Personalized Cardiovascular Medicine and Drug Development

Joseph Loscalzo, M.D., Ph.D.
Brigham and Women's Hospital
Harvard Medical School
Boston, MA

Outline

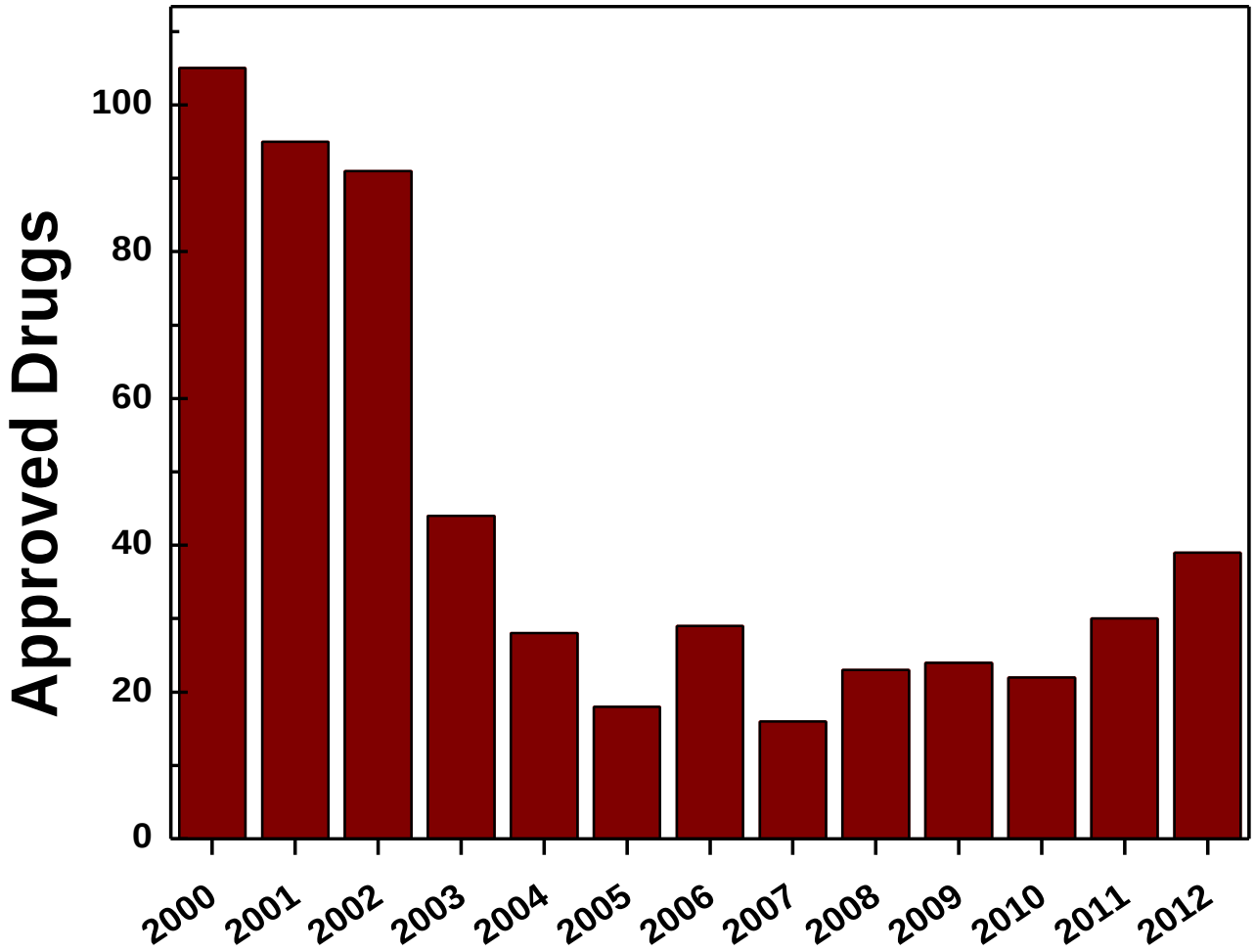
- Overview of Pharmacology and Drug Development
- Disease Networks and Identification of Drug Targets
- Quantitative (Patho)phenotypes in Clinical Trials
- Network Dynamics and Implications for Clinical Trial Design
- Approaches to Clinical Trial Design in the Era of Personalized Therapies

Overview of Pharmacology and Drug Development

Brief History: Key Paradigms

- *Empirical Physiological Effects*: Phenotypic Screening
- *Toxicity Assessment*: Animal (and Human) Experimentation
- *Reductionist Drug Target Identification*— Ehrlich's 'Magic Bullet' Concept
- *Chemotherapy & Receptor Constructs*
- *Medicinal Chemistry, Structure-Activity Relationship, and Mechanisms of Drug Action*: Semi-empiric Drug Screening
- *Protein Structure and Rational Drug Design*

FDA Approved Drugs: 2000-2012



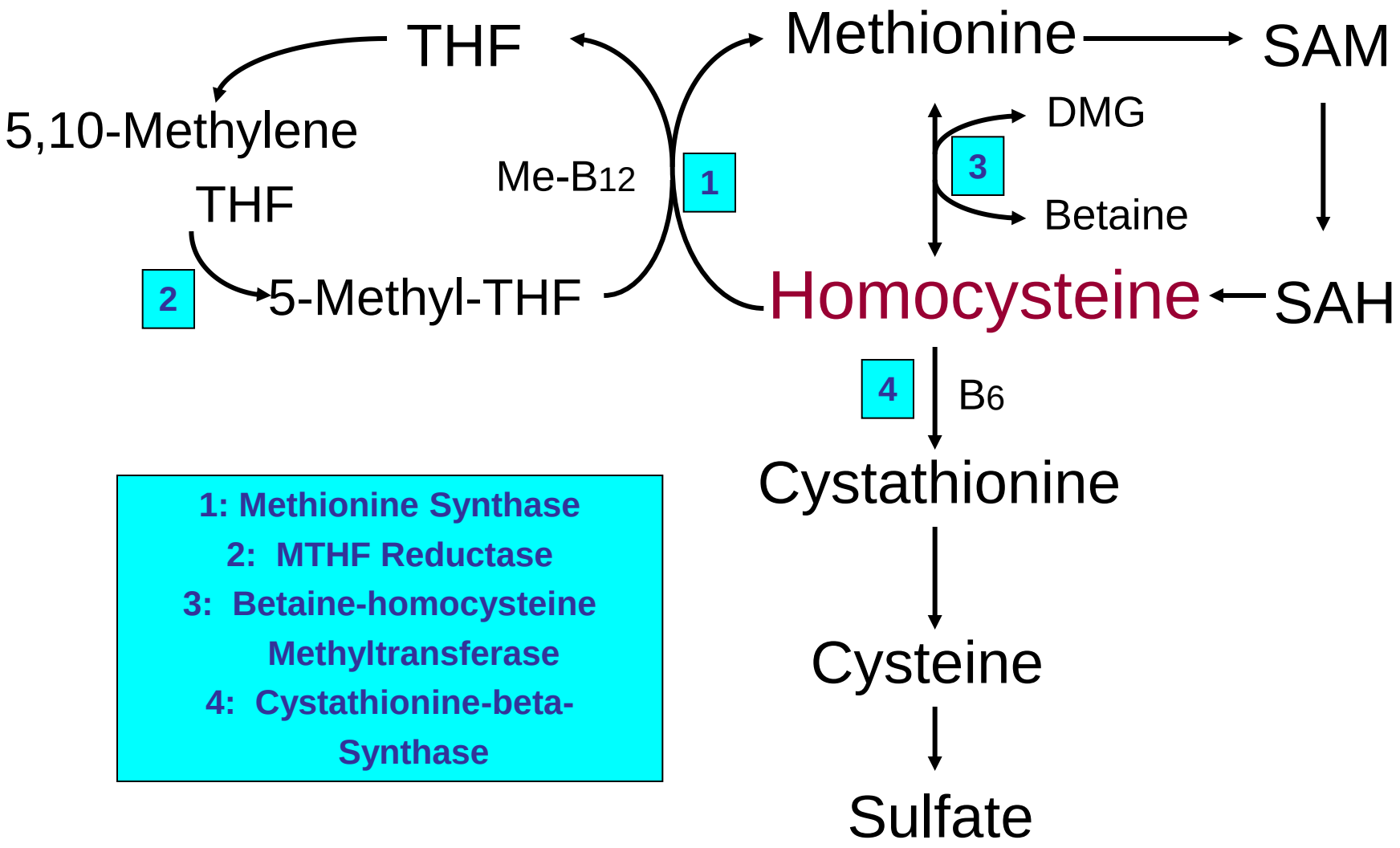
Reasons for Declining Productivity

- Regulatory environment
- Increasing need to explore novel targets
- Easy targets have been exhausted.
- Increasing attrition rate for developing drugs
- *The intrinsically flawed reductionist approach to drug development, i.e., the need to identify a single drug target with a single "magic bullet"…a timely example follows.*

Homocysteine Theory of Atherothrombosis

- First proposed by McCully (*Am.J.Path.* 1969; 56:111)
- Evidence from over 30 studies suggests that even mild-to-moderate elevations of plasma homocysteine confer a significant, independent risk for atherothrombosis.
- Hyperhomocysteinemia found in 20-40% of patients with vascular disease, but in only 2% of unaffected individuals

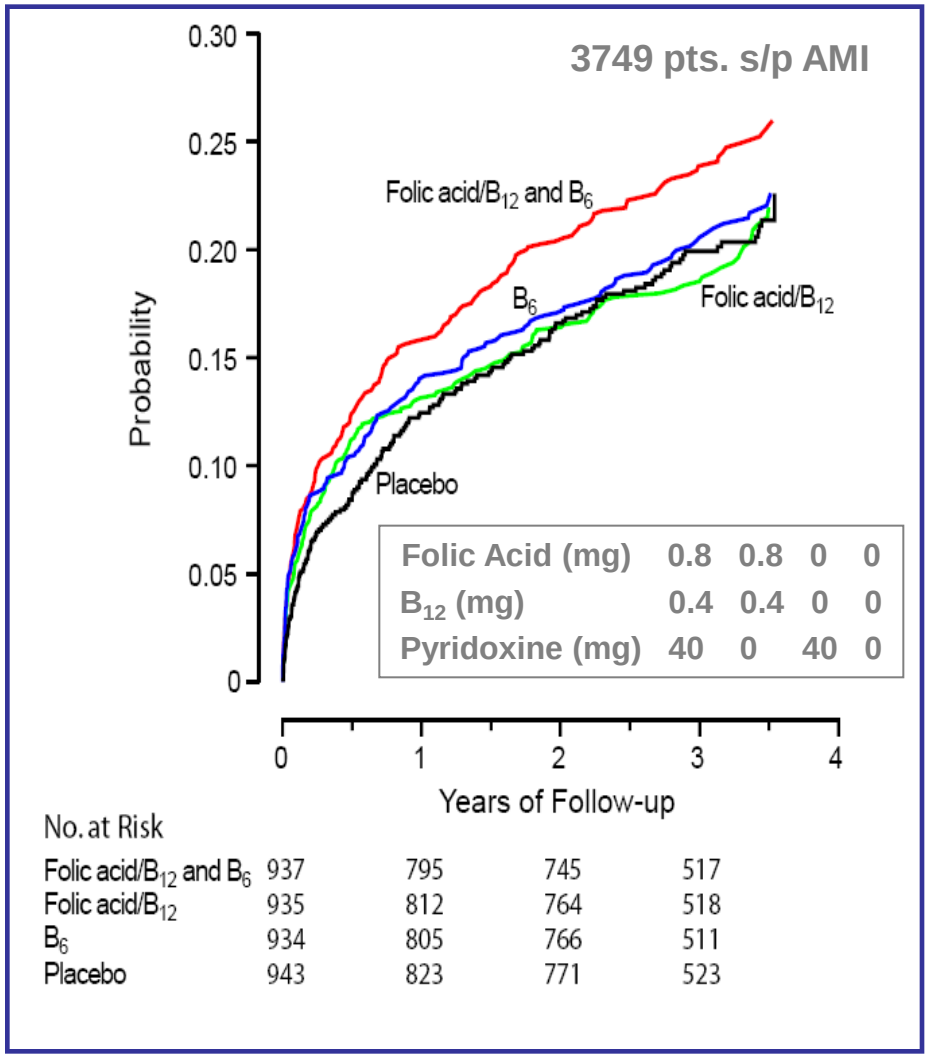
Homocysteine Metabolism



1: Methionine Synthase
2: MTHF Reductase
3: Betaine-homocysteine Methyltransferase
4: Cystathionine-beta-Synthase

