SOT 2014 Poster/Platform Abstract

Category: Bioinformatics

Title: AOPs & Biomarkers: Bridging High Throughput Screening and Regulatory Decision Making

Author: Stephen W. Edwards

As high throughput screening (HTS) plays a larger role in toxicity testing, computational toxicology has emerged as a critical component in interpreting the large volume of data produced. Computational models designed to quantify potential adverse effects based on HTS data will benefit from additional data sources that connect the magnitude of perturbation from the in vitro system to a level of concern at the organism or population level. The adverse outcome pathway (AOP) concept provides an ideal framework for combining these complementary data. Recent international efforts under the auspices of the Organization for Economic Co-operation and Development (OECD) have resulted in an AOP wiki designed to house formal descriptions of AOPs suitable for use in regulatory decision making. Recent efforts have built upon this to include an ontology describing the AOP with linkages to biological pathways, physiological terminology, and taxonomic applicability domains. Incorporation of an AOP network tool developed by the U.S. Army Core of Engineers also allows consideration of cumulative risk from chemical and non-chemical stressors.

Biomarkers are an important complement to formal AOP descriptions, particularly when dealing with susceptible subpopulations or lifestages in human health risk assessment. To address the issue of non-chemical stressors than may modify effects of criteria air pollutants, a novel method was used to integrate blood gene expression data with hematologic, immunologic, and cardiopulmonary covariates resulting in a recursive partitioning tree that segregates individuals according to their asthma status. The resulting tree model assembles asthmatic subjects into purely data-driven mechanistically distinct subtypes (or endotypes). Functional characterization of the genes and associated covariates revealed a complex interaction among Th2 mediated lung inflammation, heightened systemic innate immune response, and metabolic syndrome in discriminating asthma endotypes. The context provided by the clinical covariate data was essential in interpreting gene expression patterns and emphasizes the importance of a systems approach in understanding complex etiologies. These findings support a prominent role for systemic inflammation due to heightened innate immune responsiveness across the asthma syndrome and suggest new biomarkers and therapies that would better identify and treat mechanistically distinct non-Th2 driven endotypes. The information obtained from this study will enable the development of specific AOPs covering mechanistically distinct asthma endotypes and the indentification of informative bioindicators linked to the key events within those AOPs.