

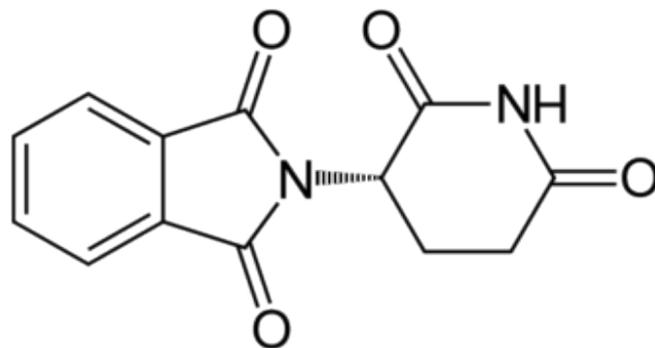
An integrative approach to drug repositioning: a use case for semantic web technologies

Paul Rigor

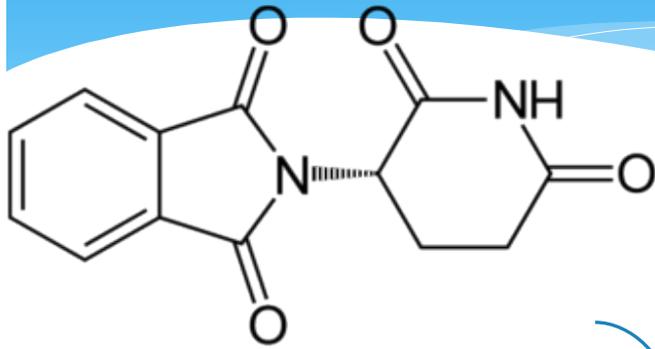
Institute for Genomics and Bioinformatics
Donald Bren School for Information and Computer Science
University of California in Irvine

Mentor: Dr. Olivier Bodenreider
Lister Hill National Center for Biomedical Communications
National Library of Medicine
National Institutes of Health

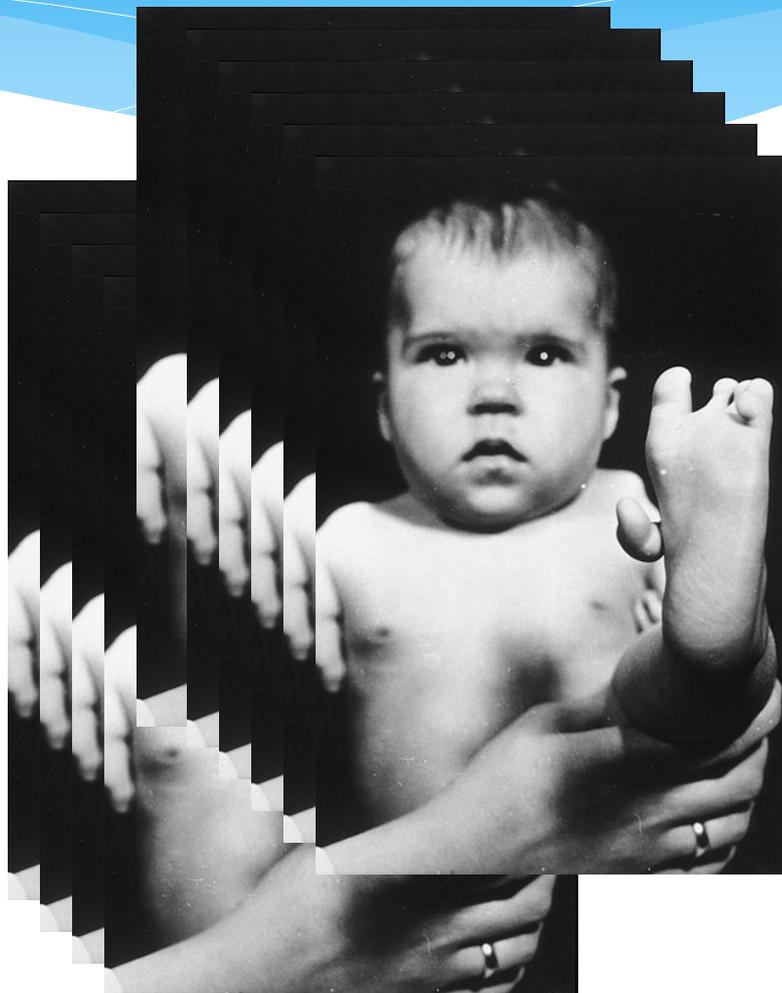
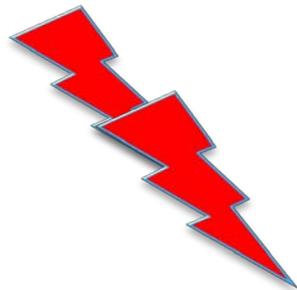
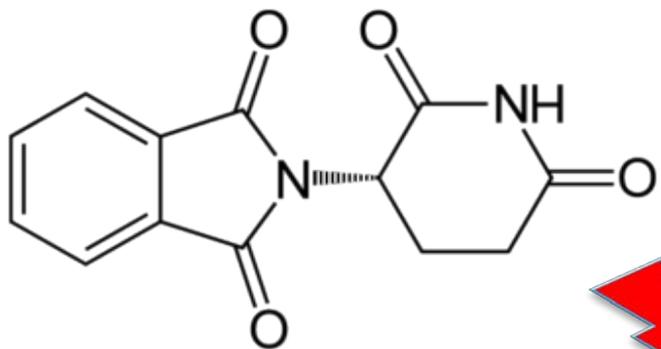
A little history



