

Pharmatropo Titanium

Predicting Toxicity Based On Data In Humans

April 29, 2009

Prediction of Adverse Events Has Been Limited by Access To Data

- *In vitro* and *in vivo* models have been used as surrogates
 - Well suited to mechanistic studies
 - Predictivity for humans difficult validate
- FDA's Adverse Events Reporting System (AERS) now gives access to human data
 - 70,000,000 records since 1999
 - 8,000,000 total events
 - 1,700 unique drugs

Pharmatropo Titanium Predicts Human Clinical Adverse Events

- Models based on ***Human Clinical Data***
- Predicts human events, **not animal models or surrogates.**
- Statistically significant models have been created for over 200 adverse events
- ***Fragment-based approach provides insight into modifications that may improve the adverse event profile***
 - *Models suggest with chemical structures are correlated with each adverse event*

Titanium Is Updated Quarterly

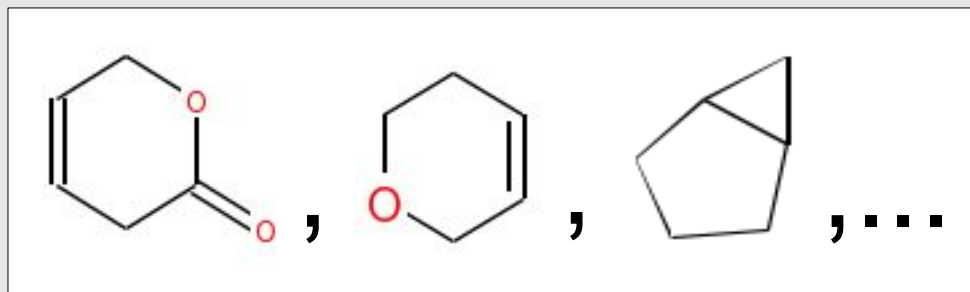
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- Download quarterly AERS updates
- Clean data
 - Extract useable records
 - Rationalize drug names
- Link chemical structures to drug names

Structure-Event Analysis Is Fragment-Based

- 325 fragments



- Fragments selected from biologically active molecules
- QSAR performed on linear combination of fragments

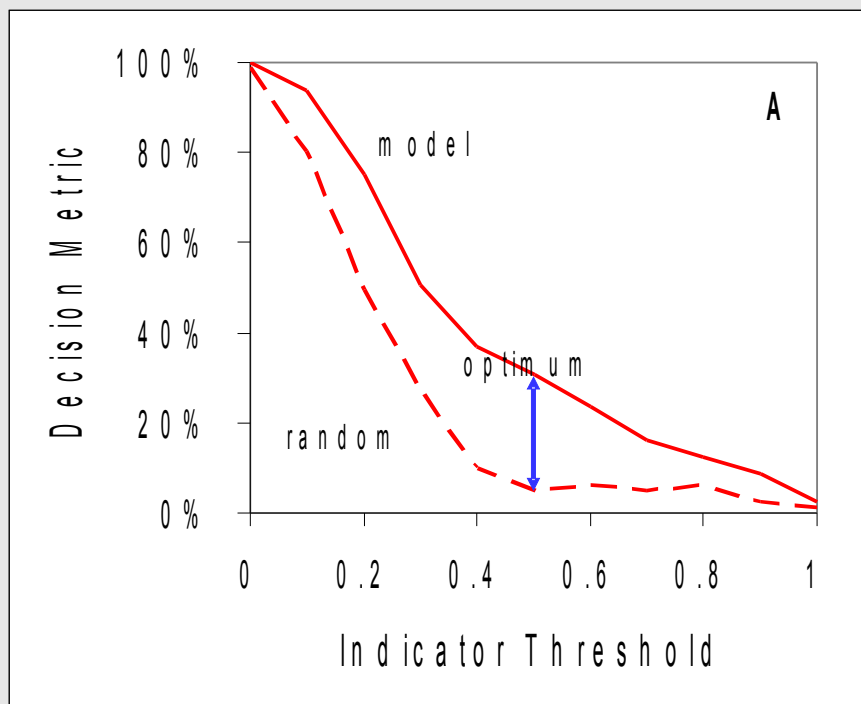
Titanium Is Tuned For “Fail Early, Fail Cheap”

