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Conventional targeted drugs, RNA drugs, and radiopharmaceuticals: targeting from drivers to passengers

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Abstract: Targeted therapy targets the driver genes of tumor cells and effective inhibitors were developed to treat tumors by inhibiting tumor cell proliferation, interfering with the cell cycle, inducing tumor cell apoptosis, and inhibiting tumor angiogenesis. The emergence of RNA therapeutics provides more opportunities to target some driver genes which cannot be targeted with conventional drugs. However, the response of these targeted drugs in patients may be limited by their potential drug toxicity and tolerance. With the development of positron emission tomography (PET) and molecular biology, a number of passenger genes that do not have a driving role in tumor growth such as prostate-specific membrane antigen (PSMA) in prostate cancer, have been developed for widespread use in the diagnosis and treatment of cancer through radiolabeled molecular tracers. Radiopharmaceutical targets exhibit high specificity, which contributes to enhancing inhibitory activity in tumor but avoiding toxic effects on normal tissues. In addition, these radiopharmaceuticals have been continuously upgraded through chemical structure optimization such as regulating linkage lengths, hydrophobicity and charge, introducing albumin-binding entities, increasing the amphiphilicity of tracers enables radiopharmaceuticals to traverse cell and nuclear membranes, which have further improved diagnostic sensitivity/therapeutic specificity and reduced off-target toxicity.

Keywords: targeted drugs; RNA drugs; radiopharmaceuticals; driver genes; passenger genes

1. Introduction

There are two types of tumor-related genes: driver and passenger genes. Driver genes are the direct drivers of tumor development, while passenger genes are non-major conflicts during tumor development [1,2]. These tumor driver genes are mainly related to the regulation of proliferation, apoptosis, cell cycles, and DNA damage repair [3–7]. Conventional targeted therapy is to target the driver genes of tumor cells and develop effective blocking agents including small molecule and protein to intervene in the cellular aspects of carcinogenesis (Figure 1).

While small molecule and protein drugs are proved to be effective in many cases, there are still a large number of diseases that cannot be treated with them. RNA therapeutics can specifically target and silence any gene in theory, having a huge advantage in targeting "undruggable" targets [8]. Due to its cost effectiveness and easier development, a great deal of research has been conducted on RNA therapeutics over the past few decades. These RNA therapeutics include antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), microRNAs (miRNAs), messenger RNAs (mRNAs), and CRISPR/Cas9 [9]. However, clinical application of these targeted drugs may be hindered by primary and acquired resistance caused by mutations of multiple driver genes in tumor or the toxicity to normal tissues because of low specificity [10].

Radiopharmaceutical targets differ from traditional drug targets in that they are not key regulatory proteins and may be non-functional, but they have high specificity requirements (Figure 1). For example, the prostate-specific membrane antigen (PSMA) is specifically expressed on the membrane of prostate cancer cells (Figure 2) [11]. Thus, the radiopharmaceuticals are efficiently targeted to the tumor tissue, specifically killing the tumor cells with the α or β rays of the radionuclides and reducing the toxicity to normal tissues.

A radiopharmaceutical consists of four main moieties: a small molecule or peptide that acts as a targeting agent (ligand), a linker, a chelator, and a radioisotope [12]. In addition to developing novel and effective radiopharmaceuticals based on various molecular targets, researchers have also attempted to modify the chemical structure of these drugs to enhance specific affinity and *in vivo* pharmacokinetic (PK) properties. This aims to increase diagnostic sensitivity and therapeutic specificity while reducing off-target toxicity [13]. As shown in Figure 3, various modifications are employed in the strategies, mainly involving the regulation of linker length, hydrophobicity, and charge, the introduction of albumin binding entities, and the enhancement of tracer amphiphilicity. These modifications enable radiopharmaceuticals to penetrate the nucleus.

In this review, two types of representative drugs targeting important tumor driver genes or passenger genes including small-molecule, protein, RNA drugs and radiopharmaceuticals were summarized and future prospectives for these drugs were discussed. The detailed information of drugs approved by FDA and in clinical trials was listed in Table 1 and Table 2, respectively.

