Antisense Inhibitors of Demethylase/Mbd2 for cancer Therapy

Information Summary

Reference code: ROI 97042, 02136, 09010
Technology overview: Novel enzyme sequence, antisense directed to and inhibitors of MBD2/Demethylase operative in cancer cells
Application: Lung, liver and colorectal cancers, metastatic cancers and in vivo assay
Validation: In vitro and in vivo animal models
Inventor: Dr Moshe Szyf et al.
Opportunity: Exclusive license; partnership/drug development.
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Technology Description

One of the hallmarks of cancer cells is an aberrant pattern of methylation; hypermethylation of selected genes and global hypomethylation have been documented. The DNA methylation machinery is composed of DNA methyltransferases, demethylases and methylated DNA binding proteins (MBDs) that interpret the DNA methylation signal. Methylated cytosines are specifically recognized by MBDs. A newly characterized methylated binding protein, MBD2b isoform has been shown to possess demethylase activity. We have cloned and purified the cDNA encoding this MBD2/demethylase enzyme. We have also developed antisense oligos and identified small molecule inhibitors of this MBD2/demethylase. The patents govern the demethylase target and the antisense oligonucleotide directed to MBD2/demethylase in lung, colorectal and liver cancers and in liver cancer metastases.

Supportive Data

MBD2 is characterized by unique features: 1) MBD2 is not essential to normal cells, 2) MBD2 inhibition in normal cells does not cause toxicity, 3) MBD2 expression is essential for cancer cells and 4) MBD2 inhibition in cancer cells leads to inhibition of metastasis. This has been validated in vitro in HEK 293 human embryonal kidney cells, A549 non-small cell lung cancer cells, MCF-7 breast cancer cells, HepG2 human liver cancer cells and CaCo colon cancer cells and in vivo in nude mice treated with H1299 non-small cell lung cancer cells with pHis MBD2 antisense or empty vector. We also demonstrated that S-adenosyl methionine inhibits active demethylation, alters gene expression and inhibits tumorogenesis in HEK 293 and A549 cells.

Advantages

Antisense oligonucleotides and inhibitors of MBD2/demethylase have potential as agents for the treatment of liver, lung and colorectal cancers and in the prevention of liver cancer metastasis. We have also developed an in vitro assay to screen demethylase inhibitors and a microarray analysis of target gene expression.

Market Need and Opportunity

The oncology/cancer market was worth $23B in Y2004 and is estimated to achieve $60B by Y2011 with a CAGR of 14.7%. A significant portion of the market will be captured by targeted therapies such as demethylase.