Method of determination of cancer cell drug sensitivity towards Aurora kinase inhibitors and overcoming their resistance

Introduction:
Recently, Aurora kinases (A, B, and C/serine threonine kinases) gained much attention due to their implication in several types of cancers. Aurora kinases are involved in multiple functions in mitosis. Aurora A is involved in mitotic entry, separation of centriole pairs, accurate bipolar spindle assembly, alignment of metaphase chromosomes and completion of cytokinesis. Aurora B is a chromosomal passenger protein involved in the regulation of chromosomal orientation, and regulating the association between kinetochores and microtubules, and cytokinesis. Aurora C exhibits similar functions to those assigned to Aurora B and is required for cytokinesis. The above-mentioned functions are directly involved in maintaining genomic stability. The relation between Aurora kinases overexpression and transformation has been reported in many cancers. Aurora A was shown to overexpress in colorectal, renal, melanoma, and breast cancers. Mainly Aurora B was shown to overexpress in colorectal cancer. Aurora B was also implicated in thyroid anaplastic carcinoma and glioblastoma. Apart from this, Aurora kinases were shown to overexpress in many other advanced solid carcinomas. Aurora kinases overexpression in many solid cancers is the basis of strong rational to discover and develop several Aurora kinase inhibitors. Some Aurora kinase inhibitors are already in the clinical trials and have shown promising anticancer activity in advanced solid cancers. AZD1152 (AstraZeneca) is currently in phase II studies and have proven effective in colon and melanoma cancers. It achieved stable diseases in progressive cancers. Similarly AT-9283 (Astex), PHA-739358 (Pfizer), and MLN8237 (Milliennium), MLN8054 (Milliennium), VX-680 (Vertex) were proven to be very promising in the clinical trials. CYC116 (4-methyl-5-(2-(4-morpholinophenylamino)pyrimidin-4-yl)thiazol-2-amine), discovered and developed by Cyclacel pharmaceuticals (Dundee, UK) is a novel pan-Aurora kinase inhibitor. It showed promising anticancer activity in both preclinical and early clinical studies. Apart from Aurora kinases, (Aurora A - 44 nM, Aurora B - 19 nM, Aurora C- 65 nM) CYC116 also inhibits other oncogenic kinases including VEGFR2 and Flt-3. ZM447439 (N-[4-[[6-Methoxy-7-3-(4-morpholinyl)propoxy]4quinazolinyl]amino]phenyl]- benzamide), is a first generation Aurora kinase inhibitor.

Technology description:
The present invention provides a group of genes the expression of which or the level of proteins coded by the genes changes with the resistance towards Aurora kinase inhibitors. Therefore, the present invention provides a method for determining the sensitivity of a patient suffering from a cancer disease to Aurora kinase inhibitor therapy and therapeutic approaches to overcome these drug resistance mechanisms.

Advantages:
The genes and proteins identified in the present invention can be used to monitor response to Aurora kinase inhibitors in clinical setting, to monitor the efficacy of Aurora kinase inhibitors therapy, to stratify patients according to the expression of these genes, etc. AstraZeneca's AZD1152 (Aurora B specific) is currently in phase II clinical trials. Both ZM44739 and AZD1152 have nearly identical mode of actions in cancer cells. ZM447439 and CYC116 resistant clones were highly cross-resistant to AZD1152 (AstraZeneca's Aurora B specific inhibitor), MLN8054 (Millennium's Aurora A specific inhibitor), and VX-680 (Vertex's pan-Aurora inhibitor). This strongly indicates similar mechanisms of tumor cell resistance towards these compounds. Hence the ZM447439 gene expression data and proteomics data is suitable to use in predicting AZD1152 long-term response. CYC116 data can also be used to predict AZD1152 and other Aurora kinase inhibitors response based on the fact that CYC116 clones are highly cross-resistant to AZD1152, VX-680, and MLN8054. By the use of the prediction of sensitivity of patients to Aurora kinase inhibitors, the therapy can be administered only to those patients for whom it is beneficial, thereby decreasing the overall costs of cancer therapy and side effects. Those patients for whom the Aurora kinase inhibitors therapy would not bring any benefit, can be quickly selected for another therapy with medicaments which are more suitable for them and do not need to undergo an unnecessary and ineffective treatment. Moreover, the genes and their pathways identified in this invention as hallmarks of Aurora kinase drug resistance can be used as future therapeutic targets to develop novel strategies for overcoming the drug resistance. Also, the present invention provides for the use of a Bcl-2 family of inhibitors in combination with an Aurora kinase inhibitors for use in the treatment of Aurora kinase inhibitor-resistant tumors in order to overcome the resistance.

Development status:
Laboratory scale, validation study on patients´ tissues.

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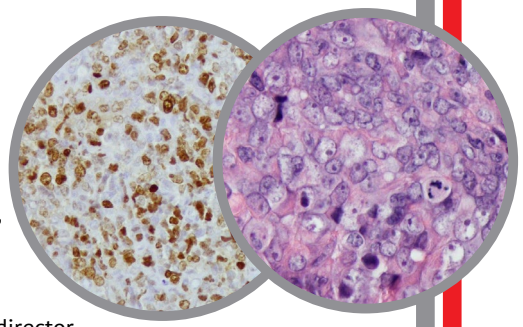

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