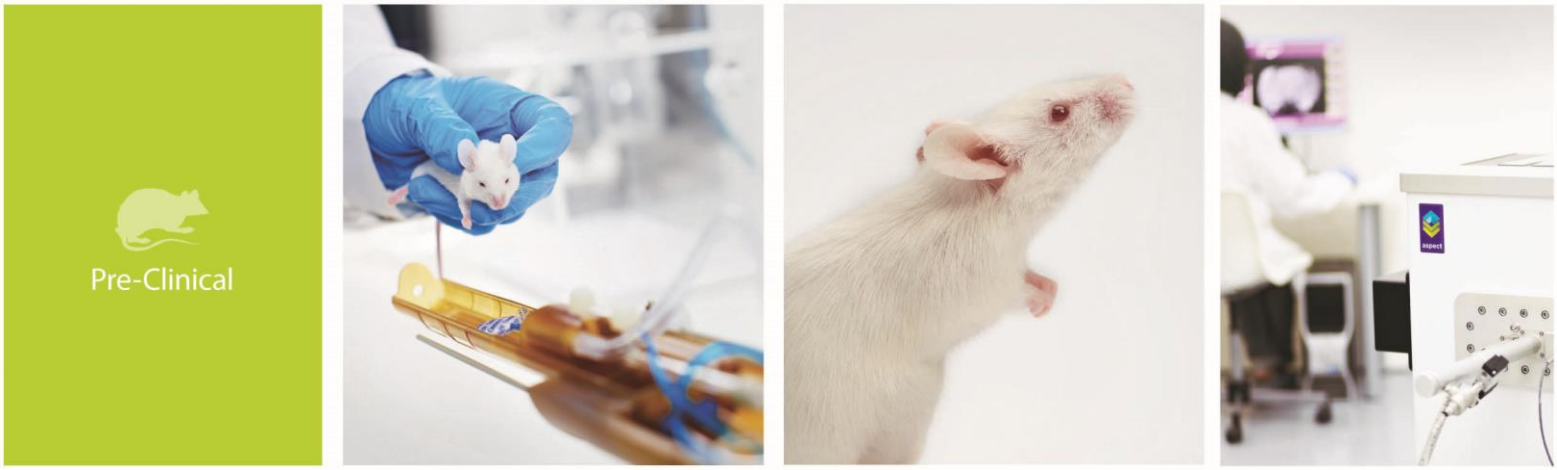
Select Listing of Scientific Papers and Posters Citing Aspect Imaging M-Series Compact MRI Systems



Aspect Imaging
www.aspectimaging.com
info@aspectimaging.com

Updated:
July 2019

Table of Contents

Tailored biological retention and efficient clearance of pegylated ultra-small MnO nanoparticles as positive MRI contrast agents for molecular imaging

Authors:

P. Chevallier[1,2], A. Walter[3], A. Garofalo[3], I. Veksler[1,2], J. Lagueux[4], S. B´egin-Colin[3], D. Felder-Flesch[3] and M.-A. Fortin[1,2,5]

Institutions:

1. Centre de recherche du Centre hospitalier universitaire de Qu´ebec (CR-CHUQ), Axe m´edecine r´eg´en´eratrice, 10 rue de l'Espinay, Qu´ebec, G1L 3L5, Canada
2. Centre de recherche sur les mat´eriaux avanc´es (CERMA), Universit´e Laval, Qu´ebec, G1V 0A6, Canada
3. Institut de Physique et Chimie des Mat´eriaux de Strasbourg (IPCMS), UMR 7504 CNRS-Universit´e de Strasbourg, 23, rue du Loess, BP 43, 67034 Strasbourg Cedex 2, France
4. Centre de recherche du Centre hospitalier universitaire de Qu´ebec (CR-CHUQ), Service d'imagerie animale (SIA), 2705, boulevard Laurier, Qu´ebec, G1V 4G2, Canada
5. D´epartement de g´enie des mines, de la m´etallurgie et des mat´eriaux, Universit´e Laval, Qu´ebec, G1V 0A6, Canada.

Abstract:

A majority of MRI procedures requiring intravascular injections of contrast agents are performed with paramagnetic chelates. Such products induce vascular signal enhancement and they are rapidly excreted by the kidneys. Unfortunately, each chelate is made of only one paramagnetic ion, which, taken individually, has a limited impact on the MRI signal. In fact, the detection of molecular events in the nanomolar range using T1-weighted MRI sequences requires the design of ultra-small particles containing hundreds of paramagnetic ions per contrast agent unit. Ultra-small nanoparticles of manganese oxide (MnO, 6–8 nm diameter) have been developed and proposed as an efficient and at least 1000□ more sensitive "positive" MRI contrast agent. However no evidence has been found until now that an adequate surface treatment of these particles could maintain their strong blood signal enhancement, while allowing their rapid and efficient excretion by the kidneys or by the hepatobiliairy pathway. Indeed, the sequestration of MnO particles by the reticuloendothelial system followed by strong uptake in the liver and in the spleen could potentially lead to Mn2+-induced toxicity effects. For ultra-small MnO particles to be applied in the clinics, it is necessary to develop coatings that also enable their efficient excretion within hours. This study demonstrates for the first time the possibility to use MnO particles as T1 vascular contrast agents, while enabling the excretion of >70% of all the Mn injected doses after 48 h. For this, small, biocompatible and highly hydrophilic pegylated bis-phosphonate dendrons (PDns) were grafted on MnO particles to confer colloidal stability, relaxometric performance, and fast excretion capacity. The chemical and colloidal stability of MnO@PDn particles were confirmed by XPS, FTIR and DLS. The relaxometric performance of MnO@PDns as "positive" MRI contrast agents was assessed (r1 ¼ 4.4 mM□1 s□1, r2/r1 ¼ 8.6; 1.41 T and 37 □C). Mice were injected with 1.21 mg Mn per kg (22 mmol Mn per kg), and scanned in MRI up to 48 h. The concentration of Mn in key organs was precisely measured by neutron activation analysis and confirmed, with MRI, the possibility to avoid RES nanoparticle sequestration through the use of phosphonate dendrons. Due to the fast kidney and hepatobiliairy clearance of MnO particles conferred by PDns, MnO nanoparticles can now be considered for promising applications in T1-weighted MRI applications requiring less toxic although highly sensitive "positive" molecular contrast agents.

Article - The Royal Society of Chemistry 2014 vol.2

Metal chelate grafting at the surface of mesoporous silica nanoparticles (MSNs): physico-chemical and biomedical imaging assessment

Authors:

Myriam Laprise-Pelletier[1,2,4], Meryem Bouchoucha[1,3,4], Jean Lagueux1,Pascale Chevallier[1,4], Roger Lecomte[5], Yves Gossuin[6], Freddy Kleitz[3,4],and Marc-Andr´e Fortin[1,2,4]

Institutions:

1. Centre de recherche du Centre hospitalier universitaire de Qu´ebec (CR-CHUQ), Axe M´edecine R´eg´en´eratrice, Qu´ebec, G1L 3L5, QC, Canada.
2. Department of Mining, Metallurgy and Materials Engineering, Universit´e Laval, Qu´ebec, G1V 0A6, QC, Canada
3. Department of Chemistry, Universit´e Laval, Qu´ebec, G1V 0A6, QC, Canada.
4. Centre de recherche sur les mat´eriaux avanc´es (CERMA), Universit´e Laval, Qu´ebec, G1V 0A6, QC, Canada
5. Sherbrooke Molecular Imaging Center, CRCHUS and Department of Nuclear Medicine and Radiobiology, Universit´e de Sherbrooke, Sherbrooke, J1H 5N4, QC, Canada
6. Service de physique biom´edicale, Universit´e de Mons, Mons, B7000, Belgium

Abstract:

Mesoporous silica nanoparticles (MSNs) are being developed as drug delivery vectors. Biomedical imaging (MRI and PET) enables their tracking in vivo, provided their surface is adequately grafted with imaging probes (metal chelates). However, MSNs are characterized by huge specific surfaces, and high-quality metal chelate anchoring procedures must be developed and validated, to demonstrate that their detection in vivo is associated to the presence of nanoparticles and not to detached metal chelates. MCM-48 nanospheres (M48SNs, 150 nm diam., 3-D pore geometry) were synthesized and functionalized with diethylenetriaminepentaacetic acid (DTPA). The strong grafting of DTPA was confirmed by 29Si MASNMR, XPS, FTIR and TGA. The particles were labeled with paramagnetic ions Gd3+ (for MRI) as well as radioactive ions 64Cu2+ (for PET; half-life: 12.7 h). Gd3+-DTPA-M48SNs formed a stable colloid in saline media for at least 6 months, without any sign of aggregation. The relaxometric properties were measured at various magnetic fields. The strength of DTPA binding at the surface of MSNs was also assessed in vivo, by injecting mice (i.v.) with Gd3+/64Cu2+-DTPA-M48SNs. Vascular retention and urinary clearance were monitored by MRI, whereas the PET modality provided dynamic and quantitative assessment of biodistribution and blood/organ clearance. No significant 64Cu activity was detectable in the bladder. The study confirmed the very limited detachment of DTPA from M48SNs cores once injected in vivo. The transit of MSNs through the liver and intestinal tract, does not lead to evidence of Gd3+/64Cu2+-DTPA in the urine. This physico-chemical and biodistribution study confirms the quality of DTPA attachment at the surface of the particles, necessary to allow further development of PET/MRI assisted MSN-vectorized drug delivery procedures.

Article - The Royal Society of Chemistry 2014

Magnetic Resonance Imaging of Human Tissue-Engineered Adipose Substitutes

Authors:

Maryse Proulx, MSc[1,2] Kim Aubin, MSc[1,2,] Jean Lagueux, PhD[1], Pierre Audet, MSc[3] Miche`le Auger, PhD[3–5], Marc-Andre´ Fortin, Ing. PhD[1,4,6], and Julie Fradette, PhD[1,2]

Institutions:

1. Division of Regenerative Medicine, CHU de Que´bec Research Centre, Que´bec, Canada.
2. De´partement de Chirurgie, Centre de Recherche en Organogene`se Expe´rimentale de l'Universite´ Laval/LOEX, Que´bec, Canada.
3. De´partement de Chimie, Universite´ Laval, Que´bec, Canada.
4. Centre de Recherche sur les Mate´riaux Avance´s (CERMA), Universite´ Laval, Que´bec, Canada.
5. Regroupement que´be´cois de recherche sur la fonction, la structure et l'inge´nierie des prote´ines (PROTEO), Universite´ Laval, Que´bec, Canada.
6. De´partement de Ge´nie des Mines, de la Me´tallurgie et des Mate´riaux, Universite´ Laval, Que´bec, Canada.

Abstract:

Adipose tissue (AT) substitutes are being developed to answer the strong demand in reconstructive surgery. To facilitate the validation of their functional performance in vivo, and to avoid resorting to excessive number of animals, it is crucial at this stage to develop biomedical imaging methodologies, enabling the follow-up of reconstructed AT substitutes. Until now, biomedical imaging of AT substitutes has scarcely been reported in the literature. Therefore, the optimal parameters enabling good resolution, appropriate contrast, and graft delineation, as well as blood perfusion validation, must be studied and reported. In this study, human adipose substitutes produced from adipose-derived stem/stromal cells using the self-assembly approach of tissue engineering were implanted into athymic mice. The fate of the reconstructed AT substitutes implanted in vivo was successfully followed by magnetic resonance imaging (MRI), which is the imaging modality of choice for visualizing soft ATs. T1-weighted images allowed clear delineation of the grafts, followed by volume integration. The magnetic resonance (MR) signal of reconstructed AT was studied in vitro by proton nuclear magnetic resonance (1H-NMR). This confirmed the presence of a strong triglyceride peak of short longitudinal proton relaxation time (T1) values (200 – 53ms) in reconstructed AT substitutes (total T1 = 813 – 76ms), which establishes a clear signal difference between adjacent muscle, connective tissue, and native fat (total T1*300ms). Graft volume retention was followed up to 6weeks after implantation, revealing a gradual resorption rate averaging at 44%of initial substitute's volume. In addition, vascular perfusion measured by dynamic contrast-enhanced-MRI confirmed the graft's vascularization Post implantation (14 and 21 days after grafting). Histological analysis of the grafted tissues revealed the persistence of numerous adipocytes without evidence of cysts or tissue necrosis. This study describes the in vivo grafting of human adipose substitutes devoid of exogenous matrix components, and for the first time, the optimal parameters necessary to achieve efficient MRI visualization of grafted tissue-engineered adipose substitutes.

TISSUE ENGINEERING: Part C Volume 00, Number 00, 2015

A Targeted Gd Nanoparticle for T1-MR Molecular Imaging of Amyloid Plaques

Authors:
Eric A Tanifum, Ketan Ghaghada, Zbigniew Starosolski and Ananth Annapragada

Institutions:
The Singleton Department of Pediatric Radiology, Texas Children's Hospital and Department of Radiology, Baylor College of Medicine, Houston, TX 77030

Presentation – RSNA 2014

Early onset and enhanced growth of autochthonous mammary carcinomas in C3-deficient Her2/neu transgenic mice

Authors:
Silvio Bandini[1], Claudia Curcio[2], Marco Macagno[1], Elena Quaglino[1], Maddalena Arigoni[1], Stefania Lanzardo[1], Albana Hysi[2], Giuseppina Barutello[1], Lorena Consolino[1], Dario Livio Longo[1], Piero Musiani[2], Guido Forni[1], Manuela Iezzi[2], and Federica Cavallo

Institutions:
1. Department of Molecular Biotechnology and Health Sciences; Molecular Biotechnology Center; University of Torino; Torino, Italy
2. Aging Research Center; G. D'Annunzio University Foundation; Chieti, Italy

Abstract:
Aside from its classical role in fighting infections, complement is an important, although poorly understood, component of the tumor microenvironment. In particular, the tumor growth-regulatory activities of complement remain under debate. To assess the role of the complement system in the progression of autochthonous mammary carcinomas, we have crossed complement component 3 (C3)-deficient (C3−/−) BALB/c male mice with BALB/c females expressing the activated rat Her2/neu oncogene (neuT). Although neuT transgenic mice develop spontaneous mammary cancers with 100% penetrance, a significantly shorter tumor latency (i.e., earlier onset of the first palpable tumor), a higher frequency of multiple tumors (multiplicity), and a dramatic increase in the tumor growth rate were found in neuT-C3−/− animals. The accelerated tumor onset observed in neuT-C3−/− mice was paralleled by an earlier onset of spontaneous lung metastases and by an increase in Her2 expression levels, primarily on the surface of tumor cells. The percentage of immune cells infiltrating neuT carcinomas was similar in C3-deficient and C3-proficient mice, with the exception of a significant increase in the frequency of regulatory T cells in neuT-C3−/− tumors. Of particular interest, the enhanced immunosuppression imparted by C3 deficiency clearly influenced the immunogenic phenotype of autochthonous mammary tumors as neuT-C3−/− malignant cells transplanted into syngeneic immunocompetent hosts gave rise to lesions with a significantly delayed kinetics and reduced incidence as compared with cells obtained from neuT C3-proficient tumors. Finally, increased blood vessel permeability was evident in neuT-C3−/− tumors, although a similar number of tumor vessels was found in neuT and neuT-C3−/− lesions. Altogether, these data suggest that complement plays a crucial role in the immunosurveillance and, possibly, the immunoediting of Her2-driven autochthonous mammary tumors.

Paper: OncoImmunology 2:9, e26137; September 2013;

Keywords:
complement; genetically engineered mice; Her2/neu; immunosurveillance; mammary cancer

Combined inhibition of PI3Kb and PI3Kg reduces fat mass by enhancing a-MSH–dependent sympathetic drive

Authors:

Alessia Perino[1], Martina Beretta[1,2], Ana Kilić[3], Alessandra Ghigo[1], Daniela Carnevale[4,5], Ivan Enrico Repetto[6], Laura Braccini[1], Dario Longo[1], Michaela Liebig-Gonglach[3], Tania Zaglia[7], Roberta Iacobucci[5], Marco Mongillo[8], Reinhard Wetzker[9], Michael Bauer[2], Silvio Aime[1], Alessandro Vercelli[6], Giuseppe Lembo[4,5], Alexander Pfeifer[3], Emilio Hirsch[1]

Institutions:

1. Molecular Biotechnology Center, Department of Molecular Biotechnology and Health Sciences, University of Turin, 10126 Turin, Italy.
2. Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, D-07747 Jena, Germany.
3. Institute of Pharmacology and Toxicology, University of Bonn, 53127 Bonn, Germany.
4. Department of Molecular Medicine, "Sapienza" University of Rome, 00161 Rome, Italy. Department of Angiocardioneurology and Translational Medicine,
5. Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Neuromed, 86077 Pozzilli (IS), Italy.
6. Neuroscience Institute Cavalieri Ottolenghi, Department of Neuroscience, University of Turin, 10043 Turin, Italy.
7. Venetian Institute of MolecularMedicine, University of Padova, 35129 Padova, Italy.
8. Department of Biomedical Sciences and Venetian Institute of Molecular Medicine, University of Padova, 35121 Padova, Italy.
9. Department of Molecular Cell Biology, Jena University Hospital, Friedrich Schiller University, 07745 Jena, Germany.

Abstract:

Obesity is defined as an abnormal increase in white adipose tissue and has become a ajor medical burden worldwide. Signals from the brain control not only appetite but also energy expenditure, both of which contribute to body weight. We showed that genetic or pharmacological inhibition of two phosphatidylinositol 3-kinases (PI3Kb and PI3Kg) in mice reduced fat mass by promoting increased energy expenditure. This effect was accompanied by stimulation of lipolysis and the acquisition of the energy burning characteristics of brown adipocytes by white adipocytes, a process referred to as browning." The browning of the white adipocytes involved increased norepinephrine release from the sympathetic nervous system. We found that PI3Kb and PI3Kg together promoted a negative feedback loop downstream of the melanocortin 4 receptor in the central nervous system, which controls appetite and energy expenditure in the periphery. Analysis of mice with drug-induced sympathetic denervation suggested that these kinases controlled the sympathetic drive in the brain. Administration of inhibitors of both PI3Kb and PI3Kg to mice by intra cerebro ventricular delivery induced a 10% reduction in fat mass as quickly as 10 days. These results suggest that combined inhibition of PI3Kb and PI3Kg might represent a promising treatment for obesity.

www.SCIENCESIGNALING.org 18 November 2014 Vol 7 Issue 352

Synthesis of a carborane-containing cholesterol derivative and evaluation as a potential dual agent for MRI/BNCT applications

Authors:

Diego Alberti[1],Antonio Toppino[2], Simonetta Geninatti Crich[1], Chiara Meraldi[2], Cristina Prandi[2], Nicoletta Protti[3,4], Silva Bortolussi[3,4], Saverio Altieri[3,4], Silvio Aime[1],and Annamaria Deagostino[2]

Institutions:

1. Department of Molecular Biotechnology and Health Sciences, University of Torino, via Nizza 52, 10126 Torino, Italy.
2. Department of Chemistry, University of Torino, via P. Giuria 7, 10125 Torino, Italy
3. Department of Nuclear and Theoretical Physics, University of Pavia, Pavia, Italy
4. Nuclear Physics National Institute (INFN), Section of Pavia, Pavia, Italy

Abstract:

In this study the synthesis and characterization of a new dual, imaging and therapeutic, agent is proposed with the aim of improving the efficacy of Boron Neutron Capture Therapy (BNCT) in cancer treatment. The agent (Gd-B-AC01) consists of a carborane unit (ten boron atoms) bearing a cholesterol unit on one side (to pursue the incorporation into the liposome bi-layer) and a Gd(III)/1,4,7,10-tetraazacyclododecane monoamide complex on the other side (as a MRI reporter to attain the quantification of the B/Gd concentration). In order to endow the BNCT agent with specific delivery properties, the liposome embedded with the MRI/BNCT dual probes has been functionalized with a pegylated phospholipid containing a folic acid residue at the end of the PEG chain. The vector allows the binding of the liposome to folate receptors that are overexpressed in many tumor types, and in particular, in human ovarian cancer cells (IGROV-1). An in vitro test on IGROV-1 cells demonstrated that Gd-B-AC01 loaded liposomes are efficient carriers for the delivery of the MRI/BNCT probes to the tumor cells. Finally, the BNCT treatment of IGROV-1 cells showed that the number of surviving cells was markedly smaller when the cells were irradiated after internalization of the folate-targeted GdB10-AC01/liposomes.

Paper: The Royal Society of Chemistry - Org. Biomol. Chem., 2014, 12, 2457–2467

Design of PLGA Based Nanoparticles for Imaging Guided Applications

Authors:
Rodolfo Nicolás Mariano[1] Diego Alberti[1], Juan Carlos Cutrin[1,2], Simonetta Geninatti Crich[1], and Silvio Aime[1]

Institutions:
1. Department of Molecular Biotechnology and Health Sciences, University of Torino, via Nizza 52, Torino, Italy
2. ININCA-CONICET, Marcelo T. de Alvear 2270, Buenos Aires, Argentina

Abstract:
An amphiphilic Gd(III) complex has been efficiently loaded in polylactic-co-glycolic acid nanoparticles (PLGA-NPs) to yield a novel, high sensitive magnetic resonance imaging (MRI) contrast agent for imaging guided drug delivery applications. As the Gd(III) complex is soluble in organic solvents, the nanoparticles were prepared as oil/water emulsions. PLGA-NPs were stable, in buffer, for more than 1week without any release of the incorporated agents. The millimolar relaxivity of the Gd(III) complex incorporated in the particles (140 nm diameter) was of 21.7 mM−1 s−1 at 21.5 MHz, a value that is about 5 times higher than that observed with the commercially available contrast agents used in clinic. The relaxometric efficiency of these particles resulted inversely proportional to the particle size measured by dynamic light scattering. The high stability and sensitivity of PLGA-NPs allowed their accumulation in vivo in murine melanoma xenograft as shown in the corresponding MR images. Once loaded with drug and contrast agents, PLGA nanoparticles can be proposed as efficient theranostic MRI agents.

Mol. Pharmaceutics 2014, 11, 4100−4106

Keywords:
poly(lactic-co-glycolic acid (PLGA) nanoparticles, MRI, Gd(III) complexes, imaging guided therapy, contrast agents

Effect of fiber length, flow rate, and concentration on velocity profiles of cellulosic fiber suspensions

Authors:
E. J. Tozzi, D. M. Lavenson, M. J. McCarthy, R. L. Powell

Institutions:
University of California, Davis, Davis, CA, USA

Abstract:
Conversion of cellulosic biomass to useful products involves pumping and mixing of fiber suspensions. Depending upon the concentration, the fibers may entangle to form flocs and networks. The fibers in these suspensions may settle both as individual fibers and fiber flocs. The flow of cellulosic suspensions has been previously modeled using generalized Newtonian rheological models. Under some flow conditions, those models do not apply due to strong gravitational effects that result in concentration gradients. Magnetic resonance flow imaging was used to obtain velocity profiles of fiber suspensions in horizontal pipe flow as a function of fiber length, concentration, and flow rates. Measures of flatness and symmetry are used to characterize the shape of the velocity profiles. The largest asymmetry is found near a crowding number of roughly three. At higher crowding numbers, the velocity profiles tended to become flat, more symmetric, and pressure drops per unit length depend strongly on concentration.

