ASU COMPLEX ADAPTIVE SYSTEMS INITIATIVE
ARIZONA STATE UNIVERSITY

Addressing Technological Challenges and the Development of New Cancer Interventions

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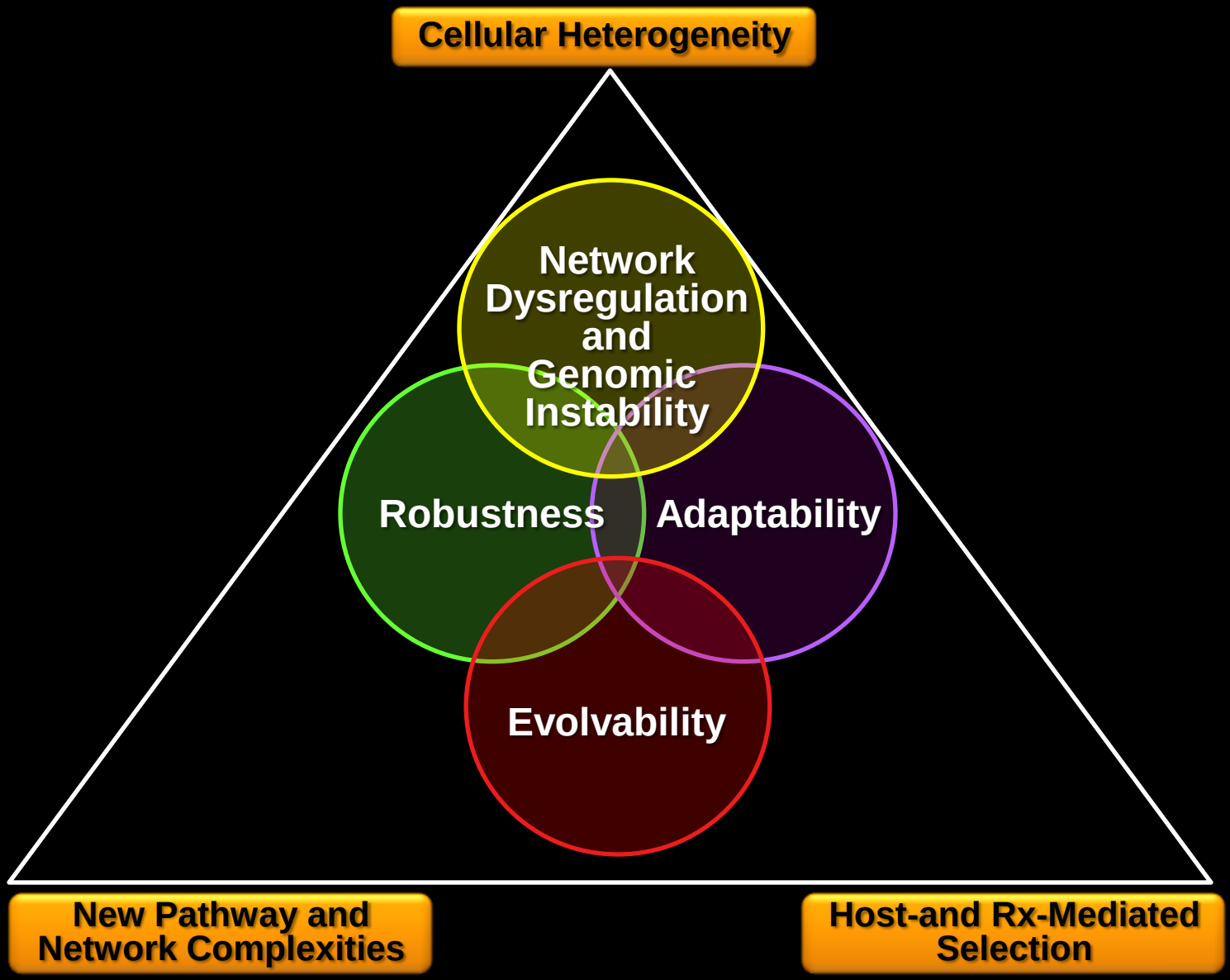
Ritz-Carlton, Pentagon City, Arlington, VA • 16 March 2010

Cancer as a Complex Adaptive System



Cancer as a Complex Adaptive System

- progressive emergence of (sub)clonal diversity
  - dynamic tumor-environment interactions
- expansion of clonal genotypic:phenotypic heterogeneity increases adaptive repertoire and survival probability
- multi-component system whose collective behavior cannot be defined or predicted by analysis of individual components and whose interactions generate novel emergent properties
  - metastasis, drug resistance

The Widespread Failure to Set Standards for Analysis and Annotation in Biomedical Research and Clinical Medicine

- predominant analysis of poorly characterized tissue samples of convenience and statistically sub-powered studies

versus

uniform QC/QA standards for sample acquisition, curation, annotation plus requisite statistical rigor

- inadequate clinical stringency in patient ‘phenotyping’ and poorly standardized criteria for patient staging, progression and outcomes

versus

consistent protocols for patient stratification and longitudinal case records for correlation of molecular pathology with clinical outcomes

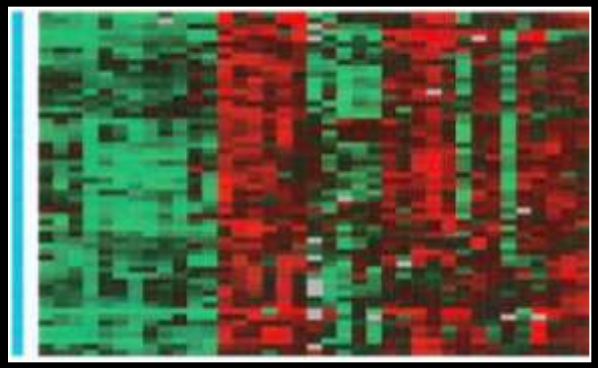
The Paucity of Biomarkers for Cancer Detection, Stratification and Rx Response Monitoring

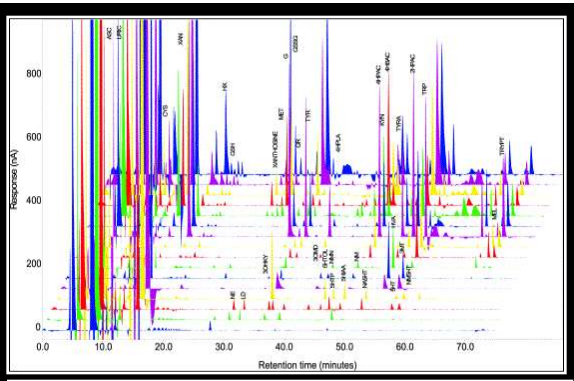
- literature dominated by anecdotal studies in poorly characterized systems
  - small patient cohorts
  - limited replication and confirmatory studies
- very few biomarkers subjected to rigorous validation
  - case-control studies with sufficient statistical power
  - inadequate stringency in clinical phenotyping
- widespread lack of understanding of regulatory requirements
  - complexities imposed by multiplex tests

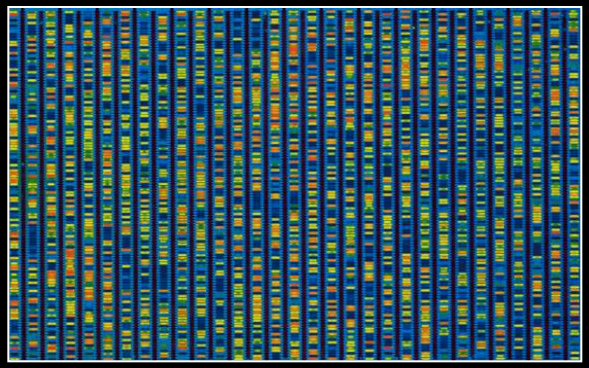
Analytical Scale and Systems-Based Integration: The Need for End-to-End R&D Solutions

