

1.

NMR-based metabolomics: Translational application and treatment of cancer.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18041668.

Serkova N J, Spratlin J L, Eckhardt S G.
Curr Opin Mol Ther. 2007;9:572-585. (Dec).

Cancer cells possess a highly unique metabolic phenotype which is characterized by high glucose uptake, increased glycolytic activity, decreased mitochondrial activity, low bioenergetic expenditure and increased phospholipid turnover. In addition to these general metabolic markers of malignancy, tissue-specific biochemistry has identified specific endogenous metabolites found in particular tumors types. These include N-acetyl aspartate in neuroblastoma, myo-inositol in gliomas and citrate in prostate cancer. Metabolic profiles can be readily assessed to monitor responsiveness and the development of resistance to novel targeted drugs, for example, where a cytostatic effect rather than cytotoxicity occurs. Using modern analytical technologies in combination with statistical approaches, a methodology termed 'metabolomics' has been developed. Metabolomics has been used to generate a global metabolic profile on patient samples, which can then be used to determine treatment response. This review describes existing NMR-based approaches for global metabolic profiling in tissue biopsies and body fluids and the use of non-invasive radiological techniques to assess metabolic biomarkers. In addition, studies on metabolic responses to novel targeted drugs, including tyrosine kinase inhibitors and metabolic modulators, are evaluated.

2.

Noninvasive delivery of gene targeting probes to live brains for transcription MRI.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18029447.

Liu C H, You Z, Ren J, et al.
Faseb J. 2007;(Nov 20).

We aimed to test the feasibility of detecting gliosis in living brains when the blood-brain barrier (BBB) is disrupted. We designed a novel magnetic resonance (MR) probe that contains superparamagnetic iron oxide nanoparticles (SPION, a T2 susceptibility contrast agent) linked to a short DNA sequence complementary to the cerebral mRNA of glial fibrillary acidic protein (GFAP) found in glia and astrocytes. As a control, we also used a sequence complementary to the mRNA of beta-actin. Our objectives are to demonstrate that this new probe, SPION-gfap, could be delivered to the brain when administered by eyedrop solution to the conjunctival sac. We induced BBB leakage by puncture wound, global cerebral ischemia, and cortical spreading depression in C57BL6 mice; 1 day after

probe delivery we acquired T2* MR images and R2* ($R2^*=1/T2^*$) maps using a transcription MRI technique in live mice. We found that the SPION-gfap probe reported foci with elevated signal in subtraction R2* maps and that these foci matched areas identified as having extensive glial network (gliosis) in postmortem immunohistochemistry. Similarly, animals administered the control probe exhibited foci of R2* elevation that matched beta-actin-expressing endothelia in the vascular wall. We conclude that our modular MR probe, delivered in an eyedrop solution, effectively reports gliosis associated with acute neurological disorders in living animals. As BBB leakage is often observed in acute neurological disorders, this study also served to validate noninvasive delivery of MR probes to the brains of live animals after acute neurological disorders.-Liu, C. H., You, Z., Ren, JQ., Kim, Y. R., Eikermann-Haerter, K., Liu, P. K. Noninvasive delivery of gene targeting probes to live brains for transcription MRI.

3.

Noninvasive imaging of apoptosis in cardiovascular disease.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18074226.

Korngold E C, Jaffer F A, Weissleder R, et al.
Heart Fail Rev. 2007;(Dec 12).

Recent advances in molecular imaging have permitted the noninvasive imaging of apoptosis, a critical process underlying the pathogenesis of many diseases of the cardiovascular system including atherosclerotic vascular disease, myocardial ischemia and reperfusion injury, chronic heart failure, myocarditis, and cardiac allograft rejection. Multiple molecular targets including phosphatidylserine, phosphatidylinositol 3-kinase, and caspases have been targeted by a variety of imaging agents and modalities such as nuclear scintigraphy, PET, MRI, and fluorescent and bioluminescent imaging. Translationally, methods utilizing radiolabeled annexin V have proven promising in several clinical trials of ischemia-reperfusion injury and cardiac allograft rejection. New approaches using novel molecular imaging agents show great potential for the ability to image apoptosis in the research and clinical setting. Ultimately the ability to detect apoptosis noninvasively would help to identify patients for emerging anti-apoptotic therapies and guide clinical management with the aim of maximal myocardial preservation.

4.

DNA-TiO(2) Nanoconjugates Labeled with Magnetic Resonance Contrast Agents.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18047347.

Endres P J, Paunesku T, Vogt S, et al.
J Am Chem Soc. 2007;(Nov 30).

