

## Selected MI References May, 2008

### **MR imaging of thrombi using EP-2104R, a fibrin-specific contrast agent: initial results in patients.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18425519](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18425519).

Spuentrup E, Botnar RM, Wiethoff AJ, et al.  
*Eur Radiol.* 2008;(epub. on Apr 19).

This study was an initial phase II trial in humans of molecular magnetic resonance (MR) imaging for improved visualization of thrombi in vessel territories potentially responsible for stroke using a new fibrin-specific contrast agent (EP-2104R). Eleven patients with thrombus in the left ventricle (n = 2), left or right atrium (n = 4), thoracic aorta (n = 4) or carotid artery (n = 1) as verified by an index examination (ultrasound, computed tomography, or conventional MR) were enrolled. All MR imaging was performed on 1.5 T whole-body MR-system using an inversion-recovery black-blood gradient-echo sequence. The same sequence was performed before and 2-6 h after low-dose intravenous administration of 4  $\mu\text{mol/kg}$  EP-2104R. Two investigators assessed image quality and signal amplification. Furthermore, contrast-to-noise ratios (CNR) between the clot and the blood pool/surrounding soft tissue before and after administration of the contrast agent were compared using Student's t-test. MR imaging and data analysis were successfully completed in 10 patients. No major adverse effects occurred. On enhanced images, thrombi demonstrated high signal amplification, typically at the clot surface, with a significantly increased contrast in comparison to the surrounding blood pool and soft tissue (CNR for clot vs. blood pool, unenhanced and enhanced: 6 +/- 8 and 29 +/- 14; CNR for clot vs. soft tissue, unenhanced and enhanced: 0 +/- 4 and 21 +/- 13;  $P < 0.01$  for both comparisons). EP-2104R allows for molecular MR imaging of thrombi potentially responsible for stroke. High contrast between thrombus and surrounding blood and soft tissues can be achieved with enhanced imaging.

### **Characterization of (111)In and (177)Lu-labeled antibodies binding to CD44v6 using a novel automated radioimmunoassay.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18438972](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18438972).

Nestor M, Andersson K, Lundqvist H.  
*J Mol Recognit.* 2008;21:179–183.

Targeted cancer therapies rely on bifunctional molecules, typically a protein that specifically recognizes tumor cells and a toxic component which is linked to the protein. Therefore, development of such therapies includes detailed characterizations of protein-cell interactions in order to find a good targeting agent. Knowledge of factors such as antibody-antigen specificity, as well as cellular uptake, retention and affinity of the antibody are necessary in order to be successful. In this paper, we have used a novel instrument, LigandTracer® Yellow, to characterize the interactions of (111)In and

(177)Lu-labeled monoclonal antibodies (MAbs) with CD44v6. Uptake studies with varying specific radioactivity of the chimeric MAb U36 and with an irrelevant antibody for the CD44v6 receptor verified the reliability of the method, as well as the specificity of the antibody-receptor binding. Uptake, retention, and affinity were very similar for the (111)In and (177)Lu-labeled conjugate, and were in line with earlier studies using manual methods. The fact that no adverse effects from labeling were seen, together with the high retention, could make these conjugates promising candidates for imaging and therapy of certain cancer types in the future. The novel LigandTracer technology reduced the workload and reagent spending while providing data with superior time resolution. The obtained results were in agreement with previously reported findings. In addition the real-time detection and higher time resolution made more detailed studies of the interactions possible. Copyright © 2008 John Wiley & Sons, Ltd.

### **Genome-free Viral Capsids as Carriers for Positron Emission Tomography Radiolabels.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18437498](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18437498).

J MH, J PON, D WR, et al.  
*Mol Imaging Biol.* 2008;(epub. on Apr 25).

**PURPOSE:** We have developed a modular synthetic strategy to append imaging agents to a viral capsid. **PROCEDURES:** The hollow protein shell of bacteriophage MS2 (mtMS2) was labeled on its inside surface with [(18)F]fluorobenzaldehyde through a multistep bioconjugation strategy. An aldehyde functional group was first attached to interior tyrosine residues through a diazonium coupling reaction. The aldehyde was further elaborated to an alkoxyamine functional group, which was then condensed with n.c.a. [(18)F]fluorobenzaldehyde. Biodistribution of the radioactive MS2 conjugates was subsequently evaluated in Sprague-Dawley rats. **RESULTS:** Relative to fluorobenzaldehyde, fluorine-18-labeled MS2 exhibited prolonged blood circulation time and a significantly altered excretion profile. It was also observed that additional small molecule cargo installed inside the capsids did not alter the biodistribution. **CONCLUSIONS:** These studies provide further insight into the pharmacokinetic behavior of nanomaterials and serve as a platform for the future development of targeted imaging and therapeutic agents based on mtMS2.

### **Quantum dot probes for bacteria distinguish Escherichia coli mutants and permit in vivo imaging.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18473060](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18473060).

Leevy WM, Lambert TN, Johnson JR, et al.  
*Chem Commun (Camb).* 2008;2331–2333.

