DRUG INTERACTION AND DRUG SAFETY – A TRANSLATIONAL BIOINFORMATICS APPROACH

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What Is Translational Bioinformatics?

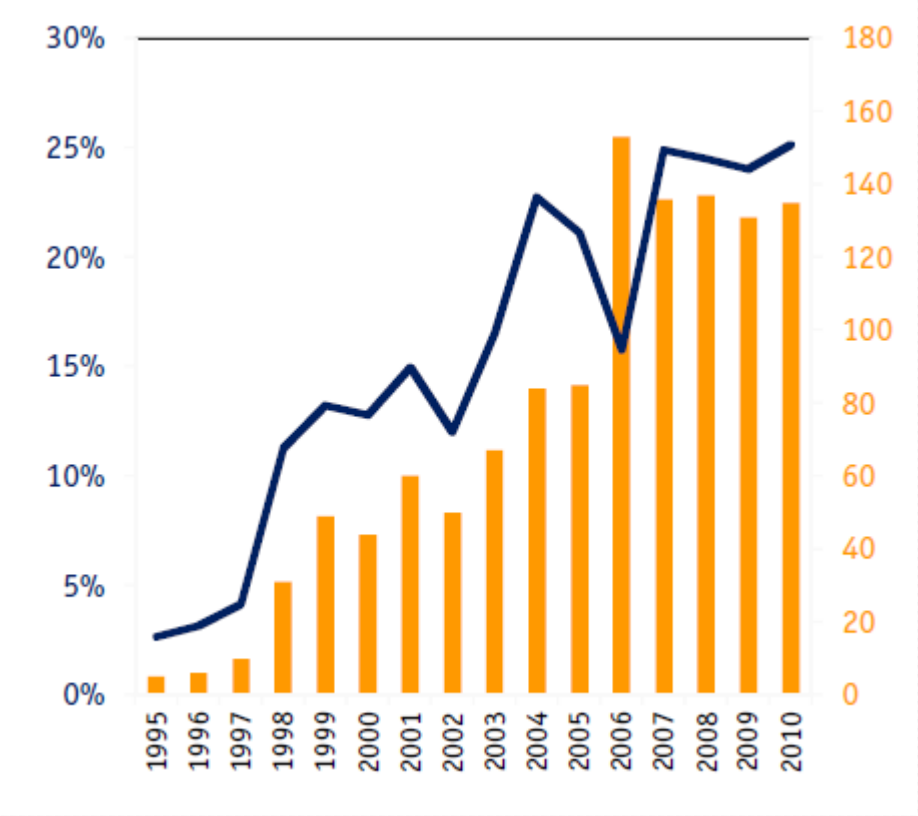
- Development of analytic, storage, and interpretive methods for large biology and/or clinical databases (e.g. IT Structure of Biobank).
- Optimize the transformation of increasingly voluminous genomic and biological data into diagnostics and therapeutics for the clinician (e.g. Pharmacogenomics studies).
- Extract and discover novel hypotheses from large biological, clinical databases, and public literatures for drug safety and drug repositioning research.

Note:

Biological Data:	GEO, DBGaP and etc.
Clinical Data:	Electronic Medical Record (EMR) and electronic Health Record
Public Literature Data:	PubMed, patents, and etc.

Why translational bioinformatics?

- New community of sharing: tools, data, and publications.
- Change in role of the bioinformatic
  question asker.
- Increased funding for this line of w
  - NIH road map starting from 2002
  - CTSA RFA mentions informatics 38
  - Dr. Francis S. Collins in 2011 Oct AM
    Informatics is one of the most impo
    difficult budget era".



Butte 2011, AMIA Tutorial

Notable Translational Biomedical Informatics Research

Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data
Marina Sirota, *et al.*
Sci Transl Med **3**, 96ra77 (2011);
DOI: 10.1126/scitranslmed.3001318

Detecting Drug Interactions From Adverse-Event Reports: Interaction Between Paroxetine and Pravastatin Increases Blood Glucose Levels

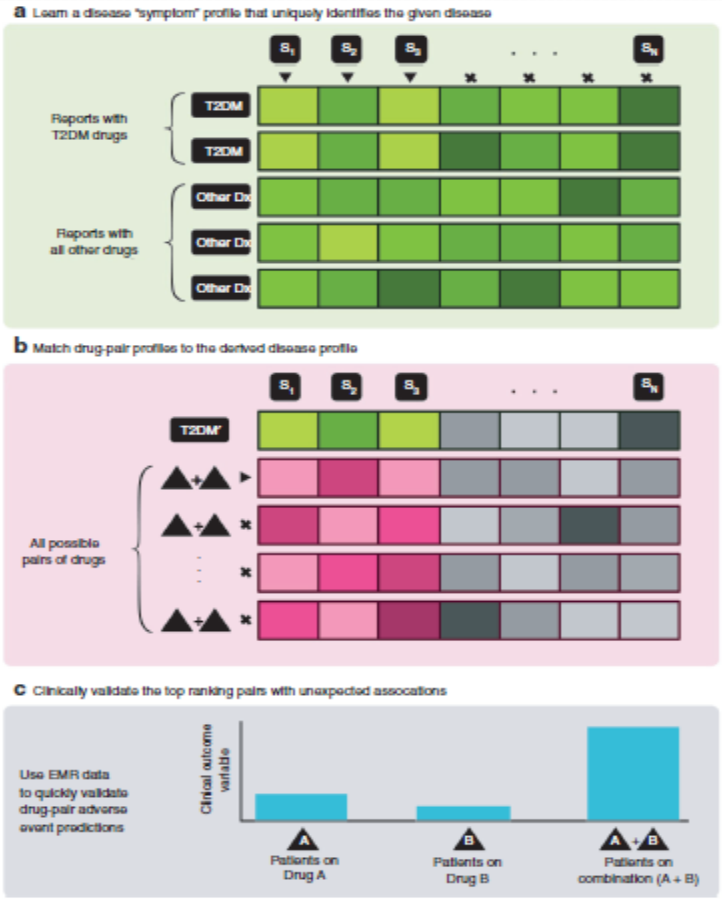
NP Tatonetti[1,2,3], JC Denny[4,5], SN Murphy[6,7], GH Fernald[1,2,3], G Krishnan[8], V Castro[6], P Yue[9], PS Tsau[9], I Kohane[7,10,11], DM Roden[5] and RB Altman[2,3]

Received 24 November 2010; accepted 1 April 2011; advance online publication 25 May 2011. doi:10.1038/clpt.2011.83

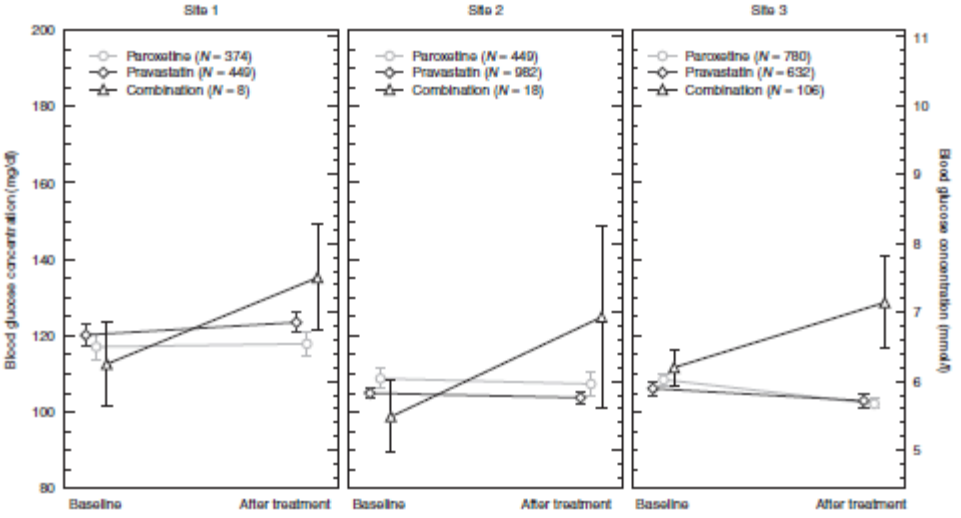
CLINICAL PHARMACOLOGY & THERAPEUTICS

Detecting drug interactions from adverse event reports: interaction between paroxetine and pravastatin increase blood glucose levels (Tatonatti et al. CPT 2011)