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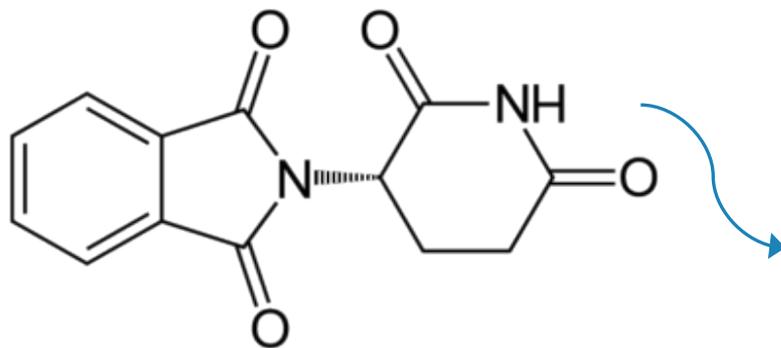


The tragic history of thalidomide



Paving a new history

- * 1964 – Serendipitous discovery as a novel treatment for symptoms of leprosy



Repositioning: novel applications of Thalidomide

Sildenafil (PDE5 inhibition)	Angina (N/A; Pfizer)	Male erectile dysfunction (Viagra; Pfizer)	Viagra, the first approved drug for male erectile dysfunction, achieved worldwide sales of US \$1.88 billion in 2003 (REF. 51).
Tadalafil (PDE5 inhibition)	Inflammation and cardiovascular disease (N/A; GSK; ICOS)	Male erectile dysfunction (Cialis; Eli Lilly & ICOS)	Tadalafil transferred to ICOS after GSK did not see any potential in the initial indication areas ⁶² . Launched in August, 2002, Cialis achieved worldwide sales of US \$1.1 billion in 2003 (REF. 64).
Thalidomide (TNF- α inhibition)	Sedation, nausea and insomnia (Contergan; Chemie Grunenthal)	Cutaneous manifestations of moderate to severe erythema nodosum leprosum in leprosy and multiple myeloma (Thalomid; Celgene)	Approval by the US FDA in 1998 for cutaneous manifestations of erythema nodosum leprosum in leprosy ⁶⁵ . It is now widely used to treat multiple myeloma and Celgene is now seeking US FDA approval for this indication. Thalomid sales reached US \$224 million in 2003 (REF. 66).
(state-dependent Na channel blockade, GABA stimulation and kainate/AMPA antagonism*)	(Topamax; Johnson & Johnson)	(N/A; Johnson & Johnson)	in overweight drug recipients. However, the side-effect profile was unacceptable using the initial formulation*. TransForm Pharmaceuticals received an approvable letter for a novel crystalline form of Topamax in late 2003 [†] , then signed a licensing agreement with J&J ⁶² .
Zidovudine (reverse-transcriptase inhibition)	Cancer (N/A; Burroughs Wellcome)	HIV/AIDS (AZT/Retrovir; GSK)	Originally developed in 1964 in oncology and was found, in 1985 to be a potent drug for AIDS ⁶ . Became the first drug approved for treatment of HIV in 1987. Worldwide sales of US \$100 million in 2003.

What is drug repositioning?

