Trey Ideker, PhD
UC San Diego

UCSF University of California San Francisco

UC San Diego School of Medicine

Fred B. Luddy Foundation

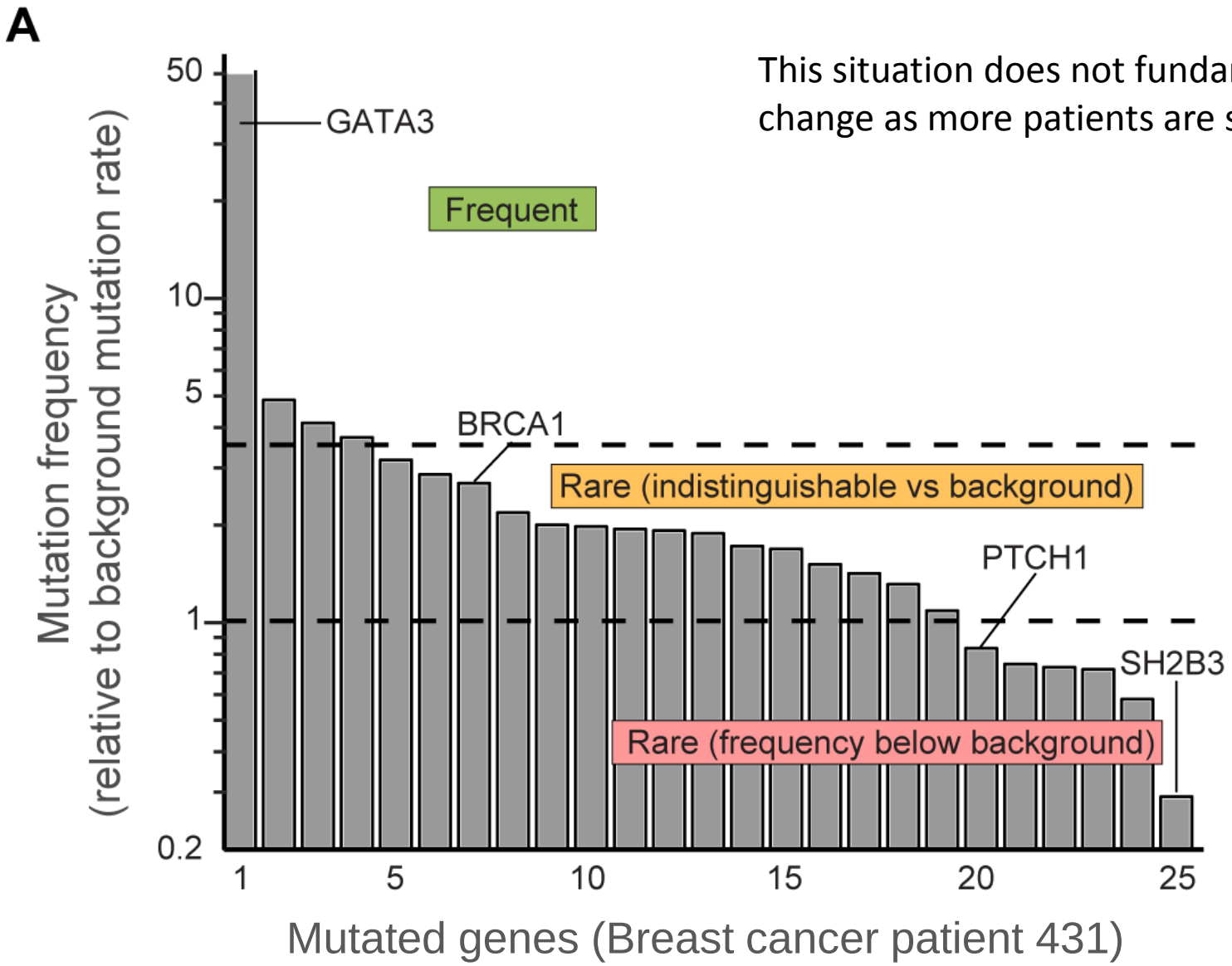
The CCMI is an initiative of the University of California, with major funding provided by the Chancellor of UC San Francisco, the Vice Chancellor of Health Sciences at UC San Diego, the California Institute for Quantitative Biosciences, and the Fred B. Luddy Foundation.

Massive DNA sequencing underway for cancer, approaching >10,000 genomes

Whole Tumor Genome Sequencing
with the Illumina HiSeq X Ten System

The challenge of heterogeneity:

Most tumor mutations are rare; completely different between patients



This situation does not fundamentally change as more patients are sequenced

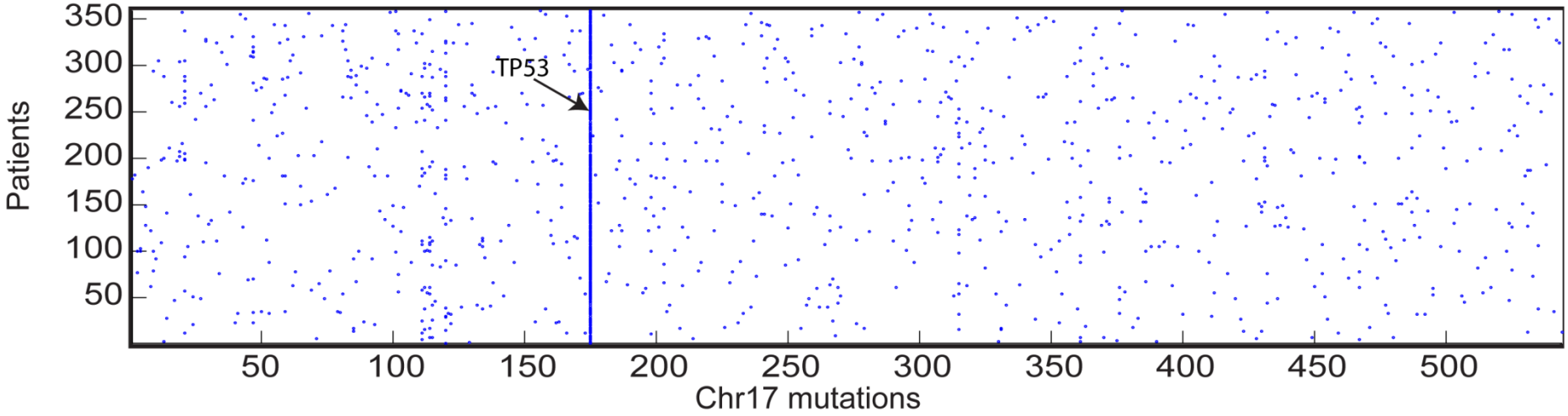
The challenge of heterogeneity:

Most tumor mutations are rare; completely different between patients

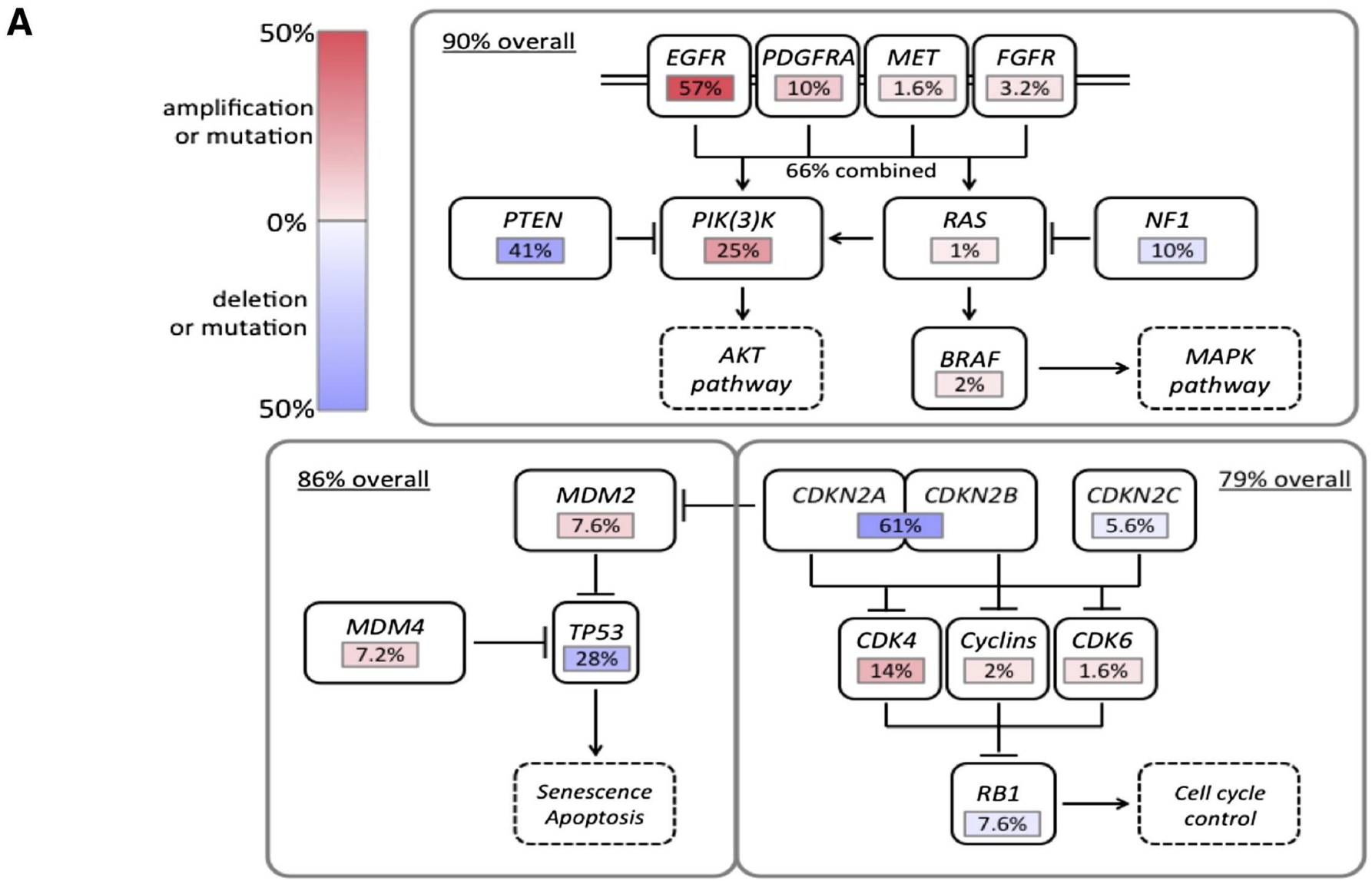
~100 somatic mutations per exome, ~10 drivers

No two patient tumors look alike

Example: TCGA ovarian cancer cohort of 351 patient tumors
Somatic mutations on Chr. 17

