Open Access Integrative bionetworks:
Why will disease biology and causal disease models enter the pre-competitive space?

Create an open access, integrative bionetwork evolved by contributor scientists working to eliminate human disease

Stephen Friend MD PhD
Sage Bionetworks
Fred Hutchinson Cancer Research Center

IOM National Policy Forum
Extending the Spectrum of Pre-Competitive
Oncology Biomedical Research
February 9th, 2010

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What drives current behavior?

Extending the Spectrum of Pre-Competitive Oncology Biomedical Research

Sharing Consultants

Trading Scientists

Sharing Revenues

Sharing Analysis Tools

Sharing Samples and Non-Compound Data

Sharing Disease Models

Sharing Clinical Compound Data

Sharing Toxicities

Sharing Compounds

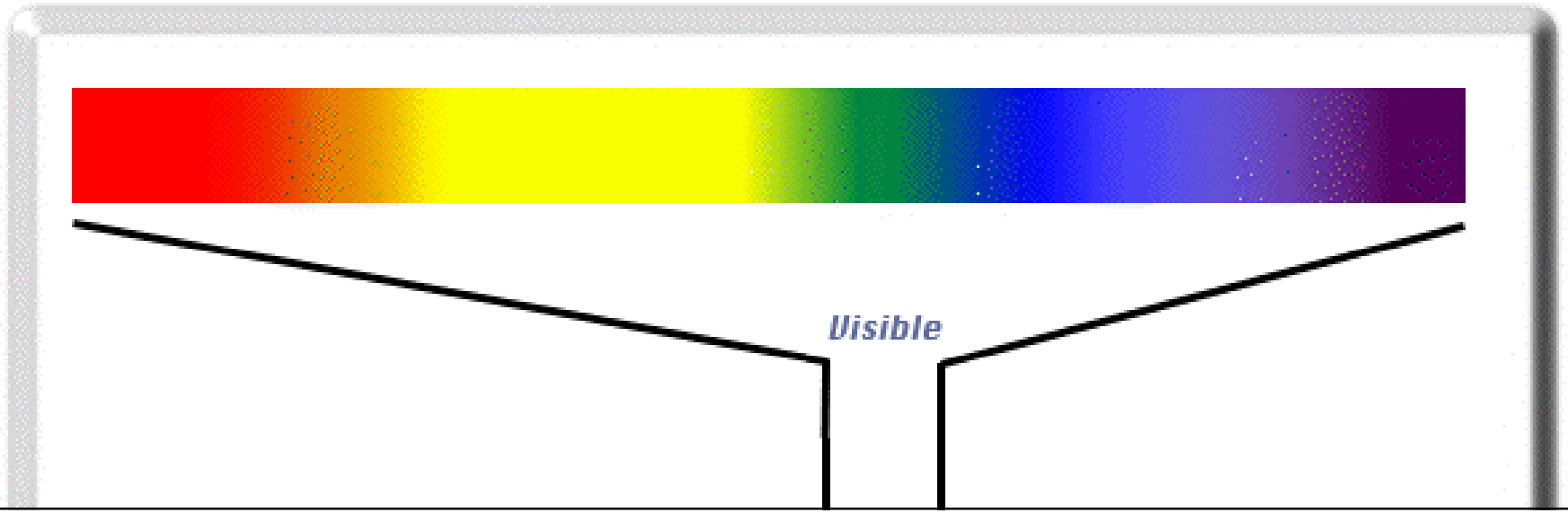
Extending the Spectrum of Pre-Competitive
Oncology Biomedical Research

Remember that if it is a company and often also if a University
they are obligated to justify
the underlying business case

Sharing ← Disease Models → Unsharing

Benefits **Costs**

Can I get there without others cheaply?
Will others beat me to it if I do not join?
Can I build a first mover advantage?
Can I sustain my advantage and sustain my return?

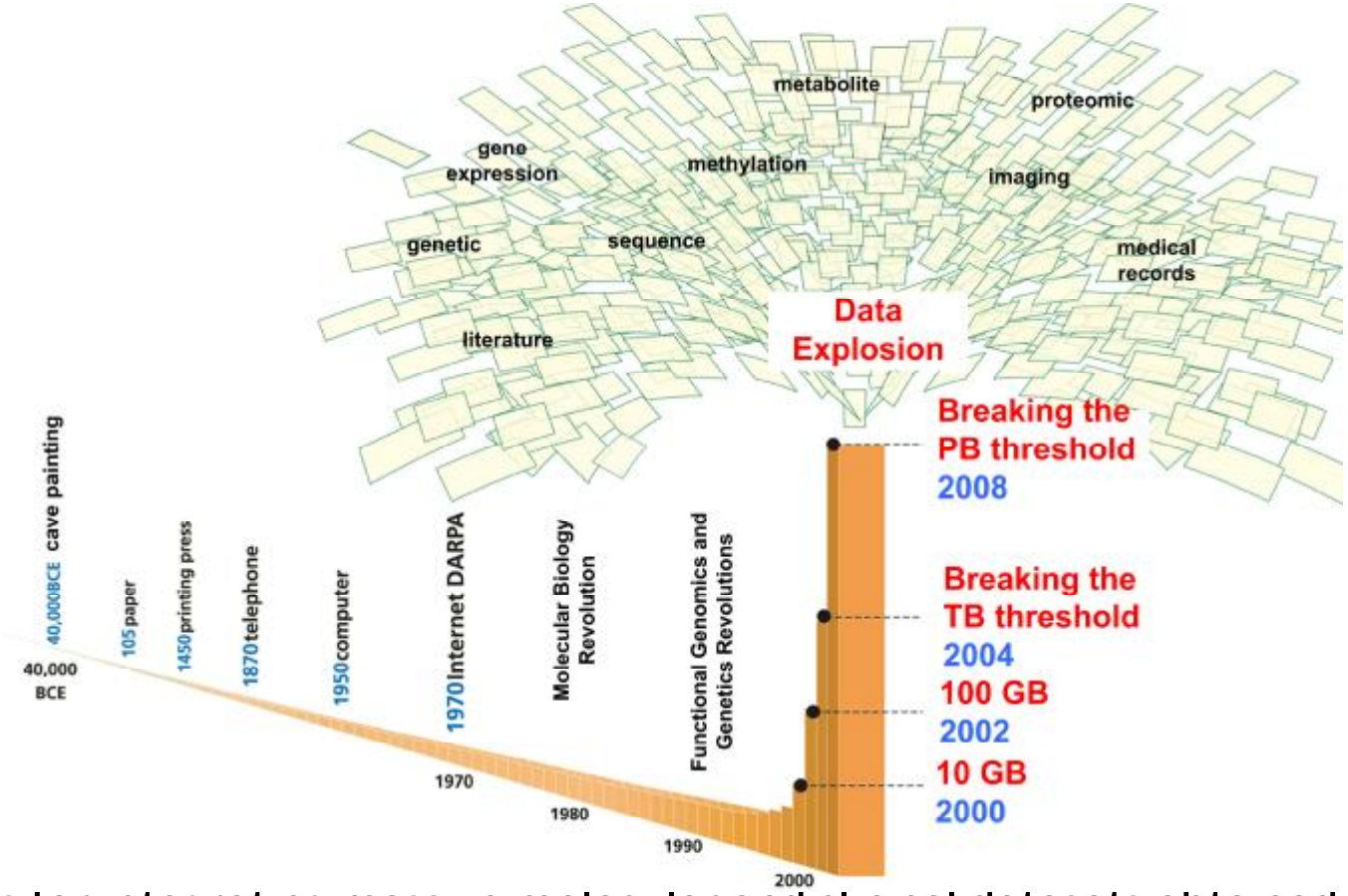


What are forces driving desire to consider precompetitive options?

Thanks to Bill Proud

"Purpose of visit?"

Explosion of Biological Genomic & Clinical Information



- Computational methods for integrating massive molecular and clinical datasets obtained across sizable populations into predictive disease models can recapitulate complex biological systems
- Data should feed and refine a set of models that inform our understanding of disease causality as well as generate new mechanisms, targets, diagnostics and knowledge.

