Published in final edited form as:

Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2019 July ; 11(4): e1551. doi:10.1002/wnan.1551.

Sugar-based biopolymers as novel imaging agents for molecular MRI

Zheng Han and

The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins School of Medicine, Baltimore, MD, USA.

Guanshu Liu

¹The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins School of Medicine, Baltimore, MD, USA.

²F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, MD, USA.

Abstract

Sugar-based biopolymers have been recognized as attractive materials to develop macromolecule- and nanoparticle-based cancer imaging and therapy. However, traditional biopolymer-based imaging approaches rely on the use of synthetic or isotopic labelling, and because of it, clinical translation often is hindered. Recently, a novel MRI technology, chemical exchange saturation transfer (CEST), has emerged, which allows the exploitation of sugar-based biopolymers as MR imaging agents by their hydroxyl protons-rich nature. In the article, we reviewed recent studies on the topic of CEST MRI detection of sugar-based biopolymers. The CEST MRI property of each biopolymer was briefly introduced, followed by the pre-clinical and clinical applications. The findings of these preliminary studies imply the enormous potential of CEST detectable sugar-based biopolymers in developing highly sensitive and translatable molecular imaging agents and constructing image-guided biopolymer-based drug delivery systems.

Graphical Abstract

<https://www.stm-assoc.org/copyright-legal-affairs/permissions/permissions-guidelines/>

Correspondence to: Guanshu Liu.

The author has declared no conflicts of interest

Introduction

Development of imaging and therapeutic delivery systems for cancers and other diseases is of great clinical significance. Biopolymers have been recognized as promising materials to develop macromolecule- and nanoparticle-based cancer imaging and therapy. Biopolymers are polymers produced by living organisms, including, categorized according to their monomeric units, polynucleotides (RNA and DNA), polypeptides, and sugar-based biopolymers (Mohanty, Misra, & Drzal, 2005). Among them, sugar-based biopolymers are particularly attractive, and their application in biomedicine area is rapidly growing in recent years. Sugar-based biopolymers possess numerous indispensable advantages, including high biocompatibility and biodegradability, low systemic toxicity, availability of different molecular weights (MW) and particle sizes, versatile physicochemical properties, and facile chemical modifications. As such, sugar-based biopolymers have been extensively studied for the preparation of a variety of targeted imaging agents or imaging guidance for drug delivery systems (Goodarzi, Varshochian, Kamalinia, Atyabi, & Dinarvand, 2013; Z. H. Liu, Jiao, Wang, Zhou, & Zhang, 2008; Swierczewska, Han, Kim, Park, & Lee, 2016). For instance, dextrans, one of the most widely used sugar-based biopolymer in the biomedical field (Larsen, 1989; Mehvar, 2000; Varshosaz, 2012), have been actively investigated for optical imaging using fluorescence dye-conjugates (Dreher et al., 2006; P. Liu et al., 2013; Morais et al., 2014; Swierczewska et al., 2016), nuclear imaging using Technetium 99m labeling (Dansereau & Line, 1994; Matsunaga et al., 2005; Morais et al., 2014) for SPECT or Gallium 68 labeling for PET (Meyer et al., 2018; Morais et al., 2014), and MR imaging using Gd-conjugates for generating T₁ contrast (Rebizak, Schaefer, & Dellacherie, 1997; Sun, Feng, Jing, Pei, & Liu, 2003; S. C. Wang et al., 1990) or dextran-coated superparamagnetic iron oxide particles for generating T₂ contrast (Anzai, McLachlan, Morris, Saxton, & Lufkin, 1994; Tassa, Shaw, & Weissleder, 2011). However, all these approaches require either isotopic or synthetic labeling, and their approval for clinical use may take a long time. To date, only few Gd-based macromolecular complexes have eventually entered clinical trials, and even many agents have been reported in pre-clinical studies (Bryson, Reineke, & Reineke, 2012). Also, there are recently rising safety concerns regarding metal-based agents, e.g., slow excretion, high tissue accumulation, and the potential risk of release of Gd(III) ions (Schmiedl et al., 1987; Wu, Feng, Jeong, Emerson, & Lu, 2009).

In context of development of highly translatable MR imaging probes, Chemical Exchange Saturation Transfer (CEST) (G. Liu, Song, Chan, & McMahon, 2013; P. C. van Zijl & Yadav, 2011; Ward, Aletras, & Balaban, 2000) MRI technology is recently developed to image diamagnetic materials possessing exchangeable protons. The mechanism for CEST detection of molecules containing exchangeable hydroxyl protons such as sugars is illustrated in Figure 1. Specifically, radiofrequency (RF) irradiation pulses are applied selectively at the dextran OH proton frequency (at a frequency offset $\omega \sim 1$ ppm with respect to the water resonance) to attenuate the NMR signal of these protons (referred to as saturation). Because of the exchange of exchangeable protons to their surrounding water molecules, the saturation is transferred to water, resulting in the decrease of the water NMR signal. While a single exchange-transfer process produces a reduction of water signal at the same concentration of exchangeable protons (i.e., $\sim$ mM), repeating this process will saturate

continuously the unsaturated protons that back-exchange from the large water pool (proton concentration $[H] \sim 110 \text{ M}$) again and again. As a result, this process can lead to great signal amplification of the NMR signal of exchangeable protons, especially for fast exchanging OH protons (exchange rate $k_{\text{ex}} \sim 1000 \text{ sec}^{-1}$). This results in a detectable decrease ($> \text{several percents}$) in the water MR signal, which is traditionally quantified by magnetization transfer ratio asymmetry (MTR_{asym}) defined by $\text{MTR}_{\text{asym}} = (S^{-\omega} - S^{+\omega})/S_0$, where $S^{+\omega}$ and $S^{-\omega}$ are the MRI signal with RF irradiation at particular offsets $+\omega$ and $-\omega$ respectively and S_0 is that acquired without RF saturation. Using CEST, one can easily gain > 1000 amplification of the NMR signal of the exchangeable protons (Ryoo et al., 2017), allowing MR detection in a high resolution manner. For more technical perspectives of CEST MRI, readers are referred to several recent review papers (Daryaei & Pagel, 2015; Kogan, Hariharan, & Reddy, 2013; G. Liu et al., 2013).

One of the unprecedented advantages of CEST MRI is the possibility to exert diamagnetic compounds for MRI contrast agents, namely diamagnetic CEST (DIACEST), either endogenously or exogenously. Recent studies have shown that many agents that are available in the clinic for other medical purposes can be directly used for CEST MRI contrast generating, including, anti-cancer drugs (Li et al., 2016; H. Liu et al., 2016; Lock et al., 2017; Ngen et al., 2016), metabolites (Cai et al., 2012; Ryoo et al., 2017), nutrients and amino acids (K. W. Chan et al., 2013; G. Liu et al., 2012), X-ray and CT contrast agents (L. Q. Chen et al., 2014; D. L. Longo et al., 2014; Moon et al., 2015a), and sugars, including glucose (K. W. Chan et al., 2012; Walker-Samuel et al., 2013; Xu et al., 2015), 2-deoxy-D-glucose (2-DG) (Jin, Mehrens, Wang, & Kim, 2016; Nasrallah, Pages, Kuchel, Golay, & Chuang, 2013; Rivlin, Horev, Tsarfaty, & Navon, 2013), 3-O-methyl-D-glucose (3OMG) (Rivlin & Navon, 2017; Rivlin, Tsarfaty, & Navon, 2014), glucosamine (Rivlin & Navon, 2016), and myo-inositol (Haris, Cai, Singh, Hariharan, & Reddy, 2011; Haris et al., 2013). As listed in Table 1, a wide range of exchangeable protons in a broad spectrum of diamagnetic compounds can be used for CEST imaging. In this review, we will focus on sugar-based biopolymers (Figure 2). For other types CEST agents, readers are referred to recent reviews (K. M. Jones, Pollard, & Pagel, 2018; Kogan et al., 2013; P. van Zijl & Sehgal, 2016).

