Genetic Resources & Drug Discovery: View from Informatics

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The Pharmacogenomics Knowledgebase

Pharmacogenomics. Knowledge. Implementation.

PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

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A message about RFA-HG-12-016:
If you are submitting a proposal to RFA-HG-12-016 "Clinically relevant genetic variants resource: a unified approach for identifying genetic variants for clinical use (U01)" and looking for a letter of support from PharmGKB, please contact us at feedback@pharmgkb.org with the request and a short description of the institutions/people involved in the proposal. Thank you.

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Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- Star (*) allele translations

find interpretations
hint: enter a gene, drug, rsid, disease

PGx-Based Drug Dosing Guidelines

- SLCO1B1/simvastatin: article and supplement
- HLA-B/abacavir: article and supplement
- more guidelines...

CPIC Gene-Drug Pairs

TPP Gene Tables

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

PGx Research

- VIP: Very Important PGx gene summaries
- PharmGKB pathways
- Annotated SNPs by gene
- Drugs with genetic information

find PGx Research
hint: enter a gene, rsid, drug, disease

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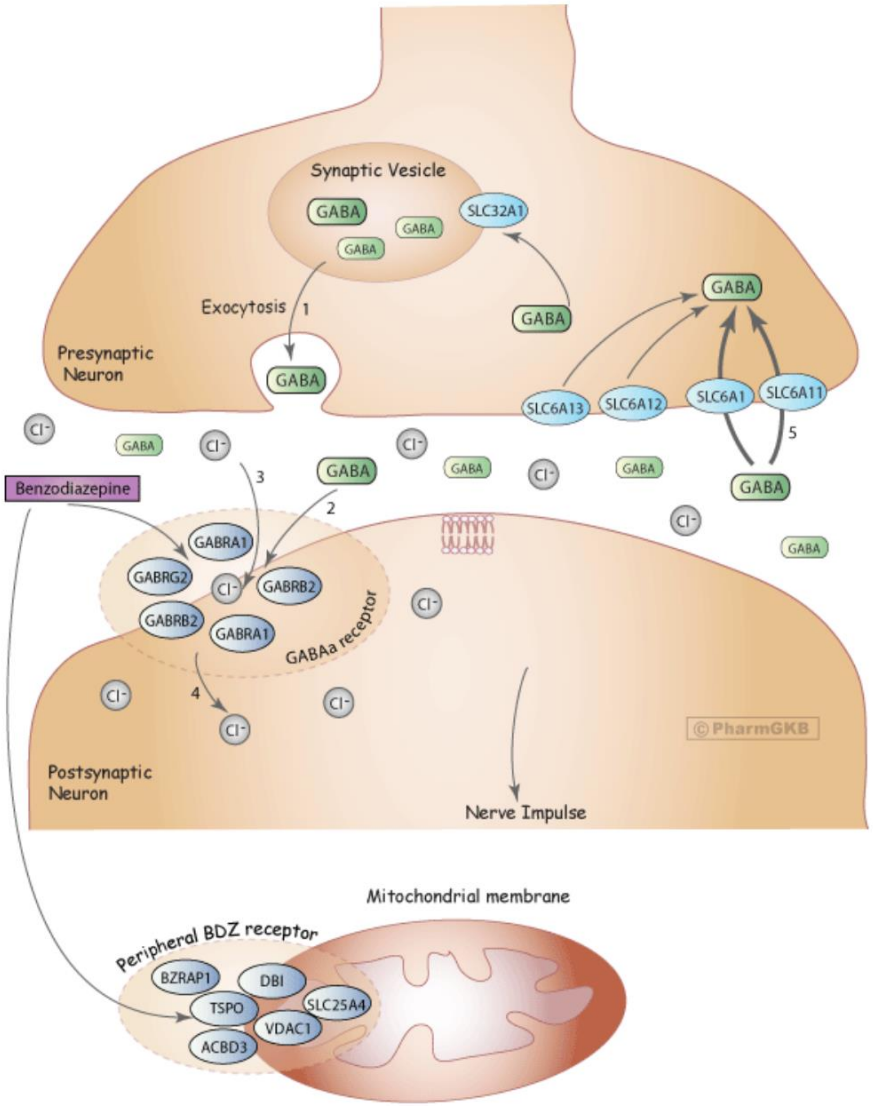
PharmGKB is a partner of the Pharmacogenomics Research Network PGRN