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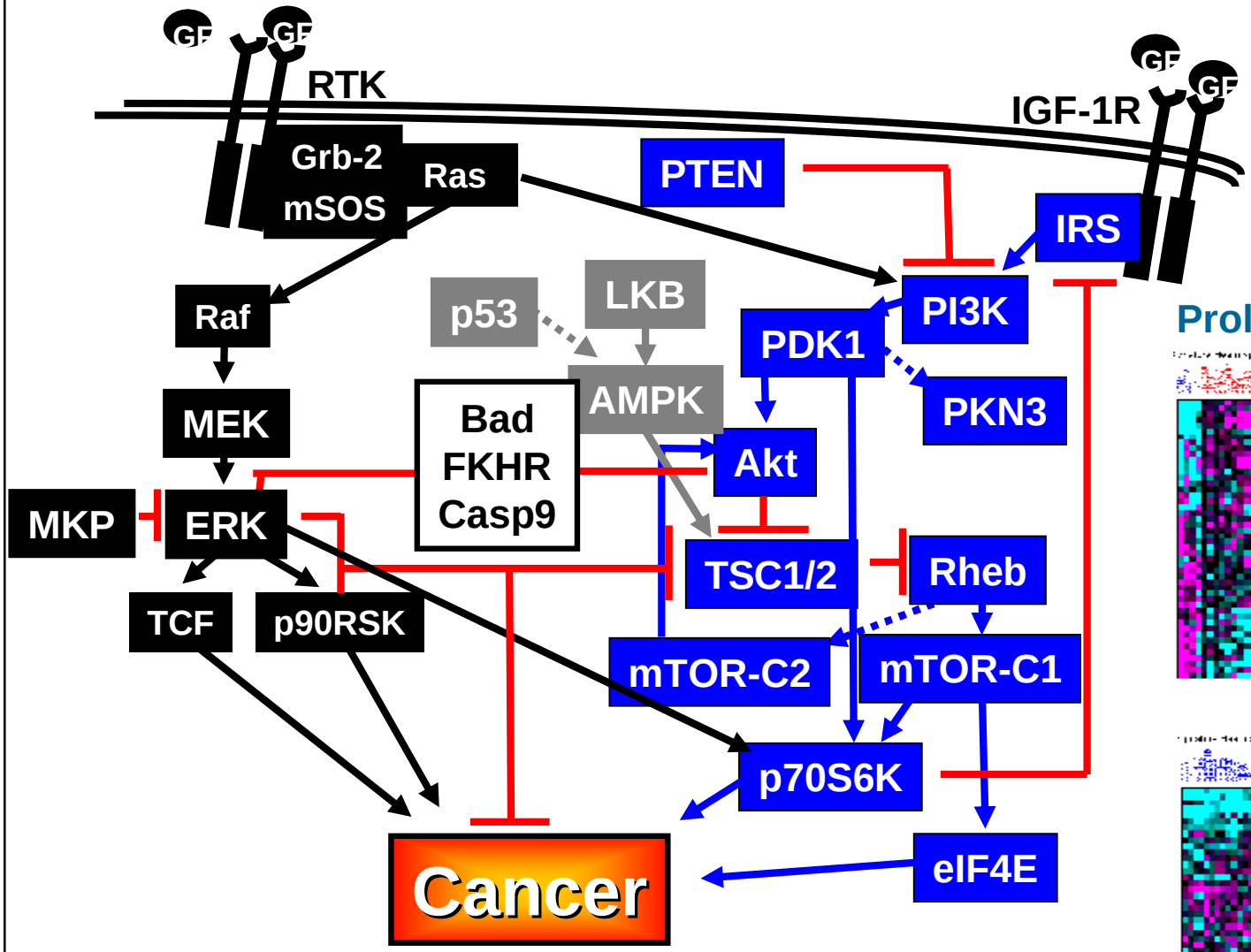
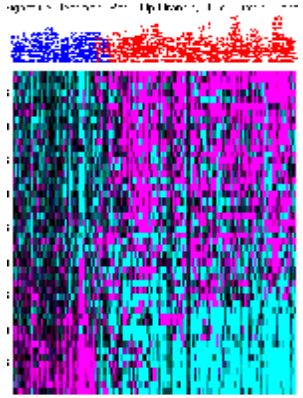
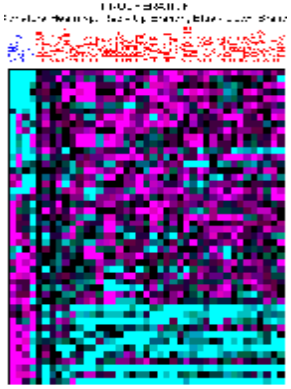
Profiling signatures to ID responder populations



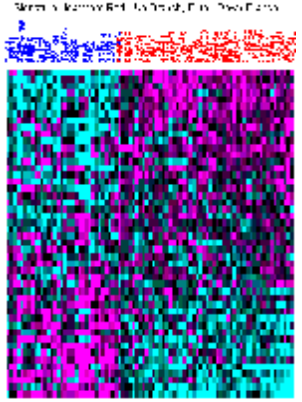
RAS activation



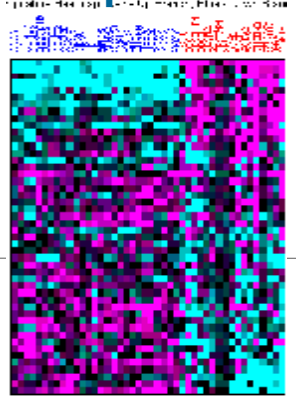
Proliferation



Growth Factors



p53



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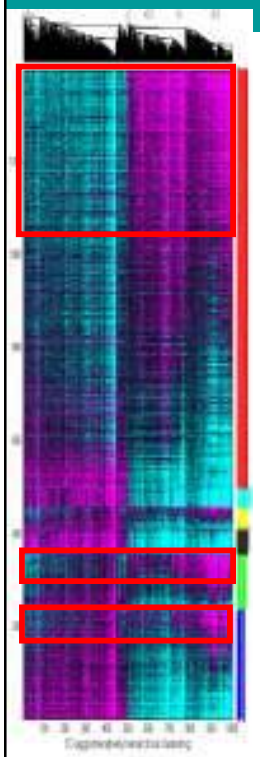
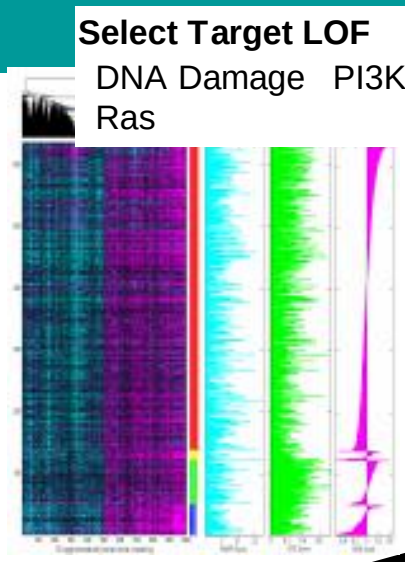
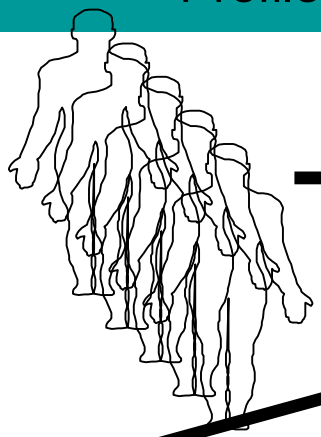
The Merck/Moffitt Strategy: Direct patient selection from database matching molecular signatures to clinical trials

