Review Article

Theranostics and its Potential Applications in Healthcare Management

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ABSTRACT

Theranostics emerges as a targeted, efficient and safe pharmacotherapy in the field of medicine. It is a novel concept involving the use of a single agent for both diagnostic and therapeutic applications, thus providing a cost-effective treatment protocol. By promoting patient-centered care, it enables a change from conventional medicine to personalised medicine. In the present review, various theranostics agents and their potential applications in disease management are described. An extensive literature search was conducted using keywords "Theranostic"; "Theranostic agents"; "Nuclear medicine"; "Nanotechnology"; Theranostics application" in the public domains of Science Direct, PubMed and Google Scholar. The articles were shortlisted based on their usefulness for the review. Theranostic agents such as nanoparticles, nuclear medicine, genetic materials, antibodies and antibody-related therapeutics are used in the management of diseases. The theranostic agents have been used for the diagnosis, delivery of therapeutic agents and monitoring the patients in response

to the treatment of cancers, neuronal diseases, atherosclerosis, and diabetes mellitus. The emerging theranostics approach has become a predictive, preventive, personalised and participatory medicine in healthcare management with the potential to improve the quality of clinical care and treatments.

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1. INTRODUCTION

Theranostics, a term coined by Funkhouser in 2002, combines the modalities of diagnosis and therapy by enabling the acquisition of diagnostic images and delivery of therapeutic agents simultaneously, hence resulting in a novel treatment paradigm [1,2]. Specific biological pathways in the human body are utilised to obtain diagnostic information, which in turn increases the probability that therapeutic agents can be targeted specifically to the disease site to limit the damage to the normal healthy tissue in the surrounding[3]. Since theranostics promotes specific and individualised treatment approaches for a variety of diseases, it enables a change from conventional trial-and-error medicine to modern personalised medicine, thus improving the quality of pharmacotherapies[4]. A study performed by Seidlin *et al*. in 1946 revealed that the first successful nuclear theranostic agent was iodine-131 (^{131}I), which was used for diagnostic imaging, target-expression confirmation and treatment of thyroid cancer [5]. After the administration of radioiodine, thyroid cancer cells were selectively harmed or killed. More iodine was deposited and the cells could be visualised using high energy gamma radiation emitted from ^{131}I in gamma cameras [5]. ^{131}I was proven to be useful in the treatment of thyrotoxicosis in the 19th century [3]. To date, ^{131}I remains the gold standard for the diagnosis and therapy of thyroid diseases[6].

In recent years, numerous efforts have been devoted to the development of highly efficient, safe and non-toxic delivery vehicles for theranostics applications. Among the most successful examples are peptide receptor radionuclide therapy (PRRT) and peptide receptor scintigraphy (PRS) of neuroendocrine tumours (NET), an orphan disease [7]. Various nanocarriers such as polymeric nanoparticles, liposomes, dendrimers, carbon nanotubes (CNTs) and quantum dots (QDs) have been explored for the targeted co-delivery of diagnostic and therapeutic agents with fewer side effects for cancer patients[8]. Biological materials such as nucleic acids, peptides and protein are designed to enable the early detection and treatment of cancers [9,10]. The goal of theranostics is to increase the quality of patient care and clinical treatments through the identification of the right drug for the right patient at the right time. The efficacy, efficiency and cost-effectiveness of treatments can be significantly improved by the implementation of appropriate theranostic agents [11]. The present review provides a detailed overview of theranostic agents and their applications in the treatment of various pathologies including cancer,

neuronal diseases and disorders, atherosclerosis and type 1 diabetes mellitus.

2. THERANOSTIC AGENTS

2.1 Nanotechnology

Nanotechnology is the study and application of materials and devices that are conducted on nanoscale, which at least one dimension sized from 1 to100 nm [12]. It is significant to take into consideration individual molecules and interacting groups of molecules concerning the bulk macroscopic properties of the material or device because usual physics and chemistry rules do not apply on the scale of atoms and molecules. It manipulates fundamental molecular structure, which in turn controls the macroscopic chemical and physical properties [13]. Nanoparticles are categorised into different classes depending on the size, morphology, chemical and physical properties.

2.1.1 Carbon-Based Nanoparticles

Carbon-based nanoparticles are divided into CNTs and fullerenes. CNTs are elongated, tubular graphene sheets mainly used for structural reinforcement. The structure of these nanotubes defines whether they are single-walled carbon nanotubes (SWCNTs) or multi-walled carbon nanotubes (MWCNTs). CNTs have the ability to conduct heat along the length but not across the tube. Deposition of carbon precursors can synthesise CNTs, particularly from atomic carbons that vaporised from graphite [14].Fullerenes possess a hollow cage composition containing sixty or more carbon atoms. These allotropes have carbon units positioned as pentagon and hexagon and each carbon atom is sp^2 hybridised. Fullerenes show excellent electrical conductivity and electron affinity. Together with their high strength and structure, they show value in the commercial [15].

2.1.2 Ceramic Nanoparticles

Ceramic nanoparticles contain oxides, carbides, carbonates and phosphates which are non-metallic inorganic solids. It is chemically inert and can be synthesised via heat and successive cooling and exerts properties to withstand high temperature. These nanoparticles act as excellent drug delivery agents in several diseases. It is known to be applied in the use as an imaging agent, photocatalysis and photodegradation of dyes [16,17].

2.1.3 Metal Nanoparticles

Metal nanoparticles can be synthesised in various ways such as chemical, electrochemical or photochemical methods. To chemically obtain a metal nanoparticle, metal-ion precursors should be reduced

using chemical reducing agents. These nanoparticles exhibit high surface energy properties to absorb small molecules. It serves as vehicles for gene and drug delivery which is excellent for targeted drug delivery. In addition, these nanoparticles have been successfully used in biomedical imaging, magnetic separation, and preconcentration of target analytes [18].