- Goal: remove liabilities early in the pipeline
 - Drug candidates with liabilities can be removed from progression or targeted for additional experimental evaluation
 - Avoid removing drug candidates with no liability
- Leads marked with liabilities only at high statistical significance
 - At the expense of identifying *all* potential liabilities
- Predicted reliability and fraction of actives missed are provided for each adverse event

Maximizing Reliability

- Drug-event links must be 99.9% significant
- At least 5 drugs must be associated with a given event
- Reliability evaluated vs. randomized data

Representative Results: Long QT Syndrome



- Results tuned to maximum signal vs. randomized data
 - Signal : random = 6x
- Reliability (test set data):
 - 31% of actives identified
 - 25 identified of 81 total
 - 96% reliability
 - 1 false positive

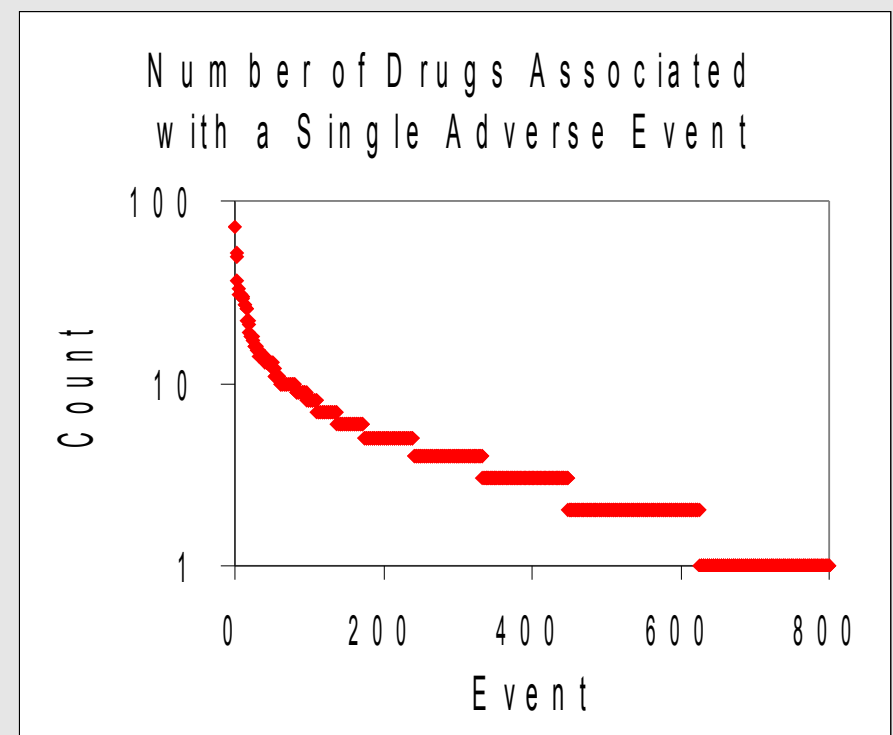
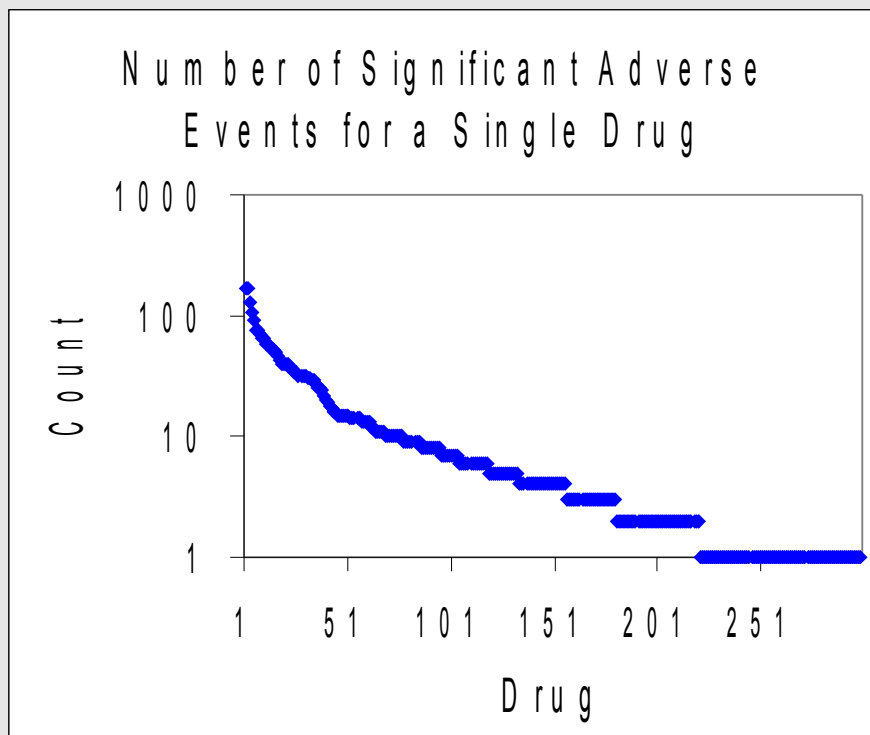
Performance Of LQS Model vs. Test Data

