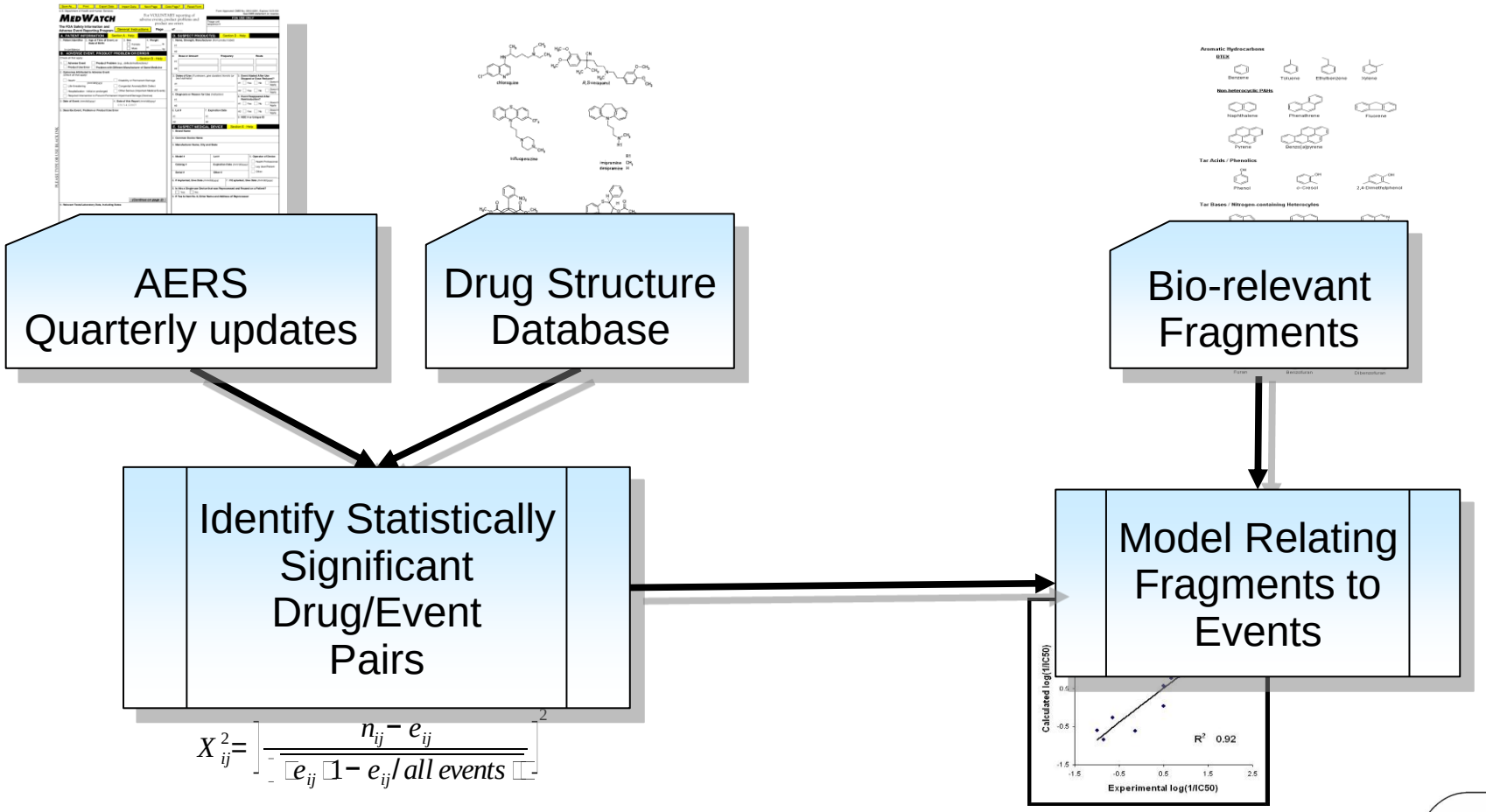
Pharmatrope Titanium™ and OpenTox

Berlin

30 May 2010

Titanium Is Two Products Derived From AERS

- Statistically filtered database for data mining
- Predictive models for 600 adverse events