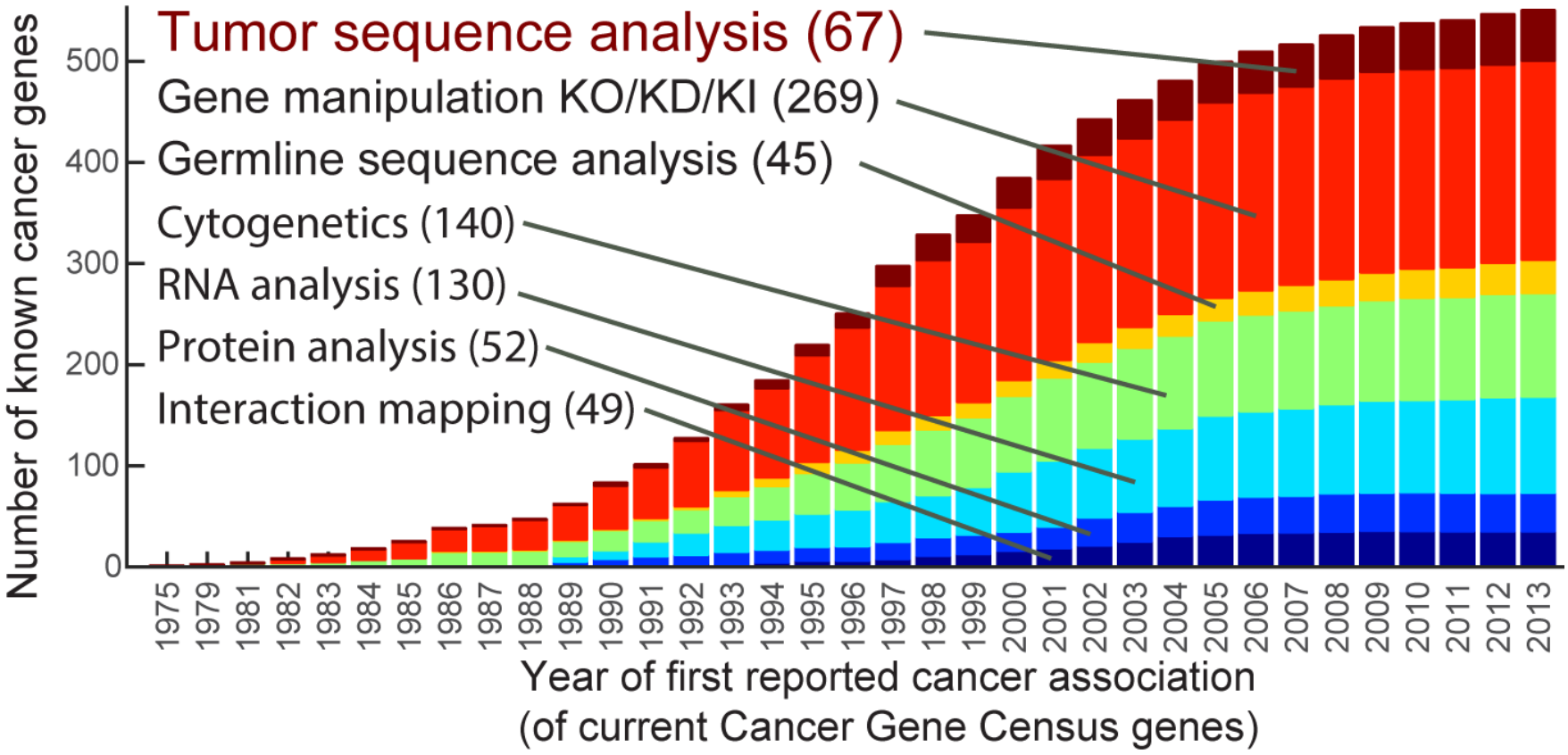


Networks address heterogeneity by integrating rare events



EGFR pathway alterations in glioblastoma; Brennan et al. *Cell* (2013)

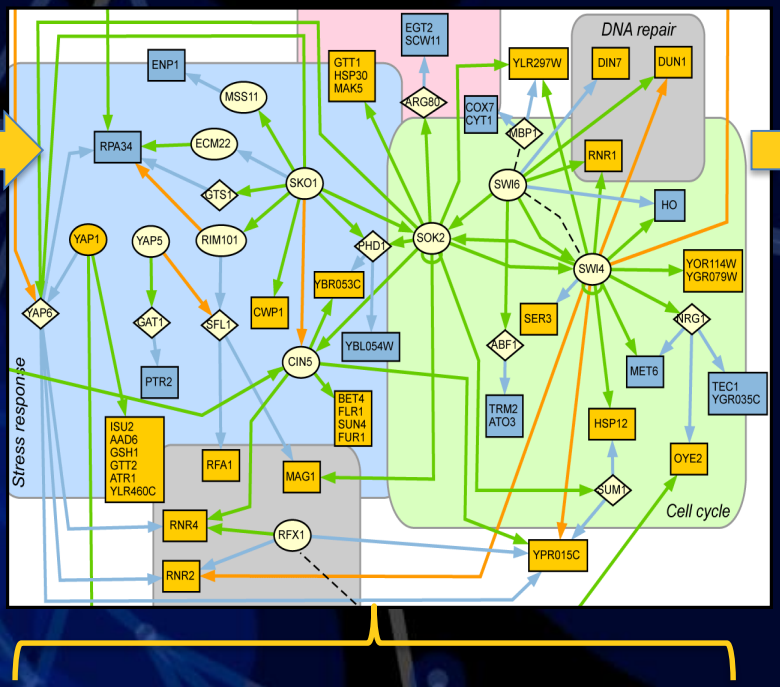
Genome analysis did not originally discover most known cancer genes



The Cancer Cell Map Initiative: Genome Interpretation *via* Networks

Cancer Cell Map

Patient genotype
Genome sequencing



Phenotype

- Disease diagnosis
- Response to therapy

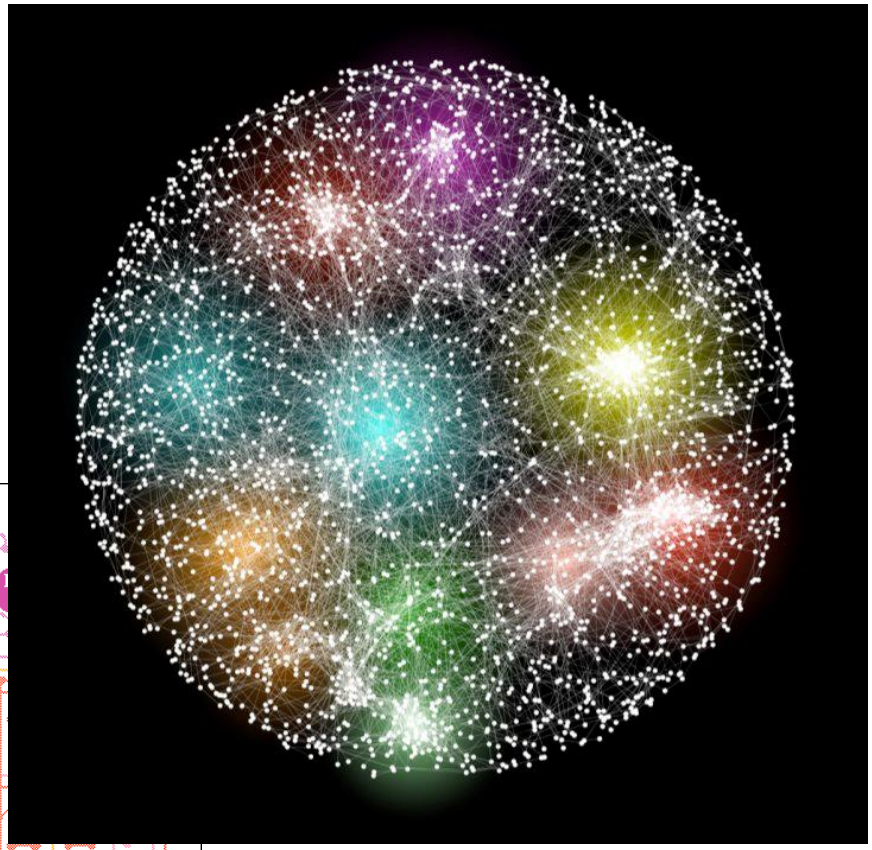
1) Integrating mol. network knowledge to translate patient genome to therapy

2) Comprehensive mapping the molecular networks under selection in cancer

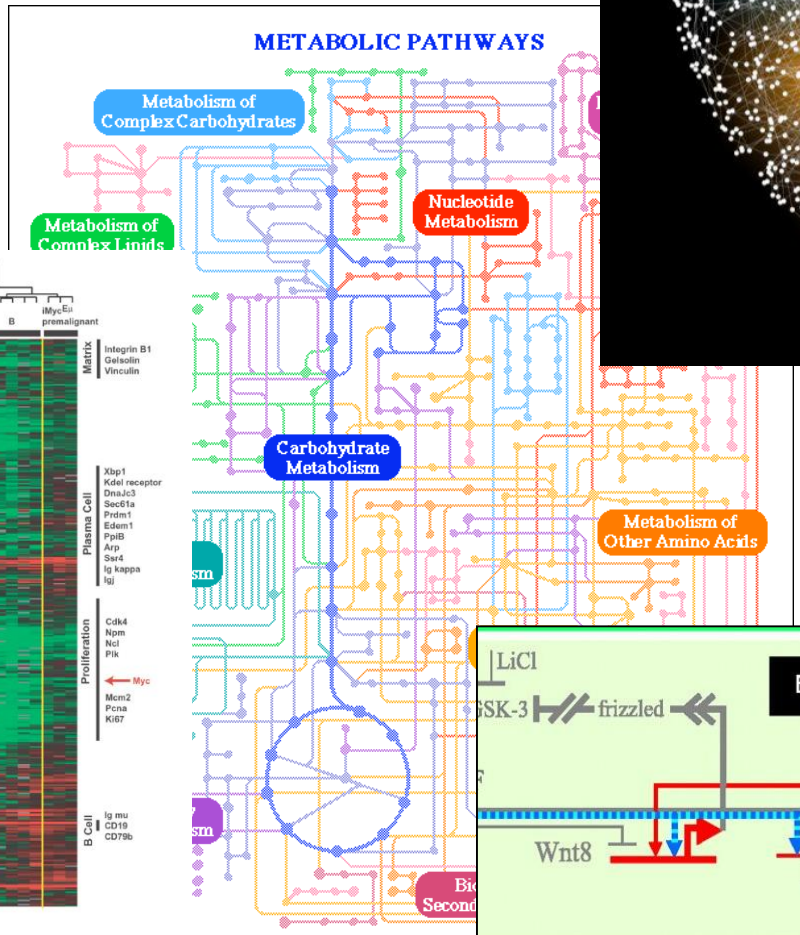
Krogan, Lippman, Agard, Ashworth, Ideker, *Molecular Cell* (2015)

Existing network data sets

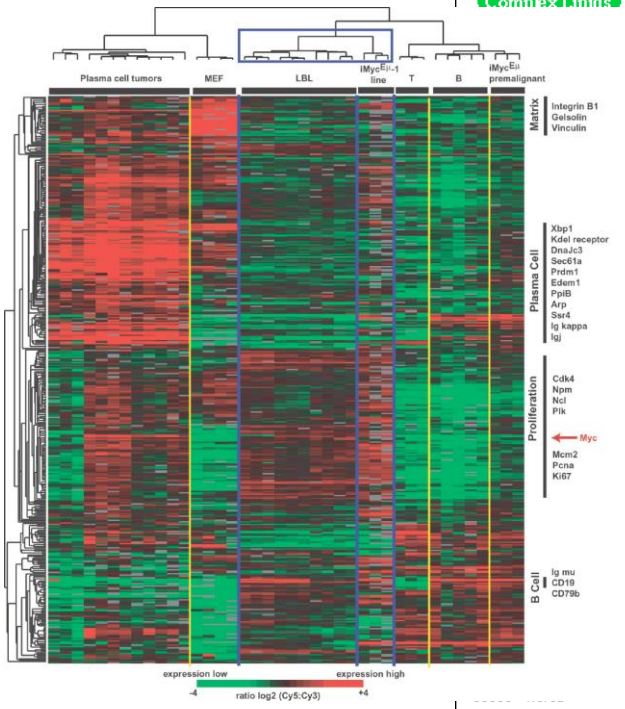
>10^6 interactions in BioGRID, IntAct, HPRD, DIP, GeneMania, HumanNet



