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Radioisotopes and Nanomedicine

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1. Introduction

Nanomedicine, the medical application of nanotechnology, is poised to make a major impact on the diagnosis and treatment of many diseases. It is a relatively new branch of science that involves harnessing the unique properties of particles that are nanometers in scale (nanoparticles) for both diagnostic and therapeutic applications. Nanoparticles (NPs) can be engineered with precise sizes, shapes, compositions and surface chemistries for specific applications. In particular, nanoparticles are uniquely suited for the treatment of cancers and cardiovascular diseases. NPs can be engineered with surface targeting ligands against cancer markers or atherosclerosis markers, which in turn allow the specific detection of as well as specific drug delivery to these diseases. In the case of cancer, nanoparticles also preferentially accumulate in tumors due to the enhanced permeability and retention (EPR) effect (Noguchi et al. 1998). Although nanomedicine is a relatively new field, it has been quickly translated into clinical medicine and has led to a number of clinically-approved agents. Today, there are more than twenty nanoparticle therapeutics in clinical use. Furthermore, a 2006 global survey conducted by the European Science and Technology Observatory (Duconge et al.) revealed that more than 150 companies are developing nanoscale therapeutics, highlighting the high enthusiasm for nanoparticle-based therapeutics (Wagner et al. 2006).

While nanomedicine has many facets, radioisotopes have been an integral component. Radioisotopes have been extensively utilized in the development of nanoparticle-based therapeutics. Radiolabeling has been the predominant method for the accurate assessment of biodistribution, circulation half-life, and pharmacokinetics of nanoparticles. In addition, there has been great interest in developing nanoparticles with dual diagnostic and therapeutic functionalities (theranostics) and radioisotopes have been a natural fit for the diagnostic component. Lastly, therapeutic radioisotopes can also be delivered by nanoparticles, especially for the treatment of cancer. In this chapter, we will review the various applications of radioisotopes in nanomedicine in detail. We also plan to discuss the methods of incorporating radioisotopes into nanoparticles as well as preclinical and clinical data on radioisotope containing nanoparticle diagnostics and therapeutics.

2. Nanoparticle platforms

Nanomedicine is a fairly new and rapidly developing branch of science. First described in 1965, liposomes are one of the first structures manufactured on a nanometer scale to be applied in medicine (Bangham 1993). Over the past 15 years, there has been a rapid growth

of interest in NPs probably due in large part to the inherent flexibility in the construction and design of the particles.

Liposomal agents were the first NP platform to make it into the clinic and have since been joined by a number of other nanoparticle classes. These various platforms include polymer-therapeutic conjugates, polymeric micelles, dendrimers, nanoshells, nucleic acid-based nanoparticles and carbon nanotubes (Wang et al. 2008). Liposomes are spherical lipid containers enclosing an aqueous space. Depending on design, they can range in size from tens of nanometers up to micrometers in size (Torchilin 2005). The outer sphere is composed of a phospholipid bilayer which acts a hydrophobic shell around the aqueous core. This allows for entrapment of hydrophilic compounds within the liposomes. Conversely, hydrophobic drugs can be incorporated into the lipid bilayer itself. The outside surface of the bilayer is exposed and can therefore act as a point of interaction between a liposome and a biosystem. The liposomal surface can be functionalized with targeting agents such as antibodies, protective polymers such as polyethylene glycol to prevent opsonization by the immune system, or diagnostic labels such as radioisotopes (Torchilin 2005).

Most of the next generation nanoparticle therapeutics are biodegradable polymer nanoparticles, which have been extensively investigated as therapeutic carriers (Kim et al. 2005). Polymeric nanoparticles are generally formulated by the self-assembly of block-copolymers consisting of two or more polymer chains with different hydrophobicity. These copolymers spontaneously assemble into a core-shell structure in an aqueous environment through the hydrophobic hydrophilic interactions. Specifically, the hydrophobic blocks form the core to minimize their exposure to aqueous surroundings while the hydrophilic blocks form the shell to stabilize the core (Farokhzad et al. 2004). This results in a structure ideally suited for drug delivery. The hydrophobic core is capable of carrying therapeutics with high loading capacity (5-25 % weight). The hydrophilic shell not only provides a steric protection for the micelle, but also provides functional groups for further particle surface modifications. Polymeric nanoparticles have been formulated to encapsulate either hydrophilic or hydrophobic small drug molecules, and macromolecules such as proteins and nucleic acids (Gu et al. 2008).

Fullerene carriers are another well-studied nanoparticle platform which includes both spherical carbon "buckyballs" and carbon nanotubes (CNTs). Both have potential as carriers for radioisotopes, in particular because of their ability to shield the reactive radioisotopes from the biosystem while at the same time allowing for modification of the outside of the nanotube for targeted therapy (Mackeyev et al. 2005). CNTs have cylindrical architecture with an extremely high length-to-diameter ratio. Until recently this system had not been successfully tested *in vivo*. Researchers at Oxford carried out the first experiments in a mouse model with I-125-filled, single-walled carbon nanotubes. Though iodine is rapidly taken up by thyroid tissue, researchers were able to completely redirect the CNTs to lung. This suggests that the iodine was entirely shielded from the circulation. This particular platform also set a record for radiation ionizing dose per gram of carrier at 800% (70% represents a reasonable prior *in vivo* benchmark). By surface functionalizing this platform, researchers hope to show versatility of targeting which may allow for extremely high doses of radiation to be delivered very selectively (Hong et al. 2010; Strano 2010).

