ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

Opening New Investigative Directions for GBM: Confronting Complexity

Dr. George Poste
Chief Scientist, Complex Adaptive Systems
and Del E. Webb Chair in Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

Presentation at Glioblastoma Multiforme (GBM):
A Think Tank to Re-Think GBM and Set a New Course

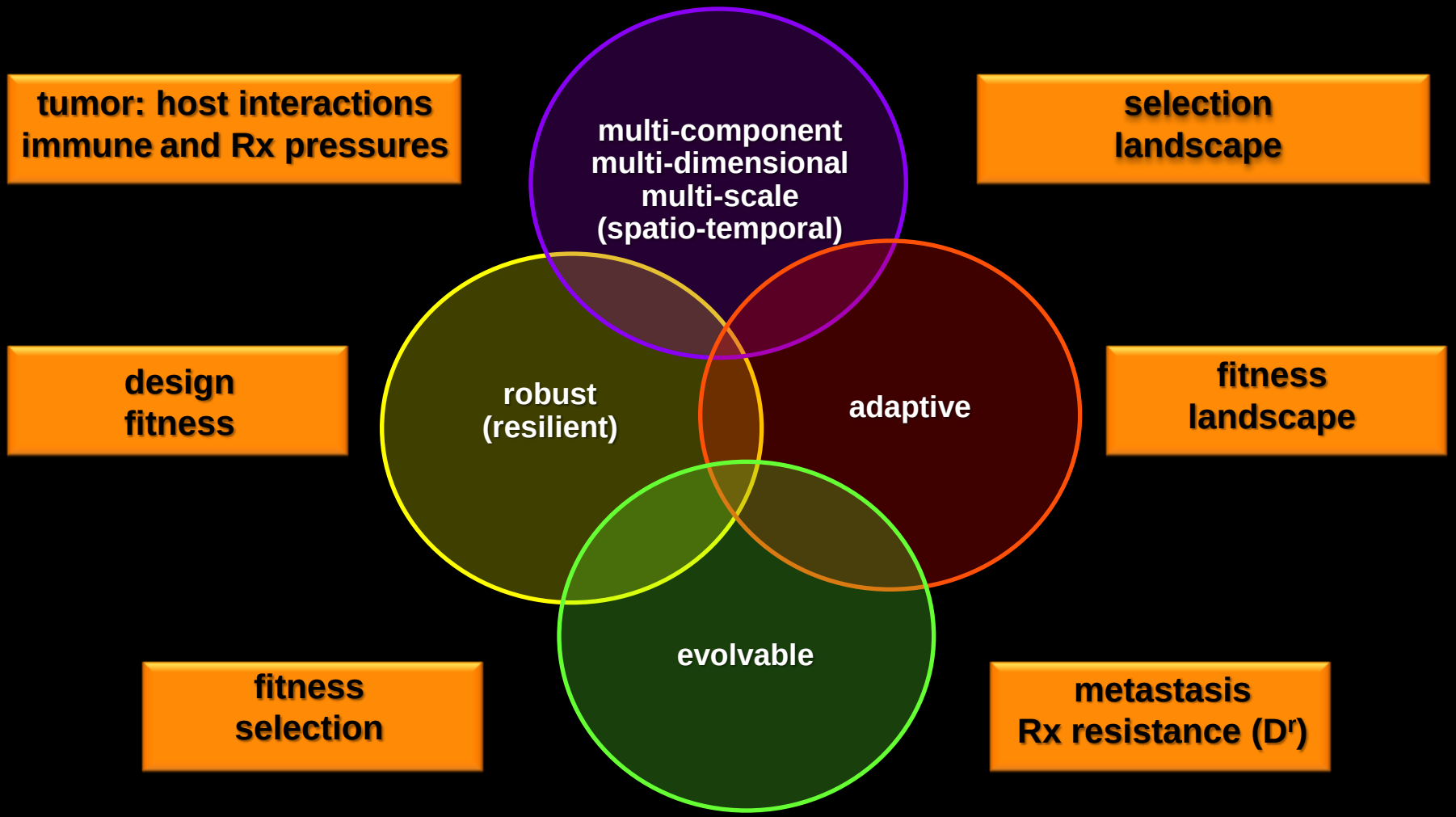
Montelucia Resort and Spa, Scottsdale, AZ
27 August 2013

Re-Thinking the Cancer Problem

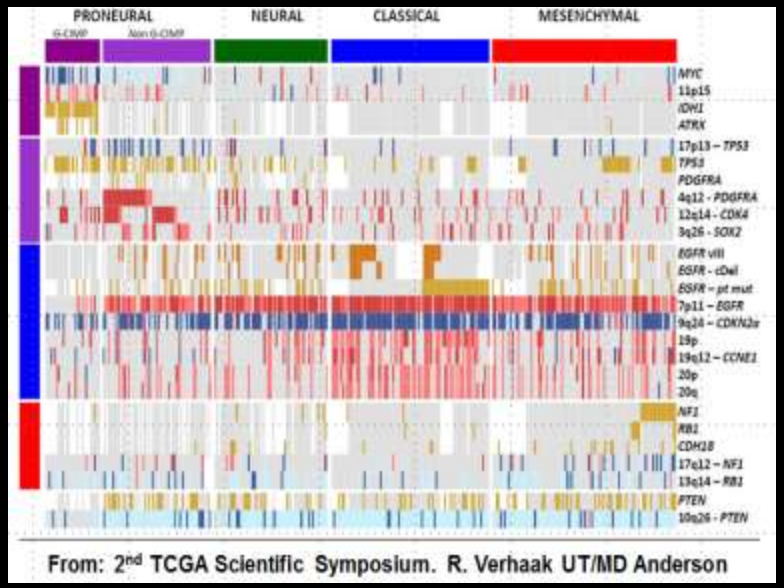
- the central challenge of tumor cell heterogeneity and the complex spatio-temporal dynamics of clonal phenotypic diversification in disease progression
- defining the molecular taxonomy of cancer and pathogenesis in terms of disruptive perturbations in the architecture, topology and regulation of complex biological networks
- cancer as a complex adaptive system (CAS)