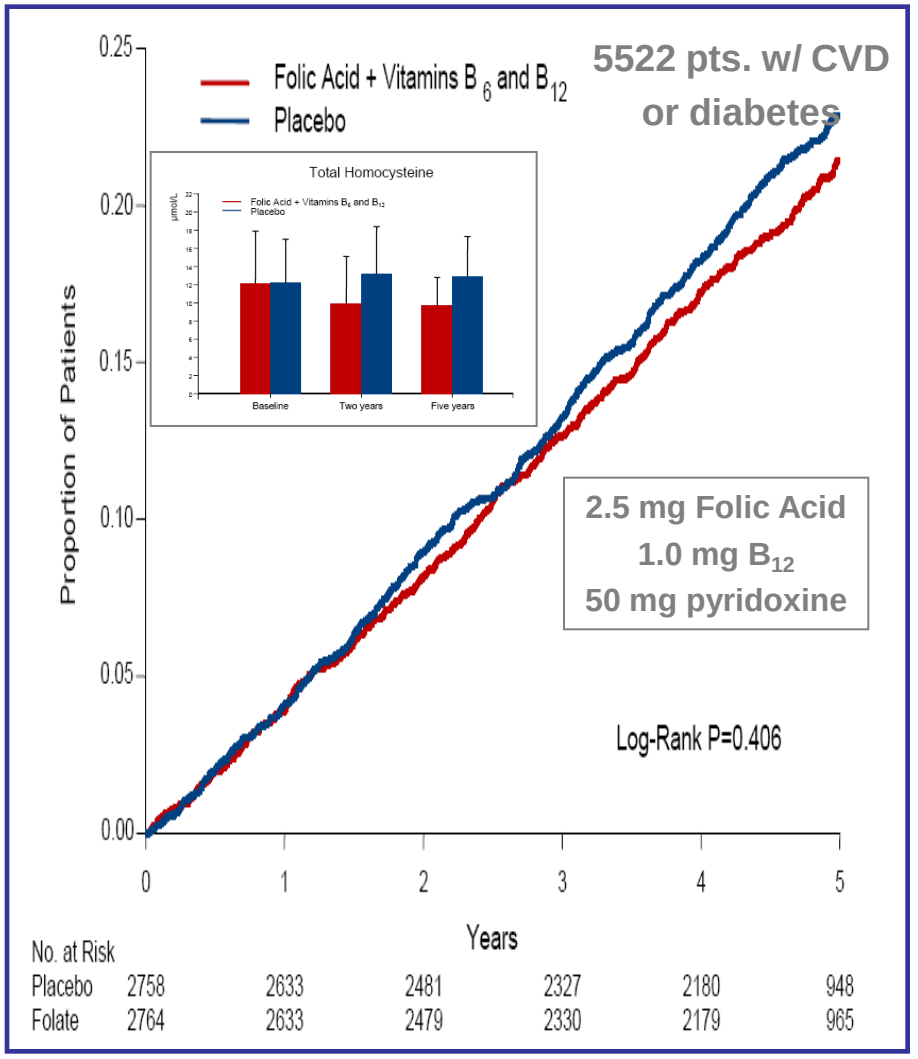
Vitamin Rx, Homocysteine, & CV Risk

NORVIT Trial



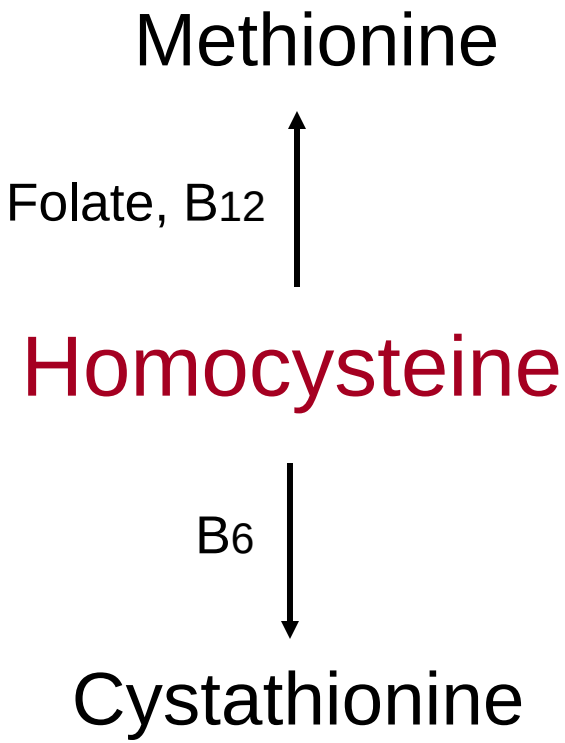
--Bonaa KH, et al., NEJM, 2006

HOPE-2 Trial

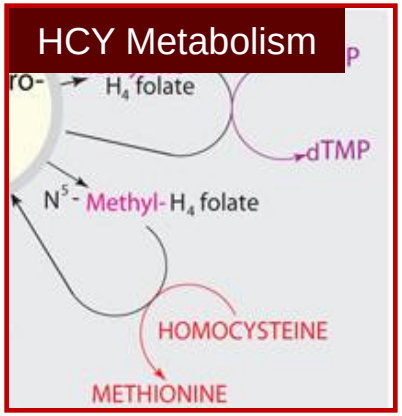


--HOPE-2 Investigators, NEJM, 2006

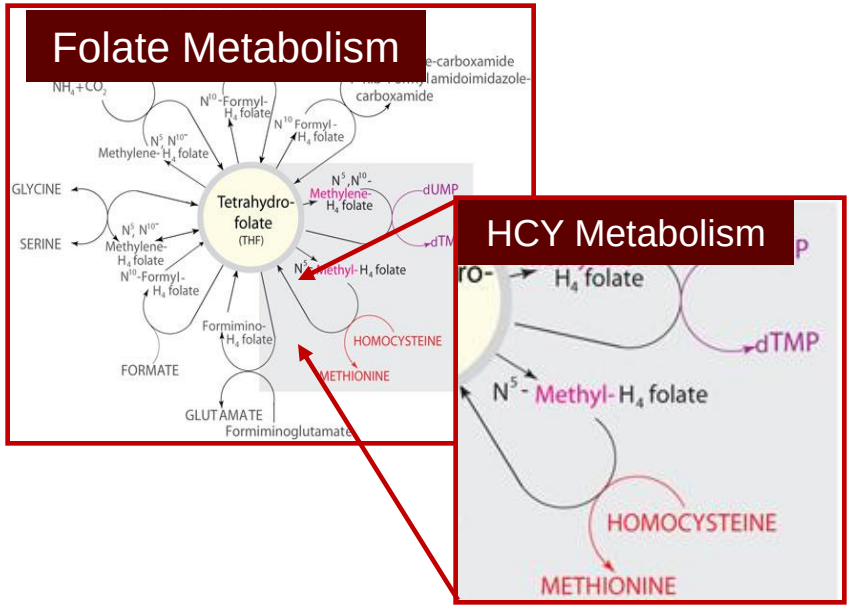
Folate, B_{12}, and Homocysteine



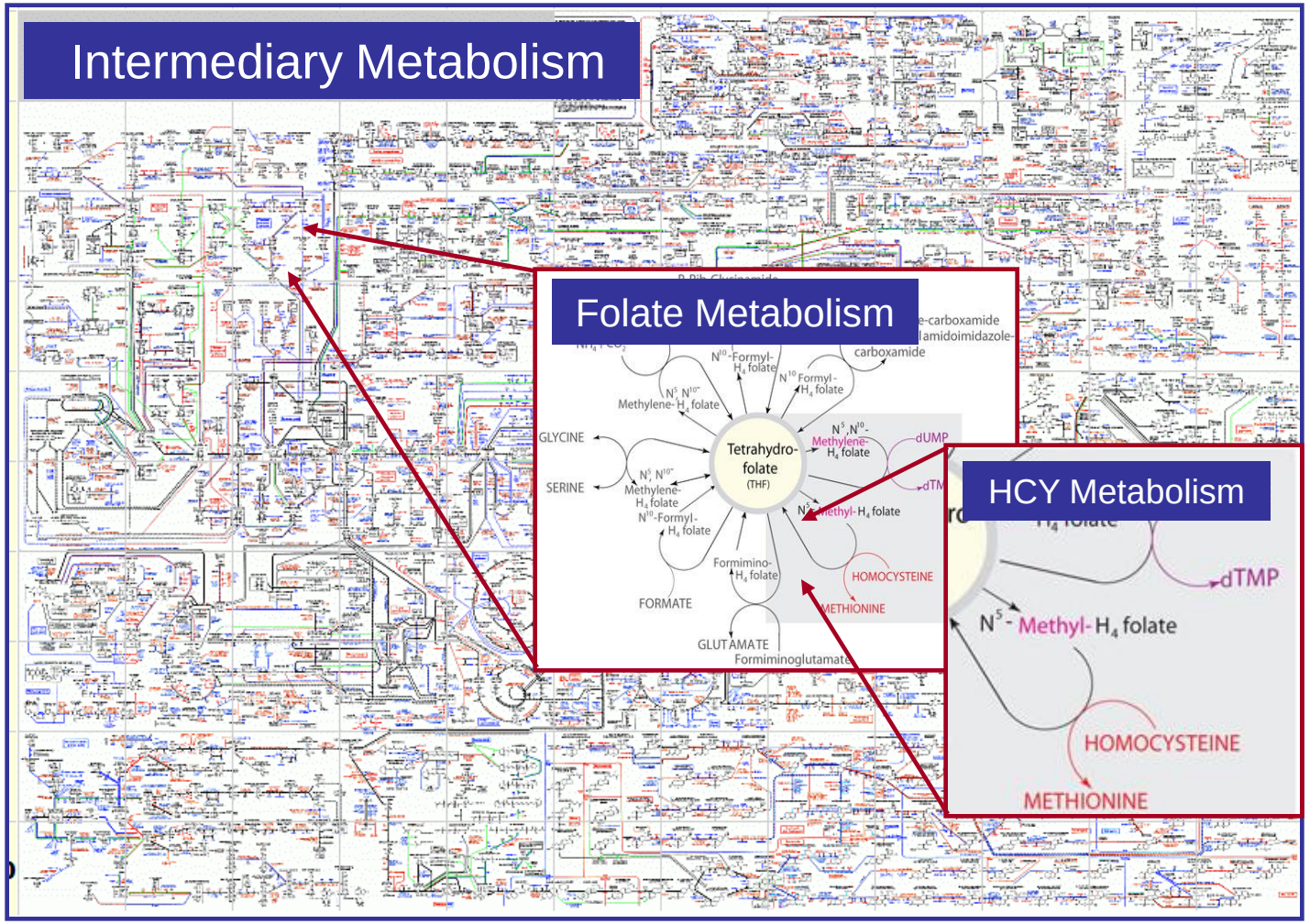
Biomedicine in Network Context



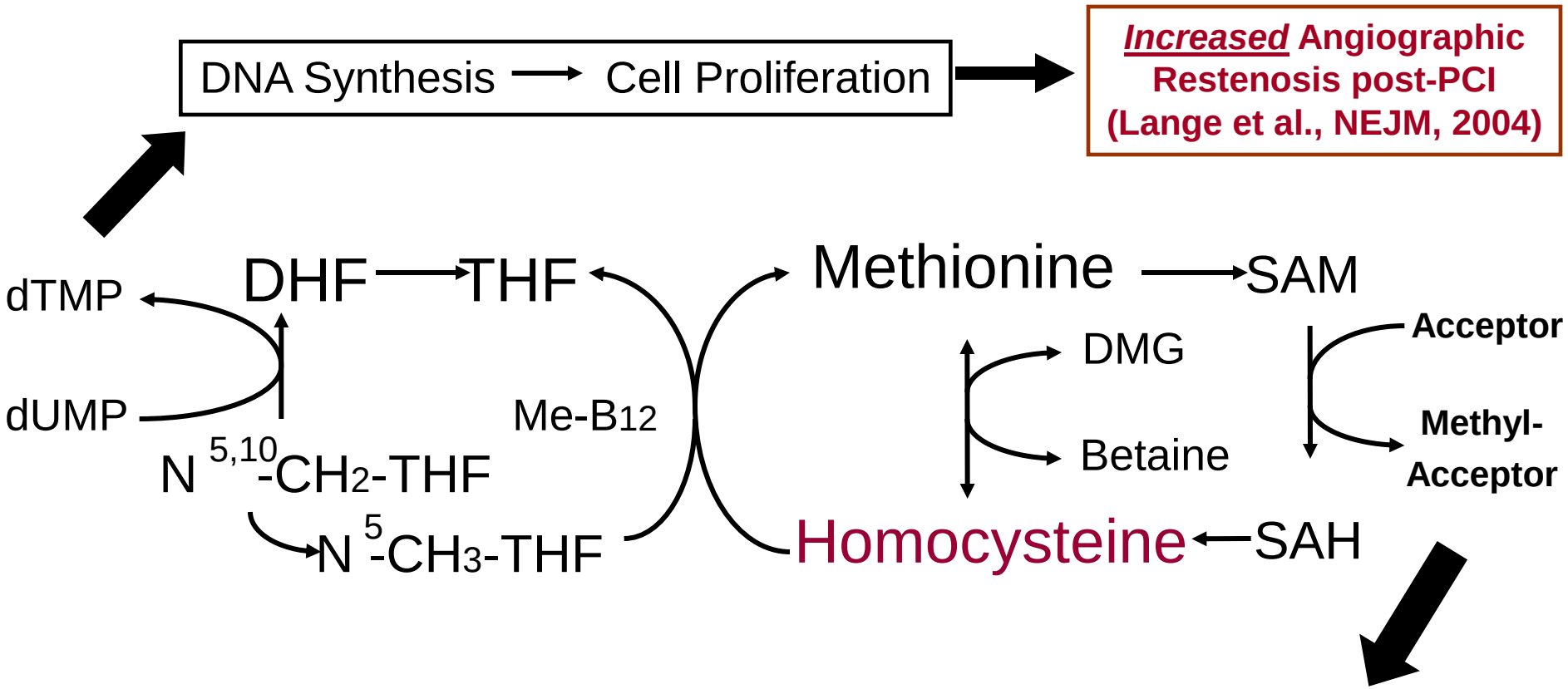
Biomedicine in Network Context



Biomedicine in Network Context



Folate, B_{12}, and Homocysteine



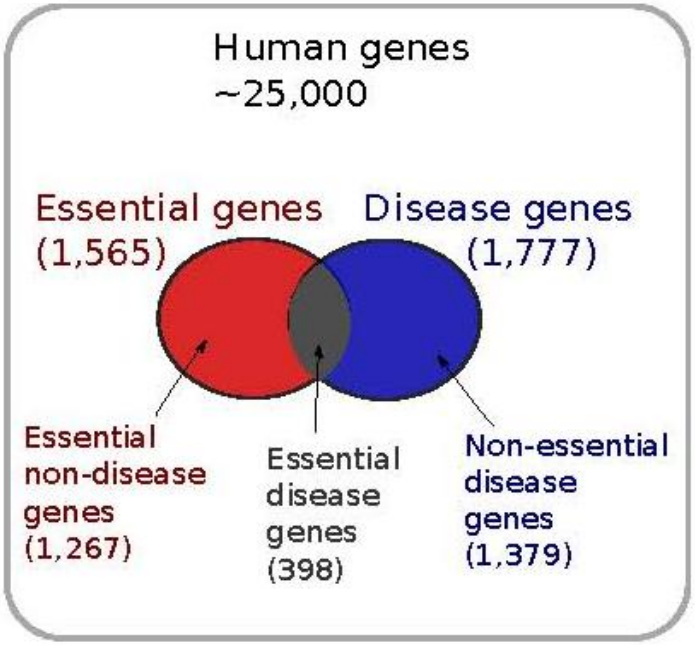
Disease Networks and Identification of Drug Targets

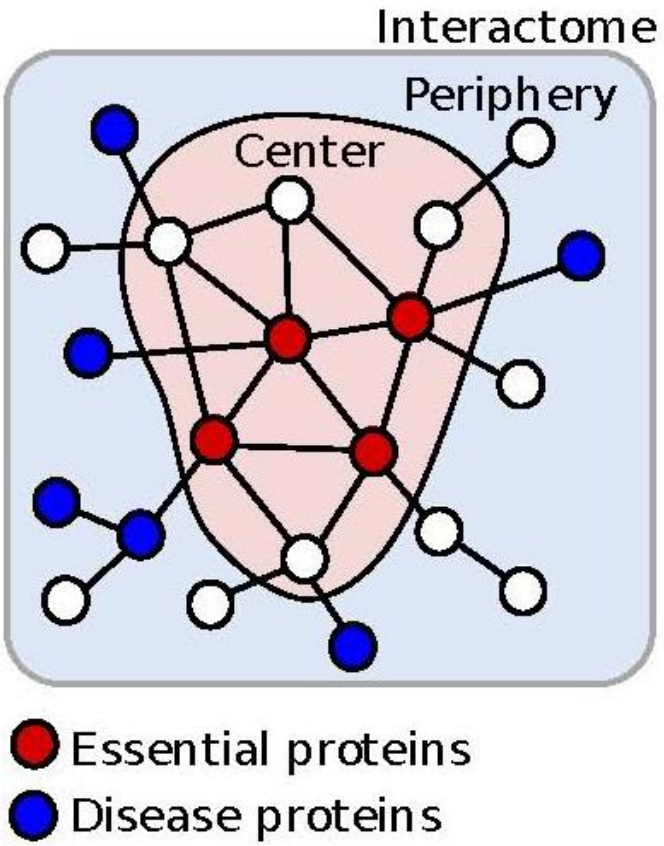
Enhancing Productivity in Drug Discovery

Can we move from reductionism to systems-based approaches in drug discovery? The universe within which a drug acts considered as a complex networked biological system….

Essential vs. Disease Genes in Network Medicine

Disease genes are largely nonessential and do not encode hubs.

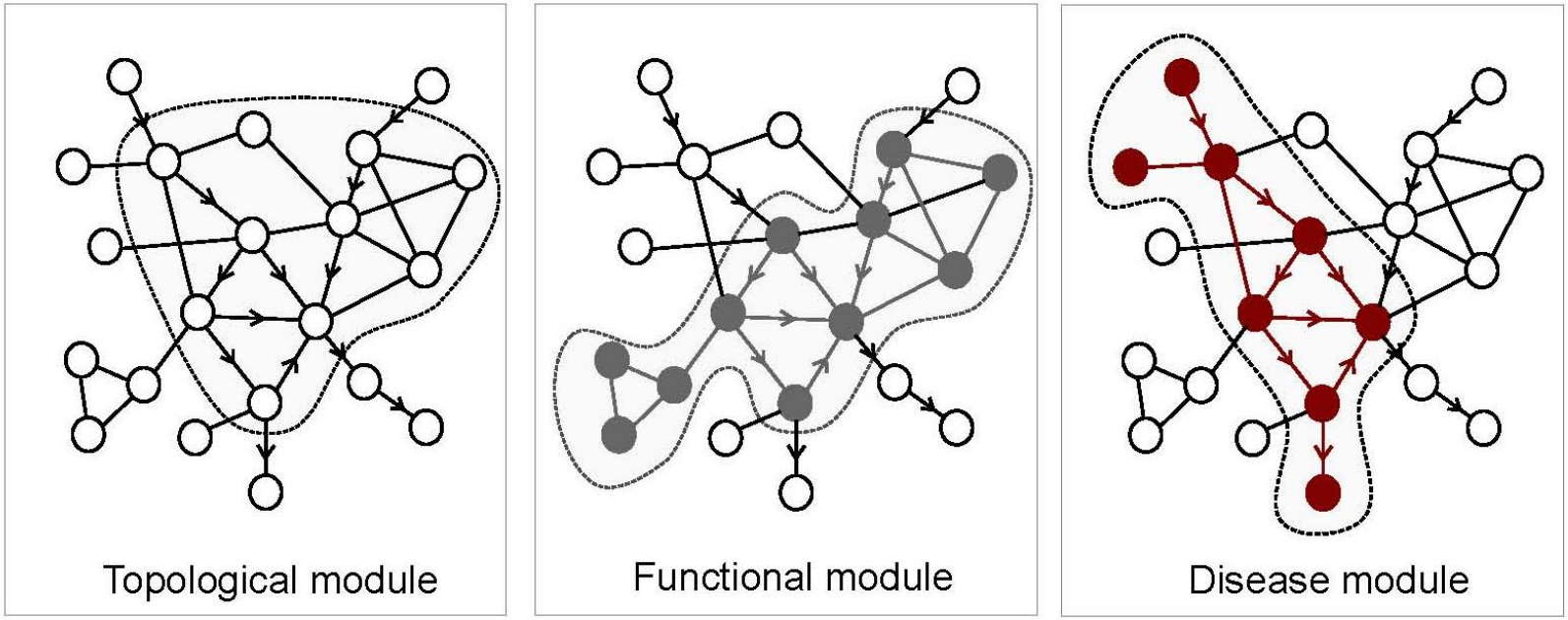




--Barabasi, et al., Nat Revs Genet 2011;12:56-68

Network Modularity and Disease

Disease modules are topologically and functionally distinct network modules.



