

Top Molecular Imaging References—January 2008

In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18157119.

Qian X, Peng XH, Ansari DO, et al.
Nat Biotechnol. 2008;26:83-90. (Jan).

We describe biocompatible and nontoxic nanoparticles for in vivo tumor targeting and detection based on pegylated gold nanoparticles and surface-enhanced Raman scattering (SERS). Colloidal gold has been safely used to treat rheumatoid arthritis for 50 years, and has recently been found to amplify the efficiency of Raman scattering by 14-15 orders of magnitude. Here we show that large optical enhancements can be achieved under in vivo conditions for tumor detection in live animals. An important finding is that small-molecule Raman reporters such as organic dyes were not displaced but were stabilized by thiol-modified polyethylene glycols. These pegylated SERS nanoparticles were considerably brighter than semiconductor quantum dots with light emission in the near-infrared window. When conjugated to tumor-targeting ligands such as single-chain variable fragment (ScFv) antibodies, the conjugated nanoparticles were able to target tumor biomarkers such as epidermal growth factor receptors on human cancer cells and in xenograft tumor models.

The promise of PET in clinical management and as a sensitive test for drug cytotoxicity in sarcomas.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18088235.

Khamly KK, Hicks RJ, McArthur GA, et al.
Expert Rev Mol Diagn. 2008;8:105–119.

Positron emission tomography (PET) is a noninvasive functional imaging technique that allows assessment of key biological processes important in cancer development and progression. It provides information complementary to conventional anatomic imaging, demonstrating utility in a range of cancer settings from diagnosis, biopsy guidance, tumor stratification and prognostication, and staging and surveillance of disease recurrence. Its ability to evaluate vital processes in tumor biology also makes it a potentially valuable and sensitive tool for assessing therapeutic response. The development of novel PET tracers and improvements in technology will only continue to augment the potential of PET and enhance its attractiveness as an instrument to facilitate drug development. This article will discuss the above issues, using the setting of sarcomas as an example.

Progress in multimodality imaging: truly simultaneous ultrasound and magnetic resonance imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18092742.

Curiel L, Chopra R, Hynynen K.
IEEE Trans Med Imaging. 2007;26:1740–1746.

Multimodality medical imaging takes advantage of the strengths of different imaging modalities to provide a more complete picture of the anatomy under investigation. Many complementary modalities have been combined to form such systems and some are gaining use clinically. One combination that has not been developed, in large part due to technical difficulties, is a combined magnetic resonance (MR) and ultrasound (US) imaging system. Such a system offers the potential to combine the strengths of these modalities in a wide range of diagnostic and therapeutic applications. The goal of this study was to evaluate the feasibility of performing simultaneous multimodality US and MR imaging. An US imaging system capable of operation in a clinical MR imager was developed, and methods to perform simultaneous imaging were investigated. Simultaneous imaging was feasible without any mutual interference by either filtering the transmitted and received US signal, or by synchronizing data acquisition between the two imaging systems. Spatial registration between the two modalities was achieved by using a reference phantom with implanted glass beads in orthogonal planes. Excellent agreement was observed between spatial measurements of an object made with both modalities, and the feasibility of using this system in vivo was demonstrated in a rabbit model. Simultaneous US and MR imaging is achievable, and can provide complementary information about an object under investigation. This demonstration of technical feasibility and the development of a prototype system open up the potential to investigate the promising clinical applications of this combined technology.

Image-guided convection-enhanced delivery platform in the treatment of neurological diseases.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18164491.

Fiandaca MS, Forsayeth JR, Dickinson PJ, et al.
Neurotherapeutics. 2008;5:123–127.

Convection-enhanced delivery (CED) of substances within the human brain is becoming a more frequent experimental treatment option in the management of brain tumors, and more recently in phase 1 trials for gene therapy in Parkinson's disease (PD). Benefits of this intracranial drug-transfer technology include a more efficient delivery of large volumes of therapeutic agent to the target region when compared with more standard delivery approaches (i.e., biopolymers, local infusion). In this article, we describe specific technical modifications we have made to the CED process to make it more effective. For example, we developed a reflux-resistant infusion cannula that allows increased infusion rates to be used. We also describe our efforts to visualize the CED process in vivo, using liposomal nanotechnology and real-time intraoperative MRI. In addition to carrying the MRI contrast agent, nanoliposomes also provide a standardized delivery vehicle for the convection of drugs to a specific brain-tissue volume. This technology provides an added level of assurance via visual confirmation of CED, allowing intraoperative alterations to the infusion if there is reflux or aberrant delivery. We propose that these specific modifications to the CED technology will improve efficacy by documenting and standardizing the treatment-volume delivery. Furthermore, we believe that this image-guided CED platform can be used in other translational neuroscience efforts, with eventual clinical application beyond neuro-oncology and PD.