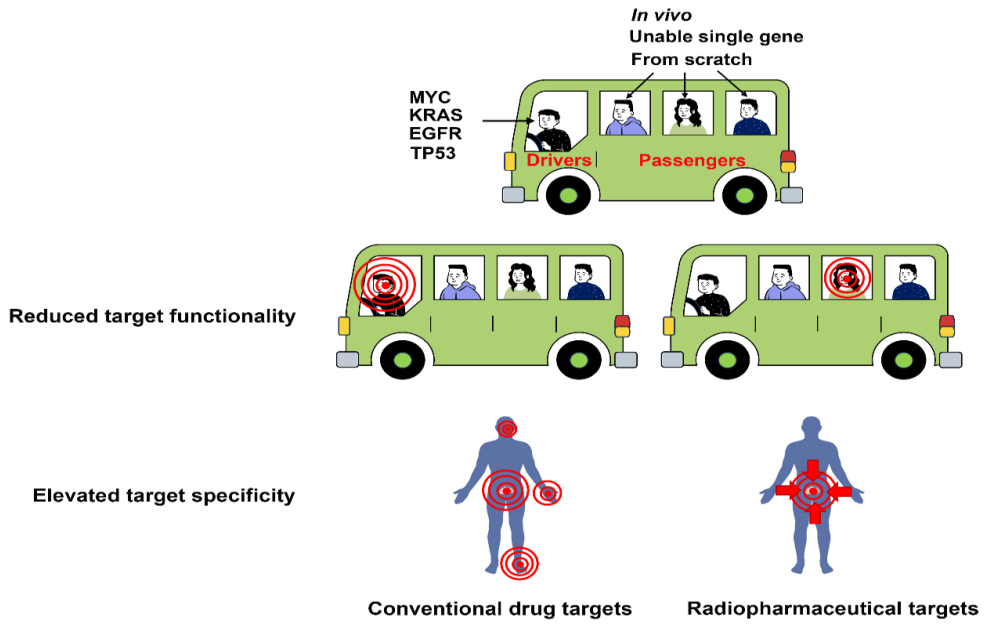

Figure 1. Different characteristics and targeting modes of conventional and radiopharmaceutical targets.

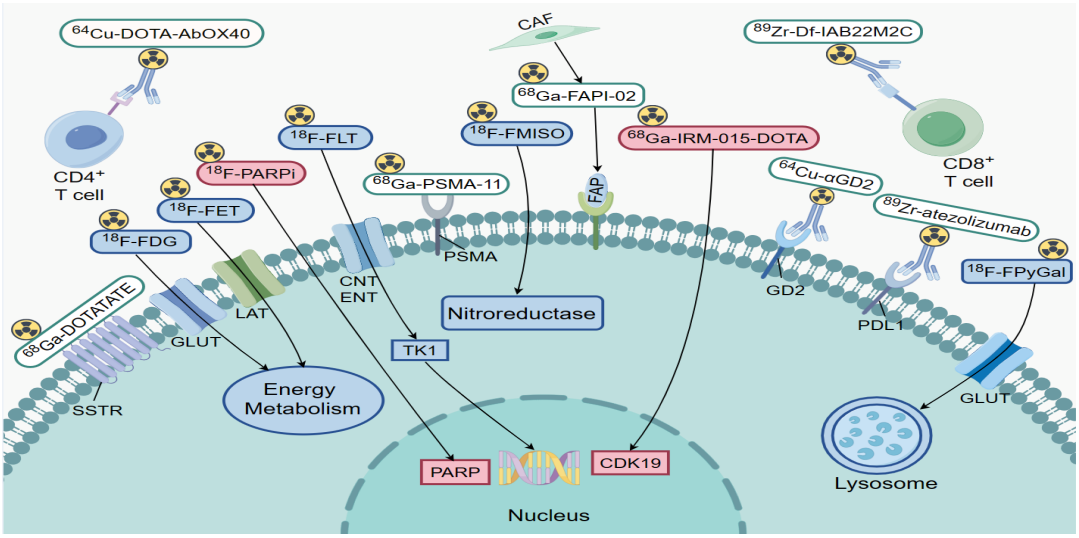

Figure 2. Radiopharmaceuticals target specific molecules in the cell membrane, cytoplasm and nucleus. CAF, Cancer-associated fibroblast; SSTR, somatostatin receptors; LAT, l-type amino acid transporter; FAP, fibroblast activation protein; GLUT, glucose transporter; PSMA, prostate-specific membrane antigen; TK1, Thymidine kinase I; PARP, Poly (ADP-ribose) polymerase; CDK19, Cyclin Dependent Kinase 19; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{18}F-FET, ^{18}F-fluoroethyl-l-tyrosine; FAPI, FAP-binding inhibitor; ^{18}F-FLT, ^{18}F-3′-deoxy-3′-fluorothymidine; ^{18}F-FMISO,^{18}F-fluoromisonidazole; PARPi, poly (ADP-ribose) polymerase inhibitor. The figure was performed using Figdraw.

