CURRENT AND FUTURE DEVELOPMENT OF THERAGNOSTIC NUCLEAR MEDICINE

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Abstract— **Theragnostic nuclear medicine has gained increasing popularity in the recent years, primarily due to the advancement in molecular medicine and nanotechnology. Theragnostics can be achieved by either using a theragnostic radionuclide that emits both therapeutic (e.g. alpha, beta or Auger electrons) and diagnostic (eg. gamma or positron) radiations simultaneously; or incorporating two radionuclides (one for imaging, another for therapy), also known as the theragnostics pair, into the same radiopharmaceutical formulation. Multiple factors need to be considered when choosing a suitable theragnostic radionuclide or theragnostics pair, including their physical half-life, radioactive decay properties, linear energy transfer (LET), therapeutic and diagnostic radiations energy, ratio of non-penetrating to penetrating radiations, radiation safety, etc. This article aims to review the currently available theragnostic radiopharmaceuticals for clinical applications or clinical trials, as well as to discuss some emerging theragnostic radionuclides for future applications.**

Keywords— **Medical Physics Teaching**

Introduction

Theragnostics (or theranostics) has become a popular term in medicine. It refers to the combination of therapeutics and diagnostics agent(s) in one delivery system for targeted therapy or personalized medicine. The concept is described as "see what you treat and treat what you see" (1). In theragnostic nuclear medicine, a molecular targeting vector is labelled with diagnostic as well as therapeutic radionuclide(s) to acquire diagnostic images while delivering a therapeutic radiation dose to the targeted tissues (Fig. 1). This can be achieved by either using a theragnostic radionuclide that emits both therapeutic (e.g. alpha, beta or Auger electrons) and diagnostic (eg. gamma or positron) radiations simultanesouly; or incorporating two radionuclides (one for imaging and another one for therapy) into the same radiopharmaceutical formulation (2). The diagnostic agents are used to localize the site or disease state as a surrogate for a potential therapeutic agent, to examine its biodistribution and predict treatment outcome, to determine the optimal therapeutic dosage or activity to be administered, as well as to monitor treatment response throughout the treatment course.

Although the term "theragnostics" was introduced in medical encyclopedia in the early 2000's, the principle is not new at all in nuclear medicine. The first example of theragnostic nuclear medicine can be back dated to 1941 when Dr Saul Hertz first applied radioiodine (I-131) for hyperthyroidism treatment (3). I-131 emits both high energetic beta (maximum energy 606 keV) and gamma (364 keV) radiations hence it can be used for diagnostic and therapeutic purposes simultaneously, which fulfil the basic principle of theragnostics. I-131 has since then been used in multiple theranostics applications, such as I-131-NaI for thyroid malignancies, I-131-MIBG for neuroblastoma, I-131-Rituximab for non-Hodgkin lymphoma, etc. Recently, due to the advancement in nanotechnology and molecular medicine, theragnostic nuclear medicine has been expanded to treat multiple diseases/conditions. This article aims to review the current and future developments of theragnostics in nuclear medicine.

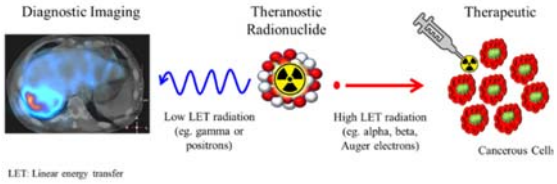

Fig. 1: Basic principle of theragnostic nuclear medicine (adapted from (2).

Selection of a Suitable Theragnostic Radionuclide

Selection of an ideal theragnostic radionuclide depends on several factors. First of all, the radionuclide should have appropriate biochemical reactivity and decay properties (4). For example, the radionuclide should have an appropriate physical half-life, usually between several hours to several days to achieve optimum treatment efficacy and radiation safety. The therapeutic radiations should have medium to high linear energy transfer (LET) and penetrate in sufficient range in tissue for the treatment purpose.

On the other hand, the diagnostic radiation energy should be suitable and sufficiently detected by a gamma camera or positron emission tomography (PET) scanner. Besides, the ratio of non-penetrating to penetrating radiations should be high, and the radionuclide should decay into a short-lived or stable daughter for safety purpose (5).

In addition, the radiopharmaceutical should have high selective concentration along with prolonged retention in the targeted tissues with minimal or no uptake in normal tissues (4).

