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## PET and SPECT Imaging of Tumor Angiogenesis

Marcian E. Van Dort<sup>1,3</sup>, Pedram Navid-Azarbaijani<sup>2</sup>,  
Rajesh Ranga<sup>2</sup>, Alnawaz Rehemtulla<sup>2,3</sup>, Brian D Ross<sup>1,3</sup>,  
Allan E David<sup>4</sup> and Mahaveer S Bhojani<sup>1,3</sup>

<sup>1</sup>Dept. of Radiology,

<sup>2</sup>Dept. of Radiation Oncology,

<sup>3</sup>Center for Molecular Imaging,

University of Michigan Medical School, Ann Arbor,

<sup>4</sup>College of Pharmacy,  
USA

### 1. Introduction

#### 1.1 PET and SPECT imaging

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) based functional imaging utilize radiolabeled tracers to provide information for real time visualization of physiological or biological processes in live animals or humans. Disease-related biomarkers involved in initiation and/or progression of a pathological condition are imaged by these nuclear imaging technologies which lead to early detection of abnormalities prior to the appearance of morphological changes visualized by other imaging modalities such as CT or MRI (1-3). Additional advantages of nuclear imaging approaches are high sensitivity of detection and high spatial resolution. Further they are either non- or minimally invasive and highly quantitative (4). Together, these characteristics of PET and SPECT make them an invaluable technique for monitoring some diseases and disorders.

There are significant differences between PET and SPECT, some of which are highlighted below. A major advantage of PET over SPECT is its 2-3 orders of magnitude greater sensitivity and quantitative capability (5). PET utilizes radioisotopes that decay via emission of positrons, whereas, SPECT radioisotopes decay by electron capture and/or gamma emission (5). Table 1 lists some of the most commonly used PET and SPECT radioisotopes and their physical properties. The synthetic chemistry behind development of these radioisotopes as tracers for imaging is dependent on the half-lives. For example, the short decay half-lives (2 – 20 min) of the PET radioisotopes: carbon-11, nitrogen-13 and oxygen-15 requires that radiotracer synthesis with these radioisotopes be conducted in close proximity to a cyclotron (3-5). On the other hand, radioisotopes such as fluorine-18, copper-64, indium-111, iodine-123 and iodine-124 are sufficiently long-lived to allow transportation from regional commercial sites (3-5). Additionally, the radioisotopes gallium-68, copper-62 and technetium-99m can be conveniently obtained from an in-house generator (3-5). At the present time, clinical SPECT

imaging is more prevalent than PET imaging due to both its cost effectiveness and the greater availability of SPECT scanners at most nuclear medicine clinics.

Isotope	Imaging Mode	Production Method	Half-Life	Decay Mode(s)
<sup>11</sup> C	PET	Cyclotron	20.4 min	β+ (99+%)
<sup>13</sup> N	PET	Cyclotron	10 min	β+ (100%)
<sup>15</sup> O	PET	Cyclotron	2.03 min	β+ (99.9%)
<sup>18</sup> F	PET	Cyclotron	110 min	β+ (97%) EC (3%)
<sup>124</sup> I	PET	Accelerator	4.2 days	EC (74.4%) β+ (25.6%)
<sup>68</sup> Ga	PET	Generator	68.3 min	β+ (90%) EC (10%)
<sup>62</sup> Cu	PET	Generator	9.73 min	β+ (98%) EC (2%)
<sup>64</sup> Cu	PET	Reactor	12.7 hours	β+ (61%) β- (39%)
<sup>99m</sup> Tc	SPECT	Generator	6.02 hours	IC (100%)
<sup>111</sup> In	Gamma Scintigraphy	Accelerator	2.8 days	EC (100%)
<sup>123</sup> I	SPECT	Accelerator	13.3 hours	β+ (100%)
<sup>192</sup> Ir	SPECT	Reactor	73.8 days	EC (4.9%) β- (95.1%)
<sup>201</sup> Tl	SPECT	Cyclotron	73 hours	EC (100%)
<sup>82</sup> Rb	PET	Generator	1.27 min	β+ (100%)
<sup>89</sup> Zr	PET	Cyclotron	3.3 days	β+ (100%)

β+ = positron emission; EC = electron capture; IC = isomeric conversion, β- = electron emission

