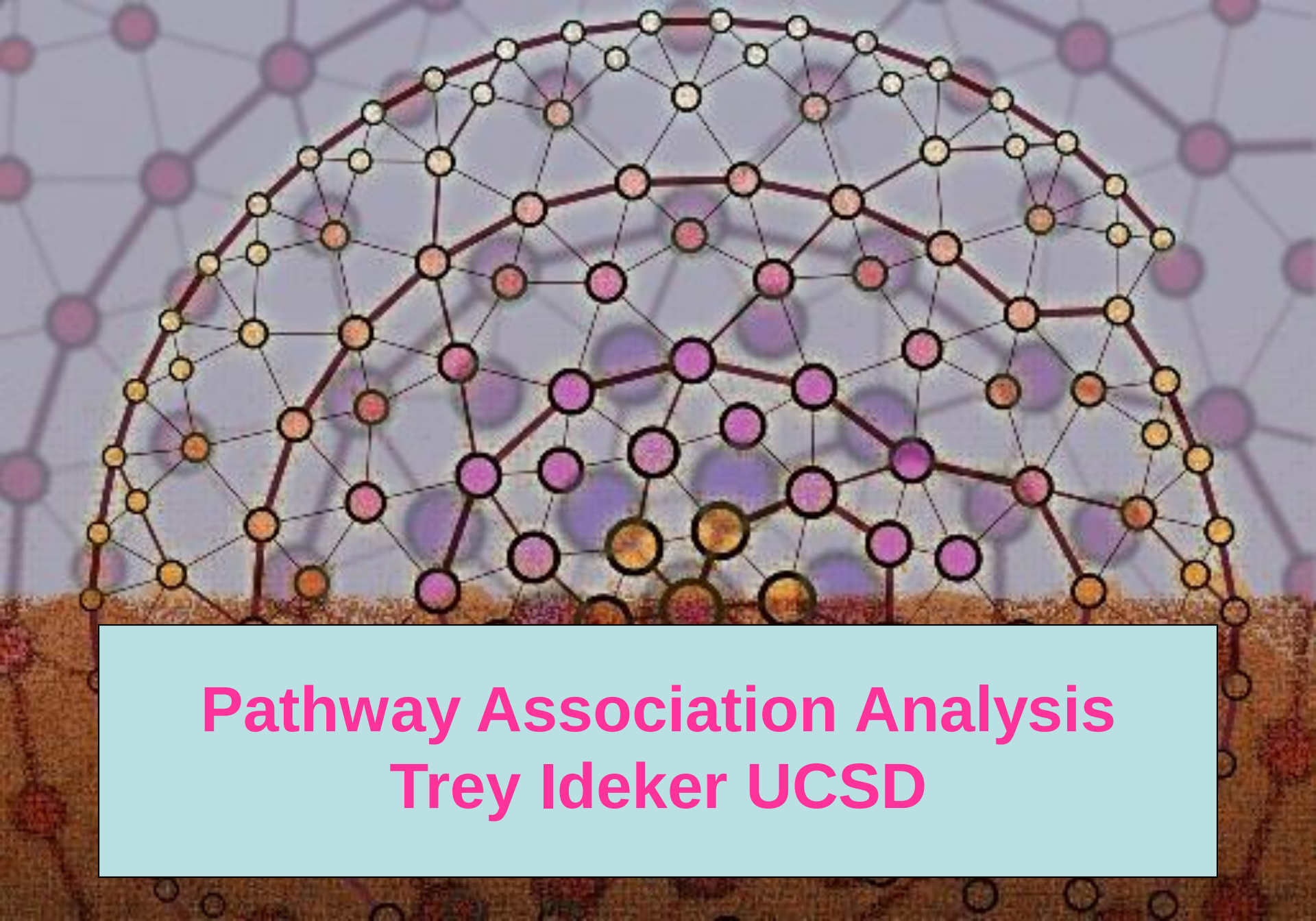

Microsoft® Research
Faculty Summit
10
YEAR ANNIVERSARY



Pathway Association Analysis

Trey Ideker UCSD

A working network map of the cell

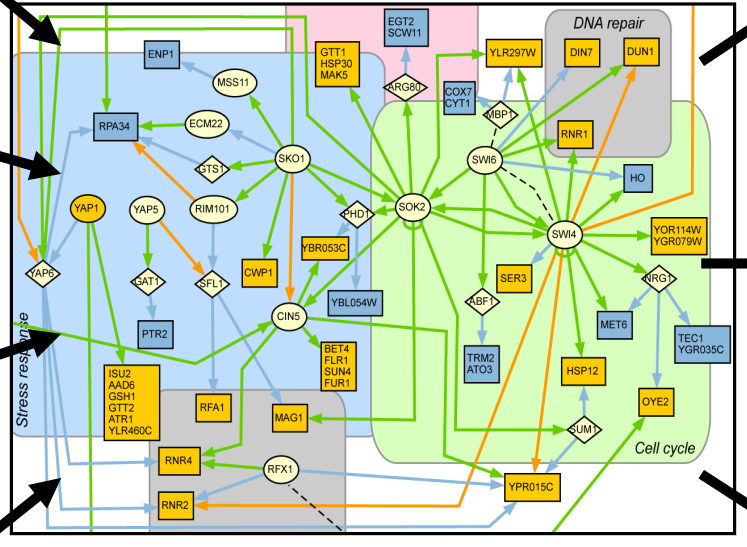
Network evolutionary comparison / cross-species alignment to identify conserved modules

Projection of molecular profiles on protein networks to reveal active modules

Integration of transcriptional interactions with causal or functional links

Alignment of physical and genetic networks

The Working Map



Network-based classification of cases vs. controls

Functional separation of gene families

Moving from genome-wide association studies (GWAS) to network-wide “pathway” association (PAS)

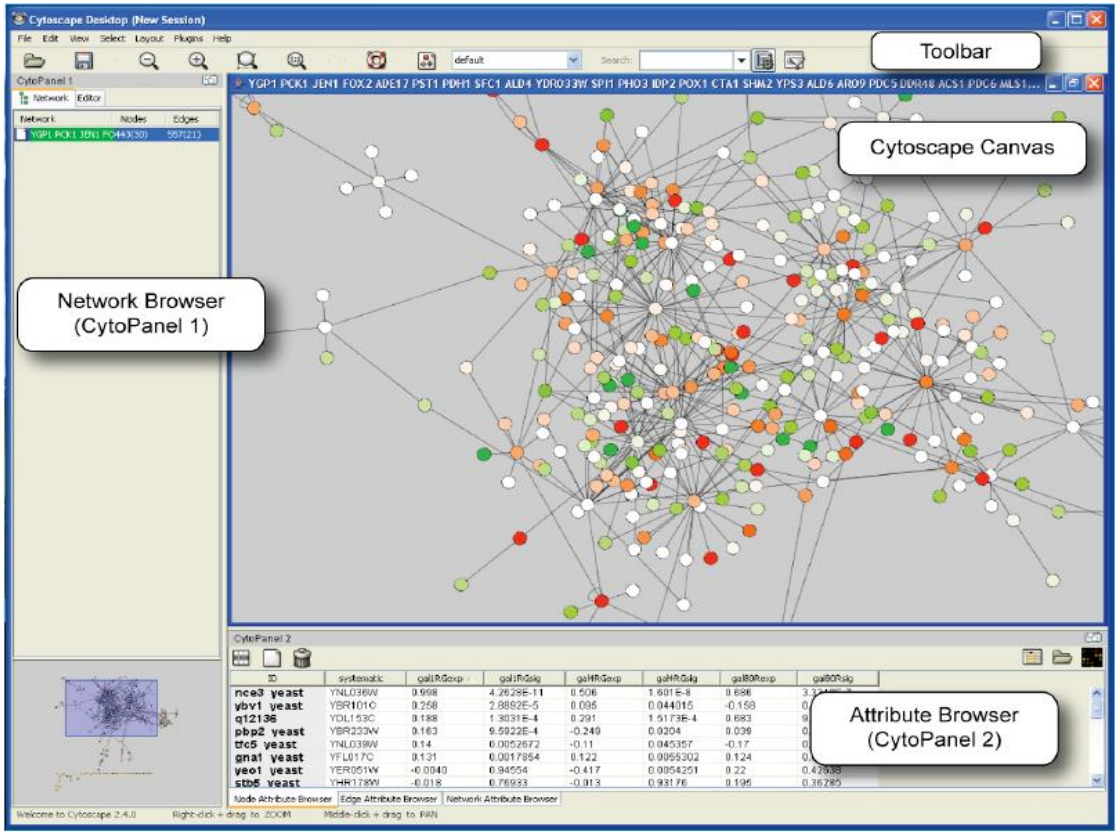
Building networks → **Using networks**

www.cytoscape.org

Shannon et al. *Genome Research* 2003
Cline et al. *Nature Protocols* 2007

OPEN SOURCE Java platform for integration of systems biology data

- Layout and query of interaction networks (physical and genetic)
- Visual and programmatic integration of molecular state data (attributes)
- The ultimate goal is to provide the tools to facilitate all aspects of pathway assembly and annotation.



RECENT NEWS

- Version 2.6 released June 2008; Scalability+efficiency now equivalent to best commercial packages
- The Cytoscape Consortium is a 501(c)3 non-for-profit in the State of California
- The Cytoscape ® Registered Trademark awarded

JOINTLY CODED with Agilent, ISB, UMich, Pasteur, Sloan-Ketter., UCSF, Unilever, Toronto

Comparison of biological networks

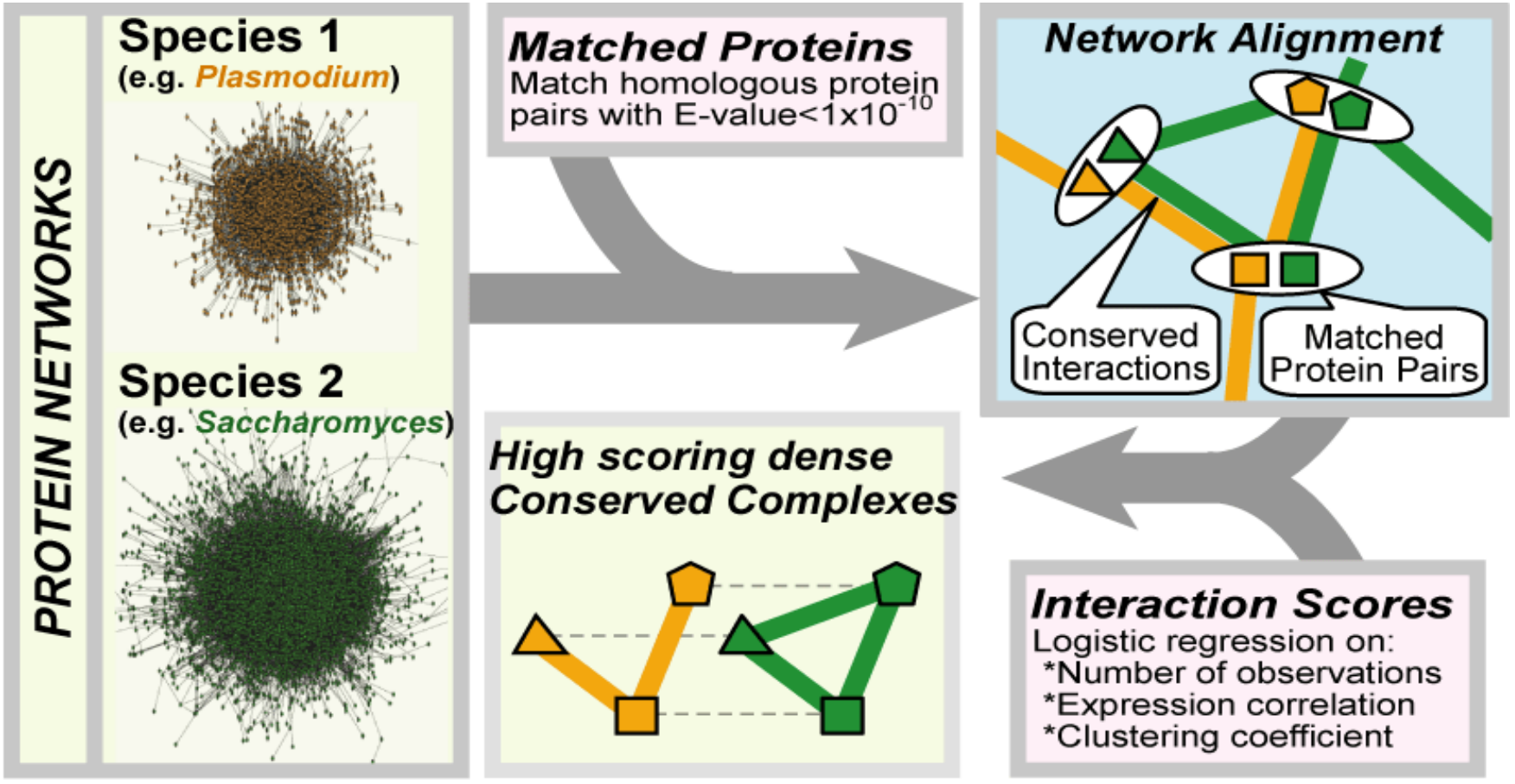
(Silpa Suthram with Roded Sharan, Richard Karp, and others)



