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The emerging role of cell surface receptor and protein binding radiopharmaceuticals in cancer diagnostics and therapy

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Abstract

Targeting specific cell membrane markers for both diagnostic imaging and radionuclide therapy is a rapidly evolving field in cancer research. Some of these applications have now found a role in routine clinical practice and have been shown to have a significant impact on patient management. Several molecular targets are being investigated in ongoing clinical trials and show promise for future implementation. Advancements in molecular biology have facilitated the identification of new cancer-specific targets for radiopharmaceutical development.

Keywords: Receptors; cell membrane proteins; positron emission tomography; targeted radionuclide therapy; radiopharmaceutical development

Introduction

The development of receptor-binding radiotracers arose out of the scientific interest for finding sensitive ways for detecting and measuring specific receptor concentrations during normal physiology, and their changes with disease [1]. The central nervous system served as the ideal model system for this field of research and is where initial development and clinical application was successful. Significant efforts were focused on identifying ligands that could adequately cross the blood brain barrier and would selectively bind to specific receptors with an affinity suitable for detecting changes in ligand binding in physiology and disease. Dr Bill Eckelman has made a very significant contribution to this field [1-4].

Research in oncological imaging has focused on methods to improve the detection and characterization of tumors, as well as identifying successful response to therapy earlier and more accurately. Cell surface receptor imaging has the potential to play a major role in these areas and has been driven by the discovery of molecular targets that can be harnessed for this in cancer cell biology [5]. Emerging research into the expression level of disease-specific biomarkers has driven the interest in targeting these cell surface receptors or proteins with radiolabeled compounds for diagnostic purposes as well as to deliver therapeutic radiation [6].

In neuroreceptor ligand development identifying the optimal trade-off between receptor affinity and receptor density is critical, as this governs the bound-to-free (B/F) ratio of the ligand and consequently changes in the signal-to-background on imaging. When the ligand affinity is very high, tracer distribution is heavily dominated by flow [7]. This is undesirable for

measuring changes in receptor concentration or occupancy related to a particular physiological condition or disease in the central nervous system. This is less relevant in oncological imaging as the aim is mostly to achieve maximum tumor binding relative to background in order to facilitate tumor detection or improve delivery of radiation. Achieving the highest possible B/F ratio is the goal in the development of most cancer targeted radionuclide imaging agents. This is a further area where Dr Eckelman has focused considerable research effort, for example in the development of radioligands targeting the IL-2 receptor [8, 9], vasoactive intestinal peptide (VIP) receptors [10], transferrin receptors [11], carbonic anhydrase IX [12] and prostate specific membrane antigen (PSMA) [13-15].

A key aspect for the development of clinically relevant diagnostics is the appreciation of the strengths and limitations of nuclear medicine approaches compared to other areas of clinical imaging. Furthermore, understanding the role of radiopharmaceuticals in oncological therapy has important implications for the development of clinically useful tools for improving treatment of advanced disease. This review focuses on some of the key areas where radionuclide-based methods have clinical impact in the management of cancer patients.

Characterization of tumor biology

A major strength of radionuclide imaging probes is the high level of biological target specificity which they demonstrate, setting them apart from most other imaging modalities used in routine clinical practice. Identifying a particular molecular or biological target can provide information on tumor grade and degree of differentiation, as well as on response to chemotherapy or radiotherapy.

For example, since the early 1980s iodine labeled metaiodobenzylguanidine ([^{123}I]- and [^{131}I]-MIBG) has been utilized for the detection of pheochromocytomas/paragangliomas [16] and neuroblastomas [17]. These tumors arise in tissues derived embryologically from the neural crest and share the common biological characteristic of expressing the norepinephrine transporter (NET) which drives uptake of the tracer [18]. Changes in uptake of this ligand during induction chemotherapy for neuroblastoma have been shown to have prognostic significance and can be utilized to guide treatment and improve patient management [19, 20]. A small percentage of neuroblastoma patients (<10%) show low or no uptake at diagnosis and are associated with a more favorable outcome [21]. On the other hand, in patients with known pheochromocytoma, the absence of MIBG uptake has been linked to specific gene mutations associated with poor prognosis [22].

Biological characterization of disease with radionuclide methods can provide information on tumor heterogeneity by identifying areas within the same tumor with different biological properties or habitats. While invasive tissue sampling is important for deep phenotyping of small volumes of tissue, imaging has the crucial and complementary role of assessing whole tumor (intratumoral heterogeneity) and multiple tumor (intertumoral heterogeneity) sites in the same patient, as well as allowing comparisons between patients (interpatient heterogeneity); in addition, imaging can monitor heterogeneity longitudinally over time, which is not practical with invasive biopsies. These multiple levels of spatial and temporal tumor heterogeneity play an important role in therapeutic success and failure, due to the potential expansion of resistant clones as different regional environmental factors can influence the selection and growth of subpopulations of cells with more aggressive behavior [23]. Utilization of multiple tracers targeting distinct biological properties in a multiplexed

approach is a powerful way for studying the spatial and temporal changes in tumor biology [24, 25]. The same concepts can be applied to monitor changes in tumor biology during treatment, providing insights into treatment response or resistance [26].

Development of sensitive imaging tools

An ideal imaging probe or radiopharmaceutical will have a high biological specificity for a particular tumor target and a low background retention due to favorable pharmacokinetics and low off-target binding. The “magic bullet” concept attributed to Paul Ehrlich and described in his Harben lectures of the early 1900s [27] was a novel pharmacological concept for developing disease-specific drugs that would only affect the intended tissue or disease while sparing normal organs. In radionuclide imaging, this concept can be applied to tumor seeking tracers which accumulate only (or mostly) in tissues with disease-specific molecular and biological properties and demonstrate high target to non-target uptake [28-30]. Even a very early example such as MIBG has sufficient biological specificity for molecular features of neural crest tumors that it remains a highly relevant tool to detect pheochromocytoma/paraganglioma [31] and neuroblastoma [32]. Additionally, it has a role in disease staging for both these conditions and for assessing treatment response as described above [33].