Table 1. Common PET and SPECT Radioisotopes

In recent years, an effort has been made to combine anatomical imaging modalities (such as CT and MRI) with molecular imaging modalities in order to capitalize on the strengths of both techniques. These multi-modality approaches can provide both high structural detail and high detection sensitivity of pathophysiological changes giving greater insight into the dynamic processes of tumor growth and progression. Advances in this field have already been made and PET-CT technology is now available for use in many clinics (6-8). Further, the recent approval by the US Food and Drug Administration (FDA) of the first PET-MRI machine for clinical imaging (9) is a major step forward in multimodal imaging. Compared with PET-CT technology, PET-MRI scans demonstrate higher structural detail, especially of soft tissues, and additionally permit the use of MRI techniques such as perfusion imaging and MR spectroscopy (10). Furthermore, MRI scans (in PET-MRI) use magnetic fields instead of x-rays, thereby decreasing patient radiation doses in comparison to PET-CT scans

(10). Boss et al. showed the effectiveness and reliability of PET-MRI in scanning intracranial tumors using [ $^{11}\text{C}$ ] methionine or [ $^{68}\text{Ga}$ ] DOTATOC (11).

The past decade has seen the investigation and validation of several radiotracers with particular emphasis in oncology. These targets include molecular biomarkers such as growth factor receptors, protein kinases, specific receptor over-expression or biological events such as angiogenesis, apoptosis, hypoxia and tumor proliferation (1-3). This review will highlight recent PET and SPECT radiotracer development for angiogenesis imaging with a major focus on their application in oncology.

## 1.2 Biology of angiogenesis

Angiogenesis, the formation of new blood vessels, plays a central role in growth of tumors beyond 1-2 mm<sup>3</sup> as neovascularization is required to supply oxygen and nutrients and for removal of cellular wastes(12-14). Further, neo-angiogenesis is critical to the metastatic potential of tumors as it aids in the dispersion of cancer cells to distant organs. Recent advances in cellular and molecular biology have led to the identification of novel angiogenic biomarkers and molecular dissection of their signaling pathways(13, 15). One of the key signaling pathways involved in initiation of new tumor blood vessels is mediated by vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase (VEGFR)(16-18). Pro-angiogenic signaling mediated by VEGF/VEGFR is critical when tumors outgrow their existing blood supply and frequently display oxygen deficiency (hypoxia). Hypoxia is known to trigger the secretion of VEGF (19-22). Binding of VEGF to its receptor initiates a signaling cascade that promotes the proliferation, migration and survival of endothelial cells, ultimately leading to angiogenesis (23-25). The angiogenic effects of the VEGF family are believed to be primarily mediated through VEGF-A. To date, VEGF-A (also referred to as VEGF) and its receptors are the most characterized signaling pathways in developmental and tumor angiogenesis(24, 26-35).

Alternative splicing of RNA has revealed the existence of at least nine different molecular isoforms for VEGF-A, comprising 121, 145, 148, 162, 165, 165b, 183, 189 or 206 amino acids(36-43). The angiogenic actions of VEGF-A are mediated primarily via two closely related endothelium-specific receptor tyrosine kinases (VEGFR-1 and VEGFR-2)(44-46). All of the VEGF-A isoforms bind to both VEGFR-1 and VEGFR-2, of which, VEGFR-2 is the major mediator of proliferation and angiogenesis (14). Thus, a variety of solid tumor cells overexpress VEGFR-2, which serves as poor prognostic marker for the survival of cancer patients (47, 48). Therefore, new therapies based on humanized monoclonal antibodies that inhibit VEGF-A are used to treat cancers of colorectal, lung, kidney and eye origin and there are many newer therapies under various stages of development (27, 49)

