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REVIEW ARTICLE

Animal tumor models for PET in drug development

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Abstract Positron emission tomography (PET) is being increasingly applied to animal tumor models due to the need for proof-of-concept testing and preclinical efficacy studies of anticancer agents. Regardless of the nature of an experiment, investigators should carefully select a suitable animal tumor model as part of the experimental design. This review introduces sources of information and the guiding principles regarding applicability of various animal tumor models for PET in anticancer agent development especially for small animals.

Keywords Animal tumor models · Positron emission tomography · Drug development · Anticancer agent

List of abbreviations

anti-[^{18}F]FACBC	Anti-1-amino-3-[^{18}F]fluorocyclobutyl-1-carboxylic acid
BOP	*N*-nitrosobis(2-oxopropyl)amine
CEA	Carcinoembryonic antigen
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ER^{+}	Estrogen receptor positive
ER^{-}	Estrogen receptor negative
ERE	Estrogen responsive element
FAS	Fatty acid synthase
[^{18}F]FES	16α-[^{18}F]Fluoroestradiol
[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
[^{18}F]FLT	3′-Deoxy-3′-[^{18}F]fluorothymidine
HDACI	Histone deacetylase inhibitors
HER2	Human epidermal growth factor receptor 2
IL	Interleukin
MEK	Mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
Morpholino-[^{124}I]IPQA	(*E*)-But-2-enedioic acid [4-(3-[^{124}I]iodoanilino)-quinazolin-6-yl]-amide-(3-morpholin-4-yl-propyl)-amide
MSH	Melanocyte-stimulating hormone
OPCT	Orthotopic prostate cancer transplantation
PET	Positron emission tomography
RGD	Arginine-glycine-aspartic
TVI	Tumor viability index
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor 2
Zebularine	1-(β-D-Ribofuranosyl)-1,2-dihydropyrimidine-2-1

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Introduction

PROGRESS in anticancer agent development has often been dependent on the use of animal tumor models for both proof-of-concept testing and for preclinical efficacy

evaluation. Despite wide usage of animal tumor models, there have been limitations based on the investigator's unfamiliarity with basic biomedical information related to these models. Regardless of the nature of the experiment, the investigators should carefully select suitable animal tumor models as part of the experimental design. Especially, the selection of suitable animal tumor models and biomarkers are prerequisites in the development of molecularly targeted anticancer agents. The purpose of this review is to introduce sources of information and the guiding principles regarding the applicability of various animal tumor models for use of positron emission tomography (PET) in anticancer agent development.

Now that high-resolution PET scanners capable of imaging small rodents at sufficient resolution are available, there can be great progress in anticancer agent development. Therefore, special emphasis is focused on rodent models. Rodents have been the main mammalian species used in preclinical studies ranging from pharmacology to safety assessment and also evaluation of PET tracers. Moreover, mice and rats are small, highly prolific, and therefore relatively cheap to breed. In addition, the development of human tumor xenograft models in immunodeficient rodents as well as techniques for transgenesis and gene knock-out have made mice and rats attractive models for the use in oncology research.

Here, we introduce available animal tumor models used in PET for anticancer agent development. Approximately 100 references recently published in four journals (*Nuclear Medicine and Biology*, *Journal of Nuclear Medicine*, *European Journal of Nuclear Medicine and Molecular Imaging*, and *Cancer Research*) were selected for this review. Transplantable animal tumor models are listed in Table 1. Animal tumor models for gene therapy and radiotherapy are beyond the scope of this review and are therefore not discussed in detail.

General considerations of animal tumor model selection

The selection of appropriate animal tumor models for PET in anticancer agent development must be based on the criteria that define both available tracers and the host or carrier species and strain. Ideally, the animal tumor models should be rapidly and simply prepared (and hence inexpensive) and should have predictive for clinical response. To date, most anticancer drug screening has been based on assessment of drug activity against rapidly growing transplantable tumors or human tumor xenografts in immunodeficient rodents. The screening of new drugs usually involves determination of the influence of a drug on survival of syngeneic tumor-bearing mice and comparison of tumor growth between treated and untreated mice. These systems are useful for identifying new drugs based on the concept of total cell killing to cure the malignant neoplasm. Several major classes of anticancer agents, including alkylating agents, anti-metabolites, and a variety of natural or semi-synthetic compounds, have been developed using these systems and have been approved for clinical use.

Many of the biological and molecular changes that occur in malignant transformation are becoming better defined, and this knowledge is being used to synthesize new types of anticancer agents, the targets of which may be more specific to tumor cells. Such targets include the products of oncogenes, molecules involved in cell signaling or cell cycle control, and growth factors or receptors that are essential for angiogenesis in tumors. For many of these newer approaches to cancer control, cell death is a less relevant end point. Inhibition of intracellular signaling may interfere with transformation and uncontrolled cell growth but may produce little or no cell killing. Similarly, inhibitors of angiogenesis are unlikely to produce cell killing. These drugs may exhibit their effects by inhibiting metabolism and proliferation of tumor cells, while cell death continues leading to gradual involution of the tumor. Therefore, new in vivo assay systems may be required to fully assess the therapeutic potential of these agents. Likewise, novel approaches may be required to evaluate the roles of new anticancer agents in clinical practice.

It goes without saying that the selection of appropriate tumor cell lines is very important. The investigators should carefully select suitable tumor cell lines not only for adopting their study design but also for the quality of each cell line. The major problems which can affect the utility of cell lines are genetic instability and phenotypic drift. Tumor cell lines tend to lack genes for monitoring and repairing DNA damage and show an increased mutation frequency. Hence, between laboratories, genetic and phenotypic changes are often seen, e.g., in stocks of the human breast cancer cell line MCF-7. To minimize genotypic and phenotypic variation of a cell line within and between laboratories, it should be expanded and frozen, and used to provide the seed stock for future work.

