[0006] Cellular myristoylated proteins have diverse biological functions in signal transduction and oncogenesis. Modification of proteins by myristoylation is required for the subcellular targeting, protein conformation and biological activity of many important proteins in eukaryotic cells, including those required for signal transduction and regulatory functions important in cell growth. Tyrosine kinases of the Src family (proto-oncogenes) are among the most extensively studied myristoylated proteins.

[0007] Myristoylation of proteins is catalyzed *N*-myristoyltransferase (NMT). NMT is responsible for this activity in eukaryotic cells and works by modifying its polypeptide substrate after the removal of the initiator methionine residue by methionyl aminopeptidase. This modification occurs primarily as a cotranslational process, although myristoylation can also occur post-translationally after proteolytic cleavage of proteins, typically during apoptosis. Two isozymes of the mammalian NMT enzymes have been cloned and are designated NMT1 and NMT2. NMTs play a pro-survival role in cells. The two NMTs are present in all normal cells.

[0008] There remains a need for compounds, composition and method for the treatment of cancer.

[0009] This background information is provided for the purpose of making known information believed by the applicant to be of possible relevance to the present invention. No admission is necessarily intended, nor should it be construed, that any of the preceding information constitutes prior art against the present invention.

SUMMARY

[0010] In accordance with one example of the present disclosure there is provided compounds and compositions for the treatment of a subject with cancer. There are also provided methods for identifying subject with cancer that are suitable for treatment with the compounds, composition and methods are described herein.

[0011] In accordance with one example of the present disclosure, there is provided a method of treating a subject having a cancer deficient in NMT2, comprising: administering to said subject an NMT inhibitor. In a specific example, said NMT inhibitor is a NMT1 inhibitor.

[0012] In a specific example, said cancer is a lymphoma. In an example, said lymphoma is a B cell lymphoma. In a more specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt's lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0013] In a specific example, said NMT inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

[0014] In a specific example, said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof. In a specific example, said antibody is a monoclonal antibody or a polyclonal antibody. In a specific example, said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

[0015] In a specific example, said subject is a human subject.

[0016] In another example of the present disclosure, the method further comprises administering a chemotherapeutic agent. In a specific example, said chemotherapeutic agent is CHOP, GAP-BOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B), CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME, MINE, MTX-CHOP, CEM, CEVD, CAVP, EVAP, or EPOCH.

[0017] In another example of the present disclosure, there is provided a method of treating a subject having cancer, comprising: measuring a sample from said subject to determine whether said sample is deficient in NMT2; and administering an inhibitor of NMT to said subject when said sample is deficient in NMT2. In a specific example, said NMT inhibitor is a NMT1 inhibitor.

[0017a] In one aspect, the present disclosure refers to a method of detecting a subject having cancer being a B cell lymphoma, comprising: measuring a sample from said subject to determine whether said sample is deficient in NMT2 by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell; wherein the B cell lymphoma is Burkett's lymphoma.

[0018] In a specific example, said NMT inhibitor is a NMT1 inhibitor.

[0019] In a specific example, said cancer is a lymphoma. In a specific example, said lymphoma is a B cell lymphoma. In a more specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt's lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0020] In a specific example, said NMT inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

[0021] In a specific example, said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof. In a specific example, said antibody is a monoclonal antibody or a polyclonal antibody. In a specific example, said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

[0022] In a specific example, said subject is a human subject.

[0023] In another example of the present disclosure, the method further comprises administering a chemotherapeutic agent. In a specific example, said chemotherapeutic agent is CHOP, GAP-BOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B), CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME, MINE, MTX-CHOP, CEM, CEVD, CAVP, EVAP, or EPOCH.

[0024] In another example, measuring of said sample is carried out using quantitative fluorescence activated cell sorting, enzyme linked immunosorbent assay, immunohistochemistry, quantitative immunohistochemistry, fluorescence resonance energy transfer, Forster resonance energy transfer, biomolecular fluorescence complementation, mass spectrometry, immunoblot assay or coimmunoprecipitation assay.

[0025] In another example of the present disclosure, there is provided a kit for treating cancer in of treating a subject having a cancer deficient in NMT2, comprising: an NMT inhibitor; and instructions for the use thereof. In one example, said NMT inhibitor is a NMT1 inhibitor.

