RADIOPHARMACEUTICALS AND THEIR THERAPEUTIC APPLICATIONS

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Abstract

Radiopharmaceutical is a pharmaceutical artefact or drug that may exert spontaneous degradation of unstable nuclei with nuclear particles or photons emission which are used in research, diagnosis, therapy, and environmental purposes. Besides, radiopharmaceuticals act as radioactive tracers among patients via gamma-ray emissions. Hence, the practises of radiopharmaceuticals as diagnostic agents to examine any biochemical, molecular biology, physiological, or anatomical abnormalities are done in patients. Therapeutic radiopharmaceutical may be directed internally for therapeutic purposes via selective effect on certain abnormal cells or organs. For instance, iodide131 is used for thyroid ablation among patients with hyperthyroid as a therapeutic radiopharmaceutical. In research, drug labelling is done with radiopharmaceutical using small quantity of radioactive substances not for diagnostic purposes, however to investigate the metabolism, bio-distribution, pharmacodynamic, and pharmacokinetic of certain drugs in a nonradioactive form. This chapter emphases primarily on preparation, environmental, pharmaceutical, diagnostic, therapeutic, and research applications of radiopharmaceuticals.

Keywords: Radiopharmaceutical, Diagnosis, Therapy, Radioactive substance, Environmental

I. Introduction

Radiopharmaceuticals are pharmaceutical products that include a radionuclide in their composition. They are used in Nuclear Medicine mainly for diagnosis but some are also used for therapeutic treatment of human diseases. Radioisotopes bound to biological molecules able to target specific organs, tissues or cells within the human body. Most radiopharmaceuticals are used for the purpose of medical diagnosis. They are usually given only once, or sometimes on a few occasions, and contain only small amounts of the active substances with a radionuclide attached to them to allow scintigraphic imaging or measurement of biodistribution·[1]. They have short physical half life time, eliminated from the body with an effective half life time approximately equalling the examination time to prevent subsequent exposure to the body. Radiopharmaceuticals emit radiation themselves, which is different from contrast media which absorb or alter external electromagnetism or ultrasound.

Radiopharmaceuticals are major contrivance used for the management of diseases and dysfunctions, but also for better understanding human diseases and developing effective treatment options, such as in the case of neurology. In this context, there is concern of continuous, impressive progress in nuclear medicine which is linked to the development of new radiopharmaceuticals and efficient production of relevant radioisotopes. Various advances in the field of radiopharmaceuticals from development, production, and use of diagnostic, therapeutic, and theranostic radioisotopes and radiopharmaceuticals are conferred. Currently, radiopharmaceutical therapy is administered by intravenous or locoregional injection and the treatment planning has typically been implemented like chemotherapy, where the activity administered is either fixed or based on a patient's body weight or body surface area (BSA). The most widely used radioisotope in diagnostic nuclear medicine is technetium-

99m. It can be attached to several specific molecules, allowing the diagnosis of many diseases, including certain types of cancers.

Nuclear medicine procedures are used in diagnosing and treating certain illnesses. These procedures use radioactive materials called radiopharmaceuticals. Examples of diseases treated with nuclear medicine procedures are hyperthyroidism, thyroid cancer, lymphomas, and bone pain from some types of cancer. A novel PET perfusion radiotracer, 18F-flurpiridaz, can diagnose coronary artery disease (CAD) in obese patients with a higher sensitivity and specificity compared to 99mTc-SPECT myocardial perfusion imaging (MPI). Hybrid molecular imaging (and the use of accompanied radiopharmaceuticals) is poised to thrive under value-based healthcare by offering clinicians best-in-class image quality and accurate early disease diagnosis and staging.[2]. Varian Edge allows radiation oncologists to treat a tumor from many directions with pinpoint accuracy and in only three to five sessions compared with 20 to 40 with standard radiation therapy. By 2030, Bibault admitted, it's likely that all radiotherapy will be automated, personalized and hypofractionated, and that FLASH will save us. “But the innovation piloting all that is going to be treatment decision and cloud computing,”

II. Mechanism and biological effects

The mechanism of action for Radiopharmaceutical therapy (RPT) is radiation-induced killing of cells. Investigation into the effects of radiation on tissues and tumours began soon after the discovery of radiation and radioactivity. RPT has the benefit of drawing on the substantial knowledge base of radiotherapy. However, RPT differs from radiotherapy, and it is important to understand how those elements unique to RPT influence therapy.

