blood disorder; hemoglobinopathy; sickle cell anemia; β -thalessemia, an inflammatory disease, and autoimmune disease e.g. rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, diarrhea, gastroesophageal reflux disease, and the like.

[0028] In some examples, the inhibition of PRMT5 may be useful in treating or preventing, in particular treating, the following non-limiting list of cancers: breast cancer, lung cancer, esophageal cancer, bladder cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenoma.

[0029] Examples of metabolic disorders which may be treated or prevented, in particular treated, include, but are not limited to, diabetes or obesity.

[0030] Examples of blood disorders which may be treated or prevented, in particular treated, include, but are not limited to, hemoglobinopathy, such as sickle cell disease or β-thalassemia.

[0031] Examples of cancers which may be treated or prevented, in particular treated, include, but are not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (e.g., lymphangio sarcoma, lymphangioendothelio sarcoma, hemangio sarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (e.g., cholangiocarcinoma), bladder cancer, breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (e.g., meningioma; glioma, e.g., astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (e.g., cervical adenocarcinoma), chordoma, choriocarcinoma, craniopharyngioma, colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endothelio sarcoma (e.g., Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (e.g. , uterine cancer, uterine sarcoma), esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett' s adenocarinoma), Ewing sarcoma, eye cancer (e.g., intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (e.g., stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma (OSCC), throat cancer (e.g., pharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), hematopoietic cancers (e.g., leukemia such as acute lymphocytic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute

ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

[0037] In a particular example, a PRMT5 inhibitor may be useful in somatic cell reprogramming, such as reprogramming somatic cells into stem cells. In a particular example, a PRMT5 inhibitors may be useful in germ cell development, and are thus envisioned useful in the areas of reproductive technology and regenerative medicine.

[0038] Other diseases which may be treated or prevented, in particular treated, include, but are not limited to, ischemic injury associated myocardial infarctions, immunological diseases, stroke, arrhythmia, toxin-induced or alcohol related liver diseases, aspirin-sensitive rhinosinusitis, cystic fibrosis, cancer pain, and haematological diseases, for example chronic anemia and aplastic anemia.

[0038a] In one aspect, there is provided a method of identifying a patient that is likely to be responsive to treatment with a protein arginine N-methyltransferase 5 (PRMT5) inhibitor comprising: evaluating a biological sample that had been obtained from the patient for the presence of a spliceosome alteration, wherein the presence of any said alteration indicates a higher likelihood for said patient to be responsive to treatment with said PRMT5 inhibitor than in the absence of any said alteration.

[0039] The present disclosure thus comprises a method of identifying a patient that is likely to be responsive to treatment with a protein arginine N-methyltransferase 5 (PRMT5) inhibitor comprising evaluating a biological sample from the patient for the presence of any of the following:

- a PIC3CA activating mutation,
- a spliceosome alteration,
- a cyclin D1 pathway amplicifation, and/or
- a WNT pathway alteration

wherein the presence of any said mutation or alteration indicates a higher likelihood for said patient to be responsive to treatment with said PRMT5 inhibitor than in the absence of any said mutation or alteration.

[0040] In an example, the splicesosome alteration comprises a mutation in a gene selected from the group consisting of U2AF1, RBM10 and KIAA1429. In a specific example, the gene is U2AF1 and the mutation is S34F. In another specific example, the gene is RBM10 and the mutation is selected from the group consisting of I696fs, I348N, G840fs. In yet another specific example, the gene is KIAA1429 and the mutation is selected from the group consisting of L837V, F1260L, D251if, T1333M, V1548L, G397A and Q962E. Other

spliceosome alterations may also indicate a higher likelihood of the patient to be responsive to treatment with a PRMT5 inhibitor.

[0041] In another example the PIC3CA activating mutation is selected from the group consisting of H1047R, PG106-R108del , T1025A and E542K. However, other activating mutation may also indicate a higher likelihood of the patient to be responsive to treatment with a PRMT5 inhibitor.

[0042] In another example, the cyclin D1 pathway amplification is an amplification of Cyclin D1, CDK4 or CDK6 expression. However, other cyclin D1 pathway amplifications may also indicate a higher likelihood of the patient to be responsive to treatment with a PRMT5 inhibitor.

[0043] In another example, the WNT pathway alteration comprises autocrine WNT signaling. Preferably, the WNT pathway alteration comprises a mutation in an APC or CTNNB1 gene. In a specific example, the gene is APC and the mutation is selected from the group consisting of R213Q, R2673G, I1177M and D2796G. In another specific example, the gene is CTNNB1 and the mutation is selected from the group consisting of Y670*, S45F, and T41A. However, other WNT pathway alterations may also indicate a higher likelihood of the patient to be responsive to treatment with a PRMT5 inhibitor.

[0044] In a particular example, the mutation or alteration according to the invention comprises a spliceosome alteration, and the patient has NSCLC.

[0045] In another particular example, the mutation or alteration according to the disclosure comprises a cyclin D1 pathway amplicifation or a WNT pathway alteration,and the patient has NSCLC.

[0046] In another particular example, the mutation or alteration according to the disclosure comprises a PIC3CA activating mutation and the patient has SCLC.

[0047] In a preferred example of the disclosure, the PRMT5 inhibitor is compound 2 or compound 80.

[0048] The present application discloses a sensitivity link to PI3K-alpha activating mutations in SCLC, and in spliceosome alterations and WNT pathway upregulation in NSCLC. Cyclin D1 pathway amplifications are associated with PRMT5 inhibitor response in NSCLC.

What is claimed:

1. A method of identifying a patient that is likely to be responsive to treatment with a protein arginine N-methyltransferase 5 (PRMT5) inhibitor comprising:

   evaluating a biological sample that had been obtained from the patient for the presence of a spliceosome alteration,

   wherein the presence of any said alteration indicates a higher likelihood for said patient to be responsive to treatment with said PRMT5 inhibitor than in the absence of any said alteration.

2. The method of claim 1, wherein the splicesosome alteration comprises a mutation in a gene selected from the group consisting of U2AF1, RBM10 and KIAA1429

3. The method of claim 2, wherein the gene is U2AF1 and the mutation is S34F.

4. The method of claim 2, wherein the gene is RBM10 and the mutation is selected from the group consisting of I696fs, I348N, G840fs

5. The method of claim 2, wherein the gene is KIAA1429 and the mutation is selected from the group consisting of L837V, F1260L, D251if, T1333M, V1548L, G397A and Q962E.

6. The method of any one of the previous claims 1-5, wherein the biological sample comprises a spliceosome alteration and the patient has NSCLC.

7. The method according to any of the previous claims, wherein the PRMT5 inhibitor is compound 2 or compound 80.