1. Glycogen

Glycogen is a multibranched polysaccharide of glucose as the primary storage form of glucose in mammalian tissues (Figure 2a), and its content is altered in many metabolic diseases (Adeva-Andany, González-Lucán, Donapetry-García, Fernández-Fernández, & Ameneiros-Rodríguez, 2016). Glycogen is the first CEST detectable polysaccharide demonstrated *in vivo* in 2007 by van Zijl et al. (P. C. van Zijl, Jones, Ren, Malloy, & Sherry, 2007a). Glycogen was characterized by a broad and strong CEST signal at 0.5–1.5 ppm, and by using this CEST MRI signal, namely glycogen CEST (glycoCEST), the changes of glycogen content in the perfused fed-mouse livers at 4.7 T was successfully assessed (Figure 3). The authors also compared the CEST detection at magnetic field strengths of 4.7 and 9.4 T and concluded that the glycoCEST detection is favorable at higher field, which is in adherence to MR exchange theory for fast exchangeable hydroxyl protons. Since then, many studies were carried out to use glycoCEST to measure the change in glycogen content in

perfused mouse livers(Miller et al., 2015), in after-meal and fasting livers in rat(S. Z. Chen et al., 2016) and human(Deng et al., 2016), and injured kidneys of diabetic mice(F. Wang et al., 2016). Interestingly, studies on 3T human scanners are also reported(S. Z. Chen et al., 2016; Deng et al., 2016), indicative of the great potential of clinical utility of glycoCEST CEST MRI. It should be noted that glycogen can also be used as an exogenous contrast agent. For example, Liu et al. reported the use of glycogen to prepare CEST detectable liposomes(G. Liu et al., 2012). Owing to its large size (MW =25–100 kDa) and therefore slow release rate, the CEST signal of glycogen labelled liposomes are more stable than those labelled using small molecular agents(G. Liu et al., 2012).

2. GAG and Mucin

Glycosaminoglycans (GAGs) are long unbranched polysaccharides consisting of repeating disaccharide units (Figure 2b). In 2008, Ling et al. first applied CEST MRI in the detection of GAG concentration in cartilage *in vivo*, which is referred to as gagCEST in the future studies(Ling, Regatte, Navon, & Jerschow, 2008). Under optimized conditions, a substantial-OH CEST effect can be achieved (~24%). As shown in Figure 4, gagCEST MRI could successfully reveal the demarcation of a cartilage lesion on the medial facet ton a patellofemoral human knee joint. Currently, extensive investigations are in progress to use gagCEST as the noninvasive clinical tool for evaluating osteoarthritis(Schleich et al., 2016), achilles tendon(Juras et al., 2015), intervertebral disc degeneration(Kim et al., 2011; Q. Liu et al., 2013; Z. Zhou et al., 2016). Recently, a phase I clinical trial was also performed to compare the sensitivity and accuracy of gagCEST on healthy volunteers with those by Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), one of the standard methods for GAG quantification *in vivo*(Wei et al., 2017). While dGEMRIC showed higher performance than gagCEST, the authors also suggested that gagCEST might be further optimized to serve as a non-contrast and non-invasive alternative to dGEMRIC. It should be noted that most recent gagCEST studies were performed at 3T, indicative of great translatability of sugar-detecting CEST MRI methods.

Another type of endogenous sugar-based biopolymer is MUC1, a glycoprotein with extensive O-linked glycosylation of its extracellular domain, which is rich in glycans containing multiple exchangeable OH protons (Figure 2c), thus readily detectable by CEST MRI. Underglycosylated mucin-1 (uMUC1) is overexpressed in most malignant adenocarcinomas of epithelial origin such as colon, breast and ovarian cancers. Song et al. showed a substantial decrease (~75%) in CEST signal at 1 ppm in the tumor cells expressing uMUC1 compared to those expressing MUC1. As shown in Figure 5, when implanted in the striatum of immunodeficient mice, uMUC1-expressing (uMUC1+) LS174T cells displayed a significantly lower CEST signal compared with U87 (uMUC1-deficient, uMUC1-) cells. Their data indicated that CEST MRI is a useful imaging tool to assess mucin glycosylation and tumor malignancy in a label-free manner (Song et al., 2015).

3. Dextran

Different from the abovementioned biopolymers, dextrans are glucose polymers produced by bacteria from sucrose or by chemical synthesis, and therefore only available as exogenous agents. As shown in Figure 2d, dextrans are glucose polymerized predominantly

(~ 95%) through α -1,6-glucosidic linkage with some degree (~ 5%) of branching via 1,3-linkage(Larsen, 1989). Dextran is available in multiple molecular weights ranging from 1 kD to 2 MD (diameters from 1 to 54 nm, respectively)(Armstrong, Wenby, Meiselman, & Fisher, 2004; Dreher et al., 2006). As important clinical materials, the pharmacokinetics of dextran has been well studied, and it has been shown to be highly dependable on molecular weights. Large dextran (> 40 kD) are excreted poorly from the kidney and can remain in the body for weeks, while small dextran (< 20 kD) are quickly cleared from the body(Chang et al., 1975). Dextran has been used clinically for more than 6 decades for plasma volume expansion, peripheral flow promotion, and as antithrombotic agents with a proven safety profile(Dubick & Wade, 1994; Thorén, 1980). Dextran 70 (dextran with MW ~ 70k) is on the WHO Model List of Essential Medicines. Owing to their versatile pharmacokinetic properties and a large number of hydroxyl groups, which can be easily conjugated to drugs and proteins by either direct attachment or through a linker, dextran is considered as ideal drug carriers for delivering drugs to specific sites of action via passive or active targeting(Heinze, Liebert, Heublein, & Hornig, 2006; Mehvar, 2000). Dextran has a well-proven safety profile even at very high doses(Dubick & Wade, 1994). While dextran-induced anaphylactic shock has been reported, the incidence is very low(Ljungstrom et al., 1983; Paull, 1987; Zinderman, Landow, & Wise, 2006), and the anaphylactic reaction can be avoided by a skin test or greatly reduced by pre-administration of dextran 1 (MW ~ 1000) (Ljungström, 2006; Zinderman et al., 2006).

Dextran (MW =10 kD - 2 MD) have been shown with a broad CEST signal resonant at around 1 ppm, and the signal is independent of molecular weights, but highly dependent on the strength of saturation RF pulse (B_1)(Li et al., 2018). On the per glucose unit basis, higher MW dextran exhibit a slightly weaker (but not significant) CEST contrast than those of smaller size, likely due to the reduced water accessibility of a small portion of hydroxyl protons shielded within larger molecules. Like D-glucose, the CEST signal of dextran exhibits a strong pH dependence. As well-documented in several early NMR studies(Hills, 1991; Symons, Benbow, & Harvey, 1980), the exchange of sugar hydroxyl protons is typically base-catalyzed when pH > 6 and acid-catalyzed when pH < 5.5. Hence, the increased CEST signal at lower pH can be attributed to the slowing down of fast-exchanging hydroxyl protons to the slow to intermediate exchange rate regime. The MRI detectability of dextran is on the order of μ M. For example, a molecule of 70 kD dextran contains approximately 400 glucose units, which lead to a 7 μ M detectability, the concentration generating a 5% CEST contrast change (MTR_{asym} = 5%).