2.1.4 Semiconductor Nanoparticles

Semiconductor nanoparticles exhibit properties between metals and non-metals. Generally, semiconductor nanoparticles possess large band gaps, that result in different properties with bandgap tuning. Common applications of these nanoparticles are in the field of photo-optics and photocatalysis. Not only that, these nanoparticles are also utilised in a number of electronic devices and water splitting applications [19,20].

2.1.5 Polymeric Nanoparticles

Two major types of polymeric nanoparticles are nano-capsules and nanospheres. They are usually organic-based nanoparticles. A nanosphere particle possesses a matrix-like structure where active constituents and the polymer are adsorbed at the outer boundary of the spherical surface. On the other hand, the nanocapsule particle possesses core-shell morphology where the active constituents are encapsulated by a shell of polymer. Polymeric nanoparticles demonstrate its advantages in the field of diagnostic imaging, combine therapy and site-specific targeting because these particles are able to control drug release and protect drug molecules. Due to the highly biodegradable and biocompatible properties, polymeric nanoparticles are used in drug delivery and diagnostics [21].

2.1.6 Lipid-Based Nanoparticles

Lipid nanoparticles consist of lipid components which have a spherical shape. These spherical lipid components usually have a diameter of 10 nm to 100 nm. A lipid nanoparticle is made up of a solid core together with a matrix. Due to the lipophilic properties of the nanoparticle, surfactants and emulsifiers are needed to stabilise the structure. Lipid-based nanoparticles are widely used as a drug carrier and delivery in the biomedical field and treatment of cancer through RNA release [22].

2.2 Nuclear Medicine

Nuclear imaging utilises gamma, positron and beta emitters. Examples of gamma emitters include technetium-99m (^{99m}Tc) and iodine-123 (^{123}I) whereas gallium-68 (^{68}Ga) and fluorine-18 (^{18}F) are characterised as positron emitters [23,24].

On the other hand, beta emitting isotopes include lutetium-177 (^{177}Lu) and yttrium-90 (^{90}Y) [25].

2.2.1 Radionuclide Therapy

Radioiodine is the first theranostic radiopharmaceutical agent in nuclear medicine history [26]. Radioiodine therapy (RIT) is the gold standard for theranostics in thyroid diseases [26]. The neutron bombardment of tellurium-131 results inthe synthesis of radioiodine, a low-cost nuclear reactor product. ^{131}I is an isotope of iodine that combines both the characteristics of gamma and beta emitters. Radioiodine imaging is useful in predicting the lesion response to ^{131}I treatment by providing detailed information on the biological status of each cancerous lesion [27]. In the case of radioiodine therapy in thyroid cancers, a gamma camera or single-photon emission computed tomography (SPECT) is used to visualise the targeted lesions during the process of ^{131}I radiation [28]

2.2.2 Radiolabelled Somatostatin Analogs Therapy

Somatostatin receptors (SSTRs) are the targetsfor the pairing of ^{111}In-/^{68}Ga-labelled diagnostic imaging and ^{90}Y-/^{177}Lu-labelled treatment compounds. SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 are five subtypes of the membrane-bound receptors in which SSTR2 is normally addressed for theranostic purposes[29]. An example of this can be seen in NET where the SSTR2 subtype is overexpressed [30]. Three somatostatin analog (SSA) tracers, which are DOTA-TATE, DOTA-TOC and DOTA-NOC, are labelled with ^{68}Ga for diagnostic purposes, mainly positron emission tomography (PET) imaging. All the three SSA tracers bind specifically with SSTRs [31]. ^{111}In-labelled SSTRs have lower sensitivity and specificity in the detection of NET when compared to ^{68}Ga-labelled SSTRs [32]. On the other hand, DOTA-TATE and DOTA-TOC are labelled with either ^{90}Y or ^{177}Lu for therapeutic purposes [30]. Longer path length of ^{90}Y beta particles produces better coverage for larger metastases whereas ^{177}Lu provides less off-target radiation and radiotoxicity for smaller metastases due to shorter path length [33]. In NET therapy, ^{177}Lu, [^{177}Lu]-Lu-DOTA-TATE and DOTA-TOC are the most widely used agents owing to the low energy, small range and less haematotoxic effects [34].PRRT is a molecular targeted therapy for NET and it involves tumour uptake in the SSTR imaging. The process of PRRT begins by receiving a dose of amino acid solution intravenously to protect the body organs from radiation. A radiopeptide is formed through the combination of a synthetic cell-targeting protein called octreotide and a small amount of radioactive substances.

High doses of radiation will be delivered to the tumour once the radiopeptide binds to the SSTRs that are located on the NET cells [30].

2.2.3 Prostate-specific Membrane Antigen Radioligand Therapy

PSMA-617 and PSMA-11 are the available radiopharmaceuticals that target prostate-specific membrane antigen (PSMA) [30].The imaging purpose is to localise and determine the extent of disease while the therapeutic use of the agent is to deliver the treatment to identify the site of injury. Between the two agents, radiolabelled PSMA-617 is mainly used for therapeutic purposes as it is the favourable kinetic for both imaging that is labelled with ^{68}Ga and therapy that is labelled with ^{177}Lu [35]. On the other hand, PSMA-11 is rarely used due to its high kidney uptake [36].