Fluorescent quantum dots coated with zinc(ii)-dipicolylamine coordination complexes can selectively stain a rough Escherichia coli mutant that lacks an O-antigen element and permit optical detection in a living mouse leg infection model.

### **Macrophage physiological function after superparamagnetic iron oxide labeling.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18470957](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18470957).

Hsiao JK, Chu HH, Wang YH, et al.  
*NMR Biomed.* 2008;(epub. on May 12).

Our goal was to analyze the changes in morphology and physiological function (phagocytosis, migratory capabilities, humoral and cellular response, and nitric oxide secretion) of murine macrophages after labeling with a clinically used superparamagnetic iron oxide (SPIO), ferucarbotran. In SPIO-treated macrophages, nanoparticles were taken up in the cytoplasm and accumulated in a membrane-bound organelle. Macrophage proliferation and viability were not modified after SPIO labeling. Phagocytic function decreased after labeling with only 10 microg Fe/mL SPIO, whereas other functions including migration and production of tumor necrosis factor-alpha and nitric oxide increased at the highest SPIO concentration (100 microg Fe/mL). Copyright © 2008 John Wiley & Sons, Ltd.

### **Sentinel lymph node detection ex vivo using ultrasound-modulated optical tomography.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18465949](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18465949).

Kim C, Song KH, Wang LV.  
*J Biomed Opt.* 2008;13:020507.

We apply ultrasound-modulated optical tomography (UOT) to image ex-vivo methylene-blue-dyed sentinel lymph nodes embedded in 3.2-cm-thick chicken breast tissues. The UOT system is implemented for the first time using ring-shaped light illumination, intense acoustic bursts, and charge-coupled device (CCD) camera-based speckle contrast detection. Since the system is noninvasive, nonionizing, portable, relatively cost effective, and easy to combine with photoacoustic imaging and single element ultrasonic pulse-echo imaging, UOT can potentially be a good imaging modality for the detection of sentinel lymph nodes in breast cancer staging in vivo.

### **3T MRI: Advances in brain imaging.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18455895](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18455895).

Alvarez-Linera J.  
*Eur J Radiol.* 2008;(epub. on May 1).

Since its approval by the FDA in 2000, brain MR imaging at 3.0T has been increasingly used in clinical practice. Theoretically, the signal-to-noise ratio (SNR) of a 3T MR scanner will be double that of a 1.5T scanner. However, the relationship between the magnetic field used and the image obtained is very complex. Today, using a 3T magnet in Neuroradiology has far more advantages than disadvantages, and the diagnostic potential of higher strength magnets for structural and vascular scans, diffusion and perfusion imaging, spectroscopy and cortical activation studies is improving. However, it is useful to have an awareness of how increasing field strength affects each of these techniques so that full advantage may be taken of them.

## **Synthesis of Fluorine-18 Functionalized Nanoparticles for use as in vivo Molecular Imaging Agents.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18452296](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18452296).

Matson JB, Grubbs RH.

*J Am Chem Soc.* 2008;(epub. on May 2).

(No abstract)

## **Update: improvement strategies for Peptide receptor scintigraphy and radionuclide therapy.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18454684](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18454684).

de Visser M, Verwijnen SM, de Jong M.

*Cancer Biother Radiopharm.* 2008;23:137–157.

Somatostatin receptor-targeting peptides are widely used for the imaging and therapy of neuroendocrine tumors. Peptide-receptor radionuclide therapy (PRRT) in neuroendocrine tumor patients with radiolabeled somatostatin analogs has resulted in symptomatic improvement, prolonged survival, and enhanced quality of life. The side-effects of PRRT are few and mostly mild, certainly when using kidney protective agents. If a more widespread use of PRRT is possible, such therapy might become the therapy of first choice in patients with metastasized or inoperable neuroendocrine gastroenteropancreatic tumors. Yet, much profit can be gained from improving the receptor-targeting strategies available and developing new strategies. This review presents an overview of several options to optimize receptor-targeted imaging and radionuclide therapy. These include the optimization of peptide analogs, increasing the number of receptors on the tumor site, and combining PRRT with other treatment strategies. The development of new peptide analogs with increased receptor-binding affinity and improved stability might lead to a higher accumulation of radioactivity inside tumor cells. Analogs of somatostatin have been widely studied. However, much profit can be gained in improving peptide analogs targeting other tumor-related receptors, including gastrin-releasing peptide (GRP) receptors, neurotensin (NT) receptors, cholecystokinin (CCK) receptors, and glucagon-like peptide-1 (GLP-1) receptors. Several peptide analogs targeting these receptors are well on their way to clinical utilization. The literature shows that it is possible to increase the receptor density on tumor cells by using different methods, which results in higher binding and internalization rates and thus a higher contrast during peptide-receptor scintigraphy. In PRRT treatment, this would enable the administration of higher therapeutic doses to tumors, which might lead to a higher cure rate in patients. Combinations of radionuclide therapy with other treatment modalities, such as chemotherapy or pretreatment with radiosensitizers, might increase the impact of the treatment. Further, the administration of higher dosages of radioactivity to the patient, enabled by combinations of PRRT with strategies reducing the radiation dose to healthy organs, will improve the outcome of tumor treatment. Also, targeting one or several tumor-specific receptors by using combinations of therapeutic agents, as well

as by reducing nontarget uptake of radioactivity, will enlarge the therapeutic window of PRRT. Clinical studies will provide more insight in the effects of combining treatment strategies in cancer patients.