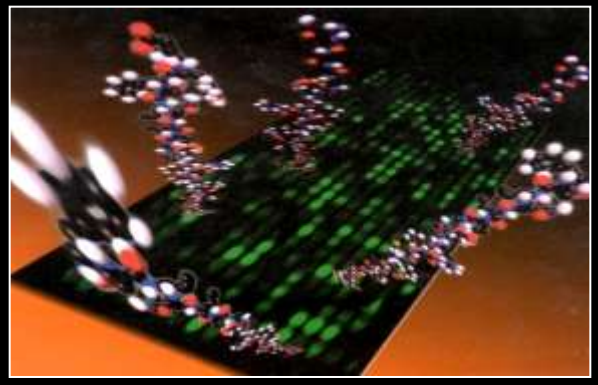
Complex Biosignature Profiling

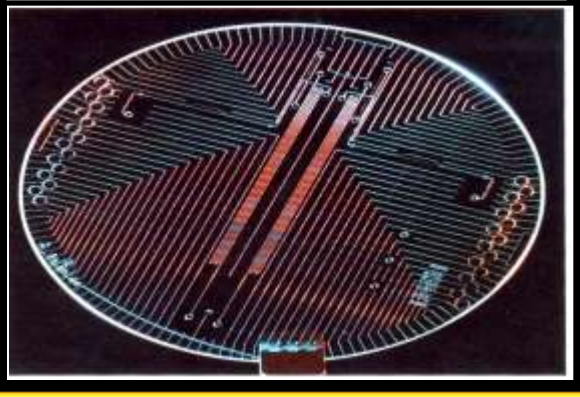
genomics	proteomics	immunosignatures

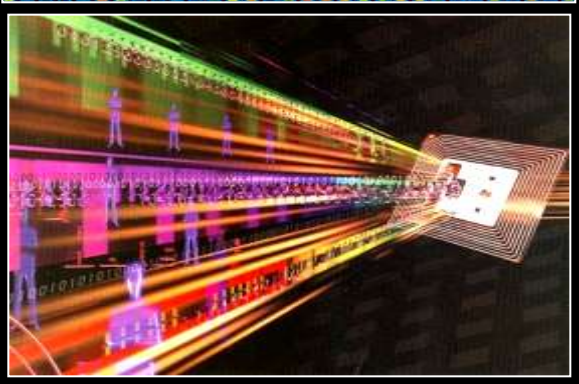












Complex Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays	miniaturized devices	new algorithms

Semantics: The Need for Adoption of Standardized Taxonomies and Ontologies in Biomedical Research

- transcending the taxonomic anarchy of descriptive biology and medicine
- standardized nomenclature for biological systems
- reporting formats for quantitative data
- crucial foundation of productive assembly and analysis of large scale and open-source datasets
- facile integration of scientific and clinical data for evidence-based treatment selection/decision-analysis

OBO Foundry Ontologies
Nature Biotechnology 25, 1251 - 1255 (2009)

The Open Biomedical Ontologies

Cell Ontology (CL)

the Gene Ontology

Gene Ontology (GO)

Foundational Model of Anatomy

ZFIN

Zebrafish Anatomical Ontology

ChEBI

Chemical Entities of Biological Interest (ChEBI)

Disease Ontology (DO)

Plant Ontology PO Consortium

Plant Ontology (PO)

SO The Sequence Ontology Project

Sequence Ontology (SO)

Ontology for Clinical Investigations (OCI)

The Open Biomedical Ontologies

Common Anatomy Reference Ontology

The Open Biomedical Ontologies

Environment Ontology

OBI

Ontology for Biomedical Investigations

Phenotypic Quality Ontology (PATO)

PIR A UniProt CONSORTIUM MEMBER Protein Information Resource

Protein Ontology (PRO)

The Relation Ontology

OBO Relation Ontology

RNA Ontology Consortium

RNA Ontology (RnaO)

Signatures and Evidentiary Standards

- epidemiological
- molecular
- longitudinal profiling of individuals
- deconvolution of combinatorial complexity
- statistical and computational tools for non-linear dynamics in CAS
- limitations of Koch's postulates/Hill's viewpoints and the challenge of demonstrating causality
- confidence to invest high cost R&D for interventions

The Evolutionary Ecology of Malignant Neoplasms

- are there discernible consistent patterns (signatures) of pathway dysregulation in neoplasms arising in specific cell types/tissues?
- what determines the kinetics of clonal diversification and emergence of metastatic clones in tumor progression?
- what is the balance between stochastic and deterministic events the genesis of clonal heterogeneity?
  - precursor signatures
  - driver versus passenger mutations
  - ‘fitness pathways’ and ‘fitness islands’
- how does the tumor microenvironment(s) attenuate or promote trajectories and kinetics of clonal heterogeneity and metastatic emergence?
- what are the effects of immune responses and Rx treatment on clonal diversity and evolutionary plasticity?

Specificity

- carcinogens exhibit tissue (cellular) specificity
- consistent patterns of macro-behavior in tumors arising in particular organs/cell types
  - metastatic localization

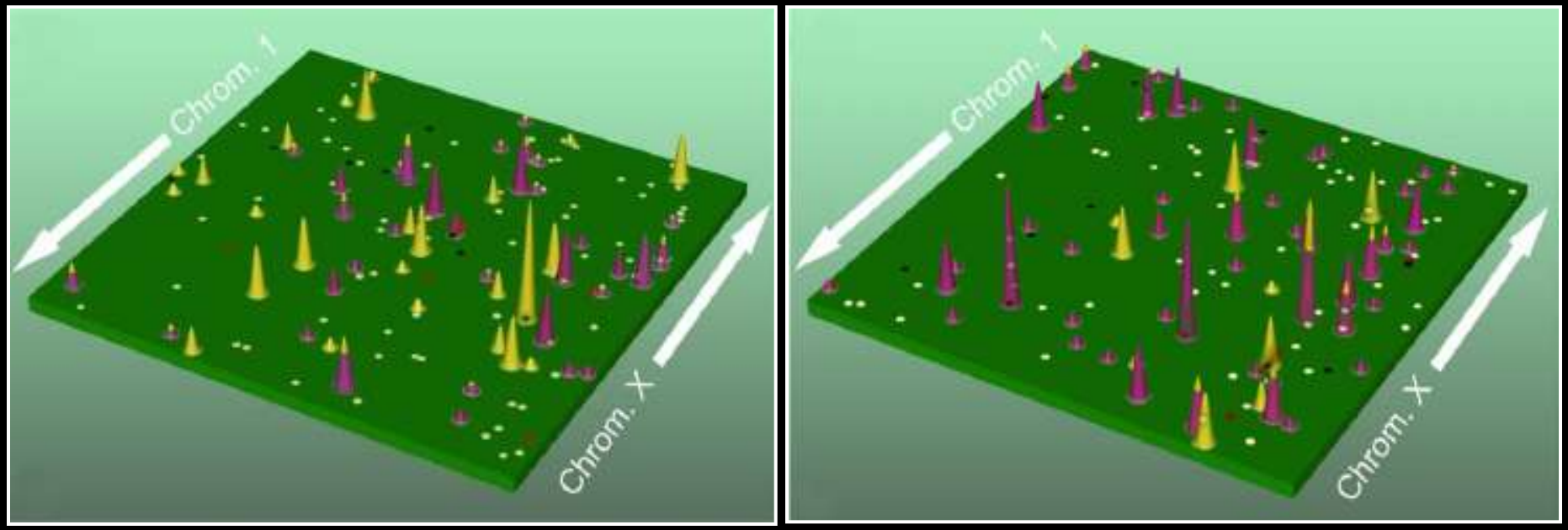
BUT

- significant inter-patient variation
  - clinical progression
  - Rx responsiveness
  - timing of recurrent disease

Mapping the Genomics Landscape of Breast and Colorectal Tumor Samples

From R. J. Leary et al (2008) PNAS 105, 16224

Breast	CRC



60 highest-ranking candidate cancer genes with peak heights reflecting the scores.

