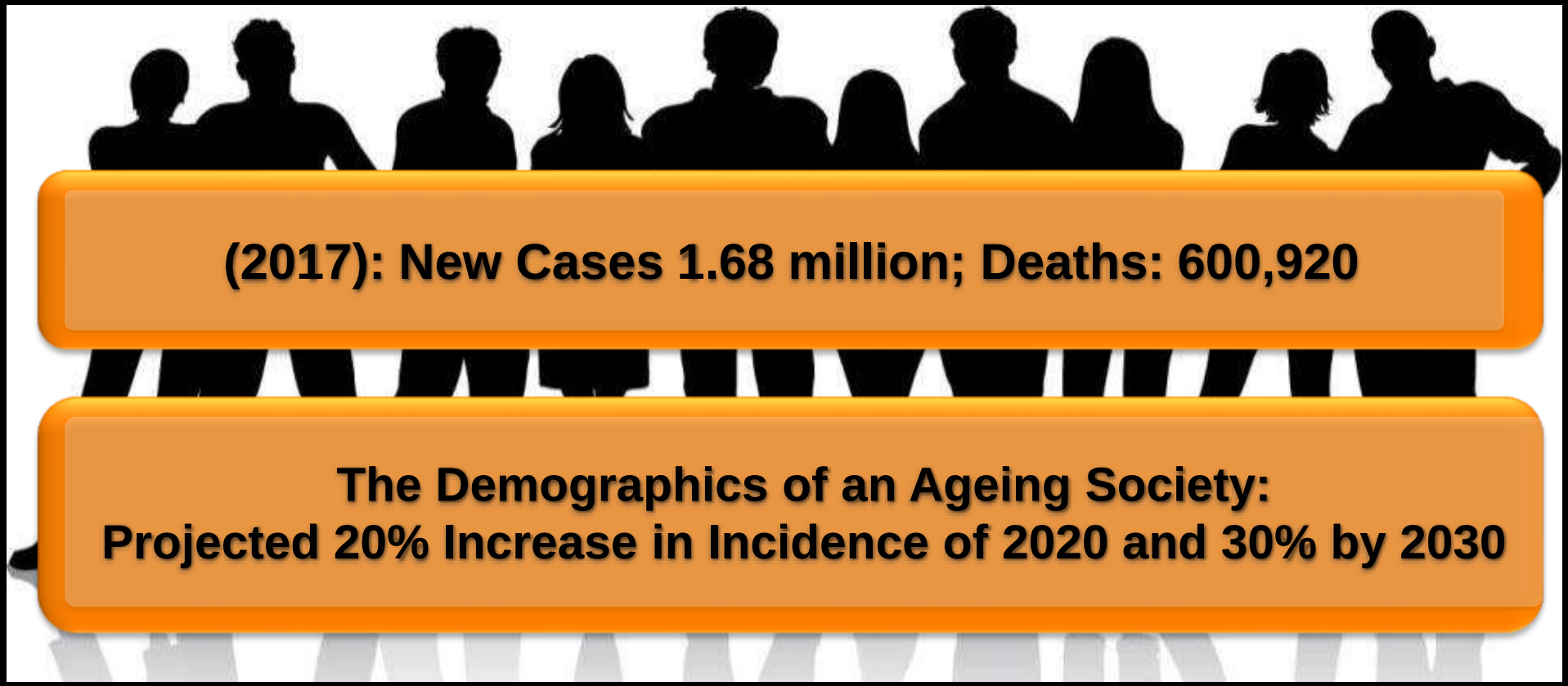
Complex Adaptive Systems Initiative
Arizona State University

BIO 302: September 26, 2018

Cancer as a Complex Adaptive System: Cancer Progression, Evolutionary Dynamics and Implications for Treatment

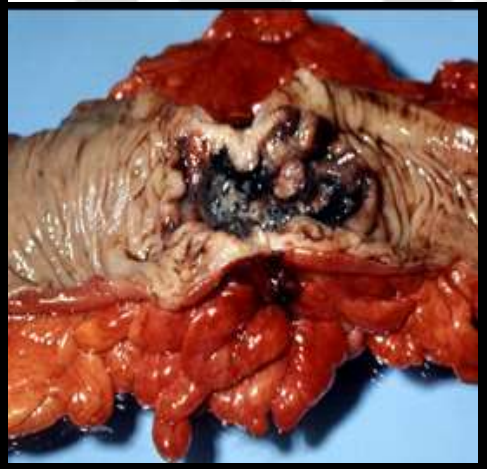
Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative
and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

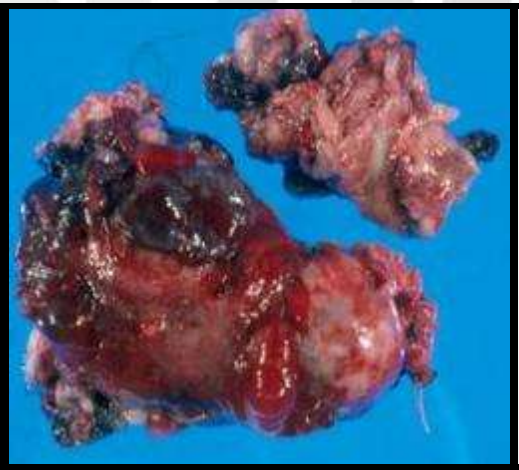
Confronting the Clinical, Economic and Human Toll of Cancer

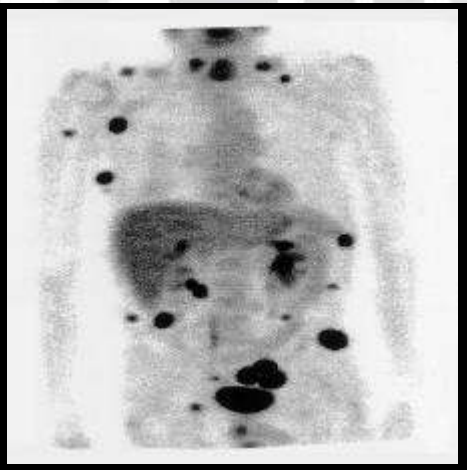


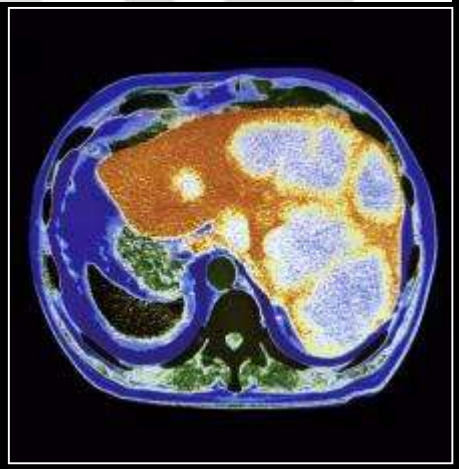
(2017): New Cases 1.68 million; Deaths: 600,920

The Demographics of an Ageing Society:
Projected 20% Increase in Incidence of 2020 and 30% by 2030



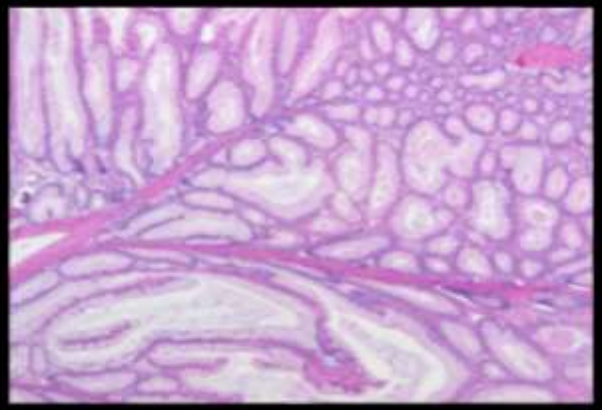






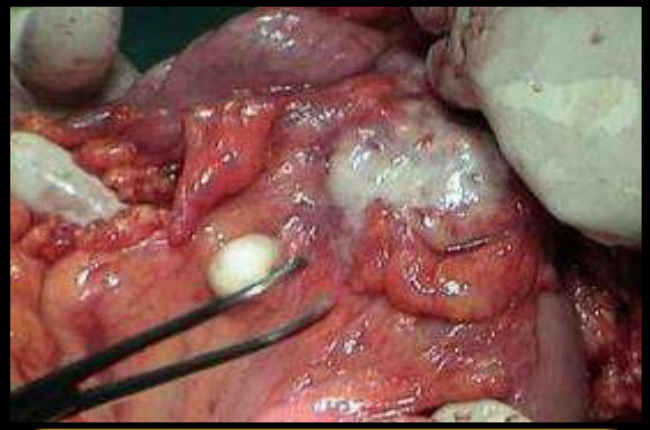
The Complex Biology of Cancer Progression and Treatment Resistance

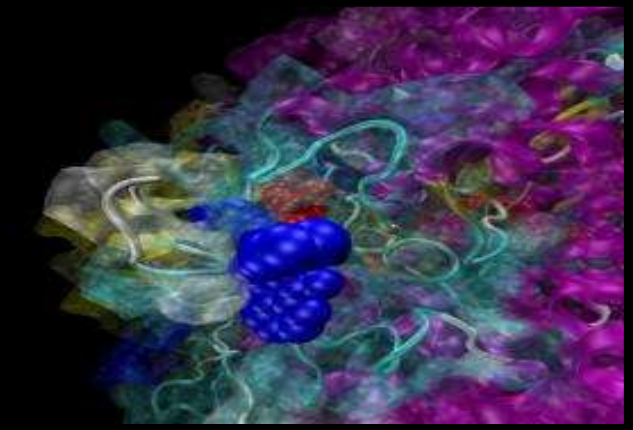
Escape From Controls for Normal Tissue Architecture



Genome Instability and Emergence of Different Clones

Evasion of Detection/ Destruction by Host Immune System





Use of Host Systems to Promote Progression

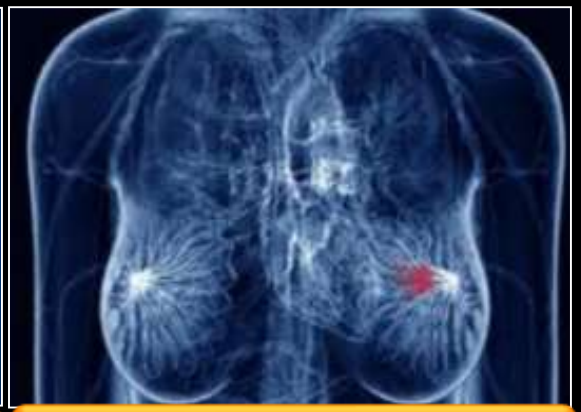
Invasion and Metastasis

Emergence of Drug-Resistant Clones

Invasion and Metastasis: The Start of the Deadly Phase of Cancer Progression

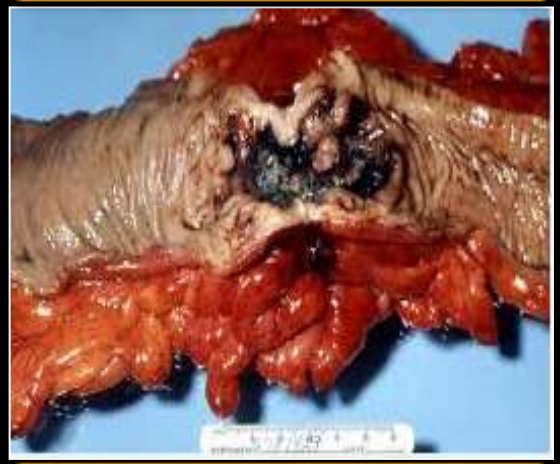
basal cell carcinoma

lung

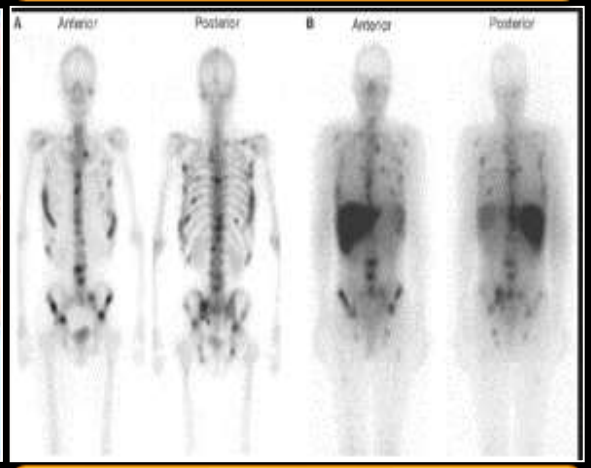


breast

glioblastoma



colorectal

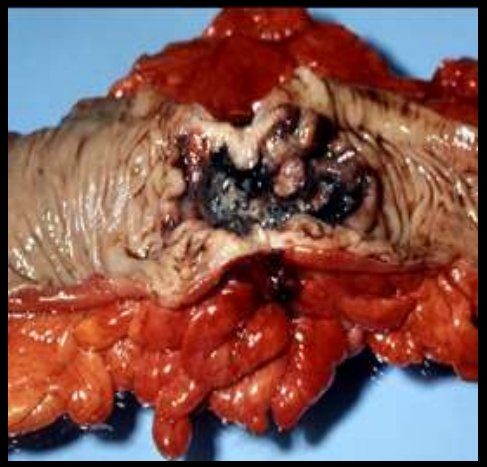


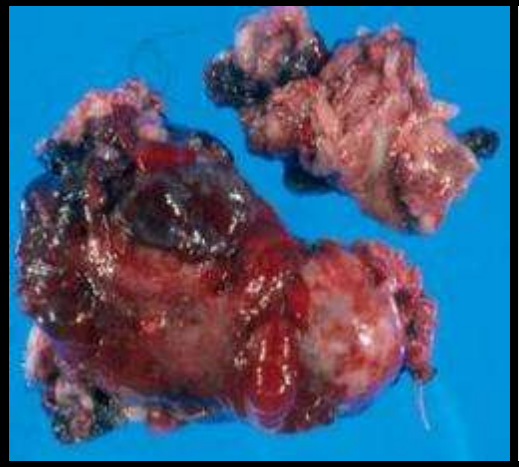
prostate

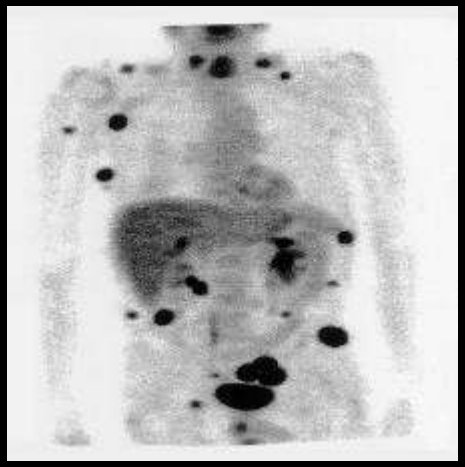
Invasion Without Metastasis

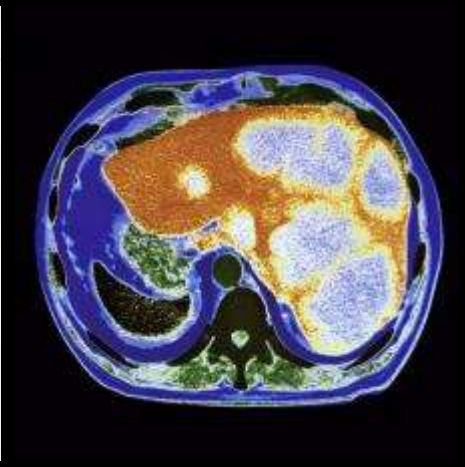
Invasion and Metastasis

Cancer as a Complex Adaptive System









Complicated Systems
Versus
Complex Systems

The Biological Complexity of Cancer

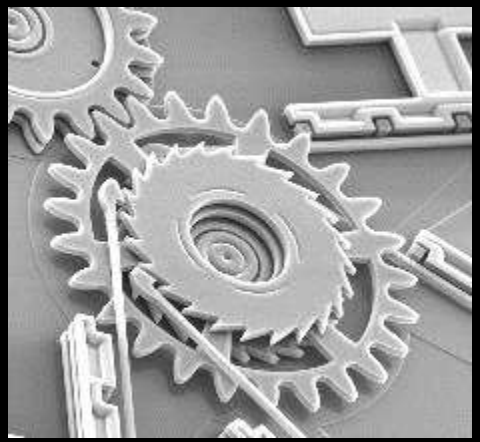
- what is the difference between complicated and complex systems?
- what features of cancer make it a complex system?
- what is meant by “emergence” in complex systems?
- what are the implications of the complex behavior of cancer for diagnosis, treatment and prevention?

