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International Journal of Cancer Biology and Clinical Oncology

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Review Article

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Radiopharmaceuticals Production for Theranostic Application and Nanoparticles in Cancer Treatment

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1 Abstract

In this review current production methods of radioisotopes and radiopharmaceuticals/reactors/Cyclotrons and the need for new theranostic radiopharmaceuticals are discussed. Radioisotopes and radiopharmaceuticals in theranostic nuclear medicine and innovation techniques in imaging/therapy are referred. Application, also, of nanomedicine in cancer disease is introduced. Nanomedicine in cancer diagnosis, prevention and treatment. Nanomedicine in theranostic approach. Alternative therapeutic and theranostic approaches are now feasible through the progress of nanotechnology. The applications of nanomedicine in tumour-related fields such as molecular imaging, hyperthermia/radiotherapy, immunotherapy, gene therapy, and chemo/radiotherapy are promising and should be incorporated into the clinical routine, providing new aspects of efficient cancer treatment.

2 Keywords: Medical radioisotopes; Radiopharmaceuticals production; Theranostic; SPECT; PET; Molecular imaging; Nanomedicine; Nanoparticles; Hyperthermia; Cancer therapy

3 Introduction

3.1. Medical radioisotopes

Advances in medical knowledge and better realizing disease processes are directing the search for early diagnosis/imaging methods and new therapy choices. Diagnostic and therapeutic applications, using radioisotopes and radiopharmaceuticals are the fundamentals in the expansion cause of these nuclear based services. Greater quantities of radioisotope products in centers around the world are essential. There is also a shift towards reduced dependence on long distance transport of radioisotope products. So, the scope for any mean change of radioactive sets is minimized. The ability to produce cost effective radiopharmaceuticals locally could have a significant impact, leading to increased need for best production procedures, quality assurance and guides. Radiopharmaceuticals are worthy tools not only for management of cancer diseases but also for better understanding human health and developing effective therapy options. In medical community, an interest for permanent, remarkable improvement in Nuclear Medicine is linked to the development of new radiopharmaceuticals and effective production of relevant radioisotopes.

Imaging remains an essential component of diagnosis, staging and response assessment in patients with cancer; clinicians increasingly seek to noninvasively inspection of tumour phenotypes and estimation of functional and molecular responses to therapy. That is theranostics - the combination of diagnostic imaging with targeted therapy - is becoming more widely applied. The study of theranostics combines molecular imaging with targeted radionuclide therapy, which involves the use of small molecules, peptides and/or antibodies as carriers for therapeutic radionuclides. Theranostics (or theragnostics) combines molecular imaging (primarily PET and SPECT) with targeted radionuclide therapy, typically with radionuclides that emit α-, β- or auger-radiation [1]. Although access to theranostics is expanding, challenges such as lack of isotope availability, shortages of trained personnel, regulatory burdens and costs might all limit the extent of global spreading [1].

3.2. Medical isotopes production

Radioactive isotopes are used in radioligand therapy -a type of cancer treatment - to target cancer cells. The radioisotopes are produced in special nuclear reactors or generators, then transported to a production facility where the radioisotope is connecting to the cell-targeting compound or ligand. One of the principal uses of medical isotopes is for diagnostic imaging of the human body. Radioactive isotope injected into the body for medical diagnostic images is assistance for examining how various tissues and internal organs of the patient are functioning. SPECT and PET studies, both diagnostic Nuclear Medicine imaging procedures, are critical using, in medical conditions where isotopes detect life-threatening. Radioligand is a radioactive biochemical substance used for diagnosis or for research-oriented study. Radioligand binding assays are extremely flexible, easy to perform [2]. More hard research and development on radioligand therapy to minimize the number of lives lost due to cancer every year, is a necessity. When radioligands attach to certain types of cancer cells in the body, there is a high possibility to obtain the proper diagnosis or treatment [3].

Radioactive medical isotopes, specific medical isotopes utilized to cancer therapeutics that effectively emit alpha (α) or beta (β) radiation, for very short periods, are applying to destroy cancer cells inside tumours. For therapeutics, high Linear Energy Transfer (LET) radiations such as alpha (α), beta (β-) or Auger electrons are utilized to kill cancerous cells locally, while saving the normal tissues surrounding the malignant tumour cells. Personalized cancer treatment obtained via Targeted Radionuclide Therapy (TRT) is of growing importance. Radionuclides with theranostic properties are proved to be clinically effective and widely used because diagnostic imaging and therapy are completing using a single preparation that avoids additional procedures and unnecessary radiation burden to the patient [4]. The availability of functional radiopharmaceuticals is one of the most significant features that lead to the sustainable development of Nuclear Medicine [5].

3.3. Current good manufacturing practices (cGMP)/ radiopharmaceutical production

The purpose of Good Manufacturing Practices (GMP) is to assure the identity, strength, quality, and purity of drug products. It includes establishing strong quality management systems, obtaining appropriate quality raw materials, creating strong operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. The current GMP conventional system of controls at a radiopharmaceutical production facility practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. It assures that drug products confront their quality criteria. This is achieved by verifying that manufacturers of pharmaceuticals adequately control production operations. The current GMP is not a management system. Instead, they are a set of principles compiled by the US Food and Drug Administration (FDA), which act as a minimum standard for operations in the pharmaceutical industry. The guidance of FDA admits the role and limitations of the cGMP and encourages organizations to adopt healthy and flexible systems for total quality management to overdo these requirements.

cGMP is designed to assist organizations verify that drug products have the correct identity, strength, purity, and quality. cGMP systems include a series of controls for quality focused operations, including:

- Management systems-quality raw materials-operating procedures.
- Detecting deviations-investigating deviations-reliable testing.

If cGMP is followed, organizations can avoid many of the most common causes of quality failure which threaten patient safety, such as drug contamination or variations. The FDA declares that cGMP is designed for flexibility to provide a universal basis for the pharmaceutical industry totally. The guidelines are a set of "minimum requirements" for entire quality management [6,7]. Current Good Manufacturing Practices (cGMP) can be summarized as the necessary level of control over the operation and administration of facilities, methods and processes which will lead to the manufacture of radiopharmaceutical products of reliably high quality and they meet the requirements for safety and effectiveness that are indicated.

3.3.1. Production environment and radiation protection

A radiopharmaceutical production facility includes several area types and the equipment that exists in those areas. Some of them in the production environment are:

- Open or Uncontrolled areas - these are the normal laboratory areas.
- Zones that are used to manufacture radiopharmaceuticals and must comply with cGMP regulations.

Production Equipment and Instruments include all the equipment to produce the radiopharmaceutical and the instruments used to analyse the final product. Radiation protection is of high concern in a production facility. There are regulations concerning the managing of radiation. Instruments are required to measure the levels of radioactivity in a laboratory to ensure it is always restricted. In Nuclear Medicine, equipment is sensitive to small amounts of radiation and to different types of radioisotopes. The radioisotopes are usually eliminated by the patient just after the study has been done in a short period of time. This time is a function of the physical half-life of the isotope and the patient excretion system. The time elapse for elimination of any radioisotope used for study is the Effective Half Life. It is related to the physical half time of the isotope and the biological half time of the patient's system [8].