Feedback | Citing PharmGKB | Acknowledgements

PATHWAY

Benzodiazepine Pathway, Pharmacodynamics

Overview | Components | Related Pathways | Downloads



- Legend
- Pathway diagram
- How to cite this pathway?
- All PharmGKB pathways

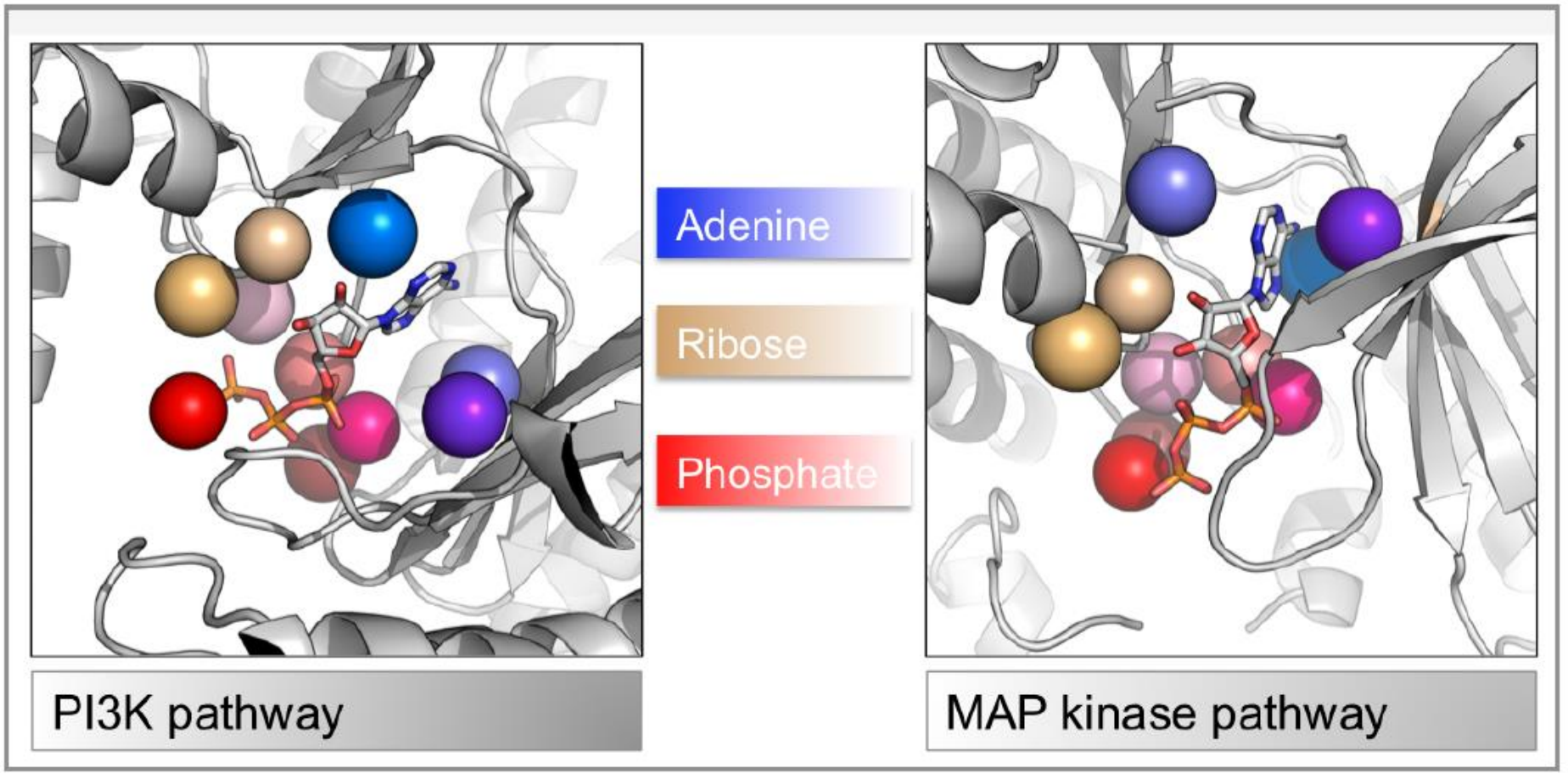
Click icons in pathway for more info

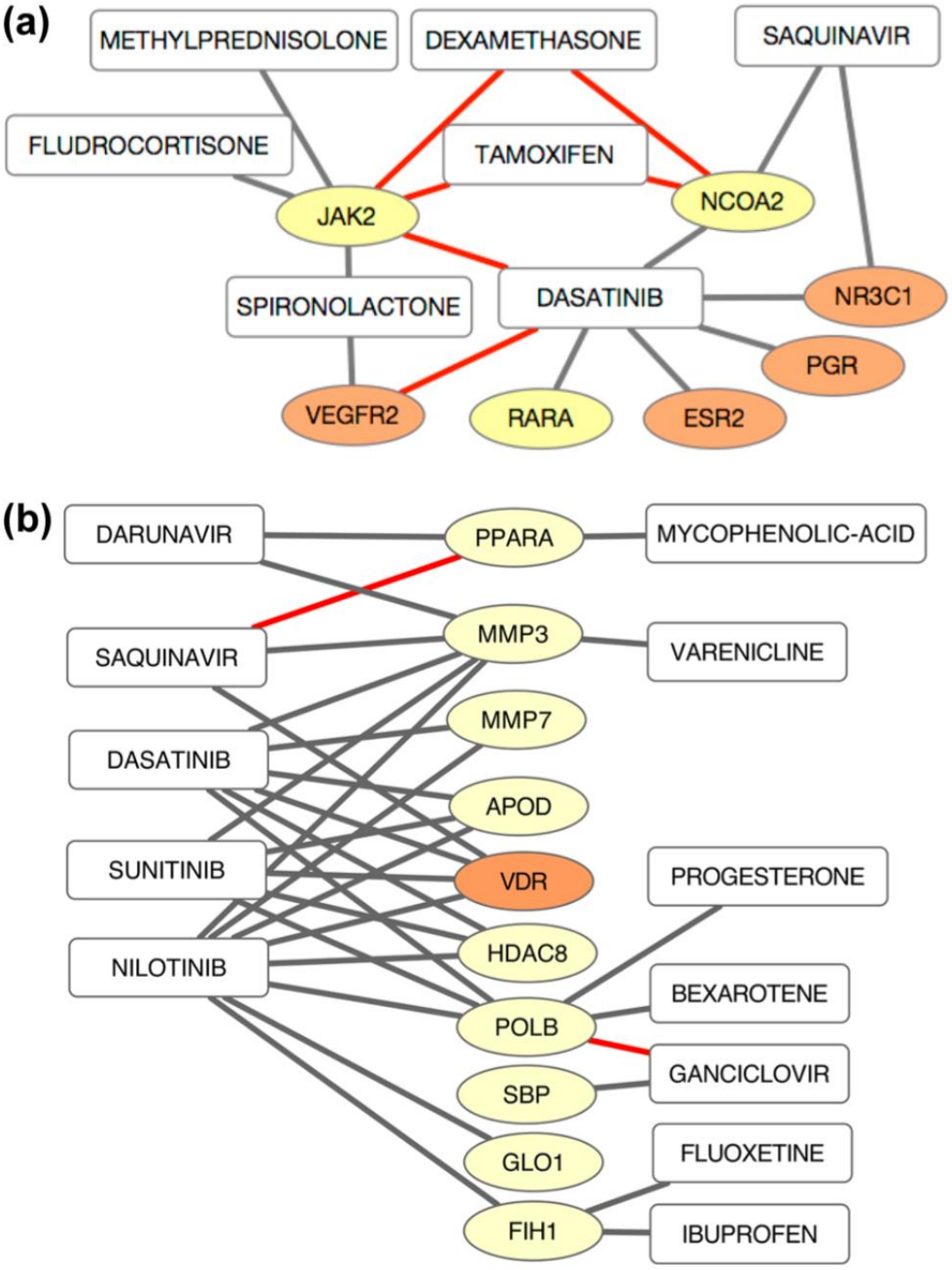
gene | drug | pathway

Key points

1. Most genetic contributors to disease are LOF (90% of OMIM), but **adding function (drug = GOF) is hard**. So need to turn search for GOF into search for LOF.
2. **Data integration** across scales (molecular, cellular, physiology, EMR, population) is mandatory to de-risk drug discovery (side effects, no effects).
3. Like genes, drugs have (vastly underestimated) **pleiotropic effects** and these should be considered during drug development.
4. **Pathway approaches** for understanding pleiotropic genes and drugs offer more opportunities to modulate biology through LOF interventions, and to predict side effects and poor efficacy.

FEATURE “sees” similarities in diverse kinase structures (PIK3CG and SRC) = repurposing opportunity (Liu & Altman, PLoS Comp Bio, 2011).



