Complex Adaptive Systems Initiative
Arizona State University

BIO 302: 26 February 2018

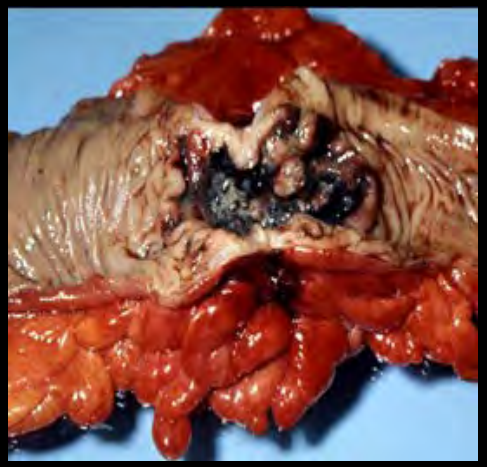
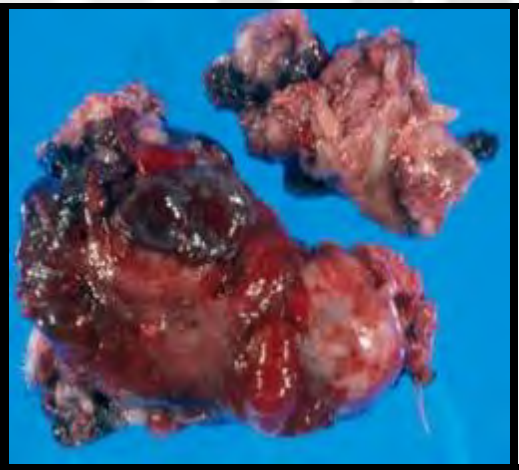
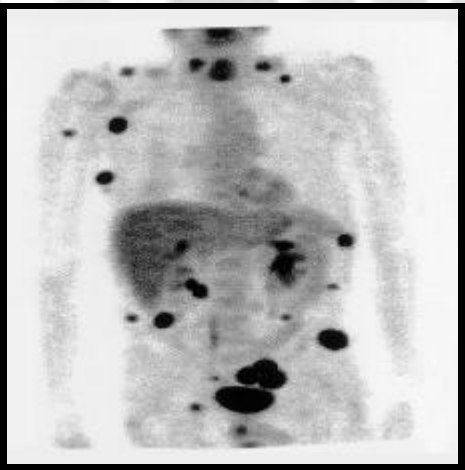
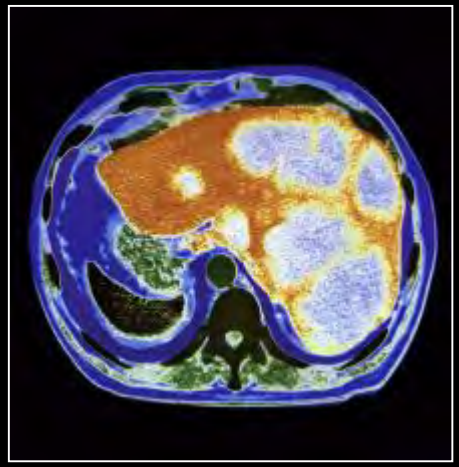
Cancer as a Complex Adaptive System: Cancer Progression, Evolutionary Dynamics and Implications for Treatment

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

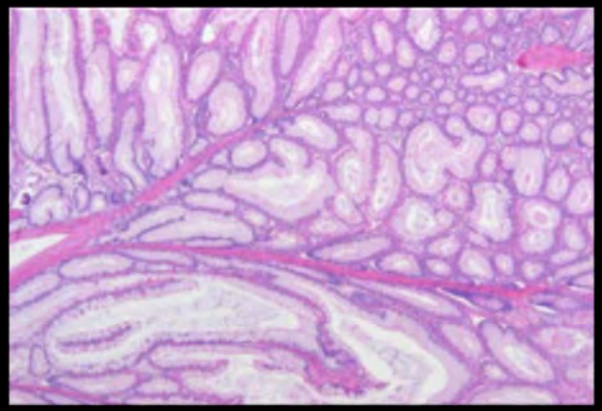
New Diagnoses: 1.2 million/year in USA

Deaths: 595,000 (2017)

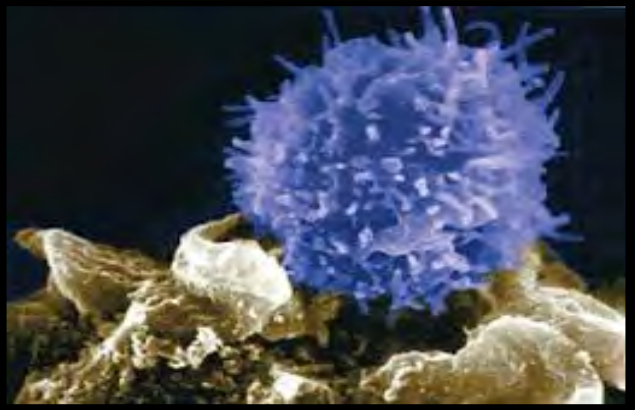
The Complex Biology of Cancer Progression and Treatment Resistance

