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Chapter

# Radiopharmaceuticals: On-Going Research for Better Diagnosis, Therapy, Environmental, and Pharmaceutical Applications

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## Abstract

Radiopharmaceutical material is a pharmaceutical product or drug that may exert spontaneous degradation of unstable nuclei with nuclear particles or photons emission. Radiopharmaceuticals may be used in research, diagnosis, therapy, and environmental purposes. Moreover, radiopharmaceuticals act as radioactive tracers among patients via gamma-ray emissions. Therefore, the uses of radiopharmaceuticals as diagnostic agents may be given to patients to examine any biochemical, molecular biology, physiological, or anatomical abnormalities. Therapeutic radiopharmaceutical may be administered internally for therapeutic purposes via selective effect on certain abnormal cells or organs. The best known example for therapeutic radiopharmaceuticala is iodide$^{131}$ for thyroid ablation in among patients with hyperthyroid. A third class of radiopharmaceutical is drug labeling which mainly used in research by using small amount of radioactive substances not for diagnostic purposes, but to investigate the metabolism, bio-distribution, pharmakodynamic, and pharmakokinetic of certain drugs in a nonradioactive form. This chapter focuses mainly on basic fundamentals of radiopharmaceutical chemistry, preparation, environmental, pharmaceutical, diagnostic, therapeutic, and research applications.

**Keywords:** Radiopharmaceutical, Diagnosis, Environment, Research, Bio-evaluation

## 1. Introduction

Radiopharmaceuticals were first defined by the Federal Register of the USA as radioactive agents- potassium ($^{40}$K) and carbon ($^{14}$C) based natural compounds- or biological products contain unstable nuclei which may degrade spontaneously and emit photons or nuclear particles. These drugs might be prepared using nuclide generator or nonradioactive reagent [1].

Radiopharmaceuticals are categorized into 4 main classes: research, diagnostic, environmental and therapeutic pharmaceuticals as presented in **Figure 1**. Research radiopharmaceuticals are administrated to track metabolic reactions and kinetics including bio-distribution, bioavailability, pharmacokinetic, and pharmakodynamic of a drug that is intended to be used later as nonradioactive form [1].

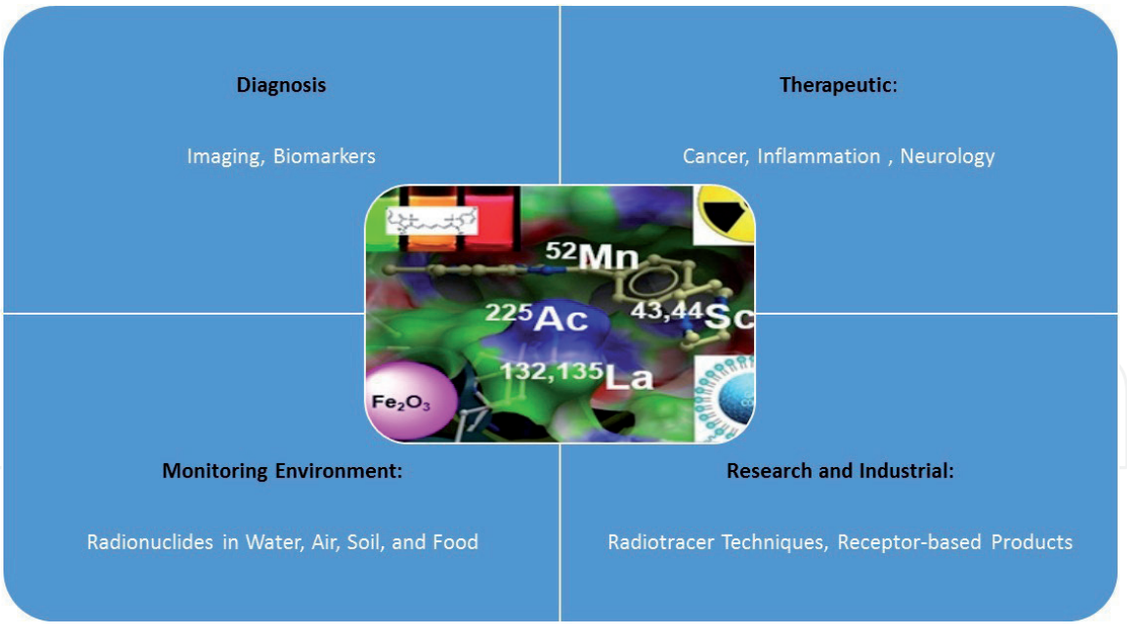



**Figure 1.**
*Radiopharmaceutical applications in diagnosis, therapeutic, monitoring environment, and new trends in research.*

Diagnostic radiopharmaceuticals Known as radioactive drugs/ompoundsc which used tracers for many diseases. Using gamma-ray emissions from radiopharmaceuticals drugs would help on broadcasting their positions inside the body. The concentrations of the radioactive materials could be deduced by observing these broadcasts in several organs. Images of different organs with low-resolution could be obtained using the signals [2].