Theragnostic Radiopharmaceuticals with Dual Functionality

Table 1 shows some examples of currently available theragnostic radionuclides with dual functionality (for therapeutic and diagnostic imaging).

Table 1: Currently available theragnostic radionuclides with dual functionality (therapy and diagnostics).

Radionuclide	Physical half-life	Therapeutic radiation, energy, keV (%)	Diagnostic radiation, energy, keV (%)	Radiopharmaceuticals (commercially available/under clinical trials)	Clinical Applications	Ref.
Gold-198 (Au-198)	2.7 d	β^- 960 (99%)	ϒ 412 (96%)	Au-198-nanoparticles	Therapy of bladder, cervix and prostate cancer, reduce fluid accumulation secondary to a cancer, relief pain in the synovial joints	(6–8)
Holmium-166 (Ho-166)	26.8 h	β^- 1854 (50%) 1774 (49%)	ϒ 81 (6%)	Ho-166-chitosan complex	HCC, skin cancer, cystic brain tumour, renal cysts, RA and hemophilic arthropathy	(9–12)
				Ho-166-DOTMP Ho-166-EDTMP	Bone metastases	
				Ho-166-PLLA microspheres	Liver malignancies, head, and neck squamous cell carcinoma	
Iodine-131 (I-131)	8.0 d	β^- 606 (89%)	ϒ 364 (82%)	I-131-NaI	Thyroid cancer and hyperthyroidism	(13–16)
				I-131-MIBG	Neuroblastoma, pheochromocytomas, paragangliomas, medullary thyroid carcinomas and other NETs	
				I-131-anti-CD45	Bone marrow ablation	
				I-131-CD276	Neuroblastoma for CNS	
				I-131-BA52	Metastatic melanoma	
				I-131-MIP-1095	Metastatic prostate cancer	
Lutetium-177 (Lu-177)	6.7 d	β^- 498 (79%) 385 (9%) 176 (12%)	ϒ 208 (11%) 113 (6%)	Lu-177-DOTATATE	Somatostatin receptor–positive gastroenteropancreatic NETs	(17–21)
				Lu-177-DOTMP Lu-177-EDTMP	Bone metastases	
				Lu-177-PSMA	mCRPC	
				Lu-177-NTSR1	Pancreatic ductal adenocarcinoma, colorectal cancer, gastric cancer	
				Lu-177-CD37	Indolent NHL, follicular lymphoma, diffuse large B-cell lymphoma	
Rhenium-186 (Re-186)	3.7 d	β^- 1069 (80%) 932 (22%) 581 (6%)	ϒ 137 (9%)	Re-186-HEDP Re-186-sulfide-colloid	Bone metastases RA	(22–24)
Rhenium-188 (Re-188)	17.0 h	β^- 2120 (71%)	ϒ 155 (15%)	Re-188-DMSA Re-188-HEDP	Bone metastases	(25–28)

		1965 (26%)		Re-188-HDD-iodized oil Re-188-HDD-lipiodol Re-188-HSA microspheres	HCC	
				Re-188-SCT	Skin cancer	
				Re-188-tin-colloid	RA	
Samarium-153 (Sm-153)	46.3 h	β^- 808 (18%) 705 (50%) 635 (32%)	γ 103 (28%) 70 (5%)	Sm-153-EDTMP	Bone metastases	(29–31)
				Sm-153-HA	RA and haemophilic arthropathy	
Tin-117m (Sn-117m)	13.6 d	Conversion electrons 152 (26%) 129 (12%) 127 (65%)	γ 159 (86%)	Sn-117m-DOTA-Annexin	Vulnerable plaque	(32–34)

Abbreviations:
CNS: central nervous system; HCC: hepatocellular carcinoma; mCRPC: metastatic castration-resistant prostate cancer; NETs: neuroendocrine tumours; NHL: non-Hodgkin lymphoma; RA: rheumatoid arthritis

Theragnostic Pairs

While there are limited choices of radionuclides that emit both therapeutic and diagnostic radiations in the suitable energy range, combining the emitting characteristics of different radionuclides with the same molecular targeting vector is an alternative approach. These radiopharmaceuticals are known as "theragnostic pairs". For example, Ga-68-DOTATATE is used for PET imaging of neuroendocrine tumours before Y-90-DOTATATE is administered to treat the tumours. Table 2 presents some examples of the theragnostic pairs used in current clinical applications/trials.

