What Needs to Be Done Differently in Cancer Control?

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**NASEM Public Workshop
How To Transform Cancer Control
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Washington, D.C.**

ASU Complex Adaptive Systems Initiative
Arizona State University

The National Academies of Sciences Engineering Medicine

Confronting the Clinical, Economic and Human Toll of Cancer

New Diagnoses: 1.68 million (2017)

Deaths: 600,920 (2017)
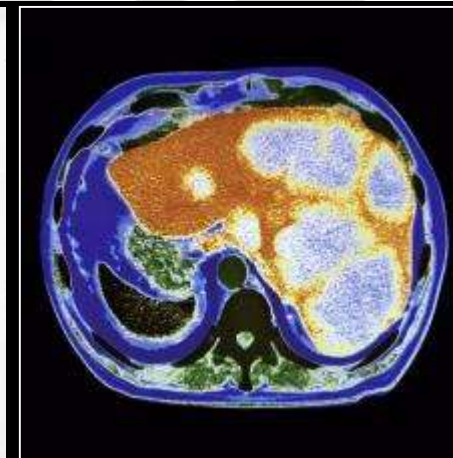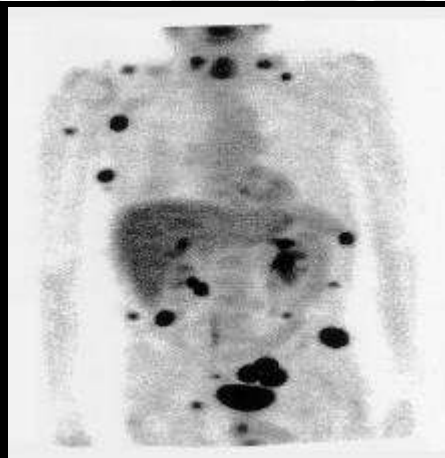
Cancer as a Complex Adaptive System

The Difference Between Complicated Systems and Complex Adaptive Systems

Complicated Systems:
Human Design and Engineering

- **behavior of the assembled system is predictable from the properties of the components**

- **proactive awareness of tolerance limits and most likely failure points**

- **system performance is fixed and not capable of autonomous evolution**
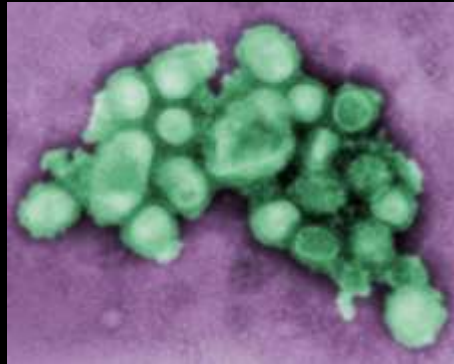
- **low degrees of design freedom**

Complex Adaptive Systems:
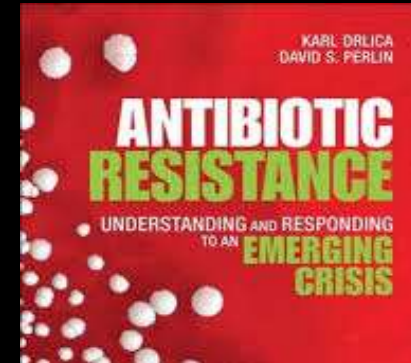## Fundamental and Ubiquitous Design Principles of Natural Systems

| weather/climate	epidemics/ pandemics	disease pathogenesis	Rx resistance

- **system behavior not predictable from knowledge of the properties of individual subcomponents**
- **dynamic behavior defined by constantly changing interactions between components in response to external inputs**
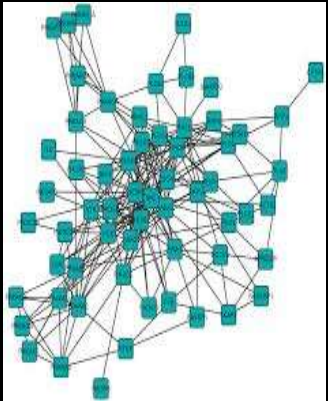- **robust, adaptive, evolvable**

Infectious Disease and Cancer as Prototypic Complex Adaptive Biological Systems
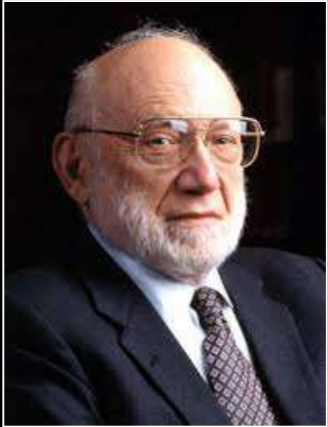
- **outpacing (not conquer!) infectious disease**

- **"a battle between their genes and our wits"**

     Joshua Lederberg, Nobel Laureate

DITTO CANCER

- **cancer as a complex adaptive system**

- **characterization of perturbations in molecular (information) networks**
  - **disease predisposition and evolution of adaptive disease progression and treatment resistance**

- **need for innovative ADAPTIVE APPROACHES TO CANCER CONTROL that address the dynamics of cancer as a CAS**

Comparison of Status of Control Strategies for Infectious Disease and Cancer as Prototypic Complex Adaptive Systems

parameter	infectious disease	cancer
need for integrated end-to-end control systems	yes (well-developed)	yes (siloed, fragmented)
threat screening and detection	yes (global surveillance)	yes (erratic success)

Comparison of Status of Control Strategies for Infectious Disease and Cancer as Prototypic Complex Adaptive Systems

parameter	infectious disease	cancer
relative rate of threat evolution (emergence of resistance)	slow (when assessed in public health terms)	high (patient lifetime)
treatment (if available)	uniform	multiple-Rx regimens plus wide variation in clinical practice