Intravascular detection of inflamed atherosclerotic plaques using a fluorescent photosensitizer targeted to the scavenger receptor.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18167594.

Tawakol A, Castano AP, Gad F, et al.
Photochem Photobiol Sci. 2008;7:33–39.

Inflammation plays an important role in the pathophysiology of atherosclerotic disease. We have previously shown that the targeted photosensitizer chlorin (e(6)) conjugated with maleylated albumin (MA-ce6) is taken up by macrophages via the scavenger receptor with high selectivity. In a rabbit model of inflamed plaque in New Zealand white rabbits via balloon injury of the aorto-iliac arteries and high cholesterol diet we showed that the targeted conjugate showed specificity towards plaques compared to free ce6. We now show that an intravascular fiber-based spectrofluorimeter advanced along the -iliac vessel through blood detects 24-fold higher fluorescence in atherosclerotic vessels compared to control rabbits ($p < 0.001$ ANOVA). Within the same animals, signal derived from the injured iliac artery was 16-fold higher than the contralateral uninjured iliac ($p < 0.001$). Arteries were removed and selective accumulation of MA-ce6 in plaques was confirmed using: (1) surface spectrofluorimetry, (2) fluorescence extraction of ce6 from aortic segments, and (3) confocal microscopy. Immunohistochemical analysis of the specimens showed a significant correlation between MA-ce6 uptake and RAM-11 macrophage staining ($R = 0.83$, $p < 0.001$) and an inverse correlation between MA-ce6 uptake and smooth muscle cell staining ($R = -0.74$, $p < 0.001$). MA-ce6 may function as a molecular imaging agent to detect and/or photodynamically treat inflamed plaques.

Detection of Cell Death in Tumors by Using MR Imaging and a Gadolinium-based Targeted Contrast Agent.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18187402.

Krishnan AS, Neves AA, de Backer MM, et al.
Radiology. 2008;(e-published on Jan 9).

Purpose: To prospectively determine in an animal model whether an ionic gadolinium (Gd(3+)) chelate conjugate of the C2A domain of synaptotagmin I can be used with magnetic resonance (MR) imaging to detect tumor cell death noninvasively in vivo. **Materials and Methods:** Animal experiments were approved by a local ethics review committee. Gd(3+) chelates and fluorescent probes were attached to the lysine epsilon-amino groups of a glutathione-S-transferase-C2A fusion protein. Binding to phosphatidylserine (PS) was characterized by using surface plasmon resonance, and binding to dying cells in vitro was characterized by using flow cytometry and MR imaging. Binding to dying tumor cells in vivo was detected with T1 mapping and T1-weighted MR imaging and compared in drug-treated animals ($n = 10$); in animals injected with a site-directed mutant, which was inactive in PS binding (PS inactive) and which showed lesser binding to dying cells ($n = 6$); and in untreated animals injected with PS-active ($n = 6$) and PS-inactive ($n = 6$) contrast agents. Among groups, differences that

were significant were analyzed by using analysis of variance and Dunnett post hoc analysis. Results: The contrast agent had a relatively high affinity for PS (dissociation constant = 333 nmol/L +/- 85 [mean +/- standard error of the mean]; n = 3) and bound to apoptotic and necrotic, but not viable, cells in vitro. There was a greater tumor accumulation of the PS-active contrast agent compared with the PS-inactive contrast agent in drug-treated animals ($P < .05$) and compared with untreated animals injected with the PS-active and PS-inactive contrast agents ($P < .01$ for both). Conclusion: A relatively small (approximately 100 kDa) Gd(3+)-based contrast agent, which gives positive contrast on MR images, can be used to detect tumor cell death in vivo, and future derivatives of it may be used to assess early tumor responses to treatment. Supplemental material: <http://radiology.rsna.org/cgi/content/full/2463070471/DC1> © RSNA, 2007.

