Lactate-Specific Shift Reagents for Active Surveillance of Cancers by CEST MRI

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Technology description

The University of Texas at Dallas is seeking companies interested in commercializing novel paramagnetic shift imaging reagents that enable discrimination of D- versus L-lactate - the unique metabolic hallmarks that distinguish cancerous tumors from benign growths and normal tissues.
In the past, the development of non-invasive differential diagnostic methods of tumor analysis has been hindered by the inability to discriminate between these key enantiomeric forms of lactate. UTD presents its novel reagents and the associated methodology for cancer diagnosis which have been demonstrated in an animal model through imaging excess lactate excreted into the bladder of a mouse.
The invention presented here takes advantages of several newly synthesized novel paramagnetic shift reagents (SR) which form selective, stable complexes with either D- or L-lactate. It has been known that cancer cells can excrete D-lactate while healthy mammalian cells only produce L-lactate. These complexes shift the lactate –OH proton resonance far away from the water while retaining the chemical exchange saturation transfer (CEST) properties of lactate itself. The magnified chemical shift of lactate complexes effectively separates them from the water signals. More importantly and significantly, these D- and L-lactate complexes generate a sufficient difference in chemical shifts between each structure that allows for enantiomeric discrimination by CEST-MRI. Given that the development of enantio-pure agents is of great interest in molecular imaging, this work is a positive advancement towards optimizing inorganic shift reagents for selective identification of important biomarkers and metabolic profiles.
Technical Summary:
The novel paramagnetic shift imaging contrast reagents, Yb_1 through Yb_4, are synthesized in a 9-step procedure. They are applied in an assay to quantify the ratios of both lactate isomers through CEST-MRI. These reagents do not discriminate between the two enantiomeric forms of lactate by forming a stable complex with either D- or L-lactate. All complexes have virtually identical molecular geometries. However, they have different chemical shifts due to the different position of the lactate proton nuclei with respect to the magnetic properties of the Yb ion. Since each agent has only one stereoisomer and forms a stable complex with either lactate isomer, they are able to provide a stronger signal than commercial contrast reagents used for this purpose, such as EuDO3A. Overall, the proton exchange rates were close to optimal at 310 K, beneficial for experiments performed at physiological

temperatures. The Yb_3 demonstrated especially strong chemical stability at various pH conditions and was further shown to be stable in severalin vivomodels.
Lactate-specific shift reagents have been synthesized and shown to provide a non-invasive method to quantitatively measure the ratios of D-/L-lactate complexes for differential diagnosis between malignant and benign tumors.
Publication:
Zhang, Lei, et al. "Enantiomeric Recognition of d- and l-Lactate by CEST with the Aid of a Paramagnetic Shift Reagent." Journal of the American Chemical Society,2017, 139 (48), pp 17431–17437. DOI: 10.1021/jacs.7b08292.

Application area

Developing Enantiopure Agents– Novel approach towards optimizing inorganic responsive agents for selective identification of biomarkers and metabolic profiles
Molecular Imaging Tool– Near-optimal proton exchange rates at physiological temperatures (310 K); Potential candidate for in vivo applications: stereoselective discrimination of D- versus L-lactate; Useful as imaging tools for chemical discrimination of enantiomeric amino acids and carboxylated enols.
Metabolite Biomarker– Research tool to quantitatively measure the ratios of both D- or L-lactate isomers, providing new insights into metabolic profiles of cancer & the Warburg effect
Clinical Diagnostics– Detection and differential diagnosis of small malignancies from benign tumors; diagnosis of Irritable Bowel Syndrome (IBS)

Advantages

Improved Resolution- Enables distinction between the chemical shifts of lactate and water proton resonances while retaining CEST properties of the lactate itself
Quantitative– Measures the ratio of D-/L-lactate complexes by CEST MRI
Enhanced Signal– Reagents have only one stereoisomer that forms a stable complex with either lactate isomer, providing a stronger signal than commercial reagents
Novel Approach– Magnifies the chemical shift of lactate OH CEST, useful for design of metabolite-specific shift reagents for functional MRI

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