Development of theranostic agents

The targeting capabilities of a radiopharmaceutical have been exploited for therapeutic applications. The ultimate goal of cancer therapy is to improve patient outcome, and targeted radionuclide therapeutics are increasingly being investigated as tools to achieve this in routine oncological practice. The ability of these radiopharmaceuticals to concentrate within

the tumor allows the delivery of lethal radiation doses while limiting exposure of normal organs, which can be difficult to achieve using external beam radiotherapy due to the geometry and tumor depth limitations. Radioisotopes with adequate decay characteristics are key for the success of this approach. In many instances, two distinct radionuclides are required to label the radiopharmaceutical: firstly, a diagnostic isotope to image the disease, and secondly an isotope which releases sufficient decay energy to elicit therapeutic effect as a companion theranostic agent. Unfortunately, there are only a few radioisotopes that can be utilized for both purposes: in the case of MIBG, for example, there has been extensive clinical experience with the ^{123}I-labelled derivative for imaging as well as with [^{131}I]MIBG which can be used for both imaging and therapy. MIBG accumulates in cells predominately through ATP-dependent active transport at low concentrations, whereas at non-physiological levels uptake occurs through passive diffusion [34]. Once localized inside the cell it is retained in intracellular vesicles providing long residence times which provide excellent image sensitivity as well high absorbed doses. MIBG is one of the oldest examples of a theranostic agent in the clinic albeit one which can only be used in these rare diseases [35].

Developing drugs intended for a theranostic path has become a major focus in cancer radiopharmaceutical research. Radiopharmaceuticals intended for therapy are usually derived from an imaging agent with identical or very similar biological properties. In general, a simple exchange of isotope or radionuclide can transform a diagnostic agent into a therapeutic one, although this can be chemically complicated. This exchange may result in differences in the biological and biodistribution characteristics of each agent that need to be taken into account when optimizing diagnostic or therapeutic efficacy. While the general concept of high sensitivity and specificity for a target is of primary importance, other factors

also have to be considered in the development of therapeutic radiopharmaceuticals such as *in vivo* stability, the retention time within the target lesion, uptake in normal organs, metabolism and route of excretion. Some of these factors are more relevant for therapy than imaging as they have important consequences on efficacy and toxicity.

Beta-emitting radionuclides are commonly utilized to deliver therapeutic radiation in this setting. These radionuclides decay emitting low mass particles (electrons) with varying emission energies. These electrons have a mean particle range in tissue varying from a few millimeters up to a centimeter. More recently, alpha emitters have received increasing attention, some even being introduced in clinical practice: these high linear energy transfer (LET) emitters have the advantage of releasing a high mass particle (a helium nucleus) which produces multiple ionizations in tissue with a short particle range (10-500 μm) resulting in significant radiation damage within a few cell widths from the site of decay, therefore minimizing normal tissue damage. The only clinically approved alpha emitting radiopharmaceutical is [^{223}Ra]$RaCl_2$ for treating bone metastases [36], but there is significant effort in expanding applications in this area with targeted compounds [37, 38].

This review will discuss clinically relevant cell surface receptor and protein binding ligands and targets which may have clinical applications in the near future. The momentum in the field has increased in recent years as a consequence of the success of early novel clinical applications. This has caught the interest of leading pharmaceutical companies and the financial sector [39] and is proving to be an important driver for investment and research in the field. There are many areas of unmet clinical need in cancer where radiolabeled drugs could play a role in diagnostics and therapy.

Three classes of cell surface targets will be discussed in detail, which have received significant attention for theranostic applications in cancer (Figure 1): the large family of G-protein coupled receptors (GPCRs); the prostate specific membrane antigen (PSMA); and the fibroblast activation protein (FAP). These targets share common features which make them suitable and appealing for radionuclide imaging and potentially for therapy. They are highly overexpressed on the cell surface of specific cancer cells (or cells within the tumor microenvironment) and they can be targeted with low molecular weight compounds with favorable biodistribution profiles such as peptides and small molecules. This enables high levels of specific targeting and retention to be achieved, both for imaging and therapeutic applications. Ligands being developed for these targets share common labelling strategies. The most successful applications for these systems have made use of coupling to macrocyclic chelators such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and subsequent labelling with radiometals such gallium-68 for Positron Emission Tomography (PET) imaging and the beta emitter lutetium-177 for therapeutic applications. Research on these targets has generated many different ligands that have reached various stages in the development pipeline with respect to clinical applications and validation. These targets provide a model for state-of-the-art in this developing field and a framework for future development of other targets.

Somatostatin receptors

Somatostatin receptors (SSTRs) are the best example to date of a theranostic target that has been translated into routine clinical care. This is a family of cell surface receptors that are widely expressed in normal tissues at low physiological levels. The evidence for

overexpression of these receptors in neuroendocrine tumors is well established [40] and they have been subsequently recognized as a potential therapeutic target. Receptor subtypes 2 and 5 are mostly expressed in these classes of tumors. The predominant expression of SSTR-2 is believed to be the most relevant target for radionuclide applications [41]. Octreotide, an analog of somatostatin designed to improve pharmacokinetics compared to the highly unstable native peptide, was developed in the 1980s. This receptor agonist was successfully employed to treat carcinoid syndrome, a common manifestation of certain neuroendocrine tumors [42]. Initial experience with radiolabeled octreotide to image neuroendocrine tumors soon followed: [^{111}In]In-DTPA-Octreotide was approved by the FDA in 1994 and was rapidly shown to effectively detect, characterize, stage and monitor disease progression of neuroendocrine tumors, outperforming standard cross-sectional anatomical imaging in many instances [43]. During the 1990s, further work targeted at improving affinity, stability, and pharmacokinetics yielded several new octreotide analogs [44, 45]. Two derivatives, DOTA[Tyr3]-Octreotide (DOTA-TOC) and DOTA[Tyr3]-Octreotate (DOTA-TATE), were identified as having suitable characteristics for nuclear medicine applications, although several other effective compounds were also developed. These molecules were originally intended for therapeutic use. Most of the chemical development was around coupling to the DOTA chelator that has superior coordination properties for the beta emitters yttrium-90 and lutetium-177 [46]. To allow these compounds' use for PET imaging, the positron emitter gallium-68 was employed in the first human applications described in the early 2000s [47]. It was very rapidly recognized that ^{68}Ga somatostatin receptor PET was clinically superior to traditional [^{111}In]In-DTPA-Octreotide SPECT. Clinical evidence soon followed, showing how somatostatin receptor targeted PET is more effective than traditional octreotide scintigraphy and single-photon emission computed tomography (SPECT) in the management of patients

