ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Novel Target Selection for Nuclear Medicine Studies

Sze Ting Lee, MD, PhD, FRACP, FAANMS,[*,†,‡] I. Burvenich, PhD,[†,‡] and A.M. Scott, MBBS, MD, FRACP, FAAHMS, FAANMS[*,†,‡,§]

Nuclear medicine techniques involving SPECT and PET are being increasingly used as a noninvasive tool for the detection, quantitation and therapy response monitoring of a myriad of disease processes through target visualization and kinetic modeling. The target selection requires a good understanding of the physiologic changes involved in the disease processes. The target selected can range from cellular proteins expressed in a particular organ, biochemical pathways in cells, or receptors on circulating blood cells. This can have a significant impact on therapeutic options for subsequent therapies, including radionuclide therapies in this evolving world of theranostic practices, which is outlined in this review.
Semin Nucl Med 49:357-368 © 2019 Published by Elsevier Inc.

Nuclear medicine has played a pivotal role in its ability to interrogate the underlying pathophysiological processes occurring in various diseases. This information can then be used to evaluate existing and novel drugs, and specific radiolabelled molecules to treat these conditions. This principle has expanded from the interrogation of available serological and protein biomarkers, to imaging based studies, now more commonly known as "theranostics". The ability to image a specific condition with radiopharmaceuticals prior to treatment with specific targeted therapies allows nuclear medicine to play a pivotal role in both diagnosis and therapy of various disease processes (Fig. 1).

The most well-known targeted radionuclide therapy is with beta-emitting radionuclides, such as the treatment of thyroid cancer with ^{131}I-NaI, which targets the NaI symporter protein (Fig. 2). However, systemic radiotherapy has increasingly been explored using radiolabeled antibodies and peptides that target cancer-specific antigens or receptors, which will be outlined below.

The expression of the target in the tumor and the suitability of the patient for treatment are usually confirmed by an imaging study performed using an analogue of the therapeutic radiopharmaceutical labeled with a positron- or gamma-emitting radionuclide. The uptake of the therapeutic radiopharmaceutical in normal tissue can stem from the expression of the target in healthy organs (eg, CD20 in the bone marrow and spleen or A33 antigen in the normal bowel) or due to the size of the protein (eg, the preferential uptake of radiolabelled peptides in the kidneys). Dosimetry analyses can also be performed to confirm that the dose delivered by the radiopharmaceutical is sufficient enough to achieve a therapeutic effect. A key goal of performing imaging studies prior to target radiotherapy is to determine the expected biodistribution of the therapeutic radiopharmaceutical and thus help avoid toxicity to healthy organs. This "theranostic" approach is exemplified by the use of ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE in patients with neuroendocrine tumours.[1] There are other newer peptide targets which are being currently explored in clinical trials, with a radiopharmaceutical targeting PSMA in metastatic prostate cancer showing impressive early clinical results.[2] These will be discussed further below.

Target Selection

The principles of target selection are based on the specific properties of the disease condition being investigated, specifically the physiologic processes involved in the condition. These targets are based on their expression, function, specificity and relevance of the target for subsequent therapies. Although these principles have been practiced widely within

*Department of Molecular Imaging and Therapy, Austin Health, Melbourne, Australia.
†Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia.
‡School of Cancer Medicine, La Trobe University, Melbourne, Australia.
§Faculty of Medicine, The University of Melbourne, Melbourne, Australia.
Address reprint requests to Sze Ting Lee MD, PhD, FRACP, FAANMS, Department of Molecular Imaging and Therapy, Austin Health, Victoria 3084, Australia. E-mail: szeting.lee@austin.org.au

https://doi.org/10.1053/j.semnuclmed.2019.06.004
0001-2998/© 2019 Published by Elsevier Inc.

the oncology field, it can also be used in the fields of neurology, cardiology, infection, musculoskeletal and other disease conditions which require functional data obtained from nuclear medicine imaging to identify and characterize the pathophysiological processes being investigated.

Target Expression

The target for radiopharmaceuticals used in nuclear medicine imaging should ideally have an abundance of expression in the cells or tissues involved in the disease processes. This would provide dynamic and quantitative information in the scans to be translated to future treatments. There are circumstances where it is the assessment of relatively abnormal distribution or measurement of a radiotracer compared to the baseline or normal tissue distribution which allows the use of a particular scanning process (eg, gated cardiac blood pool studies or gastrointestinal bleed studies). In studies where the target is preferentially expressed in diseased tissue compared to normal tissue, (eg, identification of specific cell populations, receptors or antigens in a disease process), these can be done so using SPECT or PET radiopharmaceuticals.[3-7] The low physiologic expression is especially important for targets being used for imaging and therapeutic purposes. For example, the traditional bone scan imaging of bony disease is dependent on the osteoblast uptake of MDP (labeled with ^{99m}Tc), which would allow the discrimination of diseased bone demonstrating increased uptake relative to normal bone uptake. In neurological practice, the detection of beta-amyloid in Alzheimer's disease with PET tracers usually needs threshold levels of protein in the diseased areas of the brain to increase to levels that are usually expressed after up to 10 years of the active disease process, but also predate symptoms by up to a decade.[8]

The target being investigated must also be accessible to radiopharmaceuticals for adequate uptake and imaging. The blood

