

Methods and Applications of Functional Genomics to Health Effects Research

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The primary goal of this research program was to develop genomic and bioinformatic tools for application to assessing human health risks associated with low dose chemical exposure. In response to this goal, several tools have been or currently are being developed for broader use at the CIIT Centers for Health Research and within the toxicology community. These tools can be divided into six subprojects and are organized according to the traditional risk assessment paradigm. The first two subprojects (#1 and #2) focused on developing genomic tools for aspects of hazard identification. The next three subprojects (#3 through #5) focused on developing genomic and systems biology tools for application to dose-response assessment and understanding mode-of-action. The final subproject (#6) focused on developing genomic tools for identifying susceptible subpopulations. The tools developed in this program are providing opportunities for developing predictive models for toxicological endpoints, evaluating dose-dependent transitions, assessing the mechanistic bases of non-monotonic and hormetic dose-response curves, and developing more realistic models for responses at low-level exposures. These technologies promise to revolutionize the way we look at the old problems of risk assessment including identifying hazard, evaluating dose-response, mapping modes-of-action, and extrapolating to a diverse human population to estimate low-dose risks.

Implications: Functional genomics, the branch of genomic biology that studies the genome in a cellular and functional context, is usually characterized by high-throughput, large-scale experiments. The Functional Genomics Research Program developed tools to define the cellular signaling pathways involved in toxicity and to identify the cause-and-effect relationships among altered genes and toxicity. These functional genomic tools were used in research on reactive compounds that cause tissue damage and with compounds that alter cellular function by interacting with specific receptor molecules. Application of these tools permitted incorporation of more realistic dose response relationships into risk assessments with a variety of important industrial compounds.

Start and end date: January 2004 – December 2006

Presentations:

Thomas, R. S. (2004). Application of functional genomics research to toxicology. Toxicogenomic approaches to particle-induced lung disease. Research showcase presented at Annual Science Meeting of the Long-Range Research Initiative, American Chemistry Council, Miami, FL, May 5–6, 2004.

Thomas, R. S. (2004). Methods and applications of functional genomics to health effects research. Poster presentation at Annual Science Meeting of the Long-Range Research Initiative, American Chemistry Council, Miami, FL, May 5–6, 2004.

Thomas, R. S. (2004). A systems biology approach to cross-species extrapolation. Presentation at National Academy of Sciences Committee on Emerging Issues and Data on Environmental Contaminants, Washington, DC, August 12, 2004.

Thomas, R. S. (2004). Implementing a systems biology approach in toxicology. Presentation at Department of Environmental and Molecular Toxicology, North Carolina State University, Raleigh, NC, September 14; Department of Environmental Health, Colorado State University, Fort Collins, CO, November 1, 2004.

Thomas, R. S. (2004). Implementing a functional genomics approach to toxicology. Seminar for Department of Molecular, Cellular and Craniofacial Biology at University of Louisville, School of Dentistry Birth Defects Center, Louisville, KY, November 10, 2004.

Halsey, T. A., Page, T. J., Pluta, L., and Thomas, R. S. (2005). Application of a high-coverage functional genomic screen to dissect the NFκB signaling pathway. *The Toxicologist* 84 (S-1): 249. (Abstract 1218).

Page, T., Halsey, T., Pluta, L., and Thomas, R. S. (2005). Mapping gene expression networks: Using whole genome expression analysis with RNAi to define the heat shock signal transduction cascade. *The Toxicologist* 84 (S-1): 250. (Abstract 1222).

Thomas, R. S. (2005). Molecular biology and the future of risk assessment. Lecture for Risk Assessment Course at North Carolina State University, Raleigh, NC, October 5, 2005.

Thomas, R. S. (2005). Application of functional genomics to toxicology research. Seminar at University of Texas Southwestern Medical School, Dallas, TX, November 9, 2005.

Thomas, R. S. (2005). Application of functional genomic tools for dissecting cellular signaling networks. Seminar for Molecular and Cellular Biology and Biochemistry Seminar Series at Virginia Tech University, Blacksburg, VA, February 11, 2005.

Thomas, R. S. (2005). Systems biology: A fundamental approach to dose-response assessment. Presentation at 31st Annual Summer Meeting of The Toxicology Forum at Given Institute, Aspen, CO, July 13–15, 2005.

Thomas, R. S. (2005). Application of functional genomics to toxicology research. Keynote address at 2005 Conference on the Application of Systems Biology to Environmental Health Research at University of West Virginia, Morgantown, WV, August 2, 2005.

Page, T., Yang, L., Pluta, L., Wolfinger, R., and Thomas, R. (2006). The identification of HSF-1 dependent gene transcription in response to proteotoxic stress. *The Toxicologist* 90 (S-1): 276. (Abstract 1353).

Thomas, R. S. (2006). Application of genomic technology to toxicology: Identifying predictive biomarkers and assessing the impact of chemicals on cell signaling networks. Colgate-Palmolive Student *In Vitro* Toxicology Lecture at Annual Meeting of the Society of Toxicology, March 7, 2006.

Thomas, R. S. (2006). Identifying transomic biomarkers to predict rodent cancer bioassays. Seminar presentation for Laboratory of Experimental Pathology Group at National Institutes of Environmental Health Sciences, Research Triangle Park, NC, April 19, 2006.

Thomas, R. S. (2006). Application of genomic technology to toxicology research. Plenary Talk at Annual Meeting of the Toxicology Society of South Africa. Pretoria, SA. June 11–14, 2006.