The Challenge for Comprehensive Cancer Control

- **addressing cancer as a complex adaptive system (CAS)**

- **cancer is a biological CAS embedded within a constellation of multiple other complex adaptive systems (life style, environmental exposures, patterns of care, public policy) whose interactions influence disease risk and the evolutionary dynamics of disease emergence and progression**

mapping disease mechanisms

public health and clinical care

priorities

biological complexity (the health to disease continuum)

implementation complexity (improved prevention, outcomes, detection and treatment)

policy complexity (infinite demand versus finite resources)

- public and political expectancy of meaningful progress
- demographics, escalating disease burden, insufficient clinical infrastructure and economic unsustainability
- political, ethical and legal implications of cost of care, and limits on care services

Precision Oncology

(Epi)Genomics

Causal Relationships Between Disruption of Molecular Signaling Networks and Disease
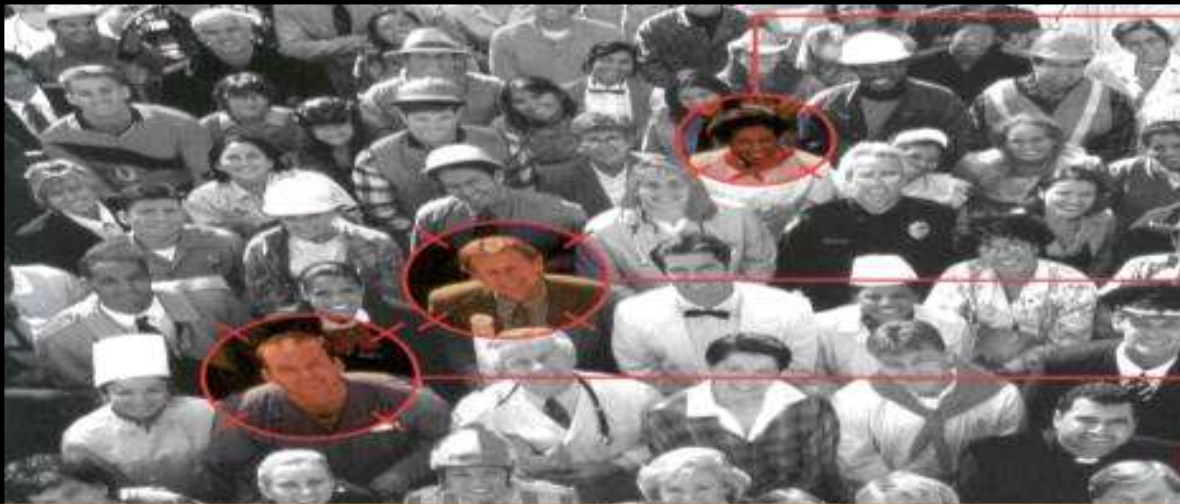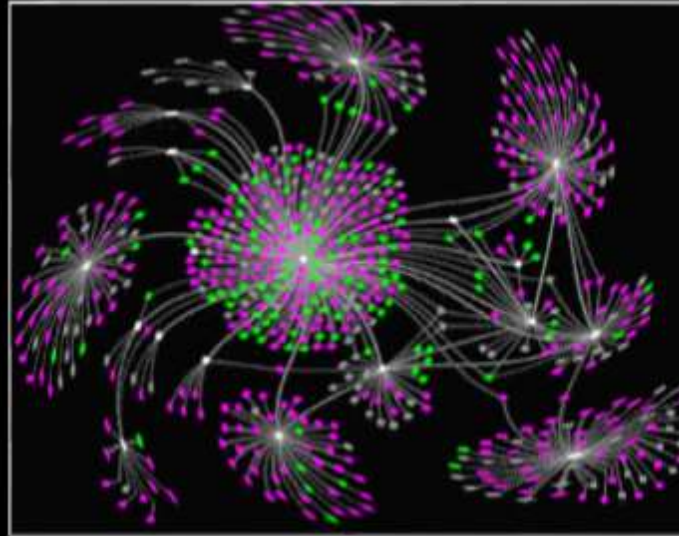
- **terabytes per individual**
- **zettabyte – yottabyte population databases**

Patient-Specific Signatures of Predisposition to Disease or Overt Disease

Big (Messy) Data

the myopic, reductionist uni-dimensional
focus on (epi)genome sequencing
(in fact very limited epigenomic data to date)

necessary but not sufficient

deep phenotyping: longitudinal integration of molecular,
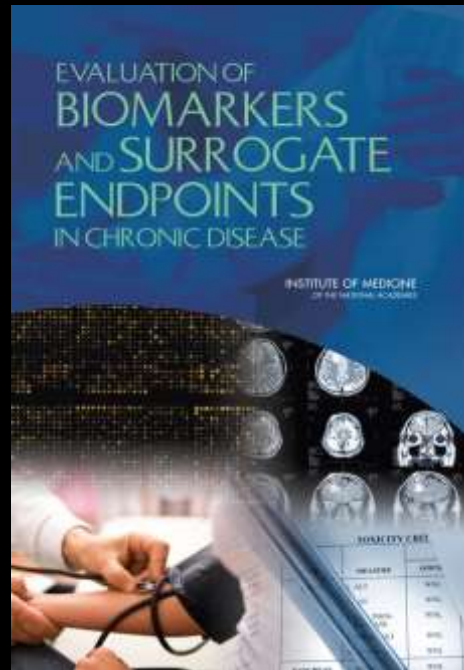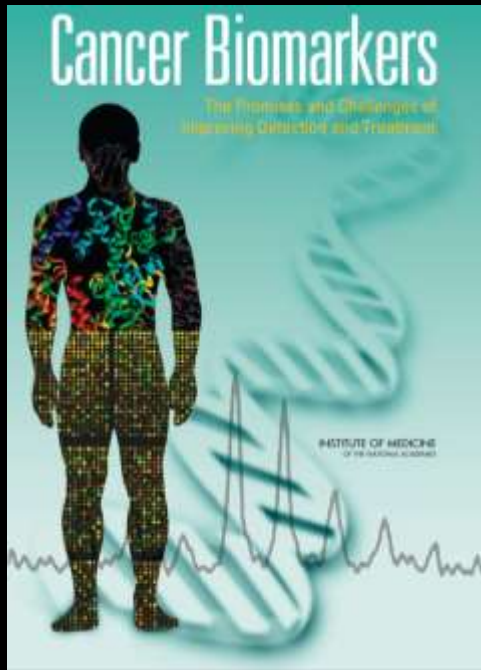clinical, environmental and socio-cultural data