The biological effects of a given absorbed dose for a tumour depend on the rate at which the dose is delivered. A dose of 30 Gy delivered to a tumour over a period of many weeks at a dose rate that is exponentially decreasing, as is typically the case with RPT, will have a very different effect from that of the same amount delivered at the much higher dose rates used in radiotherapy (for example, daily, 2-Gy fractions over 15 days). The difference in biological outcome will depend on the biological repair and radiosensitivity properties of the tumour. Dose-rate considerations also apply to normal organs [3,4,5].

Another fundamental distinguishing feature important for understanding this treatment modality is the diminishing curative potential with reduced target cell number (Figure 1). In radiotherapy the probability of killing all cells for a given absorbed dose increases as the number of target cells decreases fewer cells to kill for a given radiation absorbed dose increases the chance that all of the cells will be killed. By contrast, fewer cells do not translate into a greater tumour control probability in RPT. This is because the radiation is not delivered uniformly to all cells. If the emitted radiation originates from a radionuclide on the surface of tumour cells, fewer cells leads to a smaller fraction of the emitted energy being deposited into the targeted cells. This is balanced, in part, by the greater concentration that may be achieved in smaller clusters of cells relative to large measurable tumours [6].

RPT agents in use and in clinical development:

A number of RPT agents are currently on the market, with many more in development (Table 2). These include four β-particle and five α-particle emitters. Lead-212 decays to bismuth-212 and is used as a means to deliver ^{212}Bi, an α-emitter, without being constrained by its 1-hour half-life. The interest in α-emitters reflects a potential growth area in RPT. Other RPT agents in addition are in preclinical development.

RPT can involve the direct delivery of the radioactive element itself. A wide variety of ‘delivery vehicles’ have also been used for RPT (Fig.1), including small molecules that incorporate the radionuclide. Radiolabelled peptides and antibodies make up the majority of RPT agents investigated clinically [7,8,9]. Liposomal or nanoconstruct delivery approaches are being investigated preclinically, but these have not yet been tested in human trials. Glass and resin microspheres are relatively well established; these are used in the treatment of hepatocellular carcinoma or hepatic metastases of colorectal cancer and are administered via the hepatic artery [10].

