Selected MI References
April, 2008

Gold nanorods targeted to delta opioid receptor: plasmon-resonant contrast and photothermal agents.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18384724.

Black KC, Kirkpatrick ND, Troutman TS, et al.
Mol Imaging. 2008;7:50–57.

Molecularly targeted gold nanorods were investigated for applications in both diagnostic imaging and disease treatment with cellular resolution. The nanorods were tested in two genetically engineered cell lines derived from the human colon carcinoma HCT-116, a model for studying ligand-receptor interactions. One of these lines was modified to express delta opioid receptor (deltaOR) and green fluorescent protein, whereas the other was receptor free and expressed a red fluorescent protein, to serve as the control. Deltorphin, a high-affinity ligand for deltaOR, was stably attached to the gold nanorods through a thiol-terminated linker. In a mixed population of cells, we demonstrated selective imaging and destruction of receptor-expressing cells while sparing those cells that did not express the receptor. The molecularly targeted nanorods can be used as an in vitro ligand-binding and cytotoxic treatment assay platform and could potentially be applied in vivo for diagnostic and therapeutic purposes with endoscopic technology.

Imaging in the era of molecular oncology.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18385732.

Weissleder R, Pittet MJ.
Nature. 2008;452:580–589.

New technologies for imaging molecules, particularly optical technologies, are increasingly being used to understand the complexity, diversity and in vivo behaviour of cancers. 'Omic' approaches are providing comprehensive 'snapshots' of biological indicators, or biomarkers, of cancer, but imaging can take this information a step further, showing the activity of these markers in vivo and how their location changes over time. Advances in experimental and clinical imaging are likely to improve how cancer is understood at a systems level and, ultimately, should enable doctors not only to locate tumours but also to assess the activity of the biological processes within these tumours and to provide 'on the spot' treatment.

In vivo optical imaging of neurogenesis: watching new neurons in the intact brain.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18384721.

Couillard-Despres S, Finkl R, Winner B, et al.
Mol Imaging. 2008;7:28–34.

Adult neurogenesis is a highly dynamic process modulated by several pathologic and environmental factors, as well as by various compounds. So far, available techniques to study neurogenesis are lengthy and personnel and cost intensive. We developed a new tool based on the doublecortin promoter driving the expression of the luciferase reporter gene (DCX-promo-luciferase) in transgenic mice to perform in vivo imaging of neurogenesis. Indeed, the DCX-promo-luciferase mice allowed optical in vivo imaging of the onset of and increase in neurogenesis in developing fetal brains, as well as imaging of neurogenesis in the intact adult mouse central nervous system. Moreover, the capacity to specifically detect a small number of migrating neuronal precursors in vivo after transplantation is for the first time feasible using this DCX-promo-luciferase transgenic tool. The present imaging approach offers several crucial advantages over methods currently available, such as bromodeoxyuridine incorporation or labeling using iron oxide nanoparticles. Hence, it allows longitudinal study of neurogenesis in intact animals without the requirement of cellular prelabeling. Moreover, it guarantees that detection is specific for neuronal precursors and restricted to viable cells. Hence, our DCX-promo-luciferase transgenic model constitutes an effective tool that answers the pressing need for rapid investigation of the impact on neurogenesis of a large number of candidate compounds waiting to be tested.

Detection of colonic dysplasia in vivo using a targeted heptapeptide and confocal microendoscopy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18345013.

Hsiung PL, Hardy J, Friedland S, et al.
Nat Med. 2008;14:454–458.

A combination of targeted probes and new imaging technologies provides a powerful set of tools with the potential to improve the early detection of cancer. To develop a probe for detecting colon cancer, we screened phage display peptide libraries against fresh human colonic adenomas for high-affinity ligands with preferential binding to premalignant tissue. We identified a specific heptapeptide sequence, VRPMPLQ, which we synthesized, conjugated with fluorescein and tested in patients undergoing colonoscopy. We imaged topically administered peptide using a fluorescence confocal microendoscope delivered through the instrument channel of a standard colonoscope. In vivo images were acquired at 12 frames per second with 50-microm working distance and 2.5-microm (transverse) and 20-microm (axial) resolution. The fluorescein-conjugated peptide bound more strongly to dysplastic colonocytes than to adjacent normal cells with 81% sensitivity and 82% specificity. This methodology represents a promising diagnostic imaging approach for the early detection of colorectal cancer and potentially of other epithelial malignancies.