To date, two applications of dextran-based CEST (dexCEST) MRI have been explored. The first one is to directly use non-labeled dextran as imaging agents to assess tumor permeability. Because dextran is available at a series of sizes and therefore a wide size range from macro- to nano- size scale, they can be used to determine the permeability in a variety of tissues(Langereis, De Lussanet, Van Genderen, Backes, & Meijer, 2004). In our previous study, we successfully used natural dextran (i.e., Dextran 10 and 70) to assess the vascular permeability of CT26 colon tumors in a mouse model(Li et al., 2018). Interestingly, when sequentially injected intravenously, the enhancement patterns by the two different sizes of dextran are strikingly different in terms of dynamics, area under curve (AUC) and maximal intensity, which in turn can be used to characterize the size-dependent vascular

permeability in the different regions of the same tumor, providing a non-invasive imaging tool. Another biomedical application dexCEST is to image receptor expression in the targeted tissues using ligand-dextran conjugates. While it is considered challenging for MRI to detect receptors due to the inherently low sensitivity of MRI, dextrans provide sufficient sensitivity down to μM (per target), which would allow the detection of some highly expressing biomarkers and receptors. The first proof-of-concept study was reported in 2017 by Liu et al. (G. Liu et al., 2017), in which dextran (MW=10 kD) was conjugated with a urea-based ligand to target prostate-specific membrane antigen (PSMA), a biomarker for aggressive prostate cancer. The constructed ligand-dextran conjugates showed a strong binding affinity with PSMA and detectability of 20 μM (per dextran molecule). The dexCEST MRI enhancement in PSMA-expressing prostate tumors was about 1% (or about 1.1 M of water proton concentration), which is adequate to differentiate the PSMA expressing tumors from the control tumors (Figure 6).

4. Technical challenges

Glucose hydroxyl protons have a small chemical shift (i.e., 1.2 ppm) and very fast exchange rates (i.e., $k_{\text{ex}} > 1 \text{ KHz}$), making the detection more challenging than other exchangeable protons. To date, most of the studies were performed on high-field (i.e., 7, 9.4 and 11.7 T) scanners. Typically, CEST MRI requires the exchange rate of the exchangeable protons to be slow to intermediate in the MR time scale, i.e., of $k_{\text{ex}} < \omega$. However, the exchange rate of glucose hydroxyl protons in physiological conditions (pH = 7.4 and 37 °C) is on the order of several kHz (Cobb, Li, Xie, Gochberg, & Gore, 2014; Yadav et al., 2014). As the chemical shift of glucose hydroxyl protons is $\sim 1.2 \text{ ppm}$, it therefore requires $B_0 > 132 \text{ MHz}$ to detect them assuming the exchange rate = 1 kHz (i.e., $\omega = 2\pi \times 1.2 [\text{ppm}] \times B_0 [\text{Hz/ppm}]$). However, a number of recent studies have shown the possibility to detect glucose hydroxyl protons at 4.7T (P. C. van Zijl et al., 2007b) and even 3T (Lee, Xia, Jerschow, & Regatte, 2016), where the exchange rate falls in the intermediate to fast regime. The CEST effect of intermediate to fast exchange protons is suspected to be caused by that saturation still can be established within the brief lifetime that the hydroxyl protons remain on glucose (P. C. van Zijl et al., 2007b). In addition to carefully optimizing CEST parameters to further improve the detection of glucose hydroxyl protons, several other MRI technologies are also available and potentially can improve the applicability of sugar-based agents on 3T clinical scanners. For example, chemical exchange-sensitive spin-lock (CESL, or $T_{1\rho}$) was suggested to detect hydroxyl protons with a higher sensitivity in the intermediate range (Cobb et al., 2014; Jin & Kim, 2014). Moreover, fast exchangeable protons can be detected by their T_2 -exchange ($T_{2\text{ex}}$) effect and the optimal contrast occurs when $k_{\text{ex}} = \omega$ (Yadav et al., 2014; J. Zhang, Han, et al., 2018; J. Zhang, Li, et al., 2018). The $T_{2\text{ex}}$ MRI has been demonstrated to detect glucose (Yadav et al., 2014) and maltose (Goldenberg, Pagel, & Cárdenas-Rodríguez, 2018). Another new MRI technology, on-resonance variable delay multi-pulse (onVDMP), was also reported to improve the glucose detection (Xu et al., 2018). These new MRI methods can greatly improve the applicability of MRI detection of sugars and sugar-based biopolymers at low field strengths.

Conclusion

By their hydroxyl proton-rich nature, sugar-based polymers can be directly imaged and quantified using CEST MRI, making them a new type of MR molecular imaging agents without the need for any chemical labeling. The biopolymers can be either endogenous (GAG and Mucin1), exogenous (dextran), or both (glycogen). When using as exogenous agents, sugar-based polymers can be considered as naturally-labeled agents, i.e., not radioactive, and not paramagnetic- or super-paramagnetic-based, which can be rapidly translated to the clinic. Moreover, biopolymers such as dextrans are available in a wide size range, which can be easily tailored to different biomedical applications, for example, characterizing of the size-dependent tumor vascular permeability. The use of biopolymer also can boost the sensitivity of MR molecular imaging as a biopolymer can carry more than 1000 exchangeable protons, making the CEST MRI detectability down to μM concentration range. We, therefore, foresee that more and more sugar-based polymers will be investigated for CEST MRI detection and development of theranostic systems.

Acknowledgments

This work was supported by NIH grants R03EB021573, R01CA211087, and R21CA215860.

References

- Adeva-Andany MM, González-Lucán M, Donapetry-García C, Fernández-Fernández C, & Ameneiros-Rodríguez E (2016). Glycogen metabolism in humans. *BBA clinical*, 5, 85–100. [PubMed: 27051594]
- Anzai Y, McLachlan S, Morris M, Saxton R, & Lufkin RB (1994). Dextran-coated superparamagnetic iron oxide, an MR contrast agent for assessing lymph nodes in the head and neck. *American journal of neuroradiology*, 15(1), 87–94. [PubMed: 7511324]
- Armstrong JK, Wenby RB, Meiselman HJ, & Fisher TC (2004). The hydrodynamic radii of macromolecules and their effect on red blood cell aggregation. *Biophys J*, 87(6), 4259–4270. doi: 10.1529/biophysj.104.047746 [PubMed: 15361408]
- Bagga P, Haris M, D'Aquila K, Wilson NE, Marincola FM, Schnall MD, ... Reddy R (2017). Non-caloric sweetener provides magnetic resonance imaging contrast for cancer detection. *Journal of Translational Medicine*, 15(1), 119. doi: 10.1186/s12967-017-1221-9 [PubMed: 28558795]
- Bar-Shir A, Liu GS, Chan KKY, Oskolkov N, Song XL, Yadav NN, ... Gilad AA (2014). Human Protamine-1 as an MRI Reporter Gene Based on Chemical Exchange. *Acs Chemical Biology*, 9(1), 134–138. doi: 10.1021/cb400617q [PubMed: 24138139]
- Bar-Shir A, Liu GS, Liang YJ, Yadav NN, McMahon MT, Walczak P, ... Gilad AA (2013). Transforming Thymidine into a Magnetic Resonance Imaging Probe for Monitoring Gene Expression. *Journal of the American Chemical Society*, 135(4), 1617–1624. doi: 10.1021/ja312353e [PubMed: 23289583]
- Bryson JM, Reineke JW, & Reineke TM (2012). Macromolecular imaging agents containing lanthanides: can conceptual promise lead to clinical potential? *Macromolecules*, 45(22), 8939–8952. [PubMed: 23467737]
- Cai K, Haris M, Singh A, Kogan F, Greenberg JH, Hariharan H, ... Reddy R (2012). Magnetic resonance imaging of glutamate. *Nature Medicine*, 18(2), 302–306. doi: 10.1038/nm.2615
- Chan KW, Liu G, Song X, Kim H, Yu T, Arifin DR, ... McMahon MT (2013). MRI-detectable pH nanosensors incorporated into hydrogels for in vivo sensing of transplanted-cell viability. *Nature Materials*, 12(3), 268–275. doi: 10.1038/nmat3525 [PubMed: 23353626]