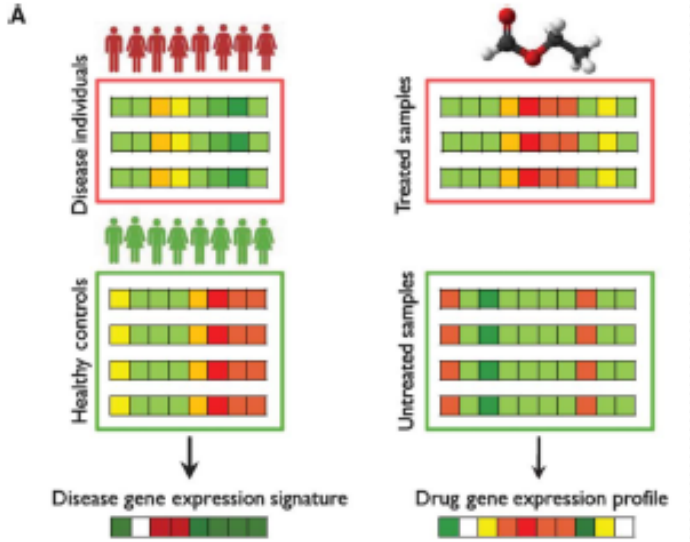
FDA Adverse Events Report System

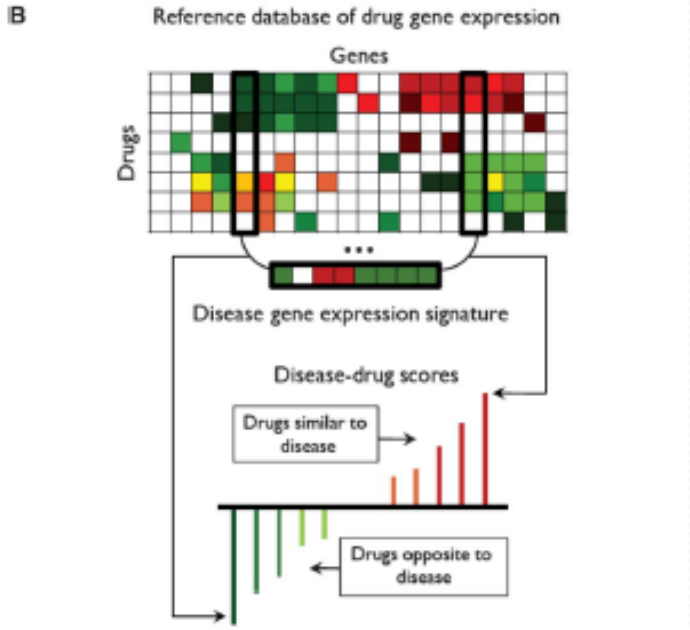


Validations in 3 EMR Databases

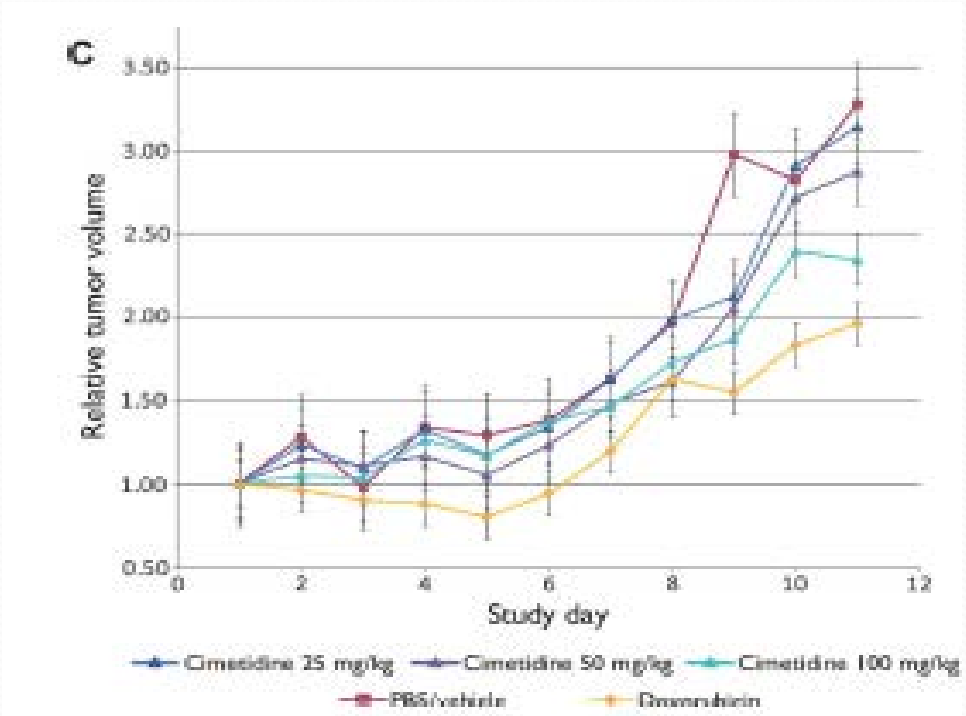


Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data, Sirota et al. Sci Transl Med 2011

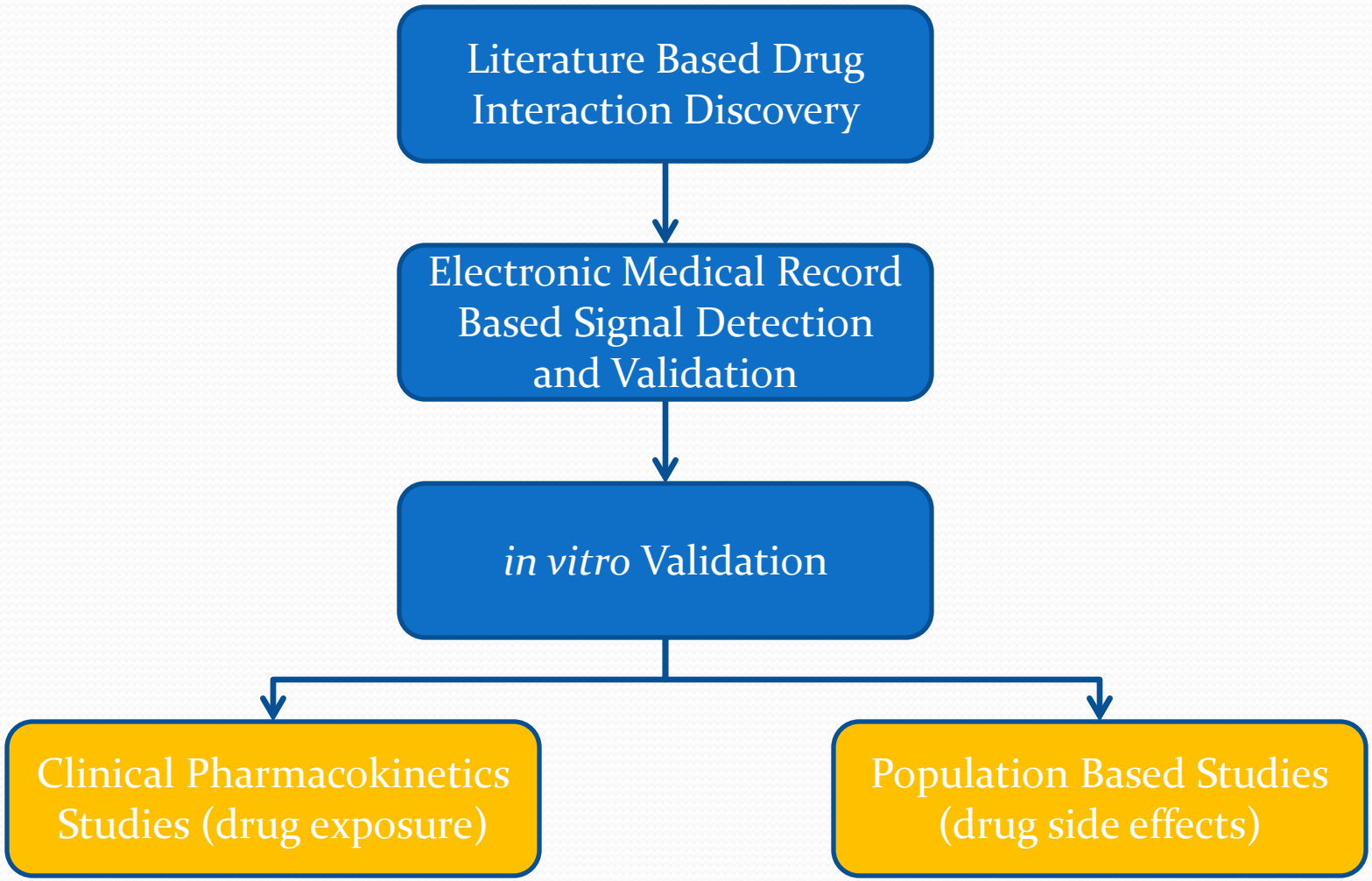




→ cimetidine for lung adenocarcinoma



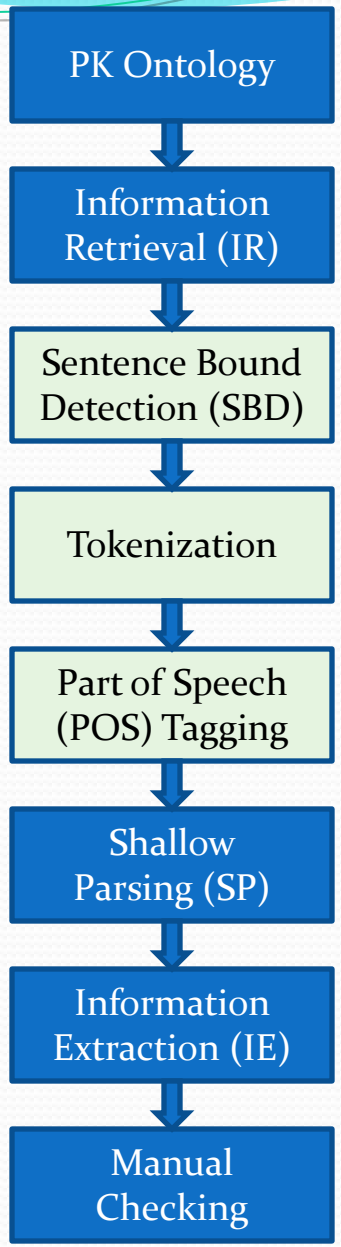
A Translational Biomedical Informatics Drug Interaction/Drug Safety Research Framework



Literature Based Discovery
Text Mining

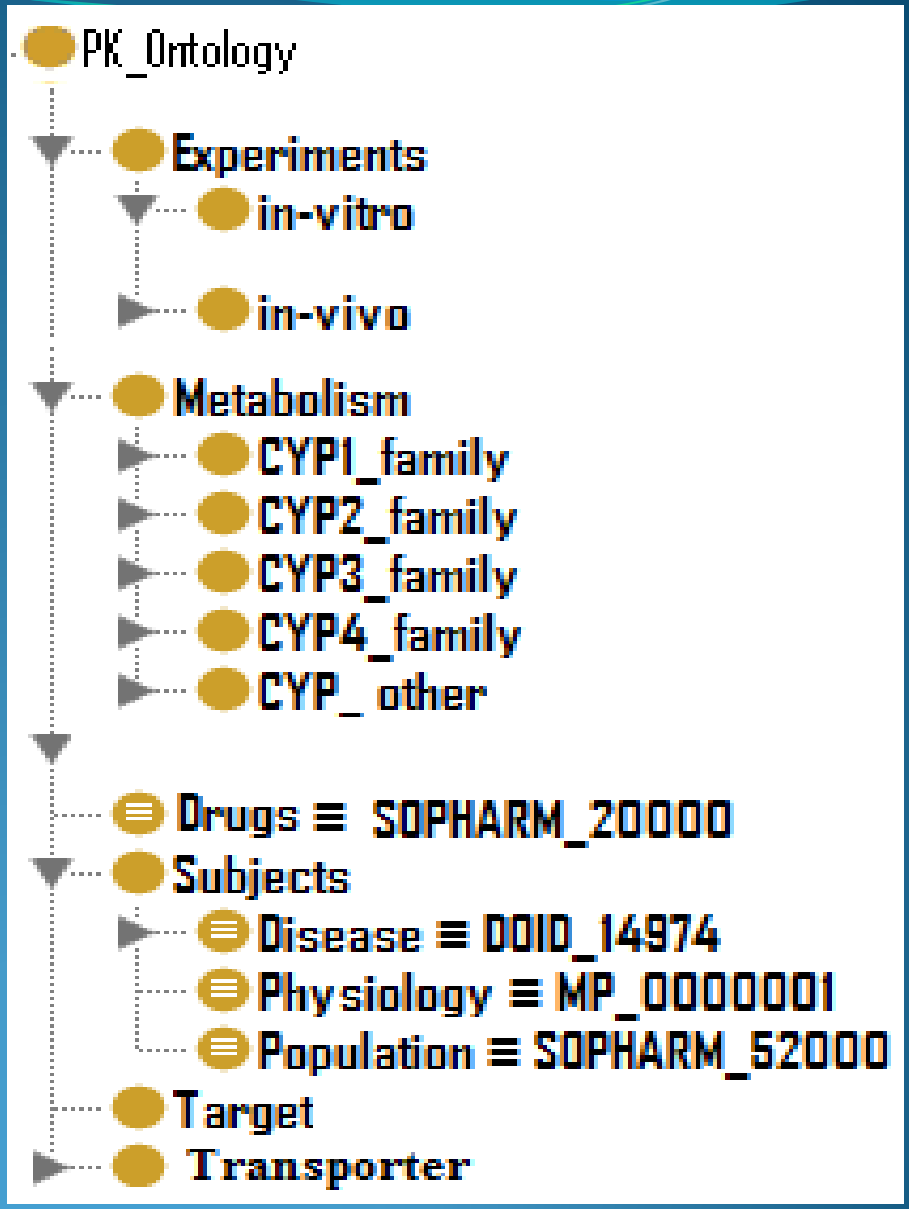
home grown algorithms
(based on domain knowledge)