Acta Mech 224, 2301–2310 (2013)

Pore-Scale Mixing and Transverse Dispersivity of Randomly Packed Monodisperse Spheres

Authors:
U. M. Scheven

Institutions:
Departamento de Qui´mica, REQUIMTE/CQFB, FCT-Universidade Nova de Lisboa, Portugal

Abstract:
We show that transverse dispersion in flow through randomly packed monodisperse spheres (sphere diameter d) is a velocity-dependent superposition of three separable random processes—diffusion with coefficient Dr, intrinsic mechanical dispersion with dispersivity lm ¼ d=33 caused by advection on streamlines, and a newly identified coupled mechanical dispersion with dispersivity lc ¼ d=11, which arises by coupled advection and transverse diffusion at the pore scale. The velocity dependence of the transverse dispersivity is derived from first principles. Our analysis is insensitive to details of the pore geometry and is verified by pulsed field gradient NMR experiments which covered 4.5 orders of magnitude in reduced velocity.

American Physical Society - Phys. Rev. Lett. 110, 214504 – Published 21 May 2013

A comparative study of semi-dilute fibre suspension flow using magnetic resonance imaging and ultrasonic Doppler velocimetry: Differences between fluid and fibre motion

Authors:
Paul Krochak[1], Richard Holm[1], Masato Hirota[2], Fredrik Lundell[2], Daniel Söderberg[1]

Institutions:
1. Innventia AB, SE-114 86 Stockholm, Sweden
2. Wallenberg Wood Science Centre, Royal Institute of Technology, Stockholm, Sweden

Abstract:
Nuclear magnetic resonance imaging (NMRI) and pulsed ultrasound Doppler velocimetry (UVP) were used concurrently to measure the phase specific velocity profiles for the flow of mono-dispersed suspensions of rayon fibres in water at various velocities in pipe flow. Phase flow encoded NMR was used to measure the motion of the water phase while UVP measured the motion of the fibre phase. Measurements were performed for fibre concentrations of nL3 = 1, 6, and 10, where n is the number density of fibres and L is the fibre length, namely 2mm. The fibre aspect ratio aspect ratio was 33 and the pipe inner diameter was 34 mm. Measurements were performed in the turbulent flow regime with water and pipe diameter based Reynolds number in the range of 9 350 – 56 100. At dilute fibre concentrations, the flow of the fibre phase is shown to be identical to that for the carrier fluid phase. Moreover both measurements techniques agree perfectly up to approximately 80% of the pipe diameter; the error being due to UVP limitations at far wall regions. As the fibre concentration is increased, small differences between the water and fibre velocity profiles are observed. Specifically, the fibre velocity is shown to lag the fluid velocity while the fluid velocity is shown to lose its symmetry. Measurements are confirmed in two independent planes normal to the flow direction. These results indicate the existence of an interphase slip velocity, even at low concentration.

ICMF 2013

EVALUATION OF COVERAGE, DISTRIBUTION AND RETENTION OF NANOCARRIER POLY(ETHYLENE) GLYCOL (PEG)-BASED VAGINAL HYDROGELS IN MICE USING MRI

Authors:
Sujata Sundara Rajan[1], Derek Adler[1], Patrick J. Sinko[1]

Institutions:
1. Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, The State university of New Jersey, New Brunswick, NJ, USA

Abstract:
The purpose of this study is to determine the coverage, distribution and retention of PEG-based hydrogels in the vagina of mice, using MRI. We hypothesize that covalently crosslinked hydrogels, by virtue of their superior viscoelastic properties will provide better coverage and retention than conventional semi-solid gel formulations. Therefore hydroxyethylcellulose (HEC) gel, used routinely as a "universal placebo" in microbicide trials were compared to nanocarrier PEG-based hydrogels.

Poster: CONRAD 2013

Assessment of pomegranate postharvest quality using nuclear magnetic resonance

Authors:
Lu Zhang[1], Michael J. McCarthy[1,2]

Institutions:
1. Department of Food Science and Technology, University of California, Davis
2. Department of Biological and Agricultural Engineering, University of California, Davis

Abstract:
Fruit quality parameters, soluble solids content (Brix), total titratable acidity, pH, and Brix/acid ratio, are often used as indicators of fruit maturity and palatability. Measurement of these fruit quality parameters requires a series of destructive methods, which can only be conducted on extracted fruit juice. The aim of this study is to investigate the relationship between spin–spin relaxation time and pomegranate quality attributes and the potential of MRI for quantitative analysis of pomegranate quality. Spin–spin relaxation time, T2, measured using a low magnetic field (0.04 T) showed correlation with the soluble solids content of pomegranate. The T2 relaxation time ranged from 837 ms to 1024 ms for the fruit with soluble solids content from 15.3 ◦Brix to 18.7 ◦Brix. However, accurate prediction was not achieved. In the MRI experiment, six MR images with varying contribution to total signal intensity from proton density, relaxation rates, and diffusion weighing were obtained for pomegranate fruit using a 1 T MR imaging system with 0.22 T/m gradient strength. The pH, Brix, total titratable acidity, and Brix/acid ratio of pomegranate were also measured by traditional destructive methods. Partial least square (PLS) analysis was applied to the statistical features of the voxel signal intensities in the MR images and quality parameters to examine the correlation between MR images results and destructive measurements. The MR image based PLS model have a R2 of 0.54, 0.6, and 0.63 for predicting titratable acidity, pH, and soluble solids/acidity levels, respectively. The correlation between MR image statistical features and soluble solids content of pomegranate was poor. In these models, T2 weighted Fast Spin Echo, diffusion weighted image, and Spin Echo image with short TE and moderate TR are the most important images in predicting the pomegranate quality attributes. Unlike traditional destructive methods, MR imaging is capable of evaluating multiple quality parameters in a single measurement.

Postharvest Biology and Technology 77 (2013)

Keywords:
Pomegranate, Quality Brix, Acidity, pH, NMR

Black heart characterization and detection in pomegranate using NMR relaxometry and MR imaging

Authors:
Lu Zhang[1], Michael J. McCarthy[1,2]

Institutions:
1. Department of Food Science and Technology, University of California
2. Department of Biological and Agricultural Engineering, University of California

Abstract:
In pomegranate, black heart disease develops inside the fruit without affecting the rind. Visual inspection is not effective for identification of black heart in pomegranate fruit because of the lack of external symptoms. It has been shown that the water proton T2 relaxation time is sensitive to cell compartmentalization. Proton NMR relaxometry was used to investigate the water T2 relaxation distribution in infected and healthy pomegranate arils, and to obtain information that indicates tissue damage. Multi-exponential inversion of the T2 data of healthy arils gave three relaxation peaks, which correspond to different water compartments in tissue. In infected arils, the three relaxation components shifted to lower relaxation time and a new fast relaxation component appeared indicating there was water redistribution among cell compartments caused by the infection. The change in cell membrane integrity in arils was also investigated with the aid of paramagnetic ions. T2-weighted fast spin echo images were acquired for healthy and pomegranates with black heart. Histogram features of images, including mean, median, mode, standard deviation, skewness, and kurtosis, were examined using partial least square discriminant analysis (PLS-DA). The PLS-DA model based on histogram features of MR image showed 92% accuracy in detecting the presence of black heart in pomegranate fruit. The significant change in T2 relaxation distribution in arils after infection proved that T2 relaxation time is a good indicator of black heart in pomegranate. The T2 based MR imaging showed its potential as a nondestructive technique for black heart detection in pomegranate.

Postharvest Biology and Technology 67 (2012) 96–101

Keywords:
Pomegranate, T2 relaxation time

Effect of Cocoa Butter Structure on Oil Migration

Authors:
Fatemeh Maleky, Kathryn L. McCarthy, Michael J. McCarthy, and Alejandro G. Marangoni

Institutions:

Abstract:
Oil migration from a high oil content filling into adjacent chocolate causes changes in product quality. The objective of this study was to quantify the oil migration from a cream filling system into cocoa butter, which provided a model for the behavior of chocolate-enrobed confectionery products with a soft, creamy center. Magnetic resonance imaging (MRI) was used to monitor spatial and temporal changes of liquid lipid content. A multislice spin echo pulse sequence was used to acquire images with a 7.8 ms echo time and a 200 ms repetition time using a 1.03 T Aspect Imaging MRI spectrometer. Samples were prepared as a 2-layer model system of cocoa butter and model cream filling. Three methods were used to prepare the cocoa butter: static, seeded, and sheared. Samples were stored at 25 ◦C for a time frame of 56 d. The rate of oil migration was quantified by a kinetic expression based on the linear dependence of oil uptake by cocoa butter and the square root of the time. Samples showed distinctly different rates of oil migration, as evidenced by quantitative differences in the kinetic rate constant

Journal of Food Science Vol. 77, Nr. 3, 2012

Keywords:
Cocoa butter, diffusion, magnetic resonance imaging (MRI), nanostructure, oil migration

Yield Stress of Pretreated Corn Stover Suspensions Using Magnetic Resonance Imaging

Authors:
David M. Lavenson[1],Emilio J. Tozzi[1] Michael J. McCarthy[2,3], Robert L. Powell[1]

Institutions:
1. Department of Chemical and Materials Science Engineering, University of California, Davis
2. Department of Food Science and Technology, University of California, Davis, California
3. Department of Biological and Agricultural Engineering, University of California, Davis, California

Abstract:
Cellulose fibers in water form networks that give rise to an apparent yield stress, especially at high solids contents. Measuring the yield stress and correlating it with fiber concentration is important for the biomass and pulp industries. Understanding how the yield stress behaves at high solids concentrations is critical to optimize enzymatic hydrolysis of biomass in the production of biofuels. Rheological studies on pretreated corn stover and various pulp fibers have shown that yield stress values correlate with fiber mass concentration through a power-law relationship. We use magnetic resonance imaging (MRI) as an in-line rheometer to measure velocity profiles during pipe flow. If coupled with pressure drop measurements, these allow yield stress values to be determined. We compare our results with literature values and discuss the accuracy and precision of the rheo-MRI measurement, along with the effects of fiber characteristics on the power-law coefficients.

Biotechnology and Bioengineering

Keywords:
biomass; corn stover; yield stress; rheology; magnetic resonance imaging

Monitoring changes in feta cheese during brining by magnetic resonance imaging and NMR relaxometry

Authors:
Aylin Altan[1,4], Mecit H. Oztop[2,3], Kathryn L. McCarthy[1,2], Michael J. McCarthy[1,2]

Institutions:
1. Department of Food Science and Technology, One Shields Avenue, University of California, Davis, Davis, CA 95616, USA
2. Department of Biological and Agricultural Engineering, One Shields Avenue, University of California, Davis, Davis, CA 95616, USA
3. Department of Food Engineering, Inonu Bulvari, Eskisehir Yolu, Middle East Technical University, Ankara, Turkiye
4. Department of Food Engineering, University of Mersin, Ciftlikkoy, Mersin 33343, Turkiye

Abstract:
Magnetic resonance imaging (MRI) and NMR relaxometry were used to monitor changes in feta cheese during 169 h of brining at 4.8%, 13.0% and 23.0% salt solutions. Image and relaxation data were acquired to study salt uptake and water loss due to dehydration of cheese during brining. Saturation recovery and Carr–Purcell–Meiboom–Gill (CPMG) sequences were used to determine the longitudinal relaxation (T1) and the transverse relaxation (T2) times, respectively. Signal intensities of T2 weighted images decreased during 169 h of brining. An excellent linear correlation between the average signal intensity and the water content was obtained (R2 = 0.984). The T1 values of cheese brined at 4.8% were almost constant but T1 values decreased for both 13.0% and 23.0% salt brined cheeses. Analysis of the CPMG decays gave relaxation spectra containing two components which decreased during brining. The short component T2a was highly correlated with salt content (R2 = 0.974). Results showed that NMR and MRI can be used to follow salt uptake and changes in water content in cheese during brining.

Journal of Food Engineering 107 (2011) 200–207

Keywords:
Brining, Feta cheese, MRI, NMR relaxometry

Yield Stress of Pretreated Corn Stover Suspensions Using Magnetic Resonance Imaging

Authors:
David M. Lavenson[1],Emilio J. Tozzi[1],Michael J. McCarthy[2], Robert L. Powell[1]

Institutions:
1. Department of Chemical and Materials Science Engineering, University of California
2. Department of Food Science and Technology, University of California, Davis, California

Abstract:
Cellulose fibers in water form networks that give rise to an apparent yield stress, especially at high solids contents. Measuring the yield stress and correlating it with fiber concentration is important for the biomass and pulp industries. Understanding how the yield stress behaves at high solids concentrations is critical to optimize enzymatic hydrolysis of biomass in the production of biofuels. Rheological studies on pretreated corn stover and various pulp fibers have shown that yield stress values correlate with fiber mass concentration through a power-law relationship. We use magnetic resonance imaging (MRI) as an in-line rheometer to measure velocity profiles during pipe flow. If coupled with pressure drop measurements, these allow yield stress values to be determined. We compare our results with literature values and discuss the accuracy and precision of the rheo-MRI measurement, along with the effects of fiber characteristics on the power-law coefficients.

Biotechnol. Bioeng. 2011;108: 2312–2319.

Keywords:
biomass; corn stover; yield stress; rheology; magnetic resonance imaging

Practical Applications of in Vivo and ex Vivo MRI in Toxicologic Pathology Using a Novel High-performance Compact MRI System

Authors:
CATHERINE TEMPEL-BRAMI[1], YAEL S. SCHIFFENBAUER[1], ABRAHAM NYSKA[2], NATI EZOV[3], ITAI SPECTOR[3], RINAT ABRAMOVITCH[4], AND ROBERT R. MARONPOT[5]

Institutions:
1. Aspect Imaging, Shoham, Israel
2. Tel Aviv University and Consultant in Toxicologic Pathology, Timrat, Tel Aviv, Israel
3. Harlan Biotech Israel, Nes Ziona, Israel
4. Hadassah Hebrew University Medical Center, Jerusalem, Israel
5. Maronpot Consulting, LLC, Raleigh, North Carolina, USA

Abstract:
Magnetic resonance imaging (MRI) is widely used in preclinical research and drug development and is a powerful noninvasive method for assessment of phenotypes and therapeutic efficacy in murine models of disease. In vivo MRI provides an opportunity for longitudinal evaluation of tissue changes and phenotypic expression in experimental animal models. Ex vivo MRI of fixed samples permits a thorough examination of multiple digital slices while leaving the specimen intact for subsequent conventional hematoxylin and eosin (H&E) histology. With the advent of new compact MRI systems that are designed to operate in most conventional labs without the cost, complexity, and infrastructure needs of conventional MRI systems, the possibility of MRI becoming a practical modality is now viable. The purpose of this study was to investigate the capabilities of a new compact, high-performance MRI platform (M22; Aspect Imaging, Israel) as it relates to preclinical toxicology studies. This overview will provide examples of major organ system pathologies with an emphasis on how compact MRI can serve as an important adjunct to conventional pathology by nondestructively providing 3-dimensional (3-D) digital data sets, detailed morphological insights, and quantitative information. Comparative data using compact MRI for both in vivo and ex vivo are provided as well as validation using conventional H&E.

Toxicological Pathology

Keywords:
MRI; ex vivo; in vivo; magnetic resonance histology (MRH); toxicology; pathology; preclinical imaging.

Histopathology of biodegradable polymers: challenges in interpretation and the use of a novel compact MRI for novel compact MRI for biocompatibility evaluation

Authors:

Abraham Nyskaa[1], Yael S. Schiffenbauer[2], Catherine T. Brami[2], Robert R. Maronpot[3] and Yuval Ramot[4]

Institutions:

1. Tel Aviv University and Consultant in Toxicologic Pathology, Timrat, Tel Aviv, Israel
2. Aspect Imaging, Shoham, Israel
3. Maronpot Consulting, LLC, Raleigh, North Carolina, USA
4. Hadassah Hebrew University Medical Center, Jerusalem, Israel

Abstract:

Toxicologic pathology is the art of assessment of potential adverse effects at the tissue level in pre-clinical studies. In the case of biomaterials and medical devices, the toxicologic pathologists assess the safety (biocompatibility) and efficacy (conditions of the use) of the implantable materials. Proper assessment of biocompatibility of biomaterials is of utmost importance, since it helps to determine their safety after implantation in humans. Biomaterial-related toxicity can be attributed to several factors, including for example leachable compounds from the material leading to thrombosis or carcinogenesis, or biodegradation of the material causing changes in its physical and compatibility properties. Evaluation of biocompatibility and biofunctionality involves assessment of cytotoxicity, allergic responses, irritation, inflammation and systemic and chronic toxicity. In many of these assessments, the toxicologic pathologist has an important role in determining product safety and potential toxicity. In this article, we review the special needs for proper toxicologic pathology assessment of biomaterials and degradable polymers. We review common adverse effects expected with biomaterials and describe their pathological picture and their clinical relevance. We also introduce a novel compact MR imaging technology as a tool for assessing biocompatibility and efficacy of implanted biodegradable materials, since it allows for the longitudinal imaging and quantification of inflammation in vivo caused by the device implantation, and enabling general inspection of shape, location and integrity of the device in vivo. Since the MR imaging technique is non-invasive, the effects of the implantable device can be monitored longitudinally in the same animal without perturbation of the pathology.

Polymers Advanced Technology: 2014, 25

Keywords:

toxicologic pathology; histopathology; MRI; safety assessment

Application of Magnetic Resonance Imaging (MRI) for histopathological examination —Detection of neural lesions in rat formalin-fixed brain by MRI

Authors:

Yoshikazu Taketa[1], Motohiro Shiotani[1], Yoshiharu Tsuru[2], Sadaharu Kotani[3], Yoshihide Osada[3], Tatsuto Fukushima[3], Akira Inomata[1], Jiro Sonoda[1], Kazuhiro Hayakawa[4], Kyoko Nakano-Ito[1], Etsuko Ohta[1], Yuki Seki[1], Aya Goto[1],Satoru Hosokawa[1]

Institutions:

1. Tsukuba Drug Safety, Eisai Co., Ltd.,
2. Research Support Dept., Primetech Corp.,
3. Neuroscience and General Medicine Product Creation Unit, Eisai Co.,Ltd.,
4. Preclinical Safety Research Laboratories, Sunplanet Co., Ltd.

Abstract:

[Introduction] Magnetic Resonance Imaging (MRI) is a clinically useful tool to detect lesions non-invasively. The present study evaluated usability of MRI for preclinical toxicity evaluation. [Methods] Pilocarpine was single dosed to male rats. After 1 week, the brains were collected, analyzed by 1T Compact MRI system with Aspect Imaging's permanent magnet, and histologically examined.
[Results and Discussion] Status epilepticus was observed by pilocarpine treatment. MRI analysis showed focal short T2 pattern in the piriform cortex, lateral thalamic nucleus, and posterior hypothalamic nucleus of the cerebrum. Histologically, neural cell degeneration/necrosis was observed in these areas. In conclusion, MRI analysis prior to histological examination will be a useful tool for preclinical toxicity evaluation.

Poster: The 31st Annual Meeting of the Japanese Society of Toxicologic Pathology

The Benefits of Compact MRI/PET/CT/3D Luminescence/Cerenkov Imaging in an Orthotopic Mammary Fat Pad Tumor Model: Complimentary Modality-Specific Anatomical, Functional and Molecular Data

Authors:
Tonya Coulthard[1], Deborah Scollard[2], Raquel De Souza[2], Jinzi Zheng[2], Meir Silver[1]

Institutions:
1. Aspect Imaging; Toronto, Canada
2. STTARR Innovation Centre, Princess Margaret Cancer Centre, University Health Network; Toronto, Canada

Abstract:
As all pre-clinical imaging modalities have their respective strengths and weaknesses, multi-modal imaging provides complementary and cumulative to better elucidate biological and molecular process as well as disease-specific biomarkers and therapeutic response.
In this study, an orthotopic mammary fat pad tumor model (MDA_MB231-luc) was chosen to show the combined value of five imaging modalities: (1) compact MRI, (2) PET, (3) CT, (4) 3D tomographic luminescence, and (5) Cerenkov imaging.
MRI is the gold standard soft tissue imaging modality, providing high resolution, high tissue-to-tumor contrast and precise localization of normal and diseased tissues.
Although PET is a highly sensitive molecular imaging modality, its disadvantages are the need for radioisotopes and lower resolution and anatomical definition compared to MR. PET images are usually co-registered with an anatomical modality to provide morphological context for the PET signal.
Cerenkov imaging utilizes radioactive PET tracers, however emitted photons are captured using an optical imaging system1 instead of PET detectors.
Luminescence is one of the most highly pervasive pre-clinical imaging modalities, due to its ease of use. The results from conventional luminescence imaging are inherently surface-weighted, and two dimensional, yielding limited information on tumor localization, and true quantification. To overcome these deficiencies, 3D tomographic luminescent imaging can be employed to enhance the visualization and localization of various tumors. LumiQuant (Aspect Imaging) is an advanced hardware and software solution which facilitates the generation of 3D tomographic luminescence coregistered with compact MR images.
Images from a novel compact MRI platform (M50, Aspect Imaging) were used quantify tumor volumes and to provide anatomical reference to all other imaging modalities. Tumor volumes were 411, 332, 329, 269 mm3 amongst the four animals imaged. CT images (eXplore Locus Ultra, GE) were also acquired on each animal, providing an additional anatomical reference.
LumiQuant (Aspect Imaging) was used to generate 3D reconstructions of the luminescence data (IVIS Spectrum, PerkinElmer). The highly sensitive luminescence signal from the luc+ cells confirmed that the tumor remained confined within the primary inoculation site.
Metabolic information about the tumors was obtained with both PET (Focus 220 microPET, Siemens) and Cerenkov (IVIS Spectrum, PerkinElmer) imaging, both utilizing glucose analog FDG (2-deoxy-2-[18F]-D-glucose) as a radioactive tracer. The tumor-to-muscle ratios for the four animals imaged were 2.7, 2.4, 3.7, and 3.0 respectively. This confirmed the increased glucose metabolic rate for the tumor cells compared to muscle cells. Cerenkov imaging was performed immediately following PET.
When combined these five imaging modalities provides complementary anatomical, functional, and molecular information, as well as cross-validation of tumor volumes and localization. This multi-modal approach to pre-clinical cancer research could be applied

easily to other tumor models, especially when a variety of imaging biomarkers of interested need to be quantified.

Poster: WMIC 2014

Comparison of Ultrasound and Compact MRI for the Assessment of Cardiac Function in Mice

Authors:
Tonya Coulthard[1], Jun Wu[2]

Institutions:
1 Aspect Imaging, Toronto, Ontario, Canada
2 STTARR, University of Toronto, Ontario, Canada

Poster: From American Heart Association's Basic Cardiovascular Sciences 2014 Scientific Sessions, Las Vegas, NV

Abstract:
Introduction: Ultrasound (US) is the standard for the assessment of cardiovascular function. Pre-clinically, this is due to the modality's translational potential, its high temporal resolution and the absence of infrastructure involved with US. Significant user variability, requirements for high-levels of operator training and the presence of imaging artifacts associated with air and bone can also render US imaging a cumbersome technique in small animal models, particularly in models of pathology where surgery is required. In addition, the lack of a "whole body" image makes anatomical land-marking with US challenging for new users. Recent advancements in novel high-performance compact MRI has made cardiac MRI a more accessible technique for assessing a variety of pathologies in murine models of cardiovascular disease, while reducing the complexity and costs traditionally associated with superconducting MRI systems. These developments may allow compact MRI to overcome some of the limitations of US meanwhile producing similar quantification capabilities.
Purpose: The purpose of this study was to evaluate the strengths and weaknesses of compact, high-performance MRI compared with high-frequency US for studying mouse models of cardiovascular disease.
Conclusions: Although compact MRI has lower frame rates, when compared with US, it has many advantages in pre-clinical cardiac imaging. In particular, because MRI signal is not attenuated by dense tissue or air, compact MRI can successfully generate artifact-free imaging and quantification of pathologies difficult or impossible to image with US. Finally, high sensitivity to Gd-based contrast agent with compact MRI enable new applications such as infarct quantification.

