ASU COMPLEX ADAPTIVE SYSTEMS INITIATIVE
ARIZONA STATE UNIVERSITY

BEYOND center for fundamental concepts in science

"The way ahead"

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The Beyond Center Cancer Forum
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MAGAZINE OF THE LIFE SCIENCES

Confronting the Cancer Challenge: The Need for Systems-Based Approaches to Biological Complexity

methodology

- scale
- standards
- semantics
- samples
- statistics
- silos

biology

- stress
- specificity
- signaling pathways
- stroma
- selection
- stem cells

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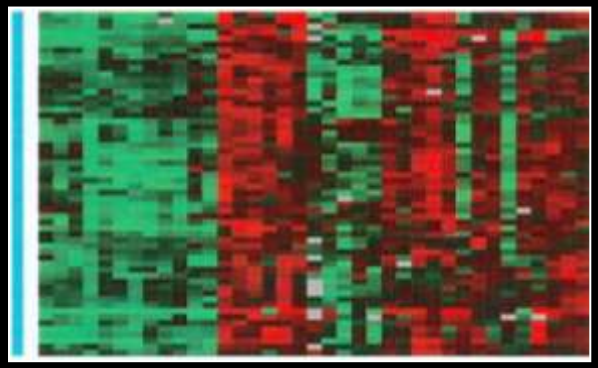
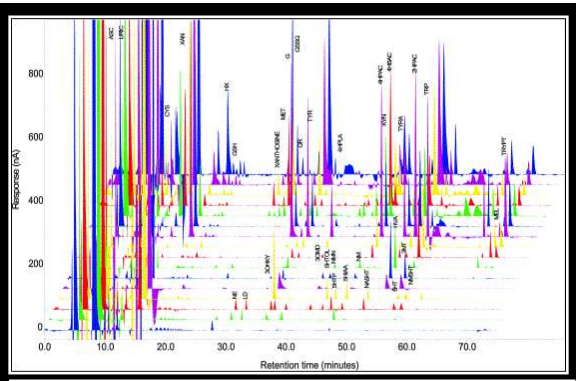
COMPLEXITY:
MAPPING THE EVOLUTIONARY ECOLOGY OF MALIGNANT NEOPLASMS

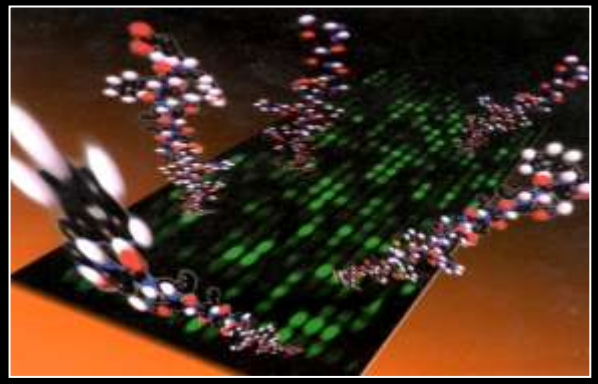
Analytical Scale and Systems-Based Integration: The Need for End-to-End R&D Solutions

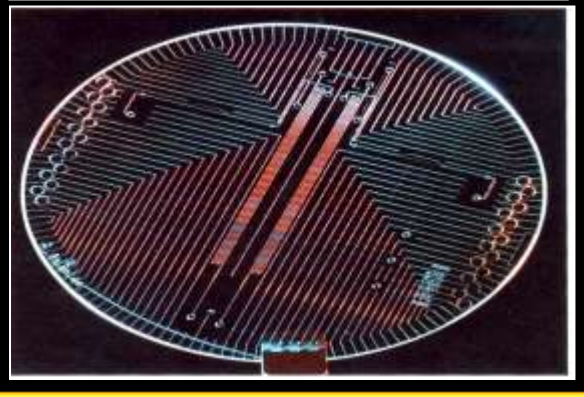
Complex Biosignature Profiling

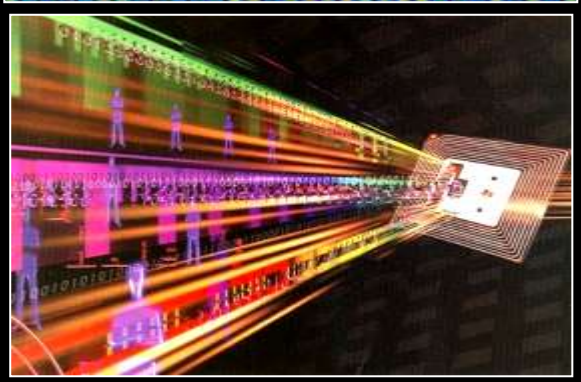
genomics	proteomics	immunosignatures











Complex Signature Detection, Deconvolution and Multivariate Analysis

multiplex assays	miniaturized devices	new algorithms

Standards

- transcending sustained reliance on disparate systems of dubious relevance to embrace more rigorous validation and QA/QC approaches
- merits of a national oncology resources center
- historical analogy with SVCP (1970s)
- role of funding and regulatory agencies in driving obligate adoption of systems-based approaches
  - organize experimental resources for systems of validated relevance to human cancers
  - research methods, materials, data, datasets
  - clinical trial methods and endpoints

Samples

- seemingly pedestrian but crucial ‘proximate’ parameter
- standardized protocols
  - excision and collection conditions
  - time lags
  - storage and transport conditions
  - prior treatment data
- analytical profiling and accurate phenotyping
  - subtyping, staging and stratification
  - defining the tumor margin (histological versus molecular perturbations)
  - zonal heterogeneity and sample analysis

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

- literature dominated by anecdotal studies in poorly characterized systems
  - academic laboratories
  - 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

Validation of Disease Associated Biomarkers

- many variables behave as QTLs with graded continuum rather than binary normal: disease separation
- the high dimensionality small sample size (HDSS) problem
  - high number of variables (2000-10000) and low sample size (10-100)
  - increased risk of selection of variables due to chance (overfitting)
- standardization and statistical powering
  - “the 20:200:2000 rule”
- new regulatory complexities for multiplex ‘signatures’

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

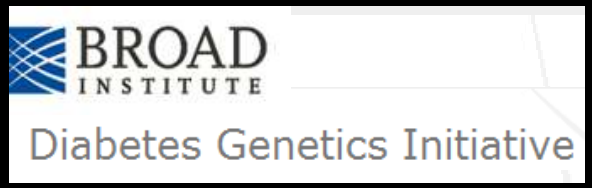
OBO Relation Ontology

RNA Ontology Consortium

RNA Ontology (RnaO)

The Rise of Open-Source Networks and Consortia

FDA/Severe Adverse Events (SAE) Consortium



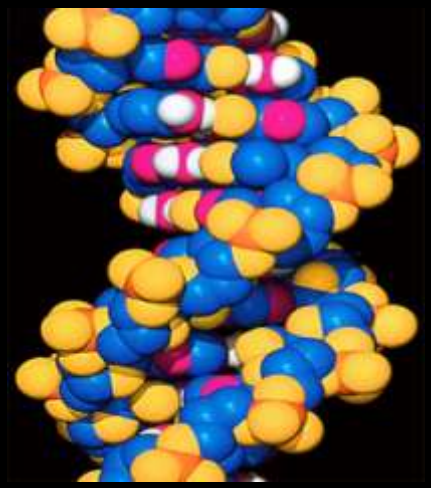
Clinical Semantics Group

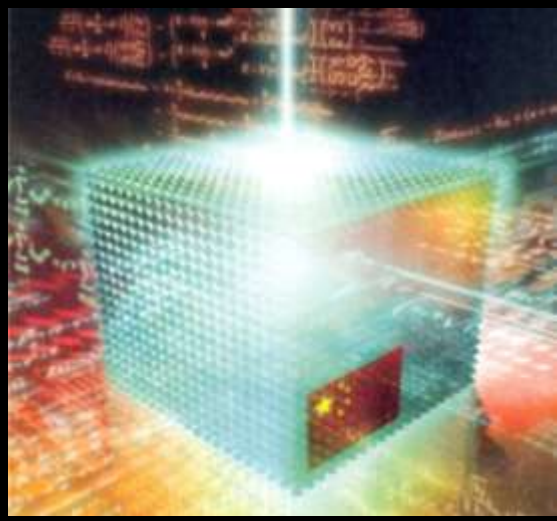
“Managing Mega-Data”

volume

scale

global networks





multiscale heterogeneity

integration

Mathematical and Computational Models of Biological Systems

- develop precise, unambiguous and standardized representations of biological data and knowledge
- develop quantitative tools to test system dynamics in biology
- algorithmic and formal methods to address state changes, concurrency and abstraction
- identification of (bio)-logic gates in biological pathways, modules and networks
- transitioning mathematical formalisms (denotational) and computational (operational) for analysis of complex biological systems