3.3.2. Quality assurance and quality management

Quality Assurance is a way of thinking to ensure that the product being produced is effective and safe for human use. Quality Assurance includes the validation of equipment, the validation of the process, and the documentation. A revised guideline has been written by members of the European Association of Nuclear Medicine (EANM) Radiopharmacy Committee and is intended to assist professionals involved in the preparation and quality control of radiopharmaceuticals. The Editorial Board of EJNMMI Radiopharmacy and Chemistry releases a biyearly highlight commentary to update the readership on trends in the field of radiopharmaceutical development. This guideline on current good Radiopharmacy Practice (GRPP) for Small-Scale Preparation of Radiopharmaceuticals (SSRP) represents the view of the Radiopharmacy Committee of the European Association of Nuclear Medicine (EANM)]. General aspects which are applicable to all levels of operations and the preparation of Small-Scale Radiopharmaceuticals (SSRP) using licensed generators and kits are considered [9]. Moreover, the more complex preparation of SSRP from non-licensed starting materials, often requiring a purification procedure and sterile filtration, is shown. The purpose is that the guideline will support radiopharmacies in the preparation of diagnostic and therapeutic SSRP's safe for human administration [10]. A Quality Management System (QMS) is the way that an organization could direct and control those activities that are related, either directly or indirectly, to achieve planned operational results [11].

3.3.3. Quality control product release and validation

Quality Control (QC) of the final product is one of the most critical steps in the production of radiopharmaceuticals. It is where the final determination is made as to whether the radiopharmaceutical can be used in a patient. There are extensive regulations from distinct governing bodies which administer these tests and regulate production. The testing, for example, that is done for PET radiopharmaceuticals has to be done promptly since the half-life of the radiopharmaceutical is short. There are a series of very specific tests which must be carried out. These include tests of both chemical and radiochemical purity, configuration of radiochemical identity, pH, sterility and to ensure that the dose does not contain dangerous levels of pyrogens. Before a product is released for clinical use, it must be approved. This can only be done by an authorized qualified person. It must be reassured that the equipment is designed to perform the tests, it is installed appropriately, it is operating correctly and it is performing properly. This is part of the Quality Assurance (QA) function [12].

Validation of the whole process is essential. Some tests such as the sterility test cannot be completed before the product is delivered. First stage in validation is to create a Validation Master Plan (VMP). The Validation Master Plan documents include the way the facility will operate, who has control over the various aspects of the validation performance; How production and quality control, or personnel management will be faced. All the equipment used in the manufacture of any radiopharmaceutical must be validated to be sure that it will give accurate and meaningful results for all the tests required before the product is released for human use [13].

3.4. Radiopharmaceutical production systems

3.4.1. Accelerators

Accelerators are machines that use electromagnetic fields to accelerate charged particles and to focus them on beams. They are mainly used for industrial and medical applications. The output of a particle accelerator can generally be directed towards multiple lines of experiments, one at a given time, by means of a deviating electromagnet. An electromagnet is a type of magnet in which the magnetic field is produced by an electric current. Electromagnets usually consist of wire wound into a coil. A current through the wire creates a magnetic field which is concentrated in the hole in the centre of the coil. The magnetic field disappears when the current is turned off (Wikipedia, free encyclopaedia). The main advantage of an electromagnet over a permanent magnet is that the magnetic field can be quickly changed by controlling the amount of electric current in the curving. However, unlike a permanent magnet, an electromagnet requires a continuous supply of current to maintain the magnetic field. Though, it operates multiple experiments without the need to shut-down the entire accelerator beam.

The purpose of an accelerator, except for synchrotron radiation sources, is to generate high-energy particles for interaction with matter. It is usually a fixed target in an accelerator which is designed as a neutron source. A positively charged particle enters a negative electrode and gets accelerated. The polarity of the electrode is reversed in order to push the particle to the next electrode. As the energy of the particle is increased the length of the electrodes is also increased (Figure 1). As there is a need for charged particles, high energy particles are used to interact and produce radioisotopes. The alpha particles are deflected when come close to the nucleus. So, particles cannot enter the nucleus of an atom unless the coulomb barrier is overcome. Hence, high energy particles are needed.

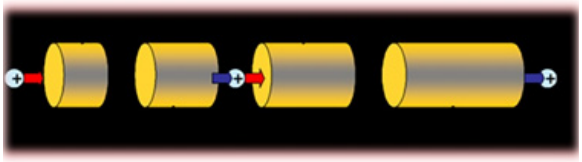

Figure 1: A particle accelerator.

An unstable nucleus can decay by emitting an alpha particle, a ß- (beta minus) particle, a ß+ (positron), a gamma ray or in some cases a single neutron (Figure 2) [14].

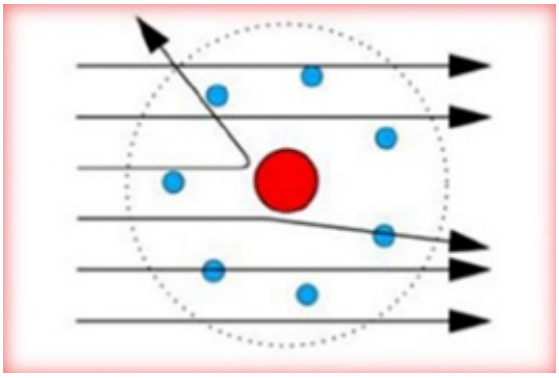

Figure 2: Charge particles are deflected by the nucleus.

There is a need of high energy charge particles, to interact with the nucleus of an atom and not be deflected. As the particle passes through the electrodes, it becomes energetic or charged particle. For example, if the nucleus is unstably large, it will emit a group of 2 protons and 2 neutrons called an alpha particle. An alpha particle is also a helium-4 nucleus, so it is written as 42He too. Alpha decay causes the mass number of the nucleus to decrease by four and the atomic number of the nucleus to decrease by two (Figure 3).

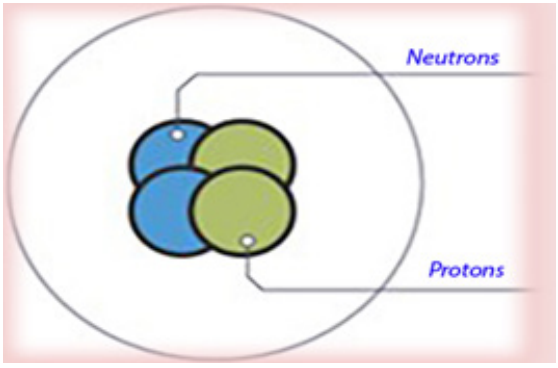

Figure 3: An alpha particle (2 protons and 2 neutrons).