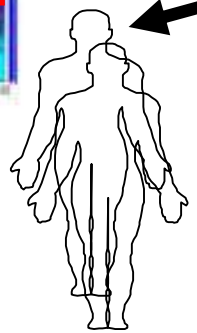




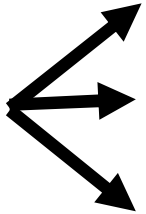
Profiles stored at hospital



Re contact
Trial design



Disease recurrence and trial eligibility



Clinical trial Portfolio

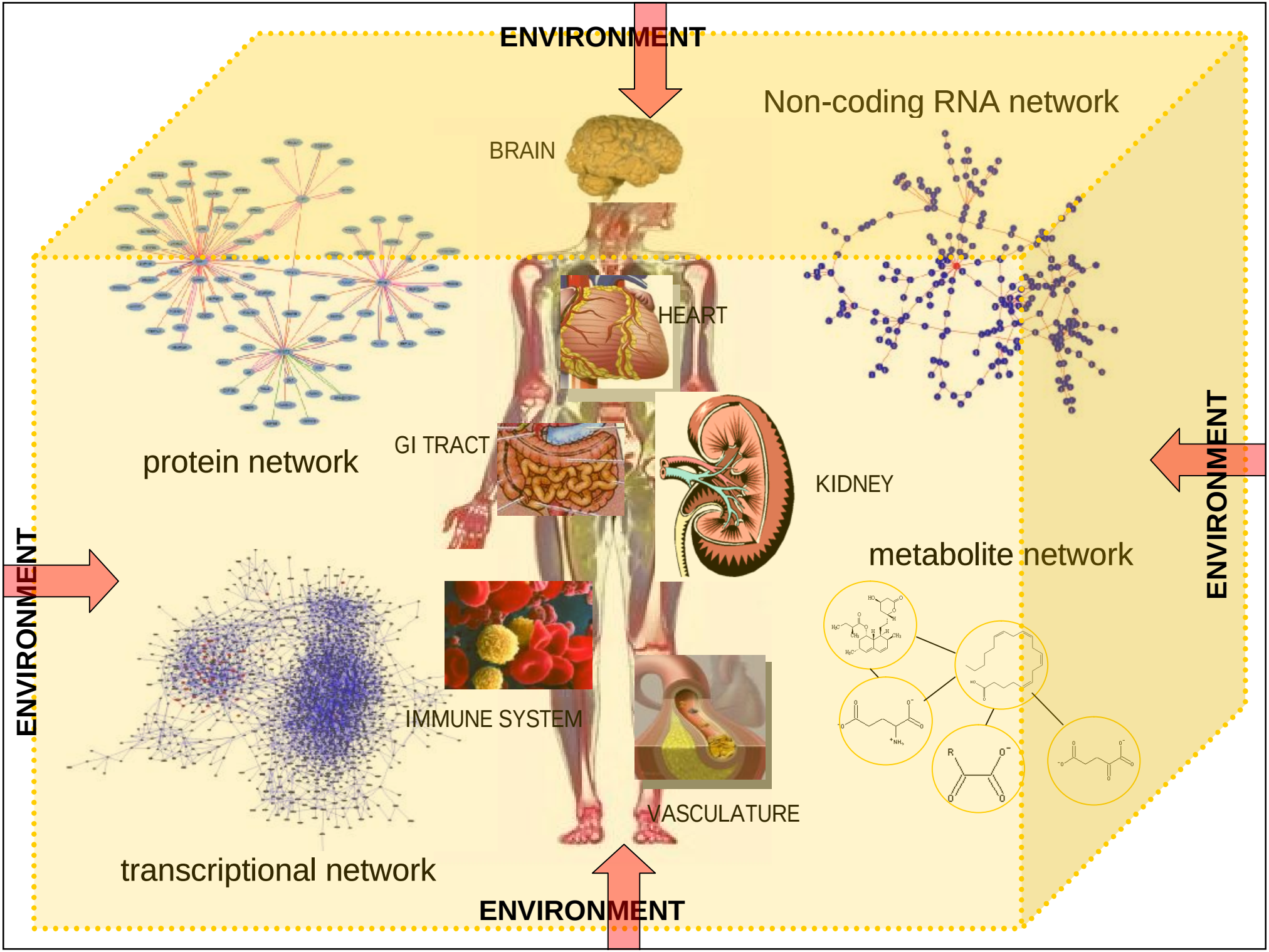
Trial sig A

Trial sig B

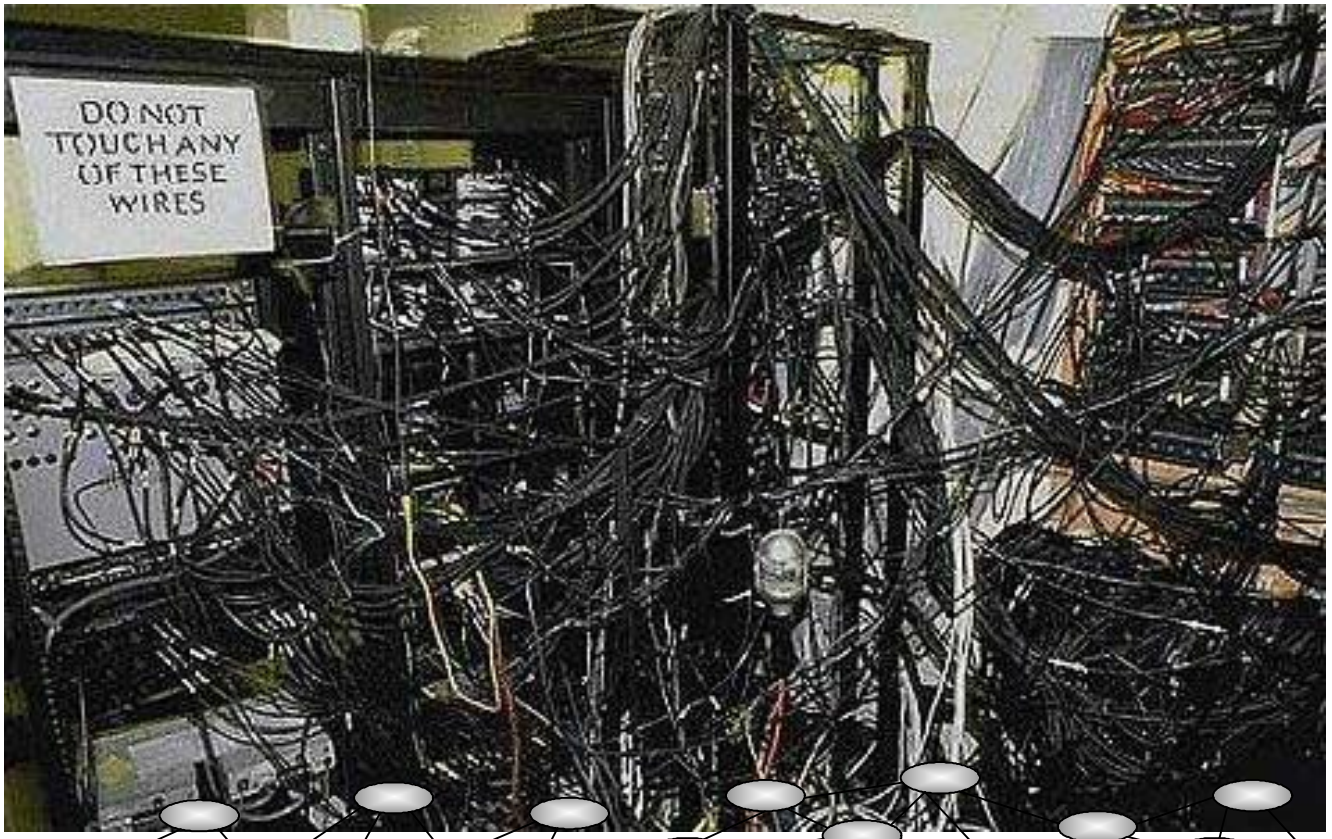
Trial sig C

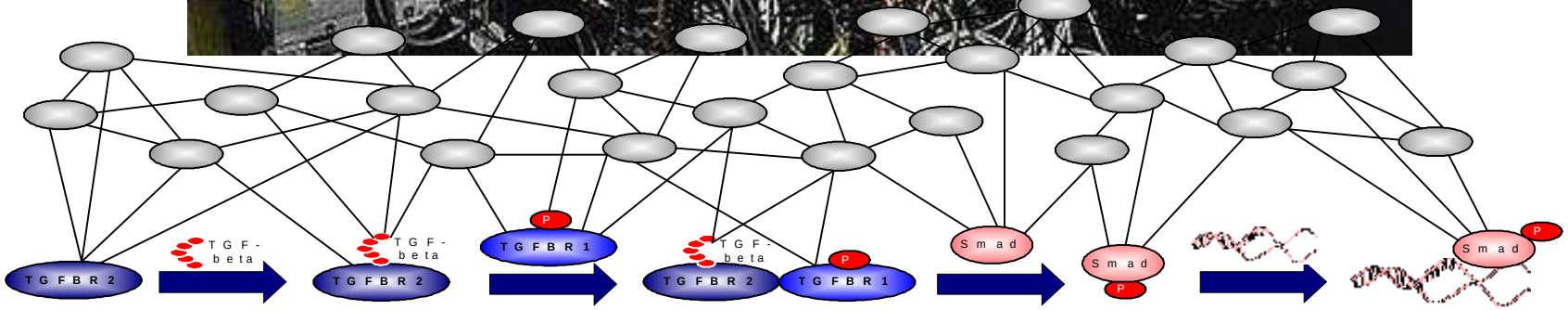
- Validation of molecular hypotheses
- Patient selection on available profiling data

Biomarker Driven Branched Subpopulation based Adaptive Trials


ENVIRONMENT
Non-coding RNA network
BRAIN
HEART
protein network
GI TRACT
KIDNEY
ENVIRONMENT
ENVIRONMENT
metabolite network
IMMUNE SYSTEM
VASCULATURE
transcriptional network
ENVIRONMENT

The Reality of Complex Behaviors Manifested by Living Systems

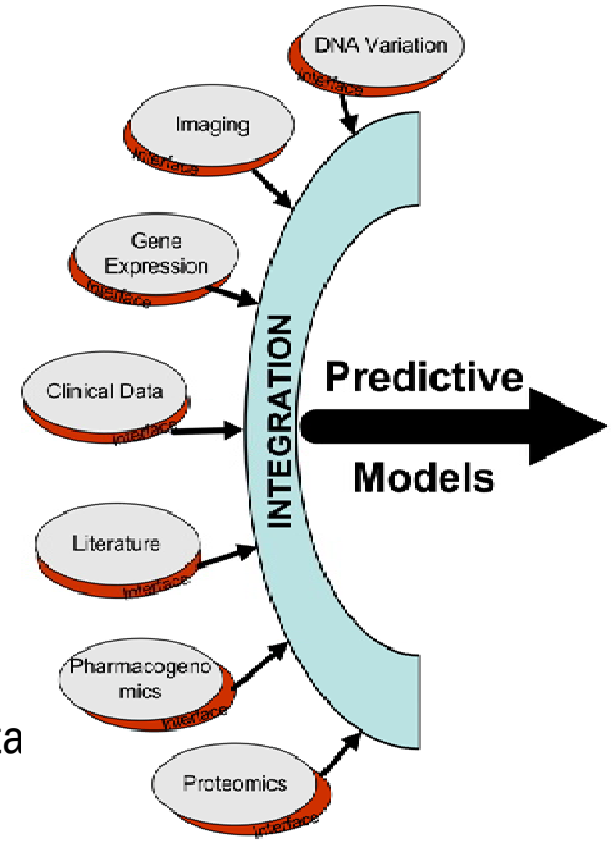


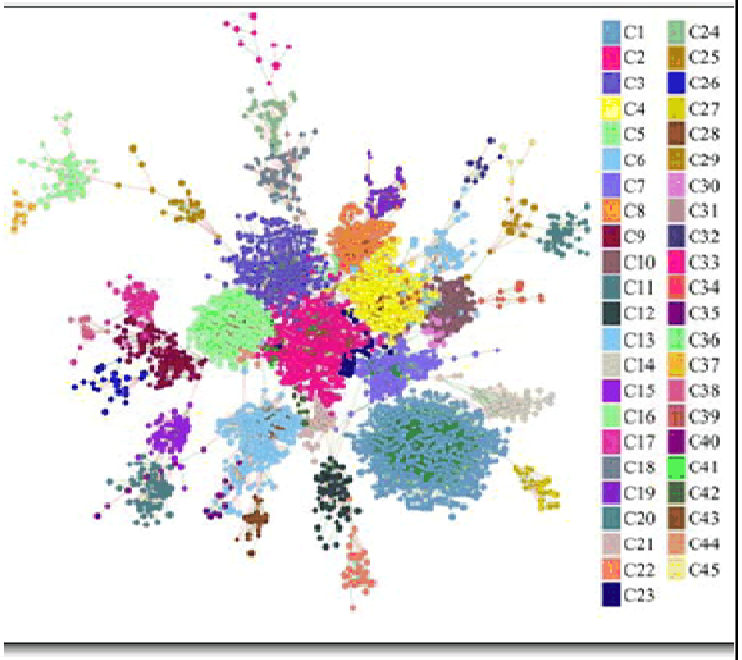


- The truth is we have little idea on the underlying causes of common human diseases.
- We need to more fully embrace the complexity to develop a better understanding.

