Drug-induced transcriptional modules in mammalian biology: Implications for drug repositioning and resistance

Murat Iskar
Peer Bork lab, EMBL Heidelberg

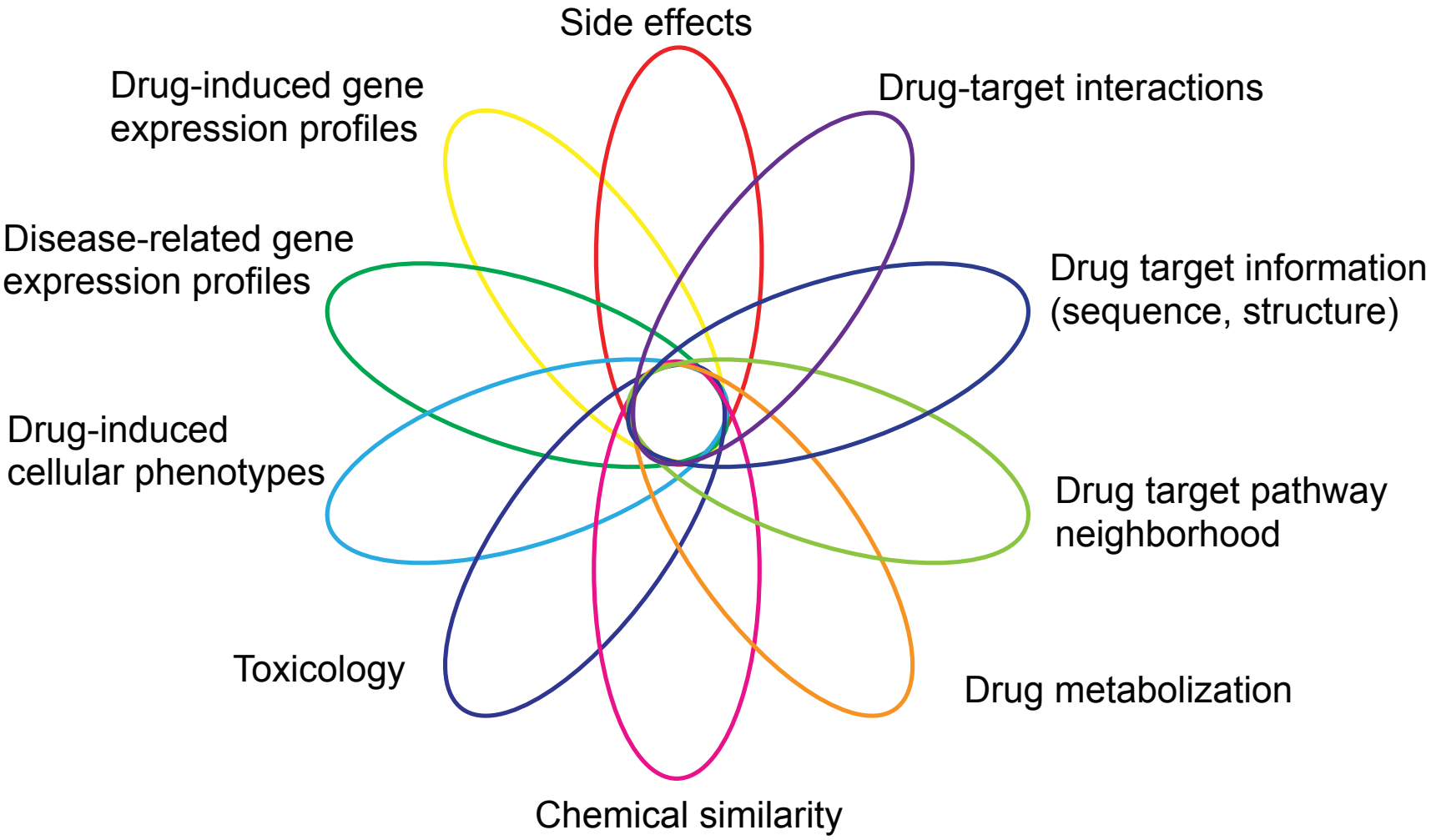
EMBL

May 19-24, 2013 Dagstuhl

Outline

- Introduction
- Drug-induced regulation of target expression
- Drug-induced transcriptional modules
  - Identification and characterization of modules
  - Functional discovery of hypothetical genes
  - Towards drug repositioning via modules

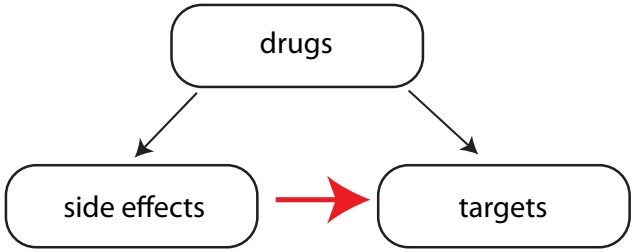
Computational approaches integrating drug-related information to gain a systems level understanding of drug action



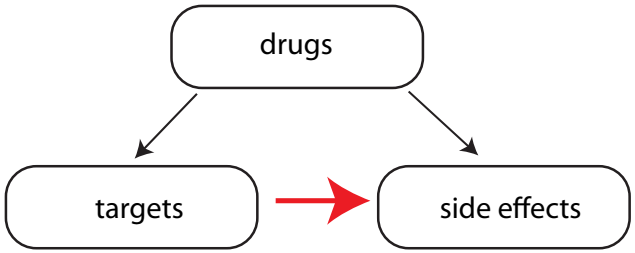
Iskar *et al*. Curr. Opin. Biotechnol. (2011)

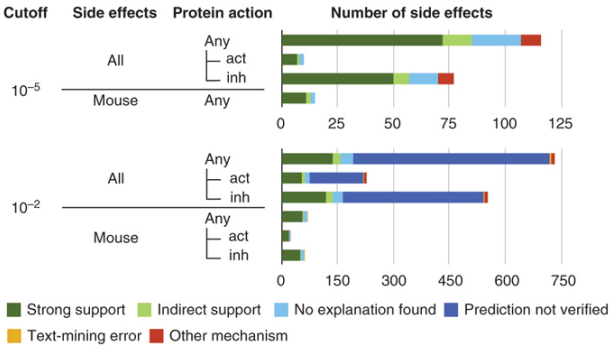
Recent studies integrating side effect information with drug-target relations

- Campillos et al. (2008) Drug target identification using side effect similarity. Science 321(5886):263-6

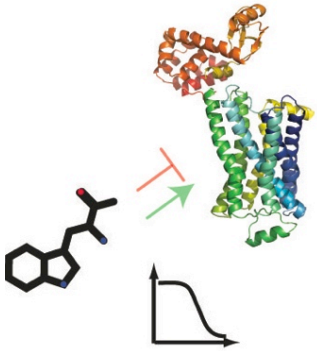


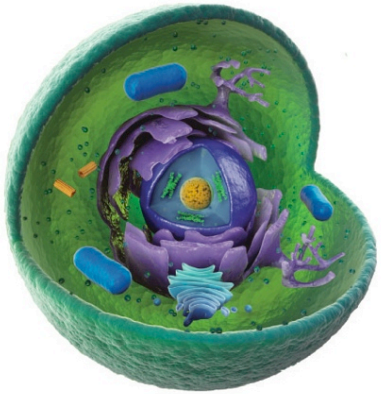
- Kuhn et al. (2013) Systematic identification of proteins that elicit drug side effects. Molecular Systems Biology 9:663

