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Molecular Imaging: the Latest Generation of Contrast Agents and Tissue Characterization Techniques

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Abstract Molecular Imaging technologies will have a profound impact on both basic research and clinical imaging in the near future. As the field covers many different specialties and scientific disciplines it is not possible to review all in a single article. In the current article we will turn our attention to those modalities that are either currently in use or in development for the medical imaging clinic. J. Cell. Biochem. 90: 443–453, 2003. © 2003 Wiley-Liss, Inc.

Key words: molecular imaging; radionuclide; contrast agent; MR; CT; SPECT; PET

The focus of this article will be to review the novel molecular imaging based contrast agents that have the greatest potential for use in clinical medicine in near future. We will discuss how the current modalities that are available for human use namely, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), single photon emission computed tomography (SPECT), or positron emission tomography (PET), and how they can be applied to the imaging of these new contrast agents.

MRI, US, AND CT

To successfully study specific receptor systems it is helpful to understand the cells expressing the receptors and the circumstances leading to changes in expression [Fischman et al., 1989]. Any receptors expressed in sufficient quantity (at least 10–50,000 copies/cell) with sufficiently high affinity for the injected agent ($>10^{-8}$ M) can be detected by external imaging [Blankenberg et al., 2000; Behr et al., 2001]. In general, radiopharmaceuticals developed for SPECT and PET have (a) high specificity (b) sensitivity requiring, (c) minimal amounts of labeled material ~0.1–10 nmoles per dose as compared with MRI and US, or iodinated contrast media for CT where concentrations ranging from ~10 μM to ~100 μM are required for imaging. While SPECT and PET offer exceptional sensitivity with respect to the amount of contrast material needed for imaging, they lack the exquisitely high anatomical spatial resolution of US, CT, and MRI. The high sensitivity of SPECT and PET to small amounts of contrast agents and high anatomic resolution with CT and MRI, however, can be combined with the current generation of PET/CT [Ketai and Hartshorne, 2001; Townsend and Beyer, 2002], SPECT/CT [Forster et al., 2003], and soon PET/MRI [Nishioka et al., 2002] clinical scanners in which co-registration of radionuclide and anatomical images (i.e., fusion imaging) is now possible as shown in Figure 1.

A variety of contrast agents have been developed for US, CT, and particularly, MRI. Most MR agents constructed thus far take advantage of either iron particulates or gadolinium (Gd)-compounds to modulate signal at the site or target of interest. Usually multiple atoms of iron or Gd are placed onto targeting molecules of interest either by attachment to polylysine, dextran, dendrimer, or coated liposome to decrease the amount of targeting material required for external imaging [Aime et al., 2002].

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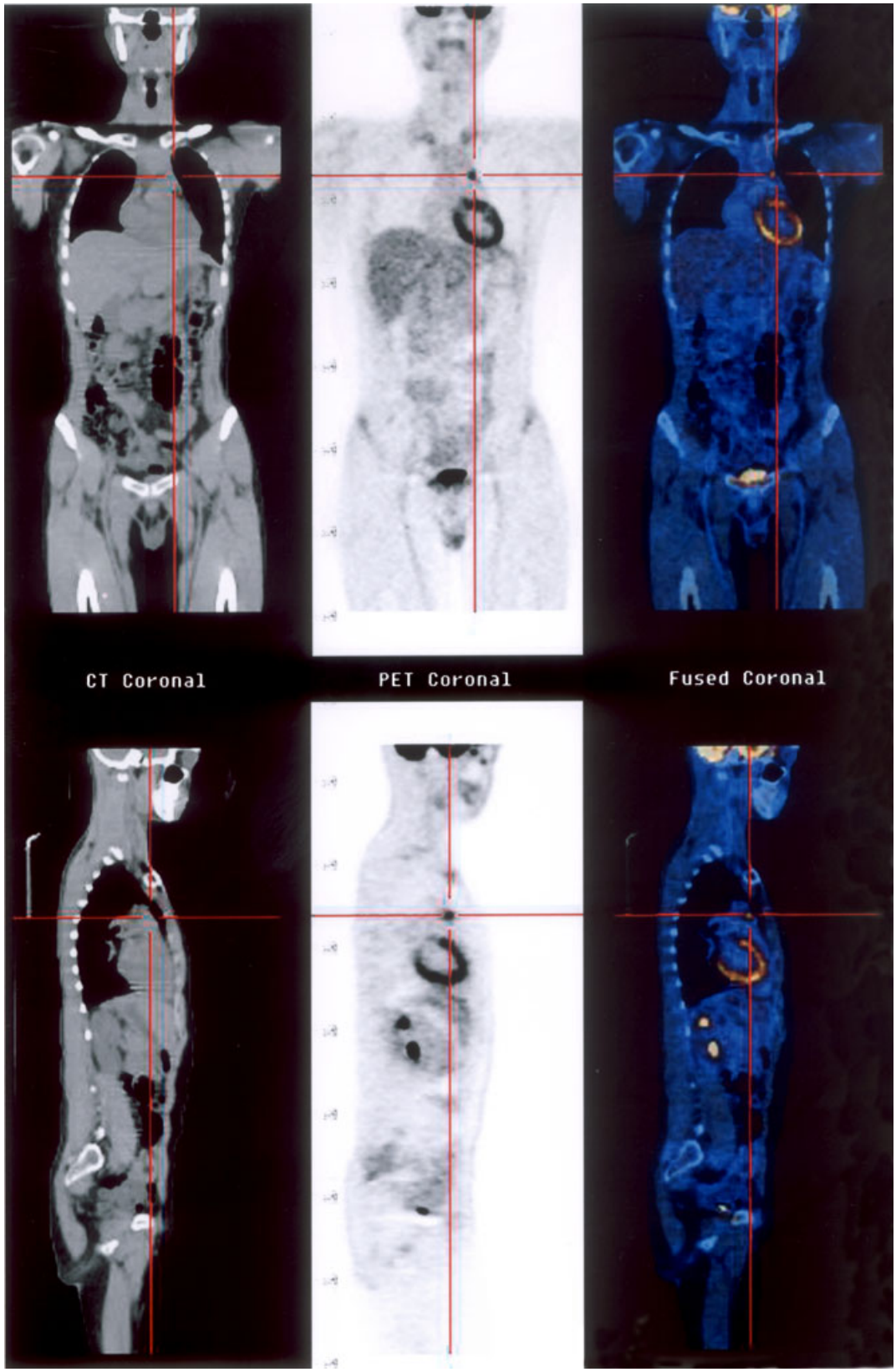