The in vivo microenvironment is known to significantly influence the tumor response to treatment. Therefore, an ideal animal tumor model should mimic the interaction of tumor cells with their relevant organ environment. Orthotropic tumor models show similarities in tumor architecture, cell morphology, and molecular characteristics to clinical cancers. Therefore, orthotropic models are now used extensively in the development of new anticancer treatments and studies of tumor biology. The tumor size also influences the tumor microenvironment. Larger tumors are known to have a poorly organized vascular system, so that tumor cells are deficient in oxygen and other nutrients. Hypoxic cells are known to be resistant to radiation and to

Table 1 Transplantable animal tumor models used in PET studies

Tumor type	Cell	Host	Radiotracer	References
Human				
Brain	U-87MG	Nude mouse	[^{64}Cu]DOTA-PEG-RGD	[1–6, 33, 54–59]
	U-87MG-fLuc	Nude rat	[^{18}F]FB-PEG-RGD	
	251T		[^{18}F]FB-RGD	
	A1207		[^{18}F]FPTA-RGD2	
	U373		[^{64}Cu]DOTA-RGD multimer	
			[^{18}F]FPRGD2	
			[^{68}Ga]NOTA–RGD1	
			[^{68}Ga]NOTA–RGD2	
			[^{68}Ga]NOTA–RGD4	
			[^{18}F]FDS	
			[^{18}F]FDG	
			[^{18}F]FB-RGD	
			[^{64}Cu]DOTA-VEGF121/rGel	
			[^{124}I]IPA	
			[^{11}C]mHED	
Head and neck squamous cell cancer	SCC-4, FaDu	Nude mouse	[^{18}F]FDG	[60–64]
	HNX-OE	Nude rat	[^{18}F]OMFD	
			[^{18}F]FLT	
			[^{18}F]FMISO	
			[^{64}Cu]ATSM	
Esophageous	SEG-1	Nude mouse	[^{18}F]FDG	[24]
			[^{18}F]FLT	
Breast	MCF-7	Nude mouse	[^{18}F]FDG	[10, 15, 17, 20, 55, 65–67]
	MCF-7 A29 clone	SCID mouse	[^{18}F]FES	
	T-47D		[^{11}C]T138067	
	MDA-MB-231		[^{18}F]T138067	
	MDA-MB-435 MDA-MB-468 MDA-361/DYT2		[^{18}F]FESP	
			[^{64}Cu]DOTA-CTT	
			[^{64}Cu]DOTA-STT	
			[^{18}F]FB-RGD	
			[^{64}Cu]DOTA-RGD	
			[^{18}F]FLT	
			[^{124}I]C6.5 diabody	
Lung	Lu-99	Nude mouse	[^{18}F]FDG	[68]
	A549	Nude rat		[59]
Alveolar	RH-30	Nude mice	[^{18}F]FDG	[69]
Pancreas	PancTuI	SCID mice	[^{18}F]FDG	[70]
	Colo357 BxPC3		[^{18}F]FLT	
			[^{18}F]FEC	
Colon	HT29	Nude mouse	[^{18}F]FAU	[8, 16, 35, 61, 71–75]
	HT29 #53 clone	SCID mouse	[^{18}F]FDG	
	LS174T	Nude rat	[^{18}F]FLT	
	HCT116		[^{18}F]OMFD	
			[^{18}F]FB-T84.66 diabody	
			[^{18}F]FMISO	
			[^{124}I]FIAU	
			[^{11}C]COX-2	

Table 1 continued

Tumor type	Cell	Host	Radiotracer	References
Kidney	SK-RC-52	Nude rat	[^{18}F]FDG	[76]
			[^{89}Zr]Df-cG250	
Ovary	SK-OV-3	Nude mouse	[^{124}I]C6.5 diabody	[15, 31, 71, 77]
	SKOV3ip1	SCID mouse	[^{18}F]FDG	
	HeyA8		[^{18}F]FBO-Z(HER2:477)	
	IGROV-1			
Cervics	HeLa	Nude mice	[^{18}F]FLT	[78]
Prostate	CWR22	Nude mouse	[^{18}F]FLT	[12, 21, 22, 33, 38, 71, 79, 80]
	PC-3	SCID mouse	[^{64}Cu]DOTA–cetuximab	
	DU145	Nude rat	[^{18}F]FACBC	
	LN-CaP		[^{11}C]Acetoacetate	
	22Rv1		[^{11}C]Acetate	
	C42B		[^{64}Cu]DOTA-[Lys^{3}]BBN, [^{64}Cu]DOTA-Aca-BBN	
	NCIPC3		[^{64}Cu]DOTA-8-AOC-BBN(7–14)NH_2	
			[^{64}Cu]CB-TE2A-8-AOC-BBN(7–14)NH_2	
			[^{18}F]Fluoride	
			[^{18}F]FDG	
Skin	A431	Nude mouse	[^{18}F]Galacto-RGD	[7, 13, 14, 31, 37, 81]
		Nude rat	[^{89}Zr]Cetuximab	
			[^{18}F]FDG	
			[^{18}F]FLT	
			[^{18}F]FAZA	
			Morpholino-[^{124}I]-IPQA	
			[^{18}F]FMISO	
			[^{124}I]IAZA	
Melanoma	M21	Nude mouse	[^{18}F]Galacto-RGD	[7, 34, 74]
	M21-L		[^{18}F]FDG	
	SKMEL-28		[^{18}F]FLT	
	BT-474			
Lymphoma	K562	Nude mouse	Morpholino-[^{124}I]-IPQA	[13, 23, 26]
	DoHH2	SCID mouse	[^{18}F]FLT	
	SUDHL-4	Nude rat		
Sarcoma	SKLMS1	Nude rat	[^{18}F]FDG	[42, 82]
	TC-71	NOD/scid mouse	[^{18}F]FEAU	
	VH-64		[^{18}F]Fluoride	
	CADO-ES1			
Unkown	HOM-T3868	Nude mouse	[^{124}I]IPA	[57]
Mouse				
SCC	SCCVII	C_3H mouse	[^{18}F]FLT	[78, 83]
			[^{18}F]FMISO	
			[^{64}Cu]ATSM	