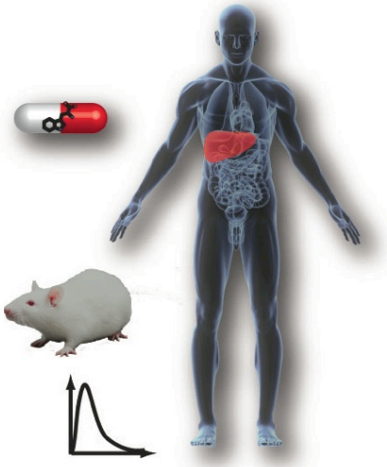




Integration of drug-information resources: a special focus on gene-expression compendium of drug treatments







Drug-target interactions
Mode of action
Structural features

Drug-induced gene expression profiles

Drug indications
Side effects

STITCH[1] *resource*
(http://stitch.embl.de)

The Connectivity Map[2]
(www.broadinstitute.org/cmap/)

The *DrugMatrix* database[3]
(GEO: GSE8858)

SIDER[4] *resource*
(http://sideeffects.embl.de)

1 Kuhn. *et al*. NAR (2012)
2 Lamb J. *et al*. Science (2006)
3 Natsoulis *et al*. MSB (2008)
4 Kuhn *et al*. MSB (2010)

Drug-induced gene expression profiles were used to generate a drug-drug similarity network

- Iorio et al. (2009) Identifying network of drug mode of action by gene expression profiling. Journal of Computational Biology 16 (2), 241-251
- Iorio et al. (2010) Discovery of drug mode of action and drug repositioning from transcriptional responses. Proceedings of the National Academy of Sciences 107 (33), 14621-14626

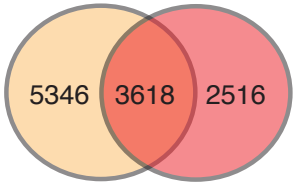
Iorio *et al*. J Comput Biol. (2009)
Iorio *et al*. PNAS (2010)

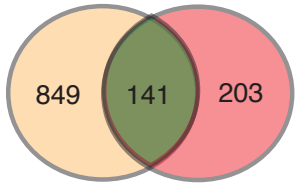
Inferring novel drug-disease associations based on anti-correlated expression profiles

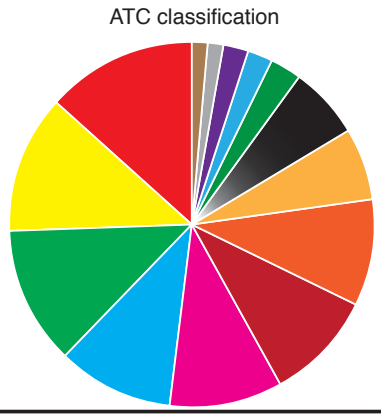
- Hu et al. (2009) Human Disease-Drug Network Based on Genomic Expression Profiles. PLoS ONE 4(8): e6536
- Sirota et al. (2011) Discovery and preclinical validation of drug indications using compendia of public gene expression data. Science Translational Medicine 3 (96), 96ra77-96ra77
- Dudley et al. (2011) Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Science Translational Medicine 3 (96), 96ra76-96ra76

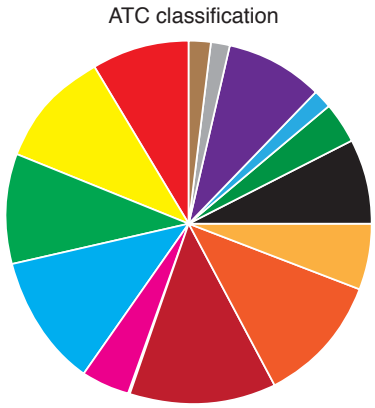
Comparison of the Connectivity Map and the DrugMatrix database

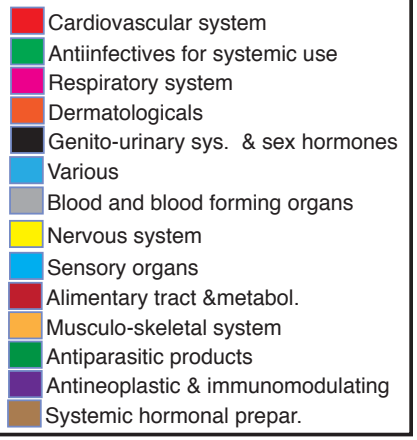
	Human cell lines	Rat liver
Source	Connectivity Map dataset (build 02)	Liver pharmacology and xenobiotic response repertoire from Iconix Biosciences (GEO: GSE8858)
Treatment duration	6 hours	mainly 6 hours, 1, 3 and 5 days
Genes	22277 probe sets ↓ Detection call filtering ↓ Unique genes 8964 genes	10455 probe sets ↓ Unique genes 7122 genes (6134 orthologous pairs) ↓ Matched orthologous pairs 3618 genes
Drugs	1309 compounds ↓ Filtering for normalization ↓ Common in all cell lines 990 compounds (>650 drugs)	344 compounds (>250 drugs)