longitudinal, dynamic data capture
versus
Isolated static snapshots

The Need for Rethinking Molecular Diagnostic and Therapeutic Strategies to Combat Cancer

Biomarkers:
The Core Technology Component of Precision Oncology

- **disease predisposition markers**
- **molecular taxonomy of cancer subtypes**
- **new clinical trial designs**
- **companion Dx for target-centric Rx choice**
- **prediction of Rx response/resistance**

Biomarkers:
The Core Technology Platform in Making Precision Oncology a Reality

- **profound mismatch between intellectual rationale and limited availability of validated biomarkers**

- **poor productivity and reproducibility of biomarker research (publish and vanish)**

- **insufficient R&D investment (public and private sectors)**

- **escalating cost of trials for multiplex biomarker validation and reimbursement barriers**

- **insufficient minimally invasive/imaging technologies for dynamic longitudinal monitoring of health to disease continuum profiling**

  – **static snapshots of dynamic disease progression**

  – **promise of liquid biopsy (ctDNA, CTC) not yet validated**

Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors
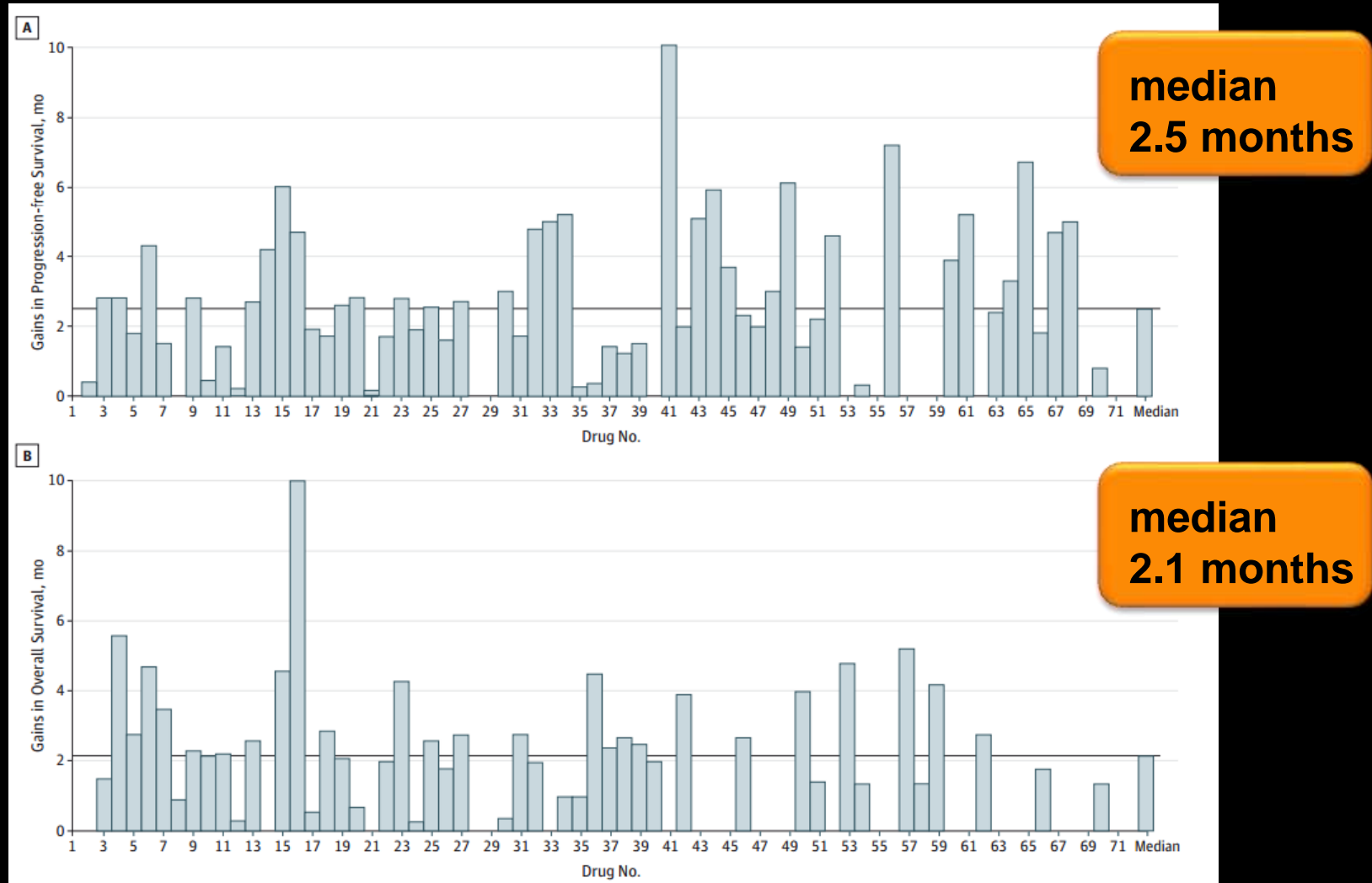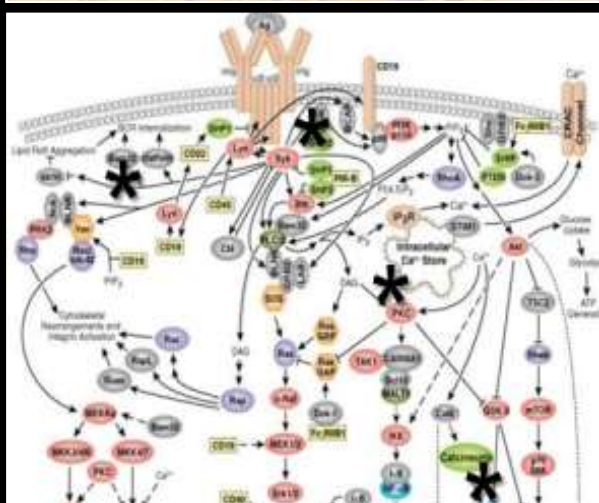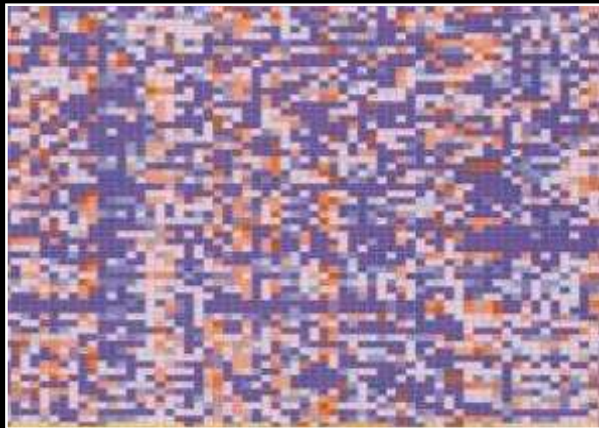