Recent efforts have shown that nanoscale materials, specifically, metal-based nanoparticles, hold particular promise for the development of multifunctional

imaging probes. These new materials provide the means to chaperone and concentrate both drugs and contrast agents in specific organs, tissues, and cells. Therefore, we have prepared a Gd(III)-modified DNA-TiO₂ semiconducting nanoparticle that is detectable in cells by MR imaging. These labeled particles are retained at specific subcellular locations via DNA hybridization to intracellular targets, hence creating the first nanoparticle system capable of targeting specific DNA sequences while being simultaneously detected via MR imaging.

5.

A p-[(18)F]Fluoroethoxyphenyl Bicyclic Nucleoside Analogue as a Potential Positron Emission Tomography Imaging Agent for Varicella-Zoster Virus Thymidine Kinase Gene Expression.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18047266.

Chitneni S K, Deroose C M, Balzarini J, et al.
J Med Chem. 2007;(Nov 30).

We recently reported a new positron emission tomography (PET) reporter gene, namely, varicella-zoster virus thymidine kinase (VZV-tk) in combination, with carbon-11 or fluorine-18 labeled m-alkoxyphenyl bicyclic nucleoside analogues (BCNAs) as PET reporter probes. We now report the synthesis and evaluation of p-alkoxyphenyl-BCNA tracers ([(11)C]- 4 and [(18)F]- 5), which are found to be superior to the m-alkoxyphenyl-BCNA tracers. In particular, the fluorine-18 labeled tracer ([(18)F]- 5, IC₅₀ of 5 is 4.2 μM) shows a higher accumulation in VZV-tk expressing cells than the previously reported m-methoxyphenyl BCNA. [(11)C]- 4 and [(18)F]- 5 were synthesized by heating the phenol precursor 3 with (11)CH₃I and (18)FCH₂CH₂Br, respectively, as alkylating agents. In vitro evaluation of [(11)C]- 4 and [(18)F]- 5 in 293T cells showed about 14- and 54-fold higher uptake, respectively, into VZV-tk gene-transduced cells compared to control cells. LC-MS analysis confirmed the formation of monophosphate derivative of 5 upon catalysis by VZV TK. In vivo studies of this new reporter gene/probe system are in progress.

6.

Hyaluronate-covered nanoparticles for the therapeutic targeting of cartilage.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18039001.

Laroui H, Grossin L, Leonard M, et al.
Biomacromolecules. 2007;8:3879-3885. (Dec).

Hyaluronic acid (HA) has a high affinity for the CD44 receptor present at the surface of articular cells, particularly of chondrocytes. HA-covered polylactide nanoparticles containing bioactive compounds such as HA and chondroitin sulfate (CS) were thus prepared in order to achieve a controlled delivery targeted to cartilage cells after injection near articular alterations/erosions. Such nanoparticles (diameter = 700 nm) were prepared by double emulsion/solvent evaporation, using amphiphilic derivatives of HA, as stabilizer of the secondary emulsion. These nanoparticles were incubated with articular cells, and several

tests were carried out. First, they proved that the nanospheres provoked no decrease in cell viability, even after 72 h of contact. Second, a confocal microscopy analysis on fluorescent HA-covered particles showed that they were captured by articular cells, while with those covered with poly(vinyl alcohol), the uptake was far lower. Third, a scattering electron microscopy analysis proved that the HA-coated nanoparticles were localized in the cell intracytoplasmic area.

7. **Molecular imaging of macrophages in atherosclerotic plaques using bimodal PEG-micelles.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18046703.

Mulder W J, Strijkers G J, Briley-Saboe K C, et al.
Magn Reson Med. 2007;58:1164-1170. (Dec).

Pegylated, fluorescent, and paramagnetic micelles were developed. The micelles were conjugated with macrophage scavenger receptor (MSR)-specific antibodies. The abdominal aortas of atherosclerotic apoE-KO mice were imaged with T(1)-weighted high-resolution MRI before and 24 h after intravenous administration of the contrast agent (CA). Pronounced signal enhancement (SE) (up to 200%) was observed for apolipoprotein E knockout (apoE-KO) mice that were injected with MSR-targeted micelles, while the aortic vessel wall of mice injected with nontargeted micelles showed little SE. To allow fluorescence microscopy and optical imaging of the excised aorta, the micelles were made fluorescent by incorporating either a quantum dot (QD) in the micelle corona or rhodamine lipids in the micelle. Ultraviolet (UV) illumination of the aorta allowed the identification of regions with high macrophage content, while MSR-targeted rhodamine micelles could be detected with fluorescence microscopy and were found to be associated with macrophages. In conclusion, this study demonstrates that macrophages in apoE-KO mice can be effectively and specifically detected by molecular MRI and optical methods upon administration of a pegylated micellar CA. *Magn Reson Med* 58:1164-1170, 2007. (c) 2007 Wiley-Liss, Inc.