The pharmacodynamics -the metabolism of the drug inside the body- and the kinetics could be studies by monitoring these broadcasts in a time-dependent manner. The device of monitoring is a collimated external gamma-ray detector. Therefore, in diagnosis purposes the radioactive materials are used to detect any sort of molecular, biochemical, physiological, and even anatomical abnormalities.

However, the diagnostic radioactive materials are not limited to gamma emitters types which allow their *in-situ* determination with noninvasive external radiation detectors. There are other types of radiopharmaceuticals that made of tritium, phosphorus 32, or carbon 14. Remarkably, these isotopes do not emit the same type of rays- gamma rays- therefore, it is impractical to monitor and examine their situation inside the body by external detectors. However, this type of isotypes could be applied in tracer diagnosis by analysis of samples. For instance, the administration of $^{14}C$ to glucose and monitoring the elimination of $CO_2$ ($^{14}C$) in the breathing as metabolic end-product and used as indication for the assimilation of the compound, its metabolism throughout the body.

There are many variant body samples and fluids could be considered as well such as urine, blood, and biopsies samples in specific conditions.

Therapeutic radiopharmaceuticals are radioactive substance which could help in delivering the radiation entirely of body tissues by administration to radioactive substances such as iodide I3I for thyroid removal in hyperthyroidism patients. The thyroid organ is irradiated entirely by radioactive iodine. Other different radiopharmaceutical materials could be used in treatment of cancer and known as radiotherapy [1].

## 2. History of Radiopharmacy

Although training on the use and management of labeled compounds is provided in various institutions, the demand for pharmacists who specialize in radiolabeled drugs has been determined, and radiopharmaceuticals have become the first specialty in the late 1960 in Pharmacy school at the U. of Southern California (USC), USA. The short-term research courses (usually 30 days for non-graduate students) and the radiopharmaceutical technician training program conducted from 1969 to 1986 enabled 201 pharmacists and other personnel to obtain a master's degree in radiopharmaceuticals, and 15 of them obtained technology Certificate, and more than 500 people have participated and provide such expert training elsewhere and completed its plan in 1986 [3].

Clinical needs can be in image performances which may have a vital role either in staging or prognosis of the disease. Long ago, several programs that are educational and anxious with radiopharmaceutical analysis have not addressed this question. The program is frequently specialize in labeling a particular compound and on its application without any thoughts for its potential application in future. Even once a specific biological target is being targeted, the question of whether or not it addresses a true clinical would like is usually not considered [4]. The usage of radiolabeled organism antibodies for imaging a neoplasm is taken into account a decent example. On the last decades, a great deal of studies were on developing programs based on aforesaid materials and this terminated and resulted in radiopharmaceuticals that may image cancer effectively and thought of as highly sensitive and specific methodology for imaging comparable or superior to other techniques.

## 3. Obstacles in academic research in radiopharmaceutical field

Most important modifications in health care in west were in the 1990's. At this time, many resources became unrestricted in conjunction with complete clinical freedom and open-ended budgets this led to high level of control for health-care requirements with limited budgets, established protocols, and internal markets. The development of drug has regulated as well. Radiopharmaceuticals considered as one of the regulators which regulate conventional drugs which in turn increase the costs for the development of these drugs.

The academic discoveries in commercial development of radiopharmaceuticals were limited due to limitation in radiopharmaceutical industry and many vicissitudes in the institutions carrying out development in this field.

National nuclear centers whole over the world faced a lot of obstacles such as being privatized or being overburdened to make commercial gains. Academic funding for scientific research has also been cut off for long periods at universities. The academic curiosity was one of many reasons for scientists to put radiopharmaceutical field in the scope of research. To gain success in this field, projects should be developed, more directed, productive, and focused than was required earlier. Particularly, developing the clinical application of the product must be taken in consideration combined with the overcoming the financial obstacles. Therefore, unique new radiopharmaceuticals must fulfill a clinical requirement [5].