From: T. Fojo et al. (2014) JAMA Otolaryngology–Head & Neck Surgery 140, 1225

Targeted Therapeutics and the Omnipresent Problem of R_x Failure Due to Emergence of Drug Resistance Clones

| Molecular Subtyping and R_x Targets	Initial R_x - Response to Targeted R_x	R_x - Resistance via Redundant Molecular Pathways

B = 15 weeks R_x (vemurafenib)

C = 23 weeks R_x and emergence of MEK1^{C121S} mutant

Wagle N, et al. *J Clin Oncol*. 2011;29(22),3085-3096.

Cancer R_x: Ugly Realities

- **in the majority of cancers the efficacy of R_x therapies (except immunotherapies) is either short-lived or completely ineffective**

- **mutations that confer R_x resistance may pre-exist prior to treatment (intrinsic resistance) or arise during treatment (acquired resistance)**

- **mutations are typically present in multiple pathways**

- **intrinsic and/or acquired mutations in non-targeted pathways can enable 'by-pass' signaling circuits that ensure tumor cell survival and ever-broadening resistance R_x spectrum**

Understanding System State Shifts (Phenomes) and Emergent Perturbations in Molecular Signaling Networks in the Health to Disease Continuum
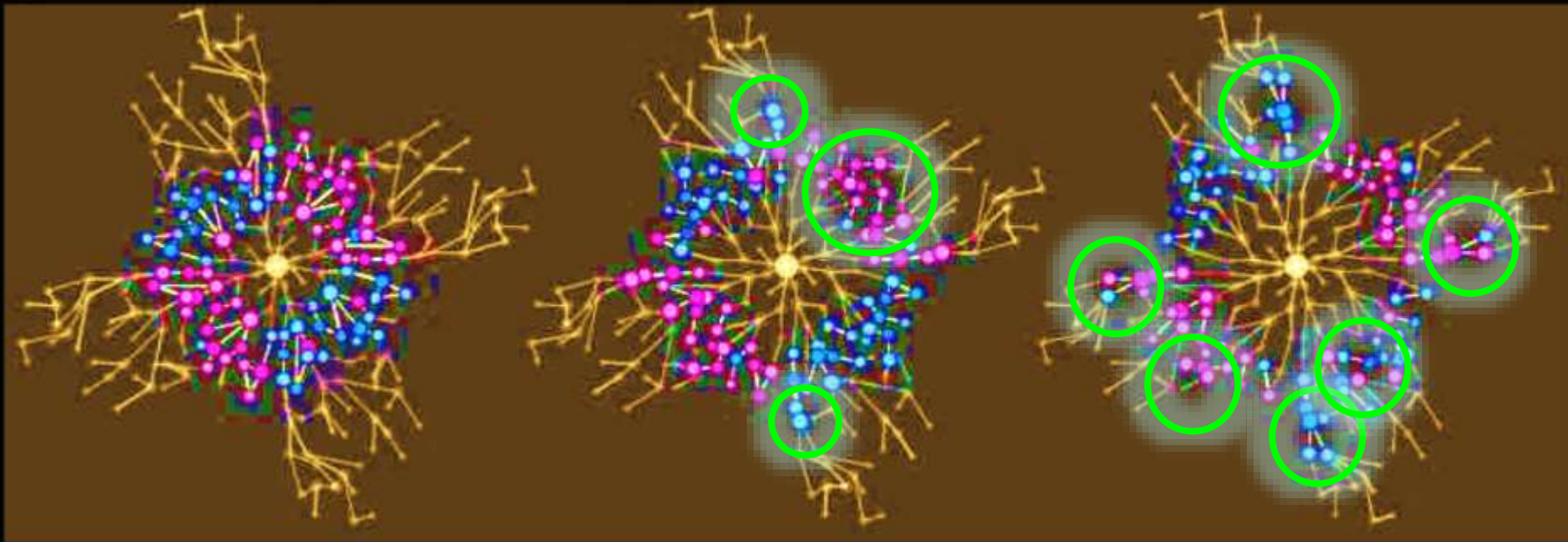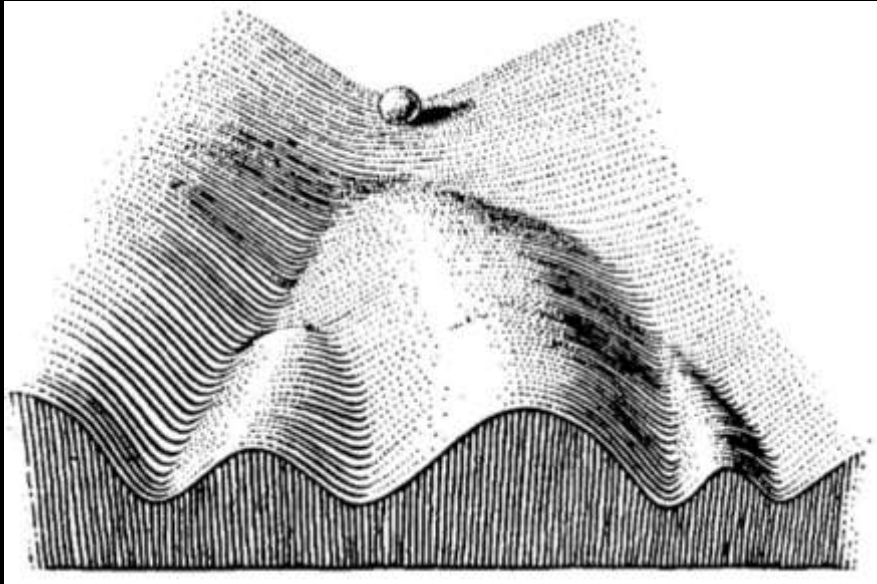