Metabolic networks

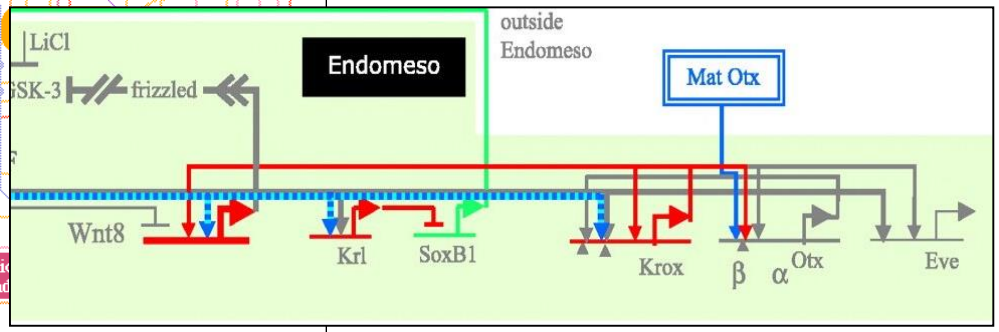


Co-expression networks



Genetic and protein interaction networks

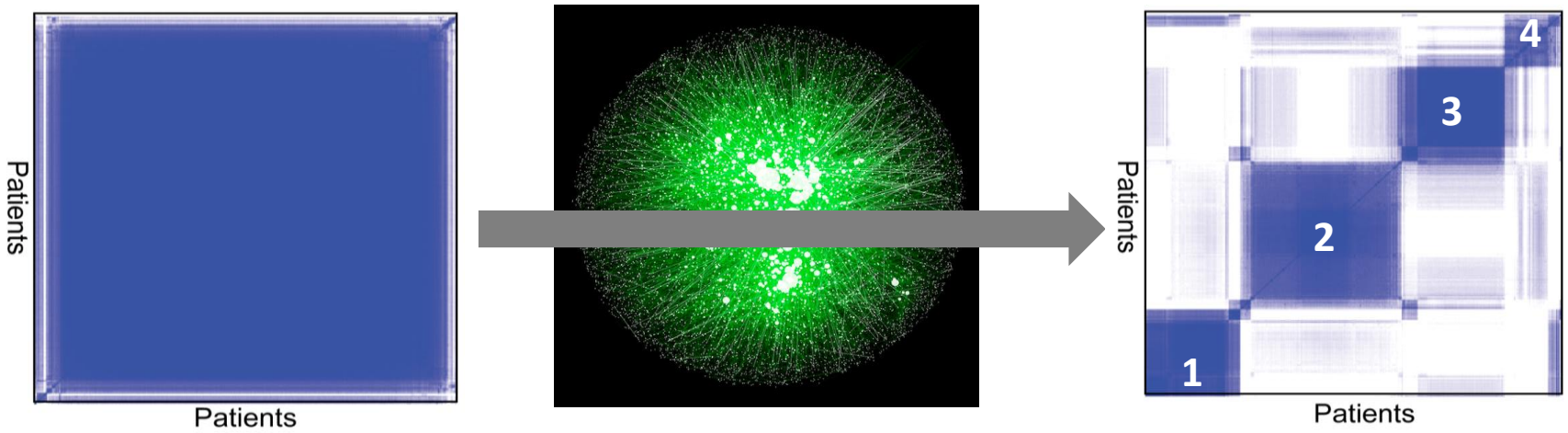
Protein-DNA networks



Network-Based Stratification of Genomes

Consensus clustering
of mutations / variants

Network-based stratification /
Consensus Clustering

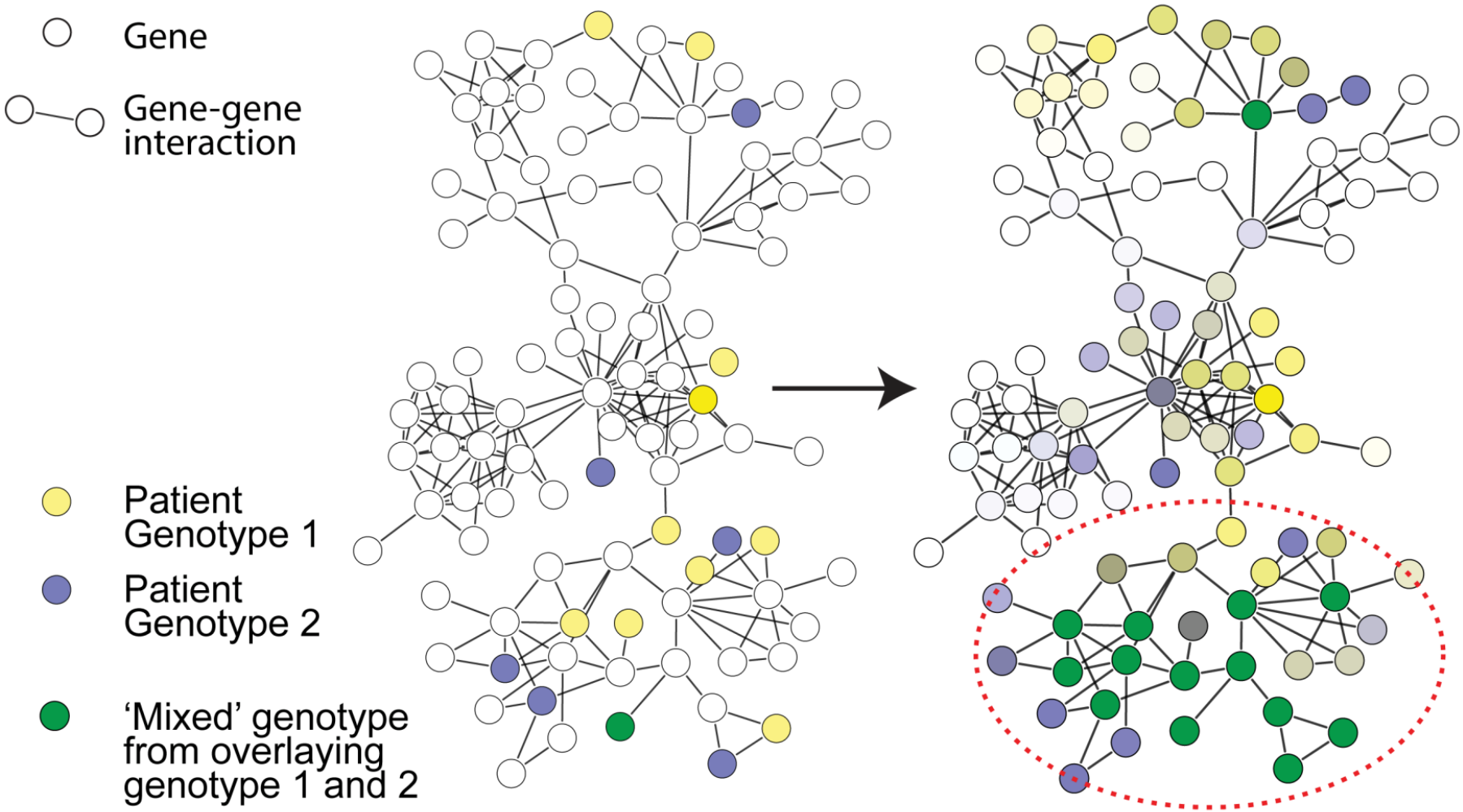


Nam Bui

Sources of molecular interactions:
Pathway Commons (MSKCC / Sander)
HumanNet (UT Austin / Marcotte)
StringDB (EMBL / Bork)

Matan Hofree et al., *Nat. Methods* (2013)
Ideker et al. *Bioinformatics* (2002); Chuang et al. *Mol Sys Biol* (2007); Lee et al. *PLoS Comp Bio* (2008); Chuang et al. *Blood* (2012)

Intuition for network smoothing



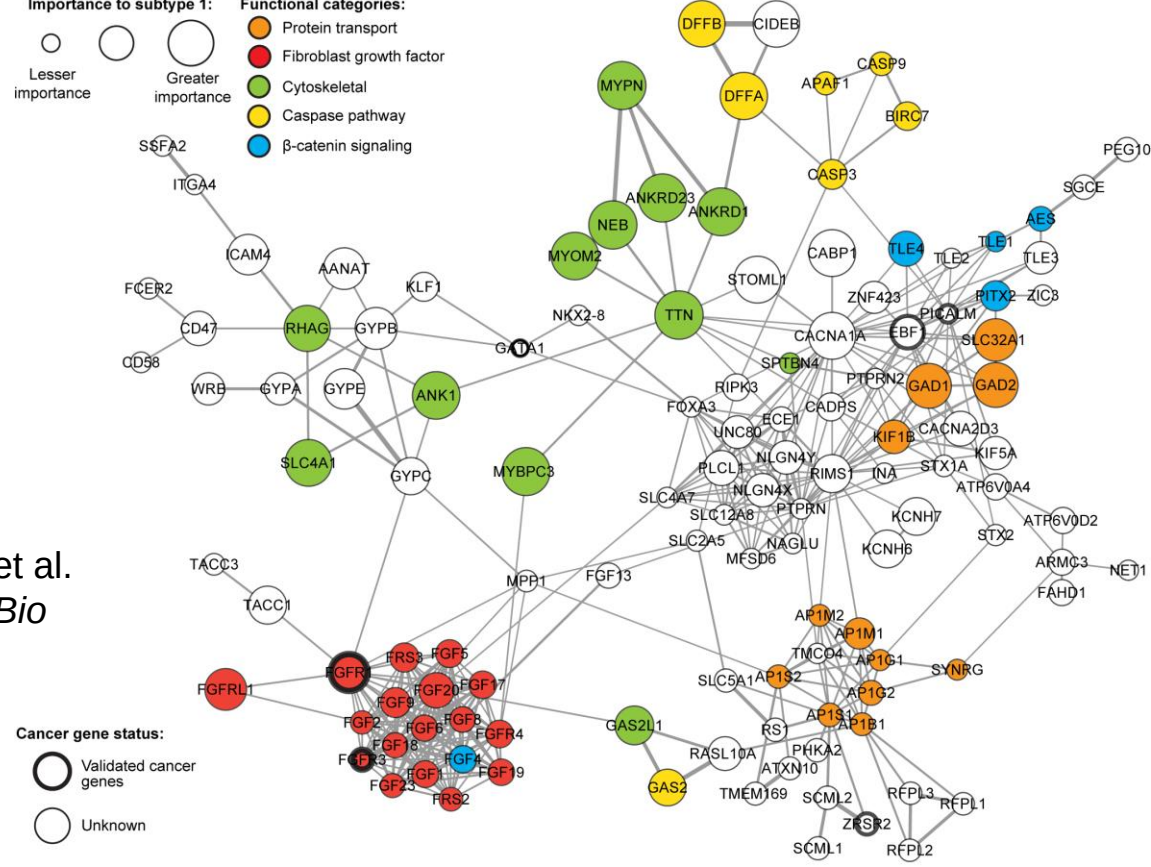
Network propagation (smoothing) in disease: Vanunu et al. PLoS CB (2010)
HotNet: Vandin et al. JCB (2011)

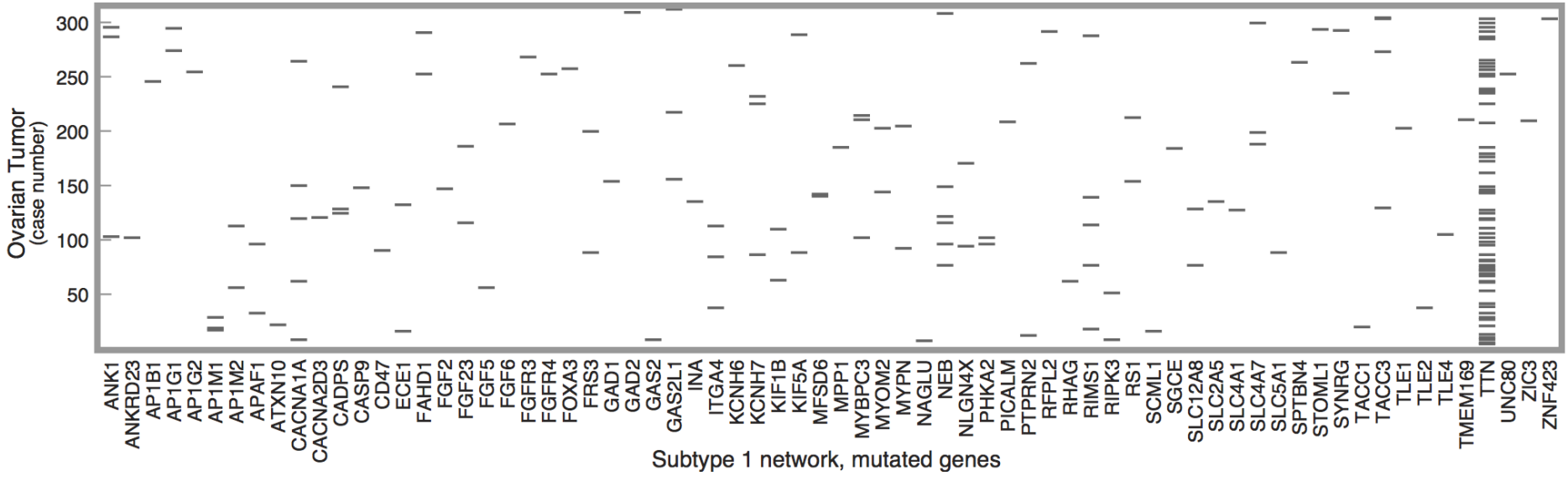
Network integrating aggressive ovarian tumor genomes