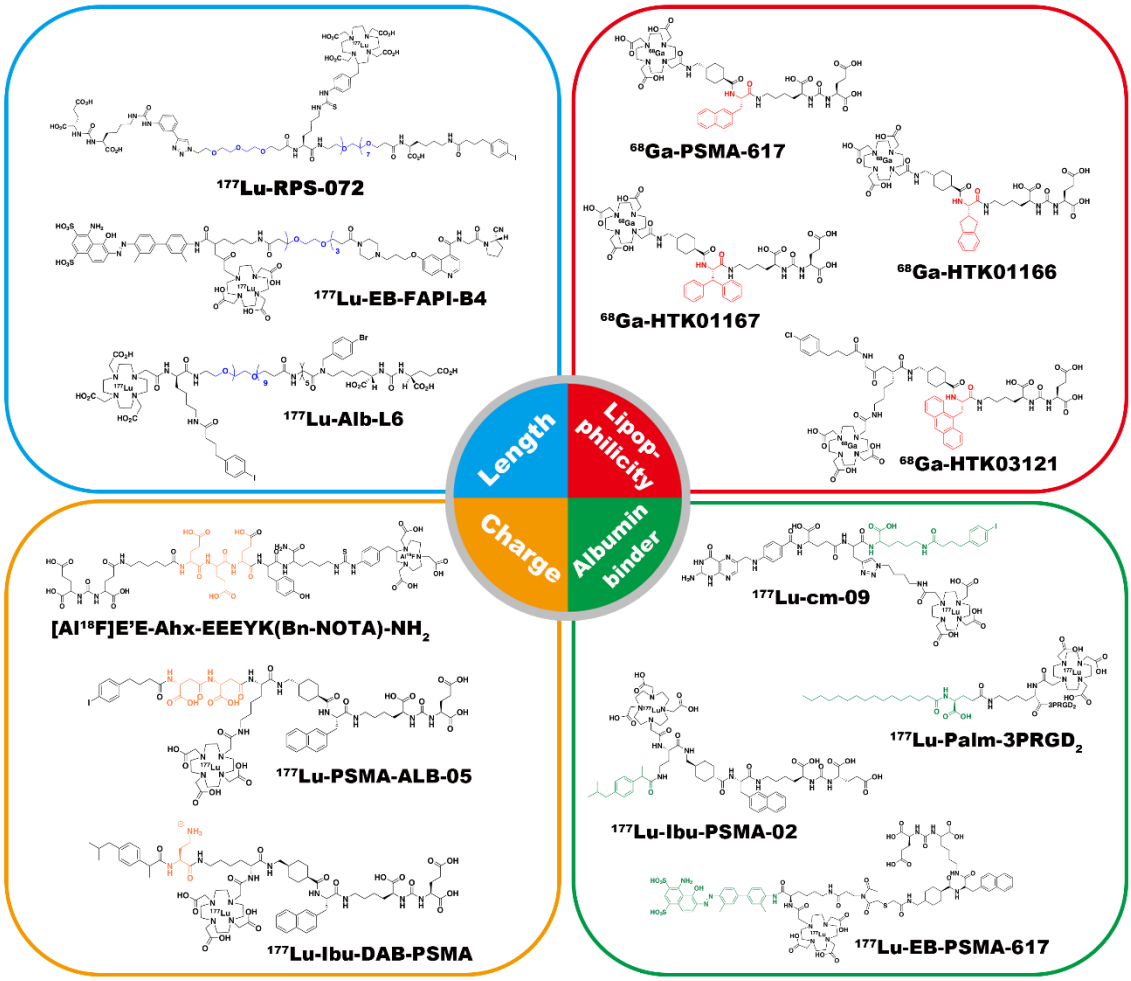

Figure 3. Representative radiopharmaceuticals based on different structure modification including introducing hydrophilic, lipophilic, and charged linkers as well as the insertion of albumin binding moieties. PSMA, prostate-specific membrane antigen; EB, Evans blue.

Table 1. FDA-approved drugs.

Drug	Trade name	Target	Indications	Approval year	Company
AMG510	Sotorasib	$KRAS^{G12C}$	NSCLC	2021	Amgen
Amivatamab	Rybrevant	EGFR	mNSCLC	2021	Johnson & Johnson
^{68}Ga-PSMA-11	Illuccix	PSMA	PCa	2020	Novartis
^{177}Lu-PSMA-617	Pluvicto	PSMA	CRPC	2022	Novartis
^{68}Ga-DOTATATE	Netspot	SSTR	NET	2016	Advanced Accelerator Applications
^{177}Lu-DOTATATE	lutathera	SSTR	GEP-NET	2018	Novartis
^{18}F-FDG	-	FDG	High glycolytic cancers	1994	Bayer AG

Table 2. Drugs in clinical trials.

Drug	Target	Indications	Phase	Trial identifier
RG7112	p53-MDM2	Advanced solid tumors,	I	NCT00559533
		Hematologic neoplasms	I	NCT00623870
RG7388	MDM2	Solid tumors	I	NCT02828930
AMG232	p53-MDM2	Acute myeloid leukemia	Ib	NCT03041688 NCT02016729
		Advanced solid tumors	I	NCT01723020
		Brain cancer	0/I	NCT03107780
		Metastatic melanoma	Ib/IIa	NCT02110355
SAR405838	p53-MDM2	Advanced cancers	I	NCT01636479
			I	NCT01985191
NVP-CGM097	p53-HDM2	Advanced solid cancers	I	NCT01760525
AZD9592	EGFR-Met	Solid tumors	I	NCT05647122
M1231	Mucin 1-EGFR	Advanced solid tumors	I	NCT04695847
BL-B01D1	EGFR-HER3	mNSCLC and other solid tumors	I	NCT05983432
			II	NCT06006169
				NCT05924841
		Metastatic gynecological malignancies	II	NCT05990803
p28	p53	Refractory Solid tumor	I	NCT00914914
		Recurrent Central Nervous System Tumors	I	NCT01975116
AZD4785	KRAS	Advanced Solid Tumors	I	NCT03101839
BP1002	Bcl-2	Acute myeloid leukemia	I/Ib	NCT05190471,
		Advanced lymphoid malignancies	I	NCT04072458
^{89}Zr-atezolizumab	PD-L1	Large B-cell lymphoma	II	NCT05404048
^{89}Zr-Df-IAB22M2C	CD8	COVID-19	I/II	NCT04874818
^{68}Ga-FAPI-02	FAP	TNBC	II	NCT06225505
^{18}F-FMISO	Nitroreductase	Head and neck cancer	II	NCT06087614
^{18}F-FET	Energy metabolism	High grade glioma	II	NCT06172595
^{18}F-FPyGal	β-galactosidase	Senescence in oncological patients	I/II	NCT04536454
^{18}F-PARPi	PARP	Head and neck cancer	I/II	NCT03631017