2.3 Genetic Materials

2.3.1 MicroRNAs

MicroRNAs (miRNAs) have been reported to regulate tumour suppressor genes and play a role as cancer biomarkers. The detection and inhibition of the miRNA function are useful as cancer theranostic probes, thus minimising side effects and invasiveness. Kim et al. developed a cancer-targeting theranostic probe in a single system using an AS1411 aptamer- and miRNA-221 molecular beacon-conjugated magnetic fluorescence nanoparticle (MFAS miRNA-221 MB) to target the cancer tissue concurrently while imaging the intracellularly expressed miRNA-221 as well as to treat carcinogenesis in which miRNA-221 is involved. Hence, it resulted in anti-tumour therapeutic effects by ceasing the function of miRNA, demonstrating an effective astrocytoma-targeting theranostics[9].

miRNAs are the main regulators of the human genome in charge of the myriad cellular pathways for the controlling of growth during physiologic and pathologic conditions. It was evident that the deregulation of miRNA promotes events which are linked to tumour initiation, metastases and drug resistance as seen in multiple myeloma (MM), which is commonly known as an invariably fatal haematologic malignancy [37]. Therefore, the degradation or blocking of the translation process of mRNA targets leads to the modulation of the expression by more than half of the protein-coding genes within the human genome by miRNAs [38]. According to genomic and bioinformatic analyses, it was reported that miRNAs play an important role in gene expression to control various biological processes which include cellular growth, differentiation, development and apoptosis[39]. Moreover,

transcriptional profiling suggests that miRNA expression profiles have the potential to classify the types of tumour. It was also identified that miRNA repertoire is a stable and unique feature that represents specific types of tumour and stages of differentiation [40].Additionally, miRNAs have the potential as diagnostics to differentiate the distinct expression signatures that determines MM from normal or monoclonal gammopathy of undetermined significance of plasma cells (MGUS PCs). Furthermore, each MM subtypes demonstrates their respective unique miRNA signatures hence the predictors may eventually replace the current available clinical and biological markers used to diagnose MM. According to a recent study, it was reported that synthetic miRNA-34a possessed not only anti-tumour properties but anti-proliferative properties, apoptotic effects and the modulation of gene expression in clinically relevant xenograft models of myeloma [41].

Cava et al. investigated the theranostic application of miRNA-429 in human epidermal growth factor receptor 2-positive (HER2-positive) breast cancer. Changes in gene expression induced by hypoxia-inducible factors(HIF) signaling contribute to many of the hallmarks of cancer that enable tumour growth, survival and invasion. The direct targeting of oncogenic miRNA-429 on von Hippel-Lindau (VHL) mRNA, an essential molecule for the degradation of HIF1α resulted in the regulation of the HIF1α pathway. Moreover, an increased proliferation and migration of breast cancer cells was observed in HER2-positive breast cancer due to the overexpression of miRNA-429. Additionally, it was found that the silencing of miRNA-429 effectively delayed tumour growth so miRNA-429 could be proposed as a therapeutic probe in HER2-positive breast cancer tumours[42].

2.3.2 Peptides

Cho et al. developed protein kinase C-delta (PKCδ) as a theranostic agent for glioma. Peptides were used for glioma treatment as they are biostable, non-toxic and small in size. A relative binding affinity for antibody and localisation in the U373 glioma cell were exhibited by the synthetic peptide produced. Moreover, the fluorescein isothiocyanate-labelled peptide with an$IC_{50}$of 1.4 μM*in vitro* inhibited the kinase activity of PKCδ. Hence, the peptide developed may have the potential to be a promising therapeutic agent against malignant brain tumours [10].

2.3.3 Functional Nucleic Acids

Functional nucleic acids (FNAs), which include aptamers, DNAzymes, andDNA-

based nanomachines (DNMs), are nucleic acids which possess functions beyond the notable genetic roles. FNAs not only possess common advantages of nucleic acid-based materials such as low cost, low immunogenicity, biocompatibility and simplicity of chemical modification, but also possess remarkable properties such as high binding affinity and specificity of aptamers, efficient and specific gene editing ability of DNAzymes, and logic-controlled designability of DNMs. These properties exhibited by FNAs make them appealing for applications in cancer theranostics. The first *in vivo* application of a DNM for cancer theranostics was recently reported. Li and colleagues decorated a flat origami sheet with thrombin enzymes which were inhibited by rolling and locking with DNA aptamers. After reaching the tumour site, the targeting nucleolin aptamers anchored the nanostructures on the cancer endothelial cell surface and binded with nucleolin to open the DNA nanotube. The thrombins that were exposed catalysed blood clotting, caused vascular occlusion, leading to tumour cell starvation and cell death. Moreover, the *in vivo* imaging results demonstrated the targeting and accumulation ability of this nanomachine at the tumour site as well as the high tumour growth inhibition efficiency of the nanomachine. The targeted delivery and logic-controlled exposure of thrombins immensely reduced the unwanted side effects and prolonged the survival time of the tumour-bearing mice [43].

2.3.4 Small Interfering RNA Nanocomplex

In a study conducted by Shi et al., polyethylene glycol (PEG)-modified manganese dioxide (MnO_2) nanosheets were connected with osteopontin (OPN) small interfering RNA (siRNA) to form a PEG-MnO_2-OPN siRNA nanocomplex using a modular streptavidin bridge for the theranostic applications of renal carcinoma *in vitro* and *in vivo*. The PEG-MnO_2nanosheets demonstrated effective tumour growth inhibition of 786-O tumour-bearing mice, thus showing that PEG-MnO_2nanosheets have the potential for the fabrication of a magnetic resonance imaging (MRI)-based theranostic system [44].