$T_{1(n)}$

health

$T_{2(n)}$

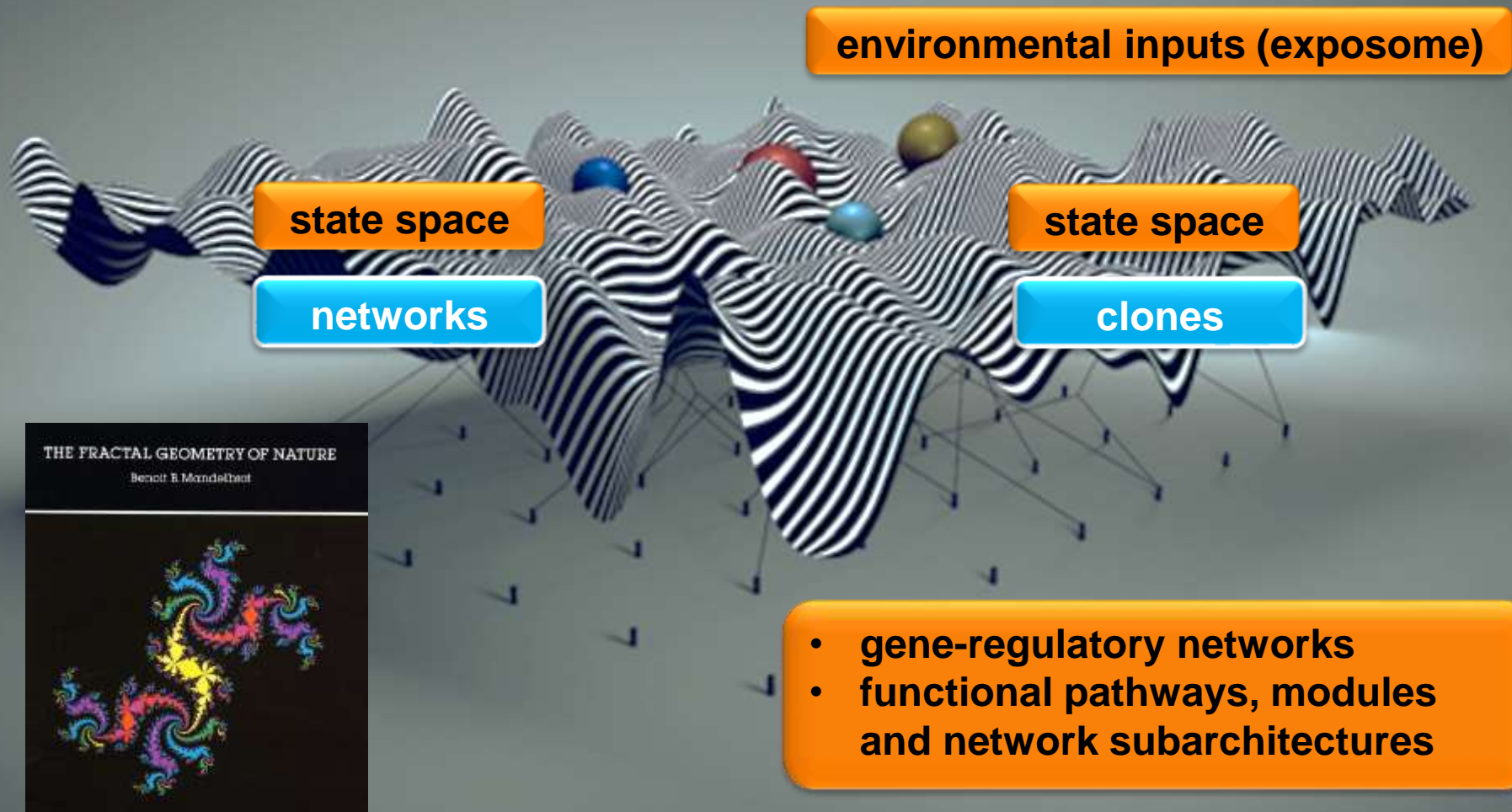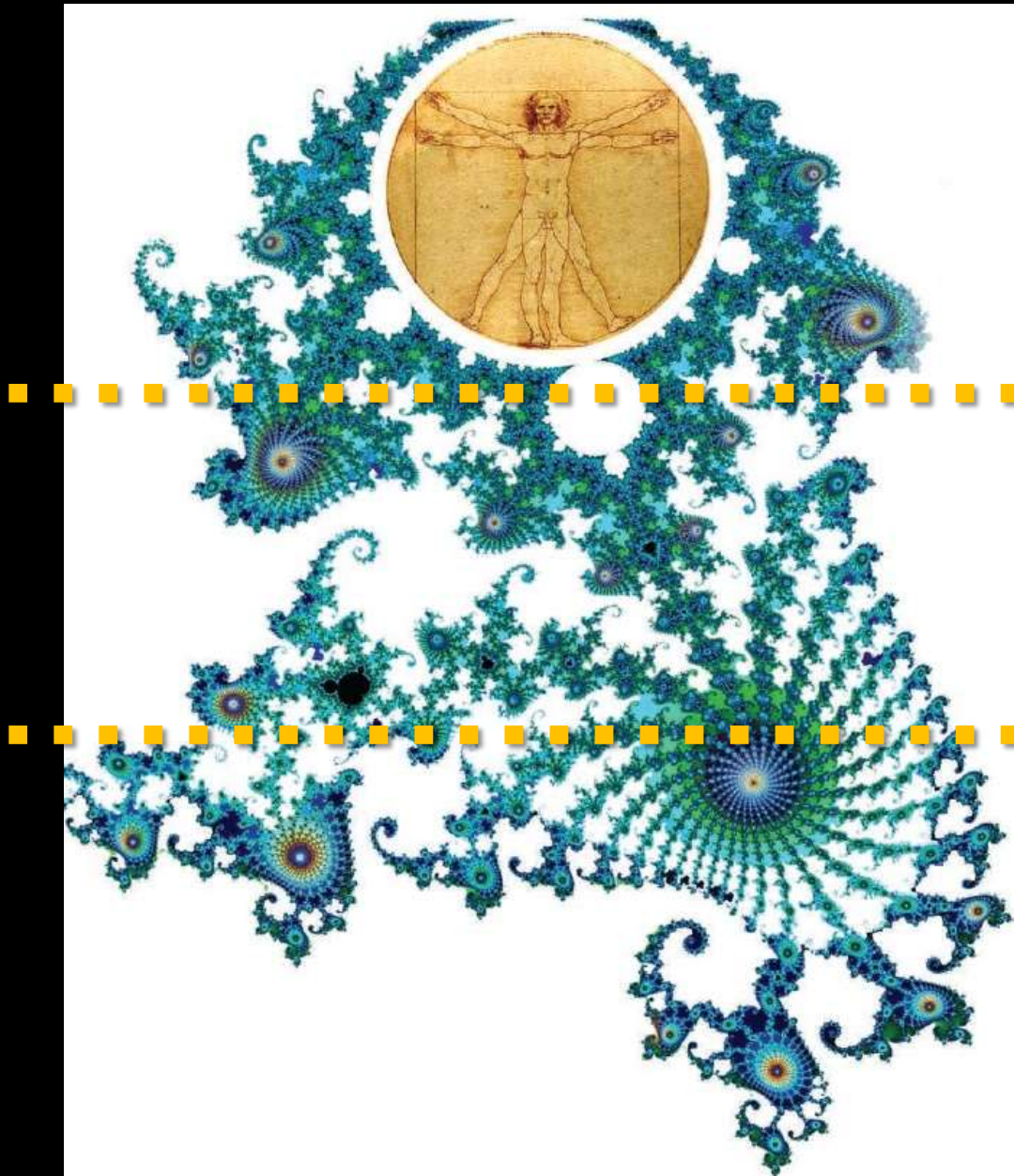subclinical disease

$T_{3(n)}$

overt disease

Multi–Attractor Landscapes and System State Space Occupancies in Biological CAS (After Haldane 1957)

Multi–Attractor Landscapes, State Space Occupancies, and Adaptive, Evolutionary Pathways in CAS