Table 1 continued

Tumor type	Cell	Host	Radiotracer	References
Breast	4T1	Balb/c mouse	[^{64}Cu]DOTA-VEGF121, [^{64}Cu]DOTA-VEGFDEE	[11, 17, 18, 65, 79]
	4T1 (fLuc4T1)		[^{18}F]FDG	
	MC4-L2		[^{18}F]FES	
	MC4-L3		[^{11}C]Acetoacetate	
	MC7-L1		[^{11}C]Acetate	
			[^{64}Cu]DOTA-IL-18bp-Fc	
	SC-115 (Shionogi)	DD/S mouse	[^{18}F]EF5	[84]
	MCaK	C_3H mouse	[^{18}F]FLT	[85]
Lung	LLC	C57BL/6	[^{18}F]FLT	[86]
Prostate	RM1 hPSMA+RFP/Rluc	SCID/beige mice	[^{18}F]FEAU	[87]
Melanoma	B16F1	B6D2F1 mouse	[^{68}Ga]DOTA-NAPamide	[9, 10, 41, 88]
	B16F10	C57BL/6 mouse	[^{64}Cu]DOTA-ReCCMSH(Arg^{11}), [^{86}Y]DOTA-ReCCMSH(Arg^{11})	
			[^{64}Cu]DOTA-CTT, [^{64}Cu]DOTA-STT	
			[^{18}F]FDG	
Lymphoma	A20	Balb/c mouse	[^{18}F]FDG	[89]
Fibrosarcoma	RIF-1	C_3J/Hej mouse	[^{18}F]FDG	[25]
			[^{18}F]FLT	
	FSAII	C_3Hf/Kam	[^{18}F]EF3	[90]
Unknown	FDC-P1	DBA/2J mouse	[^{18}F]FDG	[32]
Rat				
Brain	F98	F344 rat	[^{18}F]FBPA	[68, 91–94]
			[^{18}F]FBPA-Fr	
			[^{18}F]FDG	
			L-[^{18}F]FET	
			L-[^{18}F]FBPA-Fr	
	C6	Nude mouse	[^{18}F]FDG	[16, 28, 95–97]
	C6tk	Nude rat	[^{18}F]FLT	
		Rat: wistar, SD	[^{11}C]SA4503	
			[^{18}F]FE-SA4503	
			[^{11}C]Choline	
			[^{11}C]Methionine	
			[^{18}F]FB-T84.66 diabody	
			[^{18}F]FHPG	
	9L	F344 rat	[^{18}F]FDG	[68, 98, 99]
	9LDsRed		[^{18}F]FLT	
			[^{18}F]FMISO	
			[^{64}Cu]ATSM	
			[^{11}C]MET	
			[^{18}F]FHBG	
Liver	RH7777	Nude rat	[^{124}I]IAZGP	[68, 100]
	MH3924A		[^{15}O]H_2O	
	Ang-2-MH3924A		[^{68}Ga]DOTA-albumin	
	AH109A	Donryu rat	[^{18}F]Fluoromethylcholine	[101]
	KDH-8	WKAH rats	[^{18}F]FDG	[102]

Table 1 continued

Tumor type	Cell	Host	Radiotracer	References
Colon	RCN-9	F344/DuCrj rat	[^{18}F]FDG	[39, 40]
Prostate	MAT-Ly-Lu-B2, dunning R3327-AT	Copenhagen rat	[^{18}F]FACBC [^{18}F]FMISO [^{64}Cu]ATSM	[22, 63]
Sarcoma	R1	WAG/Rij rat	[^{18}F]FMISO	[103]
	1547	SD rat	[^{18}F]FDG	[104]
	P22	BDIX rat	[^{64}Cu]ATSE/A-G	[105]
Adrenal	PC12	Nude mouse	[^{11}C]Phenetylguanidine	[106]
Rabbit				
Carcinoma	VX2	NZ white Japanese white	[^{18}F]FDG	[50–53, 107]

the activity of several anticancer drugs. The nutritional state of the tumor tissues also influences the cellular uptake, metabolism, and toxicity of anticancer agents. In addition, larger tumor has limited penetration of drugs from tumor vessels and tends to proliferate more slowly. Hence, the tumor size is a critical factor for the procurement of successful data.

Models for PET in the screening of new tracers

Several animal tumor models for the screening of new PET tracers were developed recently. The most frequently used animal tumor models for PET tracer development can be found in the field of the design and synthesis of arginine-glycine-aspartic (RGD) peptide analogs for $\alpha_v\beta_3$ integrin expression imaging. Integrin $\alpha_v\beta_3$ plays an important role in angiogenesis and tumor cell metastasis, and is currently being evaluated as a target for new therapeutic approaches. For this purpose, U-87MG human glioblastoma xenograft in immunodeficient rodents was used as a subcutaneous or intracranial tumor model [1–6].

