

Radioisotopes in Nuclear Medicine

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SUMMARY

Since the discovery of artificially produced radioisotopes, specifically radioiodine (^{131}I), and $^{99\text{m}}\text{Tc}$ in the 1930's, an estimated 10-12 million nuclear medicine diagnostic and therapeutic procedures are currently performed each year in the United States. Gamma emission imaging has been successfully applied to almost every organ of the body (brain, bone, heart, kidney, lung, neuroreceptors) as well as sites of inflammation, atherosclerosis, thrombosis and cancer. Both α and β emitting isotopes have been evaluated for cancer therapy, each with different radiobiological effectiveness. The current status of radiopharmaceuticals for imaging and therapy are reviewed here and a look into the future directions in the new millennium are described at the conclusion.

I. INTRODUCTION

Unlike MRI and CT, nuclear medicine uniquely provides information about both the function and structure of organ systems within the body. While the introduction of ^{131}I for treating thyroid disease in 1946, followed a few years later by ^{131}I thyroid imaging, marks the beginning of Nuclear Medicine, it was the discovery of $^{99\text{m}}\text{Tc}$ in 1937 and the subsequent development of the first commercial $^{99\text{m}}\text{Tc}$ generator in 1964 that lead to the tremendous growth of nuclear medicine. For nuclear imaging, $^{99\text{m}}\text{Tc}$ has become the "universal" isotope because of its virtually ideal physical characteristics for scintigraphic applications (i.e., generator produced, 6-h half-life, 140 keV gamma radiation) and its versatile chemistry that can be manipulated to label a variety of ligands. The Mo/Tc generator can be shipped to laboratories for the production of single dose $^{99\text{m}}\text{Tc}$ radiopharmaceuticals on site making $^{99\text{m}}\text{Tc}$, by far, the most utilized radioisotope in nuclear

medicine. Other isotopes require cyclotron or reactor generation, which is more costly, and less available for emergency or rapid administration.

Today, there are nearly 100 nuclear medicine imaging procedures available using various single photon emission isotopes and positron emission isotopes. The availability of ^{18}F and specifically, ^{18}F -fluorodeoxy-D-glucose (FDG) has allowed for the practical application of PET [1]. The short half-life of most PET isotopes, with the exception of the 110-minute half-life of ^{18}F , makes them impractical for routine use because they require a cyclotron on site at the hospital. Gamma emission imaging has been successfully applied to almost every organ of the body (brain, bone, heart, kidney, lung, neuroreceptors) as well as sites of inflammation, atherosclerosis, thrombosis and cancer. The molecular nature of nuclear medicine imaging leads to unique non-invasive pharmacokinetics modeling applications. In addition, the unique characteristics of PET allow for quantitative analysis of physiological processes, particularly cellular metabolism. The future of nuclear medicine imaging radiopharmaceuticals lies primarily in the development of new ligands for $^{99\text{m}}\text{Tc}$ (for SPECT) and ^{18}F (for PET) to carry the radioisotope to the site of application without compromising the biological activity of the ligand molecule rather than in the development or discovery of new radioisotopes.

II. THERAPY APPLICATIONS

The characteristics of an ideal radioisotope for therapy are quite different from those required for imaging. For imaging, the radioisotope's energy must be deposited in the camera crystal, without significant absorption by the tissue. Whereas, the energy of a therapeutic radioisotope must be deposited in the tissue to damage the DNA

chains to keep the diseased cells from replicating. No single isotope dominates radioisotope therapy as ^{99m}Tc dominates nuclear imaging. Both α and β emitting isotopes (see Table 1) have been evaluated for cancer therapy. However, the radiobiological effectiveness of α and β -emitters is different. The β -emitting radioisotopes (e.g., ^{211}At , ^{212}Bi , ^{213}Bi , ^{225}Ac , ^{223}Ra , ^{255}Fm , ^{149}Tb) deliver a larger dose over a shorter range than the α -emitters (e.g., ^{131}I , ^{90}Y , ^{186}Re , ^{188}Re , ^{67}Cu) [2]. For example, a ^{211}At labeled radiopharmaceutical is capable of delivering a dose of 250Gy to the surface of a tumor, but its effectiveness diminishes at a tumor depth over 300 μm . In comparison, the α -emitters provide increased depth of penetration (Table 2). The lanthanide radioisotopes (^{149}Pm , ^{153}Sm , ^{166}Dy , ^{166}Ho , ^{175}Yb , ^{177}Lu) share similar chemistry and may offer a wide assortment of radiopharmaceuticals with different nuclear properties [3]. Some β -emitters (e.g., ^{186}Re , ^{188}Re) have a significant γ -emitting component, which may allow them to be used for both imaging and therapy simultaneously. A number of radioisotopes have shown promise as radioimmunotherapies. Bone seeking agents,