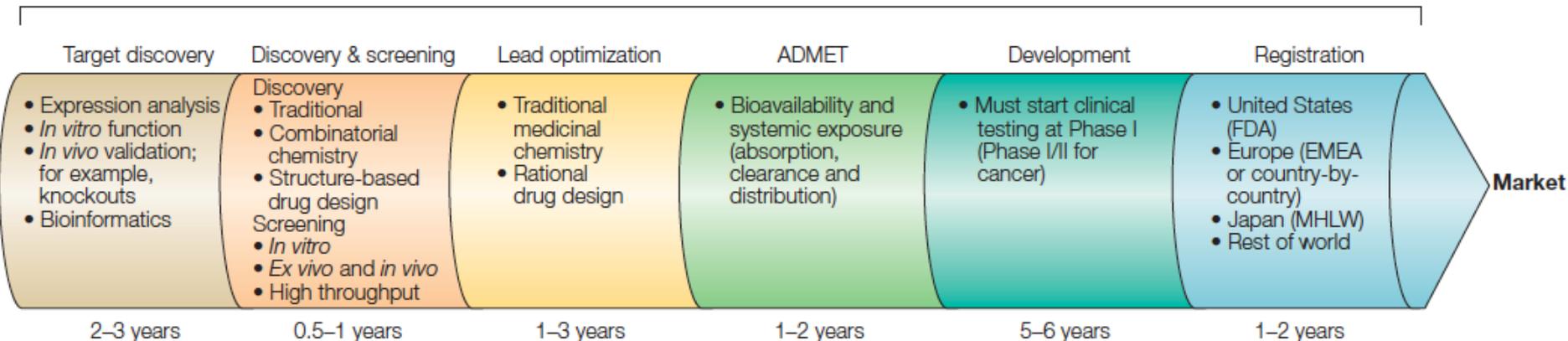
- * Discovering novel targets for existing drugs
- * Big pharma finds this approach economically attractive compared to *de novo* drug discovery
- * Three R's: Reprofileing, repurposing, and repositioning

Drug development pipelines

a

De novo drug discovery and development

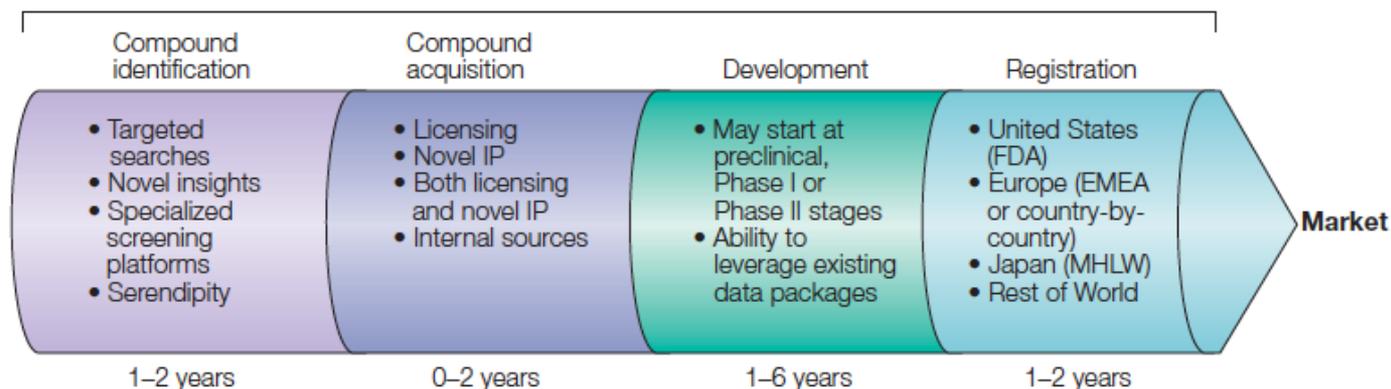
- 10–17 year process
- <10% overall probability of success



Drug repositioning

- 3–12 year process
- Reduced safety and pharmacokinetic uncertainty

b



Rational drug design

- * Drug repositioning has paved the way for rational drug design
- * Instead of phenotypic assays (trial-and-error), we are delving deeper into biological processes (and components) that underlie disease

Drug repositioning methods

- * (1) Side effects (or adverse events; Campillos, et. al. 2008)
 - * Clinical
 - * in silico
- * (2) Ligand-based (chemical similarity)
- * (3) Structure-based (simulations)
- * (4) Network-based (network pharmacology; Keiser, et.al. 2009)
 - * Polypharmacology
 - * Target promiscuity
 - * Genomics (and next generation sequencing)
- * (5) Serendipitous (clinical/experimental)!

Drug Repositioning: Side-effect

- * Campillos, et. al., 2008
- * Examples:
 - * Donepezil (original indications to treat dementia in Alzheimer's Disease)
 - * Has similar side effects as Venlafaxine (an anti-depressant, 5-HTT)
 - * Predicted and experimentally validated