Cancer as a Complex Adaptive System

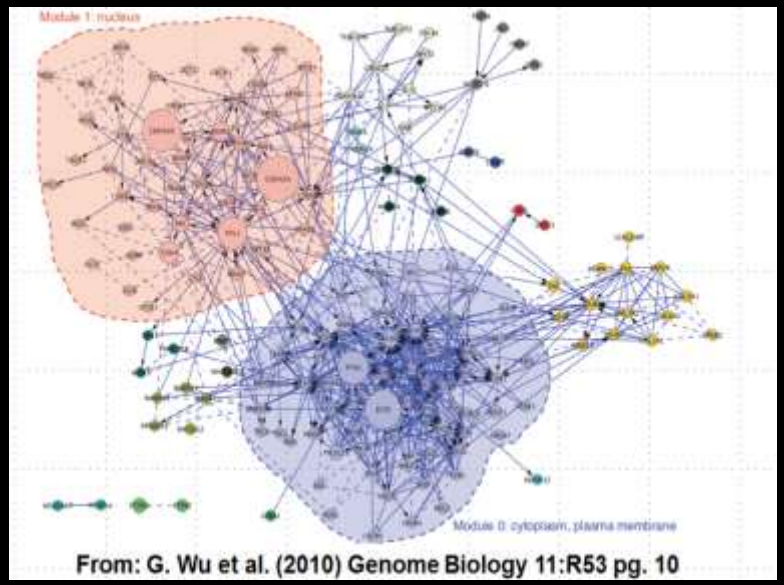
genotype: phenotype determinants and clonal heterogeneity



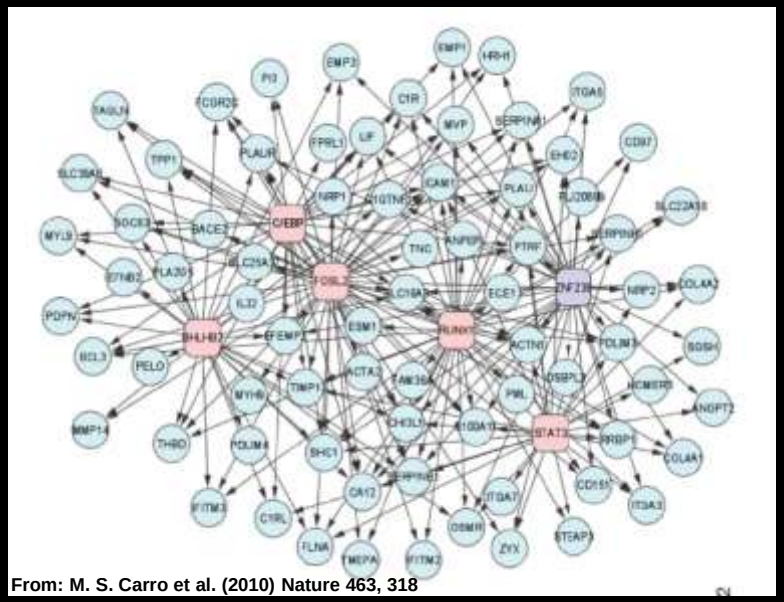
GBM Expression Subtypes and TF and miRNA-TF Regulatory Networks

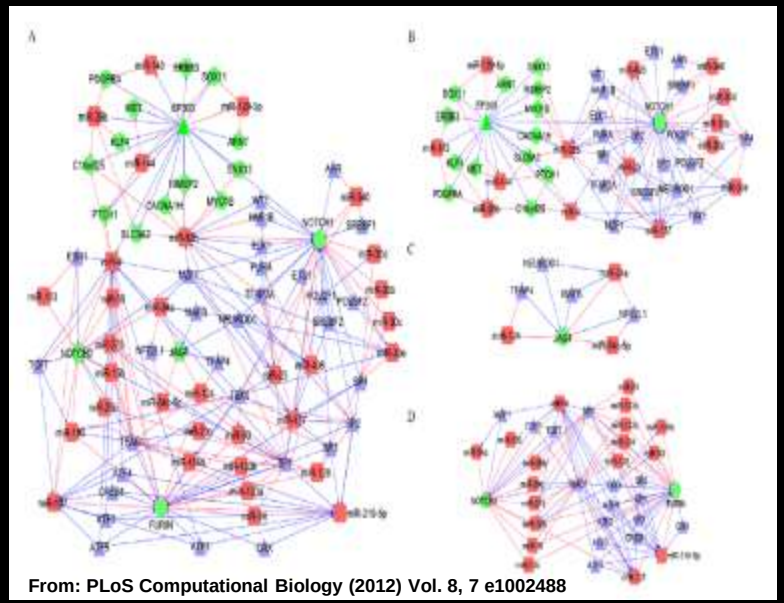


From: 2nd TCGA Scientific Symposium. R. Verhaak UT/MD Anderson



From: G. Wu et al. (2010) Genome Biology 11:R53 pg. 10


From: M. S. Carro et al. (2010) Nature 463, 318


From: PLoS Computational Biology (2012) Vol. 8, 7 e1002488

“Fate Constraints” in Biological Systems

- the *executable* program of differentiation and homeostasis (physiology)
- the *excursion state space* that represents the *disease spectrum* (pathology; MDx and disease-subtyping)
- the *trigger states* that represent *thresholds* for disease (causality; MDx)
- the determinants that elicit *emergence* in complex systems (disease progression; reversibility; irreversibility)
- the perturbed network *target space* that is amenable to *homeostatic restoration* (Rx, biological reversal, prevention)
- pathways and *networks of possibility*
  - adaptive plasticity and evolvability

The Challenge of Identification and Validation of Robust Biomarkers and Rx Targets in Oncology

- innate heterogeneity of the disease: intra-and inter-patient
- feature-rich (high dimensionality data), case poor (statistically underpowered) studies
- detection of weak signals in noisy environments plus data corruption by noise during the acquisition process
- demonstrate consistency across multiple sample sets
- demonstrate concordance across experiments from multiple types of measurements
- robustness in ‘intended use’ population(s) (‘fit for purpose’) for regulatory approval

computationally challenging, high-dimensional inference problems

Molecular Classification of Tumor Subgroups via Gene Expression Profiling

- lack of reproducibility of genomic signatures with putative associations with phenotypes
  - progression, Rx responsiveness
- network inference methods based on expression data alone are at best incomplete
- different classifiers applied to same sample sets yield different signatures
- integration of different datatypes performs better than individual datatype in prediction of regulatory mechanics
- identification of biological noise relevant to clinical phenotypes not detected by current analytic methods
- improve modeling of sources of both technical and biological noise

What is a Pathway?