Melanoma is also known as a highly metastatic and integrin $\alpha_v\beta_3$-positive tumor. Haubner et al. [7] validated [^{18}F]galacto-RGD as an integrin $\alpha_v\beta_3$-specific tracer with xenotransplanted human melanoma models (M21 and M21-L). The M21 cell line expressing $\alpha_v\beta_3$ was used as a positive control and the M21-L cell line, a stable variant of M21 that fails to transcribe the α_v genes, was used as a negative control. They showed that the uptake of [^{18}F]galacto-RGD in the tumor is correlated with the level of $\alpha_v\beta_3$ expression subsequently determined by Western blotting analysis. Moreover, using an A431 human epidermoid carcinoma model, they also demonstrated that [^{18}F]galacto-RGD PET is sufficiently sensitive to visualize $\alpha_v\beta_3$ expression. The integrin $\alpha_v\beta_3$-positive transgenic c-neu oncomouse was also used as a model animal for the screening of PET tracers [3, 6]. The c-neu oncomouse is a spontaneous tumor-bearing model that carries an activated c-neu oncogene driven by the murine mammary tumor virus promoter. Transgenic mice uniformly expressing the mouse mammary tumor virus/*c*-neu gene develop mammary adenocarcinomas 4–8 months postpartum that involve the entire epithelium in each gland.

Another application is the specific molecularly targeted PET tracer development [8–11]. Wang et al. [11] selected the 4T1 murine breast tumor model to evaluate vascular endothelial growth factor receptor 2 (VEGFR-2)-specific PET tracers. VEGFR-2 imaging is a valuable tool for the evaluation of patients with a variety of malignancies, and particularly for monitoring those undergoing anti-angiogenic therapies that block the vascular endothelial growth factor (VEGF)/VEGFR-2 function. Froidevaux et al. [9] used melanocyte-stimulating hormone (MSH) receptor-positive B16-F1 melanoma-bearing mice in PET drug development study of ^{68}Ga-labeled DOTA-α-MSH analog. PC-3 xenograft was used for bombesin receptor imaging in PET drug development study [12]. A431 epidermoid carcinoma xenografts in immunodeficient rodents have been used extensively as positive controls for high epidermal growth factor receptor (EGFR) expressing tumors in PET research [13, 14]. Pal et al. [13] evaluated (*E*)-but-2-enedioic acid [4-(3-[^{124}I]iodoanilino)-quinazolin-6-yl]-amide-(3-morpholin-4-yl-propyl)-amide (morpholino-[^{124}I]IPQA) in EGFR-positive A431 and EGFR-negative K562 human chronic myeloid leukemia xenografts of immunodeficient rodents using small animal PET.

Immuno-PET is an important field in oncological PET tracer development. Engineered antibody fragments have been developed with the appropriate targeting specificity and systemic elimination properties predicted to allow

effective imaging of cancer based on the expression of tumor-associated antigens. Robinson et al. [15] evaluated ^{124}I-labeled small engineered antibody fragment (C6.5 diabody) specific for the human epidermal growth factor receptor 2 (HER2) tyrosine kinase. They validated the antigen-specific accumulation of C6.5 diabody using HER2-positive (SK-OV-3) and HER2-negative (MDA-MB-468) tumor xenografts. Cai et al. [16] evaluated ^{18}F-labeled genetically engineered anti-carcinoembryonic antigen (anti-CEA) T84.66 diabody specific for CEA-expressing tumor. They validated the antigen-specific accumulation of diabody using CEA-positive (LS174T) and CEA-negative (C6) tumor xenografts.

Models for PET in endocrine therapy

Mammary tumor

The most widely used hormone-dependent human breast cancer cells are MCF-7, T-47D, and ZR-75-1. These cell lines were derived from malignant effusions in postmenopausal women and require estrogenic supplementation for tumorigenesis in nude mice. This estrogen-induced growth is inhibited by anti-estrogen administration. Several other human breast cancer cell lines are used to mimic the spectrum of human breast tumor characteristics, including hormone-independent growth [estrogen receptor-negative (ER^-) MDA-MB-231] and metastatic models (MDA-MB-231 and MDA-MB-435). Aliaga et al. [17] evaluated various animal tumor models of estrogen receptor positive (ER^+) and ER^- for their suitability to follow tumor response after various treatment protocols using small animal PET. They used human breast cancer (MCF-7 and T-47D) and murine mammary ductal carcinoma (MC4-L2, MC4-L3, and MC7-L1) cells lines as ER^+ tumors and MDA-MB-231 as ER^- counterparts. The human breast cancer cell lines (MCF-7, T-47D, and MDA-MB-231) grew at a slower rate in vivo and failed to accumulate 16α-[^{18}F]fluoroestradiol ([^{18}F]FES); in contrast, Balb/c MC7-L1 and MC4-L2 grew well and showed good uptake of both 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) and [^{18}F]FES. Chemotherapy (doxorubicin and methotrexate) and hormonal therapy (antiestrogen, tamoxifen and raloxifene; aromatase inhibitor, exemestane and letrozole) delayed the growth of MC7-L1 and MC4-L2 tumors, confirming their suitability as ER^+ models for therapeutic interventions. From these results, they concluded that murine MC7-L1 and MC4-L2 tumors are suitable models for monitoring the efficacy of ER^+ breast cancer therapy using small animal PET. They further investigated the feasibility of [^{18}F]FDG PET imaging to monitor tumor metabolic responses to therapy in MC7-L1 and MC4-L2 models [18]. In mice undergoing chemotherapy (doxorubicin and methotrexate) or hormonal therapy (letrozole), the level of [^{18}F]FDG uptake was markedly reduced after treatment, although flare reaction on [^{18}F]FDG PET was observed at day 7, the intensity of which varied between treatments. Interestingly, this transient increase in [^{18}F]FDG uptake has also been reported in clinical studies involving patients with metastatic breast cancer treated with tamoxifen [19].