2.4 Antibody-related Therapeutics

Monoclonal antibodies (mAbs) and antibody-related therapies are widely established in cancer treatment. They are commonly used in targeted therapies as they are designed to target specific sites, such as tumour cell membranes, immune cells and tumour microenvironment. However, not every patient that has undergone targeted therapies using antibodies will get the benefits. Moreover, the effects can be short-

lived as patients may have developed resistance [45]. Additionally, targeted therapies are very costly and may induce side effects [45]. These outcomes may be due to the heterogeneity on tumour target expression [45,46]. Therefore, it is crucial to choose the suitable patients and to monitor their response. Recently, the antibody theranostics approach has been widely used in constructing personalised antibody therapies. Antibodies are known to direct against specific targets and are easy to label [46]. At the same time, by incorporating non-invasive SPECT and PET molecular imaging techniques, it is able to provide insights on the exposure of radiolabelled mAbs and antibody-related therapeutics throughout the whole body. It has the potential to explain tumour target heterogeneity, expression of drug target, tracer uptake in the tumour and saturation of the tumour[45,46]. Those patients who are suitable to undergo antibody treatments will then be selected. To date, there are a total of 24 antibodies and antibody-related therapies approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for the treatment of cancer[45,46]. These include 20 mAbs, 1 bispecific T-cell engagers (BiTE), 2 antibody-drug conjugates (ADCs) and 1 radioimmunotherapy antibody [46].

2.4.1 Monoclonal Antibodies

The possible use of theranostic agents such as trastuzumab in making the clinical decisions has been widely investigated in several studies. Trastuzumab is a therapeutic antibody in breast cancer treatment. It was found that ^{111}In-trastuzumab SPECT imaging can identify hidden HER2-positive tumour lesions that were missed by traditional imaging in metastatic breast cancer patients [47]. This indicates that molecular antibody imaging can detect new tumour lesions that are not found using conventional imaging. Additionally, serial SPECT imaging with ^{111}In-trastuzumab is performed to examine the tumour tracer uptake before and after trastuzumab treatment [48]. Besides, a study conducted by Gebhart et al., showed that the use of zirnonium-89-(^{89}Zr)-trastuzumab PET imaging in HER2-positive breast cancer along with biopsies had successfully assessed patients' tumour heterogeneity and predicted the outcome of trastuzumabemtansine (T-DM1) treatment [49].On the other hand, angiogenesis is known to be one of the causes of cancer progression and is usually stimulated by vascular endothelial growth factor A (VEGF-A). A few studies conducted on anti-VEGF-A antibody ^{89}Zr-bevacizumab clearly showed that it can be used to visualise drugs targeting the growth factors in the microenvironment. For example, a study showed that ^{89}Zr-bevacizumab PET

can detect saturation of heterogeneous tracer in the tumour lesions [50]. Additionally, tumour detection using molecular antibody imaging has been investigated in many centres across the United States. It is believed that pre-surgical iodine-124 (^{124}I)-girentuximab PET has higher sensitivity and specificity as compared to traditional computed tomography (CT) in classifying renal lesions, both benign and malignant [46]. In short, the antibody theranostics approach is capable of helping physicians to make the clinical decisions prior to initiation of therapy.

2.4.2 Immune Checkpoint Inhibitors

Molecular imaging using immune checkpoint inhibitors (ICIs) is found to be potentially beneficial in immunotherapy. It provides insights of the immune response, thereby aids in better selection of patient and treatment. For instance, a study has demonstrated that PET imaging along with therapeutic antibody-based tracers can obtain concise information on the biological functions and importance of immune checkpoints due to its better specificity and resolution [51].An experiment was performed on ICIs targeting the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway. Mice were treated with either ^{64}Cu-NOTA-PD-1 or ^{64}Cu-NOTA-PD-L1 mAb. It showed that PD-1 immunoPET can detect PD-1+ tumour-infiltrating lymphocytes (TILs) after combined immune radio therapy and differences in intra tumoural PD-L1 expression. It also successfully identified that the lung is an organ with highly expressed interferon gamma (IFN-γ)-inducible PD-L1.

2.4.3 Bispecific T-cell Engagers

Blinatumomab is a treatment approach for relapse Philadelphia chromosome-negative or refractory B-cell precursor acute lymphoblastic leukaemia. A study has examined that kidneys exhibited the greatest uptake of ^{89}Zr-solitomab (AMG 110), followed by liver and tumour. Depending on the dose,^{89}Zr-AMG 211 directed against carcinoembryonic antigen (CEA) on tumor cells and the CD3 epsilon (CD3e) subunit of the human T-cell receptor complex on T-cells also showed CEA specific targeting in tumour xenograft of mice [52].

2.4.4 Antibody-drug Conjugates

Apart from that, the antibody theranostics approach can be applied for studying the antibodies with payload. ADCs are a subclass of antibody-related therapeutics, in which they consist of a tumour-specific mAb conjugated to a cytotoxic payload. ADCs are used as adjuvant therapy in chemotherapy by

causing cytotoxic drug to be accumulated within the cancer cells, thereby decreasing the risk of systemic toxicity [45]. A radiolabelled naked antibody of an ADC for PET imaging has the potential to assess organ biodistribution and tracer tumour uptake. A study was carried out by Strickland et al. to evaluate three doses of ^{89}Zr-labelled naked antibody of an ADC targeting mesothelin in mice bearing human pancreatic tumour xenografts. It was observed that tumour uptake reduced with increasing doses of the naked mAb [53]. This reflects that the effect and saturable tracer distribution depends on the dose. Another study investigating biodistribution and tumour uptake was performed on patients with an ^{89}Zr-labelled anti-mesothelin naked antibody subsequently treated with a mesothelin-directed ADC[54]. The outcome showed uptake of the radiolabelled naked antibody in pancreatic and ovarian tumours. Moreover, monkeys administered with a carcinoembryonic cell adhesion molecule 6-directed ADC, followed by ^{64}Cu-labelled anti-carcinoembryonic cell adhesion molecule 6 naked mAb showed that bone marrow had the greatest tracer uptake [53]. Occurrence of neutropenia and anaemia suggesting that antibody tracer uptake has the potential to predict toxicity that is tissue-specific.