3.4.2. Production by cyclotron

The cyclotron is a particle accelerator which is used to produce the radionuclides. It accelerates a charged particle to very high energies. The charged particle will be, most often, a negatively charged hydrogen ion. The particle track in a cyclotron is a spiral outward from the centre of the circular machine, so the accelerated particles emerge from a fixed point as for a linear accelerator. The alpha particles are deflected when come close to the nucleus. So, particles cannot enter the nucleus of an atom unless the Coulomb Barrier is overcome. Hence, high energy particles are needed to interact and produce radioisotopes

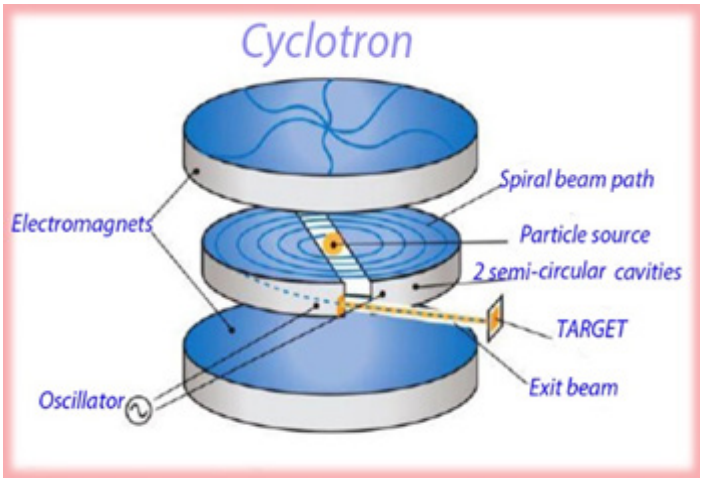

Figure 4: A cyclotron uses a pair of hollow electrodes which are of the shape of 'D' (dee) arranged in opposite configuration with a gap. These electrodesare held between the poles of a magnet which produces a uniform vertical field. An alternating voltage is applied to the electrodes.

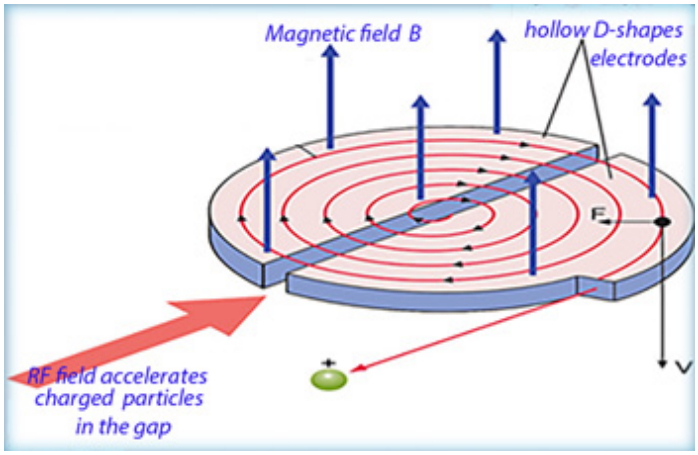

Figure 5: In a cyclotron a charged particle executes a spiral trajectory under the influence of a RF field and a perpendicular uniform magnetic field.

(Figures 4 and 5). Superconducting magnets have played an important role in the development of the cyclotron [15]. Cyclotrons have been very successful in accelerating light to heavy particles. The beam injection in a cyclotron is done using either a linear accelerator or by an electron cyclotron resonance (ECR) source. This class of accelerators have been very popular in the production of radioisotopes used as particle therapy for the treatment of cancer. ECR is a phenomenon observed in plasma physics, condensed matter physics and accelerator physics (ECR, Wikipedia) [15,16].

Beams available in cyclotrons could be Proton beam (H+), made by ionization of hydrogen, Deuteron beam (d+), Deuterium beam made by ionization of deuterium gas or Alpha beam (3He+ and 4He+). A proton beam comes to most Nuclear Medicine applications. An ion source kept in the gap at the center produces ions which get attracted by the first electrode. The ions execute circular motion inside the electrode -in a magnetic field-and get attracted across the gap by the second electrode when they emerge from the first electrode; the polarity of the second electrode is opposite. The ions again execute circular motion in the second electrode and get accelerated in the gap by the first electrode. Ions after acceleration gain energy and move in a larger circle. The process of acceleration in the gap lasts and the ions go on to move in circles of increasing radii till they leave the dee through an extraction route. Superconducting magnets have played an important role in the development of the cyclotron. Cyclotrons have been very successful in accelerating light to very heavy particles. Since a nucleus contains many protons and neutrons the nuclei energy will be much smaller. The beam injection in a cyclotron is done usually by a linear accelerator. These accelerators are often used in the production of radioisotopes as tracer elements and particle therapy for the treatment of cancer.

When high enough energy is obtained by the charged particle, it is directed out of the cyclotron and hits a target material, the Targetry and creates the radionuclide. Once the radionuclide is made, it may be extracted from the targetry. It must then be transferred out of the cyclotron cellar into the chemistry laboratory in the facility. This may be a short distance through a wall or a rather long distance depending on the placement of the cyclotron in the service. This time, the radiopharmaceutical will be produced. The medical cyclotron system should be located and installed either in a hospital or in industrial premises. The location area should be out of residential or public premises, within a radius of 30 m from them.

3.4.3. Targetry types

Gases, liquids or solids should be used as target materials to produce radionuclides depending on the specific radioisotope being produced. Targets are, consequently, designed to accommodate the material being irradiated. The design of the target will also vary on whether the target is placed inside (internal) or outside (external) the cyclotron. When irradiating a gaseous target material, the targets are usually of cylinder or capsule form to hold the gas under pressure. A thin beam entry foil allowing the projectile to penetrate the target is usually referred to as a window. The temperature inside the target will affect the product spreading. The effect of temperature on the density drop can be very high, depending on the beam current or the total power delivered to the gas. Temperatures inside a gas target can be several hundred Celsius degrees. Cooling is a major issue for gas targets since gases are weak heat conductors and compared with solids or liquids need more volume to contact the same irradiated mass of target material.

In the case of liquids, the target material occupies a specific volume unless the liquid is vaporized. During normal production conditions, the water reaches the boiling point and stays at that temperature during the irradiation. The boiling point of the water may be increased by pressing the target. When the target is boiling, the production of the radionuclides is lower than if the target remains liquid. By making the target much longer than the size of the particle path, production can be increased, though boiling. The liquid is typically added to and removed from the target remotely with the target attached to the cyclotron [17,18]. The density of solids is typically higher than that of liquids or gases, the path length of the beam is shorter and the target considerably smaller. The solid can be in many forms (foil or powder, electroplated, melted, vapour deposited). If the solid is a good heat conductor, the beam can typically be perpendicular to the solid.

Optimal separation techniques for cyclotron-based radionuclides are essential to achieve high specific activity and chemical purity suitable for radiopharmaceutical production. There is a significant possibility at facilities with cyclotrons for the production and development of alternative radionuclides and new radiopharmaceuticals, other than traditional radionuclides. Two of these potential radionuclides are Actinium (Ac-225) and Astatine (At-211). IAEA report4 (2021) provides guidelines and methods for developing targets and the chemistry for the separation of radionuclides from target materials, as well as many references to relevant literature [19].

3.4.4. Cyclotron targetry

The goal of cyclotron targetry is to get the target material into the beam, keep it there during irradiation and remove the produced radionuclide from the target material quickly and efficiently after irradiation, usually with some level of automation for reduction of personnel dose. The design of the target should be well matched to the characteristics of the cyclotron otherwise the production of radionuclides may be not optimal.

The design of targets associated with one cyclotron may not be optimal for a different cyclotron.

1. Further than the characteristics of mechanical design, beam energy and beam current, the beam size and profile are the major variables that impact on target design.