- a set of interactions associated with an inferred phenotype

CONTEXT

- critical component of biological information flows
- dysregulation of same pathway at different points in same or different tumor subtypes generates different phenotypes
- inter-modular interactions and context of ‘spill over’ alterations in other pathways
- role of stochastic events and ‘noise’ in defining pre-existing state space and context (condition-dependent) stimulus-response relationships

What is a Pathway?

concurrency

- pathways do not exist as sequential I/O events
- multiple execution threads are active simultaneously
- separation of causality versus correlation and dissection of the temporal ordering of observed events
- instructive insights from concurrency theory applications in design/modeling/analysis of massively parallel, distributed and mobile computing networks?
- new computational tools and programming languages for biological CAS

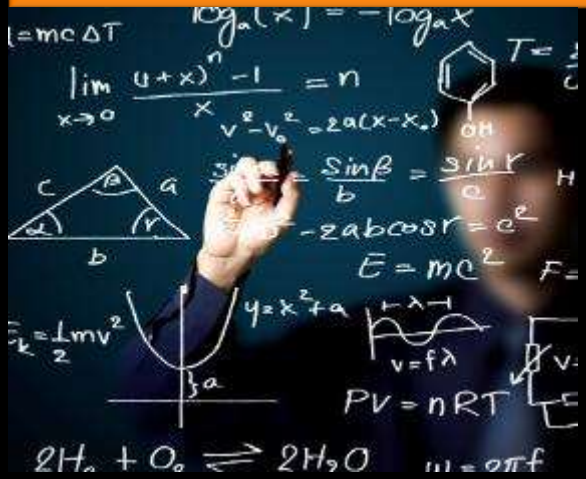
What is a Pathway?

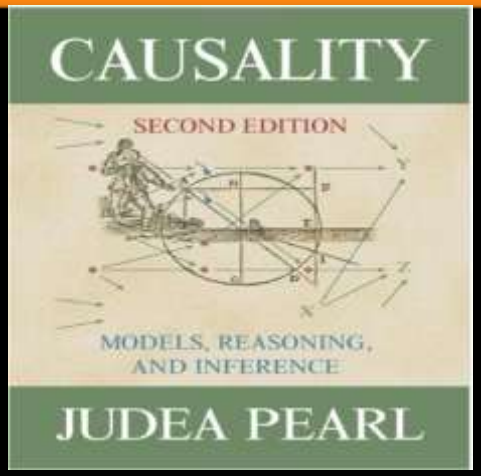
Causal Versus Correlated Events

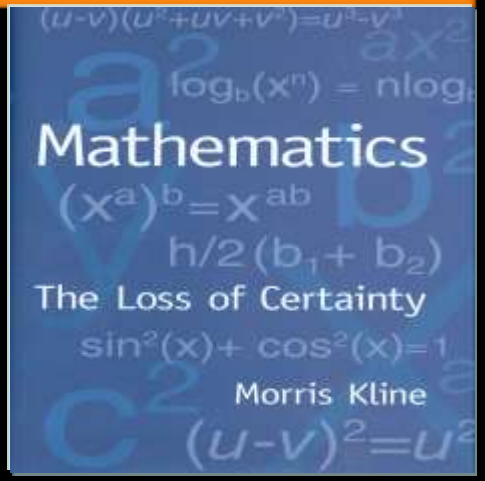
- correlations defined by both direct and indirect effects
- as size of network (graph) increases a large number of spurious indirect edges contaminate experimental measurements
  - second-, third- and higher-order interactions and resulting diffusion of information in the direct causal network
  - source of inaccuracies in network structures and network weights
- new graph theoretic tools for ‘silencing’ indirect spurious correlations

The Inadequacy of Physics-Based 'Rules' to Formulate Explanatory and Robust Prediction Tools for Biological CAS

Newtonian, Invariant Rulesets and ODEs

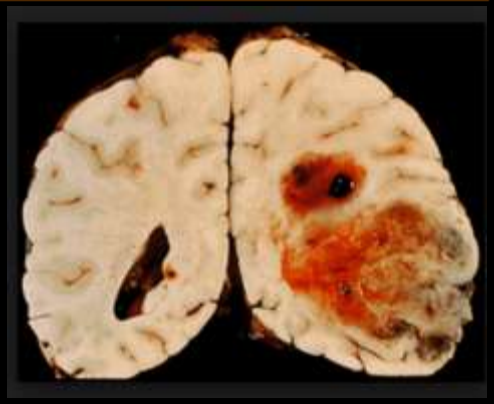






versus

New Analytics, Natural Algorithms, Models and Simulations for Non-Deterministic, Non-Linear and Stochastic 'Systems Space'



Gliomagenesis

Stem and Progenitor Cells

- ID of full spectrum of potential tumor-initiating cells
- new isolation methodologies and comparison with non-neoplastic counterparts
- determinants of different transcriptomic subtypes in primary GBM
  - mesenchymal, classical, neural, proneural
- plasticity of the differentiation repertoire
  - astrocytes, neurons, oligodendrocytes
- transdifferentiation to endothelial cells and angiogenic events