yellow = CN Changes red = point mutations only

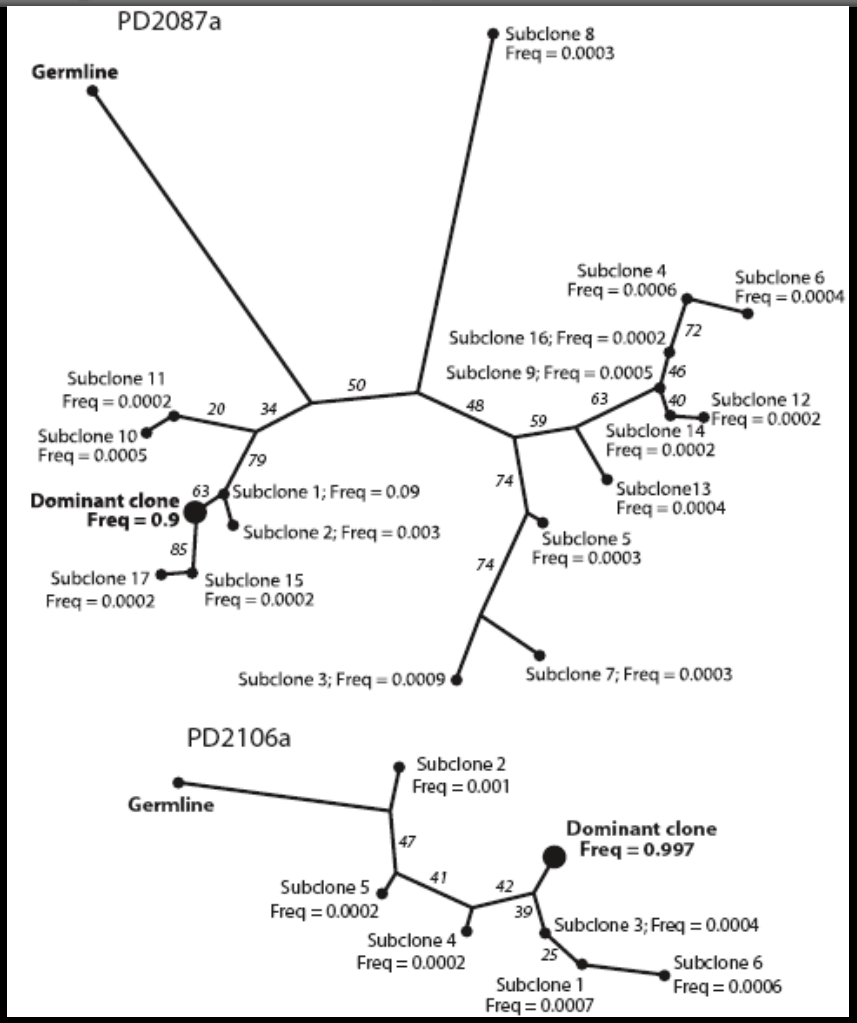
The Daunting Level of (Epi)Genomic Alterations in Cancer

- increased analytical resolution of whole genome sequencing
- significant inter-and intra-tumor heterogeneity in (epi)genomic perturbations and pathway dysregulation
- individual solid tumors contain 50 or more nonsilent mutations in coding regions
- only small fraction of these genes are mutated in a high proportion of tumors in the same cell lineage
- scale of alterations in noncoding RNA regulatory pathways unknown
- data reinforce role of stochastic events in tumor evolution

The (Epi)Genomic Landscape of Human Cancers

- very few mountains (genes mutated at moderate to high frequency in major cancers)
- the few genes that are mutated at high frequency often shared by multiple tumor types
  - TP53, PTEN, PIK3CA
  - EGFR, RAS, RAF, MEK, ERK
- multiple hills/hillocks (genes mutated at low frequency)
- anticipated need to map the entire cancer genome not only coding regions
  - mutational profiling of promoters/enhancers
  - noncoding RNAs
  - ultraconserved noncoding regions
- value of longitudinal profiling for reconstruction of disease molecular phylogeny

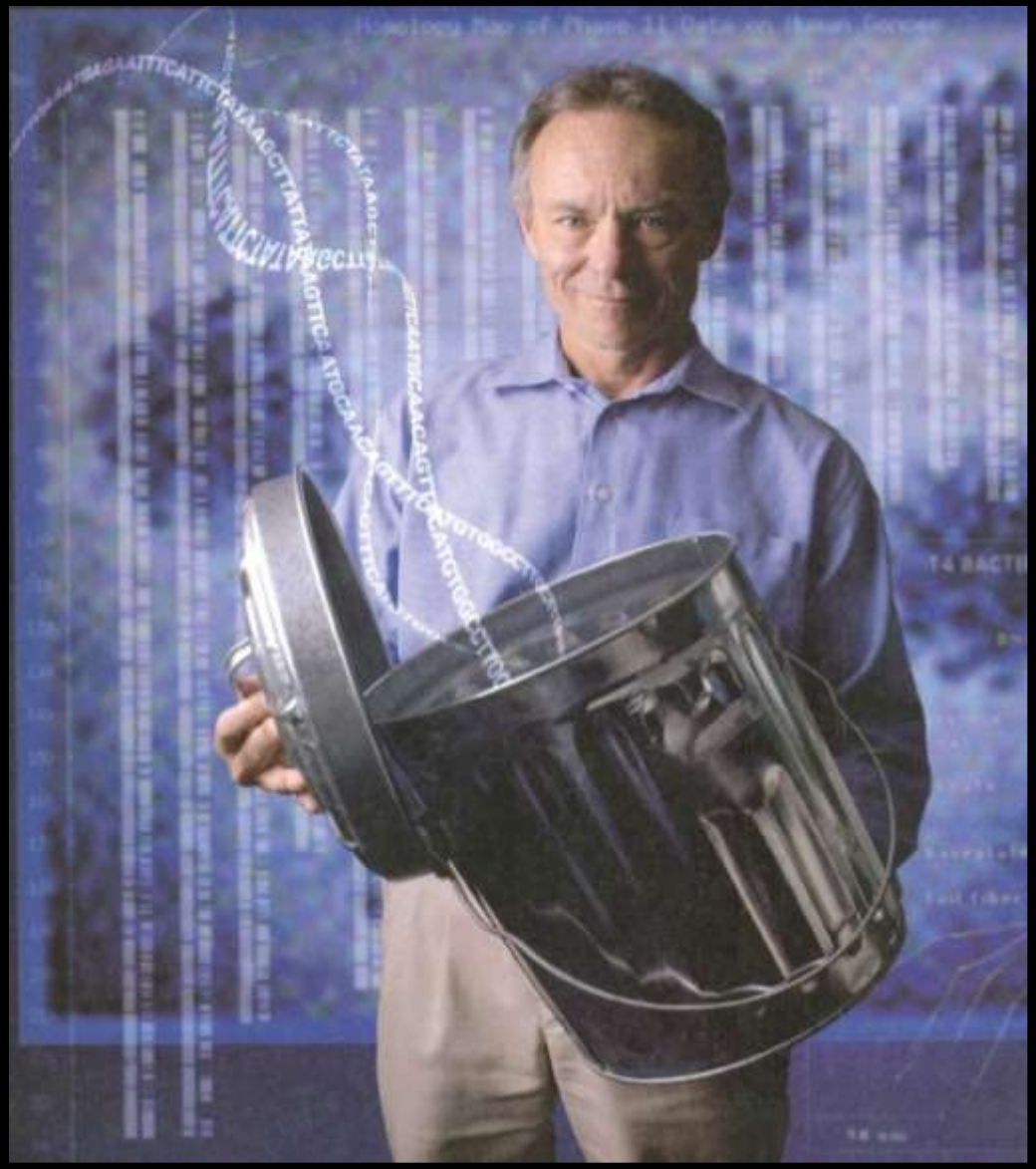
Unrooted Parsimony Tree Profiles for Clonal Evolution in B-Cell Chromic Lymphocytic Leukemia Revealed by Ultra-Deep Genome Sequencing