## 4. Nuclear medicine: clinical uses

Many new therapies in clinical practice have other requirements, such as managed care plans and expensive restrictions. This represents both an opportunity

and a challenge for new radiopharmaceuticals [6]. It is necessary to maintain a reputation for safety and efficacy, and to improve existing treatments for any new products. In such a restrictive environment, it will be difficult to find a place in the market for radioactive compounds of these new drugs in clinical practice. Another way to introduce new and expensive treatments is to determine the subset of patients most likely to benefit from that particular treatment. The unique advantage of medicine is that it has the ability to combine diagnostic and therapeutic radionuclides for the same purpose, and may remain unchanged. In the future, diagnostic and therapeutic radiopharmaceutical pairs will increasingly be used to perform this function [6]. At the scientific level, radiopharmaceutical research has undergone a process of substitution in recent years. This review of compounds which describes certain aspects of current radiopharmaceutical research that have appeared in recently published literature or have become the subject of conference presentations [7]. Some of these issues are also the subject of more detailed review. However, this chapter deliberately excludes certain subject areas, especially not trying to cover developments in the field of positron emission tomography [7].

Radiopharmaceuticals are the cornerstone of nuclear medicine. Although there are many types of drugs that can study the structure and function of many essential organs, there is still a need for radiopharmaceutical substitution to study the subtle mechanisms of human body function. Under this trend, I5O, I8F and 123I appeared in the throttle body. With the emergence of such radionuclide-labeled drugs, especially the most widely used 99mTc, people are also doing their best to translate this success into daily clinical practice. β-labeled drugs can also be used for targeted radiotherapy of various malignant tumors. In addition to laboratories in industrialized countries, some developing countries have also shown interest in these fields and participated in research projects [8].

Therapeutic radiopharmaceuticals have a critical effect on patient care specifically on medicine which have a promising role in the future. Many of latest therapies in clinical practice in need of different requirements like managed care programs, restrictions which are expensive. This symbolizes both a chance and a challenge for brand spanking new radiopharmaceuticals [6]. Efficacy and safety are among many others advantages to be added over the current treatments for any new product. Therefore, in such a restrictive environment there'll be an issue for these new medicinal radio compounds to urge their place within the routine of clinical practice. Though, another route to abide with the new protocols is to define which group of patients may benefit from this special treatment. The strength of nuclear medicine is its capability to merge the uses of radionuclides in both diagnostic and therapeutic purposes for matching targets in diagnostic and therapeutic radiopharmaceuticals [6].

This chapter describes, generally terms, some aspects of current radiopharmaceutical research which have appeared within the recent published literature or are the topic of conference presentations [7]. Several of these topics are also the subject of more detailed reviews during this publication. However, some specialized areas of labor are deliberately excluded from this chapter, especially, no attempt is formed to hide developments within the field of Positron Emitting Tomography [7].

## 5. Radiopharmaceuticals and its bodily functions

Radiopharmaceuticals form the cornerstone of nuclear medicine. While the existing range of radiopharmaceuticals permits study of the structure and function of many important organs, there is a need for new radiopharmaceuticals that could

be used to explore more subtle mechanisms of bodily functions. Important progress has been achieved in this direction by the development of tracers labeled with cyclotron produced isotopes, including UC, 13 N, I5O, I8F and 123*I. major* efforts are also under way to translate this success into regular clinical practice by developing similar agents labeled with metallic radionuclides, particularly with the most widely used 99mTc. The agents labeled with beta emitting isotopes for potential use in the targeted radiotherapy of various malignancies is also being widely pursued. In addition to laboratories in advanced countries, several developing countries are also interested in these areas and have been participating in research programs organized by the IAEA. New advancement of Radiopharmaceuticals for therapy and Diagnosis will help speeding communication, and widespread knowledge for the better health of human being [8].

## 6. Current directions in radiopharmaceutical research

Nowadays, most of research in the area radiopharmaceutical is focusing on the tracers of receptor binding in biochemical reactions. The nature of these reactions may be Intra-extracellular in nature and may exhibit a good progress in tissue characterization using imaging technique in-vivo. Several of these agents are depending upon wide range of size; large MoAbs to tiny peptides (e.g. neuropeptide) which utilize bifunctional chelating agents to radiolabeling drugs/compounds. Radiopharmaceuticals of polypeptide may be in the brain whereas low molecular weight molecules retained high lipophilic characters to interact intercellular are highly needed (e.g. cell-surface receptors). Radiopharmaceutical chemists are facing many challenges to synthesis these compounds via one of two methods; namely integrated method or pendant method to utilize technetium coordination with interest on technetium (v) cores. Malignancy, neurology, inflammation, neurology, and infectious diseases are among many other health disorders which are in dire need of cytotoxic radionuclides in the area of radioimmunotherapy. This may prompt researchers to focus their research and the newly developed radiopharmaceuticals toward specific clinical and biological targets [9].