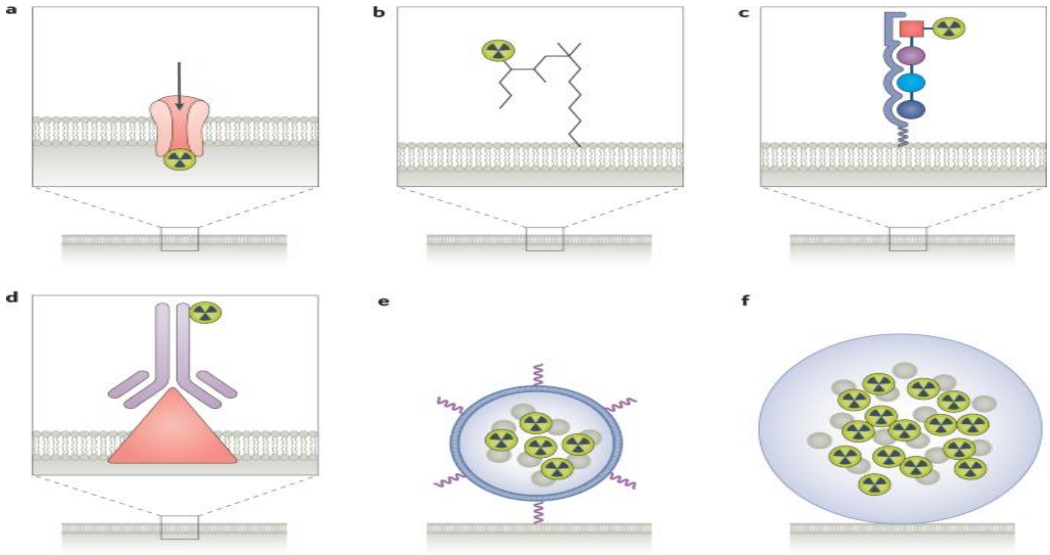

Figure 1: Basic RPT constructs used for radiation delivery.

The various radiopharmaceutical therapy (RPT) constructs that have been used to deliver radiation are illustrated: radioactive element (part **a**); small molecule (part **b**); peptide (part **c**); antibody (part **d**); nanoconstruct (part **e**); microsphere (part **f**).

The differential retention of different RPT constructs in the tumour is important but difficult to generalize. Antibody-mediated delivery is bivalent and generally leads to long retention, but the long circulating half-life of antibodies leads to greater normal organ, particularly haematological, toxicity. By contrast, small molecules and peptides have the advantage of rapid targeting and clearance, but exhibit typically shorter tumour retention. In all cases, if the agent is internalized and the radionuclide retained intracellularly, the target retention time will be very long compared with the clearance kinetics of the agent. Furthermore, in all cases, engineered agents can be designed that optimize tumour retention while increasing clearance kinetics [11].

Radiopharmaceuticals for Infection Imaging

The pandemic COVID-19 has intensified the attention for diagnosis and treatment of infectious diseases. Nuclear medicine with its prevailing scintigraphic, single photon emission computer tomography (SPECT) and positron emission tomography (PET) imaging modalities are always playing a significant protagonist in diagnosis of infections and distinguishing them from the sterile inflammation. Along with the clinically offered radiopharmaceuticals more unambiguous imaging agents like radiolabeled antibiotics and antimicrobial peptides for bacterial imaging, radiolabeled anti-fungals for fungal infections imaging, radiolabeled pathogen-specific antibodies and molecular engineered concepts are in progress.

The conventional tools still extensively used in the clinic today are ^{111}In-labeled leukocyte imaging for most indications, ^{67}Ga for imaging of opportunistic infections, pulmonary inflammation and interstitial nephritis and 2-Deoxy-2-[^{18}F]fluoroglucose ([^{18}F]FDG) for spinal osteomyelitis, vasculitis, sarcoidosis, and fever of anonymous origin and for detecting cardiovascular infection [12].

Radiolabeled Antibiotics for Imaging Bacterial Infections

Numerous antibiotics such as ciproflaxicin and nitrofuryl thiosemicarbazone, fluoroquinolone, isoniazid, ofloxacin), cephalosporin, clindamycin, doxycycline, ceftizoxime, cefotaxime, tinidazole, sulfadiazine, tazobactam and metronidazole have been radiolabeled with ^{99m}Tc to facilitate SPECT imaging in the pre-clinical models of infection. Sn(+2) salts were used as reducing agents for ^{99m}Tc which created [^{99m}Tc-O](3+) core, along with ^{99m}Tc carbonyl or [^{99m}Tc-N](2+) cores. The ^{99m}Tc carbonyl core might be less perturbing to the molecular structure of antibiotic molecules due to its smaller size. Still reduced size radiometal, PET enabling ^{68}Ga, for labeling of ciprofloxacin via two mutual bifunctional chelating agents 2,2′,2″,2‴-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA) and 2,2′,2″-(1,4,7-triazacyclononane-1,4,7-triyl)triacetic acid (NOTA) were studied. Nevertheless, both chelating agents are quite bulky macrocycles indicating labeling antibiotics with radiometals could disturb the probe entering the bacterium, or restrict with the binding to the intracellular target.