2. There are often significant differences in the characteristics of the beam profile between a positive ion cyclotron and a negative ion cyclotron.

a) The negative ion cyclotron usually has a more uniform beam profile incident on the target. This is a result of the extraction process through a peeling off foil, which tends to remove hot spots in the beam. Focusing magnets and steering magnets along the transport line, if there is one, can alter the beam to a more homogeneous shape.

b) The positive ion cyclotron may have a uniform beam profile, or the profile may be quite 'hot' in spots and not uniform at all, depending on the extraction characteristics and focusing magnets used to transport the beam. In general, the extraction process for positive ions tends to create areas of high intensity particles in the beam.

Most of the newer, commercially available cyclotrons are negative ion cyclotrons and have targets mounted directly on the cyclotron without any focusing or steering magnets to alter the beam shape. While this concept is acceptable for liquid and gaseous targets, the fact that there is no possibility to alter the beam profile may be a challenge for the irradiation of solid targets with low heat conductivity, while hot spots in the beam can damage or even destroy the irradiated material [20]. Manufacturers usually provide targets that are well suited to their cyclotron, but they are designed for radionuclides that are more commonly produced such as F-18, C-11 or I-123. Targets to produce alternative radionuclides often have very different physical and chemical characteristics from the more common ones. So, it is important to understand some of the basic principles involved in target design [18].

3.5. Nuclear research reactors in medicine

Nuclear research reactors play a vital role in the production of medical radionuclides for incorporation into clinical radiopharmaceuticals. Research reactors are nuclear reactors used for research, development, education and training next generation experts of nuclear engineers. They don't generate power. They produce vital neutrons widely used in medicine. The interruption of medical radionuclide supplies in recent years, has emphasized the importance of ongoing research reactor operation. Several types of nuclear research reactors, with their operating power and the effects of thermal neutron flux produce desirable radionuclides, with high specific activity, for clinical applications. Radioisotope production in reactors is based on neutron capture in a target material, either by activation or generation of radioisotopes from fission of the target material by bombardment with thermal neutrons [21].

The effective Quality Control (QC) processes provided by advanced technology improves the national and international capabilities of research reactor facilities. The IAEA Research Reactor Database (RRDB) is an authoritative database containing technical information on Research Reactors. 841 reactors totally are established in 70 countries, 222 are operational in 55 countries and 23 research reactors are under construction in 16countries, worldwide [22]. Research reactors and accelerators are also used to develop new radioisotopes for diagnostics and therapy in nuclear medicine, non-destructive testing and radiotracer industrial applications, as well as for radiotracer studies in scientific research. "Medical Isotopes - Challenges and opportunities for a sustainable supply" was an analytical panel discussion, in the European Research Reactor Conference, in Budapest 2022, for production and supply of medical isotopes [23].

3.6. Radionuclide generators

A radionuclide generator is a self-contained system housing an equilibrium mixture of a parent/daughter radionuclide pair and designed to provide the daughter radionuclide formed by the decay of a parent radionuclide in acceptable purity and safety. Radionuclide generators have traditionally represented

important radionuclide systems which provide both diagnostic and therapeutic radionuclides. The parent–daughter nuclear relationships would give the option of withdrawing the short-lived daughter at suitable time intervals. The radionuclide generators' technologies are subjected to a continuous innovation. At starting are the generators that provide ready-to-use solution of the radionuclide of interest, as Mo-99/Tc-99m generators, and at the end are the generators, that necessitate further manipulation of their eluate to gain radionuclide of required purity and radioactive concentration for the preparation of radiopharmaceuticals at hospital [24].

3.6.1. Generators for therapeutic radionuclides

Radionuclide generator development and use are expected to be a major area of research. The economic prospects associated with the use of radionuclide generators have led to an extension of their use in therapeutic and positron emitting radionuclides production. In the field of unsealed sources for radionuclide therapy, there are various generator-derived radionuclides which include both beta- and alpha-emitting daughters, as well as Auger emitters. Radionuclide generators providing therapeutic radionuclides are ideal for therapy as the emitted radiation has high Linear Energy Transfer (LET) and consequently high Relative Biological Effect (RBE). Targeted alpha-therapy has drawn the attention and imagination of the Nuclear Medicine community. Probably the generator derived radionuclides providing alpha-particle emitters will have an effective role in targeted therapy. From the tungsten-188/rhenium-188 (W-188/Re-188) generator, Re-188 a high energy -emitting radioisotope is obtained to be applied in various nuclear medicine therapies. Parent radionuclide, tungsten-188 (W-188) with a half-life equal to 69.4 d, is produced in a nuclear reactor by irradiation of tungsten oxide, 96.07% enrichment in tungsten-188 (W-188) with thermal and high energy neutrons. Re-188 can be produced by a W-188/Re-188 on-site generator in a convenient and inexpensive way in many hospitals. Its attractive physical properties and its potential low cost associated with a long-lived parent make it an interesting option for clinical use. The simple daily uses of W-188/Re-188 generator in nuclear medicine departments, its clinical efficacy for several therapeutic applications of a variety of Re-188-labeled agents are its use advantages. The high energy of the -emission of Re-188 is particularly well suited for effective penetration in solid tumours [25].

Radionuclide generators providing Auger electrons or perhaps conversion electron-emitting radionuclides for targeted therapy continues to be discussed, but the availability of these systems is still in its early development. Auger electron emitting radionuclides are proposed for radionuclide therapy as they deposit the energy in sub-cellular dimension providing high radiobiological effects. Less cytotoxicity is produced when the radionuclides are deposited in the cytoplasm; Auger electron emitters would be incorporated into the nucleus of the target cells [26].

3.6.2. Manual and automated generators

The technological difficulty of radionuclide generator systems has become a key area of research and development. Manual generator system remains as the mainstay for most routine preparation of radiopharmaceuticals in hospital despite individualized efforts towards automation. Automated generators provide numerous of benefits, as reduction of the radiation exposure to personnel, reduction of the probability of human errors, and provision on-line documentation of the manufacturing process thus improving GMP agreement. Other benefits of automated systems include severe devotion of sterility and pyrogenicity requirements, set reproducibility, purity and radioactive concentration. Remarkable advances in the development and availability of automated elution, concentration and radiopharmaceutical preparation systems have been done. The generator produced radionuclides must comply with pharmacopoeia requirements including the chemical, radiochemical and radionuclide purities as well as sterility.

Moreover, central radiopharmacies play a major role in supplying unit doses. Major benefits of using centralized radiopharmacy services include efficient and optimum use of resources, ability to dispense patient specific doses, same day delivery of radionuclide, simplification of regulatory and practice-based efficient storage and management of radioactive waste [25].

3.6.3. Optimization of generator performance

Optimization methods of the daughter nuclide build-up versus stand-by time and/or specific activity were developed by Van So Le et al. for increasing the performance of radionuclide generators [27]. The separation of the daughter radionuclide from its parent should be performed at a defined optimal time to avoid the deterioration in specific activity of the daughter and wasting stand-by time of the generator, while the daughter radionuclide production is maintained to a reasonably high extent. A method of "early elution schedule" was developed for increasing the daughter radionuclide production and specific radioactivity. As a result, the cost of the generator is saved and the quality of the daughter radionuclide solution is improved. Spectrometric measurements of very low activity of impure radionuclide contamination are useful in a radioisotope product of much higher activity used in molecular PET and SPECT imaging and monoclonal antibody/peptide-targeted radiotherapy.