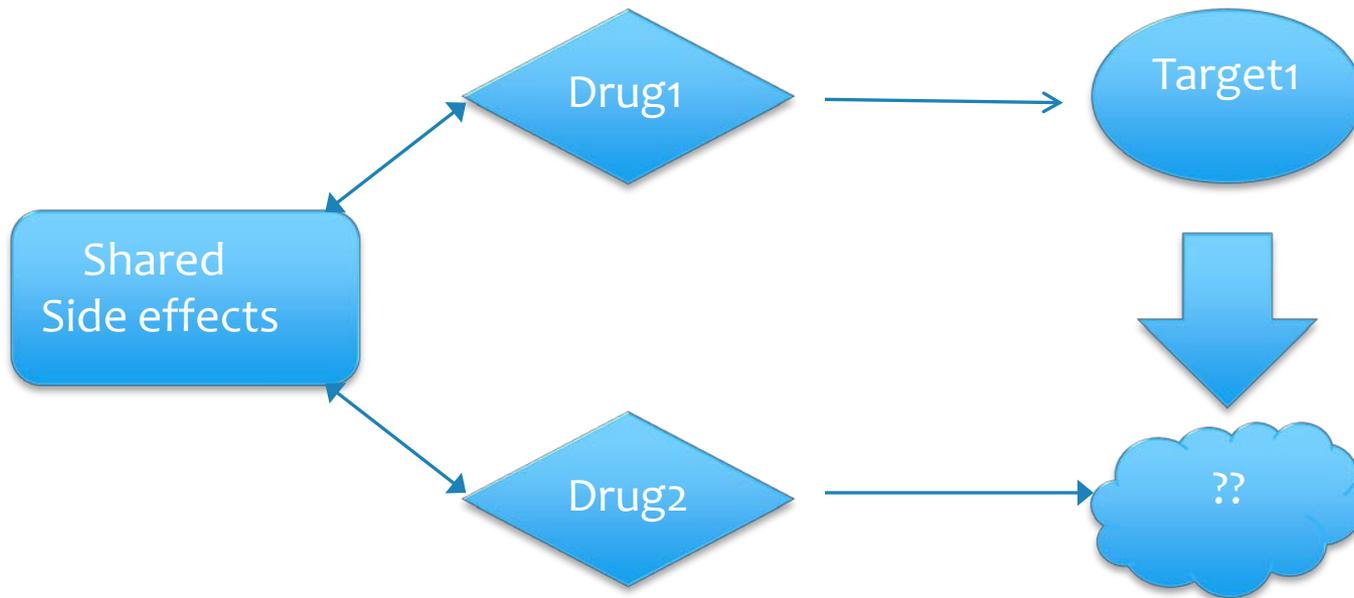
What is our strategy?

- * Our proof of concept hinges on the similarity of side-effects among drugs (Campillos, et. al. 2008)
- * We focus on existing FDA-approved drugs which are annotated in DrugBank
- * We also focus on the database of side effects called **SIDER**

What is our hypothesis?

- * In some instances, the molecular targets of drugs are known and annotated
- * However, not all FDA-approved drugs have known and experimentally validated targets
- * How do we infer targets of drugs with no known targets?

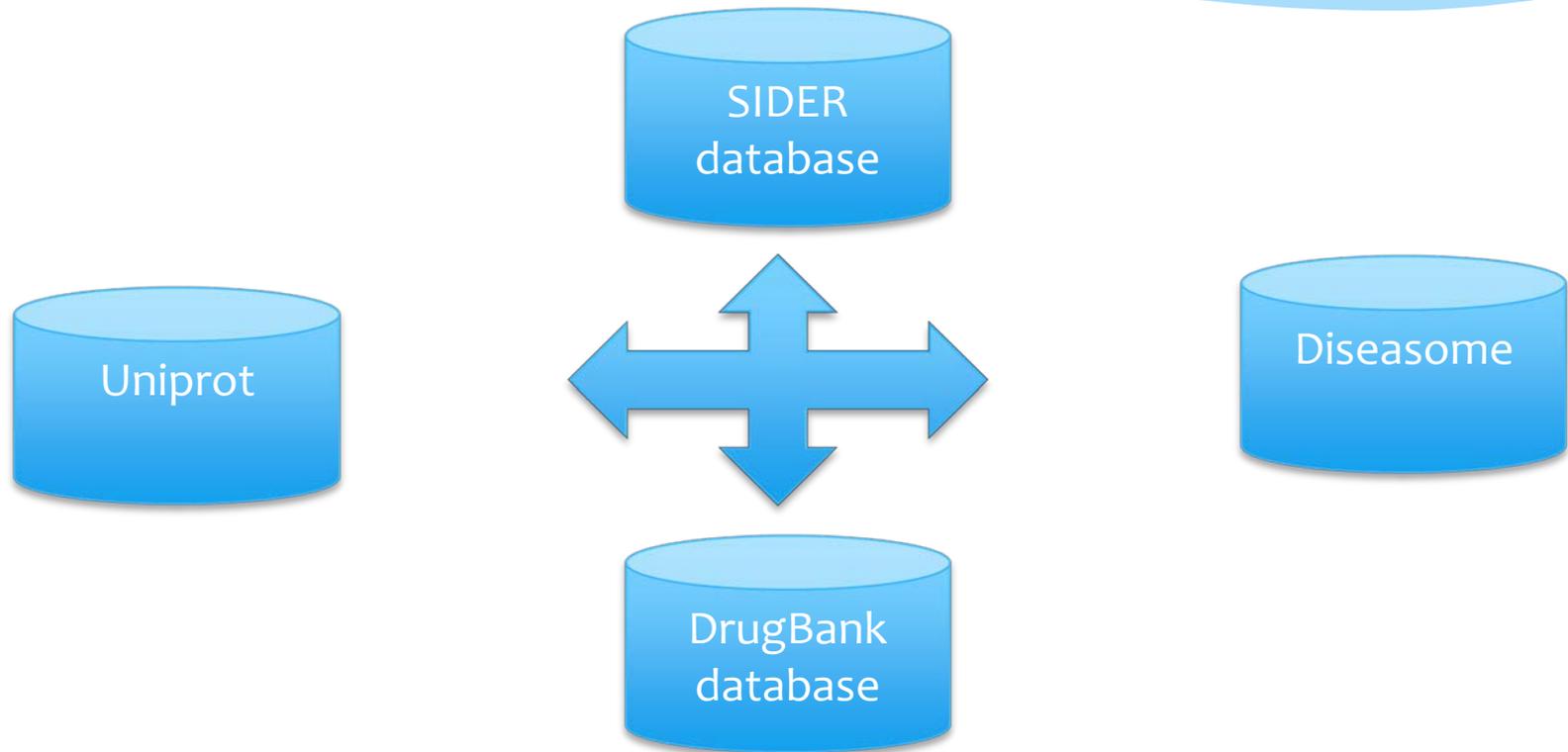
Hypothesis (graphical)