- Chan KW, McMahon MT, Kato Y, Liu G, Bulte JW, Bhujwala ZM, ... van Zijl PC (2012). Natural D-glucose as a biodegradable MRI contrast agent for detecting cancer. *Magnetic Resonance in Medicine*, 68(6), 1764–1773. doi: 10.1002/mrm.24520 [PubMed: 23074027]
- Chan K W Y, Yu T, Qiao Y, Liu Q, Yang M, Patel H, ... McMahon MT (2014). A diaCEST MRI approach for monitoring liposomal accumulation in tumors. *Journal of Controlled Release*, 180, 51–59. doi: 10.1016/j.jconrel.2014.02.005 [PubMed: 24548481]
- Chang R, Ueki I, Troy J, Deen W, Robertson CR, & Brenner B (1975). Permeability of the glomerular capillary wall to macromolecules. II. Experimental studies in rats using neutral dextran. *Biophys J*, 15(9), 887. [PubMed: 1182263]
- Chen LQ, Howison CM, Jeffery JJ, Robey IF, Kuo PH, & Pagel MD (2014). Evaluations of extracellular pH within in vivo tumors using acidoCEST MRI. *Magnetic Resonance in Medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 72(5), 1408–1417. doi: 10.1002/mrm.25053
- Chen SZ, Yuan J, Deng M, Wei J, Zhou J, & Wang YX (2016). Chemical exchange saturation transfer (CEST) MR technique for in-vivo liver imaging at 3.0 tesla. *European Radiology*, 26(6), 1792–1800. doi: 10.1007/s00330-015-3972-0 [PubMed: 26334509]
- Cobb JG, Li K, Xie J, Gochberg DF, & Gore JC (2014). Exchange-mediated contrast in CEST and spin-lock imaging. *Magnetic Resonance Imaging*, 32(1), 28–40. doi: 10.1016/j.mri.2013.08.002 [PubMed: 24239335]
- Dansereau RN, & Line BR (1994). Preparation of Dextran-70 Injection Labeled with Technetium-99m for Use as a Cardiac Blood-Pool Imaging Agent. *American Journal of Hospital Pharmacy*, 51(22), 2797–2800. [PubMed: 7531940]
- Daryaei I, & Pagel MD (2015). Double agents and secret agents: the emerging fields of exogenous chemical exchange saturation transfer and T2-exchange magnetic resonance imaging contrast agents for molecular imaging. *Res Rep Nucl Med*, 5, 19–32. doi: 10.2147/RRNM.S81742 [PubMed: 27747191]
- Deng M, Chen SZ, Yuan J, Chan Q, Zhou J, & Wang YX (2016). Chemical Exchange Saturation Transfer (CEST) MR Technique for Liver Imaging at 3.0 Tesla: an Evaluation of Different Offset Number and an After-Meal and Over-Night-Fast Comparison. *Molecular Imaging and Biology*, 18(2), 274–282. doi: 10.1007/s11307-015-0887-8 [PubMed: 26391991]
- Dreher MR, Liu W, Michelich CR, Dewhirst MW, Yuan F, & Chilkoti A (2006). Tumor vascular permeability, accumulation, and penetration of macromolecular drug carriers. *Journal of the National Cancer Institute*, 98(5), 335–344. doi: 10.1093/jnci/djj070 [PubMed: 16507830]
- Dubick MA, & Wade CE (1994). A review of the efficacy and safety of 7.5% NaCl/6% dextran 70 in experimental animals and in humans. *Journal of Trauma-Injury, Infection, and Critical Care*, 36(3), 323–330.
- Goldenberg JM, Pagel MD, & Cárdenas-Rodríguez J (2018). Characterization of D-maltose as a T2-exchange contrast agent for dynamic contrast-enhanced MRI. *Magnetic Resonance in Medicine*, 80(3), 1158–1164. doi: 10.1002/mrm.27082 [PubMed: 29369407]
- Goodarzi N, Varshochian R, Kamalinia G, Atyabi F, & Dinarvand R (2013). A review of polysaccharide cytotoxic drug conjugates for cancer therapy. *Carbohydr Polym*, 92(2), 1280–1293. doi: 10.1016/j.carbpol.2012.10.036 [PubMed: 23399156]
- Haris M, Cai K, Singh A, Hariharan H, & Reddy R (2011). In vivo mapping of brain myo-inositol. *NeuroImage*, 54(3), 2079–2085. doi: 10.1016/j.neuroimage.2010.10.017 [PubMed: 20951217]
- Haris M, Singh A, Cai K, Nath K, Crescenzi R, Kogan F, ... Reddy R (2013). MICEST: a potential tool for non-invasive detection of molecular changes in Alzheimer's disease. *Journal of Neuroscience Methods*, 212(1), 87–93. doi: 10.1016/j.jneumeth.2012.09.025 [PubMed: 23041110]
- Heinze T, Liebert T, Heublein B, & Hornig S (2006). Functional polymers based on dextran *Polysaccharides II* (pp. 199–291): Springer.
- Hills B (1991). Multinuclear NMR studies of water in solutions of simple carbohydrates. I. Proton and deuterium relaxation. *Molecular physics*, 72(5), 1099–1121.
- Jin T, & Kim SG (2014). Advantages of chemical exchange-sensitive spin-lock (CESL) over chemical exchange saturation transfer (CEST) for hydroxyl- and amine-water proton exchange studies. *NMR in Biomedicine*, 27(11), 1313–1324. doi: 10.1002/nbm.3191 [PubMed: 25199631]

