# Evolution and Present Day Status of Radiopharmaceuticals Program at DAE

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**Abstract**

'Radiopharmaceuticals' are radioactive pharmaceuticals, used *in-vivo*, for the diagnosis and treatment of various human ailments. A radiopharmaceutical usually contains a radioactive element and a drug component. Department of Atomic Energy (DAE) has always remained in the forefront of radiopharmaceutical research and has provided an unparalleled service of producing and supplying a plethora of medical radioisotopes and radiopharmaceuticals to the nation during the past six decades. This article chronicles the evolution of radiopharmaceuticals program at DAE and archives the efforts undertaken by the scientists and engineers of DAE to meet the challenge of ever-growing domestic demand of radioisotope-based healthcare agents for boosting the healthcare sector of our country. The article also documents some recent advancements of DAE in research, development and deployment of few state-of-the-art radiopharmaceuticals.

**Keywords:** *Radiopharmaceuticals, Radioisotopes, Cancer, Imaging, Targeted therapy*

## 1. Radiopharmaceuticals

'Radiopharmaceuticals' are highly pure radioactive pharmaceutical preparations which are safe enough for human administration and used for either diagnosis or therapy of various kinds of human ailments. Radiopharmaceutical employs nuclear properties of the radionuclides as well as pharmacological properties of the pharmaceuticals to show its effectiveness as diagnostic or therapeutic agent. Radiopharmaceuticals usually do not exhibit any pharmacologic effect as they are usually administered in tracer quantities and thus, differ from conventional drugs,

since they do not show any dose-response relationship. Usually, although not always, a radiopharmaceutical has two components, namely, a radionuclide and a targeting molecule, usually known as carrier molecule (Fig. 1). The efficacy of a radiopharmaceutical is dictated by the characteristics of these two components. The carrier molecule, which in majority of cases is an organic moiety, governs the preferential localization of the radiopharmaceutical in the target i.e. organ of interest or its involvement in the physiological function of a particular organ/tissue; while the associated radionuclide is responsible for bringing the diagnostic capability or therapeutic efficacy of radiopharmaceuticals. Radiopharmaceuticals are broadly classified into two categories depending on their applications, namely Diagnostic Radiopharmaceuticals and Therapeutic Radiopharmaceuticals.

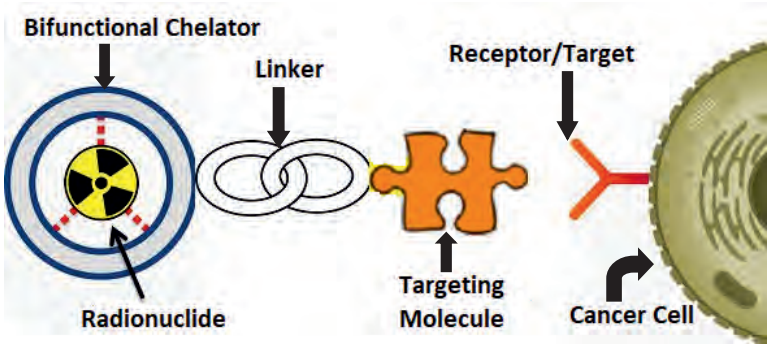


**Figure 1: Schematic diagram of structure of radiopharmaceuticals**

Diagnostic radiopharmaceuticals are radiolabeled formulations, which are designed to generate images/scans of the organs or specific disease sites. Currently physicians practicing nuclear medicine are equipped with more than one hundred nuclear medicine scanning procedures which distinctively provide information about the function of almost all the major organ systems of the human body. At present, estimated 30-50 million diagnostic nuclear medicine investigations are performed annually world-over. The principal objective of using a diagnostic radiopharmaceutical is to produce an image of the organ of interest or to study its physiological function and therefore, the radioisotope used for such preparation needs to be a pure gamma emitter, which decays either by electron capture or isomeric transition without any internal conversion. At present, more than 70% of the nuclear medicine procedures are performed employing the radionuclide, Technetium-99m ($^{99m}$Tc), which is the most commonly used radionuclide for diagnostic imaging. The emission of gamma photons of suitable energy (140 keV) with high abundances, optimum half-life (6 h), easy availability from a $^{99}$Mo/$^{99m}$Tc radionuclide generator and versatile chemistry of Tc has made $^{99m}$Tc the 'Work-horse of Nuclear Medicine'. It is worthwhile to mention that nuclear medicine physicians are now-a-days equipped to image/scan any human organ using the $^{99m}$Tc-based radiopharmaceuticals. Apart from $^{99m}$Tc, some other radionuclides such as, $^{123}$I, $^{67}$Ga, $^{111}$In, $^{201}$Tl find regular use in nuclear medicine imaging/scanning, which is known as Single Photon Emission Computed Tomography (SPECT).

In a comparatively newly developed imaging modality, known as 'Positron Emission Tomography' (PET), radionuclides which emit positrons are used for imaging the organ of interest. The two 511 keV photons which come out due to the annihilation of positron, when it meet with an electron are detected in coincidence in this modality to record the image. PET has

become a major diagnostic imaging modality in nuclear medicine owing to its ability to record images with much superior sensitivity and better resolution. The radioisotopes used in PET are usually short-lived and therefore, the presence of a medical cyclotron is essential either in the hospital premises or nearby locations. In India, although the first medical cyclotron was established only in 2002 at the 'Radiation Medicine Centre', Mumbai; the field saw a fast growth since then. Fluorine-18 ($^{18}$F) is the most commonly used radionuclide for PET imaging and 2-Deoxy-2-[$^{18}$F]-FluoroGlucose ($^{18}$F-FDG) has been termed as the 'Molecule of the Millennium' (Fig. 2) due to its widespread applications in various medical fields namely, oncology, neurology, cardiology and psychiatry.

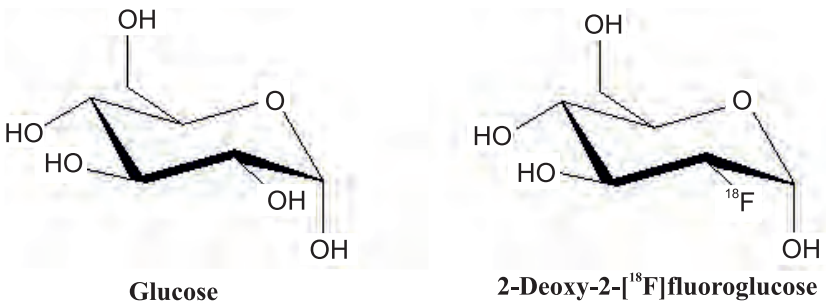


**Figure 2: Structures of Glucose and [$^{18}$F]-2-Fluoro-2-Deoxy-Glucose ($^{18}$F-FDG)**

Radionuclide therapy (RNT) or *in-vivo* targeted radiotherapy, involving administration of therapeutic radiopharmaceutical in the patient, is emerging as a safe and effective targeted approach for treating many types of cancer. Therapeutic radiopharmaceuticals may be defined as radiolabeled molecules designed to deliver therapeutic dose of ionizing radiation to specific disease sites with high specificity in the body. In RNT, radiation is systemically or locally delivered using pharmaceuticals that either bind preferentially to cancer cells or accumulate by physiological mechanisms. More than eight decades, the most widely used radionuclide for therapy is Iodine-131 ($^{131}$I), which finds extensive uses for treating the metastatic lesions from well-differentiated thyroid carcinoma and for ablation of remnant thyroid tissue after thyroidectomy as well as in the treatment of some forms of hyperthyroidism. Beside the management of thyroid related diseases, therapeutic radiopharmaceuticals are used for palliative care of cancer patients suffering from pain originating due to skeletal metastases. In the recent time, targeted radionuclide therapy employing various radiolabeled molecular carriers such as, peptides, hormones, small biomolecules and antibodies have also gained popularity and being used for the treatment for various kinds of cancers.

## 2. History of Radioisotope Production in DAE

India had made a very early entry in to the domain of atomic energy thanks to the great vision of Dr. Homi J. Bhabha. Under his prodigious leadership, 'APSARA', (Fig. 3) the first Indian and also the first Asian nuclear research reactor went critical for the first time at 3.45 PM on August 4, 1956 (Formally dedicated to the nation by the then Prime Minister of India, Pandit Jawaharlal Nehru on January 20, 1957). This helped our country to make an early entry in the arena of radioisotope production, which is one of the prime requisites for carrying out research and development work in radiopharmaceutical sciences as well as for supplying various radiolabeled agents for the treatment of a variety of human diseases. The availability of radioisotopes from

APSARA started exciting research and developmental activities for applications of radioisotopes in human healthcare. Simultaneously, the radioisotope program of Atomic Energy Establishment - Trombay (AEET) (later rechristened as Bhabha Atomic Research Centre, BARC in 1966) was started and Isotope Division was established in 1957 to undertake the production of radioisotopes. Small quantities of $^{131}$I and $^{32}$P, two medically important radioisotopes, were produced in APSARA and radiochemically processed by the end of 1958. Radioisotopes produced in APSARA were mainly used for the research work by universities and national laboratories and to a limited extent for diagnostic work by medical institutions.

