-cancer therapies.

Synthesis

Up-conversion NPs are focused on three aspects, size, phase, and shape. Two primary synthesis approach to produce Up-conversion NPs, thermolysis and hydrothermal. Choosing synthesis methods are rely on the desired shape and size for UCNPs. The composition of NPs used the solid-state synthesis approach while for size liquid synthesis is usually used.

Thermal decomposition is used commonly in UCNPs synthesis; it provides high-quality standards for produced these NPs. It is based on dissolving metal-organic material in an organic solvent; after this, it decomposed chemically. For the thermal synthesis, the crystals of NPs are produced in aqueous solutions under high pressure and temperature inside the reaction container (Zhu et al., 2019). hydrothermal provides ease of synthesis and the desired size and shape for the UCNPs.

Applications

UCNPs are used in optical imaging applications. It is used in NIR laser by exploiting their emitting features using a diode. Compared to other NPs, they need less expensive components. UCNPs have high feasibility in tumor imaging applications.

UCNPs have several features that make them perfect in imaging applications, like photostability, no autofluorescence, and nonblinking (Wu et al., 2009). UCNPs are conjugated with RGB peptide and showed promising results targeting Glioblastoma cancerous cells (Xiong

et al., 2009). UCNPs showed better tissue penetration issues than the fluorophores compounds, and much paper demonstrates that. UCNPs are stable in different solutions and high deep penetrations. UCNPs were used as a carrier for a prodrug called CA4P and showed an impressive effect on vessels' permeability, hence improving NPs targeting and UCL imaging (Wei et al., 2012). UCNPs are not just used in UCL, but they can be used in hybrid imaging modalities like UCL/PET, UCL/MRI, and UCL/ CT.

For tumor therapeutic applications, UCNPs are used in both techniques for cancer therapy, photodynamic, and photothermal. UCNPs are used as a theranostic agent in these techniques. Functionalized UCNPs are used with optical imaging techniques for cancerous cell treatment strategies. The table below summaries NPs synthesis, modification methods and materials used.

Table 3.4: Summary of Nanoparticles Materials, Modifications and Synthesis Methods

NPs	**Materials**	**Modification techniques**	**Synthesis Methods**	**Ref.**
Quantum dots (QDs)	ZnSe, ZnSe:Mn, CdSe, CdS, CdTe, InP, InAs, GaP, $GaInP_2$, PbSe, SnTe, CdTe-TGA, CdTe/ZnS-TGA, , CdSe/CdS/ZnS -PTVP, ,CdTeSe/CdS/ CdZnS-PTVP	Multidentate ligand surface modification Sulfydrylcoupling surface modification technology Amphiphilic molecules surface modification Cavity-chain surface modification technology Dendrimers surface modification	Chemical ablation Electrochemical carbonization Laser ablation Microwave irradiation Hydrothermal/solvothermal treatment	Gladyshev et al., 2013 Xing and yang et al., 2014 Namdari et al., 2017

Table 3.4 Continued

Liposomes	Natural phospholipids, -ve phospholipids, Cholesterol, Cationic lipids, High transition temperature lipids, GMI, PEG-DSPE, Long circulating liposome, Dipalmitoyl phophatidylcho line	Modification of liposomes with vitamin Modification of liposomes with carbohydrates Modification of liposomes with peptides, proteins and antibodies Modifications of liposomes with aptamers Modifications liposomes with enzymes Polymer coating modification Incorporating surfactants modification Carrier multi-layered modification Vesicular carrier modification	Passive loading techniques *Mechanical dispersion methods* *Solvent dispersion methods* *Detergent removal methods* Active loading techniques	Biju et al., 2006 Khan et al., 2020 Fakhraver et al., 2016
Dendrimers	Citric acid, Polyamido amine, Polyether,	PEG-modified dendrimers as nanocontainers with biocompatible surfaces	Cascade reactions synthesis Divergent synthesis approach	Satija et al., 2007

Table 3.4 Continued

	Polyglycerol, poly-L-Lysine, Polyphenylene, Polypropylene imine	PEG-modified PAMAM dendrimers with shells Temperature-sensitive dendrimers by surface modification Dendrimers-based amphiphiles for functional molecular assemblies Dendrimers-AuNPs hybrids	Convergent synthesis approach	Kono et al., 2012 Abbasi et al., 2014
Gold NPs (AuNPs)	Au flat, Au with TG, Au with TG and MBP, Ti substrate, AuNPs pristine, AuNPs with TG, AuNPs with TG and MBP	Electrostatic interactions modification Complementation of base pair modifications Ligand exchange modification Chemical reaction modification for Au surfaces Click chemistry modification	Physical methods *UV irradiation* *Laser ablation* *Plasma synthesis* Chemical methods *Citrate synthesis* *Turkevich method* *Wet chemical synthesis* *Chemical reduction method* Physicochemical methods *Sonochemical methods* *Sonoelectrochemical method*	Spampinato et al., 2016 Khongkow et al., 2014 Utkarsha et al., 2014

Table 3.4 Continued

Polymeric NPs (PNPs)	Gelatin, Albumin, Lectin, Legumine, Viciline, Alginate, Dextran, Chitosan, Agarose, Pullulan, poly E caprolactone, PLA, (PLGA), Polystyrene, PICA, PBCA, PHCA, PMMA	Adsorption modification technique Conjugations modification technique Polymer embedding modification technique Layer by layer deposition deposition modification technique	Two-step procedures *Solvent evaporation emulsification* *Solvent diffusion emulsification* *Reverse salting-out emulsification* One-step procedures *Nanoprecipitation method* *Dialysis method* *Supercritical fluid technology*	Arsalan et al., 2020 Crucho et al., 2017
Carbon-based NPs (CNTs)	Carbon atom with different morphologies and bindings, Citric acid, Ethylenediamine, Nitrogen-containing precursors	Noncovalent functionalization modification technique Click chemistry functionalization technique Block copolymer functionalization technique Dendritic polymers functionalization technique	Carbon arc discharge Laser vaporization Ablation techniques Catalytic chemical vapour deposition High pressure co-conversion (HiPCo)	Barman and Patra, 2018 Karkoti et al., 2018 Sahu et al., 2017

Table 3.4 Continued

Magnetic NPs (MNPs)	Iron, Nickel, Cobalt, Microbeads, MgFe2O4silica Coated, Precipitated Fe3O4	Inorganic polymers techniques (Sio2, Stöber, solgel, Nobel metals) techniques Organic molecules techniques (surfactant, citric acid) Silane coupling agent's modification techniques (amino silane, vinyl-silane)	Co-precipitation Hydrothermal synthesis Sonochemical method Arc discharge Spray pyrolysis Microemulsion Laser pyrolysis	Jaffrezic-Renault et al., 2007 Ling et al., 2019 Srivastava et al., 2017
Up-conversion NPs (UCNPs)	2+Ti, 2+Ni, 3+Mo, 4+Re, 4+Os, 3+Pr, 3+Tm	RE-doped NaYF4 modification Inorganic shell layer modification Organic capping ligands modification	Coprecipitation method Thermal decomposition method Hydrothermal/solvothermal method	Gamelan and Güdel, 2000 Wang et al., 2011

Abbreviations: TGA, thioglycolic acid; PTVP, thiol-terminated poly (vinylpirrolidone-co-maleic anhydride-co-ethylene glycol dimethacrylate) based heterobifunctional polymer; GMI, stealth liposome; PEG-DSPE, 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-Poly(ethyleneglycol); PAMAM, Poly(amidoamine); TG, 1-ß-D-thio-glucose; MBP, maltose binding protein; PLA,
Polylactic acid; PLGA, poly (lactic-co-glycolic acid); PICA, Phenolic Impregnated Carbon Ablato; PBCA, poly(butylcyanoacrylate)

3.7 Nanotheranostic Particles for Breast Cancer Diagnosis and Therapy

Tumor biomarkers can be found in different tissues in the patient's body, most of them are proteins, and they can be found in normal and abnormal tissues. For diagnosis and detection purposes, these biomarkers are used as evidence—three main types of biomarkers, intracellular, extracellular, and the one on the cell membrane. For imaging, the ones on the cell membrane are targeted for in vitro applications, and the intracellular are less targeted due to their immense size (Chen et al., 2013).

The epidermal growth factor receptor (EGFR) is a biomarker for breast tumor cells, and EGFR has roles in cell growth, apoptosis, and metastases processes (Schlessinger, 2000; Normanno et al., 2006). EGFR is coupled with itself or with human epidermal growth factor receptor 2 (HER2). Monoclonal antibodies are used in various tumor clinical applications such as cetuximab, which is used in neck, head, and colorectal cancer by coupling with EGFR and block its interaction (Dy and Adjei, 2008). EGFR targeting antibody inhibitors are coupled with NPs and used as an imaging probe for targeting imaging (Li et al., 2008; Kah et al., 2007). HER2 is considered a robust breast cancer biomarker; HER2 can be combined with EGFR and HER3 (Cai et al., 2008). Trastuzumab is used in breast cancer treatment. It is conjugated with different types of NPs and used as imaging agents in pre-clinical applications.

Vascular endothelial growth factor (VGFR) is a growth factor biomarker for tumor progression, and it has a role in the angiogenesis process that leads to abnormal activity inside healthy tissues. VEGF-A has some cell migration roles, and mitogenesis and VEGF-2 are directly related to the tumor cell development process (Ferrara et al., 2005). Bevacizumab antibodies are used to inhibit the overexpression between VEGF/VEGFR, which is related to prognosis marker for tumors and used in treatment management for cancer.

Integrins are adhesion molecules that consist of one alpha and one beta unit. They exist in the vascular, cell membrane, and other tumor cell types. Also, they have a role in metastasis and angiogenesis processes (Hood and Cheresh, 2002). these subunits are used to assist the interactions in cells. For cancer detection purposes, alpha v and beta three are used as a biomarker in various cancer types like breast, lung, and prostate (Chen et al., 2013). They are

used with RGD amino acids after coupled with NPs in drug delivery applications in cancer (Cai et al., 2008).

Folate receptors (FRs) have a low level in normal cells, and they are overexpressed in specific tumor cells like ovarian cancer (Jaracz et al., 2005). FRs are a robust biomarker for cancer due to their significant binding rate in tumor cells comparing to normal cells. Matrix metalloproteinases (MMPs) have low expression in healthy tissues, but it is rapidly activated in abnormal tissue formation and can be used as a biomarker. MMPs are overexpressed in tumor cells like in breast cancer cases and is active at a higher rate. Specific types of MMPs have an essential role in the growth, metastasis process (Scherer et al., 2008). MMPs are used in cancer applications as imaging probes for targeting purposes. MMPs, bind with peptides for tumor targeting after coupled with dye molecules, besides being used as cancer cell inhibitors (Koivunen et al., 1999).

Magnetic Nanoparticles (MNPs) have been used as probes for tumor imaging. MNPs are coupled with targeting molecules for imaging purposes. For example, the specific type of peptides is coupled with various NPs like silica and IONPs, and other molecules act as an imaging probe (Chen et al., 2013). These peptides have shown a significant result in affinity improvements for integrin (Niu and Chen, 2011). for thermal decomposition PEGylated copolymers using in IONPs coating (Chen et al., 2009). RGD-IONPs conjugation complex targets breast cancer in vivo applications (Jana et al., 2004; Woo et al., 2005).

Antibodies also can be coupled with MNPs. For example, Herceptin is coupled with MnFe2O4 and used to enhance MRI technique for ovarian and breast cancer in vivo applications (Lee et al., 2011). IONPs coupled with antibodies to detect a specific type of EGFR mutant and used for glioblastoma detection (Hadjipanayis et al., 2010). IONPs are used as a contrast agent in vivo MRI technique and providing therapeutic abilities in tumors and considered an example for theranostic approach in cancer. Paramagnetic NPs are used in tumor imaging applications. For example, MnO has been used with Herceptin, and the complex is used in locating breast cancer metastasis because of Herceptin properties (Na et al., 2007).

Histopathology is a technique used for imaging and cancer diagnosis purposes. Quantum dots (QDs) have better photostability properties, making them a good alternative for fluorophores due to their photobleaching and excitation issues (Probst et al., 2012). QDs are used in labeling biomarker applications due to their broad excitation wavelength, unlike the fluorophores. QDs are used in labeling breast cancer biomarkers: HER2, EE, and PR with 655, 605, and 565 wavelengths, respectively (Yezhelyev et al., 2007).

Gold Nanoparticles (AuNPs) with optical coherence tomography imaging (OCT) are used for tumor diagnosis purposes. Gold Nanorods (GNRs) are used with surface plasmon resonance (SPR) in optical coherence tomography imaging applications; by using OCT imaging, they get imaging for GNPs inside the breast tumor cells (Cao et al., 2012). AuNPs are used in therapy applications for breast cancer. They have been used in treatment, imaging, and clinical diagnosis. Various gold particles are used as photothermal agents, imaging agents, bio carriers, and radiosensitizers (Jain et al., 2012; Kumar et al., 2012). AuNPs are used in drug labeling applications and conjugated with peptides.

AuNPs activate the apoptosis process inside cells when activated by an external light source (Kong et al., 2008). Currently, AuNPs are used in photothermal treatment; the new particles are aimed to do both drug delivery and photothermal at the same time. AuNPs coat DOX and affect the microenvironment in breast cancer cells, act as a drug carrier, and have a beneficial role in DOX release (Nam et al., 2013). AuNPs are used with paclitaxel can be functionalized by PEG and other molecules and used in both diagnosis and therapeutic (theranostic) approaches for breast cancer (Heo et al., 2012). Nanoparticle injection may be useful in breast cancer cases because they are located near the surface and not in deep tissues. AuNPs can also be useful in promising therapy for advanced cases (Kennedy et al., 2011).

3.8 Theranostic in Cancer Targeting Therapy

Target therapy is a treatment platform. It mainly depends on how drugs are aggregate at specific sit (target cells) besides preventing normal cells' side effects. Nanocarriers are used to improve bioavailability for different compounds in the target cells, and it works on shrinking down specific molecule concentration and reduce the exposure time and toxicity inside healthy cells

caused by drugs (Din et al., 2017). drug delivery has several strategies, such as physical, local, magnetics, and passive targeting. Figure below shows the conjugation method in targeting therapy.