with neuroendocrine tumors [48, 49]. When used in combination with the glucose analog [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG), somatostatin receptor PET imaging can provide additional information regarding tumor grade, heterogeneity and changing biological properties over time relating to prognosis. This highlights the power of these functional imaging methods and their potential to serve as surrogates for histological characterization in specific clinical situations [50, 51]. [^{68}Ga]Ga-DOTA-TATE received approval by the United States Food and Drug Administration (FDA) in 2016 and [^{68}Ga]Ga-DOTA-TOC was approved by the European Medicines Agency (EMA) in the same year and by the FDA in 2019.

The concept of using these analogs to deliver target-selective radionuclide therapy was explored very soon after imaging applications in neuroendocrine tumors were introduced. Initially high doses of [^{111}In]In-DTPA-Octreotide, the imaging agent approved in the early 1990s, was utilized, although it did not result in a significant clinical impact. The need for purpose-built ligands was recognized and resulted in the development and application of ^{90}Y-labelled DOTA-TOC. This radiopharmaceutical was used in several centers in Europe in the late 1990s and showed compelling efficacy in a few small single center patient series [52]. Concerns for kidney and bone marrow toxicity from yttrium-90, led to explore alternative radionuclides better suited for therapy. Lutetium-177 has a longer half-life compared to yttrium-90 (6.7 days vs. 2.7) and lower energy beta emission (E_{max} 490 KeV vs. 2.2 MeV), resulting in longer radiation delivery and lower tissue penetration. This radionuclide also has low abundance gamma emission (11%, 211 KeV) which makes it suitable for high quality imaging with SPECT which is not possible with yttrium-90. The first clinical studies with [^{177}Lu]Lu-DOTA-TATE were published in the 2000s showing impressive response rates for the treatment of metastatic neuroendocrine tumors, particularly midgut carcinoids, an area

where systemic chemotherapy had shown very little success [53]. The toxicity profile of [^{177}Lu] Lu-DOTA-TATE also proved to be better suited than that of ^{90}Y-labeled agents. In 2011 an industry sponsored phase 3 trial (NETTER-1) was initiated in patients with midgut neuroendocrine tumors showing prolonged progression-free survival and higher response rate in patients in the [^{177}Lu]Lu-DOTA-TATE treatment arm relative to the control group [54]. This trial led to approval by the FDA and EMA in 2017 for the treatment of midgut neuroendocrine tumors. [^{177}Lu]Lu-DOTA-TATE therapy is now funded by most insurers and national healthcare systems for treatment of patients in this setting. An example of how this theranostic approach can now be routinely applied to stratify patient management is shown in Figure 2.

Achieving clinical approval is a major challenge for all new probes. The somatostatin receptor model has not only provided a very effective clinical tool in the specific setting of neuroendocrine tumors, but also serves as a model system for developing new imaging and therapeutic strategies with similar cell surface receptor/protein targeting ligands relevant in other clinical conditions. The possibility of combining targeted radionuclide treatments with chemotherapy is being actively investigated and is the subject of several registered clinical trials [55-58]. Interesting, preliminary clinical work has shown that the use of alpha emitters for somatostatin receptor targeted radionuclide therapy may be effective in patients who are refractory to treatment with traditional beta emitters [59]. There has also been significant effort on the development of somatostatin receptor 2 antagonists that show higher binding capacity than currently approved agonists [60], which has prompted clinical studies with derivatives of a compound first given the name JR11 [61]. The initial clinical experience using a ^{68}Ga-labeled DOTA coupled derivative of this peptide has shown high target-to-background

ratios and more favorable dosimetry compared to DOTA-TOC and DOTA-TATE [62]. A 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (NODAGA)-derivative of the same peptide has shown relatively higher target to background values compared to [^{68}Ga]Ga-DOTA-TOC [63] confirming its superior binding properties compared to currently used receptor agonists. A phase 1-2 clinical trial assessing safety and preliminary efficacy of [^{177}Lu]Lu-DOTA-JR11 for therapy, also known as OPS 201, is currently recruiting [64].

Prostate Specific Membrane Antigen:

The prostate specific membrane antigen (PSMA) was originally identified in the 1980s as a biomarker of prostate cancer. PSMA was rapidly recognized as a potential target for diagnostic and therapeutic applications and initial work with labelled monoclonal antibodies against this target soon followed [65]. Capromab pendetide, a monoclonal antibody labelled with indium-111, was utilized in the clinic and obtained FDA approval in 1999 [66, 67]. Subsequently, the J591 antibody, which also targets PSMA, was labeled with zirconium-89 and copper-64 for immuno-PET applications [68, 69]. However, antibody-based imaging of PSMA has had limited success in the clinical setting. This is partly accounted for by the complex nature of antibody imaging compared to other nuclear medicine imaging methods which requires multiple hospital visits since the optimal time to image is generally in the order of days following injection. This makes it less appealing for both patients and referrers. Additional drawbacks are the relatively high manufacturing costs of these imaging agents and the overall suboptimal pharmacokinetic characteristics of labeled antibodies which may not allow them to achieve the high target-to-background signal of most desirable imaging tests. A biological limitation which may have contributed to the poor success of Capromab

pendetide is that the 7E11-C5.3 murine antibody on which the agent is based recognizes an intracellular portion of the PSMA antigen which may limit its ability to detect PSMA expressing cancer cells *in vivo* since the binding target is not exposed in intact cells [70]; in contrast, the J591 antibody recognizes the extracellular domain of the PSMA protein [71].

