A Weight-of-Evidence Approach to Prioritisation based on Consensus across Multiple Sources of Information

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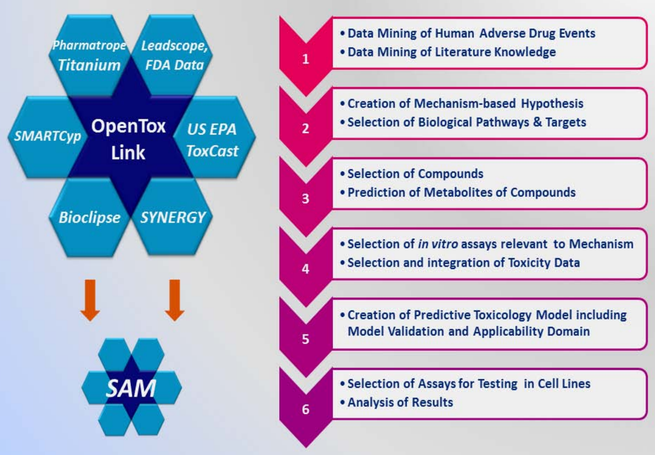
The OpenToxLink Virtual Organisation



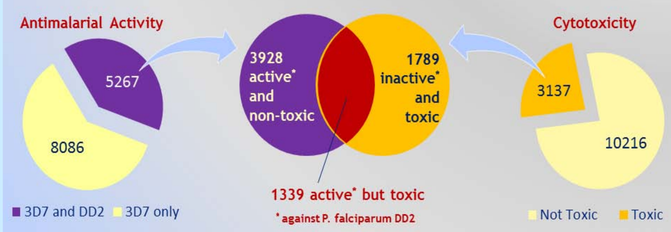
Within the FP7 SYNERGY project Douglas Connect initiated two collaborative research project pilots in 2010: one in Drug Design and one in Predictive Toxicology. The work is being carried out by a range of individual organisations from industry and academia located in several countries ie. they formed a Virtual Organisation (VO). Services developed within SYNERGY supporting the collaborative work were tested during the pilots.

OpenToxLink was formed by Douglas Connect to collaborate on the creation of a set of Linked Resources supporting predictive toxicology and to develop and test innovative strategies to predictive toxicology model building supported by Linked Resources. Eventually, the SYNERGY-supported drug discovery screening project Scientists Against Malaria (SAM) will be combined with services from the OpenToxLink VO to generate toxicology profiles for selected compounds.

The TCAMS MalariaBox

"Malaria Box": A collection of chemical compounds active against *(i.e. inhibiting growth of)* the malaria parasite *Plasmodium falciparum*

Data provided that is relevant for this project:
- Activity against (growth inhibition of) *P. falciparum* strain 3D7 (common strain)
- Activity against (growth inhibition of) *P. falciparum* strain DD2 (multi-drug resistant strain)
- Cytotoxicity against (growth inhibition of) human hepatocytes, HepG2 (hepatoma cells)

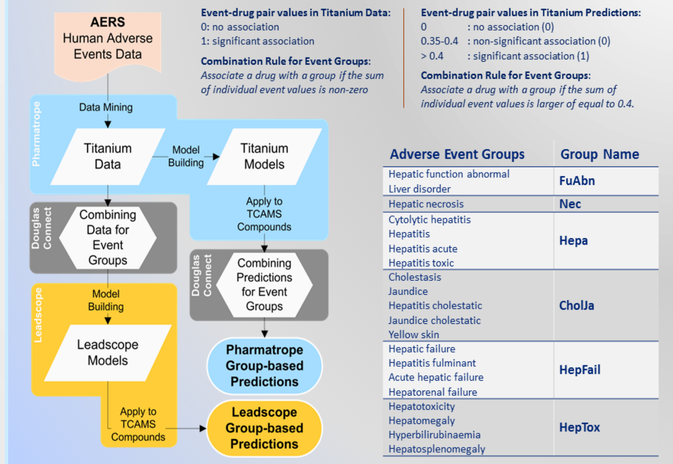


Gamo et al., *Nature* **465**(7296), 305-10 (2010)

In 2010, GlaxoSmithKline made the Tres Cantos Antimalarial Compound Set (TCAMS) publicly available by depositing it at the ChEMBL Neglected Tropical Disease Database. Each of the 13533 chemicals in the TCAMS inhibits growth of the 3D7 strain of *Plasmodium falciparum* – the malaria causing parasite – by at least 80% at a concentration of 2 µM. 5267 compounds show the same effect against the multi-drug resistant strain DD2. Evidence for liver toxicity is provided by growth inhibition data against human HepG2 cells. At 10 µM, 3137 TCAMS compounds inhibit HepG2 growth by 40% or more.

Of the ~5000 compounds active against DD2, about 1300 are to be considered toxic according to the above definition. The remaining ~4000 represent a promising starting point. To further narrow these down, we combine the TCAMS experimental data with toxicity predictions on these chemicals.