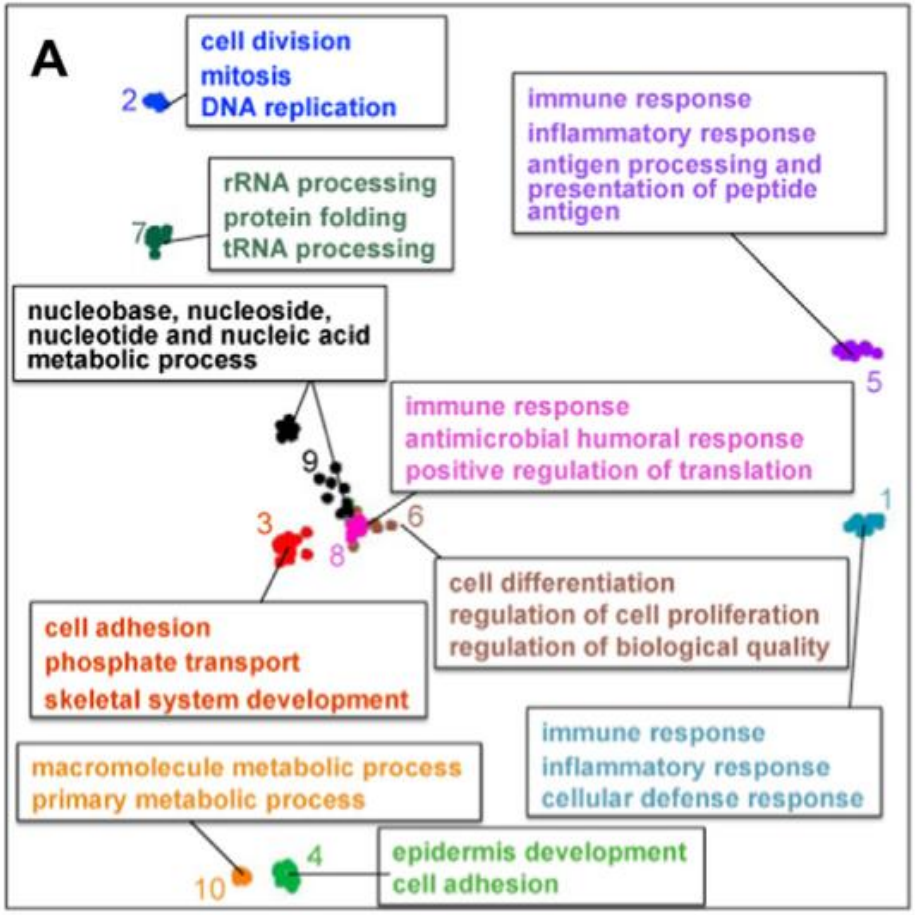


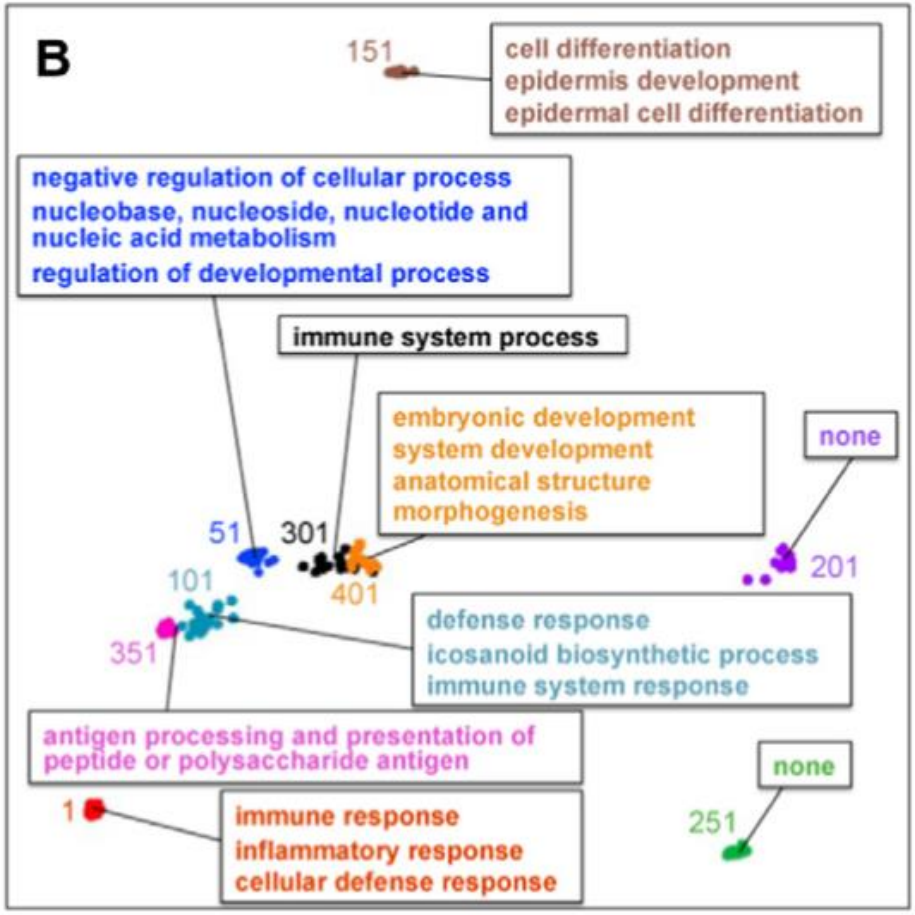
Promiscuous drug binding explains some adverse events

(a) Menstrual irregularity

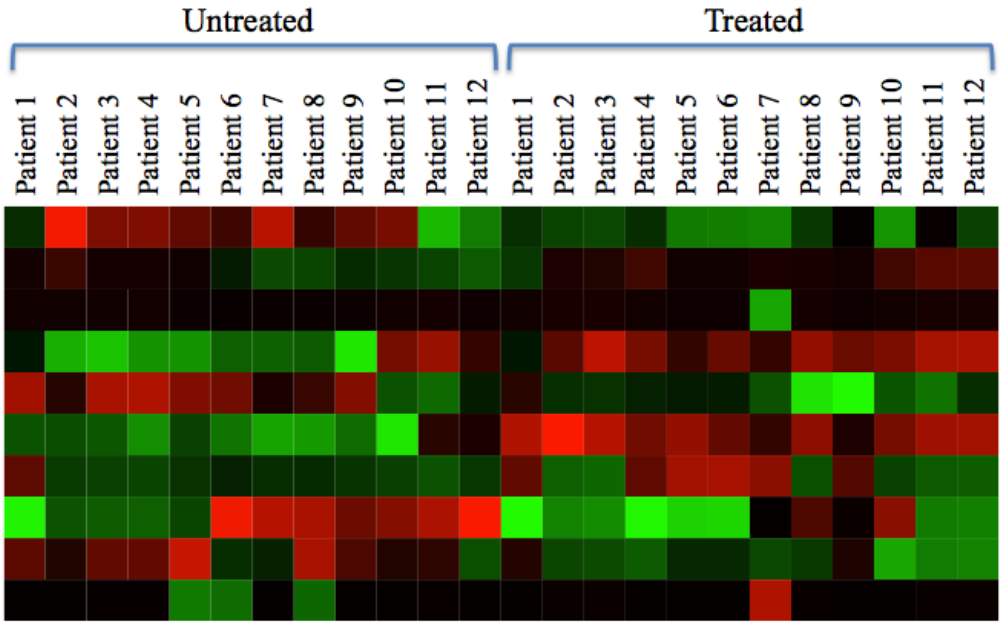
(b) Hypocalcemia

Independent Component Analysis of GEO human data yields ~450 fundamental components that explain most variability in expression experiments. (Engreitz et al, J Biomed Inform. 2010)





