

Selected MI References March, 2008

MR-optical imaging of cardiovascular molecular targets.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18324364.

Nahrendorf M, Sosnovik DE, Weissleder R.
Basic Res Cardiol. 2008;103:87–94.

Our understanding of the intricate inflammation biology underlying atherosclerosis is rapidly progressing. Molecular imaging strategies, harnessing this body of knowledge, have been developed to visualize some key cellular and molecular events in plaque evolution and vulnerability. Here, we discuss recent advances in magnetic resonance and fluorescence imaging of key biomarkers including adhesion molecules, inflammatory cells, and enzyme activity. We discuss strengths and limitations of respective imaging technologies, and comment on the potential of multi-modality imaging approaches.

Experimental research on therapeutic angiogenesis induced by hepatocyte growth factor directed by ultrasound-targeted microbubble destruction in rats.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18314523.

Li X, Wang Z, Ran H, et al.
J Ultrasound Med. 2008;27:453–460.

The purpose of this study was to explore the feasibility of therapeutic angiogenesis in myocardial infarction induced by hepatocyte growth factor (HGF) mediated by ultrasound-targeted microbubble destruction. **METHODS:** Forty Wistar rats were divided into 4 groups after the models of myocardial infarction were prepared: (1) HGF, ultrasound, and microbubbles (HGF+US/MB), (2) HGF and ultrasound, (3) HGF and microbubbles, and (4) surgery alone. Destruction of ultrasound-targeted microbubbles loaded with the HGF gene with an electrocardiographic trigger mode was performed in the HGF+US/MB group. All the rats were killed after being transfected for 14 days. Enhanced green fluorescent protein expression was examined in the myocardium, liver, and kidney in all groups by fluorescence microscopy; CD34 expression was detected by immunohistochemistry, and microvessel density (MVD) was counted in the high-power field on microscopy. Hepatocyte growth factor expression in the myocardium was detected by western blotting and an enzyme-linked immunosorbent assay. **RESULTS:** Enhanced green fluorescent protein expression was detected in the myocardium of the HGF+US/MB group, but a few areas of HGF expression were detected only in small vessels and the capillary endothelium, and no expression was found in the surgery-alone and HGF and microbubbles groups. The results of MVD counting by microscopy showed that the MVD in the myocardium of the HGF+US/MB group was the highest among all the groups. The results of western blotting and the enzyme-linked immunosorbent assay showed that the amount of HGF in the myocardium was highest in the HGF+US/MB

group. **CONCLUSIONS:** Ultrasound-targeted microbubble destruction could deliver HGF into the infarcted myocardium and produce an angiogenesis effect, which could provide a novel strategy for gene therapy of myocardial infarction.

In vivo imaging of a diabetogenic CD8+ T cell response during type 1 diabetes progression.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18302224.

Medarova Z, Tsai S, Evgenov N, et al.
Magn Reson Med. 2008;(e-published on Feb 26).

Type 1 diabetes is preceded by a long, protracted period of pancreatic islet inflammation by autoreactive lymphocytes. Noninvasive imaging of islet inflammation prior to the onset of hyperglycemia might have diagnostic and therapeutic implications, but this is not currently possible. Here, MRI is used to track, noninvasively, the accumulation of diabetogenic CD8+ T-cells during type 1 diabetes progression in nonobese diabetic (NOD) mice. The contrast agent is an MRI probe (MN-NRP-V7) that specifically labels CD8+ T-cells recognizing residues 206-214 of islet-specific glucose-6-phosphatase catalytic subunit related protein (IGRP(206-214)) in the context of the major histocompatibility complex (MHC) class I molecule H-2K(d). This probe consists of superparamagnetic iron oxide nanoparticles (MN) coated with K(d) molecules presenting NRP-V7, a high-avidity mimotope of IGRP(206-214). NOD mice of different ages (5, 8, 15, and 24 weeks) were imaged by MRI before and after a single intravenous injection of MN-NRP-V7 or unmodified MN nanoparticles. MN-NRP-V7 accumulation, as determined by semiquantitative MRI analysis of pancreas-associated T(2) relaxation time, was antigen-specific, age-dependent, and well correlated with the numbers of MN-NRP-V7-labeled CD8+ T-cells recovered from the pancreata of the treated mice. Antigen/MHC-coupled nanoparticles represent a promising new avenue for noninvasive imaging of lymphocyte inflammation in organ-specific autoimmunity and transplantation. *Magn Reson Med*, 2008. © 2008 Wiley-Liss, Inc.