Fig. 1. Positron emission tomography/computed tomography (PET/CT) scanning with ^{18}F-fluoro-deoxyglucose (FDG). Coronal (**above**) and sagittal (**below**) tomographic images of non-enhanced CT, FDG PET, and fusion of CT/PET image data sets are shown in a 50-year-old male with recurrent lung carcinoma involving a <1 cm sized malignant lymph node in the anterior mediastinum marked by cross hairs on all three sets of coronal and sagittal images. Note the marked focal uptake of FDG within recurrent tumor seen in both the PET and fusion image data sets. Note the non-specific uptake of FDG within the brain heart and kidneys, and to a lesser extent the liver, gut, and blood vessels (i.e., blood pool). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Iron nanoparticulates (superparamagnetic iron oxide particles (SPIOs) or ultra-small (USPIOs)) are usually stabilized with aminated-cross linked dextrans for in vivo administration [Kooi et al., 2003; Rydland et al., 2003]. Iron particles act as small permanent magnets that dephase proton spins in the local microenvironment thereby causing a local loss of MR signal in target tissues and cells on T2-weighted MR pulse sequences. At present these iron nanoparticles are used primarily as blood pool or macrophage (liver, spleen, lymph nodes, and bone marrow) imaging agents. Iron particulates, however, can be conjugated to any number of peptides, antibodies, enzymes, or fluorescent probes, and have even been used to track SPIO labeled dendritic cells in vivo [Lewin et al., 2000; Weissleder et al., 2000; Josephson et al., 2002; Lanza et al., 2002]. In near future it should be possible also to image intracellular production of metallomelanin, an iron containing protein whose synthesis is dependent on the expression of tyrosinase, as a part of reporter gene system for MR [Alfke et al., 2003].

Alternatively, Gadopentetate dimeglumine (Gd–DTPA) and other Gd-complexes can also be used to tag molecules of interest for MR imaging. Examples of Gd-based agents include anti-$\alpha_v\beta_3$-antibody coated Gd–DTPA liposomes for MR imaging of tumor angiogenesis [Sipkins et al., 1998], poly Gd–DTPA or Gadolinium tetra azacylcododecane tetraacetic acid labeled anti-carcino embryonic antigen (CEA)F(ab')(2) fragments that target colorectal carcinoma [Curtet et al., 1998], and Gd-labeled mesoporphyrins for the MR assessment of necrotic non-viable tumor, infarcted myocardium, and soft tissue abscesses [Ju Lee et al., 2002; Lee et al., 2003].

MR contrast agents that generate signal under certain specific physiologic and pathologic conditions are also under development [Aime et al., 2002]. The best characterized of these new micro-environment sensitive MR agents is the Egad–Gd complex [Weinmann et al., 2003]. The Egad–Gd complex is composed of a derivative of Gd–HPDO3A containing a β-galactose moiety that prevents the access of water molecules to the paramagnetic center of the molecule. In the presence of β-galactosidase encoded by the *lacZ* genes, the galactose moiety is removed allowing for the interaction of water molecules with the Gd-core and the enhancement of MR signal on T1-weighted images. Plasmids, constructed to include the gene for β-galactosidase in addition to those for gene therapy can then be directly imaged in vivo with MR when followed by intravenous injection of Egad–Gd complex. Two other more generalizable enzymatic Gd-based systems have been developed; the first a Gd–DOTA like monomer complex bearing a cathecol functionality that in the presence of peroxidase polymerizes into paramagnetic MR detectable oligomeric molecules, and the second, insoluble Gd–DTPA like complexes which when internalized by macrophages are hydrolyzed by intracellular esterases into soluble MR detectable molecules.

The development of novel micro-bubble based contrast agents for US is currently focused on blood pool and macrophage/reticulo-endothelial system (RES) for liver/spleen/lymph node and atherosclerotic plaque imaging [Harvey et al., 2002; Yucel et al., 2002; Hohmann et al., 2003]. Most of these agents are composed of lipid, albumin, or prefluorocarbon shells encapsulating microbubbles <5 μm in diameter permitting easy access to all portions of the microcirculation. Because of their size and physical characteristics these agents are confined to the imaging of the vascular space. There is, however, the potential of directing biotinylated coated microbubbles with a number of avidin labeled molecules including anti-integrin $\alpha_v\beta_3$, anti-P-selectin, and anti-ICAM-1 antibodies [Lanza et al., 1996; Lindner, 2002]. In contrast to MR and US, there has been little progress in beyond the development of lipophilic and nanoparticulate iodinated agents for blood pool, liver, spleen, lymph node, and bone marrow imaging [Choi et al., 1994; Gazelle et al., 1995; Li et al., 1996].

PET AND SPECT RADIONUCLIDE IMAGING

Molecular imaging is the natural outgrowth of the biochemical techniques and radionuclide imaging devices developed over the past several decades for the field of Nuclear Medicine. We in the next section will discuss the most salient of the newer radiopharmaceuticals that are either currently available or in route to the Nuclear Medicine clinic.

Somatostatins

Five different somatostatin receptors (SSTR)-1 through SSTR-5 [Reichlin, 1983] have been described. SSTR-2 appears to be expressed in a majority of human cancers (to varying degrees)

and on activated lymphocytes. SSTR-1, and to a lesser extent SSTR-4, have been reported only in prostate carcinoma, and human normal and hyperplastic endothelium, but not animals where SSTR-2 predominates [Curtis et al., 2000]. Caution therefore, needs to be exercised, as with all translational research, of interspecies differences in receptor type and expression.

Somatostatin itself plays a role in cancer, in particular as a tumor growth inhibitor [Lamberts et al., 1991; Denzler and Reubi, 1999]. The marked SSTR (mostly SSTR-2) density found in breast carcinoma, lymphoma, and neuroendocrine tumors permits clinical SPECT imaging of primary and metastatic tumor with currently available radiolabeled somatostatin analogs namely, ^{111}In-D-Phe-DTPA-octreotide (Octreoscan, Mallinckrodt Medical, St. Louis, MO) [Krenning et al., 1993; Vallabhajosula et al., 1996] and ^{99m}technetium (Tc)-depreotide (Neotect, Diatide Inc., Londonderry, NH) [Breeman et al., 2001]. These agents are also now being used for the detection of malignant versus benign lung modules, as well as pathologic lymphocytic processes such as lymphoma, Graves' opthalmopathy, granulomatous disease, cardiac allograft rejection, and the formation of unstable (vulnerable) atherosclerotic plaques in which T-lymphocytes accumulate and overexpress the SSTR-2 receptor [Nocaudie et al., 1999; Balon et al., 2001; Cascini et al., 2001; Mari et al., 2001].

