



Integrin $\alpha 6$ targeted cancer imaging and therapy

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Received 3 July 2022, Accepted 4 November 2022, Published online 13 January 2023

Abstract – Integrins represent ideal targets for molecular imaging and targeted therapy of cancer and their role in cancer has been reviewed extensively elsewhere. Except for $\alpha V\beta 3$ and $\alpha V\beta 5$, the remaining integrins were not systematically considered and tested as potential therapeutic targets. In recent years, the studies on integrin $\alpha 6$ as a cancer imaging and therapeutic target are increasing, due to their highly expressed in several cancers, and their expression has been associated with poor survival. Integrin $\alpha 6$ appears to be a particularly attractive target for cancer imaging and therapy, and therefore we have developed a wide array of integrin $\alpha 6$ -target molecular probes for molecular imaging and targeted therapy of different cancers. Despite the studies on integrin $\alpha 6$ as a cancer imaging and therapeutic target increasing in recent years, most of them were derived from preclinical mouse models, revealing that much more can be done in the future. The development of integrin $\alpha 6$ drugs may now be at an important point, with opportunities to learn from previous research, to explore new approaches. In this review, we will briefly introduce integrin $\alpha 6$ and highlighted the recent advances in integrin $\alpha 6$ targeted imaging and therapeutics in cancer.

Key words: Integrin $\alpha 6$, Imaging, Therapy, Cancer, Extracellular matrix.

Introduction

Integrins are a family of $\alpha\beta$ heterodimeric transmembrane receptors involved in cell-extracellular matrix (ECM) and cell-cell adhesion [1]. So far, 18 α and 8 β subunits are known in mammals to associate non-covalently forming 24 distinct integrin heterodimers [2]. Among them, integrins can be broadly divided into four subfamilies, depending on whether they bind to leukocyte-specific receptors ($\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, $\alpha D\beta 2$, $\alpha E\beta 7$, $\alpha 4\beta 7$, $\alpha 9\beta 1$, and $\alpha 4\beta 1$), arginine-glycine-aspartate (RGD) receptors ($\alpha 5\beta 1$, $\alpha V\beta 1$, $\alpha 8\beta 1$, $\alpha V\beta 3$, $\alpha IIb\beta 3$, $\alpha V\beta 5$, $\alpha V\beta 6$, and $\alpha V\beta 8$), collagen receptors ($\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$) or laminin receptors ($\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 7\beta 1$, and $\alpha 6\beta 4$) [3, 4]. Under physiological states, integrin-mediated cell adhesion plays an essential role in the formation and remodeling of tissues and organs in multicellular organisms [5]. In the pathologic state, integrin plays an important role in the inflammatory response, thrombosis, invasion, and metastasis of malignant tumors and angiogenesis [6]. As the majority of solid tumors originate from epithelial cells that are conferred with the ability to resist apoptosis, migrate, and disseminate through the epithelial-mesenchymal transition (EMT) [7], the integrins expressed by epithelial cells are retained in the tumor

[8]. Integrins $\alpha 6\beta 4$, $\alpha 6\beta 1$, $\alpha v\beta 5$, $\alpha 2\beta 1$, and $\alpha 3\beta 1$, regulate the adhesion of epithelial cells to the basement membrane, however, in tumor cells their levels and physiologic functions may be altered to involve and contribute to cell migration, proliferation, and survival [9]. In fact, the expression level of integrin subunits (including $\alpha 3$, $\alpha 5$, $\alpha 6$, αv , $\beta 1$, $\beta 3$, and $\beta 4$) in different types of cancer cells has been related to their invasive and metastatic potential [10].

As a transmembrane protein, integrins have large extracellular regions and are easily conjugation with various targeting drugs. Moreover, integrin expression is altered in cancer compared to the corresponding healthy tissue, and this altered expression was correlated with outcomes [11, 12], and therefore represents ideal targets for molecular imaging and targeted therapy of cancer [13]. The integrins, especially integrin $\alpha v\beta 3$ (binding to RGD sequence), have been extensively investigated as imaging and therapy targets for more than 25 years due to their key roles in angiogenesis, leukocytes function, and tumor development and their easy accessibility as cell surface receptors interacting with extracellular ligands [14–16]. So far, more than 100 clinical studies using more than 20 RGD-based imaging agents have been reported [3, 15, 17–19]. The role of integrins in cancer imaging and therapy has been reviewed

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extensively elsewhere about a decade ago [14]. Most of the 24 known integrins are implicated in cancer progression [20, 21], however, in addition to $\alpha V\beta 3$ and $\alpha V\beta 5$, the remainder of the integrins were not systematically considered and tested as potential therapeutic targets [22]. Although molecules that target $\alpha V\beta 3/\alpha V\beta 5$ and $\alpha 5\beta 1$ integrins generally have an acceptable safety profile, interest in using them to tackle cancer has waned, mainly owing to a lack of clinical benefits and no inhibitors has been registered as an anti-cancer drug [22]. Recently, the focus of interest is now moving away from $\alpha V\beta 3$ integrin and angiogenesis towards other integrin subtypes which are involved in a large variety of tumorigenic pathways. The laminin receptors $\alpha 6\beta 4$ and $\alpha 6\beta 1$ arguably have the largest potential next to RGD receptors, because they are expressed by several cancers, while their expression has been linked to poor survival [23], studies in integrin $\alpha 6$ as cancer imaging and therapeutic target are on the increase in recent years [3].

