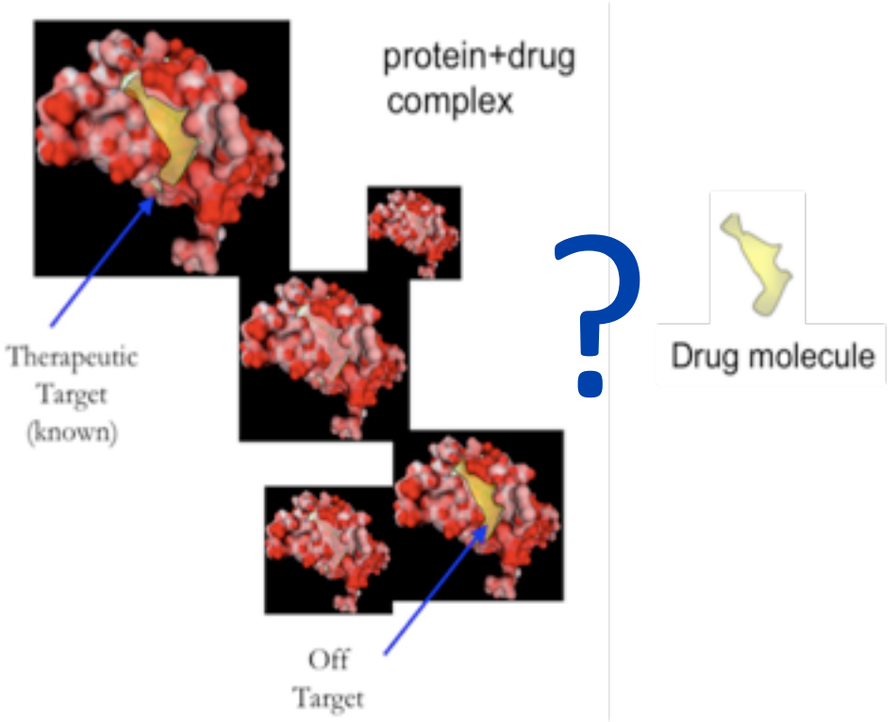
Reviews in Computational Biology

Genome-Based Drug Discovery and Re-Purposing: a new golden age for DNA microarrays?

Francesco Iorio

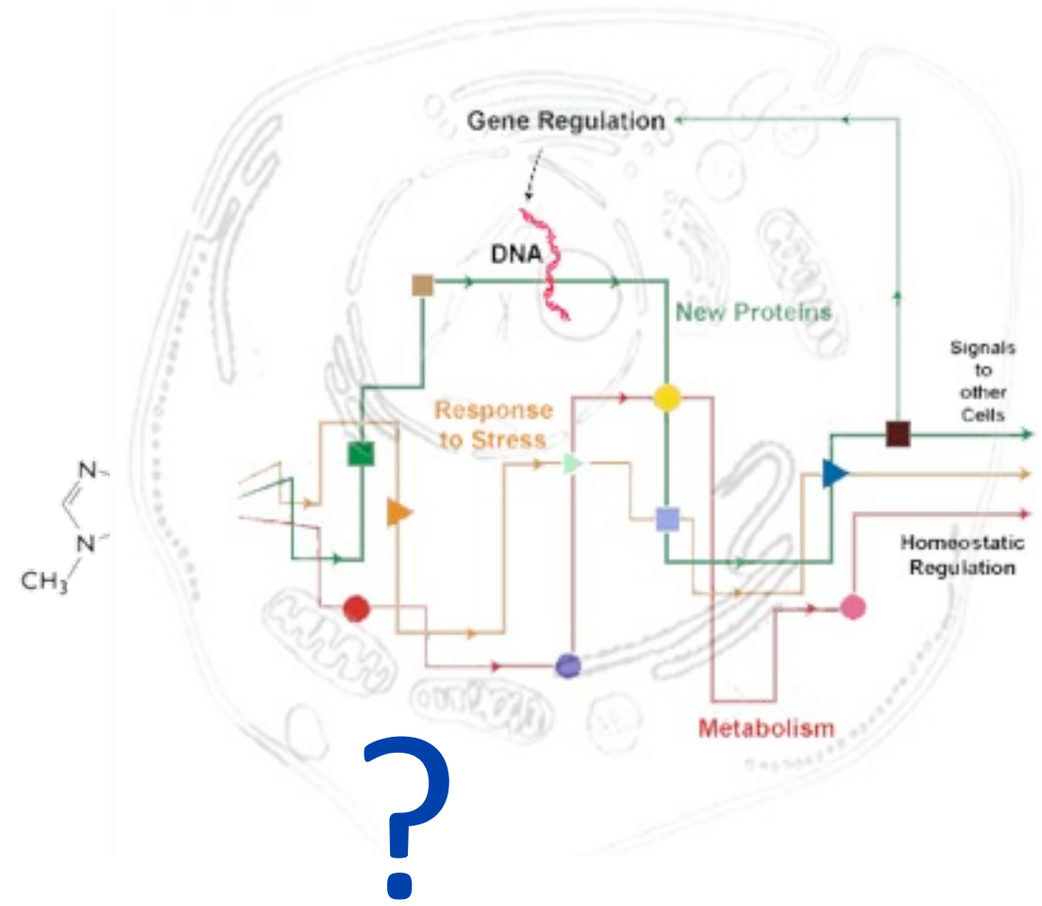
February 2012

Drug (Mode of Action) Discovery



Identifying the molecular pathways targeted by a compound and its off-target effects

Dissecting what follows the drug/substrate interaction



Drug Re-Purposing

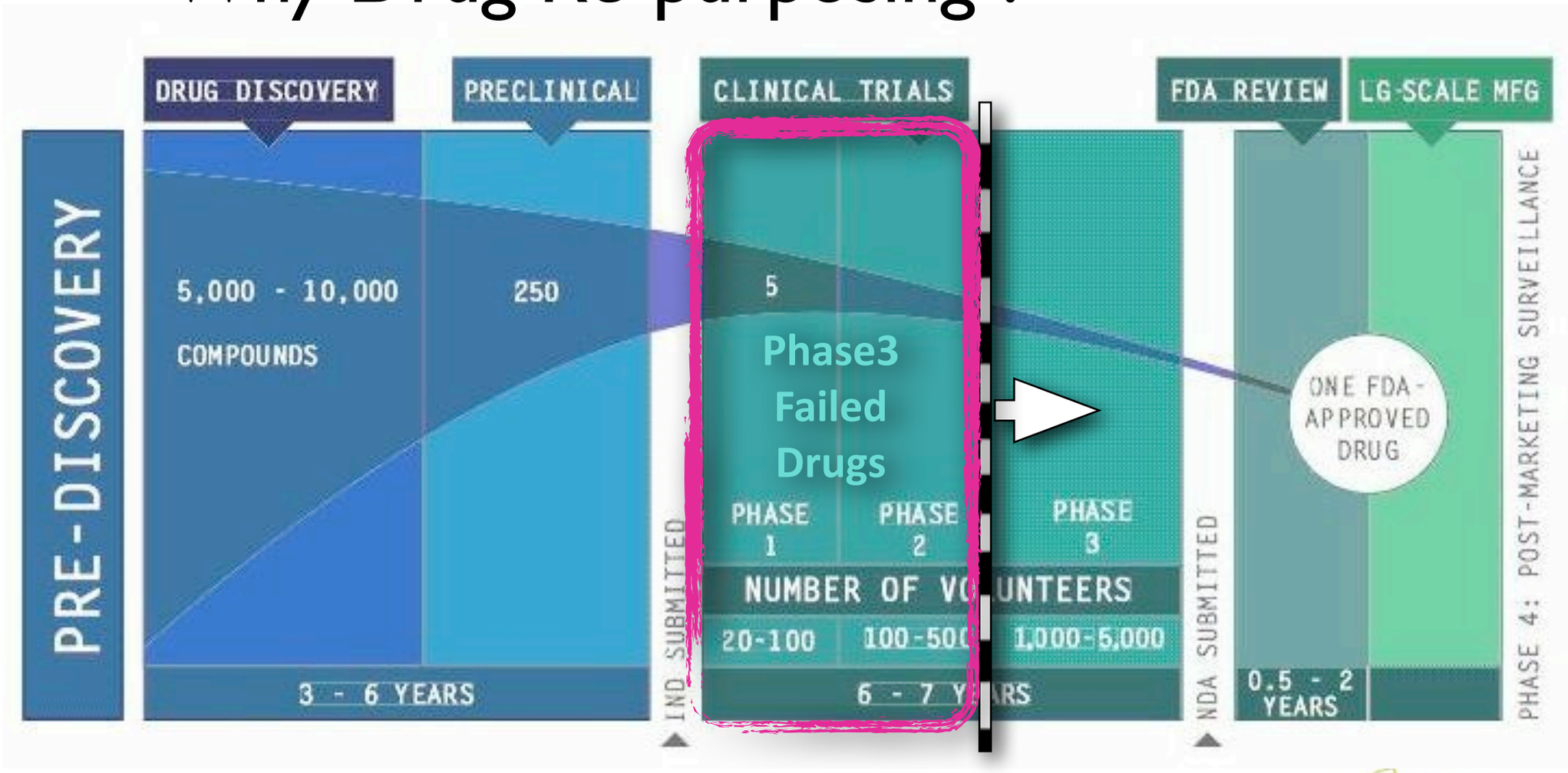
"The most fruitful basis for the discovery of a new drug is to start with an old drug."
(Nobel laureate James Black)

Application of known (safe and approved) drugs to new therapeutic indications

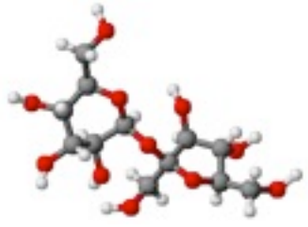
Famous Examples: **Raloxifene**, **Thalidomide**, **Sildenafil**

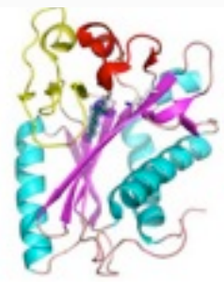
Why Drug Re-purposing ?

Drug re-positioning is easier, cheaper and faster



Drug discovery pipelines have been typically guided by knowledge of ***disease mechanisms***, ***chemical structures of drug candidates*** and ***targets***

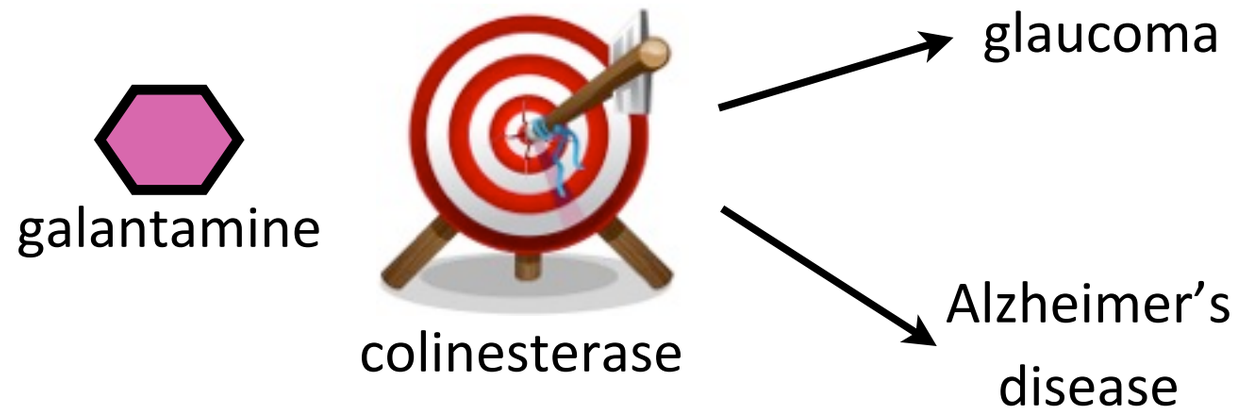


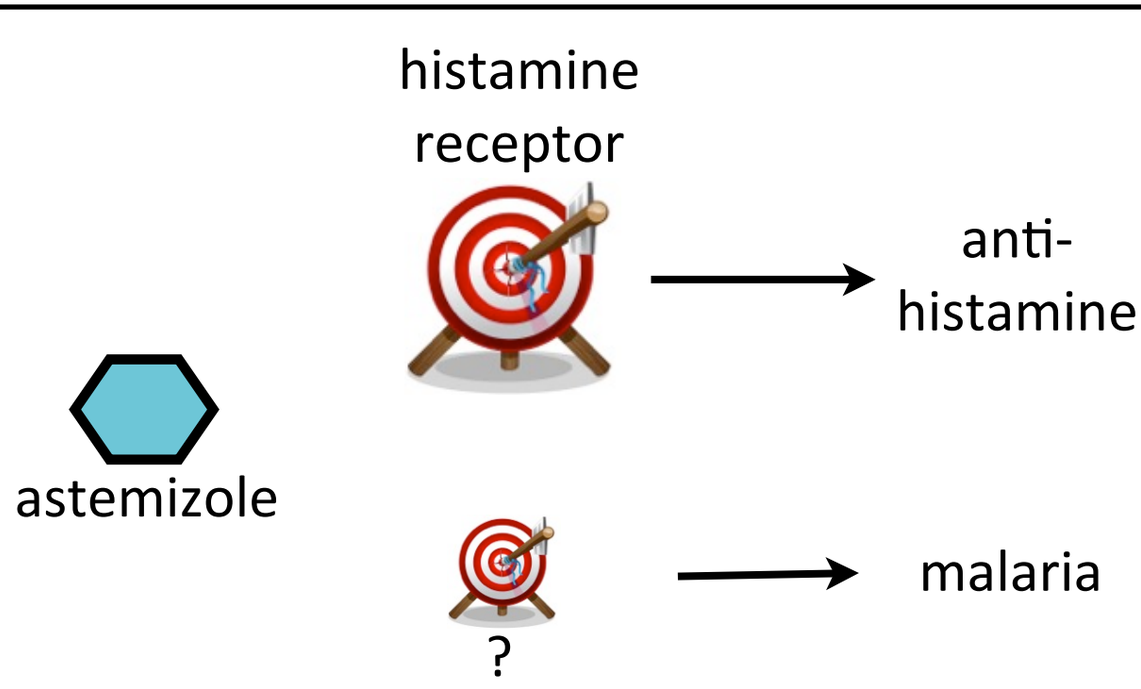


High-Throughput Screening: test hundreds of thousands of compounds a day for activity against the target protein. ***Successful identification of drug candidates*** but with ***increased process costs***