2. Methods

Research articles, systematic reviews, and clinical research relevant to the central theme of this review which were published before 25th May 2024 were retrieved in the database PubMed. Drugs targeting tumor driver or passenger genes including small-molecule drugs, protein drugs, RNA drugs, and radiopharmaceuticals were main terms for search. After the further screening, a total of 159 articles were included in the manuscript. The summary of the search strategy is outlined in Table 3.

Table 3. The search strategy summary.

Items	Specification
Date of search	25th October 2023–25th May 2024
Databases and other sources searched	PubMed
Search terms used	Tumor-targeted drugs, RNA drugs, and radiopharmaceuticals
Timeframe	Manuscripts published before 25th May 2024
Inclusion and exclusion criteria	Research articles, systematic reviews, and clinical research were included while conference proceedings, letters to editors, and articles in non-English language were excluded.
Selection process	Yichi Huang and Ting Huang conducted the search independently, and the final selection of the manuscripts were codetermined by authors.

3. Conventional drugs targeting divers

3.1. Drugs targeting MYC

MYC is one of the most extensively researched oncogenes. As a transcriptional regulator, it is involved in the regulation of various cellular processes [14,15]. Indeed, overexpression or structural alteration of the MYC gene has been reported to occur in approximately 70% of human cancers [16]. Since MYC is a driver of tumorigenesis, inhibiting its expression can reverse tumorigenesis [17,18]. Drugs primarily target MYC by inhibiting its expression or the MYC-MAX interaction to halt tumor growth. It has been reported that the BET protein BRD4 binds to the MYC promoter and regulates its transcription [19]. BET inhibitors, like the BRD4 inhibitor JQ1, have been demonstrated to downregulate MYC and inhibit tumor growth in animal models [20–22]. However, current results suggest that the existing BET inhibitors have limited efficacy as anticancer agents [23]. OmoMYC, a peptide/miniprotein, plays a crucial role in inhibiting MYC-MAX interactions. OmoMYC can form both homodimers with itself and heterodimers with MAX. The homodimer prevents the MYC-MAX heterodimer from interacting with DNA, while the heterodimer replaces the MYC-MAX heterodimer to repress MYC-induced transcription [24–26].

3.2. Drugs targeting KRAS

Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations play an essential role in driving tumorigenesis [27]. KRAS drug targets include direct targeting of KRAS mutations, as well as targeting upstream and downstream proteins [28]. Currently, $KRAS^{G12C}$ inhibitors such as AMG510 have shown promising responses in lung cancer and have been approved for use in non-small cell lung cancer (NSCLC) [29]. Except for small-molecule inhibitors, peptides were also selected to target other mutation types such as $KRAS^{G12D}$. KRpep-2d was the first reported inhibitory peptides for $KRAS^{G12D}$ [30], and KS-58 which was based on KRpep-2d, exhibited anti-tumor activity *in vivo* [31]. In terms of targeting upstream proteins, KRAS was mainly inhibited by disrupting its translocation to the cell membrane. The natural compound antroquinol inhibited the proliferation of tumor cells by inactivating KRAS through FTase and GGTase [32]. Targeting downstream proteins involves inhibiting RAF-MEK-ERK and PI3K-AKT-mTOR pathways [33–36]. However, these indirect inhibitors alone exhibited limited efficiency and required combination therapy.

3.3. Drugs targeting EGFR

Epidermal growth factor receptor (EGFR, also refer to as HER1 or ERBB1), which belongs to EGFR family, is a member of transmembrane receptor tyrosine kinases (RTKs) [37]. Due to overexpression of EGFR in various solid tumors, this receptor has regarded as one of core tumor driver genes [38]. Small-molecule tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs) are two vital classes of clinical pharmaceuticals in anti-EGFR targeted therapy [39]. However, these anti-EGFR agents are facing two main hurdles for anti-tumor activity: tumor heterogeneity and inevitable drug resistance [40]. In addition to developing the new generation of TKIs to target the specific EGFR mutations [39], bispecific antibodies (bsAbs) have emerged as a preferable method to address this challenge by simultaneously binding to two distinct targets [40]. An EGFR/mesenchymal-epithelial transition factor (MET) bsAb, amivatamab, has been approved by FDA for the treatment of patients with metastatic NSCLC (mNSCLC) [41,42]. Furthermore, several bispecific antibodies-drug conjugates (bsADCs) equipped with a bsAb and drug molecule such as AZD9592, M1231, and BL-B01D1, have been developed to prolong the clinical efficacy of EGFR-targeting therapy [43–45].