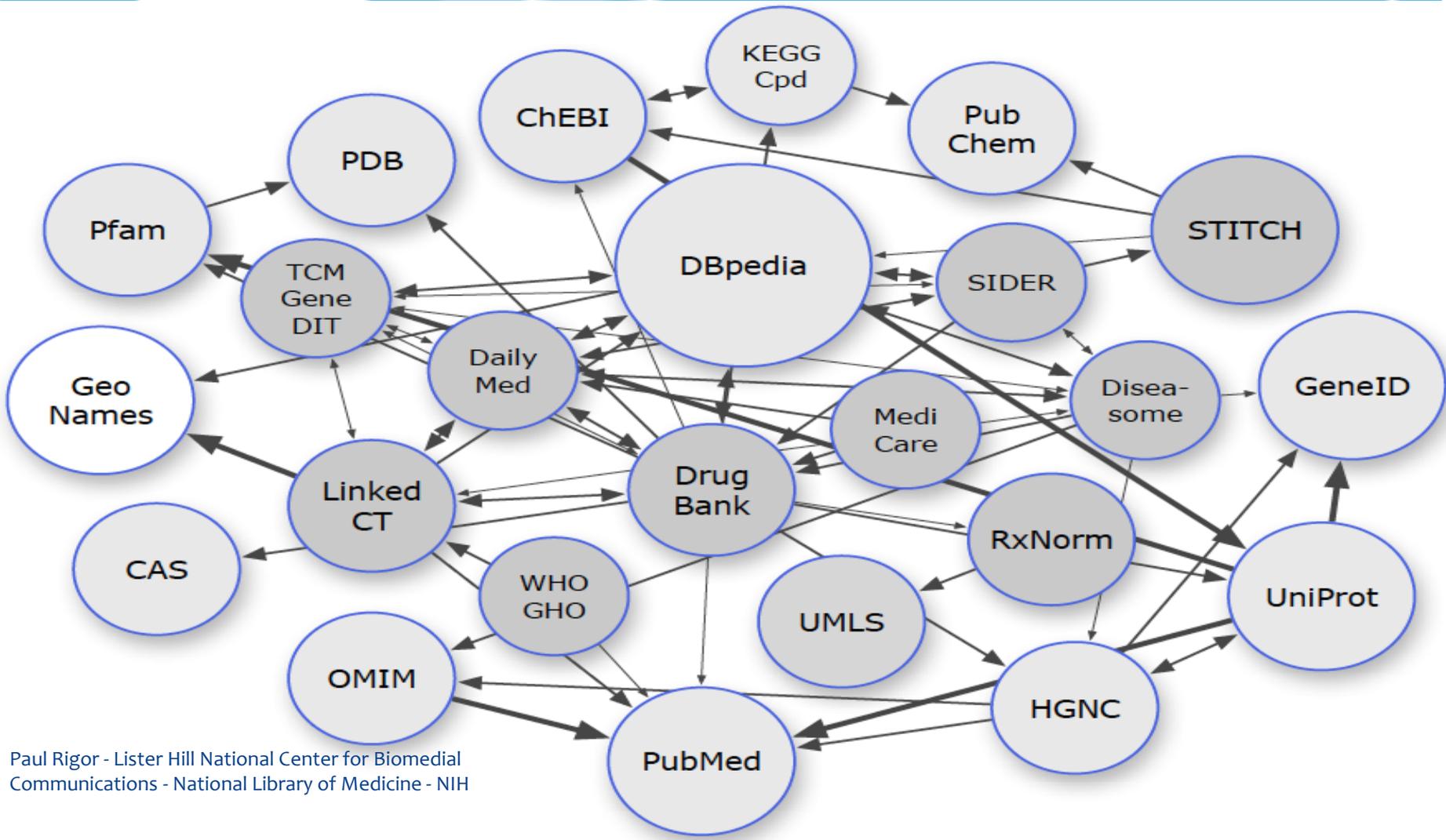
Hypotheses

- * 1) The 'unknown' target of one drug can be inferred from the 'known' target of another drug by the similarity between their side effects
- * 2) We can also infer additional targets for drugs with known targets.