open source Cognitive
Computation Group (CCG) tool
(http://l2r.cs.uiuc.edu/~cogcomp)



Abhinita et al. BMC Bioinformatics 2011 (revised)

PK Ontology


PK_Ontology
Experiments
in-vitro
in-vivo
Metabolism
CYP1_family
CYP2_family
CYP3_family
CYP4_family
CYP_ other
Drugs ≡ SOPHARM_20000
Subjects
Disease ≡ DOID_14974
Physiology ≡ MP_0000001
Population ≡ SOPHARM_52000
Target
Transporter

PK Tagger

MEDLINE 20110052

effect of the cyp3a inhibitor ketoconazole on the pharmacokinetics and pharmacodynamics of bortezomib in patients with advanced solid tumors a prospective multicenter open-label randomized two-way crossover drug-drug interaction study.

the proteasome inhibitor bortezomib undergoes oxidative biotransformation via multiple cytochrome p450 cyp enzymes with cyp3a4 identified as a partial yet potentially important contributor based on in vitro drug metabolism studies.the aim of this study was to assess the effect of concomitant administration of ketoconazole on the pharmacokinetics pk and pharmacodynamics pd of bortezomib.this was a prospective multicenter open-label randomized multiple-dose 2-way crossover study in patients with advanced solid tumors. all patients received bortezomib 1.0 mg/m 2 iv on days 1 4 8 and 11 of two 21-day cycles and were randomized to receive concomitant ketoconazole 400 mg on days 6 7 8 and 9 of cycle 1 or 2. serial blood samples were collected over the day-8 dosing interval immediately prior to bortezomib administration and from 5 minutes to 72 hours after administration in cycles 1 and 2 for measurement of plasma bortezomib concentrations for noncompartmental pk analysis and blood 20s proteasome inhibition for pd analysis. all adverse events aes were recorded during each cycle including serious aes and all neurotoxicity events for up to 30 days after the last dose of bortezomib.twenty-one patients median age 57 years sex 67% male race 86% white median body surface area 2.01 m 2 were randomized to treatment. twelve patients completed the protocol-specified dosing and pk sampling in both cycles 1 and 2. assessment of the effect of ketoconazole on bortezomib pk and pd was based on data in these 12 pk-evaluable patients. the ratio of geometric mean bortezomib auc 0-tlast auc from time 0 to last quantifiable concentration for bortezomib plus ketoconazole versus bortezomib alone was 1.352 90% ci 1 .032-1.772 . consistent with this observed mean increase in bortezomib exposure concomitant administration of ketoconazole was associated with a corresponding increase 24%-46% in the blood proteasome inhibitory effect.concomitant administration of the cyp3a inhibitor ketoconazole with bortezomib resulted in a mean increase of 35% in bortezomib exposure.

- Drugs
- in-vitro parameters
- in-vivo-parameters
- CYP Enzymes
- CYP Alleles
- AUC Units
- Patient Descriptors
- Numbers
- Clearance Units
- Annotation

PK Corpus

- Clinical PK studies (60)
- Clinical pharmacogenetic studies (60)
- Clinical DDI studies (60)
- *in vitro* drug interaction studies (60)

PK ontology is available at http://rweb.compbio.iupui.edu/corpus/ontology/, PK tagger and PK corpus are available at http://rweb.compbio.iupui.edu/corpus/.

Tagger Performance

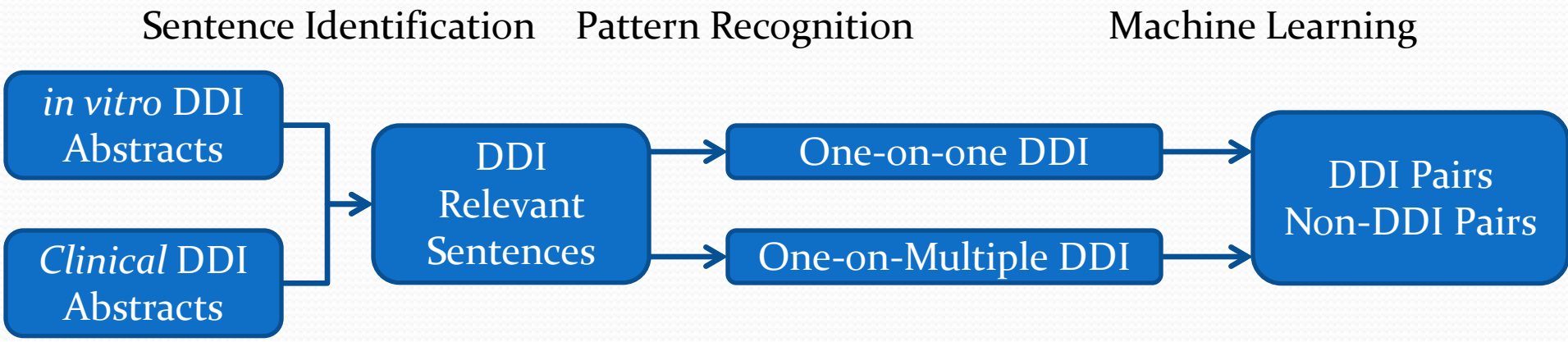
Type of Study	PK Relevant Words	Lingua:EN Tagger Error Rate	GENIA Tagger Error Rate	PK Tagger Error Rate
In-vitro Drug-Drug Interaction Studies	123	80.3%	60.4%	2.0%
Clinical Drug-Drug Interaction Studies	124	75.6%	53.1%	8.0%
Clinical Pharmacokinetic Studies	107	60.5%	40.2%	3.2%
Clinical Pharamacogenetic Studies	129	82.7%	45.2%	6.0%
Total	483	75.35%	49.99%	4.87%

Text Mining Evaluation

	text mining prediction: yes	text mining prediction: no
true positive	**n_{00}**	**n_{01}**
true negative	n_{10}	n_{11}