Without the map, these tumor genomes are heterogeneous

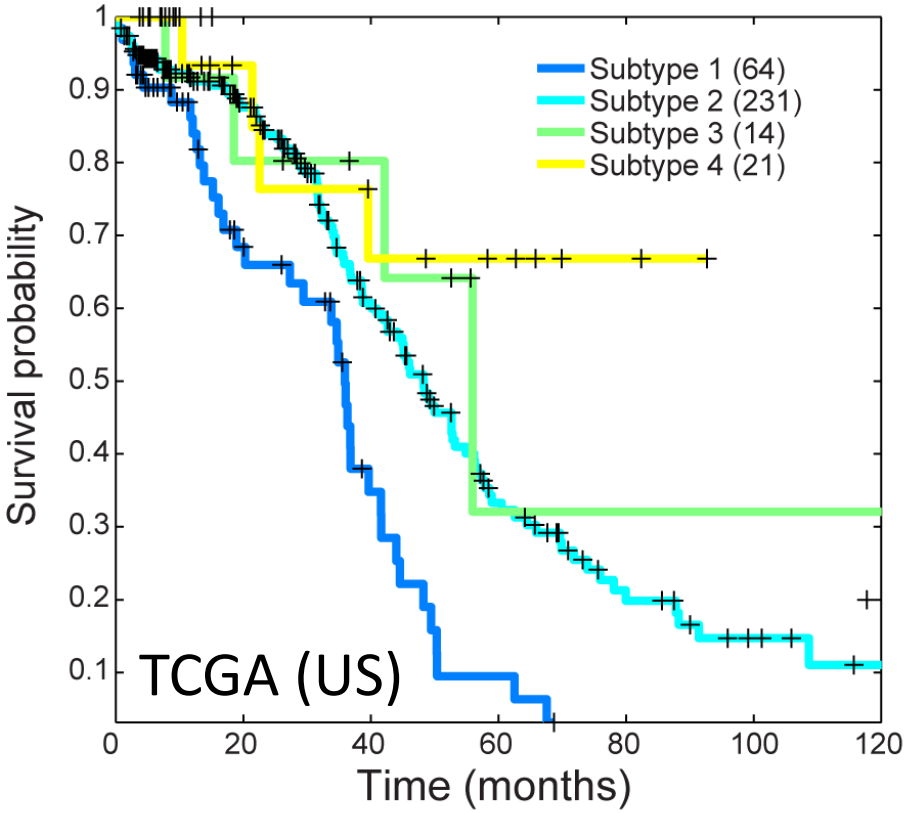
Hofree et al., *Nat. Methods* (2013)

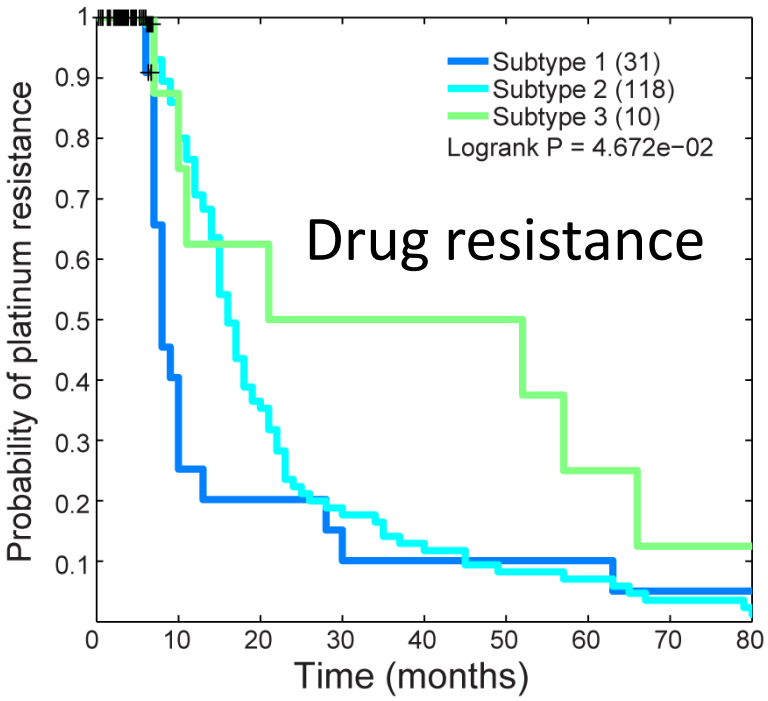
Ideker et al. *Bioinformatics* (2002); Chuang et al. *Mol Sys Biol* (2007); Lee et al. *PLoS Comp Bio* (2008); Chuang et al. *Blood* (2012)

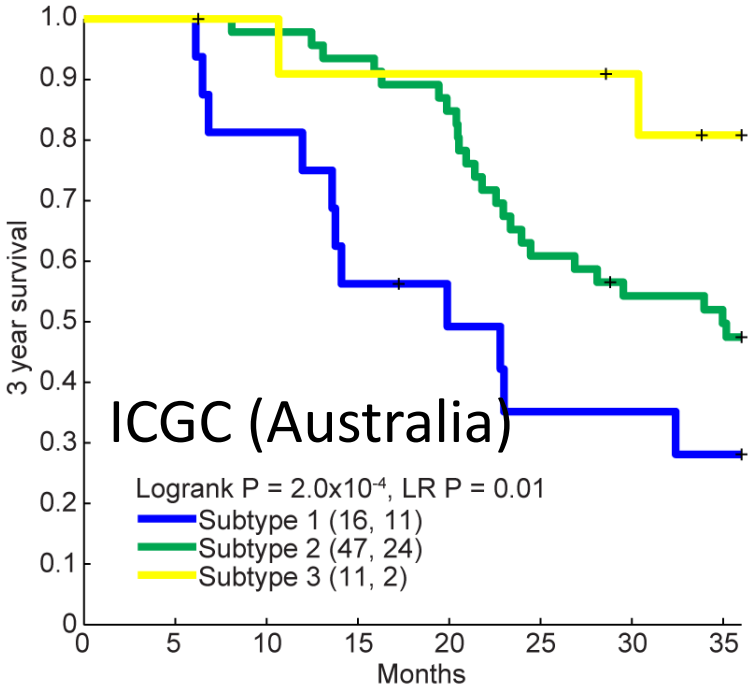




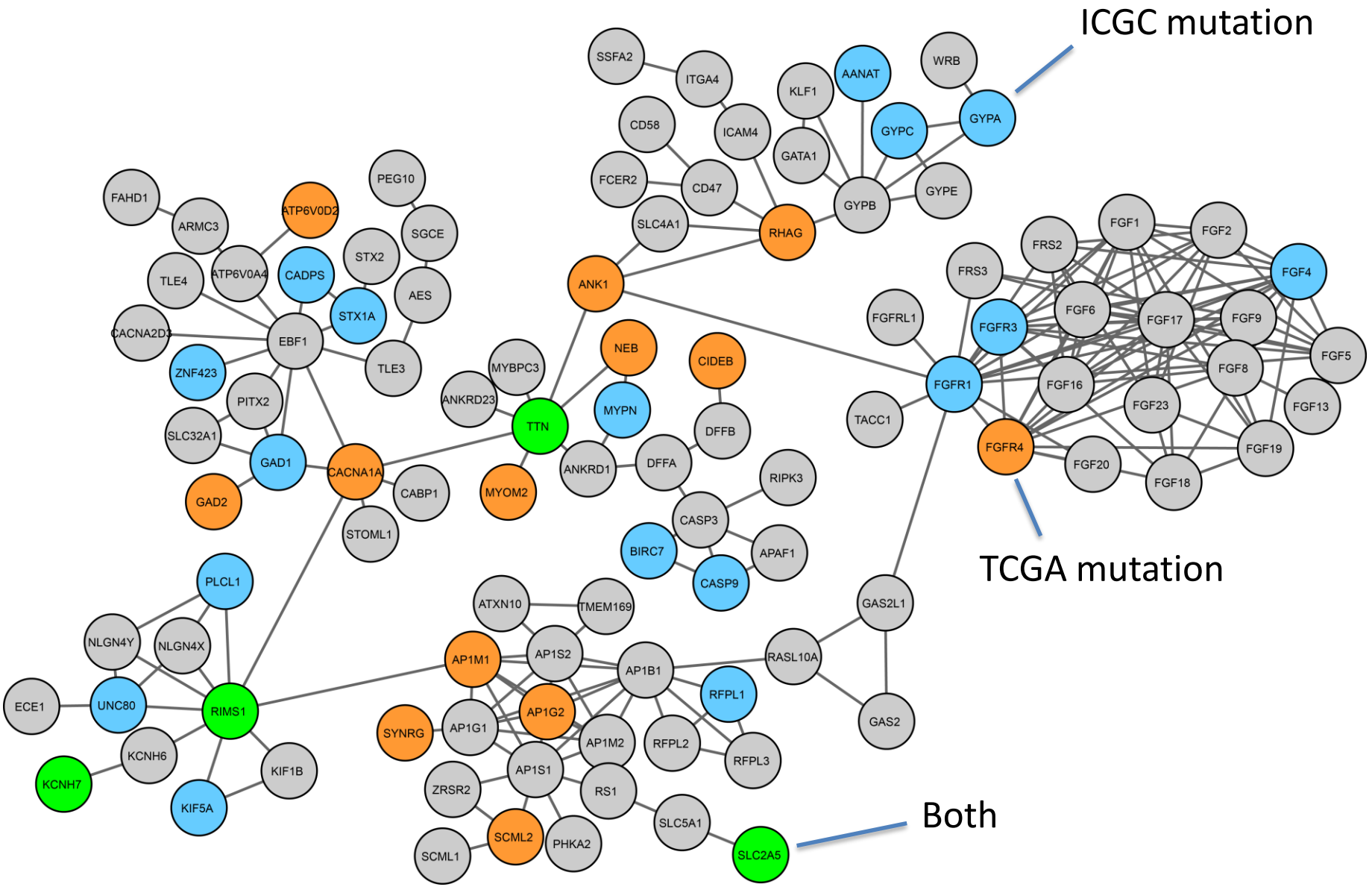
Network alterations govern survival and drug resistance