Complicated Systems:
Low Degrees of Design Freedom



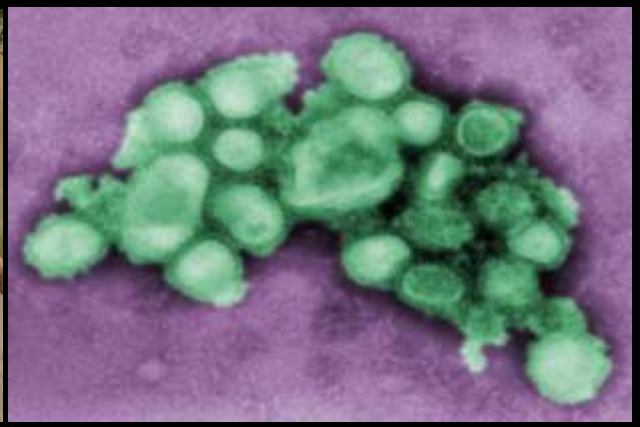
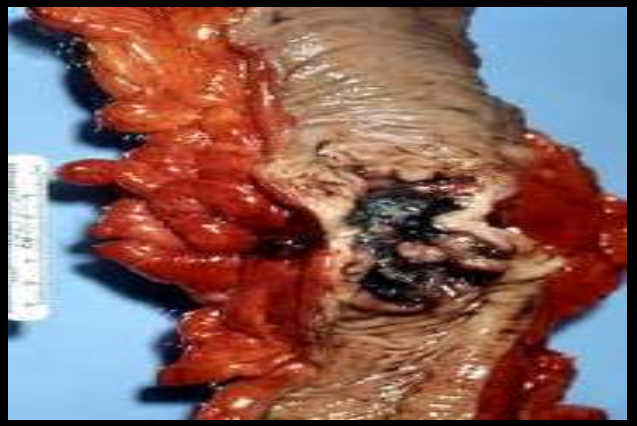







- behavior of components and the assembled whole system is predictable
- proactive awareness of tolerance limits and likely failure points
- performance of the system is fixed and not capable of autonomous evolution

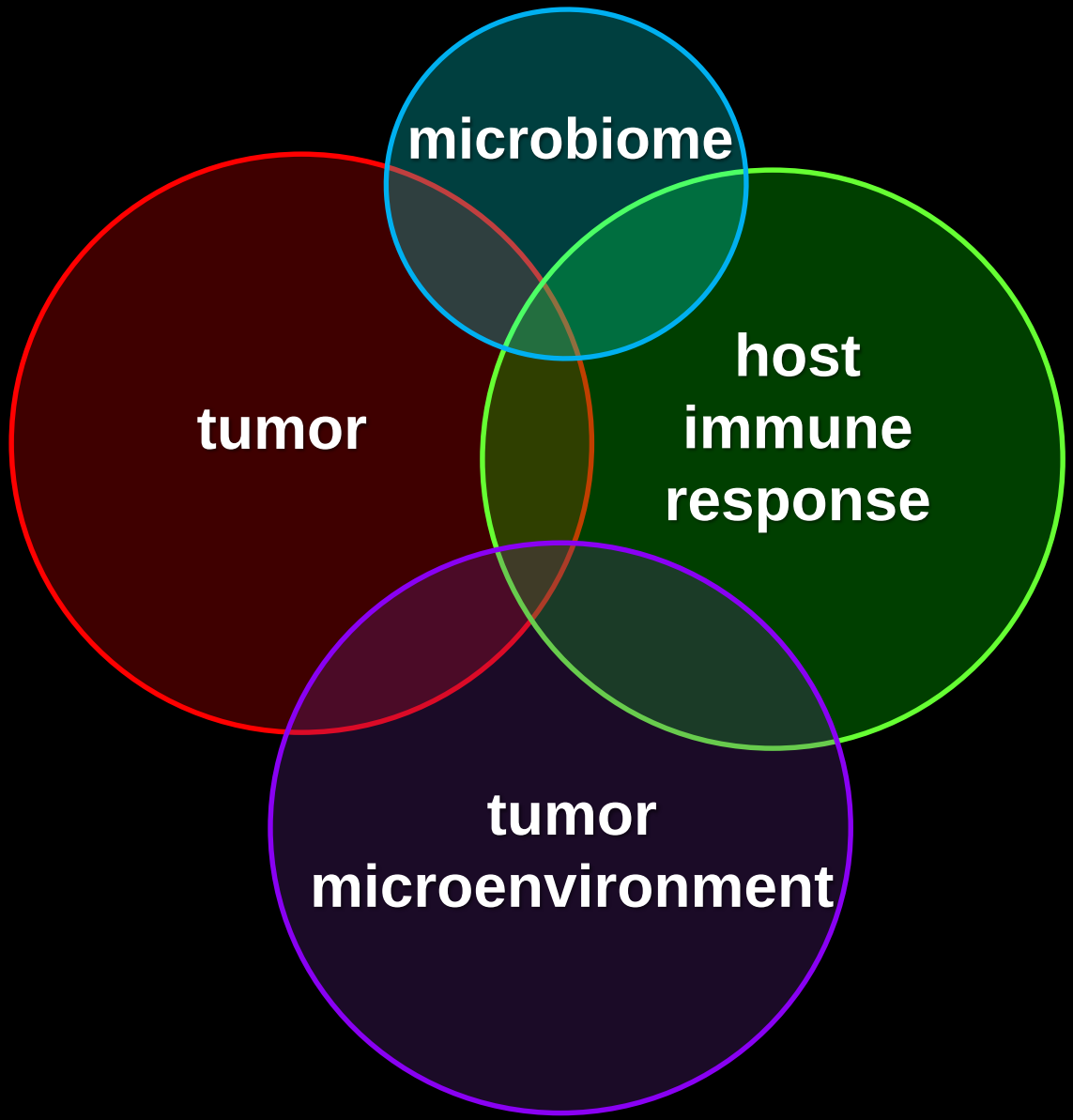
Dynamic Complex (Adaptive) Systems: Exhibit Behaviors Created by Constantly Changing Patterns of Interactions Between the Components of the System

weather/climate	stock markets	geopolitical/ national security
		
predator-prey relationships	**epidemics/pandemics**	**disease pathogenesis**
		

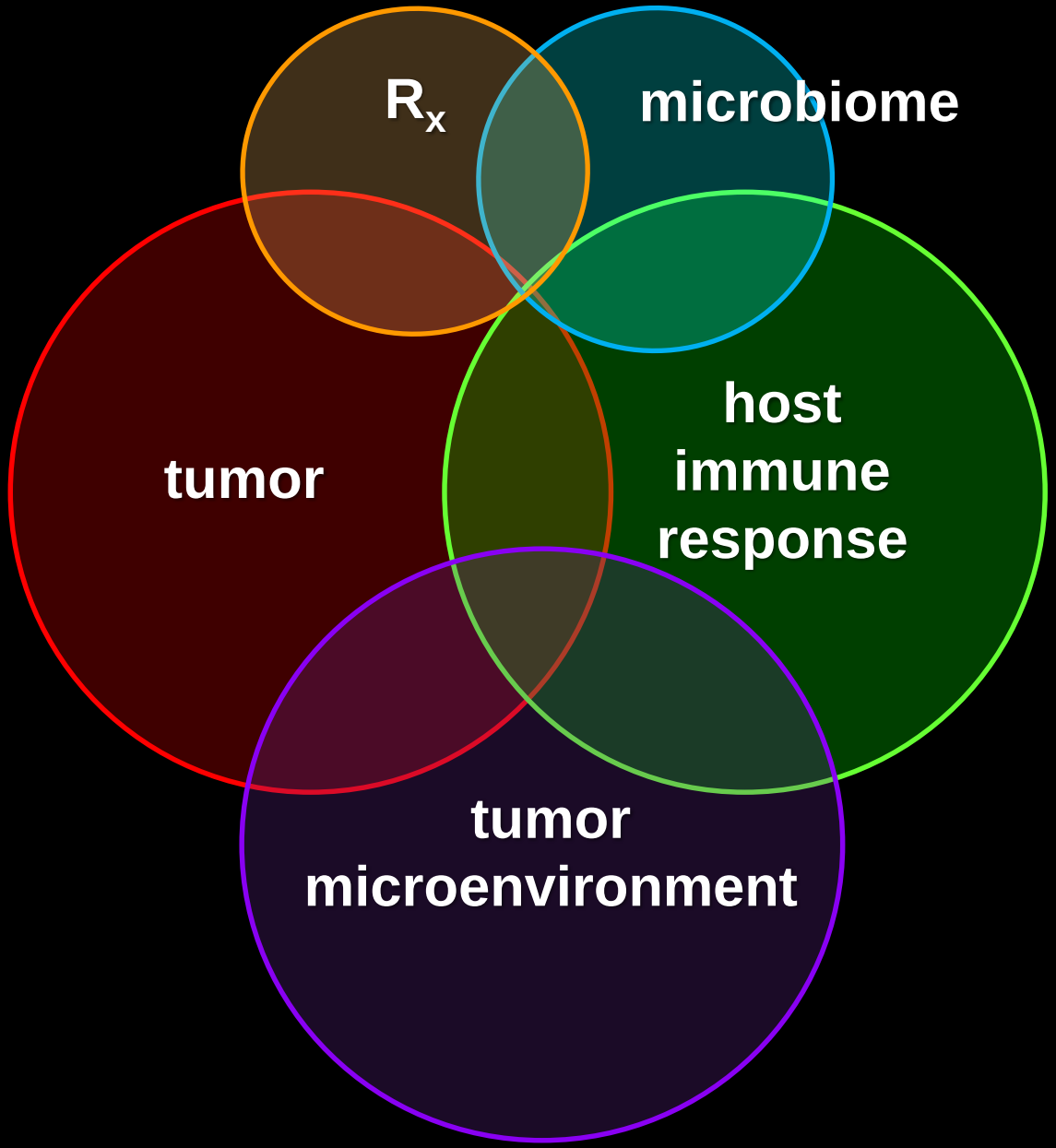
Evolvability and Emergence: The Hallmarks of Complex Systems

- new properties emerge from the interactions of simpler units (molecules, cells, organs, organisms)
- properties (behavior) of the whole system cannot be reliably predicted from knowledge of the properties of the simpler isolated units
  - "the whole is more than the sum of its parts"
- new and unexpected patterns of interactions between components can shift the system to a new state with very different properties (emergence)

Cancer: A Complex Ecosystem of Tumor and Host Dynamics

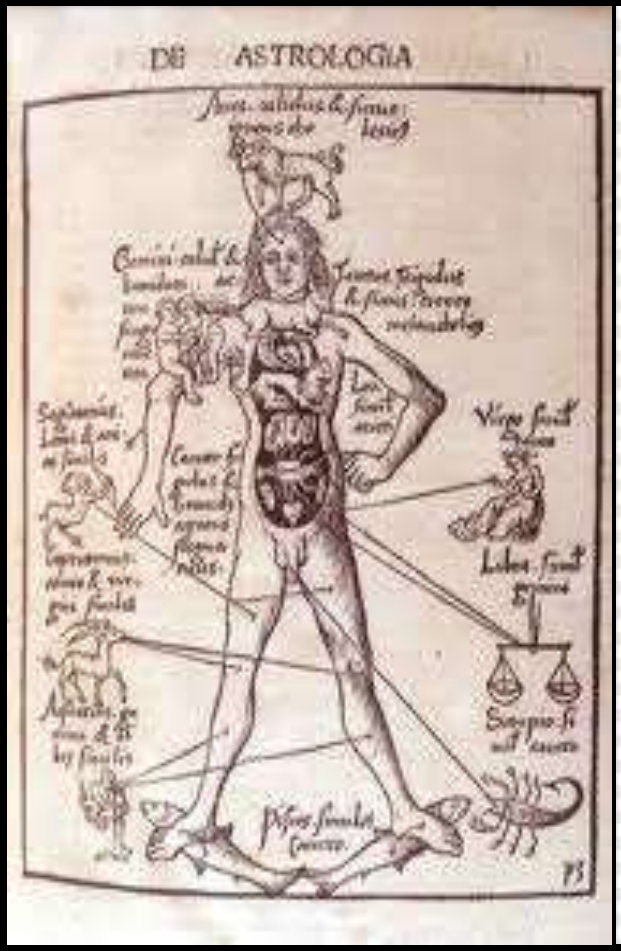


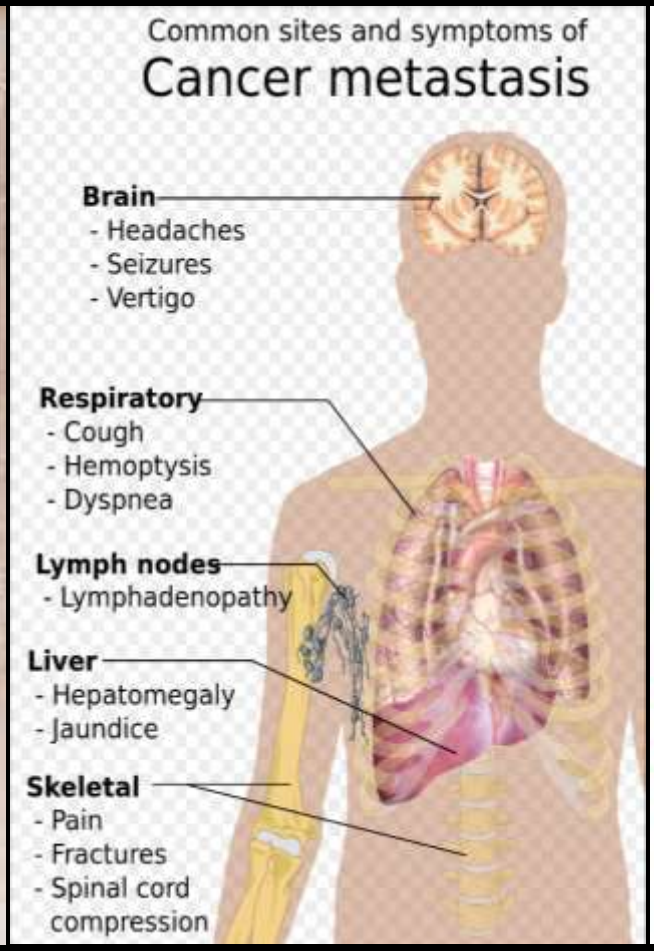
Cancer: A Complex Ecosystem of Tumor, Host Dynamics and the Effect of Treatment