Cross-comparison of networks:

(1) Conserved regions in the presence vs. absence of stimulus

(2) Conserved regions across different species



Kelley et al. *PNAS* 2003

Ideker & Sharan *Gen Res* 2008

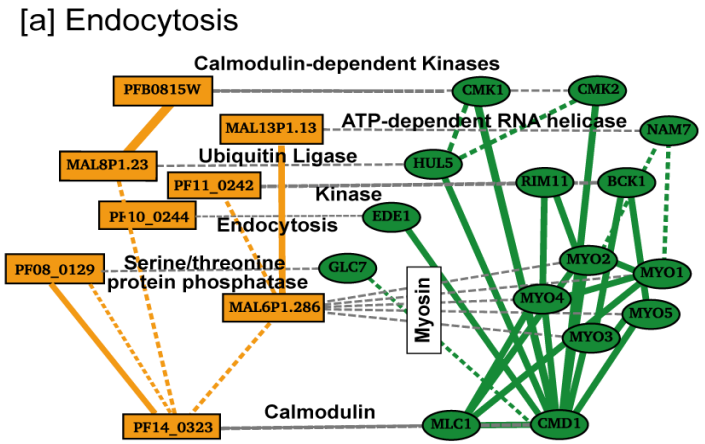
Suthram et al. *Nature* 2005

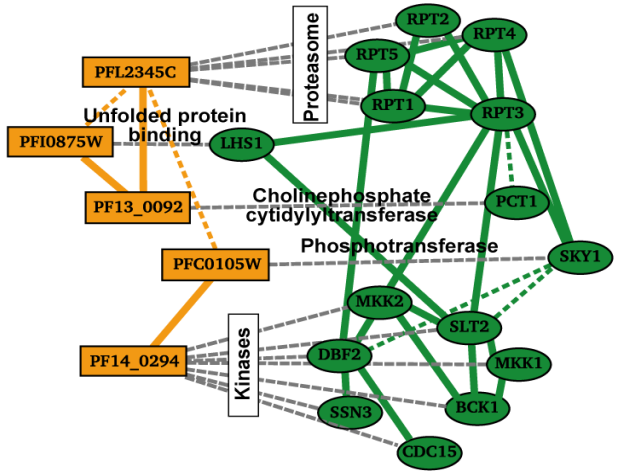
Sharan & Ideker *Nat. Biotech.* 2006

Sharan et al. *RECOMB* 2004

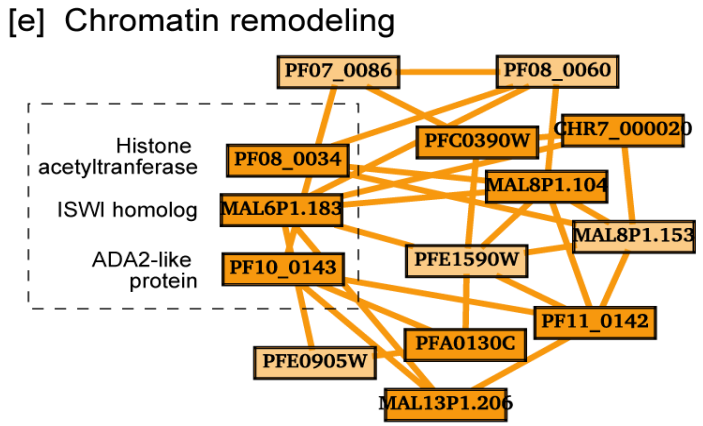
Scott et al. *RECOMB* 2005

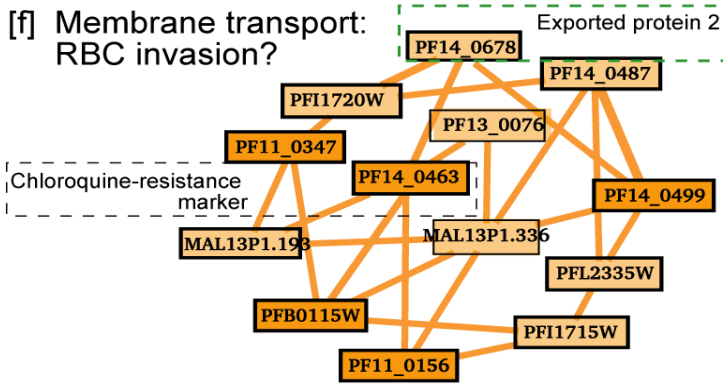
Plasmodium: a network apart?





Conserved *Plasmodium* / *Saccharomyces* protein complexes





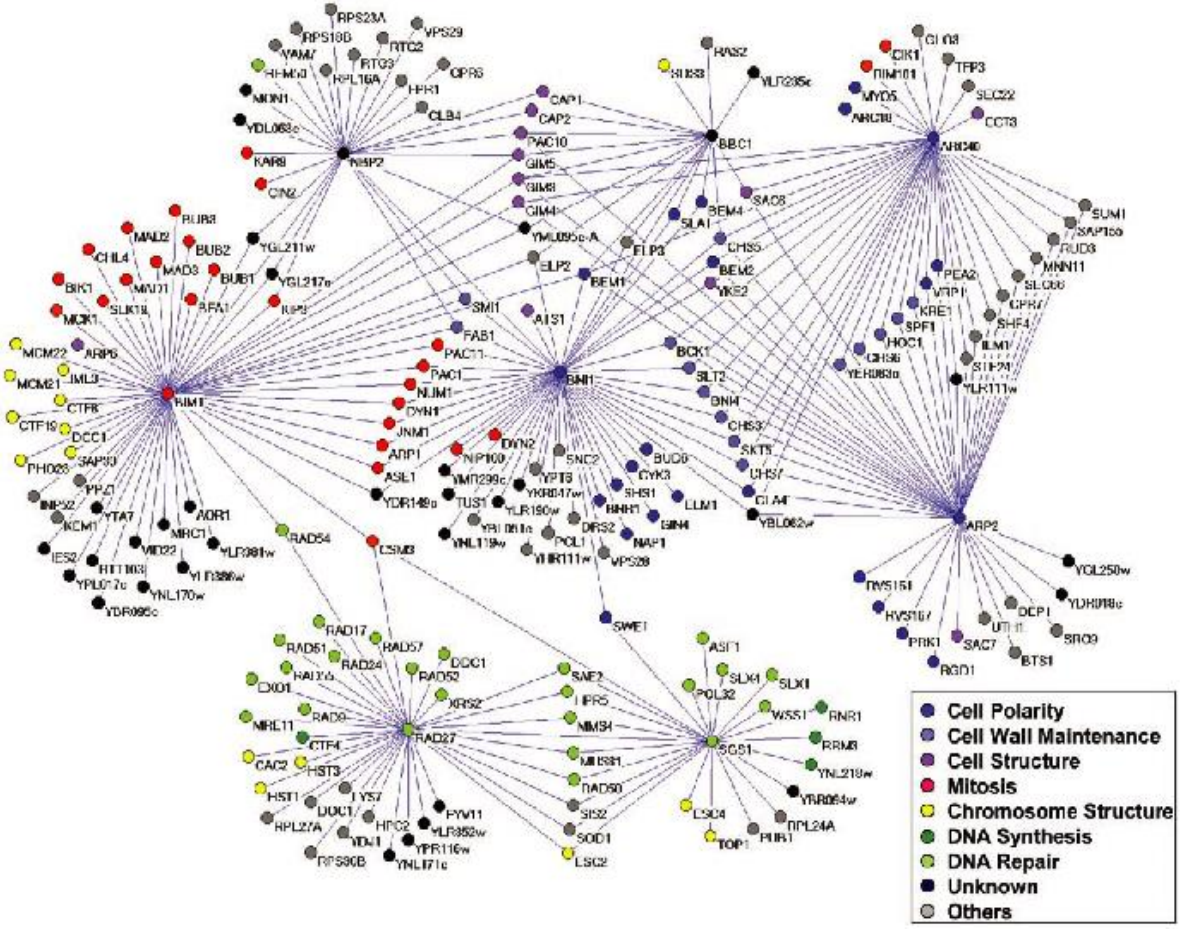
Plasmodium-specific protein complexes

Suthram et al. *Nature* 2005
La Count et al. *Nature* 2005

Synthetic lethals and epistatic interactions in model species

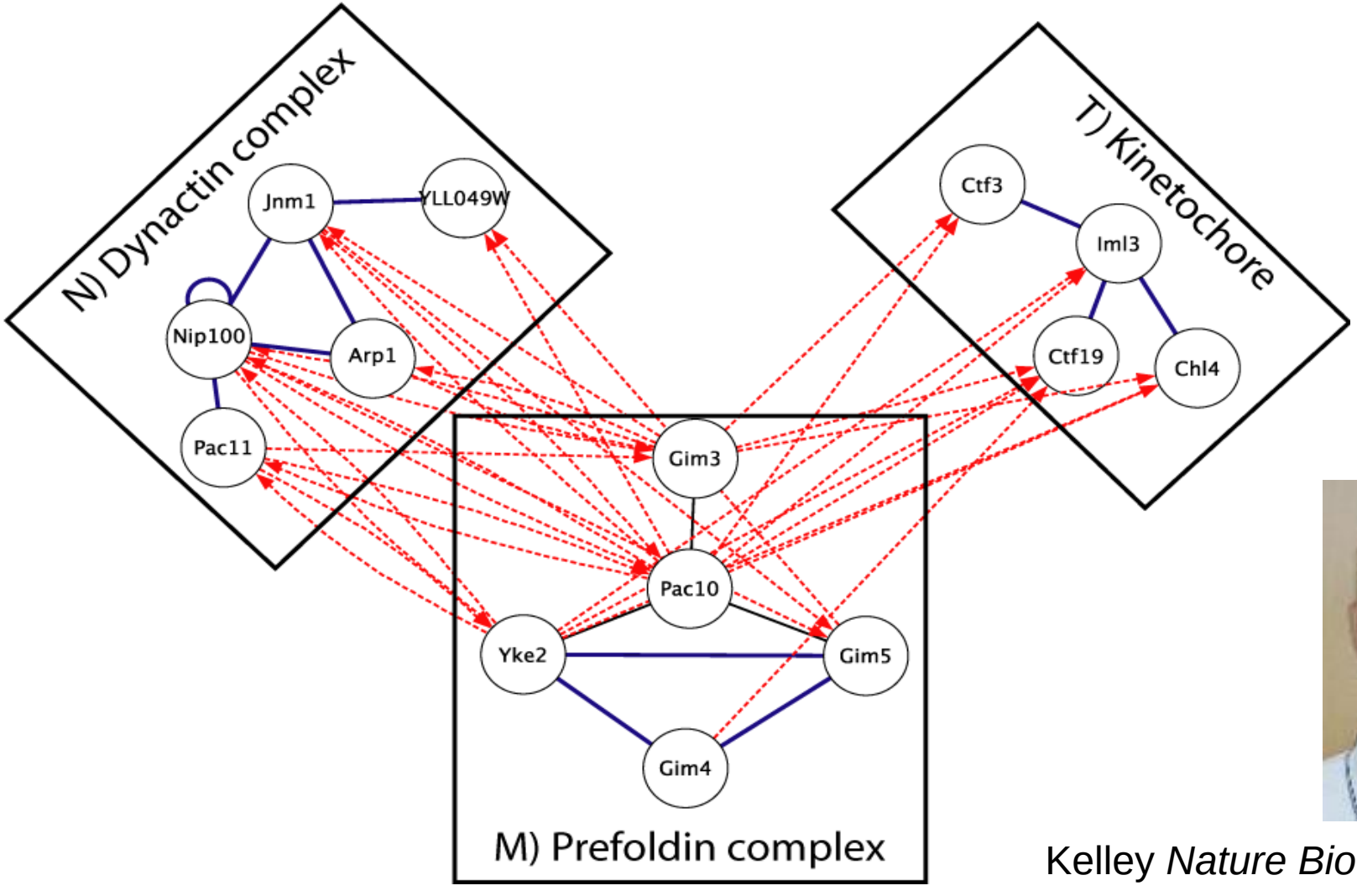
Genetic Interactions:

- Classical method used to map pathways in model species
- Highly analogous to multi-genic interaction in human disease and combination therapy
- Thousands are being uncovered through systematic studies



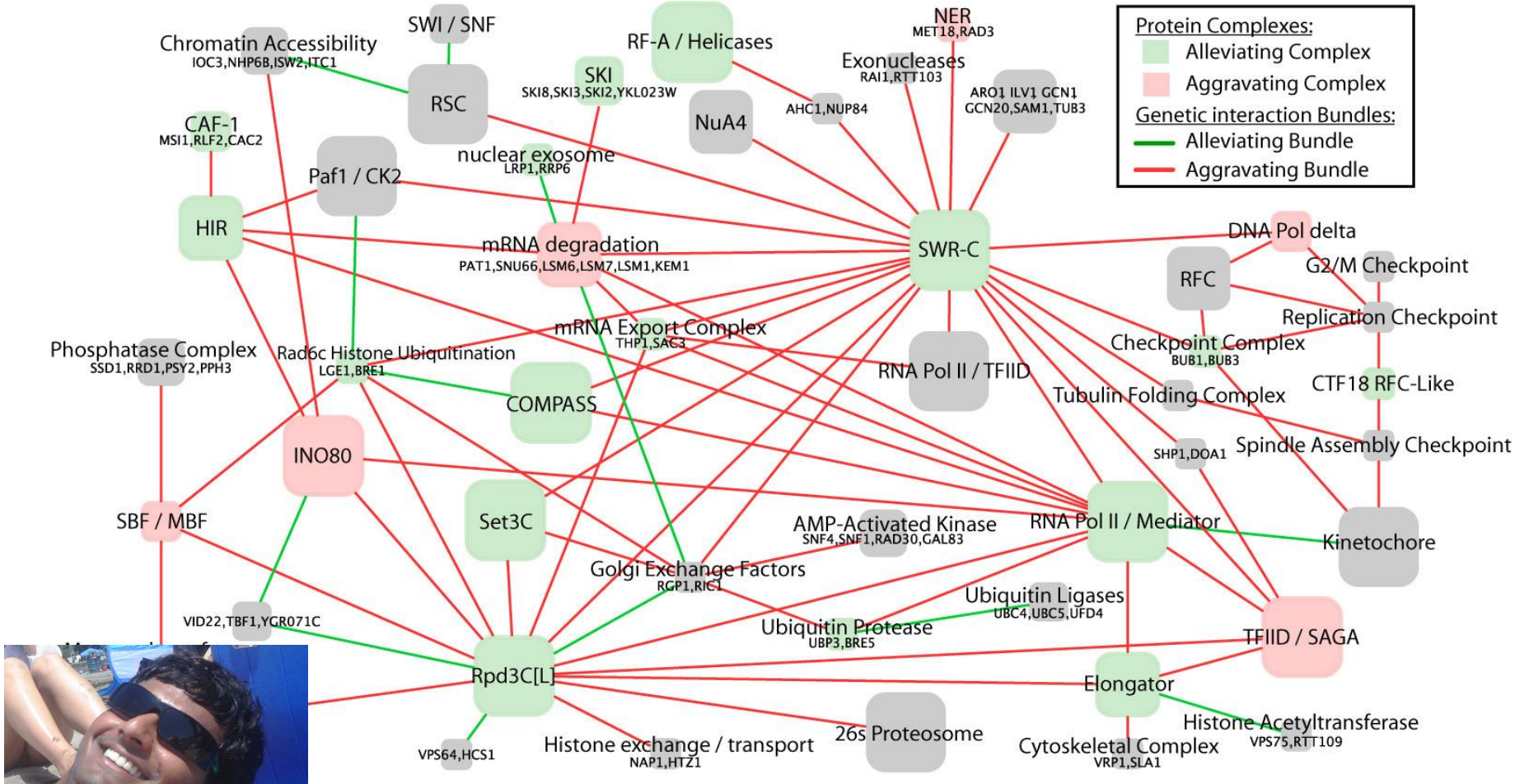
Adapted from Tong *et al.*, *Science* 2001

Genetic and physical interactions are orthogonal



Kelley *Nature Biotech*. 2005

Functional maps of protein complexes



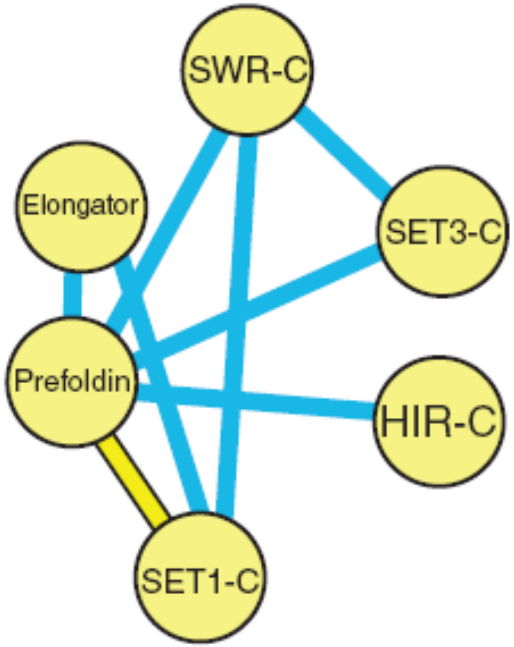
Bandyopadhyay et al. PLoS Comp Bio 2008

Comparison of genetic interaction networks across budding and fission yeasts

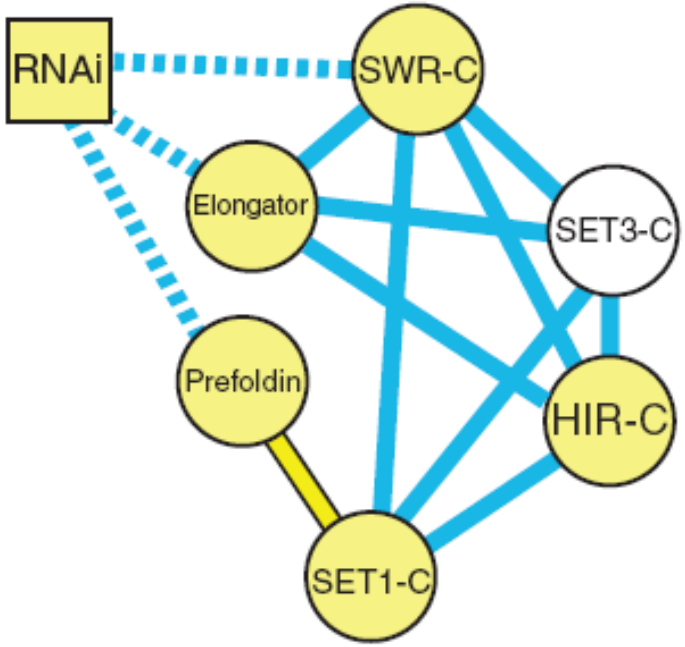
Positive Genetic Interactions

Negative Genetic Interactions

S. cerevisiae



S. pombe

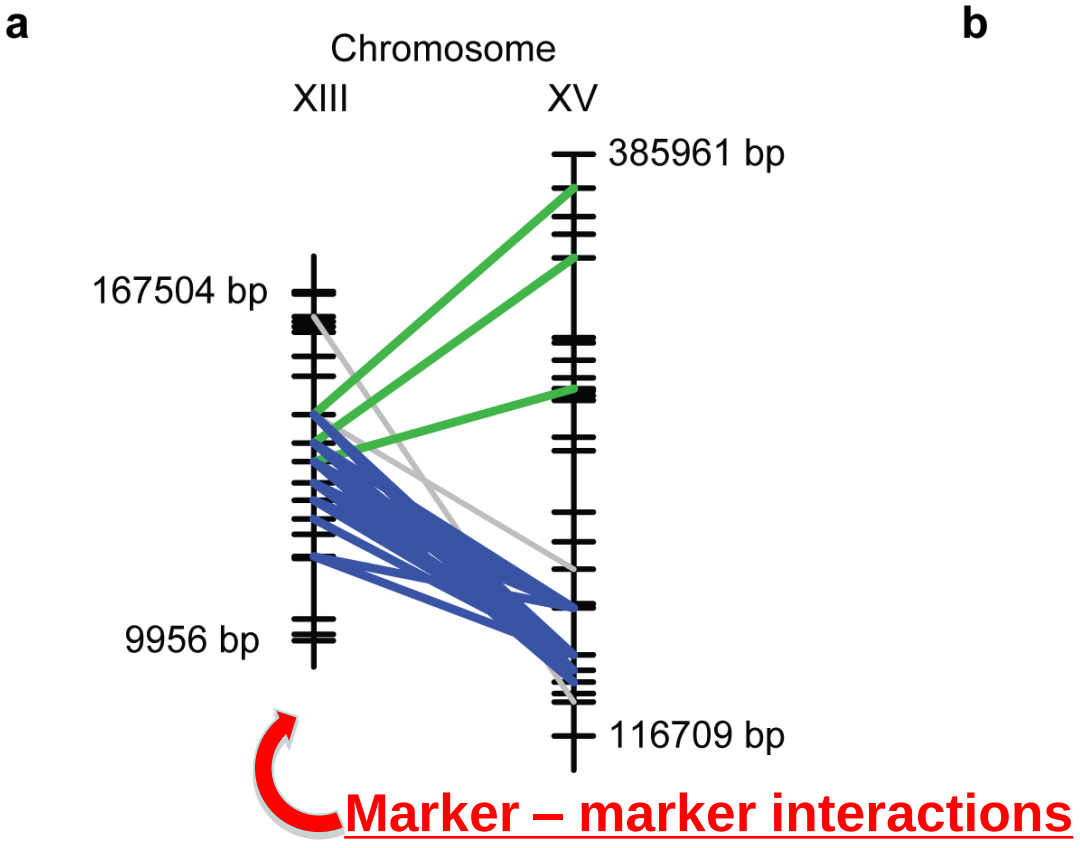


Assen Roguev,
Sourav Bandyopadhyay,
Nevan Krogan

Roguev et al. *Science* **322**: 405 (2008)

Network-based approaches to identify genetic interactions in gene association studies

