PhD Dissertation Final Oral Defense

Nour Abdo

The 1000 Genomes Toxicity Screening Project

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Incorporation of novel toxicity screening approaches is a crucial tool for tackling the complex contemporary challenges in evaluating the human health hazards of exposure to chemicals. A shift in toxicity testing from in vivo to in vitro methods may efficiently prioritize compounds, reveal new mechanisms, and enable predictive modeling. Quantitative high-throughput screening (qHTS) is a major source of data for computational toxicology. However, current in vitro testing paradigms such as Tox21 or NexGen still have major gaps that need addressing, such as population-based in vitro approaches to qHTS screening. This study evaluated the hypothesis that comparative population genomics with efficient in vitro experimental design can be used for the evaluation of the potential hazard, mode of action, and the extent of population variability in response to chemicals. In Aim 1, we intended to evaluate and assess the validity of in vitro genetically–anchored population human model system in assessing chemical toxicity and identifying candidate genetic susceptibility. We screened 81 panels of human lymphoblast cell lines with 240 chemicals at 12 different concentrations and assess the toxic response using different endpoints (cell death and caspase production). We evaluated the toxic responses to a panel of chemicals observed in lymphoblast cell lines, and compared them to other toxic responses seen with different cell lines that originate from different sources. In Aim 2, we expanded our model to include more than one population and have enough power to detect genetic variants associated with toxicological response. We intended to quantitatively assesse population-based toxicological hazard to environmental contaminants, determine the extent of human inter-individual variability in chemical toxicity, identify susceptible sub-populations or races, understand the genetic determinants of the inter-individual variability, generate testable hypotheses about toxicity pathways by leveraging genetic and genomic data from 1000 Genomes and HapMap Projects, and use the data obtained from this research to build predictive in silico models. In Aim 3, we addressed some of the remaining challenges in our model, such as limited metabolic capacity of the lymphoblasts. We also plan to explore the potential and efficiency of our model in assessing new challenges such as the evaluation of chemical mixtures and metals. In summary, this proposal not only will use novel tools to investigate population genetically anchored variability, but it will also offer exceptional methodology for incorporating scientific-based numbers for uncertainties in risk assessment.

Committee:

Ivan Rusyn, Advisor
Rebecca Fry
Avram Gold
Kari North (Epidemiology)
Fred Wright (Bioinformatics, North Carolina State University)