309 Small molecule antagonists targeting MALAT1 lncRNA

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead identification / optimization
Target(MoA)	Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) Long Non-coding RNA (lncRNA)
Brief Description	• MALAT1 expression and nuclear retention element (ENE, which assumes a triple-helical configuration) binding ligands identified • The ligands have been further studied for their ability for reverse branching morphogenesis in tumor-derived organoids • A ~50% drop in the nuclear MALAT1 copy number demonstrated after treatment with MALAT1 ENE binding ligands • Small molecules targeted to MALAT1 do not recognize a triple helix encoded by a similar lncRNA, NEAT1 • Next step is to apply X-ray crystallography to obtain a high-resolution structure of MALAT1 in complex with compounds, as a prerequisite to designing derivatives of these compounds with greater potency
Organization	National Institutes of Health

Differentiation

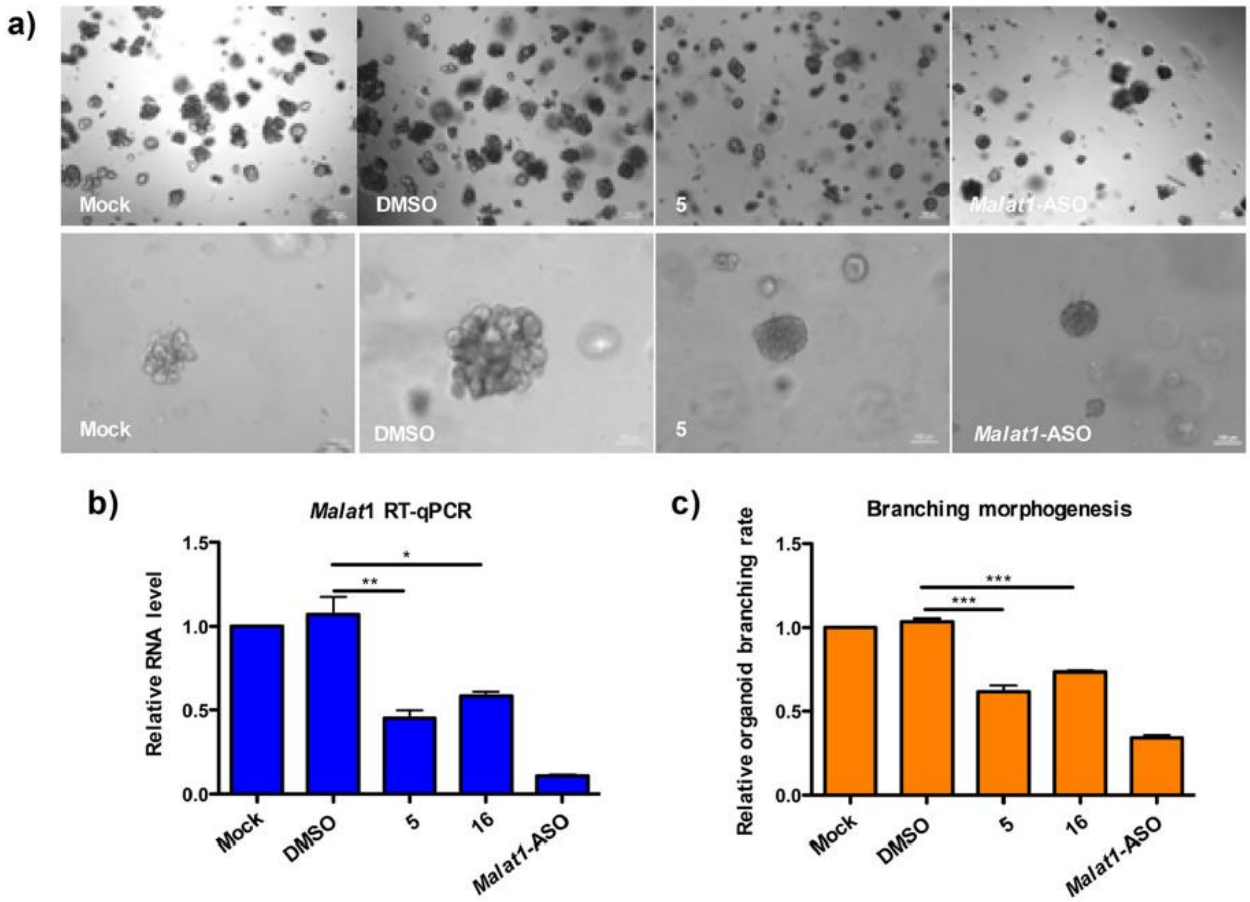
□ **MALAT1 as an anticancer target**

- Human MALAT1 is a lncRNA overexpressed in multiple human cancers
- There is a strong correlation between MALAT1 levels and increased risk of various malignancies including metastasis
- Antisense oligonucleotide inhibition of MALAT1 expression levels has shown promising anticancer effects in vivo. Additionally, depletion of MALAT1 is not lethal to normal cell growth, further supporting MALAT1 as a promising therapeutic target for cancer therapy
- Development of small molecules that recognize and disrupt MALAT1 triple helix structure (designated MALAT1 ENE), and ultimately its degradation, would provide novel therapeutics for cancers associated with enhanced levels of MALAT1
- To date, no specific small molecules capable of affecting MALAT1 nuclear copy number have been reported