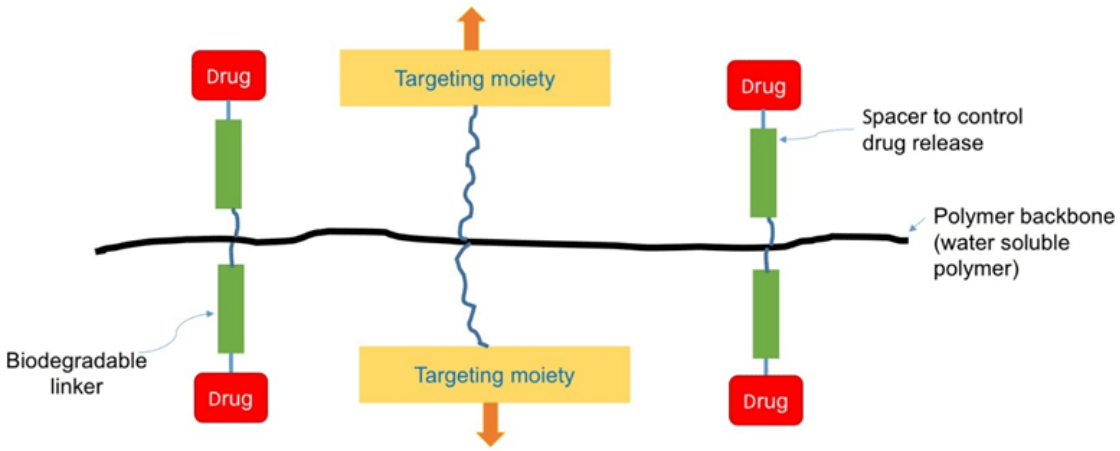

Figure 3.16: Conjugation Process in Targeting Therapy Strategy

Local targeting is used primarily for metabolic disease therapy, periodontitis, and bone abnormalities because of their potential drug availability possibilities and lengthen the drug time circulation in the area of interest. EPR is the building block for using passive targeting strategies. Macro and micro molecules aggregate favorably in tumor cell sites because of the destruction of the draining system in tumor cells; this leads to lengthening the EPR process for different molecules.

Thermal, electrical, and optical properties for bio-carriers build up the drug delivery system's physical targeting strategy. Bio-carriers destroy at specific PH levels or temperature and release the drug at a particular point for a specific target site. PH sensitive molecules are used in cancer therapy because cancerous cells are more acidic than normal ones (Karimi et al., 2016). controlling superparamagnetic bio-nano particles by external magnetic source makes NPs advantageous at targeting sites; high doses in chemotherapy can be solved using this strategy by reducing the excessive number of drugs that go into the healthy cell and lengthening the time in tumor cells. (Polyak et al., 2009). intensity, size of nanoparticles, and biological factors can

affect the super magnetic bio-carriers performance at tumor cell sites like viscosity and interaction between molecules and the blood.

Physicochemical properties are essential in passive targeting for NPs strategies, but on the other hand, the active targeting depends on the action between the carrier's surface and the antigen. Nanoparticles are functionalized with various ligands such as proteins, peptides, and aptamers because of their target site receptors' properties. The table below shows the molecules that are used in active targeting strategy in drug delivery systems.

Table 3.5: Molecules used in Active Targeting Strategy

	Ligand type	**Targeting**	**Disease**	**Ref.**
Antibodies	Trastuzumab, cetuximab, rituximab	HER2, EGFR, CD20	Breast cancer, esophageal carcinoma, pancreatic adenocarcinoma, head and neck cancer	Tokunaga et al., 2019
Peptides	Transferrin	Transferrin receptor	Cancer	Luria-Perez et al., 2016; Jhaveri et al., 2018
Small molecule (metabolic)	Folic acid	Folate receptor	Ovarian cancer, lung cancer	Dhir et al., 2018
Aptamers	A10RNA	PSMA Extracellular	Prostate cancer, breast cancer	Fan et al., 2016

Table 3.5 Continued

Abbreviations: HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; CD20, protein in B cells; A10RNA, RNA editing aptamer; PSMA, prostate specific membrane antigen.

Table 3.6: Theranostic Nanoparticles in Pre-clinical and Clinical Applications

Stage	**NP Type**	**Therapeutic agent**	**Diagnosis agent**	**Tumor**	**Target**	**Ref.**
Pre-clinical	Liposome	Paclitaxel	Ph-sensitive polymers Modified NPs	Ovarian cancer	EPR	Devalapally et al., 2016
	Silica	Paclitaxel	Superparamagnetic nanocrystals	Pancreatic cancer	Folic acid	Liong et al., 2008
	Iron oxide	Anti-EGFR	Iron oxide NPs	Glioblastoma	EGFR	Hadjipanayis et al., 2010
	Gold nanorod	Heat	Thermal/CT	Breast cancer	EPR	Von Maltzahn et al., 2009
	Quantum dots	Paclitaxel	Quantum dots	Cancers	Folic acid	Matea et al., 2017
Clinical trials	Silica	cRGDY	Hybrid NPs	Brain tumor	α1β3 integrin	Philips et al., 2014
	Cyclodextrin	RNAi	Transferrin	Solid tumors	Transferrin	Davis et al., 2010
	Silica-gold nanoshell	Photothermal ablation	Nanoshell	Head, neck, lung cancers	EPR	Singh et al., 2018

Table 3.6 Continued

Gold	Tumor necrosis factor alpha	Gold NPs	Solid tumors	EPR	Libutti et al., 2010
Iron oxide	superparamagnetic	Iron oxide	Healthy cells	N/A	Richards et al., 2012

Abbreviations: EGFR, epidermal growth factor receptor; cRGDY, peptide cyclo-(Arg-Gly-Asp-Tyr); NPs, nanoparticles; EPR, enhanced permeability and retention effect.

3.9: Theranostic Nanoparticles in Clinical Applications in Cancer

Different types of theranostic NPs can be used in cancer treatment platform. Liposomes are the most used for clinical functions. Theranostic NPs can be used as clinical procedures and pre-clinical ones. the role of theranostic applications in cancer summarize in response treatment evaluation and anticipation, develop personalized medicine by improving the current using treatment procedures. Because of their excellent biological and physicochemical properties, NPs are growing and gain much attention recently from scientists. Nowadays, scientists focus on improving various properties such as stability, accuracy, and sensitivity by representing drug delivery, target therapy, and imaging techniques strategies used as a theranostic platform for the disease, especially for cancer. The whole platform identity will rise and make magnificent advances and be significantly more than traditional cancer treatment (Maniglio et al., 2018; Saliev et al., 2018). The table below shows the latest nanoparticles used in pre-clinical and clinical applications.

Table 3.7: Theranostic Nanoparticles Applications Summary

Nanoparticles	**Size**	**Applications**
Quantum Dots (QDs)	2-10 nm	Tumor imaging Biosensing Drug delivery Cancer therapy
Liposomes	< 200 nm	Tumor diagnosis Targeting therapy Drug delivery system Anti-cancer therapy Anti-microbial therapy
Dendrimers	5-20 nm	Drug delivery system Bioimaging (imaging contrast) Radioimmunotherapy Boron neutron therapy
Polymeric Nanoparticles (PNPs)	30-100 nm	Drug delivery system Protein Inter-arterial Brain delivering Cancer Drug index improvement Molecular bioimaging Gene material detection Targeting inflammatory diseases

Table 3.7 Continued

Gold Nanoparticles (AuNPs)	5-400 nm	Diagnosis bioimaging Photothermal therapy Photodynamic therapy Imaging and therapeutic agents Drug carrier
Carbon-Based Nanoparticles (CNTs)	2-8 nm	Drug delivery Cancer therapy Biosensing
Magnetic Nanoparticles (MNPs)	1-200 nm	Improving Magnetic Resonance Imaging (contrast agents) Cancer targeting therapy Hyperthermia therapy Drug delivery system
Up-Conversion Nanoparticles (UCNPs)	1-100 nm	Molecular imaging and labelling Drug delivery system Photothermal therapy

3.10 Future Perspective of Theranostic Nanoparticles

In general, theranostic means using NPs in molecular imaging techniques and therapy platforms and considering barriers, biocompatibility, pharmacokinetics, surface modification, and other factors. Polymers are the most used nanoparticles due to their promising biological properties for molecular imaging, surface modifications, and contrast probes; thus, they provide better imaging quality and improved therapeutic function. The Figure below illustrates the main strategies for theranostic development.

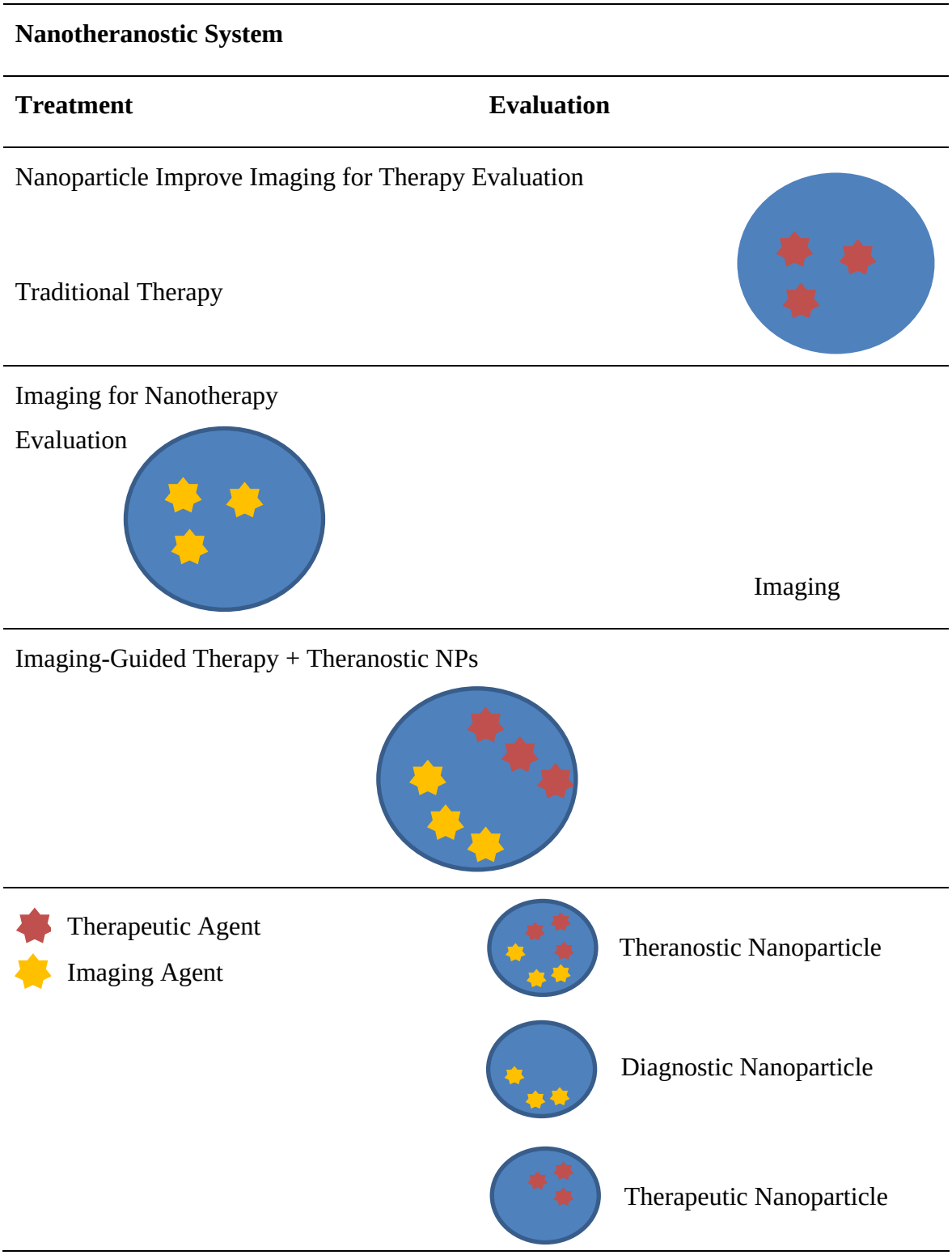

Figure 3.17: Theranostic Development Strategies

Using nanoparticles as a theranostic have three different directions (Onaciu et al., 2019):

• Using NPs as a contrast agent for assessing the therapy effects using molecular imaging.

• NPs used for estimation of theranostic platforms with imaging probes.

• Using nanoparticles as target agents and imaging tools.

For the first and second directions, NPs are evaluators or a part of the evaluation, but for the third direction, both the first and second directions are used together to produce a kind of complex processes. Annexin A5-conjugated polymeric micelles for detection apoptosis using SPECT at the same time cell apoptosis is influenced by cyclophosphamide, etoposide, polypaclitaxel and cetuximab (IMC-C255) anti-EGFR antibody and used to apoptosis observation especially for lymph cancer and breast cancer beside of that SPECT provides apoptosis visualization process inside the cancerous cells (Zhang et al., 2012).

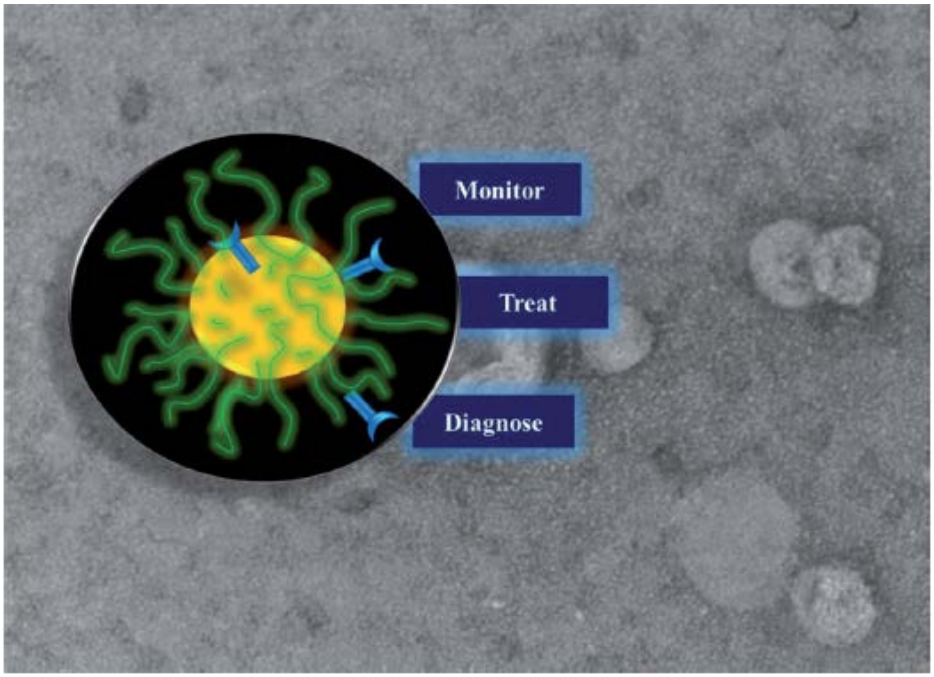

Figure 3.18: Theranostic NPs Approach

NPs are used in the evaluation process with molecular imaging probes. 2-deoxy-2-fluoro-D-glucose (F18-FDG) probe is used for metabolic measurement using PET/CT imaging technique; the labeled probe act as a biomarker for NPs besides monitoring thermal therapy treatment (PTT) strategy, especially in lung cancer (Norregaard et al., 2017). To Performing theranostic nanosystem (imaging and therapy) at the same time, nanosystems are using two different components coupled with each other to obtain a theranostic behavior; for photothermal cancer therapy, NIR with metallics NPs are used due to the sensitive optical properties the MNPs had a specific NIR wavelength.