Table 2: Examples of theragnostic pairs for current and future applications (3).

Disease	**Target**	**Companion Diagnostic agents**	**Therapeutic agents**
Currently available:			
Malignant pheochromocytoma, paraganglioma	Norepinephrine transporter	I-123-MIBG	I-131-MIBG
Neuroendocrine tumours	Somatostatin receptor	In-111-Pentetreotide Ga-68-DOTATATE Ga-68-DOTATOC	Lu-177-DOTATATE Lu-177-DOTATOC Y-90-DOTATATE Y-90-DOTATOC
Non-Hodgkin lymphoma	Anti-CD20 receptor	In-111-Ibritumomba Tiuxetan I-131-Rituximab	Y-90-Ibritumomba Tiuxetan Lu-177-Rituximab
Bone metastasis	Bone turnover	Tc-99m-MDP F-18-NaF	Sr-89 Sm-153-EDTMP Ra-223
mCRPC	PSMA	Ga-68-PSMA F-18-PSMA	Lu-177-PSMA Ac-225-PSMA
Hepatocellular carcinoma, cholangiocarcinoma, liver metastasis	Hepatic microcirculation	Tc-99m-MAA	Y-90-microspheres
Currently being evaluated:			
Multiple myeloma	CXCR4	Ga-68-CXCR4	Lu-177-CXCR4
Breast cancer	PD-1, PD-L1	Zr-89 F-18-anti-PD-1	Anti-PD-1 Anti-PD-L1

		F-18-anti-PD-L1	
Various tumours	HER2	Zr-89-anti-HER2	Anti-HER2

Emerging Theragnostics Radionuclides

A. Copper-64 (Cu-64)

Cu-64 is an interesting radionuclide as it decays via three different modes, i.e. positron decay, beta decay and electron capture (Fig. 2). Additionally, it has an unusually long physical half-life for a positron emitter. Therefore, it poses a great potential to be an excellent theragnostic agent. The positrons can be used for PET imaging while the high-energetic beta particles and Auger electrons can be used for therapeutic purposes. Recent studies showed that Cu-64 labelled to a variety of biomolecular markers demonstrated promising results for cancer treatment, such as prostate, glioblastoma, melanoma, colorectal and breast cancers (35). In a comparison study for prostate cancer (36), Cu-64-PSMA showed better image resolution than Ga-68-PSMA, and with the absence of urinary excretion it permits clear visualization of the prostate and bladder by PET. Cu-64-PSMA has a similar resolution as F-18-PSMA but Cu-64 has a longer half-life which is useful for therapeutic purposes. More clinical applications of Cu-64 are foreseen in the future with these promising theranostics characteristics.

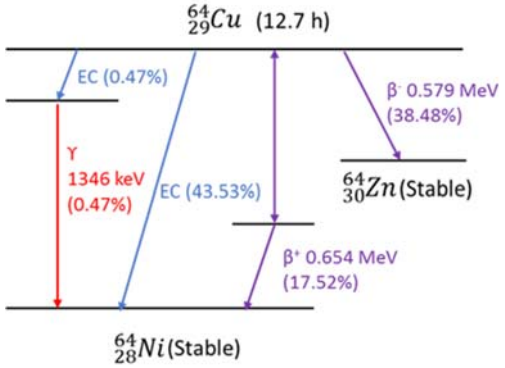

Fig. 2: Decay scheme of Cu-64 (Jalilian et al., 2017).

B. Copper-67 (Cu-67)

Cu-67 is another promising theranostic radionuclide in the copper family. It has a physical half-life of 2.58 days and it decays by beta ($E_{\beta-max}$ = 562 keV) and gamma emissions (E_{Υ} = 93 keV and 185 keV), rendering it with potential for simultaneous therapeutic and diagnostic applications. Cu-67-HER2 has shown promising results in radioimmunotheranostics of HER2-positive breast cancer (37). Furthermore, the recent breakthrough in Cu-67 production (via ^{68}Zn (ϒ, p) ^{67}Cu reaction) offers great opportunities to revitalize Cu-67 radiopharmaceuticals with high specific activity, high radionuclide purity, and with sufficient quantity (38). Interestingly, Cu-67 can also be paired with Cu-64 to perform pre-therapy biodistribution determinations and dosimetry by PET.

