



## Improving nuclear properties

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### ABSTRACT

Radiation therapy is an effective cancer treatment option in conjunction with chemotherapy and surgery. Emerging individualized internal and systemic radiation treatment promises significant improvement in efficacy and reduction of normal tissue damage; however, it requires cancer cell targeting platforms for efficient delivery of radiation sources. With recent advances in nanoscience and nanotechnology, there is great interest in developing nanomaterials as multifunctional carriers to deliver therapeutic radioisotopes for tumor targeted radiation therapy, to monitor their delivery and tumor response to the treatment. This paper provides an overview on developing nanoparticles for carrying and delivering therapeutic radioisotopes for systemic radiation treatment. Topics discussed in the review include: selecting nanoparticles and radiotherapy isotopes, strategies for targeting nanoparticles to cancers, together with challenges and potential solutions for the in vivo delivery of nanoparticles. Some examples of using nanoparticle platforms for the delivery of therapeutic radioisotopes in preclinical studies of cancer treatment are also presented.

### Keywords:

nuclear, properties, Radiation, chemotherapy.

Cancer is one of the leading causes of death worldwide. In 2008, a total of 1,437,180 new cancer cases and 565,650 cancer deaths were estimated in the United States alone.<sup>1</sup> Despite advances in our understanding of tumor biology, cancer biomarkers, surgical procedures, radio- and chemotherapy, the overall survival rate from cancer has not improved significantly in the past two decades.<sup>1</sup> Early detection, pathological characterization, and individualized treatments are recognized as important aspects for

improving the survival of cancer patients. Many novel approaches, such as imaging for the early detection of molecular events in tumors, comprehensive and personalized treatments, and targeted delivery of therapeutic agents to tumor sites, have been developed by various research groups; and some of these are already in clinical trials or applications for cancer patients. Radiation therapy, in conjunction with chemotherapy and surgery, is an effective cancer treatment option, especially for radiation-sensitive tumors. Radiation therapy

utilizes high dose ionizing radiation to kill cancer cells and prevent progression and recurrence of the tumor. In current clinical oncology practices, half of all cancer patients will be treated with radiation therapy either alone or in combination with other treatments. [1]

Traditionally, radiation therapies fall into one of three categories: external radiation, internal radiation and systemic radiation therapy. External radiation therapy delivers high-energy x-rays or electron or proton beams to a tumor from outside the body, often under imaging guidance. Internal radiation therapy (also called brachytherapy) places radiation sources within or near the tumor using minimally invasive procedures. Systemic radiation therapy delivers soluble radioactive substances, either by ingestion, catheter infusion, or intravenous administration of tumor-targeting carriers, such as antibodies or biocompatible materials, which carry selected radioisotopes. Although systemic radiation offers desirable advantages of improved efficacy as well as potentially reducing radiation dosage and side effects, in vivo delivery of radioisotopes with tumor targeted specificity needs to address many challenges that include: 1) the selection of radioisotopes with a proper half-life; 2) a delivery vehicle that can carry an optimal amount of radioisotopes and has favorable pharmacokinetics; 3) suitable tumor biomarkers that can be used to direct the delivery vehicle into cancer cells; and 4) specific tumor targeting ligands that are inexpensive to produce and can be readily conjugated to the delivery vehicles. In addition, a multifunctional carrier that not only delivers radioisotopes but also provides imaging capability for tracking and quantifying radioisotopes that have accumulated in the tumor is highly desirable. [2]

Recent advances in nanotechnology have led to the development of novel nanomaterials and integrated nanodevices for cancer detection and screening, in vivo molecular and cellular imaging, and the delivery of therapeutics such as cancer cell killing radio-isotopes. An increasing number of studies have shown that the selective delivery of therapeutic agents into

a tumor mass using nanoparticle platforms may improve the bioavailability of cytotoxic agents and minimize toxicity to normal tissues. [3]

In this review, we attempt to provide an overview on developing nanoparticles for carrying and delivering therapeutic radioisotopes for cancer treatment. We will discuss the following topics: selecting nanoparticles and radiotherapy isotopes, strategies for targeting nanoparticles to cancers, and challenges and potential solutions for in vivo delivery of nanoparticles. Some examples of using nanoparticle platforms for the delivery of therapeutic radioisotopes in preclinical studies, detection, and monitoring of therapy will also be presented.

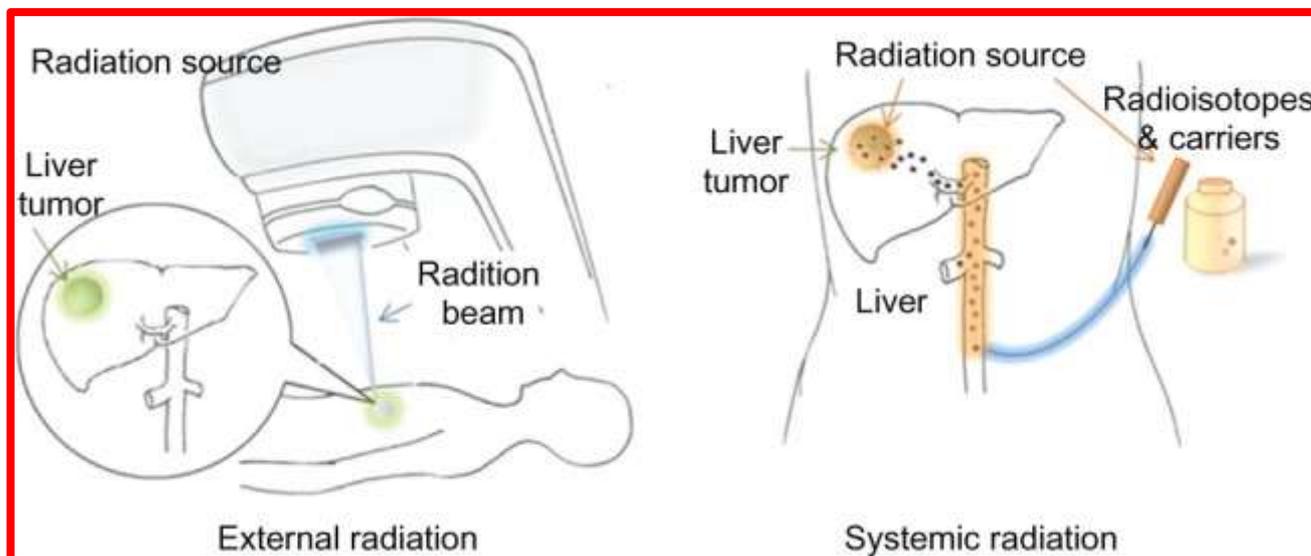
Cancer cell killing radioisotopes and radiation therapy