**Figure 3: (Clock-wise from top left): Dr. Bhabha at construction site of APSARA reactor with project engineer Shri N. B. Prasad and former controller of AEET Mr. Allerdice; Historic moment of first criticality of APSARA reactor; Dr. Bhabha with Prof. Neils Bohr, Dr. Raja Ramanna and others at APSARA reactor; Then Prime minister Pandit Jawaharlal Nehru at APSARA reactor.**

With the commissioning of CIRUS (Canada India Reactor for Utility Services) reactor in the year 1960, began a new era in the history of production of radioisotopes in India. The possibility of producing different radioisotopes in higher quantities provided a much-needed thrust in the radioisotope production and thus in the supply of radioisotope-based agents for human healthcare, which was otherwise managed through the limited capability of APSARA. In CIRUS, a number of radioisotopes for medical ($^{99}$Mo, $^{131}$I, $^{125}$I, $^{153}$Sm, $^{32}$P, $^{177}$Lu etc.), industrial ($^{60}$Co, $^{192}$Ir, $^{82}$Br, $^{46}$Sc etc.) and research ($^{35}$S, $^{45}$Ca etc.) applications were produced to meet the radioisotope demands of the country. It is noteworthy to mention that several million patients of our country have been benefitted for nearly half-a-century from the radioisotopes produced in the CIRUS reactor. Apart from radioisotope production, CIRUS provided boost to research by

permitting multiple experimental facilities to carry out materials research, neutron activation studies etc.

Foreseeing a growing demand for radioisotopes and advanced research in nuclear science, the necessity for another reactor with comparatively higher neutron flux was felt way back in 1970s, which ultimately resulted in the construction and commissioning of R-5 reactor (later renamed as Dhruva reactor) at BARC, Trombay. This completely indigenous reactor is a testimony to the resolve of Indian scientists and engineers to achieve self-reliance in nuclear reactor technology. After shut down of the CIRUS reactor in 2010, Dhruva continues to cater to the radioisotope demand of our country and at the same time providing the facilities to carry out research in nuclear sciences. Today the main source of radioisotopes in our country is Dhruva reactor, which was dedicated to the nation in 1985.

In the past six decades, Atomic Energy Establishment - Trombay (AEET) and Department of Atomic Energy (DAE) have provided an unparalleled service of producing and supplying a plethora of radioisotopes to the nation, a considerable majority of which has been for the human healthcare. The early product catalogue of radioisotopes of AEET/BARC contained numerous radioisotopes, of almost every element of the Periodic Table! However, with the progress of time, the more important and useful radioisotopes became the key drivers for subsequent developments. The rapid growth of radioisotope program of AEET for potential medical applications led to the creation of a group named 'Special Medical Products' (SMP), which later evolved as the 'Radiopharmaceutical Program' of BARC.

The targets irradiated in a nuclear reactor may require rigorous chemical processing before those can be utilized for downstream applications. This is especially true for radiopharmaceutical applications, where the radioisotopes being used should have specifications suitable for human administration. Chemical processing of radioisotopes is usually carried out inside the heavily lead-shielded plants or hot-cells. At the beginning of the radioisotope program, the targets irradiated in APSARA reactor were radio-chemically processed in a facility set-up at Bombay Dyeing Compound at Cadell Road, Prabhadevi. Initially, targets such as, tellurium metal powder, sulphur, sodium carbonate, potassium chloride etc. were irradiated for production of radioisotopes, such as $^{131}I$, $^{32}P$, $^{24}Na$, $^{42}K$, respectively. Following the commissioning of CIRUS reactor, an intermediate radioisotope processing laboratory was set-up in south-site of BARC campus at Trombay. However, as the radioisotope related activities grew exponentially, it was felt necessary to set-up full-fledged laboratories with enhanced production facilities. Accordingly, state-of-the-art radioisotope laboratories complete with hot-cells, production plants and other laboratories were established at the north-site of

**Figure 4: Radioisotope processing laboratory, then (left) and now (right)**

BARC, which is the presently known as Radiological Group (RLG) of laboratories (RLG Building). Presently, radioisotope production facilities (Fig. 4) and radiopharmaceutical development laboratories are situated at the 'Isotope Wing' of RLG and managed by the 'Radiopharmaceuticals Division' (RPhD) of 'Radiochemistry and Isotope Group' (RC & I Group) of BARC.

Dr. Bhabha's far-sightedness had led to the setting up of a dedicated wing for exploring medical applications of radioisotope-based products in 1963, which was later rechristened as Radiation Medicine Centre (RMC) of BARC. Since then, RMC, which is co-located with Tata Memorial Hospital (TMH, another DAE facility dedicated for the treatment of cancer), has remained as the nucleus for the growth of nuclear medicine in our country.

In 1989, a new Unit of DAE, namely 'Board of Radiation and Isotope Technology (BRIT)' (Fig. 5) came into existence at Vashi (Navi Mumbai) for specifically supplying products and services to users of radioisotopes, radiopharmaceuticals and radiation technology equipment. Presently BRIT supplies a plethora of radioisotope-based products – radioisotopes/radiochemicals, radiopharmaceuticals, labeled compounds, sealed sources, radiation technology equipment, low-level check sources, dosimeters, radiation indicators to name a few.

**Figure 5: BRIT (Vashi, Navi Mumbai) and one of its radioisotope handling facilities**

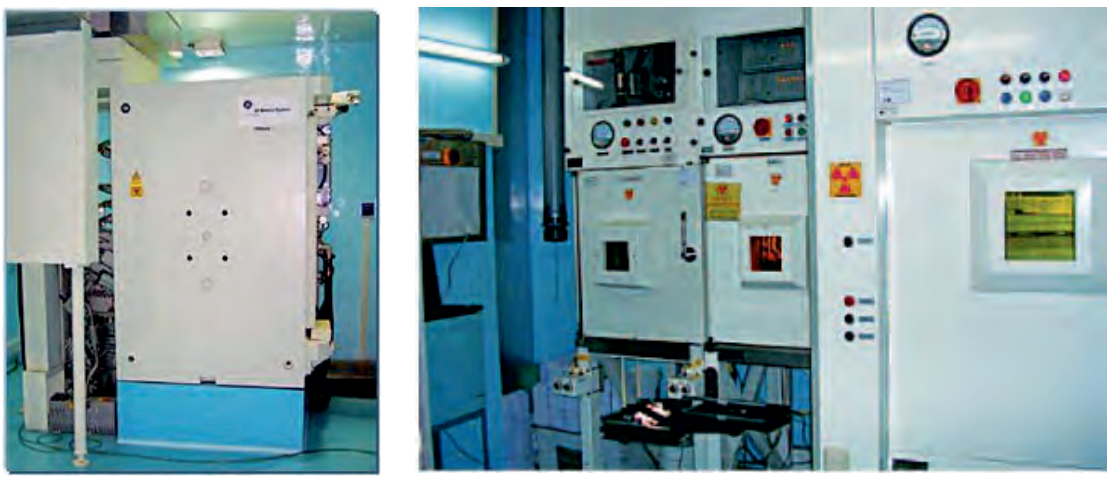

**Figure 6: India's first medical cyclotron (left) and PET-radiochemistry syntheses & dispensing module (right) at RMC, BARC**

In 1990, DAE initiated the accelerator-based radioisotope production by setting up the Variable Energy Cyclotron (VEC) at Kolkata (the then Calcutta), which was capable of producing a few radioisotopes, such as, $^{67}$Ga, $^{111}$In useful for medical purpose. In 2002, DAE further augmented the radioisotope production facility by installing the first medical cyclotron of the country at RMC, Parel (Mumbai) (Fig. 6). Since then, BARC-BRIT is operating this 16.4 MeV medical cyclotron (MC) for production of short-lived positron-emitting radioisotope $^{18}$F and several other $^{18}$F-based radiopharmaceuticals required for PET imaging.

DAE further enhanced its radioisotope production capability by commissioning APSARA-U (upgraded), a pool-type reactor like APSARA, on September 10, 2018 (Fig. 7). This indigenous reactor, by virtue of its higher fast neutron flux permits production of clinically important radioisotopes, like $^{64}$Cu, along with other important radioisotopes. Like Dhruva reactor, along with radioisotope production, APSARA-U is also expected to contribute in research of nuclear physics, material science and radiation shielding.