Detection of early prostate cancer using a hepsin-targeted imaging agent.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18381435.

Kelly KA, Setlur SR, Ross R, et al.
Cancer Res. 2008;68:2286–2291.

Early detection and diagnosis of prostate cancer is key to designing effective treatment strategies. Microarrays have resulted in the discovery of hepsin (HPN) as a biomarker for detection of prostate cancer. In this study, we explore the development of HPN imaging probes for detection of prostate cancer. We used phage display to isolate HPN binding peptides with 190 + 2.2 nmol/L affinity in monomeric form and high specificity. The identified peptides were able to detect human prostate cancer on tissue microarrays and in cell-based assays. HPN-targeted imaging agents were synthesized by conjugating multiple peptides to fluorescent nanoparticles to further improve avidity through multivalency and to improve pharmacokinetics. When injected into mouse xenograft models, HPN-targeted nanoparticles bound specifically to HPN-expressing LNCaP xenografts compared with non-HPN-expressing PC3 xenografts. HPN imaging may provide a new method for detection of prostate cancer.

Discovery of a Phosphatidylserine Recognizing Peptide and Its Utility in Molecular Imaging of Tumor Apoptosis.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18363834.

Thapa N, Kim S, So IS, et al.
J Cell Mol Med. 2008;(e-pub. Mar 17).

The exposure of phosphatidylserine (PS) molecules from the inner to the outer leaflet of the plasma membrane has been recognized as a well-defined molecular epitope of cells undergoing apoptosis. Examination and monitoring of PS exposure is an extensively used molecular marker in noninvasive apoptosis imaging under a variety of clinical conditions, including the assessment of therapeutic anticancer agents and myocardial infarction. Herein, we report the identification of a PS-recognizing peptide which was identified by the screening of an M13 phage display peptide library onto PS-coated ELISA plates. Repeated biopanning for a total of four rounds revealed a predominant enrichment of the phage clone displaying peptide sequence, CLSYYPSYC (46%). The identified phage clone evidenced enhanced binding to a number of apoptotic cells over non-apoptotic cells, and this binding was inhibited by both annexin V and synthesized peptide displayed on the phage. The binding of the fluorescein-labeled CLSYYPSYC peptide to apoptotic vs. normal cells was assessed by both FACS analysis and fluorescence microscopy. Optical imaging after the systemic administration of fluorescein-labeled CLSYYPSYC peptide to tumor-bearing nude mice (H460 cells xenograft model) treated with a single dose of an anticancer drug (camptothecin) indicated peptide homing to the tumor. The histological examination of tumor tissues showed intense staining of the tumor vasculature and apoptotic tumor cells. With these results, the CLSYYPSYC peptide is recognized as a novel PS-recognizing moiety which may possibly be developed into a

molecular probe for the imaging of apoptosis in vivo. This application would clearly be relevant to assessments of the efficacy of anticancer therapy in tumors.

Enhanced Intracellular Delivery of Quantum Dot and Adenovirus Nanoparticles Triggered by Acidic pH via Surface Charge Reversal.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18363345.

Mok H, Park JW, Park TG.
Bioconjug Chem. 2008;19:797–801.