The PSMA protein is a membrane bound enzyme homologous to a central nervous system neuropeptidase [72]. Several groups approached the problem of targeting the protein by studying small molecule inhibitors of this enzyme which had originally been developed for applications in the central nervous system. The use of small molecules as targeting agents was particularly appealing due to the favorable biodistribution characteristics that could overcome the limitations of the previous antibody-based attempts. A number of different molecules were investigated and labeled with iodine radioisotopes [73] and technetium-99m [74, 75]. While these compounds made their way to early clinical development, the radiopharmaceutical that drove the greatest initial clinical interest was a ^{68}Ga-labelled compound developed in Heidelberg, HBED-CC-PSMA (also known as PSMA-11) [76]. The first patient image with this tracer in prostate cancer was published in 2012 [77] with initial human biodistribution shortly afterwards [78]. The method was very successful with rapid clinical implementation in Germany and subsequently in the rest of Europe and other parts of the world. There is increasing evidence that PET scanning with [^{68}Ga]Ga-PSMA-11 is very sensitive at detecting disease in patients with evidence of biochemical recurrence [79]. PSMA-PET may have clinical value in monitoring response to treatment in patients with advanced disease and has potential for improving management of patients at diagnosis by providing a sensitive tool to detect disease outside of the prostate [80]. More recently ^{18}F-labelled PSMA binding agents have also become available [81, 82]. These ligands hold promise for the future given the

possibility of utilizing the same commercial distribution networks that are in place for FDG, and not having to rely on local radiopharmacies to perform ^{68}Ga-labelling. Two compounds have emerged, [^{18}F]PSMA-1007 and [^{18}F]DCFPyL, that currently show potential for widespread clinical use [83]. Accurate detection and staging of disease are key elements for best patient management in cancer and PSMA-PET provides sensitive and accurate staging information that is proving to be of great clinical utility and relevance.

Advanced stage prostate cancer has increased in incidence over the last few decades and new strategies for therapy of advanced disease are continuously being investigated [84]. Given the high target-to-background binding of PSMA ligands in prostate cancer, the potential for a theranostic approach was immediately recognized. Beta emitting radiometals have been considered in the first instance as the best approach for therapeutic applications. Since the chelator used in PSMA-11 is not suitable for labelling with lutetium-177 and yttrium-90, several other derivatives have been developed [85, 86]. The compound that has been most widely utilized is a DOTA-coupled derivative termed PSMA-617, which has been labelled with lutetium -177 and evaluated in a few small case series [87-89]. Initial results indicate anti-tumor activity with very impressive biological responses in some cases, although there is no evidence of long-term control as a single agent treatment. Some concerns remain around toxicity to the salivary and lacrimal glands, as well as impact on renal function as these organs show high expression of the target protein and are exposed to significant absorbed doses during treatment. The VISION study is a large industry sponsored phase 3 trial aimed at addressing the efficacy of [^{177}Lu]PSMA-617 in treating metastatic castrate resistant prostate cancer [90] and will likely provide information on whether this strategy has a future for widespread clinical use. The J591 antibody which has been successfully utilized for immuno-

PET imaging has also been investigated as a radioimmunotherapeutic agent [91], and there is some evidence of clinical efficacy in a small case series [92]. Results of a phase 2 study addressing treatment fractionation has been recently published [93] although larger scale validation of the approach is still pending.

Initial clinical experience with PSMA-targeted alpha therapy is on-going [94] and shows strong potential for future implementation although it is far from being applicable at large scale. Preliminary data from small case series of patients with advanced prostate cancer treated with [^{225}Ac]PSMA-617 show remarkable anti-tumoral activity with a favorable duration of tumor control compared to conventional chemotherapy and hormonal therapy in heavily pretreated subjects [95]. There is concern for marked salivary/lacrimal gland toxicities causing severe symptoms to the point of patients not being able to continue treatment. Preliminary experience with combination or tandem therapies alongside conventional [^{177}Lu]PSMA-617 may enhance response of patients with advanced stage disease, while minimizing the severity of this toxicity [96]. The use of alpha emitters coupled to antibodies has also been addressed. A phase 1 dose escalation study with [^{225}Ac]J591 is being conducted in the US, with preliminary reports indicating good tolerability in a pre-treated patient population, including a majority of patients with prior treatment using ^{177}Lu-labeled small molecule PSMA inhibitors [97].

Fibroblast activation protein:

Fibroblast activation protein (FAP) is a serine protease originally identified as a cell surface protein expressed on astrocytomas and sarcomas. FAP is a type II membrane bound glycoprotein belonging to the dipeptidase 4 family. More recently FAP has received increasing

attention as a selective marker of cancer-associated fibroblasts (CAFs) [98, 99]. FAP has known roles in embryogenesis and tissue remodeling. High expression of FAP is observed in wound healing, arthritis, atherosclerosis, fibrosis and myocardial infarction. Overexpression of FAP has been detected in over 90% of epithelial carcinomas [100, 101]. Low expression of FAP is seen in normal adult tissues such as uterus, cervix, placenta, breast and skin [102].

Interest in FAP for imaging applications was first approached with monoclonal antibodies: Tanswell *et al.* developed a murine antibody (mAbF19) for FAP which was radiolabeled with iodine-131. Initially they performed two phase I clinical trials which provided detailed information about pharmacokinetics of this antibody [103]. Later [^{99m}Tc]Tc-S-HYNIC-28H1, [^{111}In]28H1 and [^{89}Zr]28H1 antibodies were tested in rheumatoid arthritis (RA) mouse models [104, 105]. The ^{99m}Tc-labelled antibodies showed high accumulation in joints of affected animals which correlated with the severity of inflammation whereas the ^{89}Zr-labelled antibody showed less favorable characteristics due to high bone uptake [104].