The SSTR-2 receptor gene has also been successfully used as a molecular reporter of the incorporation and expression of DNA constructs in vivo [Zinn et al., 2000]. It is possible that SSTR-2 receptor gene expression (imaged with Octreoscan or Neotect) could also be used as reporter signal in non-viral molecular delivery vehicles recently described by Backer et al. [2002]. This new targeting technology relies on the non-covalent binding of standardized "payload" modules to targeting proteins expressed with a docking tag as shown in Figure 2. The payload modules are constructed by linking drug or DNA carriers to the adapter protein capable of binding to the docking tag. The system described above was originally constructed with fragments of bovine ribonuclease A used as an adapter protein and a docking tag with $VEGF_{121}$ as the internalizable targeting protein, but has been recently humanized for potential clinical use for imaging or drug delivery [unpublished data].

The advantage of this new delivery system is that it avoids the problems of (i) potential inactivation of cell binding domains by conjugation, (ii) inevitable heterogeneity of the final products, (iii) the development of custom conjugation procedures for every targeting protein, and (iv) avoids the need for development of custom heterobifunctional recombinant antibodies, the previous solution to problems (i), (ii), and (iii); large molecules which also have the problem of variable and unpredictable degrees of internalization into target cells and tissues. This particular delivery system if coupled to the SSTR-2 receptor gene (or other safe reporter gene system) has the potential to non-invasively target a variety of receptors and cellular anti-

Fig. 2. Assembly of complexes for radionuclide imaging. Docking tag is fused to a targeting protein without affecting targeting epitopes. Radionuclide chelator is conjugated to a standardized adapter protein and loaded with ^{99m}technetium (Tc). Appropriately designed, humanized adapter/docking tag system will be "non-destructive" for targeting proteins, and allow the use of multiple existing and newly discovered targeting proteins in a rapid and uniform fashion. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

gens, selectively expressed within sites of interest, with high specificity and low background.

Gamma-aminobutyric acid ($GABA_A$)–Benzodiazepine Receptor Agonists

GABA is the most abundant inhibitory transmitter in the central nervous system (CNS) and is distributed within GABAergic neurons throughout the brain [Nutt and Malizia, 2001]. When GABA inhibitory activity exceeds that of excitatory inputs (mainly glutamatergic) sedation, amnesia, and ataxia appear. Benzodiazepines work by potentiating the effects of GABA on the chloride ion channel of $GABA_A$–benzodiazepine receptor complex. Benzodiazepine derivatives [^{11}C]flumazenil for PET and [^{123}I]iomazenil for SPECT that primarily image the peripheral (as opposed to central) benzodiazepine receptors are commercially available and have been applied to the neuroimaging of a variety of neurologic disorders including anxiety and temporal lobe epilepsy characterized in part by decreases in $GABA_A$ receptors within the brain [Matheja et al., 2001; Hammers et al., 2002; Sata et al., 2002; Sauvageau et al., 2002]. In addition reductions in temporal-mesial uptake of [^{123}I]iomazenil can be found in regions that are structurally intact by MRI in patients with medically refractory temporal lobe epilepsy. It is now recommended that presurgical studies with [^{123}I]iomazenil (SPECT) or [^{11}C]flumazenil (PET) be performed as part of routine imaging along with MRI.

Interestingly, iomazenil also binds selectively to activated microglial cells (brain macrophages) that have no significant binding of tracer in their quiescent state. These cells also make up 1 out of 10 cells in the normal brain. Activated microglial cells are found in abundance with the brain (entorhinal, temporoparietal, and cingulate cortex) of patients with Alzheimer's presenile dementia and multiple sclerosis and can be readily imaged, quantified, and serially followed with [^{123}I]iomazenil SPECT or [^{11}C]flumazenil PET imaging [Cagnin et al., 2001; Debruyne et al., 2003; Versijpt et al., 2003].

Dopamine Transporter (DAT) and D2 Dopamine Receptor Imaging

The pre-synaptic DAT and the post-synaptic D2 receptor are two of the most extensively studied neurotransmitter-receptor systems in the CNS [Bergstrom et al., 1998; Voruganti et al., 2001]. Several disease states, including depression, the antipsychotic drug induced negative syndrome of schizophrenia, Parkinson's disease, and extrapyramidal Parkinson-plus neurodegenerative syndromes are characterized by focal or regional decreases in DAT and D2 receptor binding [Ilgin et al., 2001; Prunier et al., 2001; Winogrodzka et al., 2001; Wong, 2002]. Opiates and Parkinson's disease have both been shown to effect the DAT system with SPECT imaging using two novel radiopharmaceuticals; [^{123}I]β-CIT, a cocaine analog with a binding constant of 1.6 nM for the DAT and [^{123}I]FP-CIT, a tracer that has been successful at documenting the accelerated pre-synaptic dopaminergic degeneration found in Parkinson's patients [Marek et al., 2003]. Diseases characterized by abnormal increases in D2 receptor binding potential include attention order-deficit-hyperactivity disorder (ADHD), mania, and schizophrenia. ^{123}I-iodo-benzamide (IBZM) or ^{123}I-iodolisuride (ILIS) (lisuride, an ergolene derivative used in the treatment of Parkinson's disease, $k = 0.27$ nM similar to 76Br-bromolisuride used for PET) SPECT. These studies all show excellent correlations of D2 binding potential with neuropsychiatric function and may have an immediate benefit in the diagnosis and treatment of depression associated in over a third of patients undergoing anti-psychotic treatment for schizophrenia.

One fascinating area of clinical research with DAT and D2 imaging agents has been the study of substance abuse [Volkow et al., 2003]. Abuse of cocaine, methamphetamine, methylenedioxymethaphetamine (MDMA), alcohol, opiates, tobacco, marijuana, and inhalants all appeared to be associated with abnormalities of the brain dopamine system, the primary force behind the reward center in humans. Dopamine producing cell bodies are located in the midbrain within the substantia nigra and the ventral tegmental area with projections to the striatal area that is known as the reward center, the nucleus accumbens. All abused substances despite different mechanisms of action serve to increase synaptic levels of dopamine. Chronic substance abusers have stimulant-induced highs associated with increases in brain dopamine but abnormally low numbers of dopamine D2 receptors at rest as measured by the PET radioligand ^{11}C-raclopride [Doudet et al., 2003]. ^{11}C-raclopride is a radiopharmaceutical that binds to the post-synaptic D2/3 receptors and therefore is an

indirect indicator of endogenous concentrations of dopamine. This effect coupled to decreases in dopamine release in response to chemical stimuli leads to the compulsive drug seeking behavior in chronic substance abusers and is an active area of neuro-pyschiatric investigation.

Estrogen and Progesterone

Evaluating the status of estrogen receptors can be helpful in defining a treatment strategy in patients with breast cancer. In the absence of imaging, receptor status is estimated by multiple biopsies of the primary tumor and regional lymph nodes [Rose et al., 1985]. Both fluorine (F)-18 estrogen analogs [McGuire et al., 1991] and iodinated compounds have been synthesized for PET imaging [Rijks et al., 1998]. An iodinated estrogen analog, 123-labeled cis-11beta-methoxy-17alpha-iodovinyl estradiol, was successful in the determination of estrogen receptor status in a study of 22 women with primary breast carcinoma using both planar and SPECT radionuclide imaging [Bennink et al., 2001]. Progesterone receptor SPECT imaging with a progesterone analog, Z-[^{123}I]IPG2, may also be possible in near future [Rijks et al., 1998].