Other platforms of nanoparticle delivery have been extensively studied including dendrimers, metal nanoparticles, nanoemulsions and nucleic acid based nanoparticles (Wang et al. 2008). The interest in these other nanoparticle platforms is growing and several dendrimer-based antiviral therapies are currently in clinical trials. Investigators have also

developed metallic nanoshells used for controlled release of chemotherapy. Each of these platforms has unique properties and holds promise for almost every branch of medicine. Much of this work continues in the preclinical stages with a few drugs now making it to clinical trials. By improving the stealth properties and optimizing the payload capacities of these various nanomolecules, there is great hope and high expectations that this branch of science can continue to make wide-ranging contributions to medicine.

3. Common isotopes for nanomedicine and incorporation strategies

Selection of an isotope for imaging or therapy depends on a number of parameters. For imaging, radioisotopes should have decay properties conducive to detection. In positron emission tomography (PET) imaging, the energy is invariably 511 keV due to positron decay; however, for single-photon emission computed tomography (SPECT) imaging ideal energy is 100 keV to 200 keV(Phillips et al. 2009). The photons must be of sufficient energy to penetrate the body while still allowing for adequate collimation for spatial localization. The half-life of the isotope is also important to consider, particularly in relation to the duration of expected nanoparticle circulation. For instance, fluorine-18 as a component of fluorodeoxyglucose-positron emission tomography (FDG-PET) is most commonly used in clinical practice. With a half-life of 110 minutes, this allows for adequate time to allow uptake of the FDG while it retains enough activity to be clinically detected after getting a patient to the scanner, but not so much as to require long periods of detection time or as to retain substantial *in vivo* activity for more than a day. The same principles guide selection of laboratory isotope half-life, particularly when selecting PET-agents which have a wider range of half-life. Commercially available PET agents range in half-life from 2 minutes up to 4 days (Table 1) (Delbeke & Martin 2001; 2004). Naturally, nanoparticles with longer expected circulation time will require PET agents with longer half-life while those with relatively short circulation times should be tracked using isotopes with shorter half-life to improve photon yield over time. This selection process is complicated by variation in stability amongst different isotopes-nanoparticle combinations (Phillips et al. 2009). It is important to consider both *in vitro* and *in vivo* stability because unstable labeling can lead to incorrect measurements of biodistribution via isotope loss. Many methods have been described for labeling nanoparticles, most commonly liposomal platforms. The method of labeling can also greatly affect stability of the conjugate (Phillips et al. 2009).

To be useful in the laboratory setting, radiolabeled nanoparticles ideally need to meet certain criteria. Important factors include ease and efficiency of preparation as well as stability of isotope-nanoparticle conjugate without *in vitro* or *in vivo* release of the radioisotope. Steady advancements in this area have led to increasing stability of isotope labeled liposomes, some of which are being translated into the clinic for diagnostic molecular imaging (Hahn et al. 2011).

Due to the relatively short half-life of the commonly used radioisotopes, nanoparticles should be labeled shortly before being used. This is referred to as "after loading" or "remote-labeling." Though not ideal, a very simple strategy for radiolabeling liposomes is to incubate the premanufactured liposomes with a lipophilic isotope (Phillips et al. 2009). This leads to emulsion of the isotope into the lipid bilayer; however, while this method is fairly simplistic, it results in a very unstable conjugation. Several more effective "after loading" techniques have been described that yield more stable isotope-liposome conjugations (Harrington et al. 2001).

Selected radioisotopes used for nanoparticle detection and imaging			
Radionuclide	Detection Method	T½	Photon Energy (Bult et al.)
Gallium-67	SPECT	3.3 d	93, 185, 300
Indium-111	SPECT	2.8 d	171, 245
Iodine-123	SPECT	13.2 h	159
Rhenium-186	SPECT	3.72 d	137, 132
Technetium-99m	SPECT	6.01 h	141
Iodine-125	SPECT	59 d	36
Carbon-11	PET	20 min	511
Copper-64	PET	12.7 h	511
Copper-62	PET	3.5 h	511
Fluorine-18	PET	109 min	511
Gallium-68	PET	68 min	511
Iodine-124	PET	4.2 d	511
Oxygen-15	PET	2 min	511
Zirconium-89	PET	78 h	511
Hydrogen-3	Scintillation	12.3 y	(β=18.5 keV)
Carbon-14	Scintillation	5730 y	(β=156 keV)

Table 1. Common radioisotopes for nanoparticle imaging. All are generated by cyclotron with the exception of Tc-99m which comes from Molybdenum-99/Tc-99m generators, resulting in a substantially lower relative cost because it is easier to obtain.