3.7. Proton Linacs and neutron generators

Currently, cyclotrons remain the primary facilities for accelerator-based medical isotope production, although Linacs and neutron generators are rapidly becoming viable alternatives. Cyclotrons with adjustable energy ranges or medium energy can produce various kinds of medical isotopes and can cover most radiopharmaceutical production needs in a region. Though, collect and purity improvements in medical isotopes and the overall cost of cyclotron production have led researchers to explore further possibilities. The design of a Linac depends on the type of particle that is being accelerated: electrons, protons or ions. Linacs range from a short size of some cm to 3.2-kilometre-long (2.0 mi) Linac [28]. Proton Linacs is the first choice as it has advantages in providing proton beams in tens to hundreds of MeV. These Linacs can be developed in research institutes conducting

scientific experiments and physical research at the same time. The cross-section of photonuclear interactions of electron Linacs is relatively low and restricts their practical applications. Main roles in the evaluation of production methodology play the impurity products and the economic costs.

Radioisotopes are produced using linear electron accelerators and address production and separation issues of photoneutron (γ,n) and photoproton (γ,p) reactions. Though (γ,n) reactions typically result in greater quantities, separating product nuclides from the target is questioning since the chemical properties of both are the same. Produces of (γ,p) reactions are typically lower than (γ,n) ones, however they have the advantage that target and product nuclides belong to different chemical species so their separation is not such an intricated problem. Refining the neutron flux rate is a first issue for the realization of medical isotope production through neutron generators. Finally, to produce medical isotopes, the use of accelerator-based techniques has a high interest as medical isotopes generated by reactors frequently encounter supply shortages.

3.8. Radiopharmaceuticals for theranostics

In theranostics, radiopharmaceuticals can be used to perform diagnostic imaging and medical treatment. Imaging diagnosis is used to determine an optimal treatment modality and can help monitor and evaluate the medical treatment progress. Currently, radiopharmaceuticals for theranostics use either the same radiopharmaceutical, which emits rays for diagnosis and particles for treatment, or two different radiopharmaceuticals (one for diagnosis and the other for treatment). Radiopharmaceuticals for theranostics have developed rapidly in recent years with great progress in treating tumours and other diseases. The growing interest in the theranostic approach, that is, using the same vector molecule targeted to the disease lesion for delivering the diagnostic radioisotope for imaging and therapeutic radioisotope (usually beta emitters and alpha emitters) for targeted therapy, considerable research is effort in many countries. Lutetium-177 is a unique example of a therapeutic radioisotope which can be widely produced throughout the world in research reactors. High specific activity is a characteristic and relatively high specific activity of Lu177 can be readily produced in modest flux reactors by the "direct" route [29,30].

Greater availability of therapeutic radioisotopes is required to meet the demands for increasing clinical applications in nuclear medicine. Because of the need for very high specific activity products, methods other than direct neutron capture reactions are required to ensure that the highest specific activity and hopefully no carrier added (n.c.a) radioisotopes are available.

Two major methods to obtain n.c.a radioisotopes from reactors are:

- Using radionuclide generator systems by reactor produced parents and
- The formation of desired radioisotopes through beta-decay of reactor-produced species.

An example of recent development of new approaches to obtain n.c.a is Lu177 from the decay of reactor-produced Yb177 and free of the long-lived Lu-177m (T1/2= 160d) radio-contaminant.

Real advantage is that many low to modest thermal flux reactors can be used. Lutetium177 is a rare example which can be reactor produced with very high specific activity - good half-life, for distribution - good chemistry and its production capacity goes over current needs (Figure 6).

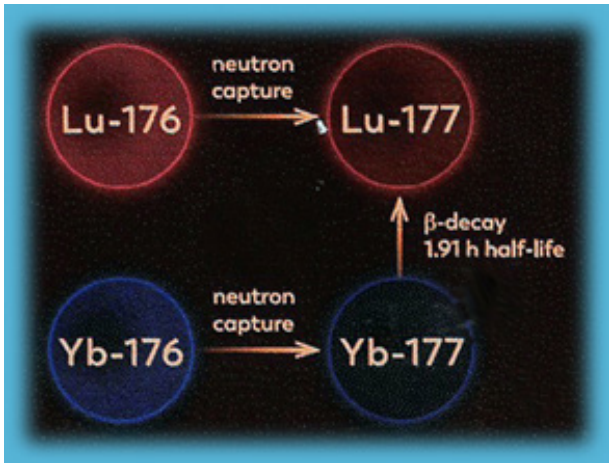

Figure 6: Diagram of possible production routes for Lu-177.

Neutron irradiation of Lu-176 produces carrier added Lu-177, while neutron irradiation of Yb-176 indirectly leads to no carrier added Lu-177 via successive decay. There is no possible production route of Lu-177 without neutron irradiation [29,30].

Another theranostic case is Cu-64 and Cu-67 isotopes.

The chemical identities of Cu-64 and Cu-67 isotopes allow for convenient use of the same chelating molecules for sequential PET imaging and radiotherapy. Copper-64 (T1/2 = 12.7 h) is a positron and beta-emitting isotope, with decay characteristics suitable for both PET imaging and radiotherapy of cancer. Copper-67 (T1/2 = 61.8 h) is a beta and gamma emitter, appropriate for radiotherapy and with a half-life suitable for SPECT imaging. A recent breakthrough in Cu-67 production opened opportunities for a reliable source of Cu-67 with high specific activity and purity [31-34].

3.9. The Status of Medical Isotope Production

Radioisotopes are divided into natural and artificial radioisotopes. At present, there are about 200 radioisotopes in use, most of which are produced artificially. With the widespread usage of radiopharmaceuticals, the constant production and supply of medical isotopes are significant. The locally used generators continue to offer easy and reliable application in Radiopharmaceutical Therapy (RPT) [35]. Medical isotopes are largely produced via either reactors or accelerators. Typically, reactor-based medical isotopes are neutron-rich isotopes generally characterized by along half-life, while accelerator-based medical isotopes tend to offer a shorter half-life and usually emit positrons or rays.

Reactor irradiation is currently the most used method to produce medical isotopes due to their high production, low cost and ease of target preparation. However, this supply is sustained

by reactors that were built in the 1950-60s. Many of these reactors will gradually shut down before 2030. Additionally, due to their age and as part of the decommissioning process, reactors can be expected to have longer periods of down time, due to maintenance or unplanned shutdown events for safety or technical reasons. This situation increases the risk of supply disruptions and continual shortages. The growing interest and recent improvements in accelerator technologies have already led some medical isotopes produced through reactors to be replaced or partly replaced by accelerator-produced isotopes [32-34]. There are many advantages to using medical isotopes produced by accelerators. These are:

1. Management is easier, and safety is improved.
2. The maintenance and decommissioning costs are lower.
3. The volume of radioactive waste formed is less than 10% of the quantity produced by a reactor and the radiation levels are lesser.
4. It has no risk of nuclear spread.