**Figure 7: APSARA-U while in operation (left) and APSARA-U reactor building (right)**

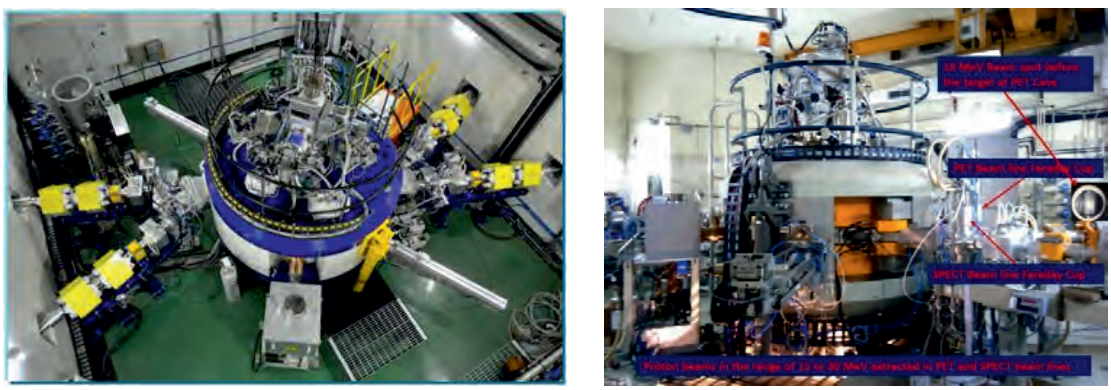


**Figure 8: Cyclone-30, India's largest cyclotron facility at Kolkata**

The recent commissioning of India's largest cyclotron facility in Kolkata, Cyclone-30 (Fig. 8), is another important milestone, which is expected to further enhance the cyclotron-based radioisotope production of our country in near future. This facility will provide affordable radioisotopes and related radiopharmaceuticals for the entire country, especially for eastern India and also have export potential for $^{68}Ge/^{68}Ga$ radionuclide generator. Commissioning of Cyclone-30 re-emphasizes the capability of Indian scientists and engineers to deliver at the highest level of science and technology. In the coming days, Cyclone-30 at Kolkata and another proposed cyclotron at ACTREC (Kharghar, Navi Mumbai) are expected to fulfill the requirement of many important and emerging cyclotron-based radioisotopes, such as, $^{43/44}Sc$, $^{64}Cu$, $^{68}Ga$, $^{89}Zr$, $^{103}Pd$, $^{123}I$ which can be useful for a variety of medical applications.

## 3. History of Radiopharmaceuticals Development in DAE

The availability of indigenously produced radioisotopes opened up a new era in the history of India's patient care, as the medical community of India seized the opportunity of using radioisotopes and radioisotope-based formulations (radiopharmaceuticals) for tracing (mapping), pre- and post-treatment staging as well as treating various types of human ailments. This proved to be much valuable in-patient management and initiated the long journey of a new branch of medical sciences, namely 'Nuclear Medicine' in India.

'Nuclear medicine' is a branch of modern medical sciences which utilizes the nuclear properties of radioactive materials in diagnosis, therapy and research to study the metabolic, physiologic and pathologic functions of human body. The real strength of nuclear medicine lies in its ability to monitor anatomical as well as physiological functions *in-vivo*, which cannot be performed by employing any of the contemporary imaging techniques, such as, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and ultrasound imaging. Nuclear medicine imaging procedures often detect the abnormalities/irregularities of the organs/physiologic functions at the very early stage of the diseases, particularly in comparison with other alternative diagnostic modalities and this provides the unique opportunity to treat the diseases early in its course. At present, nuclear medicine procedures are capable of providing information about the function of virtually every major organ/tissue of the human body (Fig. 9) and thus, considered as an integral part of patient care in hospitals and health-care centers across the globe.

Although nuclear medicine procedures are predominantly used for diagnostic purposes, it finds valuable therapeutic applications which include treatment of various thyroid disorders, Hodgkin's disease, rheumatoid arthritis, and a wide range of cancers, like cancers in prostate, ovary, breast, blood, liver, lung, colon and endocrine glands. Nuclear medicine procedures are also being extensively used to treat various heart diseases and for providing pain relief to the patients suffering from metastatic skeletal carcinoma.

AEET/BARC started to produce a variety of radioisotopes in the earlier days. Some of these radioisotopes such as, $^{131}I$, $^{32}P$ and $^{31}Cr$ belonging to the group of first-generation radioisotopes still have the relevance in nuclear medicine; while many other first-generation radioisotopes such as, $^{24}Na$, $^{57/58}Co$, $^{59}Fe$, $^{82}Br$, $^{203}Hg$ have mostly lost their utility in clinical medicine. Of these, $^{131}I$ still continues to play a very important role in the diagnosis and therapy of various thyroid-related disorders. AEET/BARC has been producing $^{131}I$ (as $Na^{131}I$) for supplying to various nuclear medicine centers of our country uninterruptedly for the past six decades.

The discovery of $^{99}Mo/^{99m}Tc$ radionuclide generator in 1958 (by Walter Tucker and Margaret Greene of Brookhaven National Laboratory, USA), suggestion regarding the possibility of using

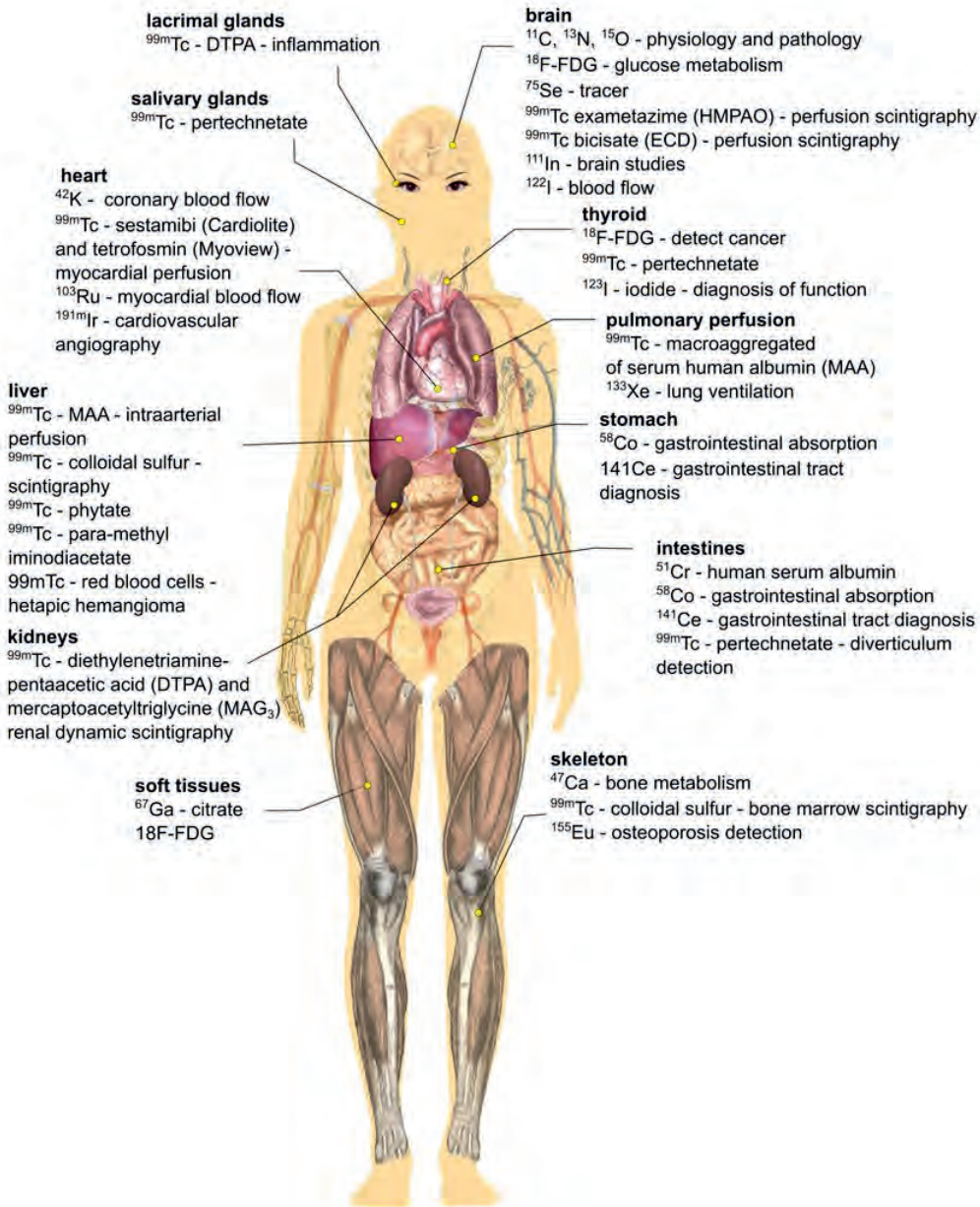


**Figure 9: Radiopharmaceuticals are available for imaging every major organ/tissue of the human body**
***[Image Reference: Filipe P, Massabni A & Orvig C (2019). Radiopharmaceuticals for diagnosis in nuclear medicine: a short review. Eclética Química Journal, 44. 11-19].***
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$^{99m}$Tc as a potential medical radiotracer in 1960 (by Powell Richards of Brookhaven National Laboratory, USA), and invention of gamma camera for scintigraphy (imaging) in 1957 (by Hal Oscar Anger of University of California, Berkeley, USA) paved the use of radioisotopes for diagnostic nuclear imaging, which later on became a force to reckon with for patient

management. The scientists working in the radioisotope production facility of AEET rose to the occasion by providing a practical source of $^{99m}$Tc, which involved supplying of $^{99}$Mo, produced in Trombay reactors and methyl ethyl ketone, the solvent required for extraction apparatus system developed locally. This preliminary radionuclide generator system was popularly known as 'Trombay $^{99m}$Tc cow'. The efforts undertaken by the scientists helped AEET/BARC to initiate the supply of various 'Freeze-dried kits' (reagent mixture, mostly in the lyophilized form) for preparing organ-specific $^{99m}$Tc-labeled radiopharmaceuticals, which enabled nuclear medicine physicians of our country to perform numerous clinical procedures. This trend has since continued and grown further. Today 75-80% of all nuclear medicine imaging procedures performed in our country involve the use of $^{99m}$Tc products. BARC/BRIT regularly produces $^{99}$Mo and supplies different types of $^{99}$Mo/$^{99m}$Tc radionuclide generators (alumina-based column generator, solvent extraction generator and gel generator) (Fig. 10) to the nuclear medicine centers, where a variety of diagnostic radiopharmaceuticals are formulated on daily basis for patient care using the $^{99m}$Tc eluted from these generators. Taking into consideration the pivotal role being played by the $^{99m}$Tc radiopharmaceuticals since its inception and their sustained importance in human healthcare, DAE is in the process of setting-up a fission-moly ($^{99}$Mo produced through nuclear fission of $^{235}$U) plant at Trombay, which is expected to provide a significant boost to the production of $^{99}$Mo. Completion of this project will assure reliable availability of $^{99m}$Tc (without the need of import) and ensure sustainability of $^{99m}$Tc-based radiopharmaceuticals for the patient care in India.