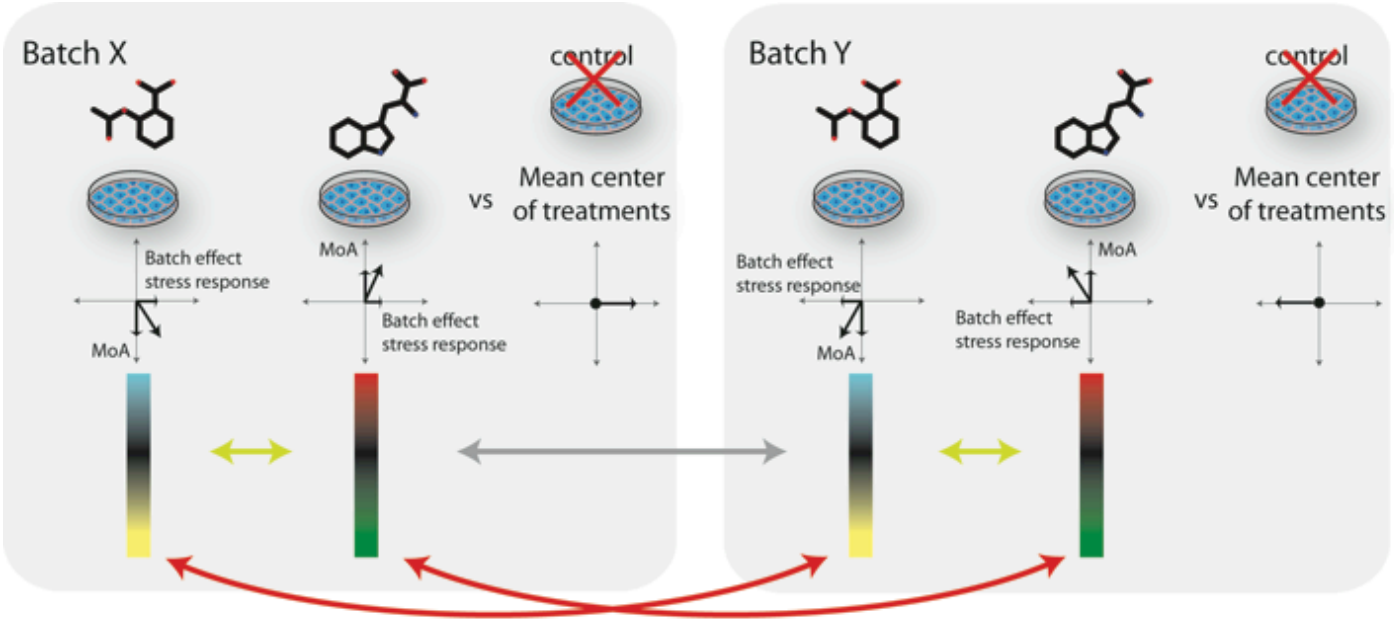


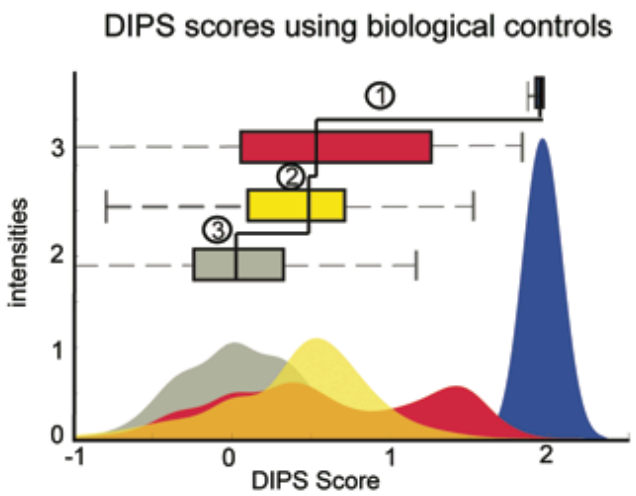


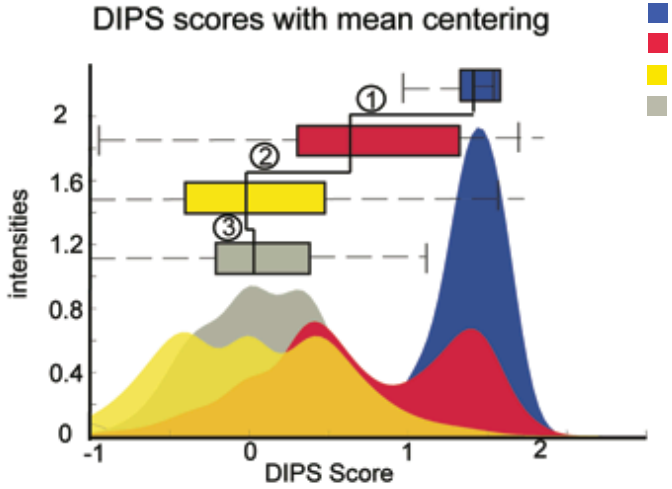




Mean centering among treatments eliminates batch effect in the Connectivity Map resource



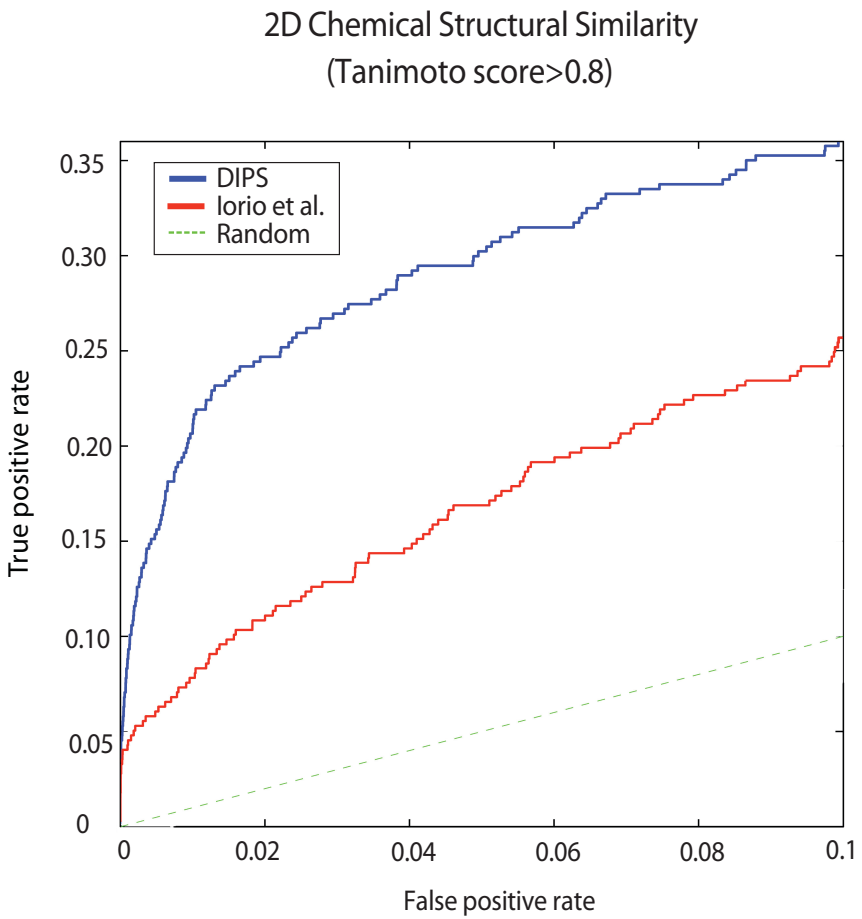


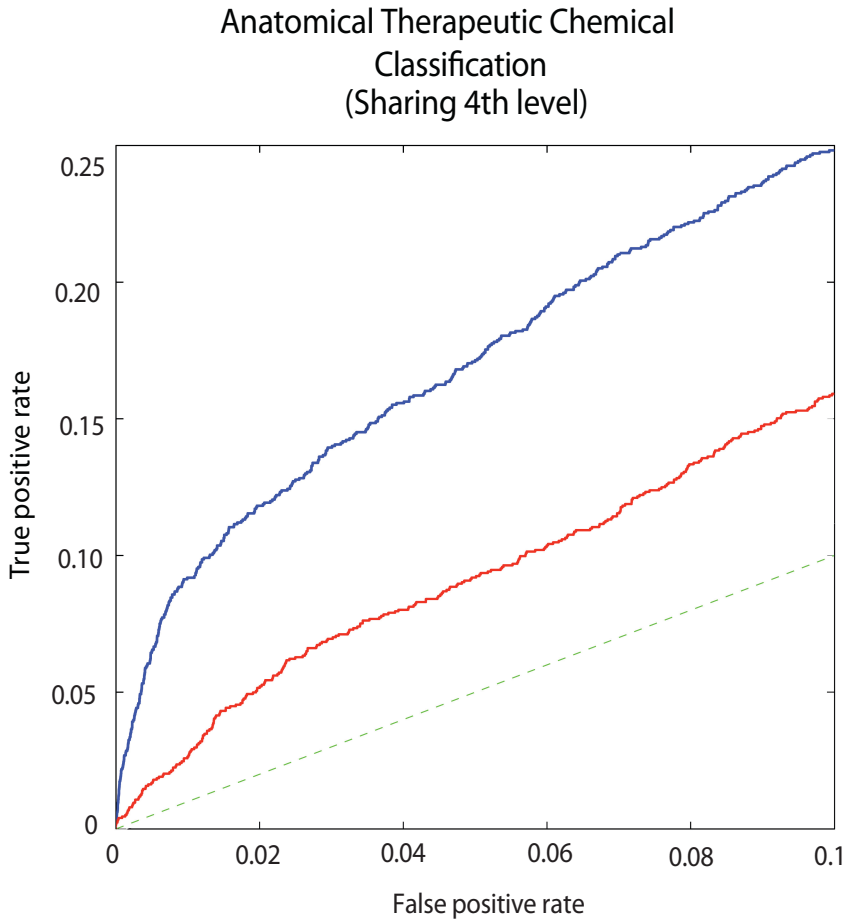


Same Drug/Same Batch
Same Drug/Different Batch
Different Drug/Same Batch
Different Drug/Different Batch

Iskar *et al*. PLoS Comput Biol. (2010)

Assessment of drug-induced gene expression profile similarity (DIPS) with structural similarity and ATC classification