Radiation therapy utilizes radiation energy to induce cell death. By directly delivering external radiation beams to a tumor in the patient, external radiation therapy offers a relatively simple and practical approach to cause radiation damage in the tumor. Although the intensity, location and timing for external radiation can be well controlled and modulated, its main disadvantages include: 1) the destruction of normal tissue adjacent to tumors and in the path of the beam; 2) the need of high radiation doses for penetrating tissues with a large field or volume; 3) prolonged treatment with the requirement of daily hospital visits for 5–6 weeks; and 4) the use of only selected radiation sources due to the technical requirements and limitations of radiation devices and radiation sources (eg, high energy x-rays). Therefore, external radiation treatment may not be applicable to certain cancers and not effective in the improvement of clinical symptoms. [4]

In contrast to external radiation treatment, systemic radiotherapy delivers radiation energy from the radioisotopes that are conjugated to a suitable delivery carrier, such as antibodies, liposome emulsions or nanoparticles with tumor targeting ligands, and transported to the tumor site as illustrated in Figure 1. If the tumor can be accessed from major arteries, the conjugated radioisotopes can be directly infused through a catheter or by

intravenous administration. Since tumor targeted and localized delivery of radiation enhances the treatment effect and reduces the toxicity to normal tissue, systemic radiotherapy is considered to be a promising approach for

personalized oncology. Although systemic radiotherapy presents major challenges in the design and production of delivery vehicles, it offers great opportunities for the application of novel nanomaterials and nanotechnologies. [5]



**Figure 1.1: External radiation therapy and systemic radiation therapy.**

### 1.1 Literature Review

(Alan T.D. Nakashima a, Sergio L. Dutra a, Paulo V. Trevizoli b, Jader R. Barbosa Jr.: 2014) In this part of the paper, an existing regenerator model was extended to predict the experimental data generated in Part I on the influence of the blow time fraction on the performance of a Gd packed bed AMR. The effect of mass imbalance between the hot and cold blows was evaluated numerically, and a significant improvement of the model predictions was obtained when the numerical and experimental mass imbalance set points were equal. A numerical assessment of the system performance beyond the conditions of Part I indicated optimal utilization factors and blow time fractions for temperature spans of 10 and 20 K, and operating frequencies of 0.25 and 0.5 Hz. For an operating point specified by fixed values of cooling capacity (20 W), temperature span (10 K) and frequency (0.5 Hz), the maximum COP was generated for a blow time fraction of 31% and a utilization factor of approximately 0.6.

(Y. Lazcano-Véliz a, J.A. Hernández b, D. Juárez-Romero b, A. Huicochea-Rodríguez b, A. Álvarez-Gallegos b, J. Siqueiros c: 2016)

This work was performed in the generator of an absorption heat transformer (AHT) applied for water purification, which has two concentric helical coils. The AHT used LiBr-H<sub>2</sub>O to 55%wt for the heat transfer through a heat exchange by falling film. The objective of this study was to define the operating condition of the generator. Different falling film regimes were analyzed: drop mode, liquid column, and jet mode. The effective area of heat transfer of the two helical coils, wetting efficiency, and experimental film thickness were determined for the four operating flows (0.003, 0.008, 0.014, 0.019 kg/s) through digital image processing. The theoretical film thickness was measured and compared with the one calculated by the Nusselt equation. The flow of 0.008 kg/s maintained a drop mode distribution favoring a homogeneous fall along the helical test bank. A wetting efficiency of 99.52% was obtained, so it is proposed as operating flow in the generator. The theoretical film thickness for this flow was 0.289 cm and the one obtained experimentally through digital

image processing was 0.293 cm. It was concluded that the distribution in the drop mode was more favorable for a better efficiency in the values of the falling film exchangers.

**(Thomas B. McConnaughy, Eric W. McFarland:2018)** Nuclear power is one of the means for large-scale CO<sub>2</sub>-free heat and electricity generation. Commercial designs, developed decades ago, have not adopted technological innovations and struggle to be cost-competitive with state-of-the-art fossil-fuel power systems. Though fuel is relatively inexpensive, nuclear power plants are expensive to build and produce only low-value electricity. One strategy to improve the process economics is to use unique characteristics of nuclear reactors to provide additional sources of revenue by co-producing higher value products. A conceptual process is analysed, which combines a molten salt nuclear power reactor and a chemical process using the reactor's gamma radiation to facilitate the production of propylene. This facility is able to co-produce electricity and high volume commodity chemicals using, otherwise wasted radiation. The conceptual process model suggests that integration of units producing an energy product with one that produces more valuable chemicals leads to significant economic benefits for the overall facility. Despite the improvements, the system studied is unable to deliver an acceptable return on investment for small power plants independent of the size of the chemical plant integrated. Conversely, large plants are capable of delivering acceptable return on investment, in some cases generating returns comparable to other modern investment options.

**In (2022) F.M. El-Hossary** studied investigates the effect of RF plasma on the commercial SS201 and Steel alloys physical, structural and nuclear properties, using an atmosphere of nitrogen (85%) plus acetylene (15%) at 500 W working for 0.5 h. The results were compared with untreated alloys and AISI304L. The study indicated the ability of RF plasma to improve both the mechanical and tribological properties of treated alloys compared to the original commercial alloys and

the AISI304L, and achieve good shielding properties for industrial/nuclear applications.

**In (2023) Guilherme Grams, Jérôme Margueron** A compressible liquid-drop approach adjusted to uniform matter many-body calculations based on chiral EFT interactions and to the experimental nuclear masses is used to investigate the neutron star crust properties. Eight chiral EFT hamiltonians and a representative phenomenological force (SLy4) are confronted. We show that some properties of the crust, e.g. clusters mass, charge, and asymmetry, are mostly determined by symmetric matter properties close to saturation density and are therefore mainly constrained by experimental nuclear masses, while other properties, e.g., energy per particle, pressure, sound speed, are mostly influenced by low-density predictions in neutron matter, where chiral EFT and phenomenological forces substantially differ.

**In (2023) Samah A. Al-Shelkamy** . In the present contribution, the reliability and accuracy of recent nuclear theories are discussed for most of the quantities needed to estimate reaction cross sections and beta-decay rates, namely nuclear masses, nuclear level densities, gamma-ray strength, fission properties and beta-strength functions. It is shown that nowadays, mean-field models can be tuned at the same level of accuracy as the phenomenological models, renormalized on experimental data if needed, and therefore can replace the phenomenological inputs in the prediction of nuclear data. While fundamental nuclear physicists keep on improving state-of-the-art models, in particular the shell or ab-initio models, nuclear applications could make use of their most recent results as quantitative constraints or guides to improve the predictions in energy or mass domain that will remain inaccessible experimentally.