Key components expressed at different levels in treated vs. untreated

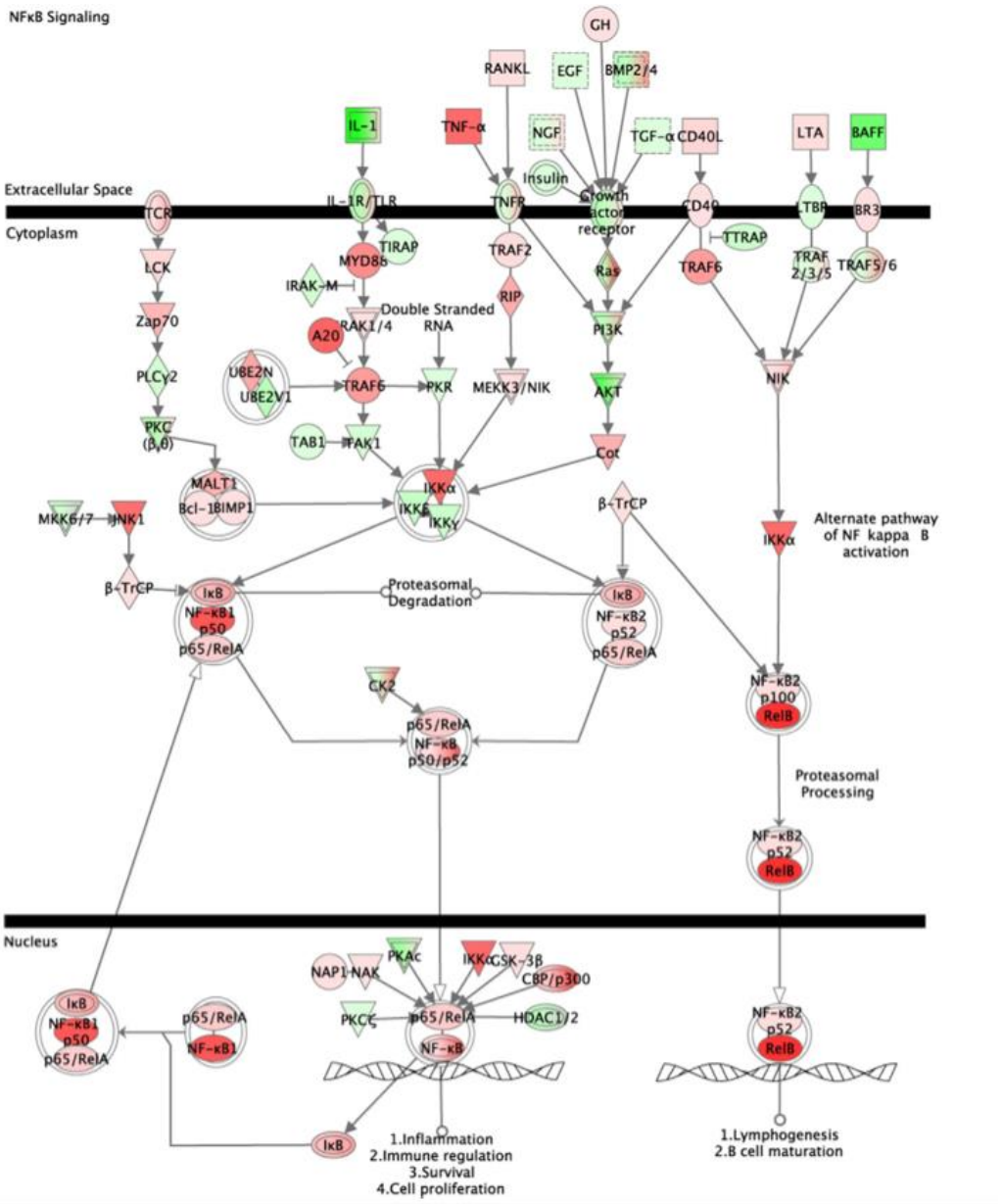


Component	Relative Fold Change	Corrected P-Value
373	-0.0311	4.86E-04
183	-0.023	2.43E-03
289	-0.0268	1.08E-04
56	0.026	6.46E-04
223	-0.0238	2.40E-03
325	0.0234	5.73E-05
345	0.0195	1.56E-05
32	-0.0185	1.08E-01
328	-0.0184	3.98E-03
34	0.0173	5.73E-05

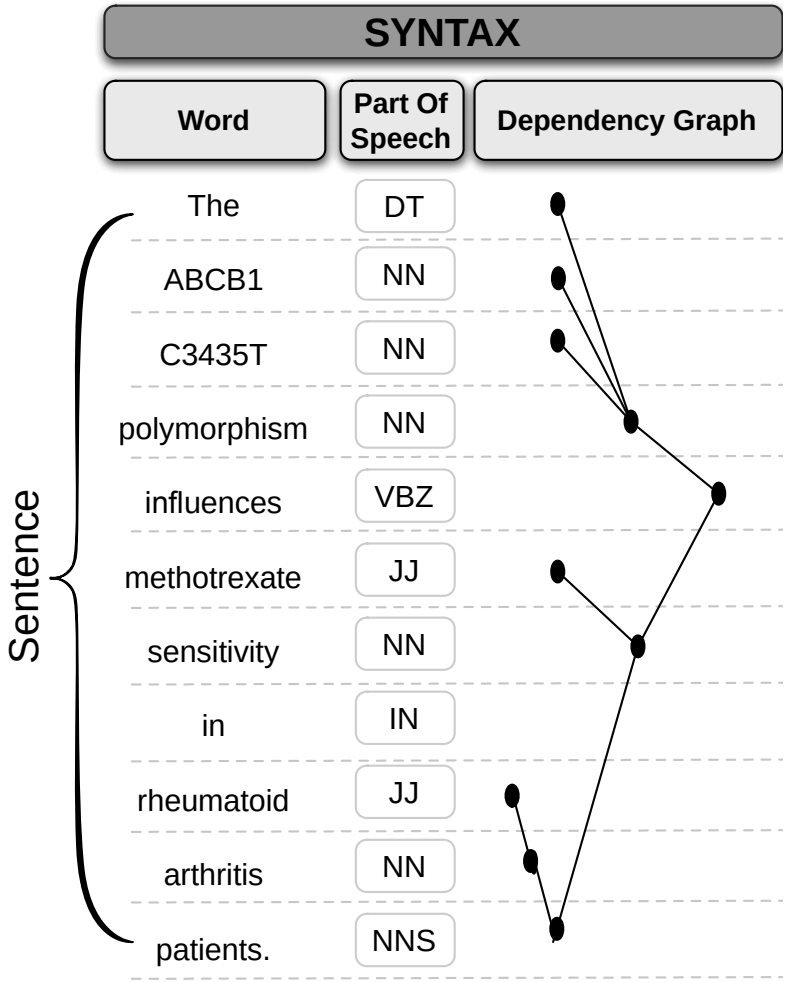
Parthenolide effects NFKB signaling. Pathways suggests new diseases and new targets.