Standards: Relevance

- discarding biologically and/or clinically irrelevant research methods/strategies
- insidious cultural and organizational barriers to change
  - propagation of funding for historical conceptual paradigms and experimental models despite evidence of low productivity
  - inadequate mechanisms for review/funding of ambitious cross-disciplinary programs
  - abundant evidence of shortcomings in many cell/animal systems as predictive models for human cancer
  - pressure for continued publication/funding sustains irrelevant models

Confronting the Cancer Challenge: The Need for Systems-Based Approaches to Biological Complexity

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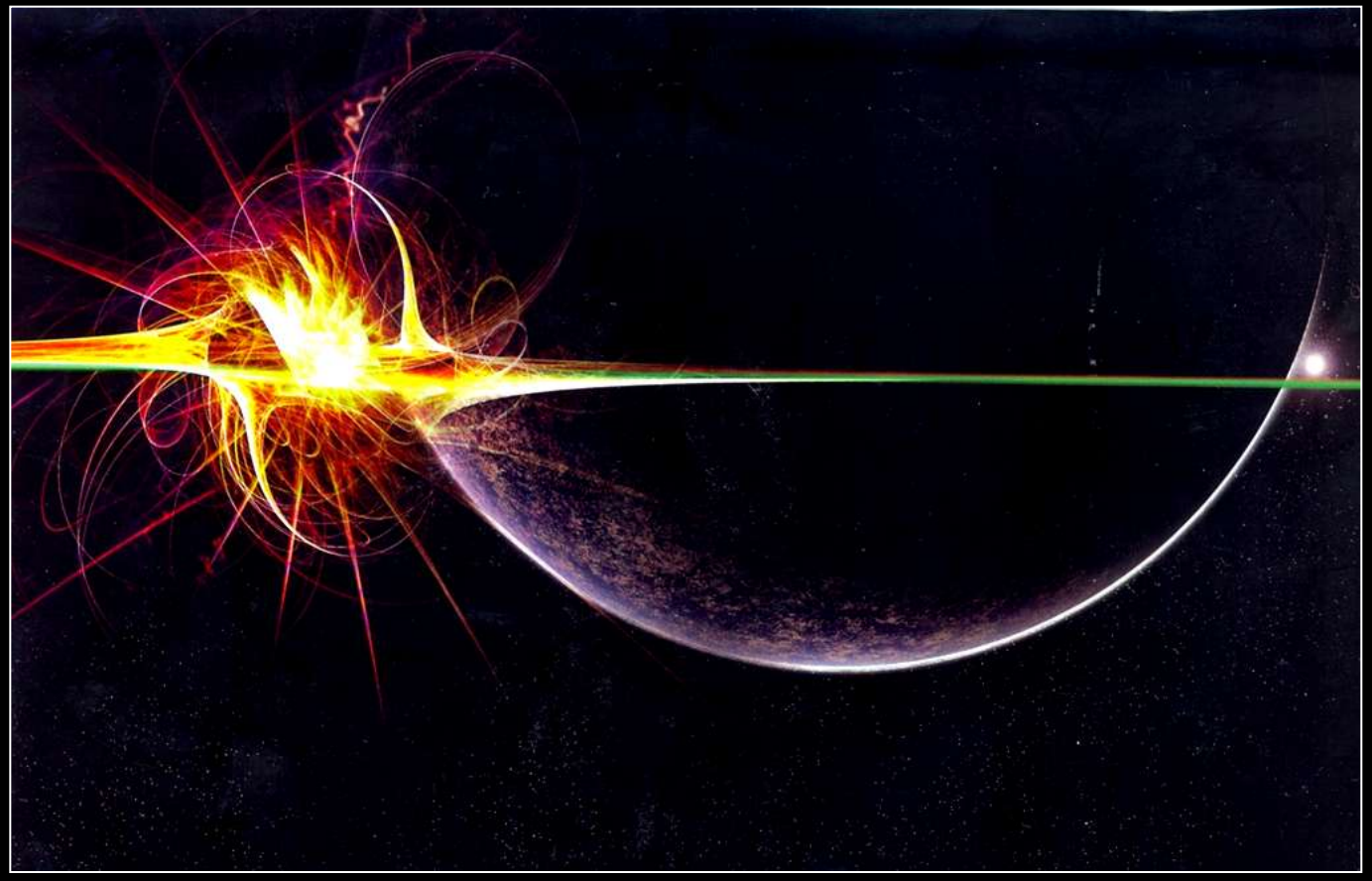
SOLUTIONS

Confronting the Cancer Challenge

Systems
Complexity

The Behavior of Far-From-Equilibrium Systems: The Evolutionary Ecology of Tumor Progression



Complex Adaptive Systems

- complex behavior arising from dynamic interaction of multiple agents
- cancer ecosystem involves highly diverse but poorly defined repertoire of interacting agents
  - multiscale (molecular networks to whole body pathophysiology)
  - multiagent (tumor cell heterogeneity, tumor-host interactions, Rx)
- consistent with other complex biological systems, cancer is a far-from-equilibrium system with non-linear characteristics
- identification of triggers of ‘emergence’ of increasingly dangerous phenotypes in tumor progression
  - immune evasion, metastasis, Rx resistance

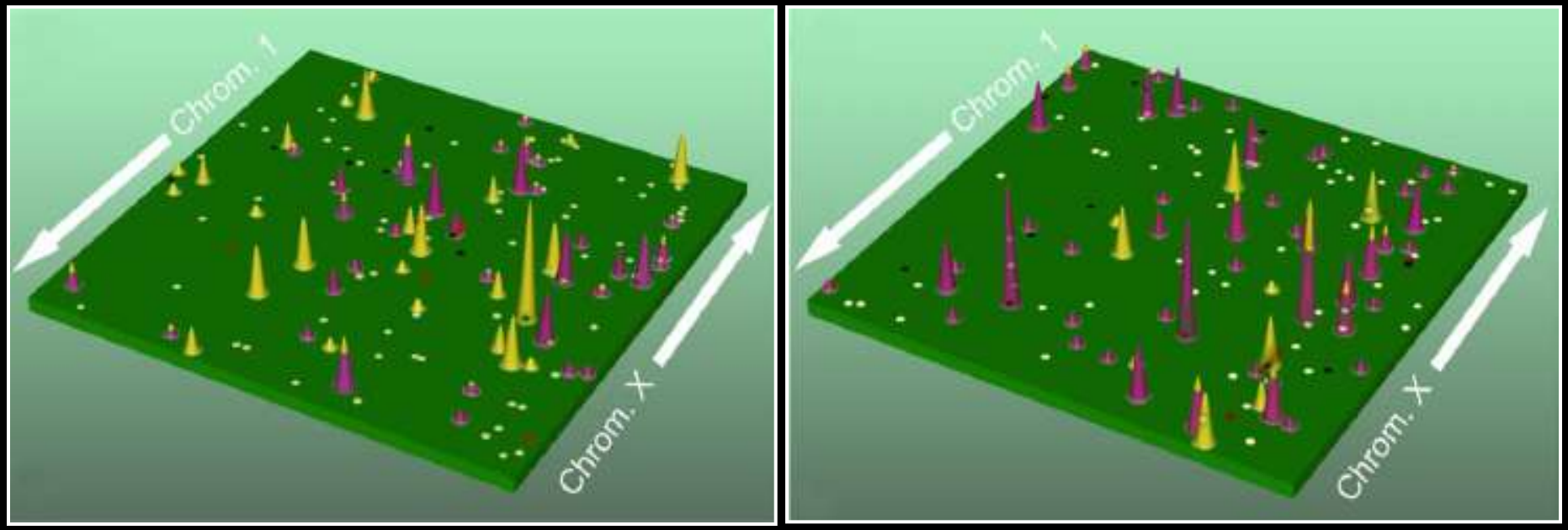
The Genomic Landscape of Cancer

- multistep accumulation of random somatic mutations in oncogene and suppressor gene networks
- progressive genomic instability and increasingly extravagant genomic/epigenetic alterations
- genetic heterogeneity and the analytical challenge of distinguishing causal (driver) versus non-causal (passenger) mutations
- both driver and passenger mutations may confer adaptive advantage
- additional importance of multiple pathways in enhancing cellular stress responses