**Figure 10: Facility for construction of $^{99}$Mo/$^{99m}$Tc radionuclide generator at BRIT (left), Geltech $^{99}$Mo/$^{99m}$Tc generator supplied by BARC/BRIT (right)**

The installation of first medical cyclotron and PET imaging facility of our country at RMC in 2002 is another important milestone in the history of India's radiopharmaceutical program. This pioneering effort of BARC (this can be considered as extremely timely response of DAE to the major turning point in the history of nuclear medicine i.e. the introduction of highly sophisticated PET-CT imaging procedure in 2001) not only ensured the availability of short-lived positron emitter, $^{18}$F for PET imaging in India; but also initiated a rapid growth in the arena of more sophisticated PET scintigraphy. This is clearly reflected in the presence of over 20 operational medical cyclotrons and more than 250 PET-CT centers, which currently provide clinical services across our country. Since then the medical cyclotron facility at RMC, jointly operated by BARC and BRIT, has produced $^{18}$F-FDG on regular basis and not only used this agent for the treatment of cancer patients at its own premises, but also supplied it to various nearby hospitals to facilitate

the cancer diagnosis. The scientists and engineers of BARC are not only producing the ubiquitous $^{18}$F-FDG, but also producing many other PET radiopharmaceuticals on regular basis for specific applications like hypoxia imaging or whole-body scintigraphy.

The deleterious radiation emerging during the decay of therapeutic radionuclides at the target lesion site leads to death of cells and this helps therapeutic radiopharmaceuticals either to exert a curative effect (e.g. treatment of cancers) or to provide palliative care (e.g., for metastatic bone pain palliation). This branch, called radionuclide therapy, has made significant progress in the past two decades and presently has become an integral part in the management of cancers. BARC has not only managed to keep pace with the development of therapeutic radiopharmaceuticals, but also taken the leadership role in the case of many products. The promotion of $^{153}$Sm-EDTMP (ethylenediamine-tetramethylene phosphonic acid) by BRIT and BARC since late 1990s has helped the cancer care hospitals to provide palliative care to a large number of late-stage cancer patients. India took a leading role in the development, demonstration and deployment of $^{177}$Lu-labeled EDTMP (based on comparatively long-lived $^{177}$Lu; hence less decay loss as well as easy to produce) for palliative care and presently this radiopharmaceutical is used for bone pain palliation in India as well as in few other countries. The untiring efforts undertaken by the radiopharmaceutical scientists of BARC and BRIT have ensured the availability of a basket of radiopharmaceuticals, such as $^{153}$Sm-EDTMP, $^{177}$Lu-EDTMP, $^{188}$Re-HEDP (hydroxyethylidene diphosphonic acid), $^{177}$Lu-DOTMP (1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetic acid) for palliative care in our country.

The scientists working in the radiopharmaceuticals program has made pioneering and significant contribution in popularizing $^{177}$Lu-based radionuclide therapy in India. The contribution made by this group towards production of $^{177}$Lu and formulation of various $^{177}$Lu-based radiopharmaceuticals is well-recognized not only in our country, but also among various groups working all over the world with the similar objectives. It is worthwhile to mention that the use of $^{177}$Lu is currently second only to that of $^{131}$I in nuclear medicine therapy. Lutetium-177-labeled radio-conjugates, specifically for targeting the tumors of neuroendocrine origin (using octreotate/octreotide analogues as target-specific ligands) and prostate cancer (using enzyme inhibitor PSMA-617, PSMA: Prostate Specific Membrane Antigen) are now available and in regular use in India, thanks to the work carried out in BARC in collaboration with the interested nuclear medicine physicians of select hospitals. Recently availability of these two important therapeutic radiopharmaceuticals in ready-to-use form from BRIT has ensured the accessibility of radionuclide therapy for neuroendocrine cancers and prostate cancer to a significant number of nuclear medicine centers of our country. The recent success of BARC scientists in in-house syntheses of clinical-grade peptides, such as DOTA-TATE, PSMA-617 etc. has added a new dimension in the research, development and deployment of peptide-based radiopharmaceuticals in India.

One of the important non-cancerous applications of therapeutic radiopharmaceuticals is their use for loco-regional administration (in contrast to systemic administration) for the treatment of rheumatoid arthritis. This treatment modality, which is known as 'Radiation Synovectomy' or 'Radiosynoviorthesis', employs administration of radiolabeled particulates or radiolabeled colloids in the synovial cavities of the affected joints. Another important loco-regional administration of therapeutic radiopharmaceuticals is reported for the treatment of hepatocellular carcinoma (liver cancer), where radiolabeled micro-spheres of specific size or radiolabeled lipiodol (a highly viscous liquid - ethyl ester of fatty acid derived from poppy seed oil) are injected through the hepatic artery of the patient. BARC has much success stories to cite in these cases too, though the volume of such procedures is rather limited in India.

The early promise of radioimmunotherapy (RIT) using radiolabeled monoclonal antibodies to target tumor associated antigens has had very limited success till date. However, monoclonal antibodies, which are already in use for chemotherapeutic intervention, have been successfully radiolabeled with different therapeutic radionuclides such as, $^{131}$I, $^{90}$Y, and $^{177}$Lu at BARC and clinical potential of such agents for the treatment of non-Hodgkin's lymphoma and breast cancer are presently being explored in collaboration with Tata Memorial Hospital and other nuclear medicine centers of our country. The preliminary dosimetric studies, conducted in limited number of cancer patients till date, have shown promising results. Presently efforts are being directed to obtain the regulatory approval for initiating full-fledged clinical application of such agents.

In the recent time, the concept of 'Theranostics', is gaining momentum. Theranostics refers to a combination of two interdependent applications namely therapy and diagnosis, using the same agent. In radiopharmaceutical, theranostics can be effected by replacing a diagnostic radioisotope in a radiopharmaceutical with a therapeutic radioisotope, usually with similar chemical properties (e.g. $^{186/188}$Re for $^{99m}$Tc, $^{177}$Lu for $^{68}$Ga) while using the same molecular vector, thereby not compromising the biological avidity of the radiopharmaceuticals. However, perhaps the most desirable option is the use of a single radioisotope, which has imageable gamma photon(s) for pre-therapeutic diagnosis and dosimetry as well as particulate emission ($\beta^-$ or $\alpha$ or Auger electron) for effecting therapy (e.g. $^{64}$Cu, $^{177}$Lu). The well-known use of $^{131}$I for both diagnosis and therapy of differentiated thyroid cancer metastases is an apt and old example of theranostics. The recent success in the production of clinical-grade $^{64}$Cu using research reactors and successful translation of $^{64}CuCl_2$ to the clinics for PET imaging of cancer patients is another important contribution of the BARC scientists to the radiopharmaceutical development program of our country.

The frequency and/or volume of production and supply of different medically important radioisotopes, ready-to-use radiopharmaceuticals, freeze-dried kits, and radionuclide generators reported in the annual reports of DAE bears the testimony of the performance, achievements and deliverables of the radiopharmaceuticals program of BARC/BRIT. It is indeed a proud privilege of the radiopharmaceutical scientists working in DAE to be of help to well over-half a million patients of India annually, by fulfilling the requirement of state-of-the-art radiochemicals, radiopharmaceuticals and allied services at an economic and affordable price for the healthcare management.