## 2.1 Radioisotopes for radiation therapy

Although many radioisotopes can be used as radiation sources, only a few have been developed and applied in preclinical and in vivo studies. When selecting a candidate for

experimental and clinical studies, the advantages and disadvantages of radioisotopes should be evaluated based on their physical and chemical properties, patient and environmental safety, specific requirements for in vivo applications, and technical feasibility. Table 1 summarizes the physical and radiation properties of therapeutic radioisotopes that have been used in previous studies. These radioisotopes can be categorized into three types, ie,  $\alpha$ ,  $\beta$  and auger particles. [5]

**Table 1** Characteristics of some therapeutic radioisotopes

Radioisotopes	Particle(s) emitted	Half-life	Particle energy (keV)	Maximum particle range
<b><math>\alpha</math>-particle</b>				
<b>At</b>	$\alpha$	7.2 hours	6,000	0.08
<b>Ac</b>	$\alpha$ and $\beta$	10 days	6-8,000	0.1 mm
<b>Bi</b>	$\alpha$ and $\beta$	60.6 minutes	6,000	0.09 mm
<b>Bi</b>	$\alpha$ and $\beta$	46 minutes	6,000	<0.1 mm
<b>Ra</b>	$\alpha$ and $\beta$	11.4 days	6-7,000	<0.1 mm
<b>Pb</b>	$\alpha$ and $\beta$	10.6 hours	7,800	<0.1 mm
<b>Tb</b>	$\alpha$	4.2 hours	4,00	<0.1 mm
<b><math>\beta</math>-particle</b>				
<b>I</b>	$\beta$ and $\gamma$	193 hours	610	2.0 mm
<b>Y</b>	$\beta$	64 hours	2,280	12.0 mm
<b>Cu</b>	$\beta$ and $\gamma$	62 hours	577	1.8 mm

<b>Re</b>	$\beta$ and $\gamma$	91 hours	1,080	5.0 mm
<b>Lu</b>	$\beta$ and $\gamma$	161 hours	496	1.5 mm
<b>Cu</b>	$\beta$	12.7 hours	1,670	2.0 mm
<b>Auger-particle</b>				
<sup>67</sup> Ga	Auger, $\gamma$	78.3 hours	90	10 nm
<sup>123</sup> I	Auger, $\gamma$	13.3 hours	159	10 nm
<sup>125</sup> I	Auger, $\gamma$	60.5 days	27	10 nm

**Abbreviation: keV, kilo electron volts.**

**2-1-  $\alpha$ -emitters**

More than 100 different radioisotopes emit  $\alpha$ -particles; however, most of them decay too quickly to be considered for therapeutic use. Only a few  $\alpha$ -emitters, including actinium-225 (<sup>225</sup>Ac), astatine-211 (<sup>211</sup>At), bismuth-213 (<sup>213</sup>Bi) and bismuth-212 (<sup>212</sup>Bi), have therapeutic potential and these have been investigated in animal models or humans.  $\alpha$ -particles are positively charged helium nuclei with a higher energy (5,000–8,000 keV) and shorter range (50–80  $\mu$ m) than  $\beta$ -particles. Correspondingly,  $\alpha$ -particles have a higher linear energy transfer (LET), approximately 100 keV/ $\mu$ m, than  $\beta$ -particles. LET refers to the average radiation energy deposited in tissue per unit length of track (keV/ $\mu$ m). Cell death occurs only when  $\alpha$ -particles traverse the cell nucleus rather than going directly to the cytoplasm. Owing to these features,  $\alpha$ -particles are better suited to the treatment of microscopic and small-volume tumors, or residual tumors. In these instances,  $\alpha$ -particles are more efficient and specific in causing tumor cell death than  $\beta$ -particles, as shown in many studies. [6]

Earlier studies using the single-cell model showed that one cell-surface decay of the  $\alpha$ -emitter At resulted in the same degree of cell killing as approximately 1,000 cell-surface decays of the  $\beta$ -emitter <sup>90</sup>Y. The therapeutic

effect of several  $\alpha$ -emitters has been investigated for decades. Recently,  $\alpha$ -emitter therapy has received renewed interest, especially for the treatment of microscopic, small tumors or minimal residual tumors in a variety of cancer types, including leukemia, lymphoma, glioma, melanoma, and peritoneal carcinomatosis. However, poor radionuclide supply, complicated methodologies for calculating the radiation dosimetry and the need for relevant data relating to normal organ toxicity limit the applications of  $\alpha$ -emitter radioisotopes and impede the development of targeted  $\alpha$ -emitters. [7]

## 2.2 Beta particle emitters ( $\beta$ )

Radioisotopes that function as  $\beta$ -emitters are widely used in radio immunotherapy trials. Commonly used  $\beta$ -emitter radioisotopes are iodine-131 (I), yttrium-90 (Y); copper-67 (Cu), rhenium-186 (Re), lutetium-177 (Lu), and copper-64 ( $^{64}\text{Cu}$ ). I and Y are the most popular candidates since these two isotopes are readily available and inexpensive.

I has a long half-life (8 days) and also provides  $\gamma$ -emissions that can be used in imaging for tracking and quantifying the radioisotope in vivo. Furthermore, relatively straight forward chemical modifications can be applied to crosslink I chelates to the proteins, allowing for the labeling of tumor targeting antibodies with radioisotopes.

However, I has some drawbacks, such as rapid degradation and a short retention time in the tumor. Additionally, the high energy  $\gamma$ -emission presents some safety concerns to patients and the environment.

Y has fewer environmental radiation restrictions than I because of its pure  $\beta$ -emitter nature, higher energy and low-range (12 mm), and a longer residence time in the tumor, making it more suitable for the irradiation of large tumors that require a higher radiation dose and a stable link between radioisotopes and the tumor targeting antibody. [8]

$\beta$ -particles have lower LET and longer radiation ranges than  $\alpha$ -particles. Because of their long radiation range (several millimeters),  $\beta$ -particles can destroy tumor cells through the

“crossfire effect,” even though the radioimmunoconjugate is not directly bound to the cells. Therefore, they are particularly useful in overcoming treatment resistance. However, longrange  $\beta$ -particles can produce nonspecific cytotoxic effects by destroying surrounding normal cells. Thus,  $\beta$ -particles are considered to be most suitable for the treatment of bulky or large volume tumors. [9]

## 2.3 Auger-emitters

An auger is a high LET (4–26 keV/ $\mu\text{m}$ ), low energy ( $\leq 1.6$  keV), and short-range ( $\leq 150$  nm) electron derived from inner-shell electron transitioning. During the decay of these radioisotopes, the vacancy formed in the K shell as a consequence of electron capture or internal conversion is rapidly filled by electrons dropping in from higher shells, resulting in a cascade of atomic electron transitions and emitting a characteristic X-ray photon or an auger. Auger emitters, such as gallium-67 (Ga), iodine-123 (I) and iodine-125 ( $^{125}\text{I}$ ), have also been used for cancer radiotherapy. Auger emitters deposit high LET over extremely short distances and are therefore most effective when the decay occurs in the nucleus and less so when the decay occurs in the cytoplasm. The dimensions of many mammalian cell nucleus components, such as 30-nm chromatin fiber, fall in the range of the auger emitter ( $< 150$  nm); therefore, auger emitters are more damaging to those cellular structures. As a result, the use of auger emitters has been relatively restricted because of the extreme toxicity of such radioisotopes. [10]