Quantum dot (QD) and adenovirus (ADV) nanoparticles were surface-modified with graft copolymers that exhibited a charge reversal behavior under acidic condition. Poly(l-lysine) (PLL) was grafted with multiple biotin-PEG chains (biotin-PEG-PLL graft copolymer), and the remaining primary amine groups in the PLL backbone were postmodified using citraconic anhydride, a pH-sensitive primary amine blocker, to generate carboxylate groups. The surfaces of streptavidin-conjugated QDs were modified with citraconylated biotin-PEG-PLL copolymer, producing net negatively charged QD nanoparticles. Under acidic conditions, citraconylated amide linkages were cleaved, resulting in the recovery of positively charged amine groups with subsequent alteration of surface charge values. Intracellular delivery of QD nanoparticles was greatly enhanced in an acidic pH condition due to the surface charge reversal. The surface of avidin-conjugated adenovirus (ADV-Avi) encoding an exogenous green fluorescent protein (GFP) gene was also modified in the same fashion. The expression extent of GFP was significantly increased at more acidic pH than pH 7.4. This study demonstrates that various nanosized drug carriers, imaging agents, and viruses could be surface-engineered to enhance their cellular uptake specifically at a low pH microenvironment like solid tumor tissue.

Evaluation of unusual neuroendocrine tumours by means of (68)Ga-DOTA-NOC PET.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18358680.

Fanti S, Ambrosini V, Tomassetti P, et al.
Biomed Pharmacother. 2008;(e-pub. Mar 3).

(18)F-FDG PET value for the assessment of neuroendocrine tumours (NET) is limited. Preliminary studies indicate that somatostatin receptor PET using (68)Ga-DOTA-peptides is more accurate for disease assessment and provide additional data on receptor status, that are crucial for targeted radionuclide therapy. At present, however, few papers investigated the role of (68)Ga-DOTA-NOC PET in NET, especially in unusual situations. The purpose of the present study was to evaluate (68)Ga-DOTA-NOC for the evaluation of NET of uncommon presentation. Patients with biopsy-proven NET were scheduled for (68)Ga-DOTA-NOC PET; we excluded from further evaluation cases with most common NET tumours (gastro-entero-pancreatic and pulmonary localization of

primary lesion, MEN syndromes, medullary thyroid carcinoma, pheochromocytomas). PET results were compared with findings of conventional imaging, including CT, ultrasonography, MR and somatostatin receptor scintigraphy; finally PET results were compared with follow-up data with respect to the impact on patient management. Fourteen patients were finally enrolled; primary tumours were located at uterine level (3 cases), prostate (3 cases), ovary (1 case), kidney (1 case), breast (1 case), ear (1 case); also 3 cases of paraganglioma (at neck, abdominal and mediastinum level) and 1 case of lymphoma were included. (68)Ga-DOTA-NOC PET was positive, showing at least 1 lesion, in 6/14 cases while 5 cases turned out negative and 2 inconclusive. On a clinical basis, (68)Ga-DOTA-NOC provided additional information in comparison to conventional imaging procedures in 7/14 cases, and was considered useful in 12/14 patients, with 8 patients in which (68)Ga-DOTA-NOC PET was determinant for patient's management. Although the number of patients studied is limited, our data show that (68)Ga-DOTA-NOC can be usefully applied for the evaluation of NET of uncommon presentation; in particular very promising results were obtained in paraganglioma. On the other hand, care has to be paid when studying lesions localized at sites of physiological concentration of the tracer, and in presence of inflammation.

Bioluminescence imaging of hematopoietic stem cell repopulation in murine models.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18370307.

Lin Y, Molter J, Lee Z, et al.
Methods Mol Biol. 2008;430:295–306.

Hematopoietic stem cells (HSCs) have been studied for decades in order to understand their stem cell biology and their potential as treatments in gene therapy, and those studies have resulted in tremendous advancement of understanding HSCs. However, most of the studies required the sacrifice of cohorts of the animals in order to obtain data for analysis, resulting in the use of large animal numbers along with difficult long-term studies. The dynamic engraftment and expansion of HSC are not fully observed and analyzed. Until recently, with the development of optical imaging, HSC repopulation can be continuously monitored in the same animal over a long period of time, reducing animal numbers and opening a new dimension for investigation. In this chapter, bioluminescence imaging of murine HSC is described for observing the dynamic repopulation process after transplantation. Photons emitted from transplanted murine HSCs expressing firefly luciferase within the mice can be visualized in light-sealed chamber with a highly sensitive digital camera after injection of substrate D-luciferin. Xenogen IVIS200 imaging system is used to record the process, and other similar imaging systems can also be used for this process.