Quantification of Mouse Model of Myocardial Infarction Using Compact, High-Resolution MRI

Authors:
Clinton Hupple[1], Tonya Coulthard[1], Jun Wu[2]

Institutions:
1 Aspect Imaging, Toronto, Ontario, Canada
2 STTARR, University of Toronto, Ontario, Canada

Poster: From American Heart Association's Basic Cardiovascular Sciences 2014 Scientific Sessions, Las Vegas, NV

Abstract:
Introduction: Cardiovascular Magnetic Resonance Imaging (cMRI) allows for non-invasive assessment of cardiovascular function and anatomy. Delayed Enhancement Imaging (DEI) is a contrast agent-based cMRI technique for characterizing myocardial infarction and predicting therapeutic efficacy following coronary ischemia. Typically gadolinium-based (Gd) contrast agents are injected intravenously and accumulate in the lesion over time, providing differentiation between normal and diseased myocardium. Traditionally, DEI has been explored using superconducting high-field MRI. It has been shown that by using a novel compact, high-performance MRI operating at 1 Tesla, an increase in sensitivity to Gd-based contrast agents compared with higher field systems is observed[1].
Purpose: In this study, cMRI was employed to characterize myocardial infarcts *in vivo* in mice. Three analysis methods were explored: cine analysis, strain analysis and delayed enhancement imaging (DEI). To leverage the increased sensitivity to Gd agents at 1 Tesla, DEI was used to measure infarct size *in vivo,* and then compared to post mortem histological analysis for validation.
Conclusions: Our preliminary results demonstrate the ability to successfully monitor cardiac function while performing DEI to effectively visualize and quantify myocardial infarction at 1 Tesla and leverage the benefits of the increased sensitivity of Gd-based contrast imaging with this novel compact, high-performance MRI.

Significant Lessening of Local Reactions Following Continuous SC Administration of ND0701 (Apo-ND), a New Apomorphine Formulation for Parkinson's Disease using MRI and Histopathology

Authors:

Ronit Shaltiel Karyo[1], Hanita Ovadia[1], Yonit Tzarfati[1], Oron Yacoby-Zeevi, Yael S Schiffenbauer[2] and Abraham Nyska[3]

Institutions:

1 Neuroderm, Ness Ziona, Israel
2 Aspect Imaging, Shoham Israel
3 Consultant in Toxicologic Pathology, Timrat, and Tel Aviv University, Israel

Poster: From Society of Toxicologic Pathology (STP) 2014, Washington, DC

Abstract:

Background: Subcutaneous administration of Apomorphin is suggested as a replacement therapy for Levodopa in Parkinson's disease patients. Continuous subcutaneous infusion of drug formulations often results in local damage at the administration site. *In vivo* and *ex vivo* MRI were used to evaluate the local damage of commercial Apo-Go® and a newly developed apomorphine formulation ND0701 (Apo-ND) in live pigs and *ex vivo* using tissue biopsies. The results were compared to histopathology.

Experimental design and methods: The drug formulations Apo-ND and Apo- Go® were administered to domestic pigs by 24 hour continuous subcutaneous infusion using an infusion pump. Follow-up of damage at the infusion site was performed using *in vivo* MRI, two and four weeks post drug administration in a Magnetom-C MRI machine (Siemens). *Ex vivo* MRI was performed there after onexcised formalin-fixed skin tissues, using the novel compact 3D-MR based histology system (Aspect Imaging), which allows for a pathologist with no prior MRI expertise to perform 3D non-destructive MR-based imaging of fixed or *in vivo* animals without the expertise, cost, and infrastructure or conventional superconducting MRI. This protocol is followed by histopathology. The histological evaluation consisted of a subjective description of the observed tissue reaction and was scored according to its severity.

Conclusions: Conventional MRI was proven useful in evaluating local toxicologicdamage as a result of subcutaneous drug administrations in pigs. While *in vivo* MRI was highly efficient in following the recovery at the injection sites, *ex vivo* compact MRI allowed quantification of the damage, manifested as subcutaneous necrosis and inflammation, with strong correlation to histopathology. Based on our experiment, Apo-ND was proved to be better locally tolerated than the commercial Apo-Go®. Applying this method of assessing fixed tissue samples (using *in vivo* and *ex vivo* compact MRI) derived from different dose formulations provides a quantitative determination of relative irritancy of different injected formulations.

Detecting and Quantifying Liver Pathologies Using Compact, High-Resolution 3D MRI-Based Histology

Authors:

Yael S Schiffenbauer[1], Catherine Brami[1], Rinat Abramovitch[2], Tali Lanton[2], Jonathan H. Axelrod[2], Eithan Galun[2], Abraham Nyska[3] and Robert Maronpot[4]

Institutions:

1 Aspect Imaging, Shoham Israel
2 Hadassah Hebrew University Medical Center, Ein Karem, Jerusalem, Israel
3 Consultant in Toxicologic Pathology, Timrat and Tel Aviv University, Israel
4 Maronpot Consulting, LLC, Raleigh, NC, USA

Poster: From European Congress of Toxicologic Pathology (ESTP) 2014, Berlin, Germany

Abstract:

Background: Magnetic Resonance Imaging (MRI) is widely used in pre-clinical research and is a powerful method for *in vivo* assessment of phenotypes in murine models of disease. 3D MR-based histology (MRH)[1] of fixed tissue specimens is gaining recognition as a technique to provide complimentary information to conventional histological techniques, as numerous digital slices from any plane of the intact sample can be acquired in 3D, quantified and then followed-up by conventional histology.

Goal and Biological Model: The purpose of this study was to investigate the capabilities of a new compact, high-performance 3D MR-based histology platform (M2™, Aspect Imaging) as a complementary method in toxicology studies. This imaging platform enables a technician to generate diagnostic-quality *in vivo* and *ex vivo* images with MRI and to operate the system without any prior imaging or physics experience due to the pre-programed imaging protocols for toxicology applications. The system is also self-shielded allowing for its ease of installation and operation. In this study, we were interested in detecting and quantifying liver pathologies manifested in mice with homozygous disruption of the mdr2 P-glycoprotein gene.[2] These mice are unable to secrete phospholipids into bile causing chronic hepatic inflammation manifested shortly after birth leading to the development of pre-neoplastic lesions which progress thereafter to hepatocellular carcinomas (HCC).[3,4]

Conclusions: We have demonstrated the utility of compact, high-performance MRI and 3D MR-based histology (MRH) as valuable tools to complement conventional toxicological studies. While *in vivo* MRI provides invaluable functional, morphological and quantitative information of disease progression and regression by non-invasively imaging the same animals over time, non destructive *ex vivo* MRI provides an additional benefit of high throughput and high-resolution 3D digital data sets of intact organs, with exquisite morphological and quantitative information. With a high degree of correlation to conventional H&E, 3D MR-based histology can provide both additional insights into disease pathology as well as directing conventional histology to ensure key targets are fully assessed, considered and calculated in toxicological work-ups.

Vulnerabilities of PTEN-p53-deficient prostate cancers to compound PARP/PI3K inhibition

Authors:
Enrique González-Billalabeitia[1, 2*], Nina Seitzer[1*], Su Jung Song[1], Min Sup Song[1], Akash Patnaik[3,4,5], Xue-Song Liu[1], Mirjam T. Epping[1], Antonella Papa[1], Robin M. Hobbs[1], Ming Chen[1], Andrea Lunardi[1], Christopher Ng[1], Kaitlyn A. Webster[1], Sabina Signoretti[7,8], Massimo Loda[7,8,9,10], John M. Asara[4], Caterina Nardella[1,6], John G. Clohessy[1,6], Lewis C. Cantley[4,5] and Pier Paolo Pandolfi[1]

Institutions:
1 Cancer Genetics Program, Beth Israel Deaconess Cancer Center, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
2 In leave of absence: Servicio de Hematología y Oncología Médica. Hospital Universitario Morales Meseguer, Spain
3 Division of Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
4 Department of Systems Biology, Harvard Medical School
5 Division of Signal Transduction, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School
6 Preclinical Murine Pharmacogenetics Facility, Beth Israel Deaconess Medical Center, Harvard Medical School
7 Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute
8 Department of Medical Oncology, Dana-Farber Cancer Institute
9 Department of Pathology, Brigham and Women's Hospital, Harvard Medical School
10 Broad Institute of Harvard and Massachusetts Institute of Technology

Cancer Discovery Published OnlineFirst May 27, 2014. doi: 10.1158/2159-8290.CD-13-0230

Abstract:
Prostate cancer (CaP) is the most prevalent cancer in males and treatment options are limited for advanced forms of the disease. Loss of the PTEN and p53 tumor suppressor genes is commonly observed in CaP, while their compound loss is often observed in advanced CaP. Here we show, that PARP inhibition triggers a p53-dependent cellular senescence in a PTEN-deficient setting in the prostate. Surprisingly, we also find that PARP-induced cellular senescence is morphed into an apoptotic response upon compound loss of PTEN and p53. We further show that superactivation of the pro-survival signalling PI3K-AKT pathway limits the efficacy of a PARP-single-agent treatment, and that PARP and PI3K inhibitors effectively synergize to suppress tumorigenesis in human CaP cell lines and in a Pten/p53 deficient mouse model of advanced CaP. Our findings therefore identify a combinatorial treatment with PARP and PI3K inhibitors as an effective option for PTEN-deficient CaP.

Keywords:
PTEN, Prostate, PARP, PI3K, Senescence

http://cancerdiscovery.aacrjournals.org/content/early/2014/05/24/2159-8290.CD-13-0230.abstract

Role of orexin in respiratory and sleep homeostasis during upper airway obstruction in rats

Authors:
Tarasiuk A[1], Levi A[2], Berdugo-Boura N[2], Yahalom A[2], Segev Y[3]

Institutions:
1 Sleep-Wake Disorders Unit, Soroka University Medical Center and Department of Physiology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
2 Sleep-Wake Disorders Unit, Soroka University Medical Center and Department of Physiology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel ; Shraga Segal Department of Microbiology and Immunology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
3 Shraga Segal Department of Microbiology and Immunology, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Sleep. 2014 May 1;37(5):987-98. doi: 10.5665/sleep.3676.

Abstract:
Study Objective: Chronic upper airway obstruction (UAO) elicits a cascade of complex endocrine derangements that affect growth, sleep, and energy metabolism. We hypothesized that elevated hypothalamic orexin has a role in maintaining ventilation during UAO, while at the same time altering sleep-wake activity and energy metabolism. Here, we sought to explore the UAO-induced changes in hypothalamic orexin and their role in sleep-wake balance, respiratory activity, and energy metabolism.
Interventions: The tracheae of 22-day-old Sprague-Dawley rats were surgically narrowed; UAO and sham-operated control animals were monitored for 7 weeks. We measured food intake, body weight, temperature, locomotion, and sleep-wake activity. Magnetic resonance imaging was used to quantify subcutaneous and visceral fat tissue volumes. In week 7, the rats were sacrificed and levels of hypothalamic orexin, serum leptin, and corticosterone were determined. The effect of dual orexin receptor antagonist (almorexant 300 mg/kg) on sleep and respiration was also explored.
Measurements and Results: UAO increased hypothalamic orexin mRNA and protein content by 64% and 65%, respectively. UAO led to 30% chronic sleep loss, excessive active phase sleepiness, decreased body temperature, increased food intake, reduction of abdominal and subcutaneous fat tissue volume, and growth retardation. Administration of almorexant normalized sleep but induced severe breathing difficulties in UAO rats, while it had no effect on sleep or on breathing of control animals.
Conclusions: In upper airway obstruction animals, enhanced orexin secretion, while crucially important for respiratory homeostasis maintenance, is also responsible for chronic partial sleep loss, as well as considerable impairment of energy metabolism and growth.

Keywords:
orexin; rat; sleep; upper airway loading

http://www.journalsleep.org/ViewAbstract.aspx?pid=29465

Multidentate block copolymer stabilized ultrasmall superparamagnetic iron oxide nanoparticles with enhanced colloidal stability for magnetic resonance imaging

Authors:
Nicky Chan[1], Myriam Laprise-Pelletier[2], Pascale Chevallier[2], Andrea Bianchi[3], Marc-André Fortin[2, 4], and Jung Kwon John Oh[1,4]

Institutions:
1 Department of Chemistry and Biochemistry and Center for Nanoscience Research, Concordia University
2 Centre de recherche du Centre hospitalier universitaire de Quebec (CR-CHUQ), axe Medecine Regeneratrice; Centre de recherche sur les materiaux avances (CERMA), Department of Mining, Metallurgy and Materials Engineering, Universite Laval
3 Departement de physique, Universite de Montreal
4 Centre Quebecois sur les Materiaux Fonctionnels (CQMF)

Biomacromolecules, 2014, 15 (6), pp 2146–2156; DOI: 10.1021/bm500311k

Abstract:
Ultrasmall superparamagnetic iron oxide nanoparticles (USPIOs) with diameters < 5 nm hold great promise as *T1*-positive contrast agents for *in vivo* magnetic resonance imaging (MRI). However, control of the surface chemistry of USPIOs to ensure individual colloidal USPIOs with a ligand monolayer and to impart biocompatibility and enhanced colloidal stability is essential for successful clinical applications. Herein, an effective and versatile strategy enabling the development of aqueous colloidal USPIOs stabilized with well-defined multidentate block copolymers (MDBCs) is reported. The multifunctional MDBCs are designed to consist of an anchoring block possessing pendant carboxylates as multidentate anchoring groups strongly bound to USPIO surfaces, and a hydrophilic block having pendant hydrophilic oligo (ethylene oxide) chains to confer water-dispersibility and biocompatibility. The surface of USPIOs are saturated with multiple anchoring groups of MDBCs, thus exhibiting excellent long-term colloidal stability as well as enhanced colloidal stability at biologically relevant electrolyte, pH, and temperature conditions. Further, relaxometric properties as well as *in vitro* and *in vivo* MR imaging results demonstrate that the MDBCs stabilized USPIO colloids hold as great potential as effective *T1* contrast agent.

Keywords:
block copolymers, atom transfer radical polymerization, magnetic resonance imaging, iron oxide nanoparticles, relaxometry

http://pubs.acs.org/doi/abs/10.1021/bm500311k

Histopathology of biodegradable polymers: challenges in interpretation and the use of a novel compact MRI for biocompatibility evaluation

Authors:
Abraham Nyska[a]*, Yael S. Schiffenbauer[b], Catherine T. Brami[b], Robert R. Maronpot[c] and Yuval Ramot[d]

Institutions:
a Toxicologic Pathology, Sackler School of Medicine, Tel Aviv University
b Aspect Imaging Ltd.
c Maronpot Consulting LLC
d Hadassah-Hebrew University Medical Center

Polymers for Advanced Technologies Special Issue: Biodegradable polymers, Volume 25, Issue 5, pages 461–467, May 2014; DOI: 10.1002/pat.3238

Abstract:
Toxicologic pathology is the art of assessment of potential adverse effects at the tissue level in pre-clinical studies. In the case of biomaterials and medical devices, the toxicologic pathologists assess the safety (biocompatibility) and efficacy (conditions of the use) of the implantable materials. Proper assessment of biocompatibility of biomaterials is of utmost importance, since it helps to determine their safety after implantation in humans. Biomaterial-related toxicity can be attributed to several factors, including for example leachable compounds from the material leading to thrombosis or carcinogenesis, or biodegradation of the material causing changes in its physical and compatibility properties. Evaluation of biocompatibility and biofunctionality involves assessment of cytotoxicity, allergic responses, irritation, inflammation and systemic and chronic toxicity. In many of these assessments, the toxicologic pathologist has an important role in determining product safety and potential toxicity. In this article, we review the special needs for proper toxicologic pathology assessment of biomaterials and degradable polymers. We review common adverse effects expected with biomaterials and describe their pathological picture and their clinical relevance. We also introduce a novel compact MR imaging technology as a tool for assessing biocompatibility and efficacy of implanted biodegradable materials, since it allows for the longitudinal imaging and quantification of inflammation *in vivo* caused by the device implantation, and enabling general inspection of shape, location and integrity of the device *in vivo*. Since the MR imaging technique is non-invasive, the effects of the implantable device can be monitored longitudinally in the same
animal without perturbation of the pathology.

Keywords:
toxicologic pathology; histopathology; MRI; safety assessment

http://onlinelibrary.wiley.com/doi/10.1002/pat.3238/abstract

Tumor-Targeted Responsive Nanoparticle-Based Systems for Magnetic Resonance Imaging and Therapy

Authors:
Ronak Savla[1] & Olga B. Garbuzenko[1] & Suzie Chen[2,3,4] & Lorna Rodriguez-Rodriguez[3,5] & Tamara Minko[1,3,4]

Institutions:
1 Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers The State University of New Jersey
2 Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey
3 Rutgers Cancer Institute of New Jersey
4 Environmental and Occupational Health Sciences Institute
5 Department of Obstetrics and Gynecology, Robert Wood Johnson Medical School, Rutgers The State University of New Jersey

Pharm Res. 2014 Jun 13. [Epub ahead of print]; DOI 10.1007/s11095-014-1436-x

Abstract:
Purpose: Design and synthesis of a tumor responsive nanoparticle based system for imaging and treatment of various cancers.
Methods: Manganese oxide nanoparticles (Mn3O4 NPs) were synthesized and modified with LHRH targeting peptide or antimelanoma antibodies (cancer targeting moieties) and a MMP2 cleavable peptide (a possible chemotactic factor). Nanostructured lipid carriers (NLCs) were used to entrap the BRAF inhibitor, vemurafenib, and enhance cytotoxicity of the drug. Size distribution, stability, drug entrapment, cytotoxicity and genotoxicity of synthesized nanoparticles were studied *in vitro*. Enhancement of MRI signal by nanoparticles and their body distribution were examined *in vivo* on mouse models of melanoma, ovarian and lung cancers.
Results: Uniform, stable cancer-targeted nanoparticles (PEGylated water-soluble Mn3O4 NPs and NLCs) were synthesized. No signs of cyto-genotoxicity and DNA damage were detected for nanoparticles that do not contain an anticancer drug. Entrapment of vemurafenib into nanoparticles significantly enhanced drug toxicity in cancer cells with targeted V600E mutation. The developed nanoparticles containing LHRH and MMP2 peptides showed preferential accumulation in primary and metastatic tumors increasing the MRI signal in mice with melanoma, lung and ovarian cancers.
Conclusions: The proposed nanoparticle-based systems provide the foundation for building an integrated MRI diagnostic and therapeutic approach for various types of cancer.

Keywords:
LHRH targeting peptide, manganese oxide nanoparticles, MMP2 cleavable peptide, nanostructured lipid carriers, vemurafenib

http://www.ncbi.nlm.nih.gov/pubmed/24919932

Heat-activated thermosensitive liposomal cisplatin (HTLC) results in effective growth delay of cervical carcinoma in mice

Authors:
Yannan N. Dou[a], Jinzi Zheng[b,c], Warren D. Foltz[b,c], Robert Weersink[c], Naz Chaudary[d], David A. Jaffray[b,c,e,f,g], Christine Allen[a,b]

Institutions:
a Leslie Dan Faculty of Pharmacy, University of Toronto, Canada
b STTARR Innovation Center, University Health Network, Canada
c Techna Institute, Radiation Medicine Program, Princess Margaret Cancer Center, University Health Network, Canada
d Ontario Cancer Institute, University Health Network, Canada
e Department of Medical Biophysics, University of Toronto, Canada
f Department of Radiation Oncology, University of Toronto, Canada
g Institute of Biomaterials & Biomedical Engineering, University of Toronto, Canada

Journal of Controlled Release (Impact Factor: 7.63). 01/2014;
DOI:10.1016/j.jconrel.2014.01.009

Abstract:
Cisplatin (CDDP) has been identified as the primary chemotherapeutic agent for the treatment of cervical cancer, but dose limiting toxicity is a key issue associated with its clinical application. A suite of liposome formulations of CDDP has been developed in efforts to reduce systemic toxicity, but their therapeutic advantage over the free drug has been modest due to insufficient drug release at the tumor site. This report describes the development of a novel heat-activated thermosensitive liposome formulation containing CDDP (HTLC) designed to release approximately 90% of the loaded drug in less than 5min under mild heating conditions (42°C). Physico-chemical characteristics of HTLC were assessed in terms of gel to liquid crystalline phase transition temperature (Tm), drug loading efficiency, particle size, and stability. The pharmacokinetic profile and biodistribution of HTLC in non-tumor-bearing mice were evaluated over a 24h period. A sophisticated spatio-temporal elucidation of HTLC release in tumor-bearing mice was achieved by way of real-time monitoring using a magnetic resonance (MR) imaging protocol, wherein a custom-built laser-based conformal heat source was applied at the tumor volume to trigger the release of HTLC co-encapsulated with the MR contrast agent gadoteridol (Gd-HP-DO3A). MR thermometry (MRT) demonstrated that a relatively uniform temperature distribution was achieved in the tumor volume using the external laser-based heating setup. In mice bearing subcutaneously-implanted ME-180 cervical tumors, the combination of HTLC and heat resulted in a 2-fold increase in tumor drug levels at 1h post-administration compared to HTLC without heating. Furthermore, the overall tumor accumulation levels for the HTLC groups (with and without heat) at 1h post-injection were significantly higher than the corresponding free CDDP group. This translated into a significant improvement in therapeutic efficacy evaluated as tumor growth delay ($p<0.05$) for the heated HTLC treatment group compared to the unheated HTLC, heated or unheated free CDDP, and saline groups. Overall, findings from this study demonstrate that a heat-activated, triggered release formulation of CDDP results in a significant enhancement in the therapeutic index of this drug.