An examination and comparison of cyclotrons that are available in the international market about the production of imaging and therapeutic radioisotopes, for the diagnosis and treatment of cancer, shows that 23 different cyclotron models manufactured by 6 suppliers. The types of radioisotopes that can be produced with those cyclotrons have been studied [36], with a division between their use either for imaging or for radiopharmaceutical therapy. Superconducting cyclotrons suitable for irradiating cancerous tissues with protons are increased. We indicate that the field of Radiopharmaceutical Therapy is expanding, and new standards and reliable applications are producing.

4. New Trends in Radiopharmaceuticals

4.1. 'New' needs

Nowadays, world keeps changing in all aspects, such as technologically, financially, politically and sociologically. These changes affect all aspects of life on earth. One of them is the health system and more specifically the new potentials of nuclear medicine towards the diagnosis and therapy of a wide range of pathologies. Technology progress in molecular imaging is gigantic: new materials are used in the manufacturing of the detectors allowing a more efficient and reliable operation, faster computer processors along with larger memory allow the capture of images while simultaneously reconstruction of images is achieved at high number of frames per second, new data analysis software packages have been developed that allow a wide range of data analysis capabilities, both qualitatively and quantitatively. In parallel, in radiopharmacy various clinical as well as meta-analysis studies have demonstrated the potential of new radio complex molecules that could act as diagnostic or therapeutic radiopharmaceuticals. All above could cover the medical needs for new radiopharmaceuticals for a wide range of pathologies that nuclear medicine could contribute constructively either on the basis of diagnosis, such as differential diagnosis and extent of pathology, or on the basis of therapy.

The fulfillment of such a need for new radiopharmaceuticals is a mirror of the so-called nuclear market, i.e. type of market, type and number of available technologies, quantity and type of demand, production lines and capabilities, national radioprotection rules, health infrastructure, social-financial characteristics, geographical characteristics and transportation infrastructure.

The orientation and the speed of developing new radiopharmaceuticals can be assessed considering the needs of the so-called demand group, such as the medical doctors, surgeons, radiotherapists and radiologists and those of the so-called supply group, such as R&D, suppliers, sales, marketing, distributors' possibilities and priorities. All those can be assessed in accordance to the various International Societies and Associations of Nuclear Medicine. The trends towards the development of new radiopharmaceuticals are a function of the requests by the attending physicians of a wide range of specialties, such as neurologists, oncologists, cardiologists, rheumatologists, etc. The major current trend is the generation of α-radioimmunotherapy treatment schemes regarding the therapy part, while for diagnosis is the optimization of 99Mo generators and its guaranteed supply. Nowadays, nuclear medicine has to fulfill the need generated by increasing incidence throughout pathologies and in the meantime maintain the spectrum of targeted pathologies. A major drawback towards the development of new radiopharmaceuticals is the value of the half-time: a short half-time of a new radiopharmaceutical is limiting its use on certain nuclear medicine departments that they either accommodate their own cyclotrons or they are at close distance to other production lines. Half-time is a unique characteristic of each radionuclide and it cannot be manipulated according to needs and therefore it is a factor that limits the use of new radiopharmaceuticals.

Currently, neurology is a fruitful field for the generation of new radiopharmaceuticals, mainly towards diagnosis having to compete an alternative imaging modality that of Magnetic Resonance Imaging (MRI) and its various techniques: Magnetic Resonance Spectroscopy (MRS), Functional (fMRI), Perfusion, Diffusion, Diffusion Tensor Imaging (DTI), etc. Furthermore, market size, competition, product portfolios, healthcare budgets and running costs paly a fundamental role towards decision-making [37-46].

4.2. Diagnosis and therapy in nuclear medicine

Radionuclides are classified with respect to their use, i.e. diagnostic and therapeutical ones. Radionuclides used in therapeutical procedures are classified as alpha, beta and brachytherapy ones. Radionuclides used in diagnostic procedures are classified as SPECT and PET [37]. Radionuclides currently used in SPECT are 99mTc, 102Tl, 123I, 67Ga, while those used in PET are 18F, 82Rb and other. Low prices, availability, in house generation and handling, binding properties, easy transportation, suited lifetime for diagnostic processes and low dose are their characteristics that established them in nuclear medicine [37-39]. Radionuclides used in therapies are the 223Ra as an alpha emitter; 131I, 90Y, 177Lu, 153Sm, 186Rn, etc as beta emitters and 125I, 192Ir, 103Pd, 131Cs, etc in brachytherapy procedures [42, 43, 46].

4.2.1. Radionuclides in SPECT studies

Currently, diagnostic nuclear medicine accounts for the larger portion of nuclear medicine procedures, almost 60%. Almost 60% of this portion is occupied by SPECT exams and the other 40% by PET exams. Increase in the SPECT and PET procedures worldwide is expected for the next decade as well as the introduction of new radionuclides due to the following facts: i) higher life expectancy, ii) increased population worldwide, iii) increased number of detected tumors, iv) increased numbers of cardiological pathologies, v) increased availability and accessibility of nuclear medicine services and vi) hardware and software developments in molecular imaging modalities. Especially, a further increase of PET examinations is expected due to the development of new radionuclides which will be more specific and more sensitive to the type of tumor [37-40]. Regarding SPECT radionuclides, such as 99mTc, 201Tl, 123I have been used successfully more decades in nuclear medicine diagnosis. Most of the nuclear medicine procedures use 99mTc as radionuclide along with a specific binding molecule (agents). It is used in approximately 85% of diagnostic scans worldwide for brain, bone, lungs, kidneys, etc. Recently, lack of supply of 99Mo/99mTc worldwide is experienced due to the increased number of such examinations taking place worldwide, lack of raw materials and shutdown of nuclear reactors producing 99mTc. Therefore, currently alternate routes of producing 99mTc are explored, such as 99mTc cyclotron generated, or using low-enriched uranium [38-41].

18F as NaF (in PET/CT) is currently explored as an alternative to 99mTc for Bone Scans, as it is easily produced in cyclotrons, with the same radiation dose and high diagnostic accuracy [46]. 82Rb in PET/CT could be used alternatively in myocardial perfusion imaging, instead of 99mTc Sestamibi, considering that it has lower radiation dose, high diagnostic accuracy and it is generator produced. Furthermore, 201Tl could be used for the same type of examination with the advantage of better viable myocardium imaging. 201Tl covers the needs of patients with cardiac problems, such as myocardial blood flow, angiography of coronary arteries, etc. Increase incidence of heart diseases will prompt an equal increase of using 201Tl in nuclear medicine examinations [46]. 123I is a radionuclide used in diagnosis due to the fact that it emits gamma rays and its advantage is that a small activity of it is required reducing like this exposure to radiation. It is mainly used for thyroid cancer and the adrenal medulla [46].

67Ga is another radionuclide used in diagnosis. Its use is expected to increase further in the future due to i) its long halftime, ii) capability to image infections, such as sarcoidosis, lymphoma, hepatoma, etc [37,41]. Use of other radiotracers, such as 133Xe, used in brain blood flow and 111In for blood examinations are increasingly used due to their unique advantages. Development of new SPECT radiotracers are limited due to the fact that the already used ones cover the diagnostic needs for all anatomies and pathologies satisfactory [46].