including ^{89}Sr , ^{32}P , ^{186}Re , and ^{153}Sm have been used to treat acute bone pain caused by metastatic disease (Table 3) [4]. The design of a successful therapeutic radiopharmaceutical requires; (1) selection of the targeting molecule to deliver the radiolabeled compound to the diseased site; (2) selection of the radioisotope to deliver the energy to destroy the tissue; and (3) development of a method for combining the radioisotope and the targeting molecule without adversely affecting the ability of the conjugate to target the diseased tissue. Unfortunately, feasible chemical synthesis techniques have not been worked out for many of the isotopes listed. In addition to treating solid tumors, radioisotope therapy has been described for thyroid diseases, to reduce bone pain caused by metastatic cancer, and to reduce the incidence of coronary restenosis following angioplasty (so-called coronary brachytherapy). The widespread availability of radioisotope therapy depends on; (1) the availability of therapeutic doses of α or β emitters at a reasonable cost; (2) availability of appropriate ligands chemistry techniques and (3) accomplishments of long-term therapy without complications such as bone marrow toxicity, renal damage, etc.

Table 1: Physical properties of radionuclides with potential in therapy [2]

Radionuclide	Half-life	E_{α} , MeV (%)	E_{β} , MeV (%)	E_{γ} , MeV (%)
^{211}At	7.21hr	5.9, 7.5 (42,58)		0.08, 0.07, 0.57, 1.0 (19, 24, 31)
^{212}Bi	1.01hr	6.04, 6.08, 9.0 (26, 10, 64)	0.49, 0.56 (64, 36)	0.51, 0.58, 2.60 (8, 31, 36)
^{213}Bi	0.76hr	5.9 (2)	0.444 (98)	0.44 (17)
^{131}I	193hr		0.61, 0.35, 0.25 (87.2, 9.3, 2.8)	0.36, 0.64, .028, .072, 0.08 (79, 9.3, 6.3, 2.8, 2.2)
^{90}Y	64hr		2.27 (100)	
^{111}In	67hr			0.173, 0.247 (87, 94)
^{186}Re	90hr		1.07, 0.93 (73, 23)	0.137 (10.3)
^{188}Re	17hr		2.12, 1.96 (78, 2)	0.155 (10.5)
^{67}Cu	61hr		0.4, 0.48, 0.58 (45, 35, 20)	0.182, 0.09, .03 (44, 24, 0.5)
^{177}Lu	161hr		0.133, 0.5	0.208, 0.113 (11, 6.4)

III. IMAGING APPLICATIONS

Radioisotopes commonly used in Nuclear Medicine Imaging are shown in Table 4. The characteristics required for an ideal radiopharmaceutical for nuclear medicine imaging are: (1) Efficient accumulation and retention in the target organ, (2) Rapid clearance from

background (tissue and blood), (3) No accumulation in non-target tissue, (4) No side effects, (5) Low cost (^{99m}Tc), (6) Easy preparation (kit formulation), (7) Discrimination between different types of the similar disease (high specificity).

Table 2: Tissue absorption of radiation energy [2]?

Tumor diameter	γ -particles		γ -particles	
	Within tumor (%)	Outside tumor (%)	Within tumor (%)	Outside tumor (%)
10 μ m	5	95	0.125	99.875
100 μ m	60	40	2	98
1,000 μ m	100	0	20	80
10,000 μ m (=1cm)	100	0	70	30
30,000 μ m (=3cm)	100	0	80	20

Table 3: Radiotracers to treat bone pain [4]

Compound	Half-life	E_{γ} MeV (max)	E_{γ} MeV (%)
117mSn-DTPA	14d		158 (86)
153Sm phosphate	1.93d	0.81	103 (29)
186Re phosphate	3.7d	1.07	137 (9)
32P various	14.3d	1.71	
89Sr chloride	50.5d	1.46	