From: P. J. Campbell et al. (2008) PNAS 105, 13081

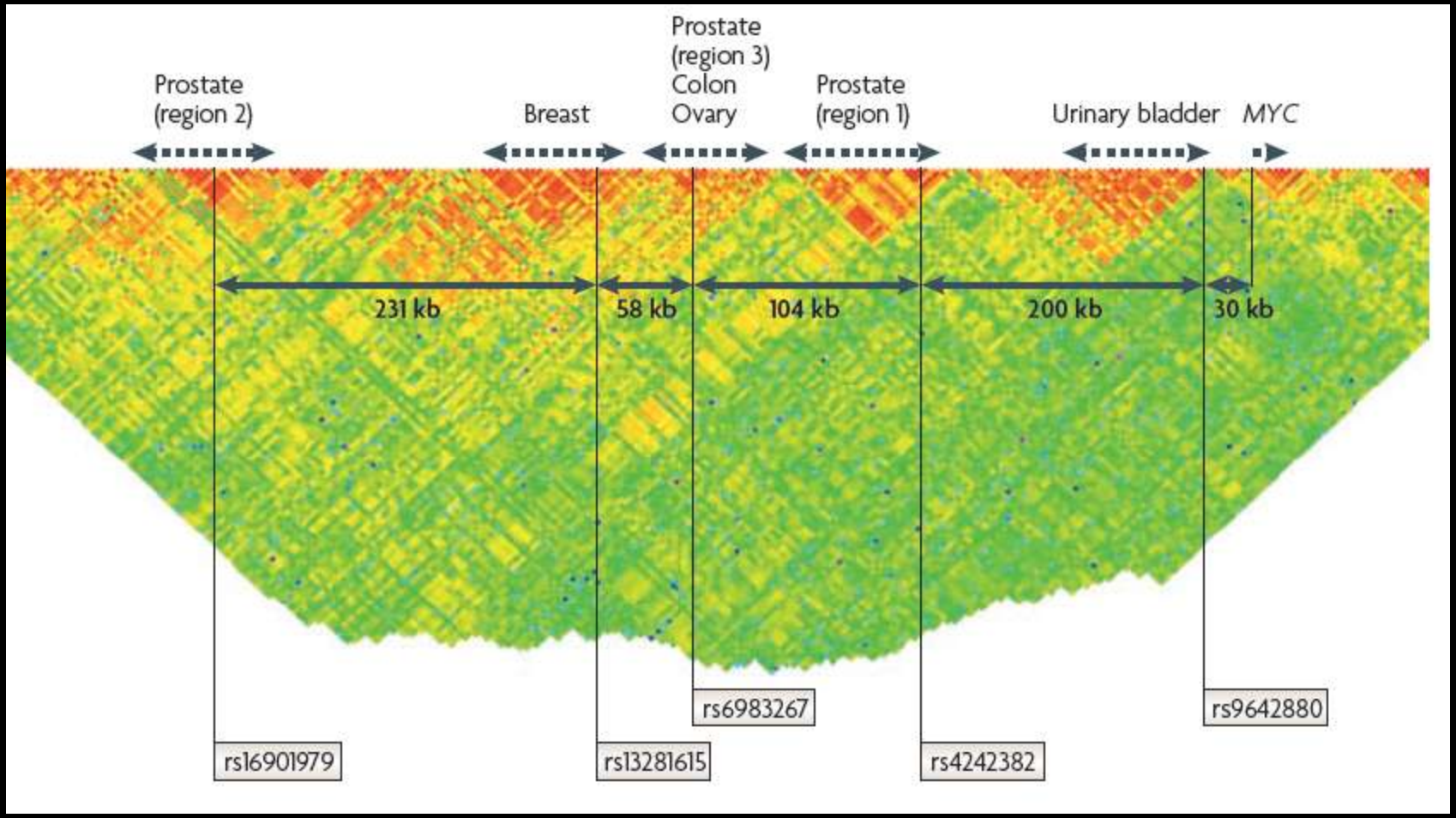
Length of branch is proportional to number of varying bases (evolutionary distance)

Mapping the Complexity of Genome Organization



- recognition of increasing levels of organizational and regulatory complexity
  - haplotypes
  - CNV
  - indels
  - RNA universe
  - ‘dark’ elements
  - epigenetics
  - epistasis
  - nuclear compartmentalization and trans-expression

Gene Deserts: The 8q24 Region and Cancer Susceptibility



From: J. P. A. Ioannidis et al. (May 2009) Nature Rev. Genetics 10, 318

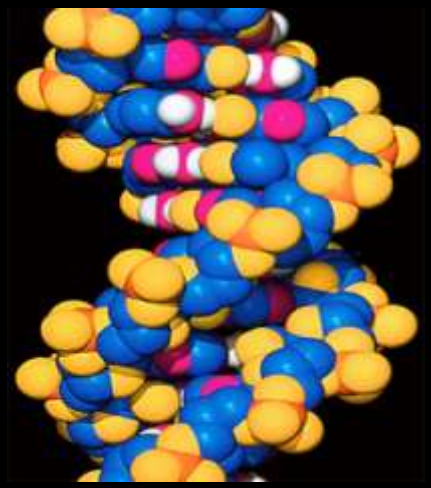
The Sequencing Race

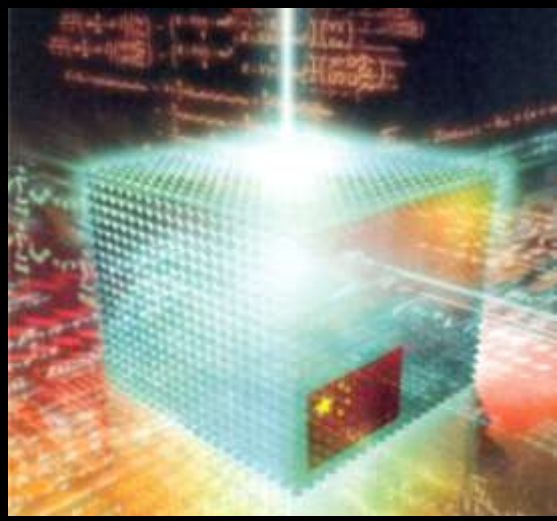
“Managing Mega-Data”