Multi-Attractor CAS Landscapes and State-Space Occupancies in the Health to Disease Continuum
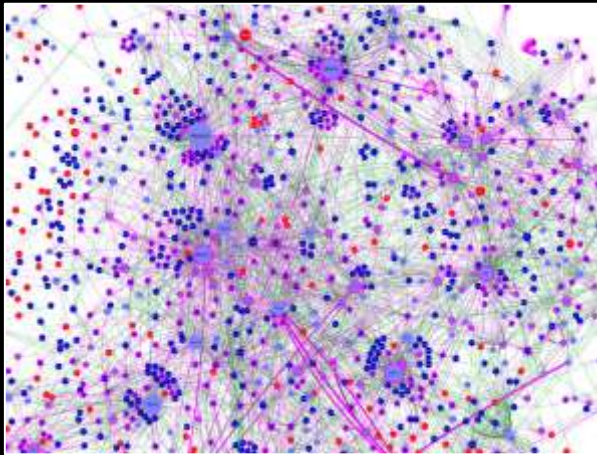

physiology (homeostasis)

- **graded perturbations**
- **disease predisposition and/or subclinical disease**

clinical disease (pathology)

- **disease subtypes and phenotypes**

A Disturbing Question:
Is Unifocal R_x Modulation of Complex Network Dysregulation in Advanced Chronic Diseases Feasible or a Delusion?