Imaging of the $\alpha_v\beta_3$ Integrin

The integrins, a family of heterodimeric endothelial cell membrane proteins, serve as adhesion receptors for extracellular matrix proteins that contain exposed arginine, glycine, and, aspartate (single letter coding RGD) amino acid sequences [Ruoslahti and Engvall, 1997]. These include laminin, fibronectin, collagens, and vitronectin that help form blood vessels. The most abundant integrin expressed on the surface of proliferating endothelial cells is the $\alpha_v\beta_3$ receptor [Brooks et al., 1994]. In the adult human the $\alpha_v\beta_3$ integrin has a limited tissue distribution. It is not expressed on quiescent epithelial cells and appears at minimal levels on smooth muscle cells. In contrast, both activated endothelial cells in tumor capillaries [Eliceiri and Cheresh, 1999], and some tumor cells [Cheresh, 1991] express high levels of $\alpha_v\beta_3$.

The cyclic pentapeptide cyclo(-Arg-Gly-Asp-D-Phe-Val-) has been identified as a potent ($k_d < 10$ nmol/L) inhibitor of $\alpha_v\beta_3$ integrin binding to extracellular matrix proteins [Pfaff et al., 1994]. Modifications of this peptide at position four or five have allowed radiolabeling with iodine for SPECT, and F-18 for PET imaging [Haubner et al., 2001]. Contrast between tumor and normal tissues (especially liver) has been since improved by addition of sugar to the amino acids of the peptide [Haubner et al., 1999]. Radiolabeled RGD-peptides have been recently used to image $\alpha_v\beta_3$ expression in tumor prior to the administration of $\alpha_v\beta_3$ antagonists such as EMD-121974 to allow selection of patients entering clinical trials. These peptides in near future will be used to assess the effectiveness of $\alpha_v\beta_3$ integrin blockade by specific doses of other $\alpha_v\beta_3$ antagonists. This approach will permit optimization of dose for a specific patient and tumor type.

Hypoxia

Angiogenic factors, including vascular endothelial growth factor (VEGF), are induced by tissue hypoxia [Brogi et al., 1994]. The amount of tumor hypoxia may therefore be related to the amount of angiogenesis. One of the effects of successful anti-angiogenic drug therapy is a reduction of blood supply to the tumor, which increases hypoxia. Hypoxia imaging can therefore be used in two different ways: to study angiogenesis itself and to determine the efficacy of drugs. Nitroimidazoles are a class of compounds that undergo biochemical reduction forming covalent bonds to intracellular protein thiols thus trapping the tracer in viable cells with abnormally low oxygen concentrations [Chapman et al., 1983]. In normoxic conditions however, these compounds enter and freely leave the cell unmodified thus distinguishing normal from hypoxic tissues. Misonidazole analogs and 2-nitroimadazole analogs have been labeled with ^{123}I and ^{99m}Tc for SPECT, and F-18 for PET imaging of hypoxia. These agents have demonstrated increased uptake in hypoxic and low flow ischemic myocardium and brain as well as in tumors [Parliament et al., 1992; Ballinger et al., 1996; Cook et al., 1998; Melo et al., 2000; Markus et al., 2002; Tolvanen et al., 2002; Hoffend et al., 2003; Song et al., 2003]. ^{99m}Tc labeled HL91 and BRU 59-21 as well as F-18 labeled fluoromisonidazole (^{18}F-FMISO) have been recently been used to study temporal changes in tumor hypoxia in patients undergoing radiation and chemotherapy for primary and recurrent squamous head and neck carcinoma [Rischin et al., 2001; Van De Wiele et al., 2001; Hoebers et al., 2002].

Imaging Apoptosis

Apoptosis, also known as "programmed cell death", was named for the series of character-

istic energy dependent biochemical and morphologic changes that a cell undergoes as it commits to its own destruction and removal [Allen et al., 1997]. One of the earliest detectable changes in the apoptotic cascade is the externalization of phosphatidylserine (PS) due to the enzymatically controlled redistribution of PS from the inner to outer leaflet of the plasma membrane phospholipid bilayer [van Engeland et al., 1998]. Annexin V, an endogenous human protein, binds specifically to membrane bound PS, which is externalized on the cell surface [van Heerde et al., 1995]. Annexin V, because of its nanomolar affinity for PS, has been used in the flow cytometric detection of apoptotic cells in vitro, in vivo in animal models, and most recently in humans for the detection apoptosis and necrosis found in acute cardiac transplant rejection [Narula et al., 2001], tumor response to chemotherapy [Belhocine et al., 2002], and acute myocardial infarction [Thimister et al., 2003]. While annexin V has been labeled with ^{99m}Tc for SPECT imaging in humans, in near future it should be possible to label annexin V with ^{18}F, allowing higher resolution PET imaging, or via the substitution of ^{94m}Tc (a positron-emitting Tc isotope) using existing ^{99m}Tc protein labeling technologies [Tanaka et al., 1996].

MR techniques can also be used to directly detect apoptosis using suppressed lipid proton spectroscopic pulse sequences that can detect cells undergoing apoptosis both in vitro [Blankenberg et al., 1997] and in vivo [Hakumaki et al., 1999]. Cells undergoing apoptosis have an associated increase in membrane and cytoplasmic neutral mobile lipid droplets composed of polyunsaturated fatty acids, cholesterol esters, and triglycerides [Al-Saffar et al., 2002; Ferretti et al., 2003]. Outside the brain, however, water suppressed lipid proton MR spectroscopy remains a challenge due to physiologic motion and the non-specific "bleeding in" of lipid signal from adipose tissue as well as the low signal to noise and relatively poor spatial resolution of the technique.