Parthenolide alters expression of TNF, NFKB, kinases.

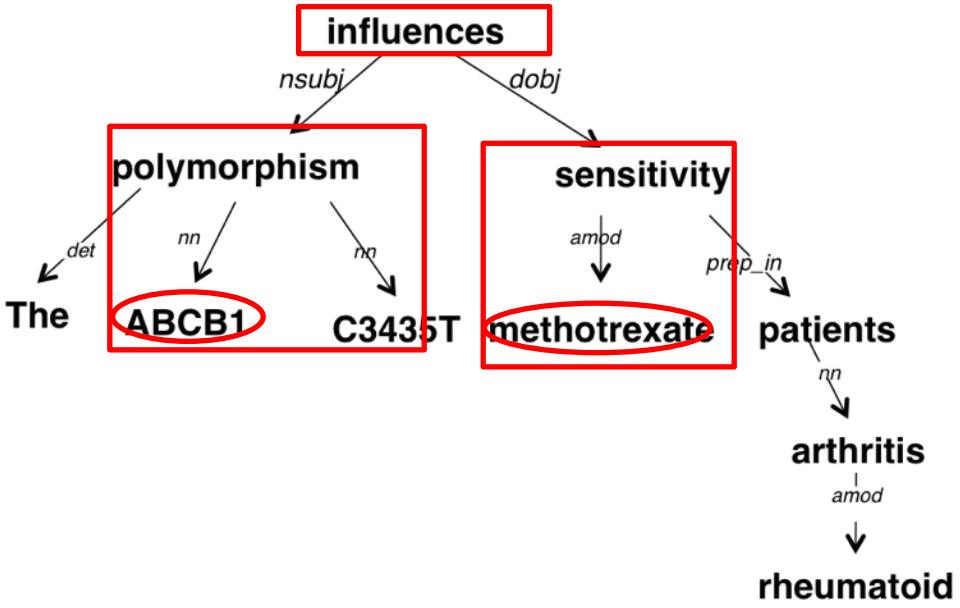
Immediately suggests a way to decide if Parthenolide is appropriate for other cancers, based on their gene expression.



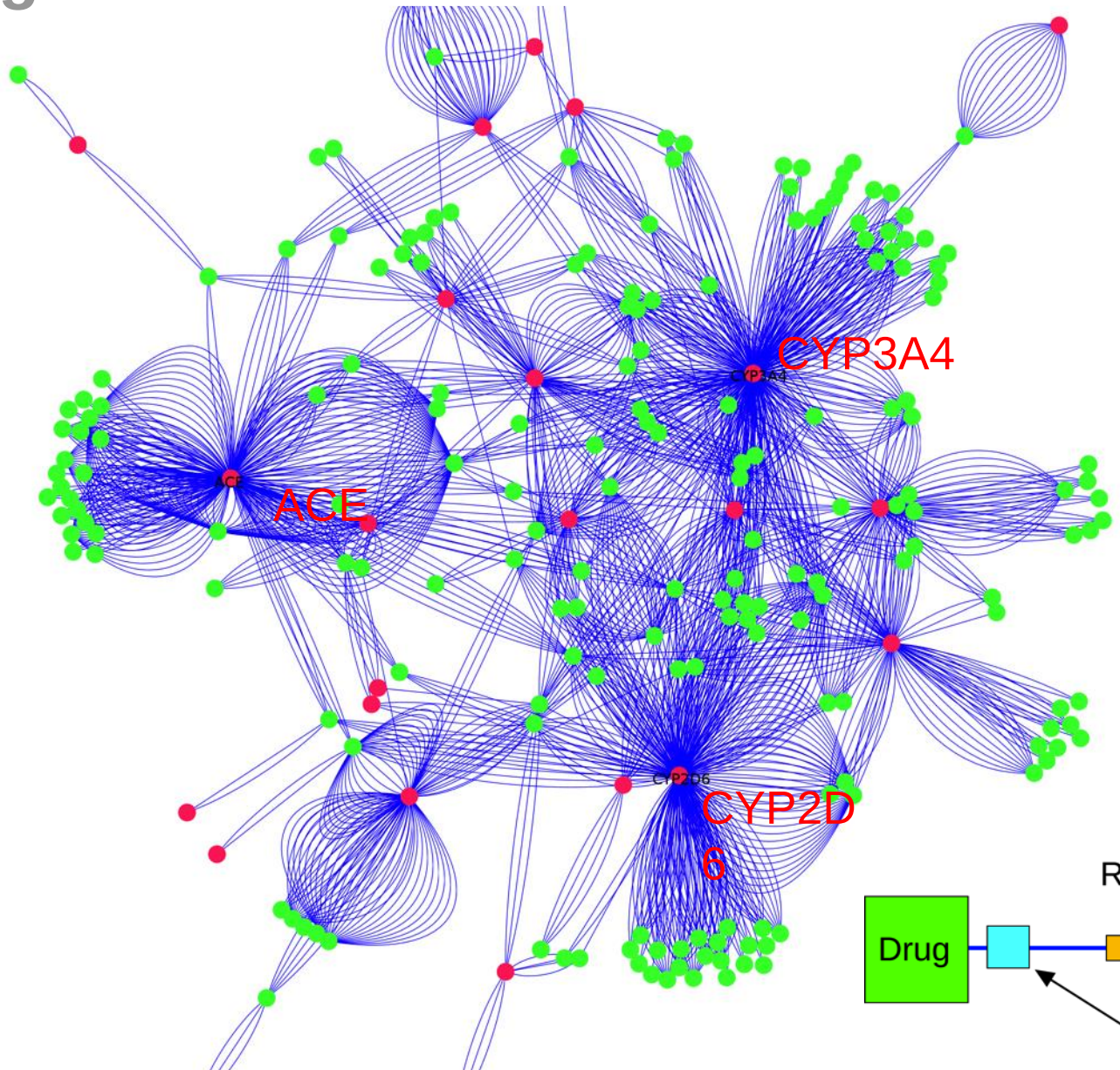
Advances in natural language parsing enable high fidelity extraction of relations

