

1. Reduced Prefrontal Oxygenation in Alzheimer Disease During Verbal Fluency Tasks.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17998307

Herrmann M J, Langer J B, Jacob C, et al.

Am J Geriatr Psychiatry. 2007;(Nov 12).

Objective: Near-infrared spectroscopy (NIRS) is an optical method to measure changes in the concentration of oxygenated hemoglobin (O₂Hb) and deoxygenated hemoglobin (HHb) in the vascular system of the brain tissue. Because NIRS is easy to assess and does not have any side effects, it seems perfectly suitable for functional measurements in psychiatric patients or fragile subjects. As previous research suggested changes in functional brain activation in prefrontal brain areas of patients with dementia, the aim of this study was to replicate these findings by means of multichannel NIRS. Methods: In the present study, the authors investigated 16 patients with Alzheimer disease and 16 healthy subjects (similar in age and sex) during performance of a verbal fluency task. Results: The results clearly showed an activation pattern during active phase as compared to baseline phase in the form of decreases in HHb and increases in O₂Hb, with a reduced increase of O₂Hb for patients. Conclusion: These results indicate a diminished activation of the dorsolateral prefrontal cortex in patients with Alzheimer disease. Future research has to show whether this decreased activation pattern might be a suitable predictor for the effectiveness of treatment in dementias.

2. Design and development of a hand-held optical probe toward fluorescence diagnostic imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17994902

Jayachandran B, Ge J, Regalado S, et al.

J Biomed Opt. 2007;12:054014. (Sep-Oct).

Near-infrared optical imaging is an emerging noninvasive technology toward breast cancer diagnosis. The optical imaging systems available to date are limited either by flexibility to image any given breast volume, patient comfort, or instrument portability. Here, a hand-held optical probe is designed and developed, 1. employing a unique measurement scheme of simultaneous multiple point illumination and collection for rapid data acquisition and minimal patient discomfort, and 2. employing a curved probe head such that it allows flexible imaging of tissue curvatures. Simulation studies are carried out on homogeneous slab phantoms (5x10x8 cc) to determine an appropriate source-detector configuration for the probe head. These design features are implemented in the development of the probe, which consisted of six simultaneous illuminating and 165 simultaneous collecting fibers, spaced 0.5 cm apart on a 5x10 sq-cm probe head. Simulation studies on 3-D slab and curved phantoms demonstrate an increase in the total area of predicted fluorescence amplitude and overall signal strength on using simultaneous multiple point sources over a single point source. The probe is designed and developed such

that on coupling with a detection system in the future, the hand-held probe based imager can be clinically assessed toward cancer diagnostic imaging.

3. Molecular imaging of vascular endothelial growth factor receptor 2 expression using targeted contrast-enhanced high-frequency ultrasonography.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17957052

Lyshchik A, Fleischer A C, Huamani J, et al.

J Ultrasound Med. 2007;26:1575-1586. (Nov).

OBJECTIVE: The aim of our study was to investigate the use of targeted contrast-enhanced high-frequency ultrasonography for molecular imaging of vascular endothelial growth factor receptor 2 (VEGFR2) expression on tumor vascular endothelium in murine models of breast cancer. **METHODS:** Highly invasive metastatic (4T1) and nonmetastatic (67NR) breast cancer cells were implanted in athymic nude mice. Tumors were examined in vivo with targeted contrast-enhanced high-frequency ultrasonography using a scanner with a 40-MHz probe. Randomized boluses of ultrasound contrast agents (UCAs) conjugated with an anti-VEGFR2 monoclonal antibody or an isotype control antibody (immunoglobulin G) were injected into the animals. Sonograms were analyzed by calculation of the normalized video intensity amplitudes caused by backscatter of the bound UCA. After ultrasonography, the tumor samples were harvested for analysis of VEGFR2 expression by immunoblotting and immunocytochemistry. **RESULTS:** The mean video intensity amplitude caused by backscatter of the retained VEGFR2-targeted UCA was significantly higher than that of the control UCA (mean +/- SD: 4T1 tumors, 15 +/- 3.5 versus 7 +/- 1.6 dB; $P < .01$; 67NR tumors, 50 +/- 12.3 versus 12 +/- 2.6 dB; $P < .01$). There was a significant difference in VEGFR2-targeted UCA retention between 4T1 and 67NR tumors (normalized video intensity amplitudes, 15 +/- 3.5 and 50 +/- 12.3 dB, respectively; $P < .001$), and this correlated well with relative VEGFR2 expression in the two tumor types. **CONCLUSIONS:** Targeted contrast-enhanced high-frequency ultrasonography may enable in vivo molecular imaging of VEGFR2 expression on the tumor vascular endothelium and may be used for noninvasive longitudinal evaluation of tumor angiogenesis in preclinical studies.