What information do we need?

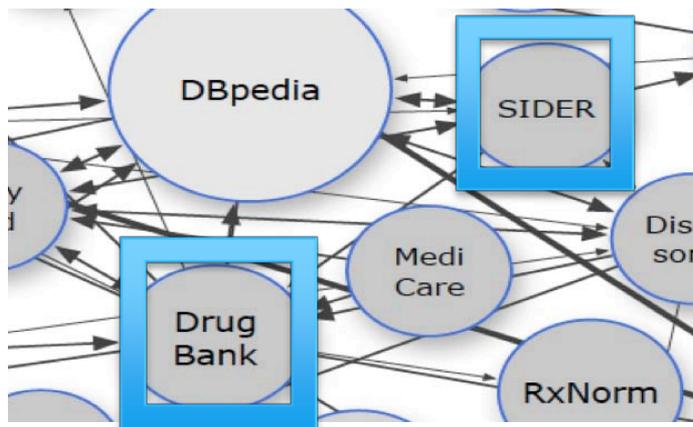


What islands of knowledge are we navigating?



Which data?

- * We have deployed SPARQL databases in-house which include
 - * 1) **DrugBank**
 - * 2) **Side effect database**

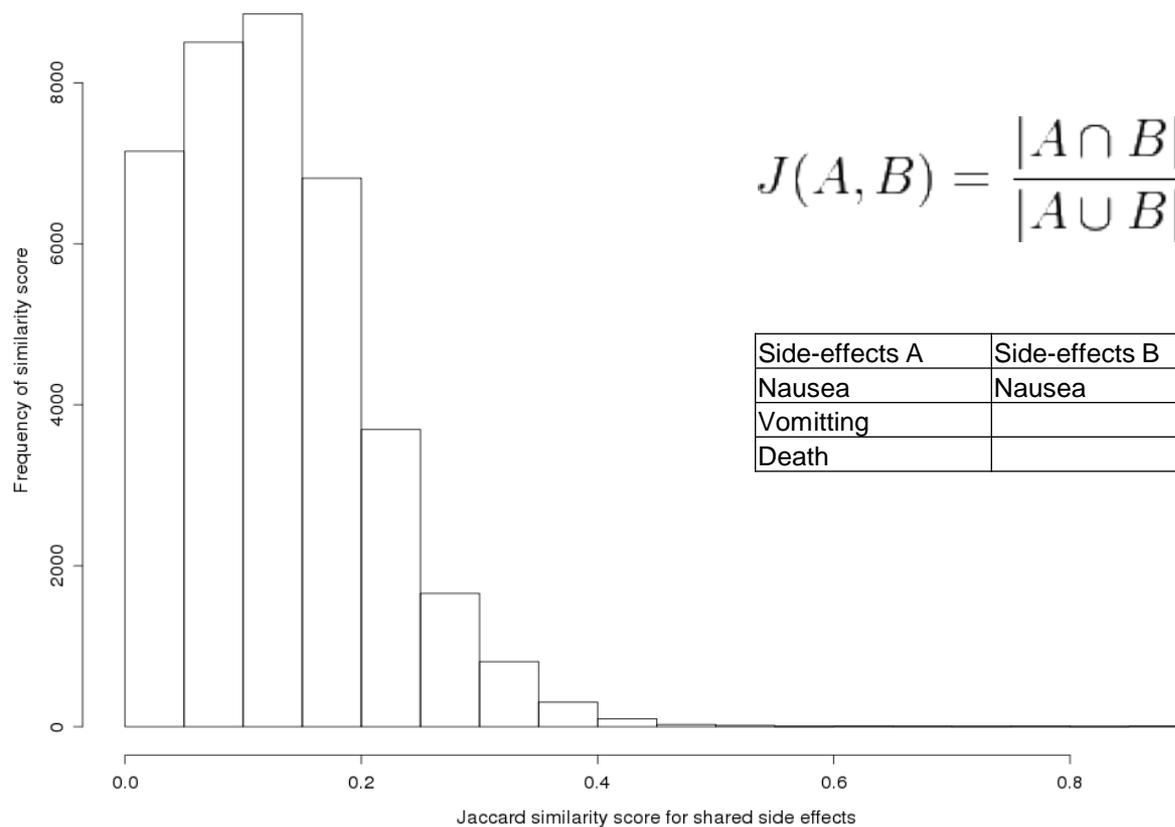


Method

- * Technical:
 - * Linked Open Drug Data
 - * Virtuoso Instances with SIDER and Drug Bank
- * Integration:
 - * SIDER for drug side-effects
 - * DrugBank for drug targets
- * Data Analysis:
 - * Calculate pair-wise drug-drug Jaccard similarity measure on shared side-effects