To avoid radiometals, one can potentially use PET-enabling "organic" radionuclides such as ^{13}N or ^{11}C, or ^{18}F shall not disturb the molecular structure of an antibiotic due to small atomic radius. Potential use of "organic" radionuclides by radiolabeling anti-TB chemotherapeutics isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) with ^{11}C and carrying out the whole body PET imaging of each radiolabeled drug in baboons was done. They also used the polyethylene glycol (PEG)ylated forms of the same anti-TB drugs for PET imaging and made an assumption about the potential utility of the PEGylated isoniazid conjugates as long-circulating carriers for enhanced therapy of TB.

Murine were used widely as the infection models in the pre-clinical studies of radiolabeled antibiotics, along with rabbits, since the immune system of rabbits is considered to be closer to human immune system. *Staphylococcus aureus* was used most often to induce infection in experimental animals, however *Mycobaterium tuberculosis*, *Bacteroides fragilis* and *Dentamoeba fragilis*, *E. coli*, *Pseudomonas aeruginosa* and *Salmonella enterica* were also utilized. Images not only depicted the localization of the radiolabeled antibiotics with SPECT or PET but also computed the biodistribution in addition to imaging. Studies conveyed retention of ^{99m}Tc-labeled isoniazid at the sites of *M. tuberculosis* infection in rabbits for 72 h.

The bio distribution results in mouse model indicated that accumulation of ^{99m}Tc-ofloxacin in the infected muscle reached target to non-target (T/NT) ratio of 2 at 4 h post injection though ^{68}Ga-ciprofloxacin tested in rats infected with *S. aureus* demonstrated T/NT ratio of 3-6 at 2 h depending on the chelating agent used. In *E. coli* rabbit model the accumulation of ^{99m}Tc-metronidazole at 1 h post injection reached T/NT ratio of 5.57. Results were promising for the clinical translation of these relatively cheap radiopharmaceuticals [13].

Neutron-Activatable Radioembolic Agent for Hepatic Radioembolization

Advanced-stage liver cancers utilises radioembolization as a great potential for treatment. Since radioembolic agents are expensive its use is currently limited, compared to other methods. A study, related to samarium carbonate-polymethacrylate [$^{152}Sm_2(CO_3)_3$-PMA] microspheres as neutron activatable radioembolic microspheres for hepatic radioembolization was developed. It revealed that the developed microspheres emitted both therapeutic beta and diagnostic gamma radiations for post-procedural imaging. Microspheres of $^{152}Sm_2(CO_3)_3$-PMA were produced from commercially available PMA microspheres by in situ formation of $^{152}Sm_2(CO_3)_3$ within the pores of the PMA microspheres. ^{153}Sm on the microspheres showed greater retention than 98% over 120 h when compared to conventionally radiolabeling method at ~85%. The $^{153}Sm_2(CO_3)_3$-PMA microspheres attained suitable physicochemical properties as theragnostic agent for hepatic radioembolization with high radionuclide purity and ^{153}Sm retention efficiency in human blood plasma [14].

Radioimmune Imaging in Inflammatory Bowel Disease

Molecular information acquired by imaging with radiolabelled monoclonal antibodies can non-invasively afford, for planning of best treatment and for observing the therapeutic response in cancer and chronic inflammatory diseases. Based on a comparative study, between radiolabelled anti-$\alpha_4\beta_7$ integrin or radiolabelled anti-TNFα mAb with unlabelled anti-$\alpha_4\beta_7$ integrin or anti-TNFα mAb prediction of therapeutic outcome was