US Imaging of Tumor Angiogenesis with Microbubbles Targeted to Vascular Endothelial Growth Factor Receptor Type 2 in Mice.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18180339.

Willmann JK, Paulmurugan R, Chen K, et al.
Radiology. 2008;(e-published on Jan 7).

Purpose: To prospectively evaluate contrast material-enhanced ultrasonography (US) with microbubbles targeted to vascular endothelial growth factor receptor type 2 (VEGFR2) for imaging tumor angiogenesis in two murine tumor models. Materials and Methods: Animal protocols were approved by the Institutional Administrative Panel on Laboratory Animal Care. A US contrast agent, consisting of encapsulated gaseous microbubbles, was developed specifically to bind to VEGFR2 (by using anti-VEGFR2 antibodies and biotin-streptavidin interaction) which is up-regulated on endothelial cells of tumor blood vessels. VEGFR2-targeted microbubbles (MB(V)), control microbubbles (MB©), and nonlabeled microbubbles (MB(N)) were tested for binding specificity on cells expressing VEGFR2 (mouse angiosarcoma SVR cells) and control cells (mouse skeletal myoblast C2C12 cells). Expression of mouse VEGFR2 in culture cells was tested with immunocytochemical and Western blot analysis. Contrast-enhanced US imaging with MB(V) and MB© was performed in 28 tumor-bearing nude mice (mouse angiosarcoma, n = 18; rat malignant glioma, n = 10). Differences were calculated by using analysis of variance. Results: In cell culture, adherence of MB(V) on SVR cells (2.1 microbubbles per SVR cell) was significantly higher than adherence of control microbubbles (0.01-0.10 microbubble per SVR cell; $P < .001$) and significantly more MB(V) attached to SVR cells than to C2C12 cells (0.15 microbubble per C2C12 cell; $P < .001$). In vivo, contrast-enhanced US imaging showed significantly higher average video intensity when using MB(V) compared with MB© for angiosarcoma and malignant glioma tumors ($P < .001$). Results of immunohistochemical analysis confirmed VEGFR2 expression on vascular endothelial cells of both tumor types. Conclusion: US imaging with contrast microbubbles targeted to VEGFR2 allows noninvasive visualization of VEGFR2 expression in tumor vessels in mice. © RSNA, 2008 Supplemental material: <http://radiology.rsna.org/cgi/content/full/2462070536/DC1/>

Sodium Iodide Symporter (hNIS) Permits Molecular Imaging of Gene Transduction in Cardiac Transplantation.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18165779.

Rao VP, Miyagi N, Ricci D, et al.
Transplantation. 2007;84:1662–1666.

BACKGROUND: We evaluated the feasibility of noninvasive micro-single photon emission computed tomography (SPECT)/computed tomography (CT) imaging and quantification of cardiac gene expression after sodium iodide symporter (hNIS) gene transfer in cardiac transplantation. **METHODS.:** Donor rat hearts were perfused *ex vivo* with adenovirus expressing hNIS (Ad-hNIS), Ad-Null, or University of Wisconsin (UW) solution prior to heterotopic transplantation into syngeneic recipients. In the first group of recipients, imaging of the transplanted hearts with micro-SPECT/CT on day 5 was followed by immediate explant of the organs for *ex vivo* analyses. Radioactivity counts in the explanted hearts were obtained *ex vivo* and expressed as a percentage of the injected dose per gram of tissue (%ID/g). Intensities of the SPECT images of the transplanted hearts were quantified and converted to radioactive counts using a standard equation. The second group of recipients was imaged sequentially after injection of I on days 2 to 14 after transplantation. **RESULTS.:** Higher *ex vivo* radioiodine counts were noted in the hearts perfused with Ad-hNIS (1.04+/-0.2) compared to either the UW group (0.31+/-0.11, P<0.001) or the Ad-Null group (0.32+/-0.08, P<0.001). Image intensity in the Ad-NIS group (0.9+/-0.2) was also significantly higher than in the UW group (0.4+/-0.03, P=0.003) or the Ad-Null group (0.5+/-0.1, P<0.05). Sequential imaging of Ad-NIS-perfused hearts between postoperative days 2 and 14 revealed peak image intensity at day 5. Overall, image intensities correlated with *ex vivo* counts of radioactivity ($\rho=0.74$, P<0.05). **CONCLUSIONS.:** These data demonstrate that hNIS gene transfer permits sequential real-time detection and quantification of reporter gene expression in the transplanted heart with micro-SPECT/CT imaging.