In vivo optical imaging of CD13/APN-expression in tumor xenografts.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18315356.

von Wallbrunn A, Waldeck J, Holtke C, et al.
J Biomed Opt. 2008;13:011007.

The metalloexopeptidase CD13/aminopeptidase N (APN) has been shown to be involved in cancer angiogenesis, invasion, and metastasis. Therefore, a CD13/APN-targeted NGR-peptide was labeled with the cyanine dye Cy 5.5 and applied to image tumor xenografts with different APN-expression levels using both planar and tomographic optical imaging methods. In vitro, the peptide-dye conjugate showed a clear binding affinity to APN-

positive HT-1080 cells, while negative MCF-7 cells and predosing with the free NGR-peptide revealed little to no fluorescence. In vivo, tumor xenografts ($n \geq 5$) were clearly visualized by two-dimensional (2-D) planar fluorescence reflectance imaging (FRI) and three-dimensional (3-D) fluorescence mediated tomography (FMT) up to 24 h after injection. FMT also allowed us to quantify fluorochrome distribution in deeper tissue sections, showing an average fluorochrome concentration of 306.7 ± 54.3 nM Cy 5.5 (HT-1080) and 116.0 ± 18.3 nM Cy 5.5 (MCF-7) in the target tissue after 5 h. Competition with the free NGR-peptide resulted in a reduction of fluorochrome concentration in HT-1080 tumor tissue (195.3 ± 21.9 nM; 5 h). We thus conclude that NGR-Cy 5.5 combined with novel tomographic optical imaging methods allows us to image and quantify tumor-associated CD13/APN expression noninvasively. This may be a promising strategy for a sensitive evaluation of tumor angiogenesis in vivo.

3D-FRET Reconstruction Microscopy for Analysis of Dynamic Molecular Interactions in Live Cells.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18339754.

Hoppe AD, Shorte SL, Swanson JA, et al.
Biophys J. 2008;(e-published on Mar 13).

Analysis of cellular pathways requires concentration measurements of dynamically interacting molecules within the 3D space of single living cells. Forster Resonance Energy Transfer (FRET) microscopy from widefield, confocal, and potentially from super-resolution microscopes can access this information; however, these measurements are distorted by the inherent 3D-blurring of optical imaging, spectral overlap of fluorophores and detection noise. We propose a mathematical model of these processes and demonstrate, through simulation, how these distortions limit the dynamic range and sensitivity of conventional FRET microscopy. Using this model, we devise and validate a new approach (called 3D-FRET Stoichiometry Reconstruction, 3DFSR) for reconstructing 3D distributions of bound and free fluorescent molecules. Previous attempts to reconstruct 3D-FRET data relied on sequential spectral unmixing and deconvolution, a process that corrupts the detection statistics. We demonstrate that 3DFSR is superior to these approaches since it simultaneously models spectral mixing, optical blurring and the detection noise. To achieve the full potential of this technique, we developed an instrument capable of acquiring 3D-FRET data rapidly and sensitively from single living cells. Compared with conventional FRET microscopy, our 3D-FRET reconstruction technique and new instrumentation provides orders of magnitude gains in both sensitivity and accuracy wherein sustained high resolution four-dimensional (4D; x,y,z,t) imaging of molecular interactions inside living cells was achieved. These results verify previous observations that Cdc42 signaling is localized to the advancing margins of forming phagosomes in macrophages.

Brain N-acetylaspartate is Reduced in Parkinson Disease With Dementia.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18317247.

Griffith HR, den Hollander JA, Okonkwo OC, et al.
Alzheimer Dis Assoc Disord. 2008;22:54–60.

Persons with Parkinson disease (PD) are at risk of developing dementia. Of the dementias affecting patients with PD, PD with dementia (PDD) is not well understood, although brain imaging studies to date have observed characteristic patterns of brain atrophy. Metabolic differences have been observed in magnetic resonance spectroscopy (MRS) studies comparing patients with PDD to nondemented PD patients, although it is unclear whether PDD patients have abnormally low MRS ratios compared with healthy age-matched adults. In this study, 12 patients with PDD, 12 patients with PD and no dementia, and 12 age-matched healthy older adults underwent MRS of the posterior cingulate gyrus. Patients with PDD showed lower N-acetylaspartate/creatine (NAA/Cr) compared with controls ($P=0.004$) and compared with nondemented PD patients ($P=0.003$). No abnormalities were observed in choline/Cr or myo-Inositol/Cr. NAA/Cr was correlated with mental status in patients with PD and in patients with PDD ($r=0.56$; $P=0.029$). The findings suggest that reduced NAA/Cr of the posterior cingulate could be used as a marker for dementia in patients with PD. Future studies investigating the utility of brain MRS as a predictor of dementia in PD and comparing brain metabolism in PDD with other dementias seem warranted.