C. Terbium-161 (Tb-161)

Tb-161 has interesting decay characteristics that make it a promising theranostic radionuclide for oncology. It decays with a physical half-life of 6.9 days to stable Dy-161 by emitting beta particles ($E_{\beta-average}$ = 154 keV) associated with several conversion and Auger electrons, as well as gamma radiations (E_{Υ} = 49 keV and 75 keV). The co-emission of a large number of conversion and Auger electrons adds to the value of therapeutic effect as compared to Lu-177. On an average, 2.24 conversion and Auger electrons are emitted along with one beta particle decay (39). Based on some pre-clinical studies, the use of Tb-161 for cancer therapy showed minimal or no side effects to kidneys, as compared to Lu-177 (40). Furthermore, Tb-161 can be produced in high specific activity and radionuclide purity, rending it a potential theragnostic radionuclide for future applications.

D. Lead-212 (Pb-212)

Generator-produced Pb-212 is a particularly promising radionuclide for α-particle therapy of metastatic melanoma, neuroendocrine tumors, and other cancers. It has a physical half-life of 11 h and it decays 100% via beta decay to alpha emitters, Bi-212 and Po-212 (Fig. 3). The multiple alpha and beta particles emissions make it a useful therapeutic radionuclide. However, due to the lack of diagnostic imaging characteristic, a surrogate imaging agent is necessary to fulfil the theragnostics application.

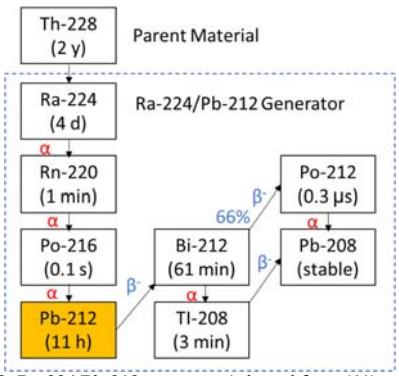

Fig. 3: Ra-224/Pb-212 generator (adapted from (41)

E. Actinium-225 (Ac-225)

Ac-225 is a pure alpha emitter. It decays via a cascade of six relatively short-lived radionuclides to long lived Bi-209 with a number of α-particles (high cumulative energy of 28 MeV) and β^- particles ($E_{\beta-max}$ = 1.6 and 0.6 MeV). It has a relatively long half-life (10 days) and rapid decay chain, render it a particularly cytotoxic radionuclide. However, similarly to Pb-212, it needs a surrogate imaging agent to perform biodistribution and treatment assessment imaging. Some clinical trials have demonstrated remarkable therapeutic efficacy of Ac-225 radiopharmaceuticals in treating various types of cancer including brain tumours, NETs, bladder cancer and prostate cancer (42).

F. F-18-FDG as a Theragnostic Agent

F-18-FDG is extensively used in PET imaging in oncology. F-18 emits energetic positrons with high abundance (96%) and a path length in tissue of 1 to 2 mm. Theoretically, these positrons can kill cancer cells in the same manner as electrons. Besides, F-18-FDG has a potential role as an immunomodulator to upregulate PD-L1 expression in tumours to enhance the efficacy of immunotherapy using ani-PD-L1. In a much recent study (43), a group of researchers from China and Singapore explored the potential of using F-18-FDG to induce PD-L1 expression in tumour and to create an immune-favourable microenvironment for anti-PD-L1 immunotherapy. The group has tested the method in different tumour cell lines (melanoma, breast, and colorectal cancer) and found that F-18-FDG significantly increased the expression of PD-L1 mRNA on tumour cells in a dose-dependent manner. The study was continued with in-vivo animal (mice) study using MC38 and CT26 colorectal tumour models. Their results showed that F-18-FDG induced significant PD-L1 upregulation and remodelled the tumour microenvironment, and subsequently enhanced the efficacy of immunotherapy using αPD-L1. As F-18-FDG is routinely used in cancer diagnosis, the combination of F-18-FDG and αPD-L1 mAb treatment would provide a new paradigm for cancer therapy.

Conclusion

In conclusion, theragnostic nuclear medicine has broadened the opportunities for innovative, safer and effective strategies towards personalized medicine. The field is currently undergoing rapid and exciting development that would mark the future of nuclear medicine. However, a sustainable development that provides continuous supply, reliable quality and affordable costs of theragnostic radiopharmaceuticals should be considered and maintained.

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