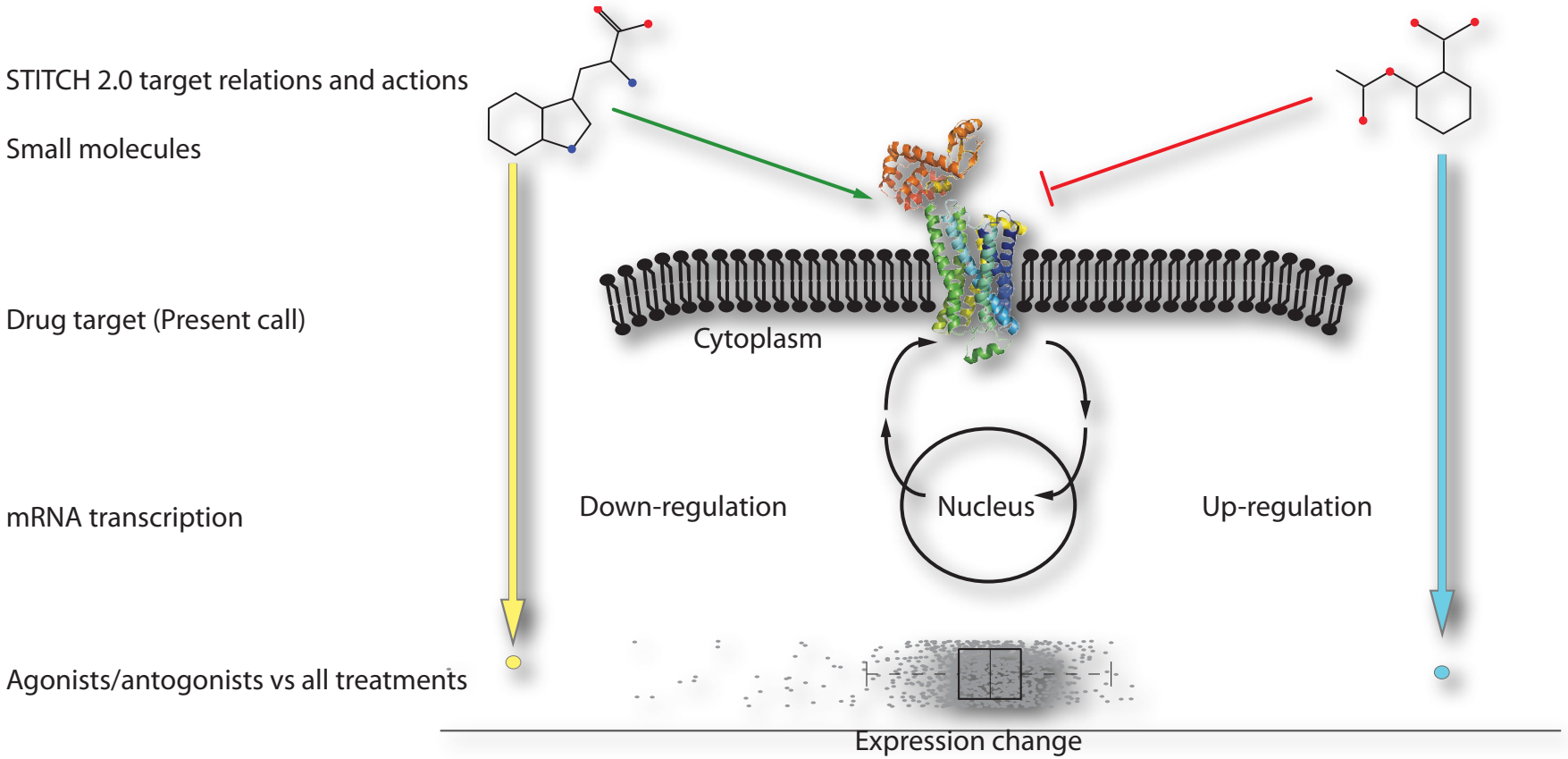




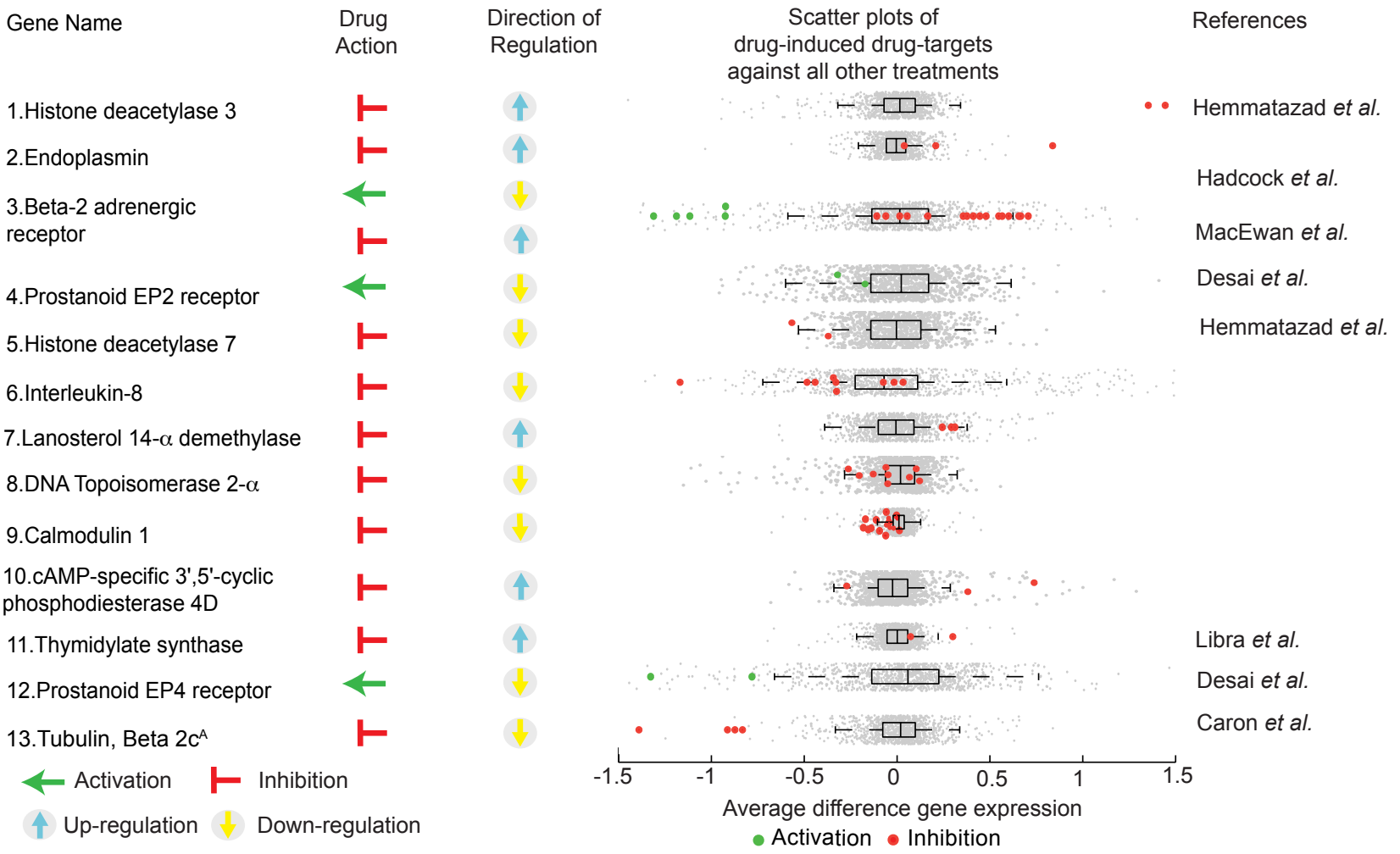
Iorio *et al*. J Comput Biol. (2009)
Iorio *et al*. PNAS (2010)

Drug-induced regulation of target expression

Aim: Systematic analysis of feedback regulation of drug targets induced by its inhibitors/activators



8% of drug targets are differentially regulated at the expression level upon drug perturbation



Iskar *et al*. PLoS Comput Biol. (2010)

Conclusions I

- Batch effect in the Connectivity Map resource can be eliminated by using treatments rather than untreated controls to estimate background.

