India's Growing Nuclear Medicine Infrastructure and Emergence of Radiotheranostics in Cancer Care: Associated Challenges and the Opportunities to Collaborate

Background

A historical pledge to use "atoms for peace" was taken after the landmark and maiden speech of 34th US president Dwight David Eisenhower in 1st UN assembly meet in 1953. This strategic UN meet was chaired by Mrs. Vijaya Laxmi Pandit. Later, an eminent Indian and a nuclear physicist Sir Dr. Homi J Bhabha was made the president of the 1st UN Congress on "atoms for peace" that was held in Vienna, Austria in 1955. These two landmark UN initiatives spearheaded by the Indian stalwarts, disseminated the drive of using the atoms for peace globally. The radiation cell laboratory was set up in Delhi (DRDO) in 1953 that is immediately after the 1st UN assembly passed the resolution to harness the peaceful uses of radiation. Under the mentorship of Dr. Brigadier SK Mazumdar, this radiation cell laboratory was upgraded to a full-fledged Institute – the Institute of Nuclear Medicine and Allied Sciences (INMAS) under DRDO, the ministry of defence, Government of India in 1961. He was the first Indian physician having put the use of radioiodine in to clinical practice for the treatment of thyrotoxicosis and thyroid cancer. Brigadier Mazumdar named as the Father of Nuclear Medicine in India, introduced in INMAS in 1968 – the world's first formal nuclear medicine training course (DRM) for medical graduates. Subsequently, an another prominent institute, namely, Radiation Medicine Centre (RMC) was built-up in Mumbai under BARC, Department of Atomic Energy (DAE) in 1963. RMC started its first formal training in nuclear medicine in 1973 both for medical (DRM) and nonmedical (DMRIT) graduates. These two giant nuclear medicine institutes (INMAS and RMC) played a leading mentorship role in producing great leaders, and with this, the specialty of nuclear medicine expanded gradually throughout the country.

Expansion of Nuclear Medicine: Workforce Generation and Infrastructure Built-up

Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS, Lucknow), the All India Institute of Medical Sciences (AIIMS), New Delhi, the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, and JIPMER, Pondicherry introduced 3-year residency (MD) program in nuclear medicine. Many private sector institutes/hospitals also introduced 3-year residency (DNB) in nuclear medicine. Subsequently, MD nuclear medicine was also introduced in RMC, TMH Mumbai and in many new AIIMS institutes across the country. Similarly, many institutes in the country have also introduced M. Sc and B. Sc Nuclear Medicine technological courses. The country (in about 25 public and private sector institutes) on an average produces about fifty medical (MD/DNB) postgraduates (PGs) and 150 technological (MSc./BSc.) graduates. Many premiere institutes of the country are also running highly competitive PhD programs. AIIMS, New Delhi is the only medical institute in the country imparting superspecialization (DM) in radionuclide therapy which is the first formal course of its kind not only in India but also in the world. Few premiere institutes of the country are also offering PET fellowships of 1-year duration. The Government of India has opened and is planning to open at least one (even 2) AIIMS/state with the current number of 22 AIIMS in various states across the country. Each of these AIIMS institutes has provision for starting nuclear medicine facility including MD program. Over the past 10 years as an exercise of revamping and escalating the health services by the Indian Government, the total number of PGs seats per year has been increased to 65,335 in the country which is double than (31,185) that was available in 2014. The anticipated and proportionate increase in the number of PG seats in nuclear medicine can be achieved if the prominent central and state medical colleges in the country also introduce the requisite technological infrastructure and MD nuclear medicine residency programs. At present, the country is producing only about fifty nuclear medicine PGs which is a very small number in proportion to the overall projected expansion of the health-care services in the country.