The two reporter gene systems driven by the same regulatory sequence containing an estrogen responsive element (ERE) were used for multimodality imaging of estrogen receptor (ER) activity in a MCF-7 xenograft model [20]. Two reporters were chosen: a mutated form of the dopaminergic D_2 receptor for PET imaging, and firefly luciferase for bioluminescence imaging. This cell line successfully couples the sensitivity and repeatability of bioluminescence imaging with three-dimensional quantitative imaging of D_2 receptor expression to monitor ER-dependent transcription.

Prostate tumor models

There are a few established animal models for prostate cancer despite its status as one of the leading causes of cancer-related mortality. The most commonly studied human prostate cancer cell lines are PC-3, DU-145, and LNCaP. PC-3 and DU-145 are poorly differentiated; they lack androgen receptors and 5α-reductase and do not produce prostate-specific antigen. LNCaP is the most commonly used cell line, and it expresses both prostate-specific antigen and prostatic acid phosphatase and is androgen sensitive.

There is a substantial evidence that androgens are involved in the etiology of prostate cancer. The pharmacological treatment of prostate cancer is based upon its marked sensitivity to androgen deprivation. Surgical and medical (diethylstilbestrol) castration have been reported to produce marked reductions in cancer mass and to lead to good rates of clinical remission. Therefore, the aim of all current endocrine treatments for prostate cancer is to diminish androgen levels. Oyama et al. [21] examined whether 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) is useful for monitoring the therapeutic effects of androgen ablation therapy on androgen-dependent human prostate tumor CWR22 xenografts. Androgen ablation therapy was conducted in this model with either diethylstilbestrol or surgical castration. Marked reductions in [^{18}F]FLT uptake were observed in tumors after castration or diethylstilbestrol treatment, while there were no differences in [^{18}F]FLT uptake in tumors in the control group. These changes in [^{18}F]FLT uptake in tumors parallel the changes in actual tumor size. These results indicate that [^{18}F]FLT PET with androgen-dependent tumor models is useful for monitoring the therapeutic effects of androgen ablation therapy in prostate cancer.

Oka et al. [22] reported another prostate cancer model useful for PET studies in anticancer agent development. They established a rat orthotopic prostate cancer transplantation (OPCT) model, and used it for the preclinical evaluation of anti-1-amino-3-[^{18}F]fluorocyclobutyl-1-carboxylic acid (anti-[^{18}F]FACBC). The OPCT model was established by transplanting the human prostate cancer cell line DU145 into the ventral prostate of F344 nude rats. Small animal PET imaging with anti-[^{18}F]FACBC facilitated visualization of prostate cancer tissues of the OPCT rats with higher contrast than that using [^{18}F]FDG.

Models for PET studies of cytotoxic drugs

[^{18}F]FLT and [^{18}F]FDG PET are valuable tools for monitoring cytotoxic treatment in various animal tumor models. Graf et al. [23] reported that the early response to doxorubicin treatment in human diffuse large B-cell lymphoma (SUDHL-4) xenografts can be visualized with [^{18}F]FLT PET. These changes in tracer uptake after therapy are correlated with both cell cycle arrest and apoptosis. Apisarnthanarax et al. [24] assessed the ability of [^{18}F]FLT PET to detect early changes in tumor proliferation after chemoradiotherapy in SEG-1 human esophageal adenocarcinoma xenografts in nude mice. They found that [^{18}F]FLT PET is suitable and more specific than [^{18}F]FDG PET for detecting early reductions in tumor proliferation that precede changes in tumor size after chemoradiotherapy. Leyton et al. [25] assessed the potential of [^{18}F]FLT to measure early cytostasis and cytotoxicity induced by cisplatin treatment of radiation-induced fibrosarcoma 1 tumor-bearing C3J/Hej mice. They found that [^{18}F]FLT PET can be used to provide early assessment of chemosensitivity in this tumor-bearing mouse model. They also proposed that [^{18}F]FLT PET may be feasible as a generic pharmacodynamic method for early quantitative imaging of drug-induced changes in cell proliferation in vivo. Buck et al. [26] examined whether [^{18}F]FLT PET is adequate for early evaluation of the response of malignant lymphoma to antiproliferative treatment in human CD20-positive B-cell follicular lymphoma DoHH2 xenografts in SCID mice. They found significant reduction of [^{18}F]FLT uptake in the tumors after high-dose chemotherapy (cyclophosphamide), immunotherapy (CD20 mAb, ibritumomab tiuxetan) and radioimmunotherapy ([^{90}Y]CD20 mAb, zevalin). None of the animals showed a significant change in tumor size. Therefore, in a lymphoma xenotransplant model, [^{18}F]FLT can detect early antiproliferative drug activity before changes in the tumor size are visible. These preclinical results suggested that [^{18}F]FLT is probably a better cancer-specific tracer than [^{18}F]FDG and may be useful for evaluating early responses to cytotoxic drugs.

Models for PET in molecularly targeted drugs

There is a growing need for means of evaluating the therapeutic effects of molecularly targeted drug candidates by small animal PET imaging, and there has been a corresponding increase in the number of reports regarding molecularly targeted drug evaluation combined with small animal PET. [^{18}F]FDG and [^{18}F]FLT PET are the most commonly used tracers for evaluation of molecularly targeted drugs. These investigations demonstrated that animal tumor models and small animal PET are useful to accelerate the preclinical evaluation of new drug candidates and may be able to predict the success of clinical trials. A successful example is discussed below.