In this review, we briefly overviewed integrin $\alpha 6$ and highlighted the recent advances in integrin $\alpha 6$ targeted imaging and therapeutics in cancer. We apologize for may not be able to cite all published work on the topic due to the specific focus of the review and space limitations.

Overview of the integrin $\alpha 6$

Integrin $\alpha 6$ subunit (140 kDa) [24], also known as CD49f [25], is encoded by the *ITGA6* gene and heterodimerized with either integrin $\beta 1$ or $\beta 4$ to form integrin $\alpha 6\beta 1$ and $\alpha 6\beta 4$ [26, 27], which binding specifically to extracellular matrix laminin [28]. Integrin $\alpha 6$ was first identified in 1998 as a stem cell marker of keratinocyte stem cells [29] and further identified as the only biomarker commonly found in more than 30 different populations of stem cells, including pluripotent and multipotent stem cells, and cancer stem cells (CSCs) [30]. In particular, integrin $\alpha 6$ is expressed in a wide variety of CSCs in breast, prostate, colorectal, brain, and non-small cell lung cancers [22]. Integrin $\alpha 6$ is subject to alternative splicing to generate two different cytoplasmic variants call $\alpha 6A$ and $\alpha 6B$, having distinct cytoplasmic domains but no difference in laminin specificity [31, 32]. In addition to the cytoplasmic variants, human integrin $\alpha 6$ has two extracellular domain variants called $\alpha 6X1$ and $\alpha 6X1X2$ [33], which appear no difference in ligand specificity and affinity [34]. Moreover, a smaller structural variant of integrin $\alpha 6$ called $\alpha 6p$ (70 kDa) has been identified in human prostate, colon, and epithelial cancer cell lines [35]. The $\alpha 6p$ is believed to function as an inactive receptor for cell adhesion to the extracellular ligand due to the lack of the entire β -propeller domain associated with ligand binding, but it remains bound to its β integrin partner [35].

Integrin $\alpha 6\beta 1$ and $\alpha 6\beta 4$ are well-known “classical” laminin receptors, of which integrin $\alpha 6\beta 1$ binds laminin-1, -2, and -4, while integrin $\alpha 6\beta 4$ binds laminin-1 and -5 [32]. Integrin $\alpha 6\beta 4$ is a receptor for laminin and is expressed by a variety of epithelial tissues and cell types [36]. Integrin $\alpha 6\beta 4$ is exclusively expressed on the basal surface of basal cells, where it is found in specialized adhesion structures called hemidesmosomes [37]. Integrin $\alpha 6\beta 4$ has been reported to promote tumor invasion by activating the PI3K/AKT, Ras, and NF- κ B signaling pathway [38, 39]. Integrin $\alpha 6\beta 4$ may also promote tumor angiogenesis

by activating NF- κ B and ERK signaling pathways [40], and promote the origin of breast cancer by amplifying ErbB2 signaling [41]. Integrin $\alpha 6\beta 1$ is expressed at high levels in capillary endothelial cells and mediated VEGF-induced angiogenesis [42]. Integrin $\alpha 6\beta 1$ has also been shown to contribute to maintaining tumor stemness in glioblastoma stem cells and triple-negative breast cancer [43, 44]. Studies indicated that *ITGA6* expression is regulated by hypoxia-inducible factor-1 (HIF-1) [26]. According to the GEPIA database (<http://gepia.cancerpku.cn/>) [45], *ITGA6* was significantly overexpressed in 13 types of cancers, including colon adenocarcinoma, esophageal carcinoma, glioblastoma multiforme, head and neck squamous cell carcinoma, kidney chromophobe, acute myeloid leukemia, brain lower grade glioma, liver hepatocellular carcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, and thymoma [46]. It is currently known that integrin $\alpha 6$ is overexpressed in 14 cancer types including head and neck squamous cell carcinomas, lung cancer, breast cancer, liver cancer, colorectal cancer, prostate cancer, cervical cancer, gastric carcinoma, human epidermal neoplasia, pancreatic cancer, glioblastoma, esophageal squamous cell carcinoma, acute lymphoblastic leukemia, and nasopharyngeal carcinoma [46]. In addition, integrin $\alpha 6$ was present abundantly in lung-tropic exosomes and mediate exosomes homing to the lung [47]. The abnormally high expression of integrin $\alpha 6$ has been correlated with cancer progression and poor prognosis of multiple tumor types [48]. This resulted in integrin $\alpha 6$ being an attractive target for cancer imaging and therapy. To study the potential of integrin $\alpha 6$ for molecular imaging and therapy, we have developed a series of target probes for molecular imaging and targeted therapy of a diverse array of cancers. Below, we mainly summarized our study as well as others' studies about integrin $\alpha 6$ targeted cancer imaging and therapy.