Cell-Surface labeling and internalization by a fluorescent inhibitor of prostate-specific membrane antigen.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18361407.

Liu T, Wu LY, Kazak M, et al.
Prostate. 2008;(e-pub. Mar 24).

BACKROUND: Prostate-specific membrane antigen (PSMA) remains an attractive target for imaging and therapeutic applications for prostate cancer. Recent efforts have been made to conjugate inhibitors of PSMA with imaging agents. Compared to antibodies, small-molecule inhibitors of PSMA possess apparent advantages for in vivo applications. To date, there are no reports on the cellular fate of such constructs once bound the extracellular domain of PSMA. The present study was focused on precisely defining the binding specificity, time-dependent internalization, cellular localization, and retention of inhibitor conjugates targeted to PSMA on LNCaP cells. A novel fluorescent inhibitor was prepared as a model to examine these processes. METHODS: Fluorescence microscopy of LNCaP and PC-3 cell lines was used to monitor the specificity, time-dependent internalization, cellular localization, and retention of a fluorescent PSMA inhibitor. RESULTS: Fluorescent inhibitor 2 was found to be a potent inhibitor (IC(50) = 0.35 nM) of purified PSMA. Its high affinity for PSMA on living cells was confirmed by antibody blocking and competitive binding experiments. Specificity for LNCaP cells was demonstrated as no labeling by 2 was observed for negative control PC-3 cells. Internalization of 2 by viable LNCaP cells was detected after 30 min incubation at 37 degrees C, followed by accumulation in the perinuclear endosomes. It was noted that internalized fluorescent inhibitor can be retained within endosomes for up to 150 min without loss of signal. CONCLUSIONS: Our results suggest that potent, small-molecule inhibitors of PSMA can be utilized as carriers for targeted delivery for prostate cancer for future imaging and therapeutic applications. Prostate © 2008 Wiley-Liss, Inc.

Cancer Detection Using a PET Tracer, 11C-Glycylsarcosine, Targeted to H+/Peptide Transporter.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18344442.

Mitsuoka K, Miyoshi S, Kato Y, et al.
J Nucl Med. 2008;49:615–622.

H(+)/peptide transporter, PEPT1, is functionally expressed in some human cancer cell lines and might be a candidate molecular target for detection of cancers in vivo using PET. The aim of the present study was to establish a novel tumor-imaging technology using a PET tracer targeted to H(+)/peptide transporter(s). We also compared the tracer with (18)F-FDG, focusing on the specificity of their accumulation between tumor and inflammatory tissues. METHODS: A dipeptide PET tracer, (11)C-glycylsarcosine ((11)C-Gly-Sar), was injected intravenously into athymic mice transplanted with human pancreatic, prostate, and gastric cancer cells. The distribution patterns of (11)C-Gly-Sar and (18)F-FDG in the tumor-bearing mice, and in mice with inflammatory tissue, were assessed by imaging with a positron planar imaging system (PPIS). Tissue distributions of tracer radioactivity were also measured. The expression levels of PEPT1 and PEPT2 (PEPTs) proteins in tumor xenografts and inflammatory tissue were examined by immunohistochemical analysis. The messenger RNA expression levels of PEPTs in 58 available cancer cell lines were quantified by means of real-time polymerase chain

reaction. RESULTS: All 3 tumor xenografts were well visualized with the PPIS after injection of (11)C-Gly-Sar. Expression of PEPTs in those xenografts was confirmed by immunohistochemical analysis. Tumor-to-blood concentration ratios of (11)C-Gly-Sar increased in a time-dependent manner and were much higher than unity. Most of the radioactivity found in the tumor tissue was recovered as the intact tracer. These results indicated that (11)C-Gly-Sar was taken up by the PEPTs in tumor xenografts. It is noteworthy that (11)C-Gly-Sar was minimally present in inflammatory tissues that expressed no PEPT1 or PEPT2 protein, whereas (18)F-FDG was highly accumulated, with the values of the selectivity index being >25.1 and 0.72 for (11)C-Gly-Sar and (18)F-FDG, respectively. The mRNAs of PEPT1 and PEPT2 were expressed in 27.6% and 93.1%, respectively, of the cancer cell lines examined in the present study. CONCLUSION: The present study indicates that (11)C-Gly-Sar is a promising tumor-imaging agent and is superior to (18)F-FDG for distinguishing between tumors and inflammatory tissue. Because PEPTs were ubiquitously expressed in various types of tumor cells examined, (11)C-Gly-Sar could be useful for the detection of many types of cancers.