volume

scale

global networks

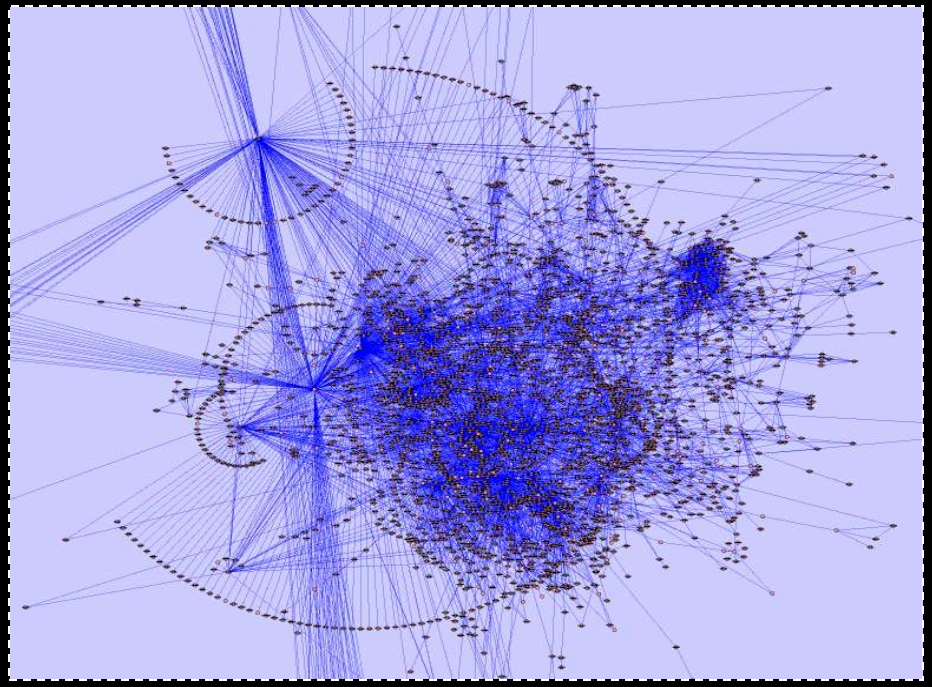


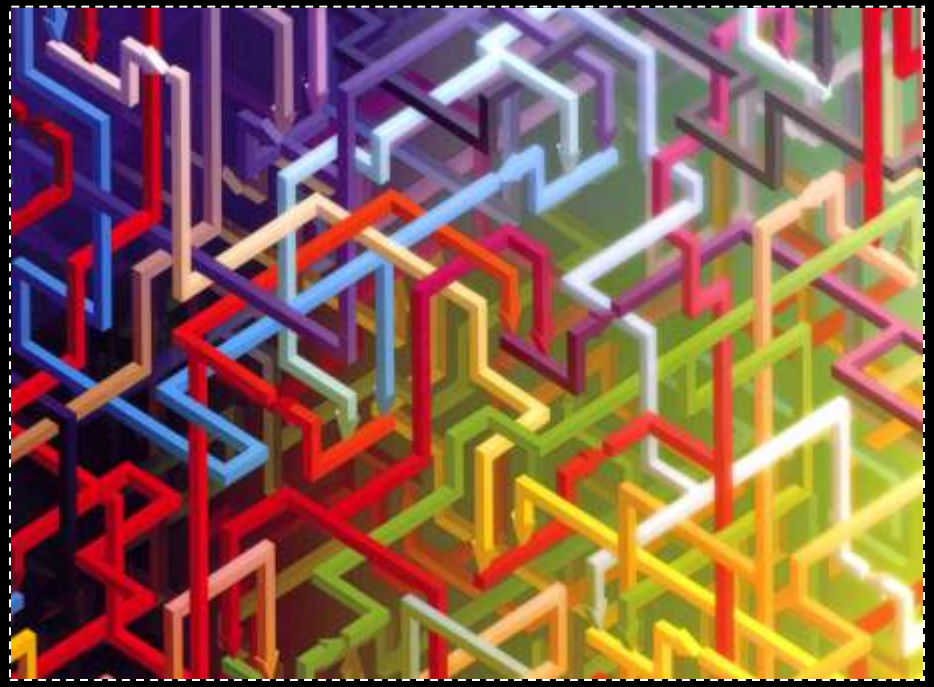


multiscale heterogeneity

integration

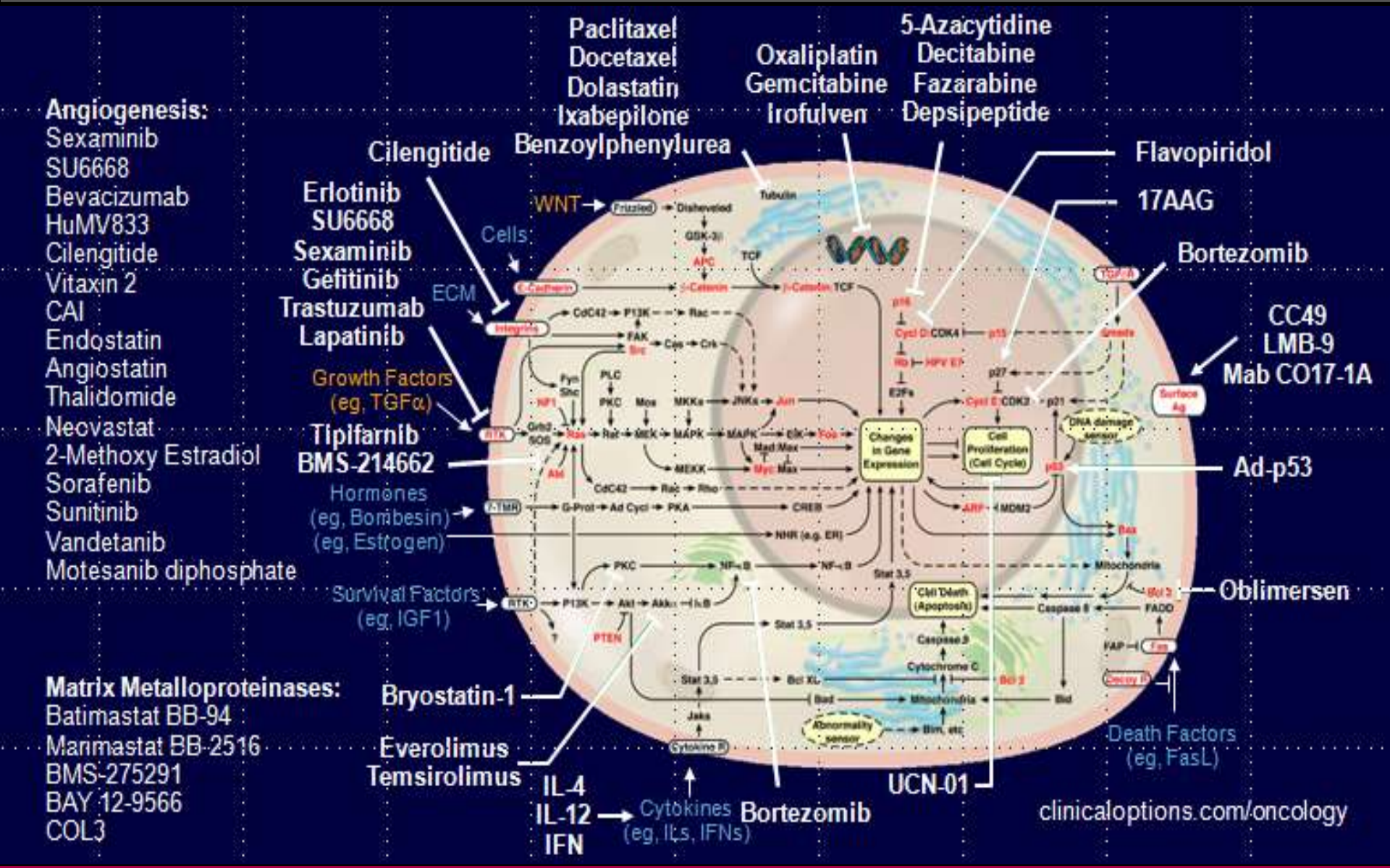
Mapping the Molecular Networks of Human Diseases