- Recall: $n_{00}/(n_{00} + n_{01})$
- Precision: $n_{00}/(n_{00} + n_{10})$

Drug Interaction Information Extraction



Recall: 95%
Precision: 60%

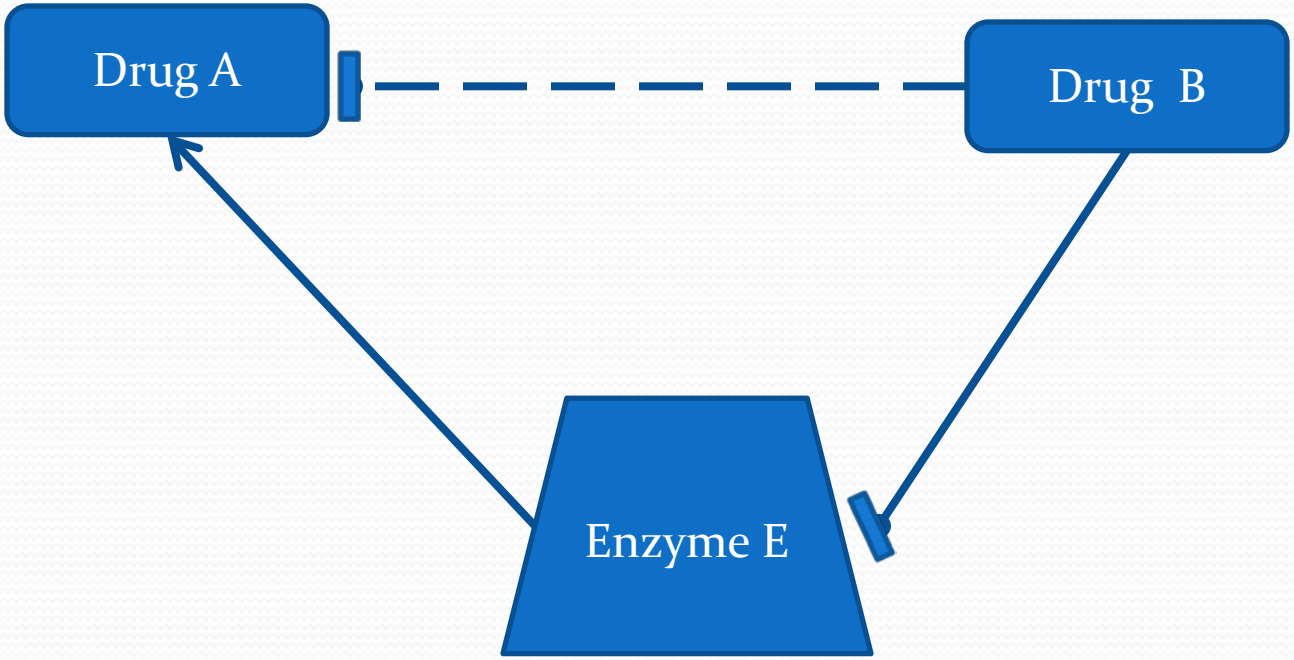
Recall: 100%
Precision: 98%

Recall: 90%
Precision: **65%**

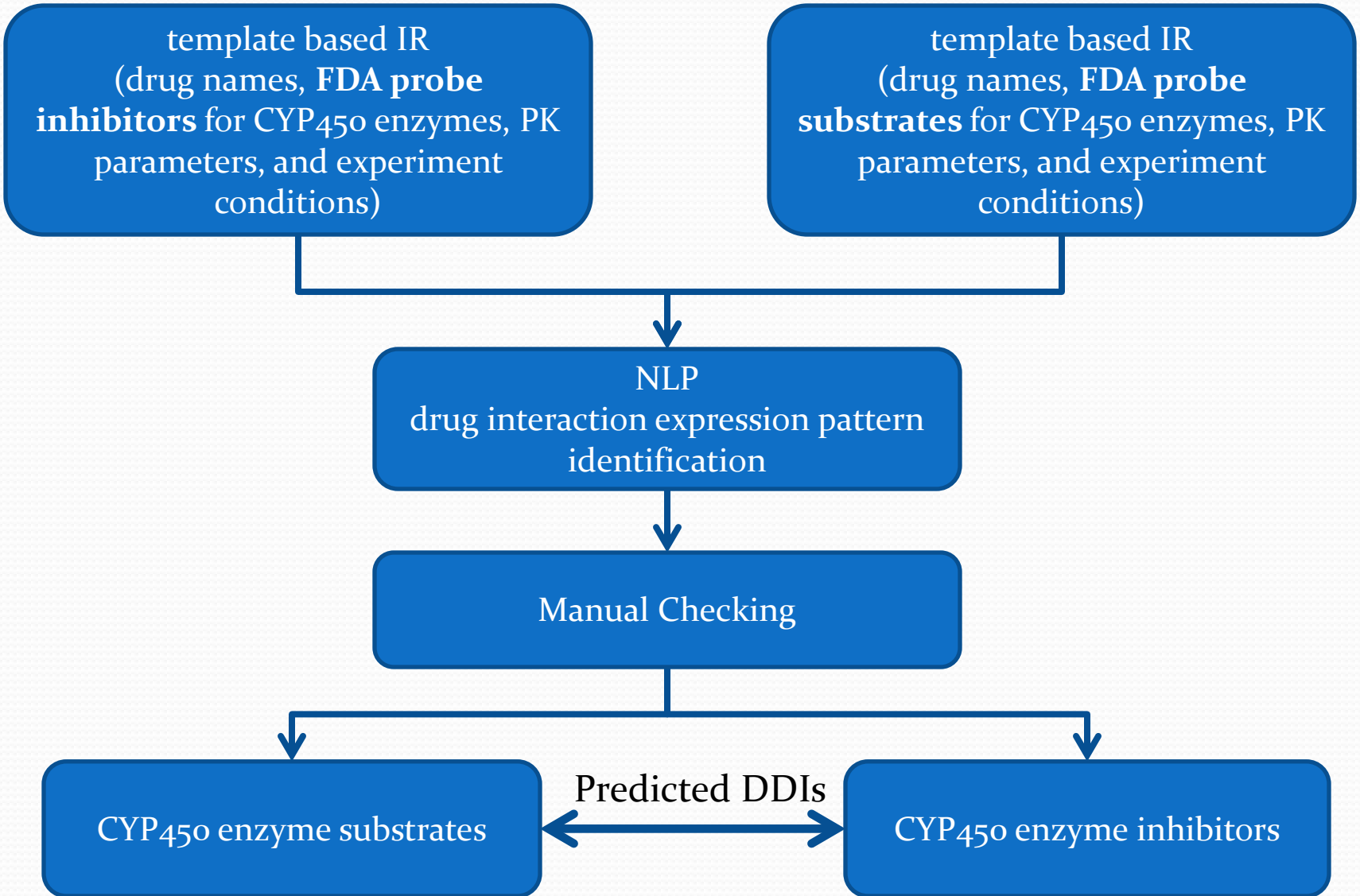
Machine Learning: conditional random field and graphic model
Our IE performance is better than the published results.

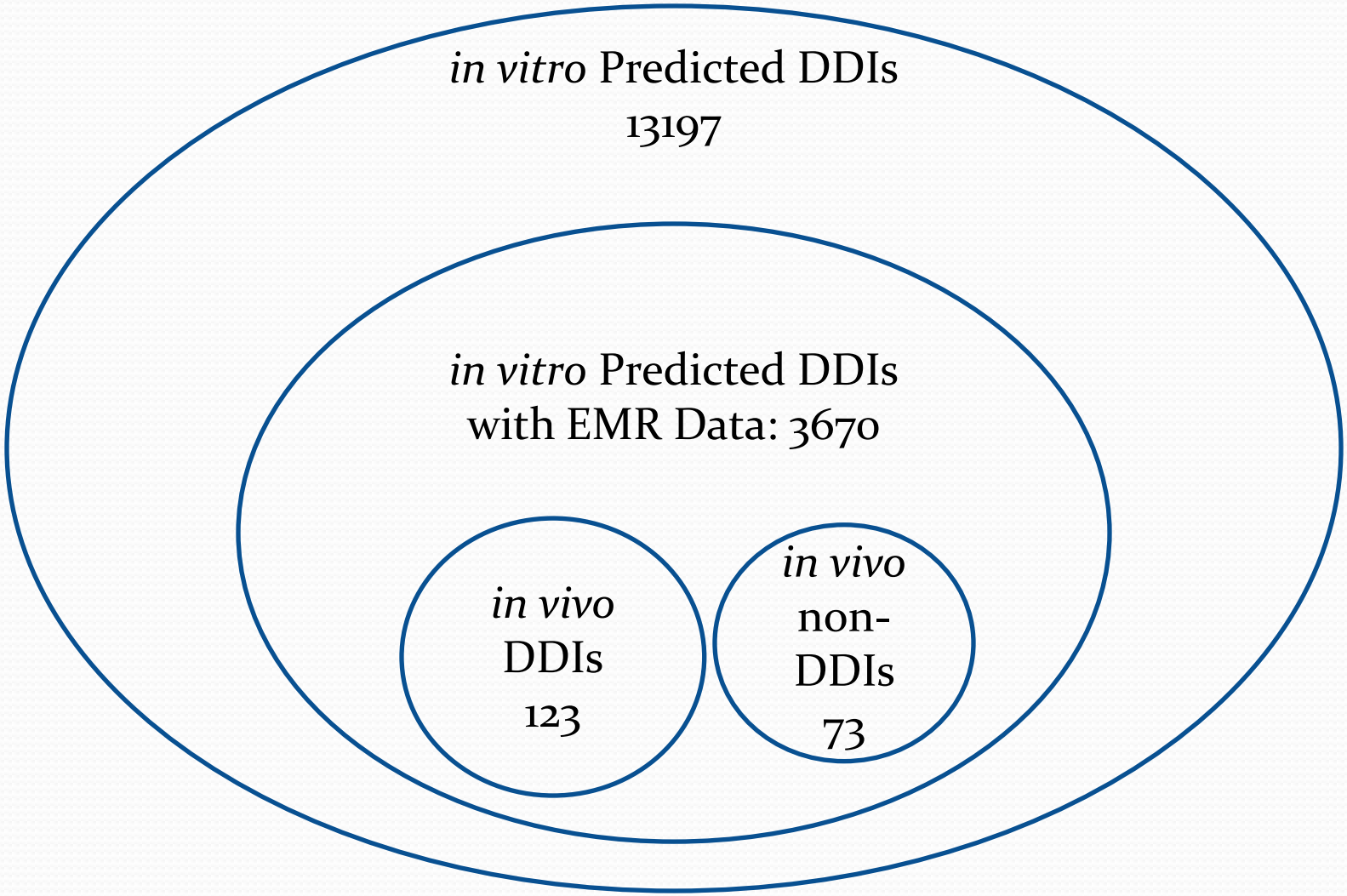
Shreyas et al. Bioinformatics 2011 (under review)

Novel DDI Prediction Based on in-vitro DDI Studies



in vitro DDI Text Mining Work Flow





Only (123+73)/3670 = 5% of predicted DDIs were tested *in vivo* or clinically.

Observational Medical Outcomes Partnership (OMOP)

- Public-Private collaboration (Pharma, academic, FDA, NIH)
- Goal is to evaluate use of observational databases in pharmacovigilance.
- Aggregated data from 11 clinical repositories (EHR / claims) accounting for >300M pts.

Regenstrief CDM

- Subset of INPC data from 2004-2009
- 2.2 million unique patients (9 county area)
  - De-identified
  - Dates perturbed
- 60 million drug exposures
- 140 million condition occurrences
- 360 million observations

Drug Safety Outcome - Myopathy

Table I. The clinical spectrum of statin-induced myopathy[11]

Condition	Definition
Myopathy	General term to describe all skeletal muscle-related adverse effects
Asymptomatic CK elevation	CK elevation without muscle symptoms
Myalgia	Muscle pain or weakness without CK elevation
Myositis	Muscle symptoms with CK elevation typically <10 × ULN
Rhabdomyolysis	Muscle symptoms with CK elevation typically >10 × ULN, and with creatinine elevation (usually with brown urine and urinary myoglobin)