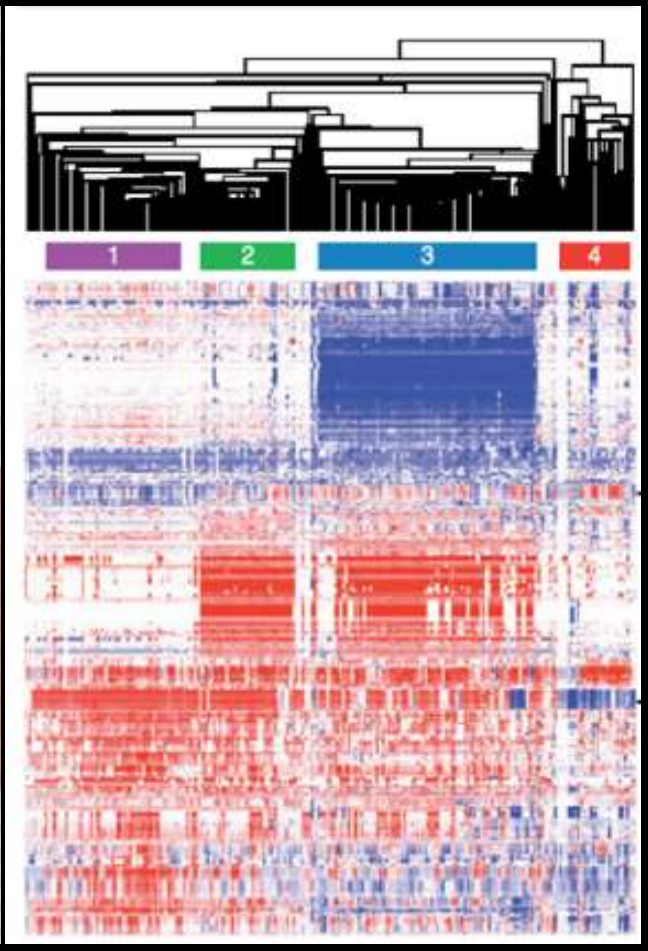


The Path to Precision Oncology:

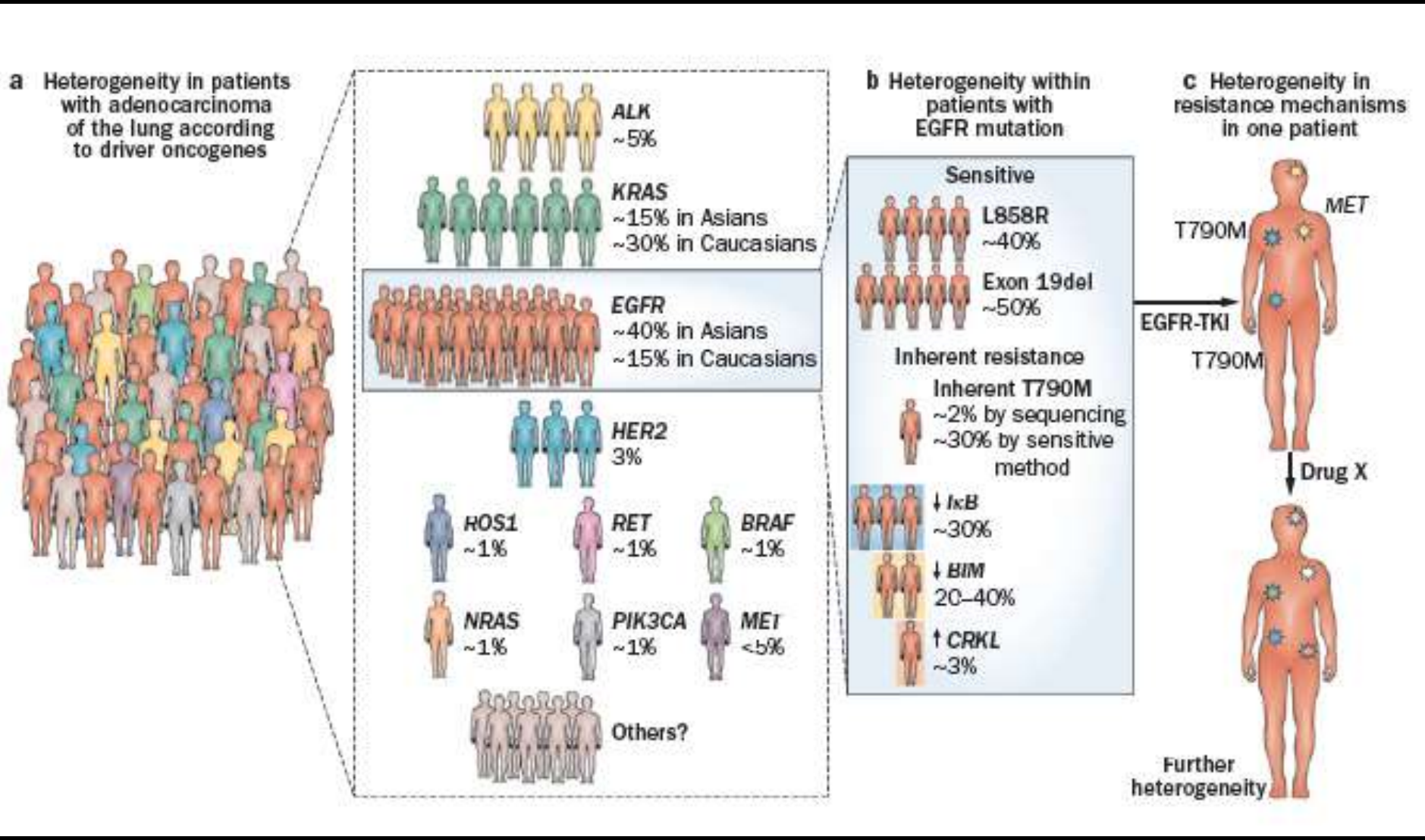
Superstitions	Symptoms	(Molecular) Signatures





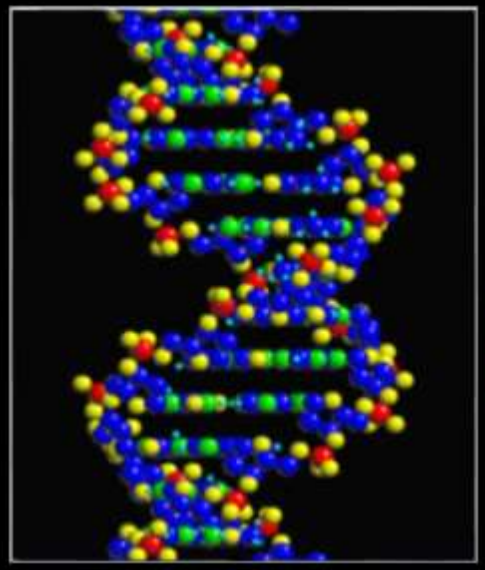


Molecular Profiling and Classification of Subtypes of NSCLC

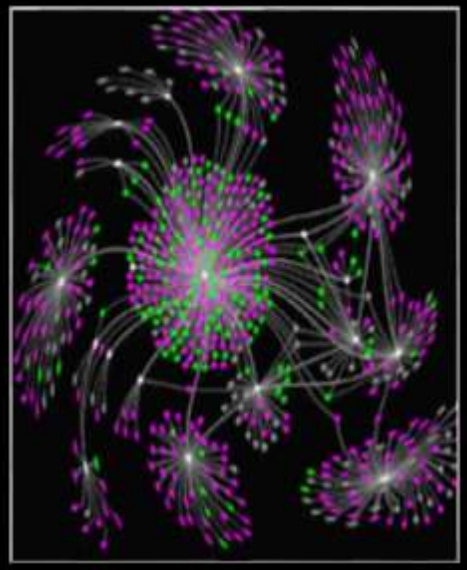


From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Precision Medicine: Understanding the Disruption of Molecular Information Networks in Disease

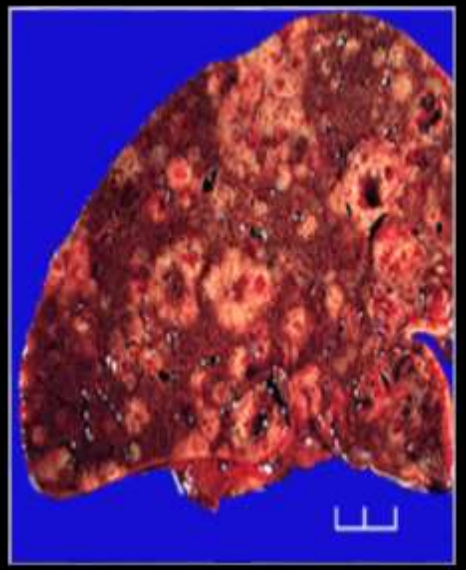


encoded information and expression as cell-specific signaling networks



patterns of information flow within signaling networks

stable networks and information fidelity (health)

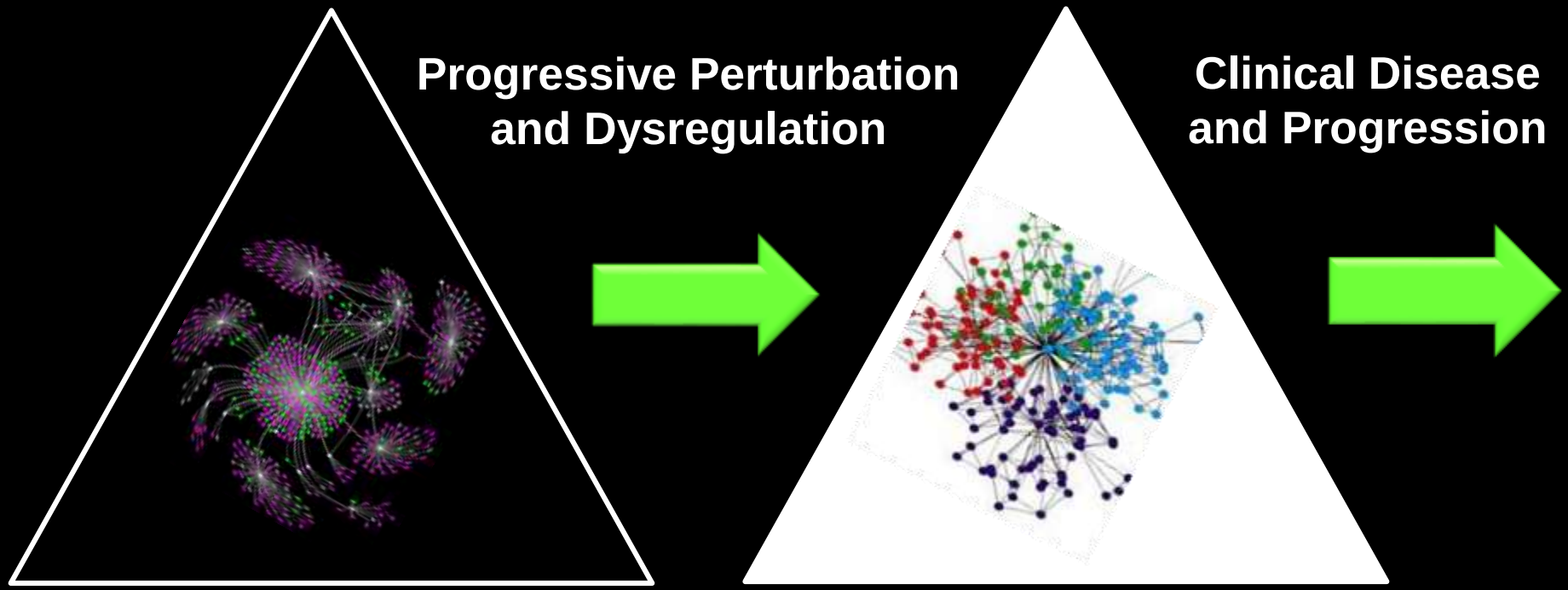


dysregulated networks and altered information patterns (disease)

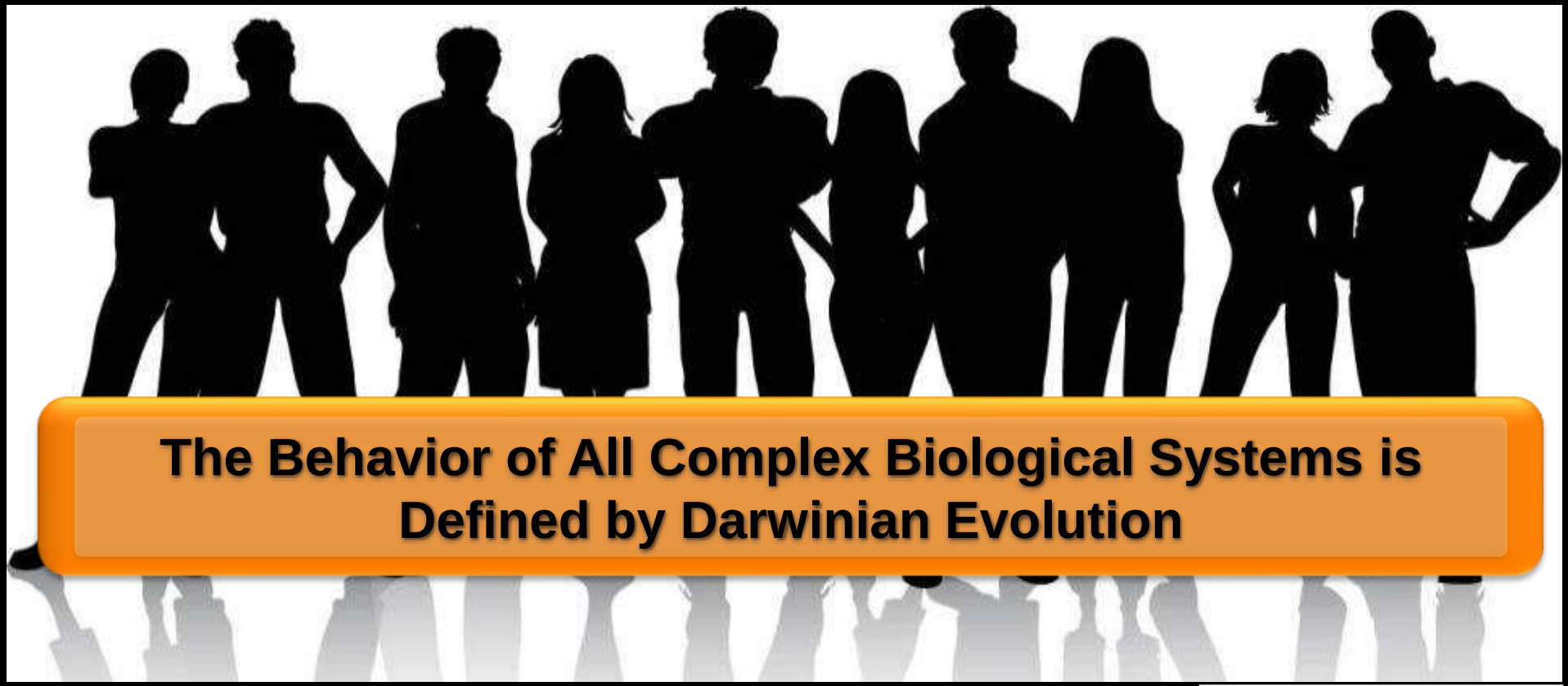
Understanding Molecular Signaling Networks (Circuit Diagrams) and Identification of Targets for Rx Action and How Rx Resistance Emerges