Imaging of Cellular Stress With Annexin V

New data suggest that the PS expression can occur with non-lethal cell injury prior to the irreversible morphologic changes such as DNA fragmentation [Lejeune et al., 1998; Hammill et al., 1999; Furukawa et al., 2000; Lin et al., 2000; Maiese and Vincent, 2000; Martin et al., 2000; Geske et al., 2001; Yang et al., 2002]. These in vitro studies showed that intermediate levels of PS exposure were noted in cells with no other morphologic features of apoptosis could be readily reversed upon removal of physiologic stressors such as nitric-oxide, p53 activation, allergic mediators, and growth factor deprivation. Studies of the surfaces of tumor endothelial cells also showed that PS expression could be reversibly increased by exposure to hypoxia/reoxygenation, acidity, thrombin, inflammatory cytokines, and hydrogen peroxide, all factors that are variably present in tumors, without inducing apoptosis [Ran et al., 2002]. Annexin V could therefore be useful as an imaging marker of tumor vessels. Thimister's clinical study found that annexin V localization partially resolved by day 3–4 and completely by day 8 in regions of ischemic injury following acute myocardial infarction [Thimister et al., 2003]. These results suggest that either injured cells that concentrated tracer were removed from the ischemic zone or the recovery of these cells in terms of both function and viability with loss of PS positivity. The reduction of perfusion abnormalities with restoration of regional wall motion 1 week following infarction suggests the latter explanation. If true then annexin V imaging maybe vastly more sensitive to cellular stress than previously thought and maybe a true marker of tissues at risk that have the potential for salvage with prompt therapeutic intervention [Strauss et al., 2000; Narula and Strauss, 2003].

REFERENCES

Aime S, Cabella C, Colombatto S, Crich SG, Gianolio E, Maggioni F. 2002. Insights into the use of paramagentic Gd(III) complexes in MR-molecular imaging investigations. J Magn Reson Imaging 16:394–406.

Al-Saffar NM, Titley JC, Robertson D, Clarke PA, Jackson LE, Leach MO, Ronen SM. 2002. Apoptosis is associated with triacylglycerol accumulation in Jurkat T-cells. Br J Cancer 86:963–970.

Alfke H, Stoppler H, Nocken F, Heverhagen JT, Kleb B, Czubayko F, Klose KJ. 2003. In vitro MR imaging of regulated gene expression. Radiology 228:488–492.

Allen RT, Hunter WJ III, Agrawal DK. 1997. Morphological and biochemical characterization and analysis of apoptosis. J Pharmacol Toxicol Methods 37:215–228.

Backer MV, Aloise R, Przekop K, Stoletov K, Backer JM. 2002. Molecular vehicles for targeted drug delivery. Bioconjug Chem 13:462–467.

Ballinger JR, Kee JW, Rauth AM. 1996. In vitro and in vivo evaluation of a technetium-99m-labeled 2-nitroimidazole (BMS181321) as a marker of tumor hypoxia. J Nucl Med 37:1023–1031.

Balon HR, Goldsmith SJ, Siegal BA, Silberstein EB, Krenning EP, Lang O, Donohoe KJ. 2001. Procedure guideline for somatostatin receptor scintigraphy with 111In-pentetreotide. J Nucl Med 42:1134–1138.

Behr TM, Gotthardt M, Barth A, Behe M. 2001. Imaging tumors with peptide-based radioligands. Q J Nucl Med 45:189–200.

Belhocine T, Steinmetz N, Hustinx R, Bartsch P, Jerusalem G, Seidel L, Rigo P, Green A. 2002. Increased uptake of the apoptosis-imaging agent (99m)Tc recombinant human Annexin V in human tumors after one course of chemotherapy as a predictor of tumor response and patient prognosis. Clin Cancer Res 8:2766–2774.

Bennink RJ, Rijks LJ, van Tienhoven G, Noorduyn LA, Janssen AG, Sloof GW. 2001. Estrogen receptor status in primary breast cancer: Iodine 123-labeled cis-11beta-methoxy-17alpha-iodovinyl estradiol scintigraphy. Radiology 220:774–779.

Bergstrom KA, Jolkkonen XX, Kuikka JT, Arkerman KK, Viinamaki H, Airaksinen O, Lansimies E, Tiihonen J. 1998. Fentanyl decreases β-CIT binding to the dopamine transporter. Synapse 29:413–415.

Blankenberg FG, Katsikis PD, Storrs RW, Beaulieu C, Spielman D, Chen JY, Naumovski L, Tait JF. 1997. Quantitative analysis of apoptotic cell death using proton nuclear magnetic resonance spectroscopy. Blood 89: 3778–3786.

Blankenberg FG, Eckelman WC, Strauss HW, Welch MJ, Alvi A, Anderson C, Bacharach S, Blasberg RG, Graham MM, Weber W. 2000. Role of radionuclide imaging in trials of antiangiogenic therapy. Acad Radiol 7:851–867.

Breeman WA, de Jong M, Kwekkeboom DJ, Valkema R, Bakker WH, Kooij PP, Visser TJ, Krenning EP. 2001. Somatostatin receptor-mediated imaging and therapy: Basic science, current knowledge, limitations and future perspectives. Eur J Nucl Med 28:1421–1429.

Brogi E, Wu T, Namiki A, Isner JM. 1994. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. Circulation 90:649–652.

Brooks PC, Clark RA, Cheresh DA. 1994. Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science 264:569–571.

Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, Jones T, Banati RB. 2001. In-vivo measurement of activated microglia in dementia. Lancet 358:461–467.

Cascini GL, Cuccurullo V, Rambaldi PF, Mansi L. 2001. Immunological imaging using marked octreotide. Minerva Endocrinol 26:129–133.

Chapman JD, Baer K, Lee J. 1983. Characteristics of the metabolism-induced binding of misonidazole to hypoxic mammalian cells. Cancer Res 43:1523–1528.

Cheresh DA. 1991. Structure, function and biological properties of integrin alpha v beta 3 on human melanoma cells. Cancer Metastasis Rev 10:3–10.

Choi BI, Han JK, Kim YI, Kim HC, Park JH, Kim CW, Han MC. 1994. Combined hepatocellular and cholangiocarcinoma of the liver: Sonography, CT, angiography, and iodized-oil CT with pathologic correlation. Abdom Imaging 19:43–46.

Cook GJ, Houston S, Barrington SF, Fogelman I. 1998. Technetium-99m-labeled HL91 to identify tumor hypoxia: Correlation with fluorine-18-FDG. J Nucl Med 39:99–103.

Curtet C, Maton F, Havet T, Slinkin M, Mishra A, Chatal JF, Muller RN. 1998. Polylysine-Gd–DTPAn and polylysine–Gd–DOTAn coupled to anti-CEA F(ab′)2 fragments as potential immunocontrast agents. Relaxometry, biodistribution, and magnetic resonance imaging in nude mice grafted with human colorectal carcinoma. Invest Radiol 33:752–761.

Curtis SB, Hewitt J, Yakubovitz S, Anzarut A, Hsiang YN, Buchan AM. 2000. Somatostatin receptor subtype expression and function in human vascular tissue. Am J Physiol Heart Circ Physiol 278:H1815–H1822.

Debruyne JC, Versijpt J, Van Laere KJ, De Vos F, Keppens J, Strijckmans K, Achten E, Slegers G, Dierckx RA, Korf J, De Reuck JL. 2003. PET visualization of microglia in multiple sclerosis patients using [11C]PK11195. Eur J Neurol 10:257–264.