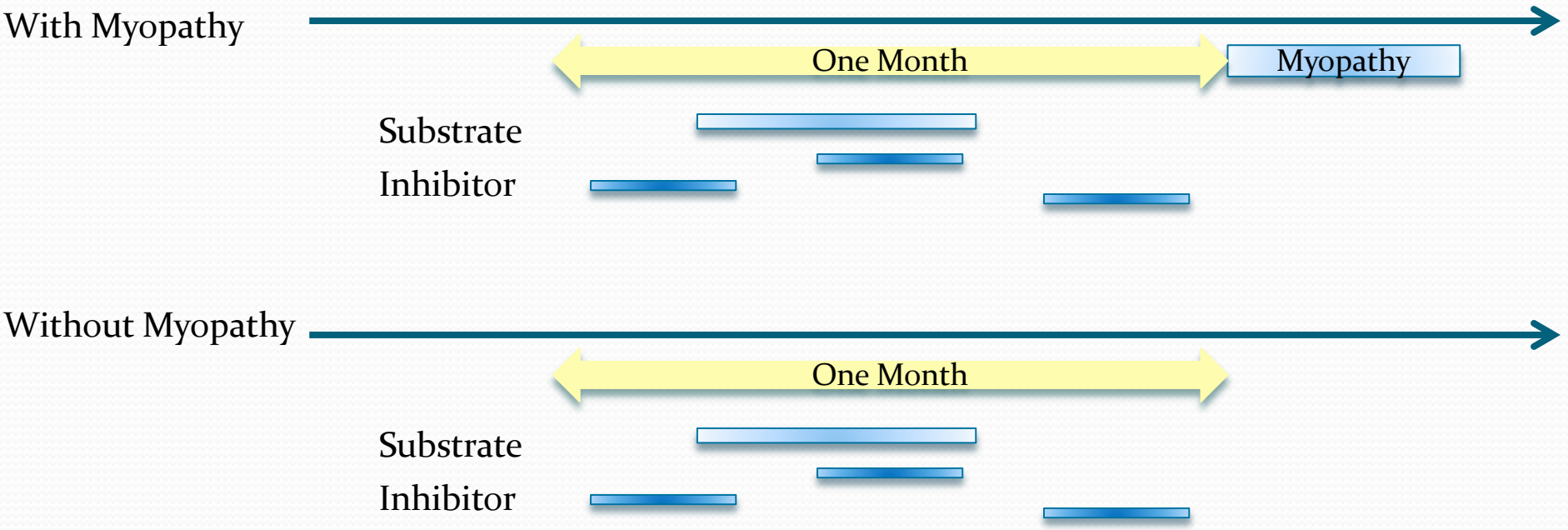
CK = creatine kinase; **ULN** = upper limit of normal.

Chatzizisis et al. Drug Safety 2010, 33, (3), 171-187

Drug Safety Outcome – Myopathy CDM Code (54 items)

Myositis	Muscle weakness (generalized)	Polymyositis
Muscle weakness	Polymyositis	Polymyositis
Polymyositis	Myoglobinuria	Myopathy toxic
Myoglobinuria	Rhabdomyolysis	Myopathy toxic
Myositis unspecified	Other myopathies	Muscle weakness conditions
[D]Myoglobinuria	Toxic myopathy	Myositis
March myoglobinuria	Antilipemic and antiarteriosclerotic drugs causing adverse effects in therapeutic use	Myositis-like syndrome
Idiopathic myoglobinuria	Myoglobinuria	Myopathy
Exertional rhabdomyolysis	Rhabdomyolysis	Rhabdomyolysis
Rhabdomyolysis	Polymyositis	Myositis
Traumatic rhabdomyolysis	Muscle Weakness	Myositis-like syndrome
Non-traumatic rhabdomyolysis	Myositis	Muscle weakness
Rhabdomyolysis	Muscle Weakness	Generalised muscle weakness
Myopathy, unspecified	Myoglobinuria	Generalized muscle weakness
Myopathy, unspecified	Myoglobinuria	Myopathy
Myalgia and myositis, unspecified		Myopathy, unspecified
		Rhabdomyolysis
		Rhabdomyolysis-induced renal failure
		Myalgia and myositis, unspecified
		Antilipemic and antiarteriosclerotic drugs causing adverse effects in therapeutic use
		Myopathy unspecified
		Mylagia and myositis unspecified
		Muscle weakness

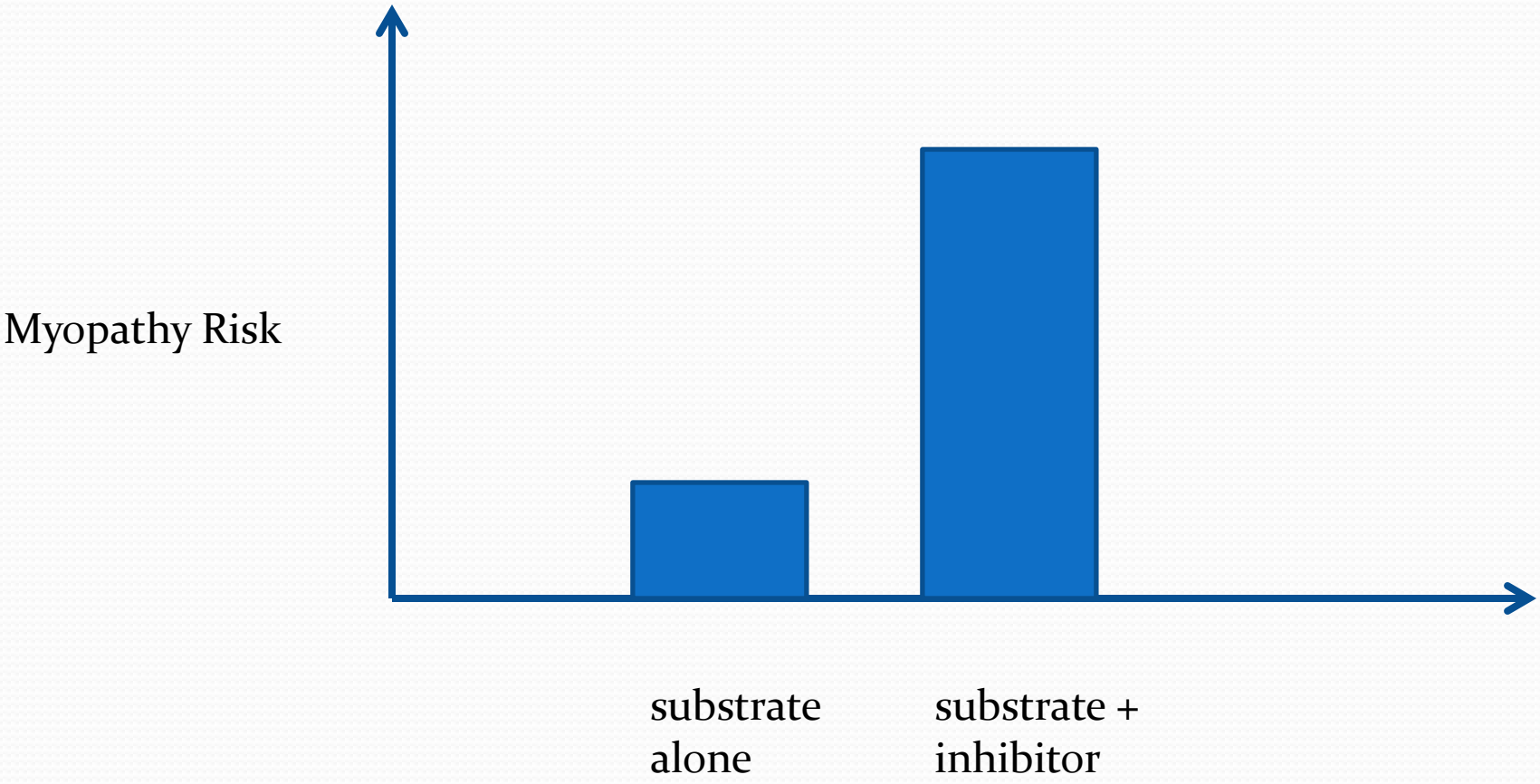
Pharmaco-epidemiologic Study Design



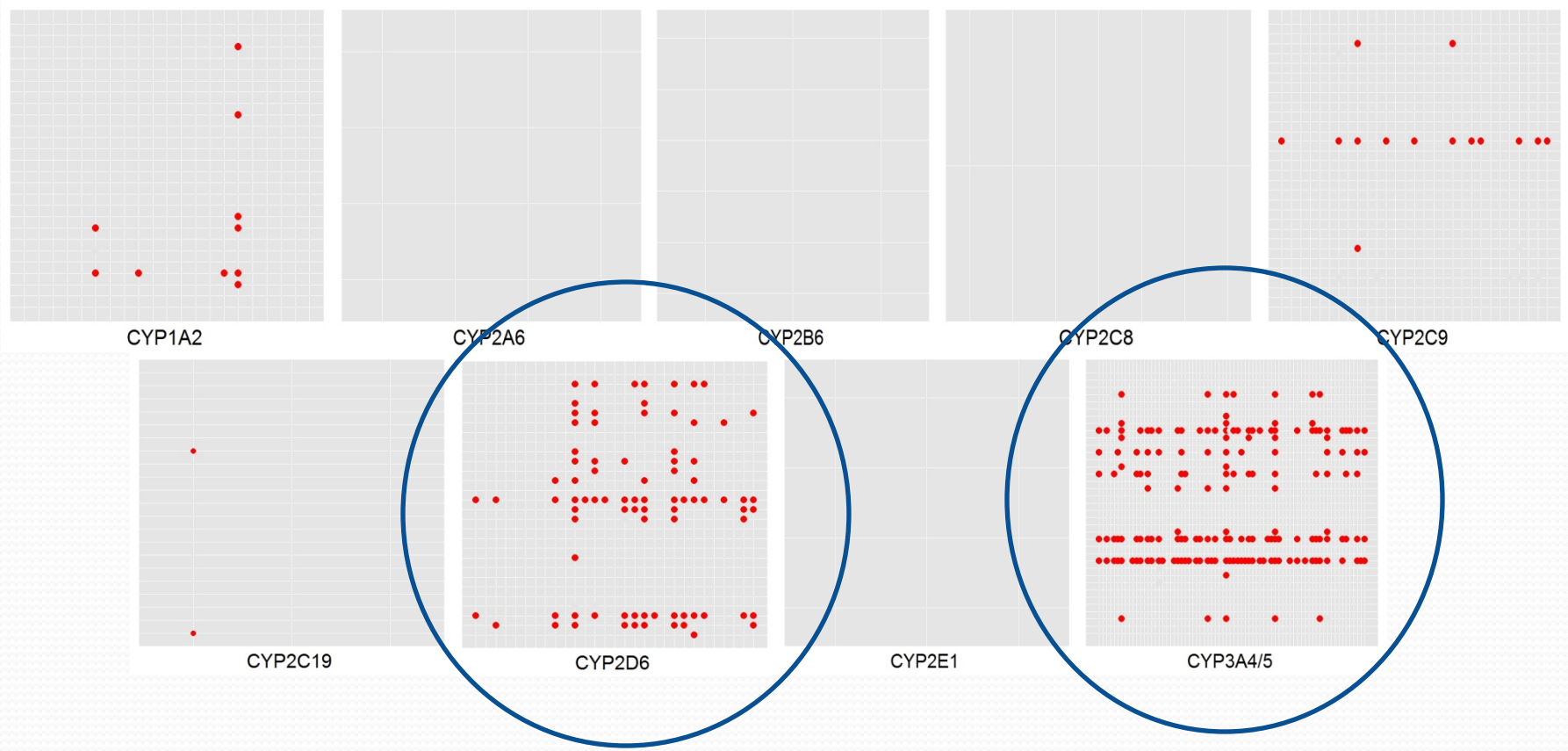
An Additive Model for Testing Drug Interactions