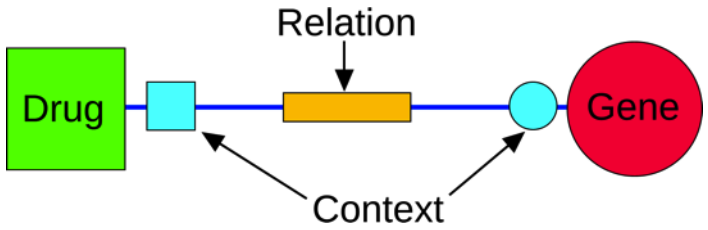


Dependency graph

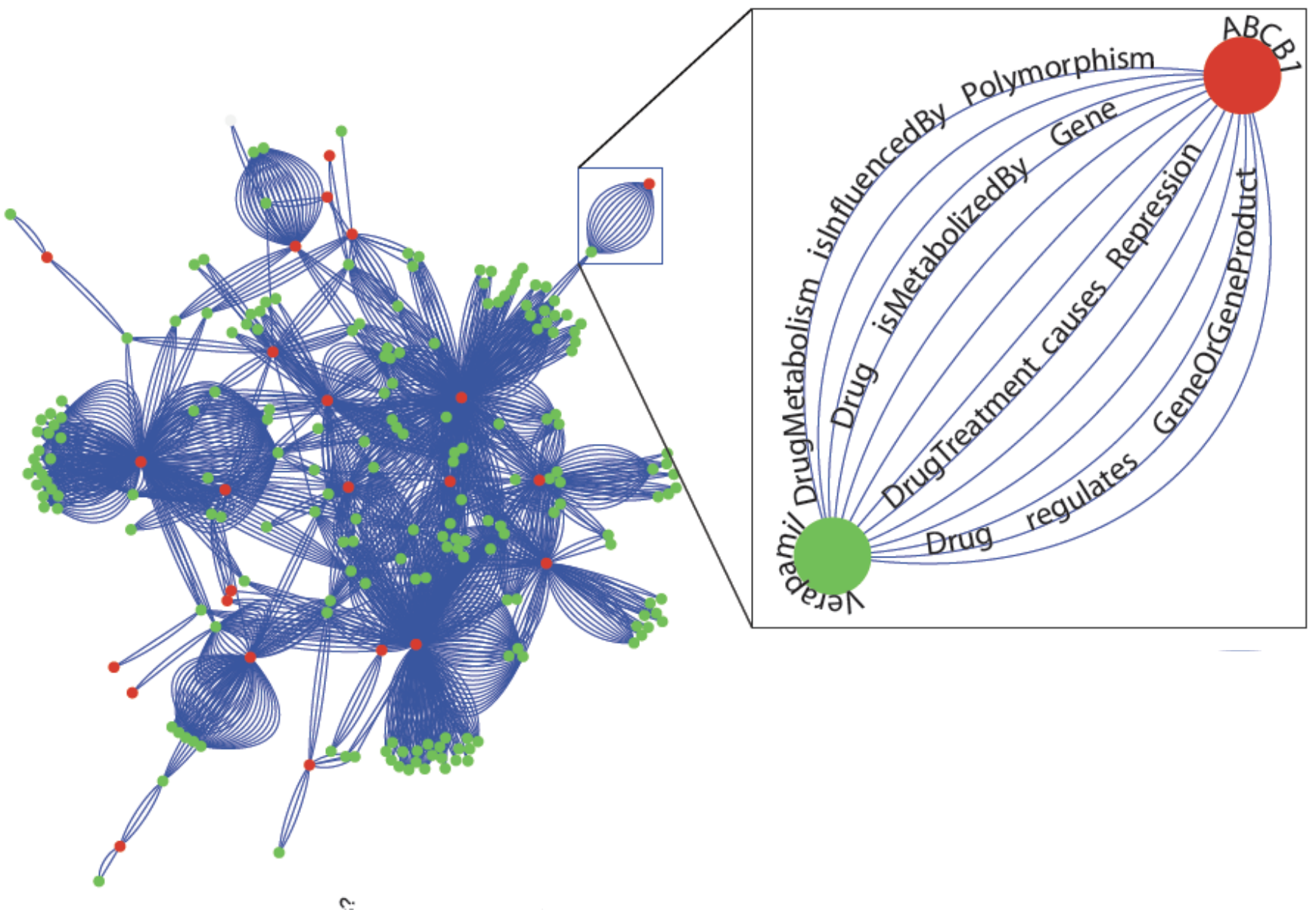


Semantic network of 170,598 normalized gene-drug relations from PubMed abstracts.