Keywords:
Thermosensitive liposome, Cisplatin (CDDP), Gadoteridol (ProHance® Gd-HP-DO3A), Magnetic resonance (MR) imaging, Laser heating, Cervical cancer

http://www.ncbi.nlm.nih.gov/pubmed/24440663

Dendrimersomes: a new vesicular nanoplatform for theranostic applications

Authors:
Miriam Filippi[1], Marisa Ferraretto[1], Gilberto Mulas[1], Jonathan Martinelli[2], Lorenzo Tei[2], Mauro Botta[2], Silvio Aime[1,3], and Enzo Terreno[1,3]

Institutions:
1 Molecular Biotechnologies and Health Sciences, University of Turin, Italy
2 Department of Sciences and Technological Innovation, University of Eastern Piedmont, Italy
3 Center for Preclinical Imaging, University of Turin, Italy

Poster: From International Society for Magnetic Resonance in Medicine (ISMRM) 2014, Milan, Italy

Abstract:
Introduction: Dendrimersomes are a new class of nanovesicles constituted by amphiphilic Janus dendrimers.1 Unlike other similar nanoparticles such as liposomes or polymersomes, the potential of dendrimersomes in biomedical imaging has not been explored yet. In this contribution, we report for the first time the preparation and *in vitro* characterization of dendrimersomes loaded with MRI probes. The probes were encapsulated in the aqueous core or incorporated in the bilayer through the synthesis of a novel dendrimer covalently conjugated to a Gd-complex. The ability of dendrimersomes to load drugs was also explored. Besides a preliminary *in vitro* characterization, the nanovesicles were also tested *in vivo* to assess biodistribution, blood half-time, as well as their overall imaging performance.
Results: Dendrimersomes composed by (3,5)12G1-PE-BMPA-G2-(OH)8 only were not stable enough in isotonic buffer. However, the addition of a small amount (5 % in moles) of DSPE-PEG2000-carboxylate significantly increased the stability of the vesicles due to electrostatic repulsion. Vesicles size ranged from 150 to 200 nm (PDI < 0.2) and Gadoteridol was encapsulated in the inner core with good efficiency. Relaxometric studies showed a relatively fast water exchange across the vesicle bilayer, and a high longitudinal relaxivity was measured for the vesicles incorporated with the Gd-based dendrimer (Chart 2). Due to the high motional freedom provided by the six carbon atoms spacer (Chart 1), the relaxivity of this system was found to be slightly lower than for the vesicles incorporating the more rigid GdDOTAMA(C18)2 complex. The *in vivo* data indicated the typical biodistribution pattern of a nanoparticle (e.g. liver and spleen accumulation) with no acute toxicity.
Conclusions: The results obtained indicate that dendrimersomes assembled from Janus dendrimers have potential to represent a new nano-platform for molecular magnetic resonance imaging experiments, particularly in the field of theranosis.

Thermal T1 measurements for frequently used 13C hyperpolarization agents at clinically available field strengths

Authors:
Stephan Düwel[1,2], Patrick Christ[1,3], Ulrich Köllisch[1,3], Markus Durst[1,3], Concetta V Gringeri[3,4], Franz Schilling[4], Marion I Menzel[3], Rolf F Schulte[3], Steffen Glaser[2], Markus Schwaiger[4], and Axel Haase[1]

Institutions:
1 Institute of Medical Engineering, Technische Universität München, Germany
2 Department of Chemistry, Technische Universität München, Germany
3 GE Global Research, Germany
4 Institute of Nuclear Medicine, Klinikum Rechts der Isar, Germany

Poster: From International Society for Magnetic Resonance in Medicine (ISMRM) 2014, Milan, Italy

Abstract:
Introduction: Hyperpolarized ^{13}C metabolic MR spectroscopic imaging of pyruvate and its down-stream metabolites alanine and lactate allows real-time in-vivo studies of energy metabolism in healthy and tumor tissue [1]. At the same time, tumor perfusion can be studied using metabolically inactive hyperpolarized agents such as urea [2], whereas hyperpolarized acetate can be used to examine short chain fatty acid metabolism *in vivo* [3]. Research facilities and clinics perform spectroscopic magnetic resonance imaging (MRSI) experiments at increasingly higher magnetic field strengths B_0 (1T, 3T, 7T, 14T) because of availability, higher spectral resolution and better thermal signal to noise ratio (SNR). Recently, it was shown that hyperpolarized experiments at even lower fields can theoretically be more sensitive than high-field MRI [4]. Long longitudinal relaxation times (T1) could favor experiments at low magnetic field strengths even further. In this study, we systematically measured T1 times for the aforementioned ^{13}C hyperpolarization agents at clinically available field strengths (1.05T, 3.0T, 7.0T) and 14.1T under constant conditions (pH, temperature, concentration), facilitating a proper design of time critical hyperpolarization experiments at varying field strengths.
Conclusion and Discussion: The T_1 times for acetate are comparable to the ones measured from Miéville et al. for a 3M solution in D_20 using the shuttling technique [7]. The T_1 for pyruvate at 1T is comparable to the one measured by Chattergoon et al. using hyperpolarized field cycling. The goal of this study was to investigate T_1 times for a larger number of frequently used hyperpolarization agents under comparable experimental conditions at all field strengths currently clinically available.
While pH and temperature could be held constant, concentrations were initially chosen to avoid solubility problems for each compound separately. A series of current experiments studies the dependence of T_1 on compound concentration and TRIS buffer concentration to also allow for a comparison between different compounds. Planning of hyperpolarized experiments could not only take into account the spectral resolution dependency on B_0, but could also consider the type of biological information that can be extracted from the varying duration of the experiment due to the T_1 dependency of the ^{13}C hyperpolarized agent on B_0.

Development of Novel Tumor-Targeted Theranostic Nanoparticles Activated by Membrane-Type Matrix Metalloproteinases for Combined Cancer Magnetic Resonance Imaging and Therapy

Authors:

Celina Ansari[1], Grigory A. Tikhomirov[1], Su Hyun Hong[1], Robert A. Falconer[2], Paul M. Loadman[2], Jason H. Gill[3], Rosalinda Castaneda[1], Florette K. Hazard[4], Ling Tong[5], Olga D. Lenkov[1], Dean W. Felsher[4,5], Jianghong Rao[1]*, and Heike E. Daldrup-Link[1]*

Institutions:

1 Molecular Imaging Program at Stanford and Department of Radiology, Stanford University
2 Institute of Cancer Therapeutics, School of Life Sciences, University of Bradford
3 School of Medicine, Pharmacy and Health, Durham University
4 Department of Pathology, Stanford University
5 Division of Oncology, Department of Medicine, Stanford University

Small. 2014 Feb 12;10(3):566-75, 417. doi: 10.1002/smll.201301456. Epub 2013 Aug 27.

Abstract:

A major drawback with current cancer therapy is the prevalence of unrequired dose limiting toxicity to non-cancerous tissues and organs, which is further compounded by a limited ability to rapidly and easily monitor drug delivery, pharmacodynamics and therapeutic response. In this report, the design and characterization of novel multifunctional "theranostic" nanoparticles (TNPs) is described for enzyme-specific drug activation at tumor sites and simultaneous *in vivo* magnetic resonance imaging (MRI) of drug delivery. TNPs are synthesized by conjugation of FDA-approved iron oxide nanoparticles ferumoxytol to an MMP-activatable peptide conjugate of azademethylcolchicine (ICT), creating CLIOICTs (TNPs). Significant cell death is observed in TNP-treated MMP-14 positive MMTVPyMT breast cancer cells *in vitro*, but not MMP-14 negative fibroblasts or cells treated with ferumoxytol alone. Intravenous administration of TNPs to MMTV-PyMT tumor-bearing mice and subsequent MRI demonstrates significant tumor selective accumulation of the TNP, an observation confirmed by histopathology. Treatment with CLIO-ICTs induces a significant antitumor effect and tumor necrosis, a response not observed with ferumoxytol. Furthermore, no toxicity or cell death is observed in normal tissues following treatment with CLIO-ICTs, ICT, or ferumoxytol. These findings demonstrate proof of concept for a new nanotemplate that integrates tumor specificity, drug delivery and *in vivo* imaging into a single TNP entity through attachment of enzyme-activated prodrugs onto magnetic nanoparticles. This novel approach holds the potential to significantly improve targeted cancer therapies, and ultimately enable personalized therapy regimens.

Keywords:

MMP-14; MR imaging; cancer therapy; iron oxide; nanoparticles; theranostic

http://www.ncbi.nlm.nih.gov/pubmed/24038954

MRI tracking of macrophages labeled with glucan particles entrapping a water insoluble paramagnetic Gd-based agent

Authors:
Sara Figueiredo[1,4,5], Juan Carlos Cutrin[1,2], Silvia Rizzitelli[1], Elisa De Luca[1], João Nuno Moreira[3,5], Carlos F. G. C. Geraldes[4,5,6], Silvio Aime[1], Enzo Terreno[1]

Institutions:
1 Department of Molecular Biotechnology and Health Sciences and Molecular and Preclinical Imaging Centers, University of Turin, Italy
2 ININCA (UBA-CONICET), Buenos Aires, Argentina
3 FFUC-Faculty of Pharmacy, University of Coimbra, Portugal
4 Department of Life Sciences, Faculty of Sciences and Technology, University of Coimbra, Portugal
5 CNC-Center of Neurosciences and Cell Biology, University of Coimbra, Portugal
6 Coimbra Chemistry Center, University of Coimbra, Portugal

Molecular Imaging and Biology (2013) 15(3):307-315; DOI: 10.1007/s11307-012-0603-x

Abstract:
Purpose: This study is aimed at demonstrating the *in vivo* potential of Gd(III)-loaded glucan particles (Gd-GPs) as magnetic resonance imaging (MRI)-positive agents for labeling and tracking phagocytic cells.
Procedure: GPs were obtained from Saccharomyces cerevisae and loaded with the water-insoluble complex Gd-DOTAMA(C_{18})$_2$. The uptake kinetics of Gd-GPs by murine macrophages was studied *in vitro* and the internalization mechanism was assessed by competition assays. The *in vivo* performance of Gd-GPs was tested at 7.05 T on a mouse model of acute liver inflammation.
Results: The minimum number of Gd-GPs-labeled J774.A1 macrophages detected *in vitro* by MRI was ca. 300 cells/μl of agar, which is the lowest number ever reported for cells labeled with a positive T_1 agent. Intravenous injection of macrophages labeled with Gd-GPs in a mouse model of liver inflammation enabled the MRI visualization of the cellular infiltration in the diseased area.
Conclusions: Gd-GPs represent a promising platform for tracking macrophages by MRI as a T_1 alternative to the golden standard T_2-based iron oxide particles.

Keywords:
MRI, Gadolinium, Paramagnetic MRI agents, Glucan particles, Cell tracking

http://link.springer.com/article/10.1007%2Fs11307-012-0603-x

Supplemental Materials: **http://link.springer.com/content/esm/art:10.1007/s11307-012-0603-x/file/MediaObjects/11307_2012_603_MOESM1_ESM.pdf**

Validation and Workflow Enhancements for Three-Dimensional Luminescence Tomography

Authors:
Jacob Hesterman[1], Matthew D. Silva[1], Balázs Viszoczki[1], Tonya Coulthard[2], Rob Sandler[2], Jack Hoppin[1]

Institutions:
1 inviCRO, LLC, Boston, MA
2 Aspect Imaging, Toronto, ON, Canada

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
Introduction: Luminescence imaging remains the most prevalent *in vivo* pre-clinical imaging modality due to its high-sensitivity for detecting viable cell populations, relatively low instrument and experiment cost, capability for high-throughput experimentation, and ease of use. While 2D imaging remains the standard, increasing success has been reported with tomographic reconstructions.
The continued adoption of 3D luminescence relies on increasing the value to the scientist and experiment in four key areas:
1. Accurate localization of signal source,
2. A quantitative link between reconstructed volume radiance and cellular light output,
3. Sustained high throughput
4. Continued ease of use
Building on previous example data [1], this work employed rigorous phantom experiments to test the reconstruction performance in these areas. This work includes a series of imaging experiment using a tissue phantom to test the 3D luminescence reconstruction software LumiQuant™ (Aspect Imaging).
Goals: This work aims to test the accuracy of the reconstruction methods for
1. Source localization
2. Source size estimation
3. Multiple source object resolution
4. Correlation of the 2D signal intensity (photons/sec) to the intensity of the 3D reconstructed object.
Conclusion: Validation and ease of use are critical components to creating successful image processing tools. These encouraging phantom data are a positive sign in the validation of this 3D BLI reconstruction approach and, along with successful implementation in preclinical cancer models, highlight the future value of this tool. Future phantom and animal studies are planned to evaluate more complex signal distributions and more realistic image study designs.

MRI and NMR Study of Engineered Adipose Tissue Developed for Reconstructive Surgery

Authors:
Marc-André Fortin[1,2], Julie Fradette[3], Jean Lagueux[1], Maryse Proulx[3]

Institutions:
1 Axe endocrinilogie-néprologie, Centre hospitalier universitaire de Québec, and Centre de recherche sur les matériaux avancés (CERMA)
2 Département de Génie des mines, de la métallurgie et des matériaux, Université Laval
3 Centre LOEX de l'Université Laval, Génie tissulaire et régénération : LOEX - Centre de recherche FRSQ du Centre hospitalier affilié universitaire de Québec, and Département de Chirurgie, Faculté de Médecine, Université Laval

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
Introduction: Adipose tissue substitutes are being developed to answer the strong demand in reconstructive and plastic surgery : trauma, tumor resection, congenital or acquired anomalies (USA 2009 > 5.2 M patients[1]

- Autologous fat transplantation is widely used; however, there are significant limitations to this approach:
  - Variable rate of graft survival (volume loss)
  - Limited availability of adipose tissue reserve
- Tissue engineering is a promising alternative to address the low predictability of autologous fat transplantation
- Reconstructed adipose tissue can be fabricated from adipose-derived stromal cells, and used as substitutes in reconstructive surgery[2]
  - Volume maintenance is the key factor to measure
  - Undervascularization is strongly associated to volume loss

MRI is necessary for following-up volume retention and to confirm tissue vascularization. NMR/MRS provide fat chemical information.

Conclusions and Perspectives: Reconstructed adipose tissue is efficiently visualized with MRI, and the grafts are clearly delineated against native fat using *T1*-w.imaging and STIR

- MRI allows efficient assessment of volume maintenance over time, as well as the confirmation of vascularization (with DCE-MRI)
- In the perspective of translational studies, MRS could be used to discriminate reconstructed adipose tissue from high extracellular matrix –containing tissue (e.g. conjunctive tissue, collagen).

3D MRI-Based Histology Using Compact, High-Resolution MRI for Toxicology Applications

Authors:
Yael S Schiffenbauer[1], Catherine Brami[1], Rinat Abramovitch[2], Abraham Nyska[3] and Robert Maronpot[4]

Institution:
1 Aspect Imaging, Shoham Israel
2 Hadassah Hebrew University Medical Center, Ein Karem, Jerusalem Israel
3 Consultant in Toxicologic Pathology, Timrat and Tel Aviv University, Israel
4 Maronpot Consulting LLC, Raleigh, NC, USA

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
Background: Magnetic Resonance Imaging (MRI) is widely used in pre-clinical research and is a powerful method for *in vivo* assessment of phenotypes in murine models of disease. 3D MR-based histology (MRH)1,2 of fixed tissue specimens is gaining recognition as a technique to provide complimentary information to conventional histological techniques, as numerous digital slices from any plane of the intact sample can be acquired in 3D, quantified and then followed-up by conventional histology.
Goal: The purpose of this study was to investigate the capabilities of a new compact, high-performance 3D MR-based histology platform (M2™, Aspect Imaging) as a complementary method in toxicology studies. This imaging platform enables a technician to generate diagnostic-quality images with MRI but without prior imaging or physics experience due to the pre-programmed imaging protocols for toxicology applications. The system is also self-shielded allowing for its ease of installation and operation.
Conclusions: We have demonstrated the utility of compact, high-performance MRI and 3D MR-based histology as valuable tools to complement conventional toxicological studies. While *in vivo* MRI provides invaluable functional, morphological and quantitative information of disease progression and regression by non-invasively imaging the same animals over time, non destructive *ex vivo* MRI provides high throughput and high-resolution 3D digital data sets of intact organs, with exquisite morphological and quantitative information. With a high degree of correlation to conventional H&E, 3D MR-based histology can provide both additional insights into disease pathology as well as directing conventional histology to ensure key targets are fully assessed, considered and calculated in toxicological work-ups.

MRI and NMR study of engineered adipose tissues developed for reconstructive surgery

Authors:
Marc-Andre Fortin[1,3], Jean Lagueux[3], Maryse Proulx[2,4], Julie Fradette[2,4]

Institutions:
1 Génie des MInes, Métallurgie et Matériaux, Universite Laval, Canada
2 Chirurgie, Université Laval, Canada
3 Axe Métabolisme, Santé Vasculaire et Rénale, CHUQ, Canada
4 LOEX, CHA-U.Laval, Canada

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
Introduction: Adipose tissue substitutes are being developed as promising alternatives to autologous grafts, to answer the strong demand in reconstructive and plastic surgery (1) Trauma, tumour resection, congenital or acquired anomalies are the main causes justifying the need for such substitutes. Once developed *in vitro*, the adipose tissue grafts must be implanted *in vivo*, and their volume retention, vascularisation, as well as 1H spectroscopic properties, assessed by MR imaging. These are crucial for the development of future clinical implantation follow-up studies as well as for planning MRS studies. The characteristics of adipose grafts were studied *in vitro* with NMR, then *in vivo* in rodents at 1 Tesla MRI.
Methods: Reconstructed adipose grafts were developed with adipose-derived stem/stromal cells extracted from lipoaspirated subcutaneous tissue of a female donor (1). The endogenous production of extracellular matrix components was stimulated *in vitro*, leading to matrix deposition in the form of cell sheets which can be by lifted from culture plates with forceps and superimposed to create thicker tissues (~125mm3). Each one of these tissues was analysed in 1H-NMR (60 MHz) to quantify the water-to-lipid ratio, and also to measure T1 and T2 of each peak. The grafts were then subcutaneously implanted on the flanks of athymic mice. Native human and murine fat grafts were also implanted in animals, as well as reconstructed connective tissue grown without adipocytes. A 1T-MRI procedure was designed to scan animals (t = 0, 7, 14, 21 days) using T1-w. 2D SE (graft volume quantification), short-tau IR (fat signal nulling), as well as a rapid gradient IR sequence (for T1 maps). Finally, the blood volume in grafts was measured by DCE-MRI using a blood pool contrast agent (Gadomer).
Results: For reconstructed adipose tissues and for grafted native fat, NMR scans (Figure SI1) revealed the presence of two major proton populations (4.7 ppm: water; 0.9 – 2.24 ppm for 1H bound to lipids). For connective tissue, there was no major peak associated to lipids; strong indications of extracellular matrix were found (3.2 – 4.8: proteoglycans, hyaluronic acid, collagen), correlating with the weak signal in T1-w. MRI (Figure 1). A strong correlation was found between the fat content (0.9 – 2.24 NMR peak), and the brightness of T1-w. imaged tissues (Figure 1). The grafts were successfully visualised at 1 T MRI over a period of 21 days, and the delineation of the grafts allowed for the precise measurement of volumes over time. Short-Tau IR images (TI : 115 ms) were used to allow the delineation of adipose grafts from the host native fat (Figure SI2). DCE MRI indicated the vascularisation of adipose tissues at day 14 and 21 post-implantation.
Conclusion: Adipose tissues were successfully implanted in athymic mice, and the volume retention and remodeling over time, measured. IR procedures could be used to differentiate reconstructed tissues from the native fat. The tissues were vascularised by day 14, which is essential to achieve viable grafts. Finally, NMR data confirmed the strong potential of these grafts for MRS. REF.: 1) Vermette et al., Biomaterials 2007.

DCE-MRI evaluation of an antiangiogenic DNA-based vaccine treatment comparing two image analysis methods

Authors:
Dario L. Longo[1,3], Miklos Espak[1], Walter Dastrù[1,3], Lorena Consolino[1], Maddalena Arigoni[2], Giuseppina Barutello[2], Stefania Lanzardo[2], Federica Cavallo[2], Silvio Aime[1,3]

Institutions:
1 Department of Chemistry, University of Turin, Italy
2 Department of Clinical and Biological Sciences, University of Turin, Italy
3 Molecular Imaging Center, University of Turin, Italy

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
DCE-MRI is a non-invasive imaging technique sensitive to differences in blood volume and vascular permeability, currently used in phase I clinical trials as a potential biomarker for characterizing the tumour response to antiangiogenic treatment. Several studies have shown that reliable assessments of therapy response can only be attained if macromolecular contrast agents are used. In this context, we recently have shown the advantage of combining HSA-bound Gd-complexes with a 1 Tesla scanner [1] to evaluate the permeability changes following a new DNA-based vaccine therapy [2]. As the employed image analysis method has a considerable influence on the derived parameters, herein we compare quantitative and semiquantitative procedures to measure the response to the vascular changes induced by the vaccine, taking into account the spatial heterogeneity of the tumour. BALB/c mice were subcutaneously injected with TUBO carcinoma cells and vaccinated at 4 mm tumor mean diameter and 9 days after with empty pcDNA3 plasmid or with plasmid coding for human p80 Amot. MR images were acquired with an Aspect MRI scanner at 1.0 Tesla before and after the second treatment. Six animals per group undergone DCE-MRI protocol by injecting B22956/1, a protein-binding Gd-based CA, into the tail vein at a dose of 0.05 mmol/kg. After acquisition, raw DCE-MRI data were analyzed by two methods: i) a semi-quantitative analysis was applied to fit the shape of the time-intensity curve of the enhanced pixels. Five readout terms (peak, slope, washout, clearance, AUC) were determined; ii) the pharmacokinetic Tofts model was implemented by an in-house C++ developed software, with a completely automatic procedure to extract the AIF and the kinetic parameters (Ktrans, Kep, Vep) from a twocompartments model. An unpaired two-tailed t-test was used to compare delta values of the parameters extracted from the two methods between the control and the treated group, clustering the entire tumour volume in three groups, according to the contrast enhancement. The good contrast between rich and poor vascularised regions inside the tumours was used to cluster pixels in three groups, allowing to detect the heterogeneity of the tumour. For the quantitative method, significant changes in Ktrans were observed after the vaccine treatment (ΔKtrans = 448.1% and 33.2% $p<0.05$ for amot and PcDNA3, respectively) for pixels belonging to high enhancement regions and in Vep (ΔVep = 157.6 ±61.6 % and -2.9% ±20.4 $p<0.05$ for amot and PcDNA3, respectively) for medium enhancing regions. For the semi-quantitative method, significant changes were observed in the peak parameter (Δpeak = 12.1 ±11.4 % and -24.4% ±10.8 $p<0.05$) both in high and medium regions, in the slope parameter (Δslope = 45.2 ±17.4 % and -34.1% ±9.7 $p<0.01$) and in the washout parameter (Δwashout = -12.1 ±6.1 % and +12.5% ±5.5 $p<0.01$) for medium enhancing regions (Fig. 1). The information provided by the two approaches are complementary and show a good correlation, allowing to assess the basic determinants of the physiological changes induced by the antiangiogenic therapy.

MM-DX-929: A novel 64Cu-liposomal PET agent for predicting antitumor treatment response to immunoliposomal chemotherapeutics

Authors:
Helen Lee[1], Jinzi Zheng[2], Daniel F. Gaddy[1], Dmitri Kirpotin[1], Michael Dunne[2], Christine Allen[2,3], David A. Jaffray[2], Bart Hendriks[1], Thomas Wickham[1]

Institutions:
1 Merrimack Pharmaceuticals, Boston, MA, USA
2 STTARR Innovation Center, Radiation Medicine Program, Princess Margaret Hospital / University Health Network, Canada
3 Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada.