Denzler B, Reubi JC. 1999. Expression of somatostatin receptors in peritumoral veins of human tumors. Cancer 85:188–198.

Doudet DJ, Jivan S, Holden JE. 2003. In vivo measurement of receptor density and affinity: Comparison of the routine sequential method with a nonsequential method in studies of dopamine D2 receptors with [11C]raclopride. J Cereb Blood Flow Metab 23:280–284.

Eliceiri BP, Cheresh DA. 1999. The role of alphav integrins during angiogenesis: Insights into potential mechanisms of action and clinical development. J Clin Invest 103: 1227–1230.

Ferretti A, Knijn A, Raggi C, Sargiacomo M. 2003. High-resolution proton NMR measures mobile lipids associated with Triton-resistant membrane domains in haematopoietic K562 cells lacking or expressing caveolin-1. Eur Biophys J 32:83–95.

Fischman AJ, Khaw BA, Strauss HW. 1989. Quo vadis radioimmune imaging. J Nucl Med 30:1911–1915.

Forster GJ, Laumann C, Nickel O, Kann P, Rieker O, Bartenstein P. 2003. SPET/CT image co-registration in the abdomen with a simple and cost-effective tool. Eur J Nucl Med Mol Imaging 30:32–39.

Furukawa Y, Bangham CRM, Taylor GP, Weber JN, Osame M. 2000. Frequent reversible membrane damage in peripheral blood B cells in human T cell lymphotrophic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Clin Exp Immunol 120:307–316.

Gazelle GS, Wolf GL, McIntire GL, Bacon ER, Na G, Halpern EF, Toner JL. 1995. Hepatic imaging with iodinated nanoparticles: A comparison with iohexol in rabbits. Acad Radiol 2:700–704.

Geske FJ, Lieberman R, Strange R, Gerschenson LE. 2001. Early stages of p53-induced apoptosis are reversible. Cell Death Differ 8:182–191.

Hakumaki JM, Poptani H, Sandmair AM, Yla-Herttuala S, Kauppinen RA. 1999. 1H MRS detects polyunsaturated fatty acid accumulation during gene therapy of glioma: Implications for the in vivo detection of apoptosis. Nat Med 5:1323–1327.

Hammers A, Koepp MJ, Hurlemann R, Thom M, Richardson MP, Brooks DJ, Duncan JS. 2002. Abnormalities of grey and white matter [11C]flumazenil binding in temporal lobe epilepsy with normal MRI. Brain 125: 2257–2271.

Hammill AK, Uhr JW, Scheuermann RH. 1999. Annexin V staining due to loss of membrane asymmetry can be reversible and precede commitment to apoptotic death. Exp Cell Res 251:16–21.

Harvey CJ, Pilcher JM, Eckersley RJ, Blomley MJK, Cosgrove DO. 2002. Advances in ultrasound. Clin Radiol 57:157–177.

Haubner R, Wester HJ, Reuning U, Senekowitsch-Schmidtke R, Diefenbach B, Keller H, Stocklin G, Schwaiger M. 1999. Radiolabeled alpha(v)beta3 integrin antagonists: A new class of tracers for tumor targeting. J Nucl Med 40:1061–1071.

Haubner R, Wester HJ, Burkhart F, Senekowitsch-Schmidtke R, Weber W, Goodman SL, Kessler H, Schwaiger M. 2001. Glycosylated RGD-containing peptides: Tracer for tumor targeting and angiogenesis imaging with improved biokinetics. J Nucl Med 42:326–336.

Hoebers FJ, Janssen HL, Olmos AV, Sprong D, Nunn AD, Balm AJ, Hoefnagel CA, Begg AC, Haustermans KM. 2002. Phase 1 study to identify tumour hypoxia in patients with head and neck cancer using technetium-99m BRU 59-21. Eur J Nucl Med Mol Imag 29:1206–1211.

Hoffend J, Linke G, Mohammed A, Tiefenbacher CP, Eisenhut M, Haberkorn U. 2003. 99mTcO(BAT-NI), a novel nitroimidazole tracer: In vivo uptake studies in ischaemic myocardium. Eur J Nucl Med Mol Imag 30:494–501.

Hohmann J, Albrecht T, Hoffmann CW, Wolf KJ. 2003. Ultrasonographic detection of focal liver lesions: Increased sensitivity and specificity with microbubble contrast agents. Eur J Radiol 46:147–159.

Ilgin N, Senol S, Gucuyener K, Gokcora N, Sener S. 2001. Is increased D2 receptor availability associated with response to stimulant medication in ADHD. Dev Med Child Neurol 43:755–760.

Josephson L, Kircher MF, Mahmood U, Tang Y, Weissleder R. 2002. Near-infrared fluorescent nanoparticles as combined MR/optical imaging probes. Bioconjug Chem 13:554–560.

Ju Lee H, Kim IO, Kim TK, Hyung Kim S, Choi JI, Woo Lee J, Kyung Moon W, Choi BI, Chung Han M, Weinmann HJ, Hyun Chang K. 2002. Dynamic enhancement features of gadophrin-2 on magnetic resonance imaging: An experimental model of VX2 carcinoma and bacterial abscess in rabbit thigh. Invest Radiol 37:663–671.

Ketai L, Hartshorne M. 2001. Potential uses of computed tomography-SPECT and computed tomography-coincidence fusion images of the chest. Clin Nucl Med 26:433–441.

Kooi ME, Cappeddijk VC, Cleutjens KBJM, Kessels AGH, Kitslaar PJEHM, Borgers M, Frederik PM, Daemen MJAP, van Engelshoven JMA. 2003. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. Circulation 107:2453–2458.

Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M, Reubi JC. 1993. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe1]- and [^{123}I- Tyr^{3}]-octreotide: The Rotterdam experience with more than 1,000 patients. Eur J Nucl Med 20:716–731.

Lamberts SW, Krenning EP, Reubi JC. 1991. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. Endocr Rev 12:450–482.

Lanza GM, Wallace KD, Scott MJ, Cacheris WP, Abendschein DR, Christy DH, Sharkey AM, Miller JG, Gaffney PJ, Wickline SA. 1996. A novel site-targeted ultrasonic contrast agent with broad biomedical application. Circulation 94:3334–3340.

Lanza GM, Yu X, Winter PM, Abendschein DR, Karukstis KK, Scott MJ, Chinen LK, Furhop RW, Scherrer DE, Wickline SA. 2002. Targeted antiproliferative drug delivery to vascular smooth muscle cells with a magnetic resonance imaging nanoparticle contrast agent. Circulation 106:2842–2847.

Lee SS, Goo HW, Park SB, Lim CH, Gong G, Seo JB, Lim TH. 2003. MR imaging of reperfused myocardial infarction: Comparison of necrosis-specific and intravascular contrast agents in a cat model. Radiology 226:739–747.