Radiolabeling via surface chelation was first described 30 years ago and is still used today. Hnatowich et al. first described chelation of both Ga-67 and Tc-99m via diethylenetriamine pentacetic acid (DTPA), a metal chelator (Hnatowich et al. 1981). More recently, Torchilin et al. published a method of radiolabeling liposomes with In-111 using phosphatidylethanolamine (PE) conjugated to DTPA (DTPA-PE). For Tc-99m a separate method has been developed by Laverman et al. (Laverman et al. 1999). A technetium chelator, *N*-hydroxysuccinimidyl hydrazine nicotinate hydrochloride (HYNIC), is conjugated to a free amino group of the liposome and incorporated via surface chelation to premanufactured liposomes. The liposomes are then incubated with Tc-99m prior to the start of the study (Laverman et al. 1999). External conjugation suffers from the potential for *in vivo* interactions between the labels and other biomolecules as well as surface crowding that could affect interactions with other functional groups on the liposome.

To help overcome this problem, other methods of "after loading" have been developed, specifically internal chelation. This approach utilizes liposomes that encapsulate a reactive species. The radiolabel is conjugated to a lipophilic chelator that can pass through the lipid bilayer (Harrington et al. 2001). Upon reaching the inside of the liposome, the complex interacts with the internal molecule, effectively entrapping it within the liposome. Numerous investigators have developed methods of radiolabeling based on this principle of internal chelation. Examples include In-111-oxine incubated with liposomes encapsulating DTPA leading to anchoring of the isotope (Harrington et al. 2001); Tc-99m-hexamethylpropyleneamine oxime incubated with liposomes encapsulating glutathione causing conversion to a hydrophilic form of the Tc-99m conjugate(Phillips et al. 1992);

Rhenium-186-*N,N*-bis(2-mercaptoethyl)-*N',N'*-diethylethylenediamine reacting with encapsulated cysteine (Bao et al. 2003); and halogenated I-123 combining with intra-liposomal arginine (Mougin-Degraef et al. 2006). Each of the reactions secures the label within the core of the nanoparticle which in general results in greater stability of the radiolabeled liposome.

Because of the wide range of methods used for incorporation of therapeutic radionuclides, discussion of these strategies is reserved for the specific examples cited later in the chapter (Table 2).

Selected radioisotopes under study for nanoparticle radiotherapy				
Radionuclide	Nanoparticle Platform	Notable Decays	$T_{1/2}$	Reference
Iodine-131	Synthetic polymer	γ, β	8 d	(Klutz et al. 2009)
Holmium-166	Acetylacetone	γ, β	27 h	(Bult et al. 2010)
Lutetium-177	Liposome, fullerene cage	β	161 h	(Helbok et al. 2010)
Rhenium-186	Liposome	γ, β	89 h	(French et al. 2010)
Rhenium-188	Liposome, iron oxide	γ, β	17 h	(Liang et al. 2007)
Yttirium-90	Lipid-polymer hybrid	β	64 h	(Wang et al. 2010)
Indium-111	Biotinylated streptavidin	Auger, γ	67 h	(Natarajan et al. 2008b)
Iodine-125	Biotinylated streptavidin	Auger, γ	60 d	(Liu et al. 2010)
Actinium-225	Mineral lattice	a	10 d	(Woodward et al. 2011)
Gold-198	Dendrimer	β	2.7 d	(Khan et al. 2008)

Table 2. Radioisotopes that have been tested in preclinical models. Radioisotopes that decay by both electron and photon emission have potential as theranostic agents.

4. Radioisotope applications in nanomedicine

Radionanoparticles have three core applications: drug development, imaging and therapy. We will discuss these applications and how they are being combined to provide unique avenues for the treatment of disease.

4.1 Radioisotopes for nanoparticle biodistribution and drug development

Nowhere have radioisotopes been more influential in nanomedicine than in their use for preclinical drug development. By successfully incorporating radioisotopes into the structure of a nanoparticle in such a way as to minimally influence external structure, nanoparticles can be tracked by radioactive decay (Ting et al. 2010). A variety of methods using an array of different isotopes have been developed for this purpose (Phillips et al. 2009). Gamma

photon imaging, in the form of positron emission tomography and single photon emission computed tomography (Racker & Spector), are the predominant methods of tracking *in vivo* particle biodistribution. Particle distribution is tracked via detection of emitted photons from isotope decay. In the case of PET, annihilation photons of 511 keV (generated when a positron and shell electron collide) emitted at 180 degrees from one another are detected and used to localize the particle (Chen & Conti 2010). SPECT uses emission of a single photon combined with collimation to allow photons of predictable trajectories to be recorded; thus, the particle decay can be localized within the body. In clinical practice, both methods have issues with spatial resolution; however, the level of localization is adequate for determining *in vivo* biodistribution.