evaluated for its use as in pre-therapy scan. The two developed radiopharmaceuticals were studied for the expression of therapeutic targets for inflammatory bowel diseases (IBD), to be used for therapy decision making. Both anti-$\alpha_4\beta_7$ integrin and anti-TNFα mAbs were successfully radiolabelled with technetium-99m with high labelling efficiency and stability [15]. Dextran sulfate sodium (DSS)-induced colitis was used as a model for murine IBD and the bowel uptake of radiolabelled mAbs was evaluated ex vivo and in vivo by planar and SPECT/CT images. Immunohistochemistry (IHC) score (partial and global) were compared to bowel uptake in four different regions. For the evaluation of biomarker expression preceding to therapy, in initial IBD, another group of DSS-treated mice was injected with radiolabelled mAb on day 2 of DSS administration (to quantify the presence of the target in the bowel) and then injected with a single therapeutic dose of unlabelled anti-$\alpha_4\beta_7$ integrin or anti-TNFα mAb [16]. Noble association was demonstrated between bowel uptake of radiolabelled mAb and immunohistochemistry (IHC) score, both in vivo and ex vivo compared with unlabelled $\alpha_4\beta_7$ integrin and anti-TNFα that had an inverse correlation between the bowel uptake of radiolabelled mAb and the histological score after therapy, proving that only mice with high $\alpha_4\beta_7$ integrin or TNFα expression will benefit of therapy with unlabelled mAb [17,18].

Radionuclide Therapy of $^{153}Sm_2O_3$-Loaded Polystyrene Microspheres

Samarium-153-oxide-loaded polystyrene ([^{153}Sm]Sm_2O_3-PS) microspheres by neutron-activation was studied as a potential theranostic agent for hepatic radioembolization. Sprague-Dawley (SD) rat model with liver cancer were assessed for therapeutic efficacy and diagnostic imaging capabilities. Roughly 37 MBq of [^{153}Sm]Sm_2O_3-PS microspheres was injected by intra-tumoural injection for study group while control group received an intra-tumoural injection of 0.1 mL of saline solution [19]. Investigation of diagnostic imaging capabilities of the microspheres was done using single photon emission computed tomography/computed tomography (SPECT/CT) system. Ultrasound images of all rats in the study group showed no tumour signs compared to tumour volumes in control group. The SPECT/CT images clearly exhibited the location of [^{153}Sm]Sm_2O_3-PS in the liver tumour of all rats at Day 5 post-injection. Additionally, the [^{153}Sm]Sm_2O_3-PS microspheres were visible on the CT images and this had supplementary benefits of ^{153}Sm as a CT contrast agent. Study revealed that the Neutron-activated [^{153}Sm]Sm_2O_3-PS microspheres demonstrated excellent therapeutic and diagnostic imaging capabilities for theranostic treatment of liver cancer in a SD rat model [20,21].

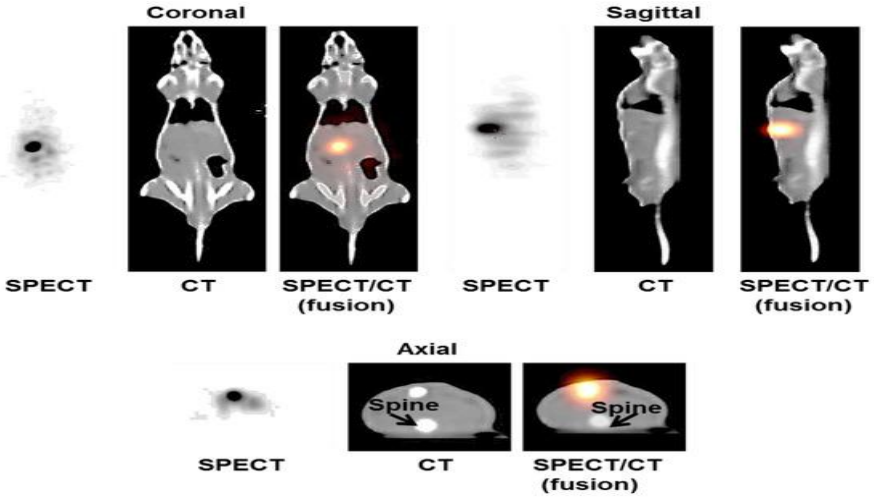

Figure 2. SPECT/CT images of a rat in the study group at Day 5 post-injection. Images displayed the location of ^{153}Sm microspheres in the liver tumour.