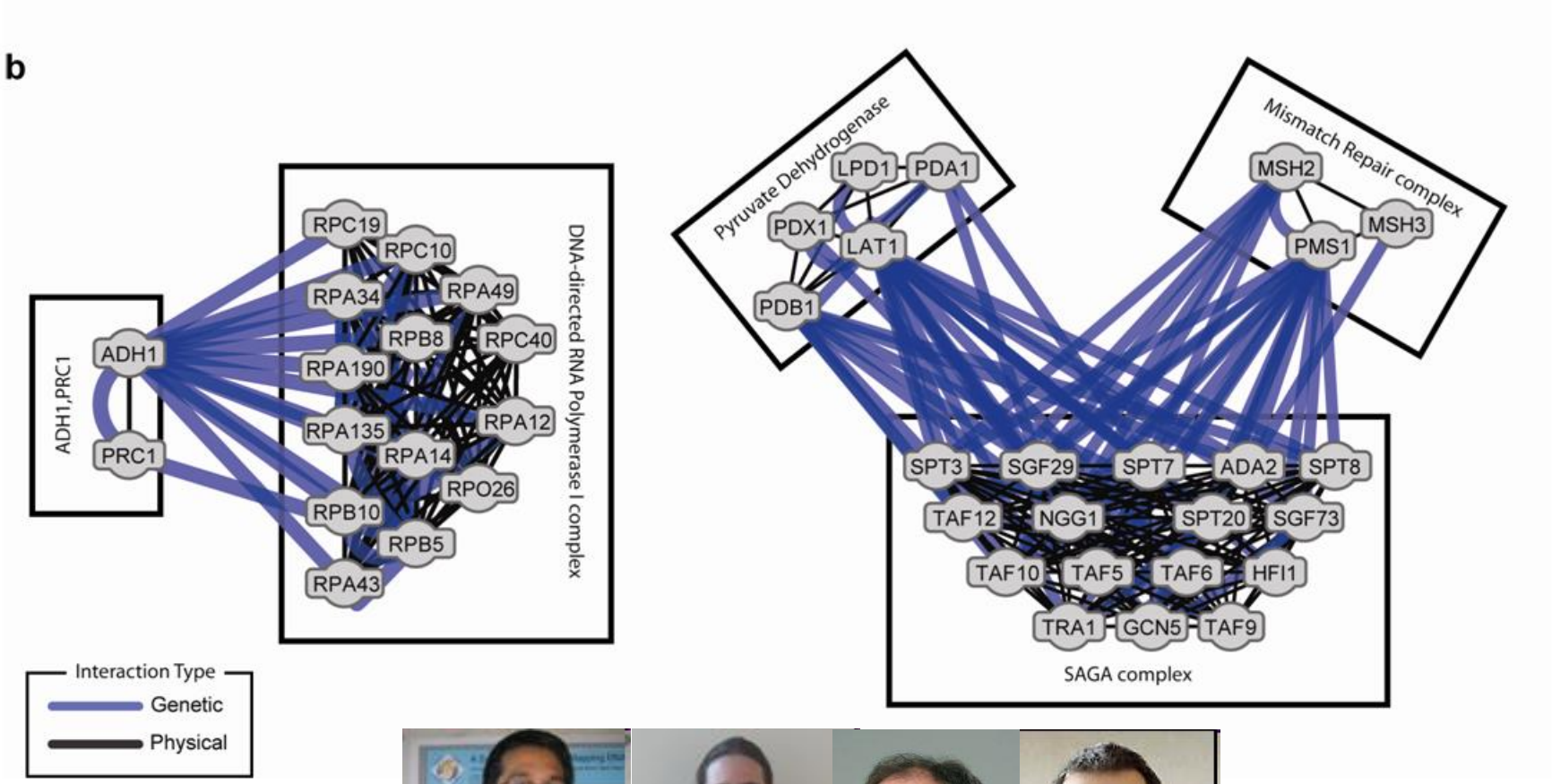
Genetic interactions occur frequently in Genome Wide Association Studies (GWAS)



Marker – marker interactions

But they are impossible to find. Marker-marker interactions are very difficult to identify in GWAS data due to lack of statistical power.

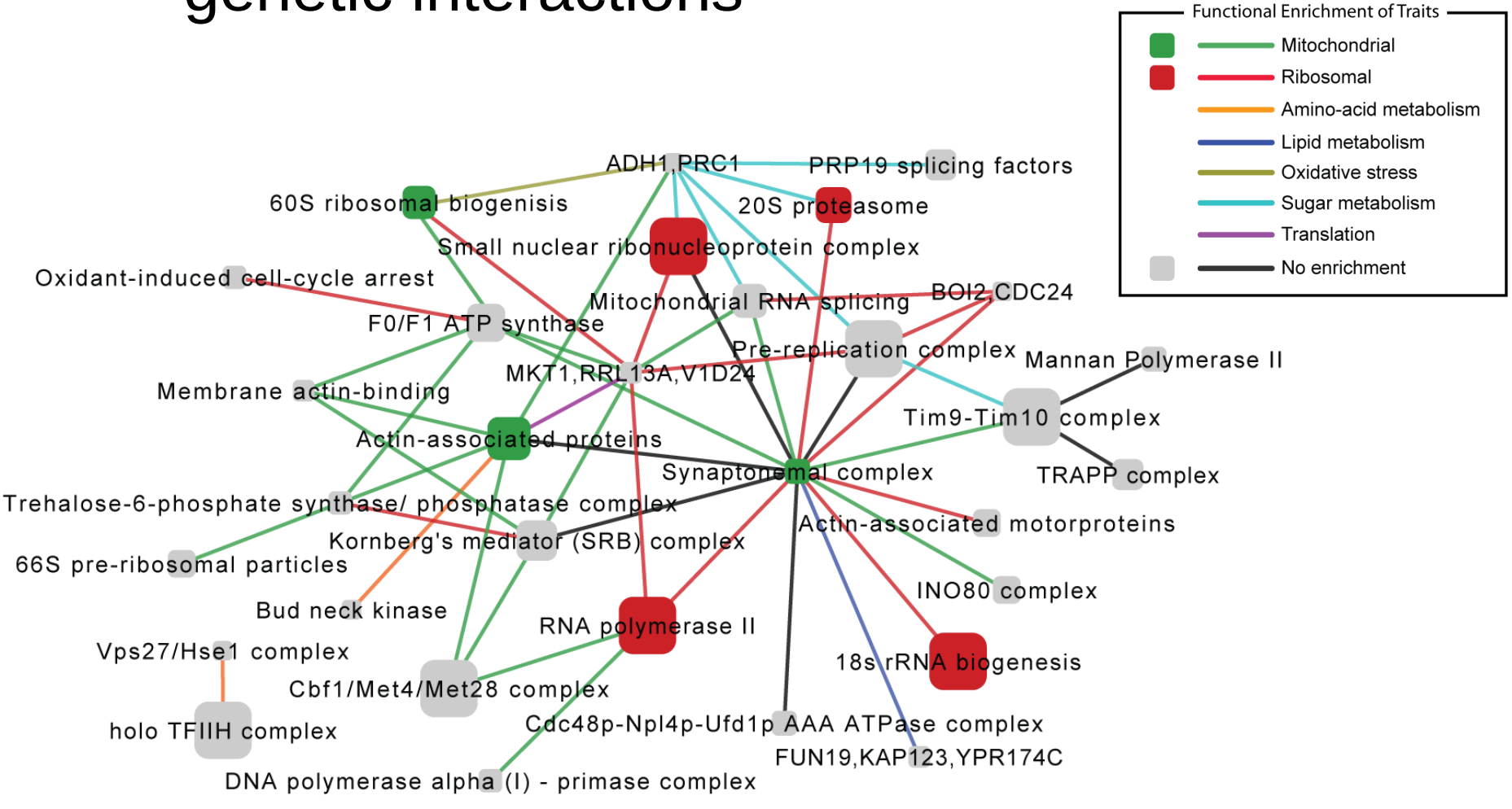
GWAS genetic interactions also run between physical networks and pathways