- "too disrupted to restore"? (homeostatic reset) ?

- multi-node/multi-module/ multi-subnetwork dysregulation

- low feasibility of multi-R_x intervention against multiple dysregulated targets ?

- even lower feasibility of design of promiscuous multi-target single R_x ?

The Promise of Cancer Immunotherapy
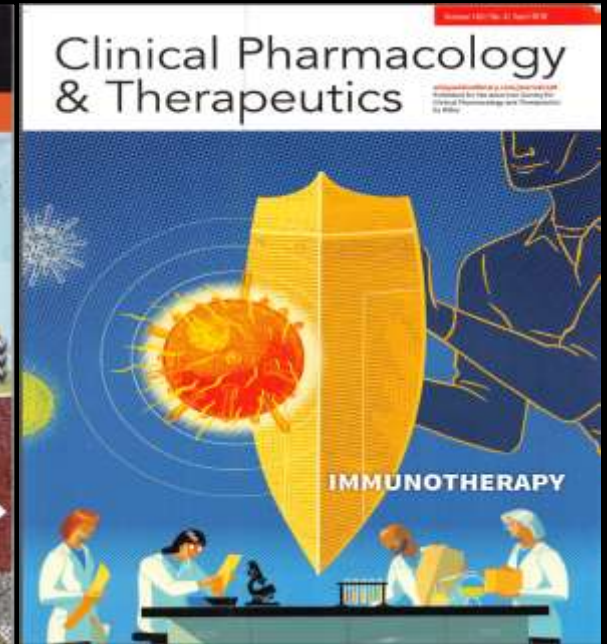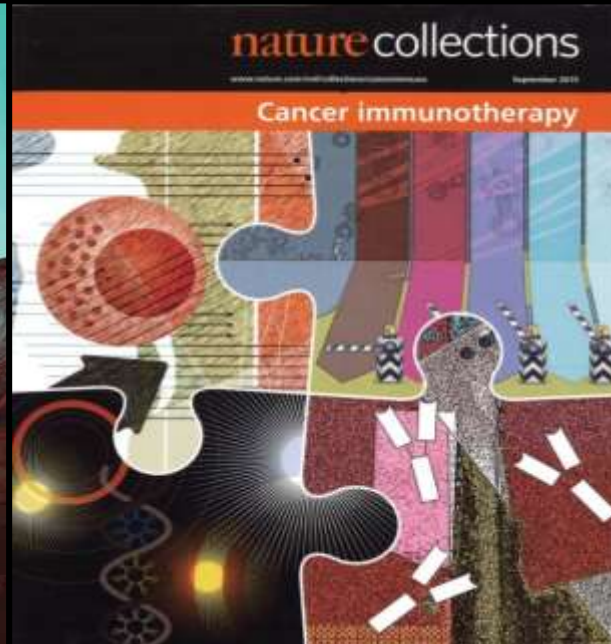
Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Therapeutic Restoration of Effective Immune Surveillance

tumor clones

tumor neoantigens

cytotoxic T cells

Rx_1

Rx_2

Rx_3

Rx_4

Rx_5

NA_1

NA_2

NA_3

NA_4

NA_5

Rx-resistant clones/

Rx refractory disease

NA_n1

NA_n2

adaptive evolution of immune response and expanded cytotoxic T cell responses
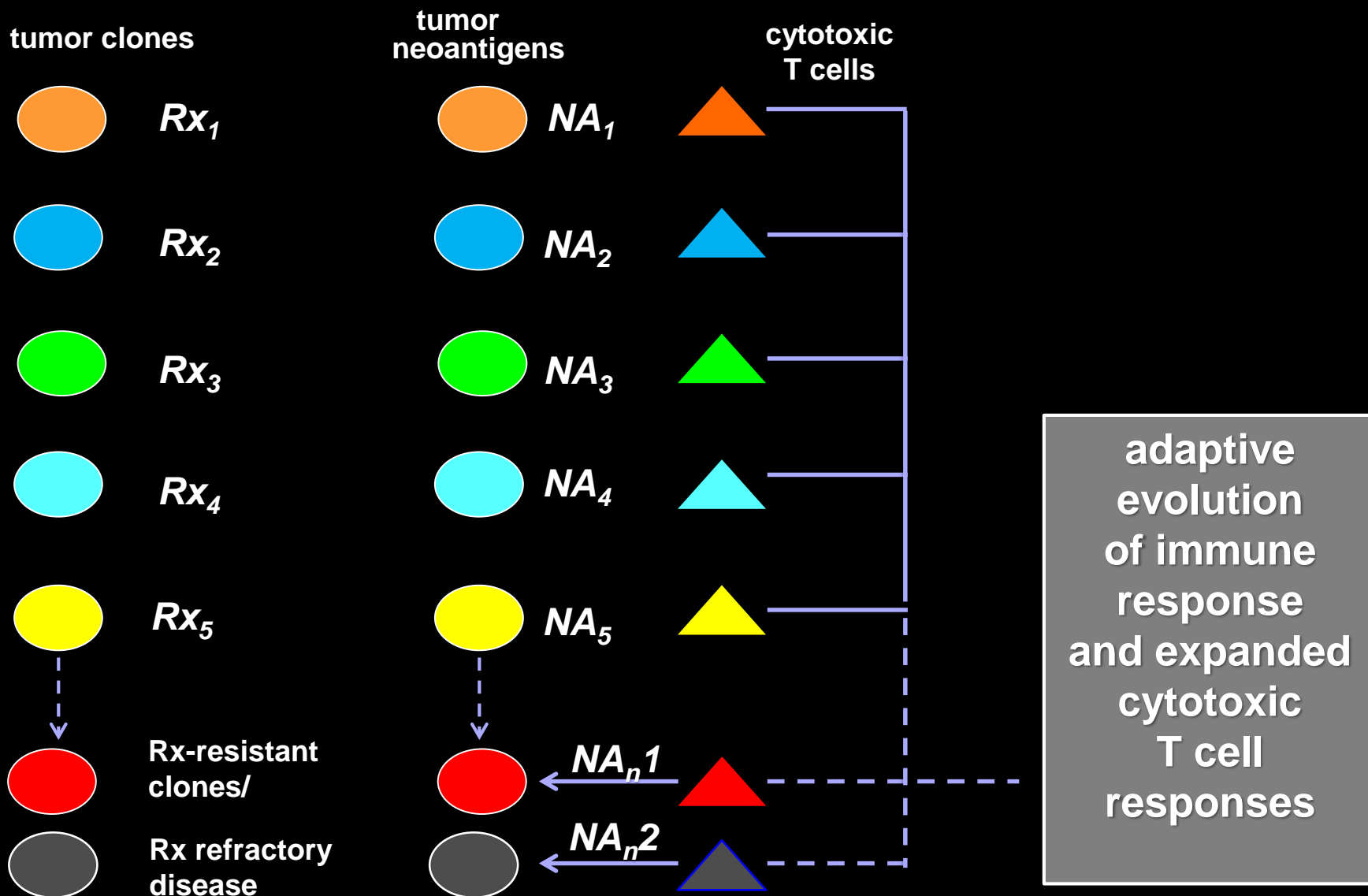
Realizing The Promise of Cancer Immunotherapy