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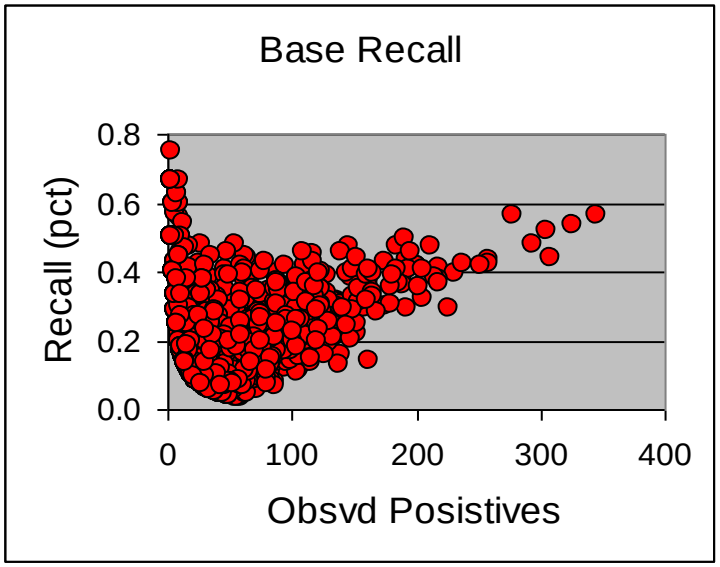
Goals

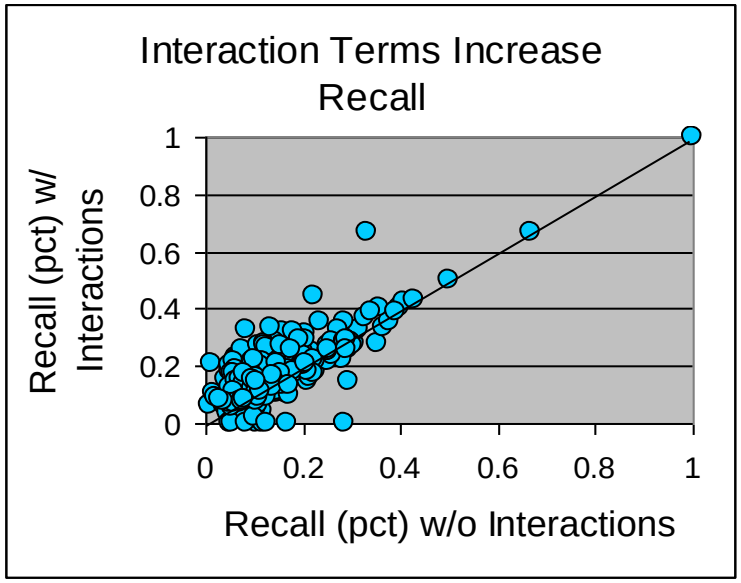
- Make human toxicity data routinely available
  - Statistical filtering is value-added component
- Provide structure-based predictions

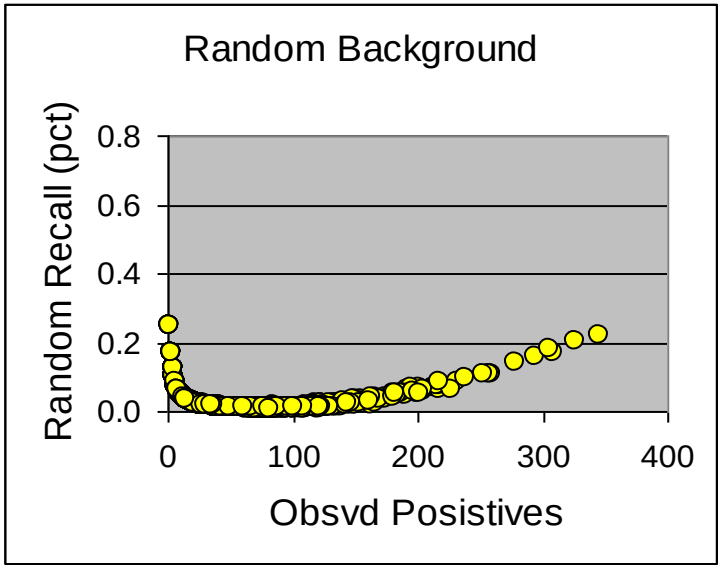
…..and then…..

