Title of Talk: Pro-CEST

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Highlights:

1) Amplification of imaging sensitivity through chemical exchange of spins with water
2) CEST contrast agents have several advantages over T1 and T2* agents which might be important for tumor imaging: switchable (on/off) contrast, sensitivity to pH, and capability of "multi-color" or "multiplex" imaging.
3) CEST imaging can be helpful for monitoring tumor grade and tumor therapy.
4) Anatomical MRI can be acquired using the same hardware.
5) CEST imaging protocols have already been established at 3T and CEST images have been collected on a number of patients to date.

Brief description of Chemical Exchange Saturation Transfer (CEST):

CEST is a newer type of MRI contrast based on the application of saturation pulses to protons in rapidly exchange with water, resulting in an amplification of signal which allows detection at millimolar to micromolar concentrations of these protons. In 2000, Balaban and colleagues showed for the first time how CEST imaging can be performed, and introduced the term "CEST contrast agents [1]. The saturation transfer contrast produced by a variety of paramagnetic and diamagnetic compounds was soon investigated by other MRI researchers [2-5], leading to the establishment of this field of research.

There are three main types of CEST contrast agents: paramagnetic agents (paraCEST) [3,6], diamagnetic agents (diaCEST) [1,2], and hyperpolarized agents (hyperCEST) [7]. ParaCEST agents are mainly lanthanide complexes with protons exchanging slow enough for detection, as first shown by Sherry and Aime et al., although complexes which include other metals such as iron are also possible[8]. This contrast is based on proton exchange of water bound to the metal center and/or exchangeable protons in the vicinity of the metal center with bulk water, with the metal perturbing the offset frequencies of these protons. DiaCEST agents are naturally occurring molecules without metal ions, with the contrast dependent on the number and type of labile protons. HyperCEST agents are slightly different, which are cages such as cryptophane designed to trap dissolved hyperpolarized material. Frequency differences are induced in the spins of the hyperpolarized material which naturally passes in and out of the cage structure. During this process, the signal is transferred from the interior of the cage to the exterior.

The process of imaging these specific pools of exchangeable protons is a useful tool for molecular imaging and has several advantages. First, because proton exchange occurs many times during the saturation pulse, the signal from

a small pool of solute protons (μM-mM) is amplified and transferred onto the much larger water signal (110 M for pure water), which improves the detection sensitivity dramatically. Second, the use of frequency selective saturation pulses to irradiate solute protons allows the contrast to be "switched on and off at will", and enables identification of these protons through their chemical shift with respect to water. As a result of these features, different exchangeable protons can be detected simultaneously but also separately identified, e.g. OH versus NH [9,10]. A third attractive feature of these agents is the potential to sense a variety of environmental factors and molecules [1,3,11]. For example, pH influences proton exchange rates through an acid and base catalysis of the exchange rate as described in detail by a number of groups previously [12-15].

Why use CEST as a part of Cancer Imaging?

There has been a tremendous amount of interest in developing new MR imaging agents for detecting the presence of tumors, determining their aggressiveness, or monitoring tumor progression. CEST imaging has been applied to brain tumors for over a decade now [5], with the first studies focusing on detecting and grading brain tumors through quantifying the amount of amide protons through Amide Proton Transfer (APT) contrast. The amount of contrast has been related to tumor grade in patients [16,17].

Exogenous contrast agents are in widespread use for clinical MRI to highlight pathology, in fact about one third of all clinical scans involve the administration of contrast agents [18]. CEST contrast agents possess several advantages for tumor imaging over paramagnetic and super paramagnetic T1 and T2* agents that are described in the previous section. In particular there are efforts underway to evaluate both paraCEST agents using Yb(III), Eu(III), and other metals [19-24] and diaCEST agents using sugars, peptides and other organic compounds [25-31] for highlighting tumors.

In addition to the traditional use of contrast material for visualizing tumors, CEST imaging has been proposed to monitor tumor therapy directly. In one example, nanocarriers of chemotherapeutics can be prepared to generate CEST contrast, allowing the monitoring of their delivery to tumors [32-34]. Two of the real attractive features of CEST contrast for this application is the switchability, potentially not requiring the pre-injection image for detection, and the "multi-color" or "multiplex" imaging capabilities. Two other examples recently described involve the use of CEST imaging to monitor bacteriolytic cancer therapy [35] and oncolytic virotherapy [36].

Translation of this technology to the clinic

Recently there has been tremendous progress in the development of CEST imaging technology, allowing the application of this technology to cancer. In particular, new imaging hardware has been developed to apply the long saturation employed in many protocols [37,38]. In addition, multiple imaging sequences have been developed which allow the acquisition of CEST images within SAR guidelines [39-46].

With respect to administration of exogenous agents, there is potential for

using previously approved compounds from other imaging modalities such as CT [47,48], or from clinical testing, i.e. glucose tolerance test [26,28] or treatment of pain [29]. Other CEST agents would require approval for human use, however existing 1H MRI hardware and protocols could still be employed for their detection. At this stage, there are several promising agents being evaluated on 3T and 7T scanners.

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