[0026] In a specific example, said cancer is a lymphoma. In a specific example, said lymphoma is a B cell lymphoma. In a more specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt's lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0027] In a specific example, said NMT inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

[0028] In a specific example, said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof. In a specific example, said antibody is a monoclonal antibody or a polyclonal antibody. In a specific example, said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

[0029] In a specific example, said subject is a human subject.

[0030] In another example of the present disclosure, the method further comprises administering a chemotherapeutic agent. In a specific example, said chemotherapeutic agent is CHOP, GAP-BOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B), CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME, MINE, MTX-CHOP, CEM, CEVD, CAVP, EVAP, or EPOCH.

[0031] In another example of the present disclosure, there is provided a use of an inhibitor NMT for treating a subject having a cancer deficient in NMT2. In a specific example, said NMT inhibitor is a NMT1 inhibitor.

[0031a] In another aspect, the present disclosure refers to use of an NMT1 inhibitor for the preparation of a medicament for treating a subject having a cancer being a B cell lymphoma deficient in NMT2 by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell, wherein the B cell lymphoma is Burkett's lymphoma.

[0032] In a specific example, said cancer is a lymphoma. In a specific example, said lymphoma is a B cell lymphoma. In a more specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt’s lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0033] In a specific example, said NMT inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

[0034] In a specific example, said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof. In a specific example, said antibody is a monoclonal antibody or a polyclonal antibody. In a specific example, said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

[0035] In a specific example, said subject is a human subject.

[0036] In another example of the present disclosure, the method further comprises administering a chemotherapeutic agent. In a specific example, said chemotherapeutic agent is CHOP, GAP-BOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B),

CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME, MINE, MTX-CHOP, CEM, CEVD, CAVP, EVAP, or EPOCH.

[0037] In another example of the present disclosure, there is provided a use of an inhibitor NMT for the preparation of a medicament for treating a subject having a cancer deficient in NMT2.

[0038] In a specific example, said NMT inhibitor is a NMT1 inhibitor.

[0039] In a specific example, said cancer is a lymphoma. In a specific example, said lymphoma is a B cell lymphoma. In a more specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt's lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0040] In a specific example, said NMT inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

[0041] In a specific example, said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof. In a specific example, said antibody is a monoclonal antibody or a polyclonal antibody. In a specific example, said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

[0042] In a specific example, said subject is a human subject.

[0043] In another example of the present disclosure, the method further comprises administering a chemotherapeutic agent. In a specific example, said chemotherapeutic agent is CHOP, GAP-BOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B), CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME, MINE, MTX-CHOP, CEM, CEVD, CAVP, EVAP, or EPOCH.

[0044] In another example of the present disclosure, there is provided a use of NMT2 as a marker for one or more of diagnosis, prognosis, classifying, or monitoring of cancer in a subject.

[0044a] In another aspect, the present disclosure refers to use of NMT2 as a marker by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell for one or more of *in vitro* diagnosis, prognosis, classifying, or monitoring of cancer being B cell lymphoma in a subject, wherein the B cell lymphoma is Burkitt's lymphoma.

[0045] In another example of the present disclosure, there is provided a use of protein myristoylation as a marker for one or more of diagnosis, prognosis, classifying or monitoring cancer in a subject.

[0045a] In another aspect, the present disclosure refers to use of protein myristoylation as a marker for one or more of *in vitro* diagnosis, prognosis, classifying or monitoring cancer being a B cell lymphoma in a subject, wherein the B cell lymphoma is Burkitt's lymphoma.

[0046] In another example of the present disclosure, there is provided a use of protein acylation as a marker for one or more of diagnosis, prognosis, classifying or monitoring cancer in a subject.

[0047] In a specific example, said cancer is lymphoma.

[0048] In a specific example, said lymphoma is B cell lymphoma.

[0049] In a specific example, said B cell lymphoma is follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, B-CLL/SLL, immunocytoma/Waldenstrom's, MALT-type/monocytoid B cell lymphoma, Burkitt's lymphoma, a pediatric lymphoma, or anaplastic large cell lymphoma.

