HHS Public Access

Author manuscript

Eur J Nucl Med Mol Imaging. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Eur J Nucl Med Mol Imaging. 2018 January ; 45(1): 132–150. doi:10.1007/s00259-017-3839-5.

PET and SPECT Imaging of Melanoma: State of the Art

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Abstract

Melanoma is the most aggressive form of skin cancer and incidences continue to rise worldwide. ^{18}F-FDG PET imaging has transformed diagnostic nuclear medicine and become an essential component in the management of melanoma, but still has its drawbacks. With the rapid growth in the field of nuclear medicine and molecular imaging, a variety of promising probes that enable early diagnosis and detection of melanoma have been developed. The substantial preclinical success of melanin- and peptide-based probes has recently resulted in translation of several radiotracers to clinical settings for noninvasive imaging and/or treatment of melanoma in human patients. In this review, we have focused on the latest developments in radiolabelled molecular imaging probes for melanoma in preclinical and clinical settings and discussed the challenges and opportunities for future development.

Keywords

Melanoma; molecular imaging; positron emission tomography (PET); single photon emission computer tomography (SPECT); cancer; theranostics; immunotherapy

1. Introduction

Although melanoma accounts for a small percentage of all skin cancer cases, it is estimated that melanoma accounted for 76,380 new cases and 10,130 deaths in the United States in 2016 [1]. Unsatisfactory 5-year survival rates for patients with distant metastases (less than

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Conflict of interest

The authors have declared no competing interest.

10%) render early detection and accurate assessment of metastatic melanoma crucial for improved outcome and disease-free survival [2]. With the gradual increase in understanding of the molecular pathogenesis of melanoma, the treatment landscape for advanced melanoma has changed markedly during the past 10 years. Novel agents such as molecularly-targeted therapies specifically inhibiting carcinogenic pathways and immunotherapies augmenting the antitumor immunity have emerged as new standards of care for patients with melanoma [3].

As elegantly reviewed by Wong et al, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) could play a pivotal role in the interpretation of therapeutic response following BRAF inhibition and immunotherapy in patients with melanoma, facilitating early assessment of drug resistance and detection of life-threatening autoimmune side effects [4]. ^{18}F-FDG PET was also recommended for staging and detecting recurrent melanoma [5, 6]. However, since ^{18}F-FDG PET monitors cellular metabolism and immunotherapy elicits a natural inflammatory response, traditional PET imaging using ^{18}F-FDG has proven inadequate in examining responses to immunotherapy in certain cancer types [7]. Moreover, owing to increased glucose metabolism in inflammatory tissues, ^{18}F-FDG displays relatively poor selectivity for distinguishing tumor from inflammatory tissue. Importantly, in one study, ^{18}F-FDG PET failed to detect melanoma in patients showing a positive sentinel lymph node biopsy for cancer, and no recurrent melanoma occurred where the ^{18}F-FDG PET scans were positive or suspicious [8]. ^{18}F-FDG PET scans also failed to detect pulmonary and brain metastases, indicating its limited value when staging patients with more advanced melanoma [9]. Currently, gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure brain metastases or to assess treatment response [10, 11].

In the era of precision medicine and molecular imaging [12], many radiolabeled probes for imaging different molecular targets or biochemical processes have been designed and evaluated for melanoma imaging. Although clinically-available ^{111}In-DOTA-lanreotide and ^{111}In-DOTA-Tyr3-octreotide may image melanoma, the detection rates may not meet the clinical requirement and their mechanisms remain unknown [13]. In the past, we and others organized reviews regarding anatomical and molecular imaging of skin cancer [14, 15]; since then, substantial amounts of molecular imaging probes for melanoma have been developed. Although nanoparticle-based multimodality imaging systems have been intensively applied to melanoma detection and therapy, it is beyond the scope of our current paper. Therefore, with an emphasis on the small molecule- and peptide- based PET imaging probes, we aim to systematically review the recent advances in the field and extend an outlook on future development. Given the multidisciplinary nature of this field, our present review is by no means exhaustive, but we intend to summarize the most recent advances for scientists to further refine these probes and for clinicians to push the clinical transition of those which are promsing, facilitating better management of patients with melanoma in the foreseeable future.

2. Small Molecule-based Probes Targeting Melanin

Melanin, an amorphous, irregular, functional biopolymer and a ubiquitous natural pigment in many organs including human skin, is a source of novel research opportunities in the

fields of biomedicine, nanotechnology, and materials science [16]. In malignant melanoma, melanin formation is highly increased because tyrosinase activity is significantly elevated [17, 18], making it a very attractive theranostic target. Many drugs, including methylene blue (MTB), chloroquine, acridine orange, benzamide (BZA) and its analogs, and other aromatic compounds, have been found to bind to melanin both in vivo and in vitro [19–24]. Melanin-targeting prodrugs also have been developed and used for in vivo melanoma imaging [25, 26].

2.1. Radiolabeled benzamide and benzamide derivatives

Various versions of radiolabeled benzamide and its analogs have been developed for targeting melanin in clinical practice [27–33]. Specifically, as evidenced by a recent prospective and multicenter phase III clinical study, ^{123}I-BZA$_2$ (Fig. 1A) [30, 34], a benzamide derivative able to bind to melanin pigment in melanoma cells, had statistically higher specificity than ^{18}F-FDG for diagnosis of melanoma metastases in a lesion-based analysis [35]. Katsifis and co-authors substituted the benzamide moiety with a nicotinamide moiety and labeled the compound with no-carrier-added ^{123}I-iodine via iododestannylation reactions. Biodistribution showed that 66% of the injected ^{123}I-1 (^{123}I-MEL008, Fig. 1B) was excreted from the urinary system at 1 h postinjection, also displaying the highest tumor uptake at that time point mainly because of its enhanced hydrophilicity and rapid clearance via renal excretion [36]. Chezal et al. then examined biological properties of aromatic or heteroaromatic BZA analogs in B16 melanoma-bearing mice and found that melanin-specific binding compound ICF01012, when labeled with ^{131}I or ^{125}I, could be applied in radionuclide diagnosis and therapy of disseminated melanoma [20, 37–39]. Furthermore, the authors developed a new multimodal approach by designing iodinated and fluorinated analogs of ICF01012, of which ^{18}F-**8** emerged as the most promising compound and demonstrated high tumor uptake, high contrast, and rapid clearance [40]. These above-mentioned efforts also led to the development of ^{123}I-MEL037 and ^{123}I-53 (Fig. 1C, D); while the former demonstrated high and prolonged tumor uptake, the latter was derived from structural modification of ^{123}I-MEL037 and performed even better than ^{123}I-ICF01012, as the tumor-to-background uptake ratios of ^{123}I-53 and ^{123}I-ICF01012 were 31.9 and 18.5, respectively [41, 42]. While the above probes accumulated at high levels in the eyes and thyroid, radioiodinated iochlonicotinamide and radioiodinated phenylacetamides (^{131}I-IHPA and ^{131}I-IHPP) had lower uptake in most normal organs and highly specific uptake in the melanotic tumor (Fig. 1E, F) [43, 44].

