Final Report Certification
for
CRADA Number ORNL04-0688

Between

UT-Battelle, LLC

and

YAHSGS LLC
(Participant)

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For the Participant:

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CEO
(Title)

9-13-05
(Date)

Use of Microarray Test Data for Toxicogenomic Prediction-Multi-Intelligent Systems for Toxicogenomic Applications (MISTA)

CRADA Final Report

CRADA No. ORNL-04-0688
UT-Battelle LLC and YAHSGS LLC

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Abstract

The YAHSGS LLC and Oak Ridge National Laboratory established a CRADA to develop a computational neural network and wavelets software to facilitate providing national needs for toxicity prediction and overcome the voracious drain of resources (money and time) being directed to the development of pharmaceutical agents. The research project was supported through a STTR Phase I task by NIEHS in 2004. The research deploys state-of-the-art computational neural networks and wavelets to make toxicity prediction on three independent bases: (1) quantitative structure-activity relationships, (2) microarray data, and (3) Massively Parallel Signature Sequencing technology. Upon completion of Phase I, a prototype software Multi-Intelligent System for Toxicogenomic and Applications (MISTA) was developed, the utility's feasibility was demonstrated, and a Phase II proposal was jointly prepared and submitted to NIEHS for funding evaluation. The goals and objectives of the program have been achieved.

Statement of Objectives

There is a critical need for inexpensive nonclinical methods to achieve rapid and accurate prediction of toxicity of potential drugs and environmental agents. Development and testing of new pharmaceuticals frequently require 12 to 15 years, with investment exceeding $500 million per drug and expenditures averaging over $150 million for drugs that fail during testing (Blackwell 2001). The CRADA No. ORNL-04-0688 with YAHSGS LLC is focused on the national need for toxicity-prediction capability and for overcoming the failures of drug development. The research deploys computational neural networks (CNNs) and wavelets to make toxicity prediction on three independent bases: (1) quantitative structure-activity relationships (QSAR), (2) microarray data, and (3) Massively Parallel Signature Sequencing (MPSS) technology. A research and development tool, the Multi-Intelligent System for Toxicogenomic and Applications (MISTA), will be developed and its feasibility tested in the Phase I performance period.

Specific research aims are:

1. Adapt QSAR-based software to function within MISTA's structure, access a web-based data-management structure that integrates existing and new data to support MISTA project data-management requirements, and make toxicological endpoint predictions.

2. Demonstrate the feasibility of developing multi-intelligent algorithms that analyze and utilize microarray test data for toxicogenomic predictions.

3. Demonstrate the feasibility of developing multi-intelligent algorithms that analyze and utilize MPSS data to enhance our toxicogenomic prediction capability.

4. Demonstrate the feasibility of the overall integrated system to make accurate predictions of chemical action on a selected target organ (liver) by challenging it with known and

interpreted test results and studies elucidating the genotoxic effects of chemicals.

Benefits to the Funding DOE Office's Mission

The STTR Phase I research was supported by the National Institute of Environmental Health Sciences (NIEHS). By way of this CRADA, ORNL and YAHSGS LLC will enhance the mission of DOE' Office of Science by collaborating to produce a software product that will help manage the huge volumes of genomic data generated through the Human Genome Project and the Genomes to Life Program.

Technical Discussion of Work Performed by All Parties

Tasks in which ORNL will participate:

1. Determined feasibility of applying ORNL Neural Net and Wavelet software to evaluate chemical effects on the genomes of single or multiple organisms, focusing on genes of significance to liver toxicity and chemicals from classes of concern to human health.

2. Developed and adapted algorithms for predicting genetic effects of chemical actions and for understanding the significance of these interactions and how these toxicological events lead to specific disease states.

3. Integrated YAHSGS advanced structure-toxicity modules to simultaneously predict chemical toxicity independent of microarray data, using a prototype to demonstrate the system's applicability by challenging it with microarray test results.

4. Created a web-based structure to store and use project data, with features that promote efficient receipt and exchange of information from linked researchers.

Tasks in which YAHSGS will participate:

1. Led project's overall technical and administrative management.

2. Evaluated toxicity data for the MISTA database.

3. Prepared and submit Phase II proposal to NIEHS.

4. Explored marketing possibilities and strategies.

Project Accomplishments

Upon completion of Phase I, two draft papers were prepared for open publication:

1. Sumpter, B.G., Nois, D.W., Lu, P.Y., Brothers, R., and Wassom, J.S. 2005. "An Integrated Toxicity Evaluation and Predictive System Based on Neural Networks and Wavelets."

2. Sumpter, B.G., Nois, D.W., Lu, P.Y., Brothers, R., and Wassom, J.S. 2005. "Computational Molecular Toxicology: A Chemical and Materials Toxicity Evaluation Module (CAMTEM)."

Commercialization Possibilities

A user-friendly database that manages microarray data on chemical agents evaluated for liver toxicity was developed (MISTA Database) to support the LiverTox software that predicts activity of chemicals evaluated for gene-expression effects in the liver. The prototype database can be further developed for a commercial product in the future.

Plans for Future Collaboration

Upon completion of Phase I, YAHSGS LLC and ORNL worked together to prepare a Phase II proposal to continue development of the LiverTox system, which applies advanced QSAR and toxicogenomic software for hepatotoxicity prediction. Specific research aims are:

1. Enhance and verify data-module interfaces.

2. Enhance and verify CNN Microarray Module.

3. Complete, train, and test MPSS Module.

4. Complete, train, and test Proteomic Module.

5. Complete, train, test Metabonomic-Metabolomic Module.

6. Complete and train MISTA for multimodule integrated liver-toxicity predictions.

Conclusions

A productive collaboration between ORNL and YAHSGS LLC during Phase I of the CRADA produced a prototype computing neural network software titled "LiverTox: Advanced QSAR and Toxicogenomic Software for Hepatotoxicity Prediction." A follow-on Phase II CRADA proposal has been jointly prepared and submitted to NIEHS for evaluation.