Functional PET Liver Imaging of Novel Radiotracers

Two novel radiotracers [^{68}Ga]Ga-TEoS-DAZA and [^{68}Ga]Ga-TMoS-DAZA are suitable for functional PET liver imaging. The tracers may be useful for segmental liver function quantification, gall tree imaging and the differential diagnosis of liver nodules due to their specific liver uptake and biliary excretion. Based on a study

done to explore complications that could occur initially during the development of the GMP compliant synthesis procedure and to evaluate the tracers in a preclinical model it was found that after low radiolabelling yields were attributed to precursor instability at high temperatures, an optimized radiolabelling procedure was established. Quality controls were in accordance with Ph. Eur. requirements and provided compliant results, though the method for the determination of the ^{68}Ga colloid is partially inhibited due to the presence of a radioactive by-product. The value of logP revealed [^{68}Ga]Ga-TEoS-DAZA (ethoxy bearing) to be more lipophilic than [^{68}Ga]Ga-TMoS-DAZA (methoxy bearing). Biodistribution readings in an in vivo model displayed a higher liver uptake for [^{68}Ga]Ga-TEoS-DAZA. Quick tracer build-up in the liver was observed in dynamic in vivo PET imaging,. Correspondingly, the activity in the intestines rose gradually within the first hour p.i., indicating biliary excretion. It was concluded that as [^{68}Ga]Ga-TEoS-DAZA and [^{68}Ga]Ga-TMoS-DAZA can be prepared according to GMP guidelines, transition into the early clinical phase could be made possible [22].

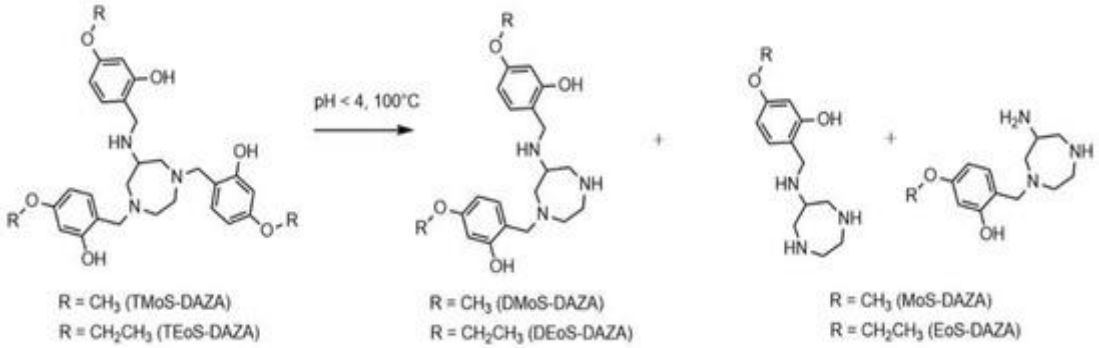

Figure 3. Structure of DEoS-DAZA and DMoS-DAZA (di-alkylated), respectively, and EoS-DAZA and MoS-DAZA (mono-alkylated), respectively, which are formed under acidic conditions. DEoS-DAZA and DMoS-DAZA are penta-dentate chelators that bind to ^{68}Ga as well, thereby forming a radioactive impurity in the final product solutions.

Radionuclide Therapy for Cancer Treatment

Radiation therapy was first used nearly a century ago in oncology, but its elementary principle is still in application, for example, radionuclide therapy (RNT) or targeted radionuclide therapy (TRT). TRT is effective in micro and macro metastasis and beneficial due to low dose, high efficacy, easy targeting and treatment. Overview of the radionuclides, as components of a TRT i.e., different types of radionuclides, vectors and chelators and highlights of TRT agents as therapeutic potential in the treatment of various types of cancers, namely, breast cancer, metastatic bone pain, thyroid cancer, neuroendocrine neoplasm, prostate tumors, malignant lymphoma, brain tumors, and hepatocellular carcinoma have been done.