Since ^{18}F-FBZA exhibited high tumor uptake and emerged as a promising candidate for clinical study (Fig. 2A) [45], Wu et al. modified the phenol moiety of benzamide with a short chain PEG and then labeled with ^{18}F to obtain ^{18}F-FPBZA (Fig. 2B). In vivo, it showed excellent tumor-to-background contrast, and this radiotracer was able to distinguish tumor from inflammatory tissue as turpentine-induced inflammation revealed low radioactivity accumulation [46]. Garg and co-authors developed 4-^{11}C-MBZA and reported that this probe displayed advantages over its ^{18}F analogs while delivering a lower radiation dose to the subject (Fig. 2C). In vitro binding studies showed specific binding of 4-^{11}C-MBZA to B16/F1 cells; however, it also accumulated to a high level in the kidneys [47]. Chang et al. developed ^{18}F–NOTA–BZA, and the melanin-specific binding ability, low bone

uptake, sustained tumor retention, high hydrophilicity (log P =−1.96), fast normal tissue clearance and low radiation burden indicated that ^{18}F–NOTA–BZA is a promising PET probe for melanin-specific imaging of melanin-positive melanoma [48]. Based on the inspiring and promising preclinical results of ^{18}F-MEL050 (Fig. 2D) [49, 50], Liu et al. successfully synthesized a series of ^{18}F-MEL050 analogs for melanoma imaging (Fig. 2E, F), of which ^{18}F-2 showed superior tumor-targeting efficacy and imaging properties [51]. Interestingly, recent research proposed that N-(2-diethylaminoethyl) rather than the aromatic ring structure in benzamide analogs is a plausible pharmacophore responsible for melanin targeting, as the synthesized probe ^{18}F-FPDA exhibited relatively high B16/F10 tumor-targeting efficacy and favorable in vivo pharmacokinetics (Fig. 2G) [52]. Besides the most commonly used PET radionuclides, ^{68}Ga ($t_{1/2}$ = 68 min) is an outstanding radioisotope for molecular imaging due to its significant 89% positron yield and its availability without the establishment of expensive cyclotron and synthesis models [53]. Trencsényi et al. conjugated PCA with two different chelators, HBED-CC and NODAGA, then labeled the compounds using Ga-68 and investigated the diagnostic value of ^{68}Ga-HBED-CC-PCA and ^{68}Ga-NODAGA-PCA in vitro and in vivo. The authors found that uptake of ^{68}Ga-NODAGA-PCA by melanin-containing melanoma was significantly higher than the accumulation of the ^{68}Ga-HBED-CC-conjugated PCA [54, 55].

2.2. Imaging of melanoma metastases

Considering that the presence of distant metastases, especially brain metastases, confers worse prognosis for patients with melanoma, their early detection is critical [56]. In a study comparing diagnostic values of ^{18}F-FDG PET/CT and MRI in melanoma patients with palpable lymph node metastases, Aukema et al. found that ^{18}F-FDG PET/CT changed the intended regional node dissection in 26 patients (37%) and resulted in a superior diagnostic accuracy of 93%, but missed 5 patients with brain metastases which were detected by MRI [57]. Other study also demonstrated that ^{18}F-FDG PET failed to detect metastatic lesions of less than 1 cm located in the lung, liver or brain [58]. Currently only contrast-enhanced MRI and ^{18}F-FET PET seem to be reliable methods to detect brain metastases from melanoma but still lack specificity [10, 59]. Moreover, in patients with surgically treatable IIIC and IV metastatic melanoma following targeted/immunotherapy, PET/CT can detect unexpected metastases that are missed with conventional imaging, and can be considered as part of preoperative workup [4, 60, 61]. Thus it is of great importance to develop novel radiotracers to identify occult lesions or distant small metastases from melanoma with high specificity and a low false positive rate. Notably, the ability of an imaging agent to cross the blood–brain barrier (BBB) is considered critical to effectively target metastatic lesions in the brain. Of the reported probes, 4-^{11}C-MBZA was able to cross the BBB and the corresponding uptake was moderate in the normal brain [47]. As observed from biodistribution and PET studies, 4-^{11}C-MBZA uptake in normal tissues was noticeably lower than that for several other ^{18}F-benzamides like ^{18}F-FPBZA [46] and ^{18}F-DAFBA [62]. In addition, newly developed radiotracers, such as ^{18}F-FBZA, ^{18}F-5-FPN,^{18}F-MEL050, ^{18}F-FITM and ^{18}F-ICF01006 (Fig. 2H), may have better performance in the delineation of small lymph node and lung metastases from melanoma than that of ^{18}F-FDG PET/CT [45, 46, 63–66]. ^{18}F-5-FPN, a probe identical to ^{18}F-2, successfully detected pigmented B16/F10 tumors as early as 1 min after injection of the tracer. The uptake increased over time and the tracer was rapidly

excreted via the kidneys. This and later studies from the same group further validated the potential of ^{18}F-5-FPN PET for the early detection of metastatic melanoma lesions (Fig. 2I) [63, 67].

^{18}F-MEL050 had excellent retention in melanin-containing tumors and rapid background clearance [49]; however it is notable that the route of administration of ^{18}F-MEL050 matters when imaging regional lymph node metastasis from melanoma. While ^{18}F-MEL050 PET correctly identified 100% of the lymph node metastases after subcutaneous administration of the tracer, only 60% of those metastases were found after systemic administration of the tracer in the lateral tail vein [50].

3. Peptide-based imaging probes

Peptides are emerging as potent and selective ligands that can be designed to bind with high affinity and specificity to cell surface receptors on a wide range of tumors [68]. Three major types of peptides, namely α-Melanocyte-stimulating hormone (α-MSH), tumor angiogenesis associated integrins, and peptides targeting both MC1R and integrin, are under intensive development for molecular imaging of melanoma.

3.1. α-Melanocyte-stimulating hormone (α-MSH)-based probes

α-MSH, a ligand specific for melanocortin receptor subtype 1 (MC1R), has been reported to be overexpressed in both melanotic and amelanotic human melanoma cases and has been widely used as a vehicle for melanoma-targeted imaging and therapy [69–73]. As native α-MSH (a linear 13 amino acid peptide, Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2) has a biological half-life of less than 3 minutes in vivo [74], tremendous work has been done in the past 20 years and several modified analogs and synthesis strategies have been developed in an effort to add biological stability and improve targeting. For example, substitution of Met^4 with Nle^4 and Phe^7 with D-Phe^7 yields NDP-α-MSH [75]. Since His^6-Phe^7-Arg^8-Trp^9 had been identified as the “essential core” of native α-MSH peptide [76], both linear and transition metal rhenium cyclized α-MSH such as NAPamide [77], DOTA-NAPamide [78], ReCCMSH [77], MTII [79], analogs of MTII [80], DOTA-CycMSH and DOTA-GlyGlu-CycMSH [81], DOTA-Nle-$CycMSH_{hex}$ [82], were constructed. Recently new highly-specific and selective ligands against MC1R for melanomas were also developed and have been explored as platforms for molecular imaging of melanoma [83, 84].