NPs can be used to enhance molecular imaging techniques outputs. DOX loaded to micelles and perfluoropentane stabilized by copolymer and used in CT and targeting therapy, especially for ovarian and breast cancer (Rapoport et al., 2007; Sorace et al., 2012). another approach for tumor visualization and targeting therapy is achieved by combining different types of NPs with ligand and drugs. Quantum dots, coupled with aptamers and DOX for tumor cell targeting therapy, control drug-releasing function and advance imaging output features for cancerous cells.

Nanoparticles can be used for photodynamic and thermal therapy to obtain an assist target therapy platform. Photodynamic therapy is a multiple level therapy procedure mainly based on using drug and energy released from light; it is using sensitizer to affect the tumor cells energy that released from light after laser energy applied on it after this process "Sensitization" activated it became toxicity environment and cause harmful effects at the targeted tumor cells site. The figure below shows the active strategies for theranostic applications.

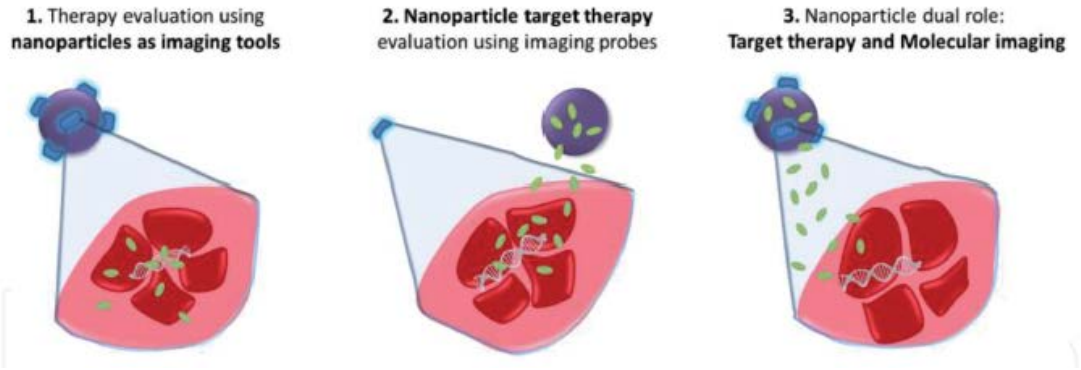

Figure 3.19: Active Theranostic Strategies

Photodynamic therapy's main task is to be a better alternative and for chemotherapy procedures in cancer therapy. Photodynamic therapy providing drug resistance for cancer. Fluorescence drugs load AuNPs; after that, it can target prostate tumor cells by their unique membrane structure. It has sometimes been used as an agent in surgical guiding systems—photodynamic therapy and immunotherapy used in colorectal cancer and liposomal nanoparticles.

Photothermal therapy (PTT) is considered a theranostic procedure because it can be providing both diagnosis and therapeutic function at the same time. The whole idea behind the PTT procedure is using NPs with thermal features and using it to target tumor cell sites and apply laser energy for heat, releasing the area of interest. PTT is based on electromagnetic radiation and infrared technique. Drug molecules coupled with targeting ligand after that it capsulated inside NPs. Au nanoshells using in targeting therapy applications for breast cancer and in NIR; besides, it is used in ovarian cancer cases in which polymer NPs are coupled with IR820 and DOX to lengthen circulation time and aggregation properties in the tumor cells, the desired temperature needed to affect the tumor cells are ranged from 42-45 Celsius degree depending on the tumor cells type (Zhu et al., 2016; Liu et al., 2018).

CHAPTER 4
BIOIMAGING FOR THERANOSTIC APPLICATIONS

4.1 Molecular Imaging Mechanism

Molecular imaging is used in diagnosis, therapeutics, and monitoring application from cells to molecular biology. Molecular imaging techniques are Computed Tomography (CT), Single-Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), Ultrasound (US), and Positron Emission Tomography (PET) besides to integrated imaging modules such as SPECT/CT or PET/MRI which provides practical information and abdominal structure information extracted from MRI, CT, and UC (Jokerst et al., 2003).

All imaging modulates depending on using contrast agents, which aggregated on the area of interest. Excess amounts of radiation are harmful to our bodies, and it might damage DNA contents and cause abnormalities in tissues; besides, it sometimes causes artifacts and side effects to patients and does not guarantee the care quality needed mostly.

4.2 Nanoparticles in Imaging Strategies

Nanoparticles are used for diagnostic functions for particular types of diseases. NPs can detect any abnormalities for specific cancerous cells, and it has capable of detecting genes, surface cell molecules, and molecules which incorporated in any diseases' environment progression, whether if it is chemical, biological, or physical changes. See the table below

Table 4.1: Nanoparticles Examples in Cancer Imaging

Imaging technique	**Sensitivity**	**Cost**	**Nanoparticle**
Positron Emission Tomography (PET)	High	High (higher than MRI)	Polymeric nanoparticles
Computed Tomography (CT)	Low	Low	AuNPs USPIONPs
Magnetic Resonance Imaging (MRI)	Low	High	Paramagnetic Liposome USPIONPs
Ultrasound	Medium	Low (lower than CT)	Microbubble

Abbreviations: AuNPs: gold Nanoparticles; USPIONPs: ultrasmall superparamagnetic iron oxide nanoparticles.

For molecular imaging applications, physical changes in NPs are suitable and applicable due to their small size. NPs size ranged from 3-150 nm in diameter; for cancer targeting applications purposes, NPs are functionalized based on their surface using specific molecule ligands; more ligands mean more efficient targeting performance. Signaling groups directly affect the sensitivity of identification and detection processes (Debbage et al., 2008).

Quantum dots, metallic nanoparticles have remarkable optical features naturally. Quantum Dots are functionalized by Arginine, Glycine, Aspartate, after labeling by F18 molecule to ensure and provide advanced optical properties for Positron Emitting Tomography (PET) and prostate cancer.

AuNPs are suitable for their optical features and it useful for CT imaging due to their high sensitivity and spatial resolution besides its conjugated with another molecule such as chitosan and this resulting in a complex with advanced characteristics used especially for adenocarcinoma imaging procedure (Sun et al., 2015) also, AuNPs coupled with antibodies for head and neck cancer and cell carcinoma theranostic applications.

Iron oxide NPs are used in MRI for their contrast features. iron oxide NPs are coupled with peptides and other polymers, forming complex structures used specifically for glioblastoma cases. For breast cancer, Positron Emission Tomography (PET) and mesoporous silica particles are used as a bio-carrier in targeting therapy platforms for cancer (Chen et al., 2015).

For real-time and non-invasive procedures in imaging, perfluorocarbon NPs are used for thyroid imaging carcinoma. Using particular NPs such as aptamers, dendrimers, liposomes, and micelles are usually need to functionalized with contrast agents and fluorophores (Barrett et al., 2009). for better performance for NPs, some characteristics are required: biocompatibility, biodegradability, target accessibility, solubility, and encapsulation properties. Photobleaching is a disadvantage for using fluorophores in imaging applications.

In medical imaging, molecular relaxation is related to various chemical and physical properties rather than emission itself; a group of factors incorporated in relaxation like temperature, presence of a specific molecule, and pressure affects the intensity profile. This phenomenon is known as quenching. Exploiting fluorescence phenomena can provide more knowledge and information about nanoparticle concentration in a specific area.

Aggregation-induced emission (AIG) was developed in 2001, and it is beneficial for both therapy and diagnosis applications. AIGgens platform system has been reliable and useful for theranostic applications; it has impressive properties such as biocompatibility, optical features, and easy to prepare and conjugation. AIEgen is coupled with a short peptide to produce a molecular complex to accelerate the Apoptosis process inside cancerous cells (Yuan et al., 2014).

4.3 Molecular Imaging and Cancer

Molecular imaging has an essential role in cancer applications; it provides detection, diagnosis, and treatment for cancer by helping the physician see what is happening deep inside the human body at the molecular level. Molecular imaging providing full detail for what is happening inside the body on a cellular scale. It is also used for functioning imaging and monitoring various biological and other processes inside the cells. The conventional methods of imaging providing physicians and scientists with anatomical images. Molecular imaging providing personalized medicine for patients in diagnosis and treatment.

Molecular imaging techniques can provide non-invasive approaches besides obtaining more specific information that other imaging modalities cannot obtain. Molecular imaging is helping in tumor localization early detection of tumor cells. It also used in the evaluation and managing care by measure the tumor spreading possibilities in other parts of the body, identify the class of tumor, selecting the best therapy based on some characteristics and some biological properties of tumor cells, monitor the post-drug response, manage the treatment regimen, offering flexibility based on any changes in biological activities in tumor cells and used in ongoing care—three advantages of molecular imaging methods that they are non-invasive and painless. The idea behind the molecular imaging technique is done by detecting the biological and chemical activities inside the cells. By detecting cancerous cells' changes like growth rate, energy consumption, blood rate changes, etc., tumor cells cause anatomical changes in organs and tissues. These changes could be detected using MRI, CT, and X-ray imaging techniques (Society of Nuclear Medicine and Molecular Imaging, 2016).

Three main components in molecular imaging techniques are device, agent, and probe. Some enormous agents can be used like MNPs, amino acids, 99mTc-pyrophosphate; after agents reach the area of interest, it becomes easy to detect by the imaging device and create a fully mapped image of these agent's properties. These mapped helps the clinicians to predict the type and the nature of the tumor cells.

Molecular imaging plays a crucial role in cancer personalized medicine approaches by using molecular imaging techniques in oncology applications and improve patient care. Molecular

imaging assists the oncology development of therapeutic procedures by detecting the molecules that significantly affect tumor cells. It is also used to detect biological characteristics; thus, support the personalized medicine approaches. Response Evaluation Criteria in Solid Tumors (RECIST) is used in monitoring patient responses for treatment, evaluation, and stabilizing (Seaman et al., 2010). molecular imaging is used in targeting therapy applications and assist clinicians in matching therapies, treatment responding, and therapeutic resistance monitoring applications (Jackson et al., 2009).

One of the biggest challenges in tumor therapeutic procedures is drug resistance, headstrong development by the cancerous cells, and poor biodistribution for the anti-cancer drug (Minchinton et al., 2006). To beat the previous challenges, aptamers and short genetic fragment oligonucleotides are used due to their significant targeting features for both diagnosis and therapeutic (theranostic) (Seaman et al., 2010). for example, aptamers and prostate cancer biomarker used as a drug carrier and theranostic agents (Lupold et al., 2002).

With time tumor cells gain a natural resistance for specific types of drugs—molecular imaging used in response therapy applications. Identifying the drug response in medicine is essential in various levels like reducing trial cost, reduce the number of patients that could suffer from the drug side effects, and improving quality of care delivered to patients. also used in pharmacodynamics markers of drugs side effects (Sarker and Workman, 2007). molecular imaging is essential in the drug development process by reducing the cost and time and increasing the treatment plan's efficiency by monitoring biological activities and pharmacodynamics and predicting the drug response.

Molecular imaging probes can predict if the patient is going to respond to a specific drug or not. It is also used to predict the treatment outgoing by comparing two groups (responders and not responders) and finding the difference between biological characteristics for both groups.

Molecular imaging techniques are improving the efficiency of tumor treatment procedures. It expands the prospects in treatment advances by supporting the tumor's structural, size, and anatomical measurement before and after treatment procedures. Tumor size alone is not enough to estimate the outgoing treatment efficiency (Wagenaar et al., 2008).

4.4 Theranostic Molecular Imaging

Nanoparticles are used widely in biomedical applications due to their unique properties such as molecular size, various morphological structures, surface functionalization abilities, and other physicochemical properties. In biomedical imaging applications, NPs act as contrast agents, which can help get better images and obtain more information at the molecular level. Nanoparticles are used clinically in therapeutic drugs bio carrier and incorporate in reducing side effects (Bobo et al., 2016). Also, nanoparticles are used in DDS and gene delivery in clinical trial phases (Anselmo et al., 2016).

Nanoparticles are used as theranostic agents due to their advances, like their unique structures and surface modifications, which can be used in various applications such as imaging and targeting therapy; besides, NPs are used in tumor cells to exploit EPR effects. Previous features make NPs capable of improving and advance classical imaging modalities such as CT, MRI, and PET. NPs are used as imaging agents for hybrid imaging modalities; thus, they can be used in various theranostic applications. The figure below illustrates theranostic NPs characteristics that make them widely used in medical applications.