on- and off- target Drug Re-Purposing

on target drug re-purposing





off target drug re-purposing

Exploiting drug–disease relationships for computational drug repositioning

Joel T. Dudley, Tarangini Deshpande and Atul J. Butte

DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical–protein interactome

Heng Luo[1], Jian Chen[1], Leming Shi[2], Mike Mikailov[3], Huang Zhu[1], Kejian Wang[1], Lin He[1,4,5,*] and Lun Yang[1,2,4,*]

PHARMACOLOGY

The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics

Ruili Huang*, Noel Southall*, Yuhong Wang, Adam Yasgar, Paul Shinn, Ajit Jadhav, Dac-Trung Nguyen and Christopher P. Austin†

A Computational Approach to Finding Novel Targets for Existing Drugs

Yvonne Y. Li*, Jianghong An, Steven J. M. Jones

DRUG REPOSITIONING

Genetic signatures uncover new uses

Drug repositioning for orphan diseases

Divya Sardana, Cheng Zhu, Minlu Zhang, Ranga C. Gudivada, Lun Yang and Anil G. Jegga

Submitted: 12th December 2010; Received (in revised form): 18th February 2011

Drug repositioning in the treatment of malaria and TB

Cheminformatic/bioinformatic analysis of large corporate databases: Application to drug repurposing

William Loging*, Raul Rodriguez-Esteban, Jon Hill, Tom Freeman, John Miglietta

TRANSLATIONAL GENETICS

Signatures for drug repositioning

Old friends in new guise: repositioning of known drugs with structural bioinformatics

V. Joachim Haupt and Michael Schroeder

PERSPECTIVE

GENOMIC MEDICINE

The Emergence of Genome-Based Drug Repositioning

Yves A. Lussier[1,2,3]* and James L. Chen[4]*

Literature mining, ontologies and information visualization for drug repurposing

Christos Andronis, Anuj Sharma, Vassilis Virvilis, Spyros Deftereos and Aris Persidis

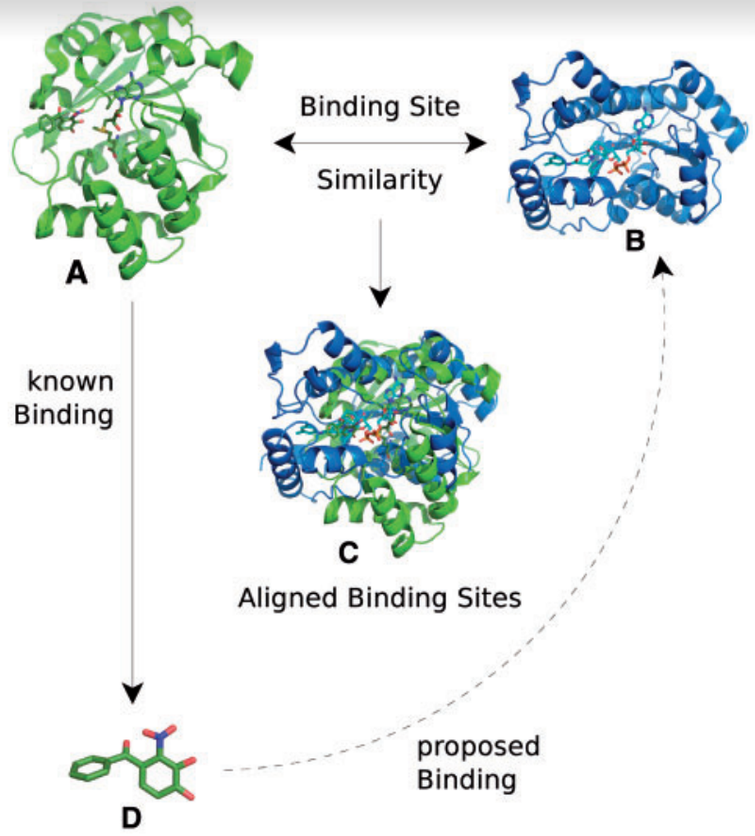
“Guilt-by-association” approaches

Structural Bioinformatics

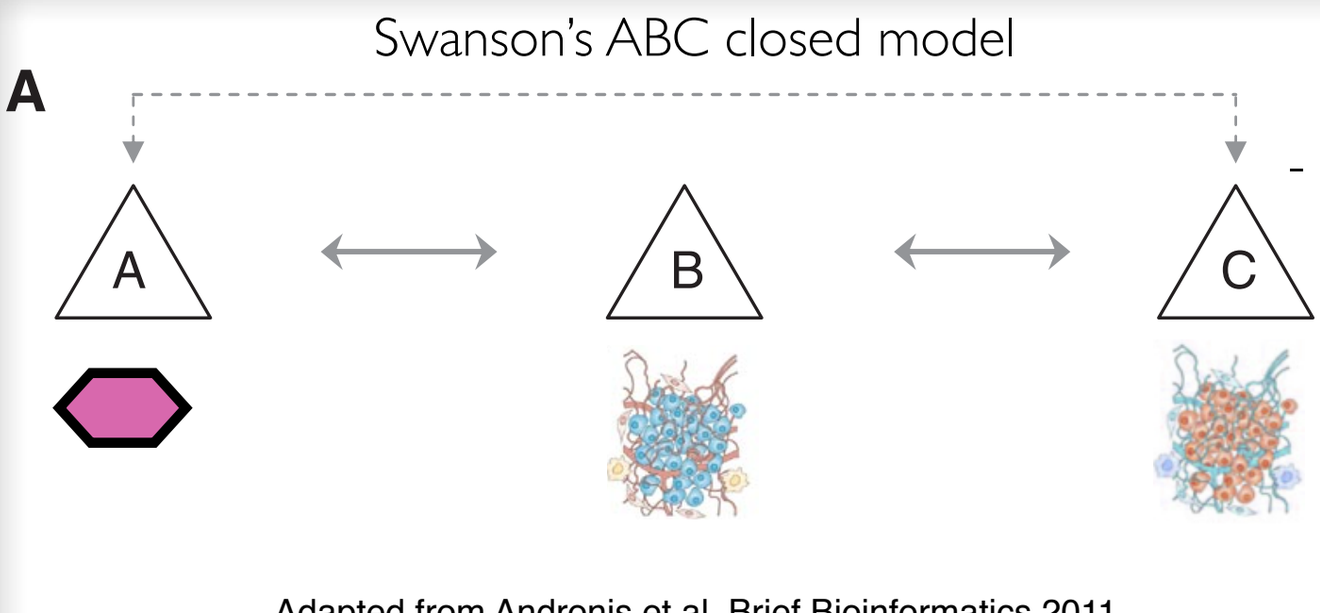
Exploiting binding site similarities between therapeutic targets

- **A** is a targeted by **D** to treat disease **1**
- **B** is a therapeutic target for disease **2**
- **A** is “similar” to **B**

D could be re-positioned for disease **2**



Haupt et al, Brief Bioinformatics 2011



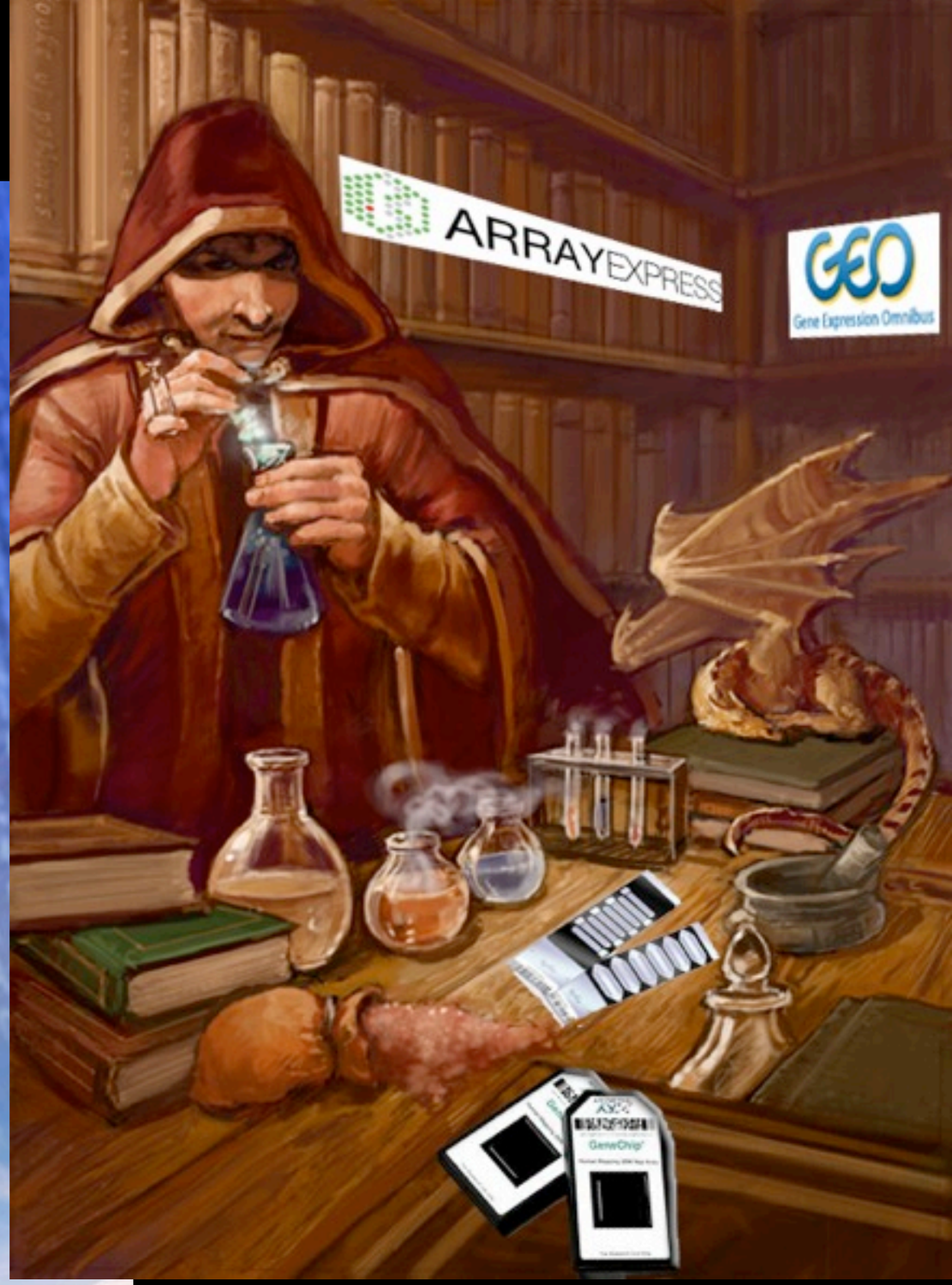
Adapted from Andronis et al, Brief Bioinformatics 2011