4.2.2. Radionuclides in PET studies

The most commonly used radionuclides in PET examinations are the 18F and 82Rb. The former is currently used in almost 99% of the diagnostic examinations due to its halftime (110 min). It is used in oncology. 68Ga is currently used as an alternate of 18F for various cancerous pathologies that targets gastro/enteron/pancreatic neuroendocrine tumors and its use is rapidly expanding. 82Rb is a radionuclide used in myocardial perfusion studies with promising preliminary results. Other PET radiotracers, such as 11C, 13N, 64Cu, 124I, etc are used in specific sites that are equipped with high tech, such as in house cyclotrons, state-of-the-art hot-labs and PET/CT or PET/MRI systems [37]. Regarding positron emitting radiometal nuclides for PET studies, on the one hand radionuclides such as 43Sc (t1/2=3.9 h), 44Sc (t1/2=4.0 h), 61Cu (t1/2=3.3 h) and 86Y (t1/2=14.7 h), provide a diagnostic role towards the diagnosis of various types of cancers. On the other hand, the radionuclides of 47Sc (t1/2=3.3 d), 67Cu (t1/2=62.0 h), and 90Y (t1/2=64.0 h), provide a therapeutic role. The combination of those two leads to a theranostic approach. Limitations towards the use of those radionuclides are the complex chemistry procedures involved and experience is ad-hoc [44]. Applications of PET/CT within Oncology, Cardiology and Neurology keep increasing as a result of higher incidence and of more access to nuclear medicine diagnosis procedures worldwide, considering that 18F PET/CT is characterized by high specificity and sensitivity with respect to other radiopharmaceuticals. Oncology will remain the main driving force for new radiopharmaceuticals in this field [37, 38, 41, 42].

4.2.3. Radionuclides in therapy

Radionuclides used in therapeutical procedures in nuclear medicine have been used for decades. The advantage of this approach is that it is non-invasive, like surgery and it lacks side-effects, as in chemotherapy. There are various radiotracers currently used depending on the type of malignancy and its extent [43-46]:

- Alpha emitters: 223Ra is the only alpha emitter radionuclide that is used. It generates high energy alpha radiation at a short distance in a small volume and it is used for bone metastasis and various types of blood cancers. Work on the use of alpha emitters in conjunction with monoclonal antibodies is currently under investigation.

- Beta emitters: 177Lu, 131I, 90Y, 153Sm have been used successfully towards the treatment of various types of cancer.

177Lu is used for treating neuroblastomas and paragangliomas. 131I is used towards the treatment of thyroid cancer, non-Hodgkin's lymphoma and neuroblastoma; 90Y is used for liver and hepatocellular cancer; 153Sm is mainly used to ease the pain generated by bone metastasis, as well as in lung, breast cancer and osteosarcoma.

All above radionuclides will be increasingly used in the future due to the expected increased incidence of those types of tumors. Nowadays, 186Re, 188Re and 117mSn are under assessment towards their therapeutical results. Furthermore, new β-emitters are developed such as 67Cu, 90Sr, 188Re, 32P, 33P for the treatment of cervical, breast, gastrointestinal and renal tumors.

The specificity and low cost of those are of high advantages. However, lack of know-how towards handling and assessing them currently slows advancement and wide use.

- Brachytherapy: in brachytherapy treatments seeds with encapsulated radionuclides that generate either low-dose-rate or high-dose-rate are delivered to the cancerous volume in a temporary or permanent plan. 125I, 103Pd, 131Cs, 137Cs, 60Co and 192Ir are the most commonly used radionuclides. Target tumors are cervical, prostate, brain, skin, etc.

The use of therapeutic radiopharmaceuticals is continuously increased driven by the oncology sector. Alternative treatments, such as surgery, radiotherapy and chemotherapy can either be not feasible or accompanied by serious toxic effects provide space for the use of therapeutic radiopharmaceuticals that target specific type of cells, with low large range radiation, without interfering with neighboring cells. Half-time of the radionuclide used can be an issue for persistent type of tumors that will require seeds replacement. This is the main drawback of the brachytherapy approach. Brachytherapy has expanded in the last decade and is expected to keep rising, although at a slower rate than the rest of therapeutic radiopharmaceuticals. Therapies involving 125I, 192Ir, 131Cs are widely used as well as new radiopharmaceuticals, such as 60Co, 106Ru and 137Cs [43-45].

5. Applications of Nanomedicine in Cancer Disease

Cancer disease is a major health issue, beginning with genetic and epigenetic alterations. Although continuous efforts have been made to improve the conventional approaches, regarding prevention, diagnosis and therapeutics, there are still aspects that can be further optimized [46]. Precision medicine, personalized medicine, artificial intelligence, and nanomedicine can significantly contribute, supplementing or replacing old-fashioned procedures [47]. In this sub-unit we will focus on the main achievements of nanomedicine in cancer disease until now, also presenting some predictions of the future perspectives in this field.

5.1. Nanomedicine in cancer prevention

Cancer is undoubtedly a serious and multivariate disease. According to World Health Organization (WHO), cancer is the second leading cause of death, worldwide [48]. A significant percentage of cancer deaths could be prevented if some risk factors had been avoided. Actually, it is generally accepted that prevention can offer a cost-effective long-term strategy to control cancer disease [49]. Two main strategies are distinguished in cancer prevention. The first one is to follow healthy habits, regarding diet, weight management, exercise, tobacco and alcohol use and general lifestyle [50]. It seems that lifestyle, job selection and location of citizenship are parameters that can affect the possibility to develop some cancer types [51]. Since cancer is a genetic disease and mutations can occur due to numerous factors, it is well established that the significant differences on cancer rates, (both rates of incidence and death) among different countries and continents can be attributed to environmental od lifestyle factors that tend to change over time [52]. The second important strategy against cancer disease regarding to prevention is through vaccination [50]. Vaccination is considered as the most effective approach to control the rapid disperse infection and it became absolutely reasonable during the pandemic of COVID-19 [53]. Nanotechnology can contribute to this field, applying nanoparticle-based carriers, such as liposomes, micelles, dendrimers, Nano emulsions, etc. to create nano vaccines that allow targeted delivery and strong immune response [54]. A pegylated (PEG) nano vaccine against pancreatic cancer has been recently developed with very promising results [55].

5.2. Nanomedicine in cancer diagnosis

As it has been already mentioned, early diagnosis leads to increased possibilities of an effective treatment and hopefully surviving [56]. Two distinct approaches are commonly considered, as means of cancer diagnosis. The first one is early diagnosis upon each and every symptom, even slight ones. Artificial intelligence promises the precise detection of every suspicious motif that might be a cancerous mass [57]. Nanoparticles can be used in these applications, allowing molecular imaging, in parallel with MRI, PET, PET/MRI, MRI/CT, PET/CT [58]. Several nanomaterials can be used in PET modalities or in hybrid systems, such as silica (SiO2)-based core-shell nanoparticles, PEGylated liposome-based 18F, poly-aspartic acid (PASP)-coated iron oxide (IO)-64Cu, solid lipid nanoparticles-based 64Cu, Single-walled (SWNTs) and Multi-walled (MWNTs) carbon nanotubes in parallel with 125I, 111I, and 99mTc administration and many others [59-64]. Also, metal-chelating lipids conjugated to Gd3+, 64Cu2+, or 111In3+, Gd-embedded iron oxide nanoparticles (T1 contrast agents (positive)) and superparamagnetic liposomes (T2 contrast agents (negative)) are used in MRI modalities, improving the diagnostic quality in imaging [65,66]. Also, theranostic procedure is highly recommended allowing parallel diagnosis and treatment. The second strategy is referred to screening of the population in order to detect individuals that have not yet developed any symptoms related to cancer disease [56]. Nanoparticles are used to optimize the characteristics of various sensors for early disease diagnosis. Rapid test technology is typically based on nanostructured colloid gold [67]. Also, nanomaterial-based colorimetric, chemo-resistors, eNoses and various other biosensors are applied for exhaled breath analysis in order to detect numerous cancer types and other diseases (e.g. lung cancer, asthma, diabetes, etc.) [68].