The country now has 442 operating nuclear medicine centers having 359 positron emission tomography-computed tomography (PET-CT) scanners (including three PET/magnetic resonance), 24 functional medical cyclotrons, and 150 high-dose radionuclide therapy facilities. India has witnessed a rapid growth and augmentation in nuclear medicine over the past two decades. Growth of nuclear medicine facilities and imaging equipment installations over the past 7 years is depicted in Figure 1a and b. However, the USA and Japan have 4.0 PET-CT scanners (highest ratio) per million population. Even to have a realistic ratio of 1.0 PET-CT scanner per million, India needs to add 1000 PET-CT scanners over the next 10 years to provide reasonable molecular imaging services for the optimal care of cancer patients. This requires huge investments both by central and state governments, in terms of economics and manpower. There is a need for making comprehensive planning to achieve the projected expansion of PET technologies uniformly throughout the country. The DAE,

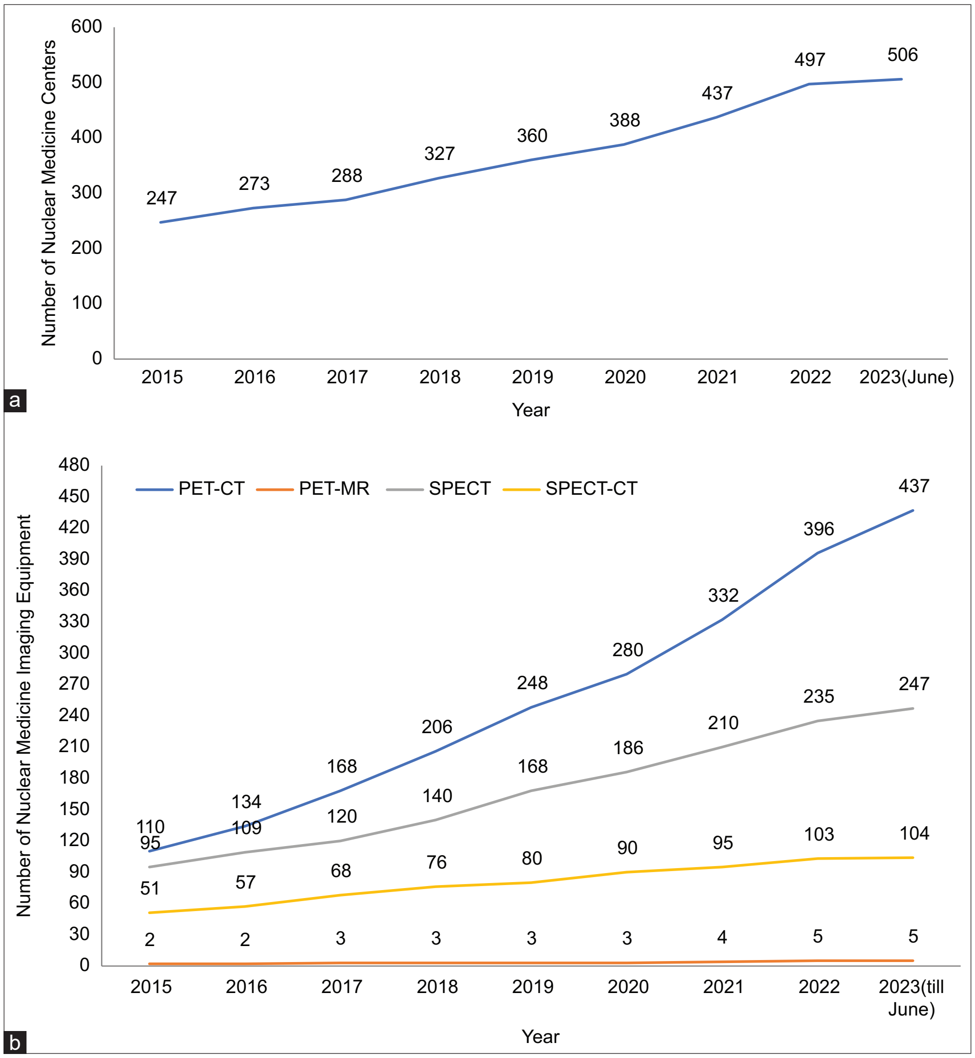

Figure 1: (a) Growth of Nuclear Medicine Facilities in India. (b) Growth of Nuclear Medicine Imaging equipment in India

the Union Health Ministry, and the concerned states need to plan and create a corpus fund to upscale these potentially life-prolonging and lifesaving services in the country. Most of the cancer patients require PET imaging for diagnosis and management including for treatment response monitoring. Molecular imaging using PET has resulted not only in improving patients' outcomes both in terms of overall survival and progression-free survival but also in improving the quality of life, social economic health as well as an early cancer detection, thereby making the dreaded disease potentially curable.