Using the previously synthesized ReCCMSH which has nanomolar affinity for MC1R, McQuade et al. labeled the peptide with PET isotopes ^{64}Cu and ^{86}Y and assessed their diagnostic efficacy in melanoma tumors. Biodistribution studies revealed that the tumor concentration of ^{86}Y-DOTA-ReCCMSH and ^{64}Cu-DOTA-ReCCMSH was two times higher compared to that of the metabolic agent ^{18}F-FDG [85]. Additionally, the use of the chelator CBTE2A provided improved stability, as uptake of ^{64}Cu-CBTE2A-ReCCMSH was significantly lower than that for ^{64}Cu-DOTA-ReCCMSH in normal organs such as liver, lung, heart, and spleen [86]. Wei et al. then successfully labeled DOTA-ReCCMSH (Arg^{11}) with ^{68}Ga and reported that the tumor uptake of ^{68}Ga-DOTA-ReCCMSH reached a maximum after 30 min and remained stable 2 h postinjection. A pretargeting strategy

employing D-lysine administration was able to significantly reduce kidney retention of the tracer [87]. ^{18}F-FB-RMSH-1 and ^{18}F-FP-RMSH-1, another two metallopeptide Ac-D-Lys-ReCCMSH(Arg^{11}) probes [88, 89], showed less optimal imaging properties than these three probes illustrated above.

Since ^{111}In-DOTA-GlyGlu-CycMSH was first developed to target MC1 receptors for primary and metastatic melanoma imaging [81, 90], recent studies determined that reduction of the ring size of ^{111}In-DOTA-GlyGlu-CycMSH, L-lysine co-injection, introduction of a -GG-linker, substitution of DOTA with NOTA, and ^{99m}Tc radiolabeling via new chelators may further increase high melanoma tumor uptake while reducing nonspecific kidney and liver uptake [82, 91–94].

In addition, MC1-R specific NAPamide analogs have been labeled with various radiometals and non-metallic radionuclides (such as ^{64}Cu, ^{68}Ga, ^{18}F, ^{111}In, ^{99m}Tc and ^{44}Sc) and have been intensively used to detect melanomas or to evaluate the expression level of MC1-R [95–101]. While ^{64}Cu–DOTA–NAPamide showed mild tumor uptake in B16/F10 xenografted melanoma (Fig. 3A) [96], ^{64}Cu-NOTA-GGNle-CycMSH$_{hex}$ showed dramatic uptake at 2 h postinjection [93]. The latter study also elucidated that the substitution of DOTA with NOTA dramatically increased the melanoma uptake and decreased the renal and liver uptake of ^{64}Cu-NOTA-GGNle-CycMSH$_{hex}$.

Due to its positron emission with a high branching ratio (I =94.27%, E_{mean} (β+) =0.63 MeV), convenient production by the ^{44}Ti/^{44}Sc generator and satisfactory physical half-life (3.97 h), ^{44}Sc is a novel radiometal which has gained significant interest as a potential radioisotope for PET imaging [102–104]. A proof-of-concept study investigated the biological properties of the ^{44}Sc-labeled DOTA-NAPamide and found that this probe showed excellent binding properties to MC1-R positive melanoma cell and tumors, slightly superior to that of ^{68}Ga-DOTA-NAPamide [95].

Most recently, three new MC1R-targeting peptides (CCZ01047, CCZ01048, and CCZ01056) were successfully developed and all the three ^{68}Ga-labeled tracers produced high contrast PET images in B16/F10 tumors, of which ^{68}Ga-CCZ01048 exhibited the most ideal tumor uptake (Fig. 3B). This study indicated that introduction of a cationic Pip linker to Nle-CycMSH$_{hex}$ could improve tumor uptake and tumor-to-normal tissue contrast in detecting melanoma [105].

3.2. Peptide-based probes targeting the integrin family

Integrins are heterodimeric αβ transmembrane receptors that connect the extracellular matrix (ECM) to the cytoskeleton, always forming dimers by combining 1 of 18 α-chains with 1 of 8 β-chains [106]. Integrin $\alpha_v\beta_3$, and less commonly integrin $\alpha_5\beta_1$, have been attractive molecular targets for developing melanoma imaging probes [107–111]. Clinically, recent studies have validated that ^{18}F-Fluciclatide (formerly known as ^{18}F-AH111585) and ^{18}F-Galacto-RGD were able to measure $\alpha_v\beta_3$ expression in melanoma and may be useful radiotracers to assess the response to the antiangiogenic therapy in melanoma patients [112–116]. Nevertheless, low concentration of these clinically-available probes in $\alpha_v\beta_3$

positive tumors and less than optimal PET/CT imaging quality warrants many sensitive and specific probes to be developed.

In the preclinical setting, as we previously reviewed [117], a large variety of imaging strategies have been successfully employed for imaging of integrin expression in various cancer types, including melanoma. One study compared the diagnostic efficacy of ^{18}F-Galacto-RGD with that of ^{68}Ga-DOTA-RGD and ^{111}In-DOTA-RGD and found that ^{18}F-Galacto-RGD remained superior for imaging $\alpha_v\beta_3$ expression [108]. Even though ^{68}Ga-Oxo-DO3A-RGD and ^{68}Ga-NS3-RGD turned out to have inferior characteristics compared to the already existing ^{68}Ga-labeled RGD peptides [118], ^{68}Ga-NODAGA-RGD possessed improved imaging properties compared to ^{68}Ga-DOTA-RGD [119], even performing similarly to ^{18}F-Galacto-RGD (Fig. 3C) [120]. To achieve an easier and more rapid radiosynthesis, fusarinine C (FSC) and SarAr have been reported to be promising Ga-68 and Zr-89 binding bifunctional chelators [110, 121–124]. The most recent study from Zhai et al. reported that ^{68}Ga-FSC(succ-RGD)$_3$ exhibited improved properties compared to ^{68}Ga-NODAGA-RGD. The half-life of the radionuclide used (^{68}Ga, 68 min) was compatible with the pharmacokinetics of RGD peptides [125].