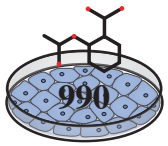
- Benchmarking highlighted that drug-induced gene expression profiles reflect the mechanism of action and chemical structure of drugs.

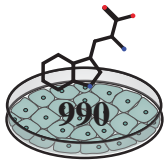
- 8% of drug targets were found to be feedback-regulated at the expression level upon drug treatment. In addition to known cases reported in literature, we also identified novel feedback loops that may have a role in the development of drug tolerance.

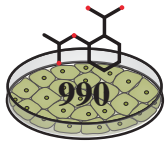
Identification and characterization of drug-induced transcriptional modules in three human cell lines and rat liver

Drug-induced gene expression profiles

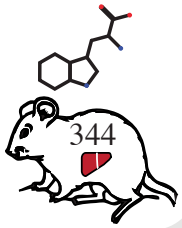
In vitro
Connectivity Map[1]

MCF7 

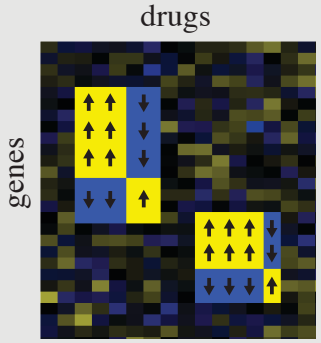
PC3 

HL60 

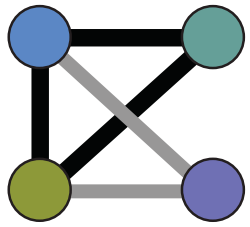
In vivo
DrugMatrix[2]



Identification of modules[3]