	With myopathy	Without myopathy
Substrate + Inhibitor	n11	n12
Substrate alone	n21	n22

An Additive Model for Testing Drug Interactions

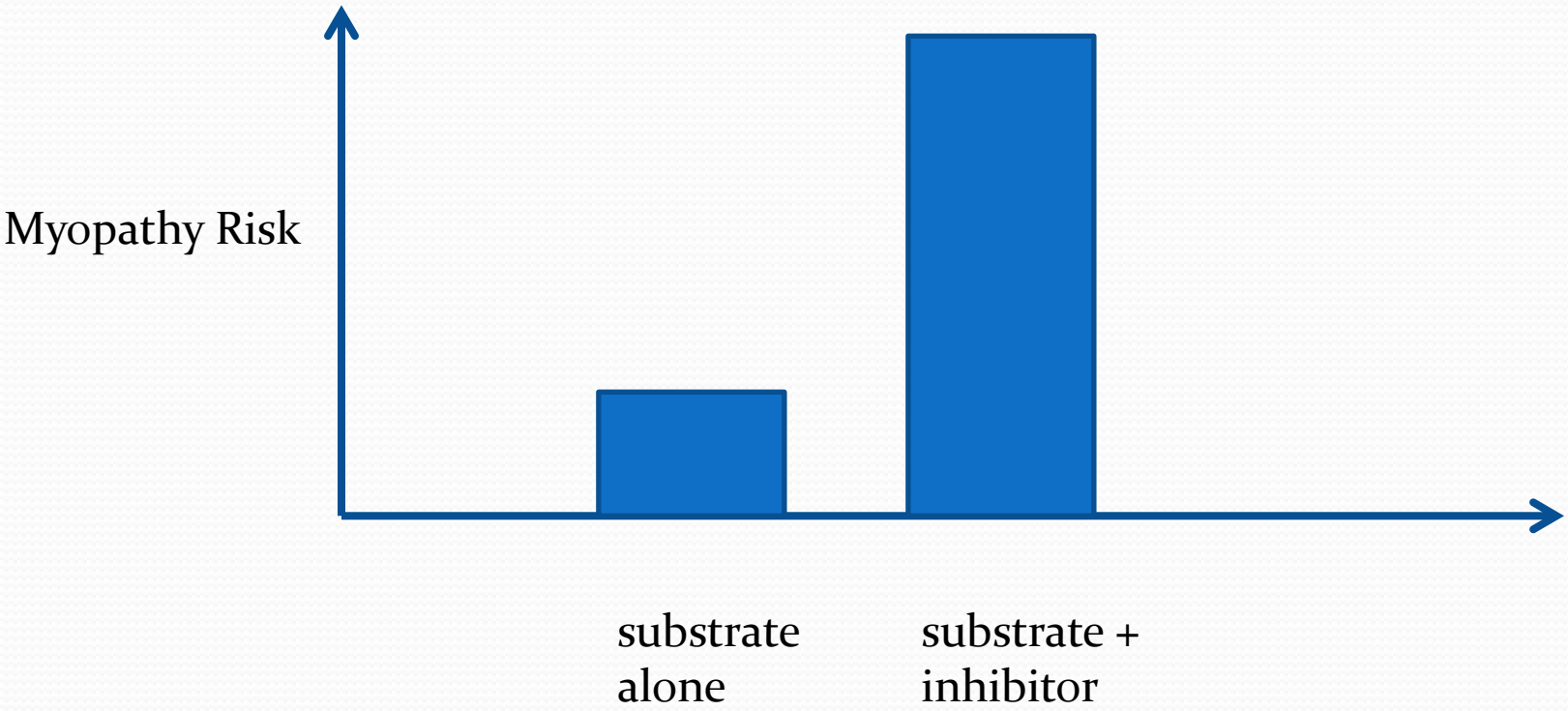


Predicted CYP450 Pathways Based DDIs and Their Associations with Myopathy Risk (p-value < 0.01)



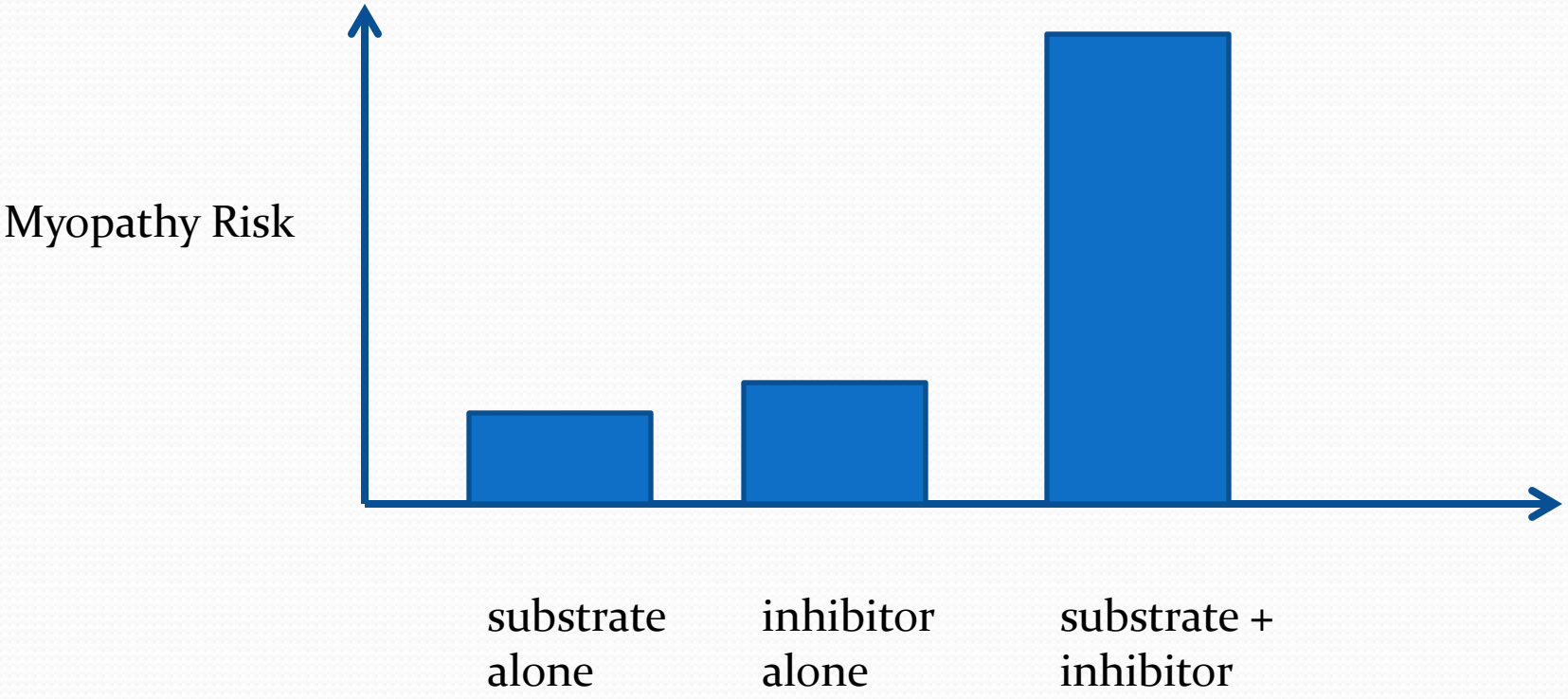
A Potential Problem of the Additive Model for Testing DDIs

The inhibitor itself can have myopathy risk.



Synergistic DDI Test

risk12 > risk1 + risk 2

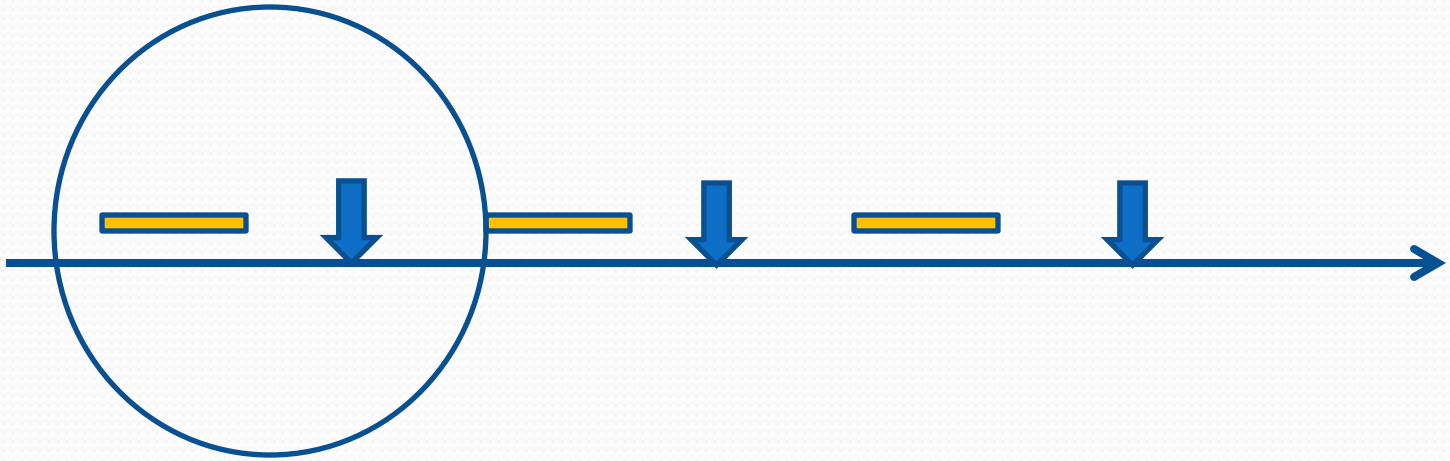


26 DDI pairs, p-value < 0.05/3713 = 0.000013

More Challenges

Remove drugs that were prescribed to treat the pain symptom

Myopathy symptom should always happen after the medication



Confounding variable justifications (age, gender, and race)