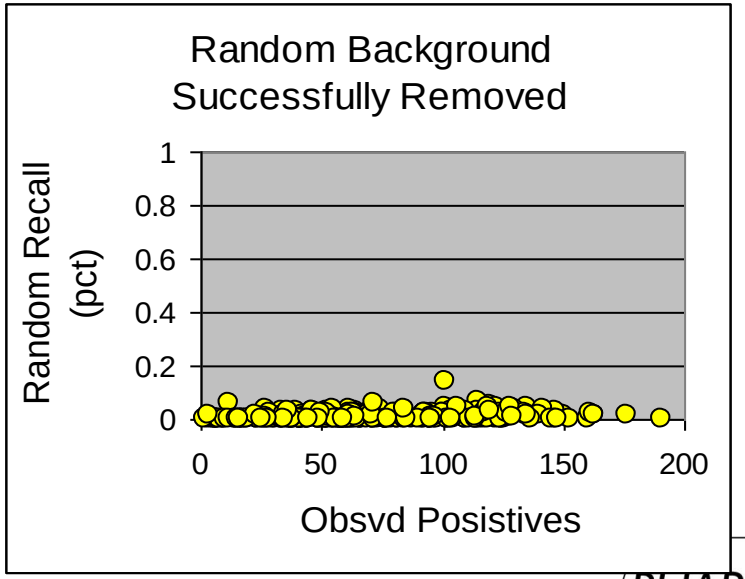
- Use signal filtering to identify mechanisms of toxicity
- Extrapolate mechanisms beyond marketed drugs

Contribution To QSAR Models: Removing Random Background Error









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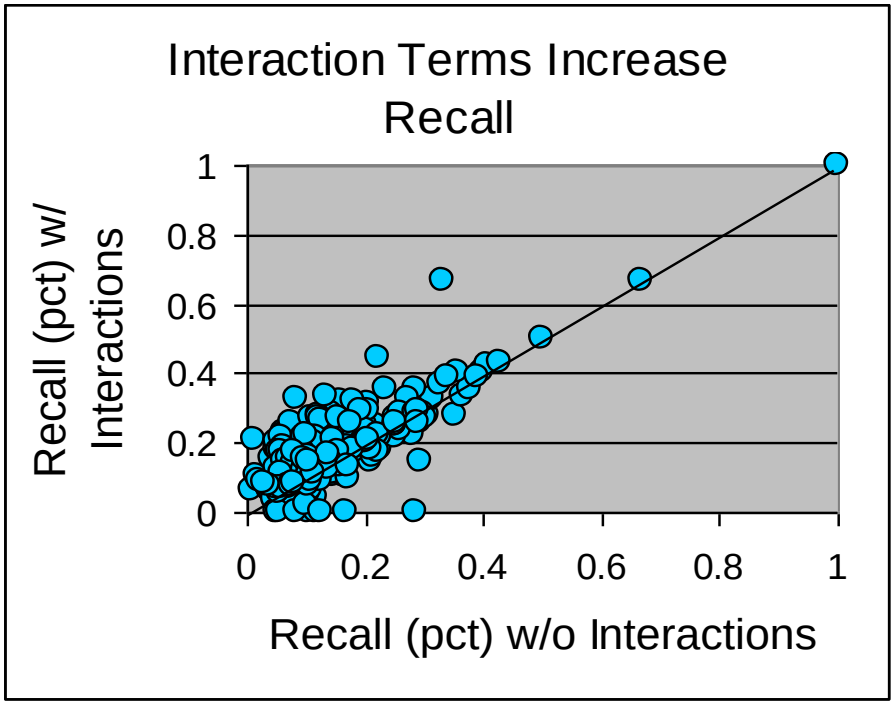
Predictive QSAR Models Are Limited By Sparseness Of Data



