Diagnostic Tools to Predict the Efficiency of Anticancer Drug Treatment Targeting Chromatin DNA or Enzymes Acting on DNA

OVERVIEW
Histone deacetylases (HDAC) regulate the expression and activity of many proteins involved in cancer initiation and progression by preventing the transcription of genes involved in tumorigenesis as well as deacetylating and binding to proteins implicated in cell growth, differentiation, and apoptosis. HDAC inhibitors (HDACIs) have been developed as potential anti-cancer drugs as cancer cells are much more sensitive to their effects than healthy cells. However, they have limited therapeutic success as monotherapies and are most often used in combination with other anticancer drugs. In an effort to optimize the selection of an anti-cancer therapeutic strategy with HDACI, UMB researchers developed an assay to predict the response of cancer cells treated with HDACI combination therapy. This patented PCR-based assay can therefore predict the therapeutic benefit of combination therapy containing HDACIs or other compounds directly acting on DNA. It may also be used to predict the optimal drug dose.

This patented technology uses PCR-Stop, real-time quantitative PCR, and specifically-designed primers to measure the amount of DNA breaks in cancer cells upon treatment with anti-cancer drugs. The extent of DNA breakage 24-48 hours following treatment with a drug combination reflects the possibility of cancer cell death, which is a direct measurement of patient response to the tested therapy.

APPLICATIONS
To date, there are no commercially-available tests for the prediction of response to combination therapy with DNA targeting agents. There are three assays currently used to assess drug sensitivity, none with a focus on DNA targeting therapies. The differential staining cytotoxicity assay and triitated thymine assay are both time and labor intensive, taking longer than one week. The histoculture drug resistance assay can assess drug sensitivity as measured by cell growth, but the concentration of drug and incubation times are not standardized nor associated with therapeutic clinical doses. This patented PCR method is quicker, may be used to predict optimal therapeutic dosage, and is to be used specifically with compounds that act on DNA, such as HDACIs and poly ADP ribose polymerase inhibitors (PARPIs). Three PARPIs have been approved by the FDA for the treatment of ovarian, fallopian tube, and peritoneal cancer. Four HDACIs have been approved for the treatment of peripheral and cutaneous T-cell lymphoma and multiple myeloma. Together, these indications represent a market of approximately 400,000 individuals who would benefit from the predictive testing of this PCR assay. With more HDACIs, PARPIs, and other DNA targeting agents currently being developed for the treatment of other neoplastic indications, this market is expected to expand in the near future.

ADVANTAGES
Predicts the efficacy of proposed combination treatment
May be used to predict optimal therapeutic dose
PCR-based method is easy to implement

STAGE OF DEVELOPMENT
These PCR-based methods are fully developed and patented. They have been tested in human colon carcinoma cells and healthy, human small intestine cells treated with an HDACI and a type II topoisomerase inhibitor. This assay has also been tested in two patients with relapsed and/or refractory acute leukemia treated with an HDACI and a type II topoisomerase inhibitor.

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LICENSE STATUS
Available for licensing; Available for sponsored research

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- Diagnostics

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ATTACHMENTS
- Download FC-2009-002 market summary FINAL.pdf

EXTERNAL RESOURCES
- Histone deacetylase inhibitors in cancer therapy

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