Production and Supply of Medical Radioisotopes in the Country

The Board of Radiation and Isotopes Technology (BRIT), an industrial unit of DAE, is our national agency entrusted to supply medical isotopes, radiopharmaceuticals, and cold lyophilized "ready to label" kit formulations for diagnostic and therapeutic use in Nuclear Medicine Departments across the country. The supply chain ranges from ^{99}Mo/^{99m}Tc-generators, radioiodine, ^{177}Lu, ^{153}Sm, and cold kits for skeletal, renal, liver, hepatobiliary, and thyroid scintigraphy studies. However, due to increased demands of these radiopharmaceuticals in tertiary care public and private medical hospitals, import dependency of ^{99}Mo/^{99}Tc generators is on the rise for many years. ^{177}Lu-PSMA and ^{177}Lu-DOTATATE supply by BRIT for the treatment of prostate and metastatic neuroendocrine tumors, respectively, has been phenomenal making these treatment affordable to a large section of the patients in different regions of the country. However, still many larger centers are dependent on import supply of these two therapeutic radiopharmaceuticals. ^{68}Ge/^{68}Ga generators, Thallium-201, and alpha emitters are not produced in India and are therefore totally imported for their extensive use both in PET/single-photon emission CT (SPECT) imaging and therapy. Their impact on the management of prostate and NETs has already been proven in several studies coming out of premium institutions in India. However, the community needs to brace itself for exponential increase in demand in coming years due to the expansion of their application in many more cancer entities.

India's Initiatives in Indigenous Production of Useful Radioisotopes

An exponential growth of nuclear medicine theranostics is seen in India for the past few years. What started with ^{131}I in Graves' disease and thyroid cancer has today evolved to the era of targeted radiopharmaceutical therapy (RPT) using beta and alpha emitters in prostate cancer and neuroendocrine tumors among others. Bhabha Atomic Research Centre (BARC), R and D unit of DAE, Government of India has been producing several medically important radioisotopes (^{99}Mo, ^{131}I, ^{125}I, ^{153}Sm, ^{32}P, ^{177}Lu, etc.), using its research reactor for their supply to the nuclear medicine centers across the India. DAE further enhanced its radioisotope production capability by commissioning APSARAU (upgraded) in 2018. This reactor is capable of producing clinically important theranostic radioisotopes, like ^{64}Cu, along with other important radioisotopes due to the availability of higher fast neutron flux. However, at present, many radioisotopes are being imported, and the exorbitant cost is one of the main reasons for the tardy pace of alpha therapy program in India. In view of this, DAE, Government of India has taken a leading role in setting up a dedicated reactor at a projected cost of 250 crores (30.0 million US $) under public–private partnership (PPP) model. This shall be a revolutionary step for the rapid growth of the specialty of nuclear medicine and in providing the cutting-edge radionuclide therapies to cancer patients at an affordable cost. The world is facing a major crisis in the production and supply of ^{99}Mo for ^{99m}Tc-based gamma imaging procedures particularly when nuclear reactors producing Mo-99 are facing temporary shutdown for repair/maintenance. India has taken a yet another lead in developing LINAC-based technology (achieving 30.0 MeV electron acceleration) as an alternate to nuclear reactor produced Mo-99/Tc-99 m radioisotopes. This system is ready for installation and will produce sufficient amount of ^{99}Mo for separating clinically useful and sufficient quantity of ^{99m}Tc. This project was funded for about 100.0 crores (13.0 million US $) by the Ministry of Electronics and Information Technology (Meity), Government of India, and the development project was executed by the Society for Applied Microwave Electronics Engineering and Research (SAMEER), Mumbai. Further, high-specific activity Mo-99 is essential for making column generator which helps nuclear medicine centers to produce Tc-99 m on daily basis to meet their requirements for gamma imaging procedures. As of now, Mo-99/Tc-99^{m} column generators are being prepared in India from the imported high-specific activity Mo-99. To become self-reliant, Board of Radiation Isotopes and Technology (BRIT), an industrial unit of DAE, Government of India has taken initiative to set up Fission Moly Plant to produce high-specific activity of Mo-99. This plant is in advanced stage of commissioning and will be operational shortly to cater to the need of the country. For the PET isotope production, RMC at BARC had installed first medical cyclotron in the year 2002 in the country at Parel, Mumbai and Medical Cyclotron is operating at 16.4 MeV for the production of short-lived positron-emitting radioisotope primarily ^{18}F for PET scanning. DAE has commissioned another Medical Cyclotron (Cyclone 30) at its VECC, Kolkata in 2018, which is capable of accelerating proton up to 30 MeV making possibilities of producing several radioisotopes in addition to ^{18}F. Today, in India, there are 24 Medical Cyclotron facilities operated by the government and private institutions for the production of medically important radioisotopes.