- Small numbers in each structural class
- Multiple mechanisms for a given event
- Multiple events for given mechanism
- Use signal filtering to deconvolute data

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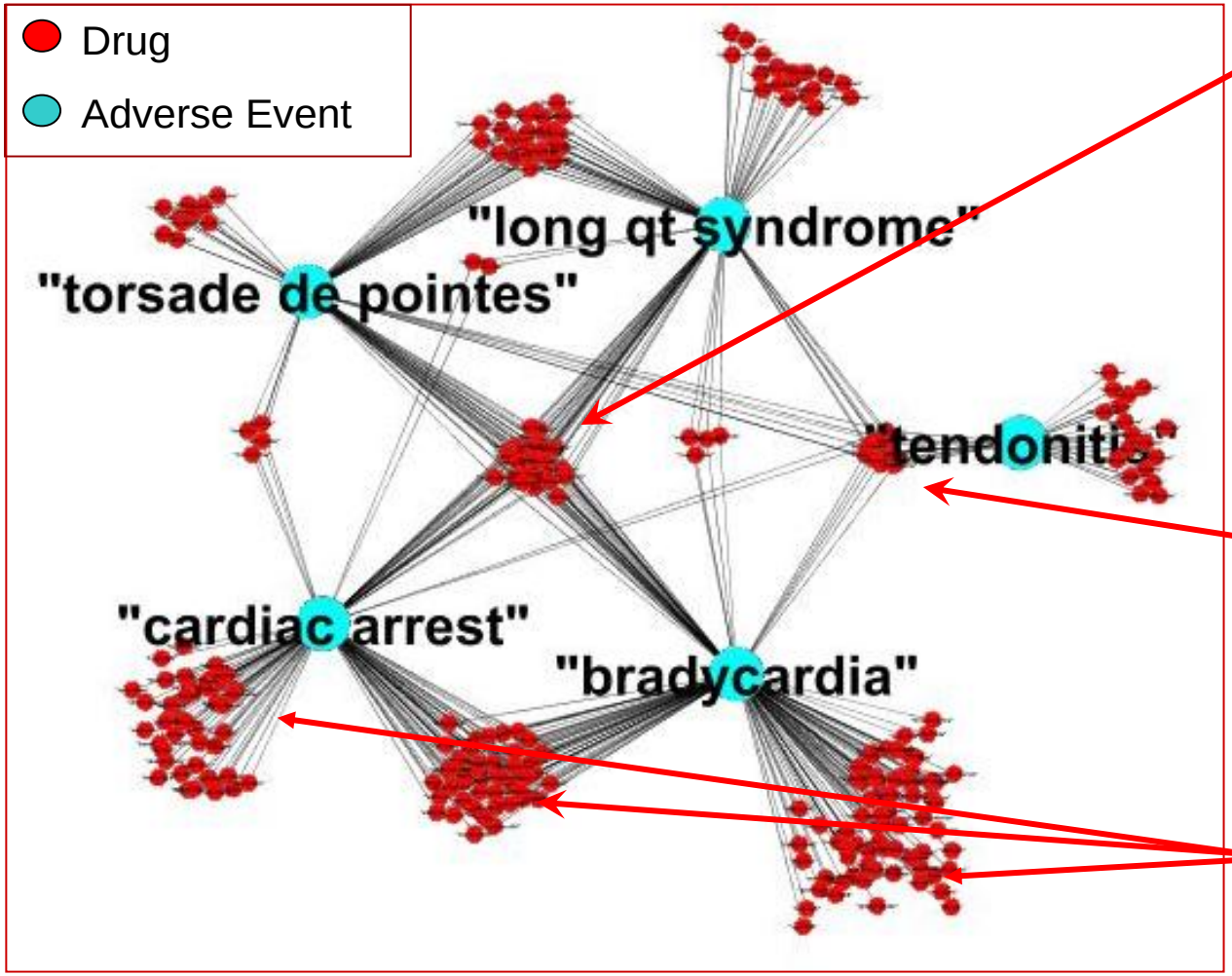
Predictive Assays: It Is Possible To Distinguish Multiple Mechanisms For A Single Adverse Event