- Jin T, Mehrens H, Wang P, & Kim SG (2016). Glucose metabolism-weighted imaging with chemical exchange-sensitive MRI of 2-deoxyglucose (2DG) in brain: Sensitivity and biological sources. *Neuroimage*, 143, 82–90. doi: 10.1016/j.neuroimage.2016.08.040 [PubMed: 27570111]
- Jin T, Wang P, Zong X, & Kim SG (2012). Magnetic resonance imaging of the Amine-Proton EXchange (APEX) dependent contrast. *NeuroImage*, 59(2), 1218–1227. doi: 10.1016/j.neuroimage.2011.08.014 [PubMed: 21871570]
- Jones CK, Huang A, Xu J, Edden RA, Schär M, Hua J, ... McMahon MT (2013). Nuclear Overhauser enhancement (NOE) imaging in the human brain at 7T. *Neuroimage*, 77, 114–124. [PubMed: 23567889]
- Jones KM, Pollard AC, & Pagel MD (2018). Clinical applications of chemical exchange saturation transfer (CEST) MRI. *Journal of magnetic resonance imaging : JMRI*, 47(1), 11–27. doi: 10.1002/jmri.25838 [PubMed: 28792646]
- Juras V, Winhofer Y, Szomolanyi P, Vosshenrich J, Hager B, Wolf P, ... Trattinig S (2015). Multiparametric MR Imaging Depicts Glycosaminoglycan Change in the Achilles Tendon during Ciprofloxacin Administration in Healthy Men: Initial Observation. *Radiology*, 275(3), 763–771. doi: 10.1148/radiol.15140484 [PubMed: 25654669]
- Kim M, Chan Q, Anthony MP, Cheung KM, Samartzis D, & Khong PL (2011). Assessment of glycosaminoglycan distribution in human lumbar intervertebral discs using chemical exchange saturation transfer at 3 T: feasibility and initial experience. *NMR Biomed*, 24(9), 1137–1144. doi: 10.1002/nbm.1671 [PubMed: 21387446]
- Kogan F, Hariharan H, & Reddy R (2013). Chemical Exchange Saturation Transfer (CEST) Imaging: Description of Technique and Potential Clinical Applications. *Curr Radiol Rep*, 1(2), 102–114. doi: 10.1007/s40134-013-0010-3 [PubMed: 23730540]
- Langereis S, De Lussanet QG, Van Genderen MH, Backes WH, & Meijer E (2004). Multivalent contrast agents based on gadolinium-diethylenetriaminepentaacetic acid-terminated poly(propylene imine) dendrimers for magnetic resonance imaging. *Macromolecules*, 37(9), 3084–3091.
- Larsen C (1989). Dextran prodrugs—structure and stability in relation to therapeutic activity. *Advanced drug delivery reviews*, 3(1), 103–154.
- Lee JS, Xia D, Jerschow A, & Regatte RR (2016). In vitro study of endogenous CEST agents at 3 T and 7 T. *Contrast Media and Molecular Imaging*, 11(1), 4–14. doi: 10.1002/cmml.1652 [PubMed: 26153196]
- Li Y, Chen H, Xu J, Yadav NN, Chan KW, Luo L, ... Liu G (2016). CEST theranostics: label-free MR imaging of anticancer drugs. *Oncotarget*, 7(6), 6369–6378. doi: 10.18632/oncotarget.7141 [PubMed: 26837220]
- Li Y, Qiao Y, Chen H, Bai R, Staedtke V, Han Z, ... Liu G (2018). Characterization of tumor vascular permeability using natural dextrans and CEST MRI. *Magnetic Resonance in Medicine*, 79(2), 1001–1009. doi: 10.1002/mrm.27014 [PubMed: 29193288]
- Ling W, Regatte RR, Navon G, & Jerschow A (2008). Assessment of glycosaminoglycan concentration in vivo by chemical exchange-dependent saturation transfer (gagCEST). *Proceedings of the National Academy of Sciences of the United States of America*, 105(7), 2266–2270. doi: 10.1073/pnas.0707666105 [PubMed: 18268341]
- Liu G, Moake M, Har-el YE, Long CM, Chan KW, Cardona A, ... McMahon MT (2012). In vivo multicolor molecular MR imaging using diamagnetic chemical exchange saturation transfer liposomes. *Magnetic Resonance in Medicine*, 67(4), 1106–1113. doi: 10.1002/mrm.23100 [PubMed: 22392814]
- Liu G, Ray Banerjee S, Yang X, Yadav N, Lisok A, Jablonska A, ... van Zijl P (2017). A dextran-based probe for the targeted magnetic resonance imaging of tumours expressing prostate-specific membrane antigen. *Nat Biomed Eng*, 1(12), 977–982. doi: 10.1038/s41551-017-0168-8 [PubMed: 29456877]
- Liu G, Song X, Chan KW, & McMahon MT (2013). Nuts and bolts of chemical exchange saturation transfer MRI. *NMR in Biomedicine*, 26(7), 810–828. doi: 10.1002/nbm.2899 [PubMed: 23303716]

- Liu GS, Liang YJ, Bar-Shir A, Chan KWY, Galpoththawela CS, Bernard SM, ... Gilad AA (2011). Monitoring Enzyme Activity Using a Diamagnetic Chemical Exchange Saturation Transfer Magnetic Resonance Imaging Contrast Agent. *Journal of the American Chemical Society*, 133(41), 16326–16329. doi: 10.1021/ja204701x [PubMed: 21919523]
- Liu H, Jablonska A, Li Y, Cao S, Liu D, Chen H, ... Liu G (2016). Label-free CEST MRI Detection of Citicoline-Liposome Drug Delivery in Ischemic Stroke. *Theranostics*, 6(10), 1588–1600. doi: 10.7150/thno.15492 [PubMed: 27446492]
- Liu P, Yue C, Shi B, Gao G, Li M, Wang B, ... Cai L (2013). Dextran based sensitive theranostic nanoparticles for near-infrared imaging and photothermal therapy in vitro. *Chemical Communications*, 49(55), 6143–6145. [PubMed: 23727789]
- Liu Q, Jin N, Fan Z, Natsuaki Y, Tawackoli W, Pelled G, ... Li D (2013). Reliable chemical exchange saturation transfer imaging of human lumbar intervertebral discs using reduced-field-of-view turbo spin echo at 3.0 T. *NMR in Biomedicine*, 26(12), 1672–1679. doi: 10.1002/nbm.3001 [PubMed: 23893565]
- Liu ZH, Jiao YP, Wang YF, Zhou CR, & Zhang ZY (2008). Polysaccharides-based nanoparticles as drug delivery systems. *Advanced drug delivery reviews*, 60(15), 1650–1662. doi: 10.1016/J.ADDR.2008.09.001 [PubMed: 18848591]
- Ljungström K-G (2006). Invited commentary: Pretreatment with dextran 1 makes dextran 40 therapy safer. *Journal of vascular surgery*, 43(5), 1070–1072. [PubMed: 16678710]
- Ljungstrom KG, Renck H, Strandberg K, Hedin H, Richter W, & Widerlov E (1983). Adverse reactions to dextran in Sweden 1970–1979. *Acta Chir Scand*, 149(3), 253–262. [PubMed: 6193664]
- Lock LL, Li Y, Mao X, Chen H, Staedtke V, Bai R, ... Cui H (2017). One-Component Supramolecular Filament Hydrogels as Theranostic Label-Free Magnetic Resonance Imaging Agents. *ACS Nano*, 11(1), 797–805. doi: 10.1021/acsnano.6b07196 [PubMed: 28075559]
- Longo DL, Dastru W, Digilio G, Keupp J, Langereis S, Lanzardo S, ... Aime S (2011). Iopamidol as a Responsive MRI-Chemical Exchange Saturation Transfer Contrast Agent for pH Mapping of Kidneys: In Vivo Studies in Mice at 7 T. *Magnetic Resonance in Medicine*, 65(1), 202–211. doi: 10.1002/mrm.22608 [PubMed: 20949634]
- Longo DL, Moustaghfir FZ, Zerbo A, Consolino L, Anemone A, Bracesco M, & Aime S (2017). EXCI-CEST: Exploiting pharmaceutical excipients as MRI-CEST contrast agents for tumor imaging. *International Journal of Pharmaceutics*, 525(1), 275–281. [PubMed: 28433532]
- Longo DL, Sun PZ, Consolino L, Michelotti FC, Uggeri F, & Aime S (2014). A general MRI-CEST ratiometric approach for pH imaging: demonstration of in vivo pH mapping with iobitridol. *Journal of the American Chemical Society*, 136(41), 14333–14336. doi: 10.1021/ja5059313 [PubMed: 25238643]
- Matsunaga K, Hara K, Imamura T, Fujioka T, Takata J, & Karube Y (2005). Technetium labeling of dextran incorporating cysteamine as a ligand. *Nuclear medicine and biology*, 32(3), 279–285. [PubMed: 15820763]
- McMahon MT, Gilad AA, Zhou JY, Sun PZ, Bulte JWM, & van Zijl PCM (2006). Quantifying exchange rates in chemical exchange saturation transfer agents using the saturation time and saturation power dependencies of the magnetization transfer effect on the magnetic resonance imaging signal (QUEST and QUESP): pH calibration for poly-L-lysine and a starburst dendrimer. *Magnetic Resonance in Medicine*, 55(4), 836–847. doi: 10.1002/mrm.20818 [PubMed: 16506187]
- Mehvar R (2000). Dextran for targeted and sustained delivery of therapeutic and imaging agents. *J Control Release*, 69(1), 1–25. [PubMed: 11018543]
- Meyer J-P, Tully KM, Jackson J, Dilling TR, Reiner T, & Lewis JS (2018). Bioorthogonal Masking of Circulating Antibody–TCO Groups Using Tetrazine-Functionalized Dextran Polymers. *Bioconjugate chemistry*, 29(2), 538–545. [PubMed: 29378403]
- Miller CO, Cao J, Chekmenev EY, Damon BM, Cherrington AD, & Gore JC (2015). Noninvasive measurements of glycogen in perfused mouse livers using chemical exchange saturation transfer NMR and comparison to (13)C NMR spectroscopy. *Analytical Chemistry*, 87(11), 5824–5830. doi: 10.1021/acs.analchem.5b01296 [PubMed: 25946616]
- Mohanty AK, Misra M, & Drzal LT (2005). Natural fibers, biopolymers, and biocomposites.