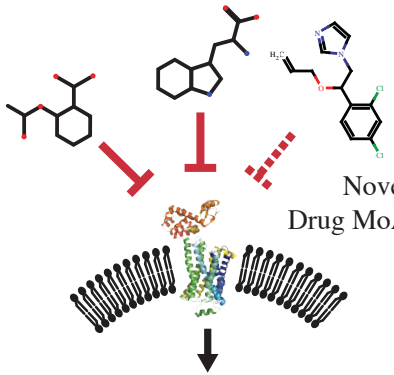


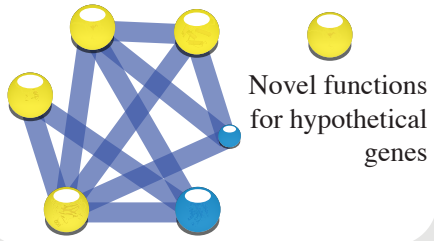
Conservation of modules



Characterization of modules

Drugs:
ATC code
Target proteins
Side effects

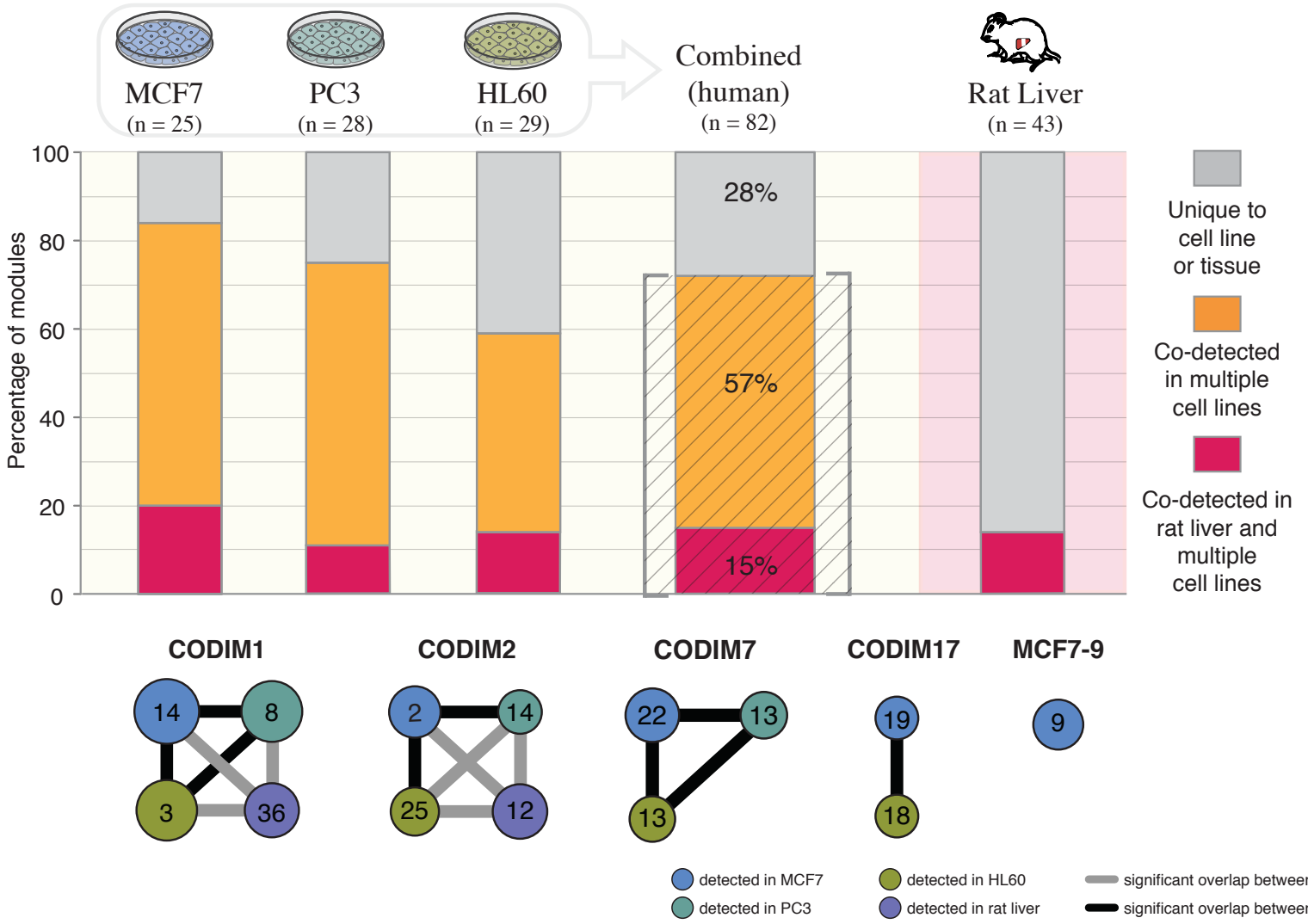




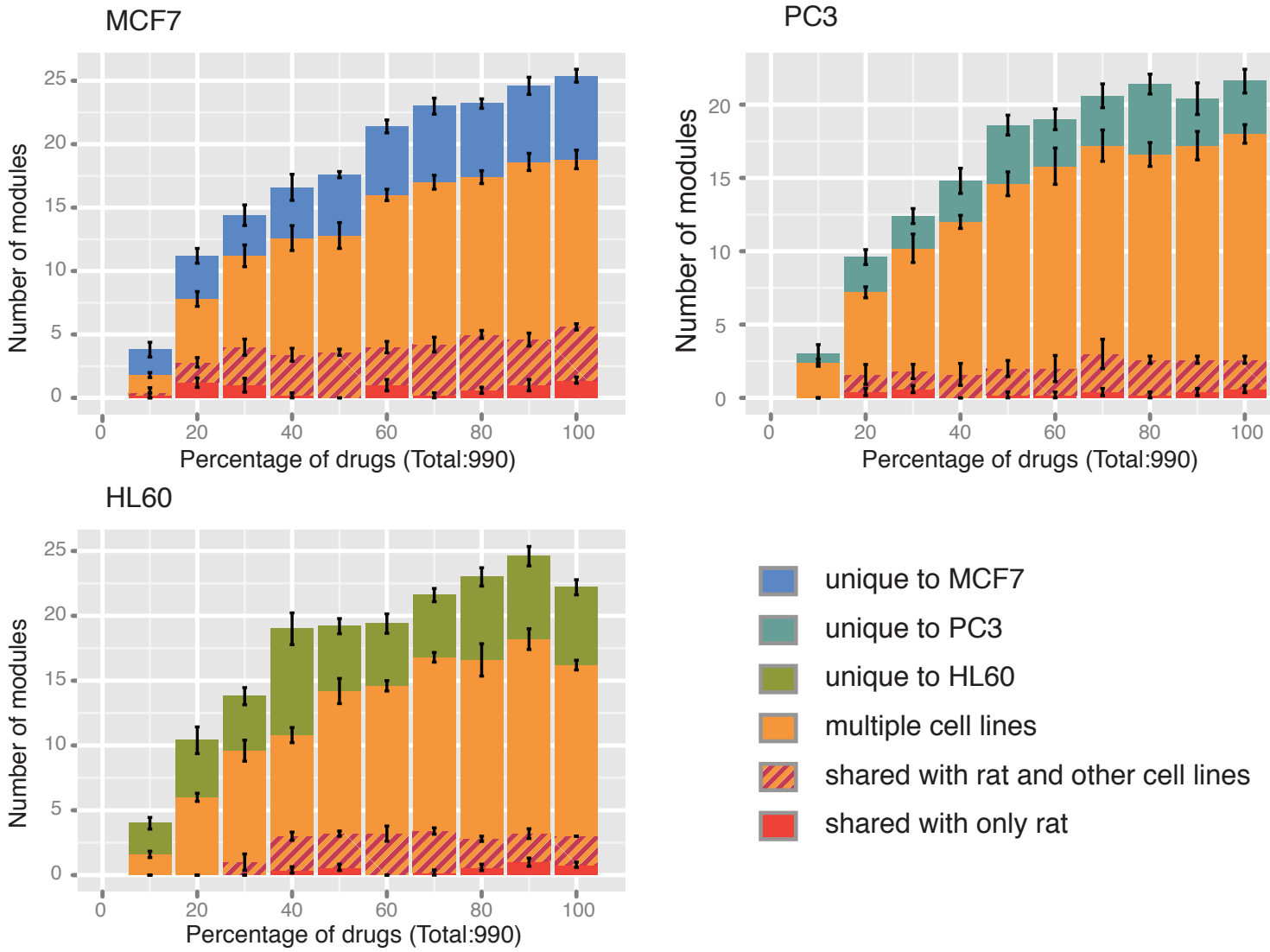
Genes:
GO terms
KEGG / BioCarta pathways
Protein-protein networks

1 Lamb J. *et al.* Science (2006)
2 Natsoulis *et al.* MSB (2008)
3 Bergmann et al. Phys Rev E Stat Nonlin Soft Matter Phys. (2003)

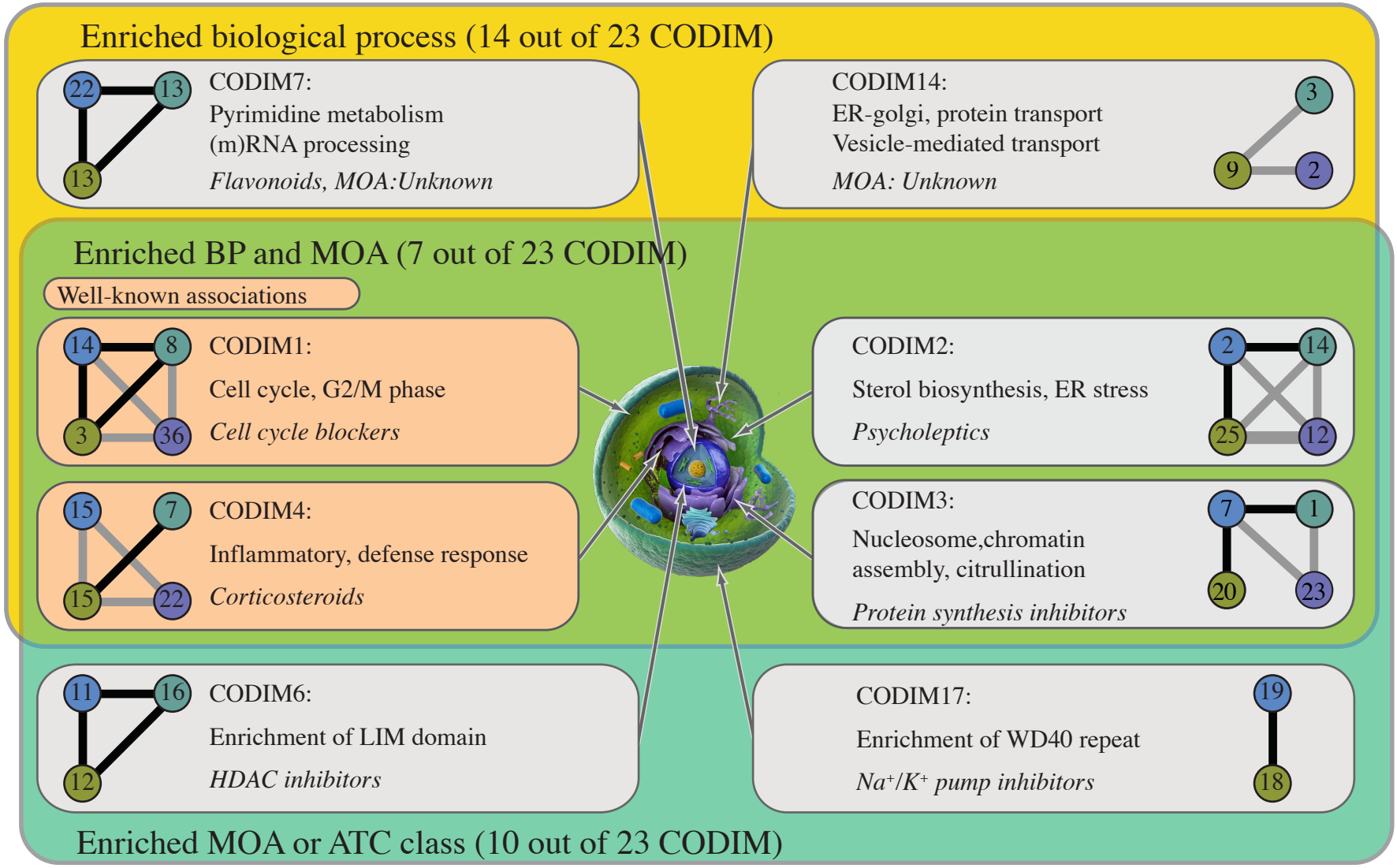
72% of human drug-induced modules are present in multiple cell lines