Visualization by Cytoscape

Subset of cardio-toxic drugs associated with LQS and TdP (e.g. terfenadine)

Cardio-toxic drugs associated with general toxicity

Cardio-toxic drugs not associated with LQS and TdP

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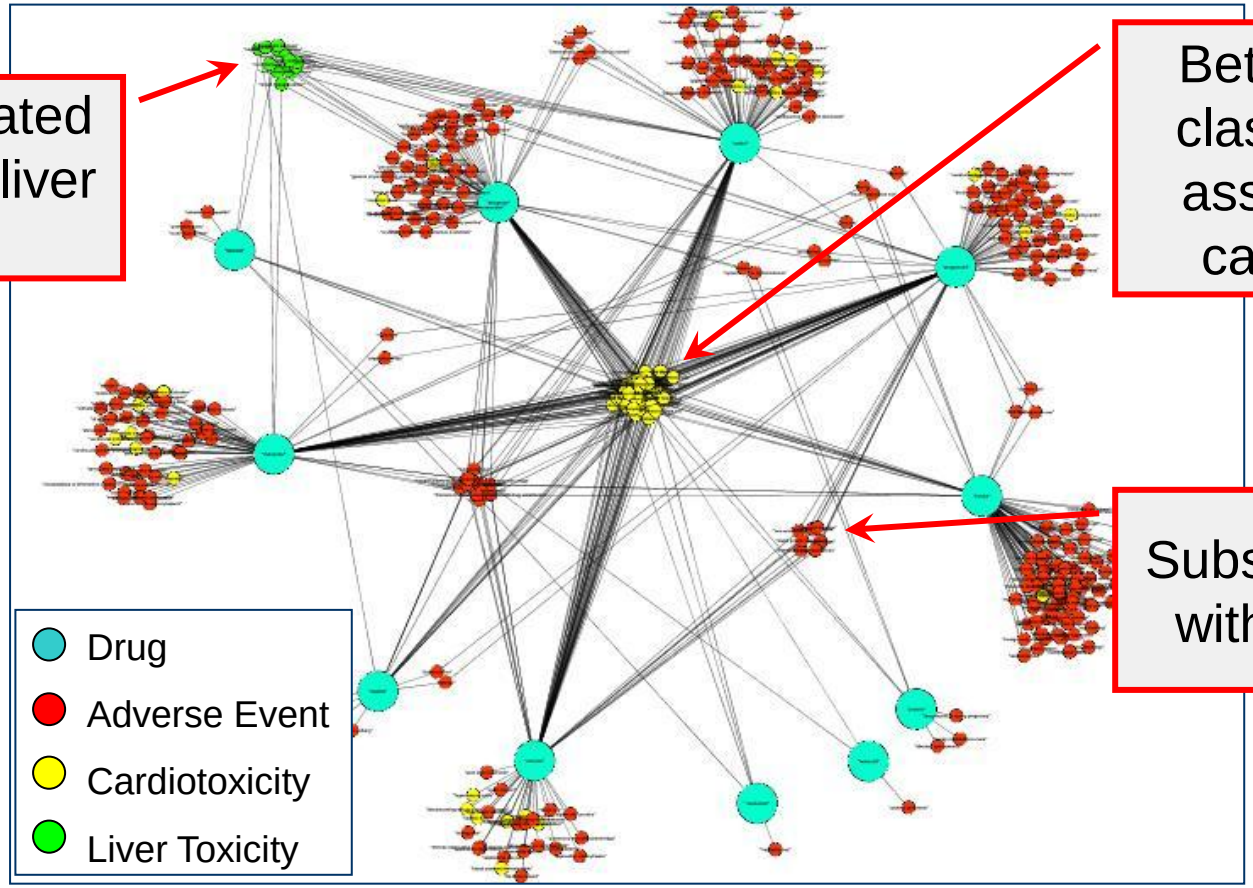
Predictive Assays: It Is Possible To Distinguish On-Target From Off-Target Mechanisms