molecular signaling network topologies in health

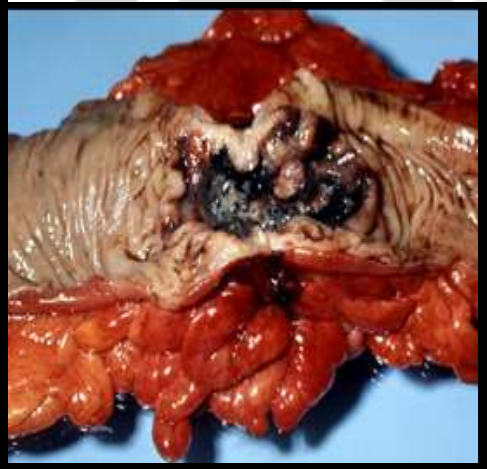
altered network topologies in disease

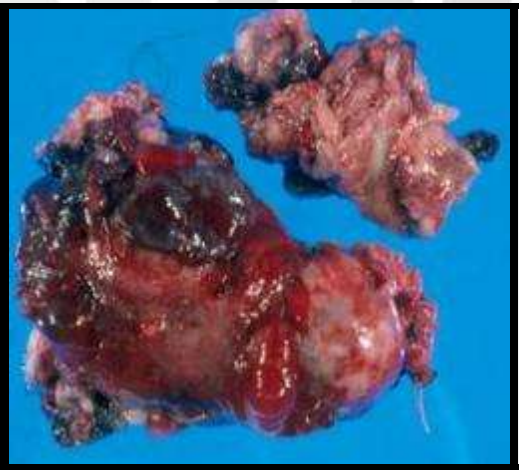


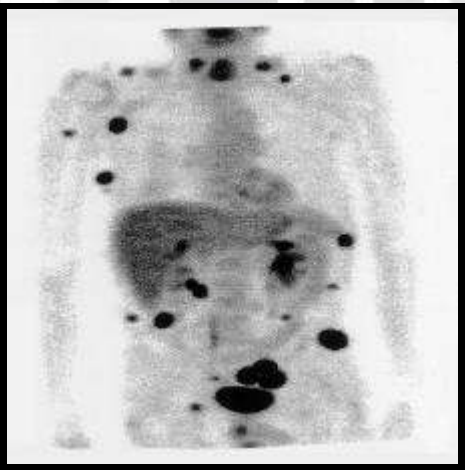
Cancer as a Complex Adaptive System

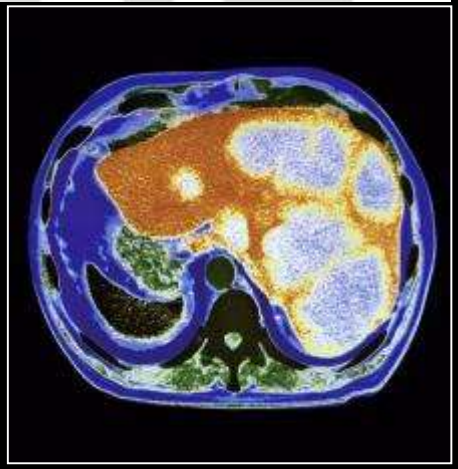


The Behavior of All Complex Biological Systems is Defined by Darwinian Evolution

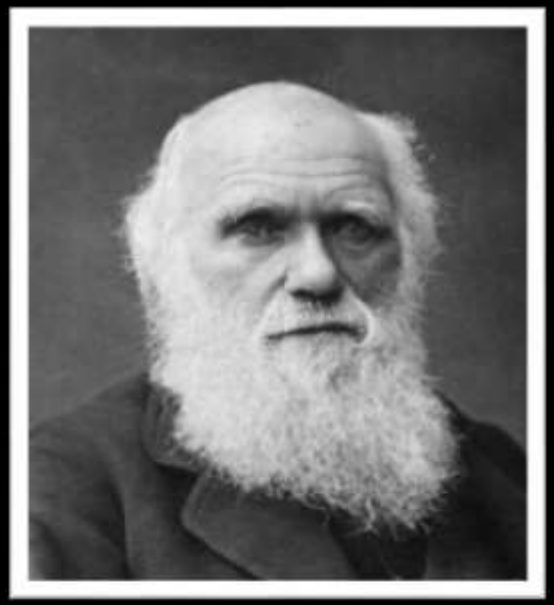






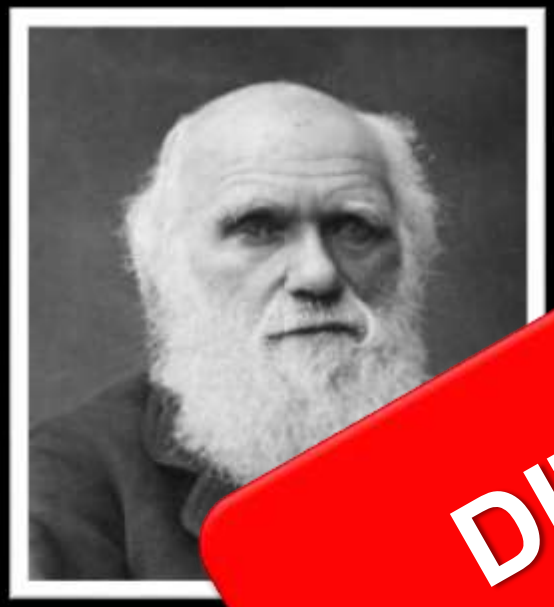


Darwinian Evolution



- variation
- selection
- adaptation
- evolvability
- “fitness” for selection pressures operating in a particular environment

Darwinian Evolution



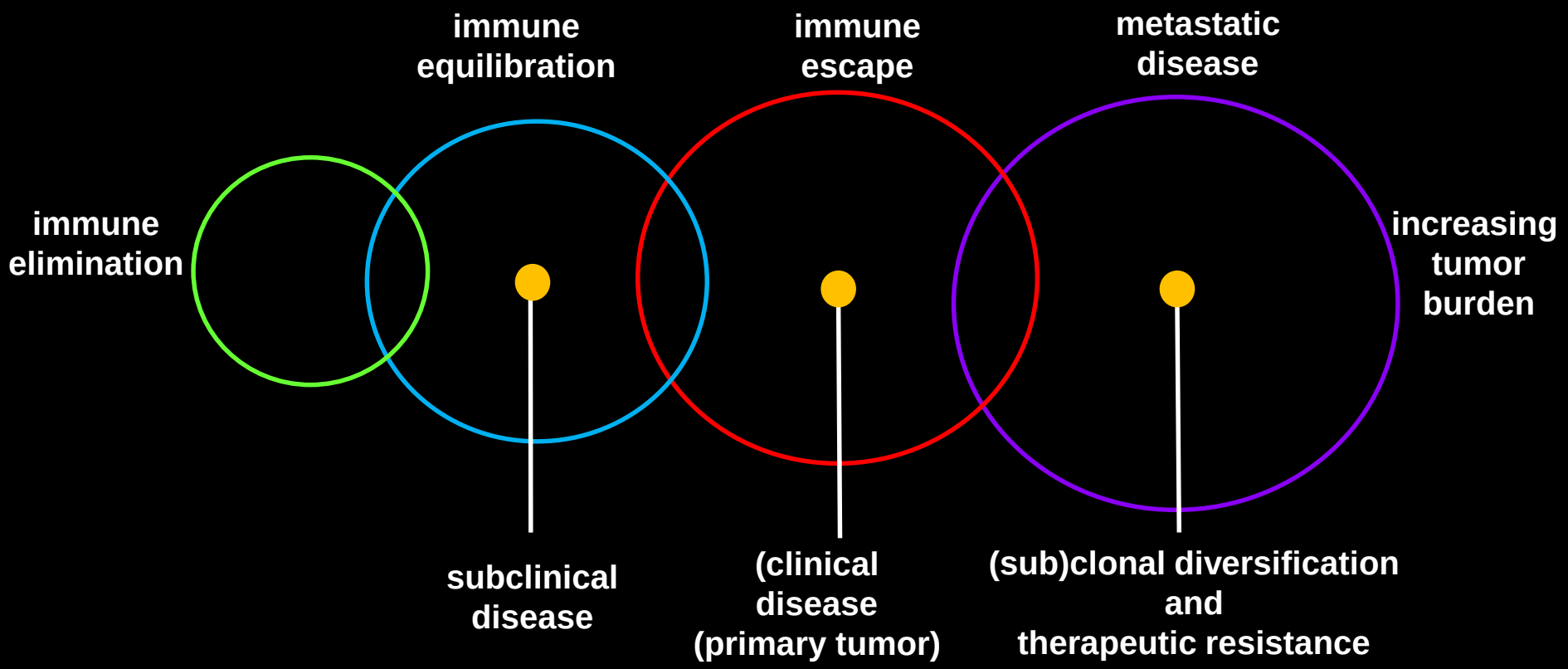
- variation
- selec
- ess" for selection pressures operating in a particular environment

DITTO CANCER

3E's: The Interplay Between Cancer and the Body's Defense Mechanisms

- elimination (detection, surveillance and destruction)
- equilibrium (cancer cells present, but contained)
- escape (breakout and evasion of destruction by the body's immune system)

Dynamic Tumor-Host Interactions in Cancer

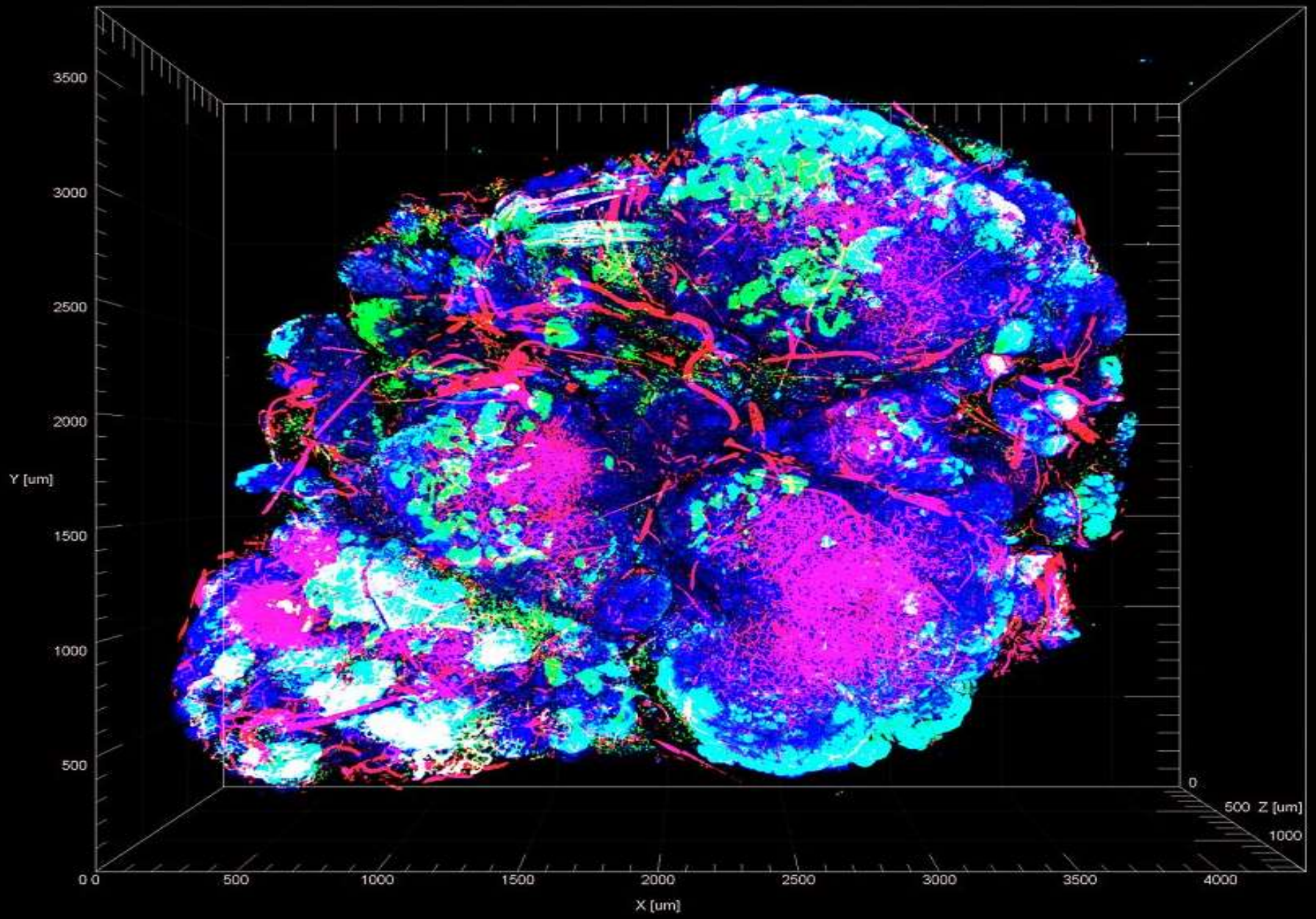


What Makes Cancer So Dangerous and Difficult to Treat ?

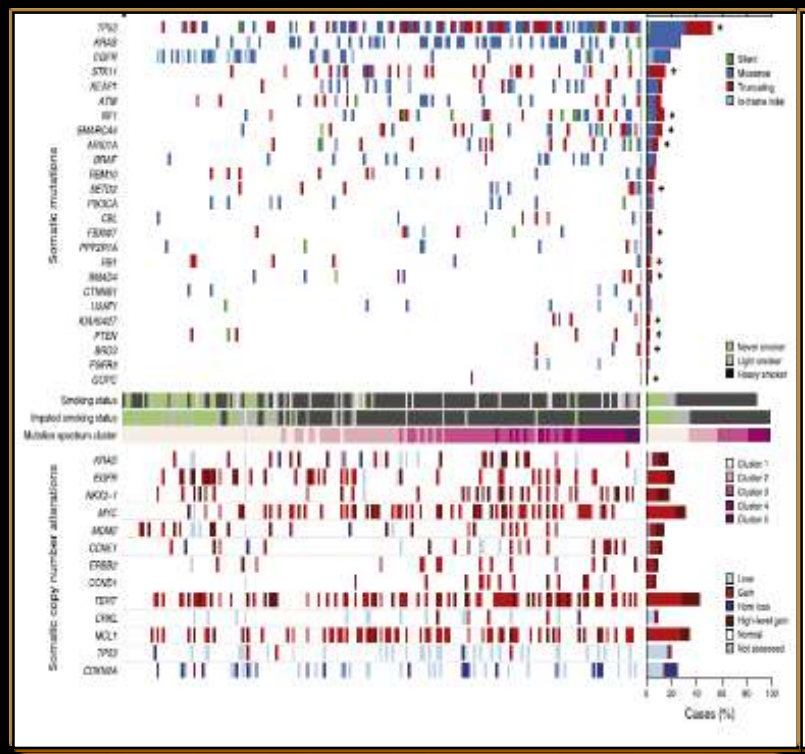
Dynamic Heterogeneity: Variation, Adaption, & Evolvability

Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression

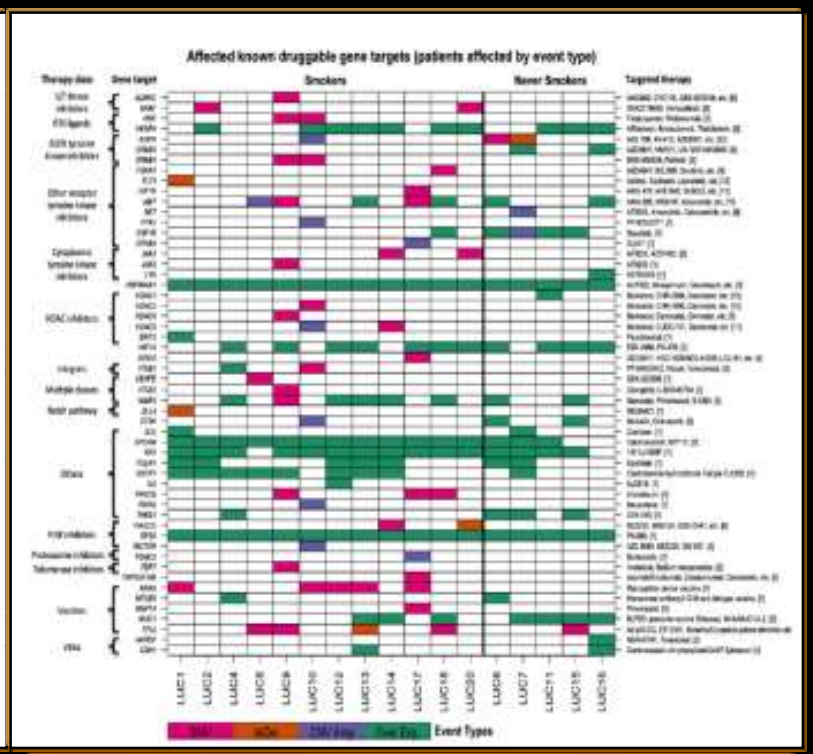
Mapping Tumor Heterogeneity: Zonal Variation



The Extravagant Landscape of Genomic Alterations in Cancer
(Cell (2012) 150, 1107 and 1121)



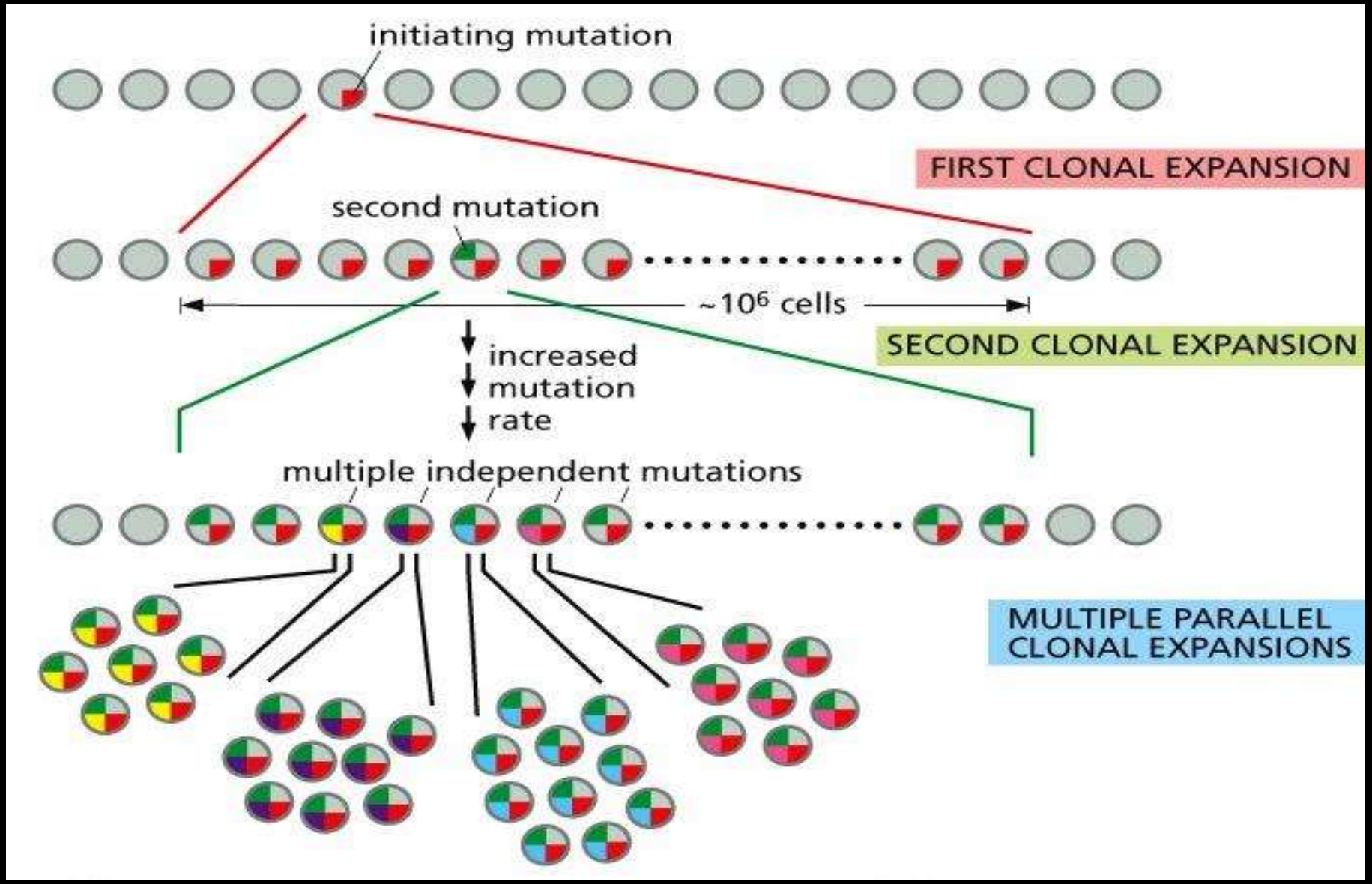
Mutations in Individual Non-Small Cell Lung Cancers



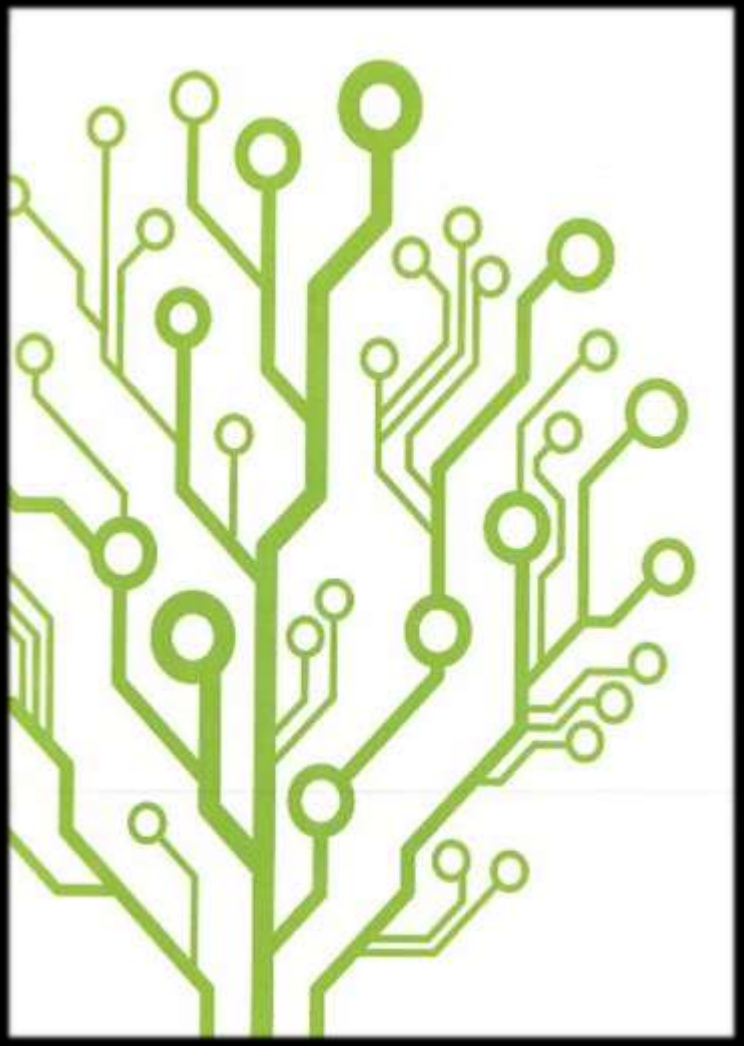
Drug Targets in Individual Non-Small Cell Lung Cancers

- "malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for therapeutic 'cure' and development of new R_x

Evolution and Phenotypic Diversification of Tumor Clones and Subclones

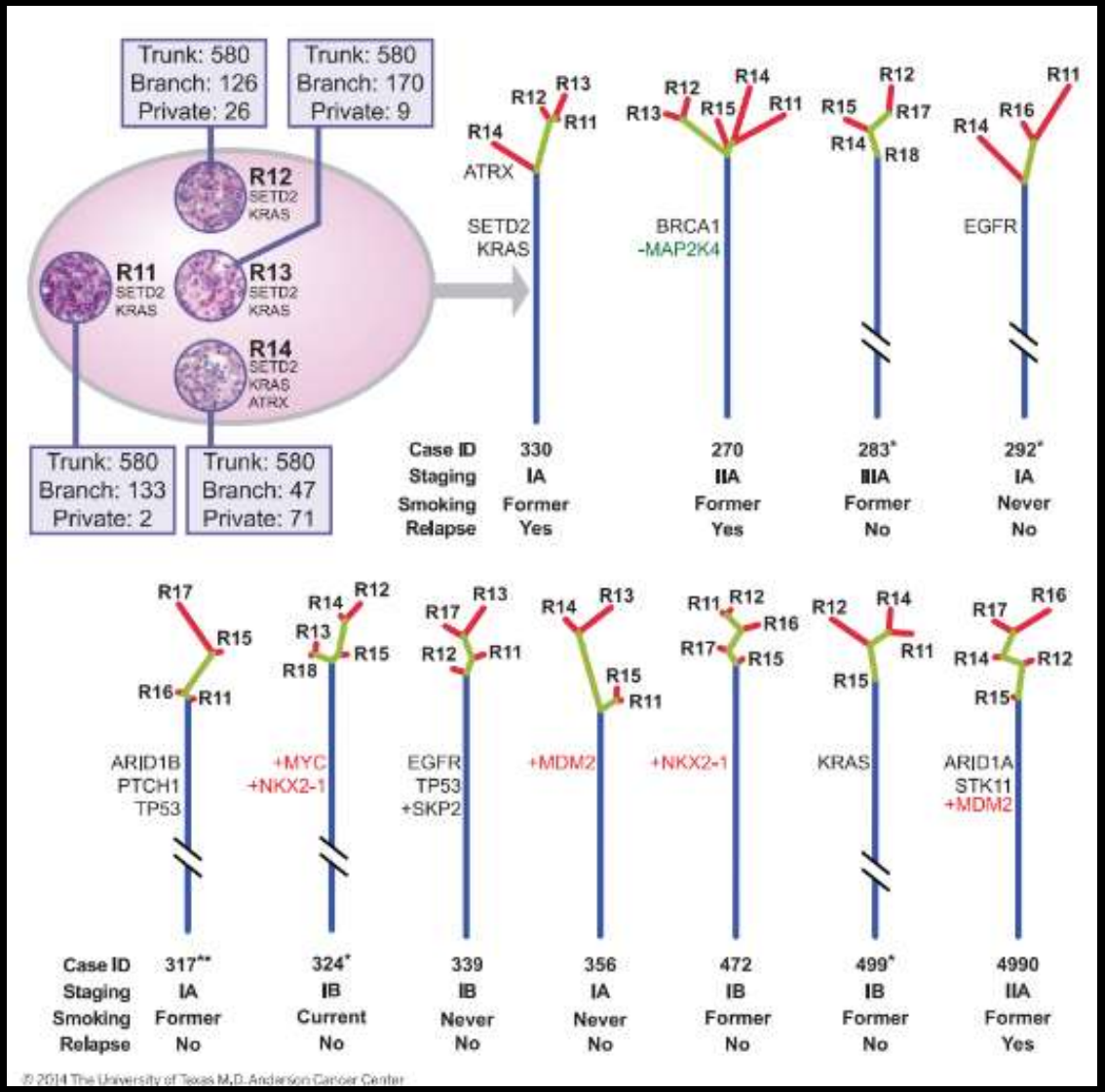


Mapping the Dynamics of Clonal Evolution in the Progression of Malignant Tumors: Clonal Branching



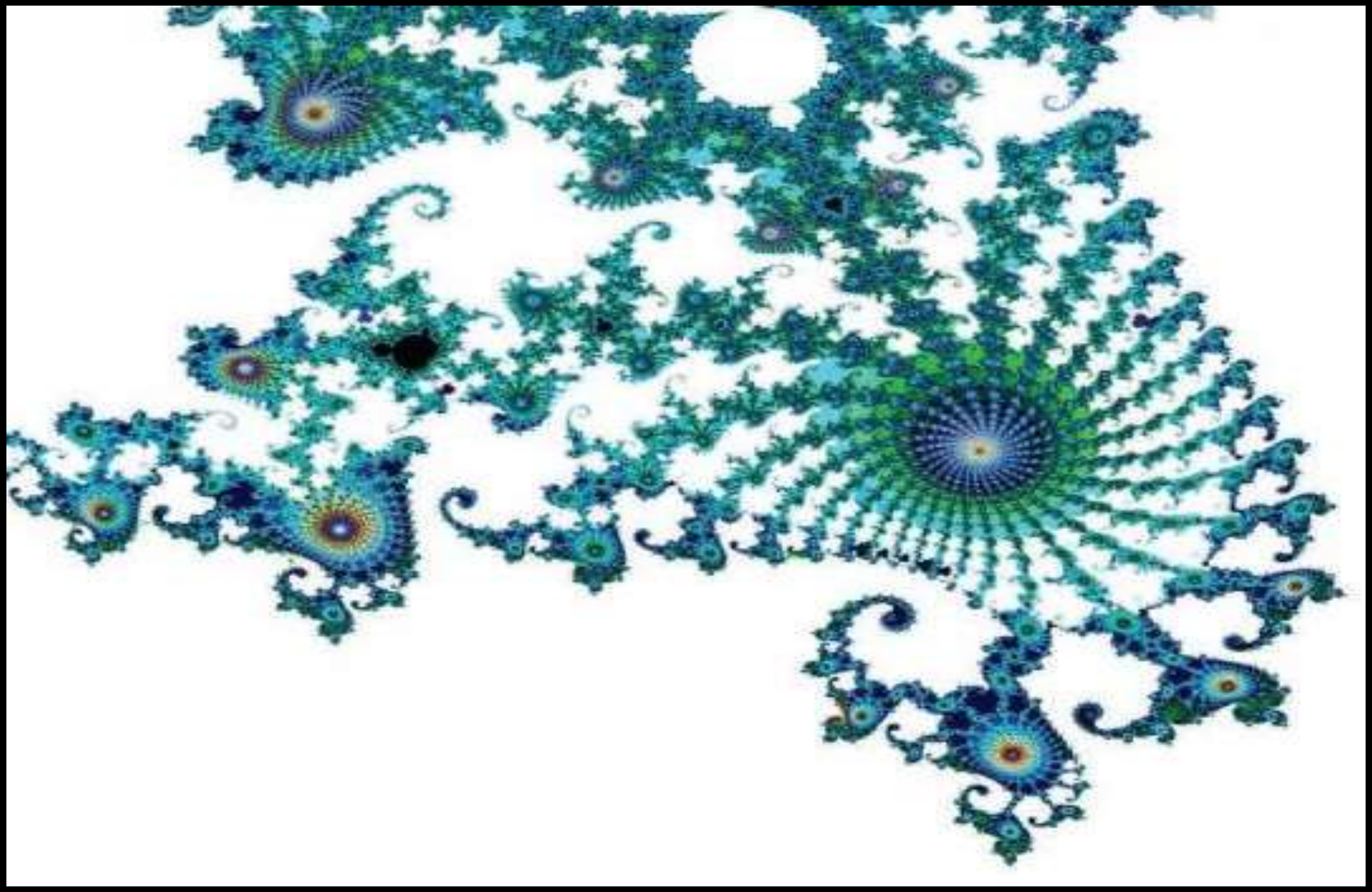
- timing of mutational events
  - ‘early events’ present in clones in both primary tumor and metastases (trunk)
  - private mutations (unique to individual patients or individual metastatic lesions in same patient) have occurred later in progression (branch)

Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches



From: J. Zhang et al. (2014) Science 346, 256

Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression



The Biological Complexity of Cancer and the Design of Treatment Strategies

- successful surgical removal of primary before metastatic spread tumor (except malignant brain tumors)
- targeting metastatic disease and circumventing R_x resistance
  - subclinical disease with evidence of probability of metastatic spread (neoadjuvant and adjuvant R_x)
  - advanced disease with clinically evident metastases
  - minimal residual disease and tumor dormancy (long term reoccurrence)

Three Generations of Cancer Therapeutics

cytotoxic agents ("chemo")

- no selectivity for cancer cells versus dividing normal cells (gut, bone marrow, hair follicles)

targeted agents

- R_x designed to inhibit specific alterations in molecular targets/pathways in cancer cells
- molecular profiling to ID patients with relevant R_x targets for improved treatment (precision oncology)

immunotherapy

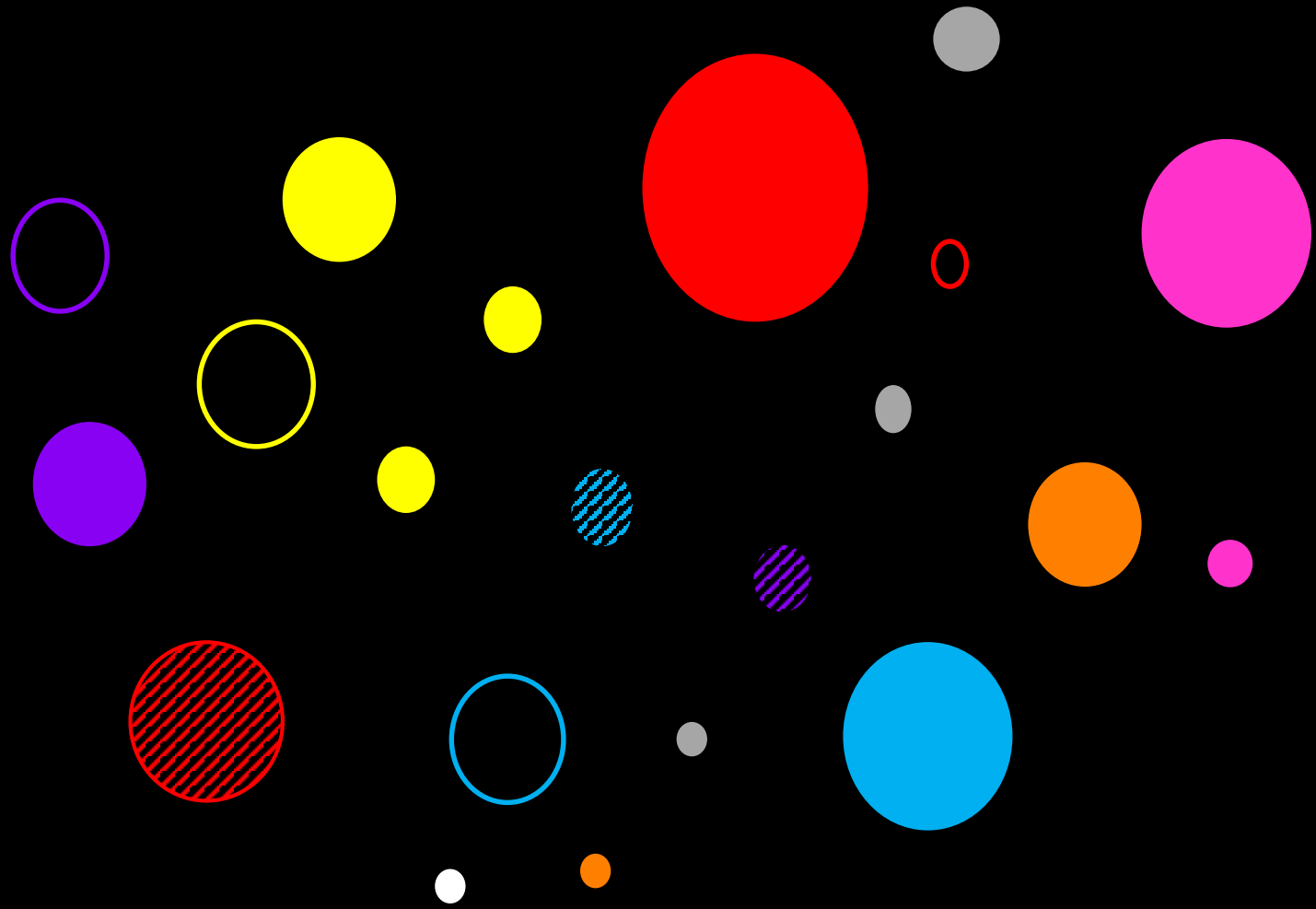
- (re) activation of body's immune defenses to detect and destroy cancer cells

The Principal Challenge in Cancer R_x Therapy

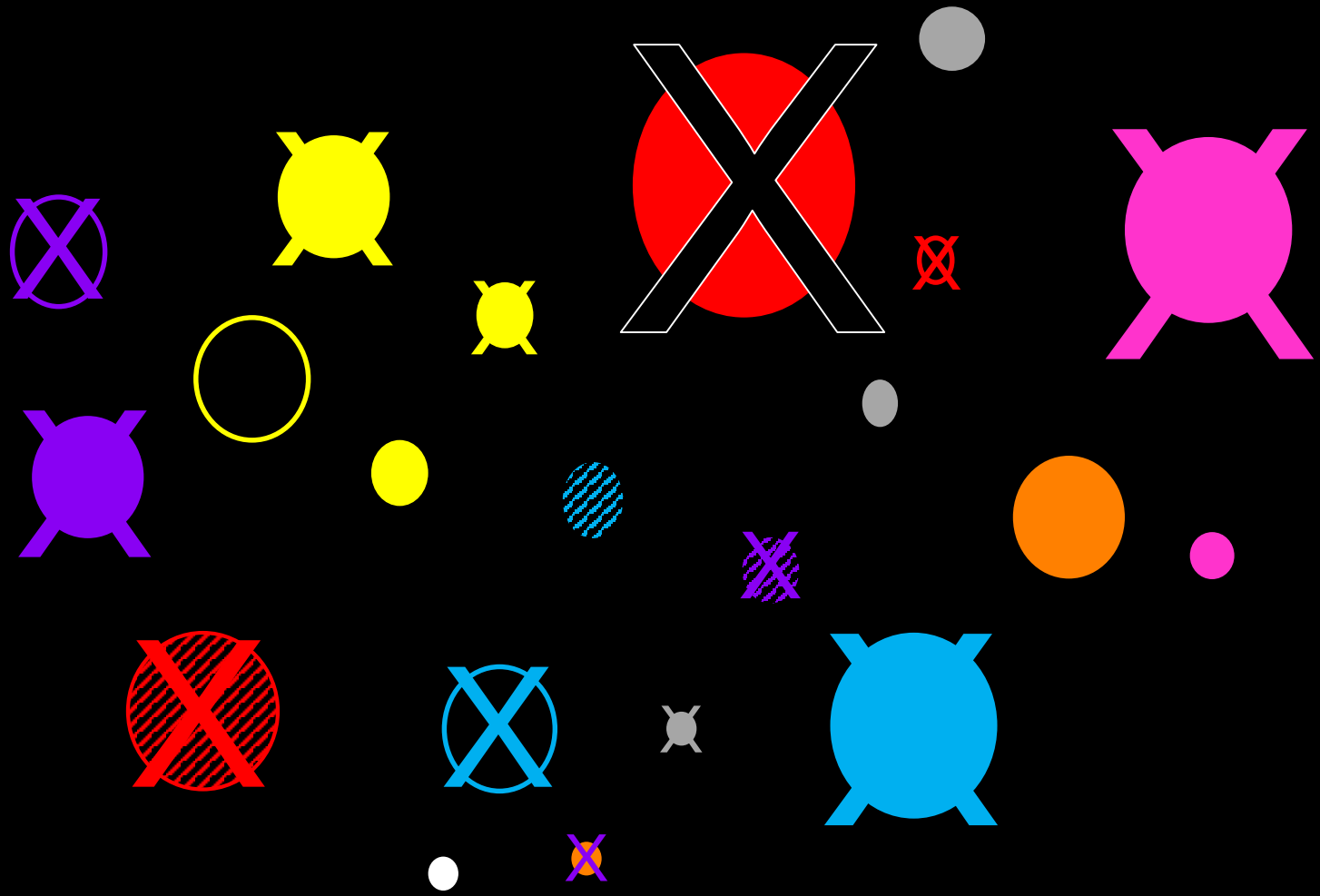
The Co-existence of Multiple Tumor Cell Clones with Varied Susceptibility to Different-R_x

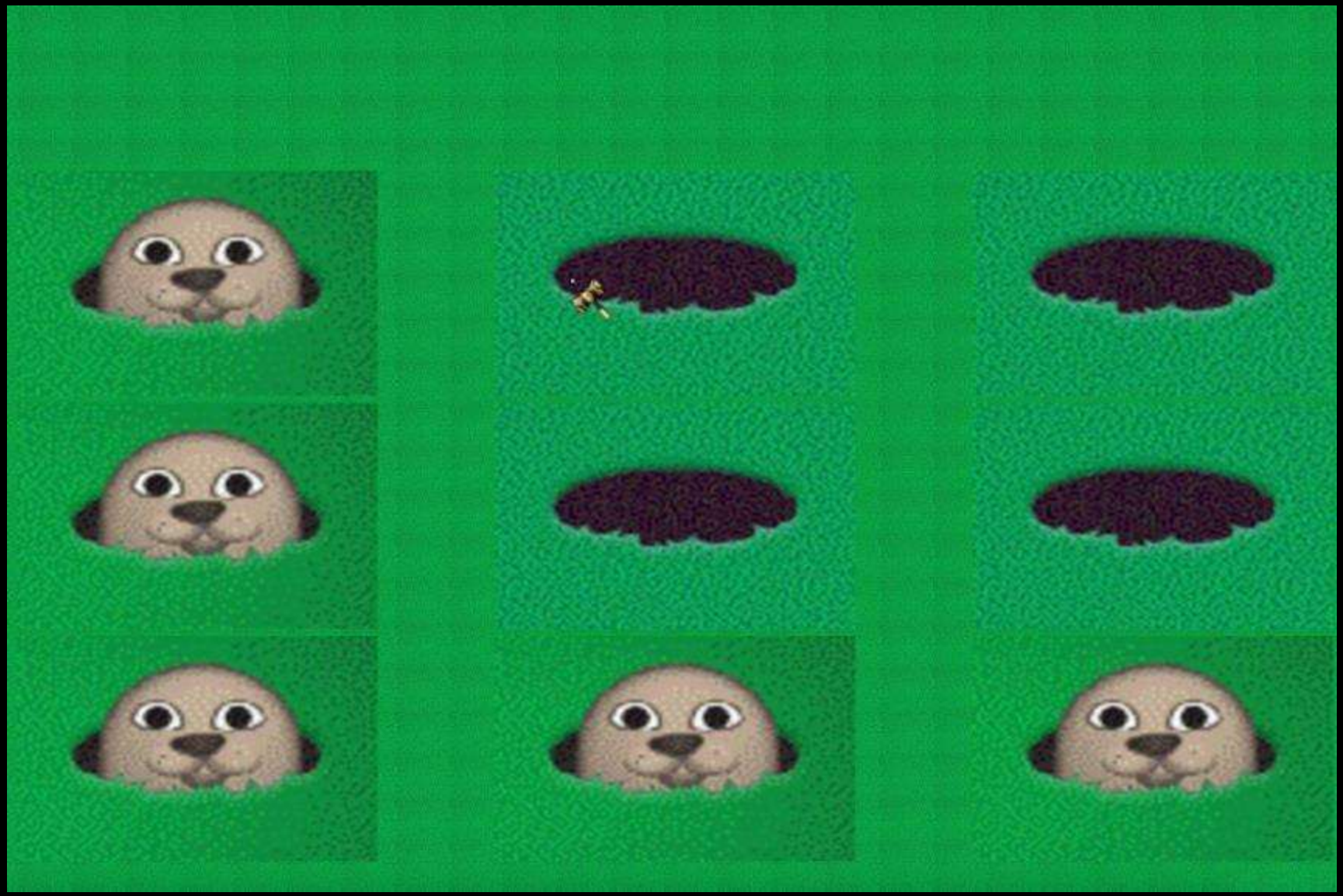
R_x - Resistance

Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy



Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy





The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple anatomic sites of metastatic disease?
- how to hit clones that emerge as escape variants driven by the selection pressure of treatment ?
  - intrinsic resistance (exist before treatment)
  - acquired resistance (mutations induced by Rx – similar to antibiotic resistance in bacteria)

Design of Cancer Treatments to Hit Multiple Targets

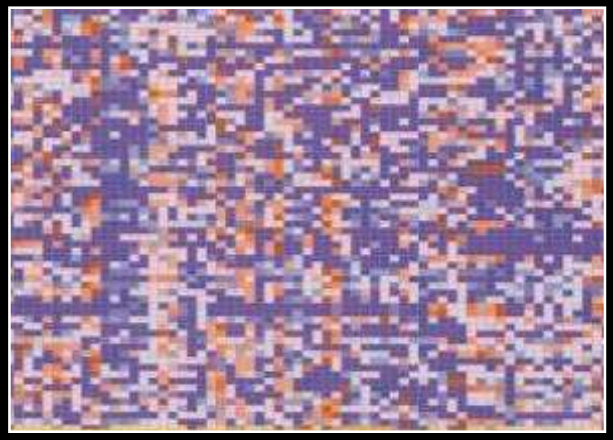
- design a single drug that hits multiple clones and multiple signaling pathways
- very low probability of technical success of creating a single molecule with multi-target pharmacological promiscuity and no off-target effects (toxicity)

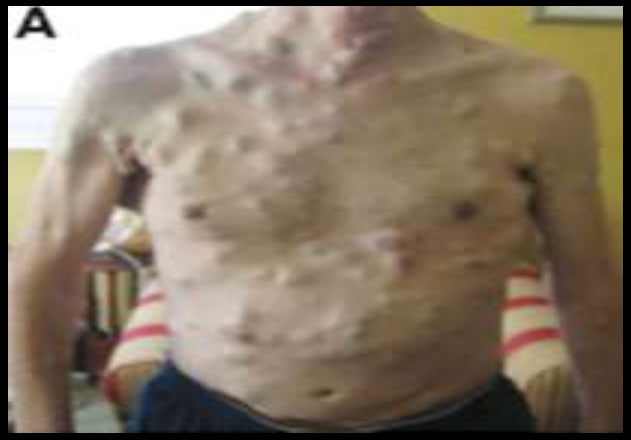
Targeted Therapeutics and the Omnipresent Problem of R_x Failure Due to Emergence of Drug Resistance Clones