4. Confocal light absorption and scattering spectroscopic microscopy monitors organelles in live cells with no exogenous labels.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17956980

Itzkan I, Qiu L, Fang H, et al.

Proc Natl Acad Sci U S A. 2007;104:17255-17260. (Oct 30).

This article reports the development of an optical imaging technique, confocal light absorption and scattering spectroscopic (CLASS) microscopy, capable of noninvasively determining the dimensions and other physical properties of single subcellular organelles. CLASS microscopy combines the principles of light-scattering spectroscopy (LSS) with confocal microscopy. LSS is an optical

technique that relates the spectroscopic properties of light elastically scattered by small particles to their size, refractive index, and shape. The multispectral nature of LSS enables it to measure internal cell structures much smaller than the diffraction limit without damaging the cell or requiring exogenous markers, which could affect cell function. Scanning the confocal volume across the sample creates an image. CLASS microscopy approaches the accuracy of electron microscopy but is nondestructive and does not require the contrast agents common to optical microscopy. It provides unique capabilities to study functions of viable cells, which are beyond the capabilities of other techniques.

5. **Pathophysiology of the blood-brain barrier: animal models and methods.**
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17950377

Hawkins B T, Egleton R D.

Curr Top Dev Biol. 2008;80:277-309. The specialized cerebral microvascular endothelium interacts with the cellular milieu of the brain and extracellular matrix to form a neurovascular unit, one aspect of which is a regulated interface between the blood and central nervous system (CNS). The concept of this blood-brain barrier (BBB) as a dynamically regulated system rather than a static barrier has wide-ranging implications for pathophysiology of the CNS. While in vitro models of the BBB are useful for screening drugs targeted to the CNS and indispensable for studies of cerebral endothelial cell biology, the complex interactions of the neurovascular unit make animal-based models and methods essential tools for understanding the pathophysiology of the BBB. BBB dysfunction is a complication of neurodegenerative disease and brain injury. Studies on animal models have shown that diseases of the periphery, such as diabetes and inflammatory pain, have deleterious effects on the BBB which may contribute to neurological complications associated with these conditions. Furthermore, genetic and/or epigenetic abnormalities in constituents of the BBB may be significant contributing factors in disease etiology. Research that approaches the BBB as a dynamic system integrated with both the CNS and the periphery is therefore critical to understanding and treating diseases of the CNS. Herein, we review various methodological approaches used to study BBB function in the context of disease. These include measurement of transport between blood and brain, imaging-based technologies, and genomic/proteomic approaches.

6. **Magnetic Resonance Imaging of Endothelial Adhesion Molecules in Mouse Atherosclerosis Using Dual-Targeted Microparticles of Iron Oxide.**
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17962629

McAteer M A, Schneider J E, Ali Z A, et al.

Arterioscler Thromb Vasc Biol. 2007;(Oct 25).

OBJECTIVE: Microparticles of iron oxide (MPIO) distort magnetic field creating marked contrast effects far exceeding their physical size. We hypothesized that antibody-conjugated MPIO would enable MRI (MRI) of endothelial cell adhesion

molecules in mouse atherosclerosis. METHODS AND RESULTS: MPIO (4.5 microm) were conjugated to monoclonal antibodies against vascular cell adhesion molecule-1 (VCAM-MPIO) or P-selectin (P-selectin-MPIO). In vitro, VCAM-MPIO bound, in dose-dependent manner, to tumor necrosis factor (TNF)-alpha stimulated sEND-1 endothelial cells, as quantified by light microscopy ($R(2)=0.94$, $P=0.03$) and by MRI ($R(2)=0.98$, $P=0.01$). VCAM-MPIO binding was blocked by preincubation with soluble VCAM-1. To mimic leukocyte binding, MPIO targeting both VCAM-1 and P-selectin were administered in apolipoprotein E(-/-) mice. By light microscopy, dual-targeted MPIO binding to endothelium overlying aortic root atherosclerosis was 5- to 7-fold more than P-selectin-MPIO ($P<0.05$) or VCAM-MPIO ($P<0.01$) alone. Dual-targeted MPIO, injected intravenously in vivo bound aortic root endothelium and were quantifiable by MRI ex vivo (3.5-fold increase versus control; $P<0.01$). MPIO were well-tolerated in vivo, with sequestration in the spleen after 24 hours. CONCLUSIONS: Dual-ligand MPIO bound to endothelium over atherosclerosis in vivo, under flow conditions. MPIO may provide a functional MRI probe for detecting endothelial-specific markers in a range of vascular pathologies.