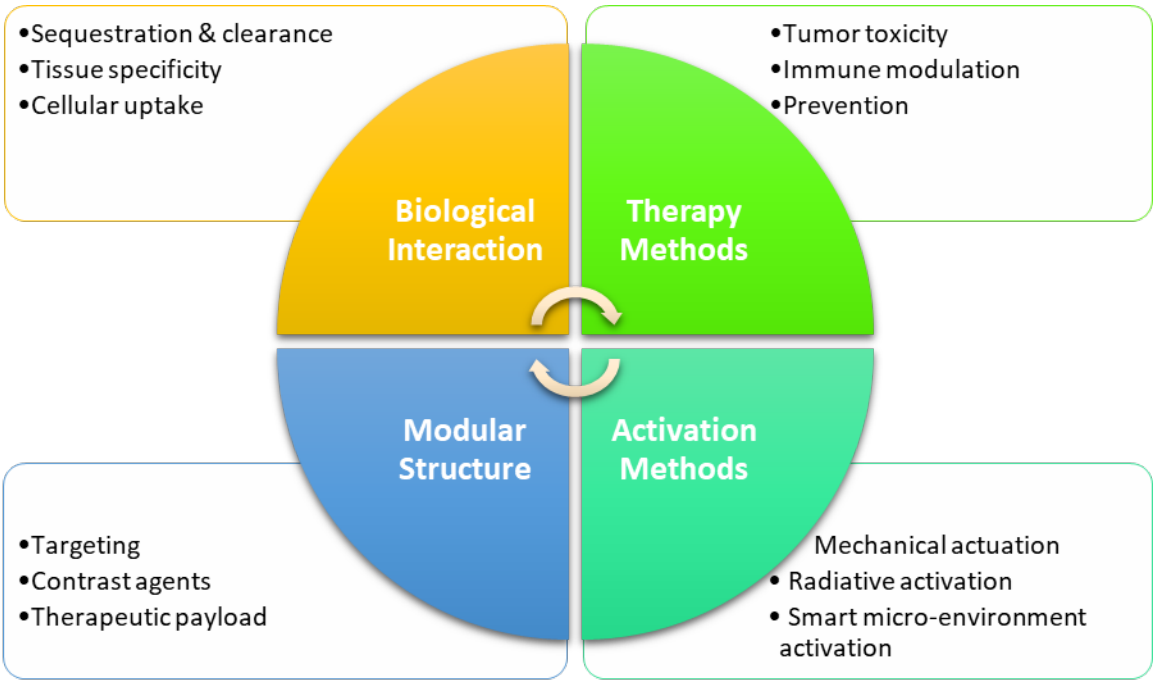

Figure 4.1: Theranostic Nanoparticles Characteristics

Imaging Applications

Superparamagnetic iron oxide NPs (SPIONs) are used as contrast agents in MRI imaging techniques. Now Ferumoxytol is used in clinical therapy applications. Ferumoxytol is related to ultrasmall SPION molecules; thus, it is beneficial in MRI imaging. It improves the MRI signal and reducing the pulse sequence loss (Bashir et al., 2015). Ferumoxytol is used in various medical applications. For example, it is used in Diabetes, neurological diseases, tumor cell imaging, tracking, and post-treatment evaluation for tumor cells (Gaglia et al., 2015; Kirschbaum et al., 2016; Deng et al., 2016; Bryant et al., 2016). Ferumoxytol used in anti-cancer for liver metastases. NPs are going to be the future of theranostic applications.

PET and SPECT are used in various medical applications like oncology, cardiology, and radiology. They are non-invasive procedures which used clinically. PET and SPECT rely on radioactive nuclides conjugated with different NPs to enhance imaging capabilities, especially for theranostic approaches like 18F-FDG and antibodies. NPs are labeled with different imaging

tracers to be used in oncology applications. The importance of NPs in labeling is summarizing as following: EPR effect, providing high radiolabeling density (DOTA, chelator), and hybrid imaging modalities. For clinical usage, NPs are preferred to be as small as possible with fast decaying radiolabels. in vivo approaches for lung cancer imaging 64Cu-labelled nanoclusters are used (Gao et al., 2015) also, 64Cu based liposome used in vivo approaches for cancer by increasing the uptake of EPR and enhance distribution properties (Hansen et al., 2015). 68Ga, 89Zr, 111ln, and 198Au used for different imaging modalities as radioisotope NPs (Madru et al., 2014; Shaffer et al., 2015; Zeng et al., 2014; Black et al., 2014). in Tumor-associated macrophages 89Zr used for labeling polymeric lipoprotein NPs for imaging purposes (Keliher et al., 2011). Cornell dots and 124I are used with positron emission tomography (PET) for localization and reducing toxicity in melanoma tumor cells (Benezra et al., 2011; Phillips et al., 2014).

Fluorescent dyes and fluorescent NPs replaced the small molecule dyes due to their significant properties and abilities such as better specificity, prolonge circulation times, and better activation features also, better signal intensity (hill et al., 2016; Kamila et al., 2016; Wang et al., 2014). Fluorescent NPs are used for detection purposes in both sentinel lymph nodes and in a solid tumor, surgery imaging-guided systems for cancer and monitoring DDS (Hill et al., 2016; Peiem et al., 2015). for photobleaching, Quantum dots are also used, there are better for multiplexing (Kamila et al., 2016). for reducing photobleaching, increasing concentration of non-fluorescent on nanoparticles surface and overcoming quenching, fluorogens with fluorescent nanoparticles by expressing aggregation-induced emission (Yan et al., 2016). On the other hand, fluorogens are not used in multiplexing, and fluorescence imaging techniques are more likely to obtained false-positive results (Tummers et al., 2015); with better specificity achieved for this imaging technique, it can be used in tumor cells resection (Stummer et al., 2006).

Surface-enhanced Raman spectroscopy (SERS) is an optical imaging technique used in tumor cell imaging. This optical imaging techniques mainly rely on enhanced surface NPs. The advantage of this technique is that the NPs are not suffering from photobleaching (Andreou et al., 2016). By exploiting the EPR effect, SERS nanoparticles can be used due to their low

threshold detection and high specificity in lesions early detection and obtained a detailed image for tumor (Harmsen et al., 2015). SERS nanoparticles are used in the sentinel lymph node, liver, and spleen cancer imaging. SERS coupled with various biological molecules such as aptamers, antibodies, or peptides to providing better imaging capabilities for tumor cells in image-guided surgical systems (Kircher et al., 2012) and used for detection in different types of cancer like ovarian, lung, and glioblastoma. SERS nanoparticles will provide a significant improvement in reducing the mortality rate for cancer patients.

In hybrid imaging techniques, NPs are excited and detected through the physical process (Andreou et al., 2017). in the photoacoustic imaging technique, the contrast agents detected ultrasound. Using NPs in hybrid imaging (Photoacoustic) techniques provides a non-invasive imaging acquisition, allowing them to obtain images for deeper tissues and high resolution than classical optical imaging. Various types of nanoparticles are used in pre-clinical procedures, which showed significant results and improvements in photoacoustic detection, photothermal, and photodynamic therapies. Iron oxide nanoparticles (IONPs) and silica nanoparticles are approved in clinical procedures (Andreou et al., 2017). MNPs with photoacoustic imaging techniques (hybrid imaging) promise to improve tumor cell detection (Li et al., 2015).

Therapy Applications

NPs are used as imaging and therapeutic agents, drug delivery systems DDS, gene delivery systems, and practical clinical procedures results (Bobo et al., 2016). In DDS, nanoparticles are used as drug vesicles for DOX and other anti-cancer drugs, releasing drugs at targeted cells in tumor sites, reducing toxicity for drugs, and protecting surrounding healthy tissues. In breast cancer cases, DOX conjugated with PLGA, injected in nanoparticles which can be stimulated by pH levels to prevent DOX from efflux and improve DOX efficiency in the tumor cell sites (Xu et al., 2016). in vivo liver cancer cases, 64CU-PEG NPs are loaded with specific anti-cancer inhibitors with positron emission tomography-photoacoustic imaging (PET-PAI) hybrid imaging technique to use in chemotherapy (Zhang et al., 2015). siRNA loaded in different types of nanoparticles and used in several medical applications such as gene delivery for lung cancer, EGFR inhibition for transdermal with no toxicity (Zheng et al., 2012).

Nanoparticles can be used in photothermal therapy applications by using heat energy to destruct tumor cells. Nanoparticles for this type of application are used for various cancer types. AuroShells was the first NPs used in photothermal applications using optical coherence tomography (OCT) (Gobin et al., 2007). NPs are also used in head and neck, lung, prostate cancers. AuNPs used in photothermal therapy. For photodynamic therapy, nanoparticles are used. Near-IR photodynamic therapy can be obtained deep imaging for tissues using silica-coated UCNPs photosensitizer (Idris et al., 2012). In pre-clinical procedures, SPIONs are used with an external magnetic field in hyperthermia therapy (Hayashi et al., 2013).

Ultrasound (US) with nanoparticles (NPs) can be used in drug delivery systems in tumor applications. US and NPs are used in drug-releasing procedures, which the US can motivate NPs to accumulate at specific sites such as cavities. Furthermore, NPs can be crossed from blood-brain barriers (BBB) (Timbie et al., 2014). copolymer blocks NPs (PEG-PDLA) with the US can beat the solubility barrier issue for anti-cancer drugs (Rapoport et al., 2013). Polymer NPs stabilize microbubbles with SPION and are used to release an MRI-US hybrid imaging technique (Morch et al., 2015).

SPIONs were used in immunotherapy applications by suppressing the growth of tumor cells. In tumor pre-clinical applications, labeled liposome and lipid NPs can be functionalized on specific immuno-cells leading to decreased tumor overload (Stephan et al., 2010). for in vivo procedures, copolymer blocks like PEG-PLGA NPs can be attached with specific dyes and amines to produce tumor antigen bodies in photothermal therapy procedures that lead to inhibiting metastasis activities (Chen et al., 2016). CNTs with PLGA NPs can be used clinically in immunotherapy applications after its surfaced functionalized by T-cells to produce antigen with carrying abilities for immuno-signaling molecule for controlling dose intake thus, can reduce side effects, the previous nanoparticles complex system incorporates in inhibiting growth in tumor cells (Fadel et al., 2014).

Positron emission tomography (PET) is used with nanoparticles in radiotherapy and is considered a perfect option due to tumor cells' distribution improvements. as mentioned before, reducing the half-life for radionuclides is essential. 225Ac nuclides are used with NPs

(McLaughlin et al., 2014). IONPs and polymeric NPs with 131I radionuclides are used in targeted therapy for thyroid in vivo procedures treatment (Chen et al., 2014; klutz et al., 2011). in vivo procedures 177Lu with lipid-calcium-phosphate NPs used as inhibitors for tumor cell growth (Satterlee et al. 2015). the nonradioactive molecule could be used in therapeutic procedures like 99mTc. The PET-folic acid-99mTc-MWCNTs imaging probe was used to enhance drug efficiency compared to the absence of 99mTc nonradioactive modules (Das et al., 2013).

Metal nanoparticles (gold, silver, iron, and titanium) used in radiotherapy applications act as photosensitizers. for example, Au nanoclusters NPs to increase uptake in tumor cells (Zhang et al., 2014) it can also be coupled with other NPs like polymeric ones (Al Zaki et al., 2014). AuNPs and AgNPs are used in glioblastoma, head, and neck cancers by advancing the survival rate in vivo procedures. SPECT imaging techniques with Au seeds incorporate in radiotherapy applications. They obtained magnificent results in tumor cells shrinking (Moeendarbari et al., 2016).

4.5 Molecular Imaging of Cancer with Imaging Agents

The cancer patient's survival rate has relied directly on early diagnosis and detection; early detection in the starting stages can prolong the survival rate by ten years (Etzioni et al., 2003). lately, molecular imaging techniques are widely used in clinical studies. MRI, CT, US, and other imaging techniques are limited to anatomical information; also, they have their drawbacks such as irregular distribution and side effects (Davis et al., 2008; Li et al., 2009; Li et al., 2013; Li et al., 2011). using nanoparticles as a contrast agent incorporate in imaging improvement by making them noninvasive and more feasible. For example, AuNPs are used as a contrast agent for Computed Tomography, See table 4.2. Using a single nanoparticle for both diagnosis and therapy in cancer is extensively used.

Table 4.2: Theranostic Imaging Agents for Various Imaging Modalities

Imaging modality	**Imaging agents**	**Functions**	**Ref.**
Optical imaging (OI)	Cy_{55} IRDye800 RhodaDOPE FITC Alexa647 DY647 IR780 Gold (Au) Quantum Dots (QDs) Y_2O_3 $NaYF_4$	Real time tracking for NPs Monitoring drug release Apoptosis real time imaging Photodynamic therapy Reducing multidrug resistance Chemotherapy Drug delivery monitoring Hyperthermia Cancer detection	Kim et al., 2010 Lai et al., 2014 Lee et al., 2011 Yoom et al., 2012 Tian et al., 2013 Grange et al., 2010 Hayashi et al., 2013 Tian et al., 2015
Ultrasound imaging (US)	Perfluorocarbon	Drug release Chemotherapy Ablation therapy	Min et al., 2015 Ma et al., 2014 Wang et al., 2014
Magnetic resonance imaging (MRI)	Gd chelates Iron Oxide Dopants	Drug delivery monitoring Hyperthermia therapy Tumor detection Gene therapy	Grange et al., 2010 Hayashi et al., 2013 Kobayashi et al., 2011
Computed tomography (CT)	Lodine Gold (Au)	Cancer imaging Chemotherapy radiosensitization	Kim et al., 2010 Huang et al., 2011

Table 4.2 Continued

Positron emission tomography (PET)	^{18}F ^{124}I ^{64}Cu ^{86}Y	Biodistribution analysis siRNA NPs efficiency	Xiao et al., 2012 Bartlett et al., 2007

4.5.1 Computed Tomography (CT)

Computed tomography relies on X-ray absorption in tissues. It used material with high atomic features for sensitivity, thus, detect contrast agents. CT imaging techniques have some advantages, such as cheap compared to other imaging modalities, high spatial resolution. The main challenge in imaging that soft tissues are hard to distinguish is the insufficient accumulation of contrast agents.

Au, Iodine, Sulfide, and ceramics compounds are used as contrast agents in the Computed Tomography imaging technique. These compounds have a high atomic number for X-ray absorption (Ma et al., 2017). ICG and iohexol are imaging agents approved by the FDA. They are used in NIR and CT imaging applications (Zheng et al., 2015). these agents are used in various in vivo approaches in cancer like breast, ovarian, lung, head, and neck (Zheng et al., 2010; Zheng et al., 2010). CF800 (lipid-based liposomal agent) with suing Computed Tomography imaging technique showed a significant result in location detection and visualization for lung cancer (Patel et al., 2016). Au-PEG NPs have been used as a contrast agent for Computed Tomography (CT) imaging techniques in breast cancer cases and showed a significant improvement in biodistribution manner (Nakagawa et al., 2016).