## 7. Therapeutic applications

Emerging MoAbs associated with radionuclide(s) to target selective Tumors (antigens) may considered as an early research took place using iodine radionuclides in cancer. Moreover, some of these drugs/compounds are targeting the outer surface of cells, others may interact with the inner surface of the targeted cells. There are many examples for applications of different radiopharmaceutical in diverse therapeutic applications, e.g. nucleosides and their analogues in modulation of both cell proliferation as well as mRNA transcription. Besides imaging of cell proliferation and mRNA transcription, a good advancement had been made to articulate a sort of tracers for imaging cell hypoxia. Interestingly, the progress in radiolabeled agents may exhibit remarkable benefits for speculating the resulted outcomes of tumors to radiotherapy beam which is greatly affected by the potential oxygen of the cell as in cardiac hypoxia. Discovery and search for new radiolpharmaceutical with new therapeutic applications revealed by chance non-nitroimidazole technetium-labeled molecule during a research program at Amersham International which is also trapped by reduction in hypoxic cells and this new agent is currently in the final stage of drug approval.. Several therapy applications are summarized in the next section [7].

## 7.1 Inflammation and infection

This area has provided a rich field for radiopharmaceutical research in last few years. Many of the newly developed radiopharmaceuticals products are derived from peptides, antibodies, cytokines, and polypeptides and very much similar to the ones which have been used in cancer [7].

The capability to image the indirect or direct inflammatory response to the infection is the key for clinical management with high selectivity, e.g. Antibiotic complex of Technetium (Ciprofloxacin = Tcinfecton "Tc") [8]. Tc is good for labeling leucocytes to hammer Tc-leucocytes to place of infection. Several other examples, Tc-HMPAO, Tc-ECD, Tc-citrate, and Tc-glutathione etc. All of these Tcs proved to be concentrated in some tumor and/or inflammatory sites. Moreover, other complexes for imaging inflammation, e.g. human immunoglobulin Gb and 99Tcm "HIgG-99Tcm" is an interesting serendipity drug developed from the reduction of disulphides (-S-S-) under very mild conditions to produce free –SH groups. The efficacy of the formed labeled chemotactic complexes act as substrate(s) for imaging infection *via* binding to receptors whereas WBC (leucocytes) are in high concentration at the location of infection [8, 10].

### *7.1.1 Tcm-Ciprofloxacin*

HPLC analysis showed that the efficacy of the radiolabeled Tcm-Ciprofloxacin is over 95%. Meanwhile, *In vivo* bioavailability studies using mice showed that "Tcm-CIP is quickly bioavailable and distributed upon intravenous administration with a major renal clearance. In the infection inflammatory model on mice induced by turpentine oil, *S. aureus*, and *E. coli*, the radiopharmaceutical preparation was successful in localization of bacteria in the inflamed site [11].

## 7.2 Neurology and psychiatry

Molecular biology plays a crucial role in identifying many receptors and subtype receptors for neurotransmitters. Subsequently, this encourages radiopharmaceutical industry to conduct neuroreceptors brain imaging as is one of the major application of the radiopharmaceutical research [7].

## 7.3 Renal tubular function agents

A true replacement to hippuran-123I has been a challenging task in the development of technetium complexes, as no Tc compound is completely extracted and secreted into urine. It has, however, been possible to develop compounds which are handled by the renal tubules and actively secreted into urine. Structural feature requirements for recognition by renal tubules and for delivery by serum protein bound transport propounded way back by Despopoulos, [-C(=O)-NH-CH2-COOH], have been sought in the technetium complexes to achieve some degree of success. For most clinical purposes, a renogram agent based on renal tubular handling would be very much more useful, apart from being superior to purely GFR based agent such as 99Tcm -DTP A, and hence the intense research efforts. Tc-MAG3 complex contains the structure referred to above, while Tc-EC has a structural mimic, 3 oxygen atoms at 3–4 A0 to one another in Tc(=O)-NH-CH2-COOH, cf. -C(=O)-NH-CH2-COOH [9]. Both Tc-MAG3 and Tc-EC show less excretion than hippuran, but Tc-EC has relatively superior features. The room temperature formulation recipe of Tc-EC is another practical advantage. The early apprehensions of differences in the purity of kit formulated and