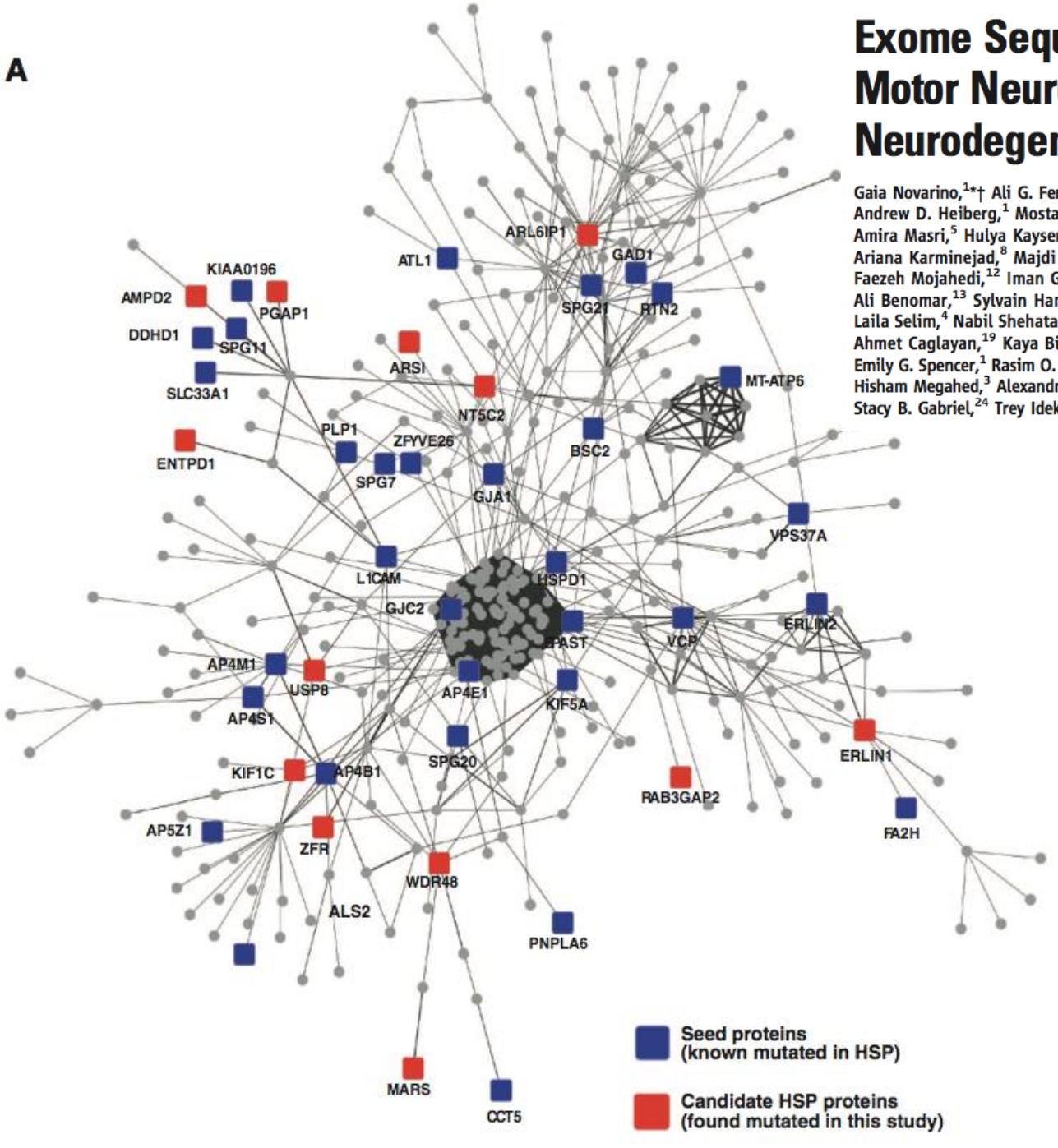


Network aggregating low-survival OVCA patients



Exome Sequencing Links Corticospinal Motor Neuron Disease to Common Neurodegenerative Disorders

Gaia Novarino,[1*†] Ali G. Fenstermaker,[1*] Maha S. Zaki,[3*] Matan Hofree,[2] Jennifer L. Silhavy,[1] Andrew D. Heiberg,[1] Mostafa Abdellateef,[1] Basak Rosti,[1] Eric Scott,[1] Lobna Mansour,[4] Amira Masri,[5] Hulya Kayserili,[6] Jumana Y. Al-Aama,[7] Ghada M. H. Abdel-Salam,[3] Ariana Karminejad,[8] Majdi Kara,[9] Bulent Kara,[10] Bita Bozorgmehri,[8] Tawfeg Ben-Omran,[11] Faezeh Mojahedi,[12] Iman Gamal El Din Mahmoud,[4] Naima Bouslam,[13] Ahmed Bouhouche,[13] Ali Benomar,[13] Sylvain Hanein,[14] Laure Raymond,[14] Sylvie Forlani,[14] Massimo Mascaro,[1] Laila Selim,[4] Nabil Shehata,[15] Nasir Al-Allawi,[16] P.S. Bindu,[17] Matloob Azam,[18] Murat Gunel,[19] Ahmet Caglayan,[19] Kaya Bilguvar,[19] Aslihan Tolun,[20] Mahmoud Y. Issa,[3] Jana Schroth,[1] Emily G. Spencer,[1] Rasim O. Rosti,[1] Naiara Akizu,[1] Keith K. Vaux,[1] Anide Johansen,[1] Alice A. Koh,[1] Hisham Megahed,[3] Alexandra Durr,[14,21] Alexis Brice,[14,21,22] Giovanni Stevanin,[14,21,22,23] Stacy B. Gabriel,[24] Trey Ideker,[2] Joseph G. Gleeson[1‡]



Gaia Novarino *et al.*
Science **343**, 506 (2014)


Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization
www.cytoscape.org
Reader
Apple Gmail Calendar LinkedIN Rhapsody Bioinformatics MBMA KhanAcademy CouncilBook iCloud Facebook Wikipedia Twitter Yahoo! AirBnB News
Inbox – trey.ideker@gmail.com – Gmail
National Resource for Network Biology
Cytoscape: An Open Source Platform for Complex Net...
Cytoscape
Intro.
Download
Apps
Docs
Community
Report a Bug
Help
Google™ Custom Search
Search
Cytoscape
Network Data Integration, Analysis, and Visualization in a Box
Introduction
Download v3.1.0

www.ndexbio.org

NDEx About Documentation API Report a Bug Contact Us Networks EGFR Network Sign In

EGFR-dependent Endothelin signaling events

Nodes: 22 **Edges:** 60

This network belongs to the NCI Pathway Interaction Database (PID) and was obtained from Pathway Commons (PC2 v.6)

Version: 07-MAR-2014
PUBLIC

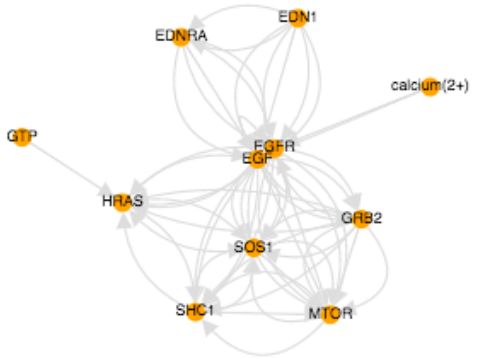
Created: Mar 7, 2015
UUID: 24319bd8-c4ab-11e4-bcc4-000c29cb28fb

Your Access Privileges: None
Other Admins:
- nci-pid

Actions

Network Properties

sourceFormat SIF
ORGANISM



Network Terms Depth: 1-step Run Query Advanced Query

Edges Nodes Provenance

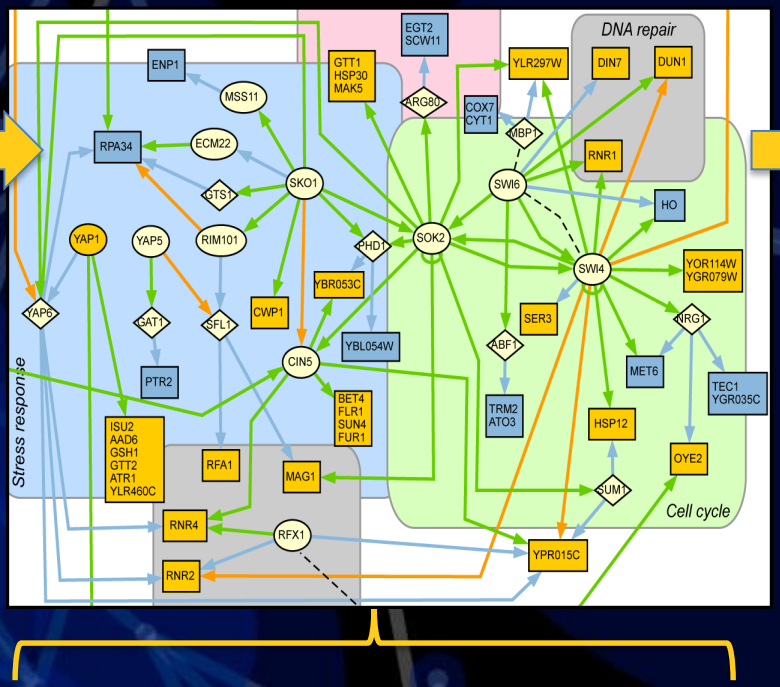
Subject	Predicate	Object	Citations
EDN1	in-complex-with	EDNRA	
EDN1	neighbor-of	EDNRA	5
EDN1	controls-state-change-of	EGFR	5
EDN1	neighbor-of	EGFR	5
EDN1	controls-state-change-of	EGF	5
EDN1	controls-transport-of	EGF	5

Funding: Pfizer, J&J, Roche, NCI U24

The Cancer Cell Map Initiative: Genome Interpretation *via* Networks

Cancer Cell Map

Patient genotype
Genome sequencing



Phenotype

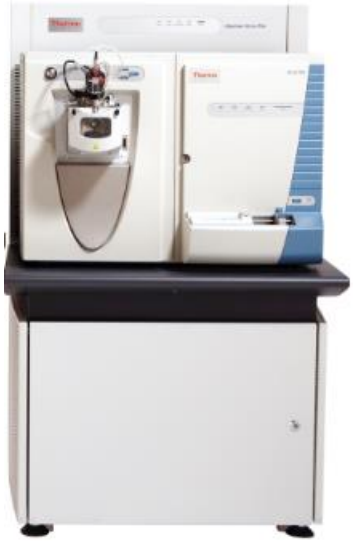
- Disease diagnosis
- Response to therapy

1) Using molecular networks to translate patient genome to therapy

2) Comprehensive mapping the molecular networks under selection in cancer

Krogan, Lippman, Agard, Ashworth, Ideker, *Molecular Cell* (2015)

Network Mapping Approach 1:
Physical protein-protein network mapping using AP/MS/MS