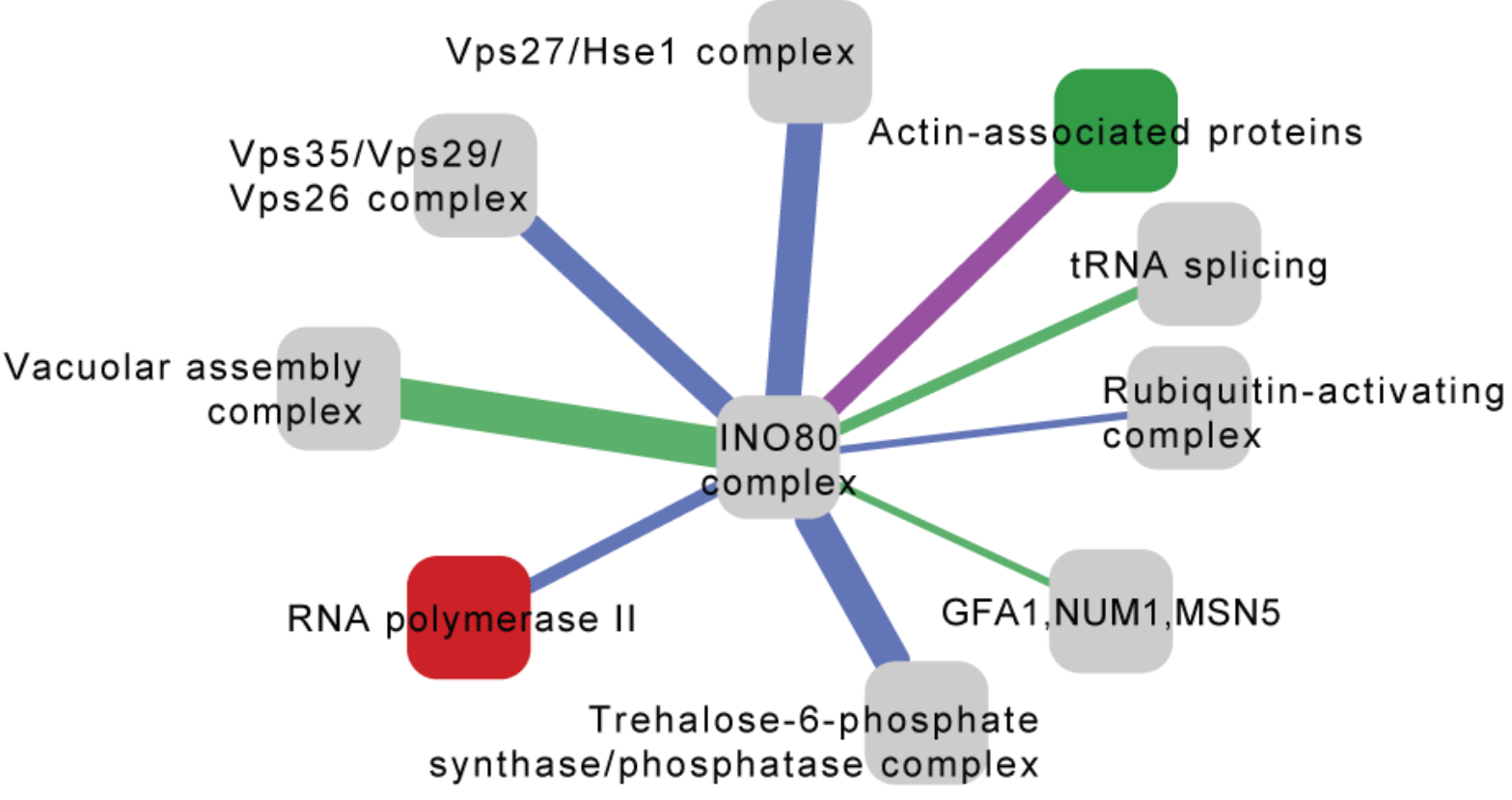
Rohith Srivas &
Greg Hannum

Richard Karp &
Nevan Krogan

Higher level maps of GWAS genetic interactions



GWAS interactions can be verified by inducing epistasis using classical genetics



Sponsors

NIGMS
NIEHS
NIMH
NSF
Packard Foundation
Agilent
Unilever
Pfizer

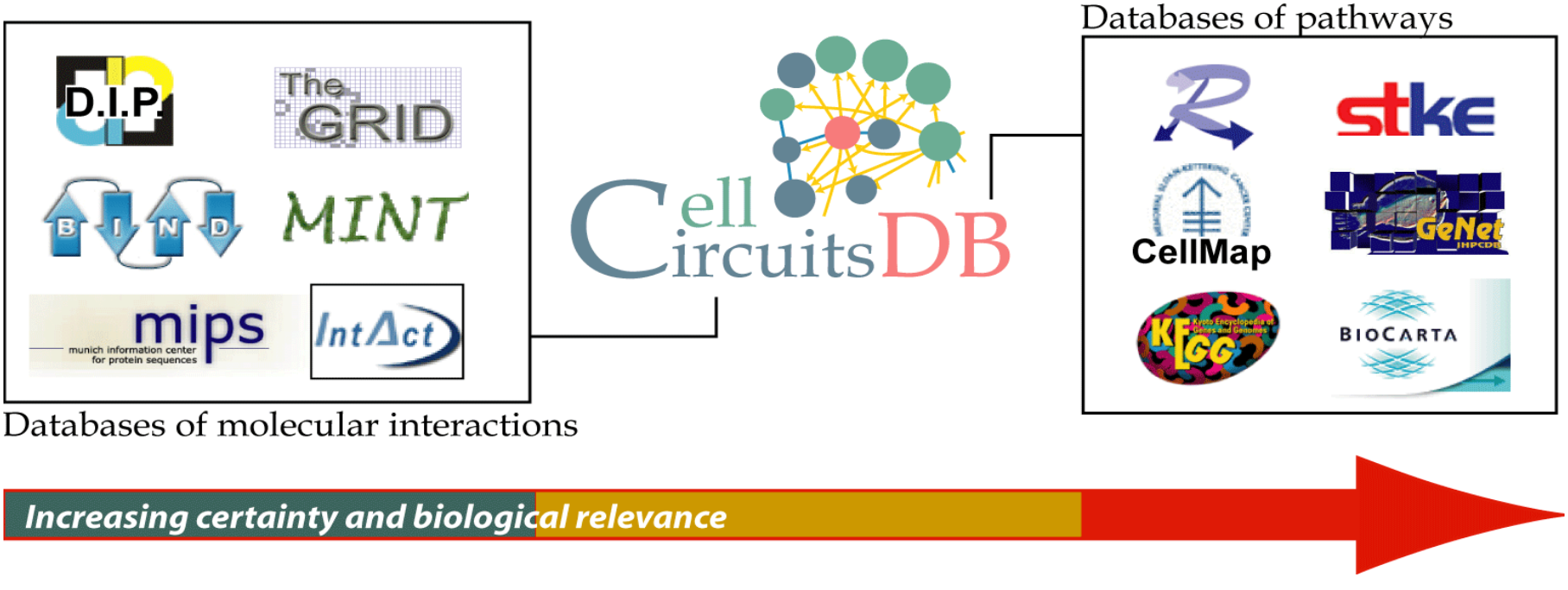
Collaborators (UCSD)

Richard Kolodner
Tom Kipps
David Perkins
Steve Briggs
Lorraine Pillus
Jean Wang

Collaborators (external)

Nevan Krogan (UCSF)
Richard Karp (UC Berkeley)
Roded Sharan (Tel Aviv)
Bas van Steensel (NKI)
Sumit Chanda (Burnham)
Howard Fox (Scripps)
Curt Wittenberg (Scripps)
Russ Finley (Wayne State)
Doheon Lee (KAIST)
Gary Bader (U Toronto)
The Cytoscape Team

http://CellCircuits.org



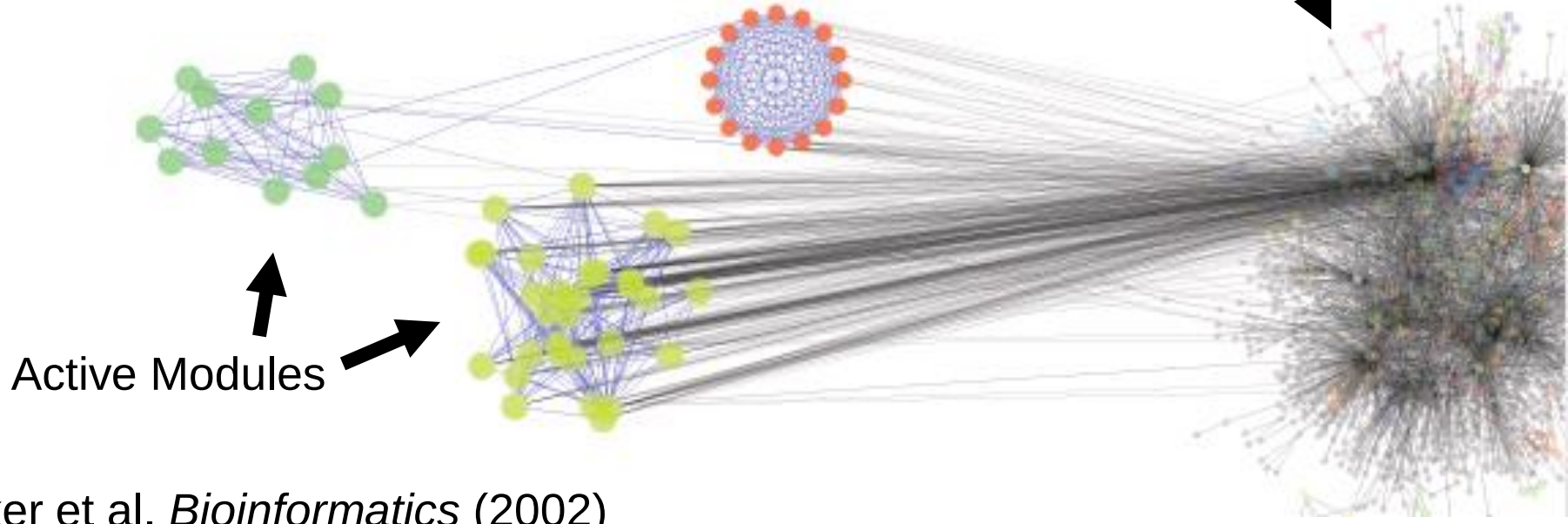
Network modules and module-based classification

Querying biological networks for “Active Modules”

Color network nodes (genes/proteins) with:

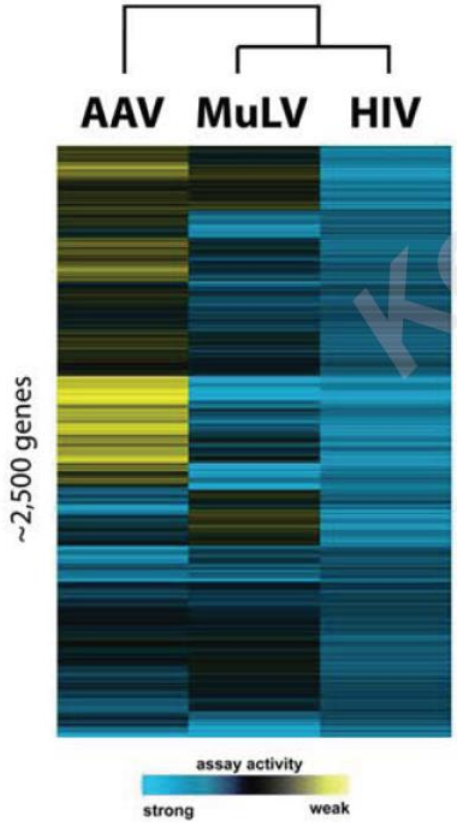
Patient expression profile
Protein states
Patient genotype (SNP state)
Enzyme activity
RNAi phenotype

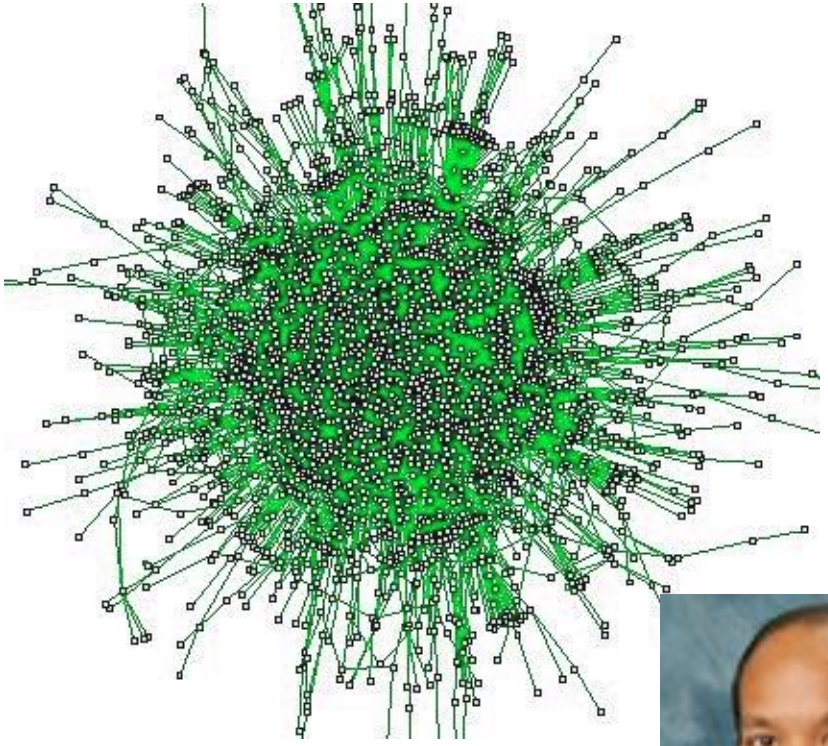
Interaction Database Dump, aka “Hairball”



Ideker et al. *Bioinformatics* (2002)

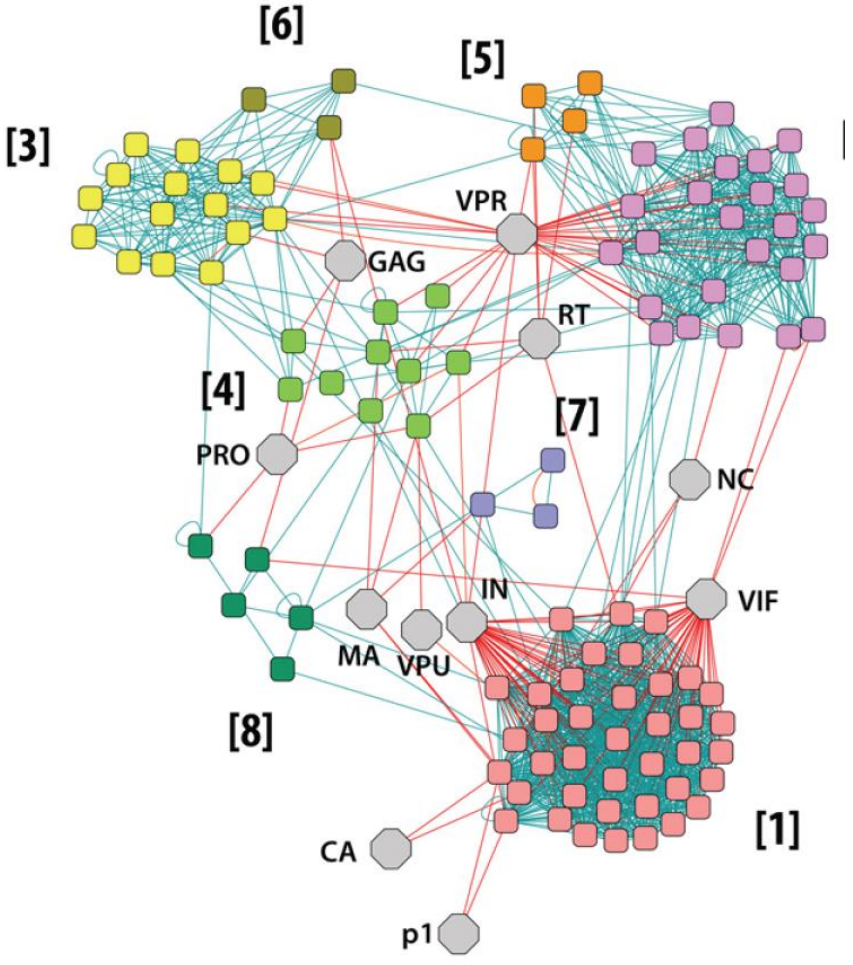
Projection of RNAi phenotypes onto a network of human-human & human-HIV protein interactions