Evaluation of molecularly targeted drugs by [^{18}F]FDG PET

Tseng et al. [27] evaluated the efficacy of CE-355621, a novel antibody against c-Met, in a subcutaneous human glioblastoma U-87MG xenograft using [^{18}F]FDG PET. c-Met is a receptor tyrosine kinase involved in multiple pathways linked to cancer and is upregulated in a large number of human cancers. They showed that CE-355621 inhibits [^{18}F]FDG accumulation earlier than changes in tumor volume, which supports the use of [^{18}F]FDG PET in human clinical trials for early therapy monitoring. Assadian et al. [28] evaluated the therapeutic effect of a novel hypoxia-inducible factor-1α inhibitor YC-1 in the rat C6 glioma model following a 3-day regimen using [^{18}F]FDG PET. The [^{18}F]FDG uptake was significantly lower in treated tumors than in control tumors during the course of treatment. Gene silencing by CpG island promoter hypermethylation has prompted interest in DNA demethylating agents such as chemotherapeutic drugs. Zebularine (1-[β-D-ribofuranosyl]-1,2-dihydropyrimidine-2-1) has recently been described as a new DNA methylation inhibitor. Herranz et al. [29] examined its effects in a mouse model of radiation-induced lymphomagenesis using [^{18}F]FDG PET. All nontreated animals showed large thymic T lymphomas and died between 4 and 5.5 months after radiation exposure. In contrast, 40% of zebularine-treated animals were still alive after 1 year. [^{18}F]FDG PET imaging showed that a specific hot spot seen in thymic lymphoma is lost in zebularine-treated mice. DNA hypomethylation induced by zebularine occurred in association with depletion of extractable DNA methyltransferase 1 protein. These data support the utility of [^{18}F]FDG PET for monitoring the DNA hypomethylation effect with antitumor activity. Fatty acid synthase (FAS) is an emerging target for anticancer therapy, and a variety of new FAS inhibitors have been explored in preclinical models. Lee et al. [30] evaluated whether the FAS inhibitor C75 affects the tumor glucose

metabolism demonstrated by [^{18}F]FDG PET in orthotopic human A549 lung cancer xenografts. Longitudinally measured metabolic volumes of interest and tumor-to-background ratios indicated a transient and reversible decrease in glucose metabolism and tumor metabolic volume after treatment, with the peak effect seen at 4 h. [^{18}F]FDG PET findings are correlated with the changes in tumor FAS activity measured ex vivo. These results demonstrated the usefulness of small animal PET in assessing the pharmacodynamics of new anticancer agents in preclinical models. Antiangiogenesis or destruction of tumor neovessels is an effective strategy to prevent tumor growth. AVE8062 is a tubulin-binding agent that belongs to a new family of low-molecular weight drugs with potent antivascular properties. Kim et al. [31] examined the therapeutic efficacy of AVE8026 alone and in combination with docetaxel in multiple orthotopic models of ovarian cancer. In addition, they performed [^{18}F]FDG PET to examine whether early functional imaging can predict therapeutic response to AVE8026. They demonstrated that AVE8026 inhibits ovarian cancer growth through direct effects on endothelial cells causing marked disruption in tumor blood flow leading to central necrosis in an orthotopic murine model. The effect was rapid in onset and could be seen clearly by [^{18}F]FDG PET. These data suggested that [^{18}F]FDG PET imaging can predict the response before anatomical reduction in tumor size in antiangiogenic therapy. Clinically, the response of gastrointestinal stromal tumors to the small molecule c-KIT inhibitor imatinib is associated with rapid reduction in [^{18}F]FDG uptake on PET. Cullinane et al. [32] developed a model based on activating mutations in c-KIT in gastrointestinal stromal tumors and applied this model to image genetic changes using the [^{18}F]FDG method. The model is comprised of murine tumors derived from FDC-P1 cell lines expressing c-KIT mutations that render the tumors either responsive (V560G) or resistant (D816V) to imatinib. A small animal PET study showed that [^{18}F]FDG uptake in V560G-expressing tumors was significantly reduced as early as after 4 h of treatment. In contrast, no changes in [^{18}F]FDG uptake were observed in resistant-D816V-expressing tumors after 48 h of treatment. As mentioned above, the FDC-P1 model and [^{18}F]FDG PET are useful for molecularly targeted drug development.

Evaluation of molecularly targeted drugs by [^{18}F]FLT PET

Hsu et al. [33] used firefly luciferase-transfected U-87MG human glioblastoma orthotopic xenograft for determination of the antiangiogenic and antitumor effects of a vascular-targeting fusion toxin ($VEGF_{121}$/rGel). [^{18}F]FLT PET revealed a significant decrease in tumor cell proliferation in $VEGF_{121}$/rGel-treated mice compared with controls. Consistent with the [^{18}F]FLT PET results, histological analysis revealed specific tumor neovascular damage with a significant decrease in peak bioluminescence signal intensity of the tumor. Activating mutations of BRAF are observed in $\sim$7% of all human tumors and are sensitive to inhibitors of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK), which causes loss of D_1-cycline expression and finally induce G_1-arrest. Solit et al. [34] hypothesized that a proliferation marker [^{18}F]FLT PET imaging may represent an ideal noninvasive early marker of G_1 arrest induced by MEK inhibition in BRAF mutant tumor. To test this hypothesis, they evaluated [^{18}F]FLT uptake in BRAF mutant tumor xenograft treated with the MEK inhibitor PD0325901. MEK inhibition completely inhibited tumor growth and induced differentiation with only modest tumor regression. MEK inhibition also resulted in a rapid decline in the [^{18}F]FLT signal in V600E BRAF mutant SKMEL-28 xenograft but not in BRAF wild-type BT-474 xenografts. These data suggest that [^{18}F]FLT PET and mutant BRAF tumors are useful for noninvasively assessing the early biological response to MEK inhibitors. Histone deacetylase inhibitors (HDACIs) have been identified as growth inhibitory compounds that modulate gene expression and inhibit tumor cell proliferation. Leyton et al. [35] examined whether [^{18}F]FLT PET could be used for noninvasive measurement of the biological activity of a novel HDACI LAQ824 in vivo. They initially confirmed that thymidine kinase 1, the enzyme responsible for [^{18}F]FLT retention, was regulated by LAQ824 in a dose-dependent manner in vitro. In HCT116 colon carcinoma xenograft, LAQ824 significantly decreased [^{18}F]FLT uptake in a dose-dependent manner. [^{18}F]FLT tumor-to-heart ratio at 60 min (NUV60) correlated significantly with cellular proliferation and was associated with drug-induced histone H4 hyperacetylation. Interestingly, [^{18}F]FLT PET imaging, both thymidine kinase 1 mRNA copy numbers and protein levels decreased in the order vehicle $>$5 mg/kg LAQ824 $>$ 25 mg/kg LAQ824. Ongoing clinical trials of HDACIs have used conventional methods of assessment, such as the maximum tolerated dose, although most HDACIs are considered to induce cytostasis at clinically acceptable doses [36]. Therefore, [^{18}F]FLT PET may be useful as a noninvasive imaging method for quantifying biological activity of HDACIs and drug development of such agents.