309 Small molecule antagonists targeting MALAT1 lncRNA

Key Data

Reduction of *Malat1* levels and organoid branching by compounds 5 and 16

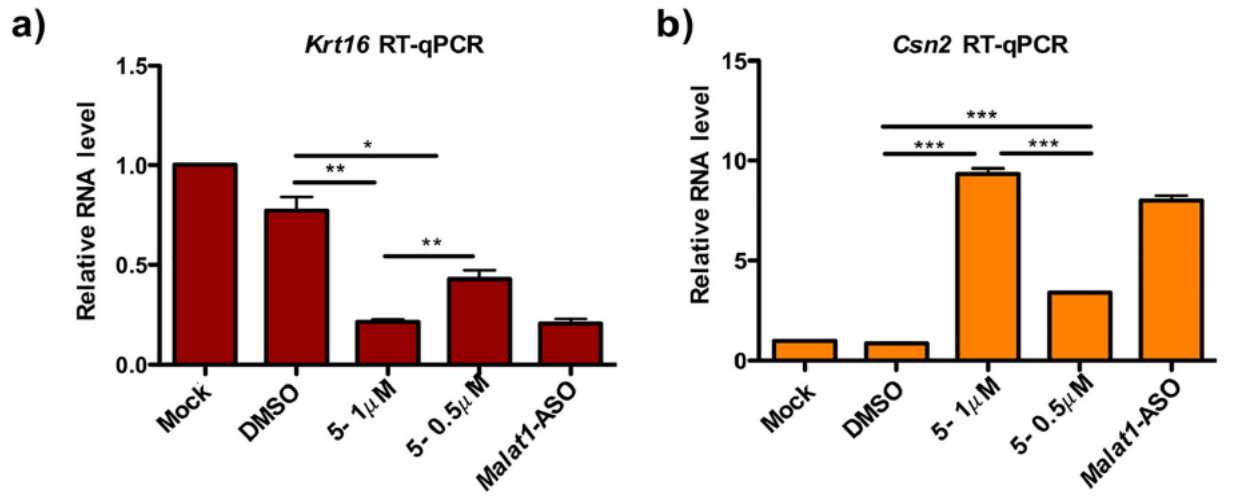


(a) Image of organoids from MMTV-PyMT* tumors after 7 days of culturing. The data for compound 5 are shown. (b) Relative Malat1 levels in MMTV-PyMT tumor organoids with treatments of Mock, DMSO, compounds 5 and 16 (final concentration of 1 μM), and Malat1-ASO (final concentration of 200 nM). (c) Relative organoid branching rate of MMTV-PyMT tumor organoids with treatment of mock, DMSO, compounds 5 and 16 (final concentration of 1 μM), and Malat1-ASO (final concentration of 200 nM). Single asterisks indicate $P < 0.05$, double asterisks indicate $P < 0.01$, and triple asterisks indicate $P < 0.001$ by Student's t test.

*The MMTV-PyMT mouse model is a well-studied mammary tumor model generated through expression of the Polyoma Virus middle T antigen oncoprotein under the direction of a mouse mammary tumor virus promoter. The model recapitulates aspects of human Luminal B breast cancer.
MMTV-PyMT tumors are undifferentiated, aggressive mammary carcinomas prone to metastasizing to the lungs.

309 Small molecule antagonists targeting MALAT1 lncRNA

Modulation of *Malat1* downstream genes by compound 5



(a) Relative RNA level of Krt16 in MMTV-PyMT tumor organoids with treatment of mock, DMSO, 1 and 0.5 μM of 5, and Malat1-ASO (final concentration of 200 nM). Single asterisks indicate $P < 0.05$ and double asterisks indicate $P < 0.01$ by Student's t test. (b) Relative RNA level of Csn2 in MMTV-PyMT tumor organoids with treatment of mock, DMSO, 1 and 0.5 μM of 5, and Malat1-ASO (final concentration of 200 nM). Triple asterisks indicate $P < 0.001$ by Student's t test.

309 Small molecule antagonists targeting MALAT1 lncRNA

Intellectual Property

Patent No.	US 62/685,026
Application Date	2018.06.14
Status	Application Pending
Country	US

Contact Information

Contact Person	John D. Hewes
Email	hewesj@mail.nih.gov
URL	https://techtransfer.cancer.gov/availabletechnologies/e-060-2018