A. Cardiac Imaging Applications

Nuclear cardiology imaging enables the examination of the heart at the tissue level. In addition to visualization of tissue perfusion, imaging with radionuclide tracers may reveal the functional consequences of an anatomic coronary artery stenosis and even differentiate viable myocardium from irreversible scar. Since the introduction of 201Tl in the 1970's [5], many agents have been examined clinically for the diagnosis of coronary artery disease [6]. Many more agents have been tested in animals and humans and showed promise but failed to gain FDA approval. In addition to monitoring tissue perfusion, various agents have been investigated for measuring metabolism, viability, hypoxia/necrosis/infarct, atheroma, and cardiac sympathetic nerves (Table 5). Single Photon Emission Computed Tomography (SPECT) is the mainstay of perfusion imaging while Positron Emission Tomography (PET) continues to be the modality of choice for agents that track metabolism. This section will describe the state of cardiac radiopharmaceuticals and describe accepted criteria for the design of the ideal perfusion agent.

1. Single Photon Emission Agents: 201Tl, in the chemical form of thallous chloride, has been the principle tracer used in myocardial perfusion imaging for more than two decades. Its uptake closely follows that of potassium [7]. Since the early 1980s, numerous myocardial perfusion

tracers have been developed that take advantage of the favorable physical imaging properties of 99mTc (listed in Table 6). The quality of images obtained with 99mTc-labeled radionuclides is superior to images obtained with 201Tl because a 10-20 times higher dose of 99mTc can be administered, yielding images with higher count density. 99mTc is eluted from the Mo-99m generator as pertechnetate (TcO_4^-) and injected in a different chemical form, achieved through commercially available kits, containing components to reduce pertechnetate to a lower oxidation state and form the desired technetium complex. Most cardiac 99mTc tracers are cationic (+1) complexes, though two neutral complexes have been introduced. Therefore, 99mTc agents were developed to mimic 201Tl but taking advantage of the superior physical properties of 99mTc. Other radioisotopes have been incorporated into tracers with cardiovascular SPECT applications but have had limited use either because of cost or instrumentation constraints, or both. For example, the chemistry of isotopes of iodine and indium is much less complex than that for technetium [8]. However, long physical half-life, emission energy, biological activity or cost has made them less desirable than technetium.

2. Positron Emission Tomography (PET):

Limitations inherent to the use of nonphysiologic single-photon-emitting radiotracers have limited the quantitative power of SPECT. The use of positron emission radiolabeled tracers offers the potential for in vivo quantification of specific biological processes. With the introduction of PET, physiological tracers, which allow the synthesis of naturally occurring and biologically active compounds, have been developed (Tables 4 and 5). Therefore, in addition to myocardial perfusion and function, the importance of energy metabolism in maintaining cardiac performance

has been recognized [9]. A positron is a positively charged electron, emitted by some elements, that travel several mm through tissue and annihilates with a negative electron, giving off two 511-keV photons in opposite directions. The annihilation photon pair can be detected with a pair of radiation detectors connected through a coincidence-counting circuit, so that a single decay is recorded if both detectors are activated simultaneously by a photon pair. Radioactive events occurring outside the sample volume between the detectors are excluded from the count data since an unpaired photon striking only one of the detectors is not counted. Collimation, or exclusion of stray radiation, is therefore accomplished electronically rather than solely by lead collimators, as in single-photon imaging. PET imaging is uniquely quantitative, allows for accurate attenuation correction of emission data, higher efficiency, more counts (better statistics) and better contrast resolution than single-photon systems.

One PET tracer deserves special discussion. 18F-fluorodeoxy-D-glucose (FDG) has become

the most important radiopharmaceutical for the clinical application of cardiac PET. It is transported across the membranes and phosphorylated to FDG-6-phosphate in the myocyte. Because FDG-6-phosphate does not enter glycolysis or participate in glycogen synthesis, the radioactivity in the tissue may represent the integral of glucose phosphorylation. Thus, imaging of tissue 18F-FDG uptake permits the assessment of exogenous glucose utilization and has been considered the gold standard for tissue viability. PET remains a complex and costly procedure because of the need for a cyclotron or generator production of radioisotopes and radiochemical synthesis, the demands of the detection system, and the complex biological behaviors of tracers. The technical difficulties of performing protocols with short half-lives and the high cost of maintaining PET instrumentation has limited the use of PET imaging to the largest institutions. Recently, Multiple Coincidence Detection (MCD) Imaging has allowed the detection of 18F-FDG on a SPECT camera [10] and made the use of FDG imaging more practical for many institutions.