Evaluation of molecularly targeted drugs by miscellaneous tracers

Dorow et al. [37] utilized A431 xenograft and multi-tracer serial small animal PET imaging as a proof-of-concept for a drug development model to characterize tumor response to molecularly targeted therapy. They showed that the pan-

Erb-B inhibitor CI-1033 treatment significantly affects tumor metabolism ([^{18}F]FDG), proliferation ([^{18}F]FLT) and hypoxia ([^{18}F]FAZA and [^{18}F]FMISO) as determined by PET. These PET findings correlated well with ex vivo biomarkers for each of the cellular processes studied. These results confirm the utility of small animal PET for evaluation of molecularly targeted therapies and simultaneously aid in identification of specific cellular processes involved in the therapeutic response. Noninvasive monitoring of the EGFR response to treatment with the Hsp90 inhibitor, 17-AAG, was evaluated by [^{64}Cu]DOTA-cetuximab in a PC-3 prostate cancer model [38]. Small animal PET imaging showed that EGFR expression demonstrated by [^{64}Cu]DOTA-cetuximab uptake was significantly reduced in 17-AAG-treated tumors. Both immunofluorescence staining and Western blotting confirmed the significantly lower EGFR expression level in the tumor tissues following 17-AAG treatment.

Metastatic tumor models

Metastasis is the major cause of death due to cancer. Patients with metastasis require chemotherapy, and one of the most crucial issues to be resolved in the treatment is how to properly evaluate the efficacy of chemotherapy. While the details of the genetic changes that contribute to metastatic ability remain incompletely understood, a number of possible therapeutic targets have been identified. Therefore, new reliable in vivo assay systems are needed to evaluate the therapeutic efficacy not only for clinical but also for preclinical drug development for metastasis. Recent advanced high-resolution PET scanners enable visualization of small tumor nodules in animals. However, it may still be difficult to visualize multiple small tumor nodules in animals. [^{18}F]FDG PET could detect only 35% of small nodules less than 2 mm in diameter. Ishiwata et al. [39] proposed the tumor viability index (TVI) as a new concept reflecting whole signals from [^{18}F]FDG taken up by all tumor tissues, including multiple and small tumor nodules. They used a liver metastatic tumor model by injection of rat colon adenocarcinoma (RCN-9) cells into Fisher 344 rats through the portal vein, and applied [^{18}F]FDG PET to this model. The TVI was defined by subtracting the signal based on the normal liver from the total signal in the whole liver including tumor nodules: (whole liver SUV−normal liver SUV) × ml of whole liver region of interest. The average TVI values increased with the tumor growth and was significantly correlated with the number of tumor nodules. Further, Liu et al. [40] applied this liver metastasis model and TVI to the evaluation of 5-fluorouracil treatment. The TVI values in the experimental model represented the viability of tumors suppressed by chemotherapy, and the values were significantly correlated with the number of nodules and the proliferating cell nuclear antigen index. Therefore, this model and index can be used to assess the efficacy of newly developed anticancer agents for liver metastasis. In addition, several other metastasis models have also been established for PET imaging studies. B16-F10 is one of the most commonly used highly metastatic cell populations in experimental lung metastasis. Using this metastasis model, Woo et al. [41] examined the impact of anesthesia on [^{18}F]FDG uptake in experimental lung metastasis models. They concluded that 0.5% isoflurane anesthesia was appropriate for detection of experimental lung metastasis using small animal [^{18}F]FDG PET. They also noted that the type and level of anesthetic should be considered carefully to ensure suitability for visualization of target tissues in experimental models. Franzius et al. [42] established a NOD/SCID mouse model for human Ewing tumor metastasis, and applied this model to diagnostic molecular imaging by small animal PET. Human Ewing tumor cells transplanted via the intravenous route produced multiple metastases in NOD/SCID mice. This pattern of metastasis was similar to those in patients with metastases in the lung, bone, and soft tissue. These metastases showed increased [^{18}F]FDG uptake. Osseous metastases were additionally visible on [^{18}F]fluoride PET by virtue of decreased [^{18}F]fluoride uptake. Bone metastasis of prostate cancer usually forms osteoblastic lesions but may also be associated with mixed or osteolytic lesions. Quantification of the osteoblastic and osteolytic components of prostate cancer lesions in vivo could be advantageous in providing an objective evaluation of different therapeutic regimens. Hsu et al. [43] reported longitudinal microPET/CT imaging of osteoblastic (LAPC-9), osteolytic (PC-3), and mixed (C42B derived from LNCaP) lesions formed by human prostate cancer cell lines in SCID mouse tibial injection model. They found that [^{18}F]FDG and [^{18}F]fluoride microPET/CT scans can localize and quantify skeletal metabolic activity in pure osteolytic and osteoblastic lesions induced by human prostate cancer cells. In contrast, for mixed lesions, [^{18}F]FDG and [^{18}F]fluoride microPET/CT scans detected only minimal metabolic activity. Further studies to determine whether microPET/CT can detect the differences in response to new treatment modalities in these models are required. Interleukin (IL)-18 plays important roles in cancer progression and metastasis. To evaluate the efficacy of IL-18 binding protein (IL-18bp)-Fc treatment, Cao et al. [44] established an experimental lung metastasis model and monitored the therapeutic response by multimodality imaging. The model was established by intravenous injection of IL-18bp-Fc-sensitive murine 4T1 breast cancer cells, which were stably transfected with firefly luciferase, into female Balb/c mice. Bioluminescence imaging, [^{18}F]FDG PET, and CT scans indicated that IL-18bp-Fc