3. APPLICATIONS OF THERANOSTICS

3.1 Cancers

3.1.1 Prostate Cancer

Prostate cancer is the leading cause of death in men worldwide after lung cancer. Effective treatments include radical prostatectomy and external beam radiotherapy but these are only applicable for localised prostate cancer [55]. Therefore, the use of PSMA ligands has been gaining a lot of attention among the medical community and researchers. PSMA, a type II trans-membrane glycoprotein associated with carboxypeptidase enzyme that has folate hydrolase activity, is found to be highly expressed during the progression of prostate cancer [56]. Several PSMA ligands incorporated with imaging studies such as PET and CT have been investigated. Current evidence suggests that the approach of combining PSMA ligands with PET/CT provides more accurate diagnosis and treatment of castration-resistant prostate cancer. One of the most common ligands used in prostate cancer is ^{68}Ga-PSMA and this has entered clinical practice for the staging of the tumour. Results from a meta-analysis have demonstrated the superiority of radiolabelled PSMA PET/CT over choline based PET/CT in detecting recurrent prostate cancer lesions with low PSA levels

(≤ 1 ng/ml) but there are fewer evidences in patients with higher PSA level [57]. Besides, ^{68}Ga-PSMA has better detection in lymph node metastases assessment before nodal salvage surgery with specificities close to 100% as compared to histological diagnosis [58,59]. ProstaScint which is an ^{111}In-capromabpendetide scan that targets the intracellular domain of PSMA also has been used for the detection of positive lymph nodes before radical prostatectomy[60]. Several PSMA-targeting radiopharmaceuticals such as ^{123}I and ^{99m}Tc in combination with SPECT imaging have been investigated in clinical trials for theranostic applications[61,62].

3.1.2 Thyroid Cancer

RIT has become the gold standard in diagnosing and treating differentiated thyroid cancer for decades [63]. By using ^{131}I combined with a gamma scan or SPECT, visualisation of targeted lesions in thyroid cancer is possible [30]. There is an improvement in the detection and localisation of ^{131}I uptake following thyroidectomy with ^{131}I-SPECT/CT. In addition,^{131}I-SPECT/CT has higher accuracy than whole-body scan (WBS) in evaluating lymph node and distant metastases [64]. ^{123}I also has improved sensitivity to detect thyroid remnants [65,66].Other than iodine, ^{18}F-fluorodeoxy-D-glucose (FDG) has been used as a theranostic agent in thyroid cancer. A study has demonstrated the benefit of ^{18}F-FDG PET/CT for diagnosing recurrent thyroid cancer in patients with negative thyroglobulin (Tg), negative ^{131}I-WBS and increased thyroglobulin antibody (TgAb) level [67].

3.1.3 Breast Cancer

Breast cancer has become the first leading cause of malignancy in women worldwide. There has been a lot of researches exploring the application of nanoparticles in breast cancer theranostics. Muthu et al., developed theranostic micelles containing conjugation of transferrin for the targeted delivery of docetaxel and ultrabright gold nanocluster (AuNC). The results demonstrated the effectiveness of the delivery system with potential advantages in imaging of tumour and its inhibition[68].Another promising nanotheranostic agent developed by Liu et al. incorporates indocyanine green (ICG) and hyaluronic acid (HA) into cationic small-sized red emission bovine serum albumin (BSA) protected AuNC to form AuNC@CBSA-ICG@HA complex. The results indicated that AuNC@CBSA-ICG@HA has an anti-tumour effect with 95% suppression of tumour growth in mice breast cancer model and this could be a great potential to perform photothermal

therapy[69]. A versatile multi-functionalised nanodevice based on orthogonal bioconjugation has been successfully developed by Cano-Cortes et al. for triple-negative breast cancer. *In vitro* and *in vivo* studies performed using doxorubicin incorporated in this nanodevice show improvement in the therapeutic index and fewer side effects as compared to free doxorubicin[70].

3.2 Neuronal Diseases and Disorders

3.2.1 Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease amongst the elderly characterised by progressive loss of neurons in the brain, leading to cognitive impairment. AD is the most common form of dementia, accounting between 60% to 80% of reported dementia cases. In 2019, over 50 million of the populationsuffered from dementia worldwide and the number is expected to be tripled by 2050[71].Amyloid beta (Aβ) peptide is the major fibrillar component of plaque deposits found in the brains of AD patients. Conventional AD pharmacotherapy remains symptomatic because effective curative therapy has not been developed despite the high medical demand and intensive research on the treatment of AD[72]. The failure in the development of new anti-AD drugs is mainly due to the physicochemical properties of drugs that make the drugs difficult to cross the blood-brain barrier (BBB), resulting in sub-optimal therapeutic concentrations in the central nervous system (CNS)[73]. Thus, it is crucial to take these considerations into account while designing and developing potential drug delivery systems for the early detection and treatment of AD[73].

Curcumin is a plant-derived compound with anti-oxidant and anti-amyloid properties beneficial for AD treatment while dexamethasone has been reported to reduce cerebrovascular inflammation and the incidence of cerebral haemorrhages [74,75]. Jaruszewski et al., developed curcumin-and dexamethasone-loaded chitosan nanoparticles conjugated with gadolinium-diethylene triamine penta acetic acid (Gd-DTPA) and IgG 4.1, an anti-amyloid antibody. It was proven that IgG4.1 on the surface of nanoparticles played a role in the specific targeting of cerebrovascular amyloid (CVA) deposits[76].Excellent distribution to the target CVA and brain vasculature was demonstrated, thus enabling SPECT and MRI specific to the CVA in the brain [76]. In a study by Mathew et al., curcumin loaded-poly (lactic-co-glycolic acid) (PLGA) nanoparticles conjugated with Tet-1 peptide are proven to exhibit anti-oxidant activity and succeed in destroying amyloid aggregates. Tet-1 peptide was

found to facilitate specific targeting on motor neurons and retrograde delivery to neuronal cells [77].