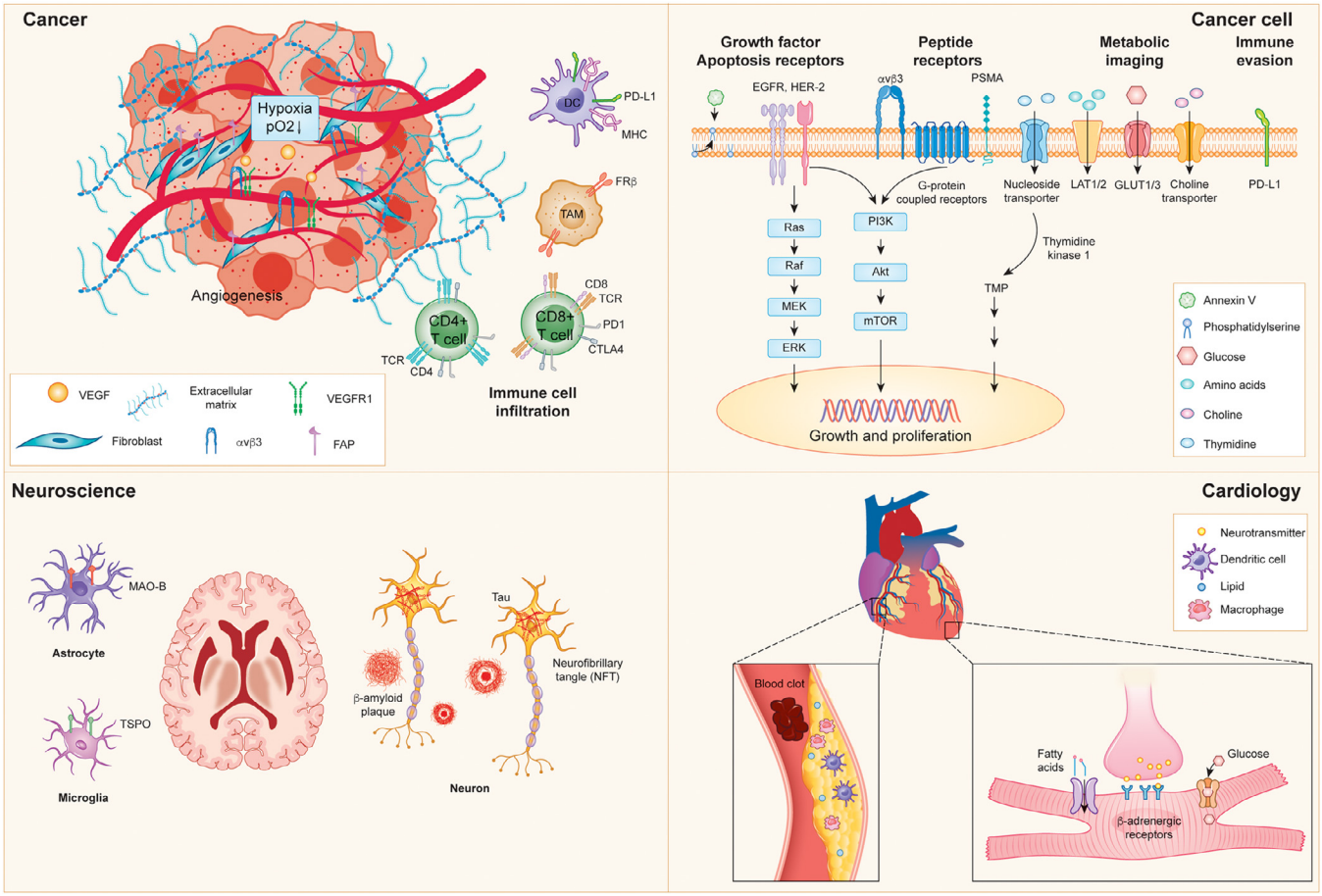

Figure 1 Targets for nuclear imaging in cancer, neuroscience and cardiology. Radiopharmaceuticals targeting metabolic pathways, physiological processes, and disease pathways can be used for nuclear imaging and targeted therapy. Akt, protein kinase B (PKB); αvβ3, alpha-v beta-3 integrin 3; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CTLA4, cytotoxic T-lymphocyte–associated antigen 4; DC, dendritic cell; FAP, fibroblast activation protein; EGFR, epidermal growth factor receptor; FRβ, folate receptor beta; GLUT1/3, glucose transporter 1 or 3; HER-2, receptor tyrosine-protein kinase erbB-2; LAT1/2, L-type amino acid transporter 1 or 2; MHC, major histocompatibility complex; MOA-B, monoamine oxidase B; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; VEGFR1, vascular endothelial growth factor receptor 1; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol-3-Kinase; PSMA, prostate-specific membrane antigen; TAM, tumor associated macrophage; TCR, T cell receptor; TMP, Thymidine monophosphate; TSPO, translocator protein 8.

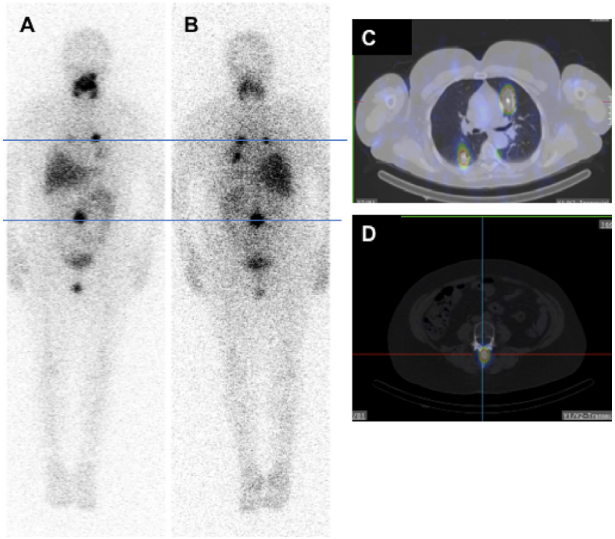

Figure 2 Metastatic follicular thyroid carcinoma. (A) Anterior whole body ^{131}I-NaI scan following treatment with 200 mCi of ^{131}I-NaI shows uptake in pulmonary nodules and lumbar spine, (B) posterior whole body planar image, (C) coregistered SPECT/CT image of the lung metastases. (D) Coregistered SPECT/CT imaging of the lumbar spine metastasis.

brain barrier may also impact on small and large molecule passage due to the lipophilicity, charge, and size restrictions on penetrance.[9,10] For peptides and large proteins, where diffusion through the interstitial membrane can restrict delivery of a tracer unless very high concentrations are delivered, must also be taken into consideration when it comes to target selection. Therefore, the validation of new radiopharmaceuticals needs careful evaluation of the biologic distribution and uptake in target cell populations or tissues to ensure target engagement is achieved and readily reproducible.

Target stability is also essential for reliable diagnosis. Any enzymatic degradation of the target, whether that be within the biochemical pathways or metabolically, can cause significant variation in the temporal pattern of uptake and retention. For example, for ^{131}I-NaI, there is a high turnover rate of the NaI symporter which may impact on the scan results and subsequent therapeutic dosimetry required in treatment of well differentiated thyroid carcinoma.[11] Furthermore, any changes in the target due to phenotypic instability (eg, HER2 or PSMA) may also impact on the sensitivity of the nuclear imaging scan for detection of a particular disease.[12] A further factor which can also impact on imaging is when the target is shed from the cells (or not trapped within the cell), resulting in rapid clearance of the radiopharmaceutical from the blood and reduced uptake in the target cell population being investigated (eg CEA or HER2).[12]

Target Function

There are various factors which influence cellular metabolism associated with many disease states, and it is the identification of these changes which permits the development of radiopharmaceuticals which can assist in the diagnosis of these diseases (Fig. 1). These changes are usually a product of transcriptional, genetic, or microenvironment influences, resulting in alterations in glucose, amino acids and lipids in cells, as well as physiologic changes such as hypoxia. There are changes which are associated with enzymatic or pump changes in cells, favoring altered metabolic states, and protein or receptor expressions linked to these conditions (eg, HIF1alpha and CAIX expression in hypoxic conditions). In addition, there are also genomic changes which result in overexpression of targets, or modified targets compared to normal (eg, mutant signaling pathways or receptors), which can be exploited for imaging and therapy.[13–16] A thorough understanding of the disease biology and identification of suitable targets would allow the development of suitable imaging probes for nuclear medicine studies to be able to noninvasively interrogate these fundamental biochemical and metabolic changes that occur in diseased tissue.

The processing of a target can also impact on the selection of optimal isotope for nuclear imaging. When the target is a cell surface receptor, the activation of the receptor may result in oligomerization and internalization of the receptor, resulting in radiopharmaceutical/receptor complex entering endosomal and lysosomal pathways and low pH conditions intracellularly.[17,18] This is not well suited to radiohalides (which are usually rapidly extruded from the cell), and radiometals are therefore much more appropriate for nuclear imaging and potential therapy.

Specificity of Disease Targets

There are many targets which are expressed in normal tissue; however, the overexpression or selective expression may provide opportunities for the development of imaging probes to specifically diagnose the disease. A typical example is that of PSMA, which is overexpressed on prostate cancer cells compared to normal tissue, and it is the upregulation of this in aggressive disease which can be imaged.[19] Hormone receptors are also selectively overexpressed in diseases (eg, cancer) compared to normal tissue. Whist it is highly unusual for these targets to only be expressed in a disease state, it is the relative abundance of the expression in disease states which allows it to be targeted for nuclear imaging.

Targets for Therapy

The specificity and stability of the target, as well as the cellular processes are key factors in the selection of suitable targets for targeted radionuclide therapy. The exception to this is where there is local administration of radiopharmaceuticals (eg, radiolabelled microspheres injection via the hepatic artery which preferentially supply hepatic tumors) (Fig. 3).

Due to the selective accumulation of internalized targets, radiometals are commonly used for detection of these targets in-vivo. Where targets are not internalized, the use of radiohalides can be highly effective, such as ^{131}I-NaI for detecting thyroid disease.[20] The ability to validate therapeutic targets needs careful preclinical assessment of area under curve

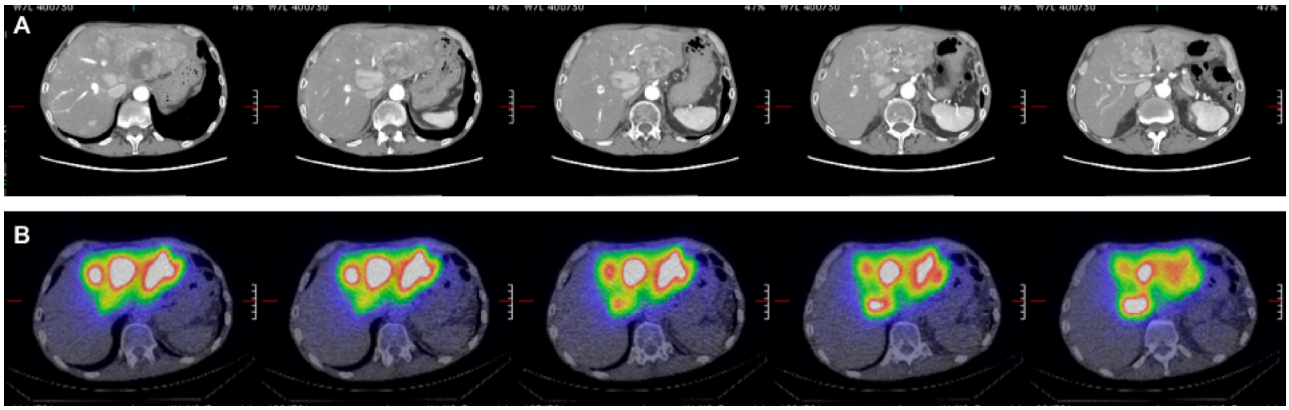

Figure 3 Treatment of primary hepatocellular carcinoma with ^{90}Y-microsphere radioembolization. (A) CT showing multifocal disease in the left lobe. (B) Post-treatment Bremstrahllung SPECT/CT imaging showing localization of the ^{90}Y-labeled microspheres in the tumor within the left lobe, without uptake outside the liver.