treatment was effective in inhibiting lung metastasis tumor progression, as determined by ex vivo examination of the lungs.

Miscellaneous tumor models for PET in drug development

Chemically induced tumor models for evaluation of carcinogenesis

In 1918, Yamagiwa and Ichikawa produced tumors by repeated painting of coal tar on the skin of rabbits. This is the first example of chemically induced experimental animal tumor models. Subsequently, several chemically induced rodent tumor models were established. These models are useful for examining early events in the process of chemical carcinogenesis and for studying malignant progression. These tumor models are also useful for the preclinical in vivo screening of chemopreventive agents. van Kouwen et al. [45] applied the *N*-nitrosobis(2-oxopropyl)amine (BOP) model for evaluation of the potential of [^{18}F]FDG PET to early detection of pancreatic cancer. The BOP hamster models developed ductular proliferation with dysplasia and pancreatic cancer within 4 months after the start of BOP treatment. Briefly, male Syrian hamsters were subcutaneously injected once a week with 10 mg/kg of BOP for 10 consecutive weeks. Terminal autopsies were performed in groups of five hamsters each from 4 until 28 weeks after first BOP treatment. Seven of 55 hamsters developed macroscopic signs of tumor lesions. Histopathological examination revealed pancreatic cancer in 13 hamsters. [^{18}F]FDG uptake increased with time and was significantly higher in the group with than in that without pancreatic cancer. Azoxymethane is a potent carcinogen that induces colorectal cancer and adenomas in rats within 5 months after commencement of treatment. The spectrum of azoxymethane-induced epithelial lesions resembles those of various types of neoplastic lesion in human colorectal cancer. To examine [^{18}F]FDG accumulation occurring during the adenoma carcinoma sequence, van Kouwen et al. [46] studied the [^{18}F]FDG uptake in azoxymethane-induced colorectal adenocarcinoma and correlated the results with histopathological findings. Briefly, male Fisher F344 rats were subcutaneously injected once a week with 15 mg/kg of azoxymethane for 3 consecutive weeks. Terminal autopsy of the rats was performed in groups of seven animals each at 2-week intervals starting at 20 weeks after the first azoxymethane treatment. Macroscopic examination revealed 21 tumors (7 located in the small bowel and 14 in the colon) in 19 rats. On histological examination, 10 colonic adenocarcinomas (the first observed on week 22) and 7 adenocarcinomas in the small bowel were found. A total of seven colon adenomas were found in five rats, six of which showed high-grade dysplasia. The [^{18}F]FDG uptake in adenocarcinoma was significantly higher than background bowl uptake. Furthermore, [^{18}F]FDG uptake in carcinoma was higher than that in adenomas. These data suggest that the azoxymethane model allows evaluation of intervention/prevention strategies with [^{18}F]FDG uptake as a varied outcome marker. The novel thioacetamide-induced rat cholangiocarcinoma models and an esophagoduodenal anastomosis rat model for carcinogenic progression of intestinal metaplasia to esophageal adenocarcinoma were also evaluated by [^{18}F]FDG PET [47, 48].

Transgenic animal models

Recently, genetically engineered mouse models of high-grade glioma applied to the development of a robust and reproducible kinetic analysis method for the quantitative evaluation of tumor proliferation by [^{18}F]FLT PET [49]. Ntv-a/Ink4a$^{-/-}$Arf$^{-/-}$ mice were intracranially injected with 10^4 DF-1 cells infected with and producing RCAS-PDGF retroviral vectors within 24 h of birth. The dynamic [^{18}F]FLT PET was successfully performed in a clinically relevant genetically engineered high-grade glioma model with the image-derived left ventricular input function. The c-neu oncomouse is described above.

VX2 rabbit tumor models

VX2 rabbit tumors are transplantable in Japanese White and New Zealand White strains. These tumors grow rapidly and reach a size that can be easily identified on imaging. In addition, catheter manipulation is easier in rabbits than in other small animals, such as mice and rats. Therefore, this model has been widely used to evaluate the curative effects of intraarterial administration of chemotherapeutic drugs and new treatment devices. However, there were only limited reports concerning the PET study of VX2 tumors on the literature recently [50–53]. Four of these 5 publications were reported from institutions within Asia. The VX2 tumor cell line is commercially available from the European Collection of Cell Cultures (ECACC).

Conclusions

Application of PET in anticancer agent development is a rapidly growing field of molecular imaging. However, available PET tracers and resolution of small animal PET scanners still have limitations for anticancer agent development. Therefore, the selection of appropriate animal tumor models and suitable validated tracers are significant

issues for successful application of PET in anticancer agent development. Tracer quality, animal handling, and kinetic analysis are also very important. Fortunately, there has been remarkable progress in addressing these methodological issues, especially in the fields of small animal imaging.

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