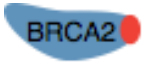
Orbitrap Velos Elite

TSQ Quantiva

Nevan Krogan, UCSF

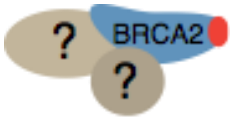
Velos Pro Ion Trap

Express a tagged protein in cells



The tagged protein interacts normally with native proteins

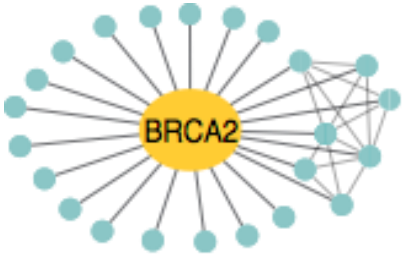
Harvest all the proteins



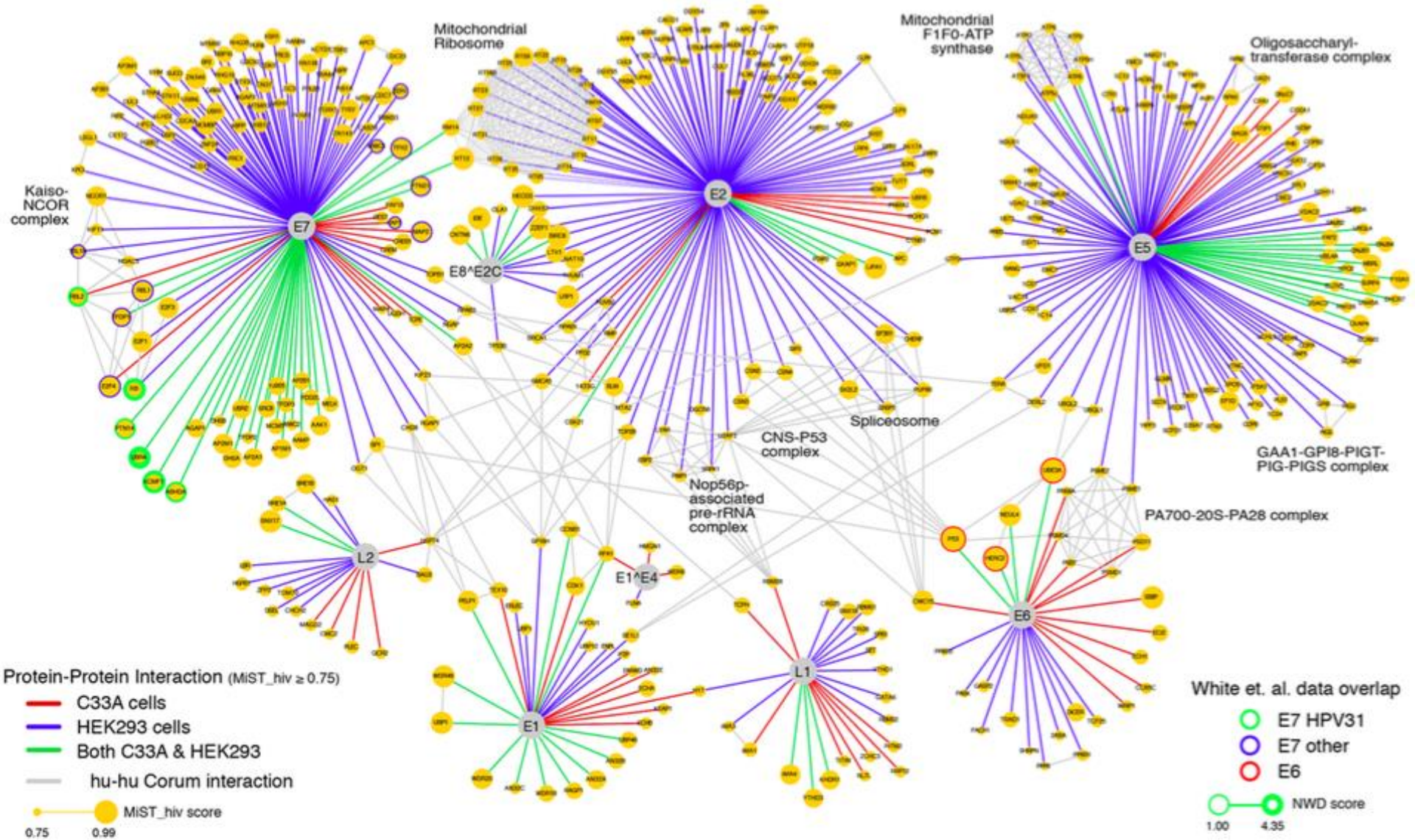
Purify the tagged BRCA2 AND all its interacting cellular proteins

Mass spectrometer identifies all of the purified proteins

Build BRCA2 interaction network

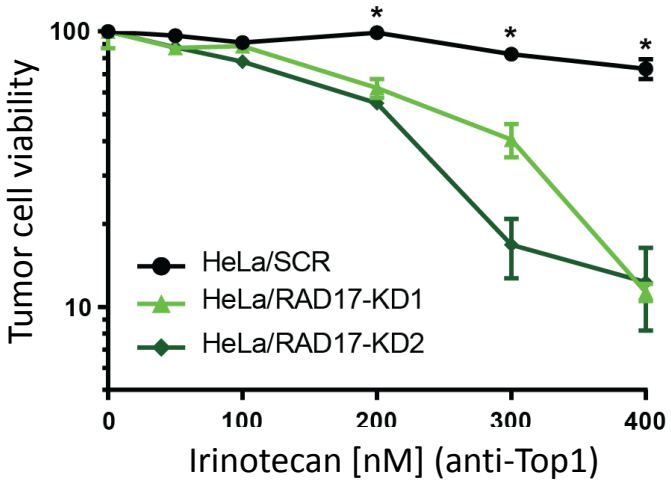


The HPV31 Interactome



Manon Eckhardt, Andy Gross, Cytoscape

Network Mapping Approach 2:
Gene-gene & chemo-genetic interactions

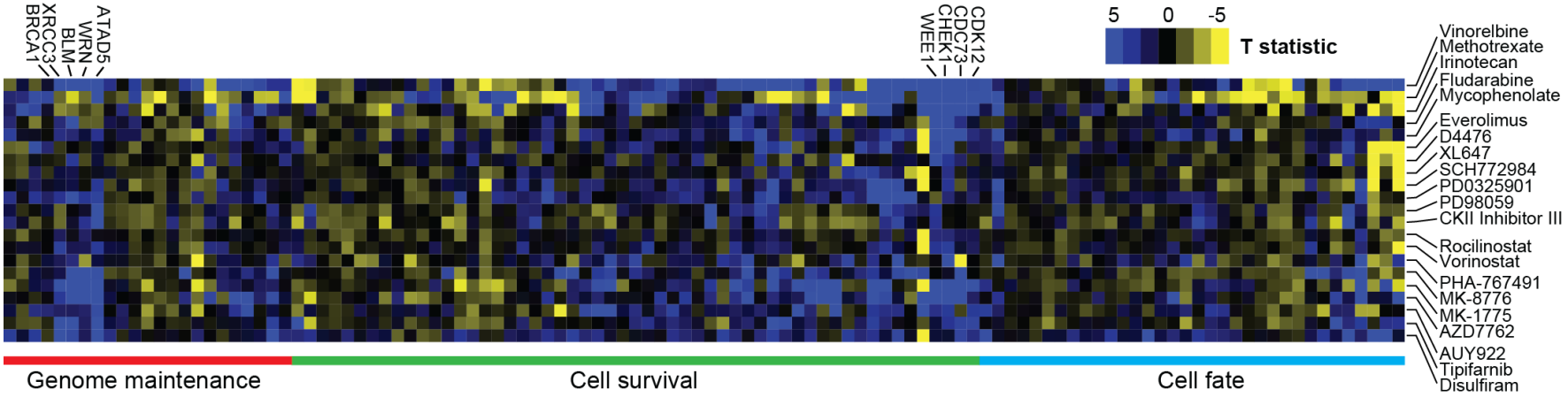


Rohith Srivas
(Fmr Student)

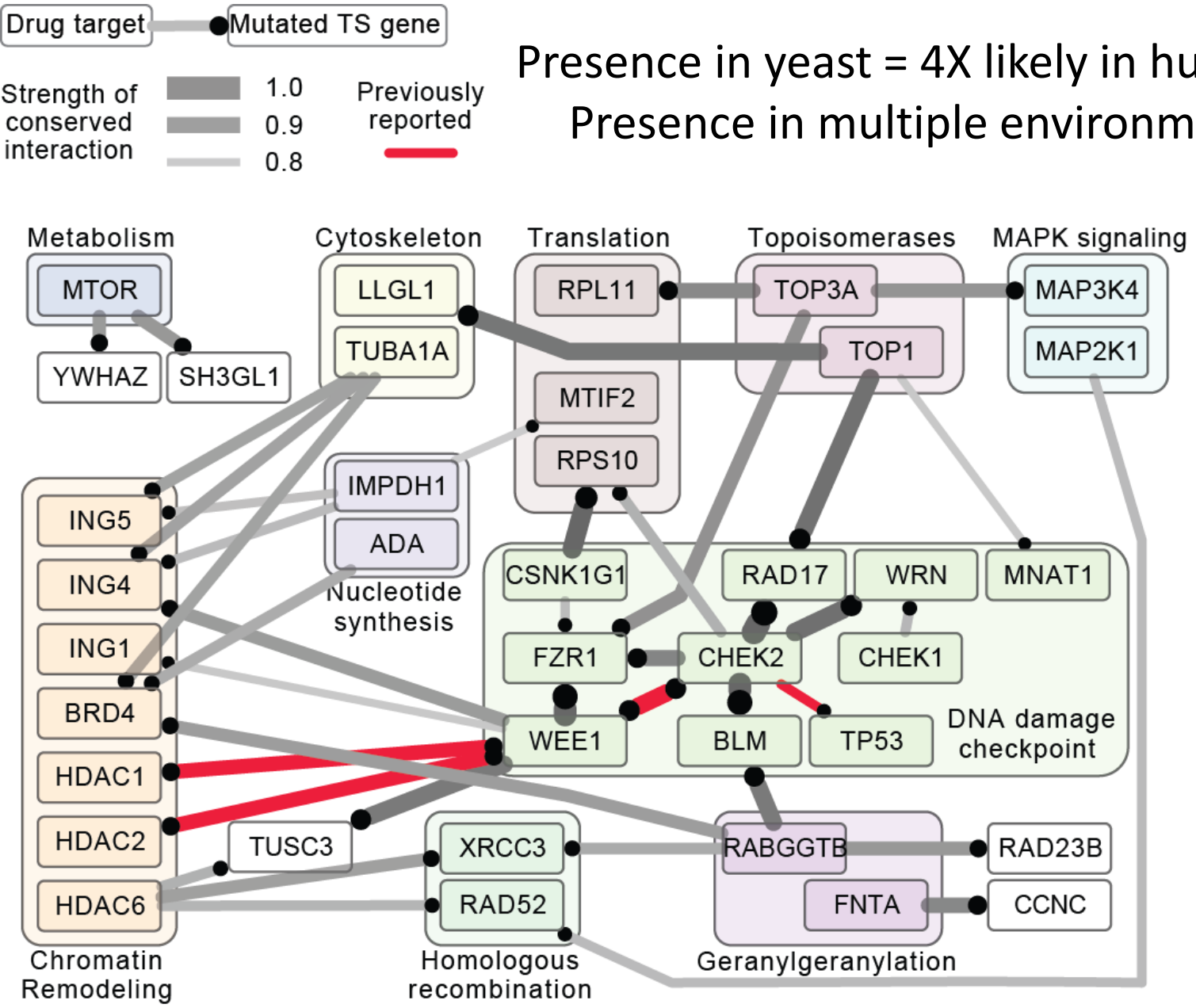
JP Shen
(MD Fellow)

ROWS:
21 targeted drugs

COLUMNS:
112 tumor suppressor knockdowns



Stability of interactions across contexts – a key property



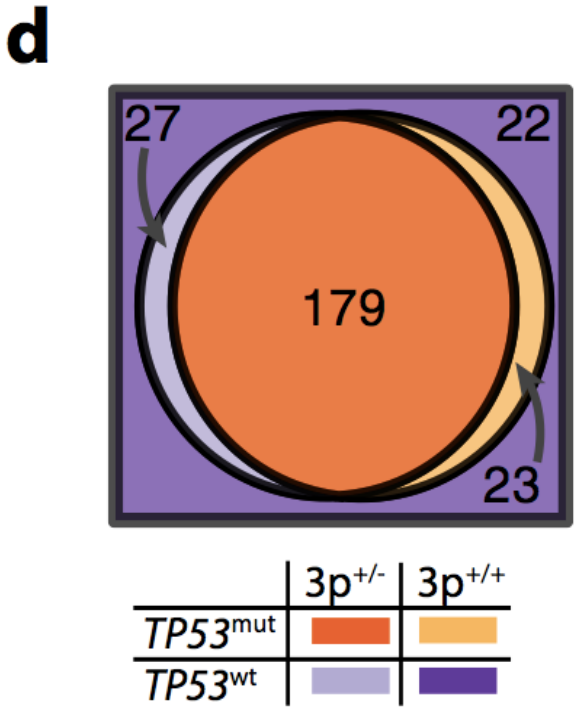
Network Mapping Approach 3:

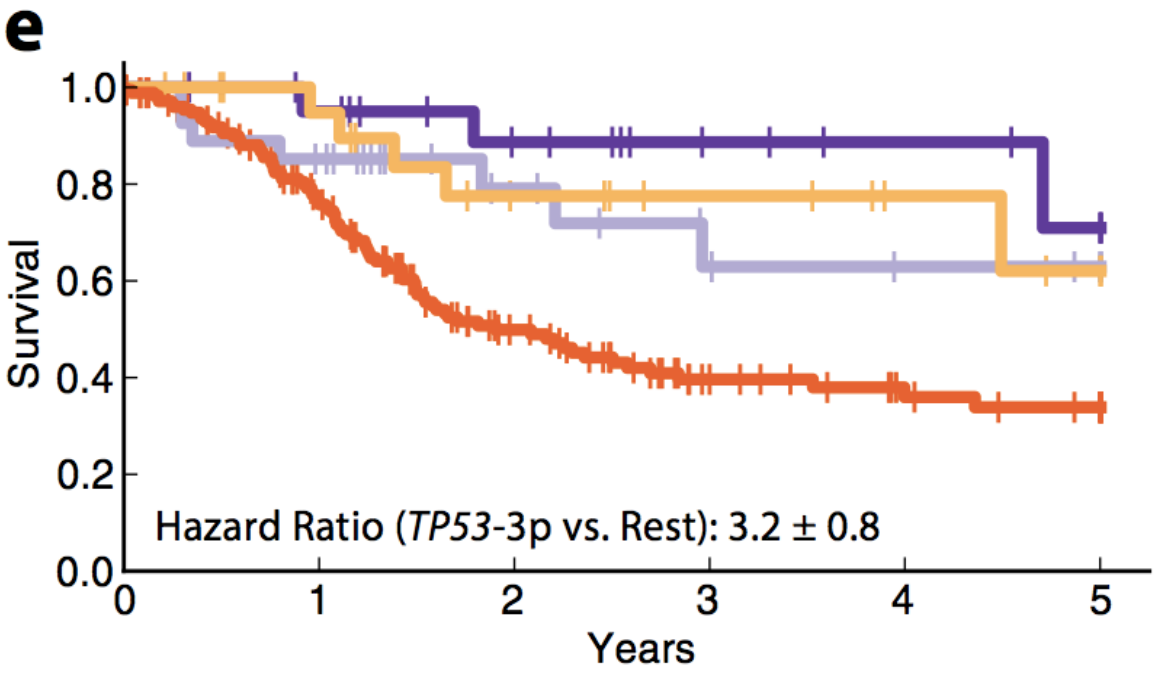
Genetic interactions in tumor populations

Andy Gross Quyen Nguyen

w/ Jenn Grandis, Neil Hayes, Ezra Cohen, Scott Lippman and the TCGA Consortium

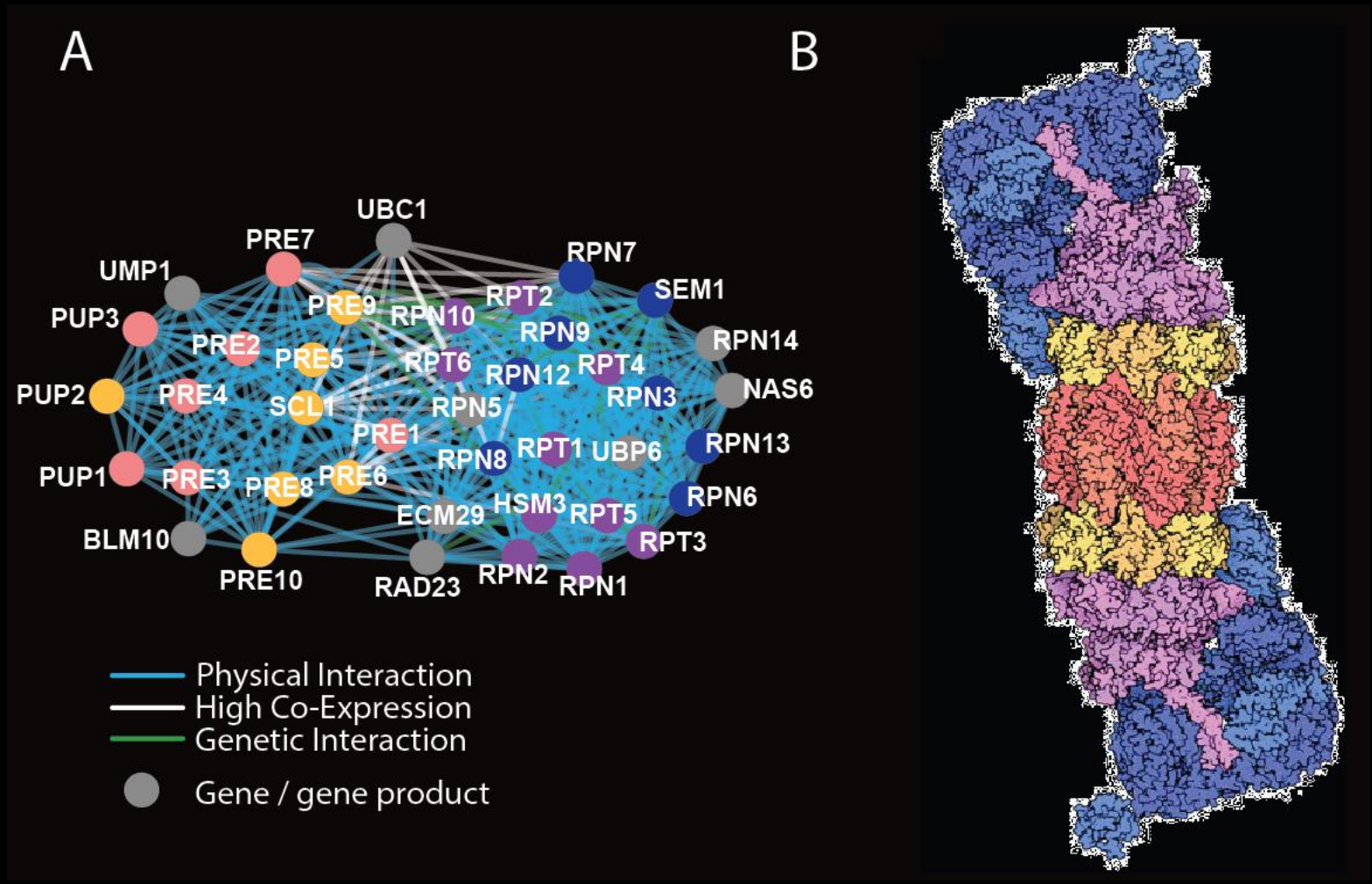
TP53 mutation interacts with chromsome 3p loss
HPV neg. head & neck tumor data
Same trend is found in pan-cancer analysis





Gross et al. *Nature Genetics* (2014)

Analysis challenge:
Networks do not look like the contents of cells

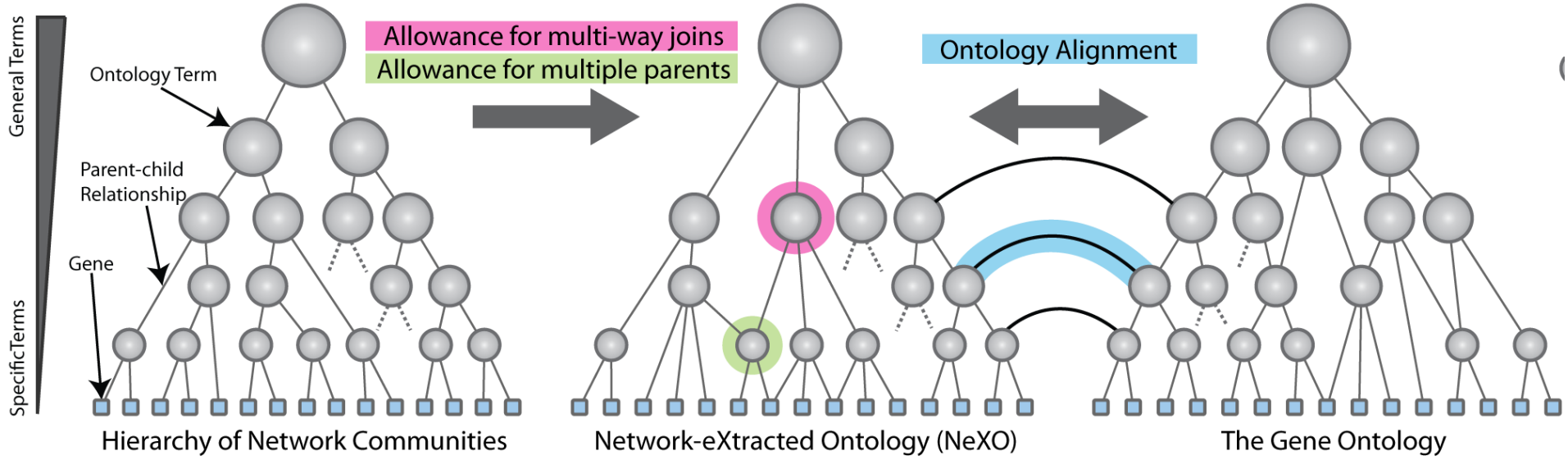


Carvunis and Ideker, *Cell* (2014)

NeXO Method – In Brief

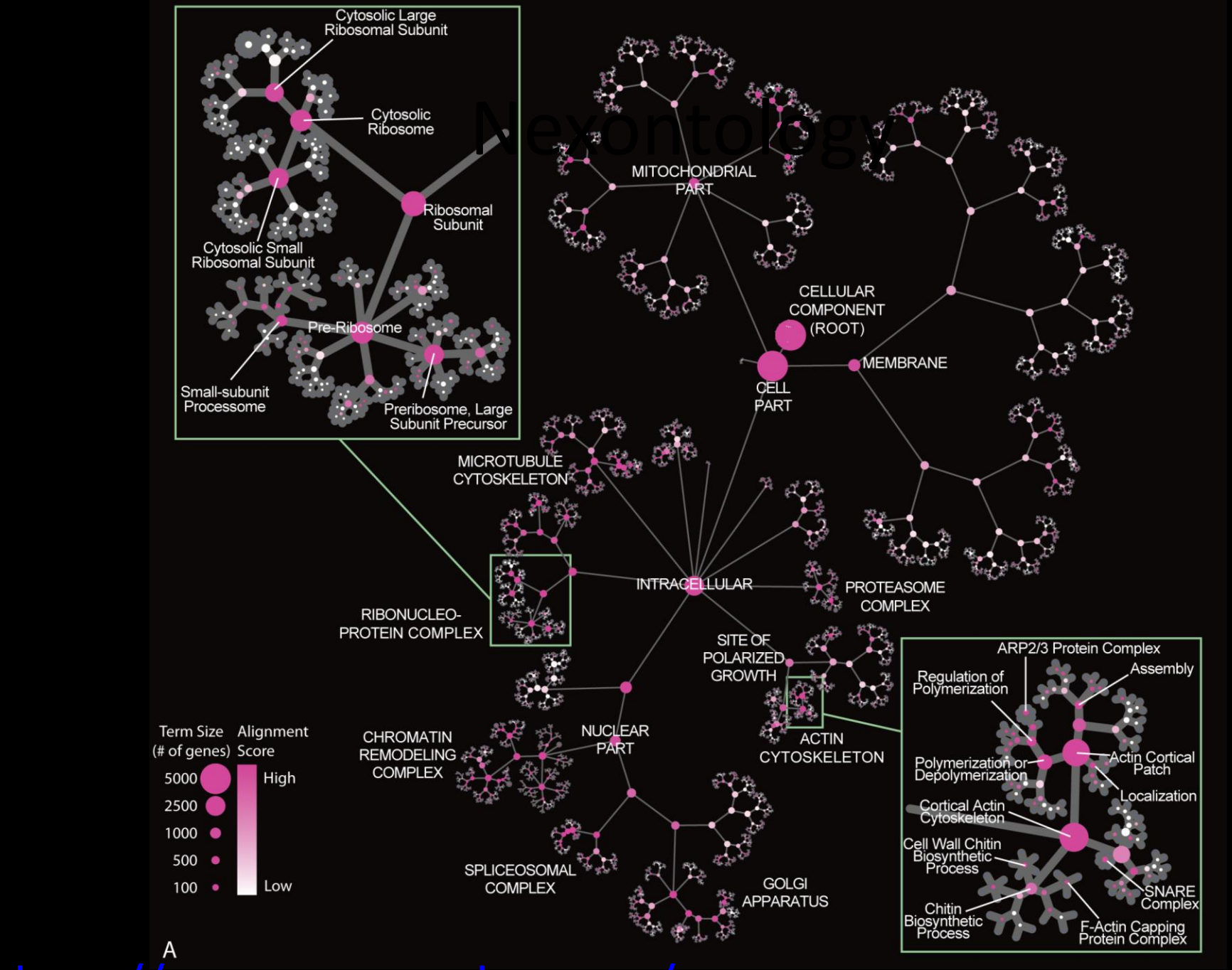
Diverse 'omics data encoded in molecular networks (here, yeast)