When compared to DOTA, the bifunctional chelator NODAGA has gained popularity because of its significant advantages in terms of labeling chemistry [119, 126]. However, the TRAP chelator possesses even better ^{68}Ga labeling properties and enables high yields and excellent reproducibility [127–129]. Notni et al. synthesized ^{68}Ga-avebetrin (formerly known as ^{68}Ga-TRAP(RGD)$_3$) and performed a comparison of biodistribution and PET data of ^{68}Ga-TRAP(RGD)$_3$ with those of ^{68}Ga-NODAGA-c(RGDyK) and ^{18}F-Galacto-RGD. Different from ^{68}Ga-NODAGA-RGD and ^{18}F-Galacto-RGD, ^{68}Ga-TRAP(RGD)$_3$ showed a very rapid blood clearance and renal excretion while maintaining activity concentration in tumor tissue, indicating the potential value of ^{68}Ga-TRAP(RGD)$_3$ as a next generation $\alpha_v\beta_3$ imaging agent (Fig. 3D) [130]. Considering that the TRAP-type chelator NOPO showed excellent ^{68}Ga labeling properties even in the presence of high concentrations of competing metal cations (Fig. 3E) [131], researchers further developed ^{68}Ga-NOPO–c(RGDfK) and found that this $\alpha_v\beta_3$ targeting probe exhibited a higher degree of hydrophilicity than similar conjugates with other chelators, resulting in rapid and specific uptake in M21 tumor xenografts, very rapid pharmacokinetics and renal clearance (Fig. 3F, G) [132].

There are a few reports on the development of $\alpha_5\beta_1$ specific radiotracers [111, 133–135]. Although there was one candidate peptide with a high specificity and affinity for $\alpha_5\beta_1$ in vitro, in vivo biodistribution studies demonstrated this radiotracer was not suitable for in vivo imaging due to its considerably high and constant radioactivity accumulation in the blood and other major organs [136]. The reported $\alpha_5\beta_1$ specific probes ^{18}F-PR_b and ^{68}Ga-NODAGAFR366 showed specific but low binding to $\alpha_5\beta_1$ positive murine melanoma tumors, and as a result, the poor tumor concentration and high kidney uptake may hinder these probe from further clinical transition [111, 137]. Recently Notni and colleagues obtained ^{68}Ga-aquibeprin by click-chemistry (CuAAC) trimerization of a $\alpha_5\beta_1$ pseudo-peptide on the TRAP chelator, followed by automated ^{68}Ga labeling. Surprisingly, the trimer ^{68}Ga-aquibeprin possessed approximately 16-times-higher $\alpha_5\beta_1$ affinity than the previously reported ^{68}Ga-labeled pseudo-peptide monomer. Although ^{68}Ga-aquibeprin

showed lower uptake than ^{68}Ga-avebetrin, low background activity and high target-to-nontarget contrast of the probe may offer great potential for elucidating biologic functions of $\alpha_5\beta_1$ and for detecting melanoma [138, 139].

RGD mimetic integrin inhibitors, like Cilengitide and Cilengitide-like RGD peptidomimetics, have also been investigated as chemical probes for the molecular imaging of angiogenesis in the literature [133, 140, 141]. In the near future, other strategies like sulfonation of tyrosine moieties in RGD peptides, which can modify the hydrophilicity of RGD peptides to increase renal clearance and to improve overall biodistribution [142], can also be applied to design novel probes for mapping $\alpha_v\beta_3$ expression in melanoma. Notably, RGD can be used as an agent for surface engineering in other imaging systems to enhance melanoma targeting efficacy and therapeutic effects [143–146].

3.3. Dual-targeted peptide-based probes

To improve the in vivo pharmacokinetics and stability of the above mentioned molecular probes, many hybrid peptides targeting both MC1R and integrin $\alpha_v\beta_3$ have been developed [147–153]. Initial synthesis and evaluation of ^{99m}Tc-RGD-Lys-(Arg^{11})CCMSH showed MC1R-mediated cellular uptake of the tracer, higher tumor uptake, and prolonged tumor retention in B16/F1 melanoma-bearing mice [148]. Substitution of Gly with Ala in the hybrid peptide not only dramatically increased the MC1R binding affinity of RAD-Lys-(Arg^{11})CCMSH compared to RGD-Lys-(Arg^{11})CCMSH (0.3 vs. 2.0 nM) but also enhanced the melanoma uptake [149]. Further studies demonstrated that ^{99m}Tc-RTD-Lys-(Arg^{11})CCMSH and ^{99m}Tc-RVD-Lys-(Arg^{11})CCMSH exhibited similar imaging properties to RAD-Lys-(Arg^{11})CCMSH, but ^{99m}Tc-RVD-Lys-(Arg11)CCMSH reached its highest concentration in melanoma lesions at a later time point [150].

Flook et al. replaced the Gly with another four amino acids (Ser, Nle, Phe, and D-Phe) and found that ^{99m}Tc-RSD-Lys-(Arg^{11})CCMSH displayed the strongest MC1R binding affinity in vitro and exhibited the most optimal melanoma uptake in vivo [151]. Importantly, linkers and charge status of the linkers between hybrid peptides may affect the renal uptake of the tracer significantly, as ^{99m}Tc-RGD-(Arg^{11})-CCMSH without a linker dramatically enhanced the tumor-to-kidney uptake ratio [154], and substitution of the Lys linker with Aoc, PEG2, β Ala or Ahx linker reduced the renal uptake of the relevant probe by 58%~63% at 2 h post-injection [155–157].

4. Other PET/SPECT probes for melanoma imaging

Besides radiolabeled melanin, MCR1, and integrin based probes, here we would like to summarize other potential radiolabelled molecular imaging probes that have been found effective in detecting not only melanoma but also other solid tumors. These probes can be divided into several categories as discussed in the following sections.

4.1. Probes targeting the metabotropic glutamate 1 receptor

Metabotropic glutamate 1 (mGlu1) receptor is a G protein-coupled receptor normally expressed in the central nervous system, essential for learning and modulating the excitatory synaptic transmission in the central nervous system [158]. Recent reports have elucidated

that mGlu1 has oncogenic characteristics in melanoma by driving constitutive activation of mitogen activated protein kinase and phoshatidylinositol-3-kinase/protein kinase B pathways [159–163]. Xie et al. initially developed ^{18}F-FITM for quantifying mGlu1 expression in the brain [164, 165], and then successfully extended ^{18}F-FITM PET imaging in melanoma [65]. However, considerable uptake and slow clearance of radioactivity in the brain undermined its usage in clinical applications. The same group elaborately introduced halogen atoms (chlorine, bromine, or iodine) rather than ^{18}F into ^{18}F-FITM and labeled these compounds using ^{11}C (half-life: 20.2 min). Of the reported compounds, the iodine analogue ^{11}C-6 showed the highest ratio of radioactivity of tumor to brain and may act as a useful PET tracer for imaging mGlu1 in melanoma (Fig. 4A, B) [166]. Notably, future studies can feasibly label ^{11}C-6 using the isotopes of ^{124}I, ^{123}I or ^{131}I for mGlu1-based theranostics of melanoma without altering their chemical structures or pharmacological profiles.