- Test set = molecules with LQS liability and dropped from market before 1999
 - 4 of 8 (50%) identified with high confidence

Compound	Identified as Active
astemizole	+
lidoflazine	+
sertindole	±
terfenadine	±
levomethadyl	-
terodiline	-
cisapride	+
grepafloxacin	+

Method Has Been Applied to All Reported Events

- 240 significant drug-adverse event relationships identified
- Distributed over 299 compounds (20% of total drugs)

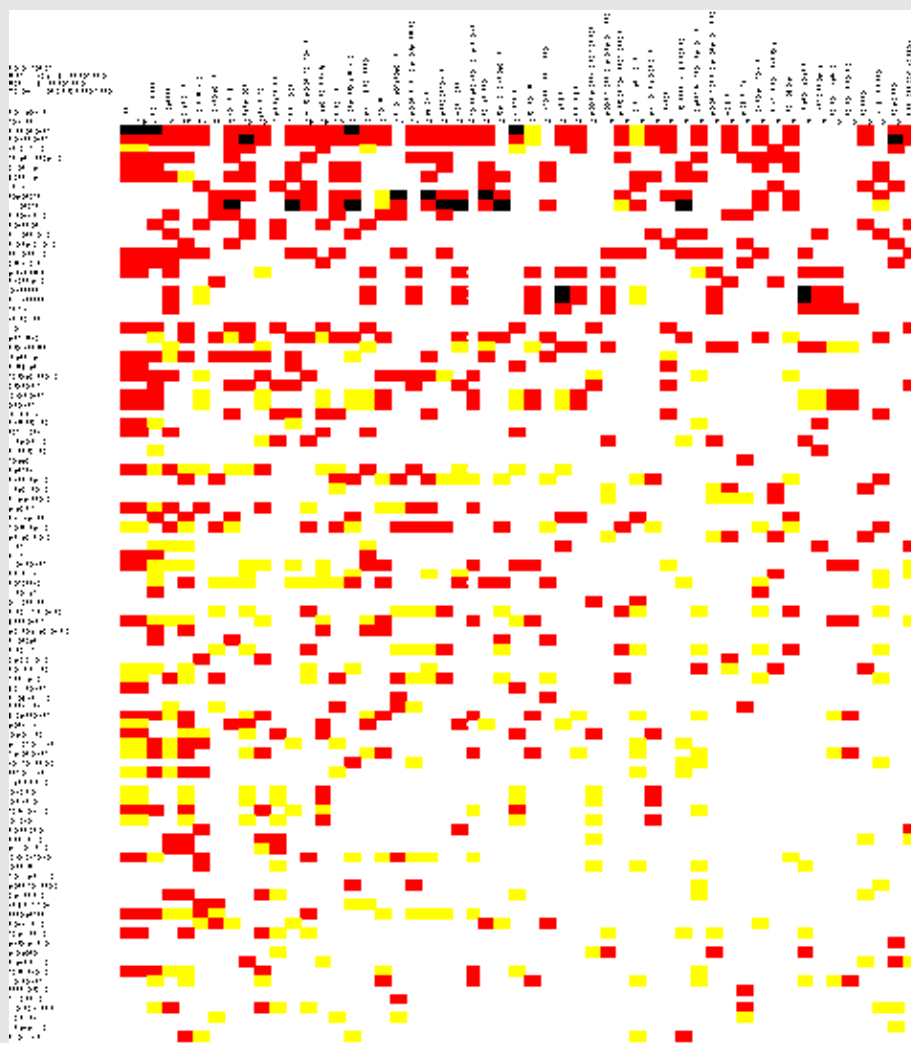


Titanium provides valuable insights

- Fast can screen large collections for potential “bad actors”
 - On compound acquisition
 - Library screening
- Fragment-based analysis provides insight
 - Can “design out” liabilities
 - Identify clusters of adverse events
- Improve performance of Phase I, II, III clinical trials

Profiling Adverse Events

- Rows are drugs, columns adverse events
 - Black – very high relationship
 - Red -high relationship
 - Yellow -moderate relationship
- Can create profiles for libraries or single compounds



Conclusions

- The relationship between chemical structures and **clinical** adverse events can be modeled
 - We no longer have to rely on *surrogates* and *animal models*
 - Unprecedented analysis of *all* adverse events
- Pharmatropo Titanium identifies drug candidates with strong liability for adverse events:
 - Identify high-risk leads
 - Screen for liabilities in compound collections
 - In-licensing due diligence
 - Reduce costs of drug discovery
 - Reduce risk to patients

Access To Titanium

- Annual license
 - Statistically significant models pre-computed
 - Models and full profile of statistically significant drug-event pairs updated quarterly
- Easy-to-use interface
 - Compound structures entered in multiple formats
 - SD files
 - ChemDraw figures
 - Single or multiple structures concurrently
 - Liabilities vs. ~200 adverse events returned
- Direct access to cleaned database negotiable