Lejeune M, Ferster A, Cantinieaux B, Sariban E. 1998. Prolonged but reversible neutrophil dyfunctions differentially sensitive to granulocyte colony-stimulating factor in children with acute lymphoblastic leukemia. Br J Haematol 102:1284–1291.

Lewin M, Carlesso N, Tung C-H, Tang X-W, Cory D, Scadden DT, Weissleder R. 2000. Tat peptide-derivatized magnetic nanoparticles allow in vivo tracking and recovery of progenitor cells. Nat Biotechnol 18:410–414.

Li C, Yu D, Kan Z, Yang DJ, Tansey W, Kuang LR, Wallace S. 1996. Biodistribution of cyclic carbonate of ioxilan: A radiopaque particulate macrophage imaging agent. Acad Radiol 3:500–506.

Lin SH, Vincent A, Shaw T, Maynard KI, Maiese K. 2000. Prevention of nitric oxide-induced neuronal injury through the modulation of independent pathways of programmed cell death. J Cereb Blood Flow Metab 20:1380–1391.

Lindner JR. 2002. Detection of inflamed plaques with contrast ultrasound. Am J Cardiol 2190(10C):32L–35L.

Maiese K, Vincent AM. 2000. Membrane asymmetry and DNA degradation: Functionally distinct determinants of neuronal programmed cell death. J Neurosci Res 59:568–580.

Marek K, Jennings D, Seibyl J. 2003. Dopamine agonists and Parkinson ' s disease progression: What can we learn from neuroimaging studies. Ann Neuorol 53(Suppl 3): S160–S169.

Mari C, Nedelman M, Blankenberg F, Ghazarossian V, Strauss HW. 2001. Detection of active atheroma in a rabbit model: Evaluation of 8 radiotracers. J Nucl Med 42(Suppl 5):45 p.

Markus R, Donnan GA, Kazui S, Read S, Hirano T, Scott AM, O'Keefe GJ, Tochon-Danguy HJ, Sachinidis JI, Reutens DC. 2002. Statistical parametric mapping of hypoxic tissue identified by [(18)F]fluoromisonidazole and positron emission tomography following acute ischemic stroke. Neuroimage 16:425–433.

Martin S, Pombo I, Poncet P, David B, Arock M, Blank U. 2000. Immunologic stimulation of mast cells leads to the reversible exposure of phosphatidylserine in the absence of apoptosis. Int Arch Allergy Immunol 123(3):249–258.

Matheja P, Ludemann P, Kuwert T, Weckesser M, Kellinghaus C, Weitemeyer, Diehl B, Schuierer G, Ringelstein EB, Schober O. 2001. Disturbed benzodiazepine receptor function at the onset of temporal lobe epilepsy-lomanzenil-binding in de-novo TLE. J Neurol 248:585–591.

McGuire AH, Dehdashti F, Siegel BA, Lyss AD, Brodack JW, Mathias CJ, Mintun MA, Katzeneltenbogen JA,

Weich MJ. 1991. Positron tomographic assessment of 16α-[^{18}F]fluoro-17β-estradiol uptake in metastatic breast carcinoma. J Nucl Med 32:1526–1531.

Melo T, Duncan J, Ballinger JR, Rauth AM. 2000. BRU59-21, a second-generation ^{99m}Tc-labeled 2-nitroimidazole for imaging hypoxia in tumors. J Nucl Med 41:169–176.

Narula J, Strauss HW. 2003. P.S.* I love you: Implications of phosphatidyl serine (PS) reversal in acute ischemic syndromes. J Nucl Med 44:397–399.

Narula J, Acio ER, Narula N, Samuels LE, Fyfe B, Wood D, Fitzpatrick JM, Raghunath PN, Tomaszewski JE, Kelly C, Steinmetz N, Green A, Tait JF, Leppo J, Blankenberg FG, Jain D, Strauss HW. 2001. Annexin-V imaging for noninvasive detection of cardiac allograft rejection. Nat Med 7:1347–1352.

Nishioka T, Shiga T, Shirato H, Tsukamoto E, Tsuchiya K, Kato T, Ohmori K, Yamazaki A, Aoyama H, Hashimoto S, Chang TC, Miyasaka K. 2002. Image fusion between 18FDG-PET and MRI/CT for radiotherapy planning of oropharyngeal and nasopharyngeal carcinomas. Int J Radiat Oncol Biol Phys 53:1051–1057.

Nocaudie M, Bailliez A, Itti E, Bauters C, Wemeau JL, Marchandise X. 1999. Somatostatin receptor scintigraphy to predict the clinical evolution and therapeutic response of thyroid-associated ophthalmopathy. Eur J Nucl Med 26:511–517.

Nutt DJ, Malizia AL. 2001. New insights into the role of the GABA(A)-benzodiazepine receptor in psychiatric disorder. Br J Psychiatry 179:390–396.

Parliament MB, Chapman JD, Urtasun RC, McEwan AJ, Goldberg L, Mercer JR, Mannan RH, Wiebe LT. 1992. Non-invasive assessment of human tumour hypoxia with ^{123}I-iodoazomycin arabinoside: Preliminary report of a clinical study. Br J Cancer 65:90–95.

Pfaff M, Tangemann K, Muller B, Gurrath M, Muller G, Kessler H, Timpl R, Engel J. 1994. Selective recognition of cyclic RGD peptides of NMR defined conformation by alpha IIb beta 3, alpha V beta 3, and alpha 5 beta 1 integrins. J Biol Chem 269:20233–20238.

Prunier C, Tranquart F, Cottier JP, Giraudeau B, Chalen S, Guillokau D, De Toffol B, Chossat F, Autret A, Besnard JC, Baulieu JL. 2001. Quantitative analysis of striatal dopamine D2 receptors with ^{123}I-iodolisuride SPECT in degenerative extrapyramidal diseases. Nucl Med Commun 22:1207–1214.

Ran S, Downes A, Thorpe PE. 2002. Increased exposure of anionic phospholipids on the surface of tumor blood vessels. Cancer Res 62:6132–6140.

Reichlin S. 1983. Somatostatin. N Engl J Med 309:1495–1501.

Rijks LJ, van den Bos JC, van Doremalen PA, Boer GJ, de Bruin K, Doornbos T, Vekemans JA, Posthumus MA, Jansseen AG, van Royen EA. 1998. Synthesis, estrogen receptor binding, and tissue distribution of a new iodovinylestradiol derivative (17alpha,20E)-21-[^{123}I]Iodo-11beta-nitrato-19-norp regna-1,3,5 (10),20-tetraene-3,17-diol (E-[123I]NIVE). Nucl Med Biol 25:411–421.