Text-Mining

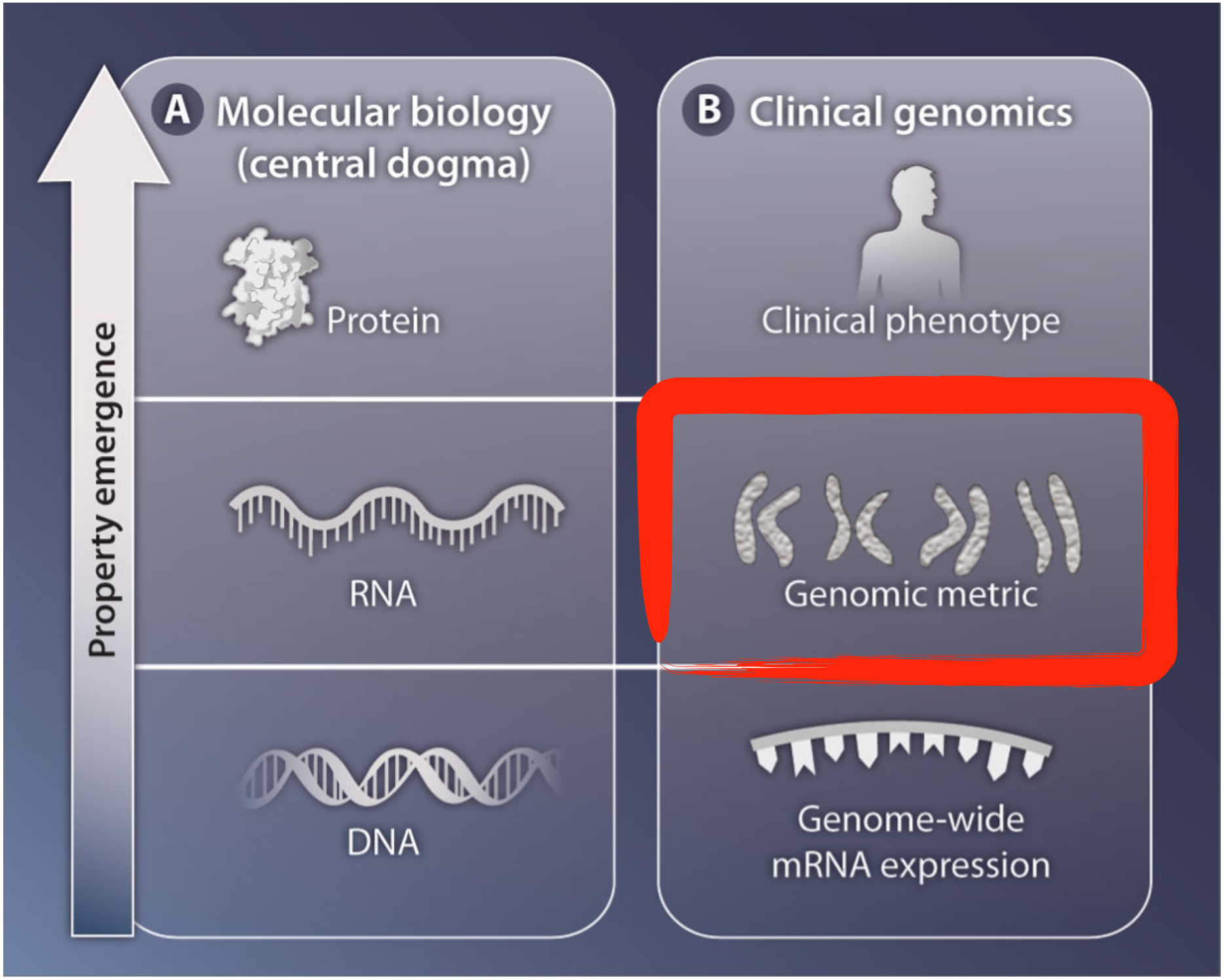
- Concept **A** (drug) is linked to concept **B** (disease 1)
- Concept **B** is linked to concept **C** (disease 2)

Concept **A** is implicitly linked
(could be re-positioned) to **C**

“Guilt-by-association” for drug re-positioning on other kind of data?

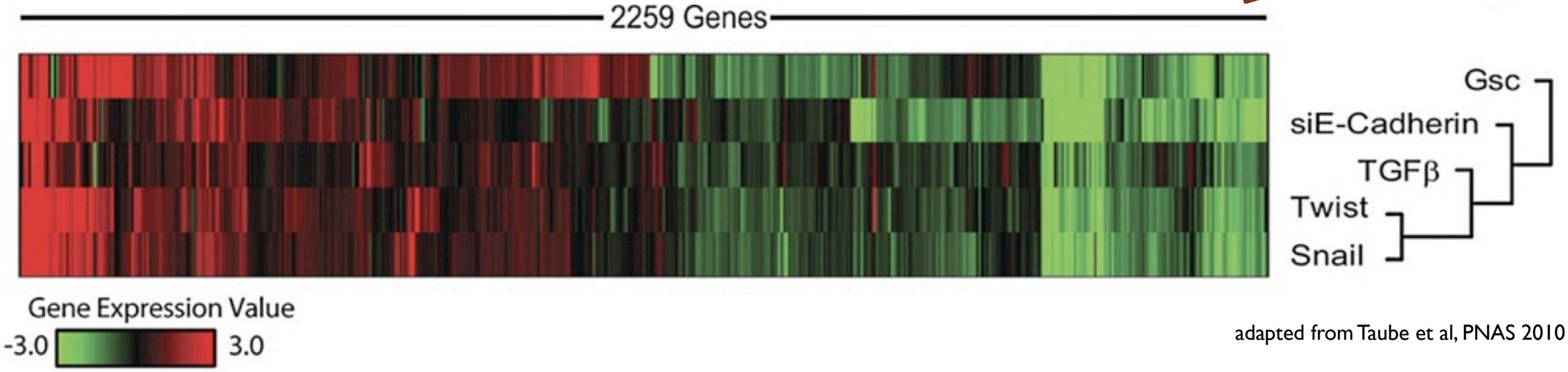

ARRAYEXPRESS
GEO
Gene Expression Omnibus

Genomic-Metrics on Transcriptional Data to Summarize clinical Phenotypes



The Emergence of Genome-Based Drug Repositioning Lussier and Chen, Sci Trans Med 2011

Leading Idea:
Every biological state can be described by a given gene expression signature



adapted from Taube et al, PNAS 2010

Harrison, C. ***Translational genetics: Signatures for drug repositioning***. Nat Rev Genet, 2011.

Lukk, M et al. ***A global map of human gene expression***. Nat Biotech, 2010.

Dudley, J.T. et al. ***Disease signatures are robust across tissues and experiments***. Mol Sys Biol, 2009.

Culhane, A.C. et al. ***GeneSigDB--a curated database of gene expression signatures***. Nucleic Acids Res, 2009.

Nevins, J.R. & Potti, A. ***Mining gene expression profiles: expression signatures as cancer phenotypes***. Nat Rev Genet, 2007.

Lamb, J. et al. **The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease**. Science, 2006.

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Bibliography

Gene expression signatures

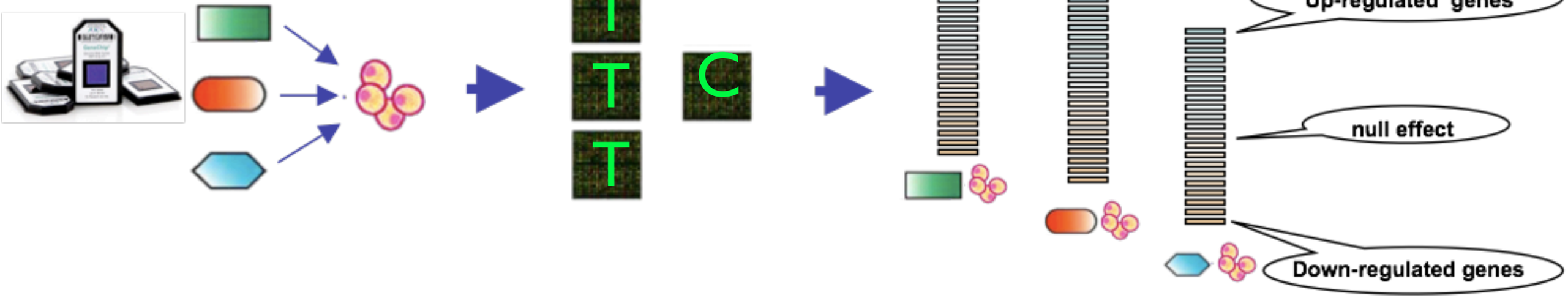
*** Nevins, J. R. & Potti, A. Mining gene expression profiles: expression signatures as cancer phenotypes. Nat Rev Genet 8, 601–609 (2007).

*** Dudley, J. T., Tibshirani, R., Deshpande, T. & Butte, A. J. Disease signatures are robust across tissues and experiments. 5, 1–8 (2009).

* Harrison, C. Translational geneticsSignatures for drug repositioning. Nat Rev Genet 12, 668–669 (2011).

CONNECTIVITY MAP

The first large reference dataset of transcriptional responses to drug



small molecules: 1309 perturbagens tested (FDA approved and nondrug bioactive compounds)

cell lines:
MCF7 (human epitelial breast cancer)
PC3 (human epitelial prostate cancer)
HL60 (human leukemia)
SKMEL5 (human melanoma)
ssMCF7 (MCF7 grown in a different veichle)

concentration and treatment
10mM (when the optimal concentration is unknown) x 6h

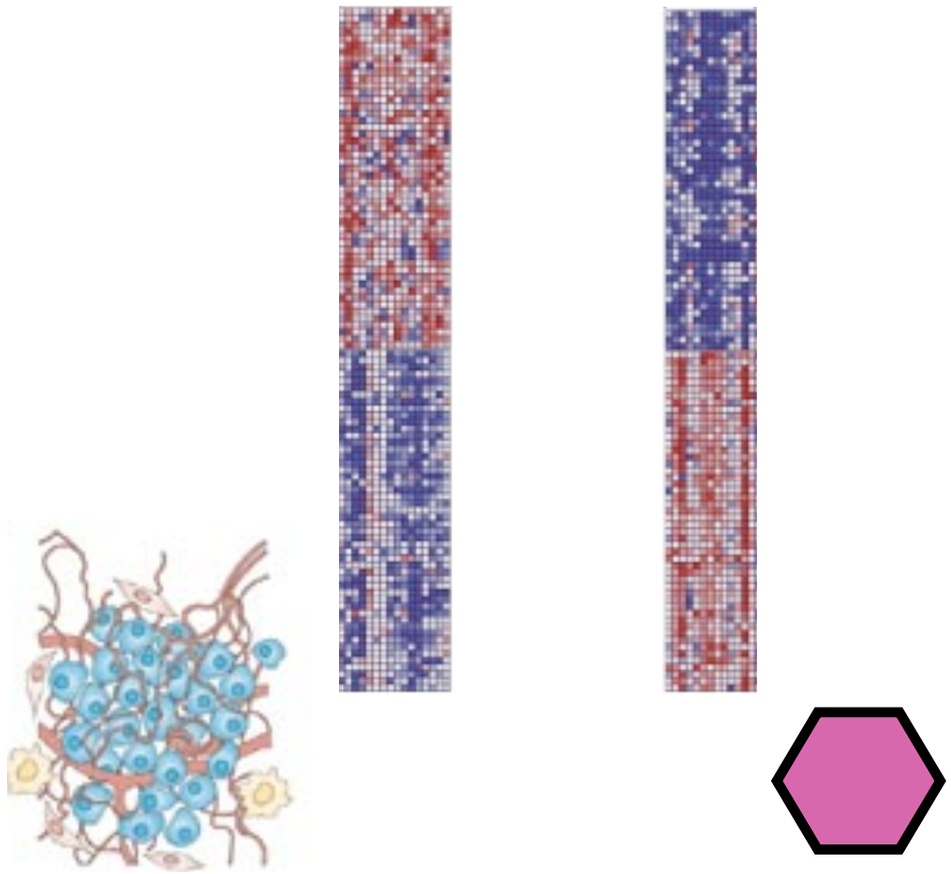
Negative Control
cells in the same plate and treated with vehicle alone (medium, DMSO…)

Lamb, J. ***The Connectivity Map: a new tool for biomedical research***. Nat Rev Cancer 7, 54-60 (2007).
Lamb, J. et al. ***The Connectivity Map: using gene-expression signatures to connect small molecules, genes, and disease***. Science 313, 1929-1935 (2006).