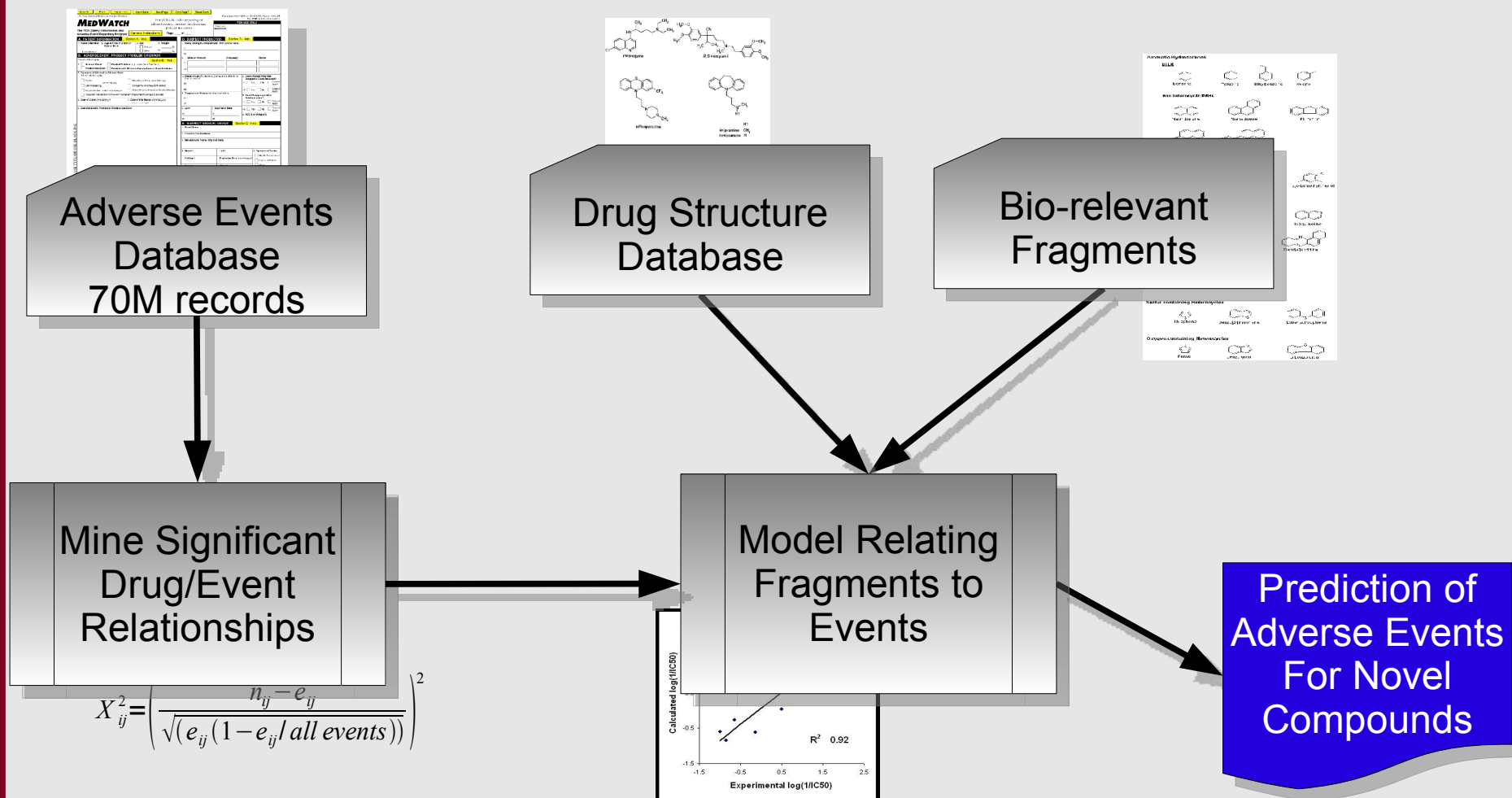
Technical Information

- Modeling Process
- Example drug/event combination
- Example of relating substructures to events
- Profiling a drug for events

Relating Chemical Structure to Adverse Events

- If we could connect chemical structural elements to adverse events we could:
 - *Reduce significant events by altering the structures*
 - *Anticipate the events associated with classes of compounds*
 - *Make better decisions on which compounds to license/progress*

Modeling Process



FDA Adverse Events Reporting System

- Collection of case reports that include:
 - Demographics of patient
 - Indication treated
 - Drugs taken
 - Adverse events
 - Outcome of case

The image shows a screenshot of the FDA MedWatch Form FDA 3500 (1005). The form is titled "MEDWATCH" and is used for the "VOLUNTARY reporting of adverse events, product problems and product use errors". It is a multi-page form with various sections for data entry. The visible sections include:

- A. PATIENT INFORMATION:** Fields for Patient Identifier, Age at Time of Event, Sex, Weight, and Date of Birth.
- B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR:** Checkboxes for Adverse Event, Product Problem, and Product Use Error. Includes a section for Outcomes Attributed to Adverse Event.
- C. PRODUCT AVAILABILITY:** Fields for Product Available for Evaluation and Return to Manufacturer.
- D. SUSPECT PRODUCT(S):** Fields for Name, Strength, Manufacturer, and other product details.