- **wide variation in R_x response rates**

  - only 20 - 40% positive responses even in the most responsive tumors

- **lack of diagnostic tests to reliably predict responder vs. non-responder patients**

- **improving response rates across all malignancies and all stages**

- **will I/O combinations increase response rates?**

Understandable Enthusiasms But With Risk of Considerable Waste in Patient Resources and Expenditure

- proliferation of I/O combination trials absent biological rationale for dose selection, sequence, timing, number of cycles and duration

  - I/O : I/O

  - I/O : chemotherapy

  - I/O : targeted Rx

  - I/O : oncolytic viruses

- patient expectations

  - informed consent vs informed risk

- market saturation and/or performance-based pricing?

The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

TIME magazine cover: "What if your immune system could be taught to kill cancer? Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy. By Alice Park"

- **unit Rx cost ($100 - 400K)**

- **indirect care cost**

- **escalating cost of combination Rx regimens**

- **extravagant cost of cell-based therapies ($500K - $1.5 million)**

- **complex clinical management challenges and compatibility with community oncology services?**

Cancer As a Complex Adaptive System: Legacy of 32 Years of Prescient Perspectives Still Alarmingly Ignored

"It may also be necessary to re-evaluate how cancer is perceived, not only as a disease but as a biological system."

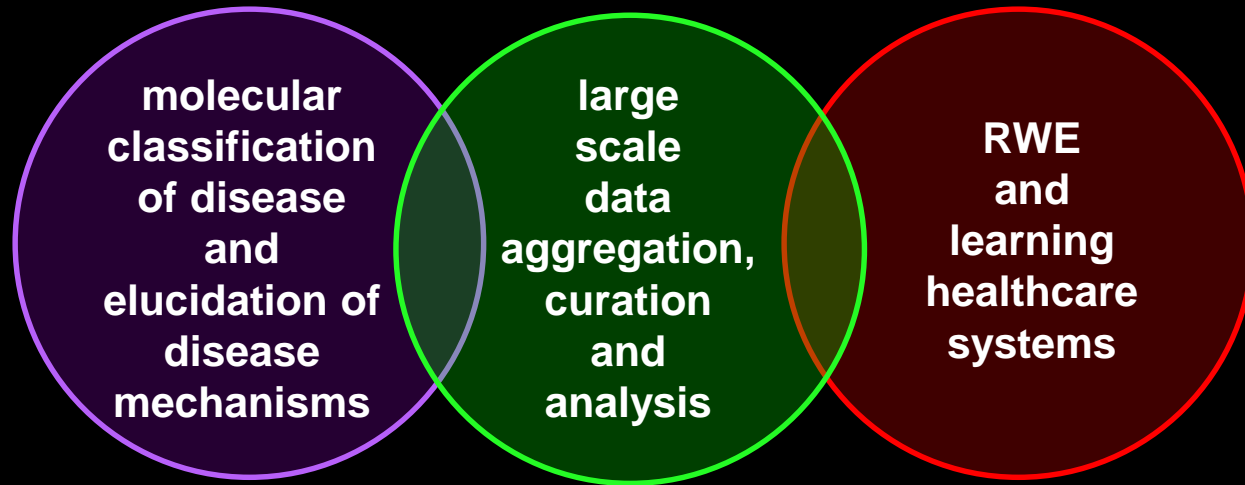E.D. Schwab and K.J. Pienta
Medical Hypotheses (1996) 47, 235

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

Ann Barker (2008)
NCI PSOP Meeting Summary

"Learning to manage cancer is learning to manage the evolutionary process."

Dr. Richard L. Schilsky
CMO, ASCO
Oncology Times 25 June 2014

Precision Medicine and Computational Medicine: Evolving Inter-dependencies

molecular classification of disease and elucidation of disease mechanisms

large scale data aggregation, curation and analysis

RWE and learning healthcare systems

The Big Data Challenge

V6: volume, variety, velocity, veracity, virtualization, value

D3: distributed, dynamic, decision support

I3: infrastructure, investment, intelligent systems

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