## 4. Glimpses of the Recent Work carried out in the Radiopharmaceuticals Division, BARC

### *4.1 Production and Supply of Radioisotopes*

The mandates of the Radiopharmaceuticals Division, BARC include production and supply of various reactor-produced radioisotopes and radioactive sources through BRIT as well as research, development and deployment of new radiopharmaceuticals. During the year 2018, total 510 units of irradiations were carried out in Dhruva reactor which produced 56,000 Ci of $^{192}$Ir for using as radiography source for industrial applications and 3,000 Ci of different medically important radioisotopes. Medical radioisotopes, such as $^{99}$Mo, $^{131}$I, $^{177}$Lu, $^{153}$Sm and $^{125}$I were radiochemically processed (Fig. 11) and supplied to various hospitals and nuclear medicine centers through BRIT for the treatment of patients suffering from a wide variety of human ailments, predominantly cancer. In the year 2019, a total of 661 units of irradiations were carried out in Dhruva reactor and 50,000 Ci of $^{192}$Ir and 3,185 Ci of medically useful radioisotopes (e.g. $^{99}$Mo, $^{131}$I, $^{177}$Lu, $^{153}$Sm and $^{125}$I) were produced and supplied for human healthcare. During 2020,

438 Ci of medical-grade $^{177}LuCl_3$ radiochemical formulation was direly deployed to 15 nuclear medicine centers all over the country and more than 1000 cancer patients were treated with therapeutic radiopharmaceuticals such as, $^{177}$Lu-DOTA-TATE and $^{177}$Lu-PSMA-617 formulated using $^{177}LuCl_3$ supplied from Radiopharmaceuticals Division. In the year 2019, 16 units of irradiations were also carried out in newly refurbished APSARA-U reactor for producing radioisotopes having applications in healthcare, industry and research. A radiochemical separation procedure based on solvent extraction were standardized for the radiochemical separation of no-carrier-added (NCA) $^{64}$Cu produced via $^{64}$Zn(n,p)$^{64}$Cu reaction in the APSARA-U reactor. Copper-64 (in its chloride form) has been successfully administered in human patients and its potential as a theranostic radiopharmaceutical has been studied in collaboration with Tata Memorial Hospital (Mumbai). At present, Radiopharmaceuticals Division is meeting 40-50% demand of $^{131}$I (annual production 1200-1500 Ci), 10-15% demand of $^{99}$Mo (annual production ~1000 Ci), 75-80% demand of $^{177}$Lu (annual production ~500 Ci) and 100% demand of $^{153}$Sm (annual production 250-300 Ci) and $^{125}$I (annual production 20-25 Ci) of our country.

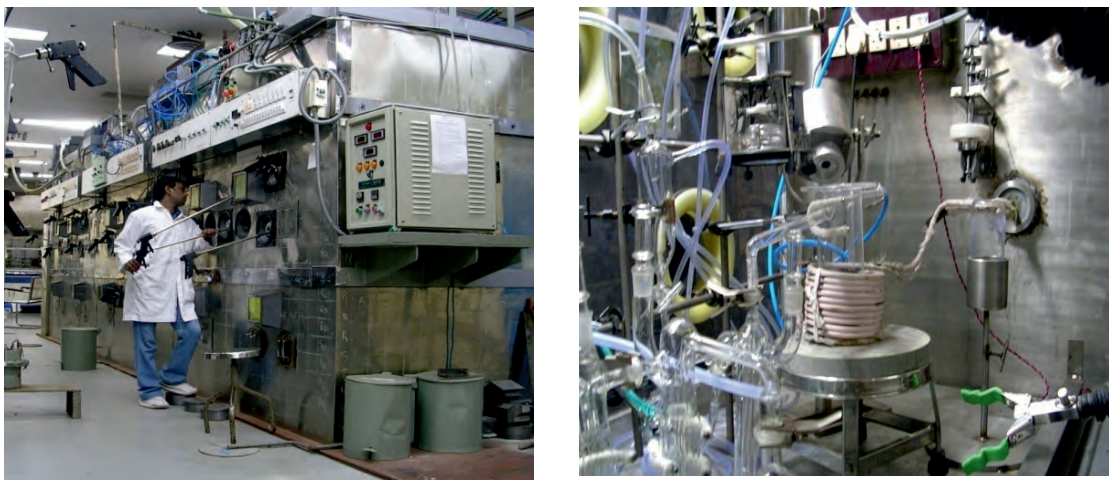


**Figure 11: $^{131}$I production cells at Radiopharmaceuticals Division - Outside (left) and inside (right) view**

### *4.2 Recent Activities on Bone Pain Palliation Radiopharmaceuticals*

Skeletal metastasis is one of the most common complications experienced by the patients suffering from prostate, breast and lung cancer at the advanced stage of their disease. These metastatic skeletal lesions often lead to excruciating pain and have a very detrimental impact on the quality of life of these patients. Such patients are subjected to palliative care, the major objective of which is to alleviate the pain and thus improving the quality of life enjoyed by these patients. Although the conventional treatment modalities such as administration of analgesics and external beam radiotherapy are continuing practices, these approaches have multiple side effects. It is reported that amongst the methodologies usually employed for metastatic bone pain palliation, use of bone-seeking radiopharmaceuticals is considered to be the most desirable for the patients having multiple metastatic lesions, as it is most well-tolerated by the patients.

BARC has developed several radiopharmaceuticals and freeze-dried kits for providing pain relief to the patients suffering from skeletal metastases - $^{177}$Lu-EDTMP (both ready-to use as well as formulation using freeze-dried EDTMP kit), $^{177}$Lu-DOTMP (both ready-to use as well as formulation using freeze-dried DOTMP kit) and $^{188}$Re-HEDP (formulation using freeze-dried

HEDP kit) (Fig. 12). Uses of most of these radiopharmaceuticals and freeze-dried kits have already been approved by DAE-RPC (DAE Radiopharmaceuticals Committee). BRIT product brochure now contains several ready-to-use radiopharmaceuticals ($^{153}$Sm-EDTMP, $^{177}$Lu-EDTMP) and freeze-dried kits (EDTMP kit for the formulation of $^{177}$Lu-EDTMP, DOTMP kit for the formulation of $^{177}$Lu-DOTMP and HEDP kit for the formulation of $^{188}$Re-HEDP) for palliative care of cancer patients and nuclear medicine centers of India are free to choose any one of these agents as per their requirements. It is worthwhile to mention that India is the first country to report the clinical administration of $^{177}$Lu-DOTMP and one of the first countries to document the clinical utility of $^{177}$Lu-EDTMP for bone pain palliation.

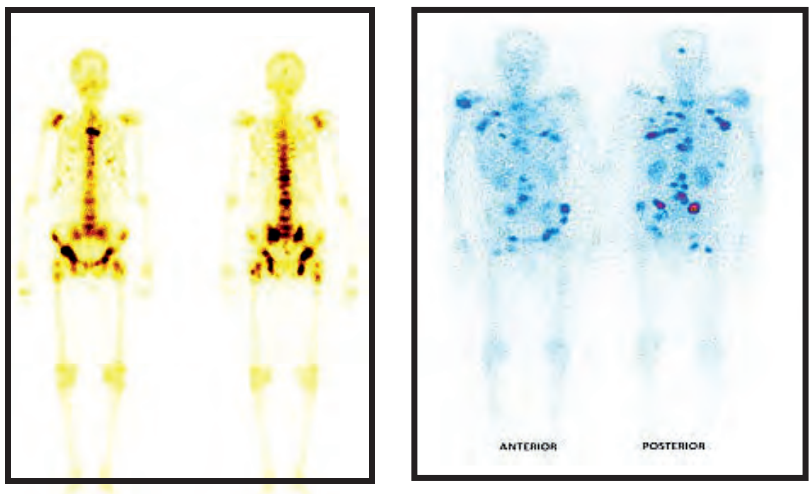



**Figure 12: Post-therapy whole-body images of the cancer patients treated with $^{177}$Lu-DOTMP (left) and $^{188}$Re-HEDP (right), prepared using freeze-dried DOTMP and HEDP kits, respectively**

### *4.3 Recent Activities on Radiolabeled Peptides*

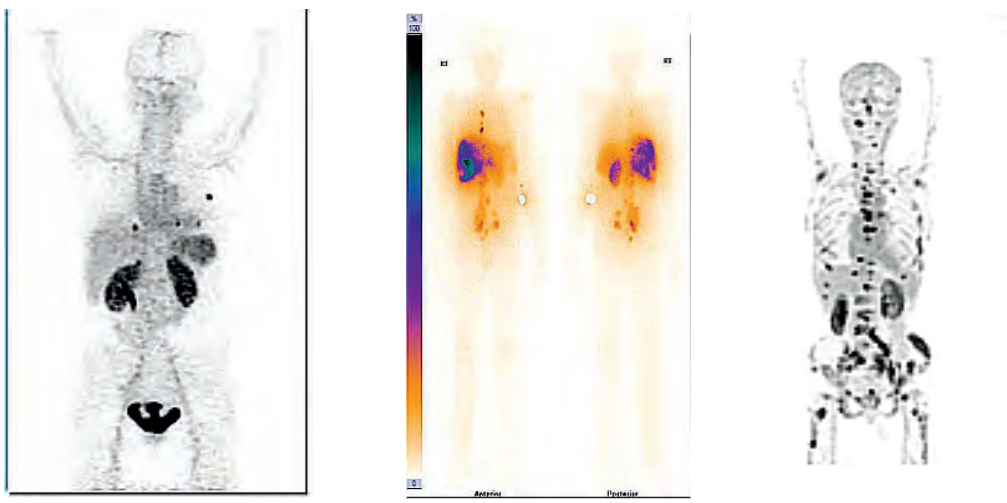
Peptides have high specificity towards their target i.e. receptors over-expressed in cancer cells and thereby selectively localize in the cancerous lesions. Several peptide-based radiopharmaceuticals are routinely used in nuclear medicine centers for SPECT and PET imaging as well as for peptide receptor radionuclide therapy (PRRT). BARC and in the recent time BRIT have made significant contribution in the deployment PRRT in our country as well as ensured the availability of state-of-the-art radiolabeled peptides on regular basis for the treatment of cancer patients.