Meletta *et al.* described a small molecule inhibitor for FAP labelled with iodine-125 which they used to localize atherosclerotic plaque [106]. Jansen *et al.* later developed small molecule inhibitors for FAP with high affinity [107]: FAPI-01 and FAPI-02. Loktev *et al.* radiolabeled these novel small molecule FAP inhibitors with iodine-125 and these two radiotracers showed high specific binding to both murine and human FAP with rapid internalization. FAPI-01 showed some limitations due to enzymatic deiodination which likely affected adequate target accumulation [108]. FAPI-02 is a DOTA coupled analogue and could be utilized for radiolabeling with gallium-68 and lutetium-177; this derivative showed more stability, rapid internalization and high tumor uptake in tumor xenografts and patients with

metastasized epithelial carcinomas [108-110]. While there is building evidence for good targeting of FAP for imaging purposes in these initial clinical studies, the potential for using this approach for therapeutic application has yet to be fully addressed. Rapid clearance of tumor-bound FAPI-02 would limit the use of this ligand for therapy [110]. There is recent preclinical data on the theranostic application of FAPI-04 to an animal model of pancreatic cancer with alpha therapy [111] showing promising results. A recently published new derivative termed FAPI-46 has more favorable tumor kinetics which may make it suitable for future theranostic application [112] and this radiopharmaceutical is being studied in registered clinical trials as an imaging tool.

C-X-C-Chemokine receptor 4

Chemokine receptors are a large family of proteins that mediate cell migration towards chemotactic gradients. The C-X-C motif chemokine receptor type 4 (CXCR4) is a member of the GPCR family with high expression found in the hematopoietic system and is widely expressed during embryonic development [113]. CXCR4 has an endogenous ligand (CXCL12, also known as stromal cell derived factor-1α), which is expressed in bone marrow, lymph nodes, lung, heart, thymus and liver [114]. CXCR4 plays a key role in tumor progression and metastasis [115, 116] and has been found to be highly upregulated in many cancers. Several literature reports have correlated high levels of CXCR4 expression in cancers with tumor aggressiveness, poor prognosis and resistance to chemotherapy [117, 118].

Different classes of CXCR4 antagonists have been studied. In the late 1990s, Tamamura *et al.* developed small peptides targeting CXCR4 and derivatives of the 14 amino acid β hairpin

peptide T140 were initially modified for radiolabeling in order to obtain CXCR4 targeting radiopharmaceuticals [119]. Biodistribution properties of these first-generation compounds proved to be unsuitable for successful application. Additional development for imaging applications were made on the radiolabeled biscyclam AMD3100 [120] and its derivatives and the cyclic pentapeptide FC131 [121]. These compounds have been used as imaging agents for PET, SPECT and fluorescence. In the early 2010s, a small cyclic peptide with more favorable biodistribution properties was identified [122]. This compound (CPCR4.2 also known as Pentixafor) has been tested in preliminary clinical studies in patients with myeloma [123], glioma [124], and lung cancer [125], showing accumulation in target lesions. As CXCR4 is a potential therapeutic target, the main role of these diagnostic agents in the clinic would be to establish and quantify receptor expression in tumors and to determine their suitability for radionuclide therapy.

Preliminary clinical experience with [^{177}Lu]Pentixather, a slightly modified structure compared to Pentixafor optimized for improved binding when labelled with lutetium-177, shows high level retention in multiple myeloma [126, 127] and other hematological malignancies [128]. Very high tumor absorbed doses have been demonstrated in this setting, although there is little evidence regarding its clinical benefit. Application of [^{177}Lu]Pentixather in non-hematological malignancies remains limited, this may be in part linked to its observed side effects on the hematopoietic system [129].

Bombesin/Gastrin Releasing Peptide Receptors

Bombesin receptors are an additional GPCR receptor family which is of increasing interest in cancer diagnosis and therapy. Bombesin receptor 2 commonly referred to as the Gastrin

Releasing Peptide Receptor (GRPR) has high physiological expression in the pancreas, but very low levels in normal tissues. Overexpression of GRPR has been documented in cancers with endocrine features, most notably prostate and breast cancers [130, 131]. Receptor agonists were originally applied for imaging purposes: technetium-99m labelled agonists have been utilized in small human studies documenting uptake in histologically-confirmed GRPR positive tumors [132]. Subsequently the focus of research shifted to receptor antagonists based on evidence that these could be superior targeting agents [133] and are expected to have fewer gastrointestinal side effects compared to agonist peptides [134]. This has driven the development of ^{68}Ga-labeled agents [135, 136] which have been utilized to image prostate cancer [135, 137] and breast cancer [138]. There is indication that these receptors are more prominently expressed in well differentiated prostate tumors and could be useful in initial staging [139]. Furthermore, heterogeneity in expression of GRPR and PSMA is seen across different lesions in the same patient, suggesting the possibility of combined use of these two classes of tracers in prostate cancer [139]. In breast cancer, expression of these targets is related to integrity and response of the estrogen receptor pathway. Imaging with these agents may be utilized to characterize lesions where estrogen receptor positivity is retained [138] in order to determine the suitability for hormonal therapy.

Development of GRPR-targeted radionuclide therapy started in the early 2000s. A receptor agonist called AMBA was labelled with lutetium-177 and was the subject of an early phase trial in prostate cancer [134] but this approach proved to be unsuccessful and was not pursued further. The later development of the above-mentioned antagonists used for PET imaging has provided the opportunity to trial potentially safer and better targeted radiopharmaceuticals in the clinical setting. Two GRPR antagonists are currently under clinical

investigation: the RM2 compound used for imaging has been labelled with lutetium-177 and has recently been evaluated in an early phase trial in prostate cancer patients [140]. Another GRPR antagonist known as Neobomb1 [141] is the subject of an international industry sponsored phase I/II clinical trial which will select patients with a range of cancer types based on [^{68}Ga]Neobomb1 PET for dose escalation treatment with [^{177}Lu]Neobomb1 [142].

Cholecystokinin (CCK) 2/Gastrin receptors

The cholecystokinin receptors (CCKR) are another class of GPCRs with important implications in cancer. Two major CCK-R subtypes have been identified (1 and 2). The CCK2R is the Gastrin receptor which is expressed throughout the central nervous system, as well as by several cell types within gastric mucosa such as parietal cells responsible for acid production, chief cells responsible for pepsinogen production, and enterochromaffin-like cells producing histamine [143]. CCK2R is overexpressed in a large percentage of medullary thyroid cancers (> 90%), as well as in other tumors of neuroendocrine origin such as small cell lung cancers and gastroenteropancreatic (GEP) tumors [144].