4.2. Probes targeting the very late antigen-4

In the past several years, very late antigen-4 (VLA-4; also called integrin $\alpha_4\beta_1$) has been found in cancers including melanoma [167]. LLP2A, a high-affinity peptidomimetic ligand for VLA-4, was identified from a 1-bead 1-compound library and has been used for cancer imaging and therapy [168–170]. Specifically, Jiang and co-authors conjugated LLP2A with two different chelators and assessed their imaging properties in melanoma models after labeling the conjugated compounds with ^{64}Cu. From the biodistribution and in vivo imaging data, both ^{64}Cu-CB-TE1A1P-LLP2A and ^{64}Cu-CB-TE2A-LLP2A clearly visualized the tumors with better contrast than was observed for ^{64}Cu-CB-TE1A1P-LLP2A [171]. When compared to ^{68}Ga-labeled NODAGA-LLP2A, ^{64}Cu-CB-TE1A1P-PEG4-LLP2A trended toward higher uptake and better tumor–to–nontarget tissue ratios (Fig. 4C, D) [172].

Recently Gai et al. designed a new probe ^{64}Cu-NE3TA-PEG4-LLP2A using the newly discovered chelator p-SCN-PhPr-NE3TA and assessed the diagnostic efficacy of the probe in melanoma xenografts. Small animal PET/CT imaging with ^{64}Cu-NE3TA-PEG4-LLP2A demonstrated high uptake with a superior tumor-to-muscle ratio at 4 h postinjection [173]. In addition, a study from Beaino et al. reported that ^{177}Lu-DOTA-PEG$_4$-LLP2A could accumulate not only in primary melanoma but also in the metastatic lesions in the lung and brain, demonstrating the potential of ^{177}Lu-DOTA-PEG$_4$-LLP2A as an alternative treatment strategy for metastatic VLA-4 expressing melanoma [174].

4.3. Probes targeting indoleamine 2,3-dioxygenase (IDO)

In recent years, immunotherapy has dramatically changed the landscape of melanoma treatment [175]. However, recent findings revealed that indoleamine 2,3-dioxygenase (IDO) can be triggered by innate responses during tumorigenesis, and also by attempted T cell activation (either spontaneous or due to immunotherapy), contributing to restrain immunity and establish immunotolerance. IDO inhibitors act as a novel class of immunomodulators with broad application in the treatment of advanced human cancer [176, 177]. In an effort to map tryptophan (Trp, a substrate of IDO) metabolism [178, 179], one group found that radionuclide labelled IDO inhibitor, 5-[18F]F-AMT, may hold great potential for melanoma imaging [180]. By using B16/F10 melanoma model, the authors found that tumors were clearly visible and this probe was possibly excreted through the urinary system as the

kidneys showed initial high uptake (Fig. 4E, F). These preliminary results implied potential usage of this series of probes because the superior tumor-to-background ratio may precisely delineate primary and metastatic melanomas, but these probes are not melanoma-specific because other tumor types like breast cancer concentrate this kind of probe as well [178].

4.4. Probes targeting the immune checkpoints

With the field of cancer immunotherapy has undergone tremendous growth during the past decade, as we recently pointed out, noninvasive molecular imaging strategies have been used to map the biodistribution of immune checkpoint molecules, monitor the efficacy and potential toxicities of the treatments, and identify potential patients who will benefit from immunotherapies [181]. Studies have shown that PET may be used for the noninvasive imaging of PD-1/PD-L1 expression in melanoma and for determining the extent of tumor-infiltration of lymphocytes [182, 183]. Recently Nedrow et al. developed a new PD-L1-targeted imaging agent, ^{111}In-DTPA-anti-PD-L1-BC and demonstrated that tumors had the greatest uptake at 24 h p.i. with a tumor-to-muscle ratio of 4.6 in mice bearing B16/F10 tumors. Whole body SPECT images demonstrated that the tumor as well as the spleen and liver were clearly defined at the later time points [184].

4.5. Probes targeting the human copper transporter 1 (CTR1)

Human copper transporter 1 (CTR1), a 190-amino acid protein of 28 kDa with three transmembrane domains [185], has been proven to be overexpressed in melanoma. The usefulness of $^{64}Cu^{2+}$ ions as PET probes is based on the fact that Cu is an essential element which plays an important role in cell proliferation and angiogenesis [186]. Therefore, copper radionuclide-based imaging of cancers have been investigated by several studies [187, 188]. $^{64}CuCl_2$ has been reported to be a novel and promising PET probe for imaging melanoma [189]. However, there have been reports that CTR1 is the specific influx copper transporter for ^{64}Cu(I) rather than ^{64}Cu(II). Using antioxidants, Jiang et al. prepared ^{64}Cu(I) and evaluated cellular uptake of ^{64}Cu(I) and ^{64}Cu(II) by melanoma cells in vitro and in vivo. The authors demonstrated that although ^{64}Cu(I) exhibited higher cellular uptake, no significant difference between ^{64}Cu(I) and ^{64}Cu(II) was observed through in vivo PET images and biodistribution [190]. However, future studies are still needed to evaluate whether or not ^{64}Cu(I) can act as a feasible PET imaging radiotracer for melanoma detection.

4.6. Antibody-based imaging probes

Radiolabeled monoclonal antibodies (mAb), antibody fragments, and engineered antibody derivatives are increasingly utilized as agents in diagnosis and therapy because of developments in antibody engineering and *in vivo stability* and high specificity of these probes [191, 192]. Twenty years have passed since the initial attempts to detect melanoma using radiolabeled antibodies [193, 194]. Besides melanin-specific antibodies [195–199], GD2 is highly expressed on the cell surface of a broad spectrum of human cancers including melanoma and has been successfully exploited as a molecular target for therapy and molecular imaging [200]. Voss et al. successfully developed a SarAr-conjugated, ^{64}Cu-labeled, anti-GD2 antibody construct, ^{64}Cu-SarAr-GD2 mAb ch14.18, and performed in vivo studies using GD2-expressing melanoma xenografts. Their results showed that about

20.5% of the injected dose accumulated in the M21 melanoma tumors [201], and further studies from the same group confirmed this finding [202, 203]. These preliminary results may indicate the feasibility of the ^{64}Cu-SarAr antibody as a platform for imaging melanoma.