The choice of radioisotope depends on a number of characteristics including the type of NP platform, ease of preparation and stability of the isotope-NP conjugate as well as availability, expense and decay characteristics of the radioisotope (Phillips et al. 2009). For instance, Tc-99m is readily available in most hospitals, and accounts for about 80% of the nuclear medicine tests worldwide (IAEA 2011); thus, it is commonly used for nanoparticle labeling. Carbon-14 was one of the first elements used to track the fate of nanoparticles by measuring urinary excretion of the isotope (Bazile et al. 1992). Tritium also has a long history of being used for tracking the fate of nanoparticles (Kukowska-Latallo et al. 2005; Takahama et al. 2009). These two radioisotopes are popular due to their long half-lives and ease of incorporation. Both radioisotopes are beta emitters and thus require dissection for *in vivo* quantification (Shokeen et al. 2008). Over the past two decades, SPECT and PET detection have emerged as facile ways of tracking internal biodistribution without the need for dissection to quantify uptake. Copper-64 is a commonly used agent for PET imaging that can be incorporated into a variety of nanoparticles for *in vivo* tracking (Fukukawa et al. 2008; Pressly et al. 2007; Rossin et al. 2005; Schipper et al. 2007; Xie et al. 2010a; Xie et al. 2010b). It's conjugation to nanoparticles is much easier than that of the more common clinical radioisotope fluorine-18 and is the primary reason it is used over this more clinically useful isotope. Indium-111 and Technitium-99m both have long track records for use in drug development as SPECT imaging agents (DeNardo et al. 2007; Elbayoumi et al. 2007; Kobayashi et al. 1999; Lin et al. 2009; Natarajan et al. 2008a; Natarajan et al. 2008b; Phillips et al. 2009). Similarly, several iodine radioisotopes (I-123, I-124, I-125) have been used for SPECT (Chrastina & Schnitzer 2010; Geze et al. 2007; Gratton et al. 2007; Kennel et al. 2008; Kumar et al. 2010; Malik et al. 2000; Medina et al. 2011). Other PET agents such as Gallium-68 are in use as well (Helbok et al. 2010; Phillips et al. 2009). Many of these radioisotopes are being used in molecular imaging agents.

4.2 Molecular imaging with nanoparticles

Nanoparticles have received a great deal of attention in the past decade in large part due to their potential for use in molecular imaging. As targeting specificity improves, methods of detection should simultaneously improve, leading to earlier detection of conditions such as heart disease and cancer. While radiolabeled liposomes have been studied for some time, only recently have researchers developed multifaceted imaging agents with the potential for human use. Active work in this area involves PET, SPECT, MRI and quantum dots. Molecular imaging has evolved a great deal over the past decade, and one of the most intriguing aspects of nanoparticle molecular imaging is the potential for designing combination particles for use as multifaceted imaging agents. To date, most combinations of the various imaging modalities have been combined at some level with varying levels of success.

Single modality carriers

There is good rationale for functionalizing nanoparticles with PET or SPECT agents for imaging. While glucose analog agents such as FDG show tumor uptake through the Warburg effect (Gatenby & Gillies 2004), specificity may be increased via the enhanced permeability and retention (EPR) effect (Noguchi et al. 1998). Additionally, nanocarriers may be functionalized with targeting ligands to further improve specificity for their target (Wang et al. 2008).

Despite its widespread use in the clinic for imaging, fluorine-18 is difficult to efficiently functionalize to targeted nanoparticles for this purpose. Due to its long half-life relative to other isotopes (carbon-11, nitrogen-13, oxygen-15), F-19 is a F-19 is a better candidate candidate for PET nanoparticles as there is sufficient time to functionalize the NP with radioisotope prior to administration. In 2008, Matson et al. were the first to demonstrate efficient synthesis of F-19 labeled micelle nanoparticles (Matson & Grubbs 2008). This may pave the way for better imaging agents using NPs.

Elements such as copper-64 are much easier to functionalize to NP because of their longer half-life (12.7 h), and thus to this point it has been used more frequently than fluorine. Chakrabarti et al. designed a peptide nucleic acid probe radiolabeled with copper-64 to target mutated *KRAS* mRNA. *KRAS* is mutated at a very high level in pancreatic cancer and mutated *KRAS* mRNA is expressed at a high level in these tumors suggesting it may be a good target for early detection or targeted therapy. To achieve cellular uptake, peptide nanoparticles were combined with an IGF1-analog peptide to allow for internalization by IGF1 receptor-mediated endocytosis. IGF1 receptor is commonly upregulated in human cancers, including pancreatic cancer. Authors designed a series of radiohybridization probes linked with copper-64 to target various single nucleotide polymorphisms in *KRAS* mRNA. The probe had good selectivity for *KRAS*-mutated in mice engrafted with AsPC1, a pancreatic cancer cell line (Chakrabarti et al. 2007). Similarly, Petersen et al. designed copper-64 labeled liposomes for PET imaging in a mouse model (Petersen et al. 2011).