The “Rosetta Integrative Genomics Experiment”: Generation, assembly, and integration of data to build models that predict clinical outcome

Merck Inc. Co.
5 Year Program
Based at Rosetta
Total Resources
>$150M

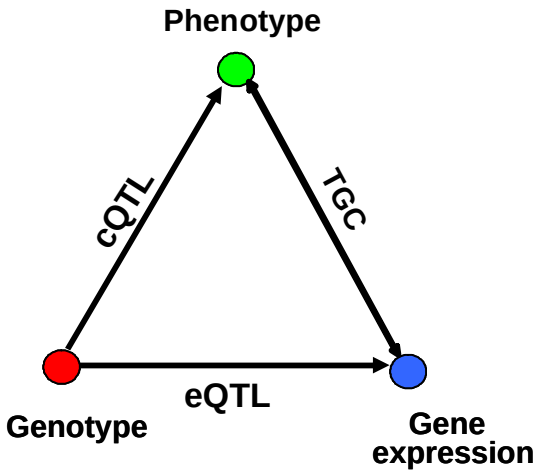


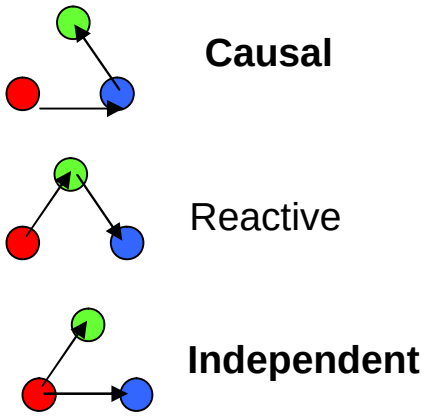


- Generate data need to build
- networks
- Assemble other available data
- Integrate and build models
- Test predictions
- Develop treatments
- Design Predictive Markers

Genetics allows Causality to be established

- **DNA Variation in populations represents complex set of perturbations that with the environment drive disease**
- **Map DNA variation to intermediate phenotypes (RNA expression) and clinical phenotypes (outcomes)**
- **For shared DNA variation that drives both intermediate traits and clinical traits can use statistical modeling to derive likely order**





Schadt et al. 2005. An integrative genomics approach to infer causal associations between gene expression and disease. *NatGenet.* 37:710-717

Network Modeling

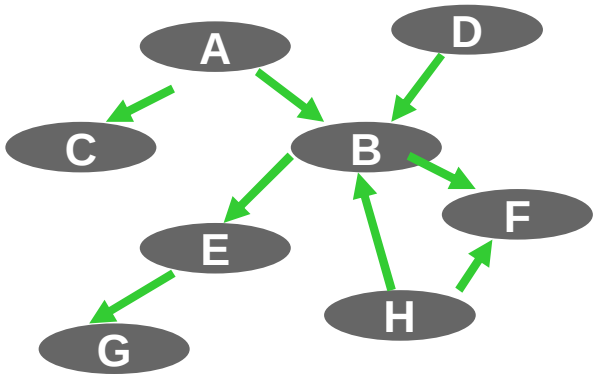
- **Probability-based networks:** Bayesian network

Bayes' theorem

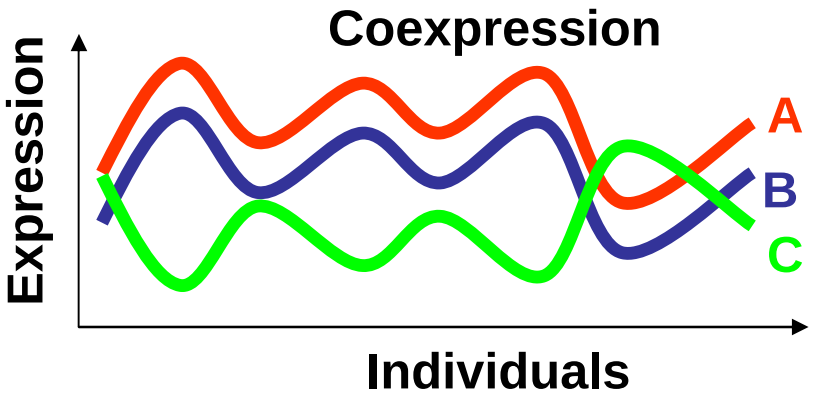
$$p(B|A) = p(A|B) \times p(B) / p(A)$$

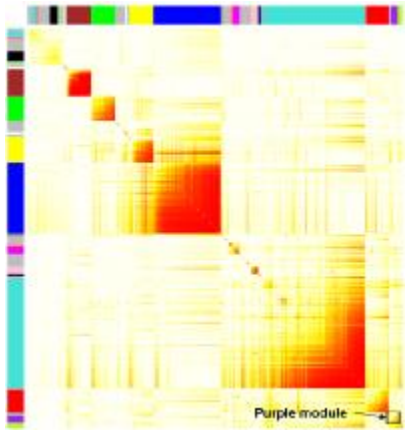
+

Priors
- Genetic
- Genomic
- Proteomic
- Metabolomic
- literature

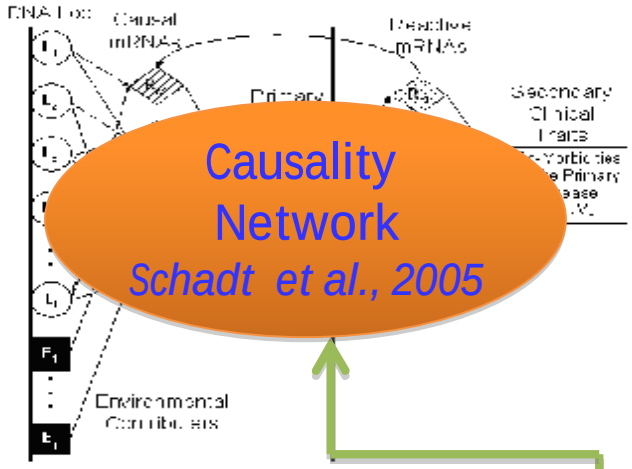


- **Correlation-based networks:**
  Weighted Co-expression network
  Tissue-tissue network





Decipher Biological Systems via Multiple Networks



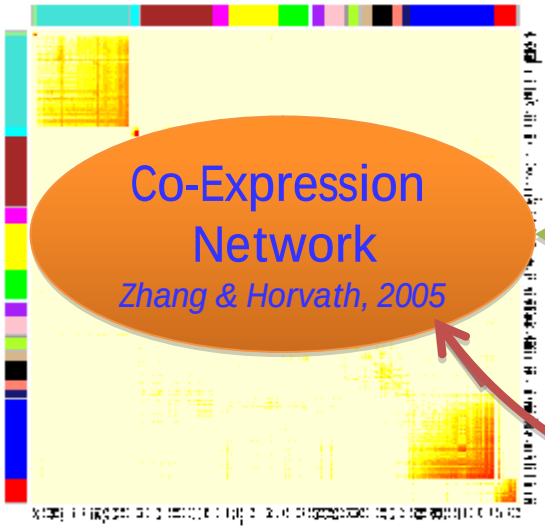
Causality Network
Schadt et al., 2005

Genotype Data

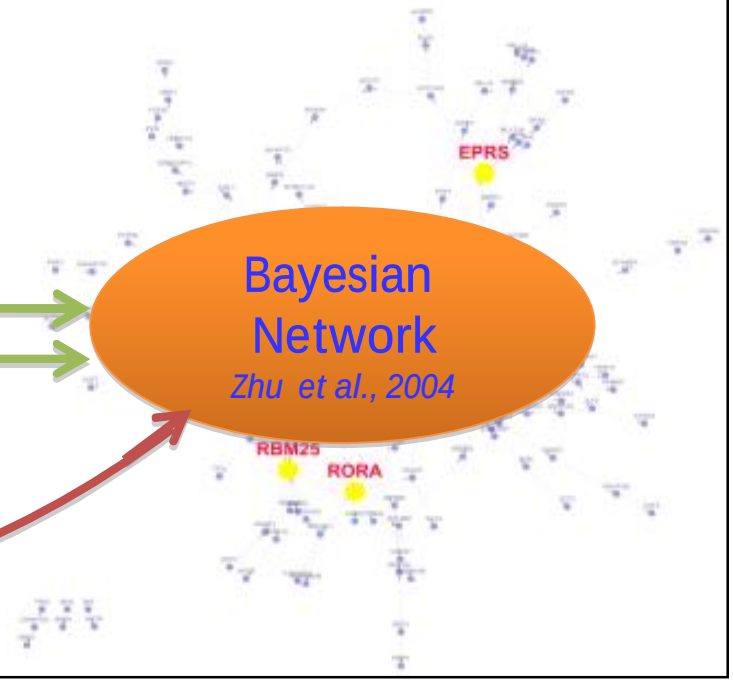
Gene Expression

Clinical Traits

Other Data



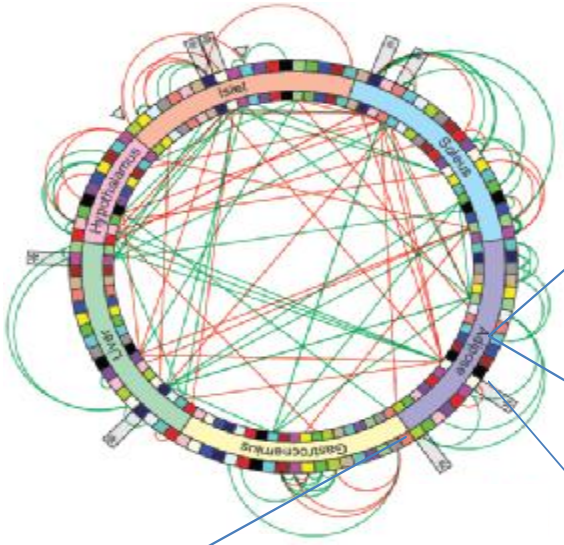
Co-Expression Network
Zhang & Horvath, 2005