Peptide-based radiopharmaceuticals have achieved huge success in identification and treatment of neuroendocrine tumors exhibiting high density of somatostatin receptors. Towards this, Radiopharmaceuticals Division has developed lyophilized kits of octreotide analogs, namely HYNIC-TOC and HYNIC-TATE for the formulation $^{99m}$Tc-HYNIC-TOC and $^{99m}$Tc-HYNIC-TATE, respectively. Both these products have been approved by the DAE-RPC for supplying to nuclear medicine centers. Correspondingly, lyophilized DOTA-TATE and DOTA-TOC kits, used for the formulation of patient dose of $^{68}$Ga-DOTA-TATE and $^{68}$Ga-DOTA-TOC, respectively have also been approved by DAE-RPC for clinical application as PET tracers for imaging of various types of neuroendocrine cancers. Recently, BRIT has started supplying ready-to-use patient doses of $^{68}$Ga-DOTA-TATE to the nearby hospitals in Mumbai and Navi-

Mumbai. On the other hand, apart from supplying medium specific activity medical-grade $^{177}$Lu (produced by Radiopharmaceuticals Division of BARC) for the formulation of therapeutic radiopharmaceuticals, BRIT has recently started supplying ready-to-use therapeutic doses of $^{177}$Lu-DOTA-TATE (for the radionuclide therapy of neuroendocrine cancers) and $^{177}$Lu-PSMA-617 (for the radionuclide therapy of prostate cancer) to the nuclear medicine centers across our country (collaborative effort of BARC and BRIT) and both these agents have become popular choices amongst hospitals owing their regular availability at an economic price.

Considering the demand and success of peptide-based radiopharmaceuticals, a peptide synthesis facility was set-up at the Radiopharmaceuticals Division, BARC for indigenous syntheses of various peptides required for imaging and therapy. In this facility, important peptides are manually synthesized using solid phase peptide synthesis (SPPS) technique. Peptides HYNIC-TATE and DOTA-TATE have been successfully synthesized at this facility and freeze-dried kits formulated using in-house synthesized HYNIC-TATE have been approved by DAE-RPC for the preparation of $^{99m}$Tc-HYNIC-TATE (an agent used for SPECT imaging of neuroendocrine cancers). Preliminary clinical studies carried out with $^{68}$Ga-labeled indigenously synthesized DOTA-TATE peptide have also demonstrated promising results (Fig. 13A). Freeze-dried kits of DOTA-TATE have also been prepared using the in-house synthesized DOTA-TATE and such kits have been employed for the formulation of $^{177}$Lu-DOTA-TATE patient dose (an agent used for radionuclide therapy of neuroendocrine cancers). Preliminary clinical studies (Fig. 13B) showed the potential of in-house developed DOTA-TATE kits in PRRT and a proposal seeking the clearance for using such kits for clinical exploitation is presently under active consideration of DAE-RPC.

Apart from radiopharmaceuticals for diagnosis and therapy of neuroendocrine cancers, lyophilized kits of commercially obtained anti-microbial peptide, ubiquicidin (UBI) have also been developed at the Radiopharmaceuticals Division for the SPECT imaging of bacterial infections. Freeze-dried kits of HYNIC-UBI for formulation of SPECT radiotracer, $^{99m}$Tc-HYNIC-UBI have already been approved by DAE-RPC for regular use in hospitals.



(A) (B) (C)

**Figure 13: Whole-body images of (A) neuroendocrine cancer patient injected with $^{68}$Ga-DOTA-TATE, (B) neuroendocrine cancer patient treated with $^{177}$Lu-DOTA-TATE, (C) prostate cancer patient injected with $^{68}$Ga-PSMA-11**

The efforts undertaken by the staff members of Radiopharmaceuticals Division resulted in the formulation of freeze-dried kits of PSMA-11, which can be used for the easy and convenient preparation of $^{68}$Ga-PSMA-11, a radiopharmaceutical regularly used for diagnosis of prostate cancer (Fig. 13C). The use of freeze-dried PSMA-11 kits has also been approved by DAE-RPC. Additionally, the on-demand supply of ready-to-use patient doses of $^{68}$Ga-PSMA-11, initiated by BRIT for the local nuclear medicine centers has ensured ready, regular and timely availability of this state-of-the-art radiopharmaceutical for the benefit of cancer patients.

Apart from this, considerable amount of work has been carried out in the Radiopharmaceuticals Division for developing suitable radiolabeled RGD derivatives for the imaging and therapy of cancerous lesions. This has resulted in the formulation of $^{99m}$Tc-HYNIC-RGD, $^{68}$Ga-NODAGA-RGD and $^{68}$Ga-DOTA-RGD, all of which have been evaluated in cancer patients. Radionuclide therapy of cancer patients have also been performed using the corresponding therapeutic analog, namely $^{177}$Lu-RGD. Recently DAE-RPC has approved the manufacture and supply use of $^{99m}$Tc-HYNIC-RGD for the treatment of cancer patients.

### *4.4 Recent Activities on Radiolabeled Antibodies*

Immunotherapy is a cancer treatment methodology which artificially stimulates the immune system of the human body and this helps the patient to fight against the disease. Radioimmunotherapy (RIT) is a special class of immunotherapeutic modality which utilizes the affinity of immune proteins toward the cancer-associated specific antigens or antigen receptors to deliver a therapeutic radionuclide to the target of interest thereby providing a lethal cytotoxic radiation dose to the cancerous lesions. RIT becomes beneficial when cancer cells fail to respond to immunotherapy, due to the fact that in RIT lethal cytotoxic doses are deliverd by the radionuclide associated with the antibody rather than the antibody itself. Additionally, the amount of antibody needed for RIT is much lower compared to that required for immunotherapy, as the role of antibody in the former is just limited to carrying the cytotoxic radiation dose at the region of interest, which in turn drastically reduces the chemotoxic dose burden of the immunotherapy.

In the recent past, considerable efforts have been directed in the Radiopharmaceuticals Division toward optimization of in-house protocols for the preparation of various radiolabeled monoclonal antibodies. One of the primary requirements for initiating wide-spread clinical evaluation of these agents is to develop a robust methodology which will enable their formulation with high degree of reproducibility at the hospital or central radiopharmacy. Therefore, attempts have been made to develop such a methodology which will enable formulation of patient doses of radiolabeled Rituximab and Trastuzumab with high radiochemical yield using radionuclides of medical interest ($^{131}$I and $^{177}$Lu) produced in DHRUVA reactor. Outcome of such efforts have resulted successful translations of some of these radiolabeled antibodies namely, $^{131}$I-Rituximab, $^{177}$Lu-Rituximab (both for the radionuclide therapy of Non-Hodgkin's Lymphoma) and $^{177}$Lu-Trastuzumab (for radionuclide therapy of metastatic breast cancer) from laboratory to clinical settings (Fig. 14 & Fig. 15). Out of these three agents, the first two have already got approval of DAE-RPC for use in cancer patients for dosimetric evaluation, whereas approval for the third radiolabeled antibody, namely $^{177}$Lu-Trastuzumab is under active consideration of DAE-RPC. It is important to note that regular clinical use of $^{177}$Lu-labeled monoclonal antibodies for the treatment of cancer is not reported in the contemporary literature.

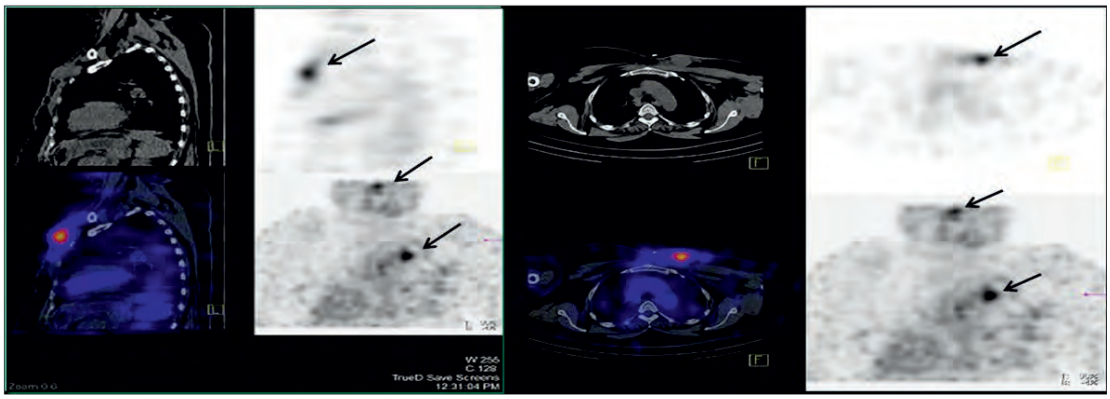
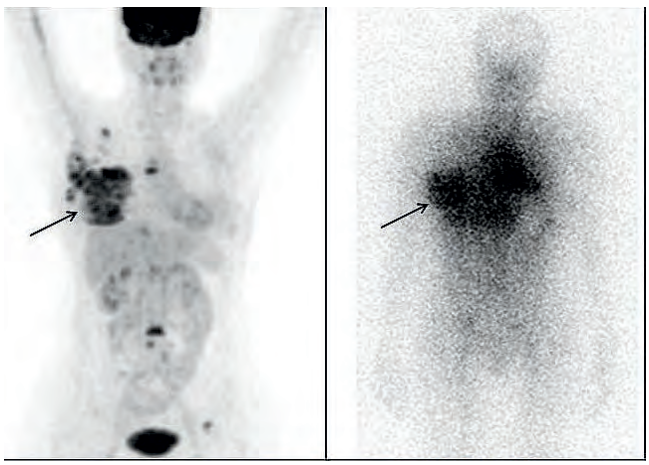


