Identifying Gene Expression Biomarkers to Predict Rodent Cancer Bioassays

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Two-year rodent bioassays play a central role in evaluating both the carcinogenic potential of a chemical and generating quantitative information on the dose-response behavior for chemical risk assessments. The bioassays involved are expensive and time-consuming, requiring nearly lifetime exposures (two years) in mice and rats and costing approximately $2 to $4 million per chemical. In this project, we present an innovative approach to efficiently and economically identify chemical carcinogens without performing a two-year bioassay for each chemical. We hypothesize that the existing two-year bioassay data generated by the National Toxicology Program (NTP) can be used to assemble a training set of chemicals that were considered positive and negative for lung tumor formation. Microarray analysis performed on the lungs of animals exposed for 13-weeks to chemicals in the training set will identify a set of gene expression biomarkers that can be used to build statistical models that can predict rodent lung tumor formation accurately in a two-year bioassay. We further propose that the dose response of the gene expression biomarkers will correlate with tumor incidence in the original bioassay. This hypothesis will be tested using a combination of genomic tools and statistical classification models. The specific aims (SAs) of this proposal are: (1) determine the gene expression profiles following a 13-week exposure to 23 chemicals that were tested for lung tumors in the NTP two-year rodent bioassay (15 positive for lung tumor formation in at least one species and sex, 10 negative in all species and sexes); (2) develop and validate one or more statistical classification procedures that predicts lung tumor formation in mice and rats using the training set of gene expression data collected in SA 1; and (3) develop dose-response curves for four chemicals that were positive for lung tumor formation using the predictive gene expression biomarkers from SA 2. Through these SAs, we have demonstrated that subchronic gene expression biomarkers can be developed to predict lung tumor formation in mice accurately.

Implications: New chemical testing methods are needed to provide higher throughput and more mechanistic information for inclusion into risk assessment decision-making. The combined application of gene expression biomarkers and statistical classification models can provide more efficient and economical approaches for chemical testing and hazard identification. In addition, information on the dose-response behavior of the gene expression biomarkers enables more quantitative risk assessments of low-level environmental exposures. Taken together, the study represents a first step in integrating genomic information into the hazard identification and risk assessment process and deriving biomarkers of carcinogenicity from short-term studies.

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Presentations:

Thomas, R. S. (2007). Chemical risk assessment improvement: Can genomic tools provide more power? Molecular Toxicology Group, National Institutes of Environmental Health Sciences, Research Triangle Park, NC, January 2007.

Thomas, R. S. (2007). Advancing toxicology by improving linkage of traditional toxicology and genomics. Symposium on Environmental Toxicology at the 2007 Meeting of the North Carolina Academy of Science, Greenville, NC, March 2007.

Thomas, R. S. (2007). Identifying gene expression biomarkers to predict rodent cancer bioassays. Symposium at the International Science Forum on Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC, May 2007.

Thomas, R. S. (2007). Carcinogenomic assessment of chemicals and pharmaceuticals: An alternative strategy to the rodent cancer bioassay. Continuing Education Course at the Society of Toxicologic Pathology Annual Meeting, Rio Grande, Puerto Rico, June 2007.

Thomas, R. S. (2007). Improving chemical and pharmaceutical safety: Can genomic tools provide more power? Seminar at the Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia, PA, July 2007.

Thomas, R. S. (2008). The application of genomic technologies to toxicology. North Carolina Science Blogging Conference, Research Triangle Park, NC, January 2008.

Peer-reviewed publications:

Thomas, R. S., Pluta, L., Yang, L., and Halsey, T. A. (2007). Application of genomic biomarkers to predict mouse lung tumor formation in two-year rodent cancer bioassays. *Toxicological Sciences* 97(1): 55−64.

Thomas, R. S., O'Connell, T. M., Pluta, L., Wolfinger, R. D., Yang, L., and Page, T. J. (2007). A comparison of transcriptomic and metabonomic technologies for identifying biomarkers predictive of two-year rodent cancer bioassays. *Toxicological Sciences* 96: 40−46.

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