Preliminary results: side effect similarity

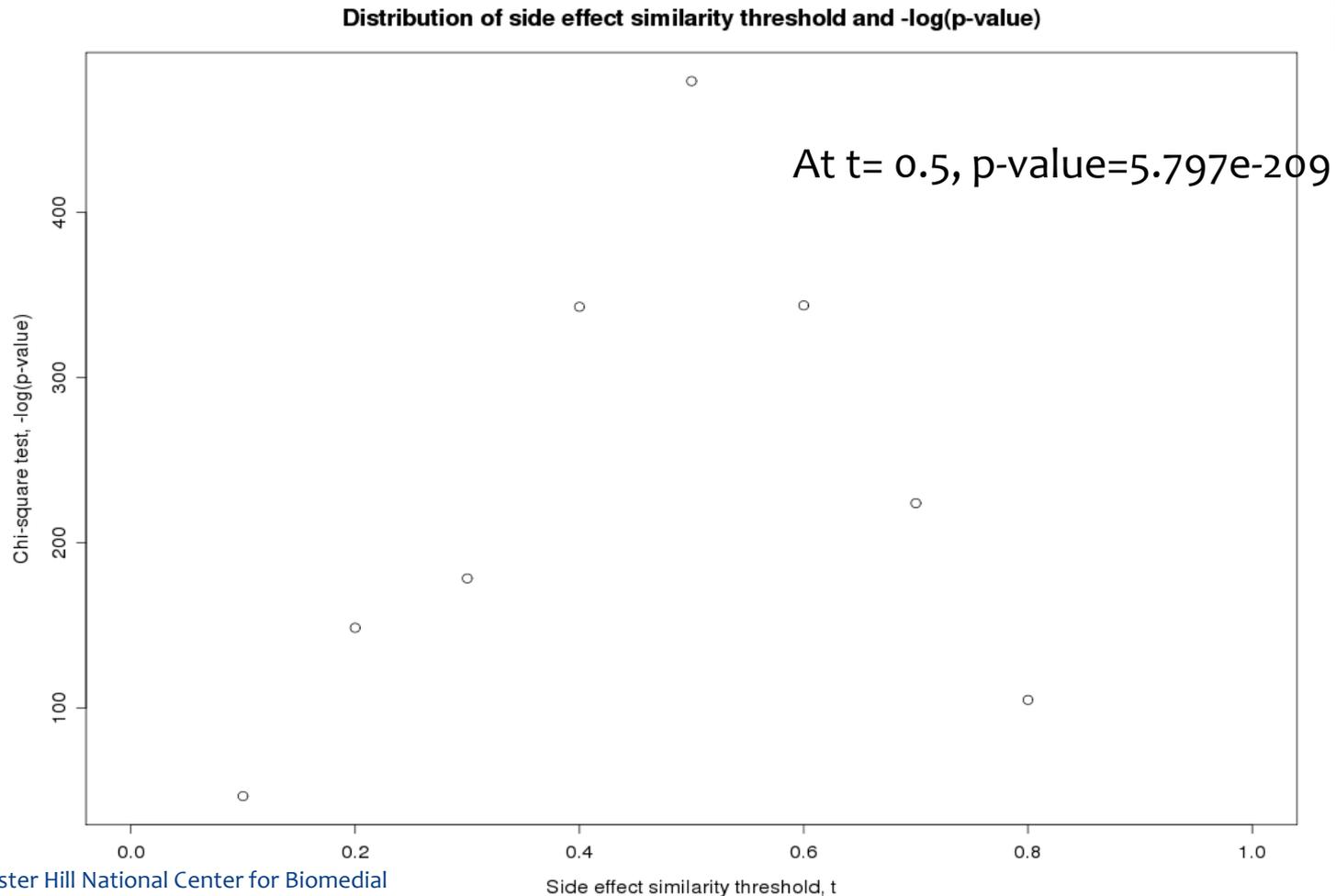
Distribution of drug pairs sharing the same side effects