-> 6 pairs ($p < 0.000013$)

Six Significant DDI Pairs

drug 1	drug 2	myopathy risk from drug 1	myopathy risk from drug2	myopathy risk from drug 1 and 2	P-value
alprazolam	loratadine	0.07	0.03	0.16	1.06E-09
duloxetine	loratadine	0.14	0.03	0.28	7.43E-09
loratadine	omeprazole	0.03	0.06	0.13	4.45E-07
loratadine	simvastatin	0.03	0.05	0.13	4.75E-07
promethazine	tegaserod	0.03	0.07	0.21	1.28E-05
loratadine	ropinirole	0.03	0.12	0.31	1.27E-05

Adverse Drug Reactions from FDA Labels

Alprazolam
muscle cramps
muscle spasticity aggravated
muscle stiffness
muscle tone abnormal
muscle tone disorder
dermatological
muscle twitch
muscle twitching
pain in limb

Duloxetine
muscle cramp
muscle rigidity
muscle spasms
muscle tightness
muscle twitching
musculoskeletal pain
myalgia

Loratadine
muscle weakness
myalgia

Ropinirole
muscle contractions involuntary
muscle contracture
muscle cramps
muscle spasm
muscle spasms
muscle tightness
muscle twitching
muscle weakness
musculoskeletal stiffness
myalgia

Omeprazole
muscle cramps
muscle weakness
myalgia

Promethazine
muscle rigidity

Simvastatin
myopathy

Tegaserod
myalgia

in vitro validation of CYP-mediated DDI

Screening Study

- High-throughput fluorometric assay to determine whether a test drug is an inhibitor of any major CYP enzyme (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4)

Yes

Kinetic Study

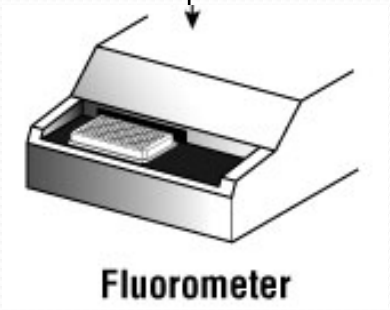
- Fluorometric assay to characterize the mechanism and kinetics of inhibition (competitive, non-competitive, mechanism-based)

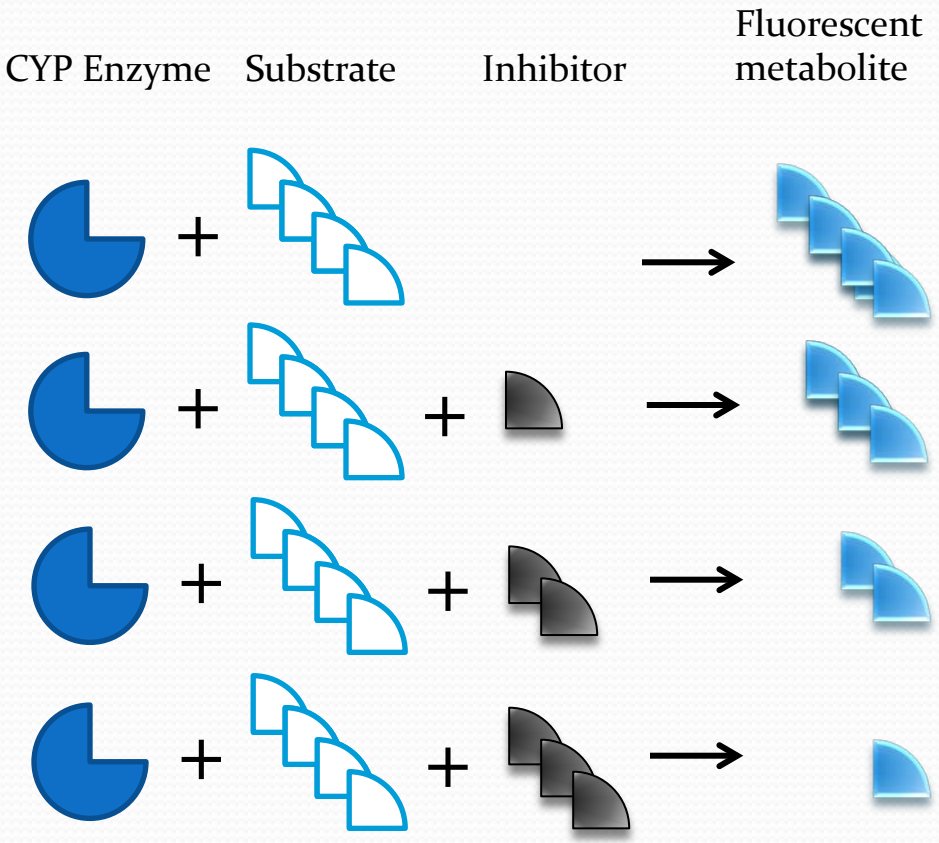
Direct Study

- Traditional incubation assay in HLMs to assess direct interaction of drug combinations of interest (% reduction in total metabolism)

CYP Fluorometric Inhibition Assay

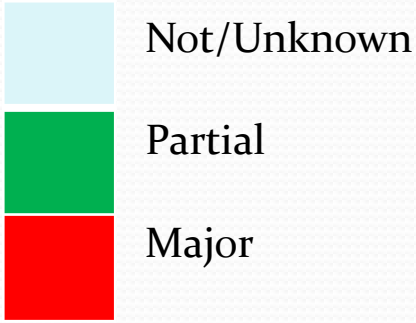
		Varying inhibitor concentrations								Negative control		Background	
		1	2	3	4	5	6	7	8	9	10	11	12
Positive inhibitor	A												
	B												
Test inhibitor 1	C												
	D												
Test inhibitor 2	E												
	F												
Test inhibitor 3	G												
	H												





Published Metabolism Pathways (CYP450)

drugs	Metabolism						
	1A2	2B6	2C8	2C9	2C19	2D6	3A
Alprazolam							Major
Duloxetine	Major					Partial	
Loratadine					Partial	Partial	Major
Ropinirole	Major						Partial
Omeprazole					Major		Partial
Promethazine		Partial					Major
Simvastatin							Major
Tegaserod						Major	



Inhibition Pathways
High-throughput Fluorometric Assay

drugs	Inhibition					
	1A2	2B6	2C9	2C19	2D6	3A
Duloxetine						
Loratadine						
Ropinirole						
Omeprazole						
Promethazine						
Simvastatin						
Tegaserod						

IC50 > 100 um

10 < IC50 < 100 um

IC50 < 10 um

Metabolism Based Inhibition Interpretation of Six DDI Pairs

Drug 1	Drug 2	pathways	metabolism	inhibition	DDI Prediction
alprazolam	loratadine	CYP3A4	major	moderate	Moderate
loratadine	duloxetine	CYP2D6	minor	strong	Moderate
omeprazole	loratadine	CYP2C19	major	moderate	Moderate
loratadine	simvastatin	CYP3A4	major	strong	**Strong**
promethazine	tegaserod	CYP2D6	major	strong	**Strong**
ropinirole	loratadine	CYP3A	minor	strong	moderate

Caveats

- The potential CYP based interactions don't mean the transporter based drug interaction or pharmacodynamic interaction don't exist.
- High-throughput Fluorometric assay shows the competitive inhibition mechanism. More experiments are needed for mechanism based inhibition.
- High-throughput Fluorometric assay can only predict the relative contributions for DDI from different enzyme pathways.
- Like any observational study, the correlation can not inferred causal relationship. Drug compliance was not part of consideration in the research.

What have we learned?

- The new translational biomedical information research paradigm works!
  - Literature Based DDI Discovery
  - EMR data based validation
  - *in vitro* validation

- Only a small fraction (5%) of predicted DDIs have been tested in the clinical pharmacologic studies.

- Simple additive DDI test coupled with pathway enrichment analysis led to the similar DDI CYP450 pathway conclusion as that from the stringent pharmaco-epidemiology data analysis combined with in vitro validation.

Prospectively, using this new translational bioinformatics paradigm, what questions can we address in the field of clinical pharmacology?

More questions need to be answered

- Among current FDA approved drugs, how many of them have established CYP450 metabolism pathway data?

- Among current FDA approved drugs, how many them have established CYP450 pathway inhibition/induction data?

Note: same questions need to be addressed for transporter based DDIs.

More questions need to be answered

- Among drug interactions reported from clinical studies or case reports, how many of them have established *in vitro* and/or *in vivo* mechanistic DDI evidence?

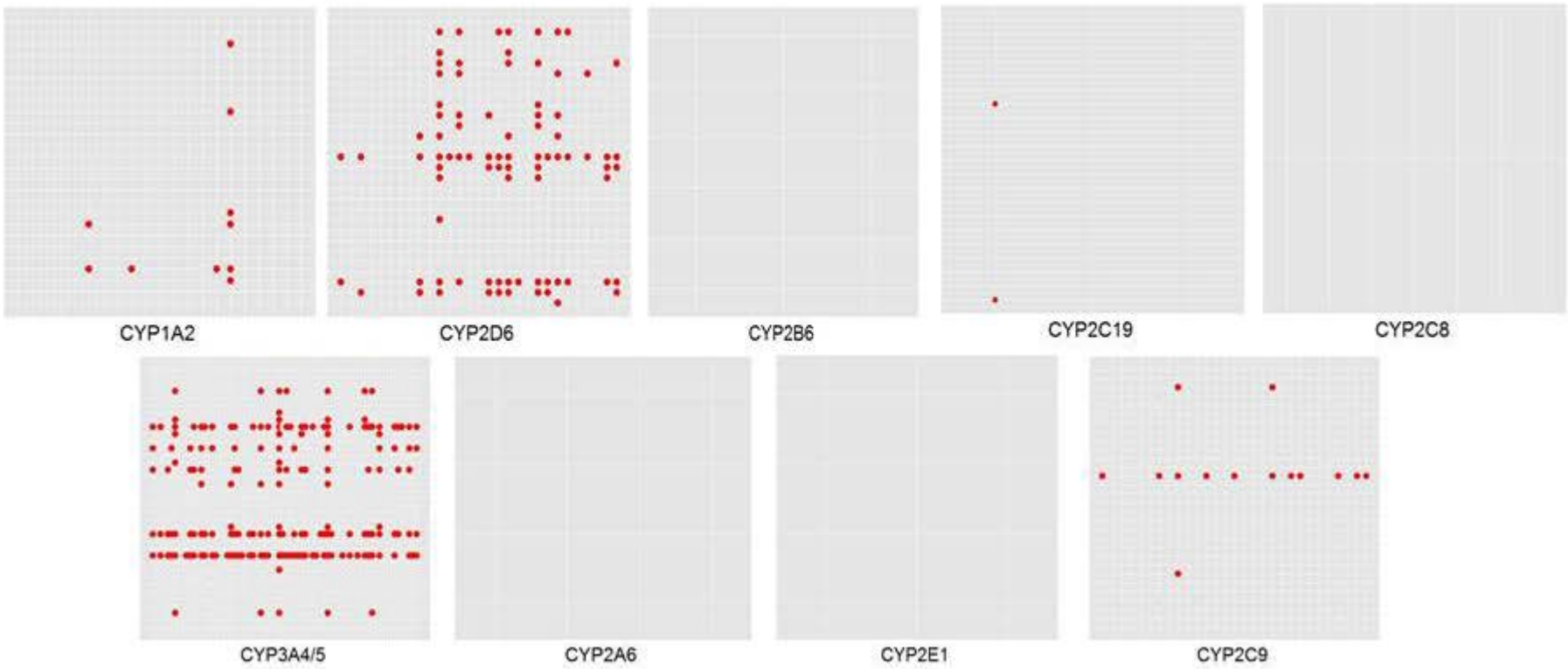
- Among different organ based drug toxicity categories, do they share the same PK DDI pathways across different drug classes?