Mapping the Genomics Landscape of Breast and Colorectal Tumor Samples

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

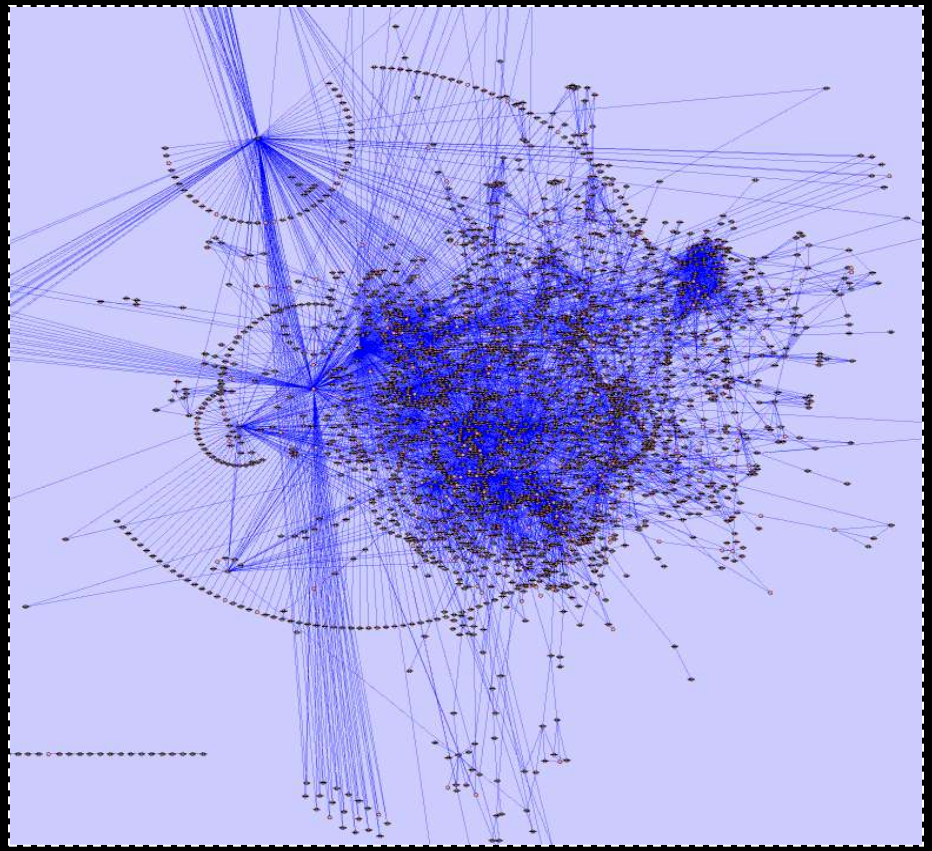
Breast	CRC

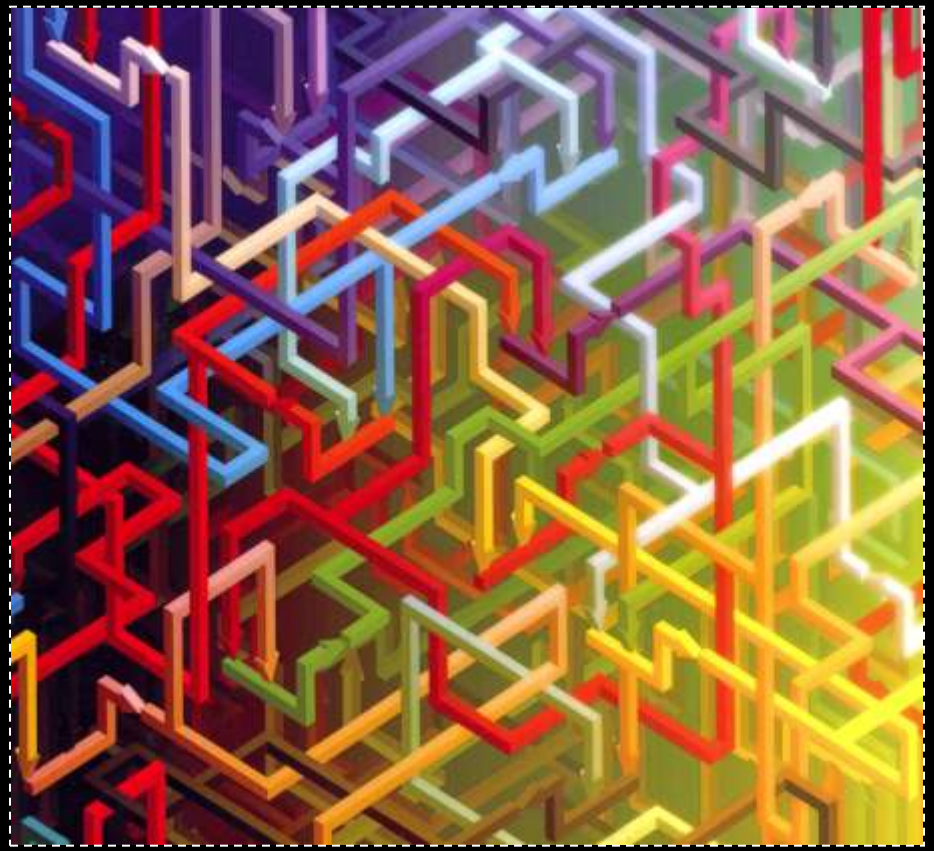


60 highest-ranking candidate cancer genes with peak heights reflecting the scores.