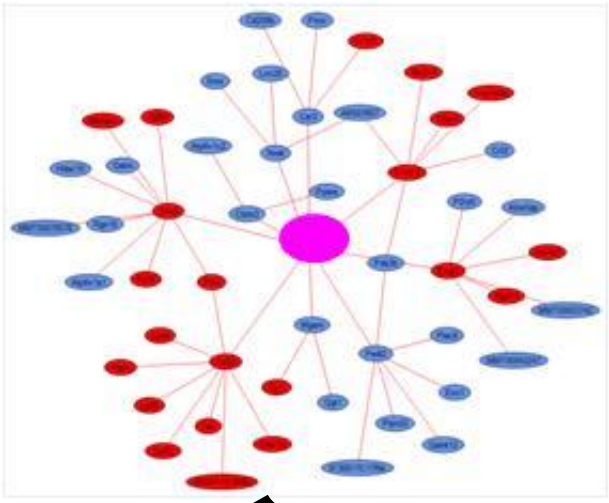
Bayesian Network
Zhu et al., 2004

Integration

Identification of Causal Regulators of Metabolic & CV Disease



Macrophage-enriched Module



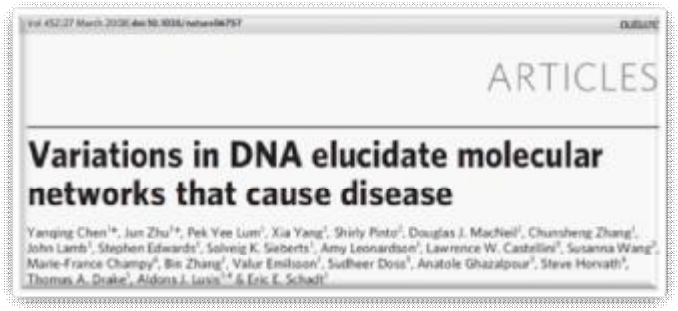
Network Causal for Diabetes, Obesity & Cardiovascular Traits

Test all sub-networks to identify those causal for disease
Identify one sub-network that contains many causal regulators:
- **75% of genes supported as causal for atherosclerotic lesions**
  - **(117 of 157 genes; p=5.6e-103)**
- **50% genes supported as causal for obesity**
  - **(366 of 735; p=3.8e-235)**
- **45% genes supported as causal for diabetes**
  - **(263 of 571; p=1.5e-133)**

Angiogenesis-enriched Module

Vascularization-enriched Module

Cell Cycle Module


ARTICLES

Variations in DNA elucidate molecular networks that cause disease

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Extensive Publication Validates Scientific Approach

- **>60 Publications from Rosetta Genetics Group (~30 scientists) over 5 years including high profile papers in Nature and Nature Genetics**

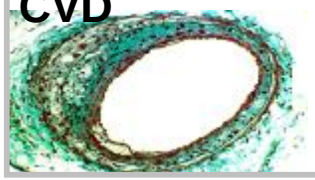
"*Genetics of gene expression surveyed in maize, mouse and man*." **Nature**. (2003)

"*Variations in DNA elucidate molecular networks that cause disease*." **Nature**. (2008)

"*Genetics of gene expression and its effect on disease*." **Nature**. (2008)

"*Validation of candidate causal genes for obesity that affect...*" **Nat Genet**. (2009)

….. Plus 10 additional papers in Genome Research, PLoS Genetics, PLoS Comp.Biology, etc



***"Identification of pathways for atherosclerosis."* Circ Res. (2007)**

"Mapping the genetic architecture of gene expression in human liver." **PLoS Biol.** (2008)

…… Plus 5 additional papers in Genome Res., Genomics, Mamm.Genome

"*Integrating genotypic and expression data …for bone traits…*" **Nat Genet.** (2005)

"..approach to identify candidate genes regulating BMD…" **J Bone Miner Res**. (2009)

"*An integrative genomics approach to infer causal associations* ..." Nat Genet. (2005)

"*Increasing the power to detect causal associations*… "PLoS Comput Biol. (2007)

"Integrating large-scale functional genomic data ..." **Nat Genet.** (2008)

…… Plus 3 additional papers in **PLoS Genet., BMC Genet.**

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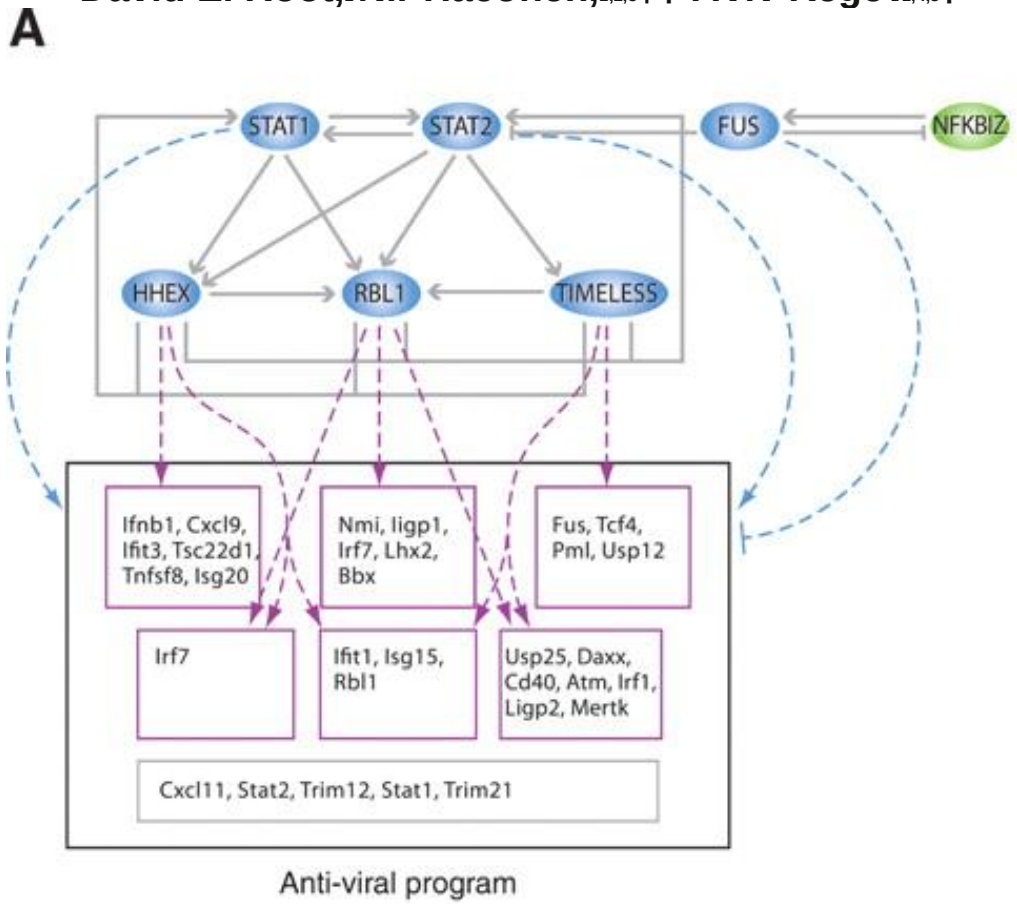
Unbiased Reconstruction of a Mammalian Transcriptional Network Mediating Pathogen Responses