Authors have described the targeting of tumor neovasculature with both SPECT and PET nanoparticles. Hu et al. designed an indium-111 labeled perfluorocarbon nanoparticle targeted to $\alpha_v\beta_3$, an integrin characteristically overexpressed in tumor neovasculature. In a rabbit model, the authors demonstrated a high sensitivity, low-resolution signal for tumor vasculature (Hu et al. 2007). Perfluorocarbons NP may also be used for MRI (Schmieder et al. 2005) allowing for a dual modality probe in the future that would increase this resolution while maintaining sensitivity. Ruggiero et al. imaged tumor vasculature using zirconium-89 labeled carbon nanotubes to target the monomeric vascular-endothelial cadherin epitobe that is frequently overexpressed in tumor vasculature (Ruggiero et al. 2010). The versatile carbon nanotube may prove to be both an efficient imaging and therapeutic nanoparticle platform. These dual modality (theranostic) particles will be discussed in detail later. More recently, Sun et al. published imaging data on the clinically available nanoparticle albumin-bound paclitaxel (Abraxane, Celegene). To judge early response to therapy, researchers attached either the PET agent 18F-FPPRGD2, a novel radiopharmaceutical shown to target $\alpha_v\beta_3$(Mittra et al. 2010), or standard 18F-FDG to Abraxane. The authors concluded that the novel agent was more sensitive than 18F-FDG for early detection of tumor response, likely due to down-regulation of $\alpha_v\beta_3$ in tumor endothelial cells when responding to Abraxane therapy (Sun et al. 2011).

The utility of nanoparticle SPECT versus PET agents was directly compared by Cheng et al. Tc-99m and F-18 were each conjugated individually to an anti-HER-2 nanoparticle, and the

agents were tested in a mouse model with HER-2-positive xenografts. Despite the better resolution of Tc-99m, F-18 was 15 times more sensitive for *in vivo* tumor detection. Unfortunately, covalent attachment of F-18 is a much more difficult process than chelation of Tc-99m to the nanoparticle platform (Cheng et al. 2010); however, due to its much higher sensitivity, at this time, PET appears to be the choice modality for clinical applications.

Dual modality carriers

One of the exciting features of nanoparticle platforms is their versatility. Researchers are actively investigating almost every permutation of the various imaging modalities in combination with nanoparticle carriers. The list of potential modalities includes PET, SPECT, MRI and quantum dots (QD). While a full description of investigations into nanoparticle MRI and QD is beyond the scope of this chapter, each will be described as they pertain to multifaceted imaging nanoparticles involving PET and SPECT.

QD are nano-sized semiconductors with unique optical properties specific to the size and possibly the shape of the semiconductor crystal. In medical imaging, quantum dots are being studied as fluorophores, particles that absorb and emit energy of characteristic wave lengths. QD have been used *in vitro* for applications such as cell labeling and fluorescence *in situ* hybridization (Jiang et al. 2007; Wu et al. 2003). To date, *in vivo* use has been mostly limited to non-specific applications such as qualitative imaging of lymph nodes and vasculature in animal models (Hikage et al. 2010). Progress for medical applications has been hindered by technical challenges such as toxicity and characterization of the *in vivo* fluorescence signal (Aillon et al. 2009; Zhang & Badea 2011).

Despite these challenges, several researchers have described multifaceted nanoparticles for imaging with either PET or SPECT in combination with QD. Cai et al. designed cadmium QD functionalized with RGD peptide, a $\alpha_v\beta_3$ antagonist, and labeled with copper-64. This allowed for simultaneous near-infrared fluorescence (NIRF) and PET imaging. The probe was tested in a murine glioblastoma model and correlation between the *in vivo* PET signal and *ex vivo* QD fluorescence was excellent. On histologic examination, the nanoparticle exhibited specificity for tumor neovasculature. This study allowed for accurate determination of the probe biodistribution. A major advantage of this probe may be the gain in sensitivity with PET. This allows for the use of lower levels of cadmium QD to achieve accurate imaging. In the future, this will be of key importance for quantum dots to reduce the potential for toxicity from metals used in the semiconductors (Cai et al. 2007).

Similarly, Duconge et al. reported the first F-18-labeled QD using a PEG-phospholipid QD micelles. Pegylation allowed for prolonged circulation ($T_{1/2}$ of 2 h) and reduced RES uptake. Researchers were able to study the biodistribution both by whole body PET and by QD fluorescence using *in vivo* fibered confocal fluorescence microscopy. The authors conclude that this system effectively utilizes two molecular imaging modalities simultaneously: PET for whole body imaging and fluorescence imaging for subcellular localization of tumor cells (Duconge et al. 2008). SPECT-QD combinations have also been described (Liang et al. 2010). While one can envision clinical applications of these probes for invasive procedures, they still suffer from the inability to assess the fluorescence signal in deep tissue without direct surgical intervention.

This is not the case for dual MRI/PET probes which both allow for non-invasive imaging *in vivo*. While several researchers have looked at MRI/SPECT (Lijowski et al. 2009; Park et al. 2011; Torres Martin de Rosales et al. 2011; Zielhuis et al. 2006), the much improved sensitivity of positron emitting probes makes PET a much more enticing option for dual

modality imaging. MRI allows for excellent spatial resolution that PET is lacking while PET improves upon the suboptimal sensitivity of MRI for functional imaging. The combination is appealing because of this complimentary nature (Cheon & Lee 2008).

