BioMAP®
Tox Alert™ Analysis

In Vitro Detection of Potential *In Vivo* Toxicity and Adverse Events

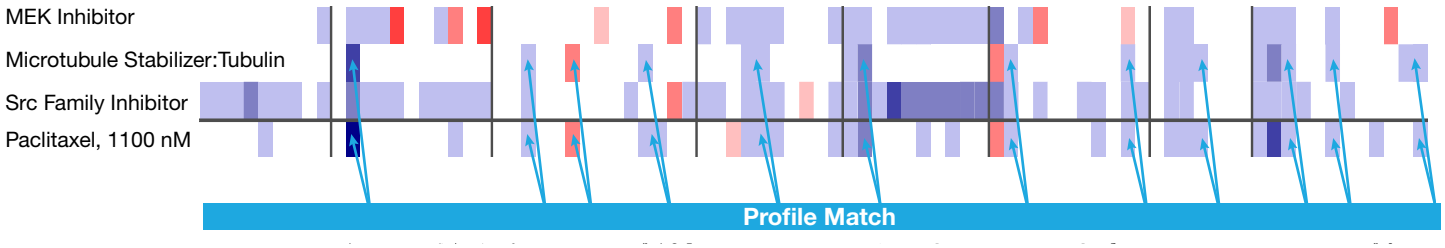
The negative impact of a Phase I clinical trial failure cannot be underestimated and highlights the critical need to identify signs of potential adverse events as early as possible. Unfortunately, current preclinical methods used to assess compound safety are undermined by both a lack of correlation to human effects and absence of large enough datasets to draw meaningful conclusions. Even animal models that are able to identify adverse events do not translate to humans and are themselves expensive and time consuming for the quality of data achieved. In contrast, by comparing the biomarker activity of a compound to a database of over 4,500 clinical, failed, and reference compounds and their clinical side effects, the BioMAP Tox Alert Analysis Service is able to accurately and affordably identify potential toxicities and classify candidates based on known mechanism classes.

Gain Better Insight into Compound Safety Prior to Entering the Clinic

Accelerate your drug development with analysis that can:

- Predict severe and potentially trial ending outcomes
- Classify lead molecules and identify unknown mechanism classes
- Expand confidence in the safety of your candidate molecules before advancing them to patients

Tox Alert Predicts Mechanism Class



Paclitaxel, an anti-proliferative chemotherapeutic agent that acts by stabilizing microtubules, was profiled in the Diversity PLUS panel and data was subsequently analyzed using Tox Alert. Analysis of 84 biomarker readouts (rows) compared to Paclitaxel and 3 of 28 consensus mechanism class profiles (columns). Vertical grey lines separate the BioMAP systems, while the horizontal grey line separates Paclitaxel from the 3 consensus mechanism profiles. Significant biomarker activities are red if protein levels are increased, blue if protein levels are decreased, and white if levels are within the envelope or unchanged as compared to control protein levels. Darker shades of color represent greater change in biomarker activity relative to vehicle control. This plot, referred to as a "Mechanism HeatMAP", compares each test compound to a set of consensus profiles that were generated from a large reference dataset of structurally distinct compounds from 28 different mechanism classes.

Predictive Results Based on a Decade of Data

Tox Alert™ starts with data from compounds profiled in the BioMAP® Diversity PLUS™ panel of human disease models spanning 84 clinical biomarkers and analyzes them in two ways:

- Identification of common signatures of toxicity that highly correlate with common adverse effects seen in the clinic
- Classification of compounds based on the statistical similarity of their activity profile to one of 28 mechanism classes with known clinical outcomes, such as corticosteroids, selective kinase inhibitors, proteasome inhibitors, microtubule stabilizers, and mitochondrial disrupters

Common Adverse Clinical Outcomes Identified by BioMAP Tox Alert Analysis Service

Toxicity Signature	Adverse Effect	Definition and Mechanism
Acute Toxicity	Death	Increased risk of death due to an inhibition of mechanisms that maintain cellular electrolyte balance.
Immune Toxicity	Immunosuppression	Increased risk of infection due to a depression of responses from immune cells.
Skin Toxicity	Irritation	Irritation of the skin with reddening and itch due to sustained production of prostaglandins leading to vascular permeability, leukocyte infiltration, and promotion of Th17 responses.
	Rash (MEK-related)	Increased incidence of acneiform skin rash due to an inhibition of growth-factor pathway dependent suppression of inflammatory pathways in the skin, leading to the recruitment of inflammatory leukocytes.
	Sensitization	Increased potential for allergic skin reactions due to reduced production of collagens in the skin, leading to barrier dysfunction.
Liver Toxicity	Hepatosteatosis	Increased incidence of hepatotoxicity and liver steatosis due to impaired endosomal trafficking in vascular cells, compromising their support of hepatocytes and leading to liver damage.
Organ Toxicity	DNA Replication-Related Toxicity	DNA replication related organ toxicity due to an inhibition of vascular cell proliferation, which impairs organ health.
Cardiovascular Toxicity	Thrombosis Related Side Effects	Increased incidence of stroke, deep vein thrombosis, or pulmonary embolism due to modulation of vascular autophagy, leading to increased thrombotic potential within the vasculature.

BioMAP Tox Alert Service

Service	Analysis of data from concurrent or previously profiled compounds in Diversity PLUS for additional safety and toxicology parameters.
Examples of Analysis Performed	Interrogation of Diversity PLUS data for the presence of one or more of the eight toxicity signatures that have been identified to highly correlate with toxicity seen in the clinic. Statistical comparison of the profiles of test agents with 28 well characterized mechanism classes derived from consensus activity profiles of multiple compounds and concentrations in that class.
Deliverables	DiscoverX provides a study report that includes: Table listing the presence of signatures of one or more adverse effects or toxicities. Results of mechanism classification and a heat map highlighting the pattern of biomarker expression as compared to each mechanism class. Annotation of biomarker activities with respect to biological significance, profile plots, graphical overlays of test and reference compound profiles, results of similarity search, and expert data interpretation and analysis.

Learn more about Tox Alert Analysis by visiting: discoverx.com/tox-alert

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