Integrin $\alpha 6$ targeted radionuclide imaging

Radionuclide imaging, including positron emission tomography (PET) and single-photon emission computed tomography (SPECT), uses radiation emitted by radioisotopes for imaging and has the advantages of high sensitivity and specificity, precise quantification and virtually no tissue penetration limit [49, 50]. Radionuclide imaging can determine the concentration of specific molecules down to the pico-molar level in the body [50], thus providing sufficient sensitivity to visualize most interactions between physiological targets and receptor ligands [51]. Biomacromolecules like peptides and antibodies can serve as targeting agents in multiple drug delivery platforms [52], many of them have been labeled with diagnostic radionuclides and used successfully to imaging tumors [51].

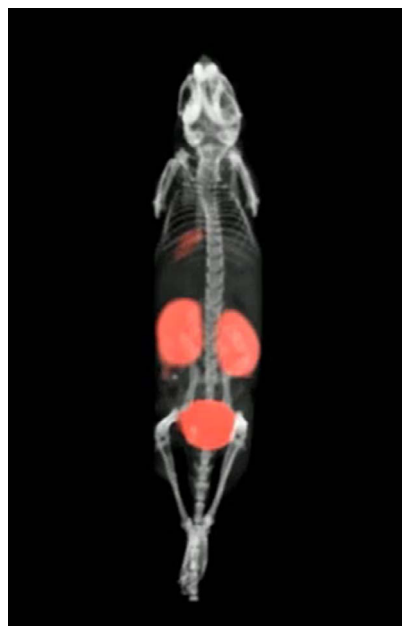
We first reported the ^{18}F -labeled derivative of the peptide sequence CRWYDENAC (abbreviated as RWY) as an integrin $\alpha 6$ targeted PET tracer ^{18}F -ALF-NOTA-RWY (abbreviated as ^{18}F -RWY) and preclinically characterized in mouse models of hepatocellular cancer (HCC) [53]. The RWY peptide was initially discovered in our laboratory with phage display on nasopharyngeal carcinoma (NPC) S18 cells and was confirmed to have high specificity and affinity for integrin $\alpha 6$ in NPC [54]. ^{18}F -RWY can produce higher sensitivities and tumor-to-liver

ratios than integrin $\alpha v\beta 3$ -targeted ^{18}F -3PRGD2 and clinical ^{18}F -FDG. Furthermore, ^{18}F -RWY is able to visualize small HCC lesions of approximately 0.2 cm in diameter that are difficult to be distinguished from surrounding hepatic vascular by enhanced magnetic resonance imaging (MRI) with hepatobiliary MR contrast agent gadoxetate disodium Gd-EOB-DTPA. **Video 1** demonstrates a visual representative dynamic PET video in an H11^{LNL-Myc} genetically engineered HCC mouse after injection with ^{18}F -RWY.

To further assess the performance of ^{18}F -RWY for PET imaging applications in tumors with high expression of integrin $\alpha 6$, we investigated the applicability of this tracer for colorectal cancer (CRC) imaging [55]. In PET imaging, ^{18}F -RWY produced high PET signals in subcutaneous, chemically induced, and genetically engineered CRC mice, which suggests its potential clinical translation in CRC. On the basis of its excellent tumor-targeting properties and safety in preclinical models, we further labeled the RWY peptide with radionuclide $^{99\text{m}}\text{Tc}$ to prepare a radiotracer $^{99\text{m}}\text{Tc}$ -RWY, which was able to clearly show tumor lesions in two breast cancer patients (Fig. 1) [56]. It was the first-in-human study of an integrin $\alpha 6$ -targeted radiotracer for SPECT imaging of breast cancer and this work was performed in collaboration with the laboratory of Prof. Wang.

Although RWY-based radionuclide imaging exhibited favorable imaging capability, the binding affinity between the current integrin $\alpha 6$ -targeted RWY peptide and integrin $\alpha 6$ (micromole affinity) is relatively low compared to the well-developed RGD peptides and integrin $\alpha v\beta 3$ (nanomole affinities). To increase the affinity of RWY to integrin $\alpha 6$, we used the alanine scanning mutagenesis to modify the RWY peptide by alanine substitution of E and obtained a peptide CRWYDANAC (abbreviated as S5) with higher affinity (approximately 1.5-fold enhanced tumor binding ability) [57]. The optimized integrin $\alpha 6$ -targeted peptide S5 was further radiolabeled with ^{18}F to form the PET radiotracer ^{18}F -S5. Considering the relatively low spatial resolution of PET and SPECT, MRI with high-resolution anatomical imaging was combined with PET, which can provide extremely sensitive and high-resolution images [58]. PET/MRI was conducted to test the imaging efficacy of ^{18}F -S5 for central nervous system leukemia (CNS-L) and pancreatic cancer [57, 59]. Our imaging experiments showed that ^{18}F -S5 enabled the detection of CNS-L, which generated nearly a 5-times tumor-to-background ratio compared to the clinically available PET radiotracer ^{18}F -FDG [59]. Additionally, ^{18}F -S5/PET imaging also enabled the detection of pancreatic ductal adenocarcinoma (PDAC) at an early stage with high sensitivity, a favorable tumor-to-muscle ratio, and low liver uptake in mice (Videos 2 and 3) [57]. PDAC is a highly lethal disease that has the worst prognosis of any major malignancy, and there are still no effective therapeutics or early detection methods [60, 61]. Imaging of PDAC not only plays a critical role in the diagnosis and therapeutic but also raises the prospect of targeted radiotherapeutics [3], however, standard tracer ^{18}F -FDG is currently not useful in small and early-stage pancreatic cancer detection [62]. Therefore, ^{18}F -S5 holds great promise for application to clinical pancreatic cancer imaging.