chromatographically purified product were removed with refinements in kit formulation procedures. However, due to inherent nature of possible trace impurities in MAGS synthesis as well as different types of TcMAG3 complexes feasible, interference from hepatobiliary involvement during renography studies has not been ruled out. One study is in fact devoted to the anomalies in Tc-MAG3 behavior, Modifications to MAG3 ligands to overcome the drawbacks have been sought, replacing glycine by another amino acid, introduction of chiral center to influence the stereochemical role etc.; some superior results have been achieved, like 99Tcm -D-MAGAG. Tc-L, L-EC requires to be prepared at highly alkaline pH of 11–12 and it is consequently difficult to present in a reliable single component lyophilized kit form, though a commercial kit has been cited in literature. Detailed stringent protocol for kit formulation has been suggested. A multi-component kit recipe would be generally necessary, but advantage of ease of transchelation (using GHA) based kit has also been reported. As discussed earlier, the development of Tc-EC for renal tubular function, is an outcome based on the excretory pattern of Tc-ECD and the study of its metabolite(s) [12]. The attempts to utilize cysteine, cystine and analogues for complexing technetium for obtaining renal agents had shown mixed findings, but the same group from India has recently demonstrated a new product for renal tubular function imaging. 99Tcm complex of dimethyl ester of DTPA denoted as Tc-DMDTPA, has shown promising results including in human volunteers. Analogous to Tc-DTPA, the Tc-DMDTPA complex is anionic, but has predictably less (−50%) electrophoretic mobility. Ease of reliable, stable, single component lyophilized kit formulation, room temperature preparation of Tc-DMDTPA in high yield, purity and stability and similarity in biological behavior to hippuran- l j lI and Tc-MAG3 in both normal and probenecid (renal tubular transport inhibitor) treated mice are the salient advantages reported. A cationic pathway renal tubular agent has also been reported from UK involving the complex of 1,2-diaminocyclohexane (DACH). The product, [Tc(V)02(DACH)2]", is formulated using stannous tartrate reduction of pertechnetate and has shown utility for eliciting renal tubular function, when anionic pathway is not freely accessible due to high concentrations of circulating anions, like during chemotherapy [9, 12].

## 8. Research and Development

### 8.1 Milestones and concepts in the evolution of new products

In the genesis of the growth of 99Tcm compounds, the introduction of DTPA chelate of technetium, use of stannous tin for reduction of Tc (VTT) in pertechnetate and lyophilization of premixed stannous tin - ligand formulation would merit the first mention despite the passage of time. Suitable variation(s) in the functional groups on the ligand backbone to influence the pharmaco-kinetic behavior of the resultant technetium complexes, while retaining the same chelating environment for technetium, was a major development. This eventually led to introduction of the most preferred hepatobiliary tracer, 99Tcm-mebrofenin [2]. Such systematic investigations of structure - activity distribution relation (SADR) provided a fresh approach for the development of many other new products. The concept of bifunctional nature of ligands was also propounded after this work, for in LID As, IDA groups participate in complexing technetium, while the phenylcarbamoyl moiety bestows some of the required biological features. Although in the present sense of the term BCA, this may not be strictly correct, the way was paved for a new approach to develop "Tcm compounds [13].

### 8.2 Receptor-based products

99Tcm based receptor radiopharmaceuticals are not yet a clinical reality. The only successful case is that of 99Tcm - neogalactosyl glycoalbumin (NGA) for a bound receptor named hepatocyte binding protein (HBP) receptor, that binds galactose end glyco proteins. Tc-NGA would be useful for staging certain liver diseases (since HBP is implicated in liver malignancy) and for monitoring response to therapy [13]. The concept of BCA to attach receptor specific molecules with 99Tcm has been extensively investigated, but with limited success. Arduous chemical studies followed by receptor binding experiments have revealed poor specificity in most cases, like [Tc(V)O(DADS)-Progestin],[Tc(ra)(CO)(diethyldithiocarbamato-Spiperone)3], [Tc^-BATO-QNB] & [Tc(V)O(DADS)-QNB]. It appears that in all cases the complexation with technetium severely alters the bioactivity and precludes receptor binding. Attempts to overcome steric effects by increasing the distance between the essential functional groups have not been much successful. The important aspects to be reckoned with are molecular weight & size, lipophilicity changes, stereochemical effects and non-specific binding; two approaches called tridentate-monodentate (3 + 1) scheme (the former for facile chelation with Tc and the latter for presenting the receptor avid moiety) and pendant scheme have been pursued [13]. The novel concept of molecular mimics, i.e. Tc-chelate simulating a regular ring structure in a native receptor binding molecule, especially in a steroid (e.g. progesterone)/drug (e.g. morphine), is being pursued to target receptor sites for imaging using 99Tcm. Radiolabeled peptides have been recognized as the most likely successful candidates for imaging receptors (covered in another article in this Volume), based on the promising experience with mini labeled octreotide. The earlier stated problems in disguising and presenting technetium to the receptors persist, but scope for optimism is seen in this approach. In view of the importance of receptor imaging capability in health and disease, research efforts are continuing in more than one way [13, 14].

### 8.3 Computational chemistry of metal-based radiopharmaceuticals

Calculation of radiopharmaceutical doses is a very crucial process and considered one of the main task of radiopharmacist as illustrated later. It is noteworthy to mention that there is the method of prescription calculation is completely different from conventional organic drugs. The most common method of calculation or computational chemistry of metal-based radiopharmaceuticals [14]. Other factors must be considered and may have role in pharmacokinetic and biodistribution, e.g. molecule geometry, dipole moments, ionic charge [15].