**Figure 14: SPECT-CT scans of a patient, suffering from Non-Hodgkin's Lymphoma, obtained using in-house formulated $^{177}$Lu-Rituximab**



(A) (B)

**Figure 15: Whole-body scans of a female patient, suffering from metastatic breast cancer, obtained using $^{18}$FDG (A) and $^{177}$Lu-Trastuzumab (B), respectively**

## Production of $^{64}$Cu in nuclear reactor for PET imaging of cancer

In nuclear medicine, the concept of 'theranostics' is gaining popularity at a remarkably fast pace. Copper-64 is a theranostic radioisotope owing to its unique nuclear decay characteristics: it decays via electron capture (44%), $\beta^+$ emission (17%, 0.655 MeV), and $\beta^-$ emission (39%, 0.573 MeV). Electron capture also leads to the release of Auger electrons, which increases the advantages of using $^{64}$Cu for radionuclide therapy. This radioisotope is generally produced in a cyclotron employing $^{64}$Ni(p,n)$^{64}$Cu reaction. Despite excellent attributes, $^{64}$Cu failed to find use in routine clinical practices till date, mainly, due to its insufficient commercial availability at an affordable price.

With an aim towards achieving widespread and cost-effective availability of this radioisotope for the benefit of cancer patients in our country, Radiopharmaceuticals Division has explored the feasibility of its indigenous production by two different routes in a nuclear reactor.

In the first approach, $^{64}$Cu was produced by irradiation of natural CuO target in the Dhruva reactor via thermal neutron bombardment on $^{63}$Cu target i.e. by $^{63}$Cu(n,γ)$^{64}$Cu reaction. In the second approach, the radioisotope was produced in a no-carrier-added (NCA) form by the irradiation of natural ZnO target inside the core of the newly commissioned APSARA-U reactor using fast neutrons employing $^{64}$Zn(n,p)$^{64}$Cu reaction.

The first route is the most facile approach for production of $^{64}$Cu as a simple radiochemical processing procedure would suffice to obtain the radioisotope in the form of $^{64}CuCl_2$ for clinical use. Depending on the amount of the target irradiated, the activity of $^{64}$Cu obtained at the end of radiochemical processing in a typical batch varies between 800-1350 mCi. The specific activity of $^{64}$Cu produced is ~80 mCi/mg and the radiochemical concentration of $^{64}CuCl_2$ product is in the range of 16-25 mCi/mL. A major concern associated with the clinical utilization of low specific activity $^{64}CuCl_2$ produced via (n,γ) route is the possible manifestation of cytotoxic effects owing to the presence of comparatively large quantity of 'cold' copper in the radioactive formulation. To alleviate this concern, elaborate toxicity studies were performed in small animal models and such studies showed that there would be no toxicity for clinically relevant doses (6-12 mCi) of $^{64}CuCl_2$ produced through (n,γ) reaction. After establishing the efficacy of (n,γ) $^{64}CuCl_2$ in pre-clinical settings, regulatory approval was obtained from the DAE-RPC for initiating the clinical studies, which were performed in prostate cancer and glioblastoma patients (Fig. 16) in collaboration with Tata Memorial Centre, Mumbai.

In the second approach, NCA $^{64}$Cu was produced by irradiation of natural ZnO target with fast neutrons in the APSARA-U reactor. An efficient radiochemical separation procedure based on solvent extraction of $^{64}$Cu as dithizonate complex was developed. The maximum available activity at the end of irradiation was found to be ~20 mCi. The overall yield of $^{64}$Cu after the separation process was >85% and it could be obtained with an effective specific activity of ~325 mCi/μg and with >99.9% radionuclidic purity and >98 % radiochemical purity. After establishing the efficacy of this production route in several batches, approval has been obtained from the DAE-RPC for clinical utilization of NCA $^{64}$Cu in India.

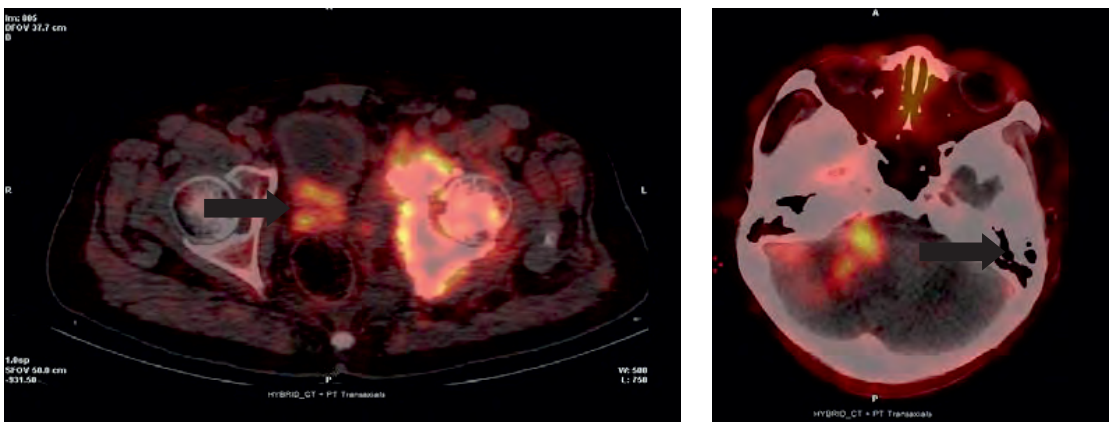


**Figure 16: PET images obtained with $^{64}CuCl_2$ in prostate cancer (left) and glioblastoma (right) patients**

In summary, the feasibility of production of clinical-grade $^{64}CuCl_2$ in research reactors has been demonstrated and successfully translated to the nuclear medicine centers for PET imaging of cancer patients. The promising results obtained in these studies would ensure larger utilization of research reactors to meet the increasing demand of $^{64}CuCl_2$ for widespread clinical studies for the benefit of cancer patients in our country.

**Some Radiochemicals, Radiopharmaceuticals and Freeze-dried Kits Developed in the Radiopharmaceuticals Division in the Recent Past**

Some of the radiochemicals, radiopharmaceuticals and freeze-dried kits, developed in the Radiopharmaceuticals Division in the recent past are tabulated below:

| Sl. No. | Product Name | Form | Application |
|---|---|---|---|
| 1 | $^{99m}$Tc HYNIC TOC[1,2] | Kit | Neuroendocrine tumor imaging |
| 2 | $^{99m}$Tc- HYNIC -TATE[3] | Kit | Neuroendocrine tumor imaging |
| 3 | $^{99m}$Tc-HSA-Nanocolloid[4] | Kit | Detection of sentinel nodes in breast and other cancers |
| 4 | $^{99m}$Tc-UBI (29-41)[5,6] | Kit | Infection imaging |
| 5 | $^{99m}$Tc-HYNIC-[cyclo(RGDfk)]$_2$[7] | Kit | Malignant tumor imaging |
| 6 | $^{68}$Ga-DOTA-TOC[8] | Kit | Neuroendocrine tumor imaging |
| 7 | $^{68}$Ga-PSMA-11[9] | Kit | Prostate cancer imaging |
| 8 | [$^{64}$Cu]$CuCl_2$ Produced by (n, γ) route in Dhruva[10] | Injection | Cancer imaging |
| 9 | [$^{64}$Cu]$CuCl_2$ (No carrier added) Produced in Apsara-U[11] | Injection | Cancer imaging & $^{64}$Cu-radiopharmaceutical preparation |
| 10 | $^{131}$I-Lipiodol[12,13] | Injection | Liver cancer therapy |
| 11 | $^{188}$Re-HEDP[14] | Kit | Bone pain palliation |
| 12 | $^{188}$Re-DEDC-Lipiodol[15] | Kit | Liver cancer therapy |
| 13 | $^{177}$Lu-DOTA-TATE[16] | Injection[#1] | Neuroendocrine cancer therapy |
| 14 | $^{177}$Lu-EDTMP[17,18] | Kit | Bone pain palliation |
| 15 | $^{177}$Lu-EDTMP[19] | Injection | Bone pain palliation |
| 16 | $^{177}$Lu-Hydroxyapatite[20] | Injection | Radiation synovectomy |
| 17 | $^{177}$Lu-PSMA-617[21,22] | Injection[#2] | Prostate cancer therapy |
| 18 | $^{177}$Lu-DOTMP[23,24] | Kit | Bone pain palliation |
| 19 | $^{177}$Lu-CHX-A-DTPA-Rituximab[25] | Injection | Therapy of Non-Hodgkin's Lymphoma |
| 20 | $^{177}$Lu-DOTA-Rituximab[26] | Injection | Therapy of Non-Hodgkin's Lymphoma |
| 21 | $^{177}$Lu-DOTA-Trastuzumab[27] | Injection | Breast cancer therapy |
| 22 | $^{90}$Y-Hydroxyapatite[28] | Injection | Radiation synovectomy |
| 23 | $^{90}$Y-glass microsphere (Bhabha-Sphere) | Injection | Treatment of liver cancer |
| 24 | $^{32}$P-Sodium orthophosphate injection[29] | Injection | Bone pain palliation |
| 25 | $^{99}$Mo/$^{99m}$Tc generator using nano sorbent (NanoTechGen-1)[30,31] | Device | Preparation of $^{99m}$Tc-Radiopharmaceuticals |
| 26 | $^{68}$Ge/$^{68}$Ga generator using nano-sorbent (GalGen-1)[31,32] | Device | Preparation of $^{68}$Ga-Radiopharmaceuticals |