Poster: From World Molecular Imaging Congress (WMIC) 2013, Georgia, USA

Abstract:
Background: Nanoparticle-based drug delivery systems, such as liposomes, are known to accumulate in tumors via the enhanced permeability and retention effect (EPR), or passive targeting. Previous studies have reported that tumor uptake of 111In-labeled liposomes is highly variable among patients. Further, imaging iodine-containing liposomes with mammography has shown liposome deposition to be predictive of response to liposomal doxorubicin (Karathanasis et al., 2009, PMID 19188313). Variability in the deposition of liposomal therapeutics within tumors leads to differences in drug exposure, thereby directly influencing tumor response to liposomal drugs. It is hypothesized that the relationship between deposition and tumor response would also hold for antibody-targeted liposomes, such as MM-302 (HER2-targeted liposomal doxorubicin, currently in clinical development) and be detectable using other imaging modalities. *Objectives:* MM-DX-929 is a novel and clinically-implementable 64Cu-liposomal PET contrast agent. The current study aims to demonstrate that the extent of tumor uptake of MM-DX-929 is predictive of tumor response to MM-302 in a mouse xenograft tumor model. Methods: Mice bearing BT474-M3 mammary tumors (n=10) were injected intravenously with MM-DX-929 prior to MM-302 treatment. PET (Focus 220, Siemens)/CT (Locus Ultra, GE) imaging was performed at 16h post MM-DX-929 injection, and tumor uptake (% i.d./g) of MM-DX-929 was determined from the PET data set (Figure 1a). The mice were then treated with MM-302 (q7d) for 3 weeks at 3 mg/kg. Response to MM-302 treatment was quantified as tumor volume changes measured over a 2-month period by MRI (M2, Aspect Imaging).
Results: Tumor deposition of MM-DX-929 was found to range between 3-6 % i.d./g, which is comparable to tumor uptake levels of MM-302. Tumor deposition of MM-DX-929 correlates with treatment response to MM-302 (Figure 1b, Spearman correlation coefficient of -0.891 and a p-value of 0.0004). Specifically, increased MM-DX-929 accumulation in tumors predicted improved tumor growth inhibition following MM-302 treatment.
Conclusion: These findings support the use of MM-DX-929 as a predictive imaging contrast agent to select patients that are most likely to respond to liposomal therapies.

Manganese-impregnated mesoporous silica nanoparticles for signal enhancement in MRI cell labelling studies

Authors:

Rémy Guillet-Nicolas[a,b], Myriam Laprise-Pelletier[b,c,d], Mahesh M. Nair[a,b], Pascale Chevallier[d], Jean Lagueux[d], Yves Gossuin[e], Sophie Laurent[f], Freddy Kleitz[a,b]*, and Marc-André Fortin[b,c,d]*

Institutions:

a Département de chimie, Université Laval
b Centre de recherche sur les matériaux avancés (CERMA), Université Laval
c Département de génie des mines, de la métallurgie et des matériaux, Université Laval
d Axe Médecine Régénératrice, Centre de recherche du Centre hospitalier universitaire de Québec (AMSVR-CRCHUQ)
e Service de physique expérimentale et biologique, Université de Mons
f Service de chimie générale, organique et biomédicale, Université de Mons

Nanoscale. 2013 Dec 7; 5(23):11499-511. doi: 10.1039/c3nr02969g. Epub 2013 Oct 31.

Abstract:

Mesoporous silica nanoparticles (MSNs) are used in drug delivery and cell tracking applications. As Mn(2+) is already implemented as a "positive" cell contrast agent in preclinical imaging procedures (in the form of MnCl2 for neurological studies), the introduction of Mn in the porous network of MSNs would allow labelling cells and tracking them using MRI. These particles are in general internalized in endosomes, an acidic environment with high saline concentration. In addition, the available MSN porosity could also serve as a carrier to deliver medical/therapeutic substances through the labelled cells. In the present study, manganese oxide was introduced in the porous network of MCM-48 silica nanoparticles (Mn-M48SNs). The particles exhibit a narrow size distribution (~140 nm diam.) and high porosity (~60% vol.), which was validated after insertion of Mn. The resulting Mn-M48SNs were characterized by TEM, N2 physisorption, and XRD. Evidence was found with H2-TPR, and XPS characterization, that Mn(II) is the main oxidation state of the paramagnetic species after suspension in water, most probably in the form of Mn-OOH. The colloidal stability as a function of time was confirmed by DLS in water, acetate buffer and cell culture medium. In NMR data, no significant evidence of Mn(2+) leaching was found in Mn-M48SNs in acidic water (pH 6), up to 96 hours after suspension. High longitudinal relaxivity values of r1 = 8.4 mM(-1) s(-1) were measured at 60 MHz and 37 °C, with the lowest relaxometric ratios (r2/r1 = 2) reported to date for a Mn-MSN system. Leukaemia cells (P388) were labelled with Mn-M48SNs and nanoparticle cell internalization was confirmed by TEM. Finally, MRI contrast enhancement provided by cell labelling with escalated incubation concentrations of Mn-M48SNs was quantified at 1 T. This study confirmed the possibility of efficiently confining Mn into M48SNs using incipient wetness, while maintaining an open porosity and relatively high pore volume. Because these Mn-labelled M48SNs express strong "positive" contrast media properties at low concentrations, they are potentially applicable for cell tracking and drug delivery methodologies.

http://www.ncbi.nlm.nih.gov/pubmed/24178890

Supplemental Materials: **http://www.rsc.org/suppdata/nr/c3/c3nr02969g/c3nr02969g.pdf**

High Relaxivities and Strong Vascular Signal Enhancement for $NaGdF_4$ Nanoparticles Designed for Dual MR/Optical Imaging

Authors:
Rafik Naccache[1], Pascale Chevallier[3], Jean Lagueux[3], Yves Gossuin[4], Sophie Laurent[5], Luce Vander Elst[5], Cornelia Chilian[6], John A. Capobianco[1],* and Marc-André Fortin[2] *

Institutions:
1 Department of Chemistry and Biochemistry and Centre for NanoScience Research, Concordia University
2 Centre de recherche du Centre hospitalier universitaire de Québec (CR-CHUQ), Département de génie des mines de la métallurgie et des matériaux and Centre de recherche sur les matériaux avancés (CERMA), Université Laval
3 Centre de recherche du Centre hospitalier universitaire de Québec (CR-CHUQ)
4 Service de physique expérimentale et biologique, Université de Mons
5 Service de chimie générale organique et biomédicale, Université de Mons
6 Ecole Polytechnique de Montréal

Advanced Healthcare Materials 2013, Volume 2, Issue 11, pg. 1478-1488; DOI: 10.1002/adhm.201300060

Abstract:
Near-infrared (NIR)-to-NIR upconverting NaY(Gd)F 4 :Tm 3 + ,Yb 3 + paramagnetic nanoparticles (NPs) are efficiently detected by NIR imaging techniques. As they contain Gd 3 + ions, they also provide efficient "positive" contrast in magnetic resonance imaging (MRI). Water-dispersible small (≈ 25 nm, "S-") and ultrasmall (< 5 nm diam., "US-") NaY(Gd)F 4 :Tm 3 + ,Yb 3 + NPs are synthesized by thermal decomposition and capped with citrate. The surface of citrate-coated US-NPs shows sodium depletion and high Gd elemental ratios, as confirmed by a comparative X-ray photoelectron spectroscopy (XPS)/neutron absorption analysis study. US-NaGd 0.745 F 4 :Tm 0.005 ,Y b0.25 NPs have hydrodynamic diameters close to that measured by TEM, with the lowest relaxometric ratios (*r* 2 / *r* 1 = 1.18) reported for NaGdF 4 nanoparticle suspensions (*r* 1 = 3.37 mM −1 s −1 at 1.4 T and 37°C). Strong relaxivity peaks in the range of 20 (0.47 T) - 300 MHz (7.05 T) are revealed in nuclear magnetic resonance dispersion profiles, with high *r* 2 / *r* 1 ratios at increasing field strengths for S-NPs. This indicates the superiority of US-NPs over S-NPs for achieving high positive contrast at clinical MRI field strengths. I.-v. injected citrate-coated US-NPs evidence long blood retention times (> 90 min) in mice. Biodistribution studies (48 h, 8 d) show elimination through the reticuloendothelial and urinary systems, similarly to other citrate-capped US-NP systems. In summary, upconverting NaY(Gd)F 4 :Tm 3 + ,Yb 3 + nanoparticles have promising luminescent, relaxometric and blood-retention properties for dual MRI/optical imaging.

Keywords:
magnetic resonance imaging; neutron activation analysis; relaxometry of paramagnetic contrast agents; sodium gadolinium fluoride; upconverting nanoparticles

http://www.ncbi.nlm.nih.gov/pubmed/24574195

A Carborane-Derivative "Click" Reaction under Heterogeneous Conditions for the Synthesis of a Promising Lipophilic MRI/GdBNCT Agent**

Authors:
Antonio Toppino[a], Maria Elena Bova[a], Simonetta Geninatti Crich[a], Diego Alberti[a], Eliano Diana[a], Alessandro Barge[b], Silvio Aime[a], Paolo Venturello[a], and Annamaria Deagostino[a]*

Institutions:
a Dipartimento di Chimica, Università degli Studi di Torino, Italy
b Dipartimento di Scienza e Tecnologia del Farmaco Università degli Studi di Torino, Italy

** MRI = magnetic resonance imaging; BNCT = boron neutron-capture therapy

Chemistry. 2013 Jan 7;19(2):721-8. doi: 10.1002/chem.201201634

Abstract:
In this study, the Huisgen reaction has been used to functionalise a carborane cage with a lipophilic moiety and a 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) ligand to obtain a new Gd boron neutron-capture therapy (BNCT)/magnetic resonance imaging (MRI) agent. The introduction of the triazole units has been accomplished under both heterogeneous conditions, by the use of a Cu-supported ionic-liquid catalyst, and homogeneous conditions. The ability of the Gd complex of the synthesised ligand to form stable adducts with low-density lipoproteins (LDLs) has been evaluated and then MRI has been performed on tumour melanoma cells incubated in the presence of a Gd-complex/LDL imaging probe. It has been concluded that the high amount of intracellular boron necessary to perform BNCT can be reached even in the presence of a relatively low-boron-containing LDL concentration.

Keywords:
Carboranes, click chemistry, cycloaddition, heterogeneous, catalysis, magnetic resonance imaging

http://www.ncbi.nlm.nih.gov/pubmed/23154917

High-Gd-Payload P22 protein cage nanoparticles for imaging vascular inflammation

Author:
Hisanori Kosuge[1]*, Masaki Uchida[2], Janice Lucon[2], Shefah Qazi[2], Trevor Douglas[2], Michael V McConnell[1]

Institution:
1 Stanford University, USA
2 Montana State University, USA

Journal of Cardiovascular Magnetic Resonance, 2013, 15(Suppl 1):O66; DOI 10.1186/1532-429X-15-S1-O66

Abstract:
The bacteriophage P22 protein cage can be bioengineered to contain a high-relaxivity gadolinium (Gd) payload internally and targeting ligands externally. It also enables phage-library-based identification of novel targets. Thus, P22 may have advantages for molecular/cellular imaging by MRI. Low dose P22-polymer-Gd showed strong enhancement for 1T vascular MRA (Figure 2). It also showed clear enhancement of the aortic wall (ApoE-/-) and ligated carotid (FVB) at 3T (Figure 3). *Ex vivo* fluorescence imaging showed the accumulation of both RGD+P22 or RGD-P22 in atherosclerotic lesions (Figure 4). RDG targeting enhanced plaque uptake (RGD+P22: 0.025 ± 0.002 counts/sec vs. RGD-P22: 0.005 ± 0.004 counts/sec, p=0.05).

Keywords:
Vascular, Inflammation, Atherosclerosis, Mice

http://link.springer.com/article/10.1186%2F1532-429X-15-S1-O66

Nanostructures based on monoolein or diolein and amphiphilic gadolinium complexes as MRI contrast agents

Authors:
Antonella Accardo[a], Eliana Gianolio[b], Francesca Arena[b], Sabine Barnert[c], Rolf Schubert[c], Diego Tesauro[a] and Giancarlo Morelli[a]*

Institutions:
a CIRPeB, Department of Pharmacy & IBB CNR, University of Naples "Federico II", Italy
b Department of Chemistry I.F.M. & Molecular Imaging Centre, University of Turin, Italy
c Department of Pharmaceutical Technology and Biopharmacy, University of Freiburg, Germany

Journal of Materials Chemistry B, 2013, 1, 617-628; DOI: 10.1039/c2tb00329e

Abstract:
Highly ordered two or three dimensional mesophases in aqueous solution could be usefully obtained by using monoolein (MO) or diolein (DO) monomers. Nanostructures (also indicated as nanoparticles, NPs) of MO or DO containing different amounts (1%, 5%, 10% and 20%) of the synthetic amphiphilic gadolinium complex (C18)2DTPA(Gd) have been prepared and characterized for their relaxometric and structural behaviors. The nanostructure is found in the 110–200 nm range for all investigated systems, while the presence of the gadolinium containing monomer produces a partial loss of the cubic symmetry, as shown by Cryo-TEM images of NPs doped with 10% w/w of (C18)2DTPA(Gd). Gadolinium containing nanostructures display high relaxivity values (in the 10–15 mM_1 s_1 range at 25_ and 20 MHz, with a further increase at 37 _C for DO based NPs), and interesting relaxometric properties for their possible use as MRI contrast agents. NPs containing 10% w/w of (C18)2DTPA(Gd) (MO3-NPs and DO3-NPs) have been also derivatized by introducing 3% wt of (C18)2–Peg3000–FA to obtain targeted aggregates (MO3-NP–FA, DO3-NP–FA). A preferential uptake efficiency of DO3-NP–FA in IGROV-1 cells with respect to DO-NPs without folic acid is observed, especially when cells are incubated with low concentrations of nanostructures or at short incubation times, thus indicating its potential use as a target-selective delivery system for MRI contrast agents on tumor cells overexpressing the folate receptor.

http://pubs.rsc.org/en/content/articlelanding/2013/tb/c2tb00329e

A co-clinical approach identifies mechanisms and potential therapies for androgen deprivation resistance in prostate cancer

Authors:

Andrea Lunardi[1], Ugo Ala[1,2], Mirjam T Epping[1], Leonardo Salmena[1,3,4], John G Clohessy[1,3,4], Kaitlyn A Webster[1], Guocan Wang[1,3–5], Roberta Mazzucchelli[6], Maristella Bianconi[7], Edward C Stack[8–10], Rosina Lis[8,9], Akash Patnaik[11], Lewis C Cantley[12,13], Glenn Bubley[11], Carlos Cordon-Cardo[14], William L Gerald[4], Rodolfo Montironi[6], Sabina Signoretti[9,10], Massimo Loda[8,9,15], Caterina Nardella[1,3,4,16] & Pier Paolo Pandolfi[1,3,4]

Institutions:

1 Cancer Genetics Program, Beth Israel Deaconess Cancer Center, Department of Medicine and Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School
2 Department of Genetics, Biology and Biochemistry, Molecular Biotechnology Center, University of Turin
3 Cancer Biology and Genetics Program, Sloan-Kettering Institute, Memorial Sloan-Kettering Cancer Center
4 Department of Pathology, Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center
5 Biochemistry, Cell & Molecular Biology Program, Weill Graduate School of Medical Sciences, Cornell University
6 Institute of Pathological Anatomy and Histopathology, Polytechnic University of the Marche Region (Ancona), United Hospitals, Ancona, Italy
7 Clinic of Oncology, Postgraduate School in Medical Oncology, Polytechnic University of the Marche Region (Ancona), United Hospitals, Ancona, Italy
8 Center for Molecular Oncologic Pathology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
9 Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School
10 Department of Pathology, Brigham and Women's Hospital, Harvard Medical School
11 Division of Hematology/Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School
12 Department of Systems Biology, Harvard Medical School
13 Division of Signal Transduction, Beth Israel Deaconess Medical Center
14 Department of Genetics and Genomic Sciences, The Mount Sinai School of Medicine
15 Broad Institute of Harvard and MIT
16 Preclinical Murine Pharmacogenetics Facility, Beth Israel Deaconess Medical Center, Harvard Medical School

Nature Genetics (2013), Volume: 45, Pg: 747–755. doi:10.1038/ng.2650

Abstract:

Here we report an integrated analysis that leverages data from treatment of genetic mouse models of prostate cancer along with clinical data from patients to elucidate new mechanisms of castration resistance. We show that castration counteracts tumor progression in a *Pten* loss–driven mouse model of prostate cancer through the induction of apoptosis and proliferation block. Conversely, this response is bypassed with deletion of either *Trp53* or *Zbtb7a* together with *Pten*, leading to the development of castration-resistant prostate cancer (CRPC). Mechanistically, the integrated acquisition of data from mouse models and patients identifies the expression patterns of XAF1, XIAP and SRD5A1 as a predictive and actionable signature for CRPC. Notably, we show that combined inhibition of XIAP, SRD5A1 and AR pathways overcomes castration resistance. Thus, our co-clinical approach facilitates the stratification of patients and the development of tailored and innovative therapeutic treatments.

http://www.nature.com/ng/journal/v45/n7/full/ng.2650.html

Gd-DTPA-loaded polymer-metal complex micelles with high relaxivity for MR cancer imaging

Authors:
Peng Mi[a], Horacio Cabral[a], Daisuke Kokuryo[b], Mohammad Rafi[c], Yasuko Terada[d], Ichio Aoki[b], Tsuneo Saga[b], Ishii Takehiko[a], Nobuhiro Nishiyama[c]**, Kazunori Kataoka[a,c,e]*

Institutions:
a Department of Bioengineering, Graduate School of Engineering, The University of Tokyo
b Molecular Imaging Center, National Institute of Radiological Sciences
c Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo
d SPring 8, JASRI
e Department of Materials Engineering, Graduate School of Engineering, The University of Tokyo

Biomaterials. 2013 Jan;34(2):492-500. doi: 10.1016/j.biomaterials.2012.09.030. Epub 2012 Oct 8.

Abstract:
Nanodevices for magnetic resonance imaging of cancer were self-assembled to coreeshell micellar structures by metal complex formation of K2PtCl6 with diethylenetriaminepentaacetic acid gadolinium (III) dihydrogen (Gd-DTPA), a T1-contrast agent, and poly(ethylene glycol)-b-poly{N-[N0-(2-aminoethyl)-2-aminoethyl]aspartamide} (PEG-b-PAsp(DET)) copolymer in aqueous solution. Gd-DTPA-loaded polymeric micelles (Gd-DTPA/m) showed a hydrodynamic diameter of 45 nm and a core size of 22 nm. Confining Gd-DTPA inside the core of the micelles increased the relaxivity of Gd-DTPA more than 13 times (48 mM (-1) (s-1)). In physiological conditions Gd-DTPA/m sustainedly released Gd-DTPA, while the Pt(IV) complexes remain bound to the polymer. Gd-DTPA/m extended the circulation time in plasma and augmented the tumor accumulation of Gd-DTPA leading to successful contrast enhancement of solid tumors. m-synchrotron radiation-X-ray fluorescence results confirmed that Gd-DTPAwas delivered to the tumor site by the micelles. Our study provides a facile strategy for incorporating contrast agents, dyes and bioactive molecules into nanodevices for developing safe and efficient drug carriers for clinical application.

Keywords:
Micelles; Drug delivery; Magnetic resonance imaging (MRI); Polymer-metal complex; Cancer diagnosis

http://www.ncbi.nlm.nih.gov/pubmed/23059004

3D MRI-Based Histology Using Compact, High-Resolution MRI

Authors:
Yael S. Schiffenbauer[1], Catherine Brami[1], Rinat Abramovitch[2], Abraham Nyska[3], Robert Maronpot[4]

Institutions:
1 Aspect Imaging, Shoham Israel
2 Hadassah Hebrew University Medical Center, Ein Karem, Jerusalem, Israel
3 Consultant in Toxicologic Pathology, Timrat, and Tel Aviv University, Israel
4 Maronpot Consulting, LLC, Raleigh, NC, USA

Poster: From Society of Toxicology (SOT) ToxExpo 2013, San Antonio, TX

Abstract:
Background: Magnetic Resonance Imaging (MRI) is widely used in pre-clinical research and is a powerful method for *in vivo* assessment of phenotypes in murine models of disease. 3D MR-based histology (MRH) (Johnson et al (1,2)) of fixed tissue specimens is gaining recognition as a technique to provide complimentary information to conventional histological techniques, as numerous digital slices from any plane of the intact sample can be acquired in 3D, quantified and then followed-up by conventional histology.
Goal: The purpose of this study was to investigate the capabilities of a new compact, high-performance 3D MR-based histology platform (M2™, Aspect Imaging) as a complementary method in toxicology studies. This imaging platform enables a technician to generate diagnostic-quality images with MRI but without prior imaging or physics experience due to the pre-programmed imaging protocols for toxicology applications. The system is also self-shielded allowing for its ease of installation and operation. Biological Model: Murine Acute Kidney Injury (AKI): Acute kidney injury (AKI) was induced in CB6F1 mice by intra-muscular injection of glycerol, producing abrupt rhabdomyolysis. Rhabdomyolysis is the breakdown of the skeletal muscle resulting in the release of the muscle fiber contents, including myoglobin, into the blood stream. The release of such content is associated with rapidly progressive renal dysfunction.
Methods: Renal morphology and cortico-medullary differentiation were evaluated over time *in vivo* in the same animals over 15 days using a compact MRI scanner (M2™ 3D MR-based histology system, Aspect Imaging) equipped with a 35 mm RF coil. Blood was collected for urea test in serum. Renal function was assessed by iv administration of Gd-DTPA, a standard MRI contrast agent. A few animals were sacrificed at the peak of disease and kidneys were removed and fixed in formalin. High-resolution 3D MR-based histology of the extracted kidneys was performed using a 10mm RF coil on the same compact MRI platform followed by H&E and further immunostained for apoptosis (TUNEL).
Conclusions: We have demonstrated the utility of compact, high-performance MRI and 3D MR-based histology (MRH) as valuable tools to complement conventional toxicological studies. While *in vivo* MRI provides invaluable functional, morphological and quantitative information of disease progression and regression by non-invasively imaging the same animals over time, non-destructive *ex vivo* MRI provides high throughput and high-resolution 3D digital data sets of intact organs, with exquisite morphological and quantitative information. With a high degree of correlation to conventional H&E, 3D MR-based histology can provide both additional insights into disease pathology as well as directing conventional histology to ensure key targets are fully assessed, considered and calculated in toxicological work-ups.

Fluorochrome-Functionalized Nanoparticles for Imaging DNA in Biological Systems

Authors:
Hoonsung Cho[1], David Alcantara[2], Hushan Yuan[1], Rahul A. Sheth[3], Howard H. Chen[4], Peng Huang[5], Sean B. Andersson[5, 6], David E. Sosnovik[4], Umar Mahmood[1,3], and Lee Josephson[1,4*]

Institutions:
1 Center for Translational Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital
2 Instituto de Nanociencia de Aragon, Universidad de Zaragoza
3 Division of Nuclear Medicine & Molecular Imaging, Department of Radiology, Massachusetts General Hospital
4 Martinos Center for Biomedical Imaging, Massachusetts General Hospital
5 Department of Mechanical Engineering, Boston University
6 Division of Systems Engineering, Boston University

ACS Nano, 2013, *7* (3), pp 2032–2041; DOI: 10.1021/nn305962n

Abstract:
Attaching DNA binding fluorochromes to nanoparticles (NPs) provides a way of obtaining NPs that bind to DNA through fluorochrome mediated interactions. To obtain a nanoparticle (NP) that bound to the DNA in biological systems, we attached the DNA binding fluorochrome, TOPRO 1 (TO), to the surface of the Feraheme (FH) NP, to obtain a fluorochrome functionalized. NP denoted TO-FH. When reacted with DNA *in vitro*, TO-FH formed microaggregates that were characterized by fluorescence, light scattering and T2 changes. The formation of DNA/TOFH microaggregates was also characterized by AFM, with microaggregates exhibiting a median size of 200 nm, and consisting of DNA and multiple TO-FH NP's whose individual diameters were only 25-35 nm. TO-FH failed to bind normal cells in culture, but treatment with chemotherapeutic agents or detergents yielded necrotic cells that bound TO-FH and vital fluorochromes similarly. The uptake of TO-FH by HT-29 xenografts (treated with 5-FU and oxaliplatin) was evident by surface fluorescence and MRI. Attaching multiple DNA binding fluorochromes to magnetic nanoparticles provides a way of generating DNA binding NP's that can be used to detect DNA detection by microaggregate formation *in vitro*, for imaging the DNA of necrotic cells in culture, and for imaging the DNA of a tumor treated with a chemotherapeutic agent. Fluorochrome functionalized NP's are a multimodal (magnetic and fluorescent), highlymultivalent (n~ 10 fluorochromes/NP) nanomaterials useful for imaging the DNA of biologicalsystems.