Beta Antagonists:
Mechanism-Based vs Off-Target Toxicities

Subset associated with renal and liver tox



Beta antagonist class is strongly associated with cardio-toxicity

Subset associated with drug abuse

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Signal Filtering Example: Distinguish Alternative Mechanisms

Event Clusters Compared To 1º Pharmacology

Event 1	Event 2	Event 3	Drug	Drug Class 1	Drug Class 2
			Compd 1		
			Compd 2		
			Compd 3		
			Compd 4		
			Compd 5		
			Compd 6		
			Compd 7		
			Compd 8		

Signal Filtering Example: Reveal Weak Patterns

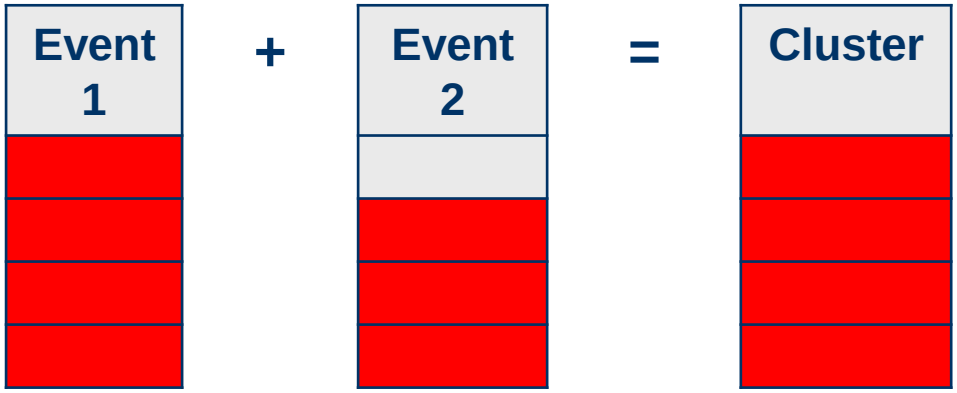
Remove 1º class effects to identify off-target toxicities

Event 1	Drug	Drug Class 1	Drug Class 2	Drug Class 3
	Compd 1			
	Compd 2			
	Compd 3			
	Compd 4			
	Compd 5			
	Compd 6			
	Compd 7			
	Compd 8			

Event 1	Drug	Drug Class 1	Drug Class 2	Drug Class 3
	Compd 1			
	Compd 2			
	Compd 3			
	Compd 4			
	Compd 5			
	Compd 6			
	Compd 7			
	Compd 8			

Clustering Is Entropy-Based

- Maximizes information gain
- Filters out random patterns



$$\Delta S = N_{cluster} \ln(N_{cluster}) - N_1 \ln(N_1) - N_2 \ln(N_2)$$

Reva, Antipin & Sander (2007)Genome Biology

Why OpenTox

- Titanium has no front end
  - Capitalize on existing data management and visualization tools
- Titanium is designed to integrate into existing infrastructure
  - Simple “structure-in”, “data-out” architecture
- Extension beyond drug discovery to ToxCast and REACH
  - Mechanistic insight from AERS verify and *extend* existing in vitro assays