Brain Metabolite Levels Assessed by Lactate-Edited MR Spectroscopy in Premature Neonates with and without Pentobarbital Sedation.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18184837.

Wang ZJ, Vigneron DB, Miller SP, et al.
AJNR Am J Neuroradiol. 2008;(e-published on Jan 9).

BACKGROUND AND PURPOSE: Pentobarbital is known to affect cerebral metabolism; pentobarbital sedation is, however, frequently used for MR imaging and MR spectroscopy, especially in children. Accurate assessment of the brain metabolite levels is important, particularly in neonates with suspected brain injury. We investigated whether pentobarbital sedation has any effect on the ratios of spectral metabolites lactate, N-acetylaspartate, or choline in a group of premature neonates. **MATERIALS AND METHODS:** MR spectroscopy was performed in 43 premature neonates, all with normal concurrent MR imaging and normal neurodevelopmental outcome at 12 months of age. Of those neonates, 14 (33%) required pentobarbital (Nembutal 1 mg/kg) sedation during MR spectroscopy; the remaining 29 neonates did not receive any sedation. Ratios of

lactate, choline, and N-acetylaspartate were calculated in the basal ganglia, thalami, and corticospinal tracts and compared between those neonates with and without sedation. RESULTS: Small amounts of brain lactate were detected in all of the premature neonates. The basal ganglia lactate/choline and lactate/N-acetylaspartate ratios were significantly lower, by 17% and 25% respectively, in the neonates with pentobarbital sedation compared with the age-matched neonates without sedation ($P < .05$). Sedation did not affect the lactate level in the thalami or the corticospinal tracts. The N-acetylaspartate/choline ratios were unaffected by pentobarbital sedation. CONCLUSION: Pentobarbital sedation is associated with lower lactate/choline and lactate/N-acetylaspartate ratios in the basal ganglia of premature neonates, as determined by proton MR spectroscopy. Investigators should be aware of this phenomenon for accurate interpretation of their MR spectroscopy results.

Applications of Mesenchymal Stem Cells Labeled with Tat Peptide Conjugated Quantum Dots to Cell Tracking in Mouse Body.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18081241.

Lei Y, Tang H, Yao L, et al.
Bioconjug Chem. 2007;(e-published on Dec 15).

Fluorescent quantum dots have great potential in cellular labeling and tracking. Here, PEG encapsulated CdSe/ZnS quantum dots have been conjugated with Tat peptide, and introduced into living mesenchymal stem cells. The Tat peptide conjugated quantum dots in mesenchymal stem cells were assessed by fluorescent microscopy, laser confocal microscope and flow cytometry. The result shows that Tat peptide conjugated quantum dots could enter mesenchymal stem cells efficiently. The Tat-quantum dots labeled stem cells were further injected into the tail veins of NOD/SCID beta2 M null mice, and the tissue distribution of these labeled cells in nude mice were examined with fluorescence microscope. The result shows that characteristic fluorescence of quantum dots was observed primarily in the liver, the lung and the spleen, with little or no quantum dots accumulation in the brain, the heart, or the kidney.

Near-Infrared Fluorescent Labeled Peptosome for Application to Cancer Imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18163535.

Tanisaka H, Kizaka-Kondoh S, Makino A, et al.
Bioconjug Chem. 2008;19:109–117.