Iodinated Au clusters are used in Computed Tomography (CT) with fluorescence for cancer applications. It enhances biocompatibility and attenuation coefficient; thus, obtain a more sensitive and accurate diagnosis procedure in thyroid cancer cases. CT/fluorescent hybrid imaging modality and iodinated Au clusters are considered a promising tool for clinical practices that can detect thyroid cancer cells in the early stages and obtained better diagnosis (Chen et al.,2017). Monodisperse spherical AuNP clusters are used in lung cancer in vivo procedures. It showed remarkable improvements in the attenuation profile when used with

Computed Tomography (CT) (Hou et al., 2017). in gastric tumor cases, folic acid is conjugated with silica and Au nanoclusters and targets small tissues (Zhou et al., 2013). WS2 nanosheets are recently used as an imaging contrast agent in Computed Tomography imaging applications (Cheng et al., 2014). Tungsten oxide nanorods are promising theranostic particles for Computed Tomography and Photoacoustic Imaging; thus, it used in theranostic cancer applications (Titan et al., 2014).

4.5.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging technique has several advantages: high soft-tissue contrast, viable, safe, and high resolution. At the same time, Magnetic Resonance Imaging (MRI) is not the perfect choice for targeting applications, but with imaging agents, Magnetic Resonance Imaging (MRI) is using in molecular imaging applications. For Molecular Magnetic Imaging, contrast agents are used, and most of them are nanoparticles (metals). The main challenge in Magnetic Resonance Imaging (MRI) is its low sensitivity, but with some advances, it can be used in clinical applications.

The first nanoparticles approved as an imaging agent for Magnetic Resonance Imaging (MRI) is SPIONs. in gastric cancer cases, silica-coated SPIONPs and labeled with near-infrared fluorescence dye and CD146 antibodies (Liu et al., 2012) can be used in Magnetic Resonance Imaging (MRI). MNPs coated with dextran used with Magnetic Resonance Imaging (MRI) to improve the diagnosis capabilities. NPs have been proven to be efficient in these applications due to their biosafety, degradability, and long circulation time in the body.

Dextran and SPIONPs are using in providing hybrid imaging agents that can be used in targeting applications. Using Magnetic Resonance Imaging with advanced imaging contrast agents (NPs) providing obtain high-resolution imaging at a molecular scale also it providing monitoring, prognosis, and early detection for tumor cells (Ma et al., 2017). in prostate cancer, lymphotropic superparamagnetic NPs are used to enhance the sensitivity of Magnetic Resonance Imaging (MRI) (Harisinghani et al., 2013). Also using MNPs can use to detect prostate cancer in the presence of lymph node metastasis.

The third generation from MNPs is used for reducing immunologic sensitivity. MNPs are used to enhance the detecting abilities in Magnetic Resonance Imaging (MRI) as well as can be used in prostate cancer (Harisinghani et al., 2007). MNPs improve Magnetic Resonance Imaging function and obtain noninvasive vascular volume fraction (Bremer et al., 2003; Tang et al., 2005). MNPs can be used with Magnetic Resonance Imaging (MRI) in pancreatic cancer as an efficient therapeutic monitor and an angiogenesis marker (Hou et al., 2017). for gastric cancer fluorescent, MNPs conjugated with specific antibodies are used to detect cancer using Magnetic Resonance Imaging (MRI) (Wang et al., 2011). For metastatic lymph node detection, SPION with ferumoxytol is used effectively.

4.5.3 Ultrasound (US)

Molecular Ultrasound imaging (US) with imaging contrast imaging agents forms an imaging strategy with several advantages: low cost, no need for ionizing or irradiation materials, fair spatial resolution, and real-time imaging (Deshpande et al., 2010). using Ultrasound Imaging (US) with advanced imaging contrast agents is a promising tool for clinical applications (Kiessling et al., 2009). Imaging guided-therapy providing a better choice than surgical resection DDS in tumor sites. Also, it has fewer side effects (Philips et al., 2014) besides Ultrasound Imaging (US) are used in drug release applications (Sirsi and Borden, 2014).

Ultrasound Imaging (US) is used in both diagnosis and therapeutic applications. For diagnosis applications, the intensity used is low, and for tumor therapy, the intensity used is high (Kiessling et al., 2014). For example, polyelectrolyte multilayer microcapsules are the promising bio carrier for Ultrasound Imaging (Gao et al., 2015). TA/PVPON carrier (Chen et al.,2017) is a promising theranostic nanocarrier that has the ability to delivering drugs in both low intensity (diagnostic) and high intensity (therapeutic) in tumor cell applications.

Ultrasound Imaging (US) using advanced imaging contrast agents can be promoted to be used in tumor angiogenesis and to be noninvasive. Microbubbles, coupled with antibodies and used as targeted molecules to Ultrasound Imaging (US), using this agent shoed promising results in tumor cells site (Willmann et al., 2008). Ultrasound Imaging (US) used with liposomal as a carrier for DOX in DDS in vivo approaches for brain tumor cases (Yang et al., 2012).

Ultrasound Imaging (US) is used in chemotherapy by vaporizing the microbubbles in drug-loaded nanodroplets. It converts the accumulated droplets in tumor cell sites to bubbles. In this process, tissue destruction and cell damage are stimulated in the tumor cells. Curcumin loaded into chitosan-perfluorohexane droplet is used as an imaging contrast agent for Ultrasound Imaging (US), and it showed useful for breast cancer toxicity (Baghbani et al., 2017).

Ultrasound Imaging (US) is used with fluorescent nanobubbles in cancerous breast cells. These nanobubbles have several advantages such as low toxicity, stability, and improving contrast features for Ultrasound Imaging (UC) for overexpressing in breast tumor cells; thus, providing early detection.

In vitro approaches, advanced imaging agents for Ultrasound Imaging (US) are used to prolong the retention time in pancreatic tumor cells, which make Ultrasound Imaging (US) a promising imaging tool for future clinical applications.

4.5.4 Positron Emission Tomography (PET)

Positron Emission Tomography (PET) is mainly used for diagnostic purposes at the molecular level. Radiopharmaceuticals are applied to promote the Positron Emission Tomography (PET) image quality. Positron Emission Tomography (PET) has several advantages that make it suitable for clinical use, such as high sensitivity and ability to monitor process inside cells while the main drawback for this imaging technique is it costly (Ma et al., 2017).

A copolymer is conjugated with prostate membrane antigen; then the substrate is evaluated using copper 64 Positron Emission Tomography (PET) to enhance accumulation activities in tumor cell sites (Wong et al., 2017). Positron Emission Tomography (PET) is mainly used in photothermal cancer strategy in localization labeled NPs (Sun and Zu, 2015; Xiao et al., 2012). Positron Emission Tomography (PET) is used to improve patient response quality by improving patient response, enhancing outcomes, and reducing time and costs. F-18 and 15F-FDG are tracers for Positron Emission Tomography (PET) and are used in treatment response assessments (Gambhir, 2002; Kelloff et al., 2005).

Plasmonic NPs heat ability and Positron Emission Tomography (PET) exploited to be used in tumor cell destruction (Jørgensen et al., 2016), it used in lung carcinoid tumor with using 18F and (fluoro-D-glucose) FDG trace. The previous experiment showed that Positron Emission Tomography (PET) could be used effectively in the treatment response for thermotherapy in the early stages.

For prostate cancer Positron Emission Tomography (PET) with follicle-stimulating hormone receptor with specific label molecule to detect the tumor cell sites (Xu et al., 2014), even so, it used with monoclonal antibodies with Positron Emission Tomography (PET) to detect the follicle hormone receptor as a marker for prostate cancer (Hong et al., 2015) also, these follicle hormones are used in ovarian cancer DDS after they get coupled with polymers or dendrimers. In breast cancer and lung cancer Positron Emission Tomography (PET) is used with modified graphene oxide to targeting (Yang et al., 2016).

4.5.5 PET/CT and PET/MRI

Hybrid imaging molecules recently used in clinical and imaging applications are used for providing both anatomical and metabolic images, thus, used in cancer treatment strategies. Positron Emission Tomography (PET) alone is the lack of detailed information in an anatomical manner. Computed Tomography (CT) integrated with Positron Emission Tomography (PET) to providing morphological images.

In clinical application, especially for tumor imaging, the hybrid imaging modality Between Positron Emission Tomography (PET) and Computed Tomography (CT) showed better results more than using Computed Tomography (CT) and Positron Emission Tomography (PET) separately, particularly in a diagnostic manner (Delbeke et al., 2009). Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) hybrid systems are now available in clinical applications. This hybrid system is costly compared to PET/CT hybrid technique. PET/MRI modality is used in cancer therapy by providing functional and anatomical abilities comparing to PET/CT hybrid modality.

PET/MRI provides a customized therapy plan and monitoring treatment response in tumor cells (Padhani et al., 2011; Padhani et al., 2009). PET/MRI surpasses PET/CT in anatomical details

due to the low contrast in soft tissue in Computed Tomography (CT). In tumor therapy applications Fluorodeoxyglucose-Positron Emission Tomography (PET) is used for treatment responses then PET/MRI.

The main challenge for these hybrid modalities is costly, but they offer future clinical applications superb capabilities.

4.6 Hybrid Imaging Modals for Cancer

Anatomical imaging techniques such as CT and MRI and molecular imaging techniques such as PET and SPECT can providing detailed images for biological activities inside the body and anatomical images for the whole human body. Recently combining these techniques are used in various medical fields such as oncology, pharmacology, cardiology, and others. For example, FDG-PET-CT is used in oncological applications. New imaging tracers have been developed in PET/CT and PET/MRI imaging applications; thus, more clinical applications can be used these types of hybrid imaging techniques for better quality care. The figure below shows the evaluation of hybrid imaging techniques and various imaging agents.

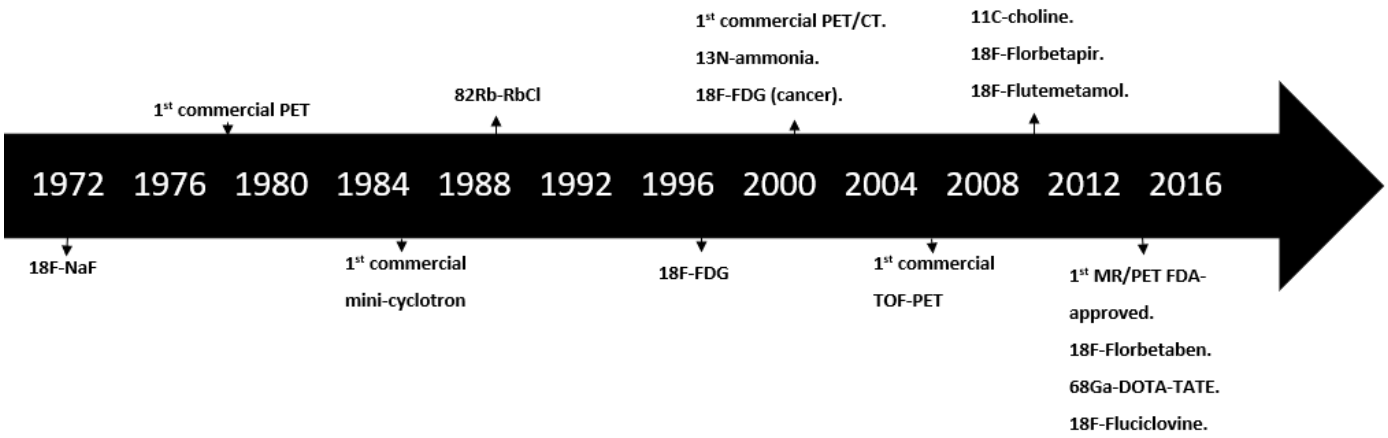

Figure 4.2: Hybrid Imaging Techniques and Imaging Agents Evaluation

Traditional imaging techniques are used in cancer applications by providing early detection, locate tumor cells, and obtained detailed imaging for activities inside them. These imaging techniques cannot provide all the required information about tumor cells like disease sites and

other specific biological information. Computed Tomography (CT) can localize tumor cells, but with some limitations such as low sensitivity and low screening resolution. The drawback in computed tomography (CT) has low contrast in soft tissues. Magnetic resonance imaging (MRI) has inconsistency issues in tumor cell screening. Positron emission tomography (PET) has some particular properties that make it perfect for molecular imaging applications like monitoring therapy response, but at the same time, it helpless in tumor early detection due to their low spatial resolution (Lim et al., 2017).

The integration of imaging techniques can mitigate the challenges and drawbacks mentioned previously in the usual imaging modalities. Hybrid imaging modalities provide more specific information essential in tumor cell diagnosis and therapy strategies like improving spatial resolution, enhancing contrast, and sensitivity. NPs are playing an essential role in hybrid imaging techniques.

Imaging probes are used in both optical and magnetic imaging; thus, providing a diagnosis in vivo approach and monitoring biological activities in situ approaches (Lim et al., 2017). Probes in MR/CT hybrid imaging technologies allow us to obtain more information about tumors and their microenvironment (ME) (Oh et al., 2011). for example, tantalum oxide NPs are used with PEG, and fluorescent dye showed remarkable results in X-ray computed tomography (CT) and fluorescence imaging, and image-guided applications (Wang et al., 2015). MNPs encapsulated with specific fluorescent molecules showed advanced improvements in specific tumor information, detection, validation, and characterization (Lim et al., 2010). Hybrid imaging modalities target imaging applications like increasing accumulation for specific molecules at the tumor cell sites (Yang et al., 2008).

4.6.1 Prostate Cancer

Fluorodeoxyglucose (FDG) is a pharma molecule used in medical imaging, especially in positron emission tomography (PET). FDG is considered a marker for prostate cancer. Most tumor metastatic diseases show a high FDG intensity. Intensity is low in the early stages of prostate cancer (Wibmer et al., 2018). FDG can be beneficial in the localization of tumor cells in the initial stages of tumor cells (Liu et al., 2016). tracers have been approved by the FDA

and used to improve the molecules targeting features. An example of these tracers is 11C-choline and 18F-Fluciclovine. In PET/CT hybrid imaging technique, 18F-Fluciclovine tracers showed better significant results than 11C-choline tracer in metastatic detection in prostate cancer (Nanni et al., 2016). More sensitive tracers are required in this field.

The targeting molecule (antigen) is called Prostate-Specific Membrane Antigen (PSMA), which is used as a targeting antigen in prostate cancer cases. It is used as a targeting molecule for bioimaging tracers. PSMA is a significant marker for prostate cancer. It overexpressed significantly in the abnormal cells (tumor cites) (Ristau et al., 2014). PSMA labeling agents showed a remarkable improvement in sensitivity and specificity for prostate tumor cells. PSMA-PET-CT is widely used in prostate cancer cases. These imaging techniques obtained outstanding results in prostate cancer early detection. PSMA is not limited to diagnosis applications. It is also used in therapeutic applications like radioisotope therapy (Baum et al., 2016).