Genome-Based drug re-purposing approaches

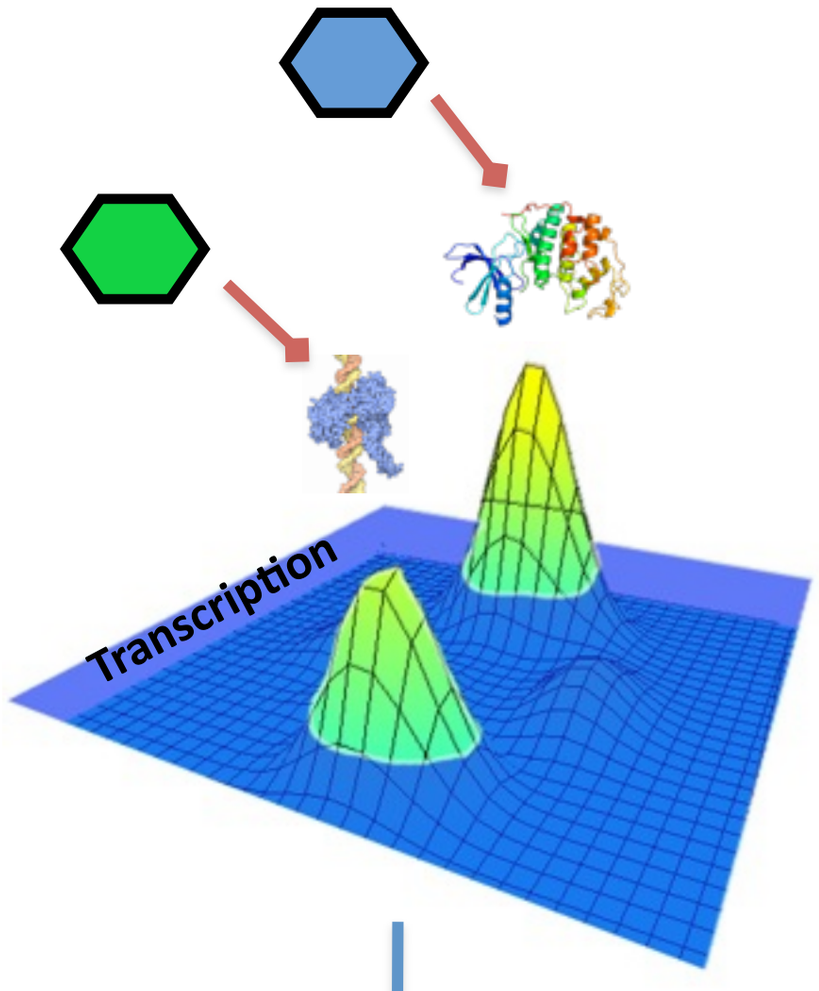
Disease signature

Drug Response Signature



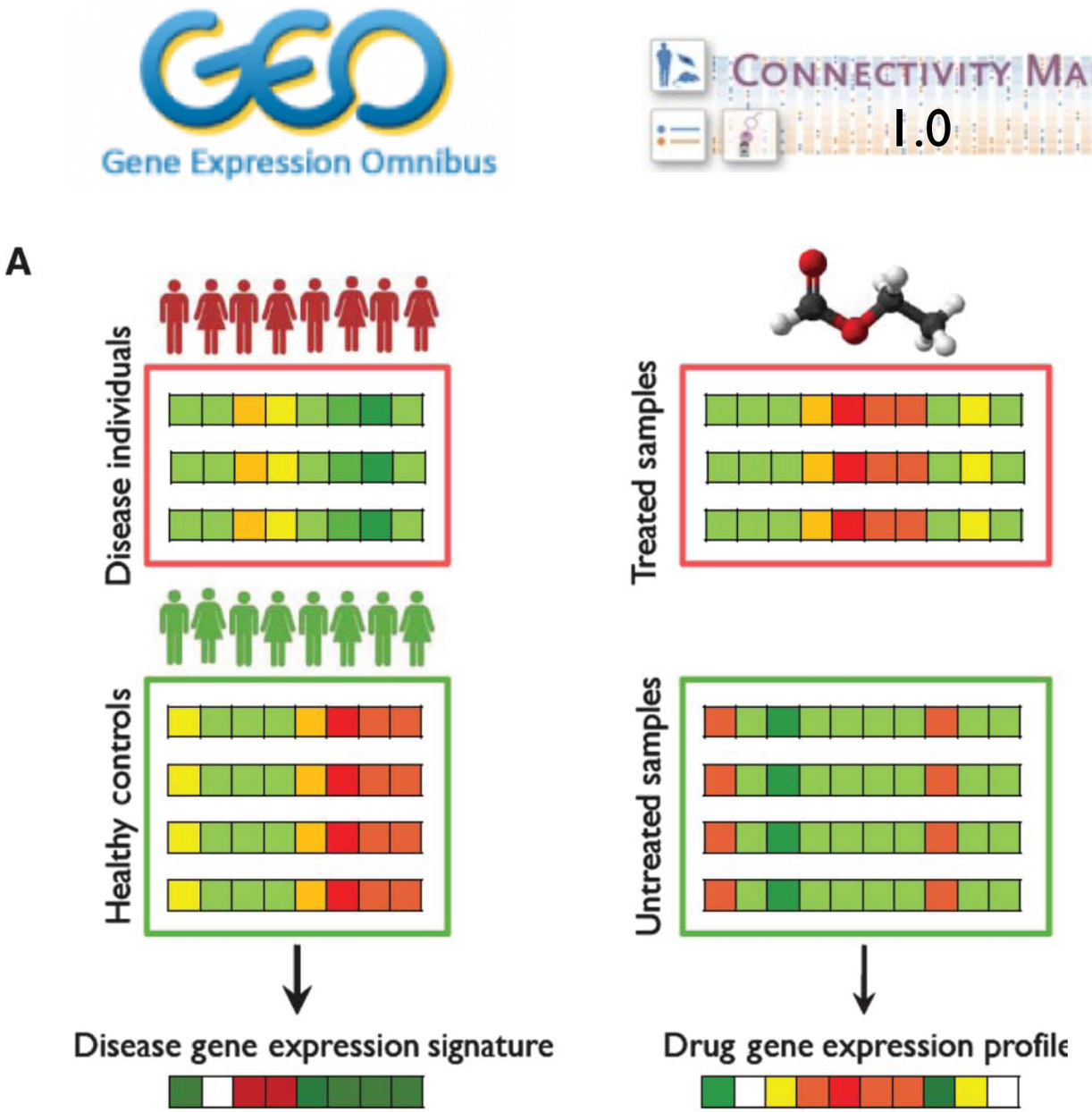
1
Drugs able to “revert” a phenotype signature could “revert the phenotype”

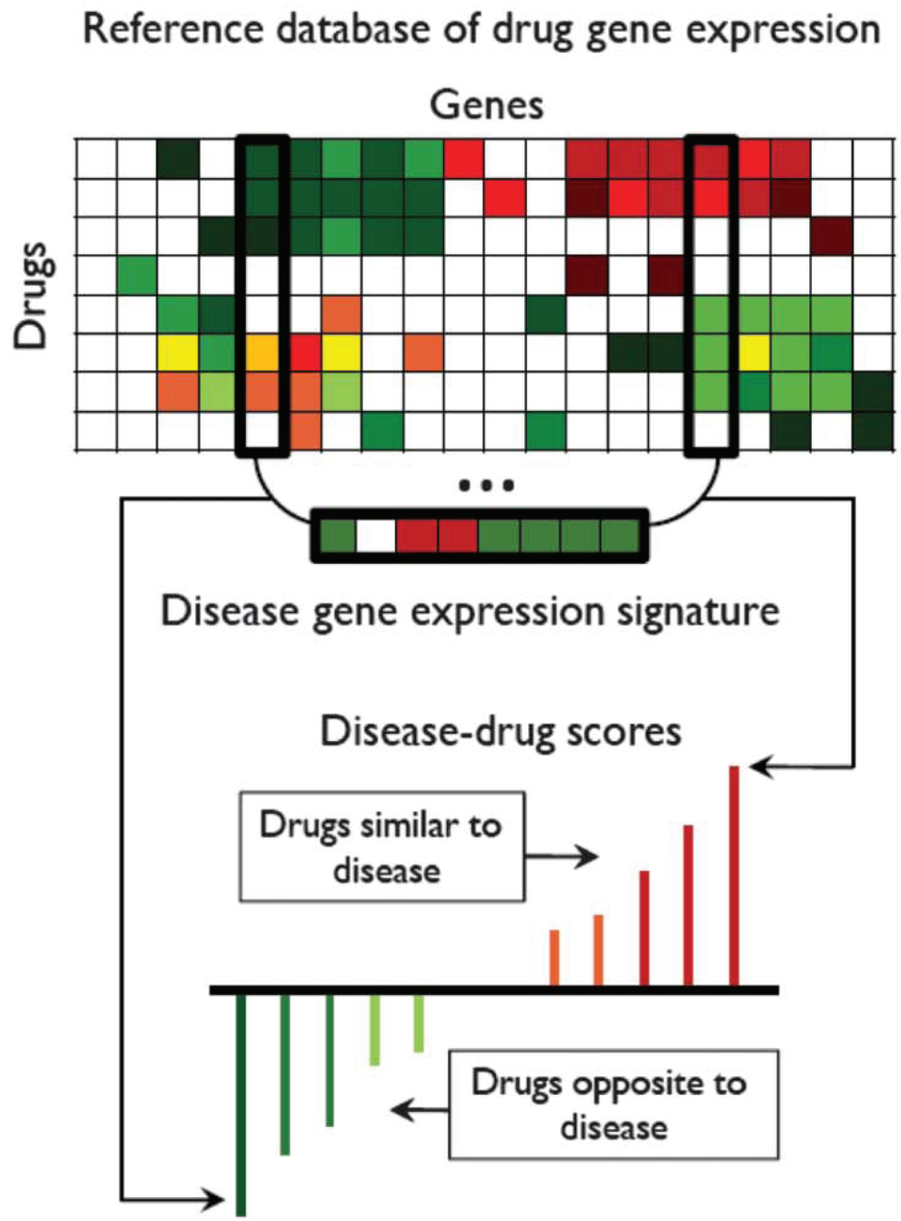
2
Drugs eliciting similar transcriptional responses could share therapeutic effects



Therapeutic Effect

Drugs “reverting” a phenotype signature “revert the phenotype”