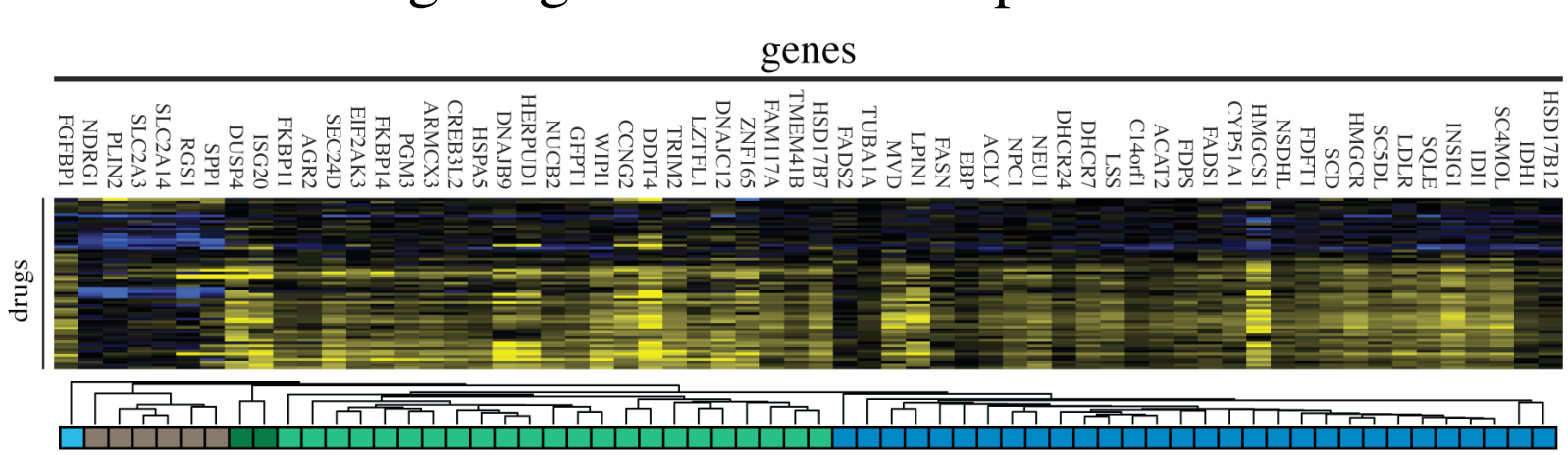
Conservation estimates across cell lines and organisms are robust to variations in chemical space

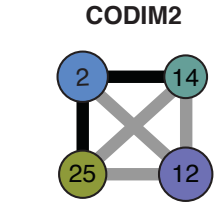


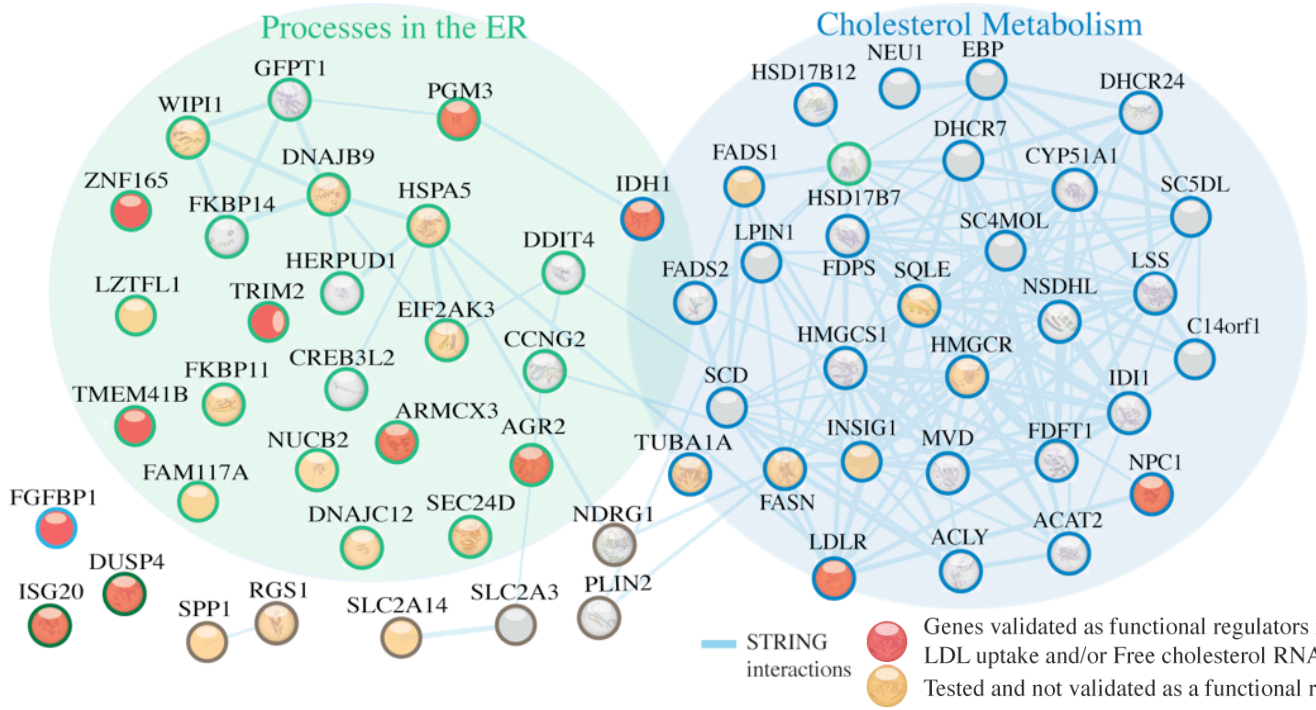
Characterization of gene and drug members of drug-induced transcriptional modules

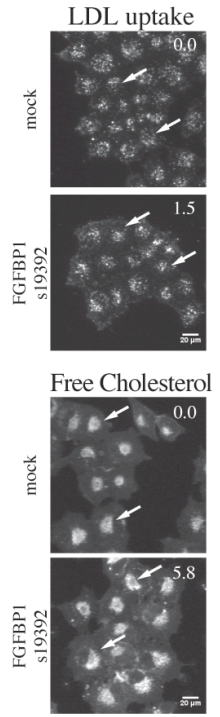


Inferring novel regulators of cellular cholesterol levels using drug-induced transcriptional modules