The selection of radioisotopes for cancer therapy should take into account the specific cancer types, characteristics of the tumor, toxicity and safety of radioisotopes, availability and production of radioisotopes, and the chemistry that is involved in assembling the radioisotopes to the delivery carriers. It has been shown that a combination of radioisotopes with different energies can be more beneficial than using a single radioisotope. For example, a previous study showed that the combination of a high energy and long tissue range radioisotope with a medium energy and shorter tissue range

radioisotope is able to destroy both large-volume tumors and micro metastases. [11]

## 2.4 Antibodies conjugated radioisotopes for tumor targeted radiation therapy

Most conventional anticancer agents do not greatly differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects, which limits the maximum allowable dose of the agent. The use of monoclonal antibodies (mAb) interacting with cancer cell surface markers is a simple tumor targeting strategy that can lead to a considerable enhancement of treatment efficacy.<sup>20</sup> Small, high affinity antibody fragments, such as single chain antibodies and affibodies, which are expressed as recombinant proteins in prokaryotic cells, have the additional advantage of cost-effective production of their targeting ligands.

mAbs or mAb fragments as ligands for the delivery of radioisotopes, as internal radiation sources, have been investigated extensively.<sup>22-24</sup> The method of using mAbs conjugated with radioisotopes for internal or systemic radiation treatment is also known as radioimmuno therapy. [12]

However, there are several limitations in using antibodyconjugated radioisotopes for the delivery of radiation therapy. Firstly, mAbs may bind to cell surface markers that are expressed at a low level in normal tissues, causing potential systemic toxicity. Secondly, mAbs have only a few sites available for conjugating radioisotopes. Therefore, delivery of a large dose of therapeutic radioisotopes may require a larger amount of antibodies. Thirdly, the use of mAbs presents potentially unwanted immune responses. Additionally, antibodies may be susceptible to protease degradation. These limitations may be addressed using nanomaterial based delivery systems. [13]

## 2.5 Biocompatible nanoparticles

### 2.5.1 The chemistry and physical properties of nanomaterials

Nanoparticles are typically colloidal materials that can be fabricated with a variety of compositions and morphologies using special

techniques and chemistries. Nanomaterials currently used in biomedical applications include fluorescent CdSe nanoparticles known as quantum dots (QDs), photosensitive gold nanoparticles, magnetic nanoparticles, as well as polymer based polymeric nanoparticles and nanoscale liposomes. Nanoparticles, especially metallic and metal oxide nanoparticles, in the “mesoscopic” size range of 5–100 nm in diameter often exhibit unique chemical and physical properties that are not possessed by their bulk or molecular counterparts. [14]

For example, QDs made from CdSe exhibit photoluminescence with a controllable wavelength ranging from the visible to near infrared depending on their size. Colloidal gold nanoparticles exhibit unique surface plasmon resonance (SPR) properties derived from the interaction of electromagnetic waves with the electrons in the conduction band.<sup>26</sup> Magnetic nanoparticles, such as iron III oxide ( $\text{Fe}_3\text{O}_4$ ), are superparamagnetic and exhibit high magnetization and yet no residual magnetization in the absence of an externally applied magnetic field.<sup>27</sup> Both the chemical properties and reactivity of the nanoparticles are controlled by the surface chemistries offered by functionalized polymer coatings or blocks, which are also important to the stability and biocompatibility of the nanoparticles, interactions between particles, biomolecules and cells, in addition to tissue distributions of the nanoparticles.

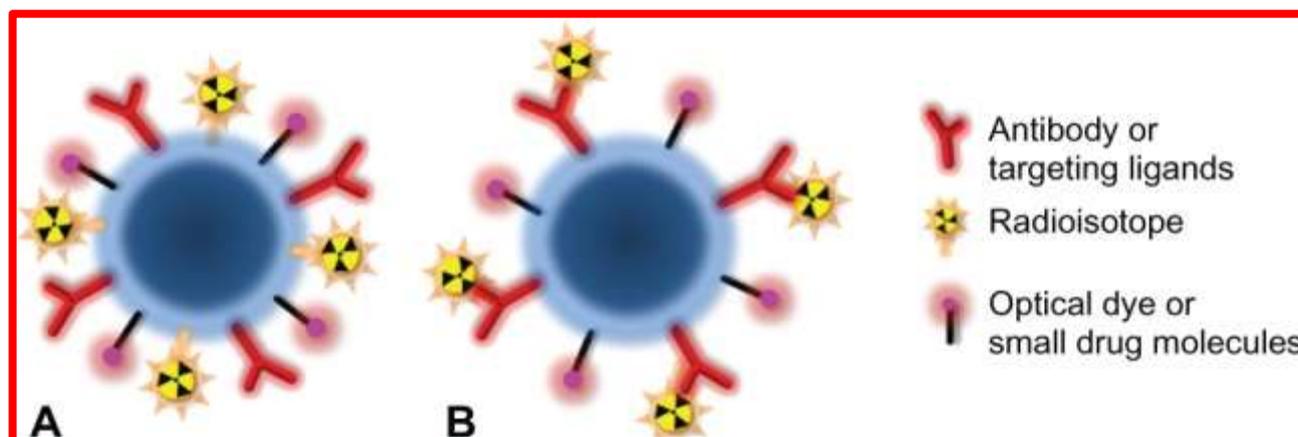
Nanoparticles provide a large surface area and various types of functional groups that allow for chemical reactions taking place on the nanoparticle surface and to assemble or load bioactive ligands or small molecular agents. Diverse nanomaterials with unique properties have been found in various biomedical applications, including in vitro or in vivo imaging, separation and purification of cells or biomolecules, and delivery of therapeutic agents. [15]

## 2.6 Biocompatibilities and functionalization of nanoparticles

Well-designed polymers can be used as coatings to stabilize metallic or metal oxide nanoparticles from aggregating and

precipitating in physiological conditions while maintaining the desired physical properties. These polymers should also provide biocompatibilities that include minimizing toxicity from metallic nanoparticles, modulating interactions between nanoparticles and biomolecules, cells and tissues, together with altering the secretion and biodistribution of the nanoparticles. Coating polymers can be

functionalized with reactive functional groups, such as  $-COOH$ ,  $-NH_2$  and  $-SH$ , which are prepared for the conjugation of the tumor targeting ligands or other agents as illustrated in Figure 2. For carrying and delivering therapeutic radioisotopes, coating polymers with reactive functional groups allows for covalent cross-linking or non-covalently incorporating chelates of radioisotopes. [16]



**Figure 2.1: Multifunctional nanoparticle platforms for tumor targeting, imaging, and delivery of drugs and/or radioisotopes. Radioisotopes can be conjugated directly on the nanoparticle surface (A) or on the tumor targeting antibodies (B).**