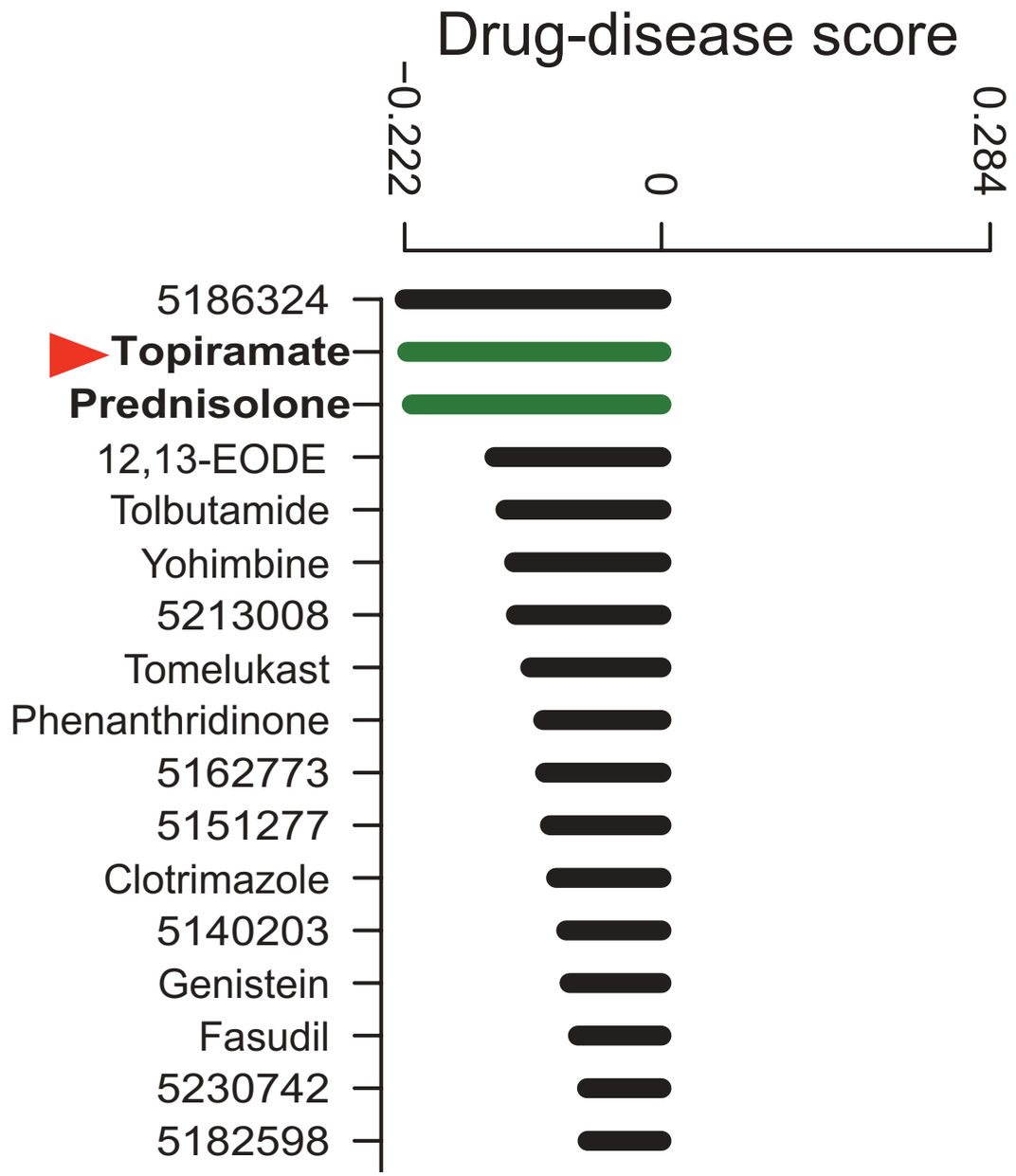


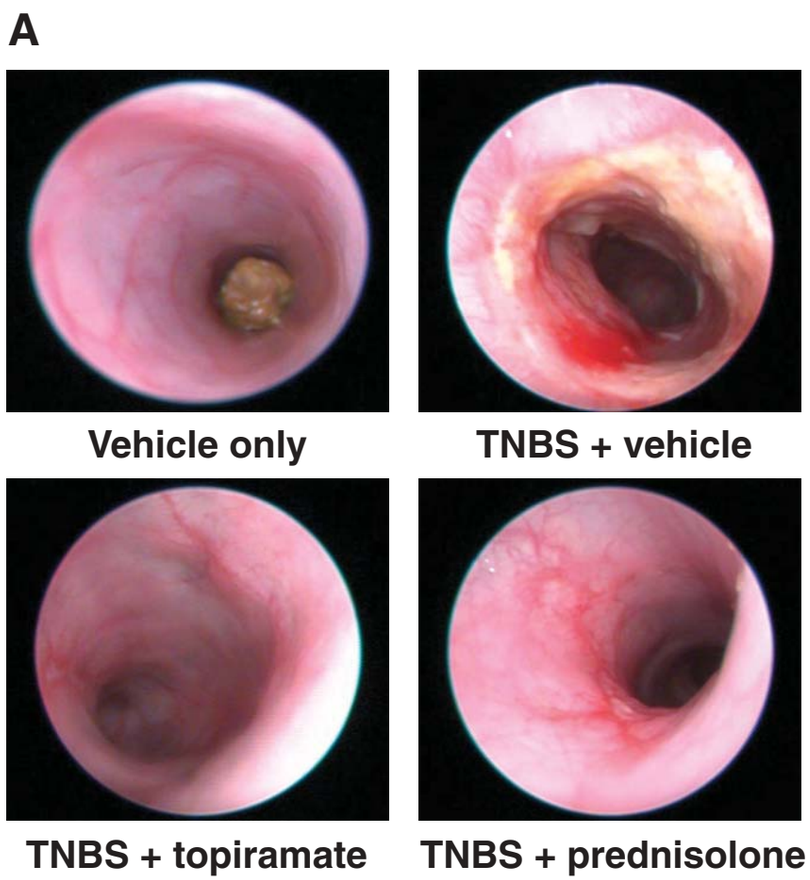
Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data

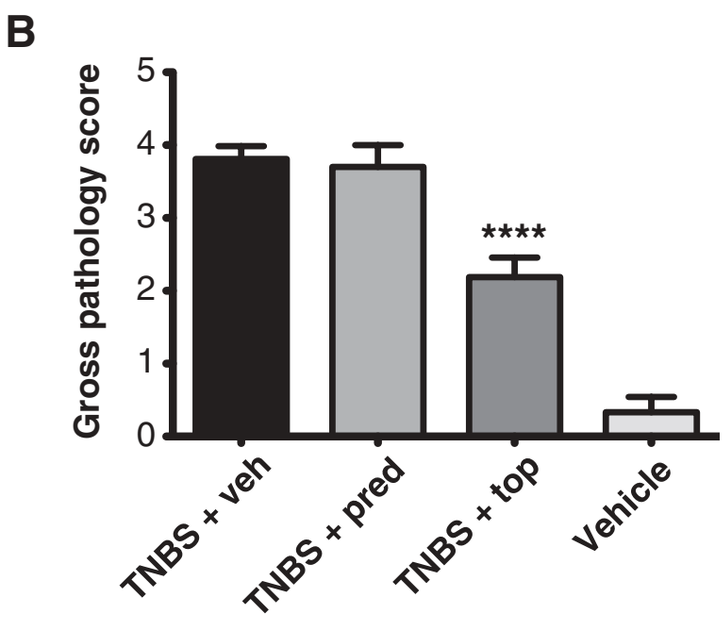
Sirota et al, Sci Trans Med 2011

Drugs “reverting” a phenotype signature “revert the phenotype”

* Prednisolone = established compound for Crohn’s disease
** Trinitobenzene Sulfonic Acid (TNBS)







Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease

Dudley et al, Sci Trans Med 2011

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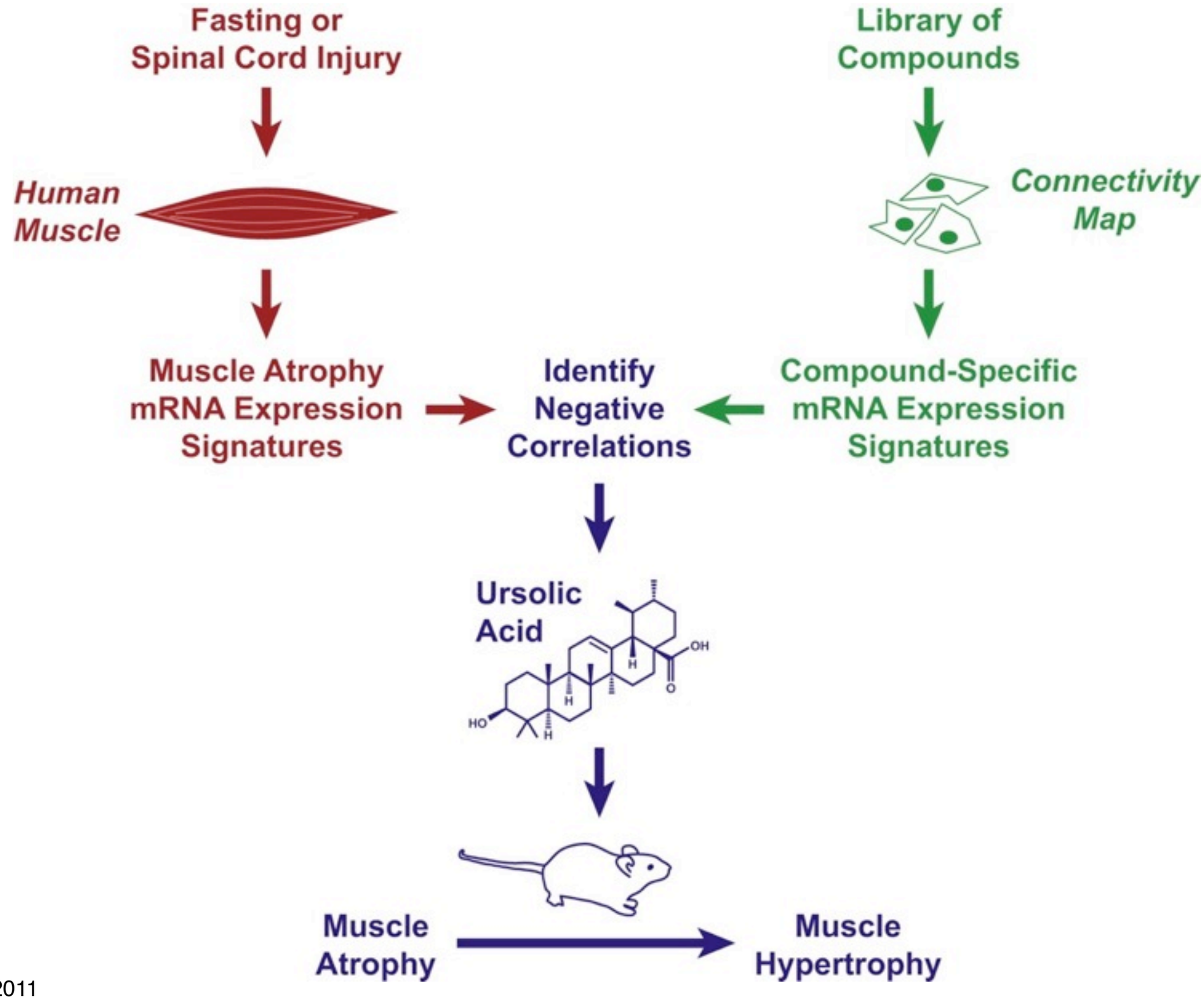


Kunkel et al, Cell 2011

mRNA Expression Signatures of Human Skeletal Muscle Atrophy Identify a Natural Compound that Increases Muscle Mass

Bibliography

Disease Signature reversion

*** Dudley, J. T. et al. Computational Repositioning of the Anticonvulsant Topiramate for Inflammatory Bowel Disease. Science Translational Medicine 3, 96ra76–96ra76 (2011).

*** Kunkel, S. D. et al. mRNA Expression Signatures of Human Skeletal Muscle Atrophy Identify a Natural Compound that Increases Muscle Mass. Cell Metabolism 13, 627–638 (2011).

*** Chen, M.-H. et al. Gene Expression-Based Chemical Genomics Identifies Potential Therapeutic Drugs in Hepatocellular Carcinoma. PLoS ONE 6, e27186 (2011).

*** Claerhout, S. et al. Gene expression signature analysis identifies vorinostat as a candidate therapy for gastric cancer. PLoS ONE 6, e24662 (2011).

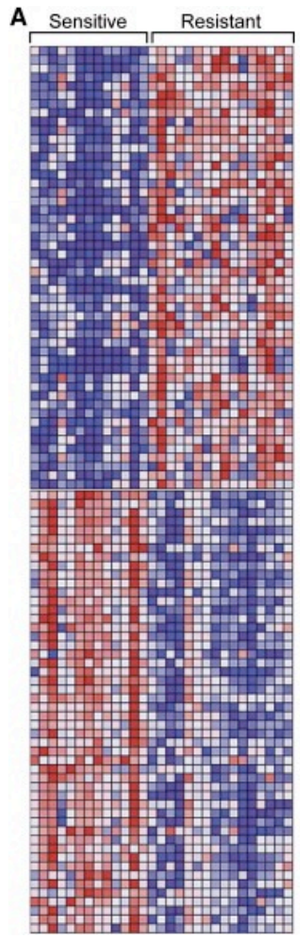
** Sirota, M. et al. Discovery and Preclinical Validation of Drug Indications Using Compendia of Public Gene Expression Data. Science Translational Medicine 3, 96ra77–96ra77 (2011).

** Mcart, D. G. & Zhang, S.-D. Identification of Candidate Small-Molecule Therapeutics to Cancer by Gene-Signature Perturbation in Connectivity Mapping. PLoS ONE 6, e16382 (2011).