## 2. Molecular targets and ligands for PET/SPECT imaging of angiogenesis

### 2.1 VEGF receptor and ligands

PET imaging of VEGFR expression *in vivo* was first demonstrated using VEGF<sub>121</sub> radiolabeled with  $^{64}\text{Cu}$ . Radiolabeling was achieved via  $^{64}\text{Cu}$  chelation to a DOTA-VEGF<sub>121</sub> conjugate (DOTA is an abbreviation for 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid). *In vivo* evaluation of  $^{64}\text{Cu}$ -DOTA-VEGF<sub>121</sub> using microPET imaging of

athymic nude mice bearing U87MG human glioblastoma xenografts showed rapid and high specific accumulation of the radioligand in small U87MG tumors (16% injected dose per gram [ID/g]) at 4 h post-injection. Larger tumors showed significantly lower uptake (1 – 3% ID/g). Differences in tumor localization between large and small tumors showed a good correlation with tumor VEGF receptor expression (VEGFR-2). *In vivo* VEGFR-2 specificity of the radioligand was also confirmed by pharmacological blocking experiments and *ex vivo* studies (immunofluorescence staining, western blot analysis). This study also demonstrated the dynamic nature of VEGFR signaling during tumor growth and proliferation. Subsequently, these authors also reported on the development of a  $^{64}\text{Cu}$ -labeled vasculature-targeting fusion toxin (VEGF<sub>121</sub>/rGel) composed of a VEGF<sub>121</sub> linked recombinant plant toxin gelonin construct (rGel) for multimodality imaging and therapy of glioblastoma. Sustained tumor accumulation and high signal-to-noise ratios were demonstrated by this radioligand in mice bearing glioblastoma xenografts up to 48 h post-injection. Based on the pharmacokinetic information obtained from the imaging studies, therapeutic administration of VEGF<sub>121</sub>/rGel to mice bearing orthotopic U87MG glioblastomas revealed specific tumor neovasculature damage by histological analysis after a multiple dose treatment regimen.

Apart from their role in tumor angiogenesis, VEGF/VEGFR signaling plays a key role in other human pathologies. For example, myocardial infarction (MI) is known to activate VEGF/VEGFR signaling. PET imaging studies conducted in a rat model of MI with  $^{64}\text{Cu}$ -DOTA-VEGF<sub>121</sub> revealed a 3 - 4 higher myocardial uptake of radioactivity for up to 2 weeks following infarction as compared to controls (50, 51). In addition, PET imaging of VEGFR expression with  $^{64}\text{Cu}$ -DOTA-VEGF<sub>121</sub> in a rat stroke model showed peak tracer uptake in the stroke border zone at approximately 10 days post-surgery indicating neovascularization as confirmed by histopathology studies(52).

$^{111}\text{In}$ -labeled recombinant VEGF isoform VEGF<sub>165</sub> ( $^{111}\text{In}$ -hn-Tf-VEGF) was reported by Chan and coworkers as a tumor angiogenic marker in experimental mice models. VEGF<sub>165</sub> was fused through a flexible polypeptide linker to the *n*-lobe of human transferrin(53). The latter construct permitted labeling of the radioligand with  $^{111}\text{In}$  at a site remote from the VEGF receptor-binding domain. In radioligand stability studies,  $^{111}\text{In}$ -hn-Tf-VEGF demonstrated a moderate loss of  $^{111}\text{In}$  to transferrin in human plasma *in vitro* over a 72 h period ( $21.3\% \pm 3.4\%$  per day). Radioligand biodistribution studies and whole-body gamma camera imaging were conducted in athymic mice bearing subcutaneous U87MG human glioblastoma xenografts.  $^{111}\text{In}$ -hn-Tf-VEGF displayed tumor and blood radioactivity accumulations of  $6.7 \pm 1.1\%$  ID/g and  $1.6 \pm 0.4\%$  ID/g, respectively, at 72 h post-injection. Co-administration of a 100-fold excess of VEGF led to a 15-fold decrease in tumor uptake of radioactivity. High uptake of radioactivity was also observed in liver ( $45.5 \pm 7.5\%$  ID/g), kidneys ( $39.4 \pm 7.0\%$  ID/g) and spleen ( $35.6 \pm 4.4\%$  ID/g) at this time interval. The authors present evidence to indicate that uptake of radioactivity in these organs is due to  $^{111}\text{In}$ -hn-Tf-VEGF and not due to  $^{111}\text{In}$ -transferrin via transchelation of  $^{111}\text{In}$  from the radioligand to transferrin.