3.4. Drugs targeting p53

Tumor protein 53 (TP53) is the most commonly mutated oncogene in tumorigenesis [5,46]. p53 is a transcription factor that binds to DNA to regulate gene expression [47,48]. p53 forms a complex with MDM2 and targets ubiquitin-dependent protein degradation in normal tissues [49]. When cells are externally stimulated, the ubiquitination of p53 is inhibited, and its expression is increased, which then blocks DNA mutations and suppresses tumors by activating various genes involved in cellular processes [50,51]. Drugs targeting MDM2 mainly consist of inhibitors that block the interaction between p53 and MDM2. These include

RG7112, RG7388, AMG232, SAR405838, and NVP-CGM097. However, these inhibitors have limitations, including wide variations in efficacy in different tumors, potential gastrointestinal side effects, and the possibility of p53 mutations and drug resistance [52–56]. In addition, protein drugs including peptides (e.g., CDB3 [57], pCAPs [58], p28 [59], and H2-scDb [60]) and nanobodies (e.g., Nb3 and Nb139 [61]) were developed to target the mutated p53 due to high specificity and security profiles , but the stability of these proteins *in vivo* still needs to be improved.

4. RNA therapeutics targeting drivers

4.1. RNA therapeutics targeting KRAS

SiRNAs are short double-stranded RNAs (19-25 base pairs) that can knockdown the target mRNA, leading to gene silencing [62]. Due to the precise control of gene expression, siRNAs have been emerged in the development of KRAS-targeted drugs. The effective delivery of siRNAs has been achieved by liposomes, nanoparticles, and exosomes [63–65]. For example, siRNA targeting $KRAS^{G12D}$ loaded by exosomes exhibited anti-tumor activity in the mice [65]. Additionally, ASOs are another alternative tactic for KRAS. ASOs are single-stranded oligonucleotides in the length of 13–25 nucleotides (nt), which degrade target transcripts by RNase H-mediated cleavage [66]. AZD4785, a ASO modified with 2'–4' constrained ethyl (cEt), has been reported to knock down KRAS in tumor tissues with high delivery efficiency and low immune response [67]. CRISPR/Cas9, served as a genome-editing system, has been successfully applied for targeting $KRAS^{G12S}$ contributing to tumor regression [68].

4.2. RNA therapeutics targeting p53

SiRNAs specifically targeting mutations of p53 mRNA were applied to ameliorate gain-of-function (GOF) activities of p53 mutants as well [69]. For example, four specific siRNAs for different mutated p53 designed by *Ubby et al.* reduced the viability of patient-derived xenografts (PDXs) with no effect on wild-type p53 mRNA [70]. In addition, *TP53* missense mutation was successfully edited into a wild-type one via CRISPR/Cas9 with the correction rate of 7.6%., demonstrating the powerful potential of this technique as an RNA therapy [71]. p53 mRNA can be efficiently delivered to tumor microenvironment by nanoparticles [72]. It has been reported that the delivery of p53 mRNA via redox-sensitive nanoparticles induced the decrease in the viability of p53-deficiency lung cancer cells and tumor size in both hepatocellular carcinoma (HCC) and NSCLC mouse models [73].

4.3. RNA therapeutics targeting STAT3

Signal transducer and activator of transcription 3 (STAT3) is implicated in many biological processes including proliferation, differentiation, angiogenesis, and apoptosis of cells [74]. Aberrant activation of STAT3 is correlated with tumorigenesis, invasion, and metastasis [75]. While conventional inhibitors failed to directly target this "undruggable" protein [76], RNA therapeutics including siRNAs and ASOs were treated as STAT3-silencing strategies *in vitro*

and *in vivo*. For instance, STX-0119 exhibited anti-tumor activity in various pancreatic cancer cell lines [77]. Gint4.T-STAT3, a siRNA delivered by aptamer agents targeting STAT3, showed cytotoxicity in glioblastoma mouse models [78]. The results in phase 1 clinical trial demonstrated that AZD9150 as an ASO with ethyl modification, was efficacious and tolerable in patients with heavily pretreated B-cell lymphoma [79].