[0050] In a specific example, said marker is measured using an assay selected from immunoassays or nucleic acid detection, or protein activity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] Embodiments of the present invention will now be described, by way of example only, with reference to the attached Figures, wherein:

[0052] Figure 1 depicts immunoblot analysis of NMT1 and NMT2 expression in one type of normal B cells (L0) and various B cell lymphomas and T cell leukemias;

[0053] Figure 2 is a graph illustrating sensitivity of various normal cells and various B cell lymphomas and T cell leukemias to the NMT inhibitors tris-dibenzylideneacetone-dipalladium (Tris-DBA);

[0054] Figure 3 is a bar graph illustrating inhibition of N-myristoyltransferase (NMT) by tris-dibenzylideneacetone-dipalladium (Tris-DBA); and

[0055] Figure 4 are immunoblotts depicting lymphoma cell lines probed with antibodies against NMT1 and NMT2.

[0056] Figure 5 is a line graph showing the sensitivity of NMT inhibitors on a Burkitt's Lymphoma cell line in comparison to an immortalized normal B lymphocytic cell line; and

[0057] Figure 6 depicts the results of transfection of Ramos B lymphoma cells with pcDNA3.1-V5-NMT2 showing increased survival to TrisDBA (5 ug/ml) 2.5 fold vs control cells transfected with empty plasmid vector (Panel A) showing cell viability, and (Panel B) an immunoblott.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method of detecting a subject having cancer being a B cell lymphoma, comprising:

measuring a sample from said subject to determine whether said sample is deficient in NMT2 by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell; wherein the B cell lymphoma is Burkett's lymphoma.

2. The method of claim 1, wherein said subject is a human subject.

3. The method of claim 1 or claim 2, wherein measuring of said sample is carried out using quantitative fluorescence activated cell sorting, enzyme linked immunosorbent assay, immunohistochemistry, quantitative immunohistochemistry, fluorescence resonance energy transfer, Forster resonance energy transfer, biomolecular fluorescence complementation, mass spectrometry, immunoblot assay or coimmunoprecipitation assay.

4. Use of an NMT1 inhibitor for the preparation of a medicament for treating a subject having a cancer being a B cell lymphoma deficient in NMT2 by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell, wherein the B cell lymphoma is Burkett's lymphoma.

5. The use of claim 4, wherein said NMT1 inhibitor is a small molecule, an antibody, a peptide fragment, or a nucleic acid.

6. The use of claim 5, wherein said small molecule is DDD85646, or a derivative thereof.

7. The use of claim 4, wherein said small molecule is Tris-DBA, HMA, or DDD85646, or a derivative thereof.

8. The use of claims 5, wherein said antibody is a monoclonal antibody or a polyclonal antibody.

9. The use of claim 5, wherein said nucleic acid comprises a dsRNA molecule, a RNAi molecule, miRNA molecule, a ribozyme, a shRNA molecule, or a siRNA molecule.

10. The use of any one of claims 4-9, wherein said subject is a human subject.

11. The use of any one of claims 4-10, wherein a chemotherapeutic agent is to be further administered, optionally wherein said chemotherapeutic agent is CHOP, GAPBOP, m-BACOD, ProMACE-MOPP, ProMACE-CytaBOM, MACOP-B, IMVP-16, MIME, DHAP, ESHAP, CEFF(B), CAMP, VABCD, ABDIC, CBVD, PCVP, CEP, EVA, MOPLACE, MIME.

12. Use of NMT2 as a marker by determining epigenetic inactivation a NMT2 gene or loss of protein function or having a level of NMT2 protein that is low or absent compared to a control being normal B cell for one or more of *in vitro* diagnosis, prognosis, classifying, or monitoring of cancer being B cell lymphoma in a subject, wherein the B cell lymphoma is Burkitt's lymphoma.

13. Use of protein myristoylation as a marker for one or more of *in vitro* diagnosis, prognosis, classifying or monitoring cancer being a B cell lymphoma in a subject, wherein the B cell lymphoma is Burkitt's lymphoma.

14. The use of claim 13, wherein said marker is measured using an assay selected from immunoassays or nucleic acid detection, or protein activity.