myopathy

hepatoxicity

cardiotoxicity

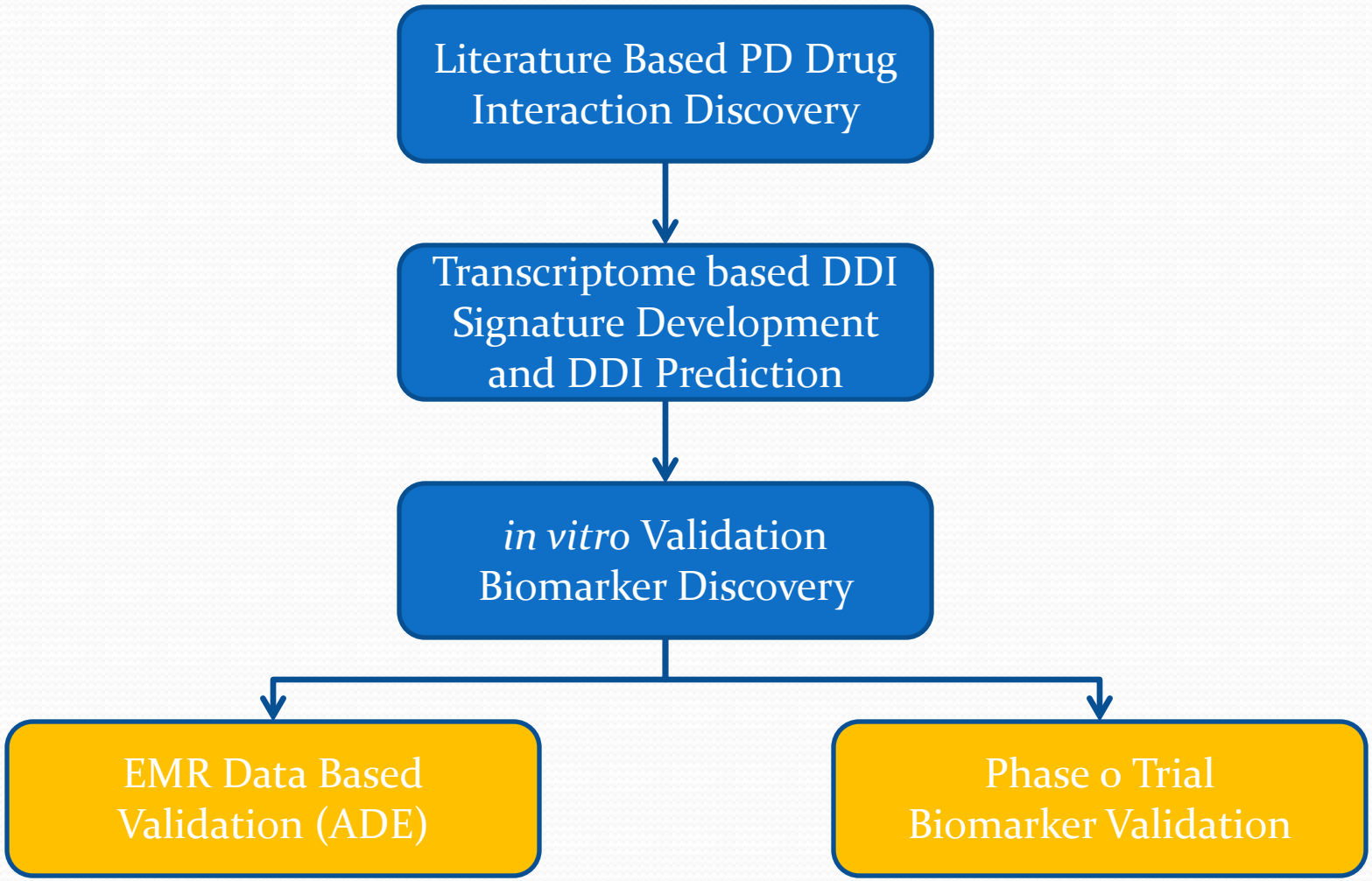
neurotoxicity



Can genetics from these shared PK DDI pathways predict different organ based drug toxicity across different drug classes?

Phenotype-Drug Wide Genetic Association Study (PDGWAS) ⇔ **Indiana Biobank**

A Translational Bioinformatics Pharmacodynamics Drug Interaction/Drug Repositioning Research Framework



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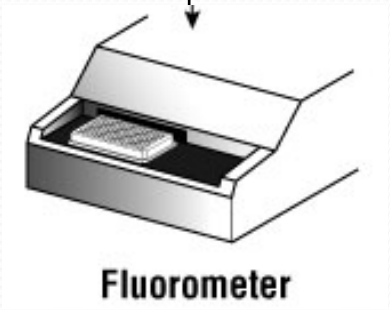
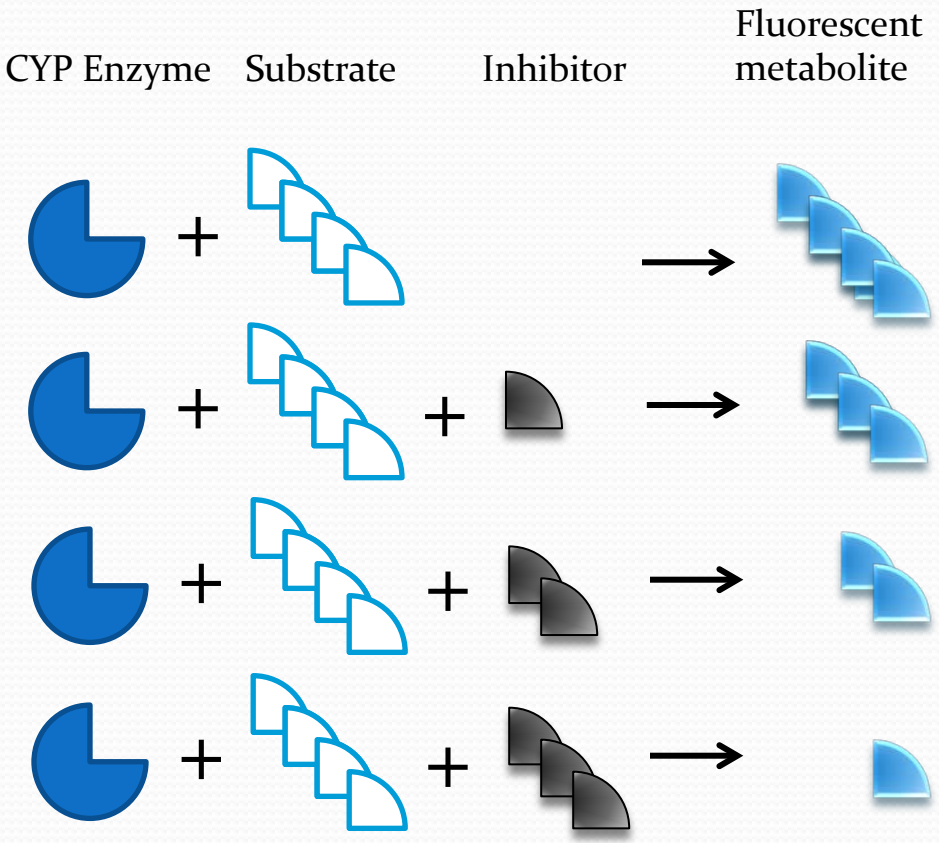
CYP Fluorometric Inhibition Assay

		Varying inhibitor concentrations								Negative control		Background	
		1	2	3	4	5	6	7	8	9	10	11	12
Positive inhibitor	A												
	B												
Test inhibitor 1	C												
	D												
Test inhibitor 2	E												
	F												
Test inhibitor 3	G												
	H												





Loratadine

- Loratadine is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis.

- Metabolized by CYP3A4/5 (75%) and CYP2D6 (25%) (Yumibe et al., Biochem Pharmacol. 1996 Jan 26;51(2): 165-72)

- An inhibitor of CYP2C19 and UGTs. (Nicolas et al., Chem Biol Interact. 1999 Nov 15;123(1):63-79)

Drug Indications

- Alprazolam is prescribed for the treatment of panic disorder, and anxiety disorders, such as generalized anxiety disorder (GAD) or social anxiety disorder (SAD).
- Loratadineis a second-generation H_1 histamine antagonist drug used to treat allergies.
- Duloxetine is effective for major depressive disorder.
- Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD), laryngopharyngeal reflux (LPR) and Zollinger–Ellison syndrome.
- Simvastatin is a hypolipidemic drug used to control elevated cholesterol, or hypercholesterolemia.
- Promethazine: It has a strong sedative effect and in some countries is prescribed for insomnia when benzodiazepines are contraindicated.
- Tegaserod is prescribed for the management of irritable bowel syndrome and constipation.
- Ropinirole is used in the treatment of Parkinson's disease.