These efforts of the Government of India are in synergy with its mission of making self-reliant India in health-care sector by developing indigenous medical technologies for accessibility and affordability by the poorest of the poor patients.

India's Emergence to the Forefront of the Clinical and Research Aspects of Newer Radio-theranostics

Our colleagues from BARC, BRIT, INMAS, and from other premiere institutes of the country having strong radiopharmacy teams have developed many radiopharmaceuticals and have validated these in clinics. Few studies from India have contributed significantly to the theranostic practices and are recognized globally. These include the use of indigenously produced ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617 in metastatic neuroendocrine tumors and prostate cancer with remarkable disease control.[1,2] The use of ^{225}Ac-DOTATATE and ^{225}Ac-PSMA has shown excellent therapeutic efficacy in NET and prostate cancer patients, respectively, who have shown disease progression after treatment with ^{177}Lu-based radioligand therapies.[3,4] This landmark work from AIIMS, New Delhi was awarded the best abstract award in 2022 SNMMI meeting and also received other international recognitions. Fortis, Gurgaon has also gained prominence in radionuclide theranostics as a first clinical user of alpha (^{225}Ac/^{213}Bi) therapy in prostate cancer.[5] They have also initiated international collaboration on the diagnostic and therapeutic applications of elementally matched radionuclide pair of ^{203}Pb/^{212}Pb in different human cancers. Targeted alpha therapy practice in prostate and NETs is picking up gradually as at least eight Indian centers have obtained NOC from AERB for the import of alpha emitters.

^{68}Ga-Pentixafor *in vivo* PET-CT imaging demonstrated high CXCR4 receptors' density overexpressed in a variety of neoplasms, particularly in multiple myeloma and lung cancer.[6-9] These studies (under funding from DST-FIST, Government of India) from PGIMER (the first center in Asia) provided a roadmap for detecting patients who may benefit from CXCR4-targetted alpha/beta radionuclide therapies. CXCR4-based (alpha/beta) therapies hold great promise for the treatment of advanced stage cancers where all the conventionally available therapies have failed. 68Ga-Pentixafor PET-CT and its counterparts 177Lu/225Ac/213Bi are viewed as very promising theranostic pair in the treatment of advanced stage hematological and solid tumor malignancies. The current progress in precision-based radiomolecular oncology practice is apparently challenging the classical statistical evidence-based medicine.[10]

Another promising PET tracer is ^{68}Ga-FAPI that targets fibroblasts has been validated clinically. Studies from the AIIMS, New Delhi have presented very encouraging results and found that [^{177}Lu] Lu-DOTAGA. (SA. FAPi)$_2$ is safe, seems effective, and most importantly, opens up a new avenue for the treatment of aggressive RR-DTC patients who have exhausted all standard line of treatments.[11,12] Another center from Bangalore (Healthcare Global Enterprises Ltd.) had been actively doing clinical studies using FAP radioligands.[13]

The approach of PET-CT-guided biopsy has gained prominence for accurate sample collection from the disease-active and tracer-avid tumor sites for histopathological and immunohistochemical correlation. PGIMER, Chandigarh has become a leading center in India in performing PET-CT-guided biopsies in a variety of human cancers including prostate cancer using ^{68}Ga-PSMA PET-CT imaging.[14] Over the past more than 5 years, PGIMER has trained a large number of nuclear medicine professionals across the country in performing the robotic arm-assisted PET-CT-guided biopsies. This practice is gaining eminence in the current era of precision oncology and is more relevant when new and noble radiotheranostics are being investigated clinically. In view of the advances in diagnostic and therapeutic practices, there had been a periodic review of the reporting guidelines of ^{68}Ga-PSMA PET-CT images. An Indian colleague from AIIMS, New Delhi had been involved with the world leaders of nuclear medicine in formulating these revised/modified guidelines for bringing in harmonization in PSMA reporting practices.[15]