Another optimized integrin $\alpha 6$ -targeted peptide dimerized cKiE peptide (abbreviated as cKiE2) was developed in



Video 1. Representative dynamic PET/CT video in an H11^{LNL-Myc} genetically engineered HCC mouse after injection with ^{18}F -RWY. In this mouse, representative dynamic PET/MR video showed high tumor uptake of ^{18}F -RWY. <https://vcm.edpsciences.org/10.1051/vcm/2022007#v1>.

Prof. Wang's laboratory [63]. They replaced Cys–Cys cyclized RWY peptide (sequence: cCRWYDENAC) with lactam-bridged cyclic cKiE peptide (sequence: cKRWYDENAisoE), leading to a new cyclic peptide c(KRWYDENAisoE) (abbreviated as cKiE). The cKiE2 was synthesized by coupling two cKiE monomers through a glutamic acid residue and two triglycine (G3) linkers and further labeled with radionuclide $^{99\text{m}}\text{Tc}$ to prepare a radiotracer $^{99\text{m}}\text{Tc}$ -cKiE2. In vitro experiments have proved that the integrin $\alpha 6$ -binding affinity of cKiE2 (IC₅₀: 252.8 nM) was about four times higher than that of RWY (IC₅₀: 1081.8 nM). In vivo experiments showed that the tumor uptake of $^{99\text{m}}\text{Tc}$ -cKiE2 related closely with the integrin $\alpha 6$ expression level. Importantly, in SPECT/CT imaging in orthotopic HCC xenograft mice experiments demonstrated that $^{99\text{m}}\text{Tc}$ -cKiE2 is superior to $^{99\text{m}}\text{Tc}$ -3PRGD2 in terms of both tumor uptake and tumor-to-liver ratio.

Integrin $\alpha 6$ targeted MR imaging

MR imaging is a widely used non-invasive clinical imaging modality that offers high spatial and temporal resolutions, unlimited tissue penetration, and tomographic capabilities [64]. Due to its excellent soft tissue contrast [65], MR imaging is widely accepted as a premier imaging modality for brain tumors [66], HCC [67], NPC [68], breast cancer [69], gynecologic cancer [70–72], rectal cancer and prostate cancer [73, 74]. Compared with PET and SPECT, MR imaging offers better anatomical resolution without the use of ionizing radiation or radiotracers and therefore appears to be the most appropriate for molecular imaging [75], however, its success in molecular imaging is limited by its intrinsic insensitivity [76]. This is