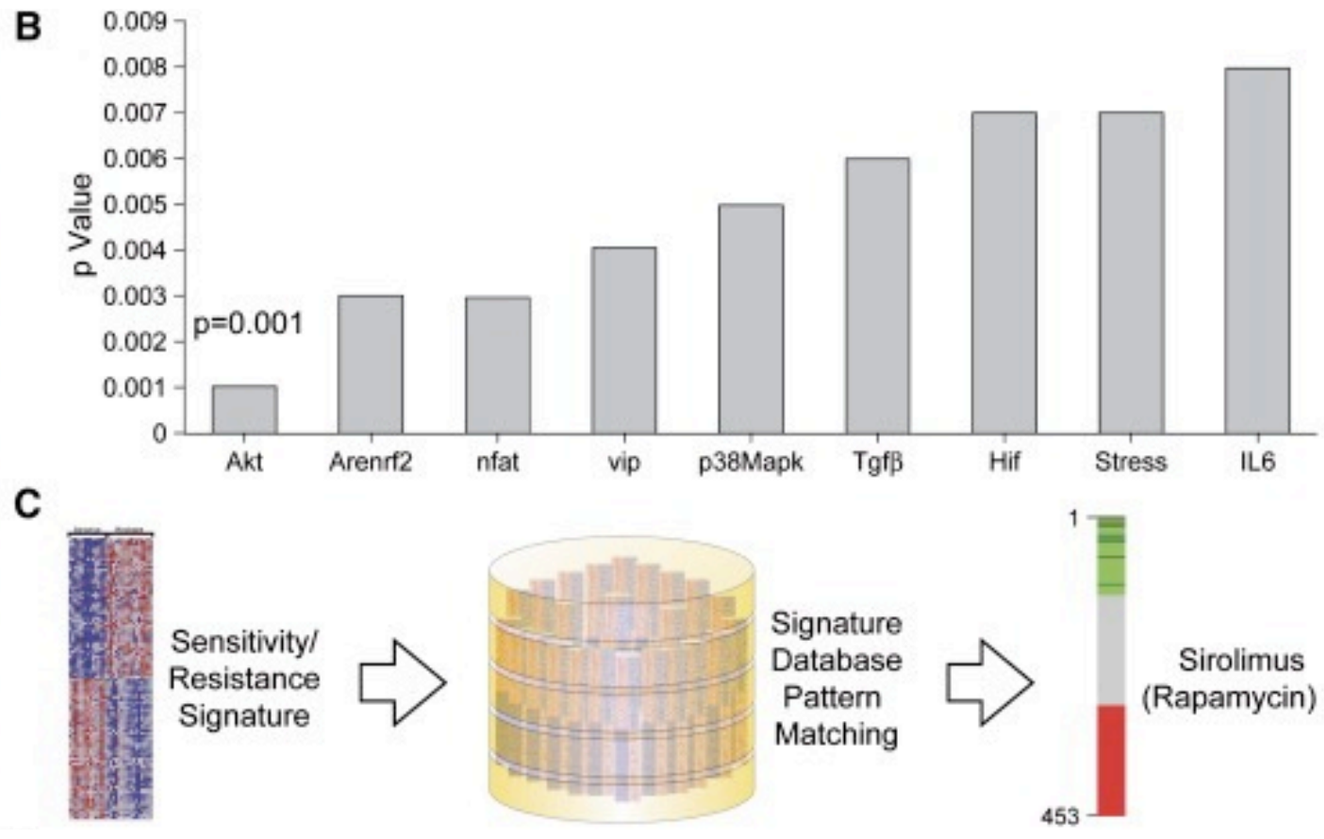
* Lussier, Y. A. & Chen, J. L. The emergence of genome-based drug repositioning. Science Translational Medicine 3, 96ps35 (2011).

Drugs “reverting” “cancer-drug-resistance” signatures could be repositioned as chemo-sensitizers

A,B) Gene expression signature of glucocorticoid resistance in childhood acute lymphoblastic leukemia



C) Query of the Connectivity Map database in order to search for compounds able to “reverse the signature”



Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance Wei et al. Cancer Cell 2006

Chemical genomic screening reveals synergism between parthenolide and inhibitors of the PI-3 kinase and mTOR pathways
Hassane et al. Blood 2010

D) Insights for combined therapy

GLUCOCORTICOIDS + RAPAMYCIN

Bibliography

Synergetic drug pairs identified by signature matching

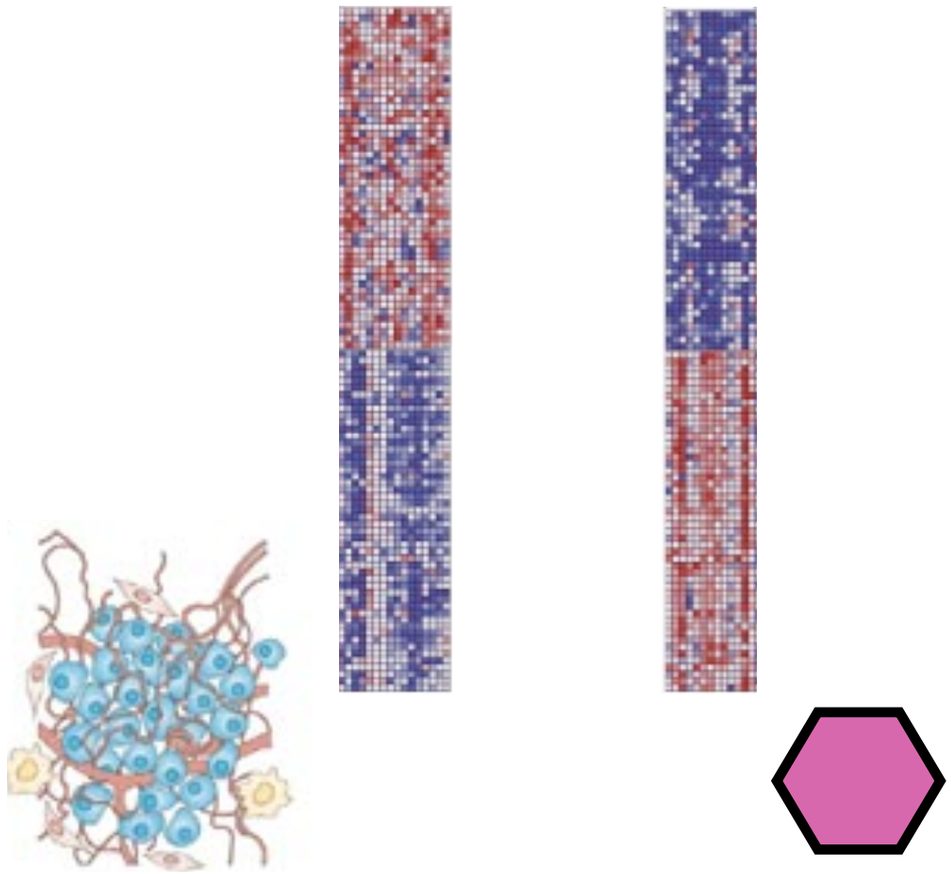
*** Wei, G. et al. Gene expression-based chemical genomics identifies rapamycin as a modulator of MCL1 and glucocorticoid resistance. Cancer Cell 10, 331–342 (2006).

*** Hassane, D. C. et al. Chemical genomic screening reveals synergism between parthenolide and inhibitors of the PI-3 kinase and mTOR pathways. Blood 116, 5983–5990 (2010).

Genome-Based drug re-purposing approaches

Disease signature

Drug Response Signature



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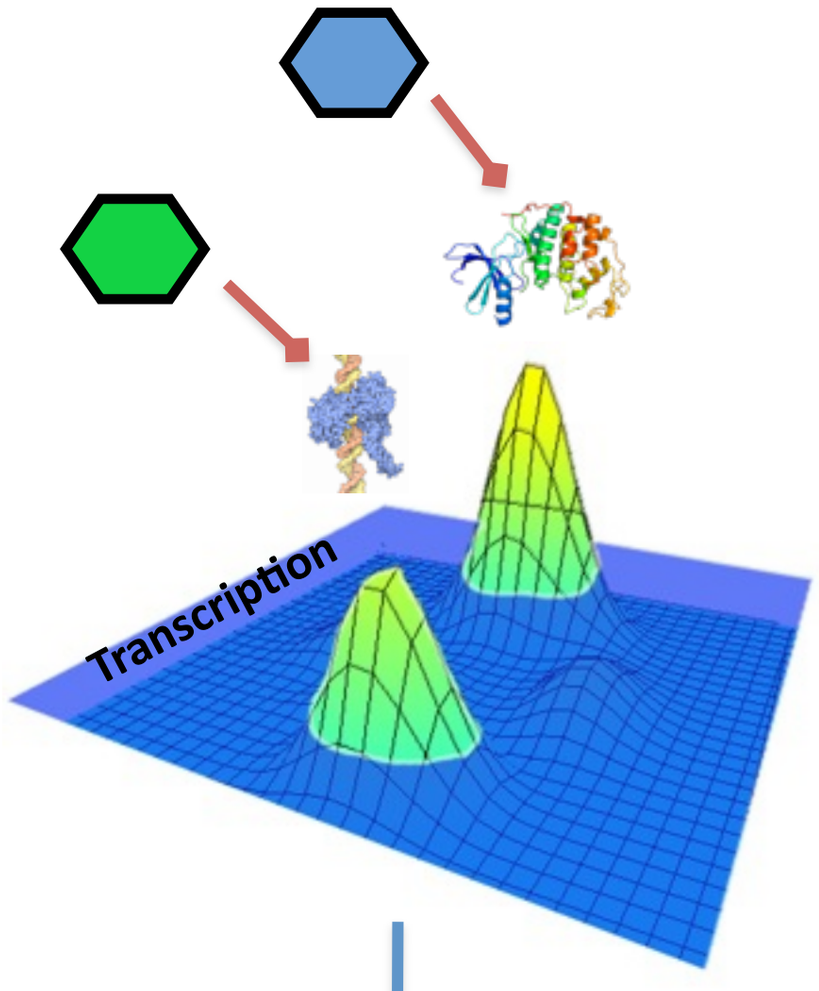
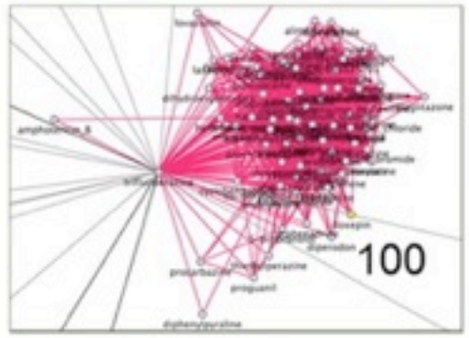
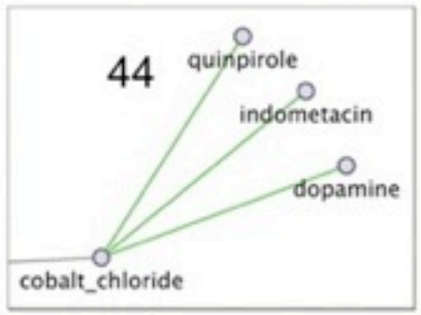