- Moon BF, Jones KM, Chen LQ, Liu P, Randtke EA, Howison CM, & Pagel MD (2015a). A comparison of iopromide and iopamidol, two acidoCEST MRI contrast media that measure tumor extracellular pH. *Contrast Media and Molecular Imaging*. doi: 10.1002/cmmi.1647
- Moon BF, Jones KM, Chen LQ, Liu PL, Randtke EA, Howison CM, & Pagel MD (2015b). A comparison of iopromide and iopamidol, two acidoCEST MRI contrast media that measure tumor extracellular pH. *Contrast Media & Molecular Imaging*, 10(6), 446–455. doi: 10.1002/cmmi.1647 [PubMed: 26108564]
- Morais M, Campello MP, Xavier C, Heemskerk J, Correia J. o. D., Lahoutte T, ... Santos I (2014). Radiolabeled mannosylated dextran derivatives bearing an NIR-fluorophore for sentinel lymph node imaging. *Bioconjugate chemistry*, 25(11), 1963–1970. [PubMed: 25265437]
- Nasrallah FA, Pages G, Kuchel PW, Golay X, & Chuang KH (2013). Imaging brain deoxyglucose uptake and metabolism by glucoCEST MRI. *Journal of Cerebral Blood Flow and Metabolism*, 33(8), 1270–1278. doi: 10.1038/jcbfm.2013.79 [PubMed: 23673434]
- Ngen EJ, Bar-Shir A, Jablonska A, Liu G, Song X, Ansari R, ... Gilad AA (2016). Imaging the DNA Alkylator Melphalan by CEST MRI: An Advanced Approach to Theranostics. *Molecular Pharmaceutics*, 13(9), 3043–3053. doi: 10.1021/acs.molpharmaceut.6b00130 [PubMed: 27398883]
- Paull J (1987). A prospective study of dextran-induced anaphylactoid reactions in 5745 patients. *Anaesthesia and intensive care*, 15(2), 163–167. [PubMed: 2440337]
- Rebizak R, Schaefer M, & Dellacherie É (1997). Polymeric conjugates of Gd3+–diethylenetriaminepentaacetic acid and dextran. 1. Synthesis, characterization, and paramagnetic properties. *Bioconjugate chemistry*, 8(4), 605–610. [PubMed: 9258461]
- Rivlin M, Horev J, Tsarfaty I, & Navon G (2013). Molecular imaging of tumors and metastases using chemical exchange saturation transfer (CEST) MRI. *Sci Rep*, 3, 3045. doi: 10.1038/srep03045 [PubMed: 24157711]
- Rivlin M, & Navon G (2016). Glucosamine and N-acetyl glucosamine as new CEST MRI agents for molecular imaging of tumors. *Sci Rep*, 6, 32648. doi: 10.1038/srep32648 [PubMed: 27600054]
- Rivlin M, & Navon G (2017). CEST MRI of 3-O-methyl-D-glucose on different breast cancer models. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. doi: 10.1002/mrm.26752
- Rivlin M, Tsarfaty I, & Navon G (2014). Functional molecular imaging of tumors by chemical exchange saturation transfer MRI of 3-O-Methyl-D-glucose. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 72(5), 1375–1380. doi: 10.1002/mrm.25467
- Ryoo D, Xu X, Li Y, Tang JA, Zhang J, van Zijl PCM, & Liu G (2017). Detection and Quantification of Hydrogen Peroxide in Aqueous Solutions Using Chemical Exchange Saturation Transfer. *Analytical Chemistry*, 89(14), 7758–7764. doi: 10.1021/acs.analchem.7b01763 [PubMed: 28627877]
- Schleich C, Bittersohl B, Miese F, Schmitt B, Muller-Lutz A, Sondern M, ... Zilkens C (2016). Glycosaminoglycan chemical exchange saturation transfer at 3T MRI in asymptomatic knee joints. *Acta Radiol*, 57(5), 627–632. doi: 10.1177/0284185115598811 [PubMed: 26253931]
- Schmiedl U, Ogan M, Paaanen H, Marotti M, Crooks LE, Brito AC, & Brasch RC (1987). Albumin Labeled with Gd-Dtpa as an Intravascular, Blood Pool Enhancing Agent for Mr Imaging - Biodistribution and Imaging Studies. *Radiology*, 162(1), 205–210. doi: DOI 10.1148/radiology.162.1.3786763 [PubMed: 3786763]
- Sehgal AA, Li Y, Lal B, Yadav NN, Xu X, Xu J, ... van Zijl PCM (2018). CEST MRI of 3-O-methyl-D-glucose uptake and accumulation in brain tumors. *Magnetic Resonance in Medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. doi: 10.1002/mrm.27489
- Snoussi K, Bulte JWM, Gueron M, & van Zijl PCM (2003). Sensitive CEST agents based on nucleic acid imino proton exchange: Detection of poly(rU) and of a dendrimer-poly(rU) model for nucleic acid delivery and pharmacology. *Magnetic Resonance in Medicine*, 49(6), 998–1005. doi: 10.1002/mrm.10463 [PubMed: 12768576]