Clinical magnetic resonance imaging of pancreatic islet grafts after iron nanoparticle labeling.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18294167.

Toso C, Vallee JP, Morel P, et al.
Am J Transplant. 2008;8:701–706.

There is a crucial need for noninvasive assessment tools after cell transplantation. This study investigates whether a magnetic resonance imaging (MRI) strategy could be clinically applied to islet transplantation. The purest fractions of seven human islet preparations were labeled with superparamagnetic iron oxide particles (SPIO, 280 microg/mL) and transplanted into four patients with type 1 diabetes. MRI studies ($T2^*$) were performed prior to and at various time points after transplantation. Viability and in vitro and in vivo functions of labeled islets were similar to those of control islets. All patients could stop insulin after transplantation. The first patient had diffuse hypointense images on her baseline liver MRI, typical for spontaneous high iron content, and transplant-related modifications could not be observed. The other three patients had normal intensity on pretransplant images, and iron-loaded islets could be identified after transplantation as hypointense spots within the liver. In one of them, i.v. iron therapy prevented subsequent visualization of the spots because of diffuse hypointense liver background. Altogether, this study demonstrates the feasibility and safety of MRI-based

islet graft monitoring in clinical practice. Iron overload (spontaneous or induced) represents the major obstacle to the technique.

Positron emission tomography and magnetic resonance imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18319342.

Catana C, Procissi D, Wu Y, et al.
Proc Natl Acad Sci U S A. 2008;105:3705–3710.

Positron emission tomography (PET) and magnetic resonance imaging (MRI) are widely used in vivo imaging technologies with both clinical and biomedical research applications. The strengths of MRI include high-resolution, high-contrast morphologic imaging of soft tissues; the ability to image physiologic parameters such as diffusion and changes in oxygenation level resulting from neuronal stimulation; and the measurement of metabolites using chemical shift imaging. PET images the distribution of biologically targeted radiotracers with high sensitivity, but images generally lack anatomic context and are of lower spatial resolution. Integration of these technologies permits the acquisition of temporally correlated data showing the distribution of PET radiotracers and MRI contrast agents or MR-detectable metabolites, with registration to the underlying anatomy. An MRI-compatible PET scanner has been built for biomedical research applications that allows data from both modalities to be acquired simultaneously. Experiments demonstrate no effect of the MRI system on the spatial resolution of the PET system and <10% reduction in the fraction of radioactive decay events detected by the PET scanner inside the MRI. The signal-to-noise ratio and uniformity of the MR images, with the exception of one particular pulse sequence, were little affected by the presence of the PET scanner. In vivo simultaneous PET and MRI studies were performed in mice. Proof-of-principle in vivo MR spectroscopy and functional MRI experiments were also demonstrated with the combined scanner.

Synthesis and Characterization of Core-Shell Star Copolymers for In Vivo PET Imaging Applications.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18338840.

Fukukawa KI, Rossin R, Hagooley A, et al.
Biomacromolecules. 2008;(e-published on Mar 13).

The synthesis of core-shell star copolymers via living free radical polymerization provides a convenient route to three-dimensional nanostructures having a poly(ethylene glycol) outer shell, a hydrophilic inner shell bearing reactive functional groups, and a central hydrophobic core. By starting with well-defined linear diblock copolymers, the thickness of each layer, overall size/molecular weight, and the number of internal reactive functional groups can be controlled accurately, permitting detailed structure/performance

information to be obtained. Functionalization of these polymeric nanoparticles with a DOTA-ligand capable of chelating radioactive (^{64}Cu) nuclei enabled the biodistribution and in vivo positron emission tomography (PET) imaging of these materials to be studied and correlated directly to the initial structure. Results indicate that nanoparticles with increasing PEG shell thickness show increased blood circulation and low accumulation in excretory organs, suggesting application as in vivo carriers for imaging, targeting, and therapeutic groups.

Targeted molecular imaging in oncology: focus on radiation therapy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18314068.

Nimmagadda S, Ford EC, Wong JW, et al.
Semin Radiat Oncol. 2008;18:136–148.