The INMAS, Delhi, has expanded the production of some useful PET radiometals (^{44}Sc, ^{64}Cu, ^{68}Ga, and ^{89}Zr) using their existing cyclotron facility. The production and labeling of ^{44}Sc with FAPI using this approach have been tested preclinically at INMAS and have wider clinical applications in PET oncology. INMAS has developed some excellent ^{99m}Tc-based tracers and has proven their diagnostic utility in clinical scenario.[16,17] The Department of Nuclear Medicine at SGPGIMS, Lucknow, using the similar approach had shown success in the production and separation of ^{64}Cu and has performed some promising clinical PET studies.

India has made a tremendous advancement in the field of nuclear medicine. The National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru has installed first simultaneous PET-MR along with cyclotron facility. Being a dedicated Neuro Institute, NIMHANS has developed radiotracers such as fluorine-18-[^{18}F] flumazenil for imaging benzodiazepine receptors, [^{18}F]-AVT-011 for assessing p-glycoprotein expression, and also started carbon-11-PBR28 TSPO PET imaging in amyotrophic lateral sclerosis.[18,19]

Institute such as INMAS, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) has done enormous contribution in translation research. These institutes have set up preclinical SPECT/PET-CT and had carried out trials for many newer anticancer drugs (in partnership with big Pharma Houses) using innovative radiopharmaceuticals. Scientists from BARC, ACTREC-TMH, Mumbai have put in their immense efforts to produce new tracers, validated through preclinical imaging, and translated to clinics.[20] Colleagues from radiopharmaceuticals chemistry section, radiochemistry, and isotope group, BARC, Mumbai have produced many therapeutic radiolabeled tracers and have shown excellent therapeutic efficacy and are offered to patients throughout the country at an affordable cost.[21-26]

ACTREC, TMH, Mumbai is coming up with 40-bedded radionuclide therapy “state of the art” ward facility for all advanced radiotheranostic applications that is possibly the largest facility in the country and in the region. Similarly, National Cancer Institute AIIMS, Jhajjar, Delhi that has been set up at cost of over 2000 crores (300 million US $) has very extensive nuclear medicine facility both for preclinical and clinical SPECT/PET-CT installations and will have a huge indoor facility for radiotheranostic applications.

Based on the cutting-edge research published by researchers from the premiere institutes, India was declared as the highlight country in the Annual Meeting of SNMMI-2023. This honor bestowed upon India, is a testimony of the consistent hard work, passion, and cutting-edge research done by the Indian Nuclear Medicine colleagues. The upfront initiatives by the Government of India in making huge investment and strengthening the nuclear medicine imaging and therapy services in the country have been greatly instrumental in getting us this honor.

Global Challenges in the Harmonization of Radiopharmaceutical Therapy Practices

The radiotheranostic practice is fast advancing in India.[27] Today’s medical use of unsealed radioactive compounds is driven by an unprecedented level of diagnostic and therapeutic molecular targeting opportunities that the human genome project and the omics of diseases, particularly in oncology, have unraveled and continue to discover. However, in a comprehensive white paper document on radiotheranotic practices complied by the world leaders of nuclear medicine, it has been highlighted that the nuclear medicine professionals across the globe are now challenged by the need to understand and eventually master a vast amount of specialized and sophisticated knowledge on various type of cancers and their cognate diagnostic and therapeutic radiopharmaceutical probes that have been or are actively being developed. Becoming proficient in this new field requires significant dedication to education and training as well as an additional level of experience and expertise.[28] This review has outlined the world's currently available offerings in education and accreditation for theranostics. It also frames the educational and proficiency challenges that countries across the globe face in developing educational and training curricula, and it offers generic guidelines toward providing physicians with sufficient knowledge and experience to confidently and safely perform nuclear theranostic procedures. This underscores a need to introduce common education and training programs and initiate research collaborations by formulating and following uniform guidelines for the harmonization of RPT practices across the globe.