Besides, a study was conducted on the immobilisation of anti-Aβ monoclonal antibodies (aAβmAb) to fluorescent iron oxide nanoparticles loaded with BAM 10 for theranostic applications of AD. A five-folds higher inhibition of Aβ40 fibrillation and a reduction in the Aβ40-induced cytotoxicity were observed with the BAM 10-conjugated nanoparticles compared to the free BAM 10[78].Aβ40 fibrils can be specifically detected *ex vivo* using MRI and fluorescence imaging owing to the selective labelling of the fibrils with the nanoparticles[78]. Targeted dual-functional nanoparticles composed of lectin-modified PEG-PLGA nanoparticles were developed for treating AD[79]. A ligand composed of 12 amino acids, TGNYKALHPHNG (TGN) and a D-enantiomeric peptide, QSHYRHISPAQV (QSH) are the two targeting peptides of PEG-PLGA nanoparticles[79]. TGN acts as the first-order targeting ligand by targeting at BBB whereas QSH is used due to its high affinity towards a component of amyloid plaques, Aβ42 peptides that are found in all AD patients [79].

3.2.2 Epilepsy

Epilepsy is a chronic neurological disorder characterised by unprovoked recurrent seizures. It was reported that the available antiepileptic drugs (AEDs) are ineffective in more than 30% of patients [80]. Thus, novel strategies are required for the treatment of epilepsy. An example is the modulation of the epilepsy phenotype by administrating miRNA mimic or inhibitory synthetic oligonucleotides[81,82]. Iori et al., used a mimic miRNA-146a injection to impair the molecular pathway of IL-1 receptor/Toll-like receptor (IL-1R1/TLR4), thus resulting in the prevention of disease progression and a significant decrease in the recurrence of chronic seizure recurrence[81]. In addition, the administration of anti-miRNA-146a into pilocarpine-induced mice models of temporal lobe epilepsy (TLE) through the intranasal route has been shown to reduce the percentage of mice with seizure onset and increase the latency of seizures [82]. Thus, it can be speculated that in the initial phase, mimic miRNA-146 is effective in the silencing of major transducers of the acute response, leading to a reduction in the epilepsy manifestation. In the second phase where activation of the complement system occurs, anti-miRNA-146 is useful to reduce the neuroinflammation associated with the epilepsy pathology by activating a repressor of the complement system [81,82].

Encapsulation of AEDs within nanoparticles is a potential approach for AD

management. A flexible chip consisting of drug-carrying core-shell magnetic nanoparticles and electrically conductive polyethylene terephthalate substrate was developed. The release of ethosuximide (ESM), an AED, from the chip is triggered by the application of a magnetic field [83]. *In vivo* studies showed that the spike-wave discharge was reduced upon drug release, thus reducing the occurrence of seizures in epileptic patients [83].Besides, polymeric nanoparticles are used owing to the high stability in biological fluids[84]. The nanoparticles incorporated with either hydrophilic or hydrophobic drugs are mostly transported across the BBB by desorption and diffusion, or through the degradation of polymers. The rapid efficient transport of polymeric nanoparticles across the BBB helps in reducing the dosage frequency [84]. Next, the potential of nanogels as a depot drug delivery system for AD treatment has been demonstrated in a study[85].The spike-wave discharge was successfully suppressed by ESM-loaded nanogels and clearance of gels from the site of administration can be visualised using MRI [85].

3.2.3 Parkinson's Disease

Parkinson's disease (PD) is associated with a progressive loss of dopaminergic neurons in the substantia nigra, leading to motor and neurological symptoms such as postural imbalance, tremors, muscle rigidity and bradykinesia[86]. The exact pathophysiology remains unknown but it is suggested that various genetic and environmental factors contribute to the progression of PD[87].The formation and accumulation of alpha-(α)-synuclein, the main component in Lewy bodies, are seen in most PD patients[87].Recently, novel nanoparticle-based approaches are used for the diagnosis and treatment of PD. A study performed by McDonagh et al. has shown that manganese oxide nanoparticles loaded with levodopa (L-DOPA) causes manganese ions and L-DOPA to be released gradually from the nanocarriers, enabling a sustained drug release for PD treatment [88]. Positive contrast in MRI given by the manganese ions is beneficial for the diagnosis of PD [88]. Other than that, the intranasal administration of odorranalectin (OL)-conjugated nanoparticles has been reported as a nose-to-brain drug delivery system with fewer immunogenic reactions in PD patients[89]. Also, OL modification can be enhanced by the pairing of a macromolecular model drug, urocortin peptide, with the nanoparticles. The increased OL modification helps in the enhancement of the therapeutic effects of urocortin-loaded nanoparticles in the management of PD [89].Hu et al. reported a biodegradable drug delivery system using lactoferrin (LF)-conjugated PEG-PLGA

nanoparticles loaded with coumarin-6. It has been demonstrated that the accumulation of LF-conjugated nanoparticles in mice brain cell line was more pronounced compared to unconjugated nanoparticles [90]. Owing to an additional clathrin-mediated endocytosis process, LF-conjugated nanoparticles were also associated with an increase in the cell uptake [90]. Thus, it can be concluded that nanoparticles are promising brain drug delivery systems for PD with reasonable toxicity.

3.2.4 Huntington's Disease

Huntington's disease (HD) is a fatal neurodegenerative disorder characterised by involuntary choreiform movements, mood changes, oxidative damage and transcriptional dysfunction. HD mainly affects the cortical and striatal medium spiny neurons[91]. The exact pathological pathway for HD remains unknown but it usually involves mitochondrial dysfunction. Thus, successful treatment of HD involves the resolve of mitochondrial impairments[91]. Solid lipid nanoparticles (SLNs) encapsulated with curcumin have been utilised in rats with 3-nitropropionic acid (3-NP)-induced HD. The results revealed marked elevations in the cytochrome levels and the activity of mitochondrial complexes, accompanied by restoration of glutathione levels and activity of superoxide dismutase, in rats treated with C-SLNs [92]. Better neuromotor coordination was observed in rats treated with C-SLNs compared to untreated rats [92]. In addition, the administration of rosmarinic acid (RA)-loaded SLNs through nasal route is useful in treating HD [93]. Nasal administration is preferred as it minimises the unnecessary transport and metabolism in other body parts as compared to intravenous (IV) administration. Improvement in behavioural abnormalities and attenuation of oxidative stress have been seen in HD patients treated with RA-loaded SLNs [93].