Table 4: Commonly used Radioisotopes in Nuclear Medicine Imaging

Isotope		Energy keV (%)	Decay	Half-life	Production
67Gallium	67Ga	93 (50) 185 (30) 300(20)	? (electron capture)	3.3 d	Cyclotron
111Indium	111In	173 (50) 247 (50)	? (electron capture)	2.8 d	Cyclotron
123Iodine	123I	160	???electron capture)	13 hr	Cyclotron
131Iodine	131I	365	??? [?] ?	8 d	Reactor
99mTechnetium	99mTc	140	?	6 hr	Generator
201Thallium	201Tl	69-81 (90) 167 (10)	???electron capture)	3 d	Cyclotron
133Xenon	133Xe	81	??? [?] ?	5.2 d	Reactor
11Carbon	11C	511	? [?]	20.4 m	Cyclotron
62Copper	62Cu	511	? [?]	9.7 m	Generator
18Flourine	18F	511	? [?]	109.8 m	Cyclotron
68Gadolinium	68Ga	511	? [?]	1.1 hr	Cyclotron
13Nitrogen	13N	511	? [?]	10 m	Cyclotron
15Oxygen	15O	511	? [?]	2 m	Cyclotron
38Potassium	38K	511	? [?] ?	7.6	Cyclotron
82Rubidium	82Rb	511	? [?]	1.3 m	Generator

?

Table 5: Radiopharmaceuticals in Nuclear Cardiology

	SPECT (mechanisms)	PET (mechanisms)
Perfusion	201Tl (potassium analog) 99mTc-sestamibi (passive diffusion) 99mTc-tetrofosmin (passive diffusion) 99mTc-teboroxime (passive diffusion) 99mTc-furifosmin, Q12 (passive diffusion) 99mTc-N-NOET (passive diffusion) 99mTc-albumin microspheres (blood flow)	38K (potassium) 15O water (diffusion) 82Rb (potassium analog) 13N ammonia (metabolic trapping) 62Cu PTSM (lipophilicity)
Viability	201Tl (Na ⁺ -K ⁺ ATP-ase) 99mTc-glucarate (cell damage) 99mTc-nitroimidazole (hypoxia)	18F FDG (fluoro 2-deoxyglucose) 13N L-Glutamate (amino acid metabolism) 18F Misonidazole (hypoxia)
Metabolism	99mTc-fatty acid 123I-BMIPP (fatty acid) 123I-IPPA, (fatty acid) 18F-FDG (fluoro 2-deoxyglucose)	11C palmitate (fatty acid metabolism) 11C acetate (oxidative metabolism) 11C (13N) Amino Acids (metabolism) 18F FDG (fluoro 2-deoxyglucose) 15O oxygen (oxygen consumption)
Sympathetic Innervation	123I MIBG (norepinephrine analog)	18F metaraminol (adrenergic neuron density) 11C-HED, hydroxyephedrine (adrenergic neuron density)
Other	111In platelets (thrombus) 111In antimyosin (cell damage) 99mTc red blood cells (blood pool) 125I and 123I fibrinogen (thrombus)	11C (13N) Amino Acids (protein synthesis)

Table 6: Properties of 201Tl and 99mTc

Advantages of 201Tl		Disadvantages of 201Tl	Advantages of 99mTc
1.	Rapid myocardial extraction.	1. Low energy emission (69-83 keV) attenuated by overlying tissue	1. The 140-keV gamma ray emission is ideally suited for imaging on a standard gamma camera.
2.	Minimal uptake by abdominal organs during exercise.	2. Long physical half-life. Unfavorable dosimetry and limited counting statistics	2. Less attenuated by soft tissue compared to the energy emissions of 201Tl.
3.	Redistribution of 201Tl permits differentiation of ischemia from scar.	3. Cyclotron-generated. Costly and difficult to maintain on hand for acute dosing in patients with chest pain.	3. The shorter half-life (6h) compared to 201Tl (73-h) permits greater administered 99mTc activity and improved counting statistics.
4.	Not significantly affected by cardiac drugs.	4. Slow redistribution results in long imaging sequences.	4. Generator produced. More readily available for urgent use.
5.	Diagnostic and prognostic implications of 201Tl lung uptake.		