Interest in CCK2R-directed radiopharmaceuticals started in the late 1990s with iodine labeled tracers [145]. Several groups across Europe studied numerous modifications of peptide derivatives of Gastrin and Cholecystokinin subsequently. A collaborative network carried out a direct comparison of a number of these derivatives which showed promise for future development [146, 147]. Following this preclinical characterization, a DOTA-coupled peptide derivative called PP-F11 (also known as CP04) labeled with indium-111 was selected for an international phase I study in patients with advanced medullary thyroid cancer, GRAN-T-MTC

[148]. A very similar compound, PP-F11N labeled with lutetium-177 is the subject of an ongoing clinical trial for therapy of patients with medullary thyroid cancer [149]. There has been recent interest in evaluating nonpeptidic antagonists to target CCK2R [150]. These may be more suitable for human use as the currently utilized agonists have acute side effects related to receptor activation. There are currently no antagonists for the CCK2R in clinical use. While remaining a very interesting target system, as the other GPCRs described, the CCK2/Gastrin receptor has overall attracted less clinical interest than anticipated. This may be due in part to the relatively low incidence of advanced medullary thyroid cancer compared to other cancers and to the overlap in the pattern of overexpression with other receptor systems such as somatostatin receptors, which are far more advanced in the theranostic development and clinical application.

Clinical outlook

The ultimate measure of success for a radiopharmaceutical is achieving clinical validation and acceptance, which is very challenging and accomplished in very few cases. For every successful probe or theranostic agent, there are many compounds that have failed to achieve their goal. In many ways, this is analogous to the research and development pathway for conventional pharmaceuticals, although the radioactive nature of these agents adds further complexity in terms of chemistry, practicality and legislation. Yet the concept of specifically targeting molecules to tumors while minimizing radiation dose to normal tissues remains very attractive. This is particularly relevant as the trend toward personalization in medicine continues to grow and these targeting methods are an excellent example of how to better characterize disease, improve patient staging, stratify patients for radionuclide or other therapies, and determine the response to these therapies earlier. There is now a clear clinical role for several of these applications in oncology. Pioneers in the field of receptor ligand development such as Dr Bill Eckelman have contributed to paving the way for the applications we are utilizing today and will develop for the future.

Table 1 provides an overview of the clinical development of cell surface receptor/protein targeting agents for cancer imaging applications, many of which have been discussed in this review. It is clear that most interest is focused on somatostatin receptor and PSMA targeting agents, which reflects the important impact these have had on patient management. There are now several somatostatin receptor ligands which have reached the end of their validation and are now licensed for specific indications and several PSMA-targeting agents in the table are likely to be licensed within the next year.

In addition to the enormous effort on development and refinement of ligands, the increasing availability of PET and gallium-68 generators have all been major contributors to these methods becoming clinically relevant. In coming years there is likely to be a shift towards fluorine-18 labeled tracers for central radiopharmacy production, which could increase availability of these diagnostic tests in smaller centers with limited or no access to gallium-68 or inadequate radiopharmacy facilities. Commercial considerations will also determine which ligands gain market share in the future. In terms of the newer ligands discussed in this review, their future role in routine diagnostics for clinical decision remains to be defined but they represent promising areas for future development. The outcome from the clinical research studies discussed in this review will help to define their potential role in the future.

Regarding therapeutic applications, there is anticipation that many of the compounds identified as suitable for imaging will be evaluated for further use as true theranostics. Somatostatin receptor targeting agents have at least partially been validated in this respect and hold a clinically defined role, being routinely used for treating patients with neuroendocrine tumors in many centers around the world. SSTR agents may see an expansion of their current indications, as well as improved strategies based on a combinational approach with other treatments. For the other targets presented here, their future role as routine clinical theranostics remains to be seen. To demonstrate the breadth of this research, Table 2 summarizes the registered radionuclide therapy trials identified as active on clinicaltrials.gov as of May 1st, 2020 with these classes of radiopharmaceuticals. This table also highlights the studies which require marker-specific imaging as part of the selection criteria for patient enrolment as a companion diagnostic, which is a key concept for developing these agents for future routine clinical use as it provides improved patient

stratification beyond conventional and often less accurate approaches. The expectation is that PSMA will provide the next approved theranostic and PSMA targeted therapy has potential to impact a significant number of patients given the increasing prevalence of advanced prostate cancer throughout the world. Appropriate validation and general clinical acceptance of PSMA-targeted therapy is still pending. Most other targets are early in the process of clinical validation and their future role is unknown. Of particular interest are some examples of clinical applications utilizing alpha emitters which have now made their way into clinical trials, albeit involving small numbers of patients. There the expectation within the radionuclide therapy community is that these radioisotopes will be more effective than the currently widely utilized beta emitters. Evaluation through proper trials will be necessary to validate this concept going forward.

To provide additional context to the review, Table 3 presents the number of clinical radionuclide therapy trials using the more traditional approach of antibodies to target tumor-specific cell surface antigens. Most of these trials are focused on hematological malignancies by targeting a range of cluster of differentiation (CD) markers, an area where there has been a degree of clinical success with some approved radioimmunotherapy applications. The discovery of immune checkpoint proteins such as CD276 (B7-H3) [151] and their functional relevance in tumor immunosuppression further catalyzed new ideas for imaging and treating tumors based on these targets in the immuno-oncology landscape. However, therapy of solid tumors with these approaches remains limited. Furthermore, while antibodies have shown a recent revival for imaging specific targets with PET, the concept of utilizing antibodies as true theranostics for routine clinical use is quite challenging as mentioned above and labeled antibodies may not be effective for high throughput imaging. On the other hand, the slow

pharmacokinetics of most antibodies may provide higher overall uptake in target tissues which could be more suitable for therapeutic applications. An interesting proposal for future theranostics could be the combination of a small molecule/peptide for highly sensitive detection of target lesions to guide stratification of patients for therapy with an antibody against the same target, which could deliver higher tumor absorbed doses. This concept is currently being investigated in some of the PSMA trials identified in Table 2.

Conclusions

There has been considerable effort in the development of receptor/membrane protein targeting radiopharmaceuticals for theranostic applications in the clinic. Important routine clinical applications are emerging, such as the role of somatostatin receptors for imaging and therapy. Progress in cancer biology, ligand development, labeling strategies and radioisotope production will help this field to identify new clinically relevant applications in the future.