Biology of IDH1

- different behavior of wt and mutant tumors

Biological Network Design and Therapeutic (Rx) Modulation

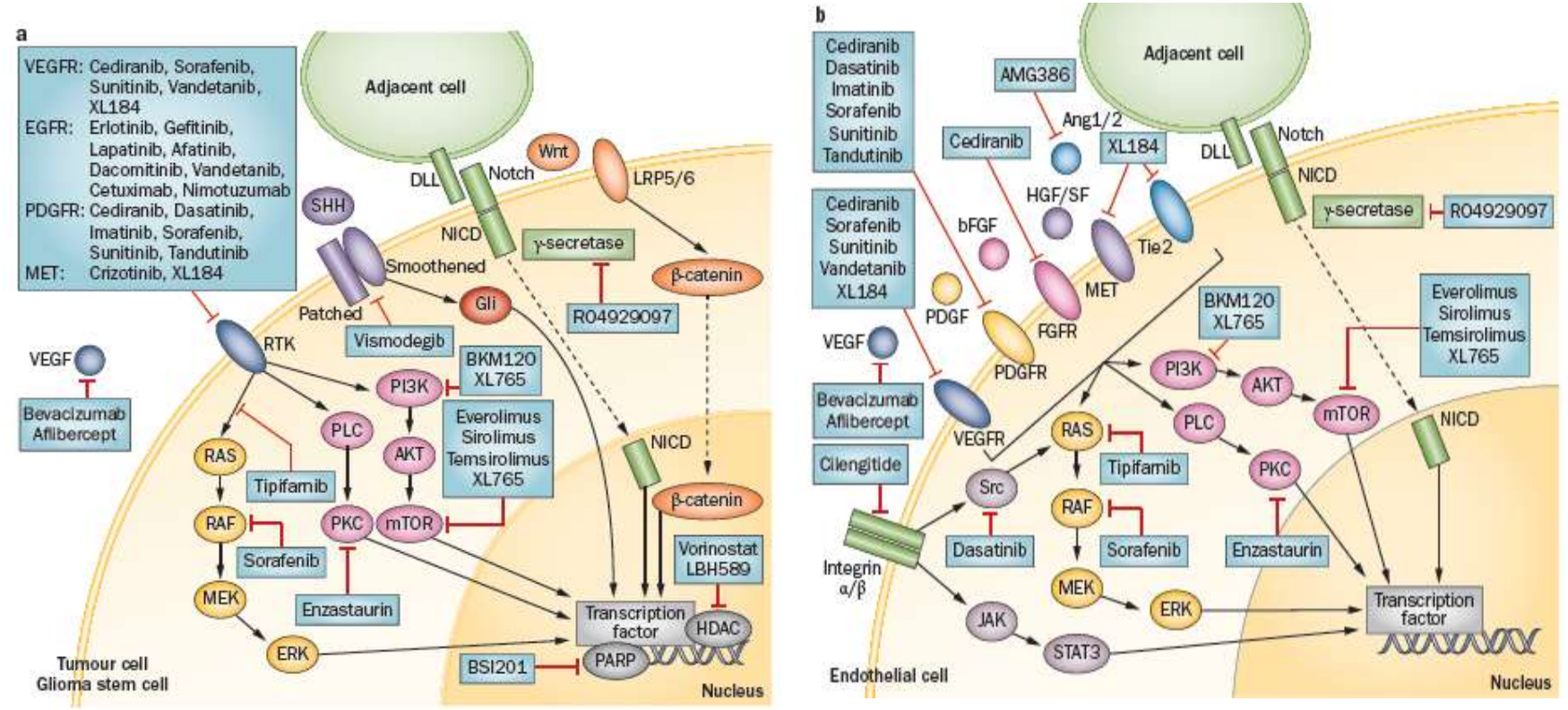
Network (Systems) Pharmacology

Prediction of Network Trajectories for Drug-Resistance (D^r) Phenotypes and Agile Therapeutic Regimens

Rx Targets for Cell Signaling in Glioblastoma and Tumor-Associated Endothelial Cells

Glioblastoma and Stem Cells

Tumor-Associated Endothelial Cells



From: S. Tanaka et al. (2013) Nature Rev. Clin. Oncol. 10,14

"Omics" Technologies and the Elucidation of Perturbations in Molecular Network 'Wiring' in Complex Diseases

- the "dead hand" of reductionism and "the trap of linearity" as barriers to progress
- delusional pursuit of individual Rx 'targets' in face of known, extravagant network-wide perturbations
  - extensive network redundancy via pathway coupling and resulting rapid shifts to compensatory "wiring circuit" options to circumvent Rx efficacy
  - redundancy = Rx resistance
- time for a serious re-assessment of current Rx target discovery strategies

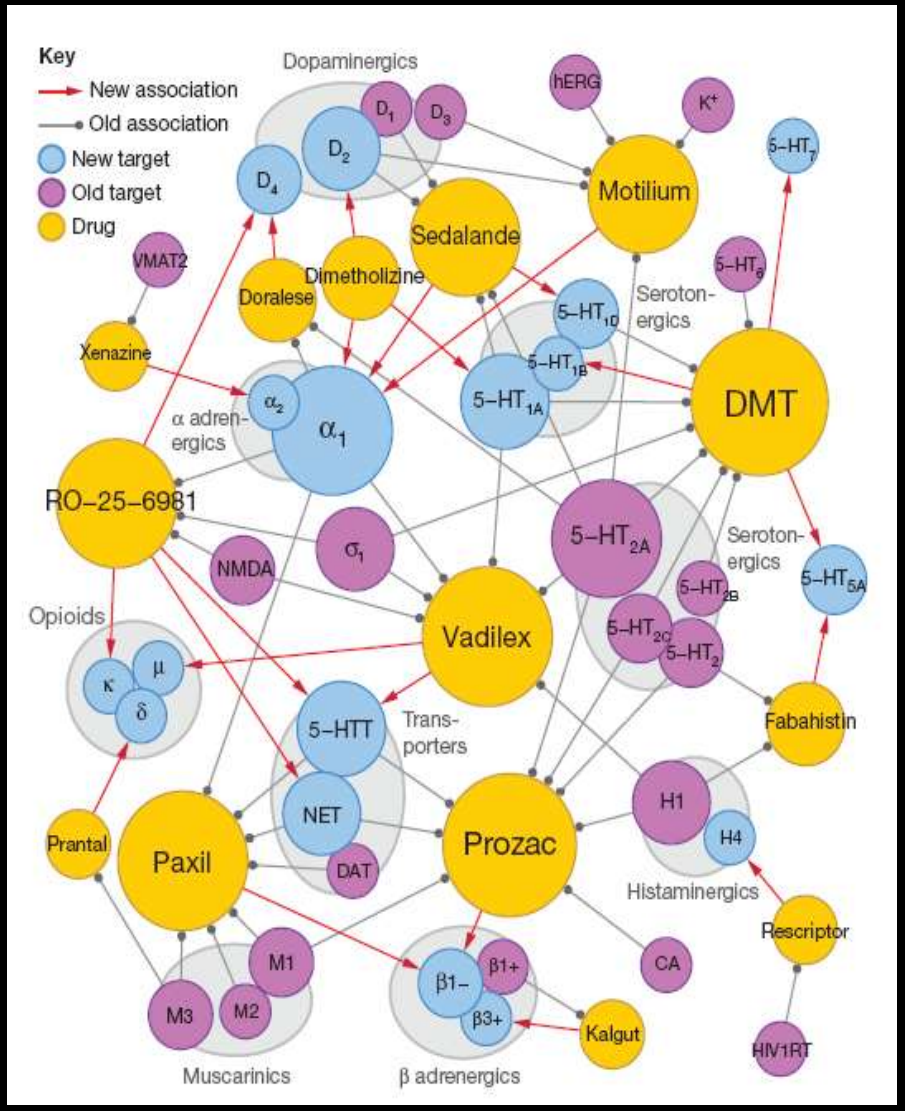
Network Pharmacology and Drug Discovery: Key Principles