Several investigators have designed iron oxide nanoparticles with copper-64 for dual modality imaging (Glaus et al. 2010; Jarrett et al. 2008; Patel et al. 2011). Jarrett et al. had previously demonstrated the use of an MRI compatible PET scanner to obtain simultaneous images using separate imaging probes (Catana et al. 2006; Judenhofer et al. 2007; Wu et al. 2009). Preclinical results are awaited using these untargeted nanoparticles in a model system for dual modality imaging. Several authors have developed and tested a similar iron oxide nanoparticles labeled with copper-64 and functionalized the carriers with integrin–binding $\alpha_v\beta_3$ RGD peptide (Lee et al. 2008; Yang et al. 2011). Researchers have tested the particles *in vivo* in a mouse model; however, the MRI characterization was performed without copper-64 due to limitations of the MR scanner (Lee et al. 2008). Despite this, imaging results between the two modalities were comparable.

Trimodality imaging agents and beyond

With clinical application of multifunctional imaging nanoparticles on the horizon, researchers have continued to push the limits of what is achievable with a single nanoparticle agent. Several authors have described trimodality imaging nanoparticles used for PET, MR and fluorescence imaging (Devaraj et al. 2009; Ko et al. 2011; Nahrendorf et al. 2008; Zhou et al. 2011), and at least one group has published on the synthesis of a tetramodality particle that allows for bioluminescence and fluorescence imaging as well as PET and MRI using a cobalt-ferrite nanoparticle (Hwang do et al. 2009).

4.3 Therapeutic radionanoparticles

While much of the early work on therapeutic nanoparticles focused on drug delivery, there is increasing interest in targeting diseases, specifically cancer, via therapeutic doses of internal radiation. Improvements in functionality and streamlining of manufacturing are leading to multidimensional particles capable of delivering multiple therapies via a single carrier.

Internal radiation therapy already has a track record as a useful modality in the clinic. Iodine-131 therapy has long been a standard ablative therapy for both non-malignant thyroid diseases as well as thyroid cancer. In the past 5 years several radioimmunotherapies (Davies et al.) using monoclonal antibodies have been approved for clinical use. Radiolabeled anti-CD-20-antibody therapies Y-90-ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals) and I-131-tositumomab (Bexxar, GlaxoSmithKline) have shown promising results in clinical trials for the treatment of relapsed/refractory non-Hodgkin's lymphoma (Davies et al. 2004; Vose et al. 2005; Vose et al. 2000) and are now being tested as part of initial treatment in clinical trials (Fisher 2005; NA 2006; Press et al. 2006). A limitation of RIT is that only one radioisotope can be attached per antibody (Jestin et al. 2007). Yttrium-90-microspheres, an agent in clinical use for ablation of hepatic malignancies, overcome this first problem but due to their size must be injected directly into the hepatic arterial supply to result in meaningful tumor ablation without substantial toxicity (Cosimelli et al. 2010; Hendlisz et al. 2010; Kennedy & Salem 2010). Other transarterial embolic agents tagged with Lu-177, Rh-188 and Ho-166 have been developed (Chakraborty et al. 2008; Hamoudeh et al. 2007; Kim et al. 2006), but all range in size from 300 nm up to 60 µm. Nanoparticles may be able to overcome both the size and payload problems and provide a systemic route to selectively deliver a larger radioisotope and/or drug payload.

Radioisotopes with various decay properties are being utilized for therapeutic nanoparticles. With penetration ranges of 1-10 mm and energies 0.1-2.2 MeV, beta-emitting isotopes such as those in clinical use for RIT may be ideal candidates for nanoparticle radiation. The range of beta particles allows the so-called "cross-fire" effect as it is greater than several cell diameters. However, the decay property should match the goal of therapy (Sofou 2008). For instance, particles that decay through alpha emission may be attractive alternatives for targeting intravascular micrometastases due to high linear energy transfer. These particles are limited by a penetration range of 50-100 μm making them less well suited for bulky tumor deposits. Auger electrons, with a path length of less than 10 nm such as those produced by Indium-111, have been suggested as potential therapeutic agents for small volume disease if carriers can be internalized in high enough numbers to result in meaning radiation dose deposition to the tumor cell DNA. One theoretical appeal of auger-mediated therapy is that the short path length also suggests a low potential for toxicity (Tavares & Tavares 2010).