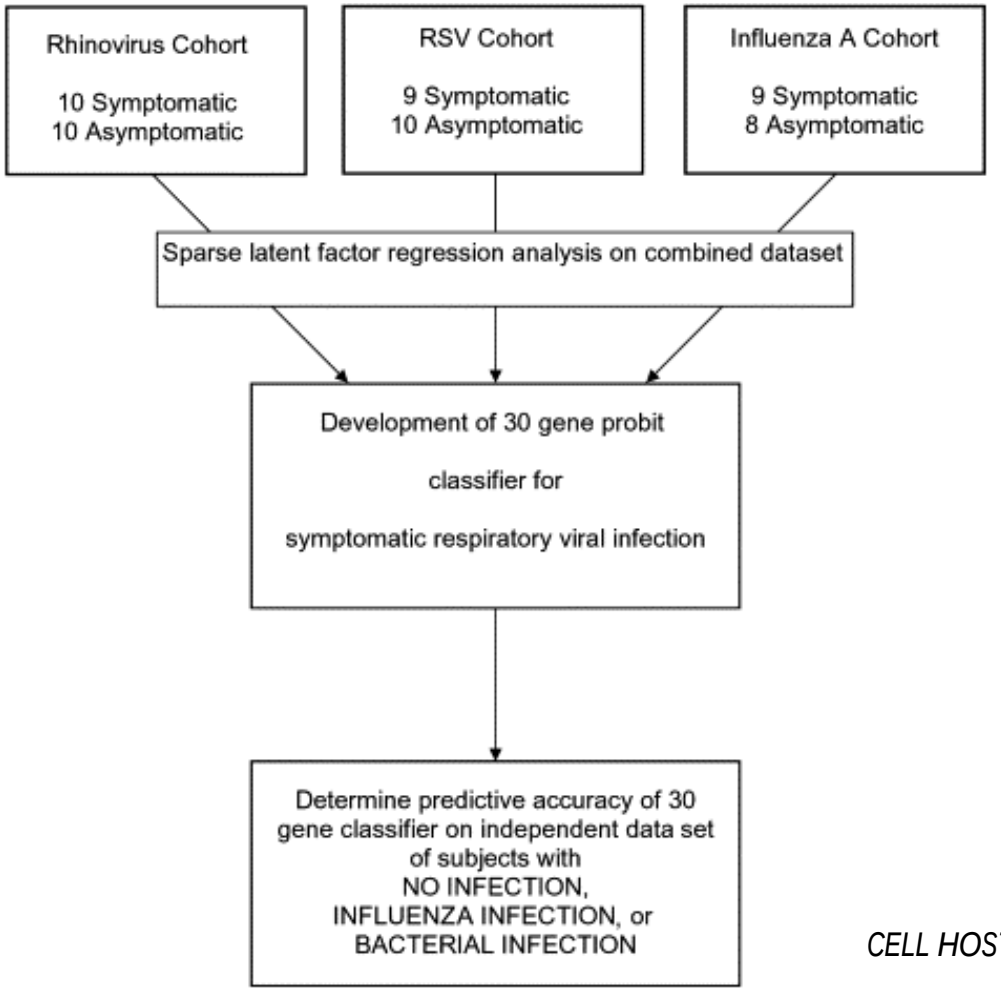
Ido Amit,[1,2,3,4] Manuel Garber,[1]* Nicolas Chevrier,[2,3]* Ana Paula Leite,[1,5]* Yoni Donner,[1]* Thomas Eisenhaure,[2,3] Mitchell Guttman,[1,4] Jennifer K. Grenier,[1] Weibo Li,[2,3] Or Zuk,[1] Lisa A. Schubert,[6] Brian Birditt,[6] Tal Shay,[1] Alon Goren,[1,7] Xiaolan Zhang,[1] Zachary Smith,[1] Raquel Deering,[2,3] Rebecca C. McDonald,[2,3] Moran Cabili,[1] Bradley E. Bernstein,[1,3,7] John L. Rinn,[1] Alex Meissner,[1] David E. Root,[1] Nir Hacohen,[1,2,3]†‡ Aviv Regev[1,4,8]‡



SCIENCE 326:263, 9 OCTOBER 2009

Gene Expression Signatures Diagnose Influenza and Other Symptomatic Respiratory Viral Infections in Humans

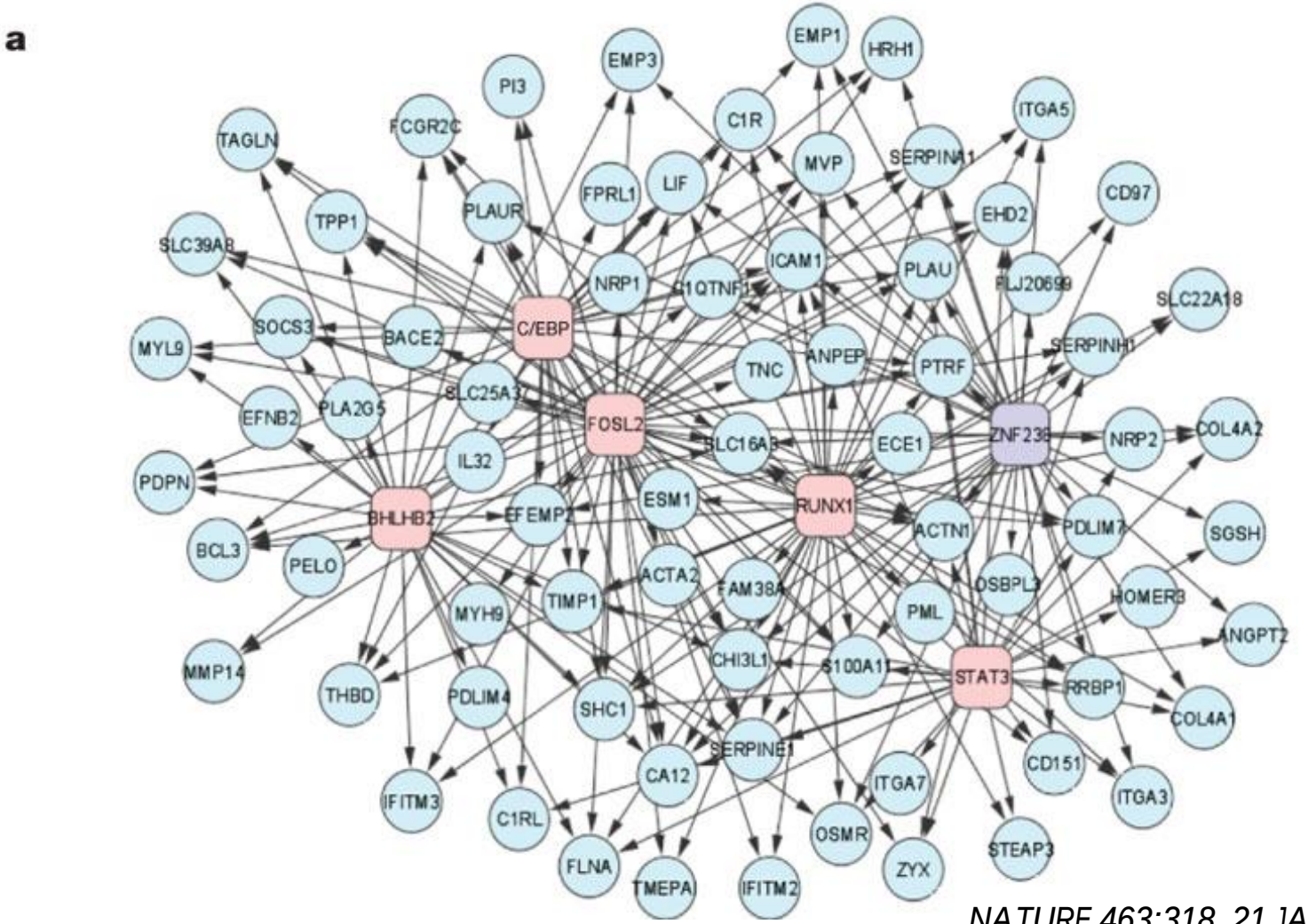
Aimee K. Zaas,[1,3,9] Minhua Chen,[2,9] Jay Varkey,[1] Timothy Veldman,[3] Alfred O. Hero III,[4] Joseph Lucas,[3] Yongsheng Huang,[4] Ronald Turner,[5] Anthony Gilbert,[6] Robert Lambkin-Williams,[6] N. Christine Øien,[3] Bradly Nicholson,[7] Stephen Kingsmore,[8] Lawrence Carin,[2] Christopher W. Woods,[1,3,7] and Geoffrey S. Ginsburg[3,*]



CELL HOST & MICROBE 6:207, 17 SEPT 2009

The transcriptional network for mesenchymal transformation of brain tumours

Maria Stella Carro[1]*{, Wei Keat Lim[2,3]*{, Mariano Javier Alvarez[3,4]*, Robert J. Bollo[8], Xudong Zhao[1], Evan Y. Snyder[9], Erik P. Sulman[10], Sandrine L. Anne[1]{, Fiona Doetsch[5], Howard Colman[11], Anna Lasorella[1,5,6], Ken Aldape[12], Andrea Califano[1,2,3,4] & Antonio Iavarone[1,5,7]

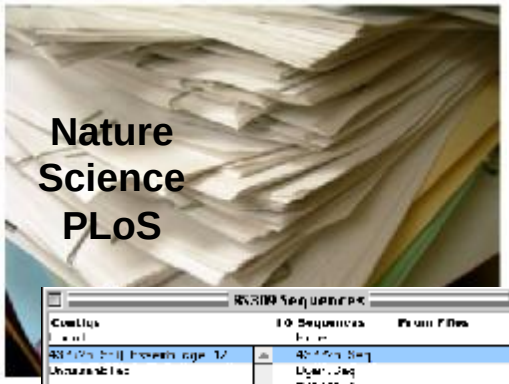


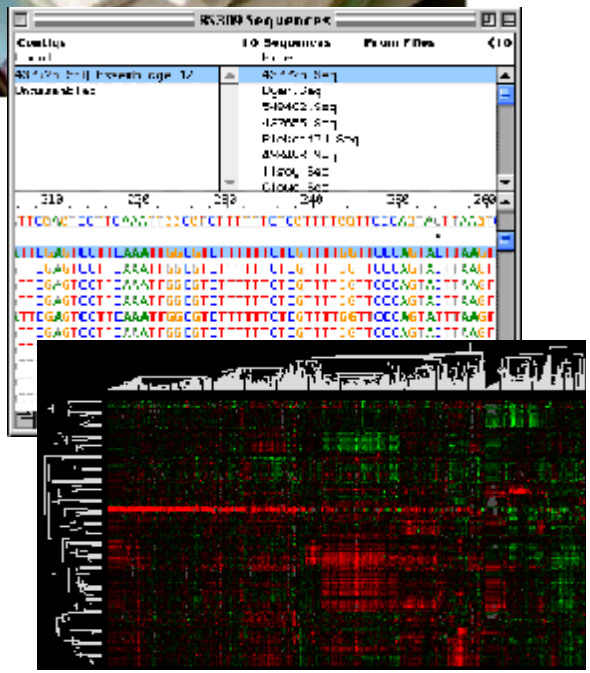
NATURE 463:318, 21 JANUARY 2010

Why Build Sage Bionetworks and a Commons?