- there are few single molecular targets for Rx action (antimicrobials?)
- effective Rx requires multi-site modulation of pathways and/or coupled modules
- there are no linear pathways, only complex patterns of graded information flow across multi-channel options
- there are also highly interconnected networks/subnetworks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network

From One Drug: One Molecular Target Strategies to Systems (Network) Pharmacology

- flawed legacy of reductionism and uncritical adoption of gene-centric HTS discovery from mid-1990's
- from animal models and cell biology (systems) to screening candidate Rx against individual cloned proteins (components) encoded by implicated gene(s)
- from serendipitous ID of multitarget promiscuity in intact cells/animals to purposeful rejection of promiscuous Rx candidates in HTS of cloned molecules
- critical importance of the genotypic:phenotypic fidelity of cell and/or animal models used for Rx selection to replicate the disease-associated network perturbations in situ

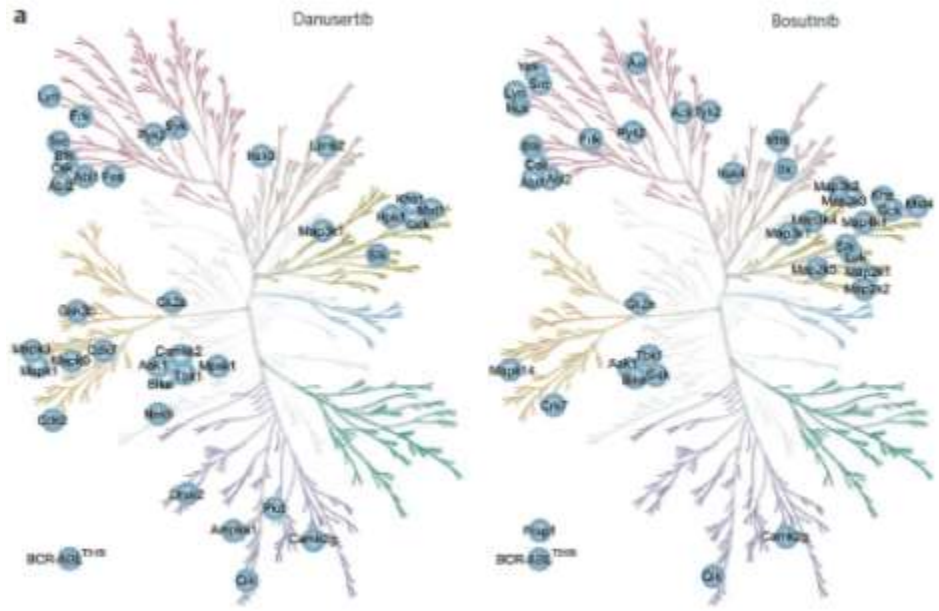
Network Pharmacology



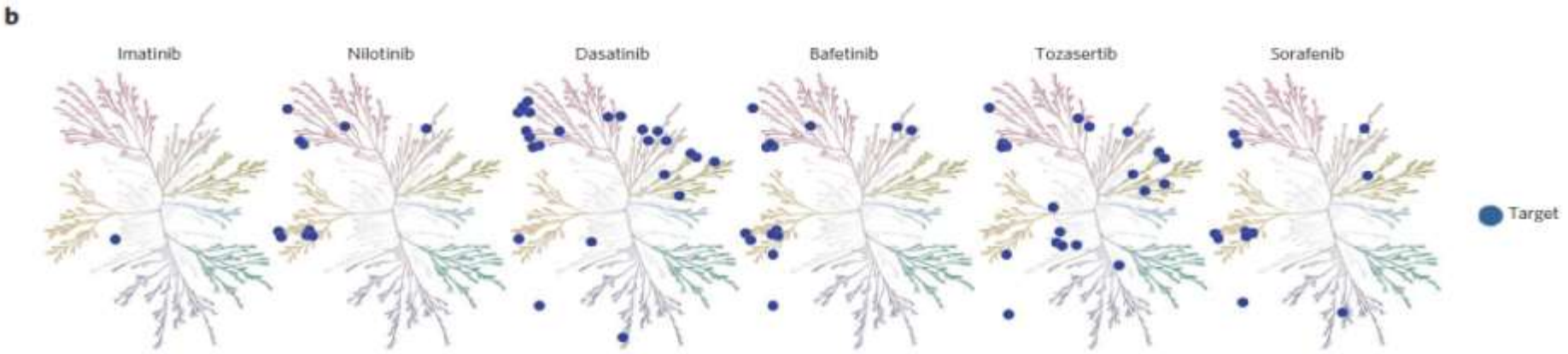
From: M. J. Keiser et al. (2011) Nature 462, 180

- analysis of Rx action in context of network topologies and dynamics
- same drug: interaction with multiple targets
- same target: interaction with multiple drugs
- mapping structural chemotypes to specific pathways and subnetworks for targeted (poly)pharmacology

Kinase Target Promiscuity in Inhibition of BCR-ABL T3151 CML Cells by Danusertib (37 Kinases) and Bosutinib (40 Kinases)



From: G. E. Winter et al. (2012)
Nature Chemical Biology 8, 905



Limited Efficacy of Multi-Target Rx in Glioblastoma

Agent	Target
sorafenib	PDGFR-α,β, VEGFR-2,3, BRAF, c-Kit, Ras
imatinib	PDGFR-α,β, c-Kit, Bcr–Abl
tandutinib	PDGFR-α,β, c-Kit, Flt3 (Phase II)
dasatinib	PDGFR-α,β, Src, Bcr–Abl, c-Kit, EphA2 (Phase II)
aflibercept	VEGF-A, VEGF-B, PlGF
cediranib	VEGFR-1,2,3, PDGFR-α,β, FGFR-1, c-Kit
sunitinib	VEGFR-2, PDGFR-β, c-Kit, RET, Flt3
vandetanib	VEGFR-2, EGFR, RET
cabozantinib	VEGFR-2, Met, RET, c-Kit, Flt3, Tie-2