$$J(A, B) = \frac{|A \cap B|}{|A \cup B|}$$

= 0.3

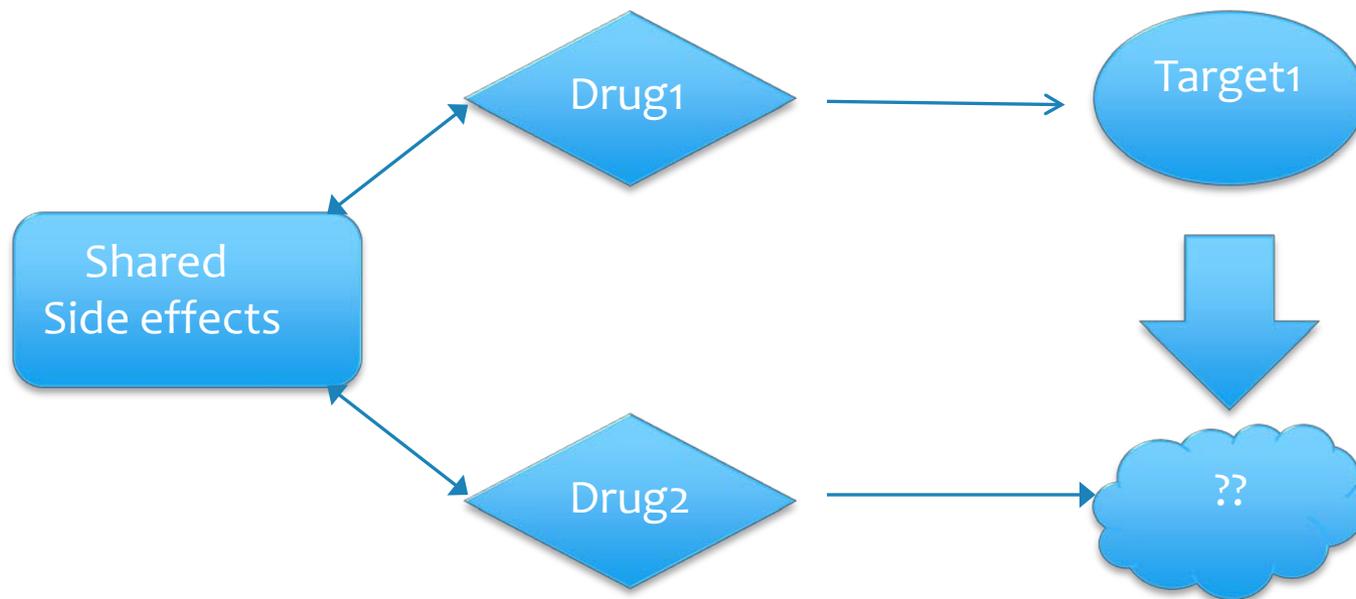
Preliminary results: significance of side effect similarity?



Preliminary results: validate high similarity score with shared targets

Name1	Name2	Side effect similarity score
CARBINOXAMINE	Dexchlorpheniramine Maleate	0.872340426
CARBINOXAMINE	Diphenhydramine	0.897959184
CARBINOXAMINE	Clemastine	0.857142857
Dexchlorpheniramine Maleate	Diphenhydramine	0.816326531
Chlorthalidone	hydroflumethiazide	0.897435897
Clemastine	Diphenhydramine	0.803921569
PENTOBARBITAL	secobarbital	0.857142857

Can we now address hypothesis #1?



Can we now address hypothesis #1: Yes?

pair-id	drug1	drug2	TS	SS
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/2315	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/2732	0	0.6730769
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/5073	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/2771	0	0.5421053
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/4934	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/4601	0	0.5384615
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/3404	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/3446	0	0.5241935
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/2771	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/5514	0	0.5226667
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/5073	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/5514	0	0.5143678
	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/2771	http://www4.wiwiss.fu-berlin.de/sider/resource/drugs/5095	0	0.5112474

Let's take the first pair:

- * Bendroflumethiazide:
 - * For the treatment of high blood pressure and management of edema
- * Chlorthalidone:
 - * For management of hypertension either as the sole therapeutic agent or to enhance the effect of other antihypertensive drugs in the more severe forms of hypertension

Initial conclusion

- * Validated side effect similarity as an indicator for drugs sharing similar targets
- * We have verified the utility of drug data from the semantic web

Discussion: what are the challenges?

- * Time: 6 weeks, new world
- * Technological hurdles
 - * The state of the technologies underlying the semantic web is still evolving (many options and resources)
- * The state of the datasets themselves are in flux
 - * Provenance
 - * Trust
 - * Currency

Moving forward: future work

- * Integrate database of regulatory motifs (MotifMap) for network-based pharmacology
- * Explore several semantic web technologies
 - * Ontologies to use and/or extend (BioRDF/LODD)
 - * Endpoint for linked data
 - * Back-end storage

Experience

- * Gained new perspective on drug discovery
 - * Exciting new technologies!
- * Exposed to international community of data integrators in the health care and life sciences
 - * Discussions with W3C HCLS/LODD
- * Exposed to resources at the NLM!
 - * UMLS/NDFRT

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