Keywords:
DNA; imaging; nanoparticle; fluorochrome; biosensing

http://pubs.acs.org/doi/abs/10.1021/nn305962n

Intracellular Aggregation of Multimodal Silica Nanoparticles for Ultrasound-Guided Stem Cell Implantation

Authors:
Jesse V. Jokerst[1], Christine Khademi[1], and Sanjiv S. Gambhir[1,2]*

Institutions:
1 Molecular Imaging Program at Stanford, Department of Radiology, Stanford University
2 Bioengineering, Materials Science and Engineering, Bio-X, Stanford University

Science Translational Medicine 20 March 2013: Vol. 5, Issue 177, p. 177ra35;
DOI:10.1126/scitranslmed.3005228

Abstract:
The promises of cardiac stem cell therapy have yet to be fully realized, in part because of poor survival and engraftment efficacy of implanted cells. Cells die after implantation owing to ischemia, inflammation, immune response, as well as mis-injection or implantation into fibrotic tissue. Imaging tools can help implant cells in areas of the heart most receptive to stem cell therapy and monitor the efficacy of treatment by reporting the viability, location, and number of implanted stem cells. We describe a multimodal, silica-based nanoparticle that can be used for cell sorting (fluorescence), real-time guided cell implantation ultrasound, and high-resolution, long-term monitoring by magnetic resonance imaging (MRI). The nanoparticle agent increased the ultrasound and MRI contrast of labeled human mesenchymal stem cells (hMSCs) 700 and 200% versus unlabeled cells, respectively, and allowed cell imaging in animal models for 13 days after implantation. The agent had no significant impact on hMSC cell metabolic activity, proliferation, or pluripotency, and it increased the production of many paracrine factors implicated in cardiac repair. Electron microscopy and ultrasound imaging suggest that the mechanism of action is *in vivo* aggregation of the 300-nm silica nanoparticles into larger silica frameworks that amplify the ultrasound backscatter. The detection limit in cardiac tissue was 250,000 hMSCs via MRI and 70,000 via ultrasound. This ultrasound-guided cell delivery and multimodal optical/ultrasound/MRI intracardiac cell-tracking platform could improve cell therapy in the clinic by minimizing misdelivery or implantation into fibrotic tissue.

http://stm.sciencemag.org/content/5/177/177ra35.abstract

Synthesis and Relaxometric Characterization of a MRI Gd-based probe responsive to Glutamic Acid Decarboxylase enzymatic activity

Authors:
Roberta Napolitano[1], Giorgio Pariani[1], Franco Fedeli[1], Zsolt Baranyai[2], Markus Aswendt[3], Silvio Aime[1] and Eliana Gianolio[1]*

Institutions:
1 Department of Molecular Biotechnologies and Health Sciences and Molecular Imaging Center, University of Torino, Italy
2 Department of Inorganic and Analytical Chemistry, Debrecen University, Hungary
3 Max-Planck-Institute for Neurological Research, In-vivo-NMR Laboratory, Germany

J Med Chem. 2013 Mar 28;56(6):2466-77. doi: 10.1021/jm301831f. Epub 2013 Mar 15.

Abstract:
Novel contrast agent based systems, which selectively visualize specific cells, e.g. neurons in the brain, would be of substantial importance for the fast developing field of molecular magnetic resonance imaging (MRI). We report here the synthesis and *in vitro* validation of a Gd(III)-based contrast agent designed to act as MRI responsive probe for imaging the activity of the enzyme Glutamic acid decarboxylase (GAD) present in neurons. Upon the action of the enzyme, the Gd(III) complex increases its hydration sphere and takes on a residual positive charge that promotes its binding to endogenous macromolecules. Both effects contribute in a synergic way to generate a marked relaxation enhancement, which directly reports enzyme activity and will allow activity detection of GAD positive cells *in vitro* and *in vivo* selectively.

Keywords:
Responsive Imaging Agents, Cell recognition, MRI, Glutamic Acid Decarboxylase, Gadolinium Complex

http://www.ncbi.nlm.nih.gov/pubmed/23469759

In vivo Monitoring of Tumor Response to Anti-cancer Therapy Using MRI and a Novel Caspase-3 Activatable Gadolinium Contrast Agent for Imaging Apoptosis

Authors:
Prachi Pandit[1], Deju Ye[1], Adam Shuhendler[1], Jianghong Rao[1,2], and Brian Rutt[1]

Institutions:
1 Radiology, Stanford University, United States
2 Chemistry, Stanford University, United States

Poster: From International Society of Magnetic Resonance in Medicine (ISMRM) 2013, Salt Lake City, UT

Abstract:
Introduction: Apoptosis is the natural suicide mechanism built into cells to maintain normal physiology. One of the hallmarks of cancer is the breakdown of this process, resulting in uncontrolled cell proliferation. Non-surgical cancer treatments like chemotherapy, irradiation, etc rely on the re induction of apoptosis to enable tumor regression. Apoptosis is preceded by the release of a number of caspase enzymes, one of which is caspase-3. Detection of this executor caspase enzyme signals imminent apoptosis and is an early indicator of therapy response. A number of optical imaging techniques have targeted caspase-3 for imaging apoptosis, but to the best of our knowledge, *in vivo* caspase-3 sensing by MRI has not yet been successfully demonstrated. Previously, our group reported on a novel generalized platform for activatable contrast agents based on intracellular biocompatible condensation1. These agents begin as small molecules that upon activation at the target site self-assemble to form nanoparticles. This work reports on a new generation of these agents. Here the condensation reaction is *intra-molecular cyclization*2 as opposed to *inter-molecular polymerization*3 in the previous generation. The new agents have the following two advantages making them more suitable for *in vivo* imaging for therapy response monitoring: (1) they are less susceptible to interaction with intracellular free cysteine, and (2) their activation is not concentration dependent. Here, we use a subcutaneous mouse.
Methods: All animal procedures were approved by the Stanford Institutional Animal Care and Use Committee. Figure 1(a) shows the experiment design. A cancer mouse model was established by subcutaneously injecting 1.5 million HeLa cells in the shoulders of athymic female nude mice. Pre-treatment MR images were acquired 10-14 days post-inoculation when the longest dimension in the tumor was ~ 0.8mm. This was followed by intra-tumoral doxorubicin treatment, which consisted of 2 injections (10mg/mL and 5 mg/mL, each in a 20μL volume) administered across an interval of 2 days. Post-treatment MR imaging was carried out 2 days after the second doxorubicin injection. All procedures were carried out under isofluorane anesthesia and the animals were euthanized after the final imaging session. A total of 8 mice were used in this study. MR imaging was performed on an Aspect M2 1T permanent magnet (Aspect Imaging, Shoham, Israel). Intravenous contrast injection at 0.1mmol/kg concentration was administered in a 100μL volume for every imaging session. Multi-slice (312um in-plane, 1mm slice) T1-weighted spin echo images (TE/TR = 8.9/250 ms) were acquired, one before contrast injection and then every 4 minutes up to 4 hours after contrast injection. Image analysis was carried out in ImageJ and tumor volume data were used to calculate % signal enhancement relative to pre-contrast injection image. Matlab was used to fit the contrast kinetics curves to a Weibull model: where a scales the curve along the horizontal axis, β defines the shape of the curve and γ scales the curve along the vertical axis.

Conclusion: We have developed a Gd-based caspase-activatable contrast agent that can self-assemble into nanoparticles and provide signal enhancement at apoptotic sites *in vivo*. We have tested these novel agents in a doxorubicin-treated mouse model of cancer and have shown statistically significant differences in enhancement in the same tumor before and after treatment. MRI is already a preferred modality for a variety of oncologic application due to its advantages over competing modalities, i.e. its non-invasive, nonionizing nature and excellent spatial and contrast resolution. With our probe it can now also achieve improved sensitivity and specificity, making MRI even more attractive for cancer theranostics.

Longitudinal Functional Imaging of the HER-2/NEU Transgenic Mouse Model Of Human Breast Cancer By DCE-MRI and Diffusion Weighted Imaging

Authors:
Dario Livio Longo[1,2], Lorena Consolino[1,2], Stefania Lanzardo[3], Walter Dastrù[1,2], Federica Cavallo[3], and Silvio Aime[1,2]

Institutions:
1 Dept. of Chemistry, University of Turin, Italy
2 Molecular Imaging Center, Torino, Italy
3 Dept. of Clinical and Biological Sciences, University of Turin, Italy

Poster: From International Society of Magnetic Resonance in Medicine (ISMRM) 2013, Salt Lake City, UT

Abstract:
Purpose: Breast cancer is the most frequent malignancy of woman worldwide. Features characterizing the progression of preinvasive ductal carcinoma to invasive breast cancer remain elusive, thus *in vivo* imaging methods are required to assess the longitudinal progression of mammary carcinogenesis exploiting the important framework provided by transgenic mouse model in preclinical settings [1]. DCE-MRI is an important non invasive tool which allows to asses changes in vessel permeability and perfusion with an increased sensitivity when done by using blood-pool contrast agents on a 1T MRI scanner [2]. Diffusion weighted imaging (DWI) is a MRI technique that reports on tissue cellularity. Both the techniques have been employed to study functional changes during the multistage process of mammary cancer progression in the HER-2/Neu transgenic mouse model.
Methods: BALB-neuT female mice develop spontaneous orthotopic mammary cancers through atypical ductal hyperplasia (7-14 weeks of age – stage I), ductal carcinoma in situ (14-21 weeks of age – stage II) and invasive lobular carcinoma (21-28 weeks of age –stage III). For each stage a total of 14 BALB-neuT mice and 6 BALB/c mice were selected for *in vivo* MR imaging looking at the left and right IV mammary glands. All procedures were done in accordance with the EU guidelines and with the approval of the university animal care use committee. MR images were acquired with an Aspect M2 1T MRI scanner (Aspect Magnet Technologies, Israel).After the scout image acquisition, T2w anatomical images were acquired with a Fast Spin Echo sequence. Baseline tumour T1 map was acquired by using a variable flip-angle Gradient-Echo (VFA-GRE) sequence (7 flip angles 15°-160°). DCE MRI dynamic protocol was carried out by using an axial T1w 3D spoiled Gradient Echo sequence with three initial pre-contrast images and 47 dynamic postcontrast images with the following parameters: TR/TE = 40/1.8 ms, flip angle = 60°, number of slices = 10, slice thickness = 1.5 mm, FOV = 40 mm, matrix = 128x128. The Gd-containing, Serum albumin binding contrast agent (Phenoquant, Cage Chemicals, Italy), was injected into the tail vein through a 27-gauge needle at a dose of 0.05 mmol/kg. The acquired raw DCE-MRI data were analyzed by a quantitative method implementing a two-compartment Tofts model by an in-house C++ developed software, yielding the relevant parametric maps (Ktrans, Kep, Vp). DWI images were acquired with a Spin-Echo sequence with seven b-values between 0 and 600 sec/mm2 with the same geometrical setting for DCE images. A Student t-test was used to compare mean parametric maps between BALB-neuT and BALB/c mice. Mice were euthanized and mammary glands excised, fixed in formalin and H&E stained. *Results and Discussion:* In BALB/c mice a slight overlap of Ktrans values was found in lymphnode and normal mammary gland area (Fig.1a-b). In BALB-neuT mice Ktrans values show higher values at stage II and III in lymphnodes and mammary glands. In both the healthy and transgenic mice Ktrans values of back muscle were similar (Fig. 1c). Analogous trends were observed

for Vp maps (Fig. 1d-e-f). BALB-neuT mice showed a significant increase of Ktrans values in mammary glands during Stage II and III, in comparison to Balb/c mice which showed a reduction (Ktrans = 7.0±1.1E-4 and 4.7±1.5E-4 for BALB-neuT mice at stage II and III; Ktrans = 4.3±0.2E-4 and 1.2±0.1E-4 for BALB/c mice at stage II and III). Vp values were significantly higher for BALB-neuT mice in comparison to BALB/c mice at Stage II and III. Therefore an increase of permeability/perfusion was found with the progression of mammary carcinogenesis, as well as an increase of heterogeneity of mammary glands tissues as depicted by the corresponding higher standard deviations values for BALB-neuT mice. Diffusion values were similar along the three stages for lymphnode and back muscle areas, for both the BALB/c an BALB-neuT mice (ADC =0.5±0.1E-3 and 1.4±0.2E-3 mm2/s for lymphnode and back muscle). In BALB-neuT mice a slight increase of diffusion was found at stage III (ADC = 0.4±0.1E-3 and 0.6±0.1E-3 mm2/s at stage II and stage III). Such changes may be related to the underlying morphological changes involved in the transition between pre-invasive and invasive lobular carcinoma.
Conclusions: There results provide new insights into the permeability/vascular/cellularity functional changes associated to the progression of early stage mammary cancer disease.

Nanostructured Lipid Carriers as Multifunctional Nanomedicine Platform for Pulmonary Co-Delivery of Anticancer Drugs and siRNA

Authors:
Oleh Taratula[1,2], Andriy Kuzmov[1], Milin Shah[1], Olga B. Garbuzenko[1], Tamara Minko[1,3*]

Institutions:
1 Department of Pharmaceutics, Ernest Mario School of Pharmacy
2 Department of Pharmaceutical Sciences, Oregon State University
3 The Cancer Institute of New Jersey, New Brunswick

J Control Release. 2013 May 3. pii: S0168-3659(13)00237-X

Abstract:
We developed, synthesized, and tested a multifunctional nanostructured lipid nanocarrierbased system (NLCS) for efficient delivery of an anticancer drug and siRNA directly into the lungs by inhalation. The system contains: (1) nanostructured lipid carriers (NLC); (2) anticancer drug (doxorubicin or paclitaxel); (3) siRNA targeted to MRP1 mRNA as a suppressor of pump drug resistance; (4) siRNA targeted to BCL2 mRNA as a suppressor of nonpump cellular resistance and (5) a modified synthetic analog of luteinizing hormonereleasing hormone (LHRH) as a targeting moiety specific to the receptors that are overexpressed in the plasma membrane of lung cancer cells. The NLCS was tested in vitro using human lung cancer cells and *in vivo* utilizing mouse orthotopic model of human lung cancer. After inhalation, the proposed NLCS effectively delivered its payload into lung cancer cells leaving healthy lung tissues intact and also significantly decreasing the exposure of healthy organs when compared with intravenous injection. The NLCS showed enhanced antitumor activity when compared with intravenous treatment. The data obtained demonstrated high efficiency of proposed NLCS for tumor-targeted local delivery by inhalation of anticancer drugs and mixture of siRNAs specifically to lung cancer cells and, as a result, efficient suppression of tumor growth and prevention of adverse side effects on healthy organs.

Keywords:
Nanostructured lipid carrier; orthotopic lung cancer model; inhalation; luteinizing hormone-releasing hormone (LHRH); imaging; drug resistance

http://www.ncbi.nlm.nih.gov/pubmed/23648833

Mn loaded apoferritin as an MRI sensor of melanin formation in melanoma cells

Authors:
Ibolya Szabó[1], Simonetta Geninatti Crich[1], Diego Alberti[1], Ferenc K. Kálmán[1,2] and Silvio Aime[1]*

Institutions:
1 Center for Molecular Imaging, Department of Chemistry IFM, University of Torino
2 Department of Inorganic and Analytical Chemistry, University of Debrecen, Hungary

Chemical Communications., 2012,48, 2436-2438; DOI: 10.1039/C2CC17801J

Abstract:
Mn(III)-loaded apoferritin is promptly reduced to Mn(II)–apoferritin by the oxidation of L-DOPA to melanin. The process is nicely witnessed by a marked relaxation enhancement of water proton relaxation rate that has been detected both in cultured melanoma cells and in tumor animal models.

Keywords:
apoferritin, melanin, MRI, contrast agent, melanoma

http://pubs.rsc.org/en/Content/ArticleLanding/2012/CC/c2cc17801j

An Extracellular MRI Polymeric Contrast Agent That Degrades at Physiological pH

Authors:
Eric Schopf[1], Jagadis Sankaranarayanan[1], Minnie Chan[2], Robert Mattrey[3], and Adah Almutairi[1,4]*

Institutions:
1 Skaggs School of Pharmacy and Pharmaceutical Sciences
2 Department of Chemistry, University of California at San Diego
3 Department of Radiology, University of California at San Diego
4 Department of NanoEngineering, University of California at San Diego

Molecular Pharmaceutics, 2012, 9 (7), pp 1911–1918, DOI: 10.1021/mp2005998

Abstract:
Macromolecular contrast agents have the potential to assist magnetic resonance imaging (MRI) due to their high relaxivity, but are not clinically useful because of toxicity due to poor clearance. We have prepared a biodegradable ketal-based polymer contrast agent which is designed to degrade rapidly at physiological pH by hydrolysis, facilitating renal clearance. *In vitro*, the agent degraded more rapidly at lower pH, with complete fragmentation after 24 h at pH 7.4. *In vitro* relaxivity measurements showed a direct correlation between molecular weight and relaxivity. We compared our polymer contrast agent with commercially available Magnevist *in vivo* by MRI imaging, as well as measuring the Gd concentration in blood. To measure the relaxivity of the polymers, an inversion recovery spin echo experiment was performed in an Aspect M2 (1 T field, Aspect Imaging, Shoham, Israel) with a 60 mm diameter whole body coil. Our results show that our polymer contrast agent gives a higher contrast and intensity in the same organs and areas as Magnevist and is cleared from the blood at a similar rate. We aim to improve our polymer contrast agent design to develop it for use as a MRI contrast agent, and explore its use as a platform for other imaging modalities.

Keywords:
contrast agents, polyketal, extracellular degradation, Gd(III) complexes, bioresponsive

http://pubs.acs.org/doi/abs/10.1021/mp2005998

Novel Gd(III)-based probes for MR molecular imaging of matrix metalloproteinases

Authors:
Concetta V. Gringeria[1], Valeria Menchise[2], Silvia Rizzitelli[3], Evelina Cittadino[3], Valeria Catanzaro[3], Gabriele Dati[4], Linda Chaabane[4], Giuseppe Digilio[1]* and Silvio Aime[3]

Institutions:
1 Department of Environmental and Life Sciences, Università del Piemonte
2 Institute for Biostructures and Bioimages (CNR) c/o Molecular Biotechnology Center (University of Turin)
3 Department of Chemistry IFM and Center for Molecular Imaging, University of Turin
4 San Raffaele Scientific Institute, INSPE-Division Neuroscience

Contrast Media and Molecular Imaging 2012 Mar-Apr;7(2):175-84. doi: 10.1002/cmmi.478.

Abstract:
Two novel Gd-based contrast agents (CAs) for the molecular imaging of matrix metalloproteinases (MMPs) were synthetized and characterized *in vitro* and *in vivo*. These probes were based on the PLG*LWAR peptide sequence, known to be hydrolyzed between Gly and Leu by a broad panel of MMPs. A Gd-DOTA chelate was conjugated to the N-terminal position through an amide bond, either directly to proline (compd Gd-K11) or through a hydrophilic spacer (compd Gd-K11N). Both CA were made strongly amphiphilic by conjugating an alkyl chain at the C-terminus of the peptide sequence. Gd-K11 and Gd-K11N have a good affinity for β-cyclodextrins (K(D) 310 and 670 μ m respectively) and for serum albumin (K(D) 350 and 90 μ m respectively), and can be efficiently cleaved *in vitro* at the expected site by MMP-2 and MMP-12. Upon MMP-dependent cleavage, the CAs lose the C-terminal tetrapeptide and the alkyl chain, thus undergoing to an amphiphilic-to-hydrophilic transformation that is expected to alter tissue pharmacokinetics. To prove this, Gd-K11 was systemically administered to mice bearing a subcutaneous B16.F10 melanoma, either pre-treated or not with the broad spectrum MMP inhibitor GM6001 (Ilomastat). The washout of the Gd-contrast enhancement in MR images was significantly faster for untreated subjects (displaying MMP activity) with respect to treated ones (MMP activity inhibited). The washout kinetics of Gd-contrast enhancement from the tumor microenvironment could be then interpreted in terms of the local activity of MMPs.

Keywords:
contrast agents, molecular imaging, matrix metalloproteinases (MMPs), Gd, gadolinium, MRI, melanoma

http://www.ncbi.nlm.nih.gov/pubmed/22434630

Use of Small Animal MRI and Cone-Beam CT for Image-Guided Radiotherapy of Orthotopic Cervical and Prostate Tumors in Mice

Authors:
Jinzi Zheng[1], Patricia E. Lindsay[1], Warren D. Foltz[1], Tonya Coulthard[2], David Jaffray[1]

Institutions:
1 Princess Margaret Hospital, Toronto, ON, Canada
2 Aspect Imaging, Toronto, ON, Canada

Poster: From American Association of Cancer Research (AACR) 2012, Chicago, IL
Abstract # 4060

Abstract:
Introduction: Recent developments in image-guided radiation therapy (IGRT) of small animals aim to adapt the radiation planning and delivery protocols employed in the clinical setting to preclinical investigations. Accurate and targeted delivery of radiation to the disease volume of interest is necessary for evaluation of new treatment strategies and their timely translation to the clinic. This abstract reports the feasibility of employing a 1T small animal MR scanner and a cone-beam CT (CBCT)-equipped small animal irradiator to effectively visualize and delineate orthotopically implanted tumors on the treatment bed prior to targeted radiotherapy.
Methods: Five male nude mice bearing an orthotopically implanted prostate tumor (DU145 and 22Rv1) and 10 female SCID mice bearing an orthotopically implanted cervical tumor (ME-180) were positioned on a transportable multimodality imaging and treatment bed (Minerve System, Bioscan) and scanned using a 1T MR scanner (M2, Aspect Imaging) and a small animal irradiator equipped with CBCT (X-rad 255Cx, Precision X-ray). The MR images were acquired using a fast spin echo sequence (TE/TR = 80/4800, NEX of 4 or 6, voxel size of 0.2 x 0.2 x 1.0 mm, 22 to 24 slices and imaging time of 6 to 8 minutes). The CBCT images were acquired at 80 and 100 kVp (for reduced streaking at the bone/soft tissue interface) and 0.5 mA (60 seconds acquisition) and reconstructed at 0.1 x 0.1 x 0.1 mm voxel size. Image matching was performed using XVI4 PilotXRad. Image analysis was conducted using Microview (GE Healthcare) by manually contouring of the tumor in selected slices and then linearly extrapolating across non-contoured slices. *Results:* The overall soft tissue contrast in the lower abdominal cavity was poor in the CBCT data set. Although there was contrast between the bladder and the tumor, and between the tumor and selected segments of the intestinal tract, it was still challenging to confidently delineate the tumor margins using the CBCT images alone (see Figure 1). Side-by-side consultation with the MR images during contouring allowed for the tumors to be more confidently delineated on the CBCT images (without co-registration with the MR data set) with a volumetric accuracy of 116.4 ± 24.6% relative to the volumes contoured using the MR data set alone (15 animals with tumor volumes ranging from 78 to 1399 mm3, Figure 2) . In addition, a built-in image matching software on the irradiator allowed for manual and automated registration of the MR and CBCT data sets which enabled more accurate placement of the treatment isocentre.
Conclusion: Precise and accurate delivery of radiation to preclinical animal models must be supplemented by imaging techniques that allow for visualization and delineation of the disease volume in the treatment position. MR images acquired with the animal on a transportable multimodality imaging and treatment bed facilitated the delineation of volumetrically accurate treatment regions using a CBCT-equipped small animal irradiator. Furthermore, the use of a built-in image matching software to register the MR and CBCT data sets allowed accurate placement of the treatment isocentre.