4.4. RNA therapeutics targeting Bcl-2

The B-cell lymphoma-2 (Bcl-2), an apoptosis-related protein, is associated with not only the development of diverse cancers in melanoma, breast, and lung, but also the resistance mechanism of drug treatment [80]. Because conventional treatments were not suitable for targeting Bcl-2 with no enzymatic activity, oligonucleotide therapeutics including ASOs and miRNAs targeting Bcl-2 mRNA are being developed. BP1002 is a novel liposome-incorporated ASO to inhibit the expression of Bcl-2 without inherent toxicity. Patients with advanced lymphoid malignancies are being recruited for the treatment of BP1002 in a phase 1 clinical trial [81]. MiRNAs are endogenous non-coding RNAs (ncRNAs) with 20-25 nt. The translation of mRNAs will be suppressed when miRNAs bind to 3'UTR of their targeted sites, promoting the degradation of mRNAs [82]. TargomiR, a miRNA mimic targeting Bcl-2 delivered by a nano-carrier, was tolerated in patients with malignant pleural mesothelioma (MPM) and NSCLC with anti-tumor activity in phase 1 clinical trial with dose escalation [83].

5. Radiopharmaceuticals targeting passengers

5.1. Radiopharmaceutical targets of cell membrane molecules

In recent years, there have been numerous advancements in radiolabeled molecular probes for the cell membranes (Figure 2) of various cancers. Among these, ^{68}Ga-PSMA-11 and ^{68}Ga-DOTATATE have been approved for cancer diagnosis, while ^{89}Zr-atezolizumab, ^{89}Zr-Df-IAB22M2C, and ^{68}Ga-fibroblast activation protein inhibitor (^{68}Ga-FAPI-02) are currently undergoing clinical phase I or II testing. Specifically, PSMA is overexpressed on the membranes of prostate cancer cells. ^{68}Ga-PSMA-11 has been utilized for visualizing prostate cancer [84], while ^{177}Lu-PSMA-617 was approved by the FDA for the treatment of prostate cancer in 2021 [85]. Furthermore, ^{68}Ga-DOTATATE, a PET tracer that targets somatostatin receptors (SSTR), has been utilized for visualizing neuroendocrine tumors (NET) [86]. ^{177}Lu-DOTATATE received FDA approval in January 2018 for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NET) that are positive for SSTR [87]. The disialoganglioside GD2 is targeted by ^{64}Cu-αGD2 for the detection of neuroblastoma [88] because of its high prevalence in many neuroectodermal tumors. In addition, cell membrane targeting is also observed in immunotherapeutic radiotracers. In cases of bladder cancer, triple-negative breast cancer (TNBC), or NSCLC, ^{89}Zr-atezolizumab [89] has been proven to be a more precise indicator of clinical response to anti-PDL1 treatment compared to established PDL1 immunohistochemistry and biomarkers. The imaging targets

representing T cells are CD4 and CD8. In cancer vaccination, ^{64}Cu-DOTA-AbOX40 [90] has been developed and may hold potential value. After treatment with a T cell bispecific antibody, ^{89}Zr-Df-IAB22M2C [91] was used to monitor cytotoxic T lymphocytes. Clinical trials [92] have already tested the safety and effectiveness of tumor targeting. Cancer-associated fibroblasts (CAFs) play a crucial role in the tumor microenvironment by promoting invasion, metastasis, and resistance to therapy. A radiolabeled FAP-binding inhibitor, ^{68}Ga-FAPI-02 [93], has been developed, and its updated versions [94,95] have been studied in patients with various types of tumors.

5.2. Radiopharmaceutical targets of cytoplasm molecules

Targets in the cytoplasm are molecules that play a crucial role in hypoxia, energy metabolism, cell proliferation, and senescence processes. Among these, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has been approved for the diagnosis of cancers, while ^{18}F-fluoromisonidazole (^{18}F-FMISO), ^{18}F-fluoroethyl-l-tyrosine (^{18}F-FET), and ^{18}F-FPyGal are still in clinical phase I-II monitoring. Hypoxia is a prevalent characteristic of most solid tumors. ^{18}F-fluoromisonidazole and ^{18}F-fluoroazomycin arabinoside [96] are the hypoxia PET tracers in clinical use. In energy metabolism, PET imaging using the radiofluorinated glucose analogue ^{18}F- FDG [97–101] is widely applied in most tumor types with the exception of prostate cancer and neuroendocrine tumors. The radiofluorinated derivative of the amino acid tyrosine, ^{18}F-FET, is used for therapy planning and treatment monitoring in neuro-oncology for both juvenile [102] and adults patients [103]. ^{18}F-FPyGal, a radiofluorinated substrate of β-galactosidase [104], was developed to meet the high medical demand for non-invasive detection of intra-tumoral senescence. The radiofluorinated thymidine analogue ^{18}F-FLT targets Thymidine kinase 1 (TK1) in the nucleus and is used to detect the proliferation of cancers [105,106].