Adapted from: S. Tanaka et al. (2013) Nature Rev. Clin. Oncol. 10,14

Expanding the Repertoire of Targets for Rx Action

minimum knockouts

- smallest number of network components (edges/nodes/hubs) needed to block a dysregulated cellular process

synthetic lethals: synergistic combinations

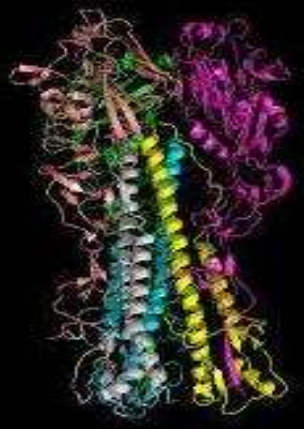
- ID of additional gene(s)/protein(s) that are ‘essential’ for maintenance of dysregulation (disease) and represent novel targets as alternatives to classical ‘resistance-loci’ targets and/or ‘non-druggable’ targets

EGFR-Targeted Therapies in Glioblastoma
SAR and Domain Relevance in Selection of Candidate-Rx

- first-generation TKIs little or no benefit
  - erlotinib, gefitinib, cetuximab, lapatinib
- efficacy of next-generation irreversible EGFR inhibitors?
  - afatinib, (NCT 00977431),
    dacomitinib (NCT 01112527),
    nimotuzumab (NCT 00753246)
- majority of EGFR mutations in glioblastoma, including EGFRvIII, involve the extracellular domain but in non-glioma cancers EGFR mutations typically occur in the intracellular domain

Expanding the Repertoire of Targets for Rx Action

Predictive Modeling of Rx Resistance Mechanisms



- analogy with epitope drift trajectory predictions in influenza hemaglutinin/neuraminidase

- directed evolution of Rx target protein to create panel of functional structural variants to ID Rx candidates active against multiple variants
  - cf. screening to ID Rx for circumvention of beta-lactamase resistance

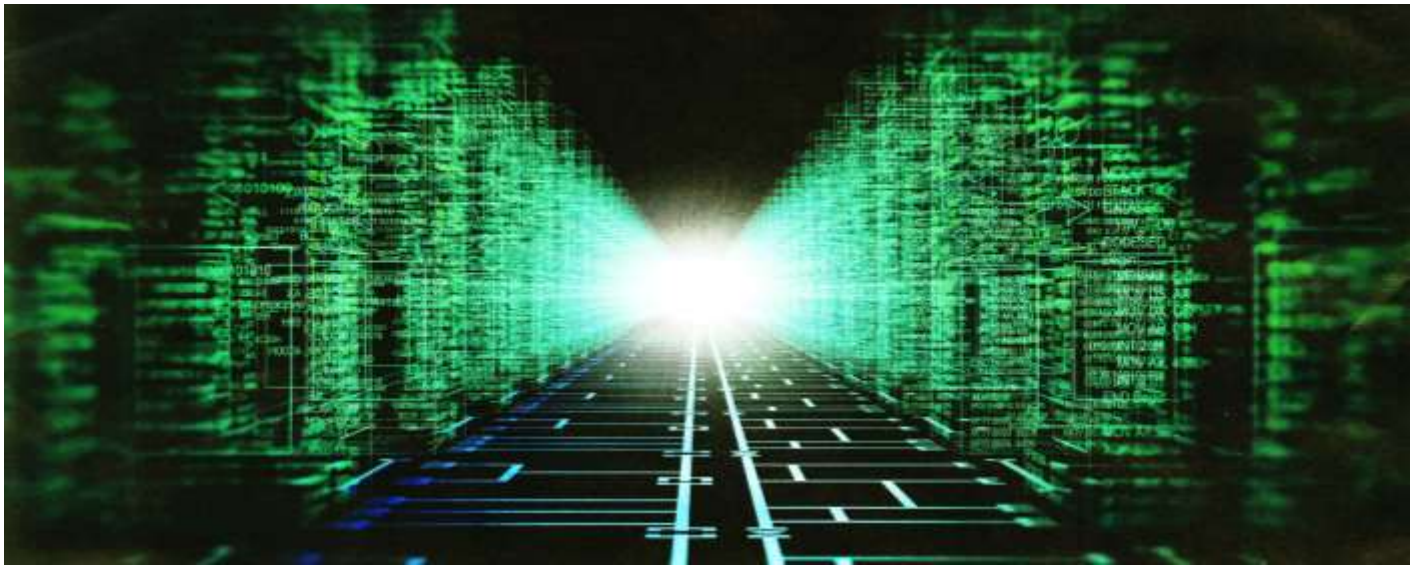
Investigational Immunotherapeutic Agents in Phase II b/III Trials for Glioblastoma

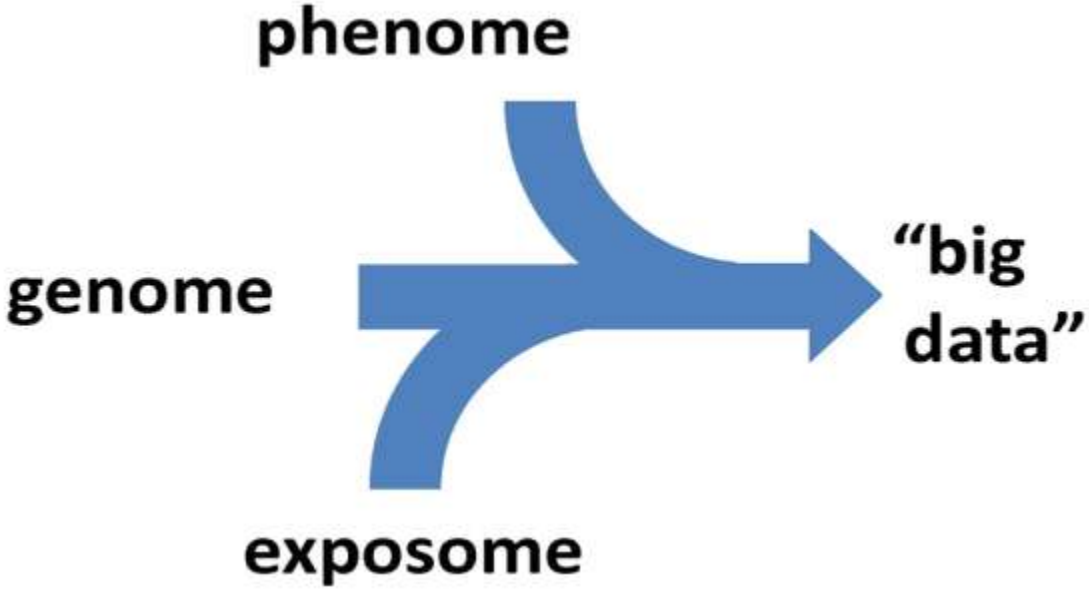
Trial	Agent	Phase I/II Outcomes	Ref.
ACT IV	EGFRv III	6 month PFS (94%)	JCO (2010) 28, 4722
DCVax-L	Dendritic Cells Pulsed with Autologous Tumor Lysate	25% survival at 6 years (original data not available)	Exp. Rev. Vaccines (2011) 10, 875
ICT-107	Dendritic Cells Pulsed with Glioma Stem Cell Antigens	2 year disease-free survival (44%)	Cancer Immunol. Immunotherap. Dx.doi.org/10.1007
Ipilimumab	Humanized anti-CTLA-4 MAB	efficacy in preclinical glioma models (FDA approval for melanoma Rx)	J. Immunotherap. (2012) 35, 385