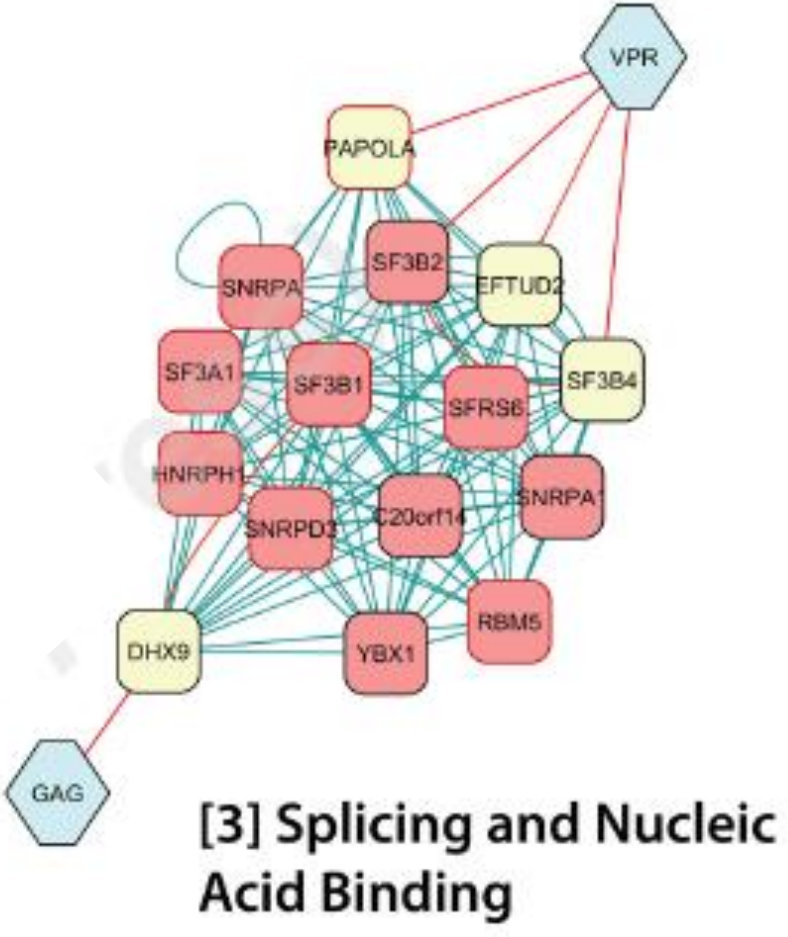




Sumit Chanda

Network modules associated with infection



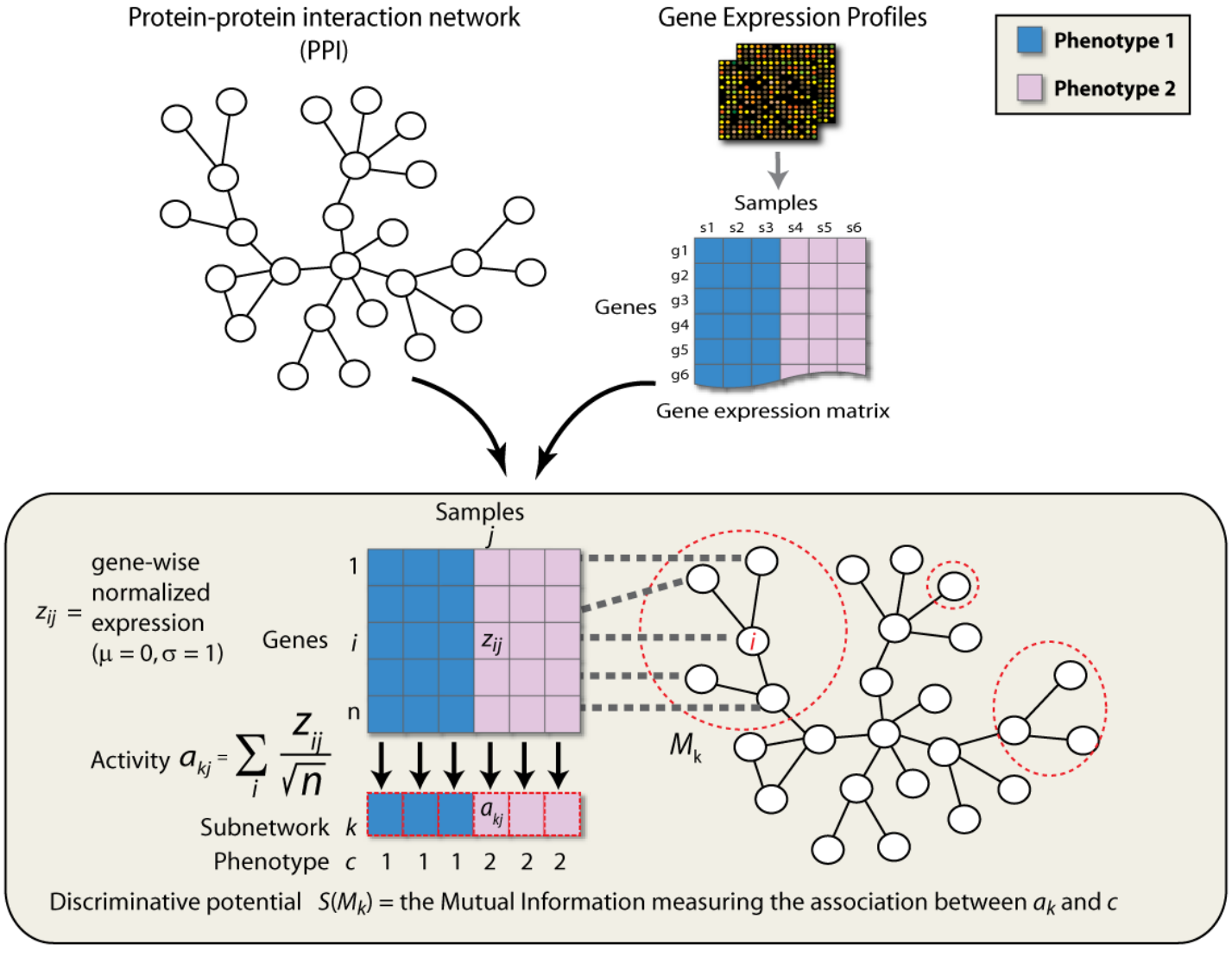


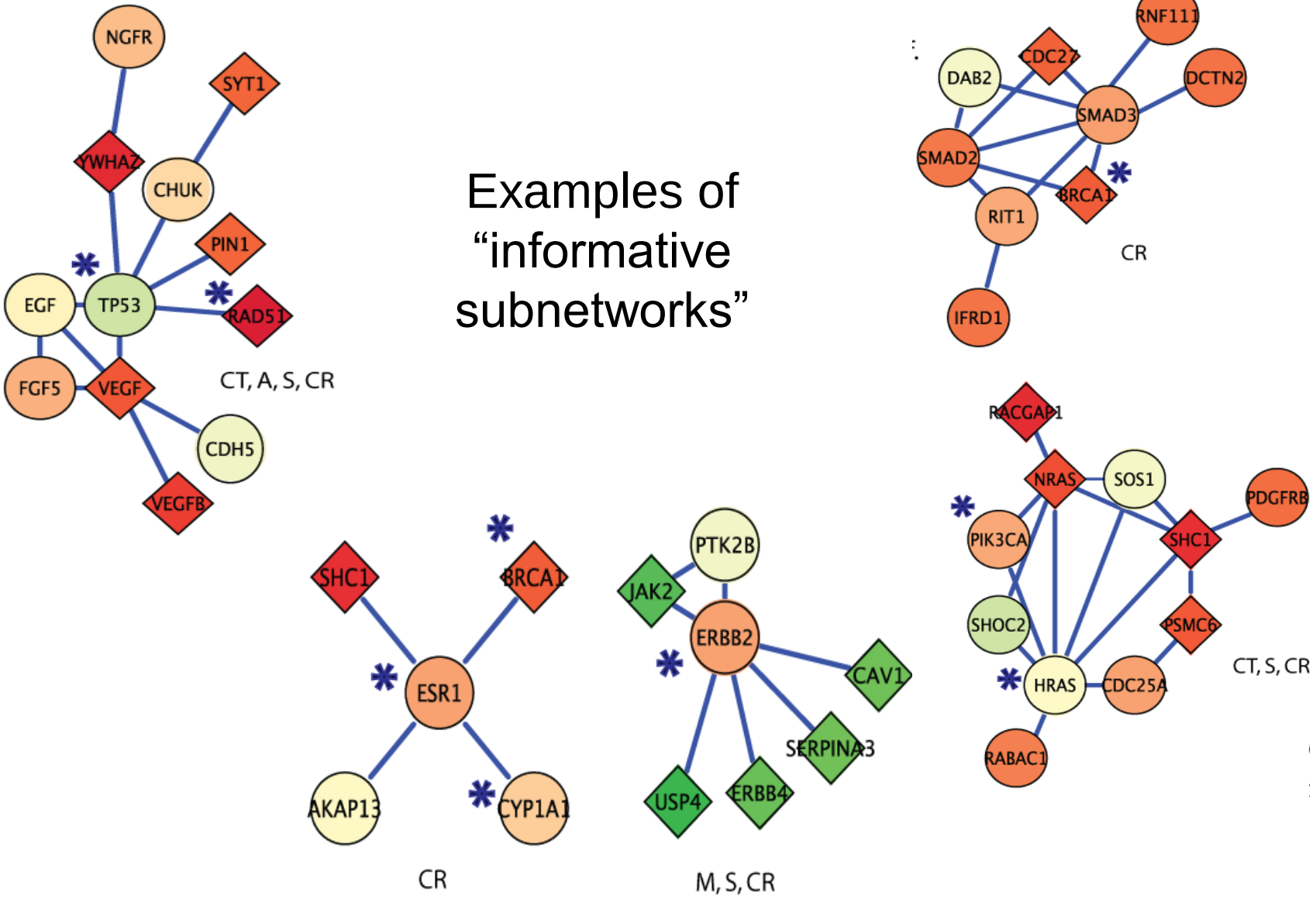
Konig et al. *Cell.* 2008

Using protein networks for diagnostics / classification

Han Yu Chuang with
Tom Kipps and Steve Briggs (UCSD)
Eunjung Lee & Doheon Lee (KAIST)

Protein network diagnosis of breast cancer metastasis





Chuang et al. *Molecular Systems Biology* 2007

LETTERS

nature biotechnology

February 2009

Dynamic modularity in protein interaction networks predicts breast cancer outcome

Ian W Taylor[1,2], Rune Linding[1,3], David Warde-Farley[4,5], Yongmei Liu[1], Catia Pesquita[6], Daniel Faria[6], Shelley Bull[1,7], Tony Pawson[1,2], Quaid Morris[4,5] & Jeffrey L Wrana[1,2]

Changes in the biochemical wiring of oncogenic cells drives phenotypic transformations that directly affect disease outcome. Here we examine the dynamic structure of the human protein interaction network (interactome) to determine whether changes in the organization of the interactome can be used to predict patient outcome. An analysis of hub proteins identified intermodular hub proteins that are co-expressed with their interacting partners in a tissue-restricted manner and intramodular hub proteins that are co-expressed with their interacting partners in all or most tissues. Substantial differences in biochemical structure were observed between the two types of hubs. Signaling domains were found more often in intermodular hub proteins, which were also more frequently associated with oncogenesis. Analysis of two breast cancer patient cohorts revealed that altered modularity of the human interactome may be useful as an indicator of breast cancer prognosis.

of hubs centered over increasing average PCC values (**Fig. 1a**, red asterisks). Randomly reassigning the expression data to different gene products in the same network resulted in an approximately normal distribution of PCC values (**Fig. 1a**, black dashed line). The shoulder (marked with a black asterisk) is largely due to strongly correlated gene products that have a high probability of reforming interactions with their true interactors when randomized (data not shown). We observed a similar multi-modal distribution using a literature-curated source alone[4] (**Supplementary Fig. 1b**) or a different high-confidence human PPI database[5] (**Supplementary Fig. 1c**).