5.3. Radiopharmaceutical targets of nucleus molecules

Currently, there is a scarcity of radiotracer targets within the cell nucleus. ^{18}F-PARPi has been used in clinic, and ^{68}Ga-IRM-015-DOTA has been developed for preclinical studies. PARP plays an important role in repairing single-strand breaks. PARP inhibitors (PARPi) can induce double-stranded breaks [107], Therefore, PARP radiotracers are primarily developed based on existing PARP inhibitors [108]. ^{18}F-PARPi has been tested in clinical trials for various types of cancer [109,110]. In addition, a new molecule, CDK19, was found to be specifically overexpressed in the nucleus in prostate cancer, and its expression levels correlated with prostate cancer progression [111]. ^{68}Ga-IRM-015-DOTA based on CDK19 inhibitor, has been developed and shown to be well-localized within the nucleus of prostate cancer cells, as well as in mouse models [112]. The PET tracker for the CDK19 inhibitor not only offers a new target for the precise treatment of prostate cancer but also sets a precedent for the research and development of nuclear radiolabeled targets in China.

6. Structural characteristics of radiopharmaceuticals

6.1. Linker length

The modification of polyethylene glycol (PEG) linkers between target and chelator has been documented to enhance renal clearance and reduce hepatobiliary excretion of radiopharmaceuticals [113]. However, excessive PEGylation may impair the recognition of ligands by the target due to conformational flexibility and hydrophilicity [114,115]. Kelly *et al.* found that the affinity of PSMA targeting constructs for PSMA and albumin was inversely proportional to the length of PEG linkers, while blood/kidney clearance was proportional [114,116]. This finding is consistent with the study results of PSMA and other ligand-targeting radioagents [117–119].

6.2. Lipophilicity moieties

The discovery of the arene-binding site (ABS) in the entrance funnel of PSMA suggests that a preference for aryl functional groups could be applied to the structural modification of PSMA inhibitors, enhancing ligand-binding activity [120]. Multiple aromatic moieties, including 2-naphthyl-L-alanine [121], 2-indanylglycine (Igl) [122], 3,3-diphenylalanine (Dip) [122], and tranexamic acid-9-anthrylalanine [123] have already been introduced into PSMA-targeting imaging agents as lipophilic linkers to enhance binding affinity and tumor-to-background absorption ratio.

6.3. Charged linkers

The linker's charge also influences the biological characteristics of radiopharmaceuticals, including tumor targeting capacity and biodistribution pattern. Huang *et al.* found that the insertion of a highly negative charged linker to PSMA targeting radiotracers resulted in reducing non-specific accumulation without affecting their binding activity to PSMA [124]. Intriguingly, *Benešová et al.* observed increased enrichment in the kidneys with the increased amount of negative charge carried by aspartate groups [125]. In addition, *Deberle et al.* found that using a positively charged diaminobutyric acid as a linker accelerated kidney elimination [126].

6.4. Albumin-binder conjugation

The introduction of various albumin binders to drugs has been documented as an effective strategy for prolonging blood half-life and avoiding rapid clearance by the kidneys [127,128]. The folate conjugate (^{177}Lu-cm09) with 4-(p-iodophenyl) butyric acid (IPBA) was initially reported to demonstrate the feasibility of radiopharmaceuticals modified with an albumin binder to enhance their poor pharmacokinetics [129]. In addition to IPBA as a potent albumin binding moiety [130], which has been extensively applied to optimize several PSMA-targeting agents due to its more flexible modification [114,116,125,131–133], multiple Evans blue (EB) [115,134–138] and fatty acid (lauric acid [139] and palmitic acid [140]) derivatives with enhanced tumor uptake and reduced renal clearance have been reported in various

diseases. Furthermore, increased tumor uptake of radiopharmaceuticals due to prolonged blood circulation may result in higher retention in healthy organs or tissues, such as the kidneys [126]. Hence, Deberle *et al.* utilized ibuprofen, a weak albumin-binding motif, to maintain the equilibrium between tumor uptake and background activity [126,141].

6.5. Nuclear accessibility

Radiopharmaceuticals currently under development mostly target cell membranes, such as ^{68}Ga-PSMA-11 and ^{68}Ga-DOTATATE. These membrane-targeted radiopharmaceuticals have several disadvantages, including short retention times in solid tumors, high blood washout impact, and limited applicability to certain tumor subtypes [142,143]. The linear structure of nuclear proteins prevents them from being targeted by radioligands, as it reduces their ability to pass through cell membranes when nuclides are added. The development of new radiopharmaceuticals targeting the nucleoprotein CDK19 involves modifying the linear molecular structure of compounds to encapsulate the nuclide, with the compound on the outside. The molecule's surface exhibits good amphiphilicity, allowing the radiopharmaceuticals to pass smoothly through the cytoplasmic and nuclear membranes and enter the nucleus [112].

7. Outlook for targeted drugs

Targeted therapy for tumor driver genes is proved to be an effective strategy to kill tumor cells directly. However, poor efficacy, high toxicity, and tumor recurrence caused by drug resistance are the main obstacles for targeted drugs. For this, additional tumor targets and resistance mechanisms need to be further identified through in-depth biochemical, genomic, molecular, and structural researches. It is necessary to discover novel drugs with diverse chemical entities or mechanisms of action. Currently, novel approaches such as next-generation sequencing techniques, the whole-genome sequencing, and deep machine learning can be used for this purpose as well [144–146]. For instance, the design of drug structure, determination of potential binding affinity, prediction of PK properties, and evaluation of side effects and toxicity can be achieved by strategies base on artificial intelligence (AI) [147].