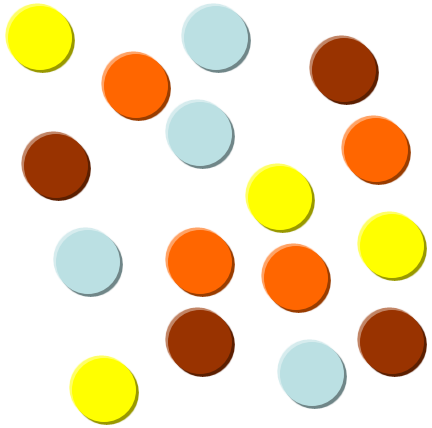
--Barabasi, et al., Nat Revs Genet 2011;12:56-68

Disease Module Derivation

- Identify disease phenotype of interest (example--pulmonary arterial hypertension).
- Ascertain disease network components.
- Construct disease network (*i.e.*, determine the structural or functional linkages among module components).
- Identify disease module(s) within network.

PAH Network Derivation

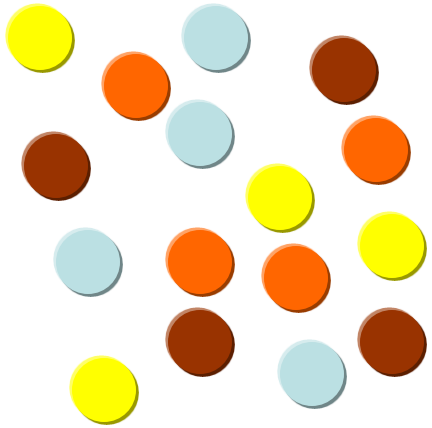
PAH Network Components *(131 Nodes, 26 Functional Pathways)*



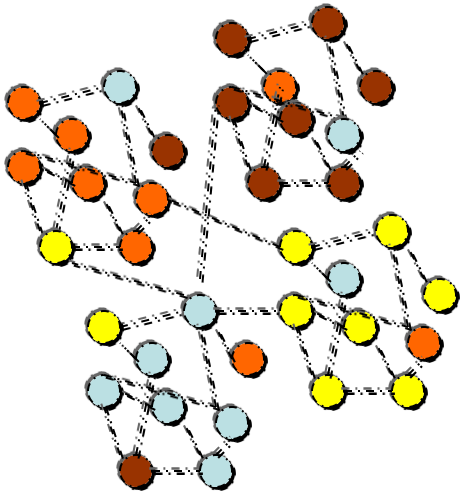
Disease components derived from curated literature, or gene, protein, or metabolite profiles.

PAH Network Derivation

PAH Network Components *(131 Nodes, 26 Functional Pathways)*



Consolidated Interactome *(11,643 Nodes 100,791 Edges)*



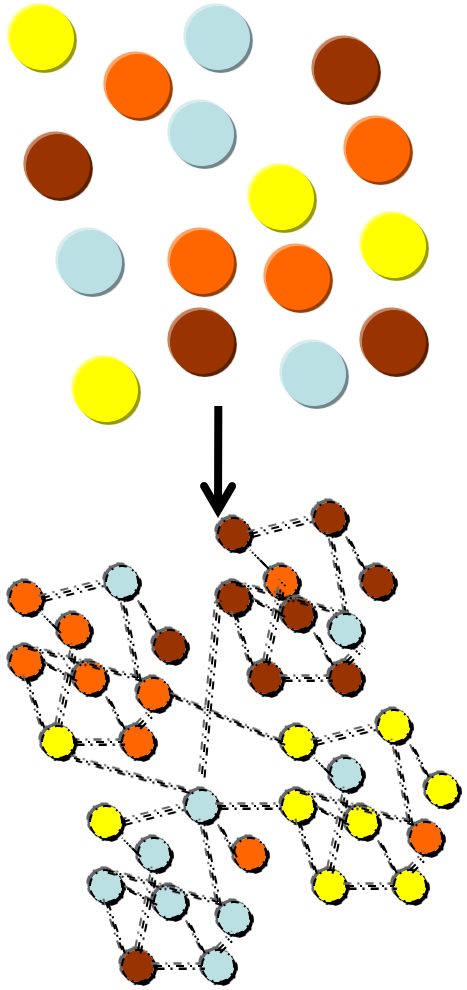
Consolidated interactome of all known physical interations: PPIs and Protein Complexes (CORUM), Regulatory Protein-DNA Interaction (TRANSFAC), Metabolic Enzyme-coupled Interactions (MCIs), Kinase Network

PAH Network Derivation

PAH Network Components *(131 Nodes, 26 Functional Pathways)*

Map

Consolidated Interactome *(11,643 Nodes 100,791 Edges)*

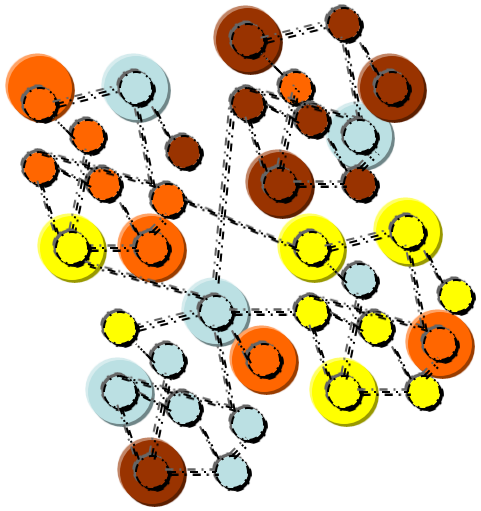


PAH Network Derivation

PAH Network Components *(131 Nodes, 26 Functional Pathways)*

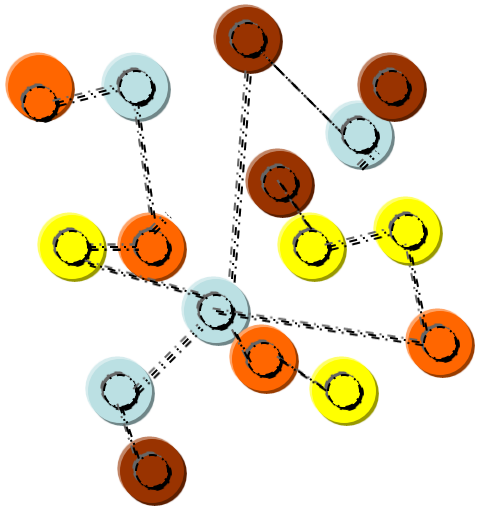
Map

Consolidated Interactome *(11,643 Nodes 100,791 Edges)*

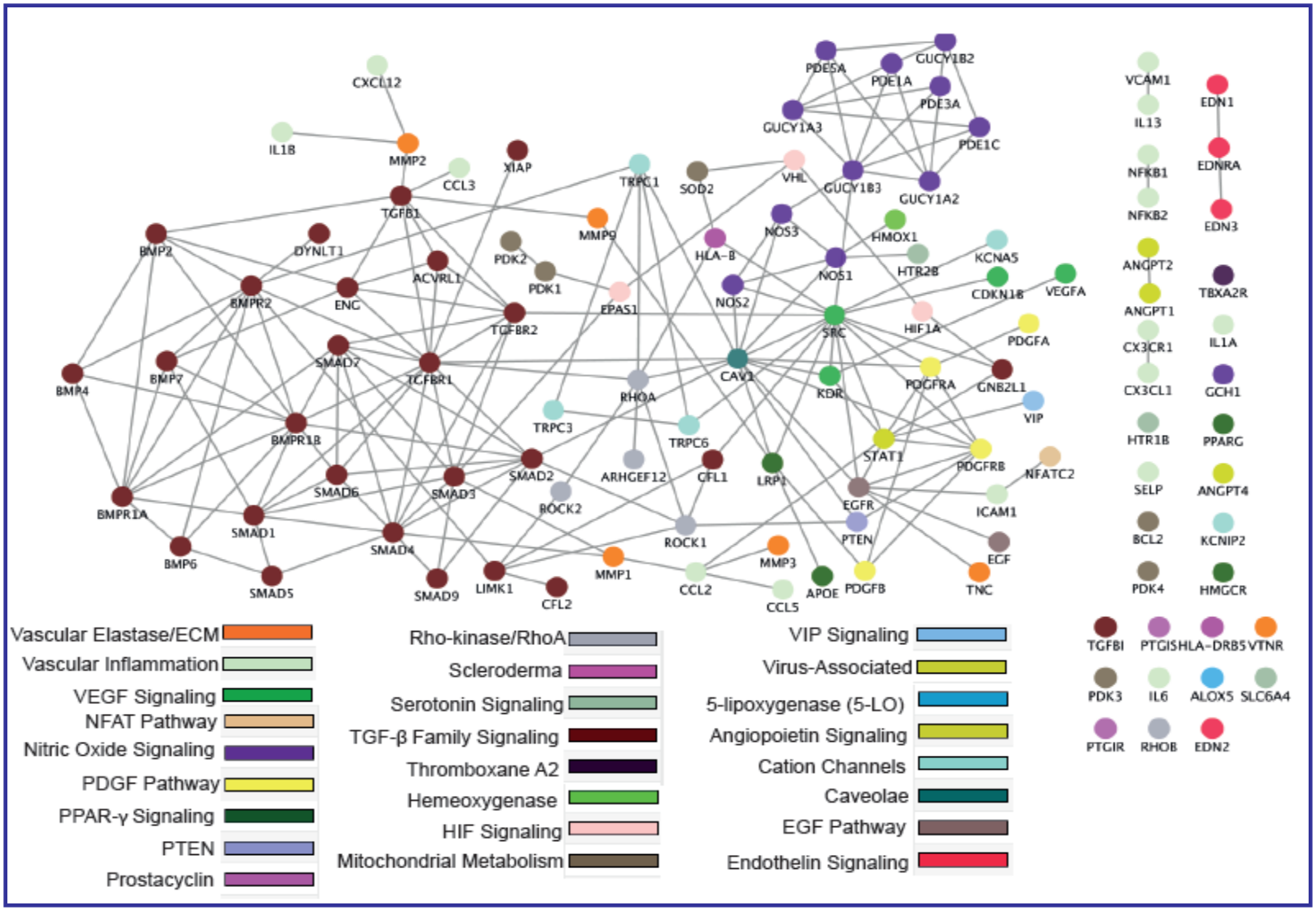


PAH Network Derivation

PAH Network
(115 Nodes, 255 Edges, Largest Connected Component = 82 Nodes)

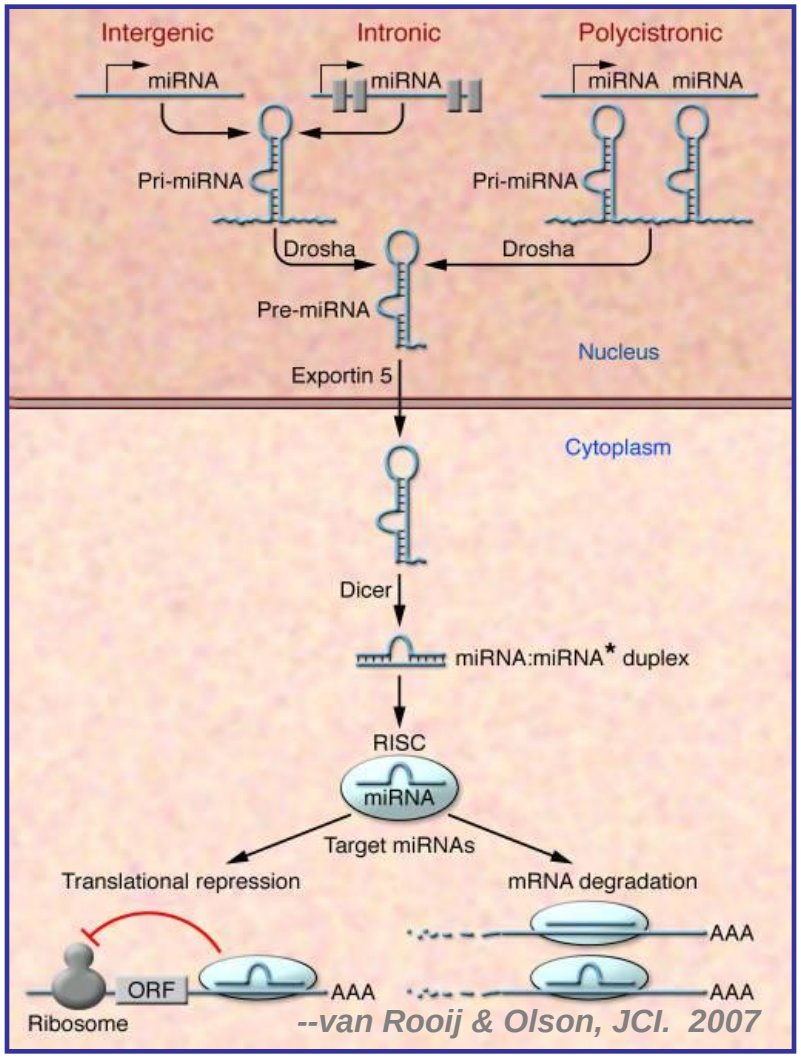


Interactome-derived PAH Network



--Parikh et al., Circulation 2012;125:1520-1532

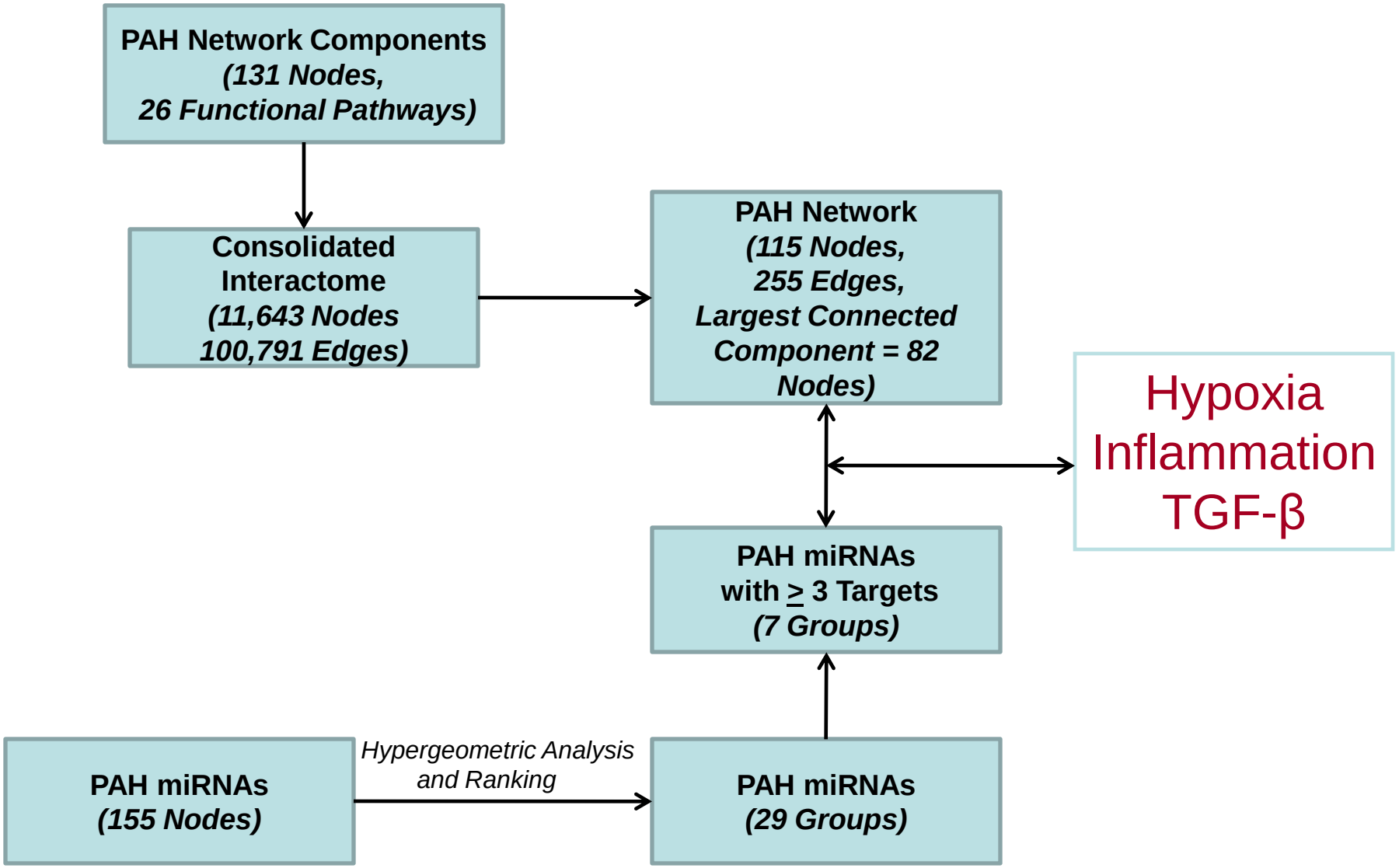
MicroRNAs as Network Filters



- Select miRNAs are induced by stresses and disease states.
- Unbiased ascertainment of miRNA targets
- Induced miRNAs target common pathways.
- Induced miRNAs suppress common mRNA targets.