4.7. Probes targeting CXCR4

C-X-C chemokine receptor type 4 (CXCR4, also called fusin, CD184) is a 7-transmembrane G-coupled receptor belonging to the chemokine receptor family and has been found to be overexpressed in various human cancers including lymphoma, neuroendocrine tumors, malignant glioma, lung cancer and multiple myeloma [204–208]. CXCR4-based imaging has also been investigated to detect melanoma recently [209]. In a clinical trial dedicated to estimate CXCR4 overexpression by using the novel CXCR4-specific probe ^{68}Ga-Pentixafor, Vag et al. included 21 patients (2 of them melanoma patients) and demonstrated the feasibility of ^{68}Ga-Pentixafor for PET imaging of solid malignancies, although the detectability of solid cancers by ^{68}Ga-Pentixafor seemed to be lower than with ^{18}F-FDG PET [210].

5. Image-guided therapy of melanoma

In addition to melanoma imaging, molecular imaging-guided therapy of melanoma has long been a hot topic in the field, as recently reviewed by Norain et al. [211]. Radionuclide-based therapy of melanoma can be realized through radiolabeled antibodies, peptides or small molecules.

5.1. Radiolabeled antibodies and peptides

Lutetium-177 (^{177}Lu) is a low energy β-emitter (497 keV, 90%) with a half-life of 6.7 days and a maximum tissue penetration of 1.6 mm. ^{177}Lu also emits γ-rays (113 and 208 keV, 6% and 11%) suitable for image-guided drug delivery using SPECT. Antibodies and peptides radiolabeled with ^{177}Lu are attractive therapeutic agents due to localized deposition of beta decay energy and a radioactive half-life which matches in vivo pharmacokinetics of targeting antibodies quite well [212–214]. Vascular endothelial growth factor (VEGF) has been extensively studied as one of the most important proteins involved in the development of physiological and pathological angiogenesis [215, 216]. Recently, ^{177}Lu-DOTA-bevacizumab (a recombinant humanized monoclonal antibody that binds to all VEGF isoforms) has shown preliminary potential as a novel radioimmunotherapy and molecular imaging agent for melanoma [217]. Building upon the success of the lactam bridge-cyclized a-MSH peptides for melanoma imaging discussed above, Guo et al. assessed the image-guided therapeutic effect of ^{177}Lu-DOTAGGNle-CycMSH$_{hex}$ in B16/F1 melanoma-bearing mice and found high melanoma uptake and fast urinary clearance of the probe, underscoring its potential as a theranostic agent for metastatic melanoma [218].

^{188}Re, a high-energy β-emitter (maximal energy: 2.12 MeV), has considerable range (several millimeters) in tissue and and relatively short half-life of 16.9 h. ^{188}Re-labeled melanin-specific antibodies for melanoma therapy have also been studied. ^{188}Re-labeled 6D2 [197], a melanin-binding IgM antibody, has been validated to be effective in treating pigmented human melanoma tumors and in augmenting the efficacy of the chemotherapeutic

agent dacarbazine (DTIC) [198]. Notably, by administering the targeting vector and radioisotope separately, in vivo pretargeting seems to be a promising approach to enhance tumor-targeting properties of radiolabeled antibodies while simultaneously skirting their pharmacokinetic limitations.

5.2. Radiolabeled small molecules

For melanin-targeted imaging-guided radionuclide therapy, many radiolabeled benzamide derivatives such as ^{131}I-MIP-1145 and ^{131}I-ICF01012 exhibited strong efficacy in murine and human melanoma xenografts [17, 219, 220]. ICF01012 was labeled with ^{123}I for melanoma imaging and with ^{131}I for melanoma treatment (Fig. 5A,B). The preliminary results not only showed a correlation between radiotracer uptake and melanin content but also demonstrated significantly reduced tumor growth and prolonged the median survival of the melanoma-bearing mice after administration of ^{131}I-ICF01012 [221]. The combination of ^{131}I-ICF01012 and coDbait, a DNA repair inhibitor, could overcome melanoma radioresistance and increase the efficacy of targeted radionuclide therapy (TRT) without increasing side effects [222]. Clinically, in a study which enrolled 26 patients with metastatic melanoma, Mier et al. reported that, out of five patients who received higher doses of treatment by administration of the melanin-binding ^{131}I-BA52 (Fig. 5C,D), three of them survived more than two years after therapy. In contrast, the mean overall survival of the untreated and insufficiently dosed patients was approximately three months [223]. Interestingly, iodinated and fluorinated radiotracers targeting melanin and offering potential for both diagnosis (SPECT and PET imaging) and therapy (iodine-131) have also been developed [224–226].

6. Conclusion and future persepectives

In this review, as summarized in Fig. 6, we provided an informative survey of the recent progress on radiolabelled molecular imaging probes for imaging different molecular targets or processes in malignant melanoma. While melanin, MCR1 and integrins are the traditional targets extensively used for melanoma detection and therapy, tumor metabolism and immune microenvironment-based molecular imaging probes have also been developed in recent years. In the era of precision medicine, devotion and efforts on radiolabelled molecular probes for mapping and treating melanoma is extremely important, and new imaging probes with optimal imaging properties are still highly demanded.

Looking into the future, we would like to put forward three proposals from our perspective. First, with the rapid development of the molecular imaging field, novel molecular imaging probes with high sensitivity and specificity enable us to characterize melanoma at the molecular level. These new probes will provide powerful platforms for early diagnosis of both primary and metastatic melanoma, monitoring of therapeutic response, accurate staging and restaging of melanoma, stratification of patients for antiangiogenesis therapy, immunotherapy and/or radionuclide therapy, and facilitation of new drug discovery for melanoma treatment. Second, melanin, MC1R, and integrins have been intensively investigated as targets for selective imaging and therapeutic agents against melanoma, and though the potential of many of these probes could be effectively demonstrated in preclinical

settings, very few of them could actually be translated to the clinics. Future studies should be dedicated to push the clinical transition of some of these most promising probes. Third, usage of humanized mice, rather than cultured cell lines and mouse xenografts [227], could examine the molecular imaging probes in the context of the human immune system and tumor microenvironment and accelerate the clinical transition of these molecular imaging probes.

To conclude, malignant melanoma represents a serious public health problem and is a deadly disease when diagnosed at late stage. With the elucidation of many important oncogenic signaling pathways and biomarkers involved in malignant melanoma pathogenesis, we belive that PET and SPECT imaging as well as image-guided therapy can undoubtedly provide better visualization and management of malignant melanoma in the forthcoming future.

Acknowledgments

This work was sponsored by Ph.D. Innovation Fund of Shanghai Jiao Tong University School of Medicine to Weijun Wei (No. BXJ201736), National Institutes of Health (1R01CA205101, P30CA014520, and T32GM008505) and the American Cancer Society (125246-RSG-13-099-01-CCE).