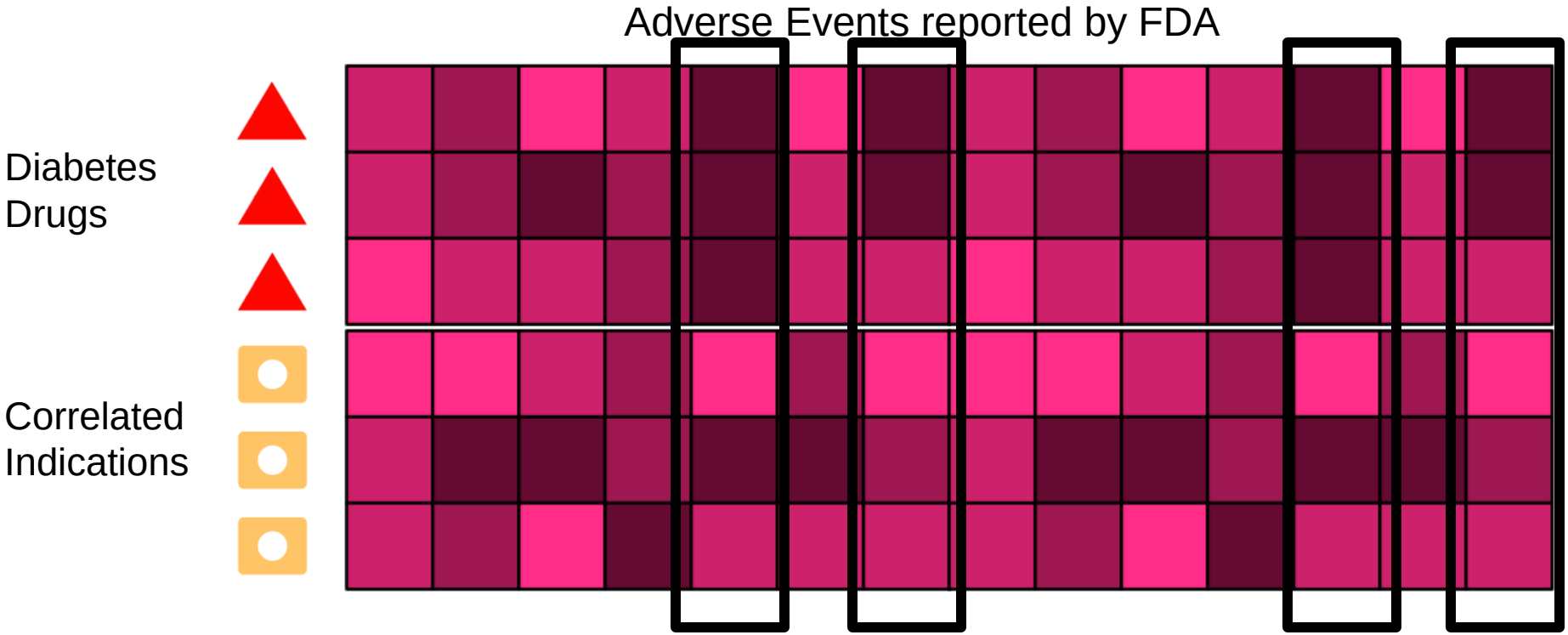




ABCB1 gene and verapamil drug



We built a statistical model able to recognize glucose-altering drugs based on their "adverse event signature"

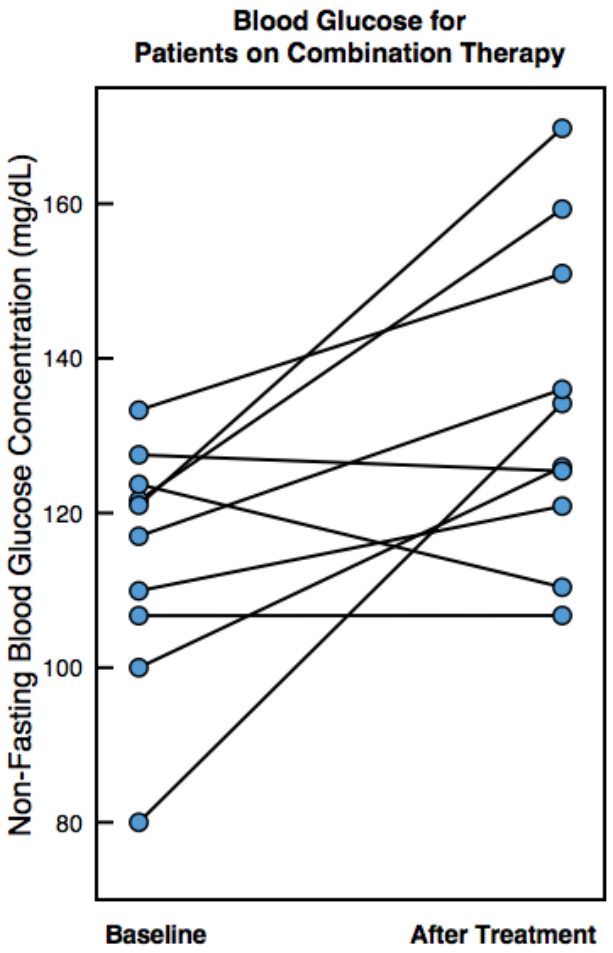


F_{ij} = frequency of AE_j for $Drug_i$

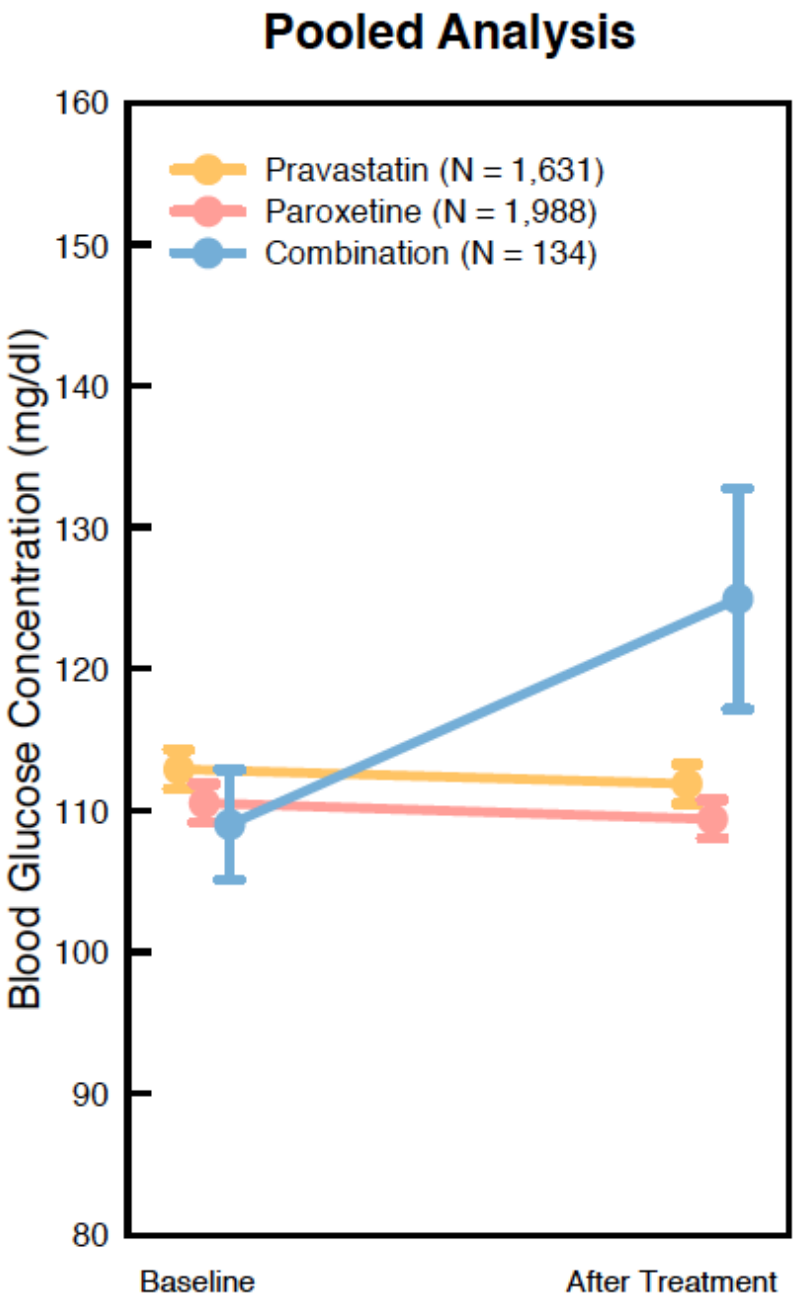
F_{ij} = frequency of AE_j for $Indication_i$