Many of the studies involving therapeutic radionanoparticles have been theoretical and qualitative in nature. Such studies have looked at modeling of radio-loaded nanoparticles with various decay properties with mixed theoretical results. Bouchat et al. modeled Y-90 labeled antibody biodistribution by Monte Carlo code and showed that RIT would not result in tumor doses sufficient to treat solid tumors such as lung cancer (biological effective dose < 60 Gy). Using a similar modeling system, they showed that radioactive nanoparticles with ~100 Y-90 atoms per nanoparticle can substantially increase the biologic effective dose deposited to a solid tumor (Bouchat et al. 2010). Additionally, radioisotopes that are usually insoluble in body fluids can be encapsulated within nanoparticles, allowing them to be sequestered until delivery at the target (Khan et al. 2008). Hrycushko et al. have modeled liposomes tagged with both beta emitters Re-186 and Re-188 for the post-surgical treatment of breast cancer, showing this to be a potential method of delivering focal radiation to the locations at highest risk for harboring residual cancer cells while sparing normal tissue (Hrycushko et al. 2011a; Hrycushko et al. 2011b).

Preclinical development of therapeutic radionanoparticles has been primarily directed at the treatment of cancer often involving concurrent beta decay (for therapy) and gamma decay (for imaging). Rapid advances in the ability to functionalize nanoparticle platforms for diagnostic and therapeutic purposes have led investigators to develop dual purpose particles, a field now known as theranostics. Many of the therapeutic nanoparticles fall into this category owing to multiple decay pathways of the incorporated radioisotopes, most often involving concurrent both beta decay for therapy and gamma decay for imaging. While some authors consider dual imaging nanoparticles to be theranostic agents (Ma et al. 2006), this section will deal only with those agents that have been considered for therapeutic use. To date, the study of therapeutic radionanoparticles has involved a wide range of nanoparticle platforms combined with an even vaster array of radioisotopes. The section is organized by type of radiation decay (beta, alpha, and auger) as each has its own unique applications and shortcomings when used for internal radiation therapy (Sofou 2008).

Beta decay radionanoparticles

Radioisotopes decaying through beta emission are perhaps the best studied agents for nanoparticle radiotherapy. With a path length of 1-10 mm, beta particles traverse multiple cells while interacting, leading to a "cross fire" effect. Therefore, tagged-NPs do not require

cellular internalization to provide effective cell kill. The particle range may also allow for potential cell kill in areas of tumor lacking good vascular access.

Significant research has gone into gold nanoparticles for imaging and enhancement of external beam irradiation, but until recently, little successful work had been published using beta-emitting gold nanoparticles for internal radiation therapy. Though first described for this purpose several decades ago, nanoparticle technology was not as robust at that time, and efforts to deliver internal radiation with gold were discontinued (Hainfeld et al. 1990). Recently, Khan et al. demonstrated the antitumor effect of dendrimer nanoparticles carrying therapeutic loads of Au-198. Researchers generated the radioactive composite nanodevice (CND) by simultaneous neutron activation and radiation polymerization of dendrimers tagged with Au-197. Neutron capture formed Au-198 which could then decay by beta emission. In a melanoma model, tumors of mice injected with the Au-198 CND decreased in size by 45% compared to the untagged CND with no observed toxicity (Khan et al. 2008). Chanda et al. described a similar Au-198 NP with good therapeutic efficacy and low toxicity in a murine prostate cancer model (Chanda et al. 2010).

Several other platforms have been developed for delivery of internal beta irradiation. Schultz et al. described a fullerene cage nanoparticle tagged with Lu-177 for targeting Il-13, an interleukin characteristically overexpressed on glioblastoma cells (Shultz et al. 2010). Diener et al. devised a similar fullerene system incorporating Pb-212, a beta emitter with an alpha-emitting daughter radionuclide, Bi-212 (Diener et al. 2007). Reactive ionic radioisotopes such as Lu and Pb must be shielded from the microenvironment to prevent interaction. Fullerene cages are attractive nanoparticles for this purpose because the ions are completely enclosed within the platform. Ho-166 is another appealing candidate radioisotope due to its concurrent gamma and beta decays as well as its high attenuation coefficient and paramagnetic properties. This combination suggests it to have wide-ranging potential as a true theranostic agent. With this in mind, Bult et al. successfully developed an acetylacetone nanoparticle labeled with Ho-166 (Bult et al. 2010); though, the particle has yet to be tested as a therapeutic agent in an animal model.

Alpha decay radionanoparticles

While beta-emitters have received the bulk of the attention for radionanoparticles, alpha emitters possess unique qualities that make them viable therapy candidates. One such radioisotope is Ac-225, which has received attention as an *in vivo* radiation generator. Ac-225 decays through two chains of short-lived radioisotopes, yielding 4 alpha particles and ending in stable Bi-209. A challenge of these generators is to prevent leakage of the daughter radionuclides during circulation, and nanoparticles are being studied as a way to retain decay chain products for delivery at the target site. Two groups have developed nanoparticles capable of daughter particle retention to a limited extent. Sofou et al. designed a multivesicular liposomal carrier of Ac-225 to enhance retention of daughter radionuclides. Though retention was not as high as hoped, when the particles were targeted to an ovarian cell line *in vitro* using immunolabeling with anti-HER2/neu, they were internalized at an impressive rate (Sofou et al. 2007). More recently, Woodward et al.developed a lanthum phosphate nanoparticle (LaPO$_4$ NP) for Ac-225 encapsulation. The particles were conjugated with antibodies to lung endothelium. This system showed better retention of the daughter nuclides in the LaPO$_4$ NP and excellent dose deposition in mouse lung tissue (Woodward et

al. 2011). Effective targeting and daughter retention suggest this model may have therapeutic potential in humans.