yellow = CN Changes red = point mutations only

Mapping the Molecular Networks of Human Diseases

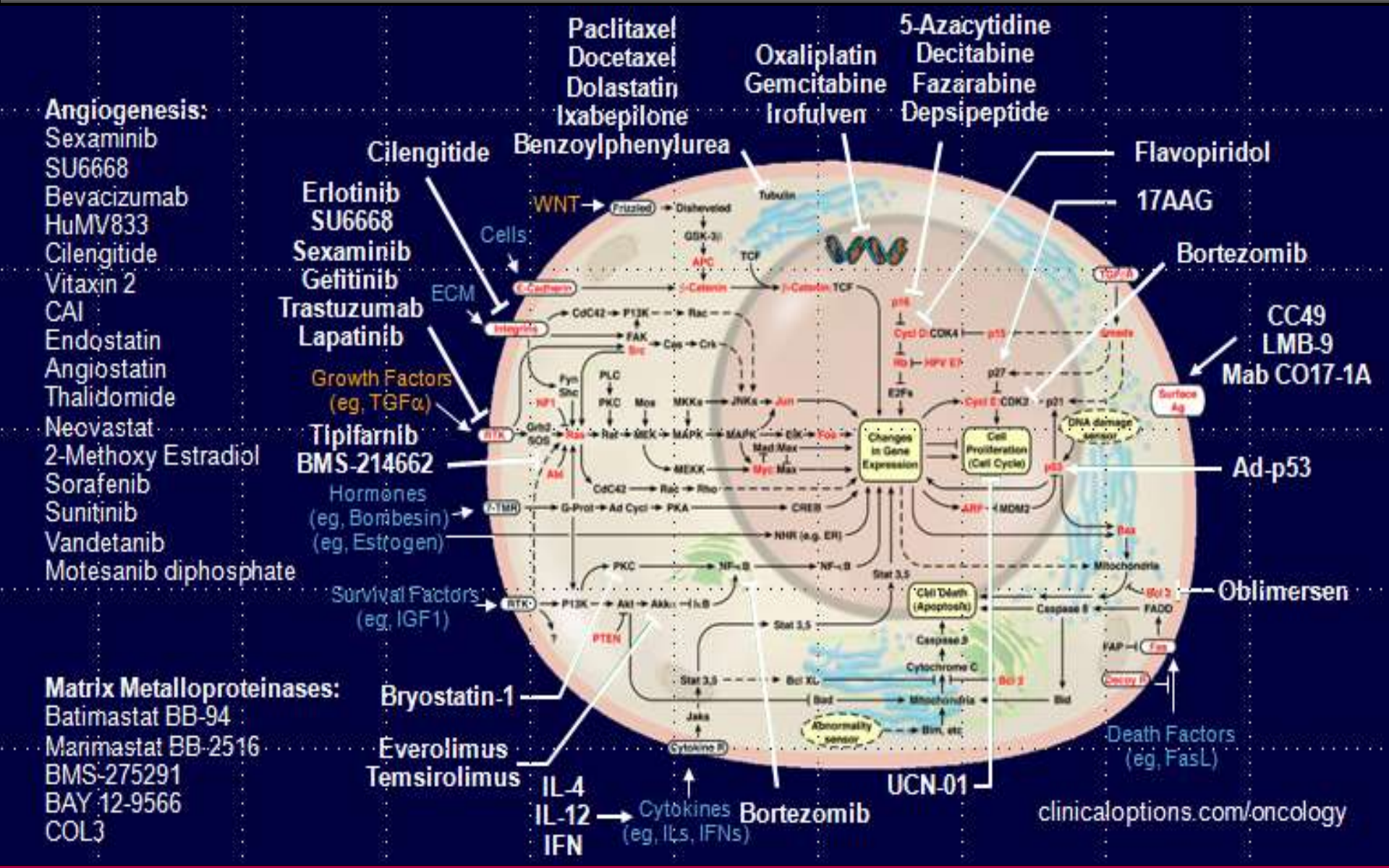




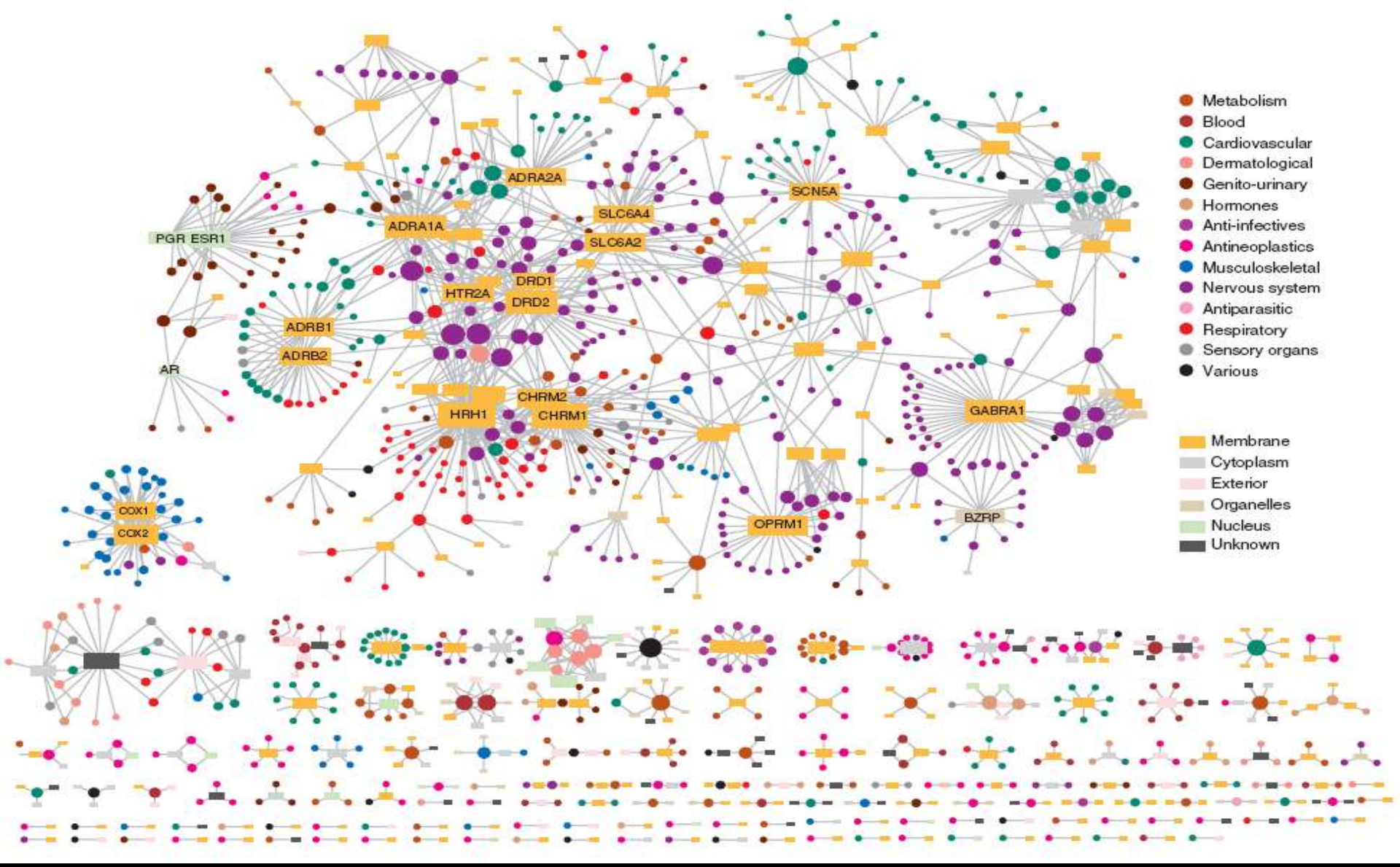
Specificity

- carcinogens exhibit tissue (cellular) specificity
- consistent patterns of macro-behavior (clinical) and pathway dysregulation (molecular) in tumors arising in particular organs/cell types
- separation of irreducible and reducible complexity
- identification of 'relevant complexity'
  - 'driver' versus 'passenger' mutations in etiology, progression and Rx responses
  - stochastic versus deterministic events in evolutionary trajectories of tumor progression
  - mapping 'directed/canalization of 'fitness pathways' /'fitness islands' in primary and metastatic lesions

Selected Targeted Agents With Potential as Breast Cancer Therapeutics



Drug-Target Networks for FDA Approved Rx:

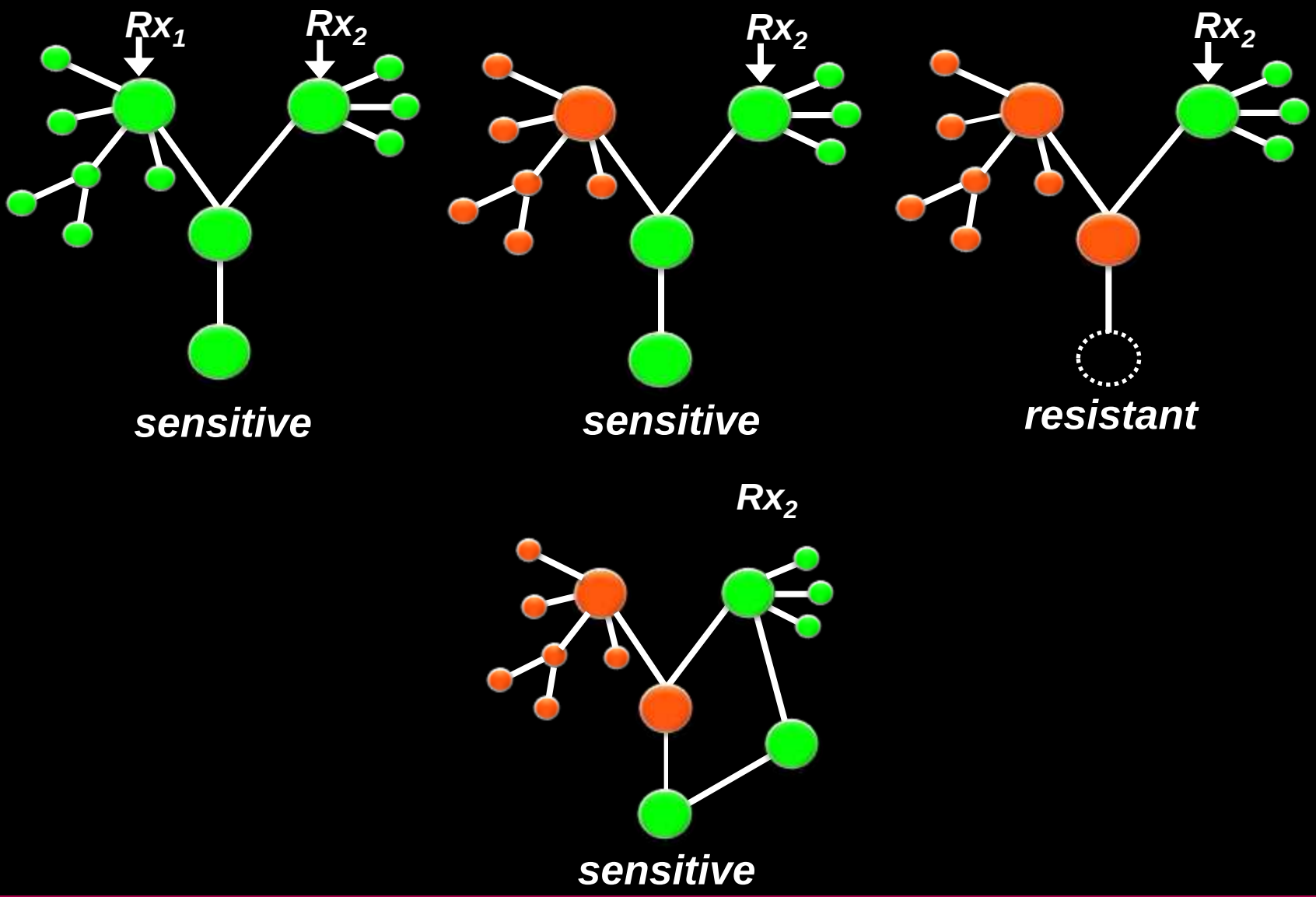


M. A. Yildirim et al. (2007) Nature Biotechnology 25, 1119

Key Principles

- there are no single molecular targets for Rx action
- there are only pathways
- there are no linear pathways only networks and subnetworks
- there are also highly interconnected networks/subnetworks between tissues
  - e.g. modulation of liver network induces changes in pancreatic islet network

