TECHNOLOGY

Development and In Vitro Testing of a Novel Trifluoromethylated Cholylsarcosine for assessment of bile acid transport using Fluorine Magnetic Resonance Imaging (MRI)

OVERVIEW

Biile Acid Malabsorption (BAM) is an underdiagnosed condition in where bile is either not adequately reabsorbed or excessive bile acid is produced causing chronic diarrhea with excess bile acids. In an effort to address this issue, University of Maryland researchers have synthesized a non-radioactive 19F labeled bile acid called **CA-sar-TFA** , to mimic naturally occurring bile acid and have developed a non-invasive method of detecting BAM. CA-sar-TFA, like endogenous bile acid, is actively absorbed by the sodium dependent bile acid transporter (ASBT) in the terminal ileum, and the NA+/taurocholate co-transporting polypeptide (NTCP), a transporter on hepatocytes responsible for the uptake of bile acids from the portal circulation. Studies conducted in first and second generation CA-lys-TFA have demonstrated the ability of CA-sar-TF to target mouse bladder as well as showing increased stability when tested in the presence of choloylglycine hydrolase (CGH), a simulated intestinal fluid with pancreatic enzymes (SIF). The ability of this synthetic compound to have in-vitro stability and bile acid uptake transporter activity makes it an attractive MRI imaging probe to detect impaired bile acid transport.

APPLICATIONS

Bile acids are synthesized in the liver, as a by-product of cholesterol metabolism, and secreted as bile. This enterohepatic circulation of bile acids is a highly efficient mechanism for their conservation. In a healthy individual, 95% of bile acid are recycled and only 3-5% of bile acids are lost in the stool each day. BAM results in excess fecal bile acid levels and chronic, intermittent diarrhea. It is largely thought to be underdiagnosed or misdiagnosed as irritable bowel syndrome, and estimated that 30-50% of unexplained chronic diarrhea could be caused by BAM. T he exact prevalence of BAM remains unclear due to the limited availability of diagnostic tests for BAM. Possible tests include the analysis of fecal bile acids in 24-hour stool collections and selenium-homocholic acid taurine (SeHCAT) retention test, which measures the loss of bile acids in a simple and reliable manner. The stool test remains available in limited numbers of laboratories and the SeHCAT has never been approved for use in the United States and is not widely available in the rest of the world. SeHCAT is mainly approved for use in Europe. Based off of an evaluation of combined 18 studies and over 1223 patients using the SeHCAT retention test, it is estimated that a potential 10 million patients suffer from bile acid diarrhea.Although bile acid diarrhea is often considered rare, there is mounting evidence that this is not the case and a need for better methods of detection is required to accurately diagnose the often misdiagnosed or underdiagnosed cases of BAM.

In Europe, BAM is clinically diagnosed using SE-HCAT, a gamma emitting synthetic bile acid. However, this is not approved in the United States since it emits low levels of radiation. The discovery of CA-sar-TFA offers a non-invasive, sensitive, and non-radioactive alternative for clinical diagnosis. Overall results show that CA-sar-TFMA, a fluorinated non-radioactive synthetic bile acid, shows favorable *in vitro* stability and bile acid uptake transporter activity, and an ideal, stable fluorine MRI imaging probe to detect impaired bile acid transport.

ADVANTAGES

19F is a stable, naturally occurring fluorine isotope that is non-radioactive

19F MRI has no background interference since there is no endogenous 19F found in tissues

19F MRI signal is directly proportional to the fluorine concentration

19F MRI imaging is non-invasive

R&D REQUIRED

LICENSING POTENTIAL

UM seeks to develop and commercialize by an exclusive or non-exclusive license agreement and/or sponsored research with a company active in the area.

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PATENT STATUS

U.S. patent issued , patent # 9,597,417

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