Simultaneous PET-MRI: a new approach for functional and morphological imaging.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18376410.

Judenhofer MS, Wehrl HF, Newport DF, et al.
Nat Med. 2008;14:459–465.

Noninvasive imaging at the molecular level is an emerging field in biomedical research. This paper introduces a new technology synergizing two leading imaging methodologies: positron emission tomography (PET) and magnetic resonance imaging (MRI). Although the value of PET lies in its high-sensitivity tracking of biomarkers in vivo, it lacks resolving morphology. MRI has lower sensitivity, but produces high soft-tissue contrast and provides spectroscopic information and functional MRI (fMRI). We have developed a three-dimensional animal PET scanner that is built into a 7-T MRI. Our evaluations show that both modalities preserve their functionality, even when operated isochronously. With this combined imaging system, we simultaneously acquired functional and morphological PET-MRI data from living mice. PET-MRI provides a powerful tool for studying biology and pathology in preclinical research and has great potential for clinical applications. Combining fMRI and spectroscopy with PET paves the way for a new perspective in molecular imaging.

Synthesis and Evaluation of a Novel Fluorescent Photoprobe for Imaging Matrix Metalloproteinases.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18396900.

Faust A, Waschkau B, Waldeck J, et al.
Bioconjug Chem. 2008;(e-pub. Apr 9).

The measurement of matrix metalloproteinase (MMP) activity in diseases like inflammation, oncogenesis, or atherosclerosis in vivo is highly desirable. Fine-tuned pyrimidine-2,4,6-triones (barbiturates) offer nonpeptidyl lead structures for developing imaging agents for specifically visualization of activated MMPs in vivo. The aim of this study was to modify a C-5-disubstituted barbiturate and thus design a highly affine, nonpeptidic, optical MMP inhibitor (MMPI)-ligand for imaging of activated MMPs in vivo. A convergent 10 step synthesis was developed, starting with a malonic ester and (4-bromophenoxy)benzene to generate 5-bromo-pyrimidine-2,4,6-trione as the key intermediate. To minimize the interactions between activated MMPs and the dye of the conjugate 6, a PEGylated piperazine derivative was used as a spacer and an azide as a protected amino function. After linking both building blocks, reducing the azide (Staudinger reaction) and labeling with Cy 5.5, we obtained the nonhydroxamate MMP inhibitor 6 with high affinity (IC 50-value: 48 nM for MMP-2) measured in a fluorogenic assay using commercially available MMP-substrates and the purified enzyme. Zymography revealed an efficient blocking of enzyme activity of purified MMP-2 and MMP-9 and of MMP-containing cell supernatants (HT-1080), (A-673) using the PEGylated barbiturate 5. Fluorescence microscopy studies using a highly (A-673) and a moderate (HT-1080) MMP-2 secreting cell line showed efficient binding of the Cy 5.5 labeled tracer 6 to the MMP-2 positive cells while MMP-2 negative cells (MCF-7) did not bind. Therefore, this new barbiturate-based MMP-probe has a high affinity and specificity toward MMP-2 and -9 and is thus a promising candidate for sensitive MMP detection in vivo.

Targeted Imaging of Hypoxia-Induced Integrin Activation in Myocardium Early After Infarction.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18356482.

Kalinowski L, Dobrucki LW, Meoli DF, et al.
J Appl Physiol. 2008;(e-pub. Mar 20).