Nonionic amphiphilic copolypeptides, which were composed of hydrophilic poly(sarcosine) and hydrophobic poly(γ -methyl l-glutamate) blocks, were synthesized with varying chain lengths of the blocks. The polypeptides having a suitable hydrophilic and hydrophobic balance were found to form vesicular assemblies of 100 nm size in buffer, which was evidenced by the TEM observation, the DLS analysis, and the encapsulation experiment. The genuine peptide vesicles, peptosomes, were labeled with a near-infrared fluorescence (NIRF) probe. In vivo retention in blood experiment showed long circulation of the peptosome in rat blood as stable as the PEGylated liposome. NIRF

imaging of a small cancer on mouse by using the peptosome as a nanocarrier was successful due to the EPR effect of the peptosome. Peptosome is shown here as a novel excellent nanocarrier for molecular imaging.

Targeted folic acid-PEG nanoparticles for noninvasive imaging of folate receptor by MRI.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18085650.

Chen TJ, Cheng TH, Hung YC, et al.
J Biomed Mater Res A. 2007;(e-published on Dec 17).

The surface of superparamagnetic iron oxide nanoparticles (SPIO) with different molecular weight of poly(ethylene glycol) (PEG) and folic acid (FA) were synthesized. The SPIO-PEG-FA nanoparticles are well-dispersed and have good stability in various pH solutions. The lack of hysteresis and remanence at ambient temperatures is characteristic of superparamagnetic materials for SPIO-PEG-FA. The uptake by macrophage for SPIO-PEG-FA is lower than that of Feridex I.V. even at higher concentration. Internalization of SPIO-PEG-FA in targeted cells (KB cells) was observed by flow-cytometric analysis and in vitro MR imaging. The intensity change of positive KB cell tumor (-20 to 25%) is significantly lower than that of negative HT-1080 cell tumor from precontrast to postcontrast images of the tumor by in vivo MR imaging. These preliminary results demonstrated that SPIO-PEG-FA have the ability to target folate receptor. © 2007 Wiley Periodicals, Inc. *J Biomed Mater Res*, 2008.

Multimodality imaging of T-cell hybridoma trafficking in collagen-induced arthritic mice: image-based estimation of the number of cells accumulating in mouse paws.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18163841.

Yaghoubi SS, Creusot RJ, Ray P, et al.
J Biomed Opt. 2007;12:064025.

Appropriate targeting of therapeutic cells is essential in adoptive cellular gene therapy (ACGT). Imaging cell trafficking in animal models and patients will guide development of ACGT protocols. Collagen type II (C-II)-specific T cell hybridomas are transduced with a lentivirus carrying a triple fusion reporter gene (TFR) construct consisting of a fluorescent reporter gene (RG), a bioluminescent RG (hRluc), and a positron emission tomography (PET) RG. Collagen-induced arthritic (CIA) mice are scanned with a bioluminescence imaging camera before and after implantation of various known cell quantities in their paws. Linear regression analysis yields equations relating two parameters of image signal intensity in mice paws to the quantity of hRluc expressing cells in the paws. Afterward, trafficking of intravenously injected cells is studied by quantitative analysis of bioluminescence images. Comparison of the average cell numbers does not demonstrate consistently higher accumulation of T-cell hybridomas in the paws with higher inflammation scores, and injecting more cells does not cause increased accumulation. MicroPET images illustrate above background signal in the

inflamed paws and chest areas of CIA mice. The procedures described in this study can be used to derive equations for cells expressing other bioluminescent RGs and in other animal models.

Visualisation of the kinetics of macrophage infiltration during experimental autoimmune encephalomyelitis by magnetic resonance imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18177950.

Baeten K, Hendriks JJ, Hellings N, et al.
J Neuroimmunol. 2008;(e-published on Jan 11).

Macrophages are considered to be the predominant effector cells in multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). Ultra small particles of iron oxide (USPIO) can be used to detect macrophage infiltrates in the CNS with magnetic resonance imaging (MRI). Here, we investigated whether the kinetics of lesion formation in EAE can be visualised by altering the time point of USPIO injection and the time interval between particle injection and MRI. When USPIO are systemically injected 24 h before MRI, hypo intense regions are detected in different brain regions depending on the disease stage. These regions correspond to sites of macrophage infiltration. A more complete visualisation of sites of inflammation is accomplished by USPIO injection at disease onset and postponing MRI to top of disease. This study demonstrates that the distribution pattern and amount of inflammatory lesions detected with USPIO, depends on timing of USPIO administration and subsequent MRI. These findings are important for a correct application and interpretation of USPIO dependent contrast imaging of CNS inflammation.