Sage: Transitioning from Clinicians as Archivists to a Contributor Community by jointly building evolving Models of Health and Disease

Current Approaches



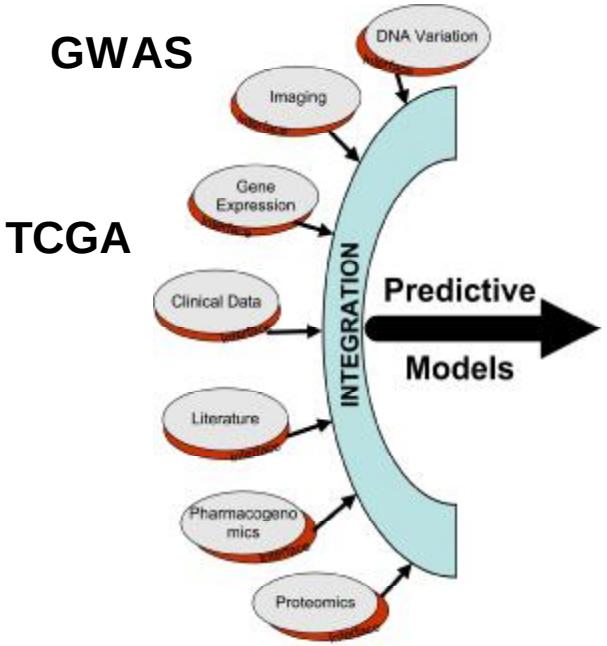


Linear files –Genome Info/Clinical
Storing / Binning
Redoing previous experiments

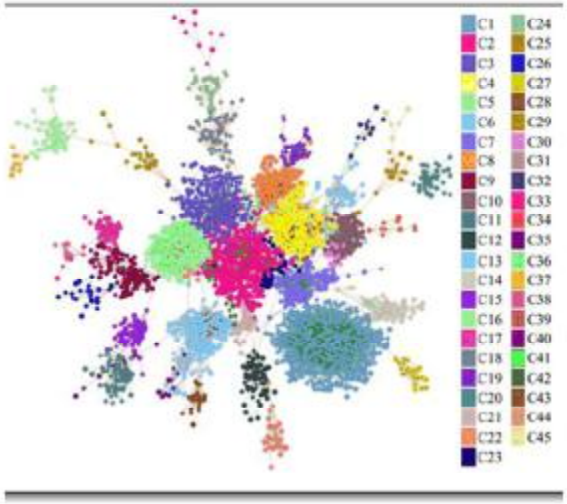
Integrative genomic approaches
Using causal bionetwork approaches
To build evolving disease models

GWAS

TCGA



N+1 Model



Requires: Reliable Data- Quality Controls
Well annotated- engage standards
Curation of platforms
Coordination of Computational Models
Tools for Interactive Work place

(leverage existing public, private efforts EBI, NCBI etc.)

How to take this forward: Jettison from a single entity

Recognition that the benefits of bionetwork based molecular models of diseases are great but that they require significant resources

Appreciation that it will require decades of evolving representations

Excited to enable patients and their advocacy groups to build models for who responds and does not respond to marketed drugs

Merck saw that by donating data, tools, know-how, it might seed a "commons" allowing a potential long term gain to the whole community provided by evolving models of disease built via a contributor network

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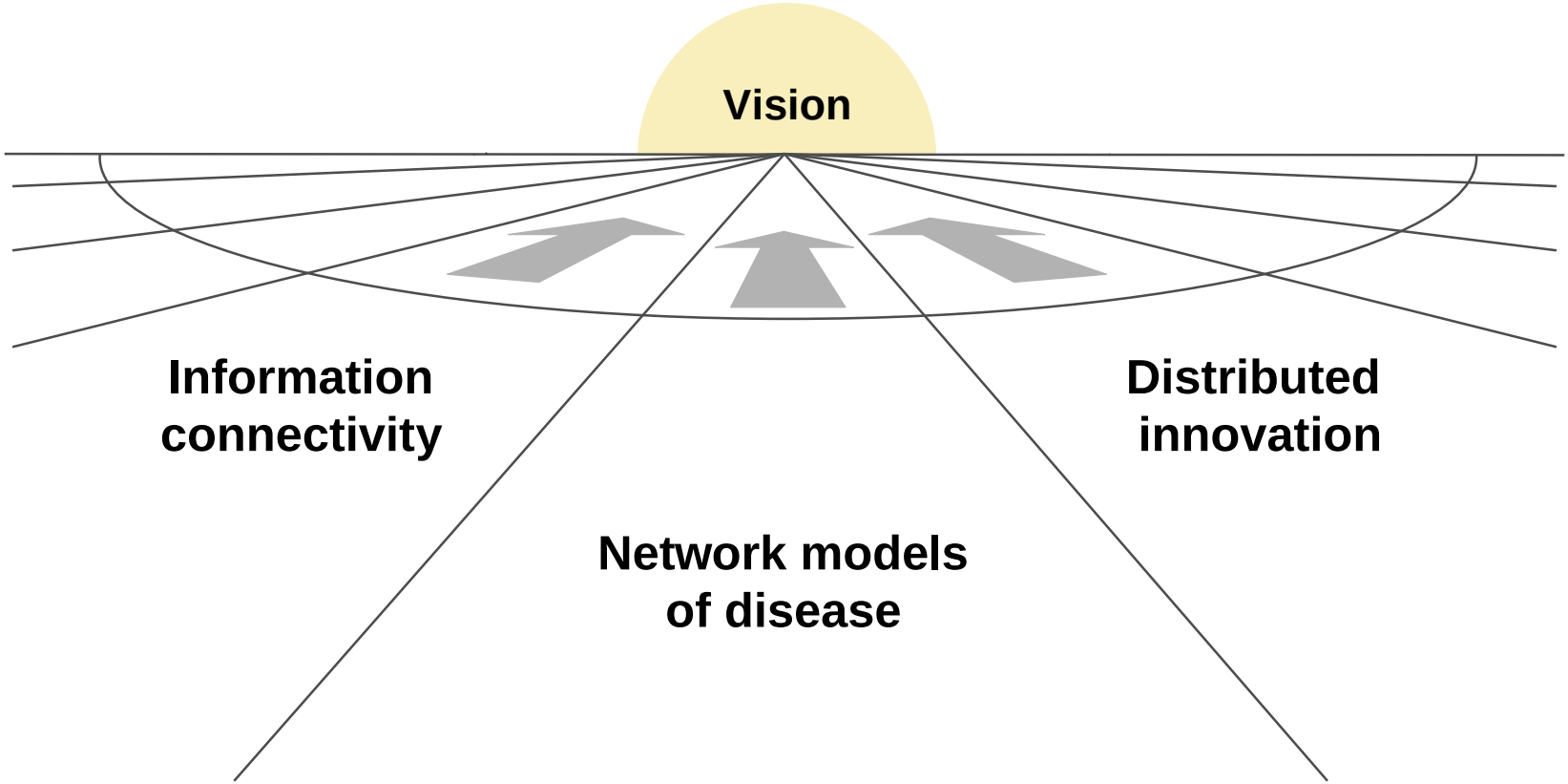
Non-profit to create a "commons" where integrative bionetworks is evolved by contributor scientists to accelerate the elimination of human diseases.



Data, Models, and Tools, with interconnectivity, data standards, governance rules
In a public/ private interface supported by Foundations, Universities, Govt, Patients

Current Status- Progress Report?

Sage Bionetworks Strategic Priorities

- Integrative genomics and network biology research
- Repository and tools to establish the Commons platform
- Interdisciplinary scientist training to enable widespread participation

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Active Partners

Clinicians- Cooperative Trial Groups

-Cambridge UK- Carlos Cordon/ UBC- Sam Aparicio

- CML –Jerry Radich

- NSABP- Soon Paik

- TCGA- Lynda Chin

Government Sources

- NCI Grant as a CCSB (awaiting formal designation)

LSDF Washington State- (finalist awaiting word in February)

- RO1- Novel Statistical methods – Sage Harvard (submitted)

Foundations

- Cure Huntington's Disease Initiative

Pharma Biotech CRO Payer Partners (Pfizer)

