Reverse Translational Studies to Understand Drug Toxicity
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The application of human genetics tools in pharmacology has led to the identification of genetic biomarkers that can predict an individual patient's risk of drug response or toxicity. Genetic association studies can also identify putative genes and pathways that are critical for drug phenotypes. We have used the National Cancer Institute cooperative group structure for pharmacogenomic studies of common adverse events associated with cancer therapies. Genome-wide genotyping and exome sequencing lead to testable hypotheses that can be investigated at the bench to uncover mechanisms underlying these toxicities, with the goal of identifying novel therapeutic approaches for prevention and treatment. I will present the results of genetic association studies of chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer patients and mechanistic studies to explain these findings. Multiple genes and pathways that converge on RhoA GTPase signaling have been associated with CIPN. Mechanistic investigation of these pathways in an induced pluripotent stem cell derived sensory neuron model have validated a role for RhoA GTPase and S1P signaling in the neurodegeneration phenotype that is the hallmark of CIPN. Transcriptional changes associated with paclitaxel treatment of sensory neurons suggest that changes in gene regulation are also critical to the neurotoxicity of microtubule targeting agents. The ability to use the findings of human genetic association studies to reveal the molecular mechanisms of drug toxicity holds great promise for improved cancer drug therapy.