Surface Modification of Gadolinium Oxide Thin Films and Nanoparticles using Poly(ethylene glycol)-Phosphate

Authors:
Andree-Anne Guay-Begin[1,2], Pascale Chevallier[1], Luc Faucher[1,2], Stephane Turgeon[1], and Marc-Andre Fortin[1,2]*

Institutions:
1 Axe metabolisme, sante vasculaire et renale, Centre hospitalier universitaire de Quebec (CRCHUQ-MSVR), Laboratoire de biomateriaux pour l'imagerie medicale (BIM), Centre de recherche sur les materiaux avances (CERMA) and Centre quebecois sur les materiaux fonctionnels (CQMF)
2 Department of Mining, Metallurgical and Materials Engineering, Universite Laval, Quebec

Langmuir. 2012 Jan 10; 28(1):774-782. Epub 2011 Dec 12.

Abstract:
The performance of nanomaterials for biomedical applications is highly dependent on the nature and the quality of surface coatings. In particular, the development of functionalized nanoparticles for magnetic resonance imaging (MRI) requires the grafting of hydrophilic, nonimmunogenic, and biocompatible polymers such as poly(ethylene glycol) (PEG). Attached at the surface of nanoparticles, this polymerenhances the steric repulsion and therefore the stability of the colloids. In this study, phosphate molecules were used as an alternative to silanes or carboxylic acids, to graft PEG at the surface of ultrasmall gadolinium oxide nanoparticles (US-Gd2O3, 2_3 nmdiameter). This emerging, high-sensitivity "positive" contrast agent is used for signal enhancement in T1-weighted molecular and cellular MRI. Comparative grafting assays were performed on Gd2O3 thin films, which demonstrated the strong reaction of phosphate with Gd2O3 compared to silane and carboxyl groups. Therefore, PEG-phosphate was preferentially used to coat US-Gd2O3 nanoparticles. The grafting of this polymer on the particles was confirmed by XPS and FTIR. These analyses also demonstrated the strong attachment of PEG-phosphate at the surface of Gd2O3, forming a protective layer on the nanoparticles. The stability in aqueous solution, the relaxometric properties, and the MRI signal of PEG-phosphate-covered Gd2O3 particles were also better than those from non-PEGylated nanoparticles. As a result, reacting PEG-phosphate with Gd2O3 particles is a promising, rapid, one-step procedure to PEGylate US-Gd2O3 nanoparticles, an emerging "positive" contrast agent for preclinical molecular and cellular applications.

Keywords:
"positive" contrast agent, preclinical molecular imaging, MRI, functionalized nanoparticles

http://pubs.acs.org/doi/abs/10.1021/la202780x

MnO-Labeled Cells: Positive Contrast Enhancement in MRI

Author:
Mathieu Létourneau[‡,§], Mélanie Tremblay[‡,§], Luc Faucher[‡,§], Dario Rojas[‡,§], Pascale Chevallier[‡], Yves Gossuin[∥], Jean Lagueux[‡], and Marc-André Fortin[‡,§*]

Institution:
‡ Axe métabolisme, santé vasculaire et rénale, Centre de recherche du Centre hospitalier universitaire de Québec, (AMSVR-CRCHUQ), Canada
§ Centre de recherche sur les matériaux avancés (CERMA) and Département de génie des mines, de la métallurgie et des matériaux, Université Laval, Canada
∥ Service de physique expérimentale et biologique, Université de Mons, Belgium

J. Phys. Chem. B, 2012, 116 (44), pp 13228–13238; DOI: 10.1021/jp3032918

Abstract:
Manganese oxide (MnO) nanoparticles have been suggested as a promising "positive" MRI contrast agent for cellular and molecular studies. Mn-based contrast agents could enable T1-weighted quantitative cell tracking procedures *in vivo* based on signal enhancement. In this study, ultrasmall MnO particles were synthesized and coated with thiolated molecules (DMSA) and polyethylene glycol (PEG) to allow enhanced cell labeling properties and colloidal stability. This coating allowed the fabrication of individual ultrasmall nanoparticles of MnO (USPMnO) as well as of nanoaggregates of the same material (SPMnO). Particle size was measured by TEM and DLS. Physico-chemical properties were characterized by XPS and FTIR. The relaxometric properties of these aqueous suspensions were measured at various magnetic fields. The suspensions provided strong positive contrast enhancement in T1-weighted imaging due to high longitudinal relaxivities (r1) and low r2/r1 ratios (USPMnO: r1 = 3.4 ± 0.1 mM–1s–1, r2/r1 = 3.2; SPMnO: r1 = 17.0 ± 0.5 mM–1s–1, r2/r1 = 4.0, at 1.41T). HT-1080 cancer cells incubated with the contrast agents were clearly visualized in MRI for Mn contents >1.1 pg Mn/cell. The viability of cells was not affected, contrarily to cells labeled with an equivalent concentration of Mn2+ ions. A higher signal per cell was found for SPMnO-labeled compared with USPMnO-labeled cells, due to the higher relaxometric properties of the agglomerates. As a result, the "positive" signal enhancement effect is not significantly affected upon agglomeration of MnO particles in endosomes. This is a major requirement in the development of reliable cell tracking procedures using T1-weighted imaging sequences. This study confirms the potential of SPMnO and USPMnO to establish more quantitative cell tracking procedures with MRI.

Keywords:
Contrast Agent, Nanoparticles, MRI, Manganese Oxide

http://www.ncbi.nlm.nih.gov/pubmed/24178890

Rapid Synthesis of PEGylated Ultrasmall Gadolinium Oxide Nanoparticles for Cell Labeling and Tracking with MRI

Authors:
Luc Faucher[1,2], Mélanie Tremblay[1,2], Jean Lagueux[1], Yves Gossuin[3] and Marc-André Fortin[1,2]*

Institutions:
1 Axe métabolisme, santé vasculaire et rénale, Centre hospitalier universitaire de Québec (CRCHUQ-MSVR)
2 Centre de recherche sur les matériaux avancés (CERMA) and Département de Génie des Mines, de la Métallurgie et des Matériaux, Université Laval, Québec
3 Service de Physique Expérimentale et Biologique, Université de Mons (UMONS)

ACS Appl. Mater. Interfaces, 2012, 4 (9), pp 4506–4515 DOI: 10.1021/am3006466 Publication Date (Web): July 26, 2012

Abstract:
Ultrasmall paramagnetic Gd(2)O(3) nanoparticles have been developed as contrast agents for molecular and cellular preclinical MRI procedures. These small particles (mean diameter <5 nm) have the highest Gd density of all paramagnetic contrast agents. They generate strong positive contrast enhancement in T1-weighted MRI. Signal enhancement is modulated by the interactions of water molecules with Gd, and very small particles provide the optimal surface-to volume ratios necessary to reach high relaxivities. Conventional Gd(2)O(3) nanocrystal synthesis techniques, and subsequent polyethylene glycol (PEG) grafting procedures are usually time-consuming and recovery losses are also limitative. The present study reports on a new, fast, and efficient one-pot Gd(2)O(3) synthesis technique that provides PEGylated nanoparticles of very small size (mean diameter = 1.3 nm). Readily coated with PEG, the particles are colloidally stable in aqueous media and provide high longitudial relaxivities and small r2/r1 ratios (r1 = 14.2 mM−1 s−1 at 60 MHz; r2/r1 = 1.20), ideal for T1-weighted MRI. In this study, F98 brain cancer cells (glioblastoma multiforme) were labeled with the contrast agent and implanted *in vivo* (mice brains). The labeled cells appeared positively contrasted at least 48 h after implantation. Each one of the implanted animals developed a brain tumor. The performance of PEG-Gd(2)O(3) was also compared with that of commercially available iron oxide nanoparticles. This study demonstrated that ultrasmall PEG-Gd(2)O(3) nanoparticles provide strong positive contrast enhancement in T1-weighted imaging, and allow the visualization of labeled cells implanted *in vivo*.

Keywords:
magnetic resonance imaging MRI, contrast agents, gadolinium oxide, nanoparticles, polyethylene glycol, cell labeling, cell tracking, glioblastoma multiforme

http://www.ncbi.nlm.nih.gov/pubmed/22834680

Iron Oxide Nanoparticle-Based Magnetic Resonance Method to Monitor Release Kinetics from Polymeric Particles with High Resolution

Authors:
Minnie Chan[2], Eric Schopf[1], Jagadis Sankaranarayanan[1], and Adah Almutairi[1,3,4*]

Institutions:
1 Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego
2 Department of Chemistry and Biochemistry, University of California San Diego
3 Department of Materials Science and Engineering, University of California San Diego
4 Department of NanoEngineering, University of California San Diego

Analytical Chemistry, 2012, 84 (18), pp 7779–7784; DOI: 10.1021/ac301344d

Abstract:
A new method to precisely monitor rapid release kinetics from polymeric particles using super paramagnetic iron oxide nanoparticles, specifically by measuring spin−spin relaxation time (T2), is reported. Previously, we have published the formulation of logic gate particles from an acid-sensitive poly-β-aminoester ketal-2 polymer. Here, a series of poly-β-aminoester ketal-2 polymers with varying hydrophobicities were synthesized and used to formulate particles. We attempted to measure fluorescence of released Nile red to determine whether the structural adjustments could finely tune the release kinetics in the range of minutes to hours; however, this standard technique did not differentiate each release rate of our series. Thus, a new method based on encapsulation of iron oxide nanoparticles was developed, which enabled us to resolve the release kinetics of our particles. Moreover, the kinetics matched the relative hydrophobicity order determined by octanol−water partition coefficients. To the best of our knowledge, this method provides the highest resolution of release kinetics to date.

http://pubs.acs.org/doi/abs/10.1021/ac301344d

A vaccine targeting angiomotin induces an antibody response which alters tumor vessel permeability and hampers the growth of established tumors

Authors:
M. Arigoni[1], G. Barutello[1], S. Lanzardo[1], F. Cavallo[1], D. Longo[2], S. Aime[2], C. Curcio[3], M. Iezzi[3], Y. Zheng[4], I. Barkefors[4], L. Holmgren[4]

Institutions:
1 Molecular Biotechnology Center, University of Turin
2 Molecular Imaging Center, Department of Chemistry IFM, University of Turin
3 Aging Research Center, ''Gabriele d'Annunzio'' University Foundation
4 Department of Oncology and Pathology, Cancer Centre Karolinska, Karolinska Institutet

Angiogenesis (2012) 15:305–316; DOI 10.1007/s10456-012-9263-3

Abstract:
Angiomotin (Amot) is one of several identified angiostatin receptors expressed by the endothelia of angiogenic tissues. We have shown that a DNA vaccine targeting Amot overcome immune tolerance and induce an antibody response that hampers the progression of incipient tumors. Following our observation of increased Amot expression on tumor endothelia concomitant with the progression from pre-neoplastic lesions to full-fledged carcinoma, we evaluated the effect of anti-Amot vaccination on clinically evident tumors. Electroporation of plasmid coding for the human Amot (pAmot) significantly delayed the progression both of autochthonous tumors in cancer prone BALB-neuT and PyMT genetically engineered mice and transplantable TUBO tumor in wild-type BALB/c mice. The intensity of the inhibition directly correlated with the titer of anti-Amot antibodies induced by the vaccine. Tumor inhibition was associated with an increase of vessels diameter with the formation of lacunar spaces, increase in vessel permeability, massive tumor perivascular necrosis and an effective epitope spreading that induces an immune response against other tumor associated antigens. Greater tumor vessel permeability also markedly enhances the antitumor effect of doxorubicin. These data provide a rationale for the development of novel anticancer treatments based on anti-Amot vaccination in conjunction with chemotherapy regimens.

Keywords:
Angiomotin, DNA vaccination, Vessel permeability, Antibodies, Chemotherapy

http://www.ncbi.nlm.nih.gov/pubmed/22426512

Image guided therapy: The advent of theranostic agents

Authors:
Enzo Terreno[1], Fulvio Uggeri[2], Silvio Aime[1]

Institutions:
1 Department of Chemistry and Molecular & Preclinical Imaging Centers, University of Turin, Italy
2 Bracco Imaging S.p.A., Centro Ricerche, Colleretto Giacosa (TO), Italy

Journal of Controlled Release 2012 Jul 20;161(2):328-37. doi: 10.1016/j.jconrel.2012.05.028. Epub 2012 May 22.

Abstract:
Theranostic agents represent a recently introduced class of imaging probes designed to offer to pharmacologists and physicians a robust tool for minimally invasive *in vivo* visualization of drug delivery/release and therapy monitoring. By means of these agents, novel strategies able to integrate diagnosis and therapy could be developed. This highly interdisciplinary research field is one of the more innovative products resulting from the synergism between molecular imaging and nanomedicine. Potential applications of theranosis include the *in vivo* assessment of drug biodistribution and accumulation at the target site, visualization of the drug release from a given nanocarrier, and real-time monitoring of the therapeutic outcome. The expected end-point of theranostic agents is to provide a fundamental support for the optimization of innovative diagnostic and therapeutic strategies that could contribute to emerging concepts in the field of the "personalized medicine". This perspective paper aims at providing the reader the basic principles of theranosis with a particular emphasis to the design of theranostic agents.

Keywords:
In vivo imaging, Drug delivery and release, Image-guided therapies, Nanomedicine

http://www.ncbi.nlm.nih.gov/pubmed/22626940

In vivo Labeling of B16 Melanoma Tumor Xenograft with a Thiol-Reactive Gadolinium Based MRI Contrast Agent

Authors:

Valeria Menchise[1], Giuseppe Digilio[2*], Eliana Gianolio[3], Evelina Cittadino[3], Valeria Catanzaro[3], Carla Carrera[3], and Silvio Aime[3]

Institutions:

1 Institute for Biostructures and Bioimages (CNR) c/o Molecular Biotechnology Center (University of Turin)
2 Department of Environmental and Life Sciences, Universita del Piemonte
3 Department of Chemistry IFM & Center for Molecular Imaging, University of Turin

Mol. Pharmaceutics, 2011, *8* (5), pp 1750–1756

Abstract:

Murine melanoma B16 cells display on the extracellular side of the plasma membrane a large number of reactive protein thiols (exofacial protein thiols, EPTs). These EPTs can be chemically labeled with Gd-DO3A-PDP, a Gd(III)-based MRI contrast agent bearing a 2-pyridinedithio chemical function for the recognition of EPTs. Uptake of gadolinium up to 109 Gd atoms per cell can be achieved. The treatment of B16 cells *ex vivo* with a reducing agent such as tris(2-carboxyethyl)phosphine (TCEP) results in an increase by 850% of available EPTs and an increase by 45% of Gd uptake. Blocking EPTs with N-ethylmaleimide (NEM) caused a decrease by 84% of available EPTs and a decrease by 55% of Gd uptake. The amount of Gd taken up by B16 cells is therefore dependent upon the availability of EPTs, whose actual level in turn changes according to the extracellular redox microenvironment. Then Gd-DO3A-PDP has been assessed for the labeling of tumor cells *in vivo* on B16.F10 melanoma tumor-bearing mice. Gd-DO3A-PDP (or Gd-DO3A as the control) has been injected directly into the tumor region at a dose level of 0.1 μmol and the signal enhancement in MR images followed over time. The washout kinetics of Gd-DO3A-PDP from tumor is very slow if compared to that of control Gd-DO3A, and 48 h post injection, the gadolinium-enhancement is still clearly visible. Therefore, B16 cells can be labeled *ex vivo* as well as *in vivo* according to a common EPTs-dependent route, provided that high levels of the thiol reactive probe can be delivered to the tumor.

Keywords:

contrast agent; gadolinium; MRI; melanoma; microenvironment; redox; tumor

http://www.ncbi.nlm.nih.gov/pubmed/21780833

β-Gal gene expression MRI reporter in melanoma tumour cells. Design, Synthesis, *in vitro* and *in vivo* testing of a Gd(III) containing probe forming a high relaxivity, melanin like structure upon β-Gal enzymatic activation

Authors:
Francesca Arena, Jebasingh Bhagavath Singh, Eliana Gianolio, Rachele Stefanìa and Silvio Aime

Institution:
Centro di Imaging Molecolare, Dipartimento di Chimica IFM, Università degli Studi di Torino, Italy

Bioconjug Chem. 2011 Dec 21;22(12):2625-35. Epub 2011 Nov 15.

Abstract:
The aim of this work is to design and test a MRI probe (Gd-DOTAtyr-gal) able to report about the gene expression of β-Galactosidase (β-Gal) in melanoma cells. The probe consists of a Gd-DOTA reporter bearing on its surface a tyrosine-galactose-pyranose functionality, that upon the release of the sugar moiety, readily transforms, in the presence of tyrosinase, into melanin oligomeric/polymeric mixture. The formation of Gd-DOTA-containing-melanin oligomers and polymers is accompanied by a marked increase of the water proton relaxation rate. The steps involving the release of the galactose-pyranose group and the formation of the melanin-like structure have been carefully investigated *in vitro* by relaxometric and UV-Vis measurements. Cellular uptake studies of Gd-DOTAtyr-gal by melanoma cells have shown that the probe enters the cells, and it appears not to be confined in endosomal vesicles. Using B16-F10*LacZ* transfected cells, the fast formation of paramagnetic melanin-Gd(III)-containing species has been assessed by the measurement of increased longitudinal relaxation rates of the cellular pellets suspensions. The *in vitro* results have been confirmed in *in vivo* MRI investigations on murine melanoma tumor bearing mice. Upon direct injection of Gd-DOTAtyr-gal, a good contrast is observed after 5 hours post injection in B16-F10*LacZ* tumors, but not in B16-F10 tumors lacking the β-Gal enzyme. Gd-DOTAtyr-gal in combination with tyrosinase introduces a novel approach for the detection of β-Gal expression by MRI *in vivo*.

Keywords:
Molecular Imaging, MRI, gene-expression reporter, Responsive Gd(III)-Contrast Agents, β-Galactosidase, Tyrosinase.

http://www.ncbi.nlm.nih.gov/pubmed/22035020

MRI of cells and mice at 1 and 7 Tesla with Gd-targeting agents: when the low field is better!

Authors:
Simonetta Geninatti-Crich, Ibolya Szabo, Diego Alberti, Dario Longo and Silvio Aime*

Institution:
Department of Chemistry I.F.M, and Center for Molecular Imaging, University of Torino, Italy

Contrast Media Mol. Imaging, 2011, 6 421–425

Abstract:
Tumor cells were targeted with Gd-loaded/LDL (low density lipoproteins) adducts consisting of ca 300 Gd(III) amphiphilic complexes incorporated in the lipophilic LDL particles. The long reorientational time of the Gd(III) complex in the supramolecular adduct yielded a relaxivity peak at ca 1 T, whereas its relaxivity at 7 T was 5 times less. The field-dependent relaxivity markedly affected the signal enhancement attainable at the two magnetic fields. As tumor cells showed up-regulation of LDL transporters, B16 melanoma cells were labeled with the Gd-loaded/LDL adduct. Each cell contained ca 2×109 Gd atoms. Upon dispersion of 5000 labeled cells in 1 μl of agar, signal intensity (SI) enhancements of about 30 and 7% were observed at 1 and 7 T, respectively. The results obtained on cellular systems were confirmed *in vivo* upon the administration of Gd-loaded/LDL particles to C57 mice bearing a transplanted melanoma (B16) tumor. From the herein reported results, one may conclude that, for slowly moving Gd complexes, it is possible to obtain *in vivo* sensitivity enhancements at 1 T several times higher than that attained at high fields.

Keywords:
MRI; low field; LDL; Gd complexes; macromolecular imaging probes, gadolinium

http://www.ncbi.nlm.nih.gov/pubmed/22144019

MR Imaging of Tumor Associated Macrophages with Clinically-Applicable Iron Oxide Nanoparticles

Authors:
Heike E. Daldrup-Link, MD[1], Daniel Golovko, MD[2], Brian Ruffell, PhD[3], David G. DeNardo, PhD[3], Rosalinda Castaneda, BA[1], Celina Ansari, MD[1], Jianghong Rao, PhD[1], Mike Wendland, PhD[4], Claire Corot, PhD[5], Lisa M. Coussens, PhD[3]

Institutions:
1 Department of Radiology, Molecular Imaging Program at Stanford, Stanford University
2 Department of Medicine, University of Massachusetts Medical School
3 Department of Pathology, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco
4 Department of Radiology and Biomedical Imaging, University of California San Francisco
5 Guerbet Group, Paris, France

Clin Cancer Research, 2011 Sep 1;17(17):5695-704. Epub 2011 Jul 26.

Abstract:
Purpose: The presence of tumor-associated macrophages (TAMs) in breast cancer correlates strongly with poor outcome. The purpose of this study was to develop a clinically applicable, non-invasive diagnostic assay for selective targeting and visualization of TAMs in breast cancer, based on magnetic resonance (MR) imaging and clinically applicable iron oxide nanoparticles.
Experimental Design: F4/80-negative mammary carcinoma cells and F4/80-positive TAMs were incubated with iron oxide nanoparticles and were compared regarding MR signal changes and iron uptake. MMTV-PyMT transgenic mice harboring mammary carcinomas underwent nanoparticle-enhanced MR up to 1 hour (h) and at 24 h post injection (p.i.). The tumor enhancement on MR images was correlated with the presence and location of TAMs and nanoparticles on confocal microscopy.
Results: In vitro studies revealed that iron oxide nanoparticles are preferentially phagocytosed by TAMs, but not by malignant tumor cells. *In vivo*, all tumors demonstrated an initial contrast agent perfusion on immediate postcontrast MR images with gradual transendothelial leakage into the tumor interstitium. At 24 h p.i., all tumors demonstrated a persistent signal decline on MR scans. TAM-depletion via aCSF1 mAb lead to significant inhibition of tumor nanoparticle enhancement. Detection of iron using DAB-enhanced Prussian Blue staining, and immunodetection of CD68 localized iron oxide nanoparticles to TAMs, indicating that the MR signal effects on delayed MR images were largely due to TAM-mediated uptake of contrast agent.
Conclusion: These data indicate that tumor-enhancement with clinically applicable iron oxide nanoparticles may serve as a new biomarker for long-term prognosis, related treatment decisions and the evaluation of new immune-targeted therapies.