Iron oxide nanoparticles are frequently used in many medical applications as they are biocompatible and biodegradable. Nanoparticles were designed for multimodal HER2-positive cancer treatment involving radionuclide therapy and magnetic hyperthermia. The magnetic core (Fe_3O_4) was coated with a gold-198 layer creating so-called core-shell nanoparticles. To attain the targeted therapy nanoparticles were then further modified with a bifunctional PEG linker and monoclonal antibody. Monoclonal antibody—trastuzumab was used to target specific breast and nipple HER2-positive cancer cells. The nanoparticles were found to be as small as 9 nm measured by transmission electron microscopy. Thermogravimetric analysis and iodine-131 labeling were the two methods used to study the bioconjugation of trastuzumab. Synthesized nanoparticles were also found to be as good heat mediators in an alternating magnetic field and reveal great specific binding and internalization capabilities towards the SKOV-3 (HER2 positive) cancer cell line. Fabricated radiobioconjugate had great potential for in vivo studies regarding magnetic hyperthermia and radionuclide combined therapy [23].

Radionuclides in Targeted Therapy

Nuclear medicine has turned into more and more projecting subspecialty utilising targeted radionuclide therapy. Earlier treatment with radionuclides has been limited to the use of iodine-131 in thyroid disorders. At present, radiopharmaceuticals, being combined to a vector for binding to a desired biological target with high specificity, are being established. Therapy is to be as selective as possible at the tumor level, while limiting the dose received at the healthy tissue level. Currently, related to better understanding of molecular mechanisms of cancer, advent of innovative targeting agents (antibodies, peptides, and small molecules) and the accessibility of new radioisotopes, significant advances in the field of vectorized radiotherapy having better therapeutic efficacy, radiation safety and personalized treatments have been evolved. For instance, targeting the tumor microenvironment, instead of cancer cells, now seems to be particularly attractive. Several radiopharmaceuticals for therapeutic targeting have shown clinical value in several types of tumors and have been or will soon be approved and authorized for clinical use. Following their clinical and commercial success, research in that domain is particularly growing, with the clinical pipeline appearing as a promising target.

Radiopharmaceuticals have been employed for use with advanced prostate cancer for decades. Recently, the alpha emitter radium-223 delivered a catalyst for the field by prolonging survival in men with metastatic castrate-resistant prostate cancer (mCRPC). The development of 177 lutetium (177Lu)-PSMA-617 (also known as lutetium Lu-177 vipivotide tetraxetan) has gained importance with FDA approval. It targets the prostate-specific membrane antigen (PSMA) expressed on the cell surface of prostate cancer cells with a beta-emitting isotope (177Lu). The present field of radiopharmaceuticals is in a rapid state of flux. Additional phase III trials are now enduring in patients with mCRPC and metastatic castrate-sensitive prostate cancer. The results from these potential practice-changing trials are highly anticipated. Earlier phase trials (I/II) are in progress examining combination therapies, radiolabeled monoclonal antibodies, and novel compounds. Targeted therapies using both beta emitters such as 177Lu and novel alpha emitters such 225 actinium related studies PSMA are in evolvement. Fortunately, radiopharmaceuticals may likely play a central role in the management of patients with advanced prostate cancer [24,25].

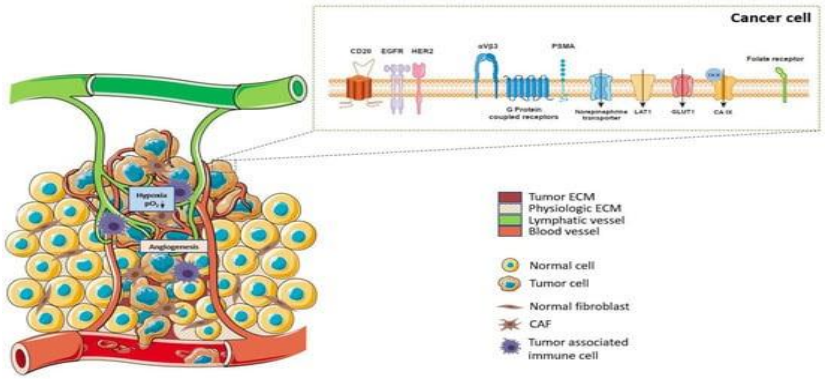

Figure 4. Possible targets for targeted radionuclide therapy.