The alphavbeta3-integrin is expressed in angiogenic vessels in response to hypoxia, and represents a potential novel target for imaging myocardial angiogenesis. This study evaluated the feasibility of non-invasively tracking hypoxia-induced alphavbeta3-integrin activation within the myocardium as a marker of angiogenesis early after myocardial infarction. Acute myocardial infarction was produced by coronary artery occlusion in rodent and canine studies. A novel (111)In-labeled radiotracer targeted at the alphavbeta3-integrin ((111)In-RP748), was used to localize regions of hypoxia-induced angiogenesis early after infarct. In rodent studies, the specificity of (111)In-RP748 for alphavbeta3-integrin was confirmed with a negative control compound ((111)In-RP790) and regional uptake of these compounds correlated with (201)Tl perfusion and a (99m)Tc-labeled nitroimidazole (BRU59-21), which was used as a quantitative marker of myocardial hypoxia. The ex vivo analysis demonstrated that only (111)In-RP748 was selectively retained in infarcted regions with reduced (201)Tl perfusion, and correlated with uptake of BRU59-21. In canine studies, myocardial uptake of (111)In-RP748 was assessed using in vivo SPECT, ex vivo planar imaging, and gamma well-counting of

myocardial tissue, and correlated with (99m)Tc-sestamibi perfusion. Dual-radiotracer in vivo SPECT imaging of (111)In-RP748 and (99m)Tc-sestamibi provided visualization of (111)In-RP748 uptake within the infarct region, which was confirmed by ex vivo planar imaging of excised myocardial slices. Myocardial (111)In-RP748 retention was associated with histological evidence of alphavbeta3-integrin activation/expression in infarct region. (111)In-RP748 imaging provides a novel non-invasive approach for evaluation of hypoxia-induced alphavbeta3-integrin activation in myocardium early after infarction, and may prove useful for directing and evaluating angiogenic therapies in patients with ischemic heart disease. Key words: angiogenesis, radiotracer imaging, myocardial infarction, hypoxia.

Towards a Noninvasive Intracranial Tumor Irradiation Using 3D Optical Imaging and Multimodal Data Registration.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18364992.

Posada R, Daul C, Wolf D, et al.
Int J Biomed Imaging. 2007;2007:62030.

Conformal radiotherapy (CRT) results in high-precision tumor volume irradiation. In fractioned radiotherapy (FRT), lesions are irradiated in several sessions so that healthy neighbouring tissues are better preserved than when treatment is carried out in one fraction. In the case of intracranial tumors, classical methods of patient positioning in the irradiation machine coordinate system are invasive and only allow for CRT in one irradiation session. This contribution presents a noninvasive positioning method representing a first step towards the combination of CRT and FRT. The 3D data used for the positioning is point clouds spread over the patient's head (CT-data usually acquired during treatment) and points distributed over the patient's face which are acquired with a structured light sensor fixed in the therapy room. The geometrical transformation linking the coordinate systems of the diagnosis device (CT-modality) and the 3D sensor of the therapy room (visible light modality) is obtained by registering the surfaces represented by the two 3D point sets. The geometrical relationship between the coordinate systems of the 3D sensor and the irradiation machine is given by a calibration of the sensor position in the therapy room. The global transformation, computed with the two previous transformations, is sufficient to predict the tumor position in the irradiation machine coordinate system with only the corresponding position in the CT-coordinate system. Results obtained for a phantom show that the mean positioning error of tumors on the treatment machine isocentre is 0.4 mm. Tests performed with human data proved that the registration algorithm is accurate (0.1 mm mean distance between homologous points) and robust even for facial expression changes.

Visualizing head and neck tumors in vivo using near-infrared fluorescent transferrin conjugate.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18384723.

Shan L, Hao Y, Wang S, et al.
Mol Imaging. 2008;7:42–49.