Keywords:
USPIO, ferumoxytol, macrophage, MRI, folate receptor

http://clincancerres.aacrjournals.org/content/early/2011/07/26/1078-0432.CCR-10-3420

Yeast cell wall particles: a promising class of nature-inspired microcarriers for multimodal imaging

Authors:
Sara Figueiredo[1,2], João Nuno Moreira[3], Carlos F. G. C. Geraldes[1], Silvia Rizzitelli[2], Silvio Aime[2] and Enzo Terreno[2]*

Institutions:
1 Department of Life Sciences, Faculty of Sciences and Technology, and Center for Neurosciences and Cell Biology, University of Coimbra, Portugal
2 Department of Chemistry IFM and Molecular & Preclinical Imaging Centers, University of Torino
3 Laboratory of Pharmaceutical Technology, Faculty of Pharmacy and Center for Neurosciences and Cell Biology, University of Coimbra, Portugal

Chemical Communications., 2011,47, 10635-10637; DOI: 10.1039/C1CC14019A

Abstract:
This communication demonstrates that yeast cell wall particles (YCWPs) are a promising class of nature-inspired biocompatible microcarriers for the delivery of amphipathic/lipophilic imaging reporters. When a paramagnetic MRI agent is loaded, the longitudinal relaxivity per particle at 0.5 T is the highest ever reported for Gd-based systems.

Keywords:
amphipathic/lipophilic imaging reporters, paramagnetic MRI contrast agent, gadolinium

http://www.ncbi.nlm.nih.gov/pubmed/21881668

Gd-loaded Yeast Cell Wall Particles as an innovative micron-sized platform for labeling and tracking immune cells by multimodal imaging

Authors:

Sara Figueiredo[1,2], João Nuno Moreira[3], Carlos F.G.C. Geraldes[1], Silvio Aime[2] and Enzo Terreno[3]

Institutions:

1 Department of Life Sciences, Faculty of Sciences and Technology and Center for Neurosciences and Cell Biology, Portugal
2 Department of Chemistry IFM And Molecular & Preclinical Imaging Centers, University of Turin
3 Laboratory of Pharmaceutical Technology, Faculty of Pharmacy and Center for Neuroscience and Cell Biology, University Of Coimbra, Portugal

Poster: From World Molecular Imaging Congress (WMIC) 2011, San Diego, CA
#P049, Poster Session 2

Abstract:

The relatively low sensitivity of paramagnetic MRI probes has prompted the development of systems able to deliver a high number of MR imaging reporters to the biological target site of interest. Several nano-sized carriers have been considered including naturally-occurring systems such as proteins, virus capsids or lipoproteins. The search for carriers able to carry a large number of paramagnetic units prompted us to consider the recently proposed micron-sized platform of yeast cell wall particles (YCWPs). Yeasts are cells whose membrane consists of β-1,3-D-glucan polymer associated with mannose-containing proteins and chitin. Such materials appear to be well tolerated by living systems and can be processed into small fragments by macrophages. Moreover, β-1,3-D-glucan is an excellent targeting vector towards several antigen presenting cells mainly through the dectin-1 receptor. We developed a procedure for entrapping paramagnetic emulsions in the inner core of YWCPs using water-insoluble Gd-complexes (e.g. Gd-DOTAMA(C18)2). Figure 1 (left) shows a TEM image of the Gd-loaded particles. The vesicles appear as pseudo spherically-shaped particles (mean diameter of 6 μm) whose cores are filled up with the Gd-based emulsion. The longitudinal relaxivity of Gd-loaded YCWPs measured at 20 MHz was ca. 50 % higher than that reported for the same chelate embedded in a liposome membrane (22.3 vs. 15 mM-1s-1). Furthermore, it was estimated that each YCWP is loaded with ca. 1.6×107 Gd3+ ions, thus yielding a relaxivity per particle of 3.5×108 mM-1s-1. To the best of our knowledge, this is the highest relaxivity ever measured for a Gd-based agent. The high affinity of YCWPs to cells of the immune system was used to exploit the labeling of macrophages with the aim of tracking them by MRI. Experiments, performed on J774 murine macrophages, have demonstrated a high and very fast uptake of the paramagnetic particles with good temporal persistence of the contrast and an extremely low cytotoxicity (Figure 1 - middle). Studies on the mechanism of phagocytosis showed that YCWPs are internalized both by clathrin-dependent endocytosis and by macropinocytosis, because both chlorpromazine and wortmannin were able to decrease the internalization of the particles, consistent with the evidences that β-glucans (as microorganisms) can be recognized either directly by membrane receptors (non-opsonic) or indirectly, by opsonic recognition (as example, complement receptor 3). Preliminary *in vivo* studies on melanoma-bearing mice showed that Gd-labeled YCWPs are able to enhance the signal in the lymph node (arrow) proximal to the tumor, after intra-muscular injection (Figure 1 - right). In summary, YCWPs may represent a very promising class of carriers for designing highly sensitive MRI probes. In addition, and analogously to other particulate systems, YCWPs can be loaded with lipophilic probes for other imaging modalities, and, moreover, glucan shells can be suitably functionalized to endow them with targeting abilities. Figure 1 - TEM image (left), J774

macrophages labeled with YCWPs (middle) and MR image of a melanoma-bearing mouse injected with Gd-loaded YCWPs (right).

Calixresorcinarenes based "theranostic" MRI agents

Authors:
Simonetta Geninatti Crich[1], Diego Alberti[1], Diana Burghelea[1], Paolo Minazzi[2,3], Camilla Cavallotti[3], Gionvanbattista Giovenzana[2,3], Silvio Aime[1]

Institutions:
1 Department of Chemistry, Center for Molecular Imaging, University of Torino, Italy
2 Scienze del Farmaco, Università degli Studi del Piemonte Orientale "Amedeo Avogadro", Novara, Italy
3 Cage Chemicals S.r.l., Novara, Italy

Poster: From World Molecular Imaging Congress (WMIC) 2011, San Diego, CA

Abstract:
Introduction: Much attention is currently devoted to the development of agents for procedures in which disease diagnosis and therapy are combined. These "theranostics" agents contain both drugs and imaging reporters within a single formulation. Usually, theranostics are made up by nanoparticles that, as a consequence of their size and versatile composition, can deliver a high number of diagnostic and therapeutic molecules in the same particle. Drawbacks associated to their nano-size are the long extravasation time (also in the presence of EPR effect) and low diffusion at thepathological target site. For these reasons, the use of nanosized carriers may reduce the omogeneous distribution of the drug and the imaging agent in the tumor region. In this work an alternative low molecular weight Gd based "theranostic" agent has been synthesized and tested on cellular systems. The agent contains up to 8 Gd-AAZTA-(CH2)9-COOH complexes linked to a calix[4]resorcinarenes moiety through a short PEG chain. Cellular uptake experiments and "*in vitro*" MRI. Folic acid is a vitamin essential for the proliferation and maintenance of cells. Normally, mammalian cells obtain their normal folate requirement via a low affinity reduced folate carrier or proton-coupled folate transporter. Accessible folate receptors are expressed in significant numbers only on cancer cells, activated macrophages, and the proximal tubule cells of the kidney. Folate conjugates bind to folate receptors on these cell types with high affinity (Kd ≈10-9 M) and they are internalized through receptor-mediated endocytosis. Inthis study, the calix[4]resorcinarene compound functionalized with two folic acid moieties (Calix-Gd-AAZTA-folate) have been considered to visualize ovarian cancer cells. (IGROV-1) These cells express about 1x106 folate receptors per cell and the amount of calix-Gd-aazta-folate taken-up after 24 h incubation has been compared to that obtained with Hela cells expressing a significantly lower amount of folate receptors (4x104 per cell.) Interaction of Rhodamine with the calix resorcinarene cavity. Calix[n]arenes and calixresorcinarenes, together with crown ethers and cyclodextrins are one of the major classes of macrocyclic organic "host" compounds in supramolecular chemistry. Calix[4]arenes form stable complexes with different classes of drugs and molecules of biological interest. For example "host-guest" complexes between fluorescent dyes and calixarenes have been studied as specific sensors of biological substances, particularly neurotransmitters of the acetylcholine and the carnitine type, steroids (cortisone, prednisone) as well as other organic analytes. In this study, the affinity of the fluorescent dye rhodamine for the calix[4]resorcinarene cavity has been determined by measuring the fluorescence intensity enhancement after the addition of calix-Gd-AAZTA to a 0.1 M rhodamine solution.
Conclusions: Calix-Gd-AAZTA-folate is selectively taken-up by ovarian cancer cells overexpressing folate receptors.- Rhodamine is able to interact with the calixresorcinarenes cavity showing an affinity constant of 2.8x106 M-1. Cell uptake studies are in progress. - Further studies will be done to test the affinity of steroids drugs (i.e prednisone) for the cali.

Registration of Small Animal Multimodal Imaging

Authors:
A. Akselrod-Ballin, H. Dafni, Y. Addadi, R. Avni, I. Biton, Y. Brenner, R. Greenman, T. Raz, M. Neeman

Institution:
Biological Regulation, Weizmann Institute of Science

Poster: From World Molecular Imaging Congress (WMIC) 2011, San Diego, CA

Abstract:
Summary: A registration based segmentation system for alignment of multimodal small animal imaging. The power stems from: 1) A multiscale, fast, automatic, segmentation representing various anatomical structures common between the modalities. 2) Flexibility of the EM-ICP feature based registration algorithms to match the structures despite their low probable differences.

Ultra-small nanoclusters of GdOx: a new, efficient contrast agent for *in vivo* cell tracking studies in T1-w. MRI

Authors:
Luc Faucher[1], Mélanie Tremblay[1], Jean Lagueux[1], Yves Gossuin[2], Marc-André Fortin[1]

Institutions:
1 Axe métabolisme, santé vasculaire et rénale, CRCHUQ-MSVR, Québec; Département de génie des mines, de la métallurgie et des matériaux and Centre de recherche sur les matériaux avancés, Université Laval
2 Service de Physique Expérimentale et Biologique, Université de Mons

Poster: From World Molecular Imaging Congress (WMIC) 2011, San Diego, CA

Abstract:
Introduction: Cell tracking studies in magnetic resonance imaging (MRI) are currently performed with "negative" contrast agents (CAs). However, FexOy-labeled cells generate susceptibility artefacts in MR-images, which can dramatically affect the anatomical information in the area of implantation. Positive CAs are being developed to allow the precise and possibly quantitative tracking of cells with T1-weighted MR imaging sequences. Of all gadolinium-based CAs, gadolinium oxide (GdOx) nanoparticles provide the highest Gd densities [1-2]and are ingested by cells[3-4].
Project objectives: The main objective of this project is to label cells *in vitro* with the smallest GdOx nanoparticles reported. Once implanted *in vivo*, the labeled cells could be detected over time with positive-T1 MRI sequences.
Aim of this study: PEG-coated ultra-small GdOx nanoparticles were used to label glioma multiforme cells (F98) *in vitro*. Then, cells were implanted in the caudoputamen of nod-scid mouse brains, and imaged for 1 month at 1 T (high performance 1T compact M2 MRI, Aspect Imaging, Toronto Canada), using a dedicated mouse brain coil and a 3D-GRE T1-weighted sequence.
Conclusions:

- F98 glioblastoma multiforme cells can be labeled with PEG-US-GdOx (1.3 nm of nanoparticle diameter)
- 100 000 labeled cells are delineated in mouse brains with "positive-T1" weighted MRI sequences
- Fine anatomical structures are visible around the cells (no artefact)
- Longitudinal and transverse relaxivities of PEG-US-GdOx are of 14.2 mM-1s-1 and 17.2 mM-1s-1 at 1.41 T (the highest of all GdOx systems)
- PEG-US-GdOx is a promising "positive-T1" cell probe since the r2/r1 ratio remains low at every magnetic field
- Future work will consist in studying more precisely cell division in mouse brains, occurrence of macrophage uptake, nanoparticle toxicity over long periods of time, as well as the fate of the particles after 1 month

Initial Experience with Coregistered PET/MRI Using a 'Desktop' 1.0T MRI Scanner

Authors:
E.P. Lunsford, K.J. Robichaud, J.V. Frangioni, & R.E. Lenkinski

Institution:
Longwood Small Animal Imaging Facility, Beth Israel Deaconess Medical Center, Boston, MA

Poster: International Society for Magnetic Resonance in Medicine (ISMRM) 2011, Montreal, QC

Abstract:
Introduction: The advent of the ASPECT 'desktop' MRI system for small animal imaging allows convenient and high quality imaging in an ordinary laboratory setting. The ASPECT is a 1.0Tpermanant magnet, with a self-shielded geometry that produces no fringe field. Because there is no need for a supercooled coil or special infrastructure, the system can be located within close proximity to PET and SPECT animal imagers, allowing for coregistration between modalities. We have tested image coregistration using a commercially available MR-compatible rodent bed, that is interchangeable between PET and MRI systems. The exact positioning of animal subjects is maintained between scans. Our efforts are focused initially on imaging brown fat: this tissue is well characterized by FDG-PET, and is also shown to be easily delineated from white adipose tissue using MRI. However there have been no studies to date which combine both PET and MRI for studying brown fat in both spatial and functional perspectives.
Methods: Mice were anesthetized using isoflurane gas at a concentration of about 2-2.5%. A standard protocol for PET imaging was performed, where approximately 0.350mCi F18-FDG was injected retroorbitally an hour before imaging on the NanoPET/CT (Bioscan). Figure 1 illustrates the laboratory workflow from PET to MRI using the multimodality mouse bed (Minerve). After PET, the mice remained anesthetized in the bed while it was exchanged and connected to the MRI system without moving the mouse. The common mouse bed, exchangeable between their PET/CT and SPECT/CT systems, was placed inside the ASPECT standard 35mm mouse coil. MR images were acquired using a T2 weighted FSE sequence (TE=127.2, TR=4000, slice thickness=1mm, FOV=80mm, 200x200 matrix) and T1 weighted SE multislice sequence (TE=11.4, TR=400, slice thickness=1mm, FOV = 100mm, 400x400 matrix). Resulting PET/MR images were analyzed and coregistered manually using InVivoScope software.
Results: Figure 2 shows a standard T2 weighted FSE using the ASPECT desktop MRI. The contrast in the kidneys is as expected, with water separation between medulla and cortex clearly shown. Figure 3 shows brown fat imaging in the same mouse, remaining anesthetized and untouched between sequential PET and MRI scans. The resulting Dicom images were imported into InVivoScope software and header files were used to automatically scale the image volumes. The reorientation tool in InVivoScope was used to manually coregister the images. Image coregistration was successful and tissue boundaries aligned as expected.
Discussion and Conclusion: PET/MRI imaging promises to make a major impact in the field of small-animal imaging by combining fine anatomical detail and functional information. Crucial to the application of multimodal imaging is accessibility and coregistration of the images. The 1.0T permanent magnet by ASPECT is a plug-and play device that can be located within any ordinary laboratory space, and operated by virtually anyone. Because there is no fringe field, it can be within close proximity to SPECT and PET nuclear imaging systems – allowing for sequential imaging while maintaining the exact position of the animal. Here we show our initial experience of combining superior soft tissue contrast of MRI with functional information offered by FDG-PET in the study of brown adipose tissue. Future

developments include coregistration of antibody-stained tissue sections with MRI and PET in order to establish a "ground truth" for interpreting imaging data using wholebody histology.

MRI of cells and mice at 1 and 7 Tesla with Gd-targeting agents: when the low field is better!

Authors:
S. Geninatti-Crich, D. Alberti, I. Szabo, D. Longo, and S. Aime

Institutions:
University of Torino, Italy

Poster: From International Society for Magnetic Resonance in Medicine (ISMRM) 2011, Montreal, QC

Abstract:
Introduction: In respect to other molecular imaging modalities such as PET or SPECT, the low sensitivity is the main limitation of the Magnetic Resonance-Molecular Imaging (MRMI) probes. Therefore, the success of a MR-Molecular Imaging protocol strongly relies on the amplification effects associated to the accumulation of the agents at the pathological site. To this purpose the use of nanoparticles as carriers for MRI contrast agents (CA) has both the advantage to transport a high number of CA units at the site of interest and an improved efficiency of their contrast enhancement properties. The relaxivity of Gd(III) complexes is field dependent and, in the case the paramagnetic complex is part of a macromolecular system, it shows a maximum efficiency at ca. 1T. The theory of paramagnetic relaxation accounts well for this experimental observation as, at around 1T, provided that the exchange rate of the metal coordinated water is fast, there is a dominant effect of the long reorientational motion of the paramagnetic slowly moving systems. Currently, most of MRI scanners for small animals employ superconducting magnets that work at fields from 4.7 to 7 T (and even higher ones). High fields provide an overall increase of the signal intensity (SI) that allows the rapid acquisition of highly resolved images. However, in the presence of slowly moving Gd(III) loaded agents, the benefit on SI brought by the relaxation enhancement observed at low fields may well counterbalance the advantages offered by the high fields. This work aims at comparing "*in vitro*" and "*in vivo*" results obtained at 1T and 7T using as Gd(III) targeting agent the supramolecular adduct formed by amphiphilic Gd(III) complexes (Gd-AAZTAC17) incorporated into Low Density Lipoproteins (LDL) particles. The used amphiphilic Gd(III) complex corresponds to the Gd-AAZTA complex in which the exocyclic carbon has been replaced by a long -C17 alkyl chain in order to pursue the incorporation in the lipidic core of LDL particles. In order to carry out the proposed comparison a newly available 1T scanner by Aspect (Aspect Magnet Technologies Ltd., Netanya, Israel) based on a NdFeB permanent magnet has been used.
Conclusions: The herein reported results indicate that, for applications in which the paramagnetic agent is part of a slowly moving system a high-resolution 1T scanner yields a markedly higher contrast enhancement with respect to a high field one. Many molecular imaging applications can be properly carried out at this (low) field when using Gd(III)-based probes possessing long molecular correlation time. The availability of low cost, easy to use 1T MRI scanners may significantly widen the number of biological groups that should come to consider "*in vivo*" MRI as a complementary or alternative tool to other imaging modalities.

IN VIVO PRECLINICAL IMAGING: an essential tool in translational research

Author:
Dr. John Comley

Institution:
HTStec Limited, Cambridge, United Kingdom

Drug Discovery World (DDW) – Summer 2011

Abstract:
In vivo imaging of small animals (mainly mice) is increasingly being deployed across the drug development process, particularly in the oncology/cancer therapeutic area. One of the main applications is monitoring the treatment response for early indications of efficacy. The most used imaging modalities are currently optical (bioluminescence and fluorescence), magnetic resonance imaging (MRI) and positron emission tomography (PET). Single modality imaging predominates, with multi-modality currently accessed mainly through coregistration with other imaging modes. The most used imaging combination today is PET+CT (x-ray computed tomography). *In vivo* imaging is expected to have greatest impact in drug development through monitoring disease progression and therapeutic response in longitudinal studies. Bioluminescent markers/reporters (eg luciferins, proluciferins) and PET Tracers (e.g. Fluorine-18 based) were the most used reagents in imaging studies. Maximising the depth of tissue penetration is perceived as the main limitation associated with optical imaging. From vendor updates it is possible to make some general observations: more compact benchtop imaging systems are being developed to promote accessibility; multi-modality imaging combinations are increasingly being offered: higher spatial resolution imaging is expected to be realised on new imagers: a broader range of imaging and contrasting reagents is under development; imaging systems are heavily reliant on advanced software systems and algorithms for reconstruction of the 3D image and co-registration of multiple imaging modalities; and finally the industry as a whole appears to be focusing on translational research applications. In summary, *in vivo* preclinical imaging is poised to rapidly advance, such that the specification and capabilities of small animal imagers will soon exceed their clinical counterparts.

Keywords:
In vivo imaging, MRI, preclinical imaging

http://www.ddw-online.com/enabling-technologies/p149260-in-vivo-preclinical-imaging:-an-essential-tool-in-translational-research-summer-11.html

Quantitative Neuromorphometry Using Magnetic Resonance Histology

Authors:
G. Allan Johnson, Alexandra Badea, Yi Jiang

Institution:
Duke Center for *In vivo* Microscopy, Durham, North Carolina, USA

Toxicologic Pathology, January 2011 vol. 39 no. 1 85-91; doi: 10.1177/0192623310389622

Abstract:
Magnetic resonance imaging (MRI), now common in the clinical domain, has been adapted for use by the neuropathologist by increasing the spatial resolution over 100,000 times what is common in human clinical imaging. This increase in spatial resolution has been accomplished through a variety of technical advances—higher magnetic fields, more sensitive receivers, and clever encoding methods. Magnetic resonance histology (MRH), that is, the application of MRI to study tissue specimens, now makes three-dimensional imaging of the fixed brain in the cranium routine. Active staining (perfusion fixation with a paramagnetic contrast agent) has allowed us to reduce the scan time by more than 8 times over earlier methods. The result is a three-dimensional isotropic image array that can be viewed along any direction without loss of spatial resolution. Homologous slices can be chosen interactively. Since the tissue is still fully hydrated in the cranium, tissue shrinkage and distortion are virtually eliminated. Volume measurements of neural structures can be made with a high degree of precision and accuracy. MRH will not replace more traditional methods, but it promises enormous value in choosing particular areas and times for more traditional sectioning and assessment.

Keywords:
contrast agents; magnetic resonance microscopy; magnetic resonance imaging; magnetic resonance histology; neuromorphometry; neuroimaging

http://www.ncbi.nlm.nih.gov/pubmed/21119052

Monitoring of NK-Cell Immunotherapy using non-invasive Imaging Modalities

Authors:
Priyanka Jha[1], Daniel Golovko[1], Sukhmine Bains[1], Daniel Hostetter[2], Reinhard Meier[1], Michael F Wendland[1], and Heike E Daldrup-Link[1]

Institutions:
1 Department of Radiology and Biomedical Imaging, University of California, San Francisco
2 Department of Pharmaceutical Chemistry, University of California, San Francisco

Cancer Res. 2010 August 1; 70(15): 6109–6113. doi:10.1158/0008-5472.CAN-09-3774.

Abstract:
Cancer immunotherapies can be guided by cellular imaging techniques, which can identify the presence or absence of immune-cell accumulation in the tumor tissue *in vivo* and in real time. This review summarizes various new and evolving imaging techniques employed for tracking and monitoring of adoptive NK-cell immunotherapies.

http://cancerres.aacrjournals.org/content/70/15/6109.abstract

A method for fat suppression in MRI based on diffusion-weighted imaging

Authors:
Peter Bendel[1], Yael Schiffenbauer[2]

Institutions:
1 Department of Chemical Research Support, The Weizmann Institute of Science
2 Aspect MR Technologies

Phys Med Biol. 2010 Nov 21;55(22):N547-55. doi: 10.1088/0031-9155/55/22/N03. Epub 2010 Nov 3.

Abstract:
The diffusion coefficient of lipid molecules is usually much smaller than that of water, and it is demonstrated here how this difference can be exploited for robust fat suppression in Magnetic Resonance Imaging (MRI). In contrast to the prevailing methods, diffusion-based fat suppression does not rely on chemical shift differences between water and lipids, and can therefore be applied easily in low or inhomogeneous magnetic fields. It is also independent on relaxation times, and can therefore be incorporated in experiments requiring conventional T1-weighted contrast. Diffusion-based fat suppression (DIFFSUP), consists of subtracting the signals acquired at low and high b-values, where the high b-value is ideally designed to achieve full suppression of the water and negligible attenuation of the lipid signal. Since high b-value images may be particularly affected by motion artifacts, a version of DIFFSUP incorporating first-order velocity compensation is also proposed and demonstrated, using phantoms and live mice, at field strengths of 4.7 and 1.0 T.

http://www.ncbi.nlm.nih.gov/pubmed/21048289