Theranostic tracers are obtained in the previous paragraph by prediction binding and calculation of the required dose. recent studies showed a high possibility to use these theranostic tracers in phase I and II in clinical trials (Rahbar et al., 2017; Brauer et al., 2017). 18F-Fluorodehydrotestosterone (FDHT) has reasonable specificity for the androgen receptor, vital for proliferation in prostate tumor cells. 18F-FDHT is used in tumor cell localization and visualization of blocking therapeutic agents used in prostate treatment protocol (Pandit-Taskar et al., 2016; Vargas et al., 2014); thus, used in treatment evaluation and determine the appropriate dose accurately. The tolerated dose strategy is essential to achieve cancer personalized medicine approaches.

4.6.2 Neuroendocrine

111In-labeled agents are used in neuroendocrine tumors. These tumors have overexpression in somatostatin receptors. Using 111ln-labeled and 68Ga-labeled chelating agents used in the PET/CT hybrid imaging technique showed improvement and resulted in better than classical imaging techniques (Sadowski et al., 2016). 111ln-pentetreotide used with SPECT/CT hybrid imaging technique and used in clinical applications, for therapeutic purposes it labeled with

177Lu. 68Ga is used in tumor cell localization and treatment monitoring by detecting the biodistribution and uptake features for the 177Lu therapeutic agent and can be beneficial in selecting proper therapy for a specific patient and can be used in determining dose calculations (Kairemo and Kangasmaki, 2013). It was used in clinical phase III and showed significant results in the neuroendocrine tumor in both diagnosis and therapeutic (theranostic system) (Strosberg et al., 2017).

4.6.3 Breast Cancer

PET and SPECT

Positron emission tomography (PET) is a radioactive imaging technique using isotopes like C, N, O, and F. Single Photon computed tomography (SPECT) relies on radioactive isotopes that emit gamma like Tc and I isotopes. SPECT has longer-lived isotopes comparing to PET. In PET imaging, it ranging from minutes to 2h; besides, PET has better sensitivity than SPECT. PET and SPECT provide real imaging for various cellular processes inside cells like blood flow and glucose metabolism (Kjaer, 2006). Due to their poor anatomical features, CT and MRI were used with PET and SPET as hybrid imaging systems. Now PET/CT is used in clinical applications. Image sensitivity means the ability to detect tumors with small sizes, and whole-body scanners provide furthermore staging information (Koolen et al.,2012). PET/MRI hybrid imaging systems provide functional information; also, they have a high contrast resolution with low radiation exposure. For lymph nodes, SPECT/CT is used (Husarik and Steinert, 2007).

Optical Imaging

For breast tumor cell imaging, molecular optical imaging relies on NIR light to excite specific fluorescent probes. NIR-fluorophores are used in diagnosis purposes in vitro applications for a tumor cell. Currently, NIR optical imaging is just limited to pre-clinical use only, lymph mapping, and tumor edge detection due to drawbacks in penetration and signal contamination issues (Oliveira et al., 2012; Van De et al., 2012; Lee et al., 2010, Verbeek et al., 2014).

Molecular Magnetic Resonance

Molecular MRI is providing detailed anatomical imaging and functional imaging; it is safe for the patient because it is not an ionizing-based imaging technique. SPIONs and gadolinium chelates are contrast agents for molecular MRI. The main disadvantage of using MRI in molecular imaging that it has low sensitivity; thus, it is not perfect for detecting small tumors. For the previous drawbacks, SPIONs contrast agents enhance sensitivity and specificity by producing strong signals (Lodhia et al., 2010; Ittrich et al., 2013). Gd nanoparticles and SPIONs are used as imaging contrast agents for molecular MRI for enhancing biocompatibility and specificity after functionalization (Huang and Tsourkas, 2013). Targeted NPs are used with molecular MRI for breast cancer imaging (li et al., 2013; Yan et al., 2013); these procedures will be used effectively in clinical applications in the future.

CHAPTER 5

METHODOLOGY

We extracted theranostic, theragnostic, and different cancer types articles for bibliometric analytical studies related to the field of oncology, especially in breast cancer. This study includes theranostic studies in oncology, which include carcinomas, sarcomas, leukemias, and lymphomas. The study included articles from 2007 to 2020 and compared and analyzed data related to cancer studies and theranostic approaches. See Table 5.1 below.

Table 5.1: Key Words and Results Extracted from Scopus Database

Keyword	Number of results	Document type	Software used
Theranostic OR Theragnostic AND Breast cancer	562	Article	Scopus BibExcel Gephi VOSviewer
Theranostic OR Theragnostic AND Colorectal cancer	80	Article	
Theranostic OR Theragnostic AND prostate cancer	236	Article	
Theranostic OR	40	Article	

Table 5.1 Continued

Theragnostic AND leukaemia		
Theranostic OR Theragnostic AND Lung cancer	158	Article
Theranostic OR Theragnostic AND Lymphoma	46	Article
Theranostic OR Theragnostic AND sarcoma	38	Article
Theranostic OR Theragnostic AND Liver cancer	60	Article

Scopus, BibExcel, VOSviewer, and Gephi, is widely used in the bibliometric analysis. Scopus is a citation database that includes more than 75 million records, 24 thousand and 600 titles, and more than 5000 publishers. It is considered of the most powerful tools for discovering and

analytics for researchers. Scopus covered health science, physical science, social science, and life science subject fields. Scopus provides search, analysis, and discovery features. Scopus provides a keyword analysis feature with detailed information about access type, year, authors, subject area, document type, source, keywords, and others; thus, more precise bibliometric analysis. BibExcel is an analytical tool developed by Olle Persson. BibExcel is used for the analysis of bibliometric data and any other data type of textual ones. It prepared the text file to be used in different processing software like Excel. VOSviwer is a tool for visualizing network data for bibliometric analysis. Data includes journals, publications, and others, it supports different constructed bibliometric data like citation, bibliographic coupling, and others, and it provides visualization for text mining. Gephi is a visualization software used with all types of data networks; it is used for link analysis, exploratory data analysis, poster creation, social network analysis, and biological network analysis. Gephi provides some metrics like centrality, density, clustering, modularity, and path lengths.

In this study, we focused just on articles published, not on other documents like reviews, notes, book chapters, and others. It includes articles published in various subjects like medicine, pharmacology, biochemistry, genetics, molecular biology, engineering, material science, etc.

We included several subject areas to provide a better and clear picture of theranostic and its applications in the oncology field, especially breast cancer. The articles from 2007-2020 are included in the study for theranostic and four main cancer types (prostate cancer, breast cancer, lung cancer, colorectal cancer), sarcomas, leukemias, and lymphomas.

We examined the analysis by three main factors year of publication, source of publication, and subject areas for six types of cancers. We used Scopus to exact proper information using theranostic, theragnostic, and different cancer types (Lung cancer, breast cancer, colorectal cancer, liver cancer, prostate cancer, leukemias, sarcomas, lymphomas) as keywords. BibExcel is used for text file preparation to be used in VOSviews and Gephi Software for visualization purposes. VOSviwer used to visualize and analyze citation for breast cancer with theranostic. Five hundred sixty-two breast cancer documents were extracted and analyzed with BibExel

(citation coupled, adding frequencies, mapping), then visualized using Gephi and VOSviewr for better understanding.

CHAPTER 6

RESULTS AND DISCUSSION

We extract 4134 articles in theranostic, theragnostic and cancer, 60 articles in theranostic, theragnostic and liver cancer, 562 articles in theranostic, theragnostic and breast cancer, 236 articles in theranostic, theragnostic and prostate cancer, 158 articles in theranostic, theragnostic and lung cancer, 80 articles in theranostic, theragnostic and colorectal cancer, 40 articles in theranostic, theragnostic and leukemia, 46 articles in theranostic, theragnostic and lymphomas and 38 articles in theranostic, theragnostic and sarcoma. Breast cancer presents more than 46 percent of all article's outcomes, and this is a clear indication of the direct relationship between theranostic Approaches and studies related to breast cancer.

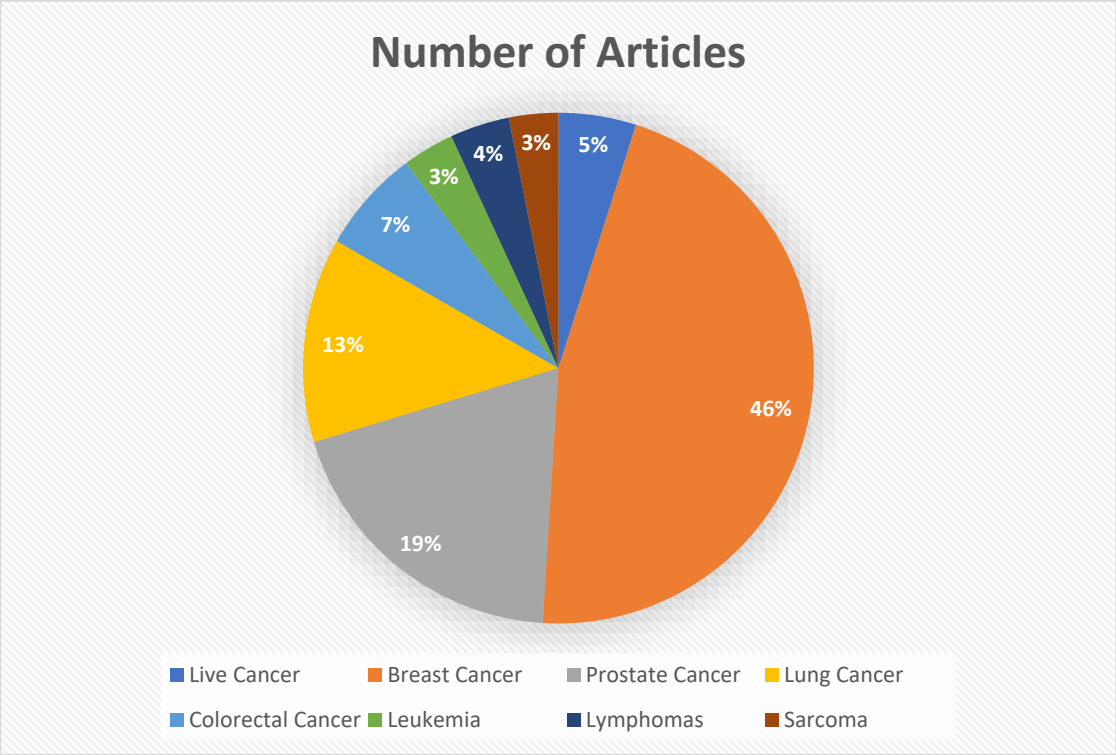

Figure 6.1: Percentage of Articles for Different Types of Cancer-related to Theranostic Approaches.

In general, the number of articles resulted from cancer and theranostic approaches is 4134, and it is a big number that gives a good indication for using this approach in various cancer applications. The number of articles published from 2007 to 2020 increased dramatically, indicating the emerging research interest in using theranostic approaches in cancer study fields. The figure below illustrates the number of articles published in the oncology and theranostic field from 2006 to 2020.

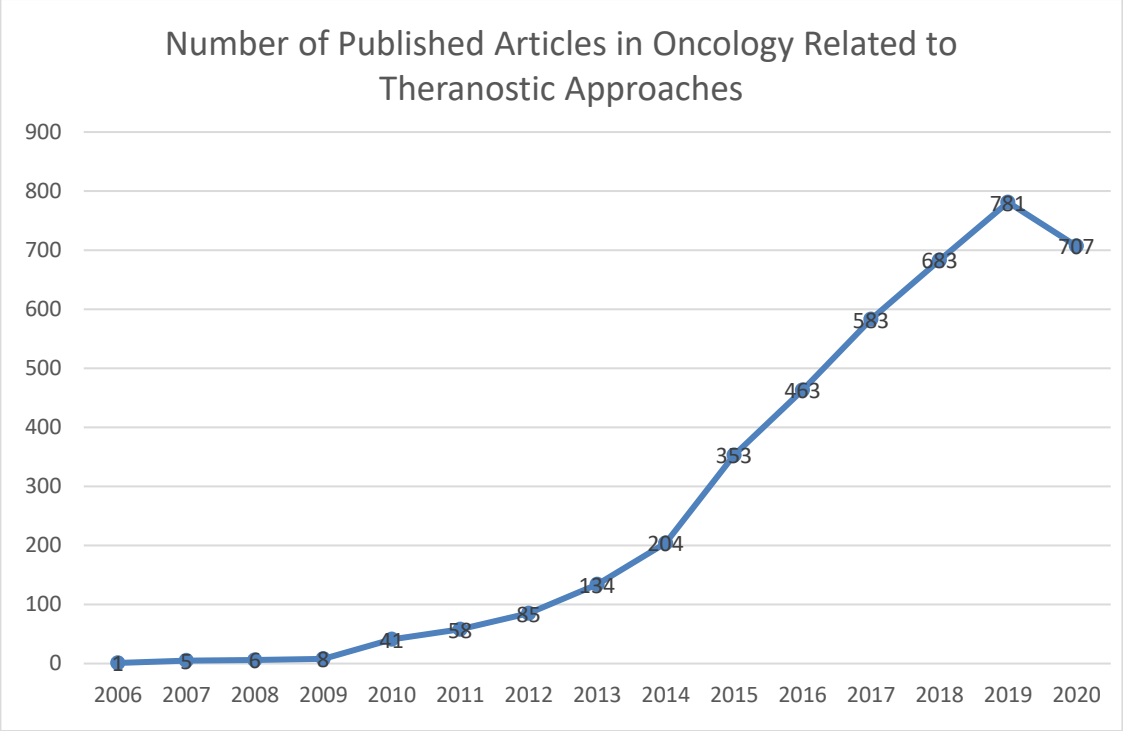

Figure 6.2: Number of Published Articles in Oncology and Theranostic Approaches

The results showed a noticed increase in the number of articles on breast cancer (carcinomas type) comparting to other types of cancers for the main types of cancers.