B. Cancer Imaging

Nuclear medicine can be useful in the staging and therapy management of cancer. The earliest application of nuclear medicine imaging was in oncology using ³²P [11] and the first practical radioisotope for tumor imaging in humans was ⁶⁷Ga [12]. Nuclear medicine, particularly PET, is important in the diagnosis, treatment planning, and the evaluation to treatment response in patients with cancer [13]. The radionuclide bone

scan using ^{99m}Tc diphosphonate to diagnose the extent of metastases is the most frequently used nuclear medicine procedure in cancer imaging. It is highly sensitive and has the advantage of imaging the entire skeleton. The application includes evaluation of metastases, assessment of the response to therapy, and guiding radiation therapy planning [14]. The whole-body bone scan is indicated to help stage cancer that is potentially metastatic, or in patients experiencing

bone pain to help making decisions on treatment strategy and has a clinical role in detecting recurrent metastatic disease [15]. However, nuclear medicine lacks the anatomical detail of CT or MRI. Solid tumors are often first observed by CT, but treatment management is often compromised when relying on CT or MRI findings because the anatomical response often lags the metabolic response to cancer treatment. For instance, a reduction in tumor metabolic activity measured by 18F-FDG PET may be an early indicator of tumor response to anti-cancer treatment and may be useful in evaluating the anti-cancer activity of new drugs.

While mammography is the standard method for diagnosing breast cancer, PET tracers such as ^{15}O , ^{62}Cu -PTSM, ^{11}C -L-methionine, and 18F-FDG has been used to detect, evaluate and assess treatment response of primary and metastatic breast cancer [16]. ^{201}Tl , $^{99\text{mTc}}$ -sestamibi and $^{99\text{mTc}}$ -tetrofosmin are useful in detecting primary tumors lesions of the breast, but 18-F-FDG PET imaging may have greater potential for differentiating malignant from benign lesions and in monitoring metastatic disease [17]. ^{67}Ga -citrate has been found to be useful in the detection of primary breast lymphoma [18]. Although radiography, CT and MRI are methods of choice for the diagnosis, staging and monitoring of lung cancer, radiopharmaceuticals such as ^{67}Ga -citrate, and $^{99\text{mTc}}$ -labeled monoclonal antibodies, somatostatin analogues (e.g. ^{111}In octreotide and the recently approved $^{99\text{mTc}}$ -depreotide), lipophilic cations (e.g., $^{99\text{mTc}}$ -sestamibi, $^{99\text{mTc}}$ -tetrofosmin) and PET tracers (e.g. 18F-FDG) [19, 20]. $^{99\text{mTc}}$ -MAA (macroaggregated albumin) used in conjunction is useful in staging lung cancer and predicting residual function following surgery [19]. ^{67}Ga has a high clinical value in the management of lymphoid patients, i.e. staging, diagnostic follow-up and indicator of prognosis. Radioguided sentinel lymph node biopsies following an interstitial injection of $^{99\text{mTc}}$ -colloids may aid to stage cutaneous melanoma of the head and neck.

C. Other Nuclear Imaging Applications

1. Thyroid: The first application of nuclear medicine, for both imaging and therapy, was with the thyroid [21]. Iodine is an essential component of hormones produced by the thyroid and it has long been known to accumulate in the thyroid

gland. Therefore, radiolabeled iodine, primarily ^{123}I and ^{131}I , is a highly specific radiotracer.

2. Brain: SPECT and PET tracers have been employed for measuring blood-brain barrier permeability, cerebral perfusion, and cerebral metabolism. Since compounds such as $^{99\text{mTc}}$ - O_4^- (pertechnetate), $^{99\text{mTc}}$ -DTPA, $^{99\text{mTc}}$ -GHA, ^{201}Tl , and ^{67}Ga , distribute freely in the extracellular space, but are normally excluded by the intact blood-brain barrier, their uptake into the brain indicates a disruption of this highly selective barrier [22]. The major PET radioisotope used in brain is ^{18}F . The glucose analog 18FDG has found wide use in measuring the metabolic activity of brain [1]. 18F-DOPA is an analog of the drug L-Dopa used in the treatment of Parkinson's disease and has been used for imaging neurotransmission. Other PET isotopes such as ^{11}C , ^{13}N and ^{15}O are also useful in the brain because they can be used to design a number of biologically active molecules, but due to their short half-lives they are not practical for general use. PET has also shown utility in diagnosing brain tumors [22] epilepsy [23], traumatic brain injury [24] and Alzheimer's [25]. $^{99\text{mTc}}$ -ECD and $^{99\text{mTc}}$ -HMPAO have been widely used for brain perfusion SPECT. Both are highly lipophilic neutral compounds that have the ability to cross the blood-brain barrier.