5.3. Nanomedicine in cancer treatment

Various therapeutic choices are nowadays available depending on the cancer type, the stage, the clinical condition of the patient and the capacity of the health system. Also, palliative care that focuses on the improvement of the quality of life of the patients and their families, is essential [69]. The conventional options for cancer treatment include surgical operations, chemotherapy, radiotherapy, immunotherapy, hormone therapy, as monotherapies or in combination. The ultimate goal is to monitor any cancer recurrence, to control the disease and to increase the possibilities of survivorship [70]. Innovative, alternative therapeutic approaches are feasible through the application of nanotechnology. Photothermal therapy is achieved,

using near-infrared electromagnetic radiation to induce heat-shock response that kills hyper thermally cancer cells [71]. Iron oxide nanoparticles, graphene oxide nanoparticles, and gold nanoparticles are the common nanoparticles that are used in hyperthermia applications, in combination with several polymers (e.g. Polydopamine (PDA), Polyaniline (PANI)) to develop hybrid multifunctional nanocomposites [72]. Hyperthermia can be applied in parallel with radiotherapy to maximize the therapeutic efficacy. In radiotherapeutic applications, it is accepted that the combined effects of ionizing radiation with high-z metallic nanoparticles (e.g. gold), can lead to radio-sensitization and maximizes the killing effect in the tumor area [73].

Photodynamic therapy is widely used for the treatment of various skin diseases including also some pre-cancerous lesions and cancer types [74]. The main idea of this application is based on the use of a light source, oxygen, and photosensitizers to develop oxidative stress environment through Reactive Oxygen Species (ROS) creation (Figure 7).

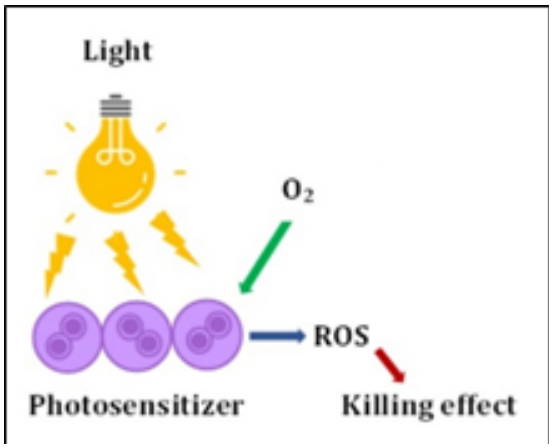

Figure 7: The schematic representation of photodynamic therapy fundamentals.

Advanced photocatalytic nanomaterials, such as TiO2, N-doped TiO2, Ag-dopes TiO2, gold and silver bimetallic nanoparticles and ZnO can be efficiently used to induce cytotoxic effects in various cancer cells upon irradiation with UV or visible light [75-80]. Also, drug delivery systems using thermos-responsive polymers [81], or other organic nanoparticles are promising platforms for targeted therapy. Gene delivery is a therapeutic approach in personalized medicine with great impact in the field of cancer treatment. Targeted delivery of genes can be achieved through pharmaceutical nanotechnology that provides several nanomaterials with the ability to load genes and transfer them to the tissue or cells of interest [82]. Nanoparticles, acting as non-viral vectors, are classified into organic (e.g. lipids, polymers, surfactants, etc.) and inorganic ones (e.g. carbon nanotubes, mesoporous silica, etc. and used to avoid the undesirable side effects of the use of conventional vectors [83]. Polymer-based gene delivery is feasible using Poly(lactic-co-glycolic acid) (PLGA), poly(L-Lysine) (PLL), Polyethyleneimine (PEI), Poly-L-arginine (PLA), Poly(ε-caprolactone) (PCL), Polymeric micelles, dendrimers, gelatin nanoparticles and various others [84-86]. Lipid-based carries, like lipoplexes of EPC, DOTAP, and DOPE with siRNA are used for GL3 luciferase gene silencing in cancer cell lines [87]. Carbon nanotubes, mesoporous silica, magnetic nanoparticles, gold nanoparticles, quantum dots, calcium phosphate are among the common inorganic nano-carriers that are successfully used in gene therapy [88]. Immunotherapy is another field that nanotechnology can play an important role. It focuses on targeting genes that induce immune responses. Lipoplexes are usually used in such cases [89]. Furthermore, the CRISPR/Cas9 system can lead to knock-out of disease-related genes, editing genetic abnormalities. Nano-based CRISPR/Cas9 employs cationic arginine gold nanoparticles increasing its efficiency [90].

Nanoparticles can be also used in biomedical applications related to scaffolds for tissue engineering, focusing on replacing damaged tissues. Carbon-based, silicate-based, as well as metal/metal oxide nanoparticles can be utilized in parallel with synthetic or natural polymers to develop advanced biomaterials [91,92]. Also 3-D printed scaffolds are developed, and their properties can be optimized, through the use of nanoparticles [93]. To sum up nanotechnology can contribute to the design of accurate and efficient therapeutic schemes, regarding photothermal, photodynamic therapy, drug delivery systems, radiotherapy, gene therapy, immunotherapy and regenerative medicine through tissue engineering, thus is very promising field that in the near future is expected to be an active part of the clinical routine.

6. Conclusion

In Nuclear Medicine, Diagnostic examinations account for 60% and Therapies for 40% of the acts. In the former, SPECT exams surpass the PET exams. However, this pattern shifts towards the PET/CT and PET/MRI modalities due to: new, more specific and sensitive radiotracers developed and the less absorbed dose involved in the PET/MRI. Applications in a wide range of Neurological pathologies offer a new under exploration 'land' for SPECT and PET procedures. Furthermore, the driving force in SPECT is the reduction of 99Mo due to scarcity of raw materials and the development of new alternative radionuclides. Regarding therapeutic applications, state-of-the-art radiotherapy could provide a better approach with better results obscuring the former. The development of new alpha emitter radiotracers is currently ongoing. The progress of Nuclear Medicine will depend upon the cost of the radionuclides (production-transport-handling), the cost of equipment (cyclotrons, reactors, generators, imaging) and the health budgets across the world. Nanotechnology allows early diagnosis, prevention, and treatment. Since a great variety of nanoparticles, both organic and inorganic ones, has been developed, it is of crucial importance in the near future, the clinical routine to incorporates these high-throughput technology, optimizing cancer treatments to maximize the therapeutic outcome.

7. Acknowledgements

D.A Verganelakis gratefully acknowledges all kind support provided by the Association of Friends of Children with Cancer 'ELPIDA' and the Oncology Clinic 'Marianna V. Vardinoyiannis' at Children's Hospital 'Aghia Sophia' in Athens.

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