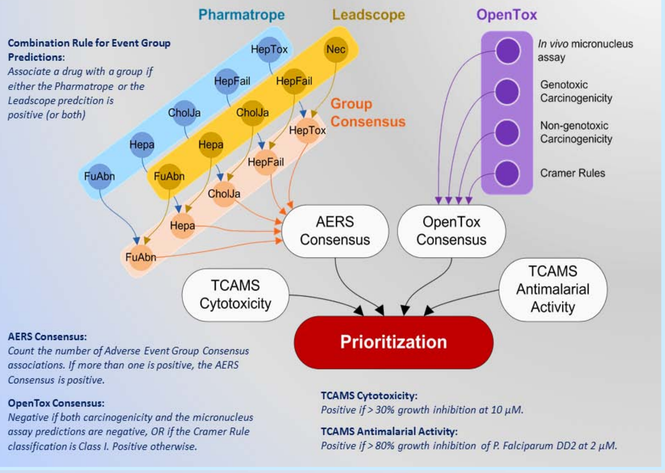
Human Adverse Events Data



The US FDA's AERS (Adverse Events Reporting System) database is a unique source of *in vivo* data on observations of human toxicities of drugs. Pharmatrope has processed the AERS data according to statistical considerations, and created the Titanium Adverse Events Database and Models. We have selected a subset of 20 adverse events related to the hepatobiliary tract, which we classified into 6 groups. Group-based predictions for the TCAMS were obtained in two ways:

1) combining the AERS data of the adverse events belonging to a group and using the combined data to train and build predictive group-based models ("Leadscope Predictions")
2) building models on each of the 20 selected adverse events and obtaining group-based predictions from a consensus across the individual predictions ("Pharmatrope Predictions").

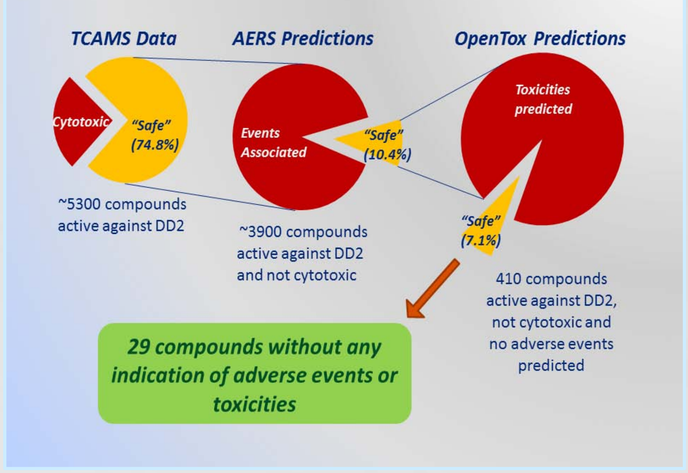
Combining Predictions and Experimental Data



The two sets of adverse events group-based predictions for the TCAMS were combined for each group using a conservative combination rule. In parallel, the TCAMS was imported as an OpenTox dataset, and three ToxTree predictive models were applied to it: the Structure Alerts for the In Vivo Micronucleus Assay in Rodents, the Benigni/Bossa Rules for Carcinogenicity and Mutagenicity, and the Cramer Rules. Again, a conservative consensus rule was applied to combine the predictions.

All toxicity predictions were combined with the experimental cytotoxicity data provided with the TCAMS, yielding an overall toxicity estimate. In combination with the antimalarial activity we prioritized the TCAMS for highly active antimalarials with a negative toxicity estimate.

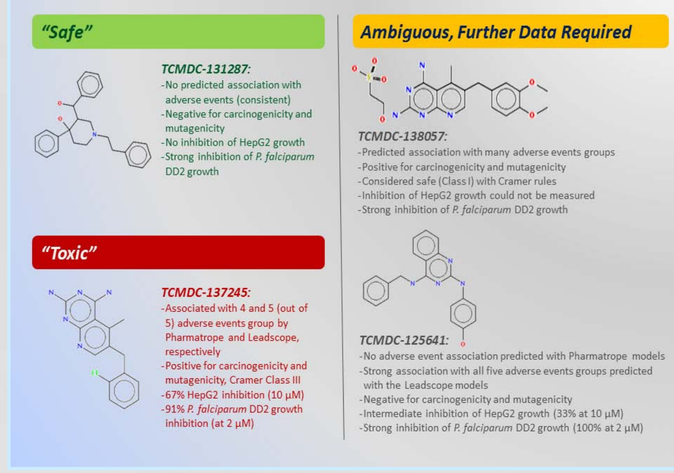
Compound Prioritization Results



Taking as a starting point the 5300 compounds that are both highly active against the multi-drug resistant P. falciparum strain DD2 and did not significantly inhibit HepG2 growth, we end up with only 29 compounds that are not associated with any adverse events or toxicities (based on the models used here). This small number allows investigating each of them individually.

A similar number (~120) is associated with all toxicities and adverse events predicted/tested. A number of compounds (~180) deserves further investigation, as they are only ambiguously associated with human adverse events (ie. the Pharmatrope and Leadscope models disagree for one or more adverse events groups).

Example compounds



Based on our gathered evidence we can still consider some compounds safe, as they have consistently yielded negative predictions and have not shown any inhibition of HepG2 growth. There are a number of chemicals that are associated with most of the adverse events included here, are predicted to be mutagenic and carcinogenic, and exhibited strong cytotoxic activity against HepG2 cells. Our results also point out compounds that need further study, as the predictions obtained for them are either inconsistent or even contradict each other.

Next steps to be taken before applying the approach to SAM compounds are the inclusion of additional classes of adverse events (eg. cardiac or renal) and of additional OpenTox models.

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www.synergy-ist.eu

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www.opentox.org

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