- *Building out specific Disease Models*

Oncology, Diabetes, Cardiovascular Disease

- Quintiles

Information Technology Partners

- *Amazon, U Miami, U of Arizona*

Software Tool Providers

- GenomeSpace-Broad

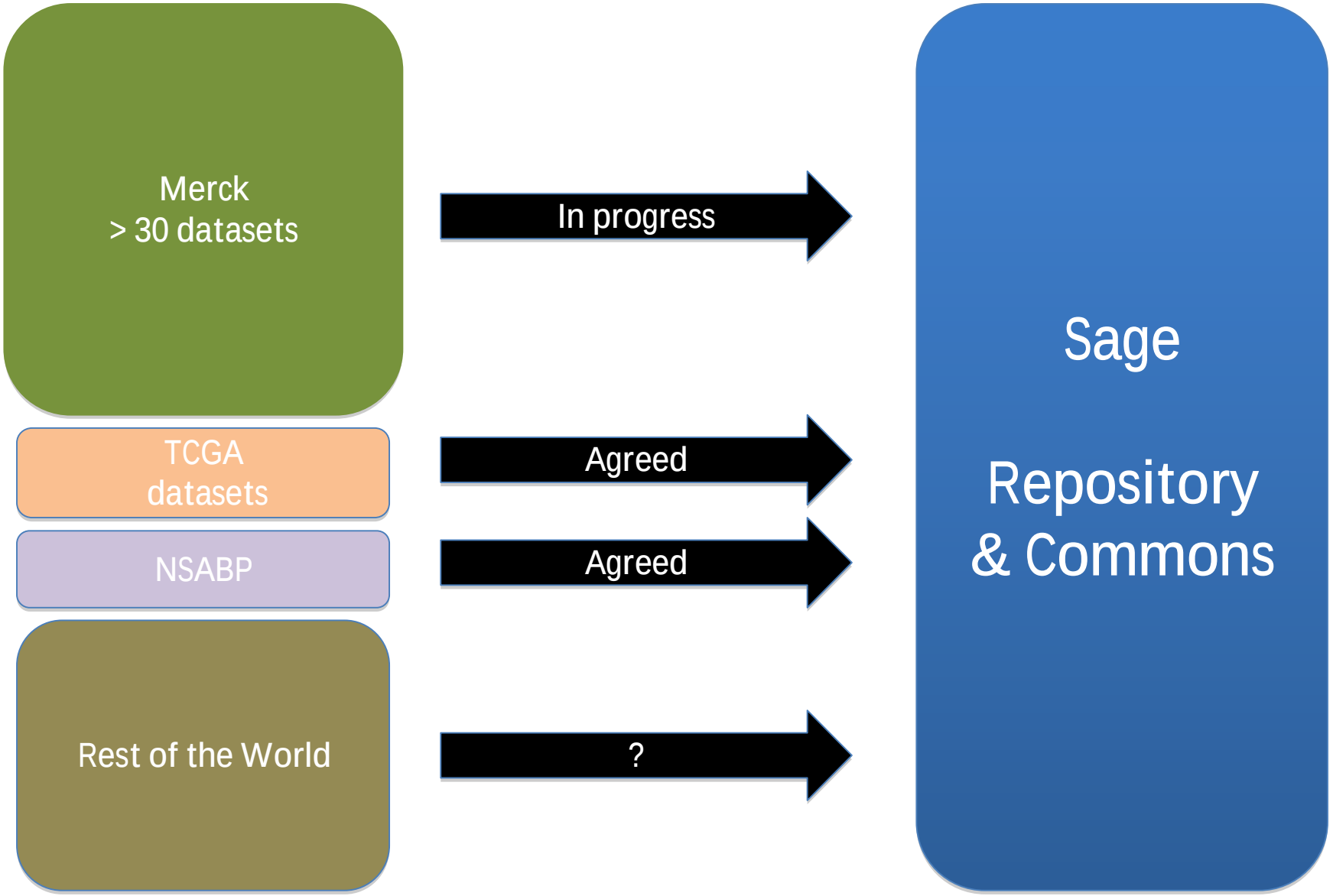
Patient Advocacy Groups

- Clearity Foundation-Ovarian Cancer

- Multiple Myeloma Research Foundation

- Live Strong

Migrating Coherent Datasets to Populate the Repository



Sage Non-Responders Project

Patient Oriented Cohort Study to ID Non-Responders to Approved CA Drugs

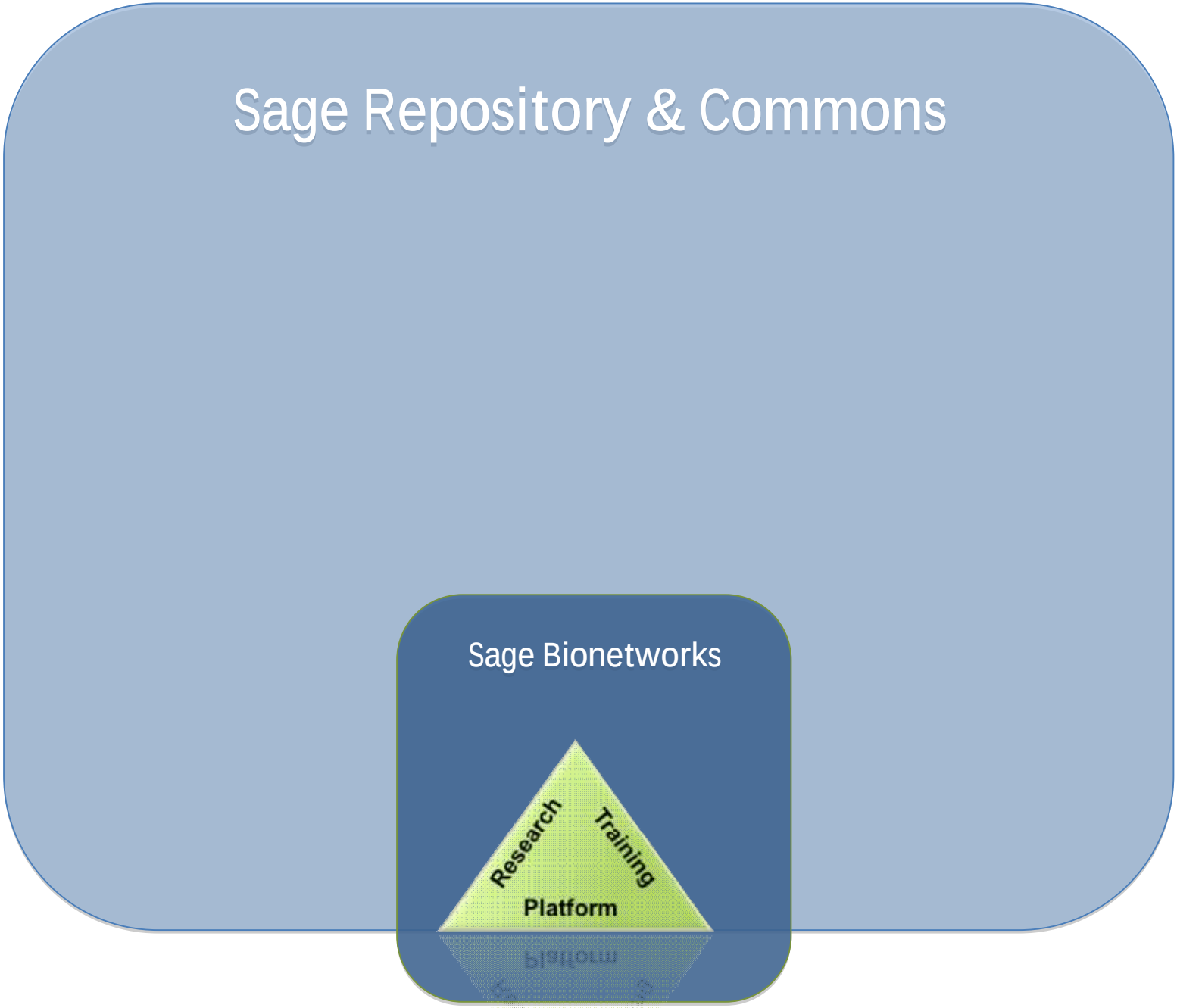
Co-Chairs- Rich Schilsky and Stephen Friend

Multiple Myeloma- Ken Anderson/ Kathy Guiste
AML at First Relapse- Fred Applebaum/
Non-Small Cell Lung Cancer- Roy Herbst/
Ovarian Cancer- Beth Karlan/ Laura Shawver

Molecular Profiling: Saywers, Golub, Levine, Polit, Levine

Patient Outreach: Anne Wojcicki 23andMe, Live Strong

Relationship between Sage Bionetworks and Sage Commons



Four Requirements to enable a Platform for Clinicians Scientists and Patients

Data Repository (Commons)

Platform Architecture System

Probabilistic Causal Network Models Of Disease

Rules And Governance

Building a Commons/ Platform; Role of a Contributor Social Network

Regional Meetings: UK, Boston, San Francisco, Beijing

First Inaugural Sage Congress April 23-24 San Francisco, Hosted by UCSF

Participants and Speakers:

- Modelers: Vamsi Mootha, Tery Ideker, Andrea Califano, Eric Schadt
- Contributor Networks: Jamie Heywood, Jeff Hammerbacher, Bob Cook-Degan
- Libraries/Publishers: Nature, PLoS, British Library, NYT, WSJ..
- Institutions: MIT/Broad, Cambridge /UK, RIKEN, Stanford, Duke, UBC..
- IT Partners: Google, MSFT, Oracle, Amazon, SONY..
- Government/Payers: NIH, NHLBI, NCI, EBI, MEDCO, FDA..
- Pharma/Biotech: Pfizer, Lilly, Genentech, GSK..

Goals and Outcomes

- Standards and Ontologies for Integration Analysis
- Citations of Probabilistic Causal Network Models
- Ratifying Commons Governance Rules for Data and Model Sharing

Extending the Spectrum of Pre-Competitive
Oncology Biomedical Research

Remember that if it is a company and often also if a University
they are obligated to justify
The underlying business case

Sharing ⟵ Disease Models ⟶ Unsharing

Can I get there without others cheaply? UNLIKELY
Will others beat me to it and I do not join? LIKELY
Can I build a first mover advantage? UNLIKELY
Can I sustain my advantage and sustain my return? UNLIKELY