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Figures

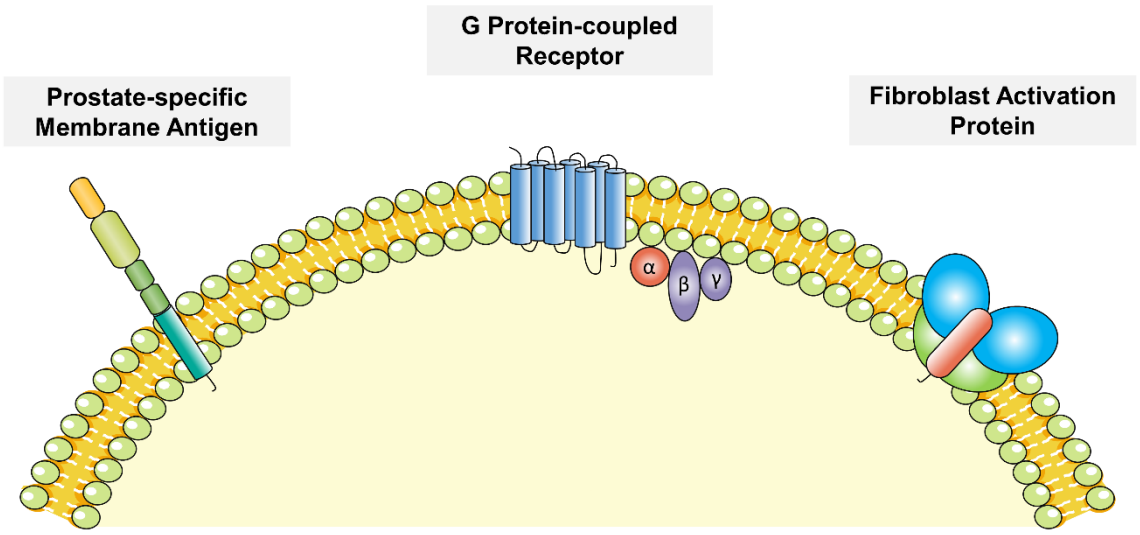

Figure 1.

Figure 1. Schematic representation of the cell surface targets addressed in this review. The Prostate Specific Membrane Antigen (PSMA) is widely overexpressed in prostate cancer as well as in the neovasculature of other tumors. G-protein coupled receptors constitute a large family of regulatory peptide receptors with similar seven transmembrane domain structure and intracellular signaling components. There are many different classes of these receptors with varying degrees of expression in normal tissues and in specific cancer types. Fibroblast Activation Protein (FAP), is expressed at high levels in cancer-associated fibroblasts present in the stroma of many epithelial tumors.

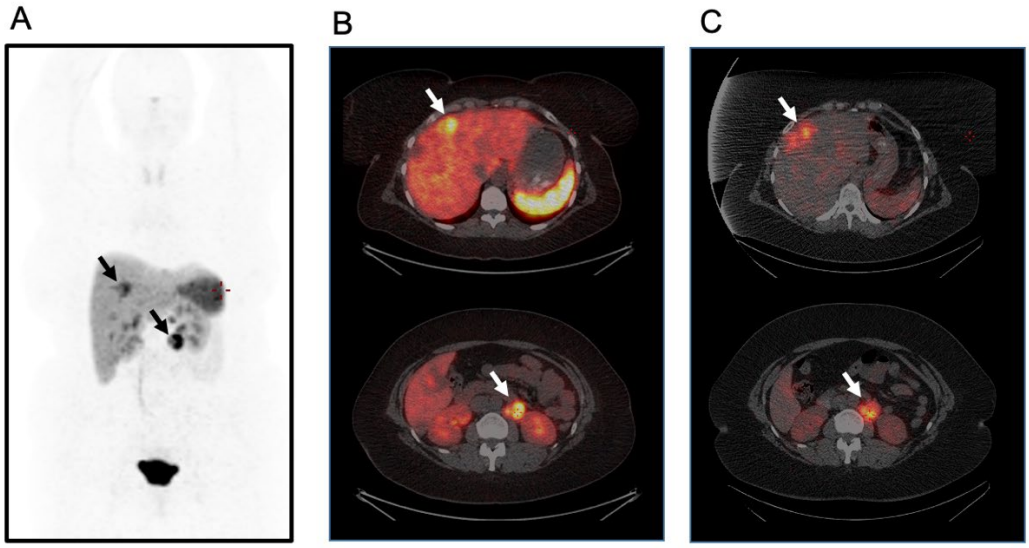

Figure 2. Maximum intensity projection (A) and fused PET/CT images (B) from a PET CT study using [^{68}Ga]Ga-DOTA-TATE in a patient with pancreatic insulinoma with liver and abdominal lymph node metastases (arrows). All lesions are identified in the PET study which allows characterization of the biological properties of the disease and identifies the patient as a candidate for somatostatin receptor targeted radionuclide therapy. C: Fused SPECT/CT images of the same patient 4 days following the first cycle of treatment with [^{177}Lu]Lu-DOTA-TATE. There is a high level uptake within the tumors previously identified with PET. The treatment resulted in long-term symptom control (dramatic reduction of the number of episodes of hypoglycemia caused by high insulin secretion from the tumors) and objective response on anatomical imaging following 4 cycles of treatment.