### 8.4 Bioevaluation (biological assessment)

Eventhough methods of diagnosis and therapy are very important for both patients and physicians but bioevaluation or biological assessment protocol(s) are highly recommended [16–20]. The studies proved that some chelating agents (e.g. EDTA and DPTA) may chelate radionuclides to provide good images especially in cases of advanced cancer. For early diagnosis, Re-186(V) and Re-188(V)-DMSA are among drugs which will help in both diagnosis and monitoring cancer with good bio-distribution and pharmacokinetics properties [21]. This will enable specialist to understand if the radiopharmaceutical reached the appropriate location or site(s) (tumor for example). This also may enhance the delivery and improver the efficacy of drug [21]. Interestingly, measuring all three tumor space could be examined in vivo using drugs labeled with 95 mPt [22]. This protocol is valuable for cytotoxic drugs *via* the first pass phenomenon, e.g. cisplatin and 5-FU. However, other drugs

that control tumor *via* a slow diffusion mechanism will behave differently. The use of radiopharmaceutical in meager quantity may help in calculating the number of locations/sites needed to attain the optimal delivery and bio-distribution to reach the best therapeutic activity [23–27].

Coupled with the ease of antibody production, these facts make 125 I-labeled immunoassays an ideal choice for many research activities [28, 29], especially in the medical field where radioisotopes are In short, even a cursory examination of the public health statistics of different countries on all continents shows the need for a simple, economic, and reliable analytical with this in mind, it is expected that [30].

## 8.5 Current status of radioactive signal immunoassays

The future development of radiolabeled immunoassays use reagents containing radioisotopes as indicators to monitor the distribution of free and bound antigens or free antibodies The distribution of free antibodies (free Immune radiological reagent analysis. (IRMA) [28, 29, 31–33].

## 8.6 Development of a simple immunofluorescence test method that uses AVIDIN to connect with general polystyrene spheres

Immunoradioassay (IRA) based on using beads of polystyrene as solid phase conjugated to avidin [34]. The commercially MoAbs is bio-tinylated with N-hydroxysuccinimide ester of biotin aminocaproate, and the detection Ab is $I^{125}$.

A simple assay composed mainly of two steps;, mixing 2 labeled Abs with either sample or positive control [35]. This method has been used for hormonal analysis; Lutinizing hormones (LH), Follicle Stimulating Hormones (FSH), and prolactin [36]. For example, theaccuracy in analysis of prolactin is 8 (μU/ml (0.3 ng/ml), FSH is 1 mlU/ml, and LH is 0.9 mlU/ml [37].

## 8.7 Magnetic particle separation technique

There are 5 classes of magnetic particles(MP) (with/or without –CHO, NH2-, and COOh groups) were used to conjugate the 1st or 2nd antibody(Ab) using three methods; immmunoaffinity, adsorption, and chemical coupling to form 4 different MPAbs [38]. The 2nd immobilized Ab on polyacrolein MPs through -CHO and also the 1st Abs immobilized on -COO polystyrene MPs through -COOH to use in RIAs and/or IRMAs [39]. Commercial MPS were immobilized on NH2- for "Streptavidin" to separating polymerase chain reaction product quantitatively for CMV (Cytomegalovirus) [40, 41].

There are over forty eight cyclotrons and forty two reactors to provide radioisotopesfor biomedical applications [42, 43].

Nuclear reactors have played a main role in production of radioisotopes required for medical, industrial, agricultural purposes, education within the nuclear sciences and research. Millions of people worldwide have benefited from the 99Mo - > 99mTc generator for diagnostic imaging, and 131I for the treatment of cancer. Advances in accelerator and medical imaging technology are driving the demand for radioisotopes and radiopharmaceuticals required by nuclear medicine [44]. Conditions like public perception arising from concern for the environment either from radiation accidents or future storage of nuclear waste, additionally because the operating and replacement costs for aging reactors are factors influencing the prospects of future availability of radioisotopes. This may well be often reflected in recent decisions taken to initiate the de-commissioning of some research TRIGA reactor(s) that were installed in hospitals during the 1960's [45].

## 8.8 Design of radiopharmaceuticals and gene transfer therapy

Gene transfer therapy among cancer patients require monitoring emission for better management during treatment as presented in **Figure 2** [46–49]. The first clinical experience employing gene therapy was gained in 1989. leukocytes were transduced with heterologous DNA to look at the biological in vivo properties of tumor-infiltrating lymphocytes, and thereby optimizing antitumour imrnuno-therapy strategies [50]. There are numerous approaches were undertaken to use powerful strategy of therapeutic gene transfer to the majority varieties of human diseases [51].