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



Network (Systems) Pharmacology

- analysis of Rx safety/efficacy in context of biological pathways/networks
- shift from one drug:one target strategy to recognition of benefits of polypharmacology and target promiscuity in Rx action
- exquisitely selective Rx may exhibit lower than desired efficacy
- Rx acting on two or more targets in disease pathway may be more efficacious
  - theoretical legitimacy but clinically impractical

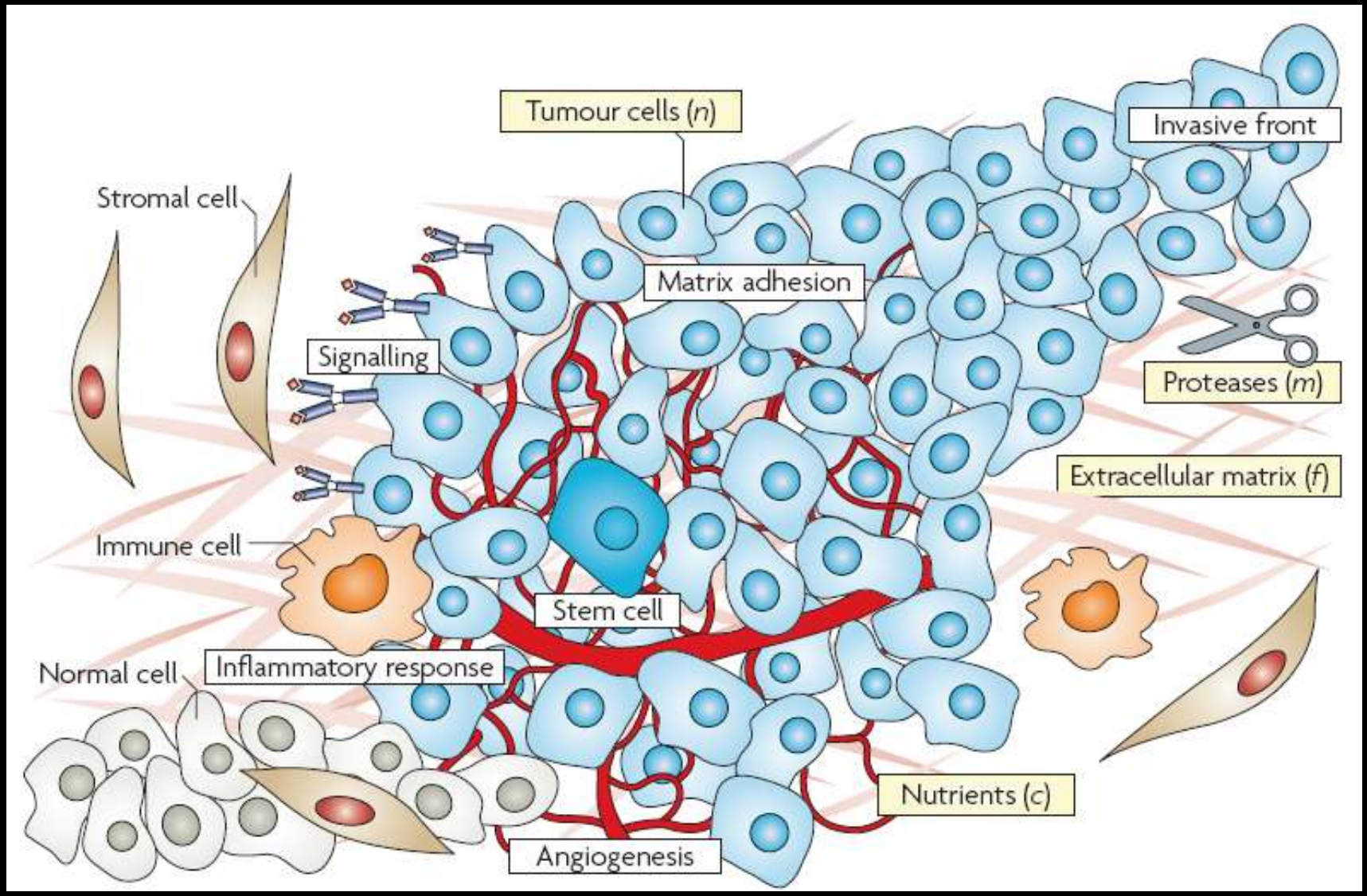
Has the Time Come to Rethink Rx Strategies in Cancer?

- defining Rx efficacy
  - DFS versus OS
  - molecular profiling and disease subphenotypes
- the looming cost:benefit debate
  - aging population demographics
  - NICE (UK), QALYS and econometric decisions
- are our current chemo-/bio-therapeutic approaches to cancer treatment conceptually flawed?
  - clonal heterogeneity and rapid adaptive plasticity as fundamental barriers to design of effective Rx

Has the Time Come to Rethink Rx Strategies in Cancer?

- merits of exploration of new therapeutic paradigms based on ‘biological control’
- cytostatic and cytotoxic agents
  - persistent problem of breakthrough of resistant clones
- cancer stem cells
  - elusive phenotype(s)
  - lack of information on emergence, regulation and molecular signatures for Dx and Rx discovery
- cancer as a dysregulation of histiotypic homeostasis
  - feasibility of engineering control by restoration of histiotypic regulatory signals?

The Complex Microenvironmental of Neoplasms

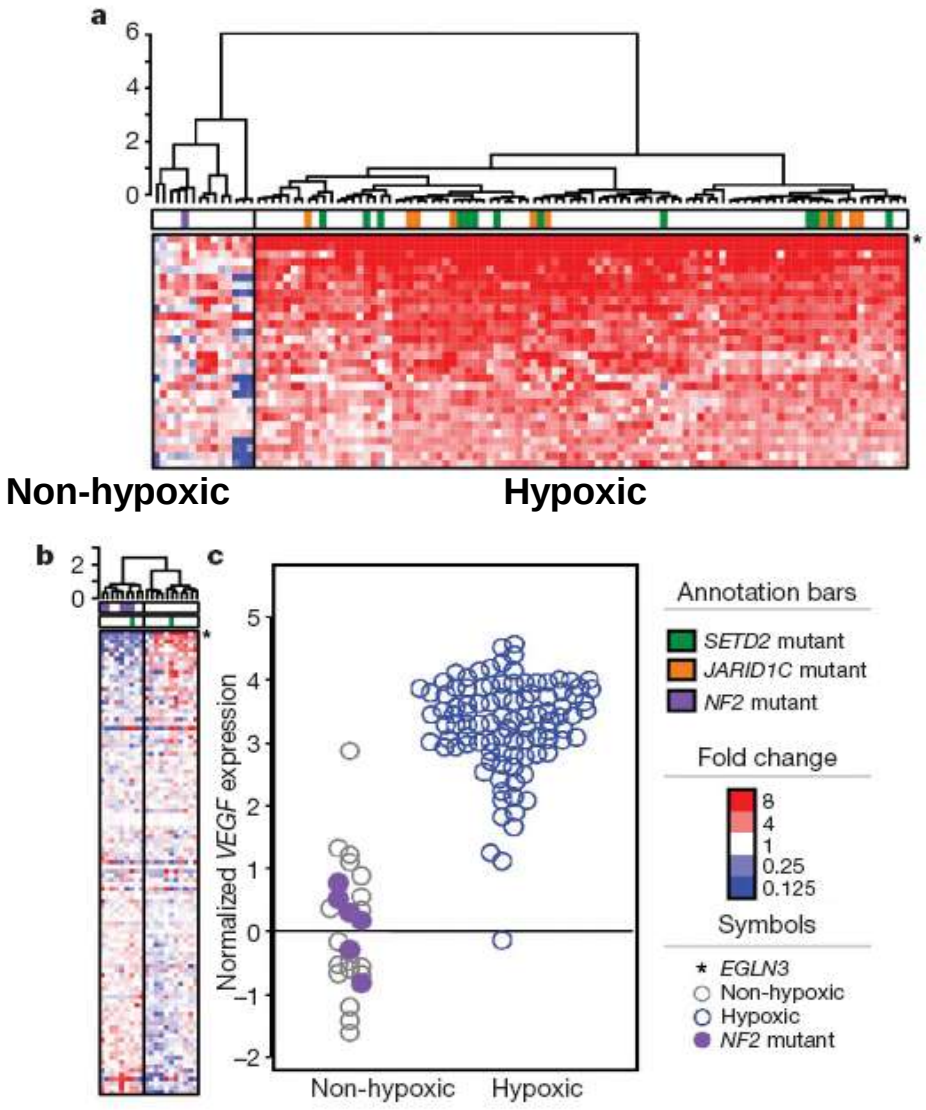


From: A. R. A. Anderson and V. Quaranta (2008) Nature Reviews Ca. 8, 227

Tumor Cell-Host Stroma Cell Interactions

- complex microenvironment
  - tumor cell adhesion, proliferation, invasion
  - evasion of host defenses
  - response to Rx: pharmacodynamics and pharmaokinetics
- roles of hypoxia, inflammatory mediators, cytokines and growth factors in tumor progression
- epithelial-stromal cell interactions as regulators of EMT and MET
- EMT and induction of stem cell-like properties and behavior
- role of non-coding RNAs in EMT/MET