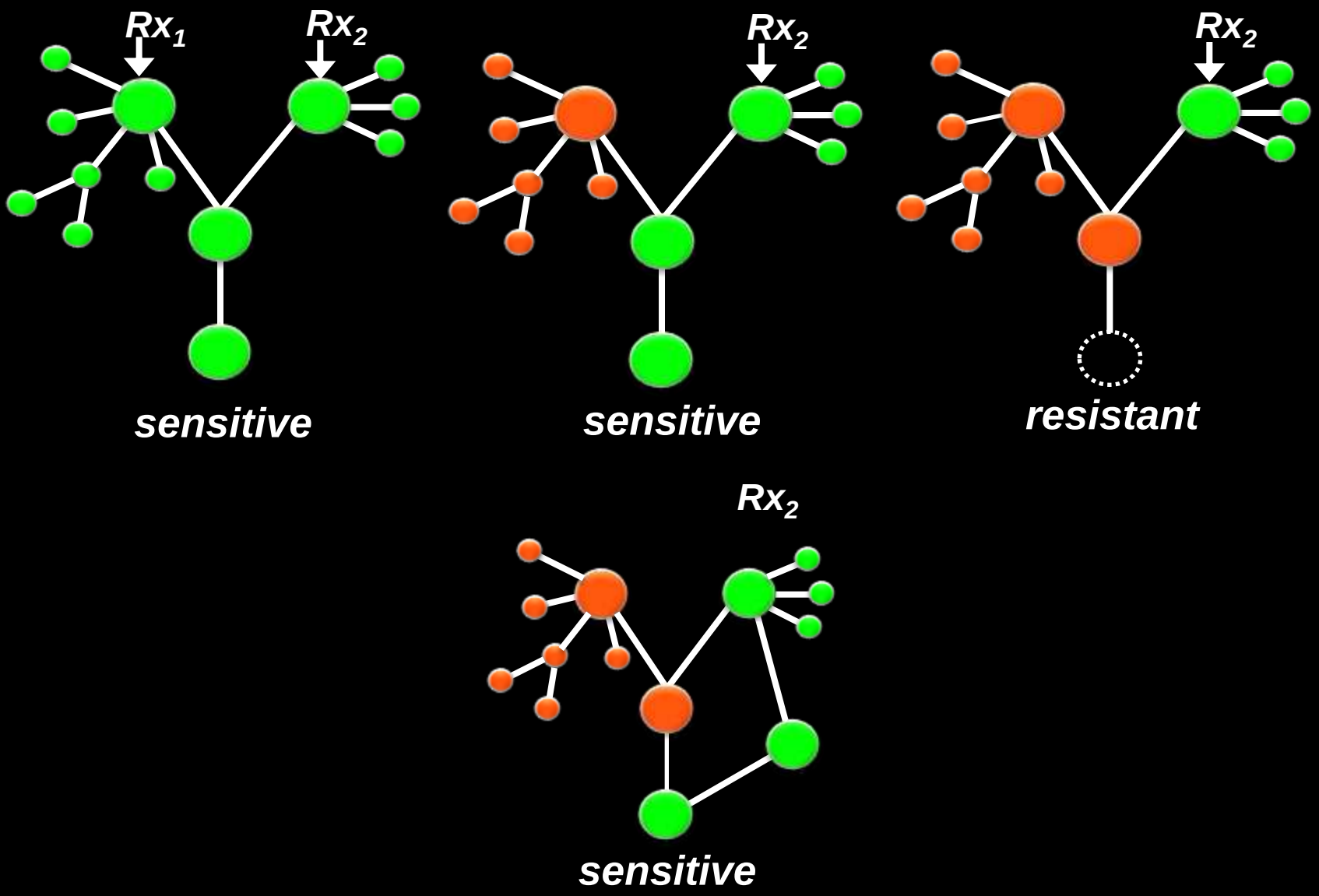


- systems-based approach to network architecture and topology
  - components and pathways (Dx)
  - heterogeneity (disease subtypes and Rx selection)
  - connectivity, redundancy and plasticity (Rx refractory/resistant)
  - identification of ‘fragility’ patterns in tumor robustness (novel Rx discovery and Rx combinations)

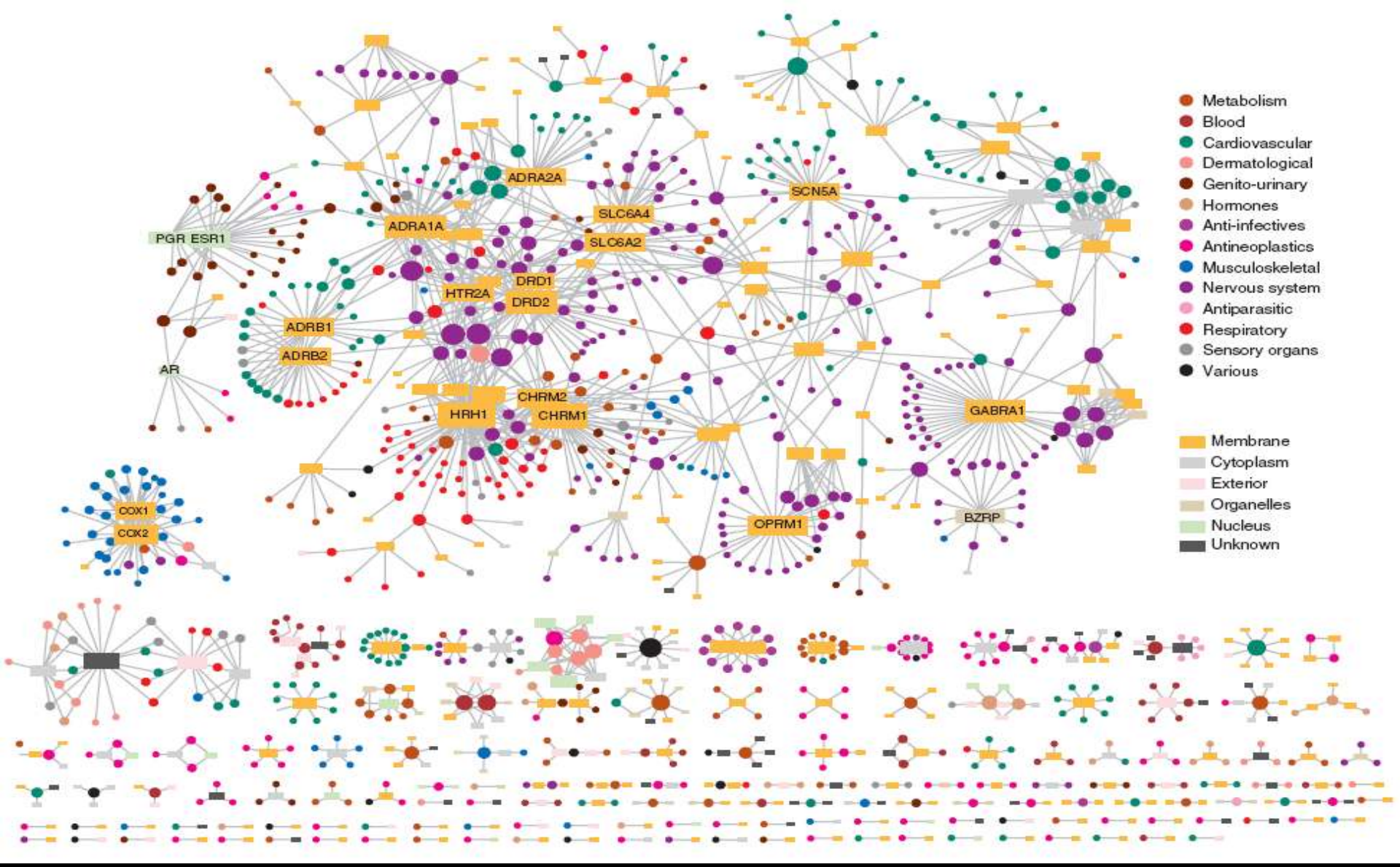
Selected Targeted Agents With Potential as Breast Cancer Therapeutics



Redundancy and Robustness in Scale-Free Networks: The Biological Foundation of Rx Resistance



Drug-Target Networks for FDA Approved Rx:



M. A. Yildirim et al. (2007) Nature Biotechnology 25, 1119

(Epi)Genomic Alterations in Cancer

- major implications of inter-and intra-tumoral heterogeneity for design of new therapeutic approaches
- target pathways versus single molecular targets
- logic of multi-agent Rx protocols but clinical/economic feasibility highly uncertain
- high probability of pre-existing Rx-resistant clones at onset of therapy
- absence of prevalently mutated genes stratifies patient population into ever smaller cohorts

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- absence of prevalently mutated genes stratifies patient population into ever smaller cohorts
  - some (or all?) cohorts may be too small to economically justify Rx development (expanding the ‘orphan’ disease pool?)

Signaling Pathways: The Challenge of Defining Biological Relevance and as Targets for New Therapeutic Interventions

Different Cell Classes Within a Tumor

- stem cells versus end-stage non-stem daughter cells
- selective blockade of progression to metastatic phenotype(s)
- targeting phenotypes unique to metastatic subpopulations
- stromal cells and epithelial-mesenchymal transition (EMT)

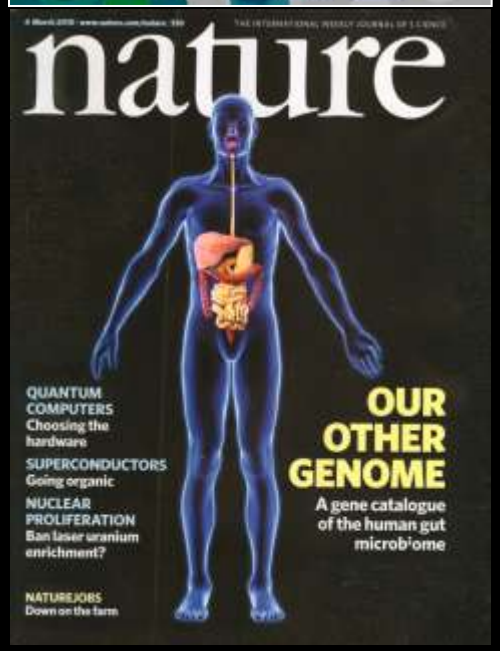
Different Biological Pathways Within a Tumor

- proliferation-related pathways as target for cell destruction by Rx
- histiotypic homeostasis pathways for new Rx class for phenotypic reversion in dysregulated cancer cells

The Evolutionary Ecology of Malignant Neoplasms

- what are the principal communication networks in histiotypic homeostasis?
  - tumor-tumor clone interactions?
  - tumor clones-host cell lineages?
- what are the mechanisms by which tumor cells acquire refractoriness to these signals and exhibit progressive behavioral autonomy?
- can insight into histiotypic homeostasis control systems offer new approaches to therapy?
  - induce phenotypic reversion in tumor clones?
  - block usurpment/subversion of histiotypic control pathways by tumor clones? (angiogenesis, EMT)
- evolution of clones completely unresponsive to hystiopic regulation

The Human Microbiome: A Barely Understood Influence in Health



- complex meta-system
  - host, microbes, viruses, other organisms, metabolites, xenobiotics
  - is there a core microbiome?
  - how do perturbations affect disease and vice-versa?
  - does the microbiome influence xenobiotic metabolism and the metabolite spectrum?
  - role in chronic diseases via carcinogen metabolism?