(AUC) and dosimetric analysis, as well as the development of imaging probes which reflect the biodistribution of the target (Fig. 4). This theranostic approach would therefore allow the development of an imaging probe which can select suitable patients for treatment and predict likely response, and is now a very powerful approach in the development of effective new therapeutic drugs and radiopharmaceutical therapies.[21,22]

Target Selection for Specific Radiotracers

Ligands

The features required for an ideal small molecule radiopharmaceutical are that it should have fast plasma clearance, high specificity and affinity for its target, low nonspecific and nonselective binding, and low peripheral metabolism. The size,

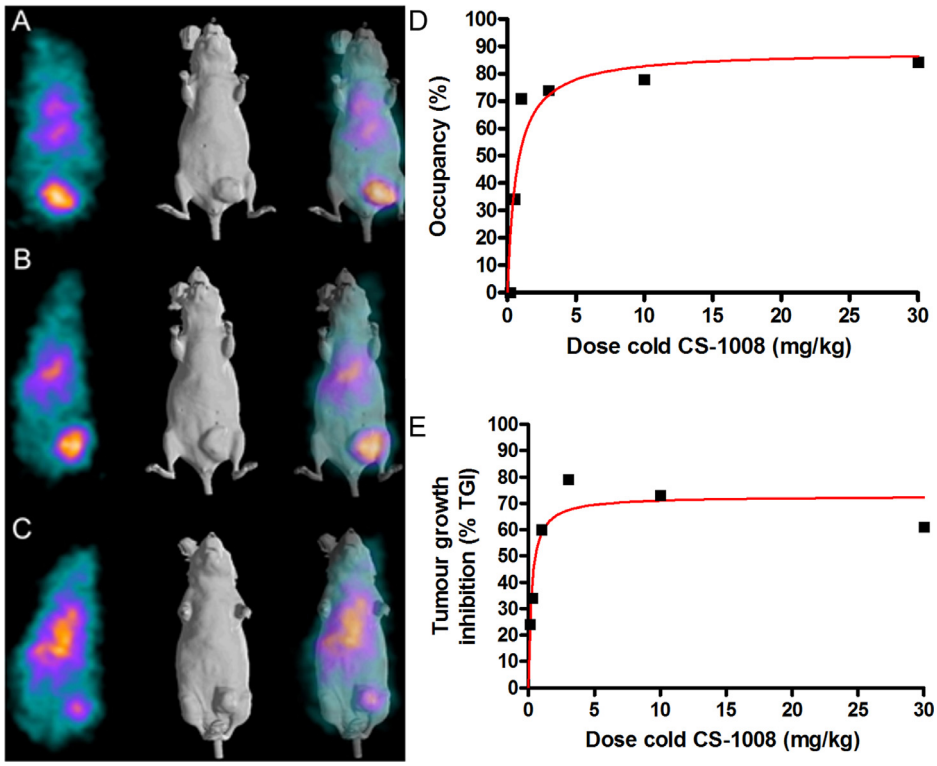

Figure 4 *In vivo* assessment of Death Receptor 5 (DR5) expression by cancer cells, and receptor occupancy relationship to therapeutic response evaluated with anti-DR5 antibody CS-1008. Uptake of ^{111}In-CHX-A″ DTPA-CS-1008 is demonstrated by planar gamma camera imaging at different dose levels (A) 0.2 mg/kg; (B) 0.5 mg/kg and (C) 10 mg/kg. Representative whole body images (*left*), surface-rendered CT (*middle*) and fused images (*right*) are shown. (D) DR5 receptor occupancy curve of ^{111}In-CHX-A″ DTPA-CS-1008 in BALB/c *nu/nu* COLO 205 tumor-bearing mice at 48 hours postinjection; (E) Tumor growth inhibition of different dose levels of CS-1008 in a COLO 205 tumor model shown as percentage tumor volume of vehicle control group at 24 days post therapy (Adapted from Yada et al 2008; adapted from Burvenich et al, 2013).

charge, and lipophilicity of the radiopharmaceutical all play important roles in determining its pharmacokinetic profile and uptake by the cell or tissue where the target is expressed.[23] The features which make small molecules more frequently used as for intracellular targets are due to their membrane permeability and the ability to design molecules for specific biochemical targets within the cytoplasm and nucleus. The targets best suited to small molecule radiotracers are metabolic pathways, kinase domains, signaling pathways, and nuclear receptors. The chemical nature of these compounds often lends itself to the creation of PET radiotracers with ^{18}F- or ^{11}C, and also SPECT radiopharmaceuticals with ^{99m}Tc as well.[24]

Peptides

There are several features peptides have which lend itself toward more advantageously over small molecules resulting in the development of radiolabelled peptides. Most importantly is their receptor specificity, as well as the design and bioconjugation advancements which allow these radiolabelled peptides to have greater potency and stability *in vivo*.[25–27] Peptides also generally have high stability at room temperature and greater ability to penetrate tissues/tumors to allow fast target uptake and blood clearance compared to larger proteins, and also less likely to cause immunogenic reactions than proteins or antibodies, compared to larger proteins.[28]

The cell surface receptors expressed by different diseases are ideal targets for radiolabelled peptides. The typical receptor targets for peptide-based radiopharmaceuticals are usually the 7-transmembrane proteins, often referred to as G-protein-coupled receptors. There are numerous G-protein-coupled receptors which have been identified, with an estimated 50% of clinically relevant drugs acting upon this class of receptors.[29] A large number of these receptors are over-expressed in disease states and are thus being evaluated as targets for nuclear imaging probes. These include somatostatin receptors, $\alpha_v\beta_3$ integrins, the gastrin releasing peptide receptor, the cholecystokinin 2 receptor, the glucagon-like peptide 1 receptor, and the chemokine receptor 4. Recent reviews have identified a large number of potential new targets for peptide-based radiopharmaceuticals.[30]

Proteins

Antibodies are large proteins which are produced by the immune system in response to antigen expression, and binds specifically to the antigen to form an antigen-antibody complex. When antibodies are administered systemically, they can take a few days to accumulate within the target tissue in a specific disease, before it is cleared from the blood.[12,31]

The complementary determining regions confer the antibody's ability to bind its target, and due to the spatial orientation of the complementary determining regions, the antibody can bind to complex antigens or receptors on the cell membrane and in the tumor microenvironment. Antibodies can target the antigens with high affinity and exquisite specificity, therefore are ideally suited to these more complex protein targets.[12]

Diseased cells and tissues express the targets for antibodies at higher concentration than the low levels expressed in normal tissues, are genetically stable, and are not shed from tissues into the bloodstream. Recent development of smaller fragments of intact antibodies (eg, scFv, minibodies) has shorter half-lives which are more suited to nuclear imaging.

The targets suited to antibodies have been explored clinically for the last few decades, and there are approved antibodies for therapy in cancer, cardiology, and immune disease indications.[32] Radiolabeled antibodies and antibody fragments are emerging as powerful tools in drug development, as they can be used to assist in the development of therapeutics through the evaluation of target expression, occupancy, and dose response in early phase clinical trials.[33]

Targets and Disease

There are new targets relevant for disease being discovered every day, but the principle clinical areas of nuclear imaging are in the fields of oncology, neuroscience, and cardiology (Fig. 5).

Oncology

There are numerous targets for the nuclear imaging of cancer, including the changes in metabolism of cancer cells, the deregulation of the expression of receptors on the surface of cells, the changes in tumoral hypoxia, angiogenesis and cell proliferation, the inactivation of apoptosis pathways, and the evasion of the immune system (Fig. 1).

The metabolic pathways involved in the pathogenesis of oncology are the most common targets for nuclear imaging, both with SPECT and PET imaging. When deliberating the most appropriate radiotracer for labeling, an important factor which needs to be taken into consideration includes the physical half-life of the radiotracer, which should be compatible with the residence time of the targeted drug, which can be fast (few hours) for a small molecule, or slow (few days) for a slow intact antibody, as has been mentioned above.

Cancer Metabolism

One of the classic "hallmarks of cancer" is cellular metabolism, which is a feature which has been exploited for nuclear imaging for decades.[34] Tumor staging with ^{18}F-FDG has been established as a cornerstone of patient management for most cancer types and has been established as an integral part of oncology practice in many countries across the world.[35–37] This is based on the cancer cells' preference for aerobic glycolysis, and FDG gets trapped within cancer cells and can be noninvasively evaluated.