Effect of Hypoxia on Gene Expression in Clear Cell Renal Cell Carinoma



From: G. L. Dalgliesh et al. (2010) Nature 463, 360

The Microenvironment in Metastases

- tissue tropism
- establishment of pre-metastatic niche primed for tumor seeding?
- recruitment and differentiation of BMDCs
  - kinetics and challenges of tumor/dormancy metastatic latency
- interaction between primary tumor and metastases
- protective niches for tumor dormancy

Confronting the Cancer Challenge

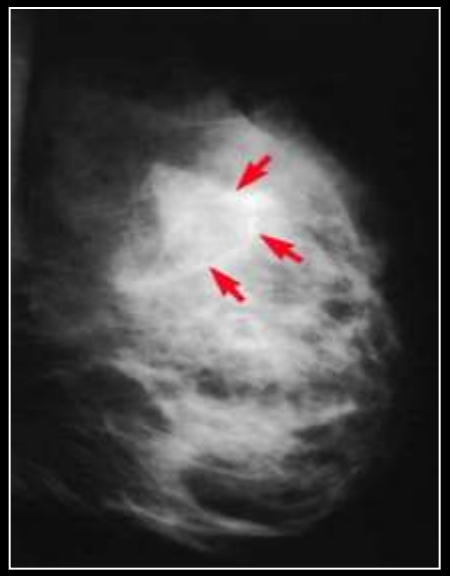
Selection

The Complex Evolutionary Ecology of Malignant Neoplasms

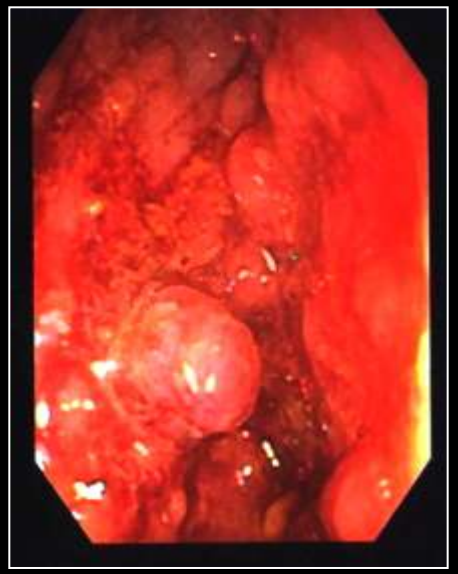
- rapid evolution of phenotypic heterogeneity in primary tumor by clonal drift
- majority of clones in early stage primary lesions are non-metastatic
- eventual emergence of clones with metastatic phenotypes
- initial metastatic dissemination and patterns of organ colonization are non-random and follow consistent patterns (seed and soil)
- circulating tumor cell burden does not correlate with timing or burden of metastatic disease
- metastatic disease can arise at long intervals (years) after apparent success in treating primary tumor (dormancy hypothesis)
- metastatic ‘storms’ can arise in some settings often after removal of primary tumor
- ‘dormancy’ and ‘storms’ suggest metastatic cells can be quiescent in organs

Have We Ignored the Biology of Tumor Progression in Our Approaches to Cancer Screening

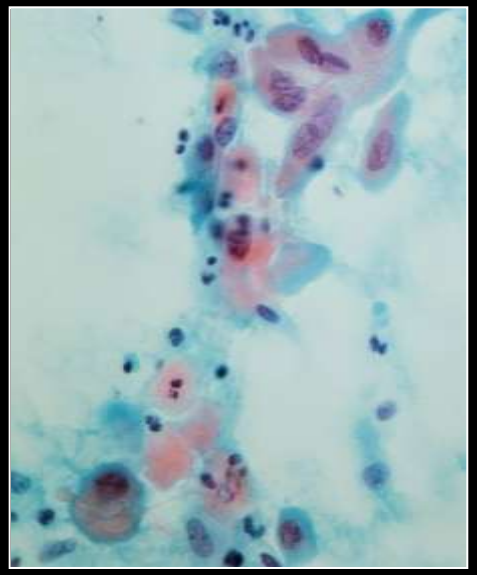
Prostate



Breast



Colon



Cervix

Have We Ignored Differences in Patterns of Tumor Progression in the Design of Breast and Prostate Cancer Screening Programs?

- L. Esserman et. al. (2009) JAMA 312, 1685-92
- Gil Andriole (2009) NEJM 360, 1310
- screening increases detection of early disease

but

incidence of disseminated fatal disease not reduced commensurately

- suggests potential overtreatment for low risk indolent lesions

and

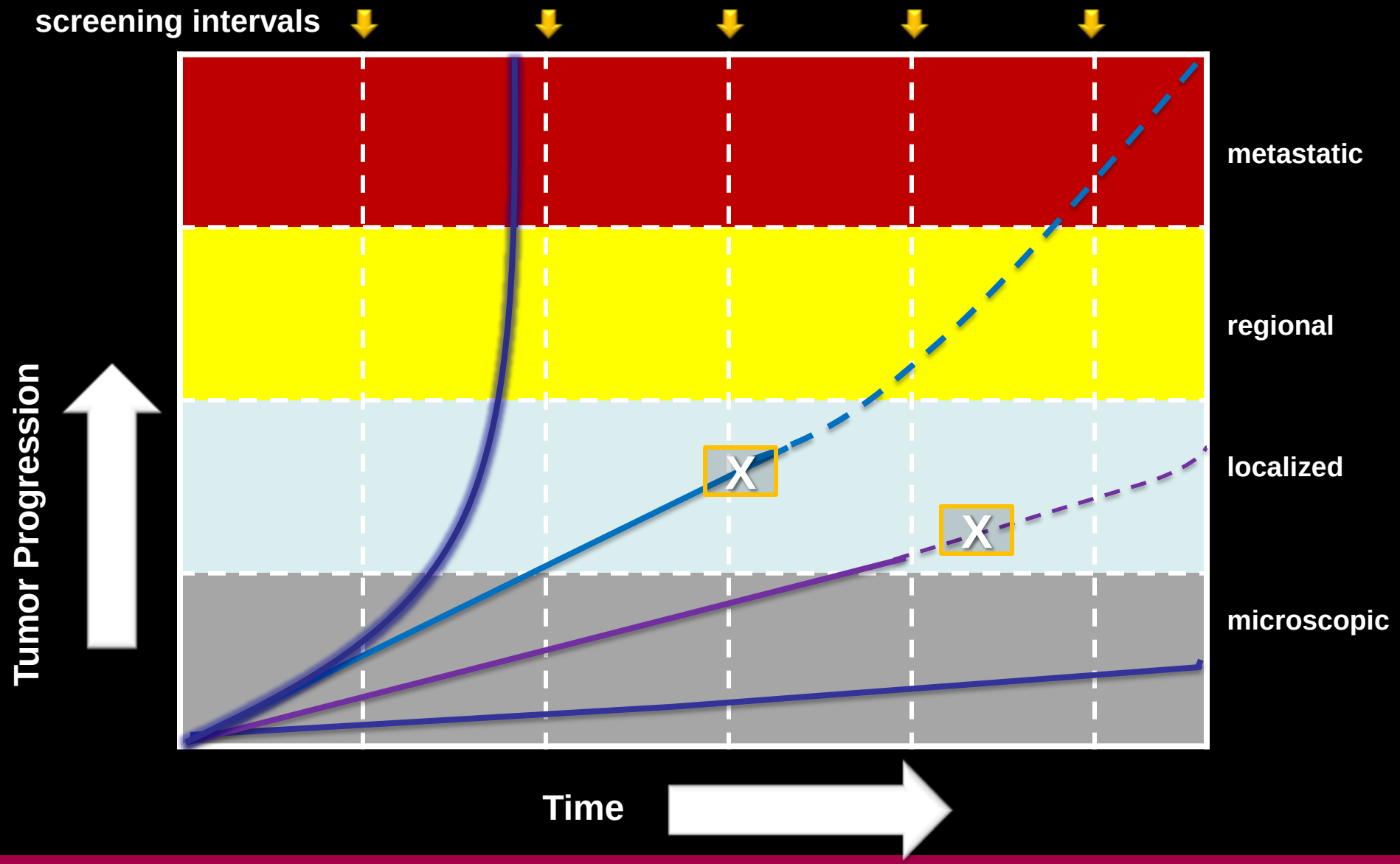
screening intervals insufficient to detect aggressive lethal tumors arising as 'inter-interval' events