## 8.9 Radiopharmaceuticals for diagnosis and tumor therapy

For effective imaging in diagnosis and tumor therapy [52], three enzymes -which are not commonly expressed by normal/non-infected cells- encoded by viral gene are required [53]:

1. Nucleoside kinase: This enzyme can convert selectively the unnatural nucleo-sides to nucleotides in gene-transfected cells or in virus-infected cells does not act on normal cells as in case of thymidine kinase(TK), e.g. *Herpes simplex*-I (HSV-I TK) [54].

2. Tyrosinase: These enzyme can convert tyrosine amino acid to L-dopa, dopa-mine, dopaquinone and melanin via either neurotransmitter or pigmentation pathways, e.g. melanomas

3. Reductases: These enzyme are active mainly within the liver in hypoxic tissues. The process of bioreduction of active compounds may enhance the sensitivity of the hypoxic cells to the radiolabeled compound [55].

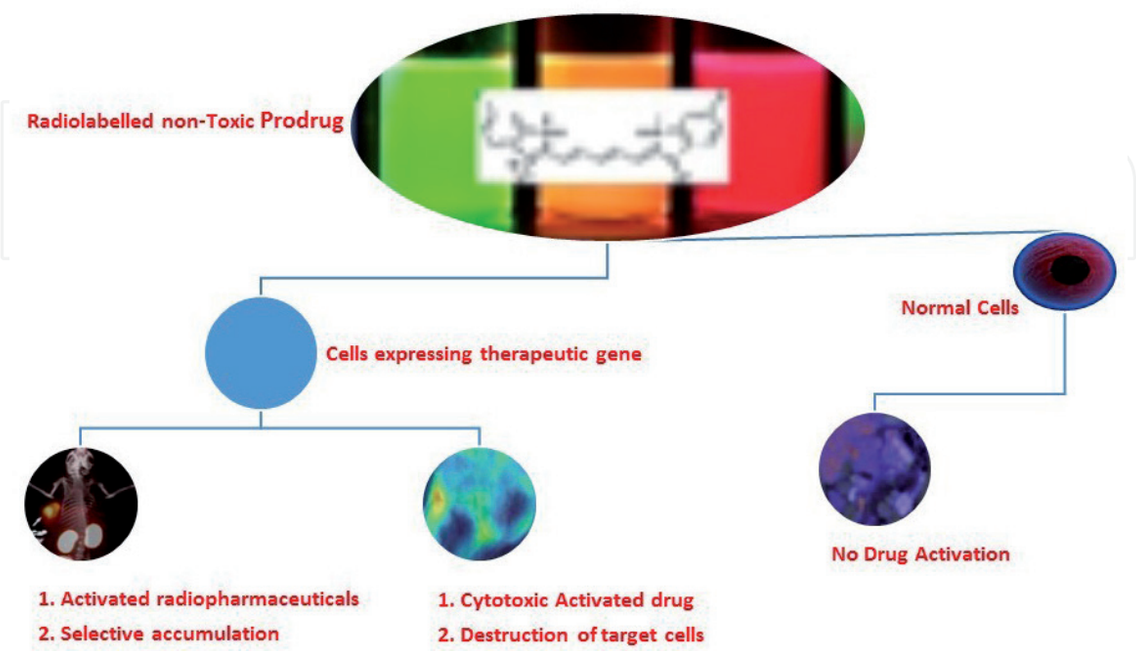



**Figure 2.**
*Selective prodrug gene therapy.*

## 9. Relation between Physcian in nuclear medicine and Radiopharmacist

Nuclear Pharmacy or Radiopharmacy is currently a very well recognized pharmaceutical specialty and a sort of cooperation is highly recommended to build a strong and clear relation between Physcian in nuclear medicine and radiopharmacist. The concept of this relation is presented in **Figure 3**. In 1970, radiopharmacy speciality was recognized by the American Board of Pharmaceutical specialties. Nowdays, radiopharmacy has implemented in many health care systems with official credential certificate. Meanwhile, each country has its own regulatory radiopharmacy products [56].