[#]1 *In collaboration with BRIT*
[#]2 *In collaboration with RMC & BRIT*

## Conclusions

Radioisotopes and radioisotope-based formulations play a pivotal role in human healthcare and millions of patients are benefitted from radioisotope-based procedures all over the world. In the past sixty years, DAE has made pioneering and significant contributions in the healthcare program of our country. From a very modest beginning in the late 1950s and early 1960s, the 'Radiopharmaceutical Program' at DAE has evolved at first pace and presently this program is considered as one of the most important contributions of the department towards societal

benefits. The efforts undertaken at DAE have always ensured the availability of various medically useful radioisotopes and state-of-the art radiopharmaceuticals for the treatment of patients, suffering from different human maladies, at a very economical price thereby bringing the benefits of contemporary healthcare to the larger section of patient population of our country. As stated in the insignia of DAE, the 'Radiopharmaceutical Program' is a true exemplar of 'Atoms in the Service of the Nation'.

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**References**

1. A. Korde, M. Mallia, A. Shinto, H. D. Sarma, G. Samuel, and S. Banerjee, Cancer Biother. Radiopharm., Vol. 29(9), pp. 387-394 (2014).
2. S. Basu, P. Kand, M. Mallia, A. Korde, and H. Shimpi, Eur. J. Nucl. Med. Mol. Imaging, Vol. 40, pp. 1622-1624 (2013).
3. A. Mukherjee, A. Korde, A. Shinto, H. D. Sarma, and A. Dash, Appl. Radiat. Isot., Vol. 145, pp. 180-186 (2018).
4. S. Subramanian, U. Pandey, S. Shah, V. Rangarajan, and G. Samuel, Nucl. Med. Commun., Vol. 36(8), pp. 848-853 (2015).
5. A. Chanda, A. Mukherjee, J. Bhatt, P. Chaudhari, K. M. Repaka, M. Venkatesh, and G. Samuel, Appl. Radiat. Isot., Vol. 107, pp. 8-12 (2016).
6. A. Shinto, A. Mukherjee, K. K. Kamaleshwaran, J. Joseph, J. Bhatt, A. Korde, I. Upadhya, A. Chanda, G. Samuel, and A. Dash, Nucl. Med. Commun., Vol. 38(4), pp. 285-290 (2017).
7. S. Chakraborty, S. Das, R. Chakravarty, H. D. Sarma, R. Vatsa, J. Shukla, B. Mittal, and A. Dash, J. Label. Compd. Radiopharm., Vol. 62(12), pp. 823-834 (2019).
8. U. Pandey, A. Korde, A. Mukherjee, A. Shinto, K. K. Kamaleshwaran, R. P. Jose, N. Gamre, and A. Dash, Appl. Radiat. Isot., Vol. 136, pp. 59-64 (2018).
9. D. Satpati, A. Shinto, K. K. Kamaleshwaran, S. Sane, and S. Banerjee, Mol. Imaging Biol., Vol. 18, pp. 420-427 (2016).
10. R. Chakravarty, P. Shetty, K. V. Vimalnath, A. Rajeswari, K. C. Jagadeesan, H. D. Sarma, V. Rangarajan, R. Krishnantry, and S. Chakraborty, Ann. Nucl. Med., Vol. 34(12), pp. 899-910 (2020).
11. R. Chakravarty, A. Rajeswari, P. Shetty, K. C. Jagadeesan, R. Ram, S. Jadhav, H. D. Sarma, A. Dash, and S. Chakraborty, Appl. Radiat. Isot., Vol. 165, 109341 (2020).

12. A. Mukherjee, S. Subramanian, R. Ambade, B. Avhad, A. Dash, and A. Korde, Cancer Biother. Radiopharm., Vol: 32, pp. 33-37 (2017).
13. A. Mukherjee, R. Ambade, S. Subramanian, B. Avhad, A. Dash, and A. Korde, BARC Newsletter, July-August, pp. 1-8 (2017).
14. M. B. Mallia, A. S. Shinto, M. Kameswaran, K. K. Kamaleshwaran, R. Kalarikal, K. K. Aswathy, and S. Banerjee, Cancer Biother. Radiopharm., Vol. 31(4), pp. 139-144 (2016).
15. M. B. Mallia, V. Chirayil, and A. Dash, Appl. Radiat. Isot., Vol. 137, pp. 147-153 (2018).
16. A. Mathur, V. Prashant, N. Sakhare, S. Chakraborty, K. V. Vimalnath, R. K. Mohan, A. Chanda, B. Karkhanis, R. Seshan, S. Basu, A. Korde, S. Banerjee, A. Dash, and S. S. Sachdev, Cancer Biother. Radiopharm., Vol. 32(7), pp. 266-273 (2017).
17. T. Das, H. D. Sarma, A. Shinto, K. K. Kamaleshwaran, and S. Banerjee, Cancer Biother. Radiopharm., Vol. 29(10), pp. 412-421 (2014).
18. P. Thapa, D. Nikam, T. Das, G. Sonawane, J. P. Agarwal, and S. Basu, J. Nucl. Med., Vol. 56(10), pp. 1513-1519 (2015).
19. C. S. Bal, G. Arora, P. Kumar, N. Damle, T. Das, S. Chakraborty, S. Banerjee, M. Venkatesh, J. J. Zaknun, and M. R. A. Pillai, Curr. Radiopharm., Vol. 9(1), pp. 71-84 (2016).
20. S. Chakraborty, K. V. Vimalnath, A. Rajeswari, A. Shinto, H. D. Sarma, K. Kamaleshwaran, P. Thirumalaisamy, and A. Dash, J. Label. Compd. Radiopharm, Vol. 57(7), pp. 453-462 (2014).
21. T. Das, M. Guleria, A. Parab, C. Kale, H. Shah, H. D. Sarma, V. R. Lele, and S. Banerjee, Nucl. Med. Biol., Vol. 43(5), pp. 296-302 (2016).
22. S. Chakraborty, K. V. Vimalnath, R. Chakravarty, H. D. Sarma, and A. Dash, Appl. Radiat. Isot., Vol. 139, pp. 91-97 (2018).
23. T. Das, S. Chakraborty, H. D. Sarma, and S. Banerjee, Radiochim. Acta, Vol. 103(8), pp. 595-604 (2015).
24. T. Das, A. Shinto, K. K. Kamaleshwaran, and S. Banerjee, Clin. Nucl. Med., Vol. 41, pp. 966-967 (2016).
25. M. Kameswaran, U. Pandey, C. Dhakan, K. Pathak, V. Gota, K. V. Vimalnath, A. Dash, and G. Samuel, Cancer Biother. Radiopharm., Vol. 30(6), pp. 240-246 (2015).
26. M. Guleria, T. Das, C. Kumar, J. Amirdhanayagam, H. D. Sarma, and S. Banerjee, J. Label. Compd. Radiopharm, Vol. 60, pp. 234-241 (2017).
27. M. Guleria, R. Sharma, J. Amirdhanayagam, H. D. Sarma, V. Rangarajan, A. Dash, and T. Das, RSC Med. Chem., Vol. 12, pp. 263-277 (2021).
28. K.V. Vimalnath, S. Chakraborty, A. Rajeswari, H. D. Sarma, J. Nuwad, U. Pandey, K. K. Kamaleshwaran, A. Shinto, and A. Dash, Nucl. Med. Biol., Vol. 42(5), pp. 455-464 (2015).
29. K. V. Vimalnath, P. Shetty, S. Chakraborty, T. Das, V. Chirayil, H. D. Sarma, K. C. Jagadeesan, and P. V. Joshi, Cancer Biother. Radiopharm., Vol. 28(5), pp. 423-428 (2013).
30. R. Chakraborty, R. Ram, R. Mishra, D. Sen, S. Majumder, M. R. A. Pillai, and A. Dash, Ind. Eng. Chem., Vol. 52(33), pp. 11673-11684 (2013).
31. A. Dash, and R. Chakravarty, Sep. Purif. Rev., Vol. 46, pp. 91-107 (2017).
32. R. Chakravarty, R. Shukla, R. Ram, A. K. Tyagi, A. Dash, and M. Venkatesh. Nucl. Med. Biol., Vol. 38(4), pp. 575-583 (2011).