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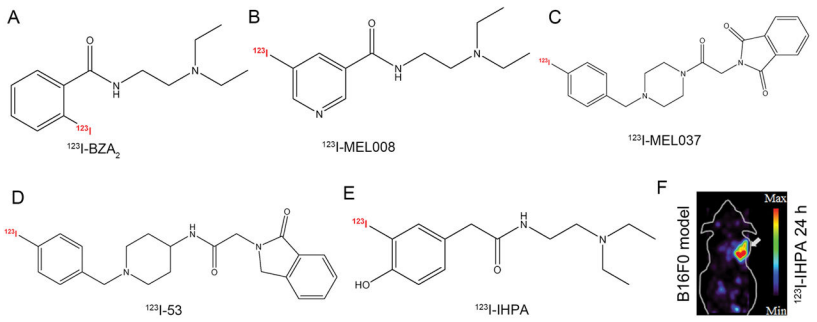

Figure 1.

Representative melanin-targeting probes. Chemical structures of (A) ^{123}I-BZA$_2$, (B) ^{123}I-MEL008, (C) ^{123}I-MEL037, (D) ^{123}I-53, and (E) ^{131}I-IHPA. (F) MicroSPECT image of C57BL/6 mice bearing B16/F0 melanotic melanoma at 24 h postinjection of approximately 11.1 MBq of ^{123}I-IHPA, the tumor is indicated by the white arrow. Adapted and modified with permission from references [34, 36, 41, 42, 44].

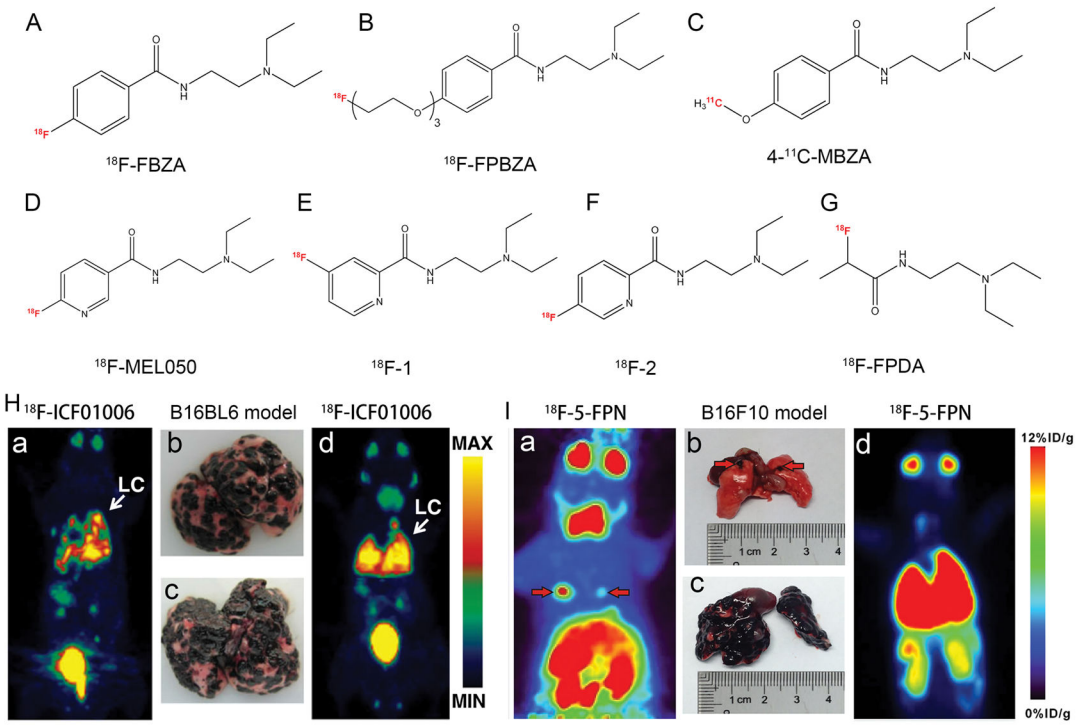

Figure 2.

Representative melanin-targeting probes and *in vivo* study images. Chemical structures of (A) ^{18}F-FBZA, (B) ^{18}F-FPBZA, (C) 4-^{11}C-MBZA, (D) ^{18}F-MEL050, (E) ^{18}F-1, (F) ^{18}F-2, and (G) ^{18}F-FPDA. (H) Whole-body maximum intensity projection (MIP) images of ^{18}F-ICF01006 and corresponding lung photographs of B16/BL6 melanoma-bearing mice at the early stage (a, b) and late stage (c, d) of tumor development. (I) ^{18}F-5-FPN PET images of two mice with lung metastases from melanoma. Note that this probe was able to detect both micrometastases (a, b) and wide spread lung metastases (c, d) from melanoma. Tumors are indicated by red arrows. Adapted and modified with permission from references [45–47, 49, 51, 52, 66, 67].

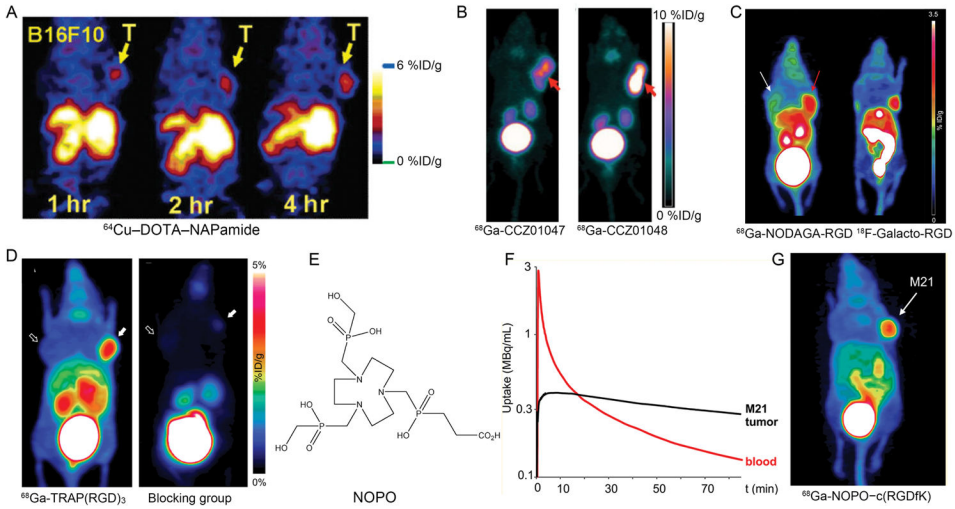

Figure 3.