There are a variety of polymers and their derivatives, such as dextran, polyethylene glycol (PEG), and dendrimer, developed for ensuring the biocompatibility and functionalization of nanoparticles. For instance, Zhang and co-workers modified the surface of iron oxide nanoparticles with trifluoroethyl ester-terminal-PEG-silane, which was then converted to an amine-terminated PEG. [17]

The terminal amine groups were used for the conjugation of Cy5.5, a near infrared (NIR) optical probe, and chlorotoxin, a targeting peptide for glioma tumors. In vitro MRI and confocal fluorescence microscopy showed a strong preferential uptake of the multimodal nanoparticles by glioma cells compared to the control nanoparticles and noncancerous cells, indicating the cancer targeting abilities of the probes for gliomas. To reduce nonspecific uptake of nanoparticles by normal tissues and extend the blood circulation time of nanoparticles to allow particle accumulation at the target site, polymer coatings must be

specifically designed to meet such applications. The physical characteristics of polymer coated nanoparticles affect their in vivo performance. Surface morphology, overall particle size and surface charge are all considered important factors that determine toxicity and biodistribution. The overall particle size must be small enough to evade uptake by reticuloendothelial system (RES) but large enough to avoid renal clearance, leaving a window of between 5.5 and 200 nm. However, it has also been demonstrated that for particles smaller than 40 nm in diameter, both the biodistribution and the half-life of nanoparticles are determined by the coating material rather than the mean size. [18]

Nanoparticles with different coating materials usually have different surface charges, which plays a critical role in blood half-lives. It has been demonstrated that both positively and strong negatively charged particles tend to nonspecifically stick to cells. Thus, it is generally considered that nanoparticles with a neutral surface charge are recommended to

extend circulation times. Additionally, nanoparticles with neutral surfaces also show a high stability for resisting protein binding and provide steric hindrance for preventing aggregation after *in vivo* administration.<sup>31</sup> Recently, new coating materials from zwitterionic polymers have been developed to provide a biocompatible surface with both positive and negative charges, which exhibit high resistance to nonspecific protein adsorption. [19]

In addition, new polymer coatings exhibit high resistance to nonspecific protein binding and uptake by macrophages in the normal liver and spleen. Combining PEG with a crosslinkable polysiloxane coating, Chen and colleagues developed an antibiofouling copolymer PEO-*b*-PγMPS for coating nanocrystals.

This new copolymer made hydrophobic iron oxide nanoparticles mono-disperse in physiological conditions with great stability. Furthermore, this amphiphilic blocked coating polymer can be functionalized with reactive amine groups on the particle surface, making it readily available for the conjugation of tumor targeting ligands and therapeutic agents such as radioisotope chelates. Furthermore, these composite nanoparticles showed a reduced nonspecific uptake.

## 2.7 Advantages of using nanoparticles to deliver therapeutic agents

One of the major obstacles in the delivery of therapeutic agents, especially small molecular agents such as radioisotope chelates, is rapid elimination of the agents and their widespread distributions into normal organs and tissues. One common solution to this problem is the administration of the agent in a large quantity, which is not cost-effective and often results in undesirable toxicity. Nanoparticles with proper biocompatible polymer coatings potentially provide better platforms for carrying therapeutic agents and subsequently delivering the agents to the tumor. [20]

There are several advantages of using nanoparticles to deliver therapeutic radioisotopes, for instance: 1) nanoparticles have prolonged blood retention time, ranging

from 30 minutes to more than 24 hours, depending on the morphology and size of the particle, coating materials, and compositions of nanoparticle conjugates; 2) nanoparticle carriers targeting cancer cells are capable of enhancing local accumulation of the nanoparticles with therapeutic agents, leading to high tumor retention times and concentrations of the agents; 3) nanoparticles can load more drug molecules or radioisotopes on a single particle than conventional carriers, sometimes more than one type of therapeutic agent or radioisotope; 4) internalization of receptor targeted nanoparticles leads to the uptake of large amounts of radioisotopes into the target cells, resulting in effective killing of tumor cells with a relatively low level of receptor-expression; and 5) the unique chemical and physical properties of nanoparticles, such as magnetization and photosensitizing, provide additional capabilities and functions for improving delivery of the radioisotopes (for example the external application of a magnetic field) and monitoring the response to radiotherapy. With the controlled formulation of nanoparticles and carefully planned drug carrying strategies, nanoparticle platforms may offer the appropriate pharmacokinetics to enable optimal delivery of therapeutic radioisotopes for cancer treatment. [21]

Biodegradable nanoparticles can be employed to gradually release drugs. For example, therapeutic agents can be interspersed within a poly(DL-lactide-co-glycolide) (PLGA) matrix. As the biocompatible polymer is degraded, the therapeutic agents are released in a sustained manner.<sup>39</sup> Additionally, particles such as micelles are useful in drug delivery since their hydrophobic centers allow for drug encapsulation while their hydrophilic surfaces allow for ease in transport. Alternatively, the particle surface allows for modifications since it provides functional groups the opportunity to conjugate small molecular agents. Radioisotopes are typically loaded onto the nanoparticles using the conjugation strategy. [22]

## 2.8 Strategies for targeting nanoparticles to cancers

Two mechanisms, passive and active targeting, are typically used in targeting nanoparticles to tumors. In passive targeting, nanoparticles and payloads reach the tumor through rich, chaotic, and highly permeable tumor vasculature and are accumulated and subsequently remain in the tumor due to its lack of lymphatic drainage. In active targeting, nanoparticles are engineered to target specific biomarker molecules that are unique and over populated in a tumor or cancer cell surface. Extensive reviews and discussions on the mechanisms of targeting nanoparticles to tumors are beyond the scope of this review and can be found elsewhere. [24]

Active targeting nanoparticles carrying therapeutic agents, such as radioisotopes, to tumors are the current research focus and the subject of intensive investigations. Differences in the expression of cellular receptors between normal and tumor cells represent a great opportunity for targeting nanoparticles to cancer cells. For engineering tumor targeted nanoparticles, different ligands, such as antibodies, peptides, and small molecules targeting the related receptors that are highly expressed in tumor cells, are usually conjugated to the surface coating polymer of nanoparticles. There have been some reports of *in vivo* tumor targeting with various targeting ligand/nanoparticle combinations, such as folic acid-modified dendrimers ( $\approx 9\%$  ID  $g^{-1}$ ; ID  $g^{-1}$  = injected dose per gram tissue), synthetic small-molecule-modified iron oxide (IO) nanoparticles ( $\approx 4\%$  ID  $g^{-1}$ ),<sup>46</sup> polyethylene glycol-coated (PEGylated) arginine – glycine – aspartic acid (RGD) peptide-modified carbon nanotubes (10%–15% ID  $g^{-1}$ ),<sup>47</sup> and PEGylated single-chain variable fragment (ScFv) antibody-modified gold nanoparticles ( $\approx 8\%$  ID  $g^{-1}$ ). Tumor-targeted nanoparticles as potential carrier vectors of therapeutic agents are believed to be the next promising platform for nanobiotechnology [25]

Using antibodies as tumor targeting ligands for magnetic or photosensitive nanoparticles has been extensively studied *in vitro* and *in vivo* in the area of cancer imaging.