The Need for More Agile Rx Regimens to Address Changes in Clonal Dynamics in Tumor Progression

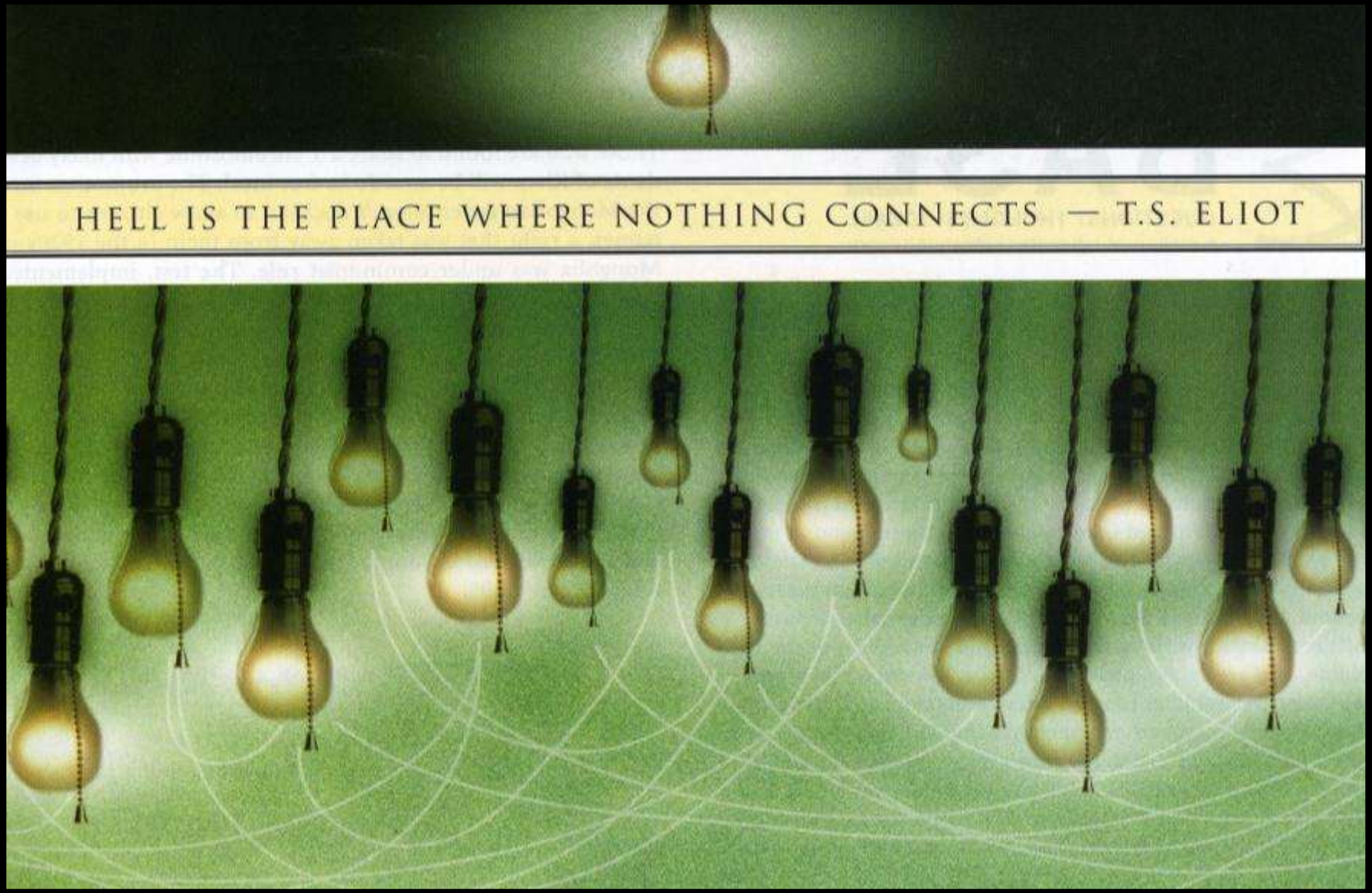
- selection of initial Rx regimen
  - guidelines
  - emerging use of MDx/NGS/WGS for patient-specific Rx selection
  - ‘static snapshot’
- need for new tools for dynamic profiling and earlier detection of emergence of D^r variants than current dependence on clinical imaging/deterioration
  - de novo and acquired resistance phenotypes
- validation of liquid biopsy methods
  - CTCs, ctDNA, exosomes
  - deep sequencing
  - Tregs and CTL4 levels