The human interactome thus has two classes of hubs. One class displays low correlation of co-expression with its partners. We call these hubs intermodular hubs, as first proposed for the yeast interactome[6,7]. A second class, termed intramodular hubs, displays more highly correlated patterns of co-expression (**Fig. 1a**). These features reflect a modular architecture. Restricting the analysis to interactions

Assembling a working network map

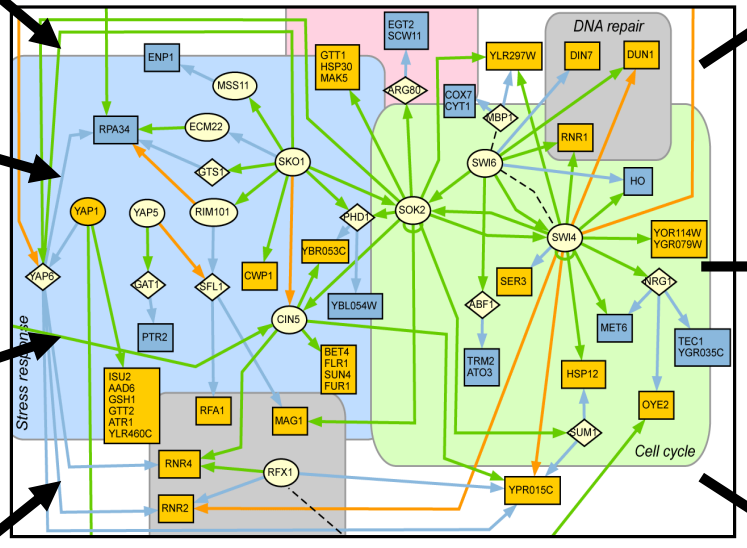
Network evolutionary comparison / cross-species alignment to identify conserved modules

Projection of molecular profiles on protein networks to reveal active modules

Integration of transcriptional interactions with causal or functional links

Alignment of physical and genetic networks

The Working Map



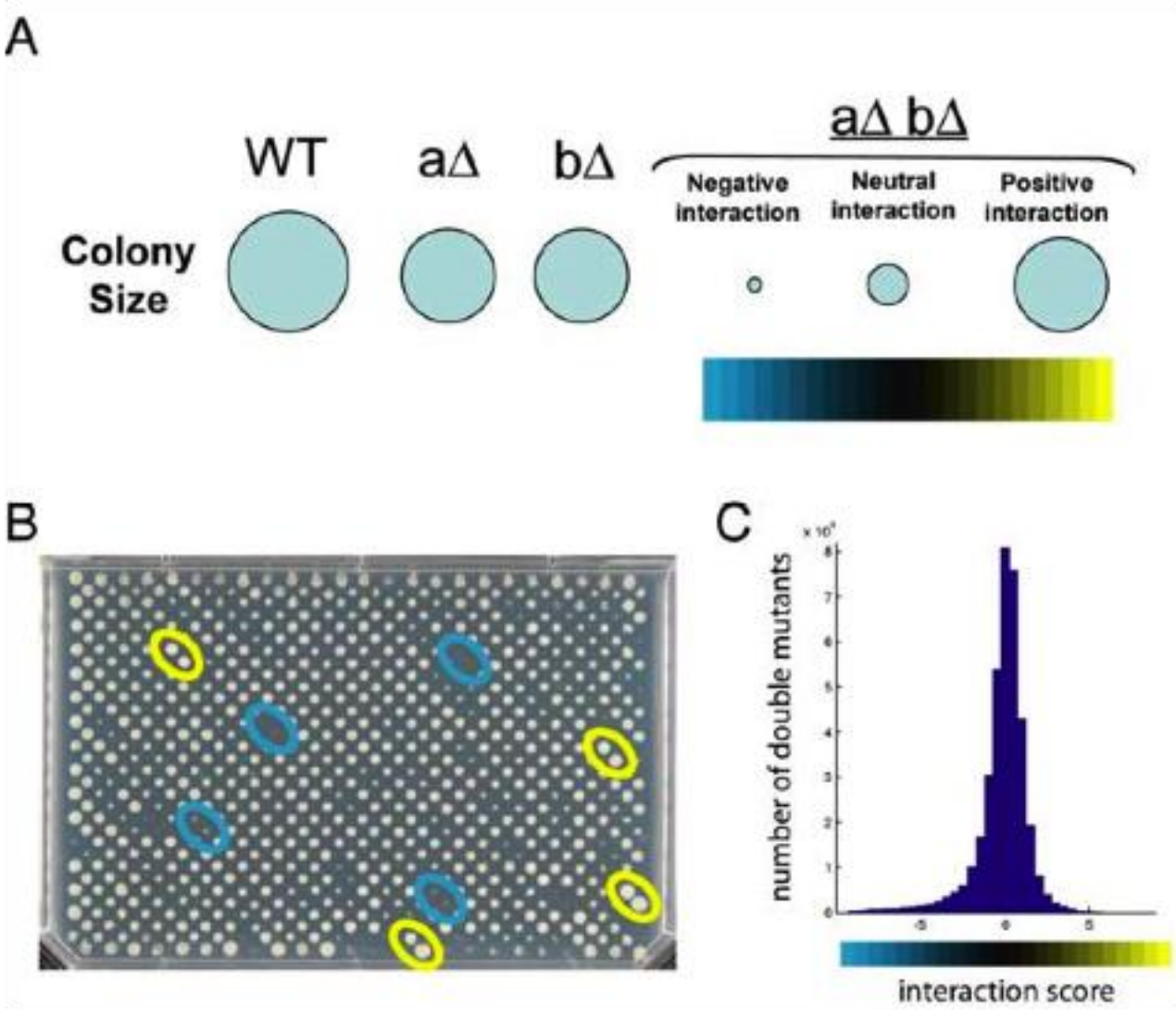
Network-based classification of cases vs. controls

Functional separation of gene families

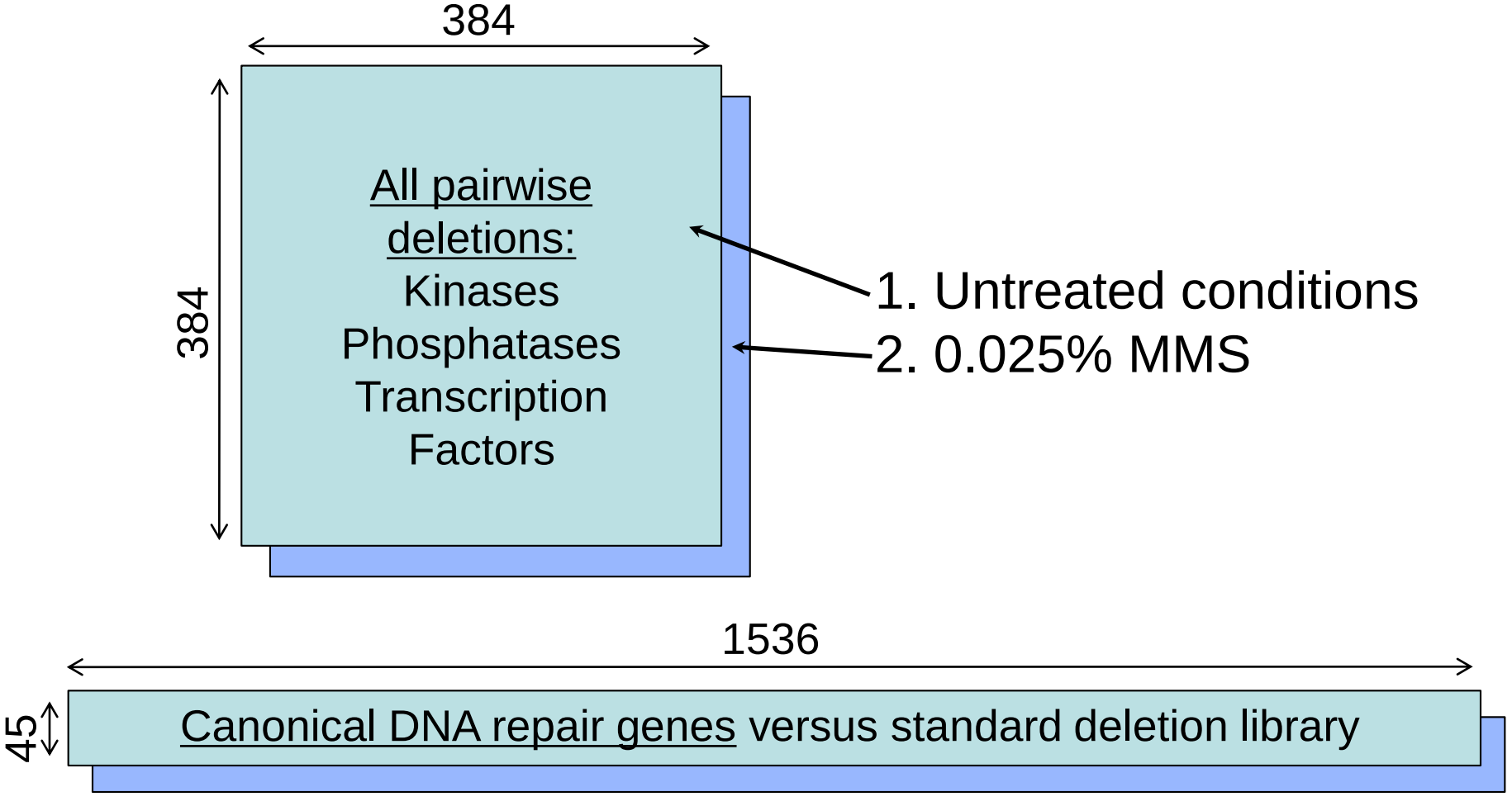
Moving from genome-wide association studies (GWAS) to network-wide “pathway” association (PAS)