Conjugates composed of nanoparticles and antibodies were found to maintain the properties of both the antibody and the nanoparticle. Conjugation of magnetic iron oxide nanoparticles with Herceptin, a well-known antibody against the HER2/*neu* receptor which is over-expressed in breast cancer cells, showed *in vivo* cancer targeting and imaging of HER2/*neu* with a high sensitivity, which enables the magnetic resonance imaging (MRI) detection of tumors as small as 50 mg. The smallest parts of the antibody, the variable regions or so called ScFv, are among the most frequently used ligands. Because antibody fragments lack the Fc domain that binds to Fc receptors on phagocytic cells, particulates derived with mAb fragments have increased circulation times in the blood compared to particulates derived with whole mAbs. [26]

In contrast to whole mAbs and antibody fragments, small molecule ligands typically can be readily obtained from chemical syntheses in a large quantity, which may be an important factor in translating novel methods into clinical practices. Small peptide ligands, such as tumor integrin  $\alpha_v \beta_3$  targeted high-affinity Arg-Gly-Asp (RGD) ligand which has a higher binding affinity in its conformationally constrained cyclic form than in its linear form, have been extensively investigated for their *in vitro* and *in vivo* applications of delivering tumor targeted nanoparticles carrying imaging and therapeutic agents. The RGD peptide, which has a higher binding affinity in cyclic conformation than its linear form, is able to bind to  $\alpha_v \beta_3$  or  $\alpha_v \beta_5$  integrins that are highly expressed in angiogenic tumor endothelial cells and subpopulations of tumor cells. It is likely that RGD-targeted nanoparticles can act on tumor endothelial cells and produce anti-angiogenesis effect. The folate receptor (FR) is an attractive molecular target for tumor targeting because it is over expressed by several types of tumor cells (eg, ovarian, colorectal, breast, nasopharyngeal carcinomas), however, it has limited expression in most normal tissues. [27]

FR-mediated tumor delivery of various agents, such as therapeutic drugs and gene products as well as imaging agents with radionuclides or nanoparticles for imaging,

have been reported. Folic acids targeting cancer cells over expressing folate receptors have been covalently conjugated to 66 nm liposomes via spacers of various lengths to target the liposomes to kB cells with a high level of folate receptor expression. The binding of folate-PEG liposomes to kB cells can be competitively inhibited by excess free folate or by antiserum against the folate receptor, demonstrating that the interaction is mediated by the cell surface folate-binding protein. These folate-PEG liposomes show potential for delivering large quantities of low molecular weight compounds into folate receptor-bearing cells.

### 2.9 Delivery of tumor targeted therapeutic radioisotopes with nanoparticles

With surface functionalized nanoparticles and a range of surface chemistries for the conjugation of peptide ligands and antibody moieties, tumor targeting antibodies cross-linked with therapeutic radioisotopes or radioisotope chelates are readily conjugated to nanoparticles. Integrin targeted nanoparticle carrying radioisotopes have demonstrated its effect on tumor vasculatures. In the study by Li and colleagues, integrin antagonist (IA) 4-[2-(3,4,5,6-tetrahydro pyrimidin-2-ylamino)ethoxy]-benzoyl-2-(5)-aminoethylsulfonamino- $\beta$ -alanine, which binds to the integrin  $\alpha_v\beta_3$ , and a monoclonal antibody against murine Flk-1, were used to target nanoparticles radiolabeled with Y.<sup>22</sup> A single treatment with IA-nanoparticle-Y caused significant tumor growth delay in murine tumor models K1735-M2 (melanoma) and CT-26 (colon adenocarcinoma), compared to untreated tumors, as well as tumors treated with anti-Flk-1 mAb, anti-Flk-1 mAb-NP, and conventional radioimmunotherapy with Y-labeled anti-Flk mAb.

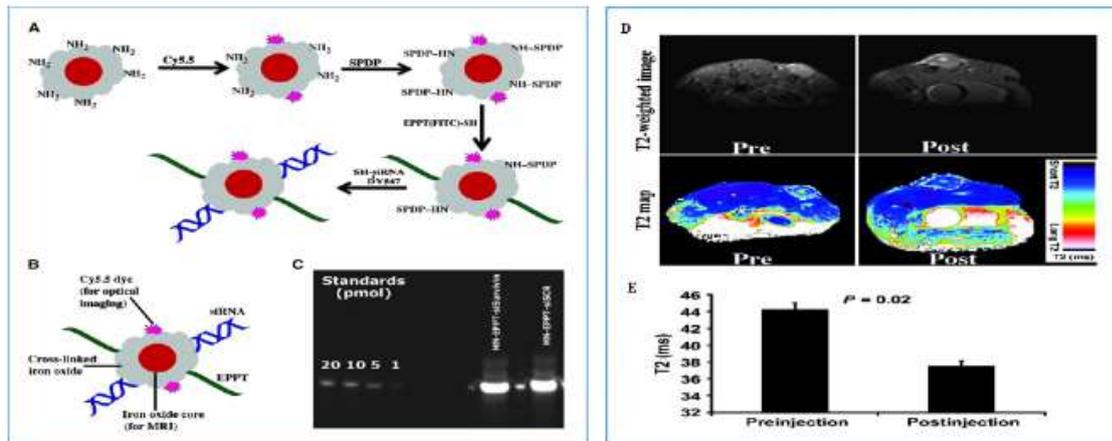
However, selection of nanoparticle carriers and radioisotopes should be based on which nanoparticle carrier can improve the pharmacokinetics and enhance the delivery of therapeutic agents, their therapeutic effects and the additional functionalities offered by nanoparticle carriers as demonstrated in several previous studies are discussed here. [28]

### 3.1 Slow clearance and prolonged blood circulation with nanoparticle carriers

One major benefit of using nanoparticles to deliver therapeutic radioisotopes for radiation treatment is that the large size and high molecular weight of nanoparticle carriers cause the nanoparticle-radioisotope conjugates to be cleared from the body slowly. Nanoparticle-radioisotope conjugates may have longer blood circulation time than radioisotopes alone or mAb-radioisotope conjugates. The slow clearance and long blood retention time of nanoparticle carriers can be demonstrated by our study on the delivery time courses of optically sensitive ATF-Cy5.5 conjugates and ATF-Cy5.5-iron oxide nanoparticle conjugates in mice bearing orthotopic pancreatic xenograft tumors. ATF-Cy5.5 conjugates were found to accumulate in the tumor in less than two hours and subsequently be secreted through the kidney in 7 hours after intravenous administration of the agent. However, ATF-Cy5.5-iron oxide nanoparticle conjugates started to accumulate in the tumor after 4 hours and the accumulation continued, peaking at 48 hours. Slow clearance and long blood retention time are critically important to the active targeting of tumors because cell surface marker targeted agents need time to reach inside the tumor and high and effective concentration of agents in the blood facilitates delivery of the agents. The unique pharmacokinetics of nanoparticle carriers has strong implications in optimizing internal radiation sources with proper consideration of the half time of the radioisotopes, radiation dosages, and treatment regime. [29]