Along with labeling VEGF-A and its isoforms, efforts have also been made to create anti-VEGF-A antibodies for imaging and therapeutic purposes. Success in this field was achieved with the creation of bevacizumab, a humanized monoclonal antibody that blocks VEGF-induced endothelial cell proliferation. A radiolabeled form of bevacizumab,  $^{89}\text{Zr}$ -



bevacizumab, was demonstrated to have high tumor uptake in small animal PET imaging (54, 55). A phase 1 clinical trial with  $^{124}\text{I}$ -labelled HuMV833 showed promising findings as well establishing the utility of radiolabeled antibodies in imaging VEGF(56, 57).

## 2.2 $\alpha_v\beta_3$ integrins and RGD peptide

An indirect approach to angiogenesis imaging has focused on radioligands targeting the  $\alpha_v\beta_3$  class of cell adhesion molecule integrins. Integrin  $\alpha_v\beta_3$  receptors are significantly up-regulated in endothelial cells during angiogenesis but not in mature vessels or non-neoplastic epithelium (Brooks PC, Science 1994; Pasqualini R, Nat Biotechnol, 1997). Integrin  $\alpha_v\beta_3$  is also expressed in a variety of tumor cells, including melanoma, late-stage glioblastoma, ovarian, breast and prostate cancer. The ability to visualize and quantify integrin  $\alpha_v\beta_3$  expression *in vivo* would allow for appropriate selection of patients for anti-integrin treatment and also monitor treatment efficacy in such patients.

Radioligand development for  $\alpha_v\beta_3$  imaging has focused primarily on small RGD peptide antagonists. The tripeptide sequence motif, arginine-glycine-aspartate (RGD), is found in proteins of the extracellular matrix. Many integrins, including  $\alpha_v\beta_3$ , link the intracellular cytoskeleton of cells with the extracellular matrix via recognition and binding to this RGD motif. [ $^{18}\text{F}$ ]GalactoRGD was the first radiotracer used for successful PET imaging of tumor  $\alpha_v\beta_3$  expression in patients. Subsequently, a hydrophilic D-amino acid containing tetrapeptide analog was also developed which demonstrated improved pharmacokinetics and proteolytic stability. Wu and coworkers have reported on the enhanced  $\alpha_v\beta_3$  receptor binding characteristics of dimeric and multimeric RGD peptides over monomeric peptides which has been attributed to an increased local concentration of RGD domains at the receptor vicinity (polyvalency effect). Accordingly, several [ $^{18}\text{F}$ ]- and [ $^{64}\text{Cu}$ ]-labeled dimeric and tetrameric RGD peptide analogs have been recently synthesized and evaluated by this group for integrin-targeted imaging in lung, brain and breast cancer. As an example, microPET imaging studies with a dimeric RGD peptide coupled to 4-[ $^{18}\text{F}$ ]Fluorobenzoate {[ $^{18}\text{F}$ ]-FB-E[c(RGDyK)]<sub>2</sub>} showed predominantly renal excretion and twice as much tumor uptake in the same animal model as the monomeric analog [ $^{18}\text{F}$ ]-FB-c(RGDyK). Binding potentials derived from tracer kinetic modeling studies showed good correlation with tumor integrin expression levels as measured by SDS-PAGE/autoradiography in the six tumor models tested.

Recently, a disulfide-based cyclic RGD called iRGD (internalizing RGD) was reported that showed binding affinity to the  $\alpha_v\beta_3$  integrin and neurophilin-1 (NRP-1) receptor and portrayed the ability to penetrate tumor tissue for both imaging and drug-delivery purposes(58). These characteristics of the peptide iRGD (CRGDKGPDC) are achieved through a sequence of steps. Initially, iRGD binds to the  $\alpha_v\beta_3$  integrins expressed on the endothelium of tumor cells through its RGD motif(59). Subsequently, the peptide is proteolytically cleaved producing a C-terminal RGDK/R sequence that both increases the peptide's affinity to NRP-1 and decreases its binding activity to  $\alpha_v\beta_3$  due to the CendR motif(59). This newfound affinity to NRP-1 provides iRGD its tumor penetrating capabilities(60). Not surprisingly, iRGD has become a major target for *in vivo* imaging as it can both home to tumor cells and also be internalized making the peptide a more effective imaging agent compared with other RGD peptides. iRGD imaging has been achieved using

optical fluorescent and MRI agents, but a nuclear imaging agent has yet to be developed for this promising peptide(58, 59).

