gene encoding for human MTAP maps to region 9p21 on human chromosome 9p. This region also contains the tumor suppressor genes $p16^{INK4A}$ (also known as CDKN2A), and $pl5^{INK4B}$. These genes code for p16 and p15, which are inhibitors of the cyclin D-dependent kinases cdk4 and cdk6, respectively.

[0008] The $pl6^{INK4A}$ transcript can alternatively be ARF spliced into a transcript encoding $pl4^{ARF}$. $pl4^{ARF}$ binds to MDM2 and prevents degradation of p53 (Pomerantz et al. (1998) Cell 92:713-723). The 9p21 chromosomal region is of interest because it is frequently homozygously deleted in a variety of cancers, including leukemias, NSLC, pancreatic cancers, gliomas, melanomas, and mesothelioma. The deletions often inactivate more than one gene. For example, Cairns et al. ((1995) Nat. Gen. 11:210--212) reported that after studying more than 500 primary tumors, almost all the deletions identified in such tumors involved a 170 kb region containing MTAP, pl4ARF and Pl6INK4A Carson *et al* (WO 99/67634) reported that a correlation exists between the stage of tumor development and loss of homozygosity of the gene encoding MTAP and the gene encoding p16. For example, deletion of the MTAP gene, but not $pl6^{INK4A}$ was reported to be indicative of a cancer at an early stage of development, whereas deletion of the genes encoding for p16 and MTAP was reported to be indicative of a cancer at a more advanced stage of tumor development. Garcia-Castellano *et al* reported that in some osteosarcoma patients, the MTAP gene was present at diagnosis but was deleted at a later time point (Garcia-Castellano et al., supra).

SUMMARY

[0009] The present disclosure provides a method for treating a cancer in a subject wherein said cancer is characterized by reduction or absence MTAP expression or absence of the MTAP gene or reduced function of MTAP protein said method comprising administering to the subject a therapeutically effective amount of a MAT2A inhibitor.

[0009a] In another aspect, the present disclosure provides use of a MAT2A inhibitor in the preparation of a medicament for treating an MTAP null cancer in a subject.

[0010] The present disclosure provides a method for determining whether survival or proliferation of a tumor cell can be inhibited by contacting said tumor cell with a MAT2A inhibitor, said method comprising determining the status of MTAP in said

tumor cell, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein indicates survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

[0010a] In another aspect, the present disclosure provides an in vitro method for determining whether survival or proliferation of a tumor cell can be inhibited by contacting said tumor cell with a MAT2A inhibitor, said method comprising determining the status of MTAP in said tumor cell, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein indicates survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

[0011] In another aspect, the present disclosure provides a method for characterizing a tumor cell comprising measuring in said tumor cell the level of MTAP gene expression, the presence or absence of an MTAP gene or the level of MTAP protein present, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein relative to a reference cell indicates that survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

[0011a] An in vitro method for characterizing a tumor cell comprising measuring in said tumor cell the level of MTAP gene expression, detecting the presence or absence of an MTAP gene or measuring the level of MTAP protein present, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein relative to a reference cell indicates that survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

[0012] In another aspect, the present disclosure provides a method of determining the responsiveness of a tumor to MAT2A inhibition comprising determining in a sample of said tumor a reduced expression level of an MTAP gene, the absence of an MTAP gene or reduction of the level or function of MTAP protein, wherein a reduced expression level of an MTAP gene, the absence of an MTAP gene or reduction of the level or function of MTAP protein indicates said tumor is responsive to a MAT2A inhibitor.

[0013] In another aspect, the present disclosure provides a kit comprising a reagent for measuring in a tumor sample the expression level of an MTAP gene, the

absence of an MTAP gene or reduction of the level or function of MTAP protein, said kit further comprising instructions for administering a therapeutically effective amount of a MAT2A inhibitor.

BRIEF DESCRIPTION OF THE FIGURES

[0014] Figure 1A-F. Functional Genomics Screening Identifies Genes that are Synthetic Lethal with MTAP loss. Schematic depicting chromosome 9 and 9p21.3 region containing *MTAP* gene in close proximity to *CDKN2A* genomic region encompassing *p16/INK4A/p14/ARF* genes. (B) Schematic depicting shRNA depletion screen in colon carcinoma HCT116 MTAP wt and $MTAP^{-/-}$ isogenic cell line pair. (C) Immunoblot analysis demonstrating a lack of MTAP protein expression in HCT116 $MTAP^{-/-}$ cells. (D) Gene scores in HCT116 $MTAP^{-/-}$ vs. MTAP wt cells. The gene score was calculated as SUM log2 fold change in the abundance of each of the 8

WE CLAIM:

1. Use of a MAT2A inhibitor in the preparation of a medicament for treating an MTAP null cancer in a subject.

2. The use of claim 1 further comprises detecting the absence of the MTAP gene in the cancer, e.g. from a sample of the cancer taken from the patient.

3. The use of claim 1 or 2, wherein said cancer incorporates a KRAS mutation.

4. The use of claim 1 or 2, wherein said cancer incorporates a p53 mutation.

5. An in vitro method for determining whether survival or proliferation of a tumor cell can be inhibited by contacting said tumor cell with a MAT2A inhibitor, said method comprising determining the status of MTAP in said tumor cell, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein indicates survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

6. The method of claim 5, wherein the absence of the MTAP gene is determined.

7. The method of claim 5 or 6 further comprising determining the presence of a KRAS mutation, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein and the presence of a KRAS mutation indicates survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

8. The method of claim 5 or 6 further comprising determining the presence of a p53 mutation, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein and the presence of a p53 mutation indicates survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor

9. An in vitro method for characterizing a tumor cell comprising measuring in said tumor cell the level of MTAP gene expression, detecting the presence or absence of an MTAP gene or measuring the level of MTAP protein present, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein relative to a reference cell indicates that survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

10. The method of claim 9, wherein the absence of MTAP gene in said tumor cell is detected.

11. The method of claim 9 or 10, further comprising detecting the presence of a KRAS mutation, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein and the presence of a KRAS mutation indicates that survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

12. The method of claim 9 or 10, further comprising detecting the presence of a p53 mutation, wherein the reduction or absence MTAP expression or absence of the MTAP gene or reduced level or function of MTAP protein and the presence of a p53 mutation indicates that survival or proliferation of said tumor cell can be inhibited by a MAT2A inhibitor.

13. A kit comprising reagents for measuring in a tumor sample the expression level of an MTAP gene, the absence of an MTAP gene or reduction of the level or function of MTAP protein, said kit further comprising instructions for administering a therapeutically effective amount of a MAT2A inhibitor.

14. The kit of claim 13, wherein the reagent are for detecting the absence of MTAP gene in the sample.

15. The kit of claim 13 or 14, wherein the kit further includes reagents for detecting the presence of a KRAS mutation.