Table 1. Cell surface receptor/ protein targeting small molecule/peptide PET and SPECT agents utilized in a clinical setting

			Stage of clinical development			
Molecular target	**Condition**	**Tracer**	**Licensed for clinical use**	**Registered clinical trials**	**Preliminary clinical experience**	**Ref.**
SSTR2	Neuroendocrine and other SSTR expressing tumors	[^{111}In]In-DTPA Octreotide	Yes			[152]
		[^{99m}Tc]Tc-EDDA-HYNIC-Octreotide	Yes, EU			[153]
		[^{68}Ga]Ga-NODAGA JR11 (OPS-202)	No	X		[63]
		[^{68}Ga]Ga-DOTA-TOC	Yes, EU+USA	X		[47]
		[^{68}Ga]Ga-DOTA-TATE	Yes, USA	X		[154]
		[^{68}Ga]Ga-DOTA-NOC	No	X		[155]
		Several others	No	X	X	
PSMA	Prostate Cancer	[^{68}Ga]Ga-PSMA-11 (HBED-CC-PSMA)	No	X		[78]
		[^{18}F]PSMA-1007	No	X		[156]
		[^{18}F]DCFPyL	No	X		[81]
		[^{68}Ga]Ga-THP-PSMA	No	X		[157]
		[^{68}Ga]Ga-PSMA-I&T	No	X		[86]
		[^{99m}Tc]Tc-MIP-1404	No	X		[158]
		Several others	No	X	X	
FAP	Various solid tumors	[^{68}Ga]Ga-FAPI 46	No	X		[112]
		[^{68}Ga]Ga-FAPI 04	No		X	[110]
		[^{68}Ga]Ga-FAPI 02	No		X	[110]
CXCR4	Hematological and solid tumors	[^{68}Ga]Ga-Pentixafor	No	X		[124]
		[^{64}Cu]Cu-Plerixafor	No	X		[159]
GRPR	Endocrine related cancers, breast, prostate, ovarian	[^{68}Ga]Ga-RM2	No	X		[136]
		[^{68}Ga]Ga-Neobomb1	No	X		[141]
		[^{68}Ga]Ga-NOTA-Aca-BBN(7-14)	No		X	[160]
		[^{68}Ga]Ga-RM26	No		X	[161]
		[^{68}Ga]Ga-SB3	No		X	[135]
CCK2/ Gastrin R	Medullary Thyroid Cancer and some Neuroendocrine Tumors	[^{111}In]In-CP04 (PP-F11)	No	X		[148]
		[^{111}In]In-DTPA Minigastrin	No		X	[162]
		[^{99m}Tc]Tc-Demogastrin	No		X	[163]

Table 2. Active radionuclide therapy trials for cell surface receptor/protein targeting small molecule/peptide agents as listed on http://clinicaltrials.gov as of May 1st, 2020. * = Number of trials where imaging and an equivalent agent/companion diagnostic is included in the selection criteria for therapy.

Molecular target (number of studies)	Condition (number of studies)	Radiopharmaceutical	Phase 1/2	Phase 3	Imaging *	Total
SSTR2 (49)	Neuroendocrine Tumors (41), Meningioma (2), Neuroblastoma (1), Small Cell Lung Cancer (2), Hepatocellular Carcinoma (1), Merkel Cell Carcinoma (1), Multiple Myeloma (1), Lymphoma (1)	[^{177}Lu]Lu-DOTA-TATE	28	3	36	36
		[^{90}Y]Y-DOTA-TOC	7	0	6	7
		[^{177}Lu]Lu-DOTA-TOC	2	1	3	3
		[^{177}Lu]Lu-JR11	1	0	2	2
		[^{212}Pb]Pb-DOTAMTATE	1	0	1	1
		[^{188}Re]Re-P2045	1	0	1	1
PSMA (22)	Prostate Cancer (20), Other Solid Tumors (1), Salivary Gland Cancer (1)	[^{177}Lu]Lu-PSMA-617	8	1	9	9
		[^{177}Lu]Lu-J591	4	0	1	4
		[^{177}Lu]Lu-PSMA-I&T	2	0	3	3
		[^{131}I]I-PSMA-1095	2	0	2	2
		[^{177}Lu]Lu-PSMA-R2	1	0	0	1
		[^{177}Lu]Lu-CTT1403	1	0	1	1
		[^{225}Ac]Ac -J591	1	0	1	1
		[^{225}Ac]Ac -PSMA-617	1	0	1	1
GRPR (1)	Tumors expressing GRP receptor	[^{177}Lu]Lu-NeoBomb1	1	0	1	1
CCK2R (2)	Medullary Thyroid Cancer	[^{177}Lu]Lu-PP-F11N	2	0	0	2
Neurotensin-1R (1)	Tumors expressing Neurotensin Type 1 Receptor	[^{177}Lu]Lu-3BP-227	1	0	0	1
IGF-1R (1)	Advanced Solid Tumors	[^{225}Ac]Ac-FPI-1434	1	0	1	1

Table 3. Active radionuclide therapy trials for cell surface antigens with antibody-based theranostics listed on http://clinicaltrials.gov as of May 1st, 2020. * number of trials where imaging with an equivalent agent/companion diagnostic is included in the selection criteria for therapy. CD = Cluster of Differentiation antigen.

Molecular target	Condition	Radiopharmaceutical	Phase 1/2	Phase 3	Imaging*	Total
CD 20	Non-Hodgkin Lymphoma, Leukemia, Multiple Myeloma	[^{90}Y]- and [^{131}I]- anti-CD20	8	3	6	11
CD 276	Sarcomas, Neuroectodermal and Central Nervous System tumors	[^{177}Lu]- and [^{131}I]- anti-CD276	5	1	1	6
CD 33	Multiple myeloma, Leukemias	[^{225}Ac]-anti-CD33	5	0	0	5
CD 45	Lymphomas, Leukemias	[^{90}Y]-, [^{211}At]- and [^{131}I]- anti-CD45	4	1	1	5
CD 37	Non-Hodgkin Lymphomas	[^{177}Lu]-anti-CD37	3	0	0	3
CD 25	Non-Hodgkin Lymphomas	[^{90}Y]-anti-CD25	2	0	1	2
CD 66	Leukemia	[^{90}Y]-anti-CD66	1	0	1	1
CA 19.9	Tumors expressing CA19.9	[^{177}Lu]-anti-CA19.9	1	0	0	1
Carbonic anhydrase IX	Clear Cell Renal Carcinoma	[^{177}Lu]-anti-CAIX	0	1	1	1
P-Cadherin	Advanced Solid Tumors	[^{90}Y]-anti-P-Cadherin	1	0	1	1
Frizzled Homolog 10	Synovial Sarcoma	[^{90}Y]-anti-FH 10	1	0	1	1
Ganglioside GD2	Multiple solid tumors	[^{131}I]-anti-GD2	1	0	0	1