There are other metabolic targets, such as choline and lipid moieties, fatty acids, and biochemical pathways have also emerged, with the recent approval of ^{11}C-choline PET in prostate cancer standing as a prominent example. The high

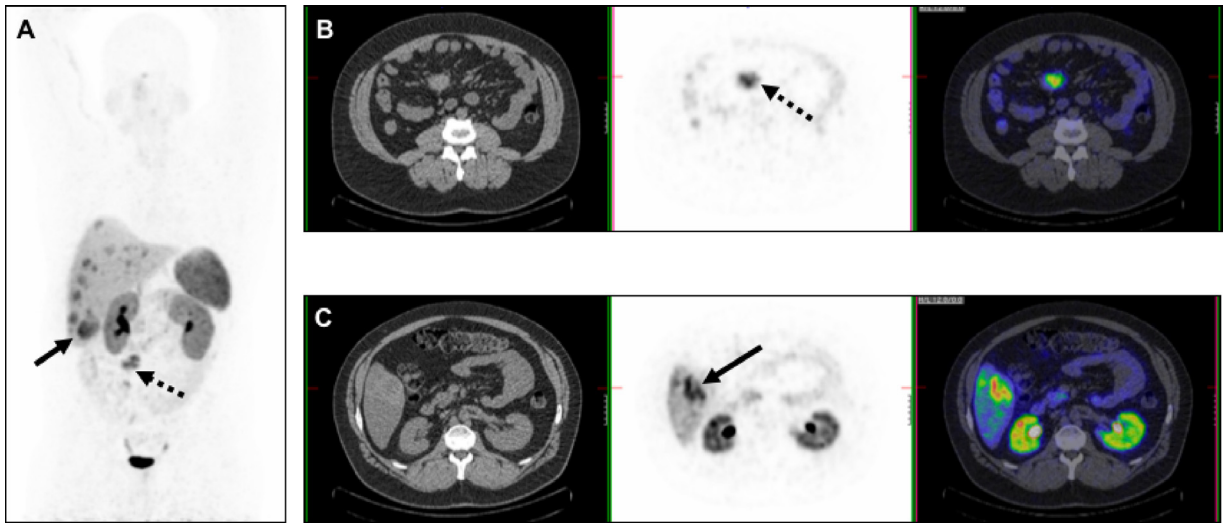

Figure 5 ^{68}Ga-DOTATATE PET scan for somatostatin receptor imaging. (A) MIP image demonstrating primary mesenteric lesion (dotted arrow) and multiple liver metastases, with the largest lesion in segment 5 (solid arrow). (B) Axial images of the mesenteric lesion on CT, PET and fused PET/CT images. (C) Axial images of the largest liver lesion on CT, PET, and fused PET/CT images.

sensitivity and accuracy of ^{18}F-FDG PET in detecting tumors and monitoring response to treatment has meant that other metabolic targets are being explored primarily to assist with the biological and functional characterization of tumors. The ability to use these PET radiopharmaceuticals in circumstances in which ^{18}F-FDG PET is not useful, would allow aid to clinicians utilizing the best clinical treatments to result in better patient management and prognosis.

Cell Proliferation

One of the most important "hallmarks" of malignant tumor growth is increased cell proliferation.[34] The imaging of cell proliferation with probes can assist with staging cancer, and assess response to treatment. The uptake of ^{18}F-fluorothymidine (^{18}F-FLT) — which is trapped in cells during the S phase of cellular growth, and therefore provides a measure of proliferation, has been shown to be highly correlated with response to treatment in certain tumours.[38]

Amino acids also enter cells via the L-type amino acid transporter (LAT1), which is overexpressed in most cancer types compared to normal tissues. Amino acid imaging has also been used to evaluate the turnover of proteins in cancer cells. There are several radiotracers which have been shown to identify recurrent tumor from postradiotherapy changes - eg, ^{18}F-fluoroethyltyrosine (^{18}F-FET) or ^{11}C-methionine (^{11}C-MET) has been shown to accurately identify recurrent tumor from post-therapy changes in a range of tumors including high grade gliomas.[39,40]

Cell Hypoxia

Hypoxia is a physiological effect which is known to be present in many tumor types, and is intricately linked with tumor angiogenesis.[41] The degree of tumor hypoxia is also an important determinant of treatment response, relapse-free survival and overall prognosis, which is independent of the treatment modality used.

Hypoxia is characterized by lower levels of oxygen in tissue than would normally be present. The imaging of hypoxia with SPECT and PET radiopharmaceuticals can provide important information on tumor biology and assist in the selection of patients for treatment with hypoxia-targeted drugs, which can impact on patient survival.[41] There are a range of radiopharmaceuticals that can be trapped within hypoxic tissues in cancer patients, including ^{18}F-labeled fluoromisonidazole (^{18}F-FMISO), ^{18}F-FAZA, and ^{64}Cu-ATSM.[42]

Receptors and Protein Kinases

The dysregulation of protein kinases can have a significant impact on cellular processes via signal transduction pathways. These include processes such as cellular proliferation, angiogenesis, transcription, and inhibition of apoptosis, which are affected in cancer cells. It is usually the activation of cell surface receptors by encoded protein tyrosine kinase (PTK) oncogenes (approximately 50% of known oncogenes). Therefore, these can serve as targets for cancer imaging and/or therapy.

Cell surface receptors on cancer cells are normally targeted by peptides or monoclonal antibodies, while cellular PTKs and intracellular ATP binding domain of PTKs receptor are usually targeted by small molecule pharmaceuticals. The extensive variety of cancer cell receptors can form the basis for a large number of therapeutic antibodies and peptides that neutralize receptor activation and inhibit tumor growth.[12,32] Receptors that are expressed in the tumor microenvironment as well as immune regulatory receptors on cancer cells and immune cells may also be targets for therapy. These targets have also been exploited for both nuclear imaging and therapy.[12,43] Intracellular tyrosine kinase domain targets may also be targets for imaging to evaluate

the suitability of tumors for therapy. To this end, radiotracers such as ^{11}C-imatinib, ^{11}C-Gefitinib, and ^{11}C-erlotinib have been developed based on FDA-approved small molecule therapeutics.[43]

There are increasing peptides being targeted for neuroendocrine tumors, where the use of peptide receptor radionuclide therapy (PRRT) targeting somatostatin receptors (Fig. 5), is the current trend. This is the basis of treatment of these tumor types after the NETTER-1 trial showed that treatment with ^{177}Lu-DOTATATE resulted in markedly longer progression-free survival and a significantly higher response rate than high dose octreotide treatment in patients with advanced midgut neuroendocrine tumors.[1] Smaller clinical trials using ^{177}Lu-DOTATATE have shown a high efficacy and tolerability, especially on the kidneys, with favorable characteristics for PRRT due to a low whole-body dose, resulting in potentially lower bone marrow toxicity.[44] Dosimetry studies have also confirmed the high specificity of PRRT against tumors, whilst being able to spare healthy tissue.[45,46] Therefore, PRRT is now integrated into multidisciplinary guidelines of this tumor type (eg, NCCN/ENETS), and is now licensed for use in Europe.[47]

In prostate cancer, prostate-specific membrane antigen (PSMA) has gained momentum in the treatment paradigm of metastatic prostate cancer. Whilst PSMA is not specific for prostate cancer,[48] it is a transmembrane protein which is highly relevant in prostate cancer theranostics in view of its marked overexpression in prostate cancer.[49,50] The value of ^{68}Ga-PSMA-directed PET imaging as a diagnostic procedure for primary and recurrent prostate cancer as well as the role of evolving PSMA radioligand therapy (PRLT) in castration-resistant prostate cancer is currently being assessed around the world (Fig. 6). Current information suggests that ^{68}Ga-PSMA PET/CT has a role in the primary staging of patients with high-risk prostate carcinoma, and the combination with pelvic multi parametric (mp) MR has the highest impact on patient management.[51] A prospective multicenter trial in Australia showed that ^{68}Ga-PSMA PET/CT scans detected previously unsuspected disease in both primary staging and restaging of patients with biochemical recurrence in patients with prostate cancer, with a change in management in 51% of patients.[52] By identifying sites of target overexpression, ^{68}Ga-PSMA PET scans permit the selection of patients eligible to receive personalized PSMA radioligand therapy, which has been found to be feasible, safe and effective in appropriately selected patients.[53] A recent phase two study has shown that radionuclide treatment with ^{177}Lu-PSMA-617 has high response rates, low toxic effects, and reduction of pain in men with metastatic castration-resistant prostate cancer who have progressed after conventional treatments.[54]

Whilst there are a few studies which show promising results with the alpha-emitter, ^{225}Ac-PSMA, this is still in relative infancy,[55,56] with potential roles in the treatment paradigm of radionuclide therapy of prostate cancer still to be determined. In particular, the combination with beta-emitters (as a cocktail or a sequence), and patient populations would need to be researched further before approval, reimbursement or standard of care in patients with metastatic prostate cancer can be determined.[56]