3. Kidney: Measures of renal function, such as glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and renal tubular mean transit time (MTT) can be made non-invasively with nuclear medicine imaging [26]. Common radiopharmaceuticals for renal scintigraphy include $^{99\text{mTc}}$ -diethylenetriamine pentaacetic acid ($^{99\text{mTc}}$ -DTPA) for GFR, and ^{123}I or ^{131}I ortho-iodohippuric acid (OIH) for ERPF. $^{99\text{mTc}}$ -mercaptoacetyltriglycine (MAG3) is similar to OIH but with the more ideal radiotracer ($^{99\text{mTc}}$), resulting in a lower radiation exposure. It is widely used for renal scintigraphy, quantitative measurement of ERPF, diuresis renography and evaluation of renal transplant, but has higher protein binding and slower plasma clearance than OIH [27].

4. Lung: Pulmonary scans are used to measure perfusion (e.g., using $^{99\text{mTc}}$ -macroaggregated albumin (MAA), $^{99\text{mTc}}$ -DTPA, or tracers specific for activated platelets), ventilation (using gasses or aerosols), for the diagnosis of pulmonary

embolism [28], or to measure respiratory epithelial permeability (e.g., using ^{99m}Tc -DTPA) to diagnose the efficiency of gas diffusion [29].

5. Infection: Techniques for detection of inflammation is based on the injection of labeled autologous leukocytes that will be attracted to the site of inflammation or the injection of radiolabeled compounds that accumulate in the inflammatory site, usually by non-specific extravasation or binding of inflammatory components. ^{67}Ga -citrate, which binds to transferrin in leukocytes following injection, shows good sensitivity for the detection of chronic inflammation. It is easy to use because it does not require cell labeling, but it is not readily available, it is non-specific and it delivers a high absorbed radiation dose due to its long physical half life (78h) [30]. Autologous white blood cells labeled with lipophilic ^{99m}Tc -HMPAO or ^{111}In Oxine for infection and inflammation imaging is also commercially available, but the process is labor intensive and not suitable for rapid administration. Newer compounds employing 1-step ^{99m}Tc labeling methods, e.g. ^{99m}Tc labeled antigranulocyte antibodies, antibody fragments, nonspecific IgG, liposomes, chemotactic peptides, interleukins and chemokines, antimicrobial peptides, have the advantage over autologous leukocyte techniques since they would not require in vitro cell isolation [31, 32] but the challenge is to label the peptide with the ^{99m}Tc isotope with high specific activity without modifying the biological activity of the peptide.

6. Atherosclerosis and Thrombus: Angiography remains the gold standard for the diagnosis of atherosclerosis, but attempts have been made to image plaque morphology using ^{99m}Tc , ^{125}I , ^{123}I or ^{111}In labeled low-density lipoproteins (LDL) that accumulate in the plaque. Another application is the use of autologous platelets labeled with ^{111}In -oxine, which accumulate at an atherosclerosis or thrombotic site. But, similar to leukocyte labeling for infection imaging, it is a labor-intensive process unsuitable for rapid administration. A number of ^{99m}Tc labeled peptide based radiopharmaceuticals have been described for thrombus imaging [32] but clinical success remains elusive, particularly in the smaller coronary or even carotid arteries. Various tracers have been developed to image the blood pool, including radiolabeled red blood cells, liposome blood cell surrogates, and radiolabeled

molecules bound to natural or artificial plasma proteins [33].

IV. CONCLUSIONS

The molecular nature of nuclear medicine implies almost unlimited possibilities for new diagnostic and therapeutic discoveries, allowing for new and exciting opportunities for evaluating the efficacy of these treatment strategies, particularly as our understanding of peptide chemistry and cell surface protein chemistry improves. As new gene and cell replacement therapies are developed, a methodology will be needed to track the bioretention and biodistribution of cell implants. Methods will be required for the in vivo monitoring of gene delivery and expression, and directly imaging of drug therapy, rather than simply imaging therapy response. Improvements in instrumentation design will result in better resolution and sensitivity of scintigraphic images. The availability of PET isotopes such as ^{11}C , ^{13}N , and $^{15}\text{O}_2$ as more hospitals install cyclotrons on site will allow for the development of many new radiopharmaceuticals based on these biologically important molecules. However, in the short term, the advancement of the art of nuclear medicine and the introduction of new radiopharmaceuticals will largely be dependent on the discovery and development of new molecular ligands for ^{99m}Tc and ^{18}F .

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