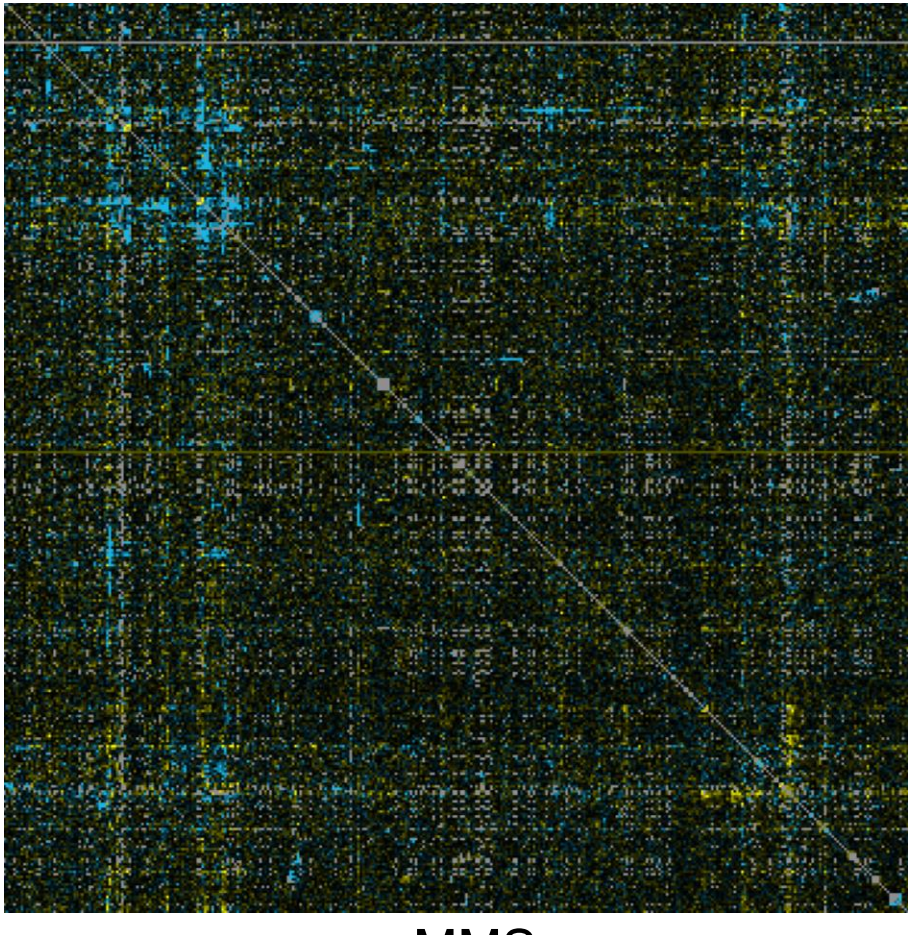
Building networks → **Using networks**

Measuring genetic interactions

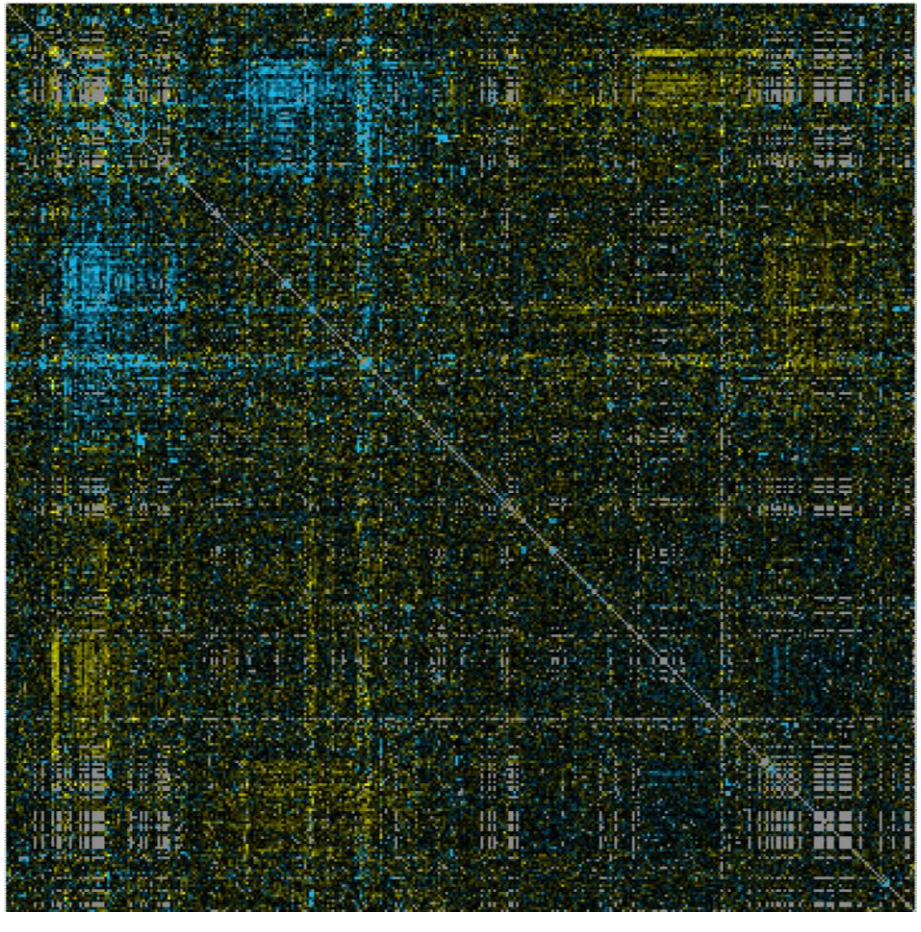


The dynamic genetic network induced by DNA damage



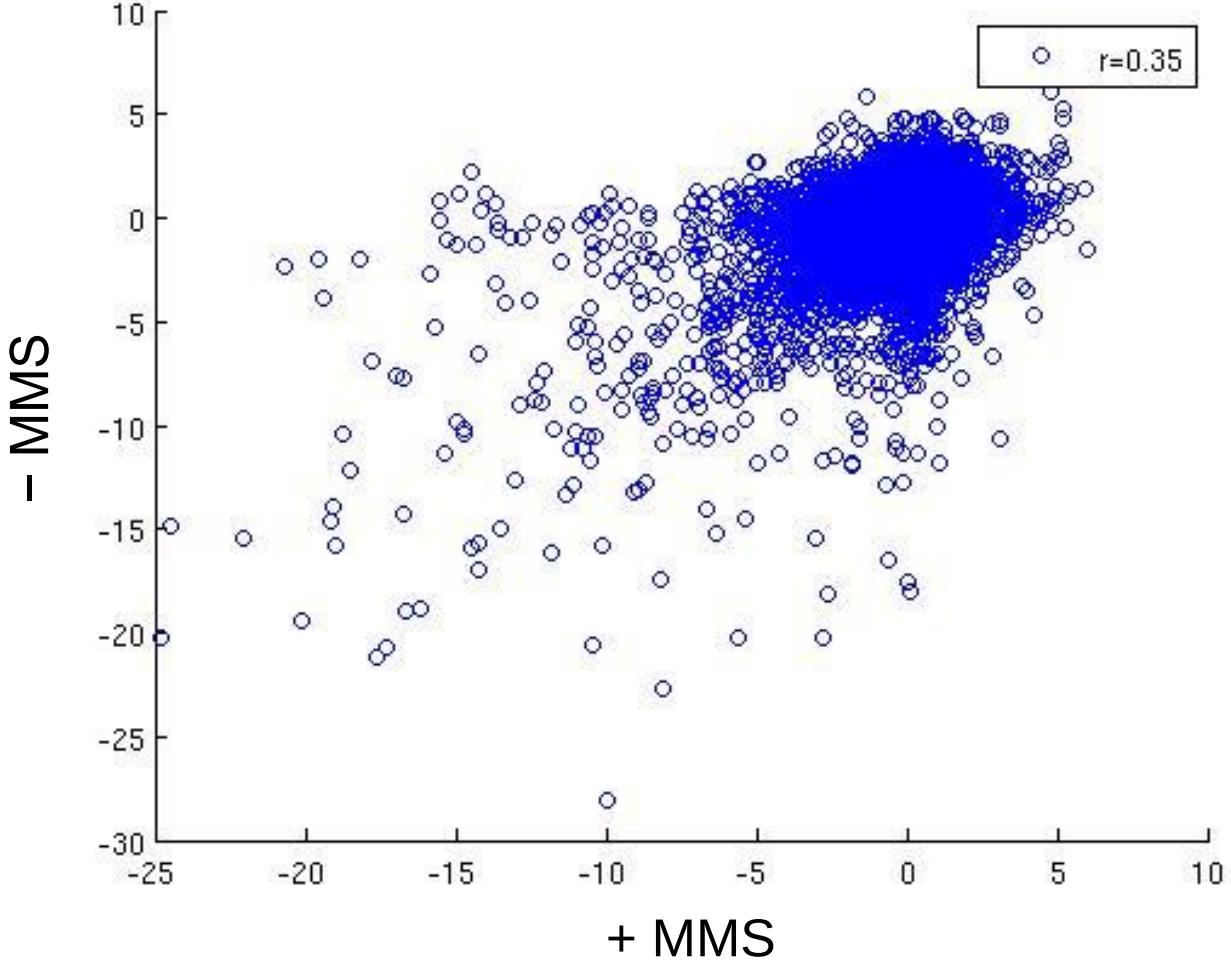


− MMS



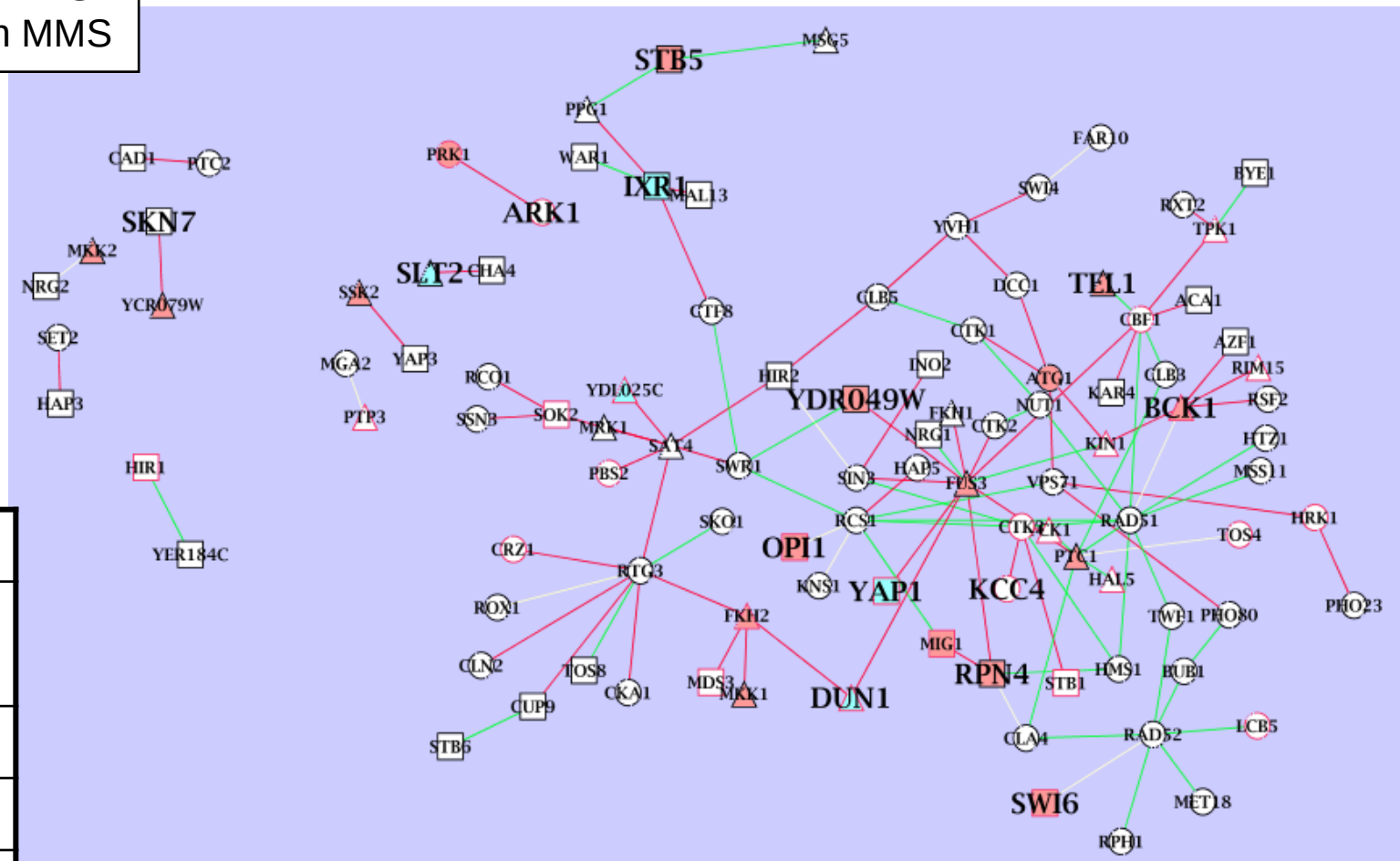
+ MMS

How in the world should we process these data ????



One answer: Develop statistics to identify only the differences

Red – Negative in MMS
Green – Positive in MMS



P	#
0.00001	228
0.0001	546
0.001	1406

Known targets of TEL1 / ATM

	Genetic Interaction Score −MMS ⇒ +MMS	**Pearson Correlation** −MMS ⇒ +MMS
DUN1		-0.03 ⇒ 0.4 ***
CBF1	-2.8 ⇒ 1.05 ***	0.03 ⇒ 0.31 **
SOK2		0.05 ⇒ 0.12
SUM1		0.03 ⇒ 0.20 *

*** < 0.00001, ** < 0.001, * < 0.05