### **In Vivo Measurement of Vascular Modulation in Experimental Tumors Using a Fluorescent Contrast Agent.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18422875](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18422875).

Valentini G, D'Andrea C, Ferrari R, et al.  
*Photochem Photobiol.* 2008;(epub. on Apr 12).

We compared the effectiveness of three optical techniques based on fluorescence imaging and spectroscopy with indocyanine green (ICG) contrast agent to evaluate in vivo the disruption of the active vasculature induced by a vascular targeting agent. The blood perfusion of the MDA-MB-435 tumor model transplanted in nude mice was estimated from the signal of the contrast agent measured immediately after its systemic injection in mice. Optical measurements were performed using a fluorescence imaging setup and a fiber-based time correlated single photon counting (TCSPC) apparatus. This latter apparatus was used to measure the tumor fluorescence in transmittance geometry and the change in the basal optical absorption induced by the contrast agent, thus providing an alternative estimation of the blood content in the tumor. Mice were divided into four groups. Three groups were treated with different doses of the vascular disrupting agent ZD6126, the fourth group (control group) received the drug vehicle only. Optical measurements were carried out 3 h after pharmacologic treatment. After 24 h, mice were killed, tumors were excised and the extent of necrosis was evaluated with standard histologic analysis. On fluorescence imaging ICG emission from tumors of mice treated with ZD6126 significantly was lower compared with the emission from control mice. The histologic sections also showed a significantly higher amount of necrosis in tumors of treated mice. Both these findings, which correlate with each other, indicate an effective vascular shutdown induced by the drug. However, ICG fluorescence measured with the TCSPC apparatus in transmittance geometry and the estimate of the change in optical absorption did not allow a statistically significant differentiation between treated and control groups.

### **Imaging transgene activity in vivo.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18413756](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18413756).

Gade TP, Koutcher JA, Spees WM, et al.  
*Cancer Res.* 2008;68:2878–2884.

The successful translation of gene therapy for clinical application will require the assessment of transgene activity as a measure of the biological function of a therapeutic transgene. Although current imaging permits the noninvasive detection of transgene expression, the critical need for quantitative imaging of the action of the expressed

transgene has not been met. In vivo magnetic resonance spectroscopic imaging (MRSI) was applied to quantitatively delineate both the concentration and activity of a cytosine deaminase-uracil phosphoribosyltransferase (CD-UPRT) fusion enzyme expressed from a transgene. MRSI enabled the generation of anatomically accurate maps of the intratumoral heterogeneity in fusion enzyme activity. We observed an excellent association between the CD-UPRT concentration and activity and the percentage of CD-UPRT(+) cells. Moreover, the regional levels of UPRT activity, as measured by imaging, correlated well with the biological affect of the enzyme. This study presents a translational imaging paradigm for precise, in vivo measurements of transgene activity with potential applications in both preclinical and clinical settings.

### **Functional imaging in Parkinson disease.**

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18413571](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18413571).

Nandhagopal R, McKeown MJ, Stoessl AJ.  
*Neurology*. 2008;70:1478–1488.

**OBJECTIVE:** Functional imaging techniques represent useful tools to assess in vivo the neurochemical alterations and functional connectivity in Parkinson disease (PD). Here, the authors review the various approaches and potential application of these imaging techniques to the study of PD. **METHOD:** Radiotracer imaging using dopaminergic markers facilitates assessment of pre- and postsynaptic nigrostriatal integrity, while imaging with other appropriate radiotracers explores nondopaminergic neurotransmitter function, local metabolism, blood flow, and mechanisms potentially related to disease progression and pathogenesis. Activation studies using functional MRI detect blood oxygen level dependent signal, as an indirect marker of neuronal activity. **RESULT:** Functional imaging techniques have been applied to infer the potential role of inflammation and other factors in etiopathogenesis as well as to study compensatory and regulatory mechanisms in early PD and subclinical disease in genetic forms of PD. Imaging studies also help to understand the neurobiological basis of motor and nonmotor complications. Recent reports suggest a role for striatal dopaminergic transmission in modulating neurobehavioral processes including the placebo effect in PD. Although functional imaging has been employed to monitor disease progression, the discordance between clinical outcome and imaging measures after therapeutic interventions precludes their use as surrogate end points in clinical trials. Beyond these limitations and potential challenges, imaging techniques continue to find wide application in the study of PD. **CONCLUSION:** Functional imaging can provide meaningful insights into mechanisms underlying various aspects of motor and nonmotor dysfunction in Parkinson disease and the role of striatal dopaminergic transmission in behavioral processes beyond motor control. These modalities hold promise to study the preclinical phase and to elucidate further the benefits and complications of surgical interventions and the utility of neuroprotective strategies.