Rijks LJ, van den Bos JC, van Doremalen PA, Boer GJ, de Bruin K, Jansseen AG, van Royen EA. 1998. New iodinated progestins as potential ligands for progesterone receptor imaging in breast cancer. Part 2: In vivo pharmacological characterization. Nucl Med Biol 25: 791–798.

Rischin D, Peters L, Hicks R, Hughes P, Fisher R, Hart R, Sexton M, D'Costa I, von Roemeling R. 2001. Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer. J Clin Oncol 19(2):535–542.

Rose C, Thorpe SM, Anderson KW, Pedersen BV, Mouridsen HT, Blicher-Toft M, Ramossen BB. 2003. Beneficial effect of adjuvant tamoxifen therapy in primary breast patients with high oestrogen receptor values. Lancet 8419:16–19.

Ruoslahti E, Engvall E. 1997. Integrins and vascular extracellular matrix assembly. J Clin Invest 100:S53–S56.

Rydland J, BjOrnerud A, Haugen O, Torheim G, Torres C, Kvistad KA, Haraldseth O. 2003. New intravascular contrast agent applied to dynamic contrast enhanced MR imaging of human breast cancer. Acta Radiol 44:275–283.

Sata Y, Matsuda K, Mihara T, Aihara M, Yagi K, Yonekura Y. 2002. Quantitative analysis of benzodiazepine receptor in temporal lobe epilepsy: [(125)I]Iomazenil autoradiographic study of surgically resected specimens. Epilepsia 43:1039–1048.

Sauvageau A, Desjardins P, Lozeva V, Rose C, Hazell AS, Bouthillier A, Butterwort RF. 2002. Increased expression of "peripheral-type" benzodiazepine receptors in human temporal lobe epilepsy: Implications for PET imaging of hippocampal sclerosis. Metab Brain Dis 17:3–11.

Sipkins DA, Cheresh DA, Kazemi MR, Nevin LM, Li KCP. 1998. Detection of tumor angiogenesis in vivo by alphaVbeta3-targeted magnetic resonace imaging. Nat Med 4:623–626.

Song HC, Bom HS, Cho KH, Kim BC, Seo JJ, Kim CG, Yang DJ, Kim EE. 2003. Prognostication of recovery in patients with acute ischemic stroke through the use of brain SPECT with technetium-99m labeled metronidazole. Stroke 34(4):982–986.

Strauss HW, Narula J, Blankenberg FG. 2000. Radioimaging to identify myocardial cell death and probably injury. Lancet 356:209–212.

Tanaka K, Einaga K, Tsuchiyama H, Tait JF, Fujikawa K. 1996. Preparation and characterization of a disulfide-linked bioconjugate of annexin V with the B-chain of urokinase: An improved fibrinolytic agent targeted to phospholipid-containing thrombi. Biochemistry 35:922–929.

Thimister PW, Hofstra L, Liem IH, Boersma HH, Kemerink G, Reutelingsperger CP, Heidendal GA. 2003. In vivo detection of cell death in the area at risk in acute myocardial infarction. J Nucl Med 44:391–396.

Tolvanen T, Lehtio K, Kulmala J, Oikonen V, Eskola O, Bergman J, Minn H. 2002. 18F-Fluoroerythronitroimidazole radiation dosimetry in cancer studies. J Nucl Med 43:1674–1680.

Townsend DW, Beyer T. 2002. A combined PET/CT scanner: The path to true image fusion. Br J Radiol 75:S24–S30.

Vallabhajosula S, Moyer BR, Lister-James J, McBride BJ, Lipszyc H, Lee H, Bastidas D, Dean RT. 1996. Preclinical evaluation of technetium-99m-labeled somatostatin receptor-binding peptides. J Nucl Med 37:1016–1022.

Van De Wiele C, Versijpt J, Dierckx RA, Moerman M, Lemmerling M, Asseler Y, Vermeersch H. 2001. 99Tc(m) labelled HL91 versus computed tomography and biopsy for the visualization of tumour recurrence of squamous head and neck carcinoma. Nucl Med Commun 22:269–275.

van Engeland M, Nieland LJ, Ramaekers FC, Schutte B, Reutelingsperger CP. 1998. Annexin V-affinity assay: A review on an apoptosis detection system based on phosphatidylserine exposure. Cytometry 31:1–9.

van Heerde WL, de Groot PG, Reutelingsperger CP. 1995. The complexity of the phospholipid binding protein Annexin V. Thromb Haemost 73:172–179.

Versijpt JJ, Dumont F, Van Laere KJ, Decoo D, Santens P, Audenaert K, Achten E, Slegers G, Dierckx RA, Korf J. 2003. Assessment of neuroinflammation and microglial activation in Alzheimer's disease with radiolabelled PK11195 and single photon emission computed tomography. A pilot study. Eur Neurol 50:39–47.

Volkow HD, Fowler JS, Wang G-J. 2003. Positron emission tomography and single-photon emission computed tomography in substance abuse research. Semin Nucl Med 33:114–128.

Voruganti L, Slomka P, Zabel P, Costa G, So A, Mattar A, Awad AG. 2001. Subjective effects of AMPT-induced dopamine depletion in schizophrenia: Correlation between dysphoric responses and striatal D(2) binding ratios on SPECT imaging. Neuropsychopharmacology 25:642–650.

Weinmann H-J, Ebert W, Misselwitz B, Schmitt-Willich H. 2003. Tissue-specific MR contrast agents. Eur J Radiol 46:33–44.

Weissleder R, Moore A, Mahmood U, Bhorade R, Benveniste H, Chiocca EA, Basilion JP. 2000. In vivo magnetic resonance imaging of transgene expression. Nat Med 6:351–354.

Winogrodzka A, Bergmans P, Booij J, van Royen EA, Janssen AGM, Wolters EC. 2001. [^{123}I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease. J Neural Transm 108:1001–1019.

Wong DF. 2002. In vivo imaging of D2 dopamine receptors in schizophrenia: The ups and downs of neuroimaging research. Arch Gen Pyschiatry 59:31–34.

Yang MY, Chuang H, Chen RF, Yang KD. 2002. Reversible phosphatidylserine expression on blood granulocytes related to membrane perturbation but not DNA strand breaks. J Leukoc Biol 71:231–237.

Yucel C, Ozdemir H, Gurel S, Ozer S, Arac M. 2002. Detection and differential diagnosis of hepatic masses using pulse inversion harmonic imaging during the liver-specific late phase of contrast enhancement with levovist. J Clin Ultrasound 30:203–212.

Zinn KR, Buchsbaum DJ, Chaudhuri TR, Mountz JM, Grizzle WE, Rogers BE. 2000. Noninvasive monitoring of gene transfer using a reporter receptor imaged with a high-affinity peptide radiolabeled with 99mTc or 188Re. J Nucl Med 41:887–895.