- Protein-protein interactions
- Co-expression information
- Synthetic-lethal interactions



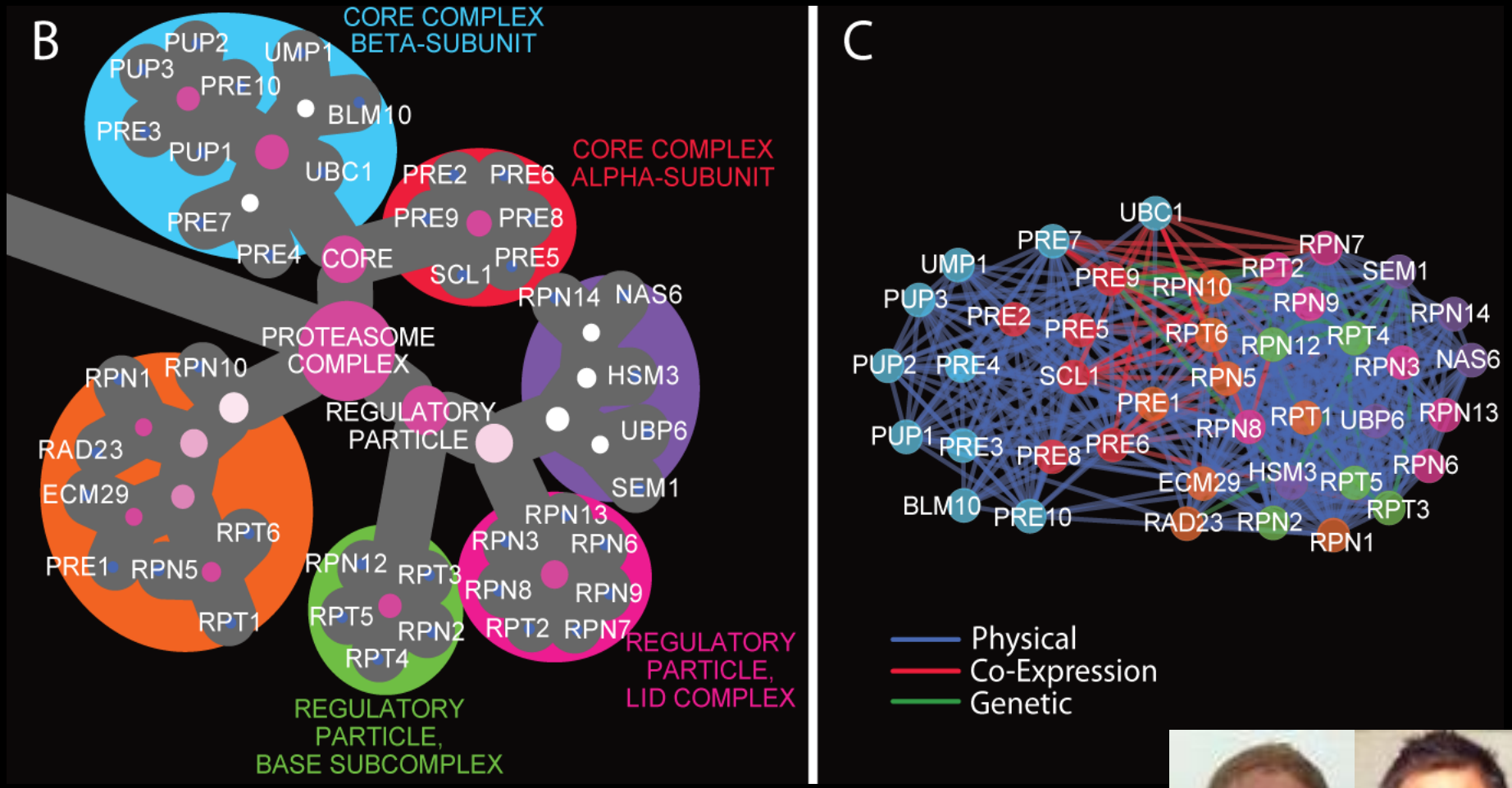
Kramer et al. *Bioinformatics* / *ISMB* 2014

Dutkowski et al. *Nat Biotech* 2013, *NAR* 2014



http://www.nexontology.org/

Gene Ontologies from Networks

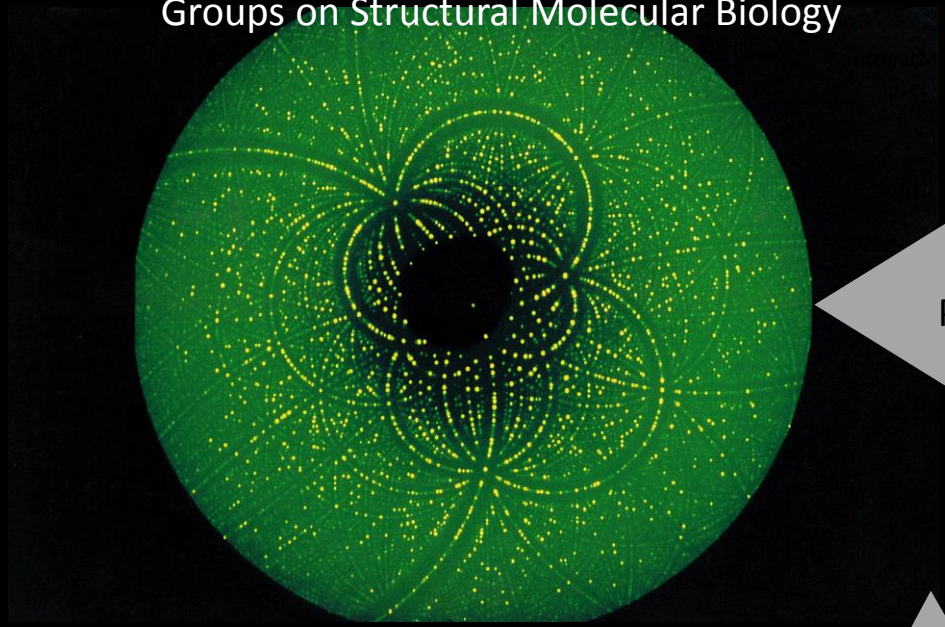


Kramer et al. *Bioinformatics* / *ISMB* 2014

Dutkowski et al. *Nat Biotech* 2013

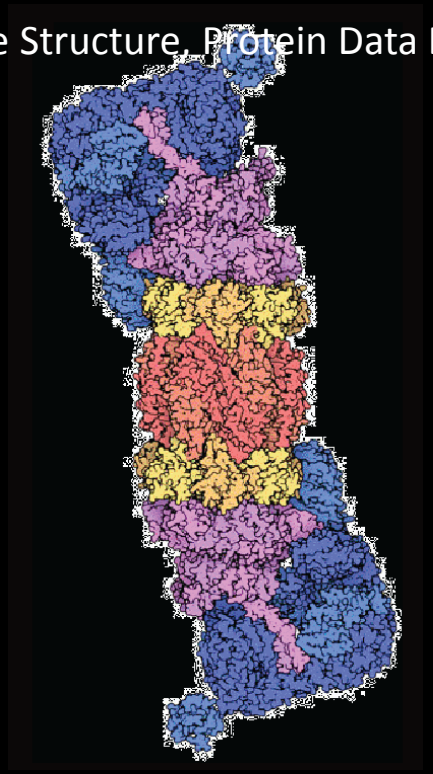
Dutkowski et al. *NAR* 2014

X-ray diffraction image, Max Planck Working Groups on Structural Molecular Biology



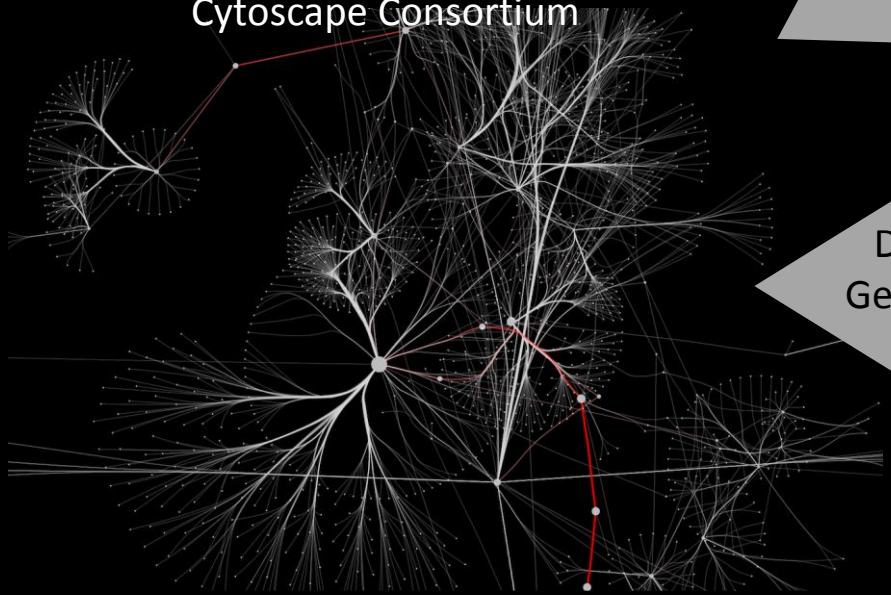
Structural Proteomics

Proteasome Structure, Protein Data Bank



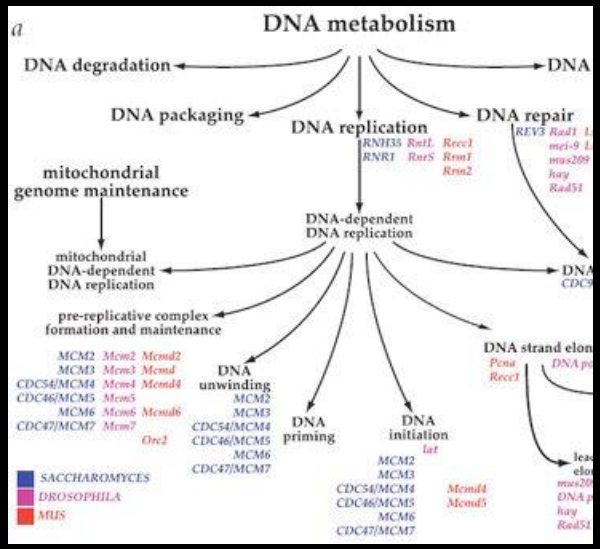
Chemical cross-linking

Molecular interaction network, Cytoscape Consortium



Data-driven Gene Ontology

Gene Ontology, DNA metabolism



Summary

- Genome sequencing has revealed thousands of genes altered in cancer
- Common patterns emerge at the level of cellular components, pathways and systems
- We have launched an open campaign to move from mapping of cancer genomes to mapping of cancer networks
- Network data can be translated into hierarchical models of the cancer cell
- Such knowledge is not just nice, it is probably necessary


Sponsors
NCI, NIGMS, NIEHS, NIMH
J&J, Pfizer, Roche, Fred Luddy
Questions?
San Diego Center for Systems Biology, National Resource for Network Biology, and the Cytoscape Community