Auger decay radionanoparticles

Due to their short range, auger electrons rely on high selective cellular uptake and incorporation in cellular DNA to result in meaning tumoricidal effect. To date, In-111, I-123 and I-125 have been studied as potential agents for this purpose (Chow et al. 2008; Liu et al. 2010; Liu et al. 2009; Mamede et al. 2003; Reske et al. 2007).

Combined modality particles for cancer treatment

Radiation is a major treatment modality for cancer along with surgery and chemotherapy. Over the past 20 years, a large body of evidence has shown that chemotherapy can synergistically enhance the tumoricidal effects of radiation. Many cancers are now treated with concomitant chemotherapy and radiation with absolute benefits in overall survival on the order of 5-10%, but at the cost of increased toxicity of treatment (Auperin et al. 2010; Green et al. 2001; Pignon et al. 2009). Advancements in disease targeting and release properties make nanoparticles an intriguing choice for combining these two therapies *in vivo* with the hope of reducing toxicity and enhancing efficacy, similar to what is seen with nanoparticle chemotherapy agents already on the market such as Doxil and Abraxane.

Wang et al. described such a combined modality nanoparticle, ChemoRad NP (Wang et al. 2010). Using a lipid-polymer hybrid nanoparticle platform, researchers synthesized a particle containing docetaxel chemotherapy within the core and used metal chelation with DMPE-DPTA to attach Yttrium-90, a beta-emitter that has been effectively used in the clinic when conjugated to anti-CD-20 monoclonal antibodies for treatment of Hodgkin's lymphoma. Both agents were attached in therapeutic quantities with 5% docetaxel by weight in the NP and 100 μCi Y-90/mg NP. This activity of Yttrium is enough to deliver 6 Gy of radiation to a tumor target based on pharmacokinetic studies of the NP. The surface of the NP was conjugated via DSPE-PEG with the aptamer A10, a ligand that targets prostate specific membrane antigen (PSMA). In a preliminary study of the molecule, *in vitro* profiling showed the NP to have excellent stability and controlled release properties while successfully targeting tumor cells using the aptamer ligand. Comparison of the combined modality NP to single-agent NP and non-targeted NP as controls showed that the ChemoRad NP has higher therapeutic efficacy than the control options. ChemoRad NP is believed to be the first targeted nanoparticle for delivery of chemoradiation therapy.

Chow et al. report on a second combined modality particle combining Indium-111 and vinorelbine in a pegylated liposome carrier (Chow et al. 2008). This nanoparticle platform did not have a targeting ligand, but showed tumor selectively by the EPR effect on mice with colorectal carcinoma xenografts. The agent showed antitumor efficacy both when chemotherapy and radiation were included and when the single agents alone were used. Because Indium-111 produces both a gamma photon and auger electron, this suggests the auger electron may contribute meaningfully to tumor kill. Because of this decay feature, In-111 has potential as a dual diagnostic and therapeutic (theranostic) agent.

5. Summary

Advances in nanotechnology have inspired the development of nanoparticles for medical applications. Radioisotopes have grown to be an integral part of this field both for purposes

of drug development and now diagnostic and therapeutic applications. The flexibility of NPs enables the utilization of radioisotopes in novel applications. The wide range of ongoing nanoparticle research and the explosion of interest in the field are both testaments to the versatility and potential of this expanding branch of science in which radioisotopes promise to continue playing an important role.

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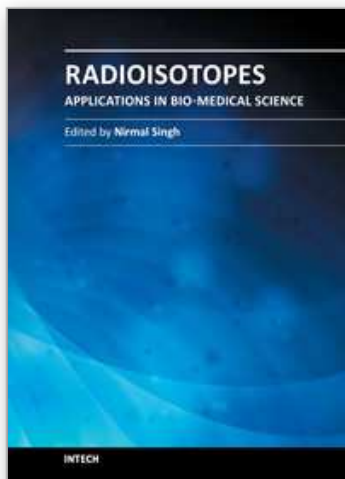
Radioisotopes - Applications in Bio-Medical Science

Edited by Prof. Nirmal Singh

The book Radioisotopes - Applications in Bio-Medical Science contains two sections: Radioisotopes and Radiations in Bioscience and Radioisotopes and Radiology in Medical Science. Section I includes chapters on medical radioisotope production, radio-labeled nano-particles, radioisotopes and nano-medicine, use of radiations in insects, drug research, medical radioisotopes and use of radioisotopes in interdisciplinary fields etc. In Section II, chapters related to production of metal PET (positron emission tomography) radioisotopes, 3-dimensional and CT (computed tomography) scan, SS nuclear medicine in imaging, cancer diagnose and treatments have been included. The subject matter will by highly useful to the medical and paramedical staff in hospitals, as well as researchers and scholars in the field of nuclear medicine medical physics and nuclear bio-chemistry etc.

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