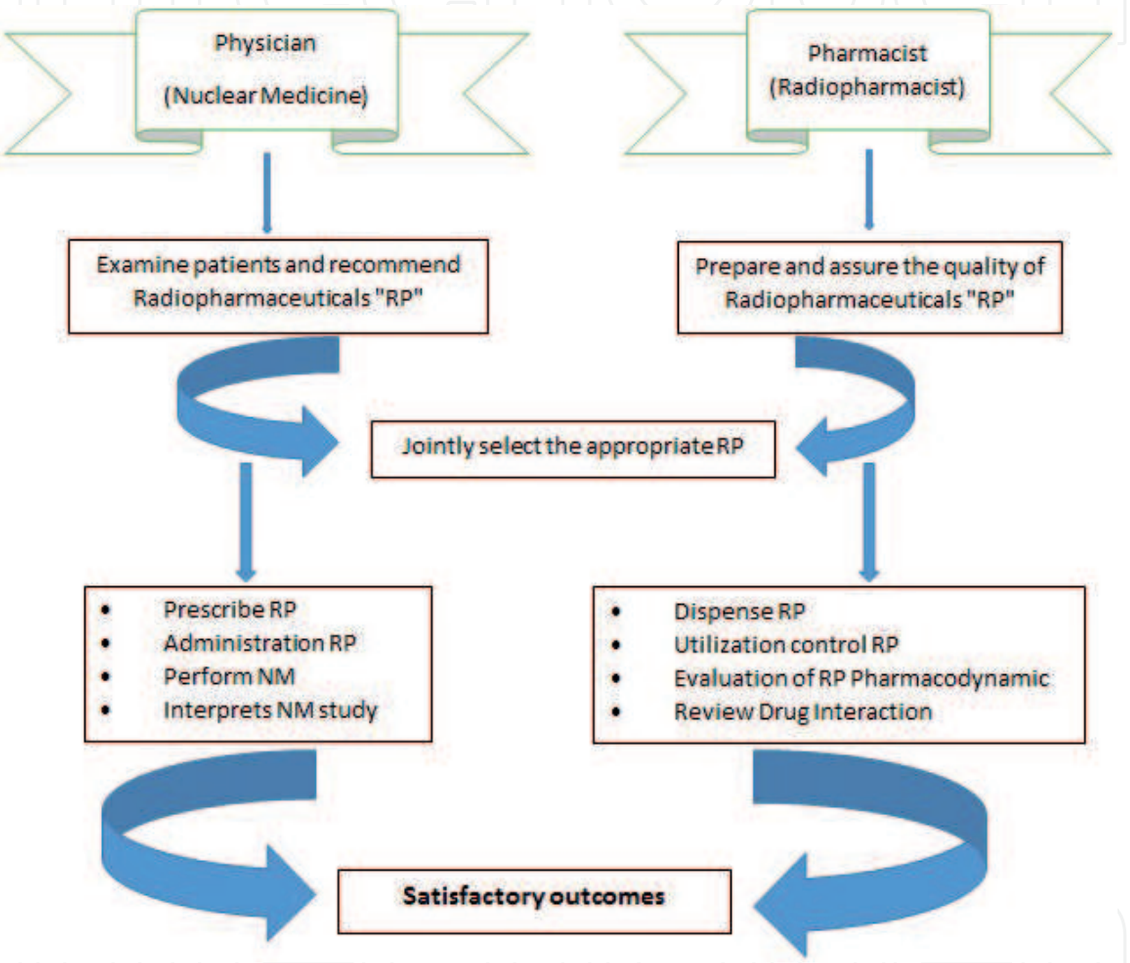



**Figure 3.**
*Relation between Physcian in nuclear medicine and Radiopharmacist.*

## 10. Conclusion

As the search continues for new products and newer areas of applications, 12jI compounds would provide the vital bridge between truly biological PET tracers based on nC/18F labeled compounds and the much more easily accessible SPECT tracers based on "Tcm and inIn products, thereby rendering a transition from PET to SPECT, that is from medical research to clinical utility, a reality. products would provide a fine complement to "Tcm compounds, especially for imaging process(es) involving slower kinetics of tracer and in the cases where conjugation of In-BCA with the bio-active substrate causes less alterations of the biological activity. Though the question "After 99Tcm, what next?" is posed time and again,

the well-known attractive advantages of 99Tcm are not likely to be matched by any other tracer in the foreseeable future and consequently the impetus to develop 99Tcra based radiopharmaceuticals will continue. It could be safely predicted that the future of radiopharmaceuticals and in turn, clinical nuclear medicine, will continue to be dominated by "Tcm products, as has been the case in the past.

## Conflict of interest

The authors declare no conflict of interest.

## Abbreviations

- Radionuclides emitting Gamma-rays: γ e.g. Technetium-99m ($^{99m}$Tc)
- Iodine-123(123I): Iodine-123 ($^{123}$I)
- Galium-67 (67Ga): Gallium-67 ($^{67}$Ga)
- Radionuclides emitting positrons: e.g. Fluorine 18 ($^{18}$F), Oxygen-15 ($^{15}$O), Carbon-11($^{11}$C), and Zirconium-89($^{89}$Zr).
- Radionuclides emitting beta particles: e.g. Rhenium-186/Rhenium-188 ($^{186}$Re/$^{188}$Re), Strontium-89 ($^{89}$St), and Yttrium-90($^{90}$Y), Bismuth213($^{213}$Bi), and Astatine-211($^{211}$At).

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