Pravastatin and paroxetine significantly increase blood glucose by 20 mg/dl

Variable	Pravastatin and Paroxetine Combination
N	10
Demographics	
Age (mean ± SD)	59.9 ± 11.09
Gender (% Female)	90.0
Race (% of group)	
White	50
African American	20
Hispanic	0
Other	30
Glucose (mg/dl mean ± SD)	
Baseline (base)	114.08 ± 14.79
After treatment(s) (post)	133.96 ± 19.54
paired t-test (t: post - base)	**0.020**
Change (base to post)	19.88 ± 21.04
N patients with increase	8 (80)

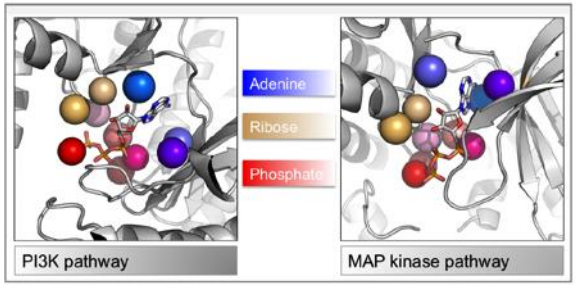


Combining all three sites



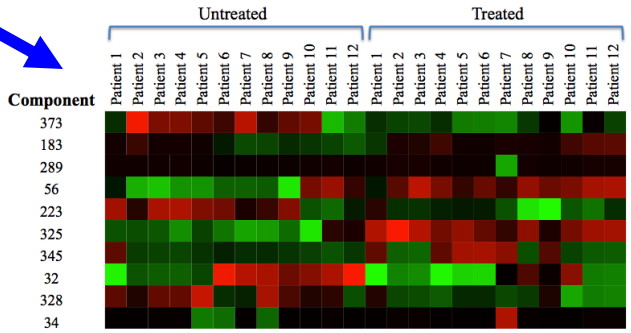
Thus, the emerging network for drugs….

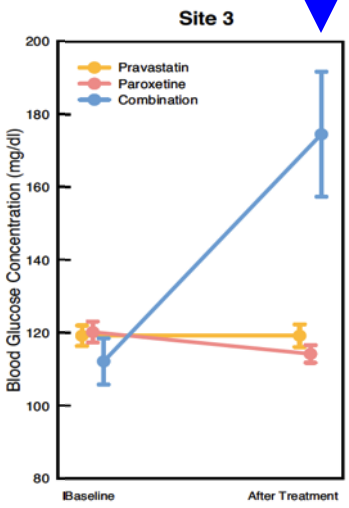
Target structure & dynamics



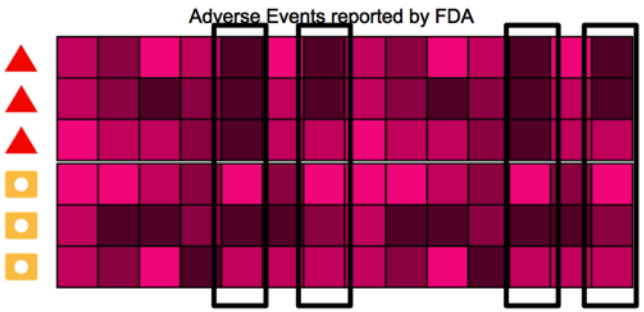
Drug recognition & binding

Cellular response & pathways



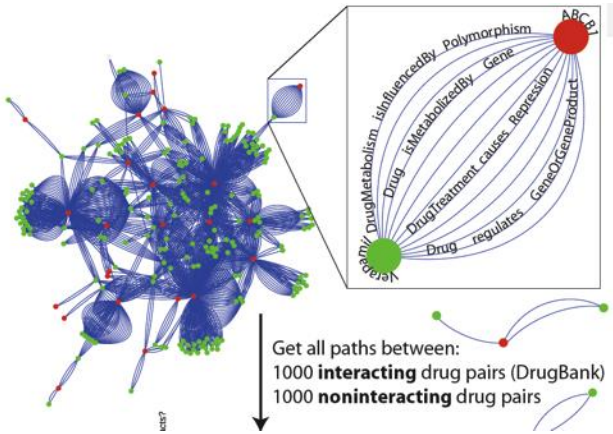


Clinical response datamining



Population effect reporting

Text mining of gene, drug, phenotype associations



PCSK9 has inspired, but exceptional?

Define relevant phenotype

↓

Find phenotypic outliers

↓

Identify causative variant(s)
(outliers + large background)

↓

Show LOF good, GOF bad

↓

Develop targeted inhibitor, refine

Define relevant cell types/tissues

↓

Define relevant molecular pathways

↓

Identify genes/variant(s) associated
with pathway function/dysfunction

↓

Find LOF pathway opportunities,
Seek genetic evidence for modulation

↓

Counter screen for promiscuity,
side effects, efficacy issues

↓

Develop inhibitor(s) of pathways,
refine

Challenges

1. 3D structures of human proteins to understand drug promiscuity/network effects (+affects of variation)
2. Gene expression response of tissues to drug exposures for promiscuity/network effects (+affects of variation)
3. Tissue-specific model systems to test pathway modulation
4. Large genetic cohorts to understand gene tolerance for mutation and GOF/LOF response of pathways.

Thanks.

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Key Papers

PharmGKB: a logical home for knowledge relating genotype to drug response phenotype. Altman RB. Nat Genet. 2007 Apr;39(4):426. No abstract available. PMID: 17392795 [PubMed - indexed for MEDLINE]

Independent component analysis: mining microarray data for fundamental human gene expression modules. Engreitz JM, Daigle BJ Jr, Marshall JJ, Altman RB. J Biomed Inform. 2010 Dec;43(6):932-44. Epub 2010 Jul 7. PMID: 20619355

Detecting drug interactions from adverse-event reports: interaction between paroxetine and pravastatin increases blood glucose levels. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, Yue P, Tsao PS, Kohane I, Roden DM, Altman RB. Clin Pharmacol Ther. 2011 Jul;90(1):133-42. doi: 10.1038/clpt.2011.83. Epub 2011 May 25. Erratum in: Clin Pharmacol Ther. 2011 Sep;90(3):480. Tsau, P S [corrected to Tsao, P S]. PMID: 21613990

Using text to build semantic networks for pharmacogenomics.Coulet A, Shah NH, Garten Y, Musen M, Altman RB. J Biomed Inform. 2010 Dec;43(6):1009-19. Epub 2010 Aug 17. PMID: 20723615 [PubMed - indexed for MEDLINE]

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A novel signal detection algorithm for identifying hidden drug-drug interactions in adverse event reports. Tatonetti NP, Fernald GH, Altman RB. J Am Med Inform Assoc. 2011 Jun 14. [Epub ahead of print] PMID: 21676938

The FEATURE framework for protein function annotation: modeling new functions, improving performance, and extending to novel applications. Halperin I, Glazer DS, Wu S, Altman RB. BMC Genomics. 2008 Sep 16;9 Suppl 2:S2. PMID: 18831785