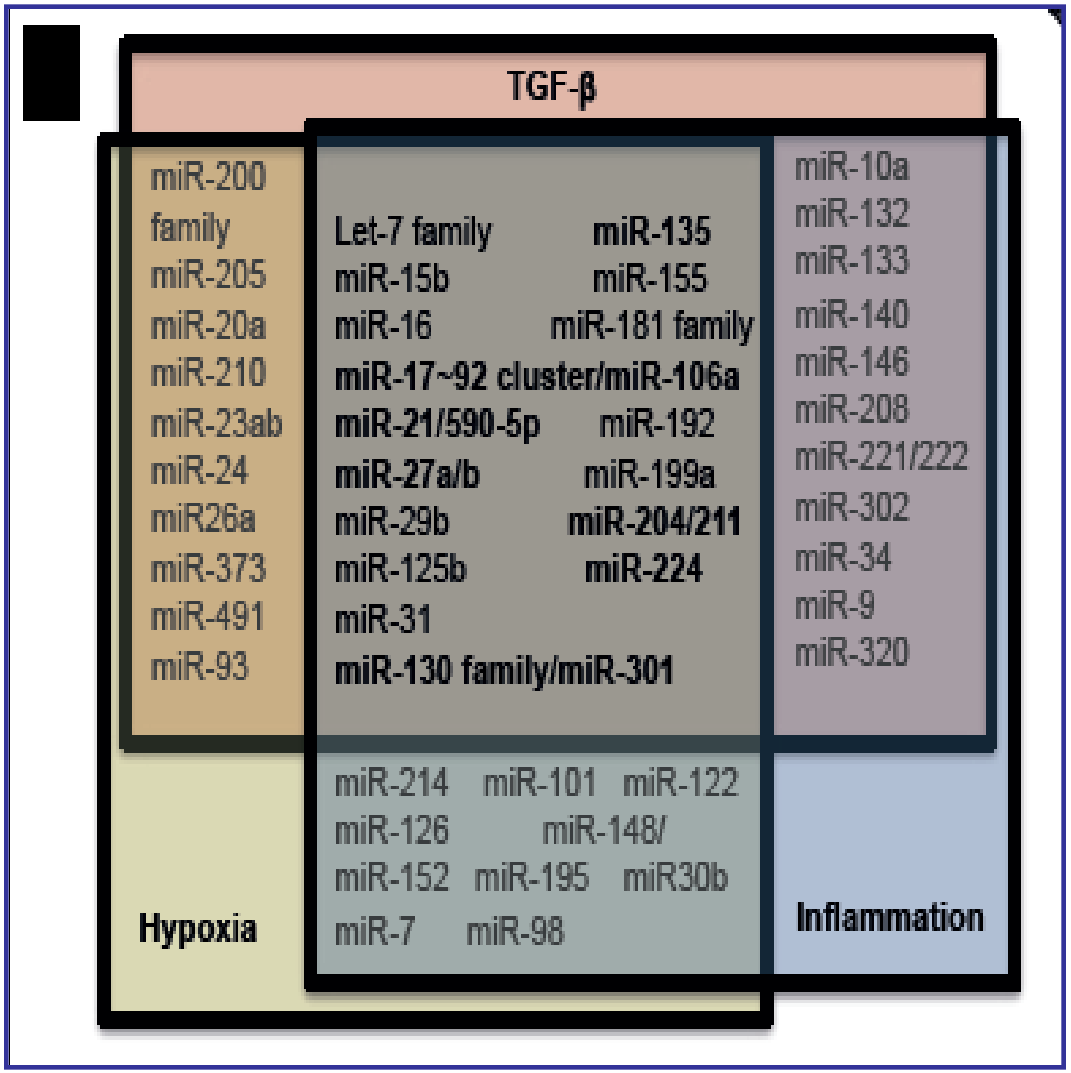
--Chan et al., Cell Metab 2009;10:273-84

PAH Network Derivation



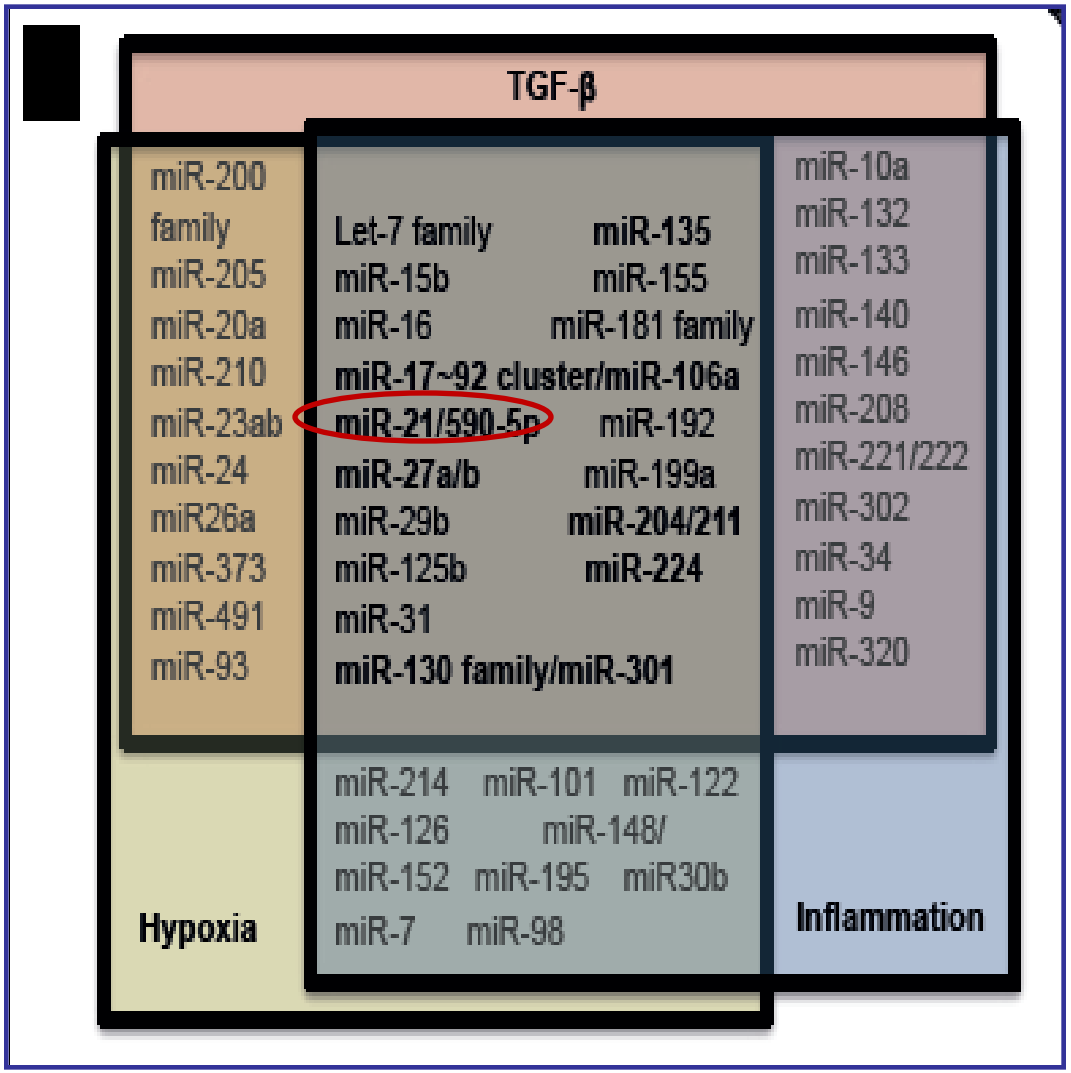
--Parikh et al., Circulation 2012;125:1520-1532

MicroRNA Network Analysis in PAH:



--Parikh et al., Circulation 2012;125:1520-1532

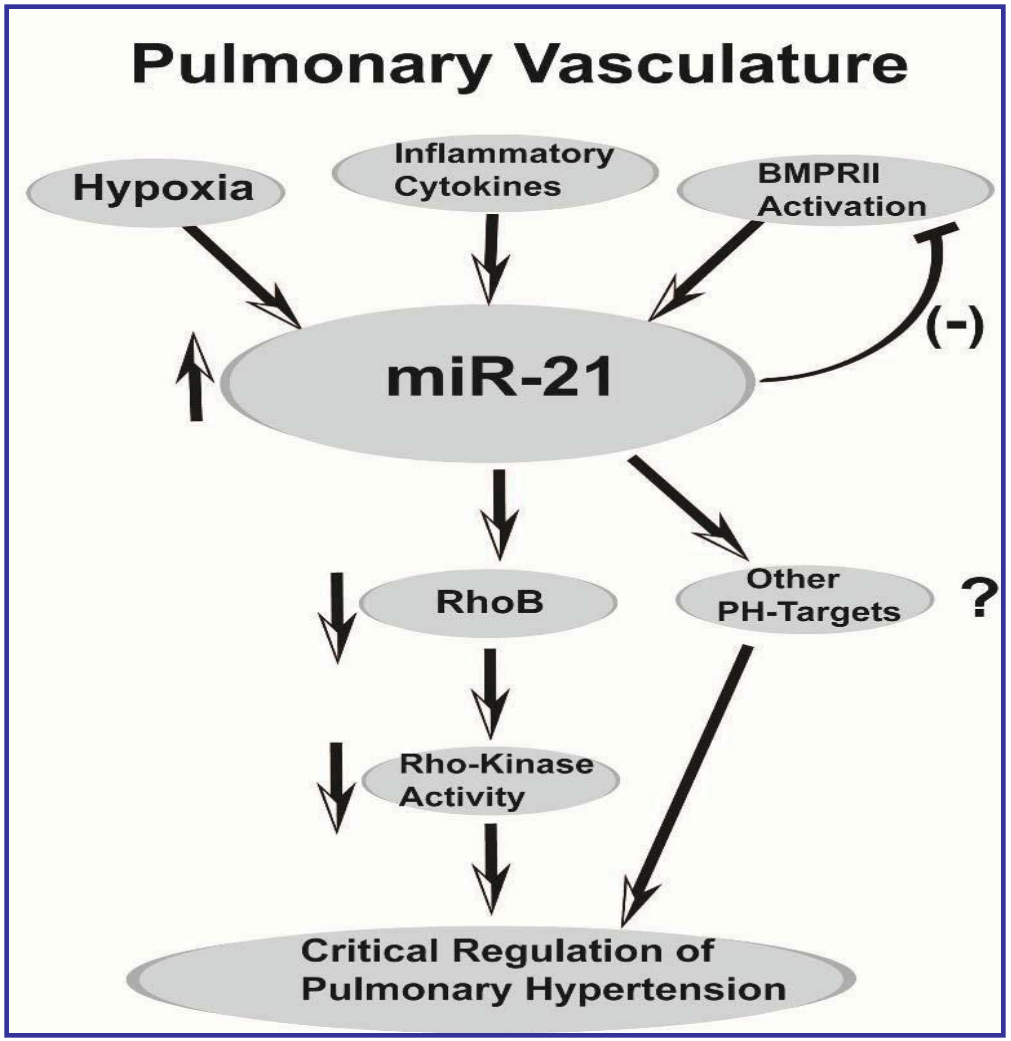
MicroRNA Network Analysis in PAH



--Parikh et al., Circulation 2012;125:1520-1532

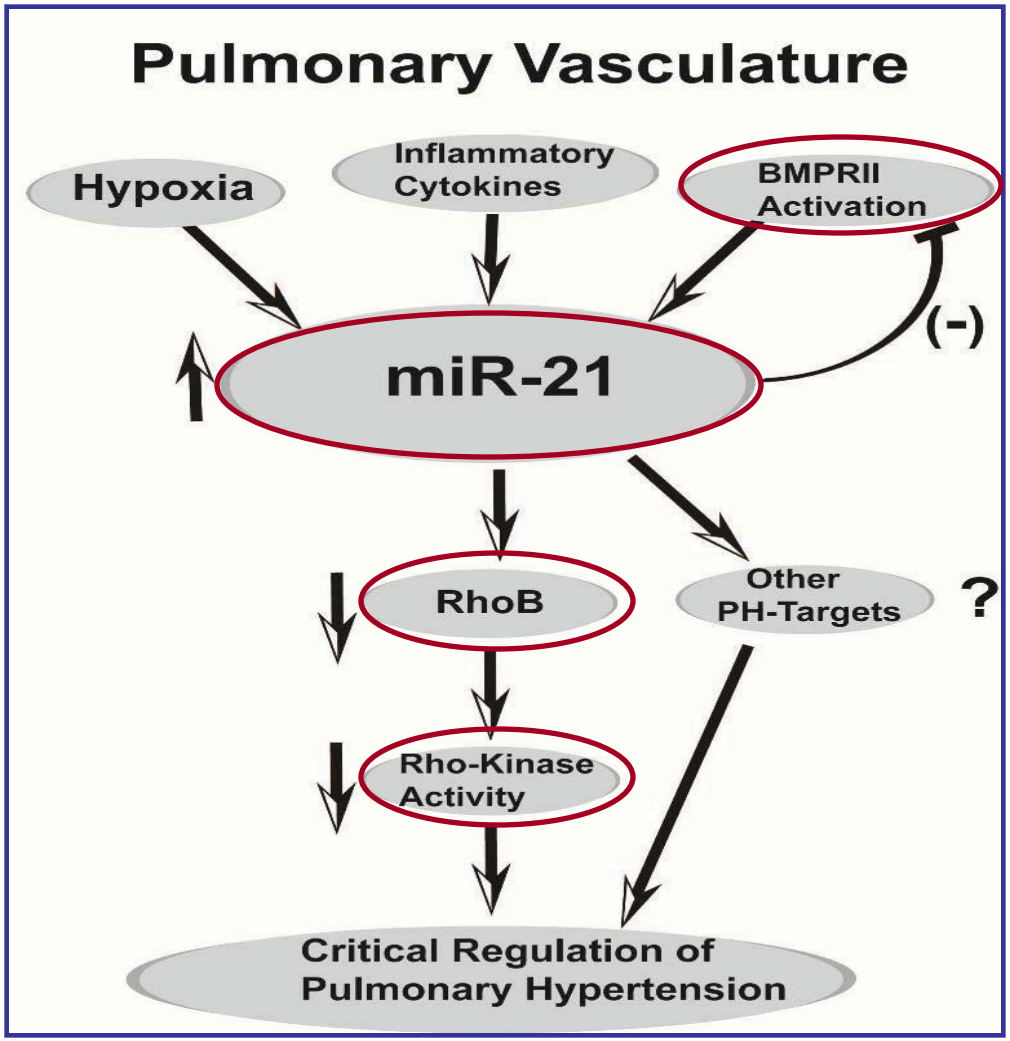
PAH and miR-21 Disease Module

miR-21 serves as a negative regulator of pathogenic pulmonary vascular responses in PAH.



--Parikh et al., Circulation 2012;125:1520-1532

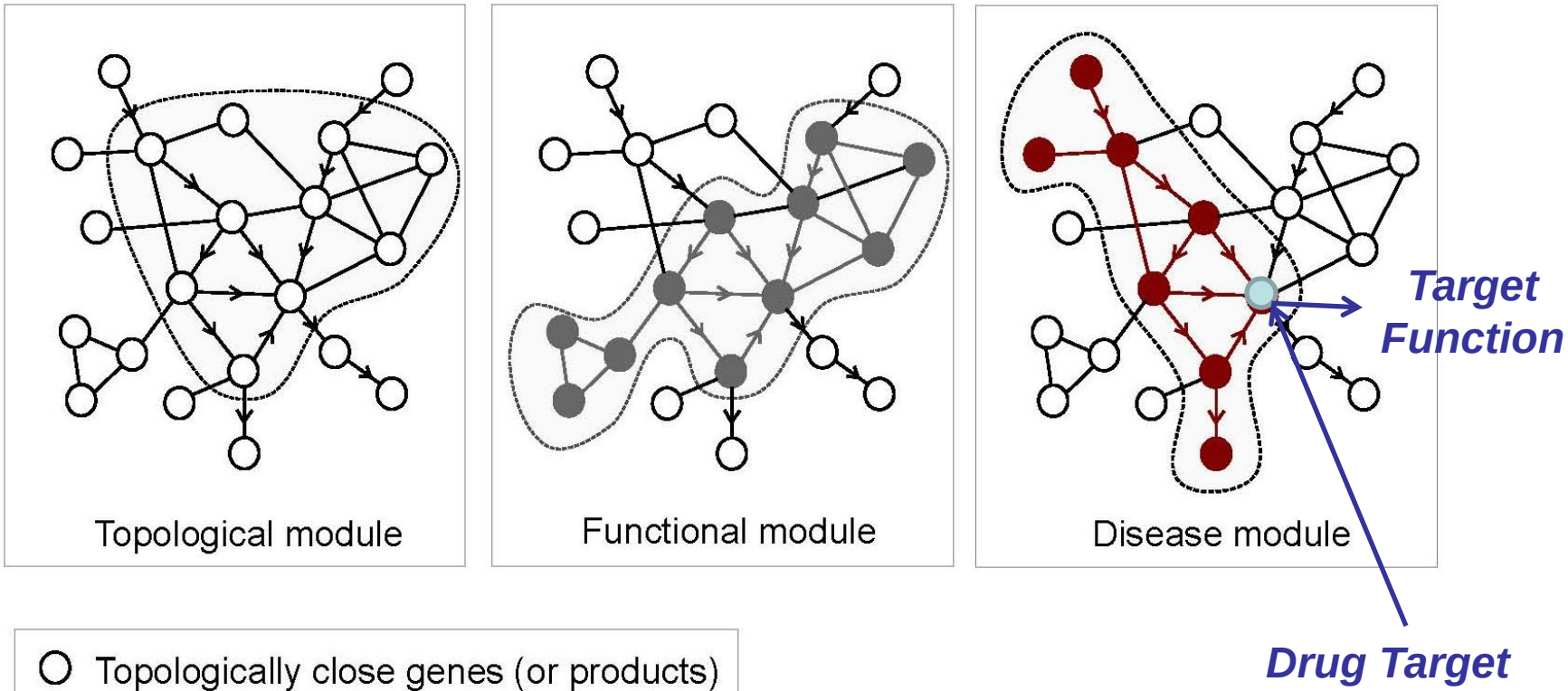
PAH and miR-21 Disease Module: Potential Drug Targets



--Parikh et al., Circulation 2012;125:1520-1532

Disease Modules and Therapeutics

Drug targets are typically characterized in isolation from the disease module.