Neuroscience

Nuclear imaging is a powerful tool for quantifying brain metabolism, visualizing alterations in regional blood flow, and aggregated proteins associated with neurodegenerative

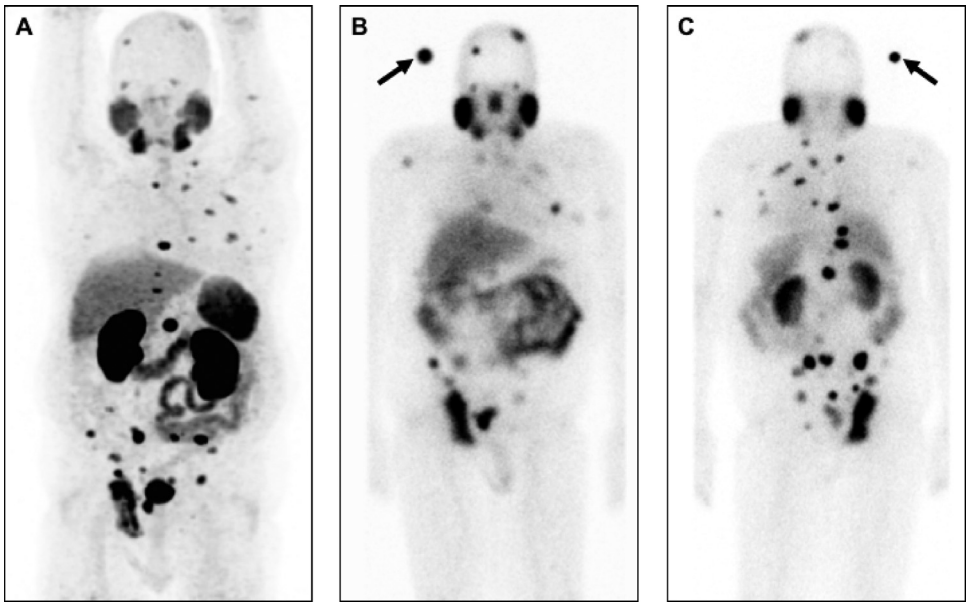

Figure 6 Theranostic pair of ^{68}Ga-PSMA PET/CT scan followed by therapeutic ^{177}Lu-PSMA therapy. (A) ^{68}Ga-PSMA PET (MIP) demonstrating extensive bony metastatic prostate carcinoma. (B) Anterior projection: ^{177}Lu-PSMA post-treatment scan 24 hours after administration demonstrating excellent localization of ^{177}Lu-PSMA to site of ^{68}Ga-PSMA avid disease. (C) Posterior projection of ^{177}Lu-PSMA post-treatment scan.

disease such as Alzheimer's disease. To investigate brain function and disease, there are a variety of compounds which have been radiolabeled as potential targets of biochemistry, and transporters. A transporter can be the primary target through the development of a specific high-affinity radioligand: examples are the multiple high-affinity radioligands for the neuronal membrane neurotransmitter or vesicular transporters, used to image nerve terminals in the brain. The goal of a radiotracer might be to study the function of a transporter through the use of a radiolabeled substrate, such as the application of 3-O-^{11}C-methylglucose to measure rates of glucose transport through the blood–brain barrier.[57]

Amyloid Plaques

The most common cause of dementia is Alzheimer's disease (AD), which is a chronic neurodegenerative disease resulting from the deposition of amyloid plaques in the brain. Amyloid plaques block cell-to-cell signaling at synapses, a process which is essential for storing memories, processing thoughts and emotions, and planning. PET imaging with small molecule amyloid-targeted radiotracers such as ^{11}C-Pittsburgh Compound B and other recently FDA-approved ^{18}F-labeled amyloid-targeted radiotracers have been used to visualize the accumulation of amyloid in the brain before cognitive deficits become clinically evident[58] (Fig. 7). In addition, amyloid radiotracers are used in AD patients to confirm their eligibility for amyloid therapy and to monitor their response to therapy.[8]

Intracellular Tau Neurofibrillary Tangle

The term tauopathies categorizes neurodegenerative conditions, such as AD, characterized by the pathologic accumulation of tau. Tau is a phosphoprotein whose major role is the stabilization of microtubules, critical for intracellular transport and cytoskeletal support. Tau hyperphosphorylation leads to tau aggregation in the form of intracellular filamentous inclusions termed neurofibrillary tangles, and although the mechanisms leading to tau hyperphosphorylation and aggregation have not been fully elucidated, tau deposition follows a stereotypical neuroanatomic pathway in the brain.[8] Studies have shown that both the amount and topographical distribution of Tau within the cerebral cortex are more tightly associated with neurodegeneration and cognitive decline.[59,60] Tau imaging studies have showed that tau retention follows the known distribution of the aggregated tau in the brain,[61] and also associated with neurodegeneration markers[62] such as FDG and cortical grey matter atrophy.

In AD, there is dysfunction of the enzymes responsible for phosphorylation of tau, which results in a hyperphosphorylated version that aggregates and forms insoluble NFT.[8] Several small molecule radiotracers with high selectivity for NFT have been recently developed, including ^{18}F-AV1451, ^{18}F-THK523, and ^{11}C-PBB3.[8,63] The mesial temporal retention of tau has been shown to be high irrespective of amyloid levels, and the association between tau levels and age increases in the presence of amyloid.[64]

Neuroreceptors

Dopaminergic neurotransmission plays an important role in regulating several aspects of basic brain function, including motor skills, behavior, motivation, and working memory.[65] It is also involved in the pathogenesis of a variety of neurological disorders, such as Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder, and drug dependence.

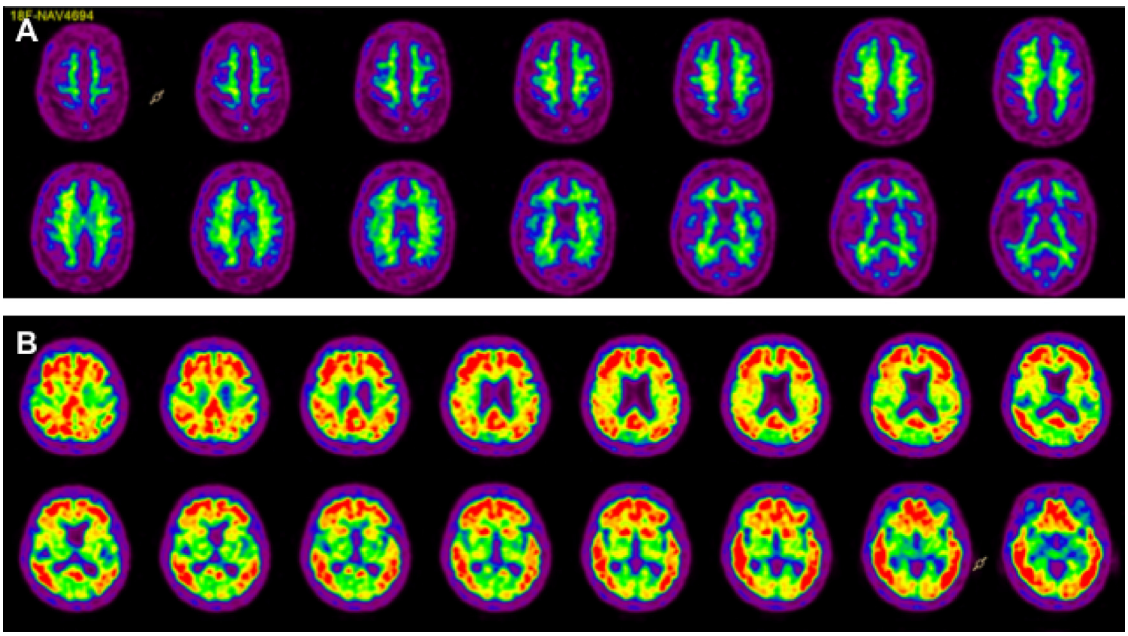

Figure 7 Axial imaging of β-amyloid with ^{18}F-NAV4694 PET/CT. (A) Negative study with normal amyloid distribution in the white matter. (B) Positive study, with significant amyloid distribution in the grey matter in both lobes, most marked in the frontal, precuneus, posterior cingulate, lateral parietal, lateral temporal cortex and striatum.

A number of small molecule PET and SPECT radiotracers have been developed to visualize the activity of dopamine synthesis, reuptake sites, and receptors in a variety of neurological disorders.[65,66]

In patients with Parkinson's disease, L-DOPA (L-dihydroxyphenylalanine) is known to be low, and therefore can be replaced with synthetic L-DOPA. ^{18}F-FDOPA is an analogue of L-DOPA, an immediate precursor for dopamine, and has been used clinically as a small molecule PET radiotracer to trace the dopaminergic pathway and evaluate striatal dopaminergic presynaptic function in patients affected by Parkinson's disease.

