

[018] "CpG" is shorthand for "—C—phosphate—G—", that is, cytosine and guanine separated by only one phosphate; phosphate links any two nucleosides together in DNA. The "CpG" notation is used to distinguish this linear sequence from the CG base-pairing of cytosine and guanine. Cytosines in CpG dinucleotides can be methylated to form 5-methylcytosine (5-mC). In mammals, methylating the cytosine within a gene can turn the gene off. Enzymes that add a methyl group to DNA are called DNA methyltransferases. In mammals, 70% to 80% of CpG cytosines are methylated. There are regions of the genome that have a higher concentration of CpG sites, known as CpG islands. These "CpG islands" also have a higher than expected GC content (i.e. >50%). Many genes in mammalian genomes have CpG islands associated with the start of the gene. Because of this, the presence of a CpG island is used to help in the prediction and annotation of genes. CpG islands are refractory to methylation, which may help maintain an open chromatin configuration. In addition, this could result in a reduced vulnerability to transition mutations and, as a consequence, a higher equilibrium density of CpGs surviving. Methylation of CpG sites within the promoters of genes can lead to their silencing, a feature found in a number of human cancers (for example the silencing of tumor suppressor genes). In contrast, the hypomethylation of CpG sites has been associated with the over-expression of oncogenes within cancer cells.

SUMMARY OF THE INVENTION

[019] ~~Disclosed is One aspect of the invention provides for a method of determining the sensitivity of tumor cell growth to inhibition by an EGFR kinase inhibitor, comprising detecting the methylation status of the ERBB2 gene in a sample tumor cell, wherein hypomethylation of the ERBB2 gene indicates that the tumor cell growth is sensitive to inhibition with the EGFR inhibitor. Also disclosed is Another aspect of the invention provides for a method of identifying a cancer patient who is likely to benefit from treatment with an EFGR inhibitor comprising detecting the methylation status of the ERBB2 gene from a sample from the patient's cancer , wherein the patient is identified as being likely to benefit from treatment with the EGFR inhibitor if the methylation status of the ERBB2 gene is detected to be hypomethylation.~~

[019a] In one aspect, there is provided a method of determining the sensitivity of tumor cell growth to inhibition by erlotinib comprising detecting the methylation status of the ERBB2 gene in a sample tumor cell, wherein hypomethylation of the ERBB2 gene indicates that the tumor cell growth is sensitive to inhibition with erlotinib.

[019b] In one aspect, there is provided a method of identifying a cancer patient who is likely to benefit from treatment with erlotinib comprising detecting the methylation status of the ERBB2 gene from a sample from the patient's cancer, wherein the patient is identified as

being likely to benefit from treatment with erlotinib if the methylation status of the ERBB2 gene is detected to be hypomethylation.

[019c] In one embodiment, the patient is administered a therapeutically effective amount of an EGFR inhibitor if the patient is identified as one who will likely benefit from treatment with the EGFR inhibitor.

[019d] In one aspect, there is provided the use of erlotinib in the manufacture of a medicament for treating cancer in a patient, wherein a sample from the patient's cancer has been subjected to detection of the methylation status of the ERBB2 gene, and erlotinib has been selected for the therapy when the ERBB2 gene is detected to be hypomethylated.

[020] ~~Further disclosed is~~ Another aspect of the invention provides for a method of treating a cancer in a patient comprising administering a therapeutically effective amount of an EGFR inhibitor to the patient, wherein the patient, prior to administration of the EGFR inhibitor, was diagnosed with a cancer which exhibits hypomethylation of the ERBB2 gene, wherein the hypomethylation of the ERBB2 gene is indicative of therapeutic responsiveness by the subject to the EGFR inhibitor.

[021] ~~Also disclosed is Another aspect of the invention provides for a method of selecting a therapy for a cancer patient, comprising the steps of detecting the methylation status of the ERBB2 gene from a sample from the patient's cancer , and selecting an EGFR inhibitor for the therapy when the ERBB2 gene is detected to be hypomethylated. In one embodiment, the patient is administered a therapeutically effective amount of the EGFR inhibitor, such as, for example, erlotinib, cetuximab, or panitumumab.~~

[022] ~~Also disclosed is Another aspect of the invention provides for a method of determining overexpression of ERBB2 gene in a cell comprising detecting the methylation status of the ERBB2 gene in the cell, wherein ERBB2 gene hypomethylation indicates overexpression of ERBB2 in the cell.~~

[023] ~~Also disclosed is Another aspect of the invention provides for a method treating a cancer in a patient comprising administering a therapeutically effective amount of a HER2 inhibitor to the patient, wherein the patient, prior to administration of the HER2 inhibitor, was diagnosed with a cancer which exhibits hypomethylation of the ERBB2 gene, wherein the hypomethylation of the ERBB2 gene is indicative of therapeutic responsiveness by the subject to the HER2 inhibitor.~~

[024] ~~Also disclosed is Another aspect of the invention provides for a method of selecting a therapy for a cancer patient, comprising the steps of detecting the methylation status of the ERBB2 gene from a sample from the patient's cancer , and selecting a HER2 inhibitor for the therapy when the ERBB2 gene is detected to be hypomethylated. In one embodiment, the patient is administered a therapeutically effective amount of the HER2 inhibitor, such as trastuzumab or T-DM1.~~

[025] In certain embodiments of the above methods, the methylation status is detected in a part of the ERBB2 gene. The part of the gene used to detect the methylation status is, for example, an enhancer region, or an enhancer region and a promoter region. In one embodiment, the part of the gene used to detect the methylation status comprises the nucleic acid sequence of SEQ ID NO:1. In one embodiment, the part of the gene used to detect the methylation status consists of the nucleic acid sequence of SEQ ID NO:1. In one embodiment, the part of the gene used to detect the methylation status comprises a 6 CpG repeat region. In one embodiment, the part of the gene used to detect the methylation status comprises the nucleic acid sequence of SEQ ID NO:2. In one embodiment, the part of the gene used to detect the methylation status consists of the nucleic acid sequence of SEQ ID NO: 2.

[026] In certain embodiments of the methods, the methylation status of the ERBB2 gene is deemed to a hypomethylation status if the ERBB2 gene, or part thereof, is less than about 50% or less than about 20% methylated. .

[027] In certain embodiments of the above methods, the methylation status is detected by pyrosequencing. In certain embodiments of the above methods, the ERBB2 gene is from a formalin-fixed paraffin embedded (FFPE) tissue or from fresh frozen tissue. In certain