Method of predicting the tumor response to DNA methylation inhibitors and alternative therapeutic regimens for overcoming resistance

Introduction:
Aberrant DNA methylation remains the consistent hallmark due to its frequent involvement in all types of cancer including myelodysplastic syndromes (MDS). Cytosine analogues currently one of the most effective epigenetic drugs inhibiting the expression of de novo DNA methyltransferases and have shown substantial potency in reactivating tumor suppressor genes. Few prototypical drugs have been approved in USA and EU for the treatment of MDS. However, like other anti-cancer drugs, resistance to these hypomethylating agents is the major barrier, reversing the effective epigenetic therapy. Molecular mechanisms dilating the cause of resistance to these drugs *in vitro* are diverse but they fail to explain the acquired resistance in patients. In congruency with the fact that the gene silencing mechanisms (DNA hypermethylation, mutations in chromatin remodeling complexes and multiple post-translational histone modifications) are not isolated from each other but interlinked, bromodomains (BRDs), chromatin effector modules that recognize and bind to ε-N-acetyl lysine motifs have rapidly emerged as exciting new targets in the quest for clinical progress in cancer. The present invention exposes such bromodomain containing genes and/or proteins coded by the genes, the expression of which was differentially regulated during the development of resistance, and targeting of which may sensitize the patients suffering from resistance towards DNA methylation inhibitors.

Technology description:
The present invention provides a method for determining the response of the patients (i.e. sensitive or resistant) towards DNA methylation inhibitors and also provides the alternative therapeutic regimens to resolve the resistance.

Advantages:
Bromodomain containing genes and/or proteins disclosed in the present invention can be used as the biomarkers for predicting the clinical response towards the epigenetic therapy, targeting aberrant DNA methylation. The varying level of expression of the genes and/or proteins and the mutations involving non-synonymous change in amino acid sequence can be used as a fundament to differentiate between the responders and the non-responders. This provides the accessibility of the method of prediction, and personalization of the therapy. The patients who do not respond to the DNA methylation inhibitors and suffer from the primary resistance can be quickly eliminated from the
ineffective treatment. This will provide the benefit to such patients by escape from the relative side effects that might associate with the drug, redundant cost of therapy, and suggests for other possible treatment protocol in time.
The patients who initially respond to the drug but during prolonged treatment develop the sign of disease progression by acquiring secondary resistance to the drug can be re-sensitized by the use of a bromodomain inhibitor in combination with a DNA methylation inhibitor. This provides the alternative therapeutic regimen to overcome the resistance and may reduce the incidence of developing resistance to a particular DNA methylation inhibitor.

Development status:
Laboratory scale, validation study on patient samples.

IP protection:
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Commercial offer:
Exclusive/non-exclusive license to the patents, related know-how and data

Ownership:
Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University, Olomouc

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More information is available upon signing a CDA/NDA. Please contact IMTM´s director (director@imtm.upol.cz) or the technology transfer office (tto@imtm.upol.cz)