7. Multiparameter Magnetic Relaxation Switch Assays.

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Taktak S, Sosnovik D, Cima M J, et al.

Anal Chem. 2007;(Nov 6).

Magnetic nanoparticles (NPs) can serve as magnetic relaxation switches (MRSw's), switching from a dispersed to a clustered state, or the reverse, due to the presence of molecular targets, with changes in the spin-spin relaxation time of water (T_2). Biotinylated NP probes reacted with an avidin molecular target to form stable NP clusters, which permitted several NMR parameters to be measured as a function of cluster size. Associated with avidin-induced NP cluster formation was an increase in the spin-spin relaxation rate ($1/T_2$), while the spin-lattice relaxation rate ($1/T_1$) was unaffected. On the basis of the selective effects of NP cluster formation on T_2 , we developed a T_1/T_2 interrogation method where NP probe concentration and avidin analyte were unknown and both were determined. A third NMR parameter examined was the replication of T_2 measurements, which were used to rapidly determine whether the ratio of avidin to biotinylated NP was optimal or whether additional biotinylated NP was needed. The T_1/T_2 and T_2 replication interrogation methods illustrate how MRSw assays can employ multiple parameters, instead of relying only on T_2 , to obtain information about the reaction of NPs with molecular targets.

8. Non-invasive radioiodine imaging for accurate quantitation of NIS reporter gene expression in transplanted hearts.

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Ricci D, Mennander A A, Pham L D, et al.

Eur J Cardiothorac Surg. 2007;(Oct 31).

Top References for Molecular Imaging – November 2007

Objective: We studied the concordance of transgene expression in the transplanted heart using bicistronic adenoviral vector coding for a transgene of interest (human carcinoembryonic antigen: hCEA - beta human chorionic gonadotropin: betahCG) and for a marker imaging transgene (human sodium iodide symporter: hNIS). Methods: Inbred Lewis rats were used for syngeneic heterotopic cardiac transplantation. Donor rat hearts were perfused ex vivo for 30min prior to transplantation with University of Wisconsin (UW) solution (n=3), with 10(9)pfu/ml of adenovirus expressing hNIS (Ad-NIS; n=6), hNIS-hCEA (Ad-NIS-CEA; n=6) and hNIS-betahCG (Ad-NIS-CG; n=6). On postoperative day (POD) 5, 10, 15 all animals underwent micro-single photon emission computed tomography/computed tomography (SPECT/CT) imaging of the donor hearts after tail vein injection of 1000muCi (123)I and blood sample collection for hCEA and betahCG quantification. Results: Significantly higher image intensity was noted in the hearts perfused with Ad-NIS (1.1+/-0.2; 0.9+/-0.07), Ad-NIS-CEA (1.2+/-0.3; 0.9+/-0.1) and Ad-NIS-CG (1.1+/-0.1; 0.9+/-0.1) compared to UW group (0.44+/-0.03; 0.47+/-0.06) on POD 5 and 10 (p<0.05). Serum levels of hCEA and betahCG increased in animals showing high cardiac (123)I uptake, but not in those with lower uptake. Above this threshold, image intensities correlated well with serum levels of hCEA and betahCG (R(2)=0.99 and R(2)=0.96, respectively). Conclusions: These data demonstrate that hNIS is an excellent reporter gene for the transplanted heart. The expression level of hNIS can be accurately and non-invasively monitored by serial radioisotopic SPECT imaging. High concordance has been demonstrated between imaging and soluble marker peptides at the maximum transgene expression on POD 5.

9. **A Novel Functional Translocator Protein Ligand for Cancer Imaging.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17979225

Bai M, Rone M B, Papadopoulos V, et al.

Bioconjug Chem. 2007;(Nov 3).

The translocator protein (TSPO) is an attractive target for tumor imaging due to its up-regulation in numerous cancer cell types. Here, we report a series of functional TSPO ligands, n-TSPOMBb732, which can be conjugated to a variety of signaling moieties and are widely applicable in TSPO-targeted molecular imaging. Two fluorescent dye-labeled 6-TSPOMBb732 displayed nanomolar binding affinities to TSPO and were successfully imaged in vitro.