### 2.3 Matrix Metalloproteinases (MMP)

Matrix metalloproteinases (MMP's), a family of zinc- and calcium-dependent endopeptidases, facilitate endothelial cell migration during angiogenesis via the enzymatic degradation of connective tissue(61). Within the family of MMP's, MMP-2 and MMP-9 have been most associated with tumor aggressiveness and metastatic potential(62). Consequently, several MMP-specific peptides as well as small-molecule inhibitors (MMPI's) have been radiolabeled with  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{64}\text{Cu}$ , or  $^{18}\text{F}$  for PET or SPECT imaging of angiogenesis(63). For example, Koivunen et al. discovered that the decapeptide *cyclo*(Cys-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys)(CTT) selectively inhibited MMP-2 and MMP-9 thus suppressing the migration of endothelial and tumor cells(63, 64). Subsequent radiolabeling with  $^{64}\text{Cu}$  and chelation to DOTA showed low tracer accumulation in tumors(63). Studies on other MMP imaging agents have shown similar results calling into question their utility for angiogenesis imaging due to their low tumor targeting capabilities, nonspecific activity in preclinical trials, and *in vivo* instability(62).

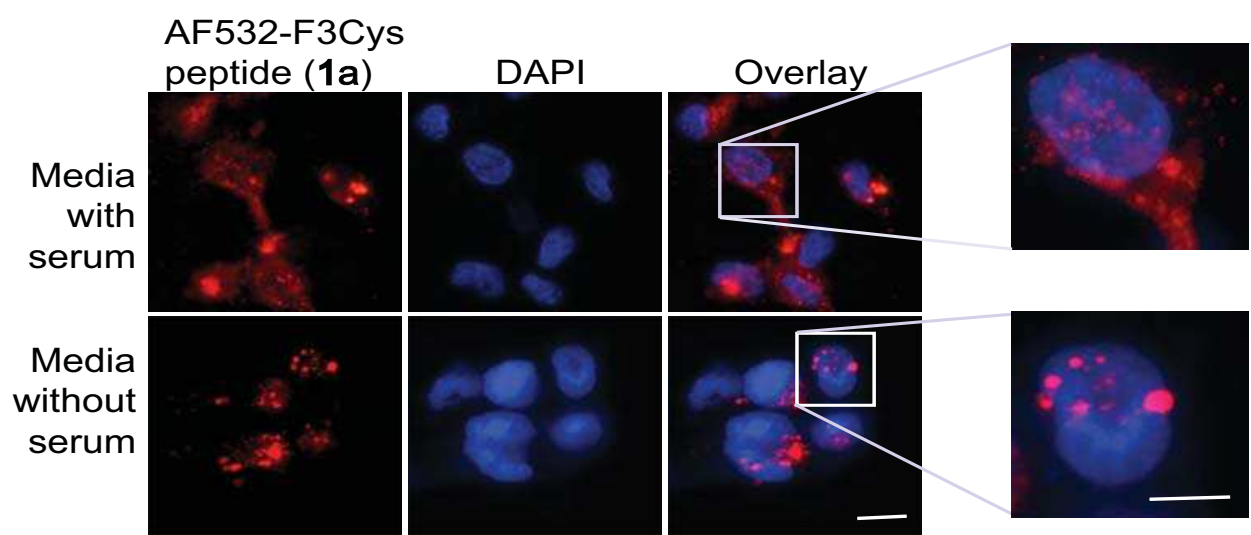
### 2.4 Nucleolin and F3 peptide

It is now commonly believed that different organs and tissues may have a distinct vasculature, and molecular profiling studies have revealed that this heterogeneity stems from expression of distinct functional biomarkers in endothelial cells and its milieu. Similarly, molecular dissections of tumor and tumor vasculature have revealed that the angiogenic network of blood vessels in tumor is unique both structurally and physiologically. Tumor vasculature expresses unique biomarkers that distinguish it from normal blood vessels and allow targeting of cargo of therapeutic or imaging agents (14).