In addition, the development of drugs which simultaneously block cancer cell proliferation and resistance, combined therapy with other antitumor therapies such as immune therapy, and personalized targeted therapy with proper selection of eligible populations by molecular diagnosis and predictive biomarkers may be other effective methods to enhance antitumor efficacy and reduce toxicity.

In 1978, mRNAs were introduced by liposome into mouse and human cells to activate protein expression, laying the foundation for mRNAs as a new class of therapeutic strategy [148]. The success of mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has inspired people’s interest in mRNA therapeutics [149]. Currently, mRNA therapeutics are mainly used to encode tumor antigens to induce immune reaction, cytokines to regulate the tumor microenvironment, suppressor such as p53 to inhibit tumor proliferation [150]. However, there is still much work needs to be done to optimize mRNA treatments for tumor.

For example, due to rare application of mRNAs targeting driver genes, considerable efforts should be devoted for the development of new mRNA vaccines for other tumor targets with rapid preparation and low cost in the future. Other mRNA candidates including circular mRNAs (circRNA), trans-amplifying mRNAs (taRNAs), and self-amplifying mRNA (saRNAs) should be further investigated to enhance the expression efficiency.

Besides, it is crucial for RNA agents to ensure safe and efficient delivery to target cells due to their poor stability and membrane permeability [151]. Advanced chemical modifications and ligands/antibodies conjugation were applied to improve the metabolic stability and therapeutic potency [152]. However, the initial chemical and physical properties of RNAs may be altered with these modifications, resulting in off-target toxicity [153]. Drug delivery platforms based on different materials including liposome, polymers, exosome, virus, and inorganic materials have been considered as another valid strategy [154]. However, it is difficult to choose the most appropriate delivery system because every kind of systems possesses its inherent shortcomings such as non-selective tissue distribution, immunogenicity, inefficient encapsulation, and off-target toxicity [154]. Therefore, novel functional vectors should be further expanded and developed to maximize the efficiency of RNA therapeutic delivery.

8. Outlook for radiopharmaceuticals

Differing from conventional drugs which directly target the driver genes, radiopharmaceuticals specifically target tumors via passenger genes and use ionizing radiation (IR) to kill tumor cells. Multiple driver gene mutations in tumors which limit the clinical application of targeted drugs, may have no influence on therapeutic effect of radiopharmaceuticals for tumors. However, current targets for radiopharmaceuticals are still limited. Exploring high-specificity targets in tumors is the priority in the development of radiopharmaceuticals in the future.

In addition, the development and optimization of targeting ligands with high specificity and safety profiles should be concerned emphatically. RNA therapeutics provide more options to expand the array of diseases that cannot be treated with small molecule and protein drugs [155]. Thus, coupling radionuclides to RNA drug backbones may contribute to develop novel radiopharmaceuticals targeting more diverse and specific targets in the diseases. These conjugates optimized by structure modification and delivery systems may be the potential candidates for the diagnosis and treatment of a wider variety of diseases.

Radionuclides may make the potential radiation damage to the non-target tissues, leading to adverse reactions. Thus, the selection of radionuclides is also very integral to minimize damage to the normal tissues. For example, the usage of α particles as radionuclides should be of particular concern. Compared with β particles, pharmaceuticals with α particles gives less dose and shorter penetrating distance to tissues, which can avoid the “escape” phenomenon existing in the treatment of β particles and reduce the damage of surrounding healthy tissues [156]. In addition to elevate the tumor specificity of radiopharmaceuticals, drug delivery systems such as nanoparticles and liposomes are another method to reduce the exposure to IR [157].

Furthermore, combining radiopharmaceuticals with AI to optimize the plans of radiopharmaceutical treatment by incorporating patient-specific factors, distribution curves and dose calculation of radiotracers, will be a future trend to improve the accuracy and effectiveness of radiopharmaceutical imaging and therapy [158]. At the same time, it can also accelerate the development of novel radiotracers and radiotherapeutic agents [159].

9. Conclusion

The ultimate goals of strategy transformation in the development of drugs from targeting driver genes to passenger genes, are to provide preferable treatment outcomes and less side effects for patients with tumors. Radiopharmaceutical targets may be non-functional proteins compared to conventional drug targets, but they all have high specificity. Due to these characteristics, it is possible for radio-targeted drugs to specifically locate tumor tissue and then kill the tumor cells by the α or β rays of the radionuclide with reduced toxicity to normal tissue. The binding affinity and PK properties of radiopharmaceuticals can be further enhanced by different structure modification. In conclusion, radiopharmaceuticals have great potential in promoting accurate diagnosis and precision therapy for patients with malignant tumors.

Conflicts of interests

The authors have no conflicts of interest to declare.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors' contribution

Conception and design: All authors; Collection and assembly of data: Yichi Huang and Ting Huang; Data analysis and interpretation: Yichi Huang and Ting Huang; Manuscript writing: All authors; Final approval of manuscript: All authors.

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