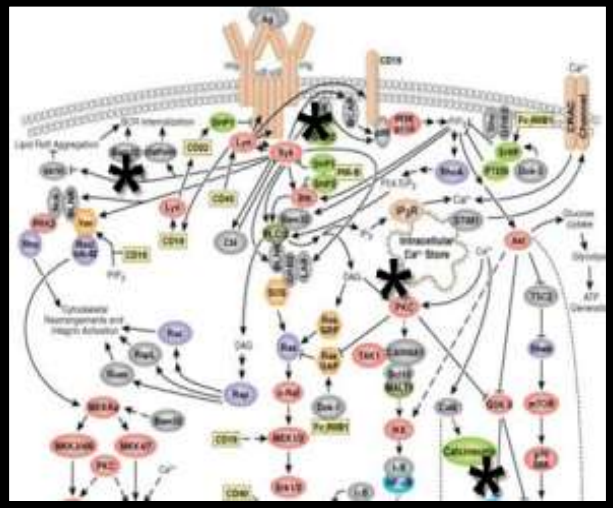
Molecular Subtyping and R_x Targets

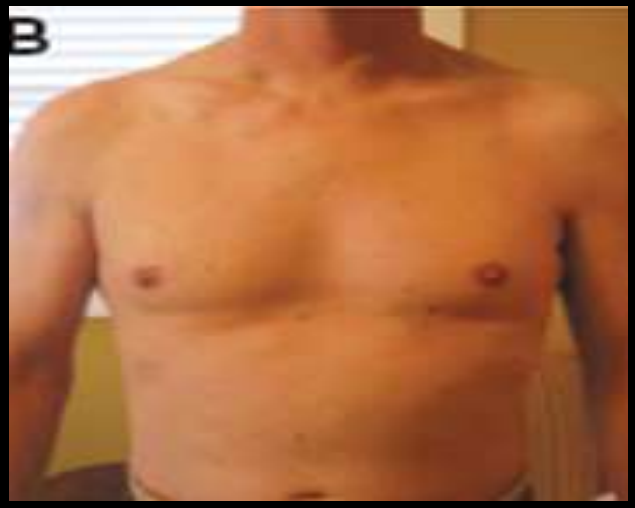
Initial R_x - Response to Targeted R_x

R_x - Resistance via Redundant Molecular Pathways









B = 15 weeks R_x (vemurafenib)

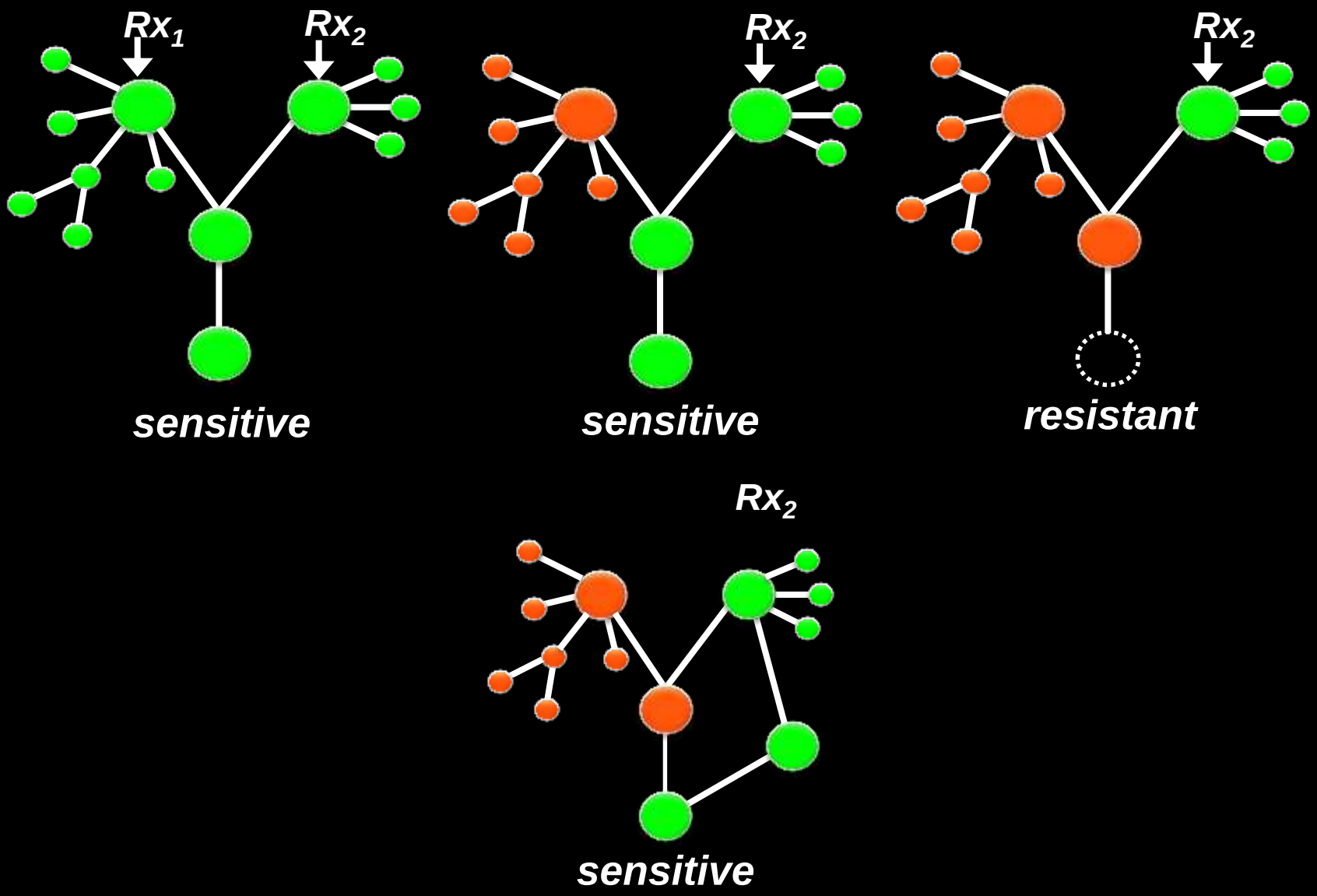
C = 23 weeks R_x and emergence of $MEK1^{C121S}$ mutant

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

‘Compensatory’ Pathways in Molecular Signaling Networks and Evolution of Drug Resistance

Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass Mechanism for Cancer Cells to Develop R_x Resistance

Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of R_x Resistance

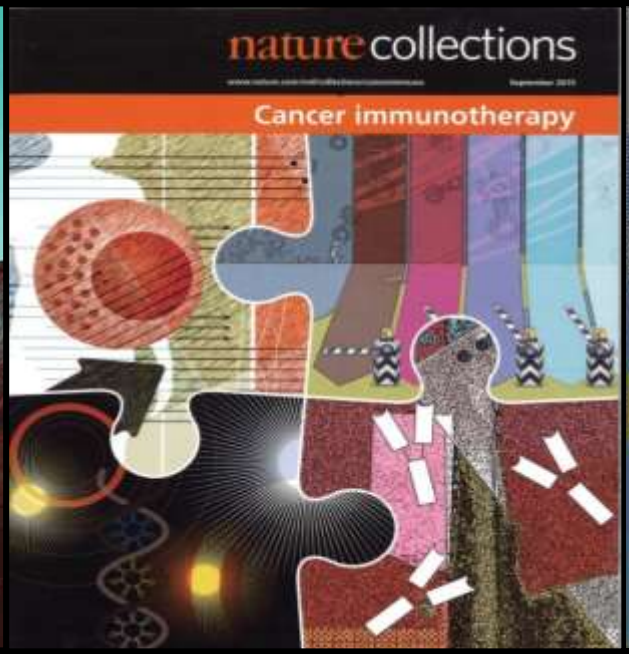


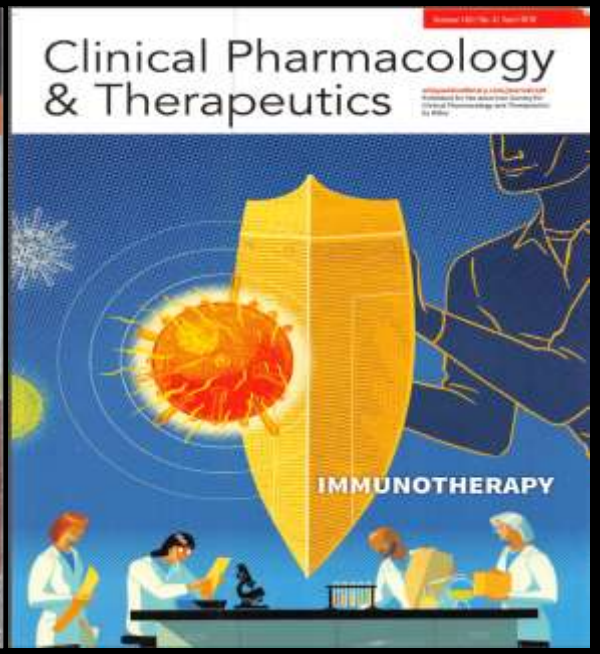
Design of Cancer Treatments to Hit Multiple Targets

- multi-drug combinations
  - patient tolerance of side effects
  - cost
- high probability that R_x-resistant variants will eventually emerge
- R_x acts as a selection pressure to generate R_x-resistant 'escape' clones
  - R_x elimination of 'dominant' clones allows pre-existing 'minor' clones to prosper (intrinsic resistance)
  - direct drug effect to cause mutations and new resistant clones (acquired resistance)

The Need for Rethinking Therapeutic Strategies to Combat Cancer

The Promise of Cancer Immunotherapy



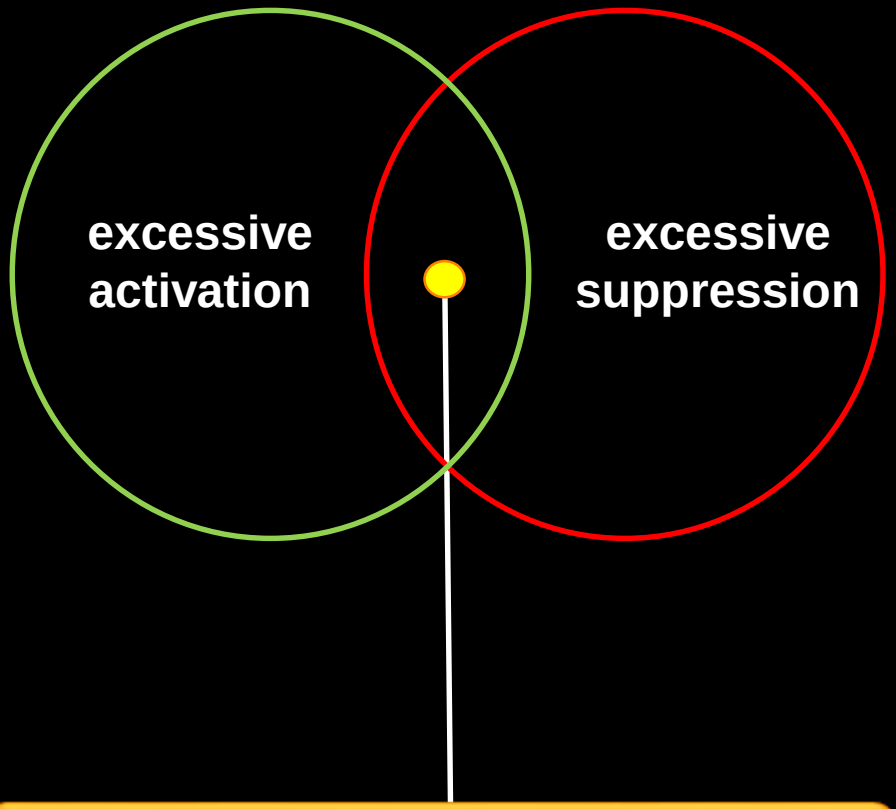


The Therapeutic Challenge of Overcoming Heterogeneity in Tumor Cell Susceptibility to Anti-Cancer Drugs

- moving from classical ‘chemo’ and “targeted” drugs to devise new ways to attack every clone
- harnessing the cognate (detection) and destruction (killing) capabilities of the body’s immune system
- therapeutic activation of immune responses
  - passive immunotherapy (designer antibodies)
  - active immunotherapy (activation of immune functions)

Balancing The Body's Immune Response

- autoimmunity
- chronic inflammation
- life - threatening activation:
  - sepsis
  - organ failure



- HIV
- cancer
- radiation
- corticosteroids
- aging
- predisposition to infections

Immune Checkpoint Controls

health

- preventing uncontrolled activation of immune system

cancer

- cancer cells send molecular signals to switch off immune system
- cancer cells ‘hijack’ host tissue cells and other immune cells (Tregs, MDSCs) to switch off immune system and inhibit infiltration of killer T cells into the tumor

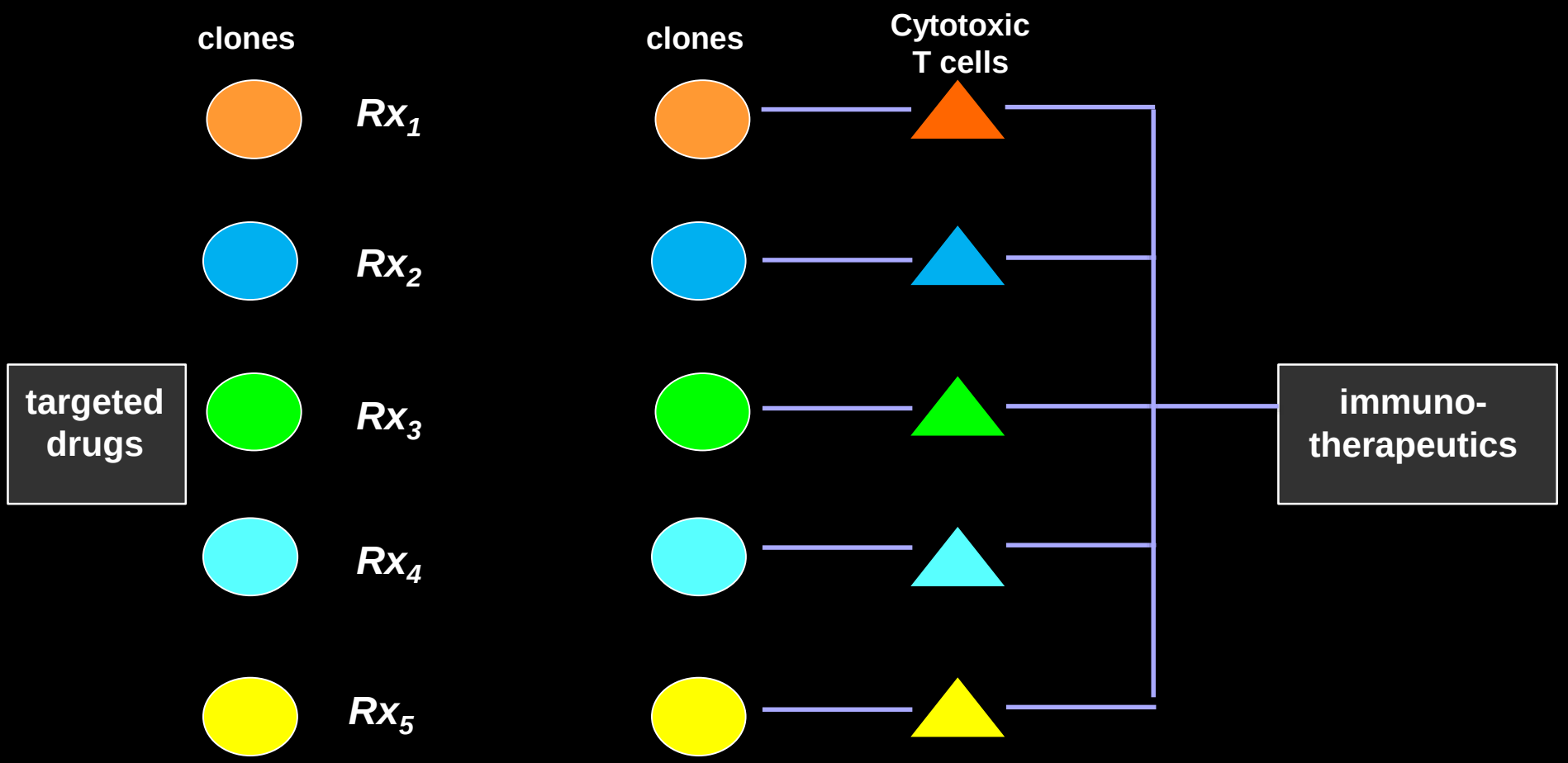
Setting the Immune System Free To Combat Cancer