- Song X, Airan RD, Arifin DR, Bar-Shir A, Kadayakkara DK, Liu G, ... Bulte JW (2015). Label-free in vivo molecular imaging of underglycosylated mucin-1 expression in tumour cells. *Nature Communications*, 6, 6719. doi: 10.1038/ncomms7719
- Sun G, Feng J, Jing F, Pei F, & Liu M (2003). Synthesis and evaluation of novel polysaccharide-Gd-DTPA compounds as contrast agent for MRI. *Journal of magnetism and magnetic materials*, 265(2), 123–129.
- Swierczewska M, Han HS, Kim K, Park JH, & Lee S (2016). Polysaccharide-based nanoparticles for theranostic nanomedicine. *Adv Drug Deliv Rev*, 99(Pt A), 70–84. doi: 10.1016/j.addr.2015.11.015 [PubMed: 26639578]
- Symons MCR, Benbow JA, & Harvey JM (1980). Hydroxyl-Proton Resonance Shifts for a Range of Aqueous Sugar Solutions. *Carbohydrate Research*, 83(1), 9–20. doi: 10.1016/S0008-6215(00)85359-8
- Tassa C, Shaw SY, & Weissleder R (2011). Dextran-coated iron oxide nanoparticles: a versatile platform for targeted molecular imaging, molecular diagnostics, and therapy. *Accounts of chemical research*, 44(10), 842–852. [PubMed: 21661727]
- Thorén L (1980). The dextrans--clinical data. *Developments in biological standardization*, 48, 157–167. [PubMed: 6168501]
- van Zijl P, & Sehgal AA (2016). Proton Chemical Exchange Saturation Transfer (CEST) MRS and MRI. *eMagRes*, 5, 1–26. doi: 10.1002/9780470034590.emrstm1482
- van Zijl PC, Jones CK, Ren J, Malloy CR, & Sherry AD (2007a). MRI detection of glycogen in vivo by using chemical exchange saturation transfer imaging (glycoCEST). *Proceedings of the National Academy of Sciences of the United States of America*, 104(11), 4359–4364. doi: 10.1073/pnas.0700281104 [PubMed: 17360529]
- van Zijl PC, Jones CK, Ren J, Malloy CR, & Sherry AD (2007b). MRI detection of glycogen in vivo by using chemical exchange saturation transfer imaging (glycoCEST). *Proceedings of the National Academy of Sciences of the United States of America*, 104(11), 4359–4364. doi: 10.1073/pnas.0700281104 [PubMed: 17360529]
- van Zijl PC, & Yadav NN (2011). Chemical exchange saturation transfer (CEST): what is in a name and what isn't? *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 65(4), 927–948. doi: 10.1002/mrm.22761
- Varshosaz J (2012). Dextran conjugates in drug delivery. *Expert opinion on drug delivery*, 9(5), 509–523. [PubMed: 22432550]
- Walker-Samuel S, Ramasawmy R, Torrealdea F, Rega M, Rajkumar V, Johnson SP, ... Golay X (2013). In vivo imaging of glucose uptake and metabolism in tumors. *Nature Medicine*, 19(8), 1067–1072. doi: 10.1038/nm.3252
- Wang F, Kopylov D, Zu Z, Takahashi K, Wang S, Quarles CC, ... Takahashi T (2016). Mapping murine diabetic kidney disease using chemical exchange saturation transfer MRI. *Magnetic Resonance in Medicine*, 76(5), 1531–1541. doi: 10.1002/mrm.26045 [PubMed: 26608660]
- Wang SC, Wikstrom MG, White DL, Klaveness J, Holtz E, Rongved P, ... Brasch RC (1990). Evaluation of Gd-DTPA-labeled dextran as an intravascular MR contrast agent: imaging characteristics in normal rat tissues. *Radiology*, 175(2), 483–488. doi: 10.1148/radiology.175.2.1691513 [PubMed: 1691513]
- Ward KM, Aletras AH, & Balaban RS (2000). A new class of contrast agents for MRI based on proton chemical exchange dependent saturation transfer (CEST). *Journal of Magnetic Resonance*, 143(1), 79–87. doi: 10.1006/jmre.1999.1956 [PubMed: 10698648]
- Wei W, Lambach B, Jia G, Kaeding C, Flanigan D, & Knopp MV (2017). A Phase I clinical trial of the knee to assess the correlation of gagCEST MRI, delayed gadolinium-enhanced MRI of cartilage and T2 mapping. *Eur J Radiol*, 90, 220–224. doi: 10.1016/j.ejrad.2017.02.030 [PubMed: 28583638]
- Wu X, Feng Y, Jeong EK, Emerson L, & Lu ZR (2009). Tumor characterization with dynamic contrast enhanced magnetic resonance imaging and biodegradable macromolecular contrast agents in mice. *Pharm Res*, 26(9), 2202–2208. doi: 10.1007/s11095-009-9935-x [PubMed: 19597972]

- Xu X, Chan KW, Knutsson L, Artemov D, Xu J, Liu G, ... van Zijl PC (2015). Dynamic glucose enhanced (DGE) MRI for combined imaging of blood-brain barrier break down and increased blood volume in brain cancer. *Magnetic Resonance in Medicine*, 74(6), 1556–1563. doi: 10.1002/mrm.25995 [PubMed: 26404120]
- Xu X, Xu J, Chan K W Y, Liu J, Liu H, Li Y, ... van Zijl PCM (2018). GlucoCEST imaging with on-resonance variable delay multiple pulse (onVDMP) MRI. *Magnetic Resonance in Medicine*. doi: 10.1002/mrm.27364
- Yadav NN, Xu J, Bar-Shir A, Qin Q, Chan KW, Grgac K, ... van Zijl PC (2014). Natural D-glucose as a biodegradable MRI relaxation agent. *Magn Reson Med*, 72(3), 823–828. doi: 10.1002/mrm.25329 [PubMed: 24975029]
- Yang X, Song XL, Banerjee SR, Li YG, Byun Y, Liu GS, ... McMahon MT (2016). Developing imidazoles as CEST MRI pH sensors. *Contrast Media & Molecular Imaging*, 11(4), 304–312. doi: 10.1002/cmmi.1693 [PubMed: 27071959]
- Yang X, Song XL, Li YG, Liu GS, Banerjee SR, Pomper MG, & McMahon MT (2013). Salicylic Acid and Analogues as diaCEST MRI Contrast Agents with Highly Shifted Exchangeable Proton Frequencies. *Angewandte Chemie-International Edition*, 52(31), 8116–8119. doi: 10.1002/anie.201302764 [PubMed: 23794432]
- Zhang J, Han Z, Lu J, Li Y, Liao X, van Zijl PCM, ... Liu G (2018). Triazoles as T2-exchange MRI contrast agents for the detection of nitrilase activity. *Chemistry*. doi: 10.1002/chem.201802663
- Zhang J, Li Y, Slania S, Yadav NN, Liu J, Wang R, ... Liu G (2018). Phenols as Diamagnetic T2-Exchange Magnetic Resonance Imaging Contrast Agents. *Chemistry*, 24(6), 1259–1263. doi: 10.1002/chem.201705772 [PubMed: 29266443]
- Zhang X-Y, Wang F, Afzal A, Xu J, Gore JC, Gochberg DF, & Zu Z (2016). A new NOE-mediated MT signal at around– 1.6 ppm for detecting ischemic stroke in rat brain. *Magnetic Resonance Imaging*, 34(8), 1100–1106. [PubMed: 27211260]
- Zhou J, Payen JF, Wilson DA, Traystman RJ, & van Zijl PC (2003). Using the amide proton signals of intracellular proteins and peptides to detect pH effects in MRI. *Nature Medicine*, 9(8), 1085–1090. doi: 10.1038/nm907
- Zhou Z, Bez M, Tawackoli W, Giaconi J, Sheyn D, de Mel S, ... Li D (2016). Quantitative chemical exchange saturation transfer MRI of intervertebral disc in a porcine model. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 76(6), 1677–1683. doi: 10.1002/mrm.26457
- Zinderman CE, Landow L, & Wise RP (2006). Anaphylactoid reactions to Dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. *Journal of vascular surgery*, 43(5), 1004–1009. [PubMed: 16678697]

