



NCER-Supported STAR Research Centers Advance the Field of Computational Toxicology

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Research Goals

The NAS report *Toxicity Testing in the 21st Century* and EPA's *Strategic Plan for Toxicity Testing of Chemicals* have called for new tools and approaches to move from a near-exclusive use of animal tests for predicting human health effects to *in vitro* assays, especially those using human cells. In line with these recommendations, ORD's National Center for Environmental Research (NCER), through its extramural STAR (Science to Achieve Results) program, is funding grants to develop computational approaches and tools for quantitative risk assessment and more efficient strategies for prioritizing chemicals for screening and testing. These Centers have formed cooperative agreements with EPA and complement ORD's intramural research program. Through the integration of modern computing and information technology with biology and chemistry, the overall goals of the STAR computational toxicology program are to:

- Improve linkages across the source-to-outcome continuum;
- Develop approaches for prioritizing chemicals for further screening and testing; and
- Produce better methods and predictive models for quantitative risk assessment.

Methods/Approach

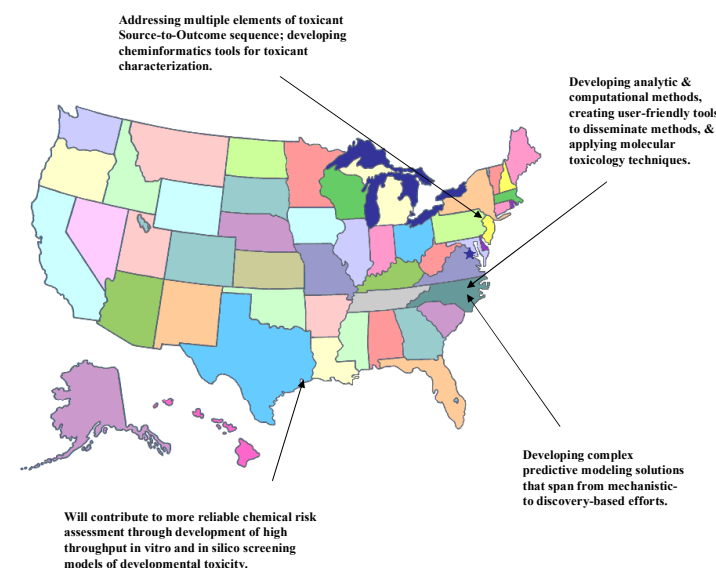
NCER has issued three Requests for Applications (RFAs) for STAR computational toxicology research centers. As a result of a 2005 RFA "Environmental Bioinformatics Research Centers," EPA funded two centers that are developing statistical and bioinformatics tools and approaches for predicting toxicity to chemical exposures. A 2007 RFA, "Computational Toxicology Centers: Development of Predictive Environmental and Biomedical Computer-Based Simulations and Models," led to an additional center. It is applying high-performance computing techniques and resources to *in silico* multi-scale modeling applications at the cellular, organ, and system-wide level to address the environmental problems and research needs facing the U.S. In July of 2009, the most recent center grant was awarded following the issuance of the RFA, "STAR Computational Toxicology Research Centers: *In vitro* and *in silico* Models of Developmental Toxicity Pathways." This center will bridge the interface of *in vitro* data generation and *in silico* model development to answer critical biological questions related to toxicity pathways important to human development.

2005 RFA – Environmental Bioinformatics Research Centers 2005-2010
The Carolina Environmental Bioinformatics Research Center
Director: Wright, Fred A., University of North Carolina, Chapel Hill
Developing novel analytic and computational methods, creating efficient user-friendly tools to disseminate methods to the wider community, and applying molecular toxicology and techniques.
New Jersey Research Center for Environmental Bioinformatics and Computational Toxicology
Director: Welsh, William J., University of Medicine and Dentistry of New Jersey, Princeton University, Rutgers University
Addressing multiple elements of the toxicant Source-to-Outcome sequence as well as developing cheminformatics tools for toxicant characterization.

2007 RFA – Development of Predictive Environmental and Biomedical Computer-Based Simulations and Models 2008-2012
Carolina Center for Computational Toxicology
Director: Rusyn, Ivan, University of North Carolina, Chapel Hill
Developing complex predictive modeling solutions that span from mechanistic- to discovery-based efforts.

2008 RFA-- STAR Computational Toxicology Research Centers: *In vitro* and *in silico* Models of Developmental Toxicity Pathways 2009-2012
Texas-Indiana Virtual STAR Center: Data-Generating *in vitro* and *in silico* Models of Developmental Toxicity in Embryonic Stem Cells and Zebrafish
Director: Jan-Åke Gustafsson, University of Houston
Will contribute to more reliable chemical risk assessment through the development of high throughput *in vitro* and *in silico* screening models of developmental toxicity.

EPA-Funded STAR Computational Research Centers



Results/Conclusions

The Research Center for Environmental Bioinformatics and Computational Toxicology has expanded the framework of the National Center for Toxicological Research/Food and Drug Administration ArrayTrack to ebTrack, an integrated bioinformatics system for environmental research and analysis. The Center has also developed computational tools for peptide identification from tandem mass spectrometry data and statistical and pattern recognition methods for clustering of gene expression data. Other accomplishments include the enhancement of Shape Signatures QSAR technology for chemical hazard identification; metabolic engineering tools for identifying pathways in hepatocyte metabolism; and computational procedures for quantifying the structure of molecular bionetworks. Major accomplishments of the Carolina Center for Environmental Bioinformatics include the development and refinement of a mouse model of variation in genetic susceptibility relevant to human populations, pathway modeling in genomic analysis, and new methods in quantitative structure activity (QSAR) modeling relevant to toxicity. In addition, the Carolina Environmental Bioinformatics Center has refined expression quantitative trait locus (eQTL) analysis procedures, and these methods greatly serve the larger goal of elucidating the underlying mechanisms of toxicity. The Center has also developed high-quality methods for testing biological pathway involvement in toxicogenomics studies and a novel hierarchical two-step approach to model chemical structure for *in vitro/in vivo* toxicity data.

Impact and Outcomes

The impacts and outcomes of STAR Center research are in line with the recommendations put forth in the National Academy of Science Report: *Toxicity Testing in the 21st Century* and the *EPA Strategic Plan for Evaluating the Toxicity of Chemicals*. They are as follows:

- Development of novel analytic & computational methods, models & tools for the scientific community, which will enable a reduction in animal testing.
- Identification of toxicity pathways & development of assays
- Tools to prioritize chemicals
- Scientific foundation for human evaluation & quantitative risk assessment

Future Directions

Development of Virtual Tissues To Elucidate the Following:

- Hazard: Identify toxicity pathways in order to prioritize chemicals for additional testing
- Exposure: Model uptake/distribution of chemicals in organism accounting for chemical life cycle
- Dosimetry: Estimate presence of active chemical at systemic target site using PBPK modeling
- Effect: Estimate target organ events/outcomes via advanced mechanistic systems-based modeling
- Risk: Estimate variability in effects across life-stages, genders & populations

References

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