

PREDICTION OF TOXICANT-SPECIFIC GENE  
EXPRESSION SIGNATURES  
FOLLOWING CHEMOTHERAPEUTIC  
TREATMENT OF BREAST CELL LINES

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Toxicogenomics

**PREDICTION OF TOXICANT-SPECIFIC GENE EXPRESSION SIGNATURES  
FOLLOWING CHEMOTHERAPEUTIC TREATMENT OF BREAST CELL  
LINES**

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Running Title: Toxicant-Specific Signatures in Breast Cell Lines

Key Words: breast cancer, class prediction, doxorubicin, etoposide, 5-fluorouracil, gene expression, microarrays

Abbreviations: doxorubicin, DOX; etoposide, ETOP; 5-fluorouracil, 5FU; human mammary epithelial cells, HME; human telomerase reverse transcriptase, hTERT; inhibitory concentration 50%, IC50; k-nearest neighbors, KNN; Prediction Analysis of Microarrays, PAM; Significance Analysis of Microarrays, SAM; topoisomerase 2A, TOP2A

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Toxicant-Specific Responses in Luminal Cell Lines

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## **ABSTRACT**

Global gene expression profiling has demonstrated that the predominant cellular response to a range of toxicants is a general stress response. This stereotyped environmental stress response commonly includes repression of protein synthesis and cell cycle regulated genes and induction of DNA damage and oxidative stress responsive genes. Our laboratory has recently characterized the general stress response of breast cell lines derived from basal-like and luminal epithelium following treatment with doxorubicin (DOX) or 5-fluorouracil (5FU) and showed that each cell type has a distinct response. However, we expected that some of the expression changes induced by DOX and 5FU would be unique to each compound and might reflect the underlying mechanisms of action of these agents. Thus, we employed supervised analyses (Significance Analysis of Microarrays) to identify genes that showed differential expression between DOX- and 5FU-treated cell lines. We then used cross-validation analyses and identified genes that afforded high predictive accuracy in classifying samples into the two treatment classes. To test whether these gene lists had good predictive accuracy in an independent data set, we treated our panel of cell lines with etoposide, a compound that is mechanistically similar to DOX. We demonstrated that using expression patterns of 100 genes, we were able to obtain 100% predictive accuracy in classifying the etoposide samples as being more similar in expression to DOX- than 5FU-treated samples. These analyses also showed that toxicant-specific gene expression patterns, similar to general stress responses, vary according to cell type.