India has produced some remarkable leaders carrying forward the torch of education in theranostics. Similarly, many of the world renowned theranostic centers in Western World have trained several Indian research fellows who have now taken center stage at the global level and are actively involved in formulating a curriculum for preparing "Nuclear Oncologists." Even international organizations such as International Centre for Precision Oncology (ICPO) have highlighted India as a country of excellence in radiopharmaceutical therapies and intend to nominate some government and private nuclear medicine centers actively engaged in treating cancer patients as "Centers of Excellence" (CoE) designated to provide training not only to Indians but also to several other countries world over. Similarly, Indian American Society of Nuclear Medicine (IASNM) has also played a significant role in expanding the umbrella of cooperation among several Indian and American RPT CoE. The memorandum of understanding (MOU) signed between SNM-India, SNMMI, and EANM in the past will further expand our research collaborations, students/faculty short-term exchanges in the COE, and by engaging ICNM, IASNM, ACNM, ICPO, and ESMIT in joint education and "hands-on" training programs.

Regulatory Framework for Safe Operation of Nuclear Medicine Facilities

Atomic Energy Act, 1962 was enacted by the Government of India to develop, control, and use atomic energy for the welfare of the people of India. The national regulatory authority, i.e. Atomic Energy Regulatory Board (AERB) was established on November 15, 1983 under the provisions of the aforesaid Act to carry out the regulatory and radiation safety functions on the use of nuclear energy and ionizing radiation in India. AERB has authority to enforce the safety provisions under the Atomic Energy Act 1962 and rules thereof, for the regulation of nuclear and radiation facilities.

AERB has the mandate and its objective is to ensure that the use of ionizing radiation and nuclear energy does not cause any undue risk to the health of humanity and the environment. To achieve and endorse its mission, AERB performs regulatory activities, namely, consenting/licensing, safety review/assessment, regulatory inspections, enforcement, and development of regulatory documents under legal provisions (Radiation Protection Rules, 2004). Under these rules, AERB issues practice specific safety codes, standards, guides, and directives time to time considering the international standards stipulating regulatory requirements. AERB safety code on "Nuclear Medicine Facilities" is issued for stipulating radiation safety requirements to protect patient, radiation workers, and public. These safety codes elaborate on safety requirements for establishing nuclear medicine facilities, operational safety, quality assurance aspects, patient protection, management of radiation emergency and radiation protection program, key personnel, and their qualifications. Safety requirements such as QA test results, radiation survey of installation, availability of qualified key personnel and personal monitoring services, and measuring and monitoring instruments are ensured before issue license to operate for ensuring safety during the operation of the equipment/facility. Periodic safety review and regulatory inspection of the facility are also carried out for the verification of safety and regulatory requirements. However, prime responsibilities lie with the licensee for safe operation of the nuclear medicine facility. India has robust regulatory framework and effective regulatory body for ensuring safe usages of radiation in nuclear medicine facilities.

Nuclear medicine practice started around six decades ago in India. The specialty over the past two decades has witnessed a sharp growth both in diagnostic and therapeutic NM practices. Several medically useful radioisotopes are being produced in the country using nuclear reactor as well as medical cyclotrons. India's growing potential in radiotheranostics has been realized by the regulatory authorities and the other concerned government agencies. Thus, to escalate the production of the medically useful radioisotopes, the government of India has taken several initiatives. These include the establishment of nuclear reactor in PPP mode, Fission Moly plant, and high energy linear accelerator to meet the growing need of a wide range of gamma, positron, alpha, and beta emitters in the effective practice of nuclear medicine in the country.

