

Evaluating Cardiotoxicity Potential: Translational Approaches and Models

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Overview

The ultimate goal of toxicology is to reduce the adverse impact of exogenous agents on biological populations. These agents can include drugs, chemicals, components of foods, etc., but the immediate goal is the same, to identify the hazard, and characterize the risk. To accomplish this goal, a variety of models are used: epidemiological, computational, in vivo animal, and in vitro. Of course, "all models are wrong, but some are useful", and the key question is how well the chosen model recapitulates the aspects of the target population that are being queried for any given potential adverse effects of any given agent.

A functional heart is critical to most animal populations, and the agents known to elicit adverse effects on it include pharmaceutical compounds (e.g. doxorubicin), natural products (e.g. digitalis), environmental pollutants (phenanthrene, TCDD) and industrial compounds (cadmium, cobalt). The heart is part of a complicated cardiovascular system, with certain differences between species and subtle differences even between individuals. Hence the models chosen to study adverse effects on this organ have to be characterized for what they do and do not recapitulate, from a temporal, mechanistic and individual response perspective.

Research at NCTR on cardiotoxicity has explored computational, in vitro, in vivo, and clinical models. Agents with known clinical adverse effects, such as proarrhythmia drugs, anthracyclines, and tyrosine kinase inhibitors, have been used to characterize these models. We have examined cellular, electrophysiological, and transcriptional endpoints in vitro; circulating and tissue biomarker, electrophysiological and histopathological endpoints in vivo; and circulating biomarker and cardiofunctional endpoints clinically. Our goal (work in progress) is to integrate these endpoints so as to best implement these models for screening and characterizing compounds for potential cardiotoxic risk.