Rossin and colleagues developed Cu-radiolabeled folate-conjugated shell cross-linked nanoparticles as candidate agents to shuttle radionuclides and drugs into tumors over expressing the folate receptor. They reported that <sup>64</sup>Cu-radiolabeled folate-conjugated shell cross-linked nanoparticles exhibited a long circulation time in blood and were able to passively accumulate in tumors. Because Cu is also a radioisotope capable of positron emission tomography (PET), Cu-radiolabeled folate-conjugated shell cross-

linked nanoparticles are a class of promising radioisotope agents for imaging and treating early-stage solid tumors. [30]



**Figure 3.1 : A, flowchart of the synthesis. B, nanodrug characterization. The nanodrug consisted of dextran-coated MNs triple labeled with Cy5.5 dye, EPPT peptides, and synthetic siRNA duplexes**

### 3.2 Improve local delivery and tumor retention time of radioisotopes with magnetic nanoparticles

Systemic radiation therapy consists of a focused radiation source that remains at the tumor site over a period time. Magnetic nanoparticles, such as biocompatible superparamagnetic iron oxide nanoparticles with core sizes of 10–50 nm, suit this purpose well. Applying an external magnetic field to magnetic nanoparticle-based radioisotopes delivered to tumors may enhance their therapeutic effect and decrease the adverse effect of systemic radiotherapy.

A static magnetic field can be applied after the radioisotopes have localized in the tumors, constraining these magnetic nanoparticles to helical paths, which would result in substantially confining the emitted particles within the tumor's boundaries, thus increasing the radiation dose to the tumor. Chen and colleagues developed a radioimmunoconjugate-I – anti-vascular endothelial growth factor (VEGF) monoclonal antibody (Sc-7269) cross-linked to dextran coated magnetic iron oxide nanoparticles and investigated their therapeutic effect and safety in nude mice bearing human liver cancer.

While I – anti-VEGF monoclonal antibody (Sc-7269) provides tumor targeting and a radiation source, the use of magnetic nanoparticles was intended to improve the delivery of the radioisotopes to the tumor and tumor retention time of the radiation source under the force of an external magnetic field. Their results suggested that the radioimmunotherapy of intratumoral injection of I – Sc-7269 – nanoparticles is safe and efficient for the treatment of liver cancer. [31]

### 3.3 Radiation treatment combined with hyperthermia induced by nanoparticles

Local hyperthermia at the site of the tumor has been shown to be an effective cancer treatment because increasing the temperature in living tissues to 42–46°C leads to cell death. Heat can be induced in cancer cells through the external application of an alternating magnetic field (AMF) and tumor targeted nanoparticles. Nanoparticle-based hyperthermia has been demonstrated to be a potential method for treating cancer. Furthermore, application of the external AMF can activate nanoparticles carrying radioisotopes to preferentially be retained in the microenvironment of the tumor tissue at higher concentrations than in the surrounding normal tissue. In an earlier study by DeNardo

and colleagues, investigators evaluated the pharmacokinetics, tumor uptake, and the therapeutic effect of In-chimeric L6 (ChL6) monoclonal antibody (mAb)-linked iron oxide nanoparticles in a thymic mice bearing human breast cancer (HBT 3477) xenografts when inductively heating these In-ChL6 mAb linked iron oxide nanoparticles with an externally applied AMF. [32]

They found significant therapeutic responses from AMF/bioprobes therapy with up to an eight times longer mean time to quintuple tumor volume with the therapy compared with no treatment. Their data suggested that mAb-conjugated nanoparticles, when given intravenously, escaped into the extravascular space and bonded to cancer cell membrane antigens, so that In-ChL6 mAb linked iron oxide nanoparticles could be used in concert with an externally applied AMF to deliver thermoablative cancer therapy. [33]

Natarajan and colleagues developed a new class of radioconjugated nanoparticles ( $^{111}\text{In}$ -DOTA-di-scFv-NP) for the imaging and therapy of anti-MUC-1-expressing cancers.

They showed the binding of radioconjugated nanoparticles to cancer cells was time dependent with increased binding over time. They also compared the ability of 20 nm, 30 nm, and 100 nm nanoparticles to conjugate In-mAb and found that 100 nm nanoparticles could be conjugated to  $^{111}\text{In}$ -mAb so that the resulting radioimmunonanoparticles (RINP) had characteristics suitable for AMF therapy. Although 100 nm RINP targeted tumors less efficiently than 20 nm RINP, their heating capacity is typically 6 times greater, suggesting the 100 nm RINP could still deliver better therapy with AMF. [34]

### 3.4 Improving boron neutron capture therapy with nanoparticles

Boron neutron capture therapy (BNCT) is based on a nuclear reaction in which a neutron of appropriate energy reacts with the stable B isotope, and a high-energy  $\alpha$ -particle is released in addition to a recoiling  $^7\text{Li}$  nucleus. The energy of the released  $\alpha$ -particle provides the main therapeutic effect and is deposited in the tissue within 10  $\mu\text{m}$  of the site of neutron capture. This

localized therapy is designed to minimize toxicities. Because the recoil range of the emitted lithium and helium particles in tissue is 5 and 7  $\mu\text{m}$ , respectively, which is comparable to the size of a single cell, the cellular internalization and subcellular localization of the boron carrier with respect to the cell nucleus is a major determinant of the therapeutic efficacy for this approach. BNCT has been effectively used in treating prostate and breast cancers in clinical oncology. Using monoclonal antibodies serving both as the targeting ligand and the delivery carrier is challenging for this therapy. Recently, various nanoparticle approaches, such as dendrimers, liposomes, cationic acrylamide copolymers and single-walled carbon nanotubes,<sup>65</sup> have been developed and tested to deliver boron isotopes that target tumors. For example, boron carbide nanoparticles are studied as a system for T cell-guided boron neutron capture therapy. Nanoparticles were produced by a method of ball milling in various atmospheres using commercially available boron carbide. In vitro thermal neutron irradiation of B16 melanoma cells incubated with sub-100 nm nanoparticles (381.5 mg/g  $^{10}\text{B}$ ) induced complete cell death, while the nanoparticles alone induced no toxicity. [35]

### 3.5 Challenges and future directions of nanoparticle delivery of therapeutic radioisotopes

#### Improving systemic delivery of nanoparticles

One of the major challenges in the application of nanoparticles in vivo is the nonspecific uptake of nanoparticles by the liver and spleen in the RES when using systemic delivery. For tumor targeted delivery of therapeutic agents, such as radioisotopes, the trapping followed by a rapid clearance of nanoparticles by the RES effectively reduces the tumor targeting efficiency of nanoparticles and potentially causes undesirable organ and normal tissue damage after agents accumulate in the liver and spleen. Therefore, minimizing and evading RES uptake and improving blood retention time of nanoparticles are active areas of research and development in the field.