Roadmap

Nuclear Medicine is one of the truly inter- and intra-disciplinary fields of medicine, resulting out of amalgamation of all the pure branches of science,

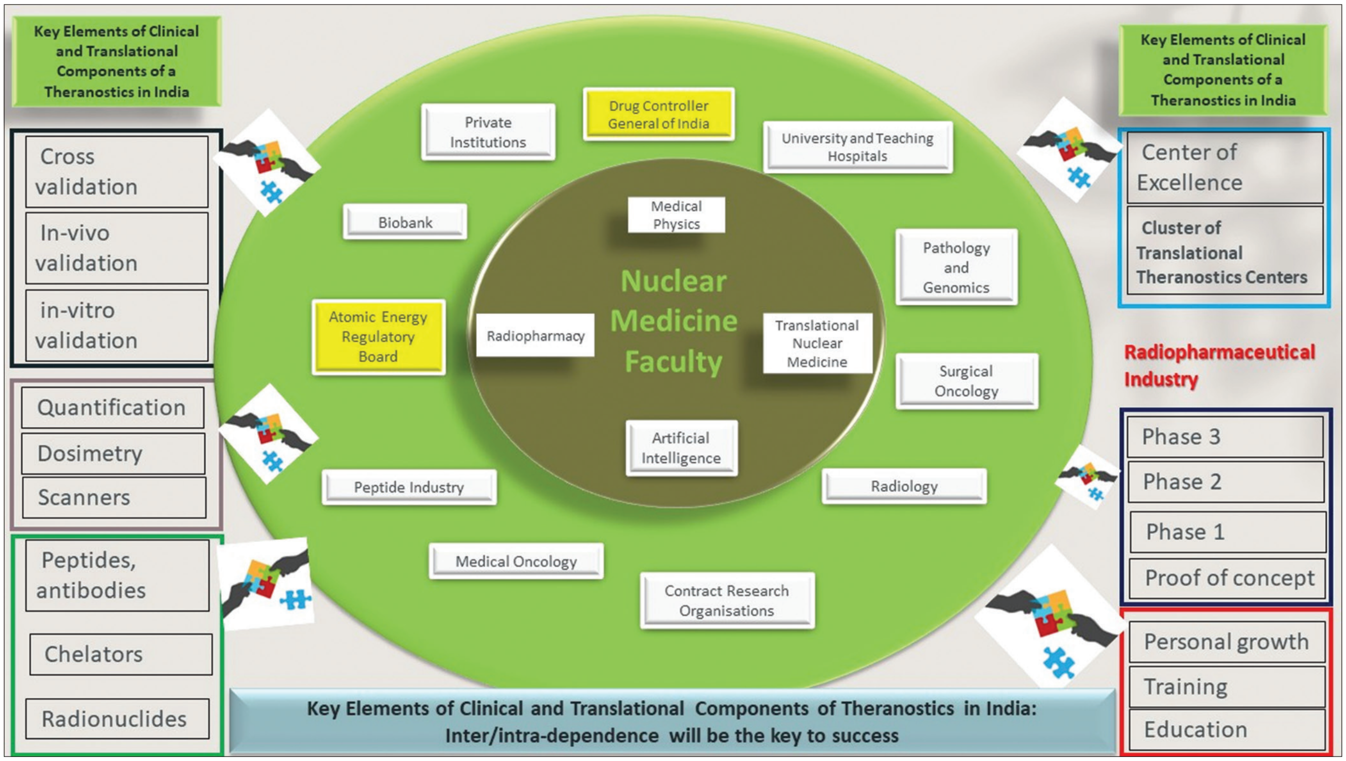

Figure 2: Roadmap for success of theranostics in India

i.e., physics, chemistry, biology, and of course mathematics. As the field of theranostics grows, it is essential to maintain coherence between different fast evolving facets of the field, which, if not orchestrated properly, may lead to loss of efficiency and efficacy of potentially life-changing treatment and diagnostic methods. India has recently shown the prowess in the field of vaccine production, which can be used to the benefit of producing peptides (used in PRRT) and antibodies in a GMP facility in India. Similarly, Indian scientists have been at the forefront of creating one of the most powerful artificial intelligence (AI) tools the world over. AI and machine learning can be so easily implemented in India because of the plethora of data already existing in various centers practicing theranostics in India. Given proper impetus, guidance, and support from academic and nonacademic centers and government as well as industries alike, theranostics in India has the potential to become the world (Citius, Altius, and Fortius) leader in precision "Radiomolecular Oncology" another name for "theranostics." It is also time, that Drug Controller General of India recognizes radiopharmaceuticals as a "drug." Figure 2 is the graphical representation of the various pillars, organizations, and partners which need to come together to make this ambitious vision a reality.

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Conflicts of interest

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