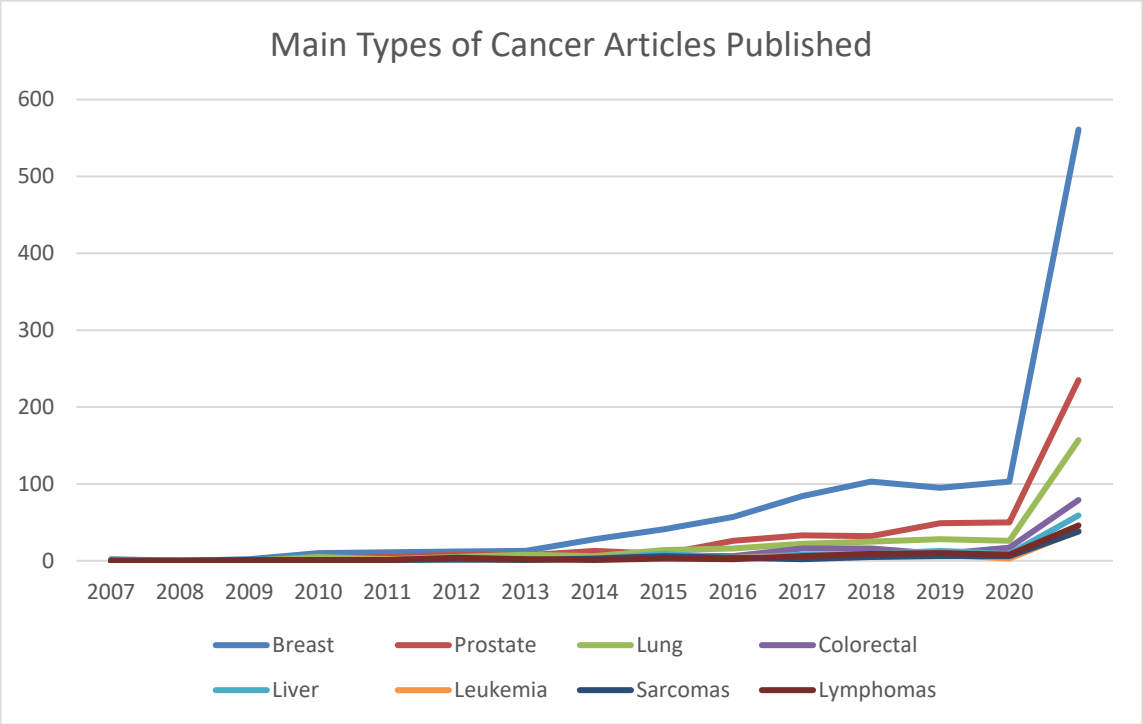

Figure 6.3: Four Main Types of Cancer Articles Published

Interest in the use of theranostic started at the beginning of 2006, like breast cancer, and in some other types, it began in 2010 like colorectal, liver, and lymphoma. This means that this approach (theranostic) is a relatively new strategy for cancer research.

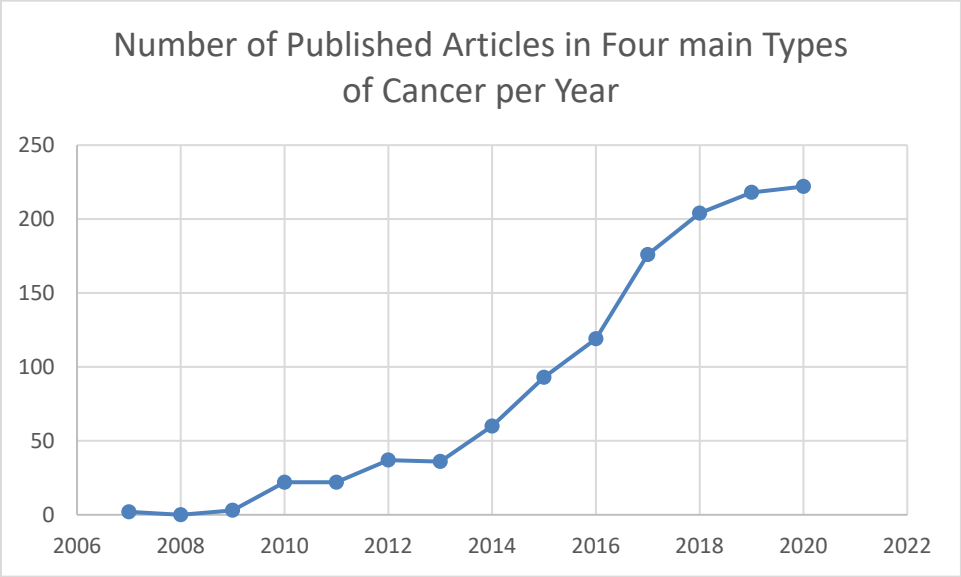

Figure 6.4: Number of Published Articles in Four main Types of Cancer from 2006-2020

In terms of the subject of area, theranostic approaches in the oncology field rely on several main subjects, as shown below in the figure. From the diagram below, it is clear that the research fields on cancer and theranostic do not mainly depend only on the medical subject, but on several different subjects of area, including chemistry, Biochemistry, Genetics, and Molecular Biology, engineering, and chemical engineering.

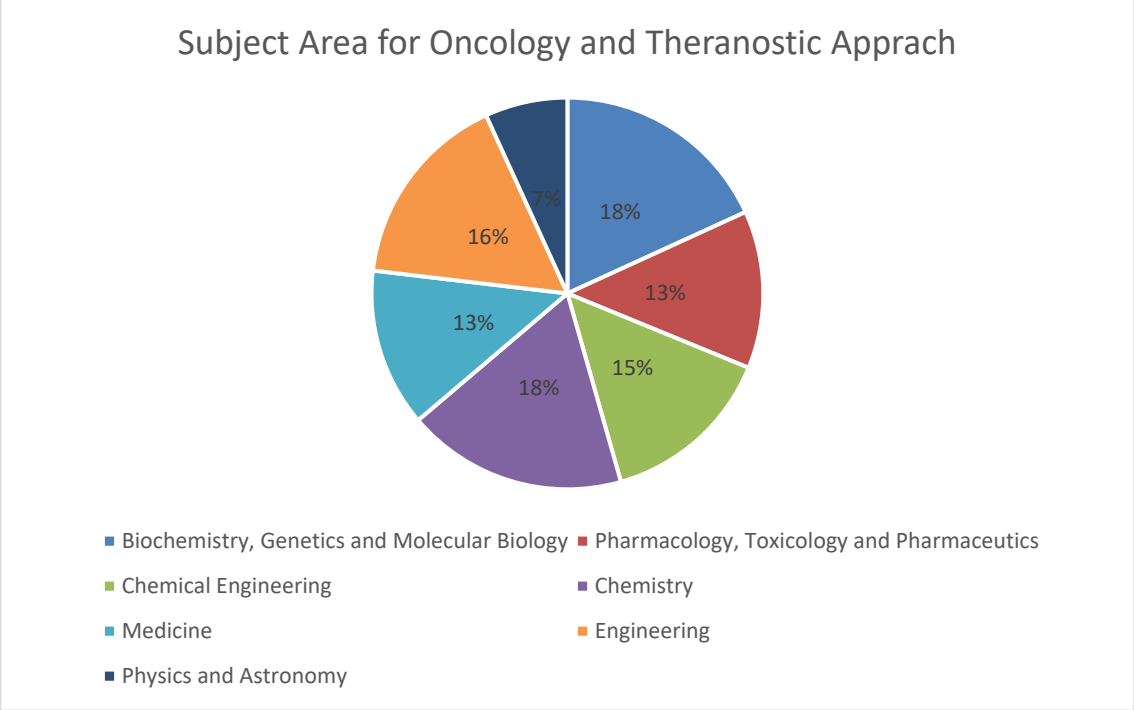

Figure 6.5: Percentage of Subject Areas for Theranostic and Oncology Field of Study

In general, breast cancer and theranostic approach depend mainly on several subjects, includes material science, Biochemistry, Genetics, and Molecular Biology, Pharmacology, Toxicology and Pharmaceutics, engineering, chemical engineering, chemistry, and medicine.

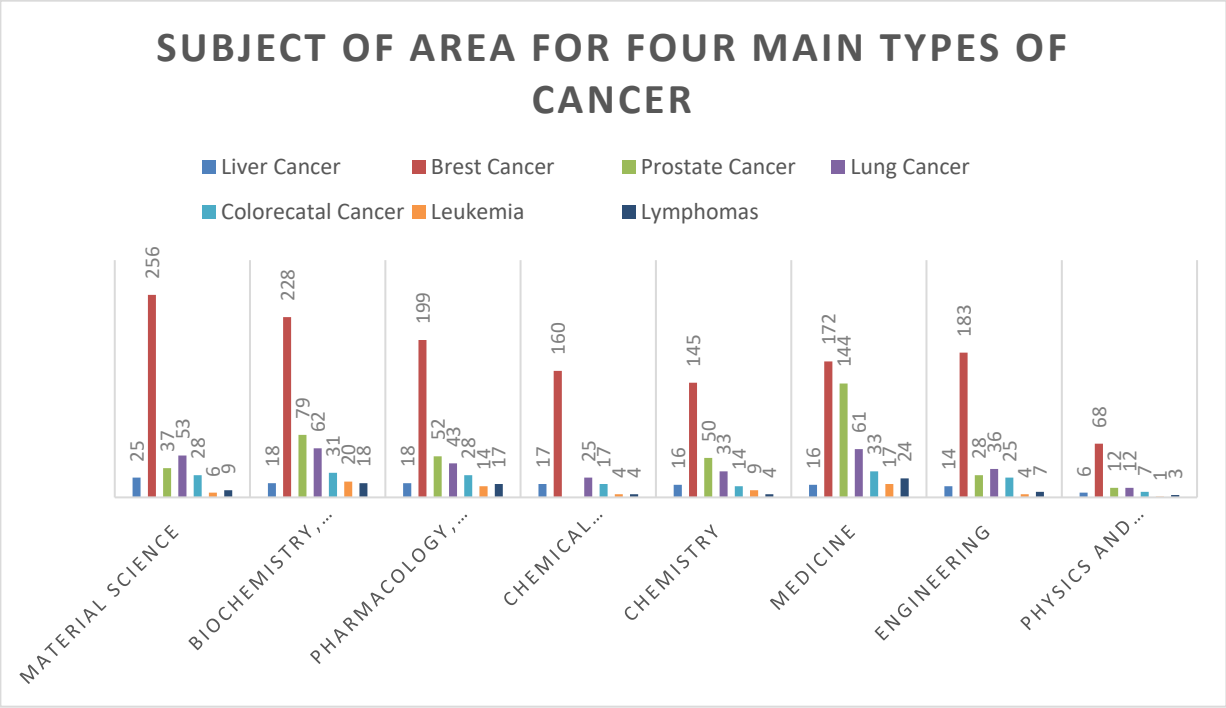

Figure 6.6: Subject of Area for Four Main Types of Cancer

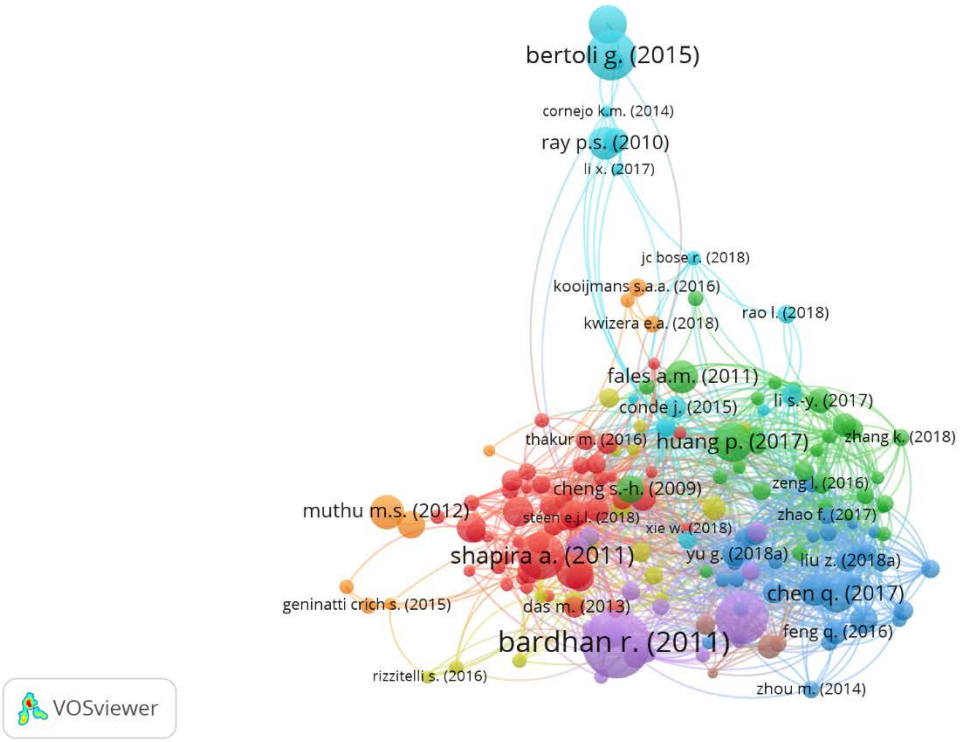

Figure 6.7: VOSviewer Citation Map Based on Citation Weight for Breast Cancer

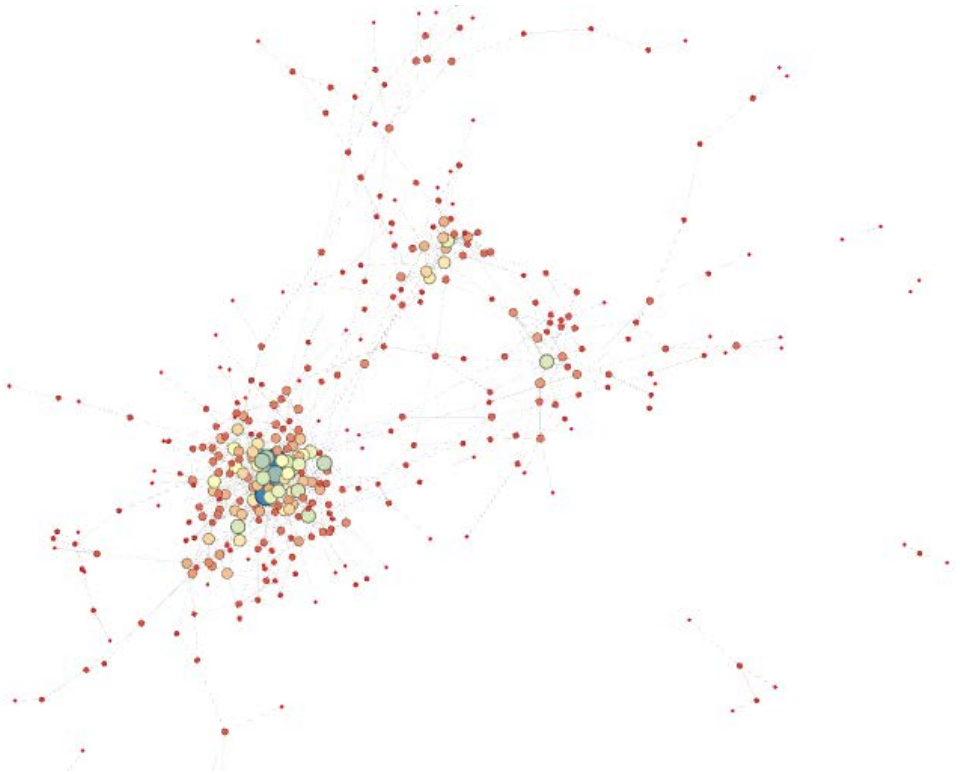

Figure 6.8: Gephi Citation Map for Breast Cancer

In VOSviewer, clusters are shown based on citation weights using bibliographic coupling with the full coupling counting method. Unit of analysis documents with a minimum number of citations, ten or more, and link strength more than 10. The results are 266 documents with nine clusters, 4424 links, and link strength are 6297, while in Gephi directed graph for breast cancer results it showed three different clusters with no filter applied. 386 articles build this network with 926 edges in total, and nodes are ranking by degree red means low and blue means high for ranking.