The Imminent Arrival of the Zettabyte (10^{21}) Era

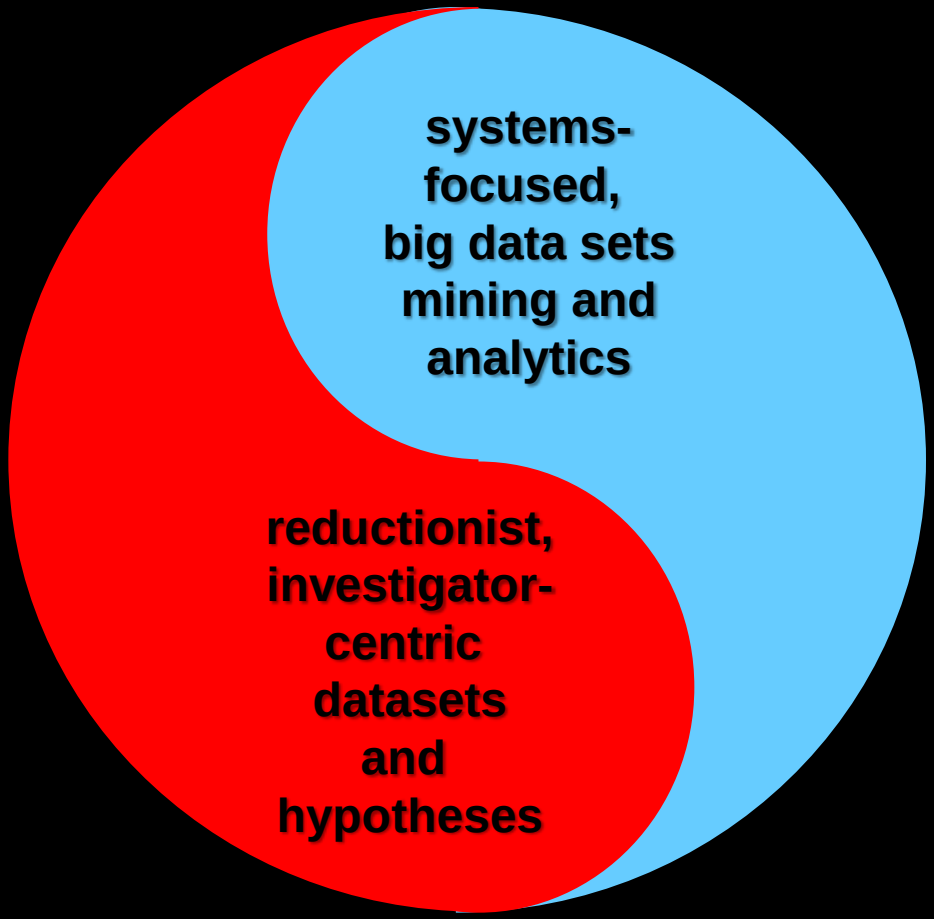




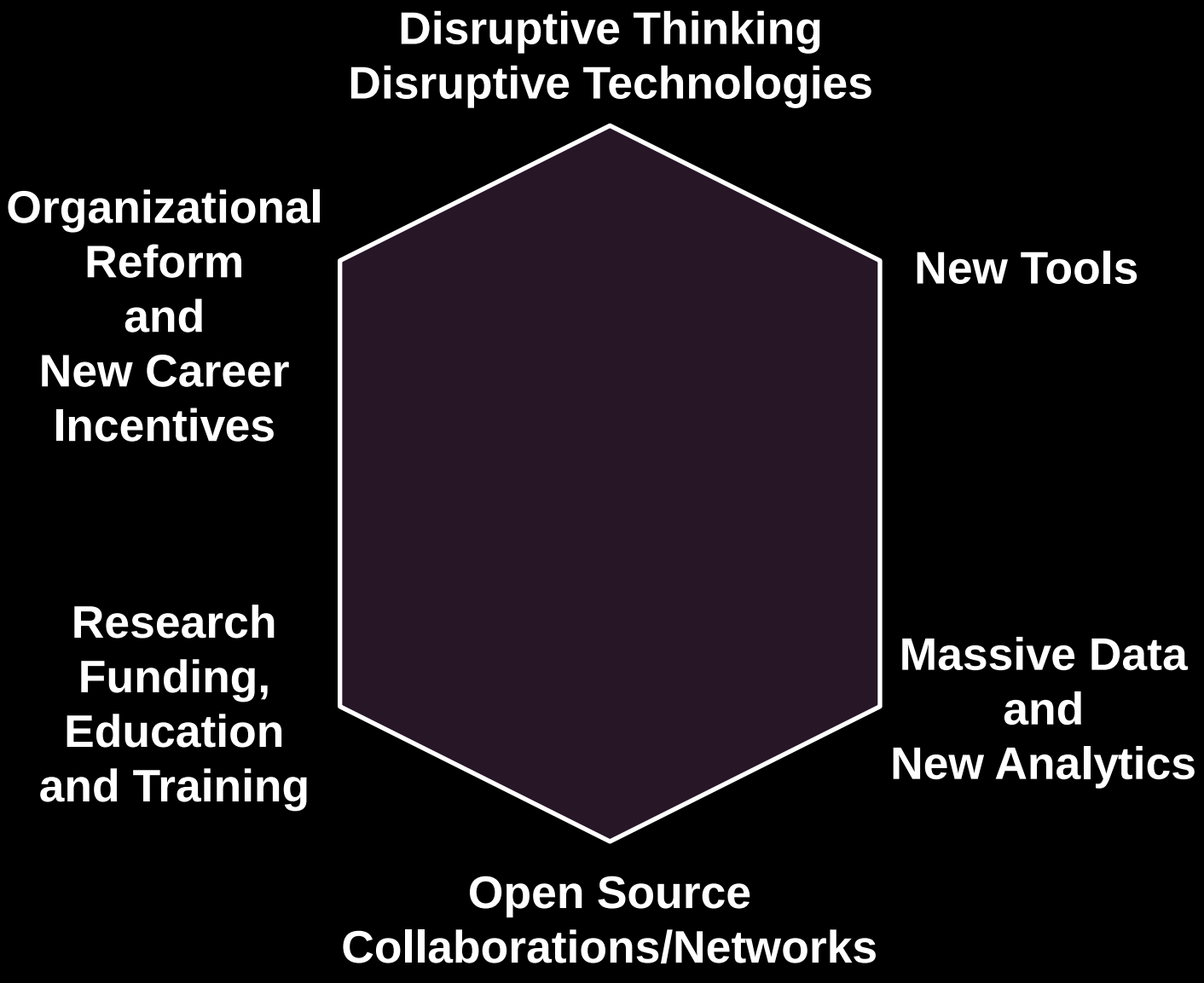
Silos Subvert Solutions: Protecting Turf and Sustaining the Status Quo



Complexity, Cross-Domain Convergence and Increasing Dependency on Data-Intensive Methods and New Knowledge Networks



Disruptive Innovation and Knowledge Networks: Silos Subvert Solutions



CAS Network Design Principles

- can commonalities in network design identified in CAS at more advanced stages of knowledge maturation be instructive in guiding research in less mature network insights (i.e., biological networks)
  - internet connectivities and analytics (e.g., social networks)
  - monitoring for internet distributed denial of service attacks
  - complex supply chain logistics
  - advanced avionics

Engaging Complexity:

“The cancer biology community by itself is unprepared to solve the difficult transdisciplinary problems such as biological complexity, information transfer and tumor cell evolution.”

Summary Remarks Meeting Report
National Cancer Institute Meeting:
Integrating and Leveraging the Physical Sciences to Open a New frontier in Oncology
February, 2008, p. 34

Are We Yet Sufficiently Engaged?