Phage display peptide libraries contain peptide motifs that can home to the tumor vasculature and bind directly to the molecules expressed on tumor vessels (65, 66). Utilizing *in vivo* phage display technology, Ruoslahti's group identified F3 peptide (KDEPQRRSARLSAKPAPPKPEPKPKKAPAKK) as a sequence that specifically binds to tumor and its angiogenic endothelial cells (67). Later studies identified Nucleolin, as the receptor for F3 peptide. Nucleolin is localized both within the nucleus and the cytoplasm and is involved in RNA transport and processing. However, in proliferating tumor cells, it is cyclically transported from the nucleus to cell surface and back by a specific shuttle mechanism (68). Subcellular distribution of fluorescently-labeled F3 peptide shadowed nucleolin localization both *in vitro* and *in vivo* (Figure 1, (69, 70)). Further, we recently performed meta-analysis of microarray data from tumor samples and found that Nucleolin is upregulated in brain, head and neck and lung cancers when compared with respective normal tissue. Taken together, the overexpression of nucleolin and its unique localization at cell surface, suggest that nucleolin may be targeted for tumor imaging and delivery of therapeutic agents.

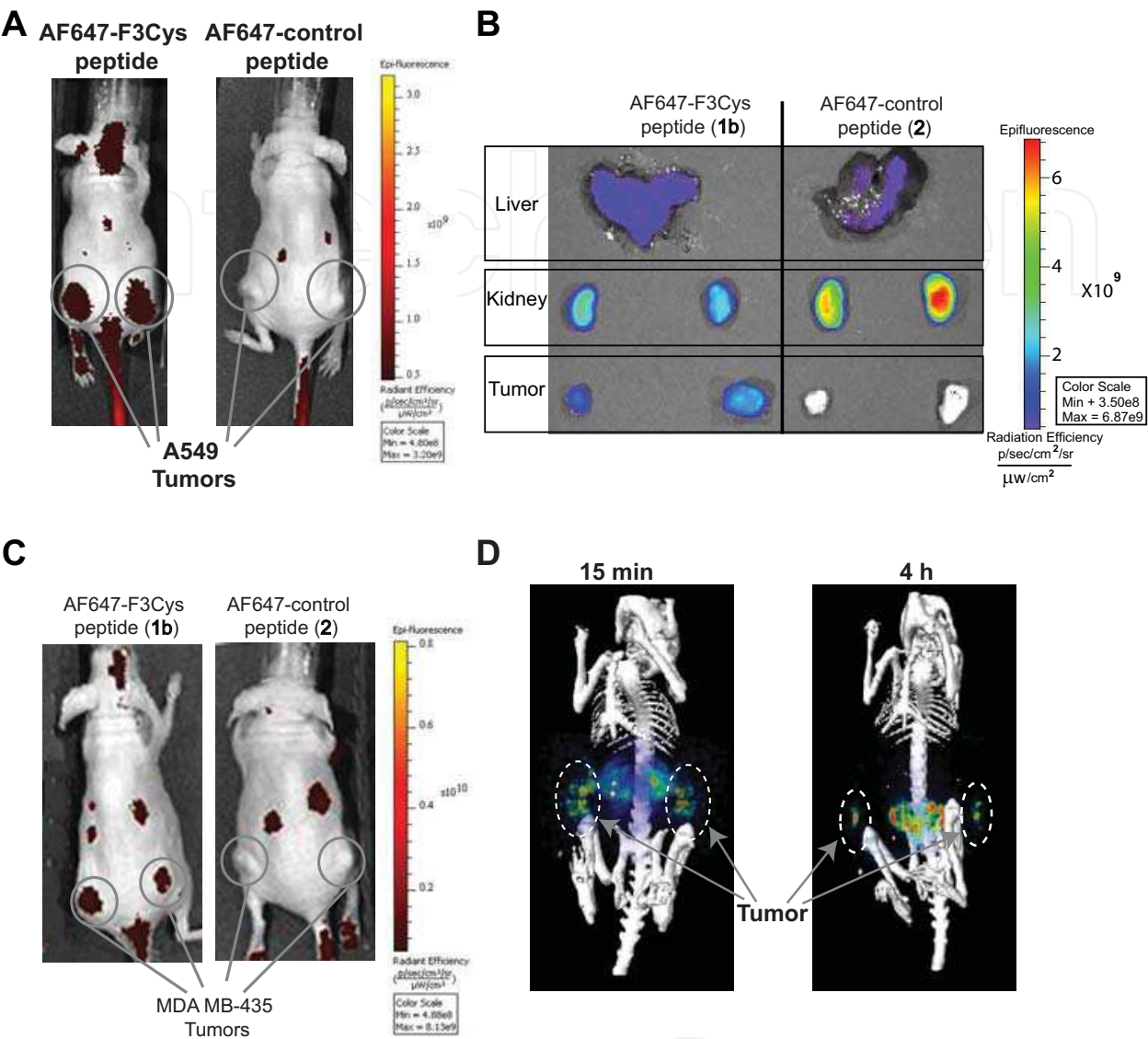
F3 peptide has been used to deliver fluorescent tags, siRNA, and therapeutic radionuclides to tumors (44, 71-75). We have recently demonstrated that this peptide sequence can carry a