Cells also have ion channels which are membrane proteins controlling the flow of ions passing through the cell membrane. Ion channel linked receptors are bound in cell membranes and mediated via the conformational interaction between ion channels and chemical ligands. The γ-aminobutyric acid-benzodiazapine (GABA) receptor is a well investigated ion channel linked receptors in the brain.[67] Decreases in GABA-A receptor expression have been observed in many brain disorders such a dystonia, epilepsy, and ischemic stroke in clinical research studies using ^{11}C and ^{18}F-flumazenil PET imaging.

The reduction in the expression of the nicotinic acetylcholine receptor has been reported in various neurodegenerative diseases, including epilepsy, depression, schizophrenia, and Parkinson's disease.[68] PET imaging with ^{18}F-2-FA has shown promise in the imaging of Alzheimer's disease and Parkinson's disease patients.[69]

Neurological Proteins

The translocator protein (TSPO) is an 18kDa mitochondrial protein in the central nervous system which has been known to involve the expression of receptors in neuroinflammation, and could potentially be targets for radiopharmaceuticals. The TSPO specifically has been shown to be an important target for the visualization of activated microglia that mediate the inflammatory process in disorders such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[70] The level of TSPO is low in the healthy brain but increases when the inflammatory pathway is activated. Many different TSPO-targeted PET radiotracers have been developed, of which ^{11}C-PK11195 is the most frequently used.[71]

There are also transporters such as p-glycoprotein that function to extrude small molecules from tissues, and can effectively work against successful uptake of radiotracers. The diversity of structures and functions of transporters, in the diagnostic and therapeutic aspects, demonstrates their importance and role in in vivo imaging of transporter location and function to establish the role in the therapeutic realm and PET radiotracer and drug development.[57]

Cardiology

In cardiovascular disease, a large number of targets associated with atherosclerotic plaque inflammation, myocardial infarction, impaired myocardial autonomic innervation, cardiac cell apoptosis, and vulnerable plaque rupture-prone lesions have been explored for nuclear imaging.[72] Even though there are many radiopharmaceuticals being developed and evaluated clinically for nuclear imaging in cardiovascular disease, probes for the visualization of myocardial perfusion imaging and myocardial metabolism are the most commonly used in current practice.

Infiltrative heart diseases such as sarcoidosis and amyloidosis are another group of cardiovascular diseases whereby nuclear medicine is playing an increasing role in developing molecularly targeted tracers to precisely phenotype infiltration. The infiltration accumulates in the heart, resulting in heart failure, morbidity, and death. The pathogenesis of infiltrative heart disease can be wide, ranging from myocyte involvement and changes in the extracellular matrix structure, resulting in hypertrophy, atrophy, apoptosis, fibrosis, or a combination of all. Changes in the composition can result in edema and amyloid fibril deposition, and complex metabolic switches affect the glucose, fatty acid and oxidative metabolism in the heart as well.[73] These structural and metabolic changes in the ventricles and atria can form substrates for electrical heterogeneity, cardiac rhythm abnormalities, heart blocks, and embolic phenomenon.[74]

There are a number of myocardial adaptations to infiltration which can be imaged noninvasively without a need for endomyocardial biopsy. Advanced phenotyping of myocardial metabolic processes and molecular adaptations evaluated by "omics" are likely to become the basis for personalized management of patients with infiltrative heart disease.[71] Due to the recent availability of effective targeted therapies which can slow the progression of cardiac amyloidosis, there has been a renewed interest in being able to diagnose the disease leading to better patient selection and outcome. Emerging imaging targets for inflammation and fibrosis and the role of imaging in the evaluation of microvascular dysfunction, innervation, and targeted imaging of sarcoidosis and amyloidosis.[71]

Myocardial Perfusion Imaging (MPI)

Cardiac SPECT and PET imaging is commonly performed to assess myocardial perfusion and left ventricular function in patients with coronary artery disease. Myocardial perfusion imaging (MPI) enables the accurate measurement of the passage of blood through the heart, and the combination of MPI and stress testing (exercise or pharmacologic) can facilitate the identification of areas of myocardial damage or impaired blood flow.[75] SPECT tracers such as ^{201}Tl-thallous chloride, ^{99m}Tc-sestamibi, and ^{99m}Tc-tetrofosmin are commonly used for MPI, while imaging with ^{99m}Tc-red blood cells is used for the assessment of left and right ventricular function and shunts. ^{18}F-FDG and ^{82}Rb-RbCl can also be used for the PET imaging of myocardial viability and blood flow.[75] In the assessment of cardiac sarcoidosis, cardiac FDG PET has been used to both identify metabolically active extracardiac granulomatous sarcoid lesions, as well as the presence of focal or multifocal increased FDG uptake associated with perfusion

defects assessed on myocardial perfusion imaging, as described above.

Cardiac Innervation Imaging

The maintenance of homeostasis in the cardiovascular system by the sympathetic nervous system is mediated in part by catecholamines such as norepinephrine (NE). The stimulation of the adrenergic receptors of the cardiac muscle is caused by NE released from sympathetic neurons. The over-expression of an NE transporter known as hNET, a transmembrane protein that facilitates the reuptake of NE in sympathetic nervous system in the heart, has been correlated with the progression of heart disease as well as increased mortality. To date, the majority of clinical myocardial innervation imaging studies have utilized radiolabeled analogues of norepinephrine using both SPECT and PET, including ^{123}I-labeled metaiodobenzylguanidine ^{123}I-MIBG and ^{11}C-labeled meta-hydroxyephinephrine (^{11}C-mHED).[76]

Cardiac Amyloid Imaging

Cardiac amyloidosis is a form of restrictive cardiomyopathy resulting in heart failure and potential risk on arrhythmia, due to amyloid infiltration of the nerve conduction system and the myocardial tissue. The prognosis in this progressive disease is poor, probably due the development of cardiac arrhythmias. Early detection of cardiac sympathetic innervation disturbances has become of major clinical interest, because its occurrence and severity limits the choice of treatment. Therefore, the use of ^{123}I-MIBG, which is well established in patients with heart failure and plays an important role in evaluation of sympathetic innervation in cardiac amyloidosis. Single photon emission computed tomography provides additional information and has advantages for evaluating abnormalities in regional distribution in the myocardium. ^{123}I-MIBG is mainly useful in patients with hereditary and wild-type ATTR cardiac amyloidosis, not in AA and AL amyloidosis.[77]

Various SPECT radiopharmaceuticals have been developed to either directly or indirectly target amyloidosis deposition.[78] There have been small studies showing that iodine-labeled serum amyloid P protein and ^{99m}Tc-aprotinin, could play a role in the diagnosis of cardiac amyloidosis, these are not readily available and have not been widely accepted. More recently, different PET radiopharmaceuticals developed to detect brain amyloid, have been investigated to image amyloid deposits in the heart. A pilot study of 14 subjects demonstrated that 18F-florbetapir accumulates in the heart of patients with cardiac amyloidosis, with higher uptake in AL compared with that in ATTR, and no significant uptake was seen in the heart of healthy controls.[79] Similar results were obtained with the ^{11}C-PiB,[80] and ^{18}F-florbetaben compounds.[81]

These studies show that amyloid imaging can differentiate between healthy controls from patients with amyloidosis with high sensitivity and specificity; and can also differentiate between patients with cardiac amyloidosis from patients suffering from left ventricular hypertrophy due to hypertensive heart disease. It was shown that amyloid tracers bind specifically to myocardial amyloid deposit in both AL and ATTR cardiac amyloidoses, confirming that the uptake observed with these tracers is related to specific binding to amyloid deposits, without binding to interstitial fibrosis and infarct.[82]

Plaque Imaging

Atherosclerosis is a lipid storage disease, and inflammatory cells are thought to be responsible for the transformation of a stable plaque into a vulnerable one. Lymphocytes constitute at least 20% of infiltrating cells in these vulnerable plaques. Therefore, the Interleukin-2 receptor (IL-2) - which is over-expressed on activated T lymphocytes - is thought to be an attractive target for the visualization plaque vulnerability. Radiotracers developed by radiolabeling IL-2 directly with technetium-99m or iodine-123 have shown high affinity to the IL-2 receptor and are used in the detection of activated T lymphocytes in atherosclerosis.[83]