Thomas, R.S. (2006). Application of functional genomics technologies to understand the topology of signaling networks. Lecture at Meeting of the Society of Industrial and Applied Mathematics. Raleigh, NC. August 2006.

Thomas, R. S. (2006). Using functional genomic technologies to understand the topology of signaling networks: Potential application to dose-response assessment. Computational Toxicology Symposium at 27th Annual American College of Toxicology Meeting, Indian Wells, CA. November 5–8, 2006.

Thomas, R. S. (2006). A comparison of transcriptomic and metabonomic technologies for identifying biomarkers predictive of two-year rodent cancer bioassays. Lecture for Metabonomics Group at University of North Carolina, Chapel Hill, NC. October 2006.

Thomas, R. S. (2006). Using omic technologies to predict long-term effects from short-term studies: Can we replace the rodent cancer bioassay? CIIT Open House Lecture for CIIT Centers for Health Research at Research Triangle Park, NC. October 2006.

Thomas, R. S. (2006). Chemical risk assessment improvement: Can genomic tools provide more power? Lecture for U.S. Environmental Protection Agency at Research Triangle Park, NC. December 2006.

Thomas, R. S., Pluta, L. H., Page, T. J., MacDonald, J. M., Winnike, J., and Wolfinger, R. D. (2006). A transomic biomarker comparison for predicting two-year rodent cancer bioassays. *The Toxicologist*. 90 (S-1): 429. (Abstract 2093).

Allen, B. C., Nong, A., Yang, L., Clewell, H. J., Andersen, M. E., and Thomas, R. S. (2008). Integration of benchmark dose analysis with genomic data to assess the functional effects of chemical exposure. *The Toxicologist* 102 (S-1): 242. (Abstract 1175). Partially funded by the Formaldehyde Council, Inc.

Andersen, M. E., Clewell, H. J., Bermudez, E., Willson, G. A., and Thomas, R. S. (2008). Concentrations dependent transitions in responses of rat nasal epithelium to inhaled formaldehyde. *The Toxicologist* 102 (S-1): 326. (Abstract 1590). Partially funded by the Formaldehyde Council, Inc.

Thomas, R. S. and Daston, G. P. (2008). Where the rubber meets the road: Current application of genomic tools in product development and decision making in the consumer product, pharmaceutical, and chemical industries. *The Toxicologist* 102 (S-1), 121. (Abstract 591).

Thomas, R. S., Allen, B. C., Yang, L., Nong, A., Clewell, H. J., and Andersen, M. E. (2008). Using genomic dose-response modeling to inform key events in a mode-of-action risk assessment. *The Toxicologist* 102 (S-1), 484. (Abstract 2350).

Peer-reviewed publication(s):

Andersen, M. E., Dennison, J. E., Thomas, R. S., and Conolly, R. B. (2005). New directions in incidence-dose modeling. *Trends in Biotechnology* 23: 122–127.

Andersen, M. E., Thomas, R. S., Gaido, K. W., and Conolly, R. B. (2005). Dose-response modeling in reproductive toxicology in the systems biology era. *Reproductive Toxicology* 19: 327–337.

Hayes, K. R., Vollrath, A. L., Zastrow, G. M., McMillan, B. J., Craven, M., Jovanovich, S., Rank, D. R., Penn, S., Walisser, J. A., Reddy, J. K., Thomas, R. S., and Bradfield, C. A. (2005). EDGE: A centralized resource for the comparison, analysis, and distribution of toxicogenomic information. *Molecular Pharmacology* 67: 1360–1368.

Page, T. J., Sikder, D., Yang, L., Pluta, L., Wolfinger, R. D., Kodadek, T., and Thomas, R. S. (2006). Genome-wide analysis of HSF1 signaling reveals a transcriptional program linked to cellular adaptation and survival. *Molecular BioSystems* 2: 627–639.

Halsey, T. A., Yang, L., Walker, J. R., Hogenesch, J. B., and Thomas, R. S. (2007). A functional map of NFκB signaling identifies novel modulators and multiple system controls. *Genome Biology* 8: R104 (doi:10.1186/gb-2007-8-6-r104).

Thomas, R. S., Allen, B. C., Nong, A., Yang, L., Bermudez, E., Clewell, H. J., and Andersen, M. E. (2007). A method to integrate benchmark dose estimates with genomic data to assess the functional effects of chemical exposure. *Toxicological Sciences* 98(1): 240–248.

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(1): 40–46.

Yang, L., Allen, B. C., and Thomas, R. S. (2007). BMDEExpress: A software tool for the benchmark dose analyses of genomic data. *BMC Genomics* 8: 387 (doi:10.1186/1471-2164-8-387).

Yang, L., Walker, J.R., Hogenesch, J.B., and Thomas, R.S. (2008). NetAtlas: A Cytoscape plugin to examine signaling networks based on tissue gene expression. *In Silico Biology* 8(1): 47–52.

Other publication(s):

Thomas, R., Nong, A., Yang, L., Bermudez, E., Clewell III, H. J., Andersen, M. E., and Allen, B. (2008). Making sense of genomic data: a dose-response analysis approach. *LRI Perspectives*, March 2008.

Thomas, R. Pluta, L., Yang, L., Halsey, T., O'Connell, T., Page, T., and Wolfinger, R. (2008). Using genomic technologies to more efficiently screen for carcinogens. *LRI Perspectives*, March 2008.

Sponsors in addition to the LRI: National Institutes of Environmental Health Sciences (RSTR21601). National Cancer Institute (RSTREG601). U.S. Army (DCDVAN601). The Formaldehyde Council, Inc.

Abstract revision date: March 2009