pay load of 80 nm multifunctional nanoparticles in a tumor specific manner (76) and that these reside at the tumor sites longer than the untargeted nanoparticles. Several groups have generated a variety of distinct F3-targeted nanoparticles and shown their efficacy in targeting mouse tumors or human xenografts in mouse (44, 71-75, 77). We recently reported the development of an new F3 peptide with cysteine at the c-terminus. Fluorescently or [<sup>125</sup>I]-labeled conjugates of this peptide localized to tumors in a mouse model, when systemically administered (Figure 2).



**Fig. 1. Subcellular localization of Fluorescent-labeled F3Cys peptides shadows that of nucleolin.** MDA-MB-435 cells, in optically clear bottom dishes, cultured in either serum free or serum containing media were stained with AF532-F3Cys, counterstained with DAPI and monitored under a fluorescent microscope. In cells grown in media containing 10% serum, cell surface and nuclear staining of F3Cys was observed while serum starved cells showed predominantly nuclear staining without significant membrane staining. This suggests that F3Cys localizes to cell surface in actively growing cells.





**Fig. 2. Fluorescent or SPECT imaging using tagged F3-cys peptide.** Mice bearing A549 (A) xenografts were injected i.v. via the tail vein with either AF647-F3Cys or AF647-Control peptide and fluorescence images were acquired over time. Tumor specific uptake at 2 h was observed only with AF647-F3Cys but not with AF647-Control peptide (A). *Ex vivo* fluorescence imaging of tumor, kidney and liver harvested 2 h after AF647-F3Cys peptide injection in animals bearing A549 Tumor xenografts show that F3 peptide is taken up by tumor, kidney and liver while AF647-Control peptide shows no tumor specific fluorescence (B). Tumor specific uptake was also seen with MDA-MB-435 (melanoma cancer cells) xenografts when AF647-F3Cys and not AF647-Control peptide was administered (C). SPECT imaging studies conducted following i.v. administration of [<sup>125</sup>I]IBMF3 to nude mice bearing MDA-MB-435 tumor xenografts showed distinct uptake of radioactivity in tumor as early as 15 min post-injection and also at 4 h post-injection (D).

## 2.5 Miscellaneous alternate targets

Prostate-specific membrane antigen (PSMA) is expressed on the neovascular endothelium of a majority of solid type tumors and not on endothelial cells of normal tissue. Thus, radiolabelled PSMA may be utilized in the detection of tumor-specific angiogenesis (78-80). For the detection of nodal metastasis in prostate cancer, the FDA approved ProstaScint, a PSMA antibody labeled with  $^{111}\text{In}$  (81, 82). Another  $^{111}\text{In}$ -labeled PSMA antibody (J591) in a phase I clinical trial was reported to accumulate in malignant sites of tumors associated with kidney, liver, colon, breast and melanomas suggesting a potential of PSMA in imaging angiogenesis (81-84). In a preclinical study, a  $^{11}\text{C}$ -labeled small molecule ligand for prostate-specific antigen was shown to localize to prostate cancer in experimental animal models.

A number of extracellular matrix (ECM) proteins have also been targeted in the imaging of angiogenesis as some of the antigens in ECM have been discovered to be associated with neoangiogenic sites. Extra domain B of fibronectin and extra domain C of tenascin have been targeted in preclinical model systems to detect neoangiogenesis in malignant sites (63, 85, 86).