Vulnerable atherosclerotic plaque is known to be responsible for most major cardiovascular events such as acute myocardial infarction and stroke. The vulnerable plaque can be imaged using molecular imaging techniques to identify the characteristic including inflammatory cells, synthesis of lipid and fatty acid in the plaque, presence of hypoxia in severely inflamed lesions, expression of factors stimulating angiogenesis, apoptosis, microcalcifications, and expression of protease enzymes in the lesion, and development of microthrombi in late-phase lesions.[84] One of the most established of these in this field uses the over-expression of integrin $\alpha_v\beta_3$, which has been associated with plaque rupture. SPECT and PET radiotracers developed from RGD peptides, including ^{99m}Tc-IDA-D-c(RGDfK)2 and ^{18}F-AlF-NOTA-PRGD2, have been reported to bind selectively to integrin $\alpha_v\beta_3$ in atherosclerotic aorta compared to normal aorta which does not express the integrin in question.[85] The expression of surface adhesion molecules such as VCAM-1 and selectins also plays a fundamental role in atherosclerotic plaque progression. These surface adhesion molecules are responsible for the receptor mediated recruitment of leukocytes, and VCAM-1 expression contributes to the inflammation after ischemic injury. ^{18}F-nanobodies against VCAM-1 have been shown to have utility in the PET imaging of atherosclerotic plaques in mouse models.[86]

Inflammation

Inflammation is also the primary infiltrative substrate in cardiac sarcoidosis, where it forms the typical noncaseating granuloma, consisting of epithelioid cells, giant cells, lymphocytes, and plasma cells.[87] Apart from IL-2, other tracers linked to the pathogenesis of inflammation include matrix metalloproteinases, tumor necrosis factor-alpha, vascular adhesion protein-1, or mannose receptor, which are in different stages of preclinical and early clinical development for use in infiltrative cardiac disease.[88]

Apoptosis – Cardiac Phosphatidylserine

Apoptosis is a critical process in cardiology diseases such as chronic heart failure, atherosclerotic vascular disease,

myocardial ischemia, and infiltrative heart disease. Apoptosis is characterized by cellular biochemical events leading to nuclear fragmentation and cell death. Whilst it is carefully regulated in normal cells, defective apoptosis can contribute to disease. The imaging of apoptosis has potential clinical utility in scenarios where cell death is uncertain and may impact clinical management decisions. For example, several clinical trials have shown that radiolabeled annexin V (a 37 kD protein) is capable of detecting apoptosis in ischemia-reperfusion injury and cardiac allograft rejection by targeting phosphatidylserine in a calcium-dependent manner.[89]

Conclusions

Disease processes involve a myriad of physiological and biochemical processes which can be exploited to select a suitable target for nuclear imaging or targeted therapies, including radionuclide therapy. This has resulted in a renewed interest in targets for theranostics based approaches to therapy of diseases ranging from oncology to cardiology and neurology, which will need to be further investigated in active preclinical and clinical research in the future.

References

1. Strosberg J, El-Haddad G, Wolin E, et al: Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. New Engl J Med 376:125-135, 2017
2. Emmett L, Willowson K, Violet J, et al: Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: A review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci 64:52-60, 2017
3. Weber J, Haberkorn U, Mier W: Cancer stratification by molecular imaging. Int J Mol Sci 16:4918-4946, 2015
4. Kenny LM, Aboagye EO: Clinical translation of molecular imaging agents used in PET studies of cancer. Adv Cancer Res 124:329-374, 2014
5. Gandal MJ, Leppa V, Won H, et al: The road to precision psychiatry: Translating genetics into disease mechanisms. Nat Neurosci 19: 1397-1407, 2016
6. Varley J, Brooks DJ, Edison P: Imaging neuroinflammation in Alzheimer's disease and other dementias: Recent advances and future directions. Alzheimer's Dement 11:1110-1120, 2015
7. Osborn EA, Kessinger CW, Tawakol A, et al: Metabolic and molecular imaging of atherosclerosis and venous thromboembolism. J Nucl Med 58:871-877, 2017
8. Villemagne VL, Dore V, Burnham SC, et al: Aβ-amyloid and tau imaging in dementia. Semin Nucl Med 47:75-88, 2017
9. Pardridge WM: Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab 32:1959-1972, 2012
10. Gan HK, van den Bent M, Lassman AB, et al: Antibody-drug conjugates in glioblastoma therapy: The right drugs to the right cells. Nat Rev Clin Oncol 14:695-707, 2017
11. van Isselt JW, Broekhuizen-de Gast: The radioiodine turnover rate as a determinant of radioiodine treatment outcome in Grave's disease. Hell J Nucl Med 13:2-5, 2010
12. Scott AM, Wolchok JD, Old LJ: Antibody therapy of cancer. Nat Rev Cancer 12:278-287, 2012
13. Thul PJ, Akesson L, Wiking M, et al: A subcellular map of the human proteome. Science 356, 2017. pii: eaal3321
14. Esteller M: Non-coding RNAs in human disease. Nat Rev Genet 12: 861-874, 2011
15. Bhullar KS, Lagaron NO, McGowan EM, et al: Kinase-target cancer therapies: Progress, challenges and future directions. Mol Cancer 17:48, 2018
16. Cardon LR, Harris T: Precision medicine, genomics and drug discovery. Hum Mol Genet 25:R166-R172, 2016
17. Goldstein JL, Anderson RGW, Brwon MS: Coated pits, coated vesicles and receptor-mediated endocytosis. Nature 279:679-685, 1979
18. Sorkin A, von Zastrow M: Endocytosis and signalling: Intertwining molecular networks. Nat Rev Mol Cell Biol 10:609-622, 2009
19. Perner S, Hofer MD, Kim R, et al: Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. Hum Path 38:696-701, 2007
20. Luster M, Pfestroff A, Hänscheid H, et al: Radioiodine therapy. Semin Nucl Med 47:126-134, 2017
21. Puranik AD, Kulkarni HR, Baum RP: Companion diagnostics and molecular imaging. Cancer J 21:213-217, 2015
22. Yordanova A, Eppard E, Kurpig S, et al: Theranostics in nuclear medicine practice. Onco Targets Ther 10:4821-4828, 2017
23. Pardridge WM: Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab 32:1959-1972, 2012
24. Braband H: High-valent technetium chemistry – new opportunities for radiopharmaceutical developments. J Labelled Comp Radiopharm 57:270-274, 2014
25. Smit Duijzentkunst DA, Kwekkeboom DJ, Bodei L: Somatostatin receptor-2 targeting compounds. J Nucl Med 58(Suppl 2):10S-16S, 2017
26. Oliveira BL, Caravan P: Peptide-based fibrin-targeting probes for thrombus imaging. Dalton Trans 46:14488-144508, 2017
27. Bjornmalm M, Thurecht KJ, Michael M, et al: Bridging bio-nano science and cancer nanomedicine. ACS Nano 11:9594-9613, 2017
28. Lee S, Xie J, Chen X: Peptides and peptide hormones for molecular imaging and disease diagnosis. Chem Rev 110:3087-3111, 2010
29. Katritch V, Cherezov V, Stevens RC: Structure-function of the G protein-coupled receptor superfamily. Annu Rev Pharmacol Toxicol 53:531-556, 2013
30. Schottelius M, Wester H-J: Molecular imaging targeting peptide receptors. Methods 48:161-177, 2009
31. Orcutt KD, Adams GP, Wu AM, et al: Molecular simulation of receptor occupancy and tumor penetration of an antibody and smaller scaffolds: Application to molecular imaging. Mol Imag Biol 19:656-664, 2017
32. Parakh S, Parslow AC, Gan HK, et al: Antibody-mediated delivery of therapeutics for cancer therapy. Expert Opin Drug Del 13:401-419, 2016
33. Moek KL, Giesen D, Kok IC, et al: Theranostics using antibodies and antibody-related therapeutics. J Nucl Med 58(Suppl 2):83S-90S, 2017
34. Hanahan D, Weinberg RA: Hallmarks of cancer. Cell 144:646-674, 2011
35. Fletcher JW, Djulbegovic B, Soares HP, et al: Recommendations on the use of ^{18}F-FDG in oncology. J Nucl Med 49:480-508, 2008
36. Zhu A, Lee D, Shim H: Metabolic PET imaging in cancer detection and therapy response. Semin Oncol 38:55-69, 2011
37. Jadvar H, Colletti PM, Delgardo-Bolton R, et al: Appropriate use criteria for ^{18}F-FDG PET/CT in restaging and treatment response assessment of malignant disease. J Nucl Med 58:2026-2037, 2017
38. Peck M, Pollack HA, Friesen A, et al: Applications of PET imaging with the proliferation marker [^{18}F]-FLT. Q J Nucl Med Mol Imaging 59: 95-104, 2015
39. Dunet V, Pomoni A, Hottinger A, et al: Performance of ^{18}F-FET versus ^{18}F-FDG-PET for the diagnosis and grading of brain tumors: Systematic review and meta-analysis. Neuro Oncol 18:426-434, 2016
40. Furuse M, Nonoguchi N, Yamada K, et al: Radiological diagnosis of brain radiation necrosis after cranial irradiation for brain tumor: A systematic review. Radiat Oncol 14:28-43, 2019
41. Lee ST, Scott AM: Hypoxia imaging with ^{18}F-Fluoromisonidazole. Semin Nucl Med 37:451-461, 2007
42. Fleming IN, Manavaki R, Blower PJ, et al: Imaging tumour hypoxia with positron emission tomography. Br J Cancer 112:238-250, 2015
43. Van Dongen GA, Poot AJ, Vugts DJ: PET imaging with radiolabeled antibodies and tyrosine kinase inhibitors: Immuno-PET and TKI-PET. Tumour Biol 33:607-615, 2012
44. Wehrmann C, Senftleben S, Zachert C, et al: Results of individual patient dosimetry in peptide receptor radionuclide therapy with 177Lu DOTA-TATE and 177Lu DOTA-NOC. Cancer Biother Radiopharm 22:406-416, 2007