Several strategies, which are mainly focused on optimizing surface coating polymers, have been investigated. PEGylation and reducing surface charge of nanoparticle coatings may significantly reduce the RES uptake and improve the tumor targeting of nanoparticles as demonstrated by many groups. Antibiofouling and increased renal excretion rather than RES clearance were observed in nanoparticles with surface modified silica containing coating polymers. [36]

### 3.6 Multifunctional nanoparticles

In recent years, there has been a tremendous interest in developing multifunctional nanomaterials for cancer detection, treatment, treatment monitoring and image-guided interventions. For example, theranostic nanoparticles are capable of simultaneous imaging and therapy. Nanoparticles carrying cancer cell killing radioisotopes represent an ideal theranostic system with the radioisotope providing both therapeutic and imaging modalities or combining its therapeutic capability with the imaging capability of nanoparticle carriers. In particular, radioisotopes In or Cu, which emit gamma rays during their decay, have been most frequently used as the imaging probes for PET. Other intrinsic properties of nanoparticles may offer additional functions to further improve tumor specific radiation treatment with the combination of other therapeutics; for example, the ability to induce hyperthermia and increase tumor retention time with magnetic iron oxide or photosensitizing and photoacoustics from gold nanoparticles. Trimodal imaging probes have also been designed by adding another imaging modality to dual MRI and optical imaging probes. The representative multimodal imaging probe is iron oxide nanoparticles coupled with fluorescent organic dyes. The iron oxide nanoparticles chemically crosslinked with dextran have been widely used for in vivo as well as in vitro MRI because of their biocompatibility, small hydrodynamic size, and stable hydrophilic polymer coating. Nahrendorf et al developed multimodal imaging probes composed of magnetic iron oxide nanoparticles conjugated with arginyl peptides, near infrared

(NIR) fluorescent indocyanine dye, Cy5.5, and DTPA to chelate PET tracer  $^{64}\text{Cu}$ , resulting in a PET, MRI, and optically detectable imaging agent. In another example, RGD peptide was used for the targeted delivery of nanoparticles into integrin  $\alpha_v\beta_3$ -positive tumors. Both small-animal PET and T<sub>2</sub>-weighted MRI showed integrin-specific delivery of conjugated RGD-polyaspartic acid-iron oxide nanoparticles and prominent RES uptake. The bifunctional imaging approach may allow for earlier tumor detection with a high degree of accuracy and provide further insight into the molecular mechanisms of cancer. [27]

### 3.7 Improving detection and follow-up of therapy effects

In addition to its therapy function, nanoconstructs that are capable of reporting responses to therapeutics, especially in the real time monitoring of tumor changes at the molecular level post-treatment, are highly desirable. Imaging techniques, especially clinically feasible modalities in MRI, single photon emission computed tomography (SPECT) and PET, play important roles in the evaluation of the therapeutic effects of radiation therapy. For example, in a recent study by Jacene and colleagues fluorine-18 fluorodeoxyglucose (F-FDG) PET/CT was used for monitoring the response of non-Hodgkin's lymphoma to radioimmunotherapy.

They found F-FDG uptake in tumors typically drops significantly after radioimmunotherapy in non-Hodgkin's lymphoma. A continued decline in tumor maximum standardized uptake values between 12 and 24 weeks without additional therapy can occur, suggesting a need for delayed-response assessment. In patients who progress after radioimmunotherapy, new sites of disease, rather than recurrence or progression at previous disease sites, is commonly detected. Large declines in F-FDG uptake tend to be seen in those with the longest progression-free survival. Another recent study investigated the efficacy and side-effects of Y ibritumomab tiuxetan in patients with early stage extranodal indolent lymphoma of the ocular adnexa with  $^{111}\text{In}$  ibritumomab tiuxetan imaging. All

patients had In ibritumomab tiuxetan imaging to confirm expected biodistribution of  $^{90}\text{Y}$ -Zevalin during the radiation therapy. Investigators concluded rituximab followed by  $^{90}\text{Y}$  ibritumomab tiuxetan was an effective and

safe frontline treatment for early-stage extranodal indolent B-cell lymphoma of the ocular adnexa. [38]



**Figure 3.2 :shows PET scan Device**

#### 4.1 Conclusion

1. With the advances in nanoscience and nanotechnology, many nanomaterials including nanoparticles made of metal oxide, dendrimers, liposomes, polymers, and micelles can be used as carriers to deliver chemical, pharmaceutical agents and/or therapeutic radioisotopes into tumors.

2. Conjugating these nanoparticles with therapeutic isotopes and targeted antibodies can enhance therapeutic efficacy and decrease the toxicity and destruction of surrounding normal tissue by radioisotopes.

3. In experimental and clinical studies, proper radioisotope selection that is specific to a particular tumor type and delivery

mechanism should be considered when planning in vivo nanoparticle delivery. For

example,  $\alpha$ -particles should be used when micrometastatic diseases or minimal residual tumors are treated, while  $\beta$ -particle isotopes are recommended for bulky tumors.

4. The half-life of radioisotopes should be considered when using an intravenous system of delivering nanoparticle-radioisotope conjugates to the tumor, given the different pharmacokinetics in nanoparticles.

5. The nanoparticles carrying therapeutic radioisotopes should be a platform capable of not only delivering radioisotopes into the targeted tumors it should be capable of real-

time imaging for the monitoring and follow-up of the treatment.

6. In addition, the external magnetic field and other functions associated with nanoparticles can be used to enhance the delivery of radiation dosages and reduce normal tissue damage.

7. The further development of nanoparticle-based carriers will offer a range of approaches for the targeted delivery of radioisotopes for use in the internal and systemic radiation therapy of cancers.

#### 4.2 Recommendations

1. Radiation therapy, also called radiation therapy, is a type of cancer treatment. It uses intense energy beams to eliminate cancer cells. Radiation therapy often uses X-rays. But there are other types of radiation therapy, including proton beam therapy.

2. Modern radiation therapy methods are precise, directing beams of radiation directly at the cancer site precisely while protecting healthy tissue from high doses of radiation.

3. Radiation therapy can be given inside or outside your body. External beam radiation therapy is the most common type. This treatment uses a large device called a linear accelerator that directs high-energy beams to precise locations in the body.

4. Radiation therapy placed inside the body is called brachytherapy, and it is a common cancer treatment. During this treatment, the doctor places a small, solid implant at or near the site of the cancer.

5. Radiation therapy kills cells by destroying the genetic material that controls cell growth and division. Healthy cells may be damaged along with cancer cells during radiation therapy. But healthy cells can repair themselves more easily than cancer cells. The goal of radiation therapy is to treat cancer while harming the least possible number of healthy cells.

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