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 an inhibitor of MAT2A enzymatic activity in the preparation of a medicament for treating an MTAP null cancer in a subject, wherein said treating an MTAP null cancer in a subject comprises detecting the

WE CLAIM:

1. Use of an inhibitor of MAT2A enzymatic activity in the preparation of a medicament for treating an MTAP null cancer in a subject, wherein said treating an MTAP null cancer in a subject comprises detecting the absence of the MTAP gene in the cancer, e.g. from a sample of the cancer taken from the patient.

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

3. The use of claim 1, wherein said cancer incorporates a p53 mutation.

4. The use of claim 2, wherein said KRAS mutation is a G12X or G13X amino acid substitution.

5. The use of claim 2, wherein said KRAS mutation is G12C, G12D G12R, G12V, or G13D.

6. The use of claim 3, wherein said p53 mutation is, Y126_splice, K132Q, M133K, R174fs, R175H, R196*, C238S, C242Y, G245S, R248W, R248Q, I255T, D259V, S261_splice, R267P, R273C, R282W, A159V or R280K.

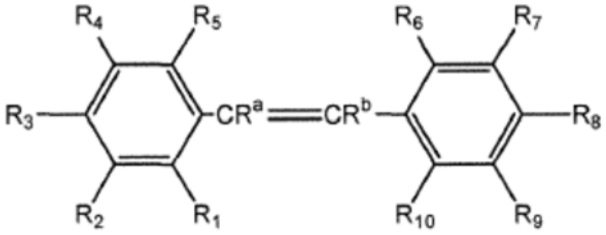
7. The use of claim 1, wherein said inhibitor of MAT2A enzymatic activity is a compound of the formula:

$$X\text{-}Ar_1\text{-}CR^a{=}CR^b\text{-}Ar_2$$

where R^a and R^b are independently H, alkyl, halo, alkoxy, cyano; X represents at least one halogen, e.g., a fluorine, chlorine, bromine, or iodine substituent, on Ar_1; each of Ar_1 and Ar_2 are aryl, e.g., phenyl, naphthyl, and heteroaryl, e.g., pyridyl, pyrolidyl, piperidyl, pyrimidyl, indolyl, thienyl, which can be further substituted with halo, amino, alkylamino, dialkylamino, arylalkylamino, N-oxides of dialkylamino, trialkylammonium, mercapto, alkylthio, alkanoyl, nitro, nitrosyl, cyano, alkoxy, alkenyloxy, aryl, heteroaryl, sulfonyl, sulfonamide, $CONR_{11}R_{12}$, $NR_{11}CO(R_{13})$, $NR_{11}COO(R_{13})$, $NR_{11}CONR_{12}R_n$ where R_{11}, R_{12}, R_{13} are independently, H, alkyl, aryl, heteroaryl or a fluorine; provided that Ar_2 contains

at least one nitrogen atom in the aryl ring or at least one nitrogen substituent on the aryl ring; e.g., an NR^cR^dZ substituent on Ar_2 where R^c is H, alkyl, alkoxy, aryl, heteroaryl, R^d is an alkyl group, Z is a an unshared pair of electrons, H, alkyl, oxygen.

8. The use of claim 1, wherein said inhibitor of MAT2A enzymatic activity is a compound of formula:



where R^a and R^b are as defined above, R_1 to R_{10} are independently H, halo, amino, alkylamino, dialkylamino, N-oxides of dialkylamino, arylalkylamino, dialkyloxyamino, trialkylammonium, mercapto, alkylthio, alkanoyl, nitro, nitrosyl, cyano, alkoxy, alkenyloxy, aryl, heteroaryl, sulfonyl, sulfonamide, $CONR_{11}R_{12}$, $NR_{11}CO(R_{13})$, $NR_{11}COO(R_{13})$, $NR_{11}CONR_{12}R_{13}$ where R_{11}, R_{12}, R_{13}, are independently, H, alkyl, aryl, heteroaryl or a fluorine; provided at least one of R_1 to R_s is a halogen, e.g. a fluorine and/or chlorine; and at least one of R_6 to R_{10} is a nitrogen containing substituent, e.g., an NR^cR^dZ substituent where R^c is H, alkyl, e.g., a lower alkyl, alkoxy, aryl, heteroaryl, R^d is an alkyl group, Z is a an unshared pair of electrons, H, alkyl, oxygen, or a pharmaceutically acceptable salt thereof, or a biotinylated derivative thereof.

9. The use of claim 8, wherein the inhibitor of MAT2A enzymatic activity is selected from the group consisting of: (E)-4-(2-Fluorostyryl)-N ,N-dimethylaniline; (E)-4-(3-Fluorostyryl)-N ,N-dimethylaniline; (E)-4-(4-Fluorostyryl)-N ,N-dimethylaniline; (E)-4-(2-Fluorostyryl)-N,N-diethylaniline; (E)-4-(2-Fluorostyryl)-N,N-di phenylaniline; (E)-1-(4-(2-Fluorostyryl)phenyl)-4-methylpiperazine; (E)-4-(2-Fluorostyryl)-N ,N-dimethylnaphthalen-1-amine; (E)-2-(4-(2-Fluorostyryl)phenyl)-1-methyl-1 H-imidazole; (E)-4-(2,3-Difluorostyryl)-N,N-dimethylaniline; (E)-4-(2,4-Difluorostyryl)-N,N-

dimethylaniline; (E)-4-(2,5-Difluorostyryl)-N,N-dimethylaniline; (E)-2-(2,6-Difluorostyryl)-N,N-dimethylaniline; (E)-3-(2,6-Difluorostyryl)-N,N-dimethylaniline; (E)-4-(2,6-Difluorostyryl)-N,N-dimethylaniline; (E)-4-(2,6-Difluorostyryl)-N,N-diethylaniline; (E)-4-(3,4-Difluorostyryl)-N,N-dimethylaniline; (E)-4-(3,5-Difluorostyryl)N, N-dimethylaniline; (E)-N,N-Dimethyl-4-(2,3,6-trifluorostyryl)aniline; (E)-N,N-Dimethyl-4-(2,4,6-trifluorostyryl)aniline; (E)-4-(2-chloro-6-fluorostyryl)-N,N-dimethylaniline; (E)-4-(2,6-dichlorostyryl)-N,N-dimethylaniline; (E)-4-(2,6-Difluorophenethyl)-N,N-dimethylaniline; and (E)-2-benzamide-4-(2,6-difluorostyryl)-N,N-dimethylaniline.