3.2.5 Post-traumatic Stress Disorders

Post-traumatic stress disorder (PTSD) is a trauma- and stressor-related disorder developed after traumatic experiences, characterised by the persistence of at least one of the symptoms from the four domains including avoidance, arousal and reactivity, intrusion, as well as negative mood and cognitive alterations for a month or longer[94]. However, only 10% to 20% of individuals will develop PTSD after trauma[95]. Once PTSD is appropriately diagnosed, the selection of treatments should be guided by the established guidelines or current research literature [96].Serotonin, also known as 5-hydroxytryptamine (5-HT), has a

theranostic potential in PTSD due to its role in the control of mood and impulse. Empirical demonstrations of abnormalities in 5-HT function were found in most PTSD patients. However, there is limited evidence on the clinical efficacy of selective serotonin reuptake inhibitors (SSRIs) andserotonin-norepinephrine reuptake inhibitors (SNRIs). In a study performed by MacNamaraet al., reappraisal-related activations in the left dorsolateral prefrontal cortex (DL-PFC) and supplementary motor area (SMA) were significantly increased in patients treated with paroxetine, an SSRI, without alterations in the amygdala[97]. DL-PFC has been proven to be associated with the initiation and maintenance of emotion regulation while SMA plays a role in the implementation of DL-PFC-initiated emotion regulatory effects [98]. Shin et al. demonstrated the potential use of SSRIs in PTSD patients by decreasing the amygdala hyperactivity [99].

Trauma-focused treatments (TFTs) including prolonged exposure therapy (PE) and cognitive processing therapy (CPT) are widely used in treating PTSD.PE consists of 10 sessions in which patients are exposed to images associated with an index trauma and real-life stimuli that can be endured and prevented with distress. PE has been shown to help in the prevention and reduction of anxiety as well as an accurate appraisal of the traumatic experience[100]. On the other hand, CPT requires patients to provide a written narrative of the index trauma. The maladaptive cognitions reinforced or formed by the trauma are examined and restructured. CPT has been proven effective in the reappraisal of maladaptive beliefs, thus providing a promising treatment for PTSD patients[101]. Both PE and CPT involve individualised and customised care depending on the needs, barriers and treatment goals of each patient [100,101].

3.2.6 Amyloidosis

Amyloidosis is a series of diseases presenting a hallmark of accretion of misfolded insoluble proteins termed amyloid fibrils. Amyloidosis is a prominent pathologic feature in numerous degenerative disorders [102]. Recently, QDs have been increasingly studied to be one of the potential theranostic tools for amyloidosis. QDs are nanoscale semiconductor crystals, offering tunable optical properties. QDs, a newly emerged class of nanomedicine, can potentially act as effective regulators of amyloidogenesis by inhibiting amyloid fibrils synthesis. There are two major groups of QDs, namely inorganic and organic QDs. Inorganic QDs comprise of a shielded metal crystalline core. Inorganic QDs inherently possess higher stability over organic QDs, indicating potentially longer shelf-lives

when applied as therapeutic drugs [103]. Biphenyl ether (BPE)-conjugated CdSe/ZnS core-shell QDs were shown to be involved in amyloid fibril disruption on preformed transthyretin fibres *in vitro* although at a relatively slower rate [104]. A study utilising a capping agent of dihydrolipoic acid (DHLA) conjugated with CdSe/ZnS core-shell QDs demonstrated a favourable reduction in Aβ fibrillation [105]. Another study by Xiao et al. reported a concentration-dependent inhibition by N-acetyl-L-cysteine capped CdTe core-shell QDs on the amyloid fibrillation through the formation of hydrogen bonds that further restrain the elongation for the fibrillation process [106]. Graphene QDs (GQDs) are organic QDs having low toxicity, high solvent solubility and are easier to be modified on the surface as compared to inorganic QDs. Studies have shown GQDs are effective Aβ peptides fibrillation and aggregation inhibitors [107,108].

Besides inhibiting or disaggregating amyloids, QDs also are shown to exhibit excellent detection ability for amyloids. Conventional thioflavin probes have certain limitations including poor photostability and emission intensity. A nano-formulated red fluorescent QD encapsulated by benzotriazole was developed [109]. This combination of intense red fluorescence, multivalent binding and low overlapping emissions from the background emerges as a more superior detection tool as compared to conventional thioflavin dye [109]. The use of BPE-QDs shows remarkable fluorescence intensity and superior contrast for imaging over the conventional instrument [104]. These studies with different model combinations provide opportunities for further development of QDs amyloidosis treatment and detection.

3.3 *Atherosclerosis*

Atherosclerosis is the arterial lesion characterised by the hardening of arteries underlying the majority of cardiovascular diseases. Recently, an increasing number of preclinical studies have shown the potential of nanoparticles in the theranostics of atherosclerosis. Certain cells and receptors can be specifically targeted by nanoparticles. One of the most extensively investigated targets is macrophages due to its abundance in the arterial plaque [110]. To date, there are multiple strategies utilised in the theranostics of atherosclerosis, namely photodynamic therapy (PDT) and photothermal therapy (PTT). PDT is a treatment mode utilising light to trigger the activation of photosensitisers, producing reactive oxygen species (ROS), singlet oxygen and radicals, which are ultimately cytotoxic to the macrophages. The activated photosensitisers are used for fluorescent

imaging. McCarthy et al., synthesised cross-linked dextran-coated iron oxide (CLIO) nanoparticles aiming for macrophage ablation in atherosclerosis [111]. Additionally, CLIO was labelled with near-infrared (NIR) fluorescent dye and a chlorine-based photosensitiser, making CLIO to be recognised by MRI and fluorescence imaging [111]. The use of chlorine-based photosensitiser in this study was unstable, therefore presenting another CLIO nanoparticles conjugated with a new chlorine-based photosensitiser, namely *meso*-tetra(*m*-hydroxyphenyl)chlorine (THPC) [112]. The results showed macrophage death after irradiating a 650 nm laser whereas fluorescence imaging displayed a build-up of CLIO-THPC in the atherosclerotic plaque.