- E. SUSPECT MEDICAL DEVICE:** Fields for Brand Name, Common Device Name, and Manufacturer.
- G. RESPONDER:** Fields for Name and Address.

The form also includes a "PLEASE TYPE OR USE BLACK INK" instruction on the left side and a footer with the form number and submission instructions.

Size and Coverage

- Data collection started 1996, superseding the older SRS system
- 2,061,597 Cases
- 1,871 Drugs
- 7,933,712 Events



Mining Drugs/Event Relationships

	Reports with drug i	Reports w/o drug i	Total
Reports with event j	a	b	a+b
Reports w/o event j	c	d	c+d
Total	a+c	b+d	a+b+c+d

- Baseline count $e_{ij} = (a+b)(a+c)/(a+b+c+d)$
- Relative ratio $rr_{ij} = n_{ij}/e_{ij}$
- Ratio measures the occurrence of an drug-event combination beyond the expected number from the baseline of all drugs

Example: Aspirin/Reye's Syndrome

	Reports with Aspirin	Reports w/o Aspirin	Total
Reports with Reye's	17	102	119
Reports w/o Reyes	15,104	7,131,022	7,146,126
Total	15,121	7,131,124	7,146,245

- Baseline expected reports is 0.25 per drug
 - $(119 * 15,121 / 7,146,245)$
- Observed 17 reports connected with Aspirin
- Ratio is $17/0.25 = 68$ times expected occurrence

Connecting Drug Structures to Adverse Events

- Break drugs into a set of chemically relevant fragments
- Create a model that associates the presence of fragments with a drug/event relationship
 - Using the drugs reported in AERS
- Use the resulting model to predict the connection of a *novel* compound with *specific adverse events*.