Transferrin receptor (TfR) is overexpressed in human head and neck squamous cell carcinomas (HNSCCs). This study was carried out to investigate the feasibility of imaging HNSCC by targeting TfR using near-infrared fluorescent transferrin conjugate (Tf(NIR)). Western blot analysis of four HNSCC cell lines revealed overexpression of TfR in all four lines compared with that in normal keratinocytes (OKFL). Immunocytochemistry further confirmed the expression of TfR and endocytosis of Tf(NIR) in JHU-013 culture cells. Following intravenous administration of Tf(NIR) (200 muL, 0.625 mug/muL), fluorescent signal was preferentially accumulated in JHU-013 tumor xenografts grown in the lower back ($n = 14$) and oral base tissues ($n = 4$) of nude mice. The signal in tumors was clearly detectable as early as 10 minutes and reached the maximum at 90 to 120 minutes postinjection. The background showed an increase, followed by a decrease at a much faster pace than tumor signal. A high fluorescent ratio of the tumor to muscle was obtained (from 1.42 to 4.15 among tumors), usually achieved within 6 hours, and correlated with the tumor size ($r = .74$, $p = .002$). Our results indicate that TfR is a promising target and that Tf(NIR)-based optical imaging is potentially useful for noninvasive detection of early HNSCC in the clinic.

Iron chelator-based amplification strategy for improved targeting of transferrin receptor with SPIO.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18367876.

Zhang CY, Lu J, Tsourkas A.
Cancer Biol Ther. 2008;7:(e-pub. Mar 12).

A major obstacle faced by magnetic resonance (MR) as a platform for molecular imaging is the low sensitivity for detecting receptor-targeted MR contrast agents. The versatility of MR imaging, however, could be improved if there existed a strategy to upregulate the receptor of interest prior to administration of the targeted contrast agent. Here, we describe an amplification strategy that uses iron chelators to upregulate the transferrin receptor (TfR) prior to administration of TfR-targeted superparamagnetic iron oxide nanoparticles (SPIO). When K562 human leukemic cells were incubated with the iron chelator desferrioxamine (DFO), followed by administration of anti-TfR SPIO, there was a 57% improvement in the T2 relaxation time compared with cells not treated with DFO and an 82% improvement compared with cells not targeted with SPIO. The effects of incubation time, temperature, SPIO concentration, and targeting molecule on contrast enhancement were also examined. The results reported here suggest that iron chelators have the potential to significantly improve the sensitivity of TfR-mediated cancer detection, providing a new paradigm for MR signal amplification.

A new transgenic mouse line to image chemically induced p53 activation in vivo.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18377420.

Briat A, Vassaux G.
Cancer Sci. 2008;99:683-688.

Monitoring p53 transcriptional activity to identify genotoxic damages induced by drugs has been proposed and validated in vitro. However, this methodology is by design limited to the cell line tested. In this study, we have fully validated a luciferase-based p53-reporter system in vitro and in vivo. We generated a mouse transgenic line to monitor non-invasively p53 activation in response to chemically induced DNA damage. Doxorubicin was used as a drug of known toxicity to validate our model. Reporter gene expression was measured using bioluminescence imaging. In females, a weak p53 luciferase activity driven by a p53-responsive promoter was detectable in the oral cavity region after doxorubicin treatment. In males, the signal increased in the lower abdominal region. Imaging of various organs revealed that the luciferase activity was mainly generated from the testes. Immunohistology demonstrated that the cells in the seminiferous tubules were damaged by the drug and confirmed that they were luciferase and p53 positive. Therefore, these transgenic mice could provide a powerful tool to predict, map and characterize at the organ and cellular levels the toxicity of compounds and help to develop new therapeutic agents in humans.

Noninvasive molecular imaging of small living subjects using Raman spectroscopy.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18378895.

Keren S, Zavaleta C, Cheng Z, et al.
Proc Natl Acad Sci U S A. 2008;(e-pub. Mar 31).

Molecular imaging of living subjects continues to rapidly evolve with bioluminescence and fluorescence strategies, in particular being frequently used for small-animal models. This article presents noninvasive deep-tissue molecular images in a living subject with the use of Raman spectroscopy. We describe a strategy for small-animal optical imaging based on Raman spectroscopy and Raman nanoparticles. Surface-enhanced Raman scattering nanoparticles and single-wall carbon nanotubes were used to demonstrate whole-body Raman imaging, nanoparticle pharmacokinetics, multiplexing, and in vivo tumor targeting, using an imaging system adapted for small-animal Raman imaging. The imaging modality reported here holds significant potential as a strategy for biomedical imaging of living subjects.