Examples of peptide-based imaging of melanoma. (A) Coronal microPET images of mice bearing B16/F10 tumors at different time points after tail vein injection of ^{64}Cu–DOTA–NAPamide. (B) PET images of ^{68}Ga-CCZ01047 and ^{68}Ga-CCZ01048 at 1 h postinjection of the corresponding tracer in mice bearing B16/F10 tumors. (C) MIP PET images of mice bearing M21 and M21L tumor xenografts on right and left shoulder, respectively. ^{68}Ga-NODAGA-RGD (left) showed more intense tumor uptake than ^{18}F-Galacto-RGD (right) in $\alpha_v\beta_3$ positive M21 melanoma models. (D) MIP images of microPET scans of M21 (solid arrows) and M21L (outline arrows) human melanoma models. ^{68}Ga-TRAP(RGD)$_3$ showed high-contrast visualization of the M21 tumor. (E) Chemical structure of bifunctional chelator NOPO. (F) The relative uptake of ^{68}Ga-NOPO–c(RGDfK) in M21 tumor tissue and blood over time. (G) MIP of ^{68}Ga-NOPO–c(RGDfK) PET imaging in M21/M21L xenografted mice. Tumor site was marked with white arrow. Adapted and modified with permission from references [96, 105, 120, 130–132].

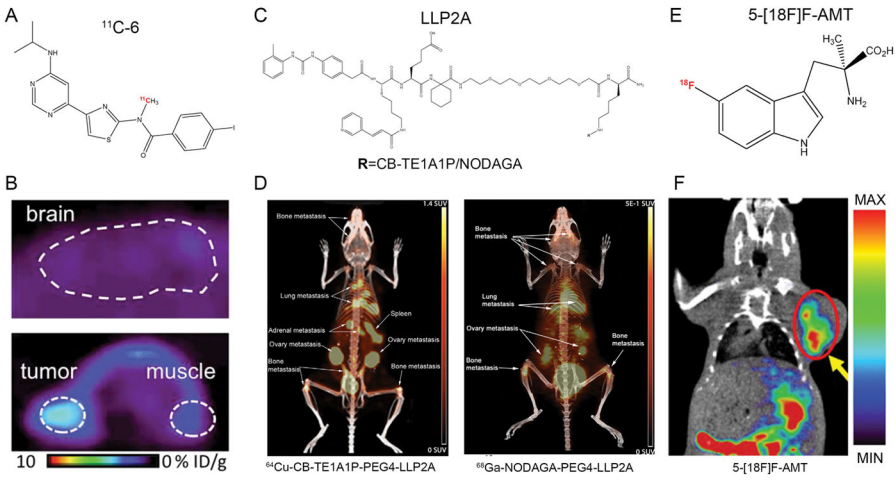

Figure 4.

Other PET probes for melanoma imaging. (A) Chemical structure of ^{11}C-**6** for imaging of mGlu1 receptor. (B) Representative PET images of mice bearing B16/F10 after injection of ^{11}C-**6**. Upper: sagittal image of the brain. Lower: Axial image of tumor and muscle. (C) Chemical structures of NODAGA-PEG4-LLP2A and CB-TE1A1P-PEG4-LLP2A. (D) Small animal PET/CT imaging at 2 h after injection of the radiotracers (7.4 MBq). Both ^{64}Cu-CB-TE1A1P-PEG4-LLP2A and ^{68}Ga-NODAGA-PEG4-LLP2A were able to image melanoma lung metastases with high contrast and minimal lung background. (E) Chemical structure of 5-[^{18}F]F-AMT. (F) Coronal PET/CT image of B16/F10 melanoma 30 min after injection of 5-[^{18}F]F-AMT. Adapted and modified with permission from references [166, 172, 180].

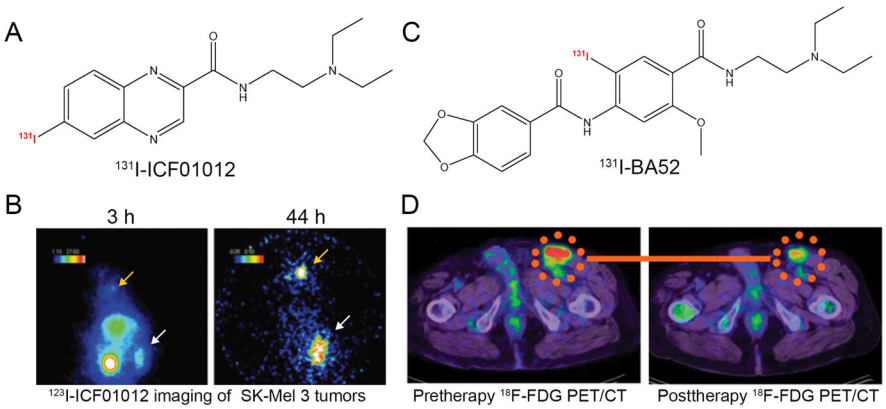

Figure 5.

Representative radionuclide-labeled therapeutic agents for melanoma. (A) Chemical structure of ^{131}I-ICF01012. (B) Gamma-camera imaging of SK-Mel 3 melanoma-bearing mice after injection of 3.7 MBq ^{123}I-ICF01012. A clear concentration of ^{123}I-ICF01012 occurred 3 hours after radiotracer administration and a rapid elimination of ^{123}I-ICF01012 from non-specific organs was observed at 44 h postinjection. Tumor and thyroid were indicated by white and orange arrows, respectively. (C) Chemical structure of ^{131}I-BA52. (D) ^{18}F-FDG PET/CT examinations in a melanoma patient before and after ^{131}I-BA52 treatment. After treatment using ^{131}I-BA52, post-therapeutic ^{18}F-FDG PET/CT examination demonstrated that SUV of the inguinal lymph node metastasis decreased from 9.02 to 5.81. Adapted and modified with permission from references [221, 223].

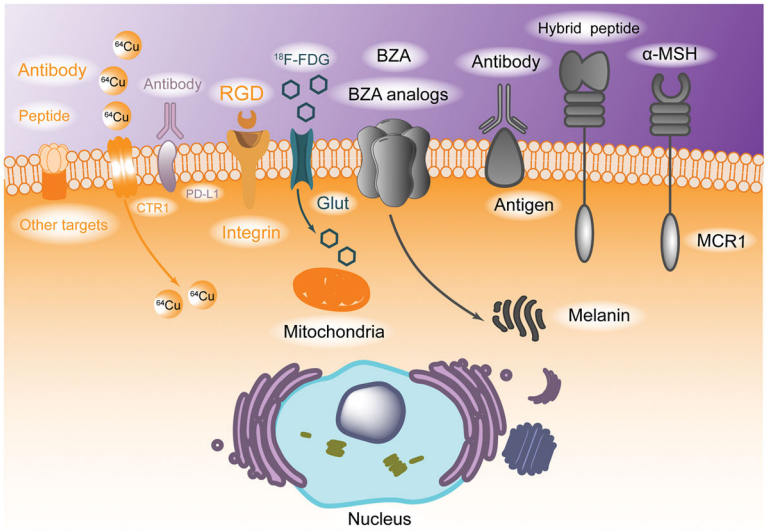

Figure 6.

Pictorial abstract showing PET and SPECT imaging probes for malignant melanoma. Molecular targets discussed above can be divided into two groups, melanoma specific targets which are indicated by grey/black models and melanoma nonspecific targets which are indicated by colorful models.