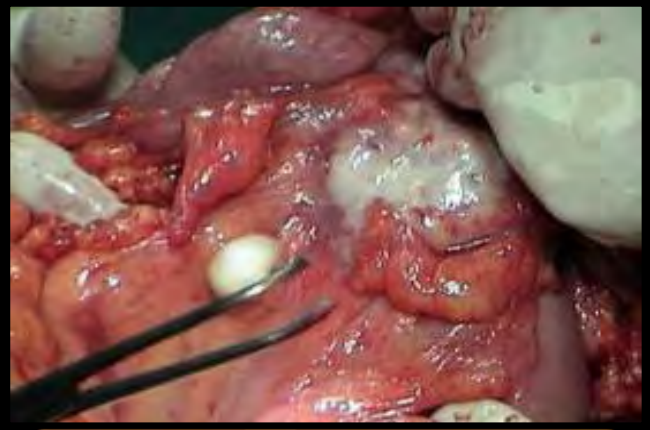
Escape From Controls for Normal Tissue Architecture

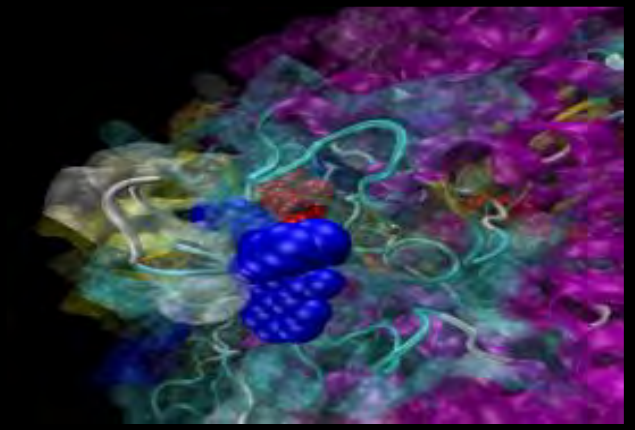


Genome Instability and Emergence of Clonal Variants

Evasion of Detection/ Destruction by Host Immune System



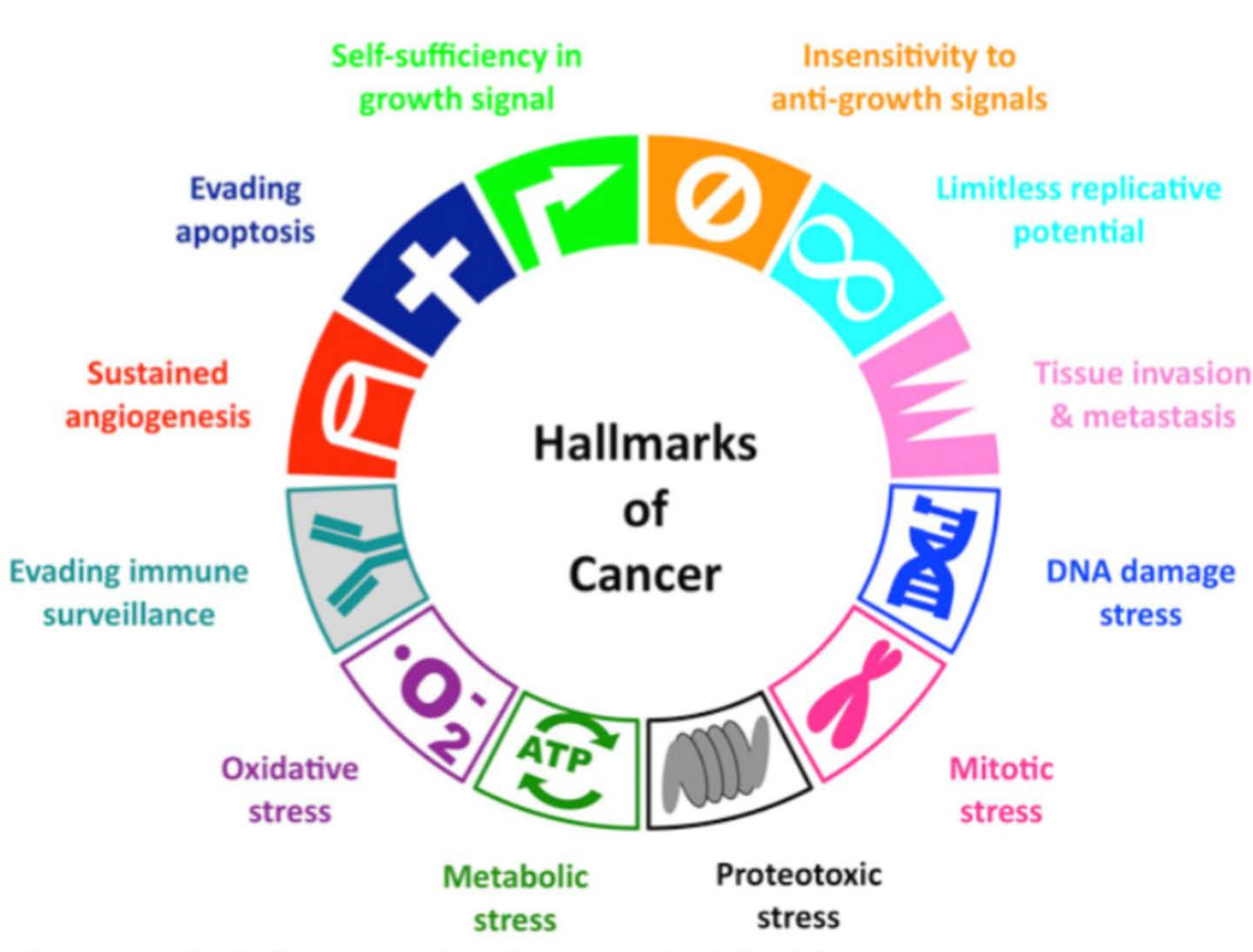




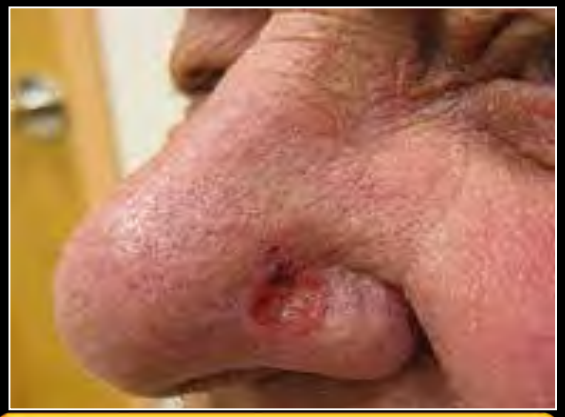
Use of Host Systems to Promote Progression

Invasion and Metastasis

Emergence of Drug-Resistant Clones

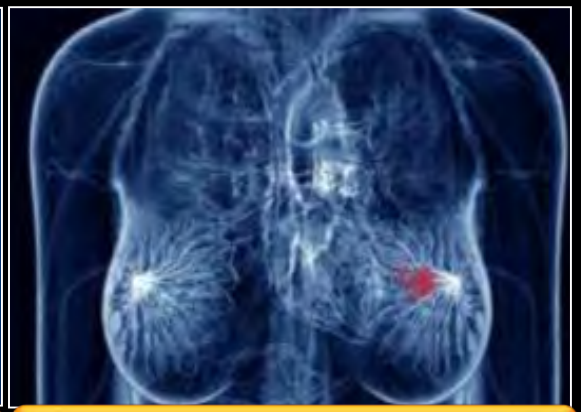

Self-sufficiency in growth signal
Insensitivity to anti-growth signals
Evading apoptosis
Limitless replicative potential
Sustained angiogenesis
Tissue invasion & metastasis
Hallmarks of Cancer
Evading immune surveillance
DNA damage stress
Oxidative stress
Mitotic stress
Metabolic stress
Proteotoxic stress
ATP