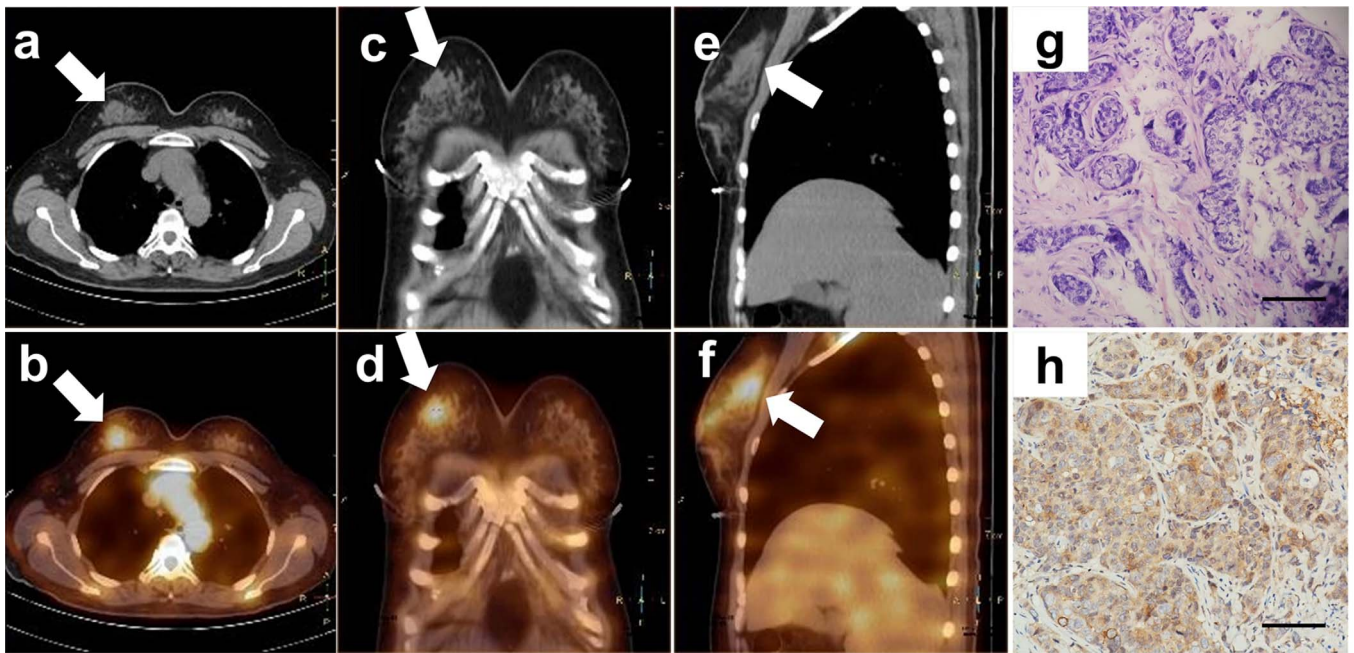
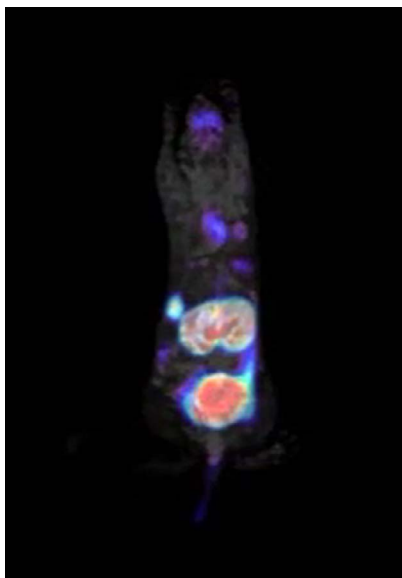
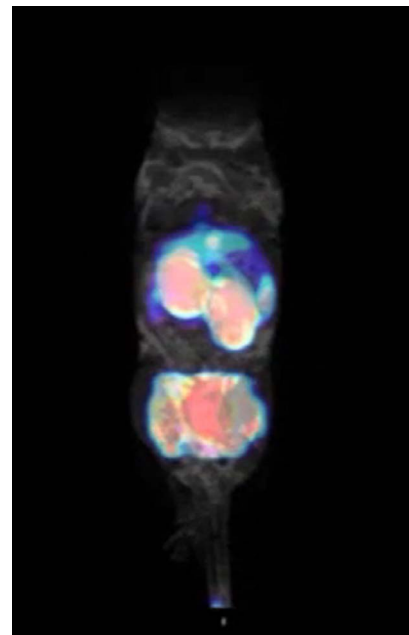


Figure 1. ^{99m}Tc -RWY SPECT/CT imaging of a 52-year-old woman with clinical stage II breast cancer in the left breast and the expression level of integrin $\alpha 6$ in breast cancer. (a, b) Transverse, (c, d) coronal, and (e, f) sagittal plane CT and SPECT/CT. SPECT/CT images of the chest obtained 0.5 h p.i. displayed intense ^{99m}Tc -RWY accumulation in the cancer tissue in the left breast (white arrow). (g) Hematoxylin–eosin (HE) staining confirmed the presence of tumor cells in the section indicated by the white arrow. Scale bar, 100 μm . (h) Immunohistochemical staining indicated high integrin $\alpha 6$ expression in the area with high radioactivity accumulation. The figure and legend are modified and reproduced with permission from [56] under the terms of the Creative Commons CC BY license.



Video 2. Representative dynamic PET/MR video in a genetically engineered KPC mouse with spontaneously developed PDAC after injection with ^{18}F -S5. In this mouse, representative dynamic PET/MR video showed high tumor uptake of ^{18}F -S5. <https://vcmedpsciences.org/10.1051/vcm/2022007#V2>.



Video 3. Representative dynamic PET/MR video in a genetically engineered KC mouse with spontaneously developed PanIN (precancerous lesion of PDAC) after injection with ^{18}F -S5. In this mouse, representative dynamic PET/MR video showed a high accumulation of ^{18}F -S5 in the possible lesion site. <https://vcmedpsciences.org/10.1051/vcm/2022007#V3>.

due to causing a detectable signal change requiring micromolar concentrations (0.01–0.1 mM) of molecular agents, while many molecules are present at much lower concentrations (in the nano- or picomolar range) [77]. To overcome the intrinsic insensitivity of MR imaging, it is necessary to design and development of targeted probes, to provide or enhance image contrast by active targeting [78]. Gadolinium (III) is particularly well-suited for use as an MRI contrast agent [79]. For Gd-based agents, high sensitivities can be attained by coupling with Gd (III) chelates and targeting ligands such as small molecules, peptides, proteins, antibodies, and cells [80]. Compared to antibodies, peptide-based systems have several major advantages, including their small size, sufficient capillary permeability, low immunogenicity, short biological half-time, rapid clearance from non-target tissues, ease of manufacture, and being readily labeled with specific nuclides [80–82]. Gd(III) chelates can be directly conjugated to targeting agents but with a lower detection signal and larger steric hindrance [83]. Gd(III) chelates are often loaded on various carriers (including polymers, dendrimers, liposomes, and micelles) to increase the concentration around the targeted. As a structurally simple and nontoxic water-soluble polymer [84], polyethylene glycol (PEG) is commonly used as a linker to space the contrast agents from the targeting agents, thus enhancing the effective binding of the targeting groups to the target sites [83]. To our knowledge, besides our laboratory, there are no reports on MR imaging probes targeting integrin $\alpha 6$ so far.