45. Severi S, Grassi I, Nicolini S, et al: Peptide receptor radionuclide therapy in the management of gastrointestinal neuroendocrine tumors: Efficacy profile, safety, and quality of life. Onco Targets Ther 10:551-557, 2017
46. Lee ST, Singh A, Kulkarni H, Baum RP: Theranostics of neuroendocrine tumours. Visc Med 33:358-366, 2017
47. Lee ST, Scott AM: Nuclear medicine in the era of personalised medicine. Int Med J 48:497-499, 2018
48. Jadvar H, Ballas LK: PSMA PET: Transformational change in prostate cancer management? J Nucl Med 52:228-229, 2018
49. Jadvar H: Radiotheranostics in prostate cancer: Introduction and overview. J Nucl Med 57(suppl 3):1S-2S, 2016
50. Ballas LK, de Castro Abreu AL, Quinn DI: What medical, urologic, and radiation oncologists want from molecular imaging of prostate cancer. J Nucl Med 57(suppl 3):6S-12S, 2016
51. Virgolini I, Decristoforo C, Haug A, et al: Current status of theranostics in prostate cancer. Eur J Nucl Med Mol Imaging 45:471-495, 2018
52. Roach PJ, Francis R, Emmett L, et al: The impact of (68)Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. J Nucl Med 59:82-88, 2018
53. Baum RP, Kulkarni HR, Schuchardt C, et al: ^{177}Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: Safety and efficacy. J Nucl Med 57:1006-1013, 2016
54. Hofman MS, Violet J, Hicks RJ, et al: [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study. Lancel Oncol 19:815-833, 2018
55. Sathekge M, Bruchertseifer F, Knoesen O, et al: 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: A pilot study. Eur J Nucl Med Mol Imaging 46:129-138, 2019
56. Jadvar H: Value proposition of PSMA-targeted alpha-particle radioligand therapy in metastatic prostate cancer. Eur J Nucl Med Mol Imaging 46:8-10, 2019
57. Kilbourn MS: Small molecule PET tracers for transporter imaging. Semin Nucl Med 47:536-552, 2017
58. Rowe CC, Villemagne VL: Brain amyloid imaging. J Nucl Med 52: 1733-1740, 2011
59. Royall DR: Location, location, location. Neurobiol Aging 28:1481-1482, 2007
60. Delacourte A, David JP, Sergeant N, et al: The biochemical pathway of neurofibrillary degeneration in ageing and Alzheimer's disease. Neurology 52:1158-1165, 1999
61. Braak H, Braak H: Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18:351-357, 1997
62. Delacourte A, Sergeant N, Wattez A, et al: Tau aggregation in the hippocampal formation: An ageing or a pathological process? Exp Gerontol. 37:1291-1296, 2002
63. Goedert M, Yamaguchi Y, Mishra SK: Tau filaments and the development of positron emission tomography tracers. Front Neur 9:70, 2018
64. Scholl M, Lockhart SM, Schonhaut DR, et al: PET imaging of Tau deposition in the aging human brain. Neuron 89:971-982, 2016
65. Suwijn SR, van Boheemen CJM, de Haan RJ, et al: The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain Parkinsonism: A systematic review. EJNMMI Res 5:12, 2015
66. Elsinga P, Ishiwata K, Hatano K: PET tracers for imaging the dopaminergic system. Med Chem 13:2139-2153, 2006
67. Slifstein M, Abi-Dargham: Recent developments in molecular brain imaging of neuropsychiatric disorders. Sem Nucl Med 47:54-63, 2017
68. Kassenbrock A, Vasdev N, Liang SH: Selected PET radioligands for ion channel linked neuroreceptor imaging: Focus on GABA, NMDA, and nACH receptors. Curr Top Med Chem 16:1830-1842, 2016
69. Meyer PM, Tiepolt S, Barthel H, et al: Radioligand imaging of α4α;2* nicotinic acetylcholine receptors in Alzheimer's disease and Parkinson's disease. Q J Nucl Med Mol Imaging 58:376-386, 2014
70. Denora N, Natile G: An updated view of the translocator protein (TSPO). Int J Mol Sci 18, 2017. pii. E2640
71. Alam MM, Lee J, Lee SY: Recent progress in the development of TSPO PET ligands for neuroinflammation imaging in neurologic diseases. Nucl Med Mol Imaging 51:283-296, 2017
72. Shaw SY: Molecular imaging in cardiovascular disease: Targets and opportunities. Nat Rev Cardiol 6:567-579, 2009
73. Dorbala S, Shaw SY: Molecular phenotyping of infiltrative cardiomyopathies: Tthe future. J Nucl Cardiol. 26:154-157.
74. Falk RH: Diagnosis and management of the cardiac amyloidoses. Circulation 112:2047-2760, 2005
75. Underwood SR, de Bondt P, Flotats A, et al: The current and future status of nuclear cardiology: A consensus report. Eur Heart J 15:949-955, 2014
76. Travin MI: Current clinical applications and next steps for cardiac innervation imaging. Curr Cardiol Rep 19:1, 2017
77. Slart RHJA, Glaudemans AWJM, Hazenberg BPC, et al: Imaging cardiac innervation in amyloidosis. J Nucl Cardiol 26:174-187, 2019
78. Pelletier-Galarneau M, Abikhzer G, Giraldeau G, et al: Molecular imaging of cardiac amyloidosis. Curr Cardiol Rep 21:12, 2019
79. Dorbala S, Vangala D, Semer J, et al: Imaging cardiac amyloidosis: A pilot study using ^{18}F-florbetapir positron emission tomography. Eur J Nucl Med Mol Imaging 41:1652-1662, 2014
80. Lee S-P, Lee ES, Choi H, et al: ^{11}C Pittsburgh B PET imaging in cardiac amyloidosis. JACC Cardiovasc Imaging 8:50-59, 2015
81. Law WP, Wang WYS, Moore PT, et al: Cardiac amyloid imaging with ^{18}F-florbetaben PET: A pilot study. J Nucl Med 57:1733-1739, 2016
82. Park M-A, Padera RF, Belanger A, et al: ^{18}F-Florbetapir binds specifically to myocardial light chain and transthyretin amyloid deposits: Autoradiography study. Circ Cardiovasc Imaging 8:e002954, 2015
83. Annovazzi A, Bonanno E, Arca M, et al: 99mTc-interleukin-2 scintigraphy for the in vivo detection of vulnerable atherosclerotic plaques. Eur J Nucl Med Mol Imaging 33:117-126, 2006
84. Nakahara T, Narula J, Strauss HW: Molecular imaging of vulnerable plaque. Semin Nucl Med 48:2910298, 2018
85. Jackson IM, Scott PJH, Thompson S: Clinical applications of radiolabeled peptides for PET. Semin Nucl Med. 47:493-523.
86. Bala G, Blykers A, Xavier C, et al: Targeting of vascular cell adhesion molecule-1 by 18F-labelled nanobodies for PET/CT imaging of inflamed atherosclerotic plaques. Eur Heart J Cardiovac Imaging 17:1001-1008, 2016
87. Schatka I, Bengel FM: Advanced imaging of cardiac sarcoidosis. J Nucl Med 55:99-106, 2014
88. Bengel F, Ross TL: Emerging imaging targets for infiltrative cardiomyopathy: Inflammation and fibrosis. J Nucl Cardiol 26:208-216, 2019
89. Laufer EM, Winkens HM, Corsten MF, et al: PET and SPECT imaging of apoptosis in vulnerable atherosclerotic plaques with radiolabeled Annexin A5. Q J Nucl Med Mol Imaging 53:26-34, 2009