PTT utilises photo absorbers in generating hyperthermia in the disease area with the help of light irradiation. There are a few studies investigated for the development of gold nanorods (GNRs) for theranostics of atherosclerosis. A study employs conjugation of GNRs and macrophage-targeting monoclonal antibodies (CD11b) as theranostic agents [113].Upon NIR irradiation, up to 80 % of targeted macrophages were killed and the fluorescent imaging portrayed a specific display of CD11b in macrophages. Similar studies have emerged including silica-coated GNRs. This study demonstrated the use of a novel imaging modality, namely combined intravascular ultrasound and photoacoustic (IVUS/IVPA) imaging for localised temperature control upon laser heating [114]. This unique imaging modality can assess the thermal damage and the dose delivered. In atherosclerotic plaques, there is a dense expression of integrin αvβ3 at activated endothelial cells and macrophages [115]. Thus, integrin αvβ3 could be a combined marker of both inflammation and angiogenesis in the lesions [116]. Winter et al. portrayed the use of αvβ3-integrin-targeted loaded with an anti-angiogenic drug called fumagillin[117]. The delivery of an anti-angiogenic drug, detection of early atherosclerosis, and non-invasive assessment of local response from treatment were illustrated. In their further study, the duration of anti-angiogenic activity from single low-dose αvβ3-integrin-targeted was investigated along with atorvastatin[118]. The results showed prolonged anti-angiogenesis, suggesting possible incorporation of this novel theranostics into the standard clinical regimen. Most novel theranostic agents for atherosclerosis portray rapid and non-invasive diagnosis, simultaneously producing desired and specific outcomes in preclinical studies.

3.4 *Type 1 Diabetes Mellitus*

Type 1 diabetes mellitus is a chronic auto-immune disease arising from the impairment of insulin synthesis from the pancreas. These patients often require life-long exogenous insulin injections for glycaemic control. The RNA interference (RNAi) including siRNA and miRNA is the main nucleic-acid based are responsible for pancreatic beta cells normal function by regulating beta-cell growth, insulin production and roles of immune cells. All of which are involved in beta-cell dysfunction [119]. Theranostic application in RNAi involves delivery of oligonucleotides to beta cells and monitoring of the delivery in a non-invasive manner. These non-invasive targeting and beta-cell imaging track the infiltrating diabetogenic T-lymphocytes, and monitor endogenous islet mass and changes throughout the diabetes progression including at the time of therapy [120]. Various imaging approaches including MRI, nuclear imaging and optical imaging could be used concomitantly with RNAi, utilising the diagnostic imaging probe to deliver therapeutic RNAi[119].Several strategies have been investigated for developing MRI probes that are specific to beta cells. Glucagon-like peptide 1 receptor (GLP-1R) targeting superparamagnetic iron oxide (SPIO) nanoparticles are one of the promising probes for theranostic MRI of endogenous islets [121]. Zhang et al. developed targeted SPIO with GLP-1 analog-exendin-4 acting as the ligand. Importantly, the results showed that SPIO-exendin4 bind specifically to and get internalised by GLP-1R-expressing INS-1 cells. This suggests that SPIO-exendin4 could be a molecularly-targeted imaging agent for in vivo insulinoma imaging. GLP-1 and its analogues have been widely recognised in the treatment of diabetes, the potential of the theranostic approach from probes containing GLP-1 analogue conjugates cannot be underestimated [122].

Immune rejection of transplanted islet can lead to graft damage due to T lymphocyte-mediated immune response. Thus, early detection of this immune rejection is required. A study developed a theranostic model with magnetic nanoparticles (MNs) conjugated with siRNA targeting beta-2 microglobulin (B2M). The MNs deliver the siRNA molecule and also provides imaging[123]. The result demonstrated a remarkably slower rate of graft volume loss induced by immune rejection in mice with transplanted MN-siB2M-treated islets as compared to control. Another study showed improved mortality in treatment of patients with transplanted pancreatic islets with theranostic targeting the caspase-3 gene [124]. Downregulation of this gene could protect the transplanted islets from apoptosis [124,125]. Similarly, this study also utilised

in vivo and *in vitro* use of MNs as imaging conjugated with siRNA targeting caspase-3. The grafts loaded with MN-siCaspase-3 presented enhanced insulin secretion and decreased apoptosis. In both *in vitro* and *in vivo*, MN-siCaspase-3 portrayed potential protection on islets [124,125]. These two models could be utilised for further investigation as theranostic, aiming to improve clinical outcomes from islet transplantation.To date, none of the imaging strategies can provide all requirements for theranostic imaging in type 1 diabetes mellitus. These requirements include specifically imaging beta-cell mass, monitoring transplanted islets, and inflammation occurring in islets.

CONCLUSIONS

In conclusion, the emerging theranostics approach has become a predictive, preventive, personalised and participatory medicine or "P4 medicine" in the healthcare management. It has the potential to improve the quality of clinical care and treatments. Ultimately, it helps to identify the right drug for the right patient at the right time, thus saving treatment costs. In other words, theranostics provide successful treatments which can be specific and cost-effective.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial orotherwise.

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