Figure. 1. Illustration of CEST MRI detection of natural dextran, which is achieved by the continuous transfer of saturated protons (red) from hydroxyl groups to surrounding water molecules, generating a reduction in the water signal (MRI contrast) proportional to the dextran concentration and the rate of exchange. The unsaturated hydroxyl protons are shown in blue. S_{sat} , the water (MRI) signal in the presence of saturation RF pulses. Reproduced from ref.(G. Liu et al., 2017)with permission.

Figure 2. Structure illustration of four sugar-based biopolymers.

a) Glycogen, b) GAG, c) Mucin1, and d) Dextran.

Figure 3.

glycoCEST imaging of a perfused fed-mouse liver at 4.7 T and 37°C. The first image (gray scale) marks the beginning of perfusion ($t = 0$) with glucose-free media containing 500 pg/ml glucagon. The liver tissue is darkened because of the CEST effect from presaturation at 1.0 ppm for 1 s at 3.0 μ T. Upon further perfusion with glucagon, the liver signal increased, corresponding to a decrease in CEST effect. The colorized glycoCEST images as a function of time during perfusion show the relative CEST intensity [MTRasym (1 ppm)] of liver tissue as a function of perfusion time. The color scale shows that there are regions of liver where the initial asymmetry difference between ± 1 ppm is as high as 55% (orange pixels) and as low as 5% (blue pixels). With time, as glycogen disappears, the CEST images become more uniformly dark blue, corresponding to minimal glycogen. The corresponding glycogen depletion for a homogeneous region of interest is quantified in the graph ($n = 4$). Reproduced from ref.(P. C. van Zijl, Jones, Ren, Malloy, & Sherry, 2007b)with permission.

Figure 4. GagCEST MR Images of a human patella in vivo with irradiation at -1.0 ppm, $+1.0$ ppm, and the difference image (a) along with the extracted CEST contrast from the femur and the lateral and medial sides of the patella (b). The total duration of the presaturation pulse sequence was 320 ms at an average RF power of 42 Hz. Reproduced from ref. (Ling et al., 2008) with permission.

Figure 5.

(a) T2w image, marked with regions of U87, LS174T, and control white matter (dashed square). (b) CEST contrast map created by averaging 1.2 and 0.9 ppm superimposed onto (a) for B1=3.6 μT . (c) MTR_{asym} curves of the three ROIs marked in (a). (d) MTR_{asym} values of the two cell lines showing a significant difference (*P<0.05, Student's t-test). Error bars represent standard deviation. (n=3). Reproduced from ref. (Song et al., 2015) with permission.

Figure 6. Changes in the dynamic CEST signal in PSMA(+) and PSMA(-) tumours.

a T2-weighted image and dynamic CEST maps at 1 ppm after the injection of 375 mg/kg urea-10KD-dextran (injection volume = 100 μL). **b** Mean changes in the CEST signal in PSMA(+) and PSMA(-) tumours in one of the mice for which time dependence was measured. CEST signal enhancement was quantified by $MTR_{asym} = MTR_{asym}(t) - MTR_{asym}(t=0)$, where the error bars are the standard errors of the CEST signal of all the pixels in each tumour. All CEST images were acquired using a 1.8 μT and 3-second-long CW pulse. **c** Average CEST signal in the tumour for five mice before (blue) and one hour after (red) the injection of urea-Dex10. The signal difference is shown in black. Error bars are standard deviations of the CEST signal of all five tumours. **d** Bar plots showing the mean changes in CEST signal as quantified by MTR_{asym} (1 h) in each type tumour (n = 5 and 3 for urea-Dex10 and non-targeted Dex10 respectively). * : $P < 0.05$ (Student's t test, two-tailed and unpaired). **e** In vivo fluorescence image of a representative mouse showing a distinctive tumour uptake of urea-Dex10 at 60 minutes after injection. **f** Sections of PSMA(+) PC3-PIP (top) and PSMA(-) PC3-flu (bottom) tumours stained with anti-PSMA. Images were acquired at 40× magnification. **g** Fluorescence microscopy of nuclei (blue, stained with DAPI) dextran (red, NIR-600-labeled). Scale bar = 500 μm for the left three panels and 100 μm for the most right panels, which are the zoomed view of the area enclosed in the dashed green box in the image on the left. On the right, a scatter plot shows the comparison of the normalized mean fluorescence intensity of three different field of views in the tumours. Reproduced from ref. (G. Liu et al., 2017) with permission.

Table1.

DIACEST library

Exchangeable proton	Signal frequency offset ω (ppm)	Examples
Hydroxyl (–OH)	0.8–2, 4.8	glucose(K. W. Chan et al., 2012; Walker-Samuel et al., 2013; Xu et al., 2015) 3-OMG(Rivlin & Navon, 2017; Rivlin et al., 2014; Sehgal et al., 2018) 2DG(Jin et al., 2016; Nasrallah et al., 2013; Rivlin et al., 2013) dextran(Li et al., 2018; G. Liu et al., 2017) sucralose(Bagga et al., 2017) sucrose(Dario Livio Longo et al., 2017) glucosamine(Rivlin & Navon, 2016) phenol(J. Zhang, Li, et al., 2018)
Amide (–NH)	3.5, 4.2, 5.6	poly-L-lysine(McMahon et al., 2006) Iopamidol(D. L. Longo et al., 2011) iopromide(Moon et al., 2015b) mobile proteins(J. Zhou, Payen, Wilson, Traystman, & van Zijl, 2003)
Amino (–NH ₂)	1.8–2.4	L-arginine(K. W. Chan et al., 2013; G. Liu et al., 2012) protamine(Bar-Shir et al., 2014) cytosine/5-FC(G. S. Liu et al., 2011) proteins(Jin, Wang, Zong, & Kim, 2012) folate acids(Li et al., 2016)
Heterocyclic ring amide (–NH)	5–6.3	barbituric acid(K. W. Y. Chan et al., 2014) thymidine(Bar-Shir et al., 2013) uridine(Snoussi, Bulte, Gueron, & van Zijl, 2003)
Hydrogen bonds	6–12	Salicylic acids(Yang et al., 2013) imidazoles(Yang et al., 2016), H ₂ O ₂ (Ryoo et al., 2017)
Aliphatic protons (rNOE)	–1.6, –3.5	Mobile proteins(C. K. Jones et al., 2013; X.-Y. Zhang et al., 2016)

Abbreviations: 3-OMG: 3-O-methyl glucose; 2DG: 2-Deoxy-D-glucose; rNOE: relayed nuclear overhauser effect