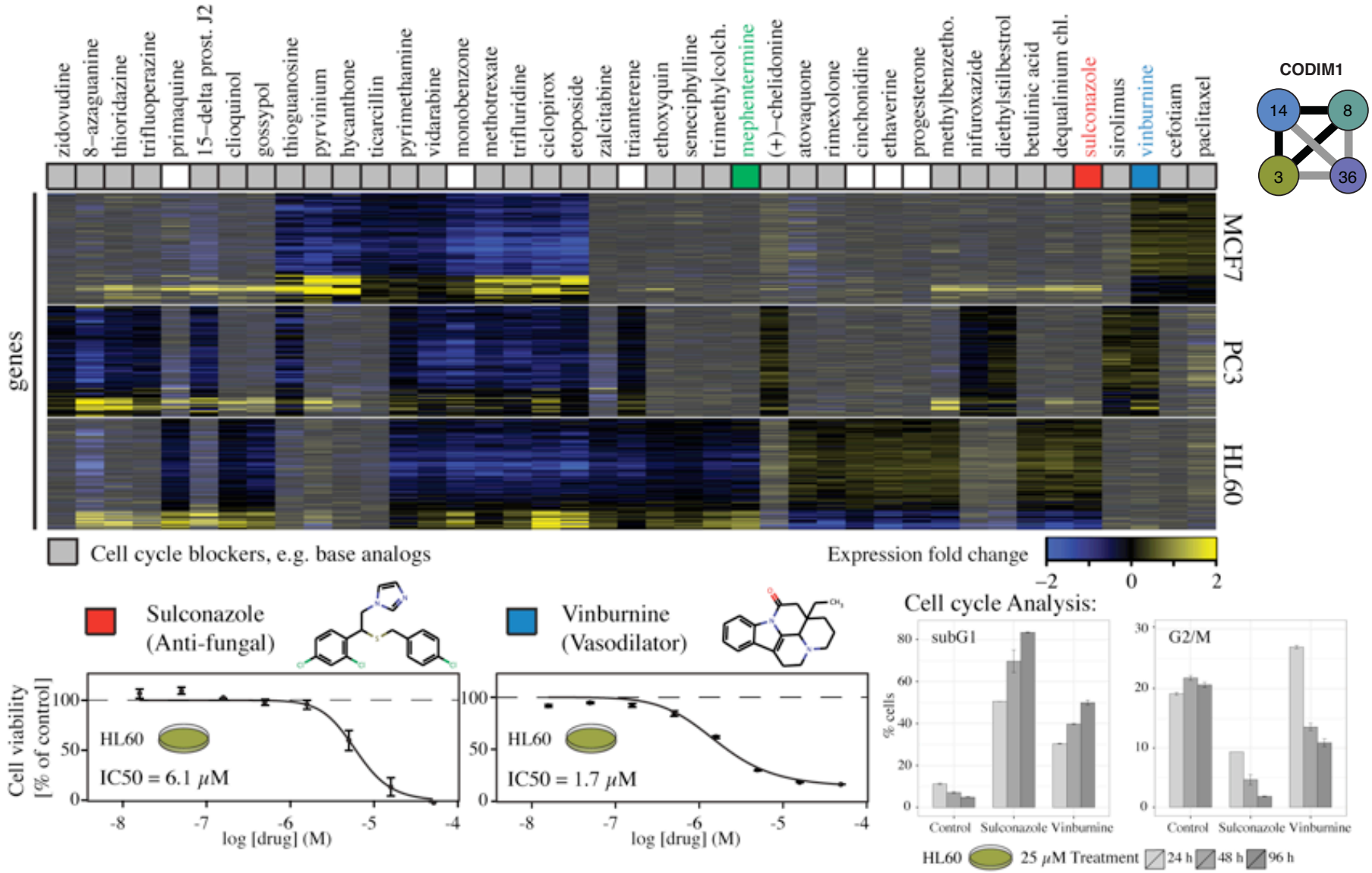




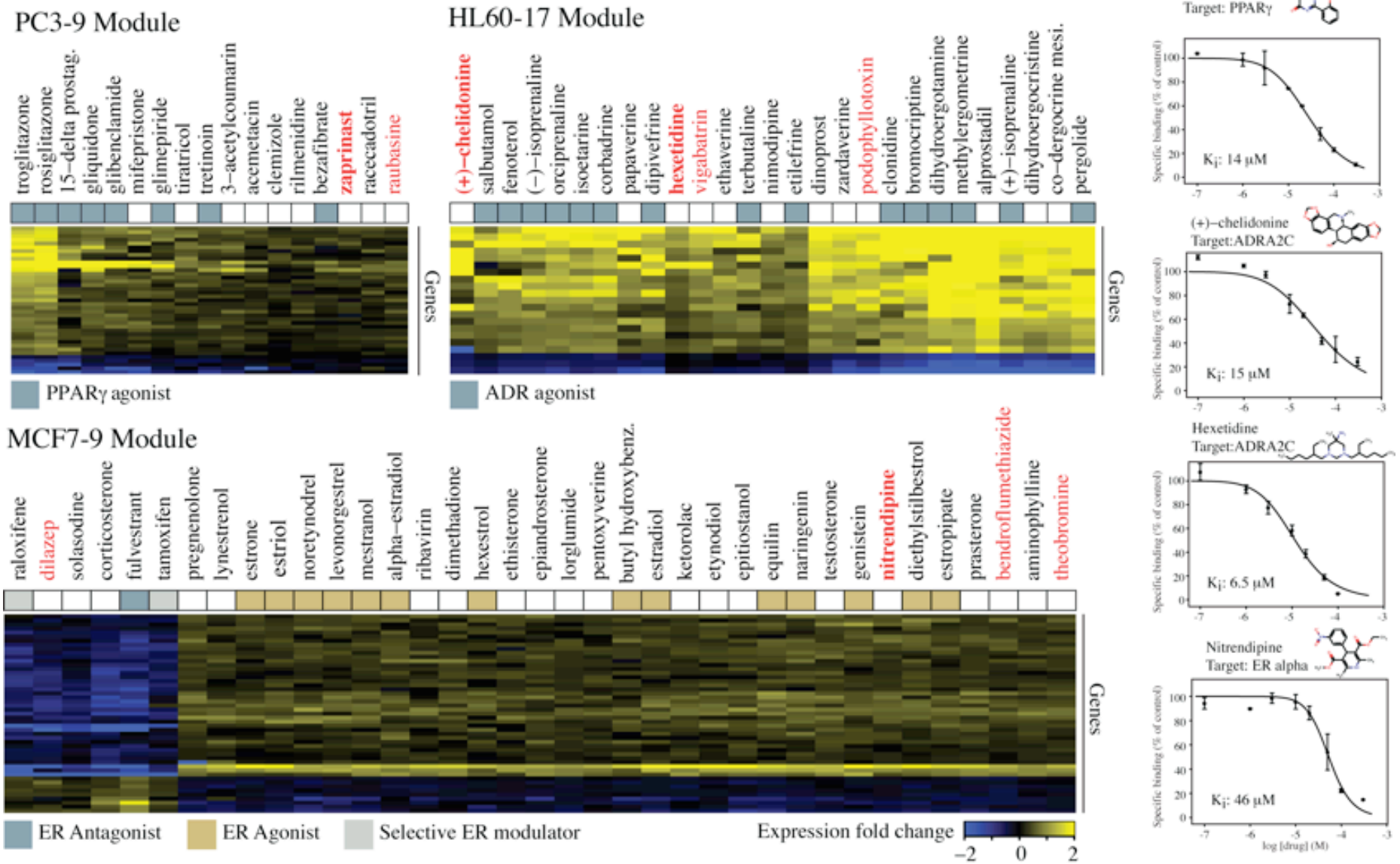




Prediction and confirmation of novel cell-cycle inhibitors via drug-induced transcriptional modules



Identification of novel drug-target relations using cell line-specific drug-induced transcriptional modules



Conclusions II

- Our analysis framework has delineated the modular architecture of regulatory networks in mammalian cells perturbed with various drugs, resulting in a compendia of drug-induced transcriptional modules.

- Drug-induced transcriptional modules are conserved across cell lines (72%) and organisms (15%).

- Drug-induced modules can be used to infer gene function (e.g. novel regulators of cholesterol levels) and drug action (e.g. new cell cycle blockers and new modulators of PPARγ, ADRA2C and ERα).

- Drug-induced transcriptional modules can be regarded as transcriptional markers for specific (off-) targets or side effects to systematically evaluate the efficacy and safety of new chemicals during early drug development.

Acknowledgements

Peer Bork

Vera van Noort
Georg Zeller
Kasia Kaminska
Bork Group

Helmholtz Zentrum München
Monica Campillos

Technical University of Dresden
Michael Kuhn

Collaborators

EMBL
Structural & Computational Biology
Anne-Claude Gavin

Cell biology and Biophysics
Peter Blattmann
Rainer Pepperkok

University of Copenhagen
Lars Juhl Jensen