Based on the integrin $\alpha 6$ -targeted RWY peptide, we developed an MR contrast agent RWY-dL-(Gd-DOTA)₄ for the MR imaging of HCC [67]. The chemical structure of RWY-dL-(Gd-DOTA)₄ is shown in Figure 2A. RWY-dL-(Gd-DOTA)₄ contains four different domains, including Gd-DOTA monoamide, RWY peptide domain, PEG4 spacer, and lysine dendrimer. Four Gd-DOTA monoamide chelates for MR signal enhancement and one integrin $\alpha 6$ -targeted peptide for tumor targeting. Lysine dendrimer was used to increase the molar ratio of Gd-DOTA monoamide to the peptide for effective targeted contrast enhancement and PEG4 spacer was used to avoid steric hindrance of Gd-DOTA monoamide for tumor targeting binding. In the MR imaging, RWY-dL-(Gd-DOTA)₄ generated significant signal enhancement in HCC-LM3 subcutaneous liver tumors, quantitative signal analysis revealed that RWY-dL-(Gd-DOTA)₄ resulted in approximately threefold more signal enhancement than control agent (Ctrl-dL-(Gd-DOTA)₄) within the first 5 min post-injection and about fourfold more signal enhancement at 50 min post-injection. For DEN-induced HCC mice, RWY-dL-(Gd-DOTA)₄ enabled the detection of some HCC lesions that are hardly distinguished by Gd-EOB-DTPA. In addition, RWY-dL-(Gd-DOTA)₄ readily penetrated the tumor tissue through the vascular endothelium and excreted in urine via kidneys.

Even though RWY-dL-(Gd-DOTA)₄ had demonstrated the efficacy for MR imaging of HCC in subcutaneous and chemical-induced HCC mouse models, its safety and contrast enhancement still need to be improved. The S5 peptide with higher affinity provides a critical raw material for the development of the second-generation integrin $\alpha 6$ -targeted MR probe. The optimized integrin $\alpha 6$ -targeted peptide S5 was further conjugated with Gd(III) chelates to develop integrin $\alpha 6$ -targeted

MR contrast agent DOTA(Gd)-ANADYWR (abbreviated as Gd-S5) [48]. The chemical structure of Gd-S5 is shown in Figure 2B. We optimized the synthetic procedure of Gd-S5 via direct condensation reaction between carboxyl groups in DOTA and amine groups in the reverse S5, thereby rendering the reaction step simpler and the product yields higher. It should be noted that the peptide used for ¹⁸F-S5 was a cyclic peptide, and for Gd-S5 peptide was a straight peptide based on the convenience and requirements of the synthesis process. The micro-scale thermophoresis (MST) experiments have confirmed that the binding affinity of straight S5 was as strong as that of cyclic S5. In MR imaging, Gd-S5 can generate more significant signal enhancement in the HCC lesions than nonspecific clinical agent gadoteridol and detect small HCC lesions (approximately 1 mm) which is hardly detected by the clinically available Gd-EOB-DTPA.

In view of the promising MR imaging of HCC in mice, we further studied the imaging efficacy of Gd-S5 in CNS-L with high expression of integrin $\alpha 6$. CNS-L refers to the central nervous system involvement of acute lymphoblastic leukemia (ALL), which is difficult to accurately diagnose and leads to delayed or excessive treatment [59]. Unlike solid tumors, CNS-L barely forms solid lesions and results in a great challenge for conventional imaging methods [85, 86]. Moreover, ¹⁸F-FDG has poor contrast in intracranial lesions due to the high uptake of glucose in normal brain tissue [87]. MR imaging in NALM6-Luciferase tumor-bearing mice showed that Gd-S5 generated superior signal enhancement at the site of meninges located between the skull bone and brain parenchyma. Relatively, Gd-DTPA did not generate the distinguishable MR signal in the same head regions. This study suggests the potential application of integrin $\alpha 6$ -targeted MR imaging probe Gd-S5 for the accurate detection of CNS-L. To our knowledge, this is the first application of the MR imaging probe to CNS-L imaging.

Integrin $\alpha 6$ targeted therapeutics

The integrins exert their functions through activation, ligand binding, focal adhesion formation, and cytoskeletal contacts. Blocking either one of these processes inhibits integrin-regulated functions [88]. In addition, integrin contains a larger N-terminal extracellular domain, which is more amenable to binding antagonists. Therefore, integrins emerge as ideal pharmacological targets [89, 90]. Several integrins, including $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 5\beta 1$, have been studied for more than 25 years as potential therapeutic targets for various cancers [16]. Integrin-targeted therapeutics have been shown to give benefits in the delivery of chemotherapeutics, oncolytic viruses, proapoptotic peptides, and radionucleotides to both tumor cells and the supporting vasculature [8]. Various integrin antagonists, such as low molecular weight inhibitors, peptidomimetics, or monoclonal antibodies, are in various stages of development for anti-cancer therapy [91]. Integrin $\alpha 6\beta 1$ and $\alpha 6\beta 4$ are subtypes of integrins that have the potential to be an attractive therapeutic target for cancer therapy, due to their highly expressed in several cancers and their expression has been associated with poor survival [3, 54]. To our knowledge, only a few integrin