- concept consistent with identification of small fraction of small, early breast cancers classified as low risk by NCI criteria but as high mortality risk by NKI 70 gene test

and

I-SPY trial data with 85% malignancies were inter-interval cancers and only 15% detected in routine screening

Effectiveness of Cancer Screens Based on Different Patterns of Tumor Biology and Screening Intervals



Proc. Natl. Acad. Sci. USA
Vol. 78, No. 10, pp. 6226–6230, October 1981
Cell Biology

Interactions among clonal subpopulations affect stability of the metastatic phenotype in polyclonal populations of B16 melanoma cells

(cancer/cellular interactions/phenotypic regulation/growth control)

GEORGE POSTE*†, JOHN DOLL*, AND ISAIAH J. FIDLER‡

*Department of Tumor Biology, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101; †Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104; and ‡Cancer Metastasis and Treatment Laboratory, National Cancer Institute–Frederick Cancer Research Center, Frederick, Maryland 21701

Communicated by Peter C. Nowell, May 4, 1981

Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 6574–6578, November 1982
Cell Biology

Evolution of tumor cell heterogeneity during progressive growth of individual lung metastases

(cancer/phenotypic stability)

GEORGE POSTE*†, JAMES TZENG†, JOHN DOLL*, RUSSELL GREIG*, DAVID RIEMAN*, AND IRVING ZEIDMAN†

*Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101; and †Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Communicated by Sidney Weinhouse, August 4, 1982

The Complex Evolutionary Ecology of Malignant Neoplasms: Patterns of Phenotypic Drift in B16 Melanoma Clones

- tumorigenic clones with varied metastatic potential
  - none (T^+M^-), low (T^+M^+L) and high (T^+M^+H)
  - organ-specific clones (T^+M^+lung, liver, brain)
- isolated T^+M^- clones exhibit high mutation rates and phenotypic drift
- rapid phenotypic drift modulated with evolution of polyclonal heterogeneity in primary lesion/in vitro co-culture
- T^+M^+L clones in heterogenous primary lesion/co-culture exhibit similar constrained drift
- successful colonization of distant organ by T^+M^+L clone reignites rapid phenotypic drift
- genesis of polyclonal heterogeniety in metastatic lesion restores slow phenotypic drift

The Complex Ecology of Malignant Neoplasms: Patterns of Phenotypic Drift in B16 Melanoma Clones

- clones with high metastatic capabilities (T^+M^+H) exhibit consistent high rates of phenotypic drift
  - co-mixed with T^+M^- and T^+M^+L as implant
  - aerosolized mixed colonies
  - co-cultivation in vitro
  - “non-stabilizable” phenotypes
- uniform refractoriness of M^+H clones to modulation indicates loss of pathways for “homeostatic signal cognition”
- ability of some M^+H clones to modulate rapid drift in T^+M^- and T^+M^+H clones suggests that “homeostatic” signal transmission pathways are retained even when signal cognition is lost

The Complex Clonal Ecology of Malignant Neoplasms
Patterns of Phenotypic Drift in B16 Melanoma Clones

Clonal Phenotype	Modulation of Rapid Phenotypic Drift by Co-Cultivation			
	Normal fibroblasts	T^+M^-	T^+M^+L	T^+M^+H
T^+M^-	Yes	Yes	Yes	
T^+M^+L	Yes	Yes	Yes	
T^+M^+H	No	No	No	No

Proposed Evolution of Clonal Autonomy from Histiotypic Regulatory Signals in Tumor Progression

Stage of Progression	Phenotypes	Rate of Drift
• initial neoplastic nidus	T^+M^-	rapid
• detectable primary tumor		
- step one	T^+M^-	slow
- step two	T^+M^+	slow
• initial wave of metastatic seeds	T^+M^+L	rapid
• evolved initial metastatic lesions	T^+M^+L	slow
• advanced primary tumor	T^+M^-	slow
	T^+M^+L	slow
	T^+M^+H	rapid
• subsequent metastatic waves	T^+M^+H	rapid

Chemical Mediators in Biological Homeostasis

- endocrine
- paracrine
- autocrine
- juxtacrine

Chemical Mediators in Biological Homeostasis

- endocrine
- paracrine
- autocrine
- juxtacrine
- vesicular
  - microvesicles
  - exosomes

Proc. Natl. Acad. Sci. USA
Vol. 77, No. 1, pp. 399–403, January 1980
Cell Biology

Arrest and metastasis of blood-borne tumor cells are modified by fusion of plasma membrane vesicles from highly metastatic cells

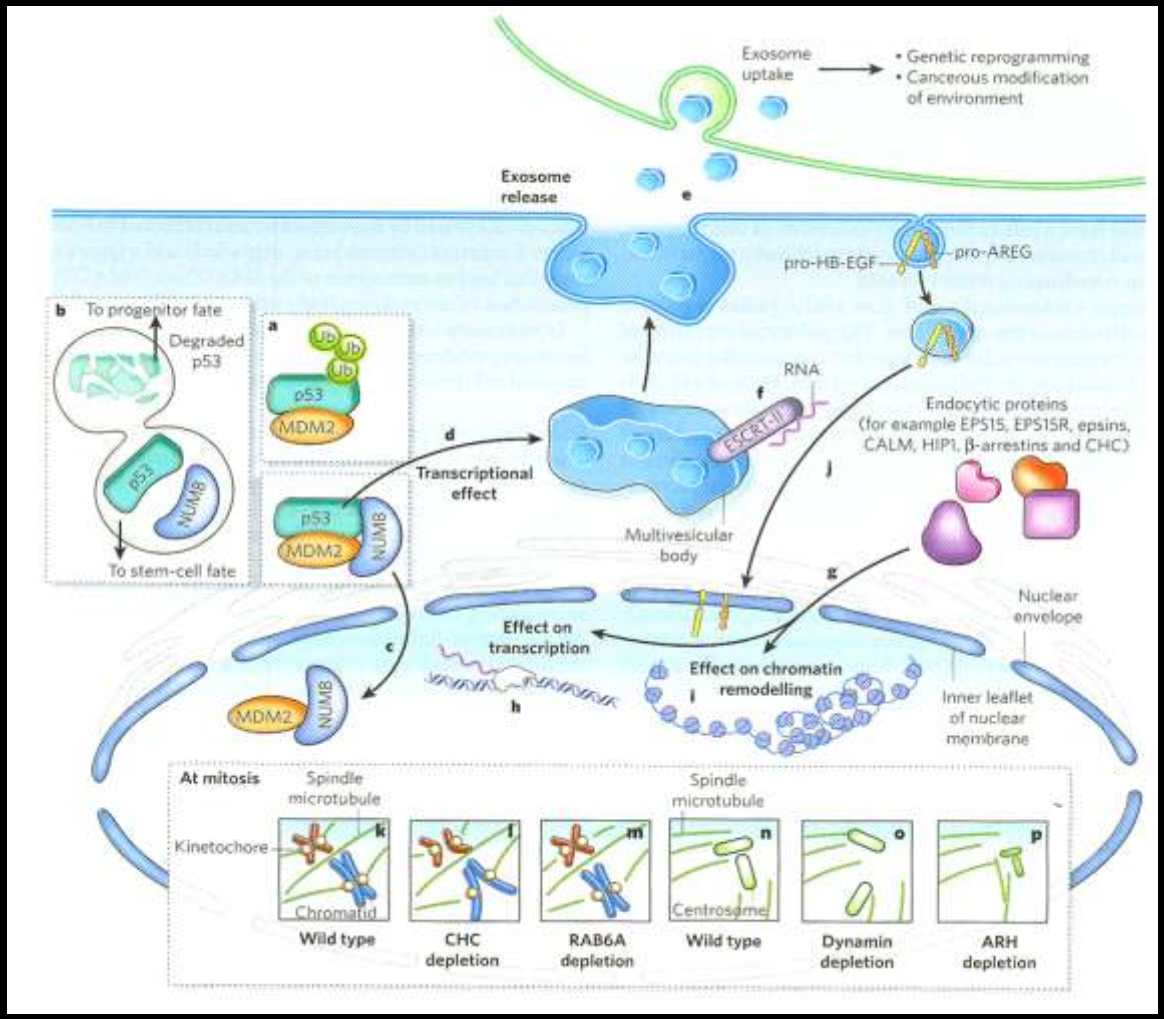
(cancer/cell surface/cell recognition/blood vessels)