--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68

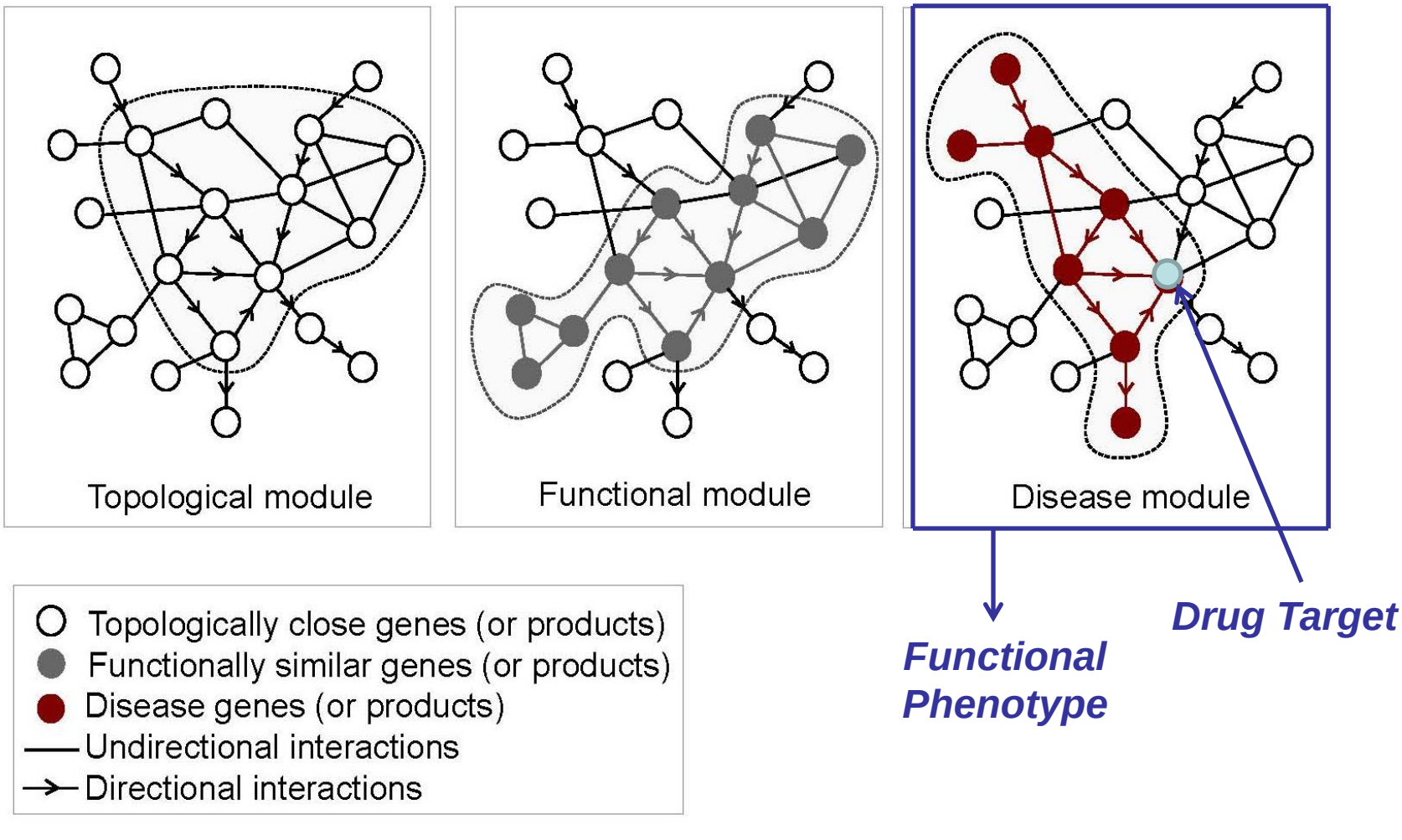
Target-based Screening

Facilitated by:

- Genomic datasets for target identification
- Structural tools, including protein X-ray crystallogaphy, NMR spectroscopy, computational modeling
- Large real and virtual compound libraries
- High-throughput screening technologies

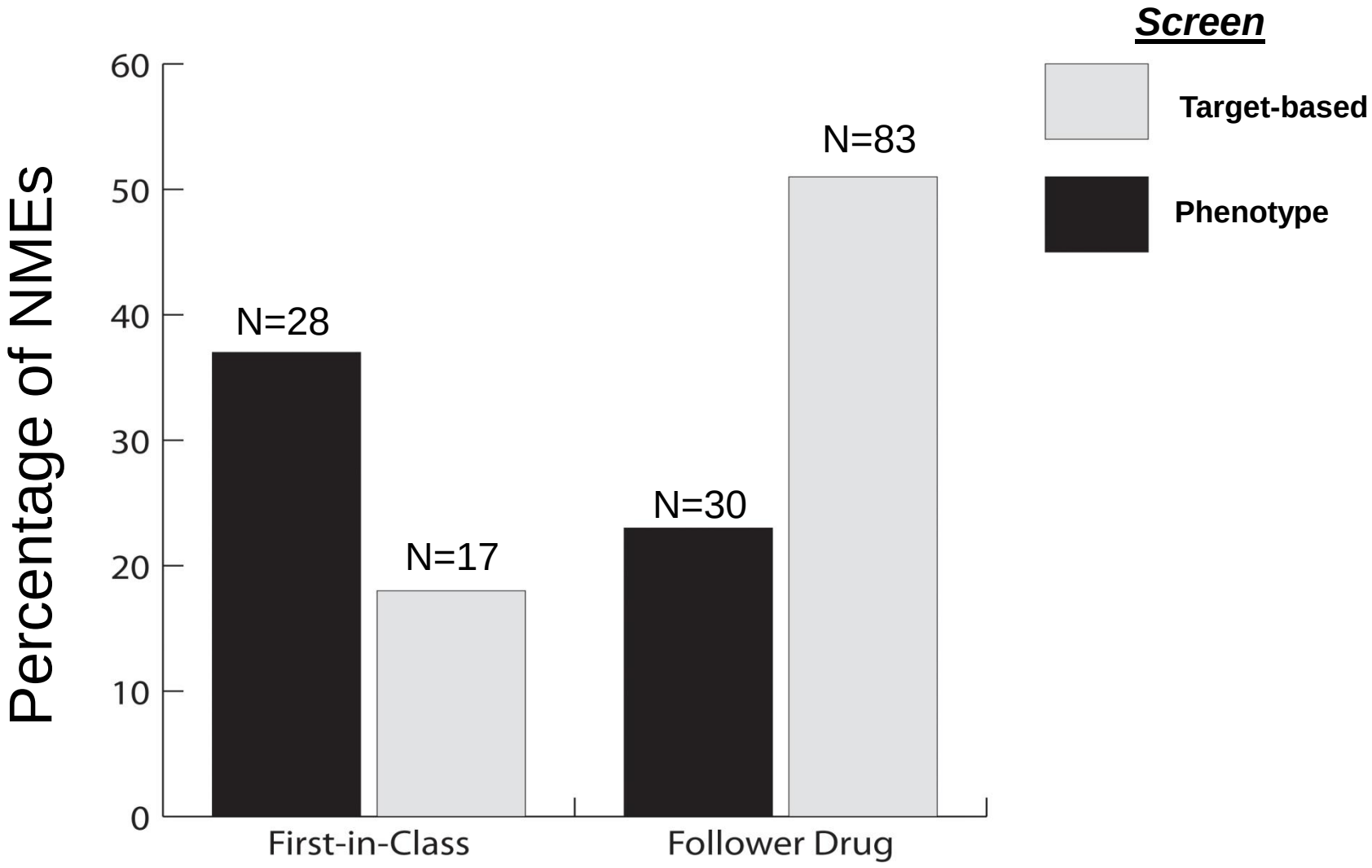
Disease Modules and Therapeutics

Drug targets are better characterized with regard to their effects on phenotype.



--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68

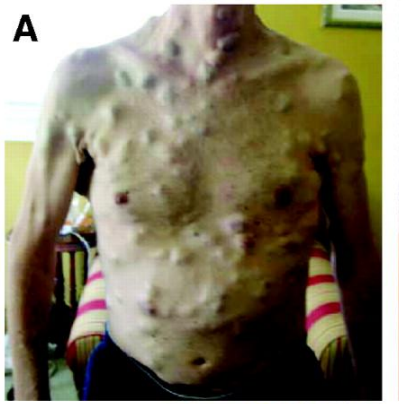
Drug Discovery Strategies: Success Rates

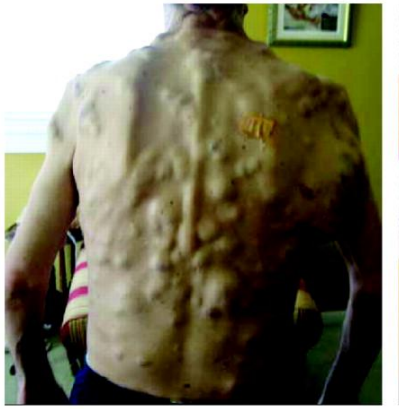


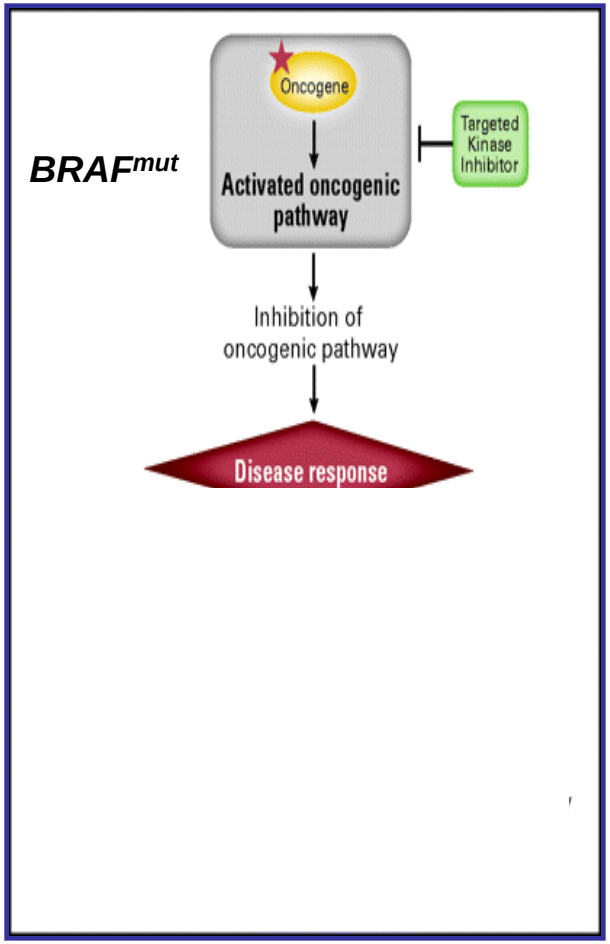
--Swinney & Anthony, Nature Rev Drug Disc 2011;10:507-519