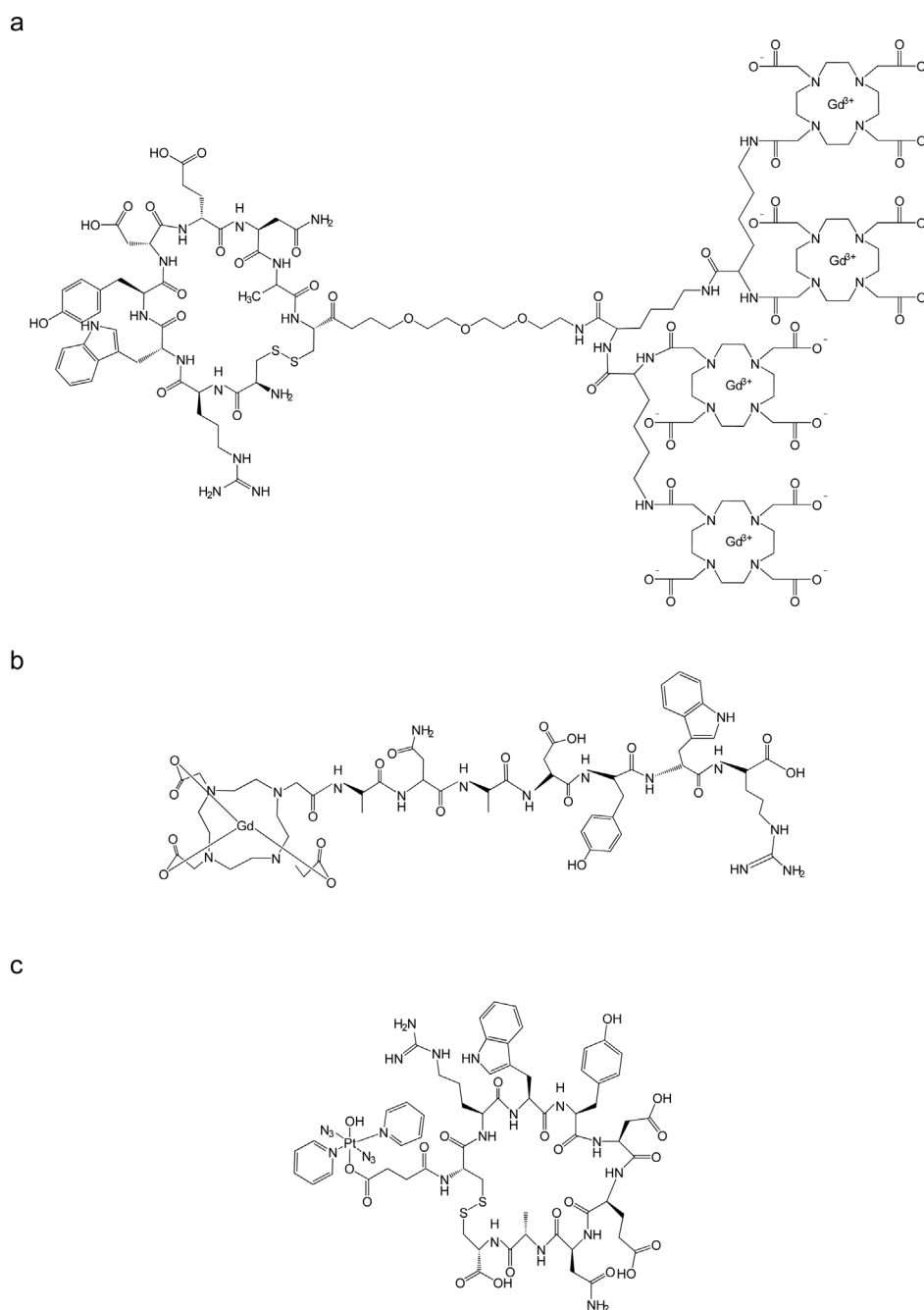


Figure 2. Chemical structures of RWY-dL-(Gd-DOTA)₄, Gd-S5, and Pt-cP. (a) Chemical structures of RWY-dL-(Gd-DOTA)₄, with a molecular weight of 3877.55. (b) Chemical structures of Gd-S5, with a molecular weight of 1480.68. (c) Chemical structures of Pt-cP, with a molecular weight of 1710.64.

$\alpha 6$ -targeted therapeutic approaches have been developed for cancer therapy to date.

Landowski et al. reported the first use of function-blocking antibody called J8H which targeted intracellular integrin $\alpha 6$ for the inhibition of osteolytic progression of metastatic prostate in mice [92]. J8H is a mouse mAb created by Hogervorst et al. [93]. J8H can recognize an extracellular epitope of $\alpha 6$ resulting in block integrin $\alpha 6$ converting to $\alpha 6_p$, but not integrin $\alpha 6$ dependent adhesion [28]. In a xenograft human prostate cancer mouse model, J8H not only retarded pre-existing cancer lesions progression in bone, but also improved survival. Interest-

ingly, the proportion of bone lesions displaying a sclerotic rim of new bone formation increased in mice that received J8H, which demonstrated that the J8H treatment can reduce osteolytic tumor activity and induce a sclerotic reaction in bone lesions [92].