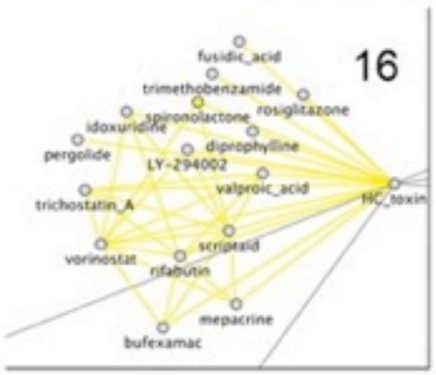
Therapeutic Effect

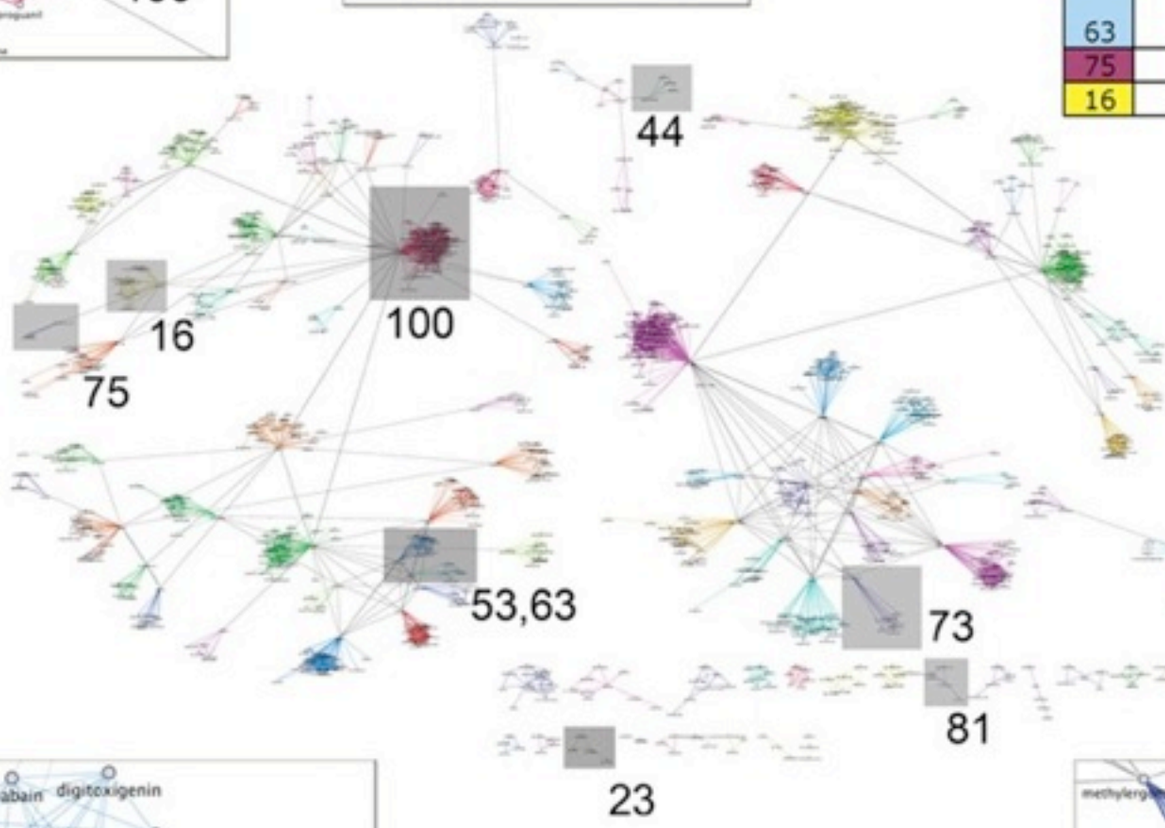
The Drug Network

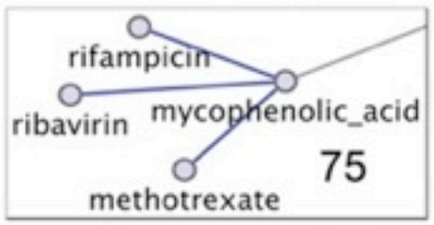


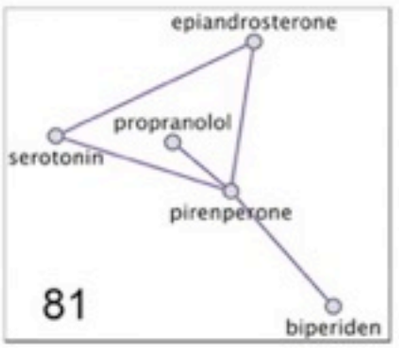


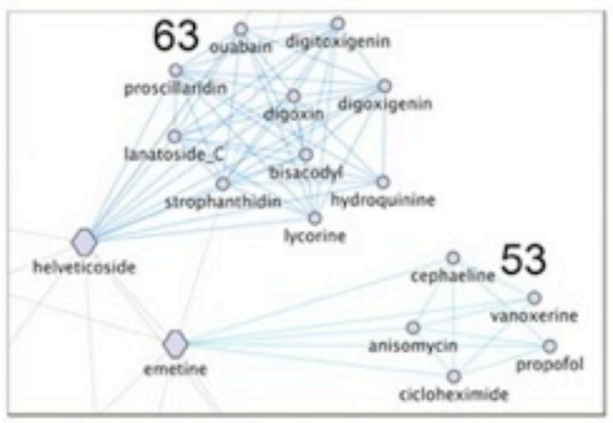
Id.	Most Enriched Function
100	Antipsychotics
23	PGE2 antagonists
44	Dopaminergic Agents
73	Alpha and Beta Adrenergic Modulators
81	Serotonin Receptor Modulators, Antiparkinsonians
53	Protein Synthesis Inhibitors
63	Na+/K+ - ATPase membrane pump inhibitors
75	Antivirals
16	Histone Deacetylase Inhibitors

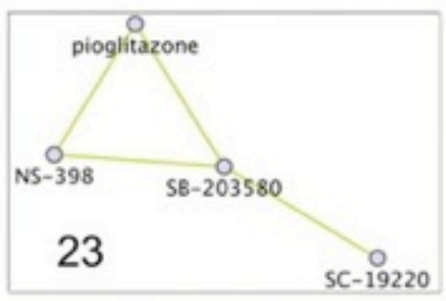


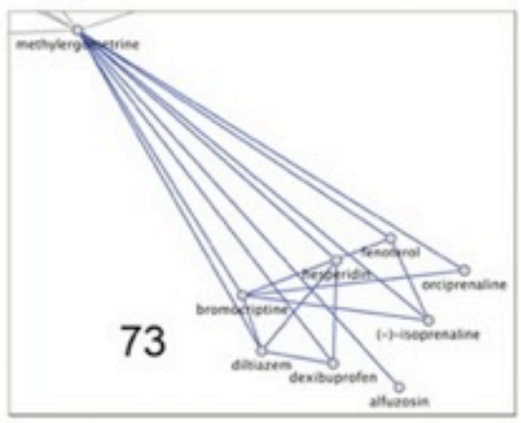






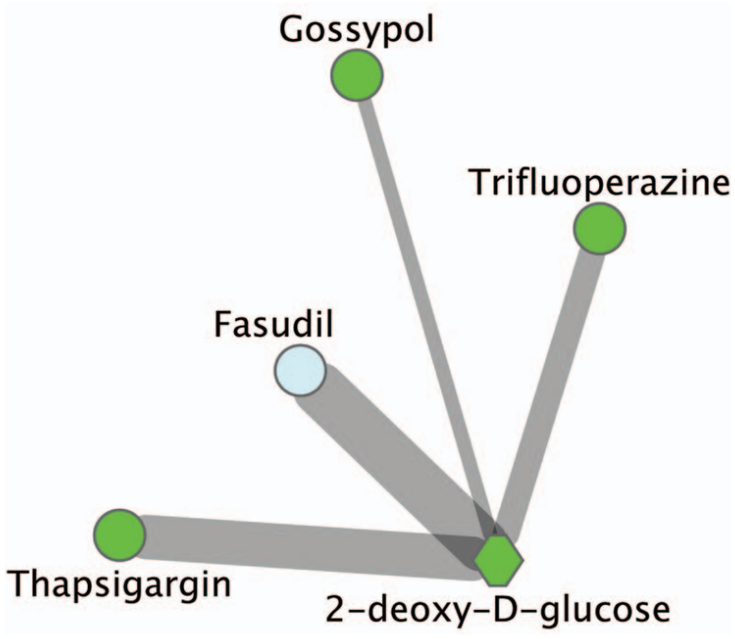






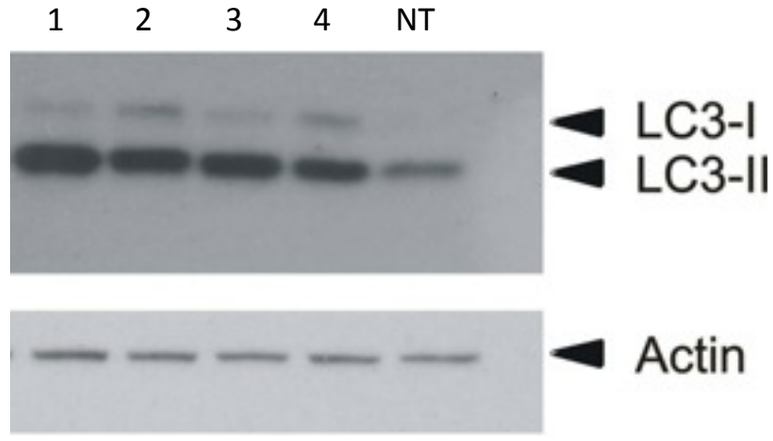
Discovery of drug mode of action and drug repositioning from transcriptional responses Iorio et al, PNAS 2010

Drugs eliciting similar signatures share therapeutic effects



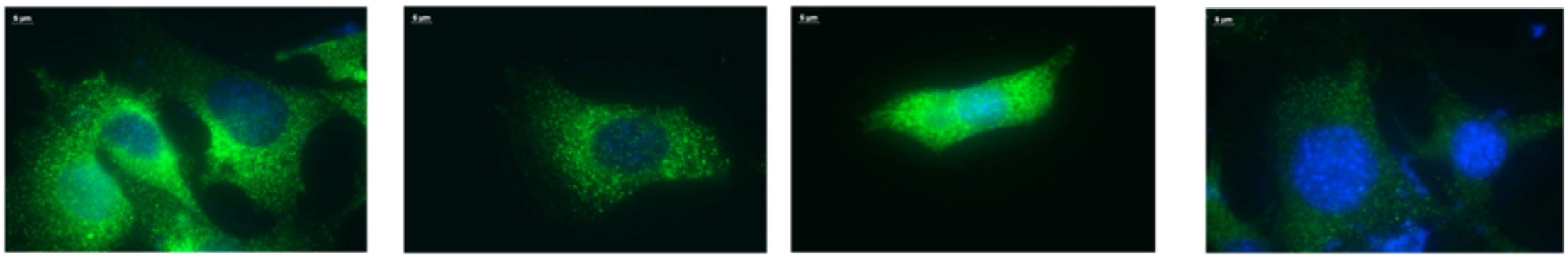
2DOG neighborhood

1	Fasudil	0.5162
2	Thapsigargin	0.5644
3	Trifluoperazine	0.577
4	Gossypol	0.633
5	Niclosamide	0.6539
...	...	...



Iorio et al, PNAS 2010

Immunofluoressence using anti-LC3 antibody



1 - Rapamycin, ***2 - Fasudil***,

3 - Trifluoperazine, 4 - 2DOG,

NT - Untreated

Identification of small molecules enhancing autophagic function from drug network analysis

Iorio et al, Autophagy 2010

Bibliography

Drug classification and re-positioning through guilt-by-association

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*** Iorio, F. et al. Discovery of drug mode of action and drug repositioning from transcriptional responses. Proceedings of the National Academy of Sciences 107, 14621 (2010).

* Wolpaw, A. J. et al. Modulatory profiling identifies mechanisms of small molecule-induced cell death. Proceedings of the National Academy of Sciences 108, E771–80 (2011).

There is a huge amount of public available data ready to be mined/integrated/exploited with existing tools

ARRAYEXPRESS

GEO Gene Expression Omnibus

MSigDB Molecular Signatures Database

CONNECTIVITY MAP

GeneSigDB Curated Gene Signatures

ProfileChaser

MarQ MicroArray Rank Query

Parkinson, H. et al. ***ArrayExpress update--an archive of microarray and high-throughput sequencing-based functional genomics experiments***. Nucleic Acids Res, 2011.

Vazquez, M. et al. ***MARQ: an online tool to mine GEO for experiments with similar or opposite gene expression signatures***. Nucleic Acids Res 38, 2010.

Engreitz, J. M. et al. ***ProfileChaser: searching microarray repositories based on genome-wide patterns of differential expression***. Bioinformatics, 2011.

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Gene Signature and Gene Expression data Repositories

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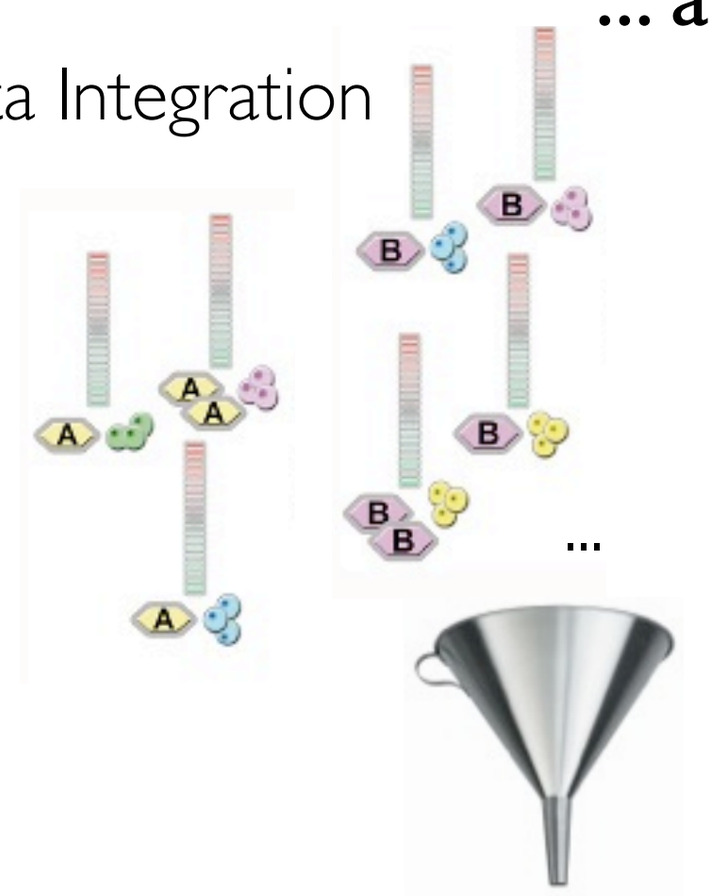
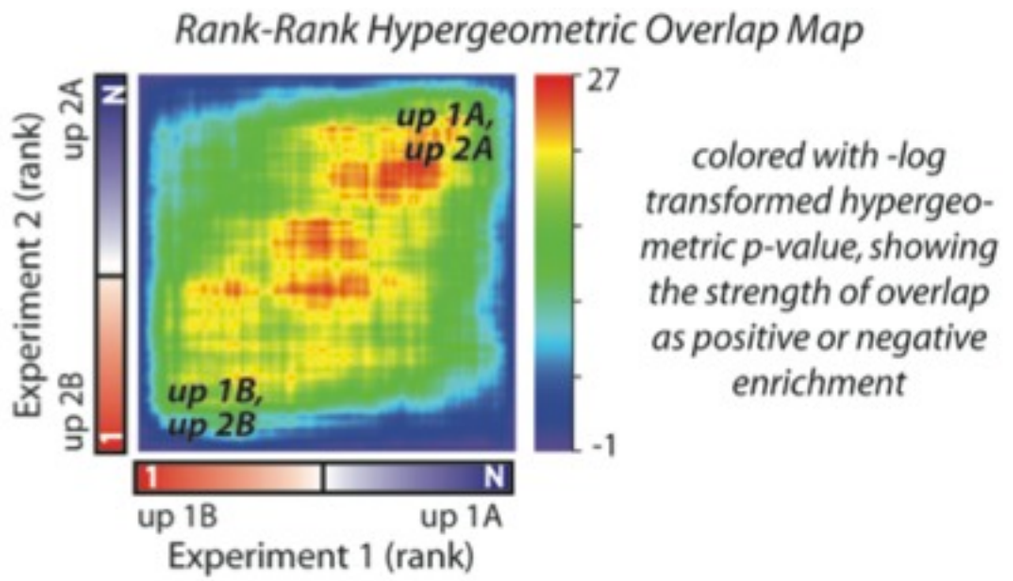
... and some challenges