The Promise of Personalized Medicine: Find the Target

Before Rx



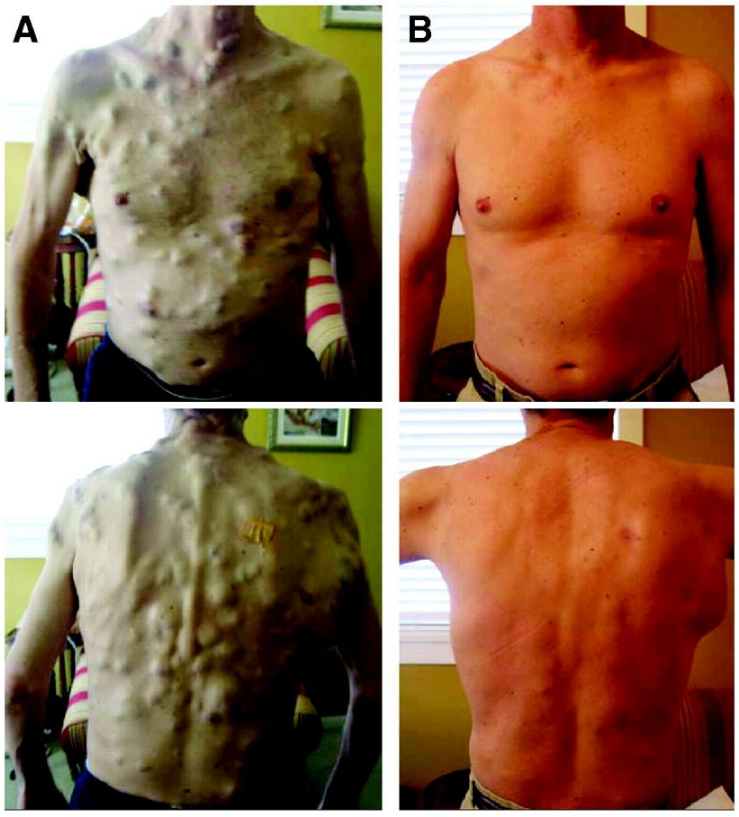


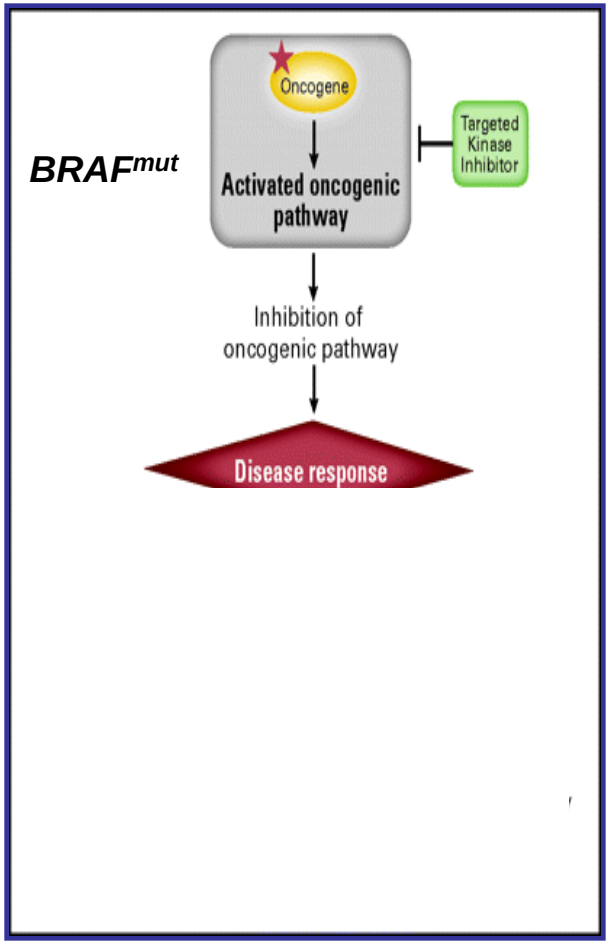


--Wagle et al., J Clin Oncol 2011;29:3085-3096

The Promise of Personalized Medicine: Inhibit the Target

Before Rx ***Vemurafenib—15 wks***

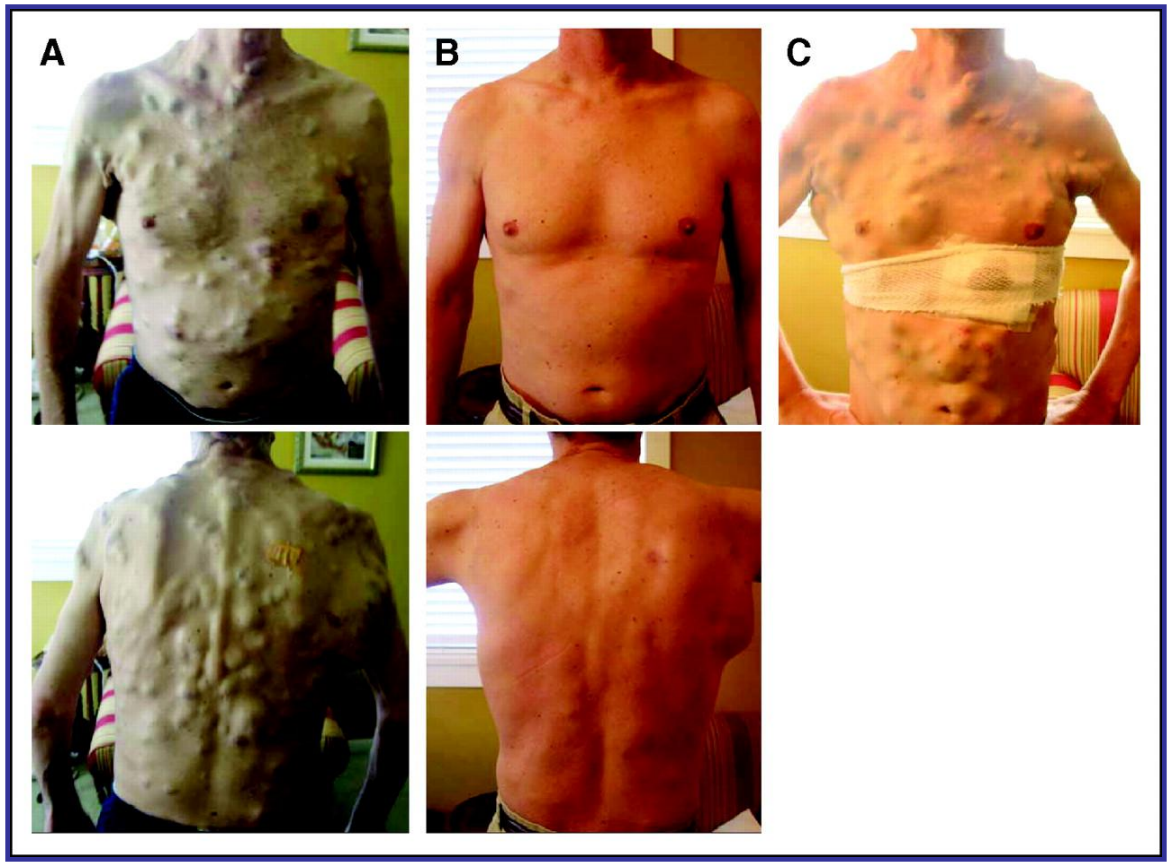


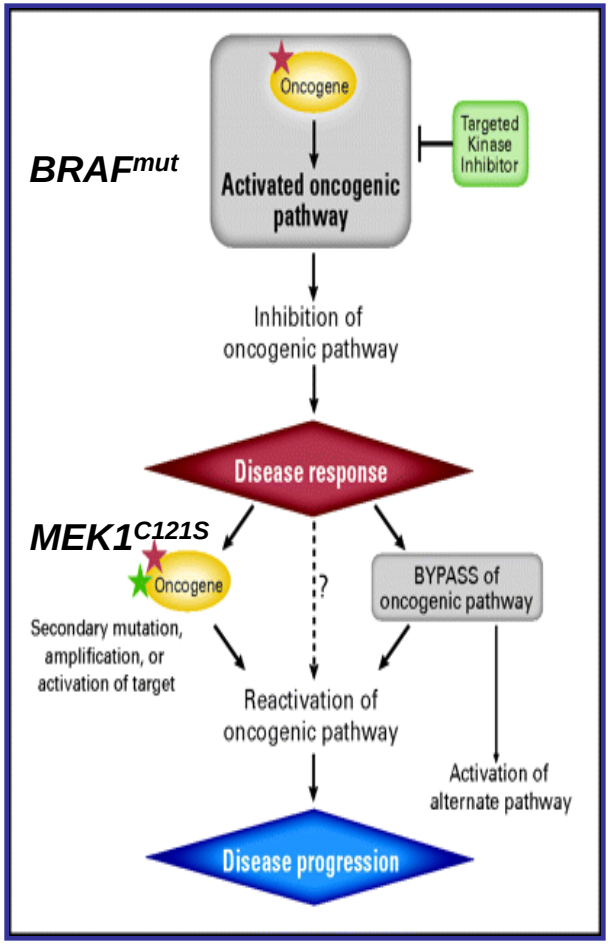


--Wagle et al., J Clin Oncol 2011;29:3085-3096

The Peril of Personalized Medicine with Conventional Strategy

Before Rx ***Vemurafenib—15 wks*** ***Vemurafenib—23 wks***

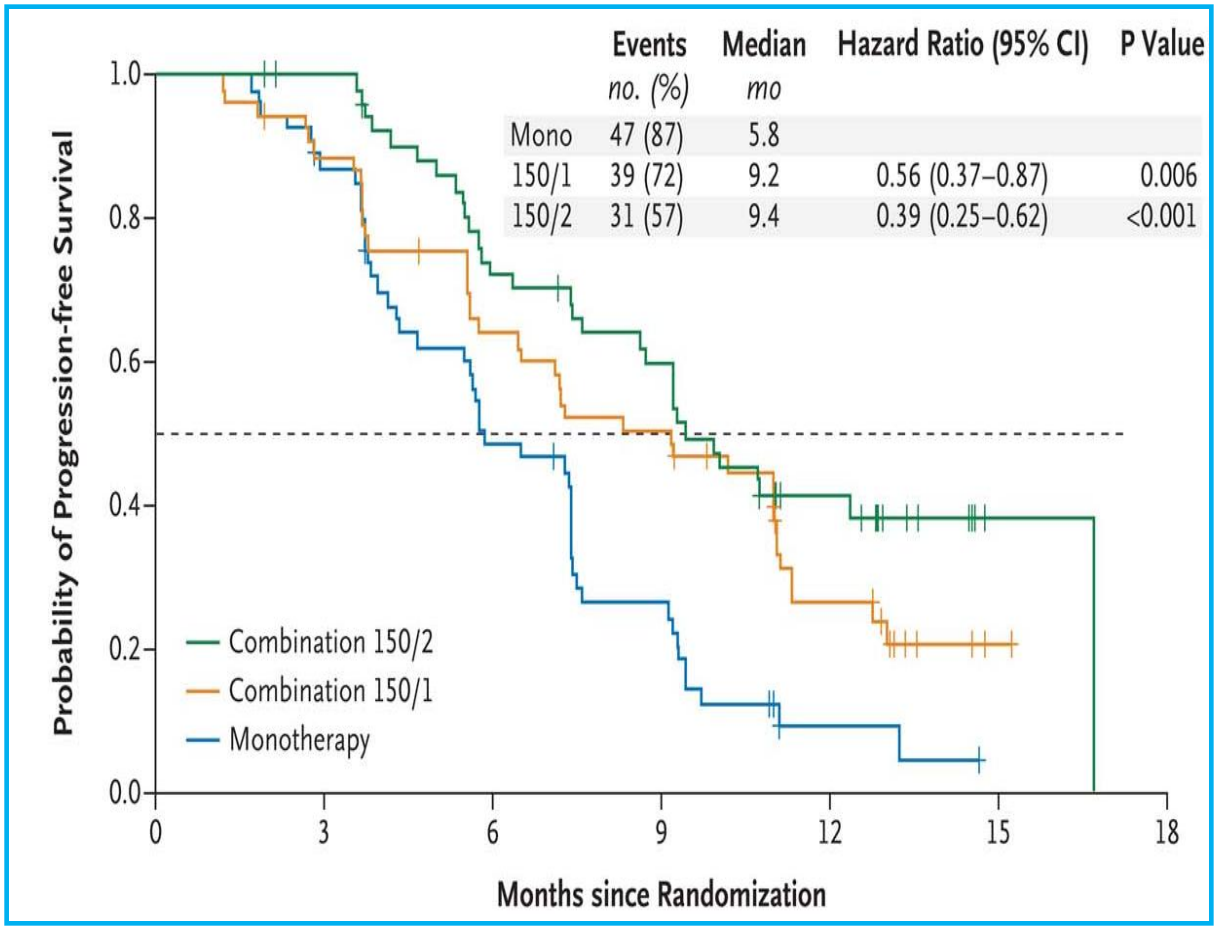




--Wagle et al., J Clin Oncol 2011;29:3085-3096

Pathway Targeting: Combination Rx

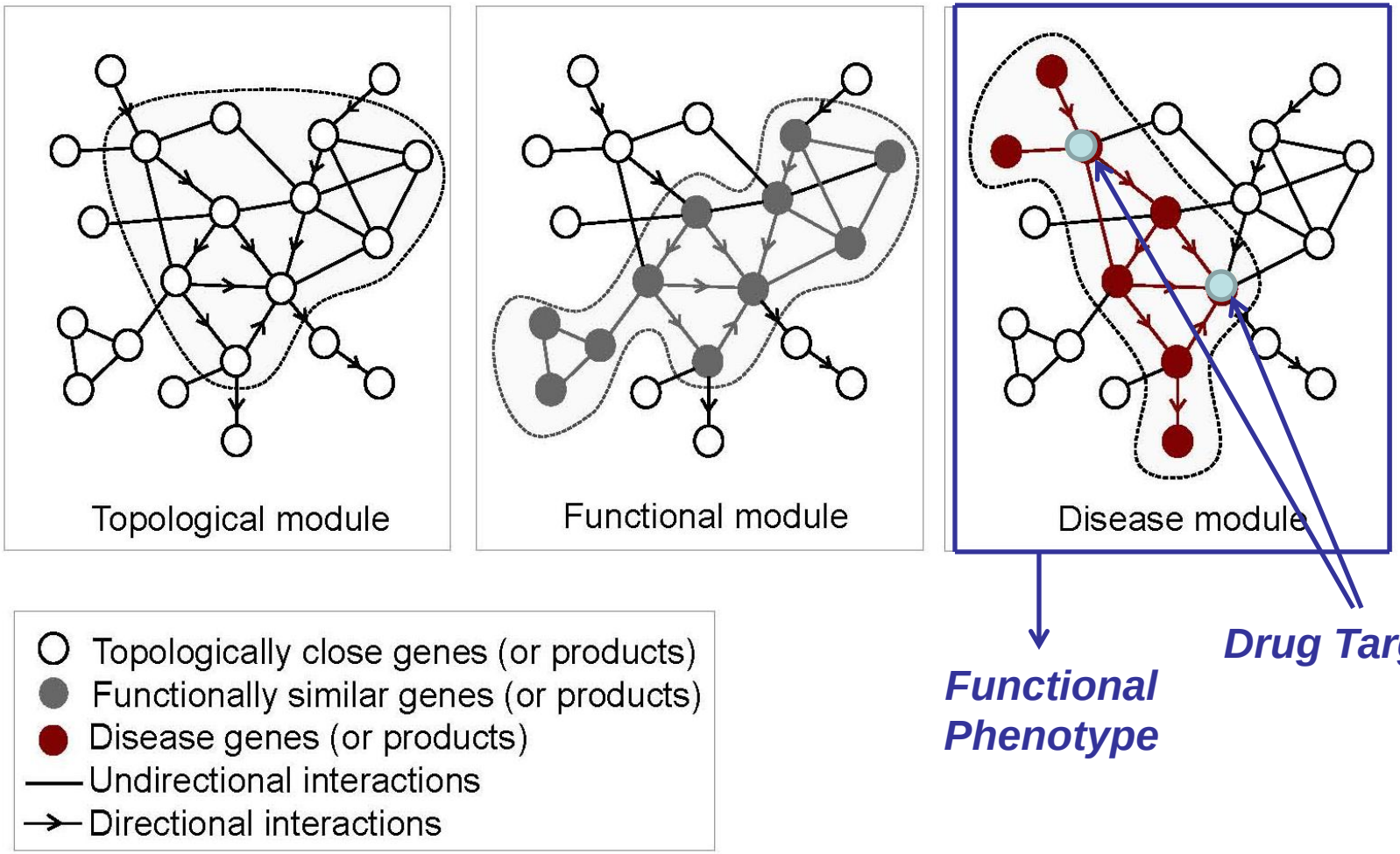
Combination therapy: dabrafenib (BRAF inhibitor) & trametinib (MEK inhibitor)



--Flaherty et al., NEJM 2012;367:1694-1703

Disease Modules and Therapeutics

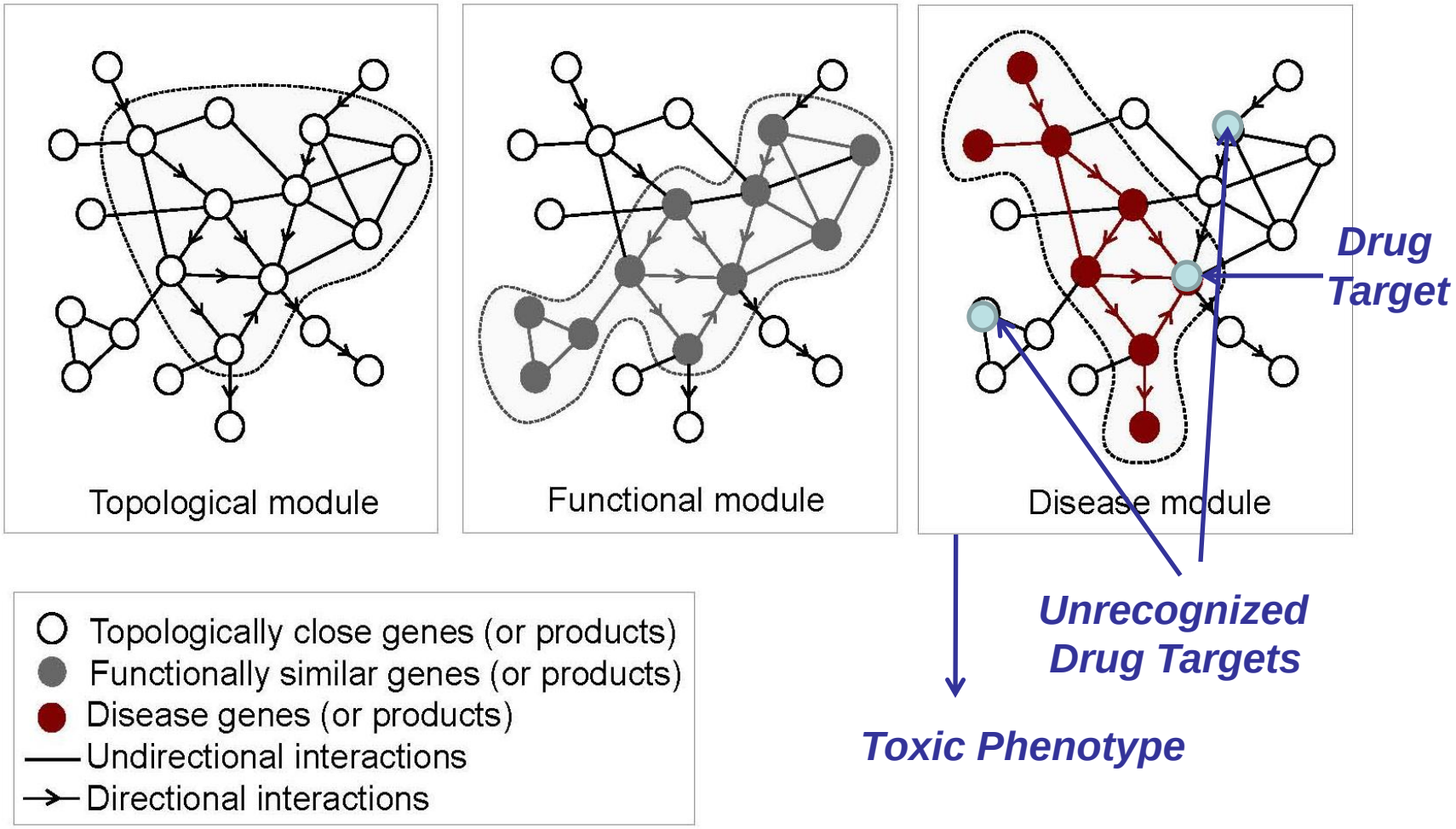
Disease modules should be targeted with rational polypharmacy for optimal effects on phenotype.