We have reported an NPC-targeted nanomedicine RWY-NP/Pt(IV), which was developed by encapsulating a cisplatin prodrug Pt(IV) with RWY-grafted polymeric nanoparticles [54]. In vitro controlled release assay showed that the RWY-NP/Pt(IV) display a 100-fold increase in cytotoxicity towards integrin $\alpha 6$ -overexpressing NPC compared to free cisplatin. Growth inhibition was about 78% for RWY-NP/Pt(IV)

treatment, but only 44% for free cisplatin. Importantly, RWY-NP/Pt(IV) not only enhances the efficacy of cisplatin treatment but also reduces potential side effects.

In association with Prof. Sadler, we have further developed a photoactive platinum(IV) complex trans- [Pt(N₃)₂(py)₂(OH)(succinate)] (Pt-cP), a conjugate of a photoactive trans-diazido platinum(IV) complex with RWY [94]. The chemical structure of Pt-cP is shown in Figure 2C. Pt-cP exhibited good dark stability and photocytotoxicity towards cancer cells, including ovarian A2780, lung A549, and prostate PC3 human cancer cells upon irradiation with blue light. Conjugation with cancer-cell-targeting peptide RWY enhances the photo-cytotoxicity and photo-accumulation of photoactive platinum(IV) complexes and their photo-selectivity towards cancer cells without reducing their dark stability.

Additional agents targeting integrin $\alpha 6$ have also shown some anti-cancer effects in some studies results to be developed as anti-cancer agents. It has been shown that siRNA oligonucleotides targeting either subunit of the integrin $\alpha 6\beta 4$ reduced the cell surface expression of this integrin and led to the reduced invasion of breast cancer cells [95]. In ALL xenografts mouse model, PI3K δ inhibitor (which decreased integrin $\alpha 6$ expression on ALL cells) or specific $\alpha 6$ integrin-neutralizing antibodies can lead to a significant reduction in ALL transit along bridging vessels, blast counts in the cerebrospinal fluid and CNS disease symptoms despite a slight reduction in bone marrow disease burden [96]. HYD-1 (peptide sequence: KIKMVISWKG) peptides that blocked integrin $\alpha 6\beta 4$ markedly decreased exosome uptake, as well as lung metastasis [47].

Summary and prospects

This review summarizes recent research development of integrin $\alpha 6$ targeted imaging and therapeutics in cancer. The studies reviewed here have provided support for integrin $\alpha 6$ as an attractive target for both cancer imaging and therapy. Overall, integrin $\alpha 6$ target cancer imaging and therapy have some potential strengths, which can be summarized as follows. First, as is highly expressed in 14 tumors, integrin $\alpha 6$ has a potential application in the imaging and therapy of these tumors. Second, integrin $\alpha 6$ target imaging exhibits great potential for early detection of HCC and PDAC, which are difficult early imaging clinically. Third, integrin $\alpha 6$ target imaging allows for imaging of CNS-L, thus offering a unique non-invasive method to evaluate the non-solid tumor. Four, integrin $\alpha 6$ target therapy contributes to CSC killing, as integrin $\alpha 6$ is a CSC maker in several types of cancers. Five, integrin $\alpha 6$ can promote cancer distant metastasis and is found expressed in several metastases, and therefore it can serve as an imaging and therapy target for these metastases.

Similarly, current integrin $\alpha 6$ target cancer imaging and therapy also face some challenges. First, integrin $\alpha 6\beta 4$ is an essential component of the basement membranes and its knock-out is embryonically lethal in mice. This indicates that integrin $\alpha 6$ target therapy may have notable adverse effects. Second, when compared to a wealth of study on molecular imaging, there is a relative paucity of work on integrin $\alpha 6$ -targeted therapy, further studies are warranted to reveal the effects and adverse effects. Third, there has been no report of

integrin $\alpha 6$ -humanized antibodies, although a few generations of specific antibodies have been reported. Four, despite the studies on integrin $\alpha 6$ as a cancer imaging and therapeutic target, are increasing in recent years, most of them were derived from preclinical mouse models. Future research should address these challenges. Increasing the affinity of integrin $\alpha 6$ binding peptides seems to be a feasible method. In fact, we have obtained a new integrin $\alpha 6$ -targeting peptide whose affinity is more than 300 times higher than RWY in our recent research, which provides a critical raw material for integrin $\alpha 6$ target cancer imaging and therapy. In sum, we optimistically envisage that integrin $\alpha 6$ will become a rising star in tumor imaging and therapy in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements. This work was supported by the Fundamental Research Funds for the Central Universities (19ykpy174).

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Cite this article as: Zhang W, Ye J, Li X, Li Y & Feng G, et al. 2023. Integrin $\alpha 6$ targeted cancer imaging and therapy. *Visualized Cancer Medicine*. 2023; 4, 4.