Data Integration



Plaisier et al Nucleic Acids Res 2010



how to compute genome-wide similarity

Drug-Induced Regulation of Target Expression Iskar et al, PLoS Comp Biol 2010

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Data Integration and Genome-wide similarity metrics

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New methods (Bayesian statistic and others)

** Jin, G. et al. A novel method of transcriptional response analysis to facilitate drug repositioning for cancer therapy. Cancer Res. (2011).doi:10.1158/0008-5472.CAN-11-2333

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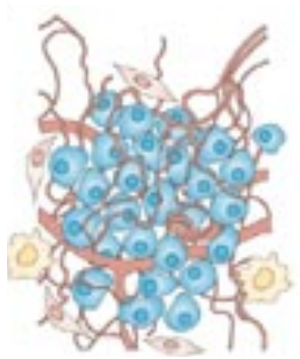
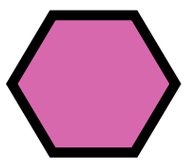
Genome-Based drug re-purposing approaches

Disease signature

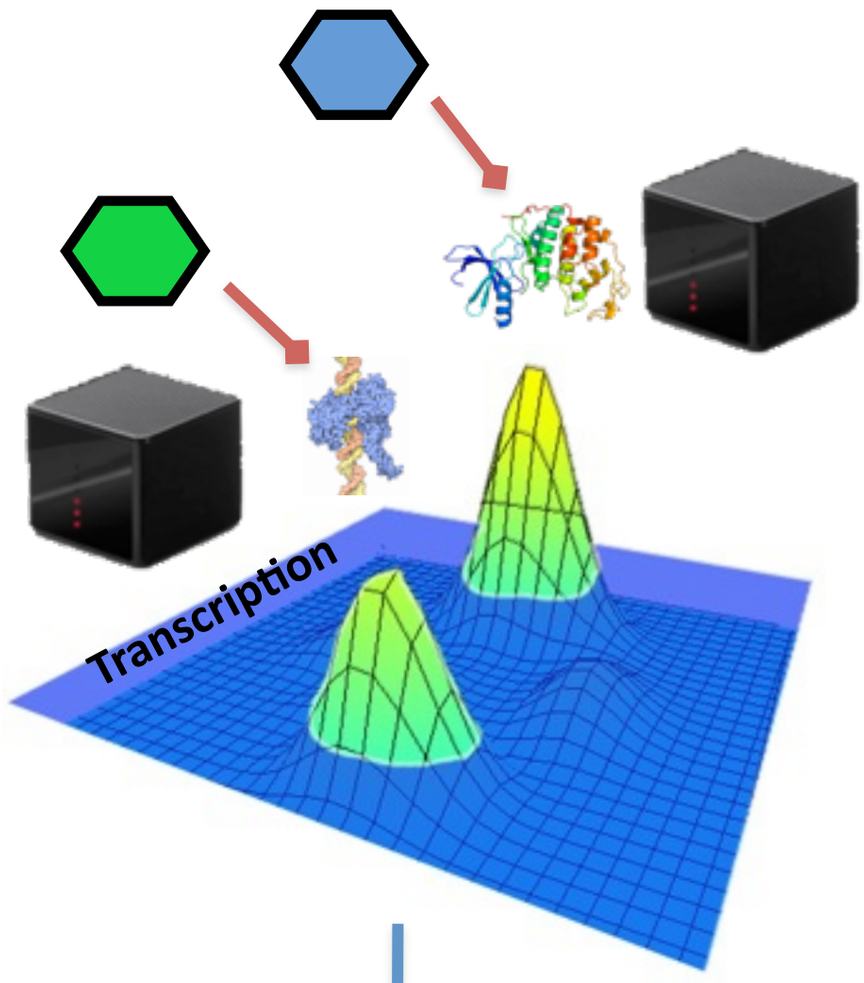
Drug Response Signature





1
Drugs able to “revert” a phenotype signature could “revert the phenotype”

2
Drugs eliciting similar transcriptional responses could share therapeutic effects

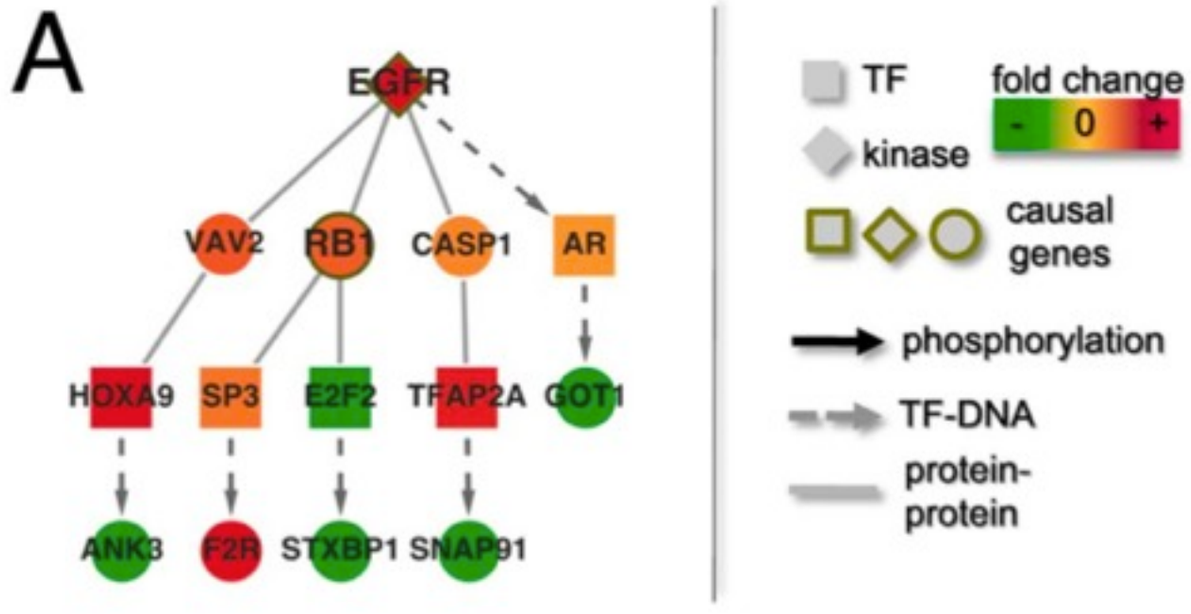


Therapeutic Effect

no mechanistic insights

Causal Reasoning upon drug treatment

Identifying Causal Genes and Dysregulated Pathways in Complex Diseases



1) identification of a disease gene expression signature

2) identification of paths from genomic alterations to the genes in the signature through a network of molecular interactions

Modeling the Mechanism of Action of a DGAT1 Inhibitor Using a Causal Reasoning Platform Kin et al, PLoS Comp Biol 2010

in this case the signature is connected to a number of literature derived hypotheses on the MoA of the drug

Network-based prediction for sources of transcriptional dysregulation using latent pathway identification analysis Pham et al, PNAS 2011

Revealing signaling pathway deregulation by using gene expression signatures and regulatory motif analysis Liu et al, Genome Biol 2007

Causal Reasoning: open problems

- It is not trivial to chose an a-priori-known map of pathways or molecular interactions that is the best trad-off between reliability and exhaustiveness and upon which experimental data can be calibrated

- different graph-theory algorithms have been proposed to link putatively causal nodes to “affected” genes but none of them is based on solid biological arguments

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On causal reasoning to dissect drug Mode of Action

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Conclusions

1) The potential of the massive quantity of public available gene expression data has not been fully exploited

2) A significant number of published works showed that it is possible to identify drug repositioning opportunities by using genome-wide signature-matching methods

3) If coupled with recently developed “causal-reasoning” techniques the methods in (2) could provide the basis for the development of robust and efficient computational platforms for systematic drug discovery and re-purposing

4) this would open “De-facto” a new Golden-Age for DNA-microarray technology

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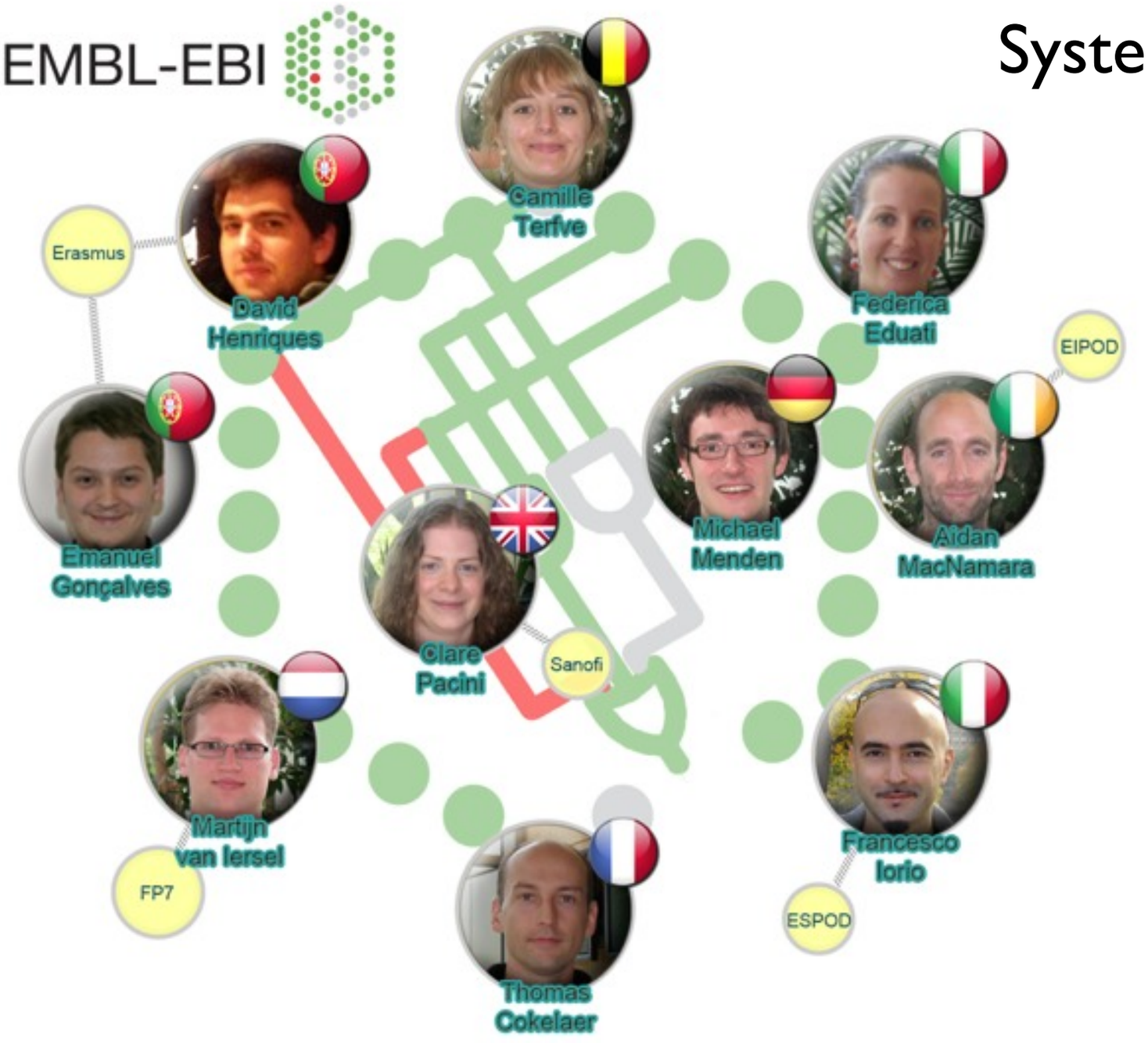

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Saez-Rodriguez Group Positions

We have a number of opportunities depending on experience and availability:

- **PhD students**: Please check the EMBL PhD Programme for deadlines and whether there is a position in our group

- **Internships**: Find out more about an internship in the Saez-Rodriguez group.

- **Postdoctoral**: we have no openings at the moment but we are open to discuss candidates who have potential external funding. Please also visit the EIPOD and ESPOD programmes.