--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68

Drug Toxicities as Systems Response

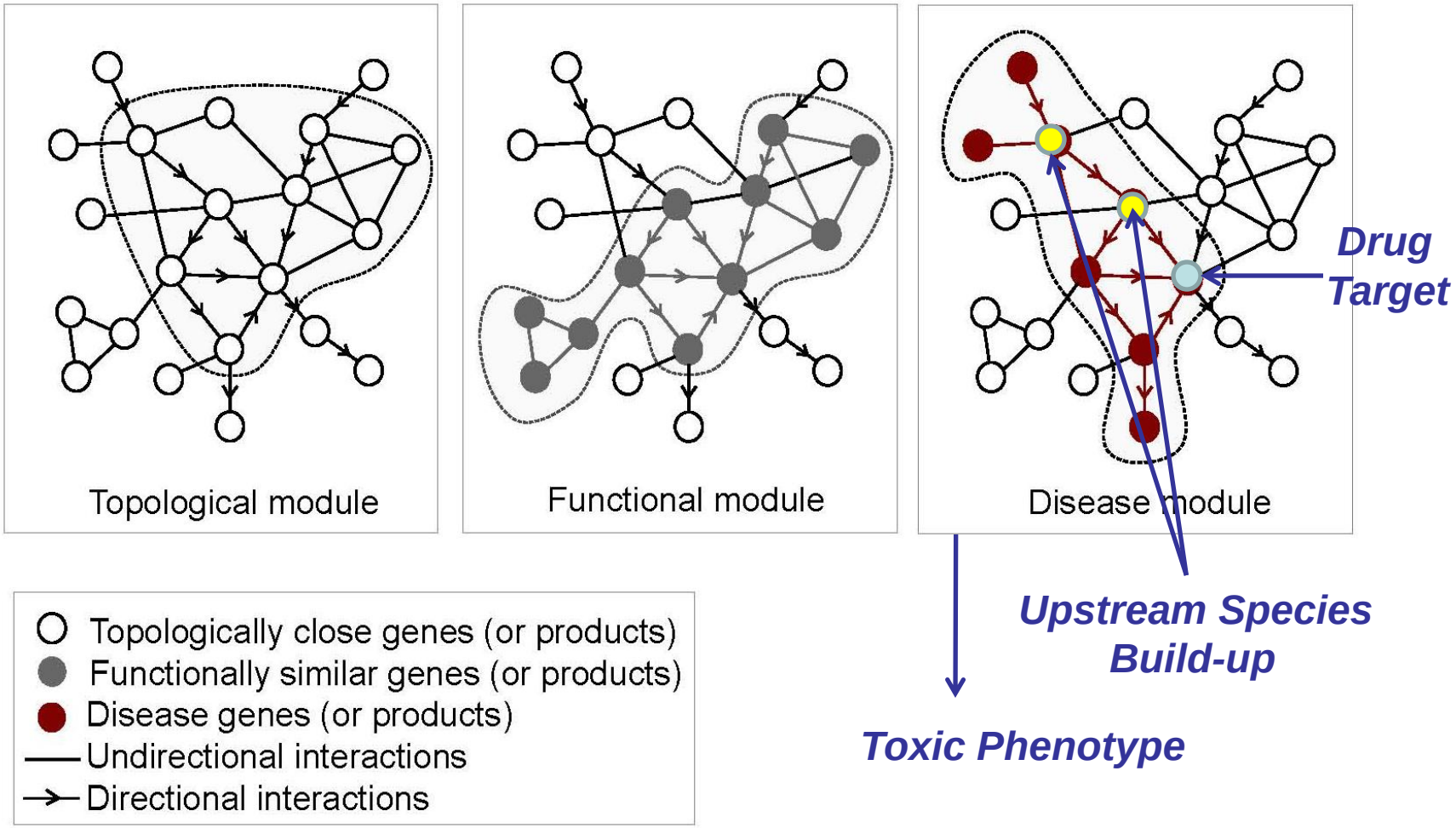
Unrecognized drug targets lead to toxic phenotypes.



--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68

Drug Toxicities as Systems Response

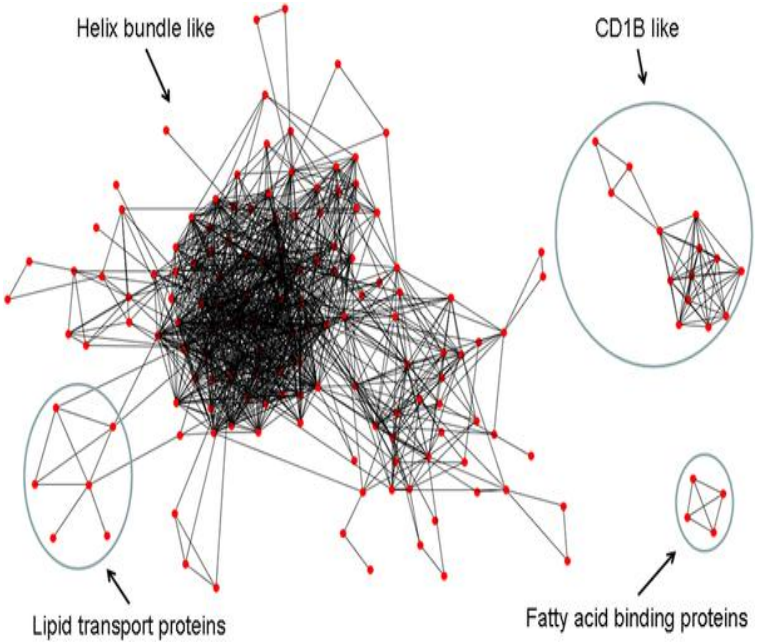
Increased upstream species can yield toxic phenotypes.

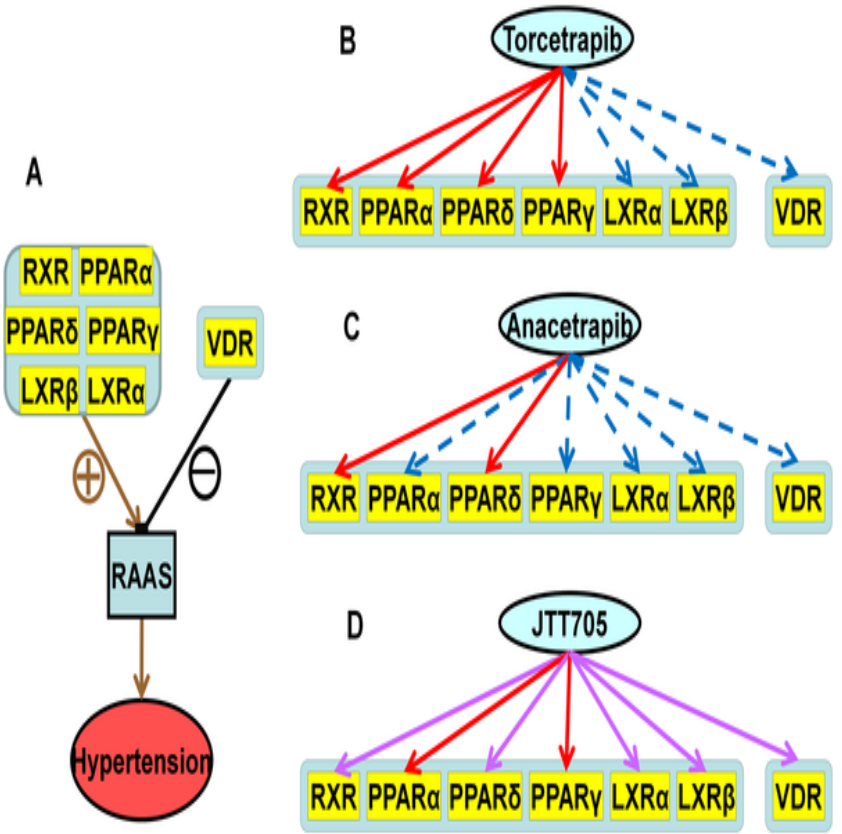


--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68

Drug Side-effect Predictions: CETP Inhibitors

Structural similarity networks coupled with systems analysis of pathways can be used to predict adverse effects of drugs.





--Xie et al., PLoS Comp Biol 2009;5:e1000387

Systems-based Drug Discovery

Experimental Focus

	Disease	*Drug*
Initial Conditions	Characterize Disease Network	Characterize Pharmacologic Action
Network Analysis		
Iterative Refinement	Perturb Network: Characterize Emergent Properties & Control Nodes	Identify Emergent Properties (‘off-target,’ unanticipated)

--after Schadt, et al., Nature Rev Drug Disc 2009;8:286-295; Barabasi, et al., Nature Rev Genet 2011; 12:56-68

Quantitative (Patho)phenotypes in Clinical Trials

Why Does Phenotype Screening Continue to Surpass Target-based Screening?

- The chosen target is wrong.
- The chosen target is reasonable, but the networked architecture of the system within which it functions is redundant, clustered, and adaptive.
- The phenotype is imprecise.
- Combinations of the above

Why Does Phenotype Screening Continue to Surpass Target-based Screening?

- The chosen target is wrong.
- The chosen target is reasonable, but the networked architecture of the system within which it functions is redundant, clustered, and adaptive.
- The phenotype is imprecise.
- Combinations of the above

Toward Precision Medicine

National Research Council

of the National Academies

Recommendation for New Disease Taxonomy

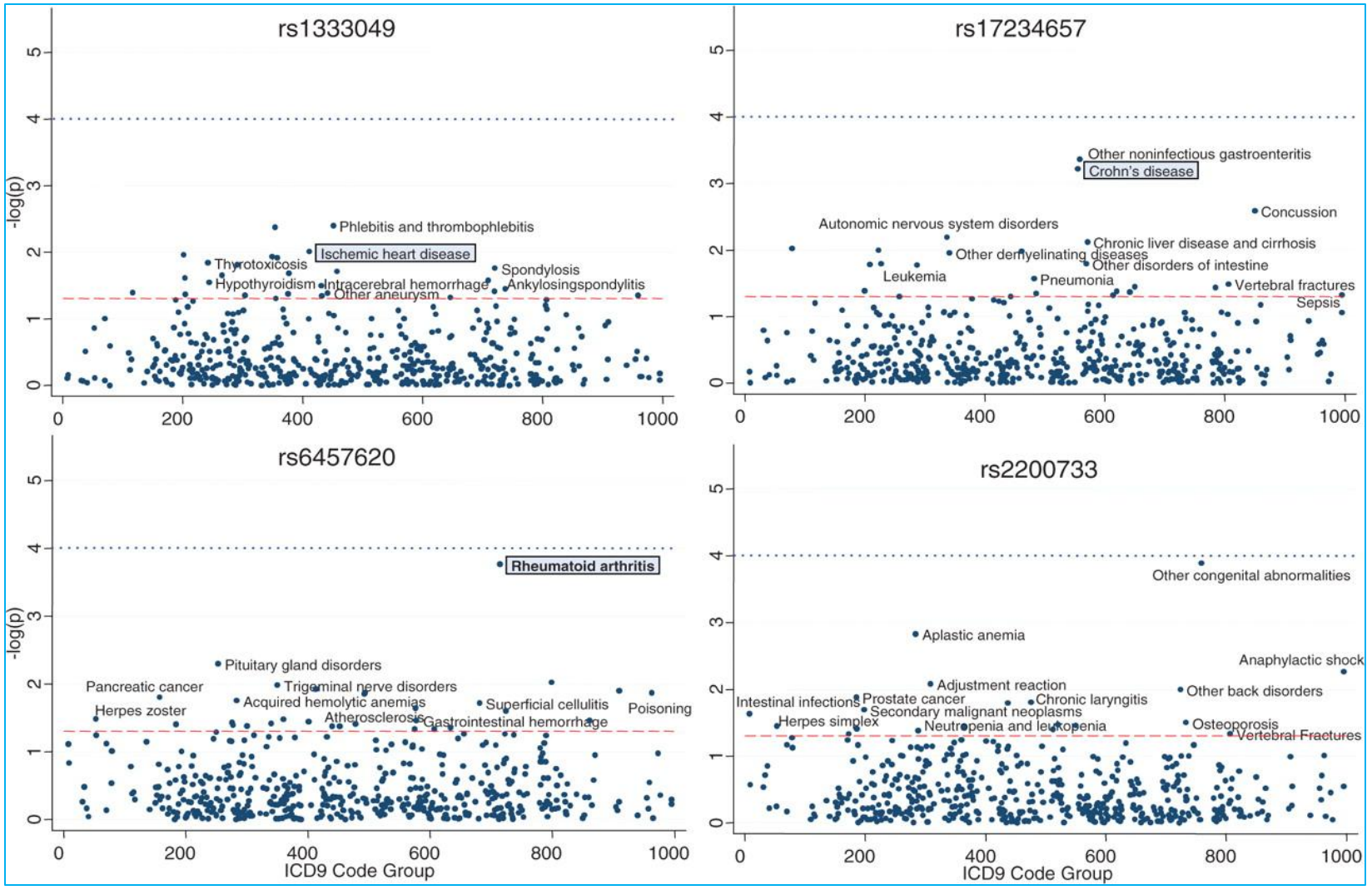
"A new disease taxonomy should be developed that would:

- describe and define diseases based on their intrinsic biology in addition to traditional physical 'signs and symptoms';
- go beyond description and be directly linked to a deeper understanding of disease mechanisms, pathogenesis, and treatments; and
- be highly dynamic…continuously incorporating newly emerging…information."

Approaches to 'Exquisite' Phenotyping: Clinical Phenotypes

- Database of Genotypes and Phenotypes (dbGaP)
- Phenome-wide Association Studies (PheWas) (cf. *Denny et al., Bioinformatics 2010;2605-1210*)
- Electronic Medical Records and Genomics (eMERGE)
- Repurposing Existing Clinical (trial) Data Sets—Drug Trials-Systems Perturbations (cf. *Tatonetti et al., Sci Transl Med 2012;4:125ra31; Campillos et al., Science 2008;321:263*)

PheWAS



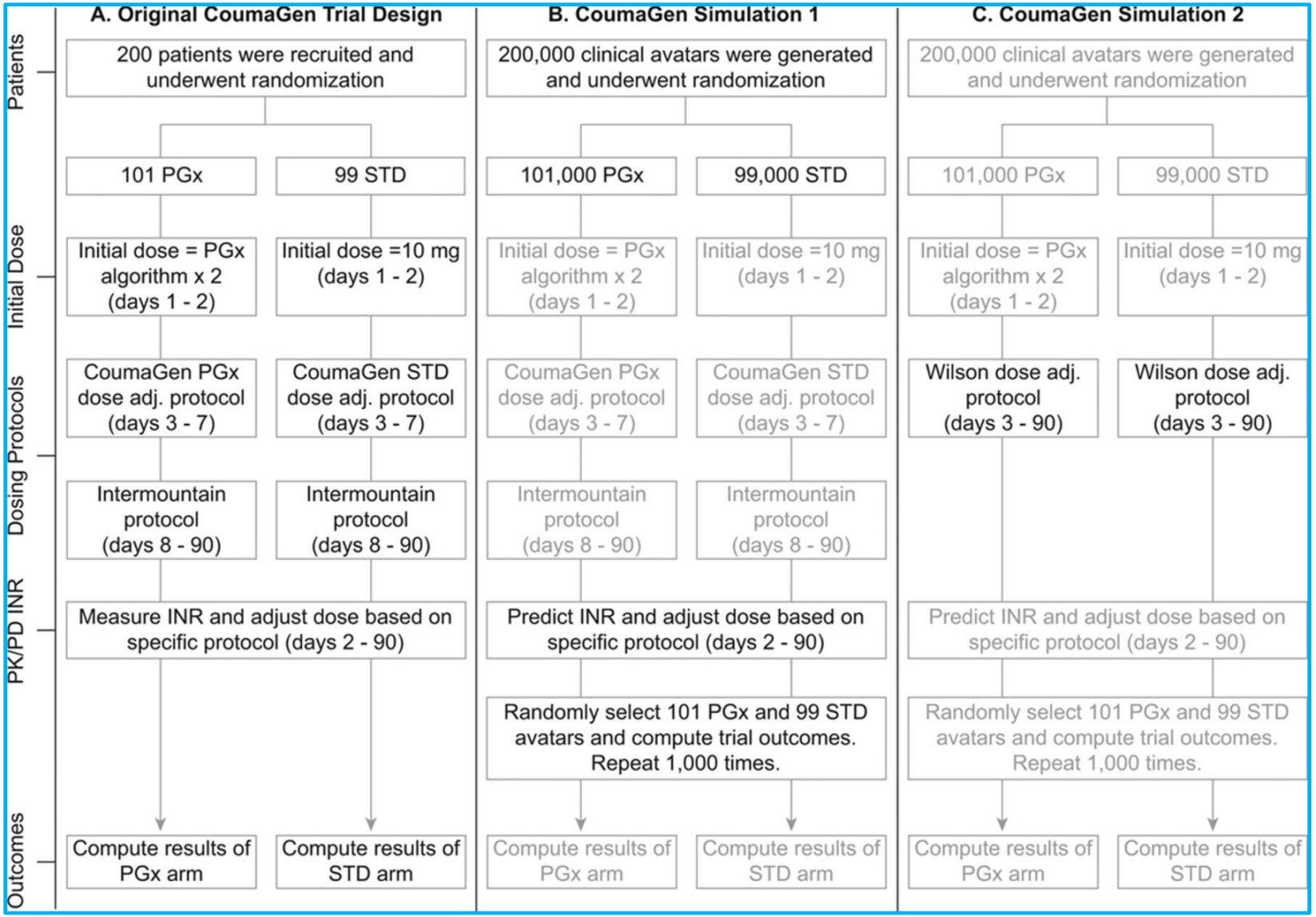
--Denny et al., Bioinformatics 2010;26:1205-1210

Approaches to ‘Exquisite’ Phenotyping: Other

- Imaging Data Sets & Machine Learning
- Orthogonal Unbiased Information (UK BioBank & Keystroke Data)
- Diagnostic and Drug Data Bases (cf. *Ponda et al., Circulation 2012;126:270-7*)