8. **HSP70-Inducible hNIS-IRES-eGFP Reporter Imaging: Response to Heat Shock.**

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18053411.

Che J, Doubrovin M, Serganova I, et al.
Mol Imaging. 2007;6:404-416. (Nov-Dec).

A retroviral vector pQHSP70/hNIS-IRES-eGFP (pQHNIG70) was constructed containing the hNIS-IRES-eGFP dual-reporter genes under the control of an inducible human heat shock protein (HSP)70 promoter and RG2-pQHSP70/hNIS-IRES-eGFP (RG2-pQHNIG70) transduced cells were generated. Heat-induced expression of both reporter genes in RG2-pQHNIG70 cells was validated by enhanced green fluorescent protein (eGFP) fluorescence-activated cell sorter, in vitro radiotracer assays, and immunoblot and immunocytochemistry. A 2.2- to 6.1-fold ((¹³¹I(-)), a 6.1- to 14.4-fold ((^{99m}TcO(4)(-)), and a 5.1- to 39-fold (fluorescence) increase above baseline

was observed in response to graded hyperthermia (39-43 degrees C). Increases in eGFP fluorescence and radiotracer uptake were first noted at 6 hours, reached a maximum at 24 hours, and fell toward baseline at 72 hours. A stable ratio of radiotracer uptake to eGFP fluorescence and to heat shock protein (HSP)70 protein was demonstrated over a wide range of expression levels, induced by different levels of heating. We also demonstrate that the local application of heat on RG2-pQHNIG70 xenografts can effectively induce hNIS and eGFP gene expression in vivo and that this expression can be efficiently visualized by fluorescence, scintigraphic, and micro-positron emission tomography imaging. Endogenous HSP70 protein and reporter expression was confirmed by postmortem tissue evaluations (immunoblot and immunohistochemistry). The pQHNIG70 reporter system can be used to study stress and drug responses in transduced cells and tissues.

9.

Transcription MRI: A New View of the Living Brain.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18024855.

Liu P K, Mandeville J B, Dai G, et al.

Neuroscientist. 2007;(Nov 16).

Altered gene activities are underlying causes of many neurological disorders. The ability to detect, image, and report endogenous gene transcription using magnetic resonance (MR) holds great potential for providing significant clinical benefits. In this review, we present the development of conjugates consisting of gene-targeting short nucleic acids (oligodeoxynucleotides, or sODN) and superparamagnetic iron oxide nanoparticles (SPION, an MR susceptibility T2 agent) for reporting gene activity using transcription MRI (tMRI). We will discuss 1) the target specificity of sODN, 2) selection of contrast agents for tMRI, 3) the distribution and uptake, 4) sequence specificity, 5) histology of SPION and sODN, 6) data acquisition and quantitative analysis for tMRI, and 7) application of gene transcript-targeting nanoparticles in biology and medicine. We will also discuss methods of validating the correlation between results from conventional assays (in situ hybridization, PCR, histology Prussian blue stain and immunohistochemistry) in postmortem samples and retention of SPION-sODN using tMRI. The application of our novel contrast probe to report and target gene transcripts in the mesolimbic pathways of living mouse brains after amphetamine exposure will be discussed. Because of the targeting ability in the nucleic acid sequence, the concept of tMRI probes with complementary nucleic acid (antisense DNA or short interfering RNA) allows not only tracking, targeting, binding to intracellular mRNA, and manipulating gene action but also tracing cells with specific gene action in living brains. Transcription MRI will lend itself to myriad applications in living organs. DOI: 10.1177/1073858407309746.

10.

Advanced MRI in the management of adult gliomas.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18071982.

Jenkinson M D, Plessis D G, Walker C, et al.

Br J Neurosurg. 2007;21:550-561. (Dec).

Gliomas are a heterogeneous group that account for approximately 86% of primary brain neoplasms, and include astrocytic and oligodendroglial tumours, as well as a variety of less common histopathological subtypes. Magnetic resonance imaging has become the accepted mode of imaging for the clinical management of these tumours. MRI features bear close resemblance to the histopathology grading and prognosis of these tumours. Currently, conventional MRI is used to aid diagnosis, plan neurosurgical approaches, and monitor response to therapy and disease progression. More recent developments in the field of MRI include MR spectroscopy, perfusion MRI, diffusion-weighted imaging, intraoperative MRI and functional MRI. These newer techniques have been adopted with varying success in the management of adult gliomas. This review focuses on the application of advanced MR imaging in the clinical management of adult gliomas.