CHAPTER 7

CONCLUSION

Recently, the interest in engineering new and different types of theranostic nanoparticles has become very important, especially concerning diagnostic and therapeutic applications. The development of nanoparticles for diagnostic and therapeutic purposes has become necessary for developing the medical sector and provides an advanced tool to overcome the most severe challenges in these fields. This approach is considered the future for clinical applications. Nanotheranostic systems are used in therapeutic and diagnostic applications for many emerging diseases that face medicine problems in diagnostic and therapeutic aspects. These systems contribute to the provision and development of many medical strategies and properties used, such as pharmacokinetics, distribution, and stability thus, providing better medical care and quality by providing accurate technology for emerging diseases. These nanotheranostic systems develop biomedical strategies such as drug delivery and drug delivery by improving and monitoring cells' response to treatment protocols and precisely understanding and identifying their properties, whether biological, physical, or chemical, to ensure adequate healthcare provided to patients. nanotheranostic has a significant advantage in developing and providing therapeutic and diagnostic methods that do not affect the patient and are safer than the usual methods used, especially in cancerous diseases.

Consequently, this results in obtaining an integrated medical service for the patient. On the other hand, these techniques contribute to a precise identification of the type of nanoparticles that should be better used in tumor cell localization and targeting sites. This approach predicts the most efficient medical treatments and protocols for treating tumor diseases and providing post-treatment monitoring, which makes a remarkable development in treating emerging diseases.

nanotheranostic systems provide accurate analysis and real-time monitoring of drug delivery systems in addition to Contrast Agent monitoring. These systems also monitor biological and functional changes at the patient's cellular level, thus ensuring a more effective system. These

systems occupy an excellent place for their contribution to obtain the personalized medicine approach with all these features. The main challenge in the field of diagnosing and treating cancerous diseases is that it has many faults that negatively affect the patient and, thus, the quality of the health care provided; for this reason, scientists aspire to develop therapeutic and diagnostic techniques free from side effects and be safe for the patient. The current studies focus massively on developing an effective and safe technology at the same time and focus on obtaining the personalized medicine approach. Nanotheranostic advances development in several different biomedical fields, including smart medicine and tissue engineering, and reaches a deep understanding of cancer cells' nature, leading to advanced diagnostic and therapeutic methods. The treatment and diagnosis of cancer must rely on hybrid methods that combine two or more techniques to provide an integrated medical service. Ultimately, an effective treatment formula must be obtained with no side effects. Studies have recently confirmed that not all nanoparticles are useful for diagnostic and therapeutic applications for cancer due to some biological, chemical, and physical defects of these particles, so these particles' development is considered an essential matter for scientists in the future. On the other hand, many studies have proven nanoparticles to be effective because of their properties and advantages that make them able to simulate biological phenomena inside the body with no harm entirely. Besides, these particles possess the ability to represent vital systems, which makes them a future for developing therapeutic and diagnostic systems (theranostic).

It focuses on promoting these particles' properties and trying to eliminate the defects to make them the ideal solution for cancerous diseases' future clinical applications. The real challenge in this field lies in changing how scientists and doctors look at these diseases and find new, innovative, and more effective ways to reach an ideal medical protocol that serves the personalized medicine approach. It focuses on each patient separately without relying on one drug for all cases, and this is the future of modern medicine. To provide an effective cancer treatment regimen, the therapeutic and diagnostic effect on healthy cells surrounding cancer cells must be minimized, and this is what Theranostic offers by delivering the various molecules to the specific location only with an effective method, which makes this field very important in turn representing an effective tool for increasing the effectiveness of diagnostic and treatment

systems for cancer. Many of the characteristics that make reaching the objective possible due to the characteristics and properties that characterize the nanoparticles, such as the varied differences in shape and periodic age commensurate with the different types of cancer and the surface functionalization processes other structural properties. These particles contribute to providing a safe and accurate solution for many drug delivery applications and the possibility of changing their chemical, physical and biological properties at the cellular level, making them an effective tool in determining and monitoring the appropriate drug dose so that it does not lead to side effects, complications and does not affect the healthy cells that surround the cancer cells, which leads to Increasing the quality of health care provided to cancer patients and making the therapeutic mechanisms more effective. Therefore, it was important that the focus be on engineering and designing high-precision particles specialized for cancer therapy and diagnostic purposes. Breast cancer studies have shown that they focus on developing theranostic nanoparticles that help develop regular cancer treatments with the developing targeted therapy systems. These theranostic nanoparticles can also be used to develop pharmaceutical systems and specialized devices in breast cancer treatment.

These theranostic nanoparticles help treat breast cancer by measuring and monitoring the signs of cancer cells' response to different anti-cancer drugs, contributing to making these therapeutic techniques more effective. Theranostic Nanoparticles are considered the future in developing diagnostic and therapeutic systems for cancer to ensure high quality of the health service. The importance of focusing on the diagnosis and treatment of cancer, in particular, is because cancer is the second cause of death.

Medical imaging systems play an essential role in achieving personalized medicine approaches in cancer. The importance of molecular imaging lies in providing doctors with functional and structural images of various biological processes in cancer cells and normal cells, which provides a greater opportunity for a deep understanding of the nature of these tumors, which facilitates the process of finding and developing advanced and more effective diagnostic and therapeutic techniques. The development of these technologies mainly requires the use of theranostic nanoparticles as modern imaging probes. These probes help to increase the effectiveness and quality of medical imaging by using them as an alternative to regular probes

that have many flaws, which constitutes a significant obstacle to reaching imaging methods suitable for advanced medical applications and the need for more accurate methods to obtain better imaging and imaging-guided therapy for different types of cancer. In the future, these technologies will be used in broader and more precise areas, such as stem cell imaging and imaging the biological environment surrounding cancer cells, which results in a comprehensive and clear understanding of the nature of these tumors in a better way which It may help in providing solutions to many of the challenges facing the medical sector in confronting the treatment of stubborn types of malignant cancers. The real challenge is to choose the appropriate and ideal nanoparticles in different medical imaging techniques to reach the desired results. With the increase in the number of treatments and drugs in cancer, the need for advanced techniques and tools to evaluate the effectiveness of these treatments and drugs on cancer cells and ensure their safety on patients has made nanoparticles the focus of scientists' attention.

The remarkable development in these theranostic nanoparticles' manufacture and production has contributed to a deeper understanding and an extraordinary development in cancer biomarkers' fields, thus achieving the personalized medicine approach in cancer. The delivery of diagnostic and therapeutic methods using a single theranostic nanoparticle at the same time is considered an effective strategy on many levels, such as reducing the amount of diagnostic or therapeutic dose in a way that reflects positively on the patient's health directly in addition to reducing the financial cost, saving time and obtaining accurate therapeutic and diagnostic results in addition to that contribute to evaluating the post-treatment plan. These particles enabled the application of more than one treatment method for cancer at one time, making these systems' efficiency more effective, especially in stubborn ones. Due to the characteristics and properties that these particles possess, they are used in the delivery of more than one strategy at the same time by providing a multifunctional approach in cancer treatment by delivering a specific treatment or diagnosis (imaging probe) or even delivering a specific dose safely to the target sites. Theranostic nanoparticles help significantly increase cancer treatment drugs' effectiveness and narrow their impact on normal cells and the surrounding cellular environment, ensuring effective and safe treatment and leading to achieving better health care delivery for cancer patients.

The possibility of using more than a nanoparticle at the same time allows for advanced and effective techniques and features in which to determine and localize cancer cells and deliver the drug targeting sites.

The use of nanoparticles in the treatment of cancers began at the beginning of the 2000s, and in 2005 in particular, the development of diagnostic and therapeutic mechanisms was used for breast cancer and in which other cancers appeared a little late. This approach does not depend only on medicine but rather on several fields, including biochemistry, engineering, chemical engineering, pharmaceutical sciences, and others, making studying this thing, especially for cancer, complicated. These techniques depend on the nature of these nanoparticles' interaction with cells and the surrounding biological environment. The final answer lies in answering the question: Do these particles cause any vital change that positively or positively affects if it is positive. Here, the journey of research begins to exploit these advantages in various diagnostic and therapeutic uses. In the end, there is no doubt that this approach is the future for diagnosis and treatments related to cancer in particular because of its great effectiveness and providing an integrated cellular environment.

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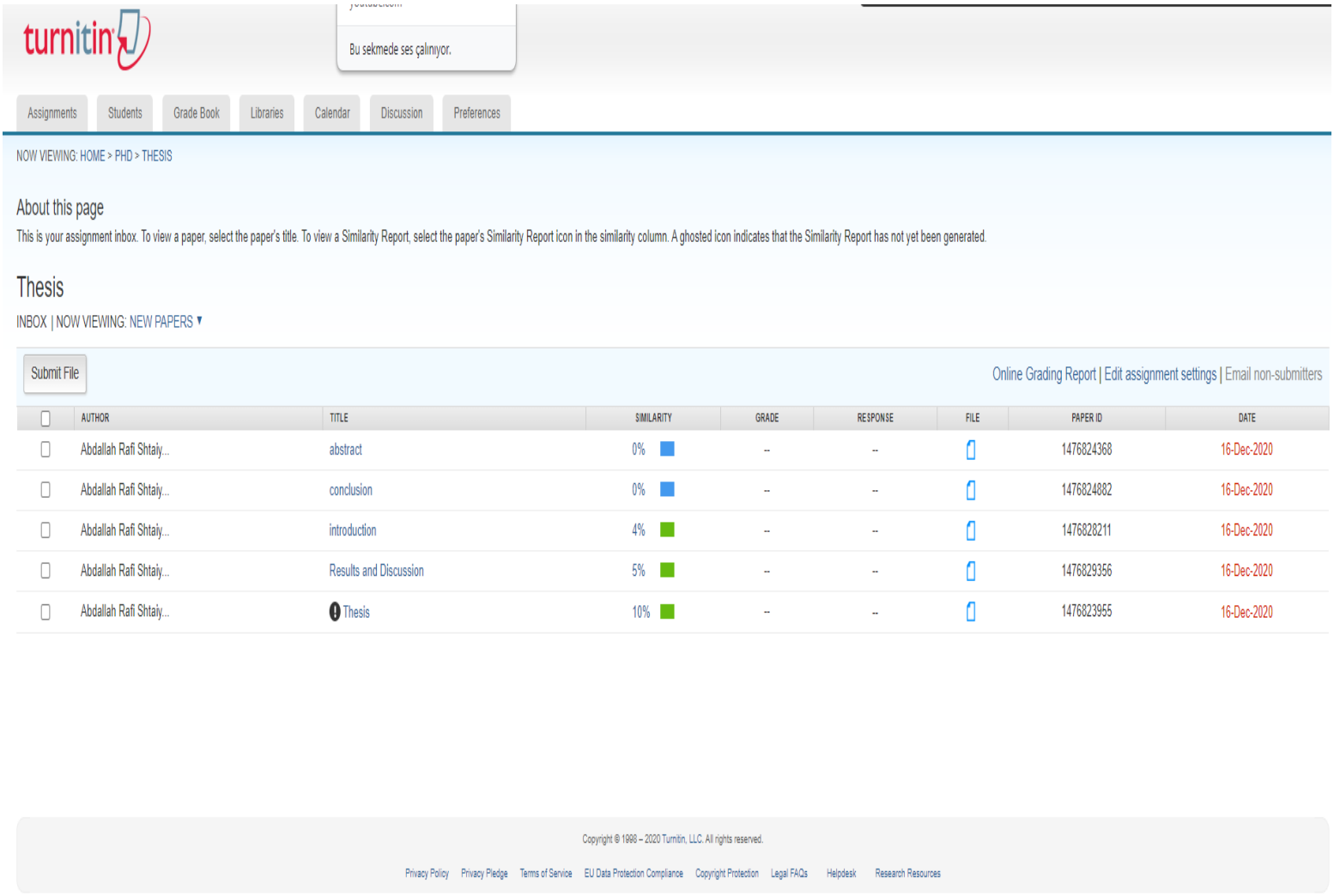
APPENDICIES

APPENDIX 1

SIMILARITY REPORT



BIOMIMETIC ANALYSIS OF THERANOSTIC NANOPARTICLES FOR CANCER APPLICATIONS

Prof. Dr. Terin Adalı

APPENDIX 2

ETHICAL APPROVAL LETTER

NEAR EAST UNIVERSITY

ETHICAL APPROVAL DOCUMENT

Date: 28/12/2020

To the Graduate School of Applied Sciences,

For the thesis project entitled as "NANOPARTICLE THERANOSTIC AGENTS APPLICATIONS IN CANCER", the researchers declare that they did not collect any data from human/animal or any other subjects. Therefore, this project does not need to go through the ethics committee evaluation.

Title: Prof. Dr.

Name Surname: Terin Adalı

Signature:

Role in Research Project: Supervisor