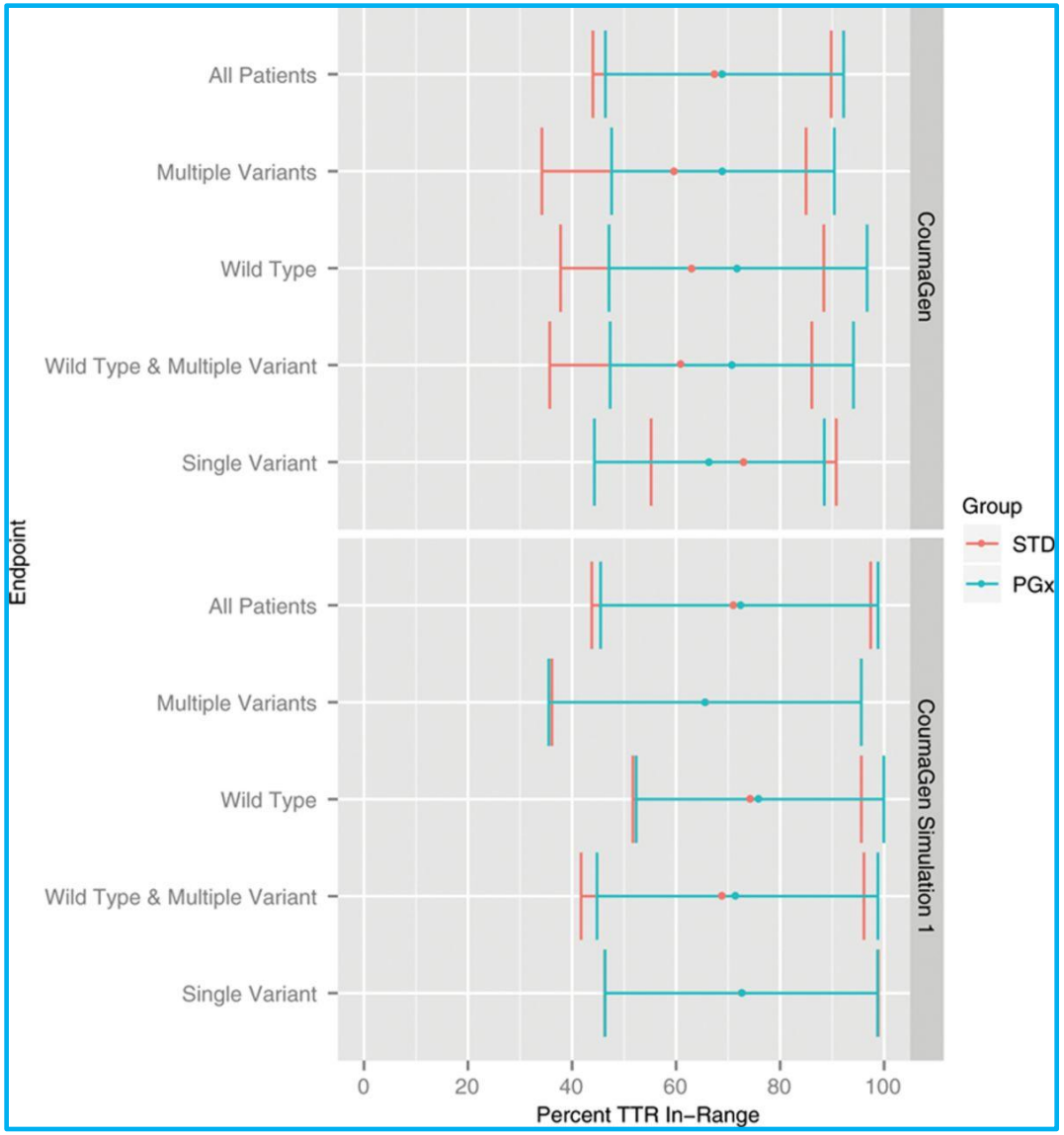
Network Dynamics and Clinical Trial Design

Systems-based Clinical Trial Design



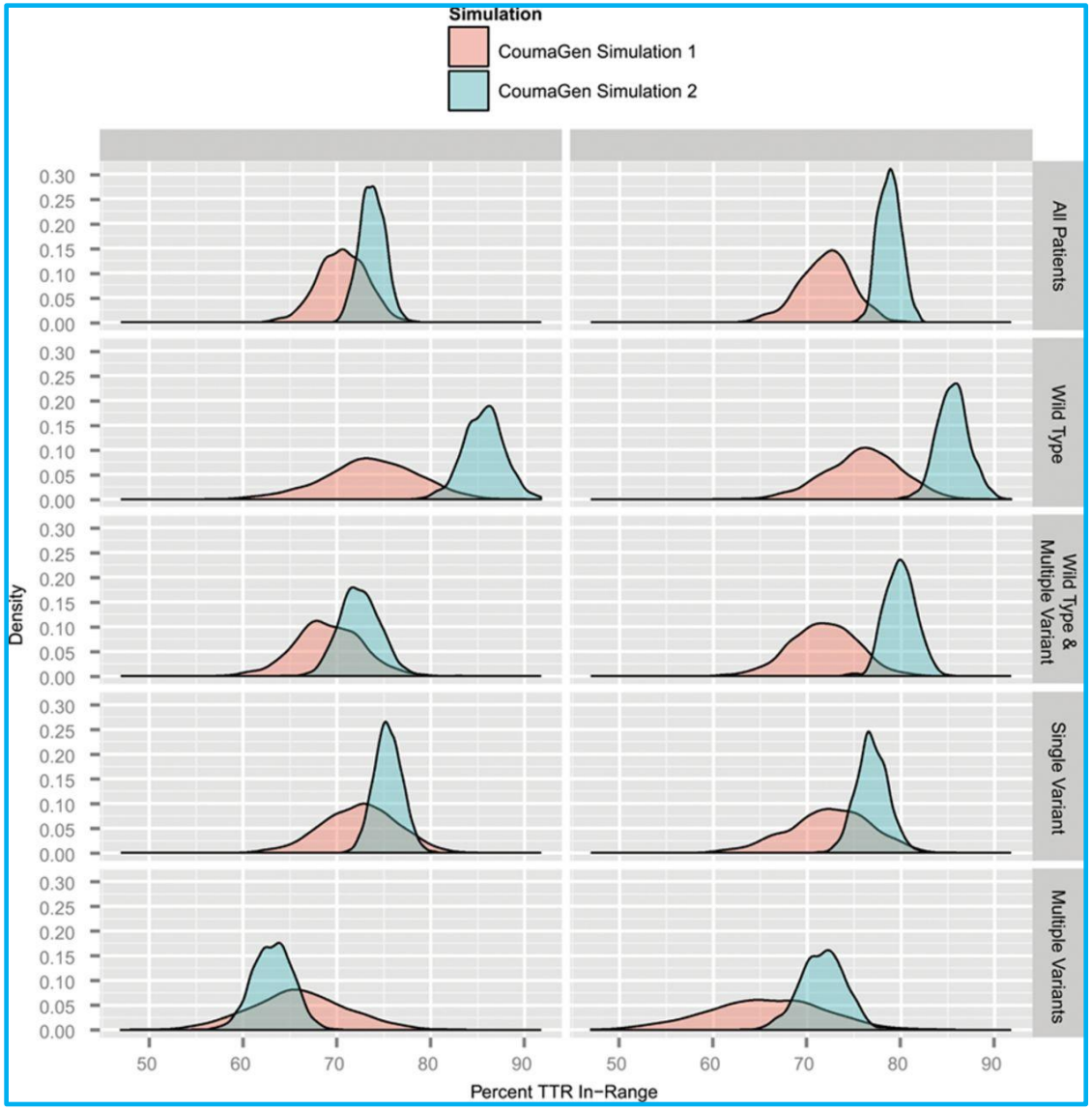
--Fusaro et al., Circulation 2013;127:517-526

Systems-based Clinical Trial Design



--Fusaro et al., Circulation 2013;127:517-526

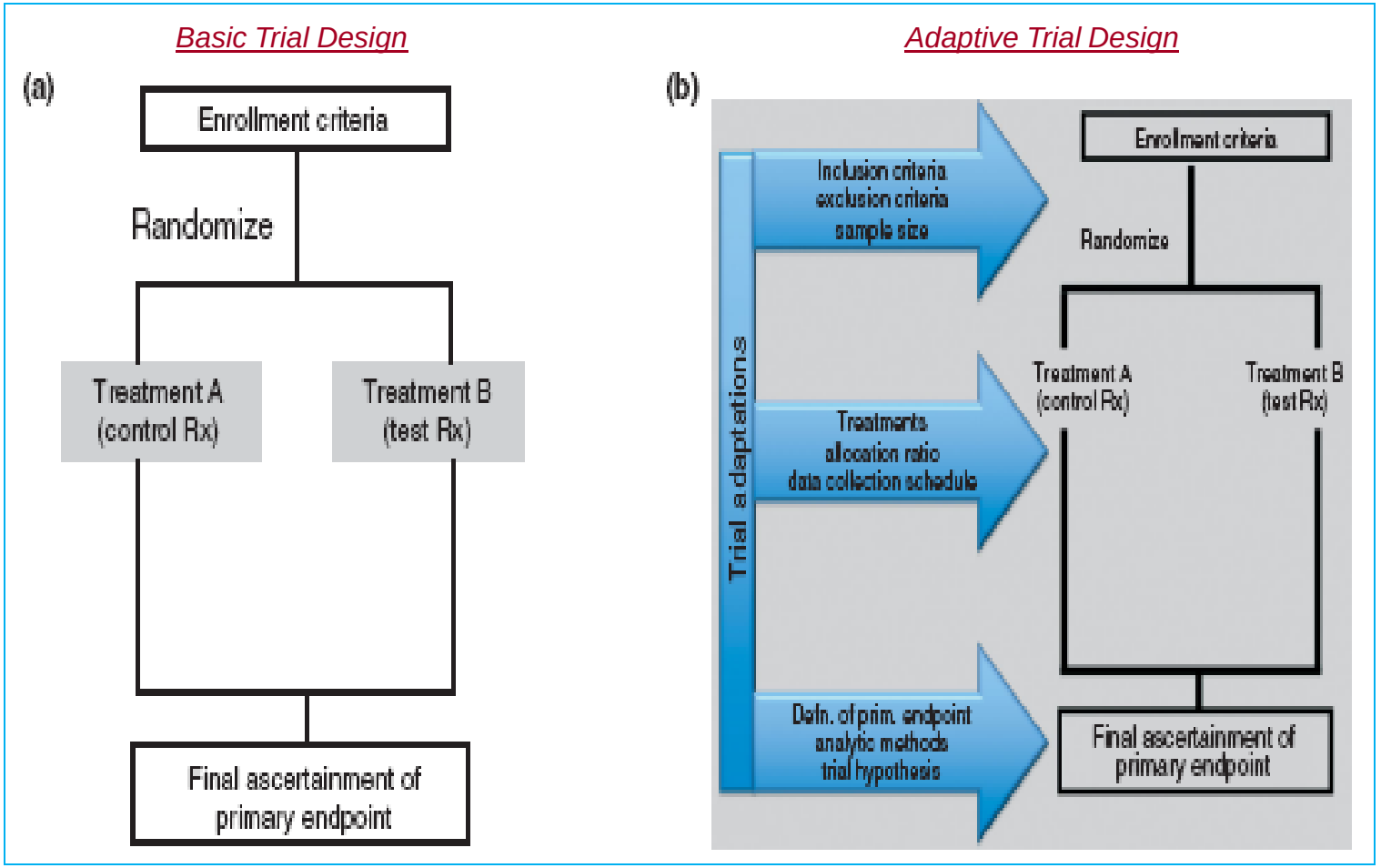
Systems-based Clinical Trial Design



--Fusaro et al., Circulation 2013;127:517-526

Approach to Clinical Trial Design in Systems Pharmacology Era

Clinical Trial Design

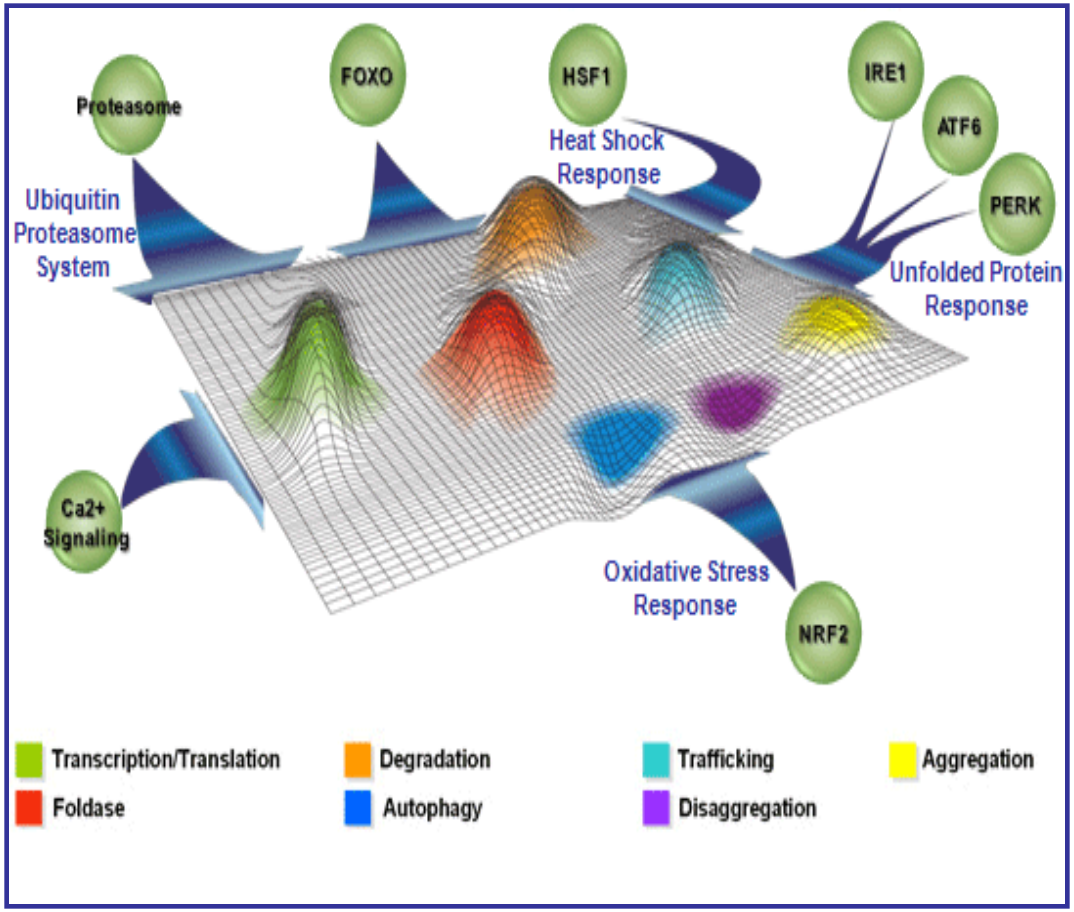


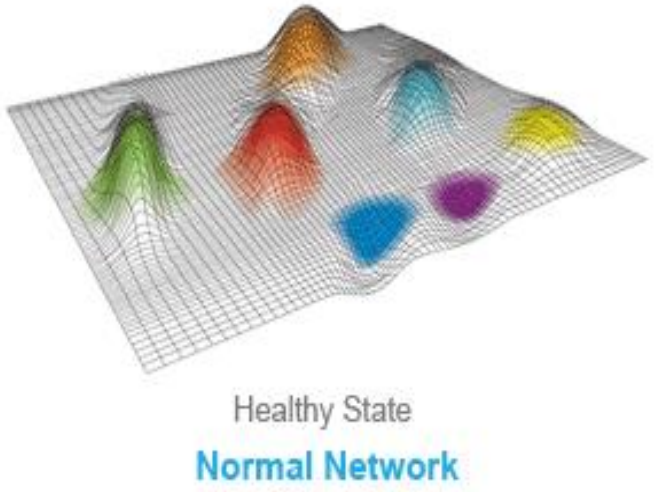
--Antman et al., WIREs Syst Biol Med 2012;10.1002

Developing New Biomarkers and Patient Reported Outcomes Measures (PROs)

- C-Path Institute (nonprofit): new biomarkers for drug-induced (renal) injury (data produced by a consortium); FDA and EMA accepted; undergoing clinical evaluation
- PROMIS (NIH PRO effort)
- C-Path Institute: PROs for specific diseases

Systems Pharmacology: Visualizing Therapeutic Actions





--From Proteostasis Web Site:
http://www.proteostasis.com/science/proteostasis_network.php

Summary

- There are major problems with current drug development paradigms.
- Systems biology and network science provide useful approaches to identifying drug targets and rational combinations of targets.
- Clinical phenotyping must become more precise and more discriminating for optimal identification of effective therapies.
- The clinical research enterprise and the drug approval process must be transformed *pari passu*.

Acknowledgements

- Stephen Chan
- Katherine Cottrill
- Farshid Garmaroudi
- Brad Maron
- Victoria Parikh
- Yingyi Zhang
- Elliott Antman
- Laszlo Barabasi
- Natalie Gulbahce
- Calum Macrae
- Scott Weiss