GEORGE POSTE* AND GARTH L. NICOLSON†

*Department of Experimental Pathology, Roswell Park Memorial Institute, Buffalo, New York 14263; and †Departments of Developmental and Cell Biology, and Physiology, College of Medicine, University of California, Irvine, California 92717

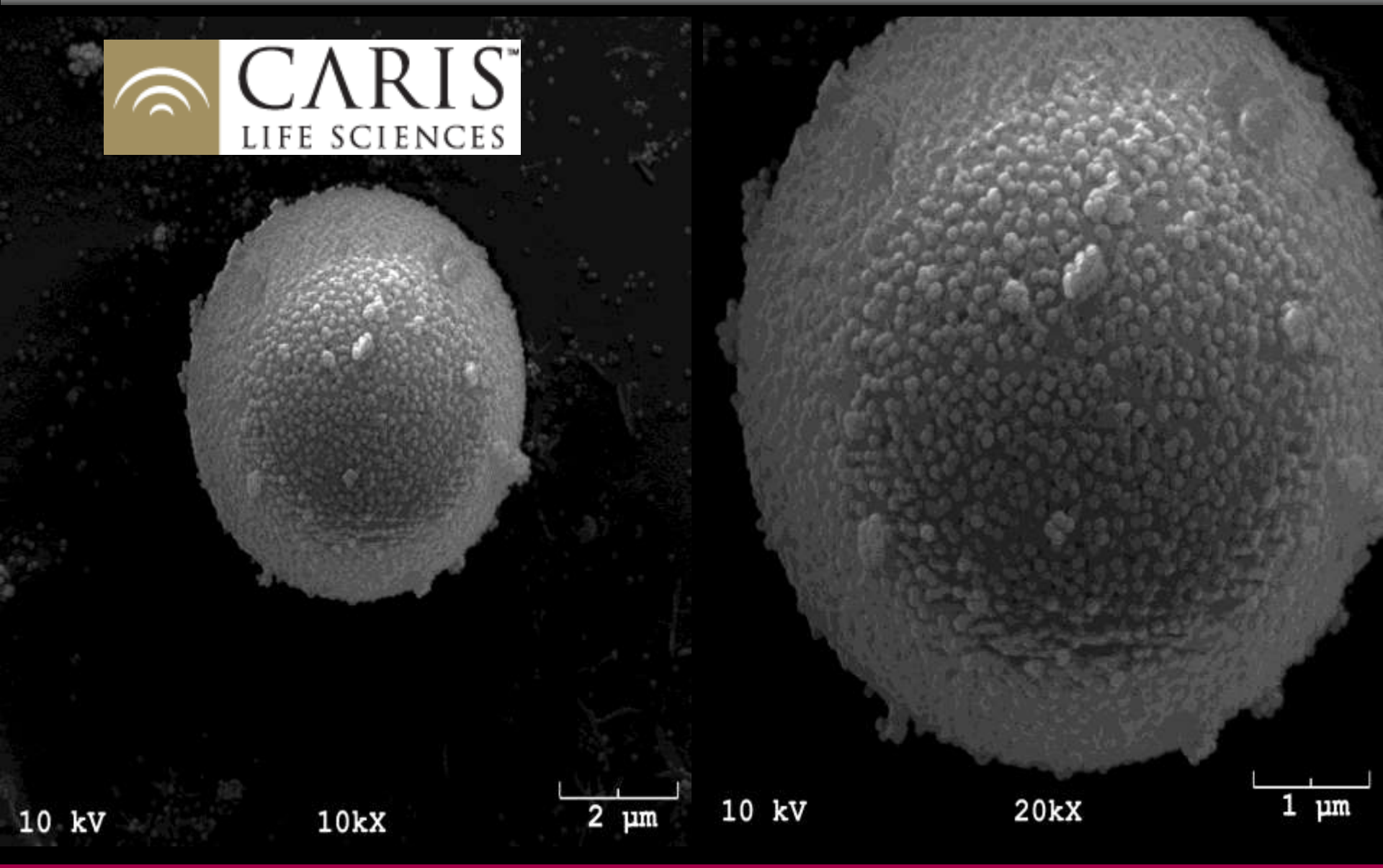
Communicated by Donald A. Glaser, October 1, 1979

Endocytic Membrane Traffic Flows



From: G. Scita et al. (2010) Nature 463, 469

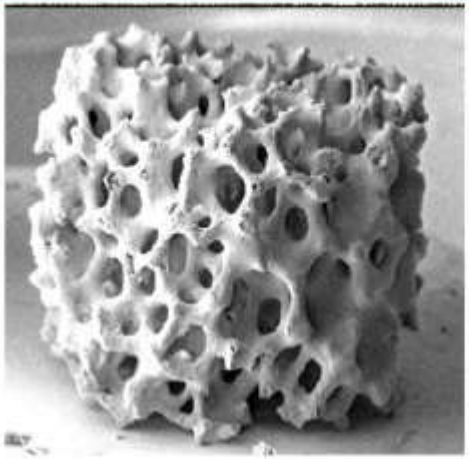
Antibody-Mediated Capture of Tumor-Derived Exosomes from Human Prostate Cancer Cells



Exploration of the Role of Exosomes in Tumor Progression

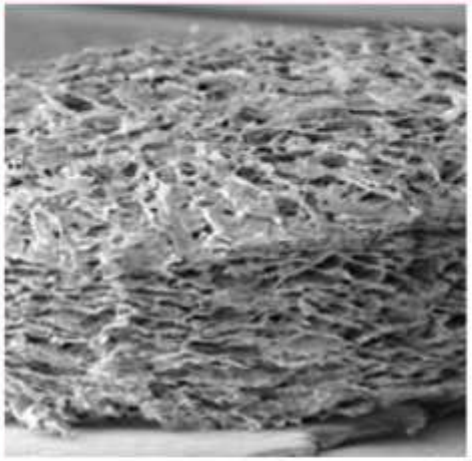
- cancer-specific signatures
  - miRNA, mRNA, proteins
  - identify tissue of origin
  - ‘cargo’ changes with progression
- role in modulating host immune defenses?
- role in epithelial-mesenchymal transition?
- role in ‘preconditioning’ of organs for metastatic seeding?
- potential value in Dx?
  - minimally invasive versus biopsy
  - longitudinal disease monitoring in patients
- potential value as markers of Rx response/resistance/relapse?

3D – Macroscaffolds as Derivatized Substrates for Evaluation of Tissue Specific Histiotypic Regulatory Mediators to Control Neoplastic Progression

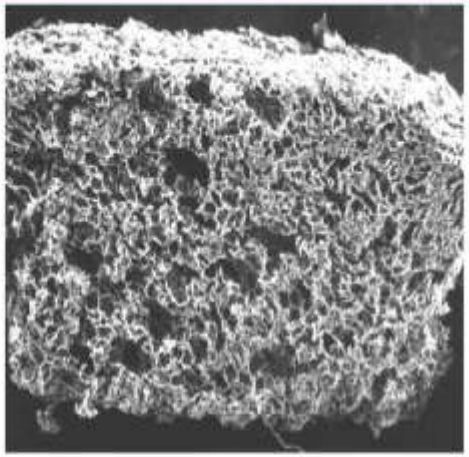


BD™ 3D Calcium Phosphate Scaffold

Cell types: *bone, cartilage*



BD™ 3D Collagen Composite Scaffold



BD™ 3D OPLA® Scaffold

Cell types: *epithelial, endothelial, smooth muscle, neuronal, bone, cartilage*

Skelite is a trademark of Octane Orthobiologics, Inc., Ontario, Canada. Collagen Composite and OPLA Scaffolds are proprietary biomaterials of Kensey Nash Corporation; OPLA is a registered trademark of Kensey Nash Corporation.

BD

Embracing 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

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
- lack of academic understanding of translational research: "the valley of dearth" → stringent funding criteria for obligate assembly of full expertise spectrum; new clinical training/ medical curriculum