Host Immune-Tumor Interactions

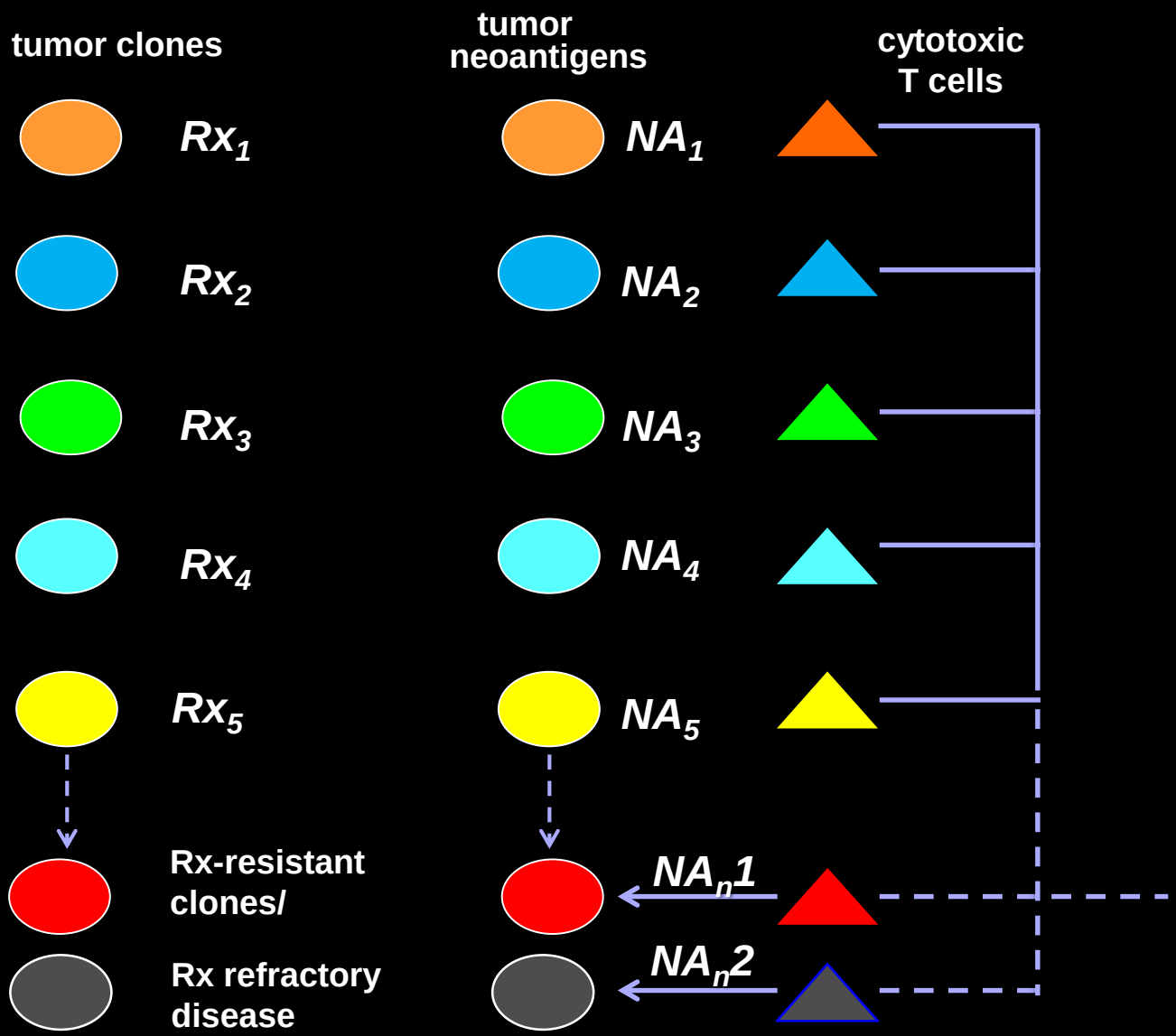
Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion
versus
Activation of Host T Lymphocyte Clones to Kill (Neo)Antigen-Specific Tumor Clones

Therapeutic Strategies for Circumvention of Clonal Diversity in Malignant Tumors: Single Target Drugs (Rx) versus Immunotherapeutics (Irx)



Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance



adaptive evolution of immune response and expanded cytotoxic T cell responses

Overcoming Tumor-Induced Immune Inhibition: Immune Checkpoint Inhibitors

MERCK

Bristol-Myers Squibb

Why Are Some Cancer Types More Responsive to Immune Checkpoint Blockade?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck
- colorectal (MSI-high)

Less Responsive

- pancreatic
- colorectal (MSI-low)
- ovarian

Immunogenic Versus Non-Immunogenic Tumors

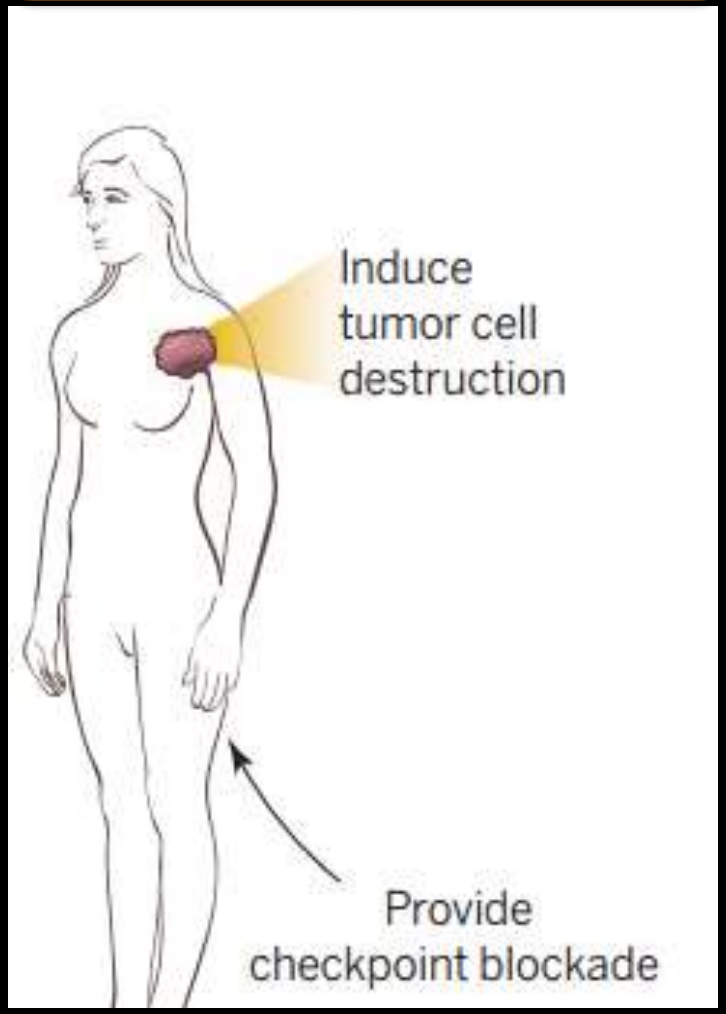
Immunogenic	Non-Immunogenic
‘hot’	‘cold’
‘inflamed’	‘non-inflamed’
‘stimulatory’	‘silent’
high mutagenic burden	low mutagenic burden
high tumor neoantigen expression	low tumor neoantigen expression

Realizing the Promise of Immune Checkpoint Inhibition

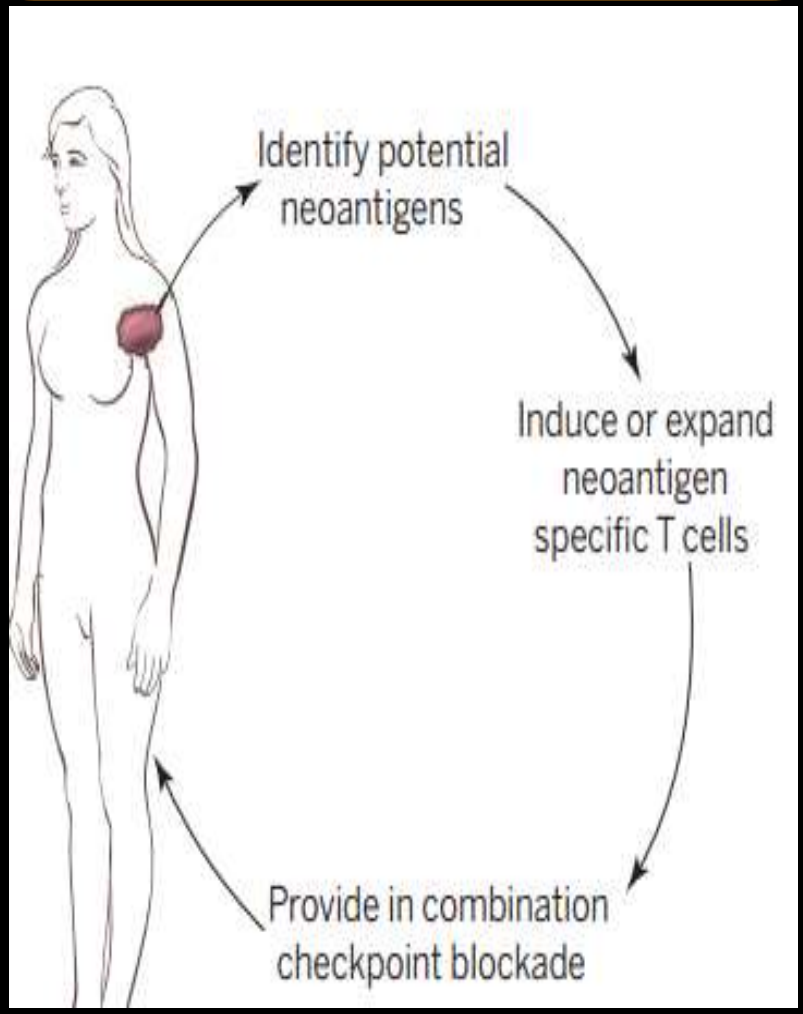
- wide variation in R_x response rates
  - only 20 - 40% positive responses in the most responsive tumors
- lack of diagnostic tests to predict responder vs. non-responder patients
- will I/O combinations increase response rates?
- cost

Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

Immune Checkpoint Modulation



Adoptive Cell Therapy TILs, TCRs, CARs



Adapted From: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69

Engineering Killer T Cells for Cancer Therapy

- killer T cells harvested from cancer patients
- harvested cells genetically engineered in vitro to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)
  - TCR/CAR genes delivered by viral vectors
  - TCRs must be genetically matched to the patients immune type
- challenge of creating TCR/CARs for diverse neoantigens
- cost and complexity of ‘individualized’ therapy

Is Widespread Adoption of Immunotherapy Economically Feasible?

- direct R_x cost
- indirect care cost
- escalating cost of combination regimens (> $200K)
- extravagant cost of cell-based therapies ($500K - $1.5 million)
- complex clinical management challenges and compatibility with community oncology services

Summary and Key Points

Cancer As a Complex Adaptive System

- cancer as multi-component, ecosystem involving complex interactions between cancer cells and host systems over extended time periods
- genotoxic insult(s), mutations and genomic instability as drivers of cancer initiation and progression
- relentless evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)
- adaptive evolution of tumor cell clones to diverse selection pressures (fitness) to escape destruction by body's immune defense and R_x
- clonal heterogeneity and phenotypic diversification pose formidable challenges for successful treatment

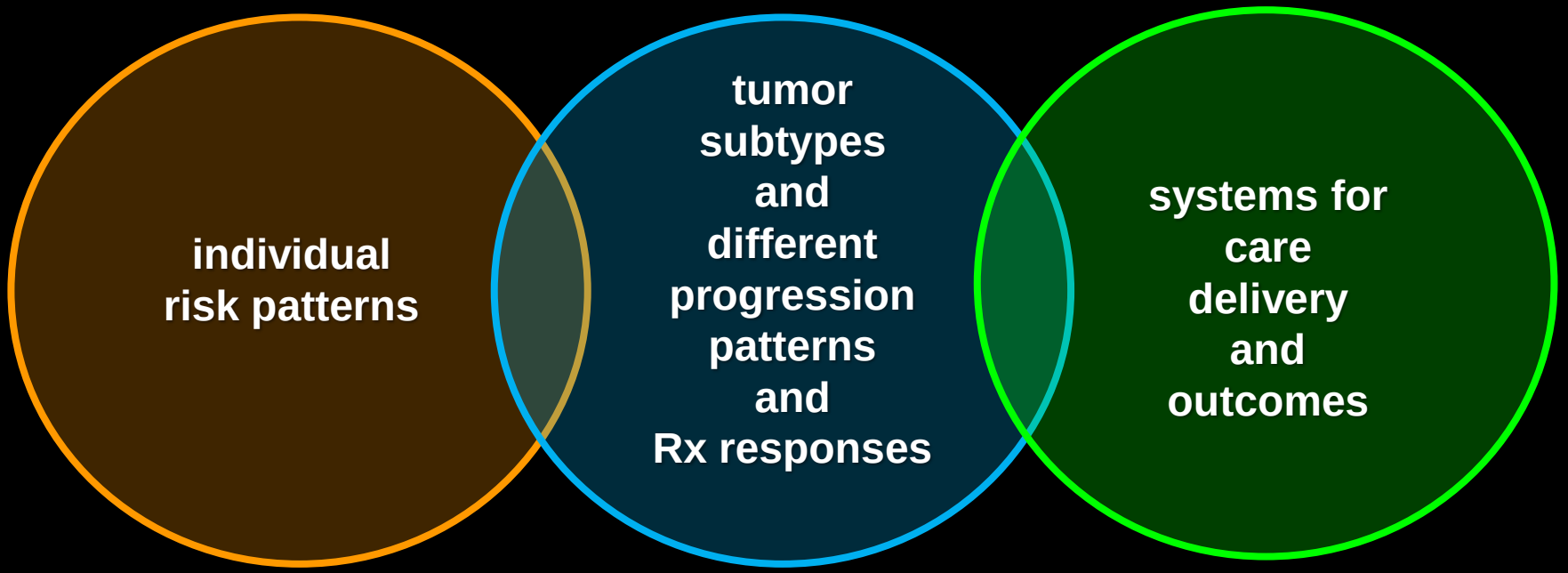
Cancer R_x: Ugly Realities

- in the majority of cancers R_x efficacy (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)

Aspirations for Improved Cancer Treatment

- maximize the efficacy and safety of therapeutic interventions against advanced (metastatic) disease
  - the promise of immunotherapy
- mobilization (reactivation) of body's immune defenses to detect and destroy all clones
  - how to expand efficacy ?
  - is the cost of immunotherapy sustainable ?

Cancer as a Multi-Dimensional Dynamic Interaction Between Multiple Complex Adaptive Systems



- germ line predisposition
- environmental carcinogens
- lifestyle

- precision oncology
- new standards for care

- access to care
- cost of care
- quality of care

Future Challenges in Cancer Care

The Demographics of an Ageing Society And Projected Increased Cancer Incidence

Infinite Demand Versus Finite Resources: The Adequacy of Clinical Infrastructure and Economic Sustainability

Defining Treatment Value: Cost, Quality-of-Life and Outcomes

Complex Clinical, Scientific, Economic, Ethical and Legal Issues