## 3. Clinical relevance of imaging angiogenesis

Radiotracer imaging techniques such as PET and SPECT offer unique advantages for investigation of angiogenesis in patients at the molecular level by virtue of its high sensitivity and adequate spatial and temporal resolution. At the clinical level, such approaches could be useful for lesion detection, to select patients likely to respond to therapies directed at such targets, to confirm successful targeting and dose optimization as well as treatment monitoring. Additionally, nuclear imaging techniques could also aid in the development of new angiogenesis-targeted drugs and their validation. For example, PET imaging can provide rapid characterization of a drug's pharmacokinetics and pharmacodynamic behavior in both pre-clinical studies and clinical trials thereby improving the speed, efficiency and cost of drug development. Taken together, these exciting developments will likely play an important clinical role in the management of human malignancies.

### 3.1 Future outlook on angiogenesis radiotracer design

The past decade has seen major advances in the field of PET and SPECT radiotracer development for visualizing the molecular events associated with angiogenesis. A vast majority of these approaches have either focused on radiolabeled analogs of vascular endothelial growth factor (VEGF) or RGD small peptide antagonists of the  $\alpha_v\beta_3$  class of cell adhesion molecule integrins. Despite these achievements, there is still a need for improvements in synthetic strategies for existing radiotracers and the development of alternate radiotracers for angiogenesis imaging. For example, approaches using radiolabeled VEGF are complicated by several factors such as the presence of multiple VEGF isoforms, high renal expression of VEGF receptors and the mitogenic activity of VEGF. Additionally, clinical trials conducted with RGD-based radiotracers have shown wide heterogeneity in tumor binding both within the same patient and between patients (87). Furthermore, RGD

peptides may have limitations for tumor imaging due to the limited number of  $\alpha_v\beta_3$  integrin receptors available per tumor cell and their low binding affinity (87). Thus, new radiotracers with improved targeting efficacy and pharmacokinetics are indispensable for successful clinical translation.

Angiogenesis is involved in a multitude of biological processes including, embryogenesis, female reproductive cycle, tissue remodeling and wound healing (88). Furthermore, imbalances or upregulation of angiogenic processes are observed in numerous disorders including rheumatoid arthritis, psoriasis, cardiac restenosis and diabetic retinopathy. Accordingly, the future availability of clinically-validated angiogenesis imaging radiotracers could have broad applicability in disease management beyond that of oncology.

#### 4. Summary

In this review, we have focused on recent developments in the design of new PET and SPECT radiotracers for imaging the tumor angiogenic process and their biological evaluation in pre-clinical animal models and initial clinical studies. Radiotracers based on VEGF and the cell adhesion molecule integrin  $\alpha_v\beta_3$  currently form the major focus for imaging agent development. Additionally, alternate approaches that focus on radiolabeled matrix metalloproteinase and prostate specific membrane antigen (PSMA) inhibitors as well as the tumor-homing F3 peptide are described. Molecular imaging techniques such as PET and SPECT continue to play an increasingly important role in both disease diagnosis at the presymptomatic stage and the monitoring of its progression and response to therapeutic intervention. The future availability of improved imaging biomarkers for angiogenesis and appropriate animal models for their validation will be crucial for unraveling this complex process in health and disease and could lead to important advances in the treatment of cancer.

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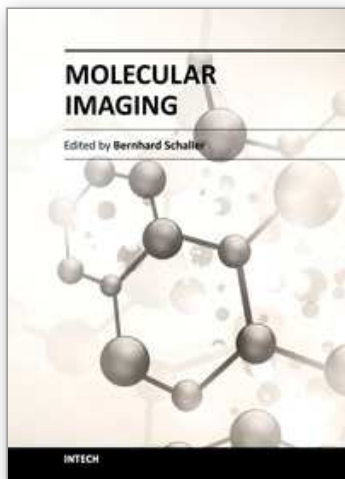


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The present book gives an exceptional overview of molecular imaging. Practical approach represents the red thread through the whole book, covering at the same time detailed background information that goes very deep into molecular as well as cellular level. Ideas how molecular imaging will develop in the near future present a special delicacy. This should be of special interest as the contributors are members of leading research groups from all over the world.

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University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
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### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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