Lutetium-177 Dotatate for Neuroendocrine Tumours

Neuroendocrine tumours (NETs) are being treated with Lutetium-177 Dotatate (^{177}Lu-DOTATATE), also known as Lutathera, a targeted radionuclide. Neuroendocrine cells dispersed throughout the body which are responsible for the production and secretion of various hormones cause these tumours. NETs arise in different organs, such as the gastrointestinal tract, pancreas, and lungs. Treatment becomes more challenging as these tumours are often slow-growing, but can sometimes be destructive and metastasise to other parts of the body. Somatostatin receptors (SSTRs) that are overexpressed on the surface of NET cells selectively binds to Lutetium-177 Dotatate a radiolabelled. Various physiological processes, including releasing other hormones, gastrointestinal motility, and cell proliferation are regulated by Somatostatin, a naturally occurring peptide hormone. ^{177}Lu-DOTATATE is preferentially taken up by NET cells, delivering a high dose of beta radiation directly to the tumour site while sparing healthy tissues by mimicking somatostatin, Side effects often associated

with conventional radiation therapy such as the risk of collateral damage to surrounding healthy cells are minimised by this targeted approach [26].

Radiopharmaceuticals cordial anti-tumour immunity

Exhaustive immunologic eradication of cancer tumour cells can be achieved by the innate and adaptive immune system, however a necessity for efficient elimination is the recognition of danger signals on tumour cells. It is conceivable that some cells could advance into an equilibrium phase and begin a chronic tug-of-war with immune system, in this state the immune system is still able to keep these cells under control. Finally interplay between the immune system and an emergent cancer is that uncontrolled tumour cells successfully escape the immunosurveillance, then grow gradually due to their reduced immunogenicity and the formation of immunosuppressive tumour microenvironment occurs.

The immunogenic cell death (ICD) provoked by radiotherapy also relates the DNA Damage Response (DDR) to anti-tumour immunity, which denotes to cell death modalities that share the susceptibility to activate an immune response. Irradiated tumour cells undergo a stressful death process, associated with the up regulation of immunomodulatory cell surface molecules, expansion of the cellular peptide pool, and the release of cytokines, which are also known as danger-associated molecular patterns (DAMPs). ICD following radiotherapy initiates the production of a plethora of mediators into the extracellular space as danger signals, which are termed DAMPs. These DAMPs are recognized by macrophages and dendritic cells (DCs) activated by diverse pathways including Toll-like receptors (TLRs), induce their maturation and promote cross-presentation of tumour antigens, kindle the release of cytokines including IL-1β, IL-23, and CXCL10, that activates infiltration and chemotaxis of immune effectors. Activated natural killer cells (NKs) and cytotoxic T lymphocytes (CTLs, which are CD8+ T cells) possess the ability to kill tumour cells with the help of CD4+ T cells. Radiotherapy also controls multiple pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), IL-6, IL-8, IL-1α, and IL-1β, to induce an acute inflammatory reaction in tumours [27].

Conclusions

Radiopharmaceuticals have great advent in clinical medicine and biological research with extraordinary benefits, allowing fast and non-invasive diagnosis and therapy of socially pertinent diseases, including inflammation, cancer, cardiovascular diseases or neurodegeneration. Prompt progresses along the path of debt of pharmacokinetics and clearance needs to afford an optimized dose and screen the efficiency of treatment, and personalized medicine, through the use of targeted drug delivery of new therapeutics, are expected to impart increasing specificity and selectivity to patient care.

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