Long QT Syndrome

- Prediction of true drug/event relationships is robust.
- May miss some positives, but the predicted drug event associations are robust

		<i>counts</i>		
		predicted		
		TRUE	FALSE	<i>total</i>
observed	TRUE	25	56	81
	FALSE	1	1139	1140
	<i>total</i>	26	1195	

Only 1 false positive

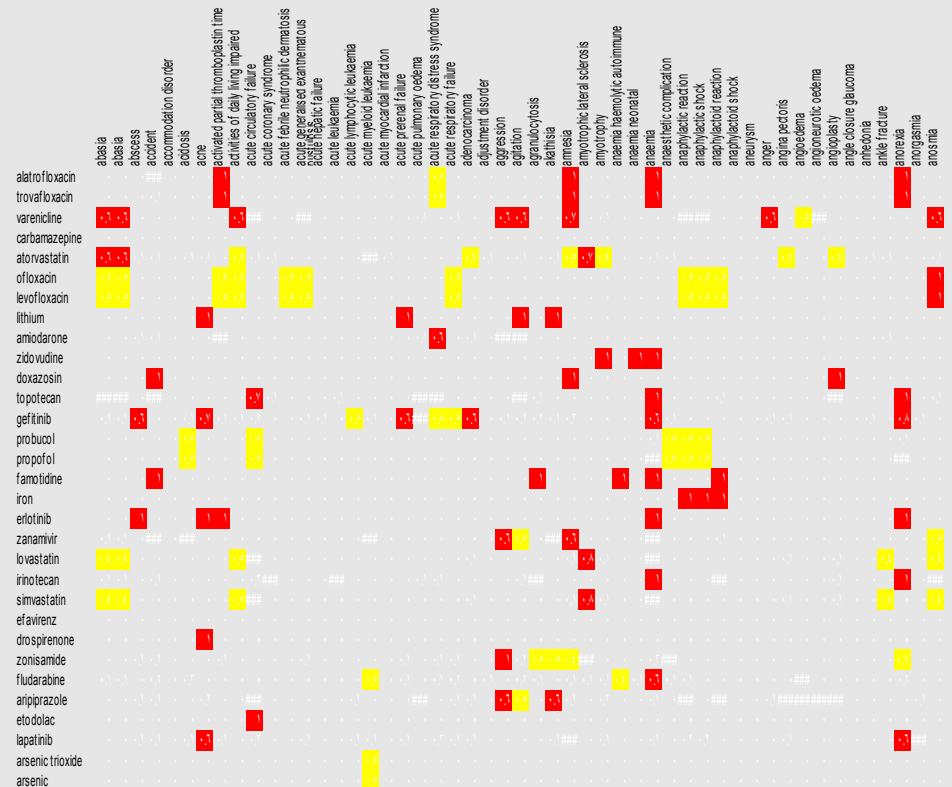
25 of 81 QT compounds detected

Method Has Been Applied to All Reported Events

- Of the 11,000 unique events in AERS, nearly 500 have statistically significant relationships to drug structure.
- Pharmatropé provides unprecedented ability to predict a broad range of events based on drug structures

Prediction of a Series of Events for A Set of Drugs

- Evaluation of a panel of drugs for a series of adverse events
- This example is for known drugs
- Provides an adverse event “panel” for evaluation



Conclusions

- The relationship between chemical structures and **clinical** adverse events can be modeled
 - We no longer have to rely on weak *surrogates* and *animal models* for these events.
- The ability to anticipate adverse events provides a powerful tool for drug discovery and development.
 - Discovery – Design molecules to reduce clinical issues associated with the target
 - Development – Focus licensing, development, and trial planning based on anticipated events