Anatomically based technologies (computed tomography scans, magnetic resonance imaging, and so on) are in routine use in radiotherapy for planning and assessment purposes. Even with improvements in imaging, however, radiotherapy is still limited in efficacy and toxicity in certain applications. Further advances may be provided by technologies that image the molecular activities of tumors and normal tissues. Possible uses for molecular imaging include better localization of tumor regions and early assay for the radiation response of tumors and normal tissues. Critical to the success of this approach is the identification and validation of molecular probes that are suitable in the radiotherapy context. Recent developments in molecular-imaging probes and integration of functional imaging with radiotherapy are promising. This review focuses on recent advances in molecular imaging strategies and probes that may aid in improving the efficacy of radiotherapy.

Therapeutic nanoparticles for drug delivery in cancer.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18316549.

Cho K, Wang X, Nie S, et al.
Clin Cancer Res. 2008;14:1310–1316.

Cancer nanotherapeutics are rapidly progressing and are being implemented to solve several limitations of conventional drug delivery systems such as nonspecific biodistribution and targeting, lack of water solubility, poor oral bioavailability, and low therapeutic indices. To improve the biodistribution of cancer drugs, nanoparticles have been designed for optimal size and surface characteristics to increase their circulation time in the bloodstream. They are also able to carry their loaded active drugs to cancer cells by selectively using the unique pathophysiology of tumors, such as their enhanced permeability and retention effect and the tumor microenvironment. In addition to this passive targeting mechanism, active targeting strategies using ligands or antibodies

directed against selected tumor targets amplify the specificity of these therapeutic nanoparticles. Drug resistance, another obstacle that impedes the efficacy of both molecularly targeted and conventional chemotherapeutic agents, might also be overcome, or at least reduced, using nanoparticles. Nanoparticles have the ability to accumulate in cells without being recognized by P-glycoprotein, one of the main mediators of multidrug resistance, resulting in the increased intracellular concentration of drugs. Multifunctional and multiplex nanoparticles are now being actively investigated and are on the horizon as the next generation of nanoparticles, facilitating personalized and tailored cancer treatment.

A preclinical model for predicting drug response in soft-tissue sarcoma with targeted AAVP molecular imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18337507.

Hajitou A, Lev DC, Hannay JA, et al.
Proc Natl Acad Sci U S A. 2008;(e-published on Mar 12).

Human sarcomas are rare but diverse malignant tumors derived from mesenchymal tissue. Clinical response to therapy is currently determined by the modified World Health Organization (WHO) criteria or the Response Evaluation Criteria in Solid Tumors (RECIST), but these standards correlate poorly with sarcoma patient outcome. We introduced ligand-directed particles with elements of AAV and phage (AAVP) to enable integration of tumor targeting to molecular imaging. We report drug-response monitoring and prediction in a nude rat model of human sarcoma by AAVP imaging. As a proof-of-concept, we imaged Herpes simplex thymidine kinase in a clinic-ready setting with PET to show that one can a priori predict tumor response to a systemic cytotoxic. Given the target expression in patient-derived sarcomas, this platform may be translated in clinical applications. Sarcoma-specific ligands and promoters may ultimately lead to an imaging transcriptome.

A ratiometric optical imaging probe for intracellular pH based on modulation of europium emission.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18327327.

Pal R, Parker D.
Org Biomol Chem. 2008;6:1020–1033.

A set of three pH-responsive ratiometric Eu(III) complexes has been synthesised incorporating a coordinated azathioxanthone sensitizer and a pH dependent alkylsulfonamide moiety. Emission properties, anion binding affinities, pH response curves and protein binding constants were studied in detail in aqueous media, and solutions containing various concentrations of interfering anions and protein were also

examined. The complex, [EuL(3)] exhibited some interference from protein and endogenous anions, e.g. lactate and hydrogen carbonate, but possessed a protonation constant of 7.2 in human serum solution. A suitable calibration curve was obtained and was used to determine the local pH using a 680/589 nm intensity ratio vs. pH plot. Confocal fluorescence microscopy images revealed fast uptake of the complex and a well distributed localisation within the cell; fast egress also occurred. Ribosomal localisation, with a high concentration within the protein-dense nucleoli was observed, in a similar manner to structurally related complexes bearing the same coordinated sensitising moiety. An IC(50) value of 67 (+/-20) microM was estimated using an MTT assay. Selected emission band ratio versus pH plots allow pH measurement in the range 6 to 8, enabling intracellular pH to be measured by microscopy. A value of 7.4 was estimated for NIH 3T3 cells in the protein rich regions of the nucleolus and ribosomes.