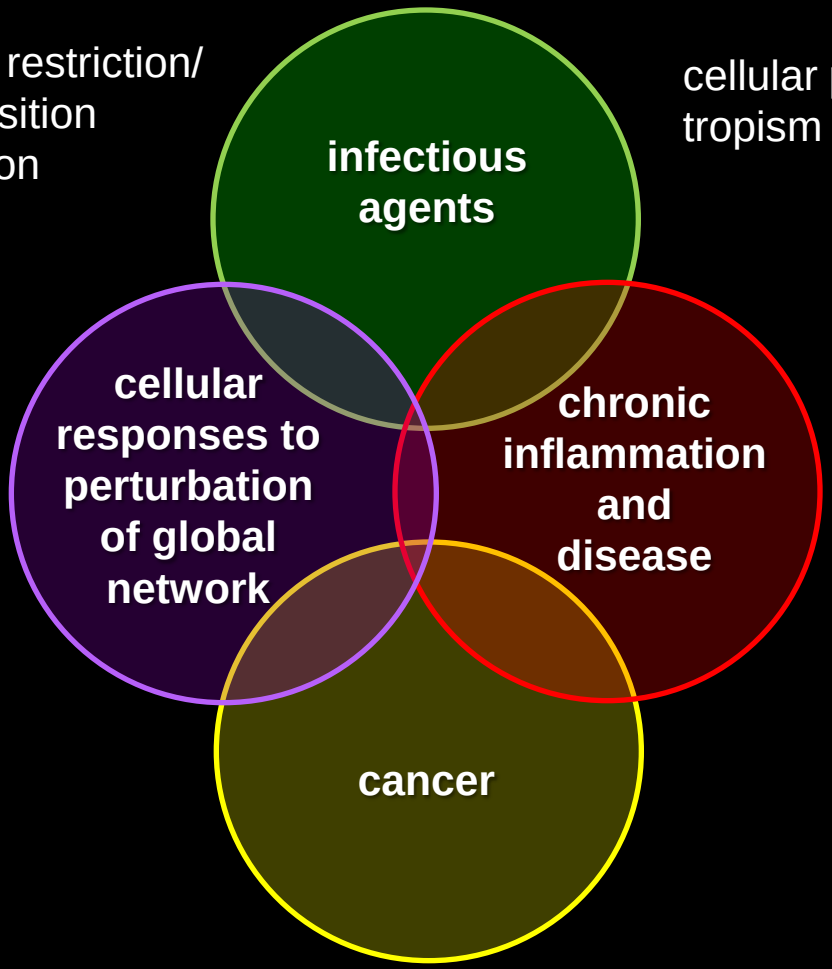
The Challenge of Identification of the Long-Term Adverse Consequences of Infection

- hunting elusive causal relationships between infections and cancer beyond the known oncogenic infectious agents
- problem of extended time between trigger event (single or repetitive) and clinical consequences
- massive noise problem due to exposure to multiple agents and non-controlled confounders
- challenge of ID of ‘signatures’ of ‘hit-and-run’ or ‘hit-and-hide’ events in specific cell lineages permissive for the suspected agent(s)

The Challenge of Identification of the Long-Term Adverse Consequences of Infection

- what role does infection play in triggering dysregulation of innate and adaptive immune responses?
- sustained asymptomatic inflammation as a cellular ‘stress-insult’ that propagates progressive genomic instability and pathway/network perturbations leading to neoplastic conversion?
- lack of quantitative methods for profiling the ‘immunostat’
  - longitudinal baseline values in large cohorts
  - profiling of amplification/restoration/persistent activation states post-infection

The Complex and Poorly Understood Relationships Between, Infection, Inflammation and Chronic Diseases



genomic restriction/ predisposition to infection

cellular permissiveness and tropism

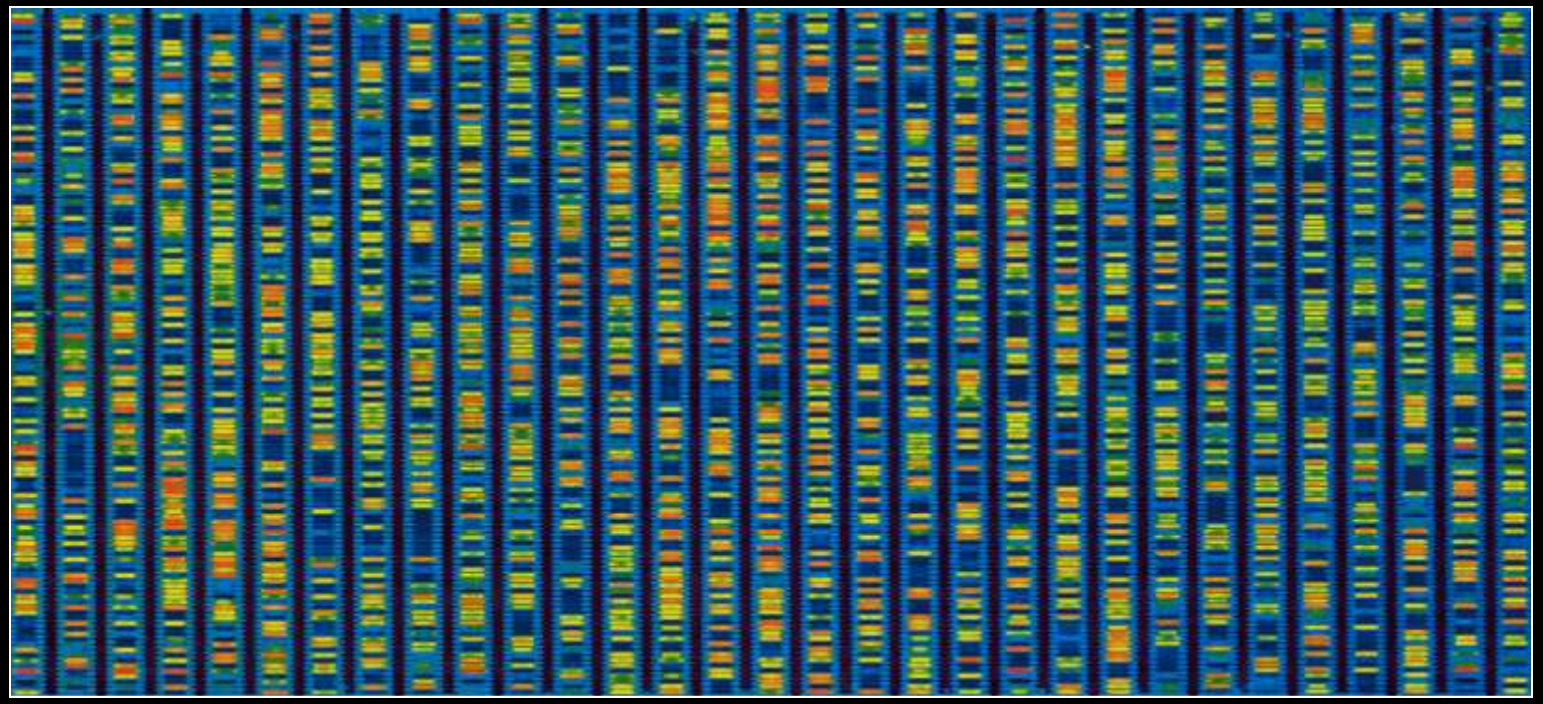
genome integrity defenses

innate and adaptive immune response

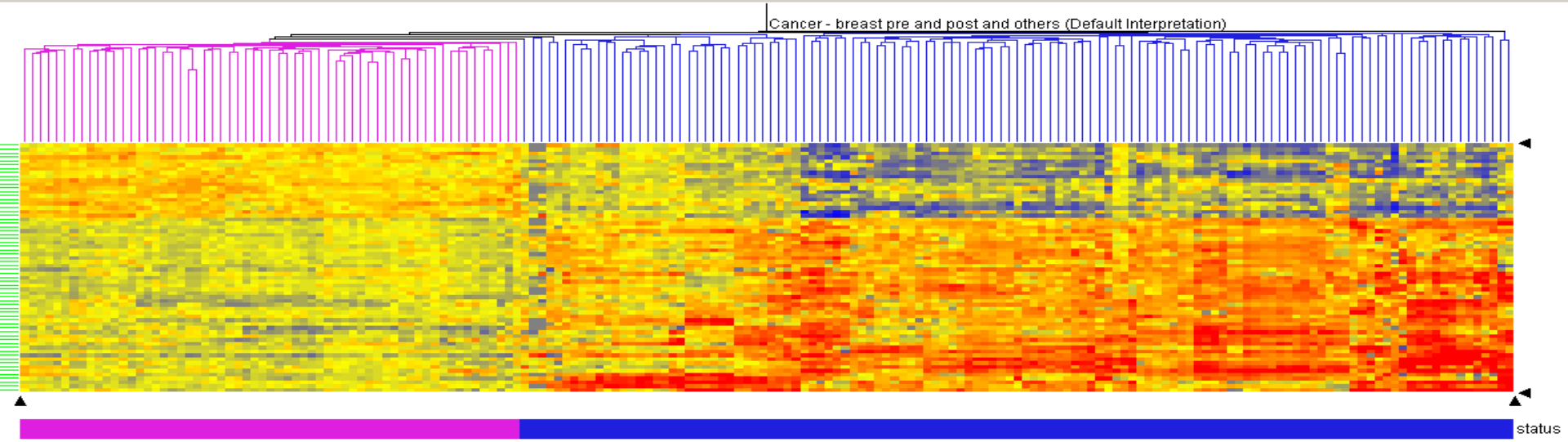
- diabetes?
- obesity?
- atherosclerosis?
- Alzheimer's?
- cancer?

multi-step insults and progressive genomic instability

Immunosignatures

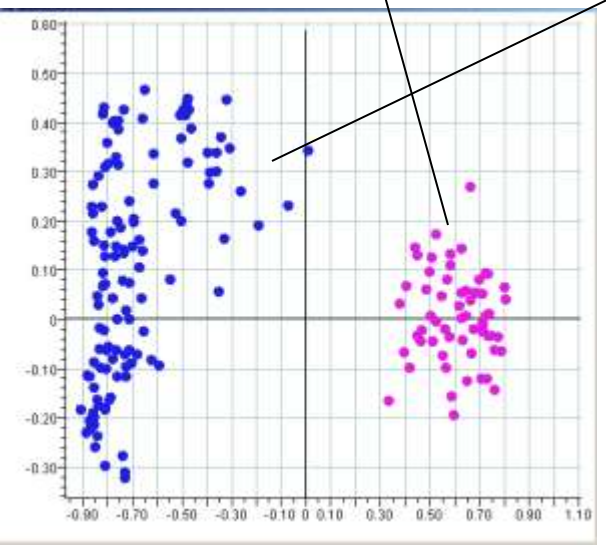


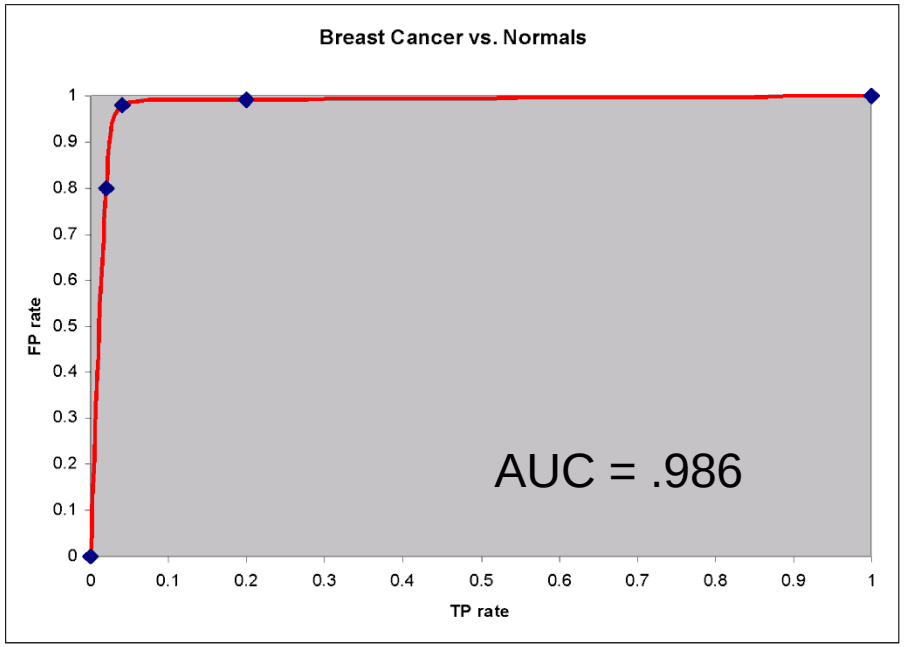
- patterns of antibody binding to large scale peptide arrays
- ability to profile banked samples
- prospective longitudinal studies
  - presymptomatic, clinical onset, progression and outcomes



CIM Breast cancer

CIM Normals





From: S. Johnston et al. The Biodesign Institute, Arizona State University

Reverse Mapping of Immunosignatures to Identify Eliciting Epitopes

- do the consistent immunosignature patterns detected in cancers in specific cell lineages ‘map’ to peptide sequences in microbial pathogens or infected cells?
  - linear versus assembled epitopes
- can host immunosignatures provide insight into the initiating trigger event(s) (and cause?)

Infectious Diseases and Cancer: Therapeutic Options

Vaccines

- therapeutic vs. prophylactic
- ID of multiplex antigen/epitope repertoire
- selection for immune escape variants
- route of immunization (mucosal immunity)
- risk of tolerance/future predisposition to cancer?
- efficacy endpoints for clinical trials, time and cost
- regulatory requirements (REMS)?

Infectious Diseases and Cancer: Therapeutic Options

Oncolytic Viruses

- targeted delivery
- specificity for neoplastic clones

Immunomodulation to Reverse Immune Tolerance

- pathogen associated molecular pattern (PAMP) agents
- improved antigen presentation to DCs
- literature reports of reduced incidence of tumors following infections but rigorous analysis needed

Viral-Encoded miRNAs as Oncomirs: New Therapeutic Targets?

- upregulation of cellular miRNA
  - miR-155 and EBV
- viral orthologs of cellular miRNAs
  - KSHV miRK-12-11 same seed as cellular miR-155 and targets same mRNAs for downregulation
  - oncogenic Marek's Disease MDV-1 encodes miR-155 ortholog but non-oncogenic MDV-2 does not
  - EBV miR-BART5 ortholog of cellular mirR-18a, 18b
- targets for miR-155
  - proteins with known role in B cell proliferation
  - TP53 inducible nuclear protein 1 and correlation with miR-155 upregulation in pancreatic cancers

Changing the Sociology of Life Sciences and Clinical Research

- transcending silo mentalities, organization and funding → cross-disciplinary initiatives and new career incentives/rewards
- rebalance public funding priorities to address scale and complexity of trans-disciplinary projects → new funding vehicles with suitable scale; new review systems
- set new balance between hypothesis-driven and data-driven research → recognize importance and intellectual merits of large scale dbase assembly, curation, analysis
- poorly standardized, fragmented data → standardized ontologies, consortia, grids, open source databases for meta-analyses
- the challenge of translational research: "the valley of dearth" → stringent funding criteria for obligate assembly of full expertise spectrum; new clinical training/ medical curriculum; private: public partnerships