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

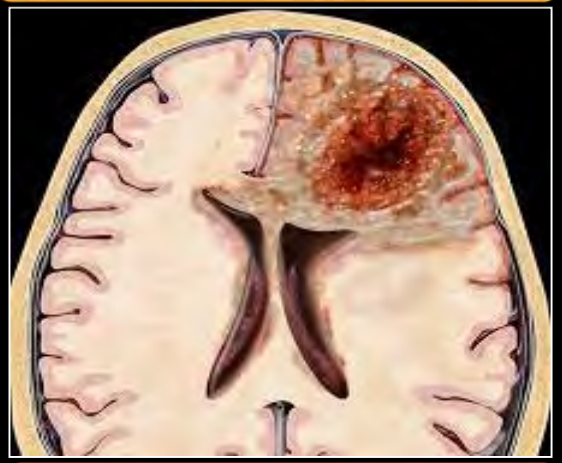


basal cell carcinoma

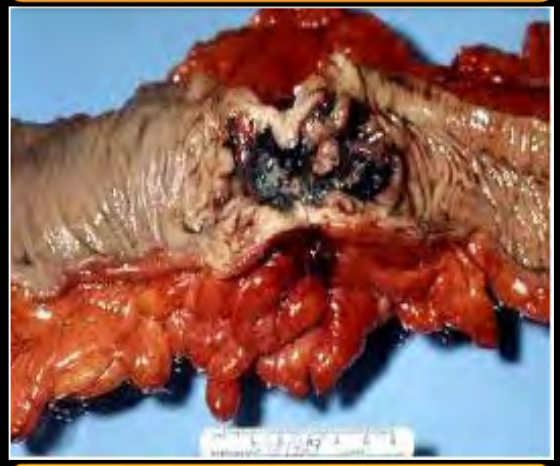
lung



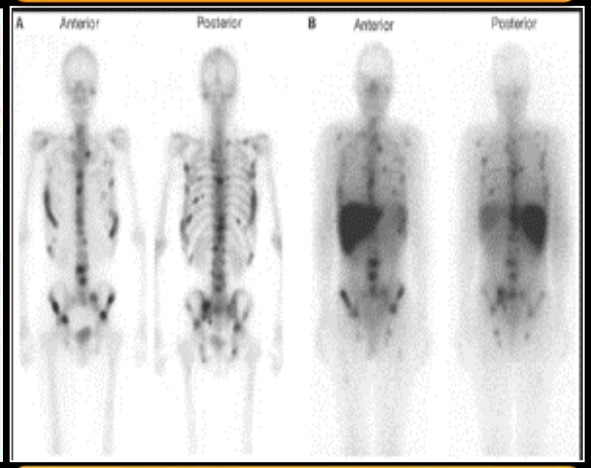
breast



glioblastoma



colorectal

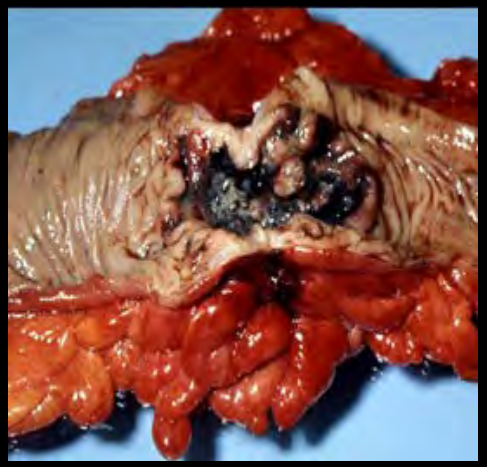


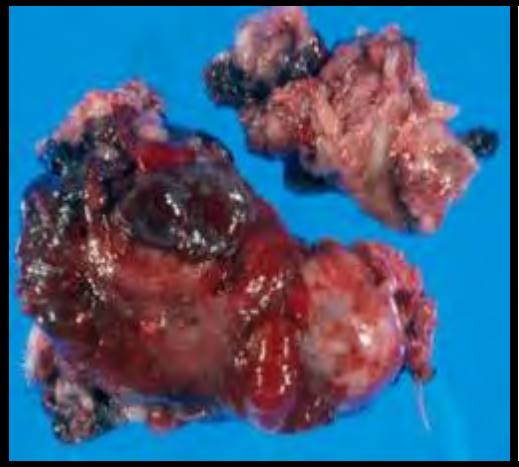
prostate

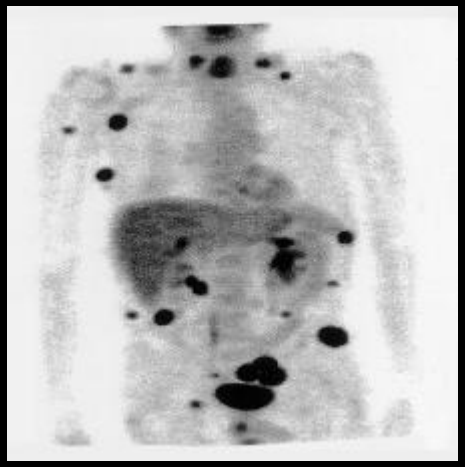
Invasion Without Metastasis

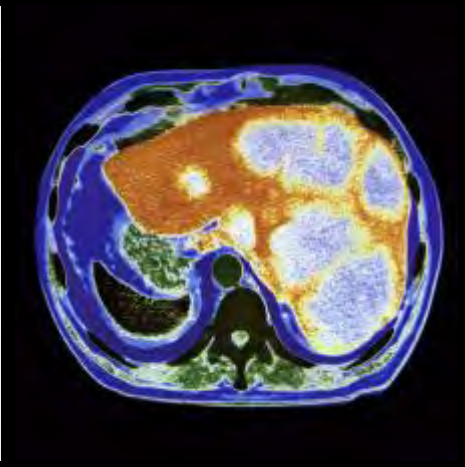
Invasion and Metastasis

Cancer as a Complex Adaptive System

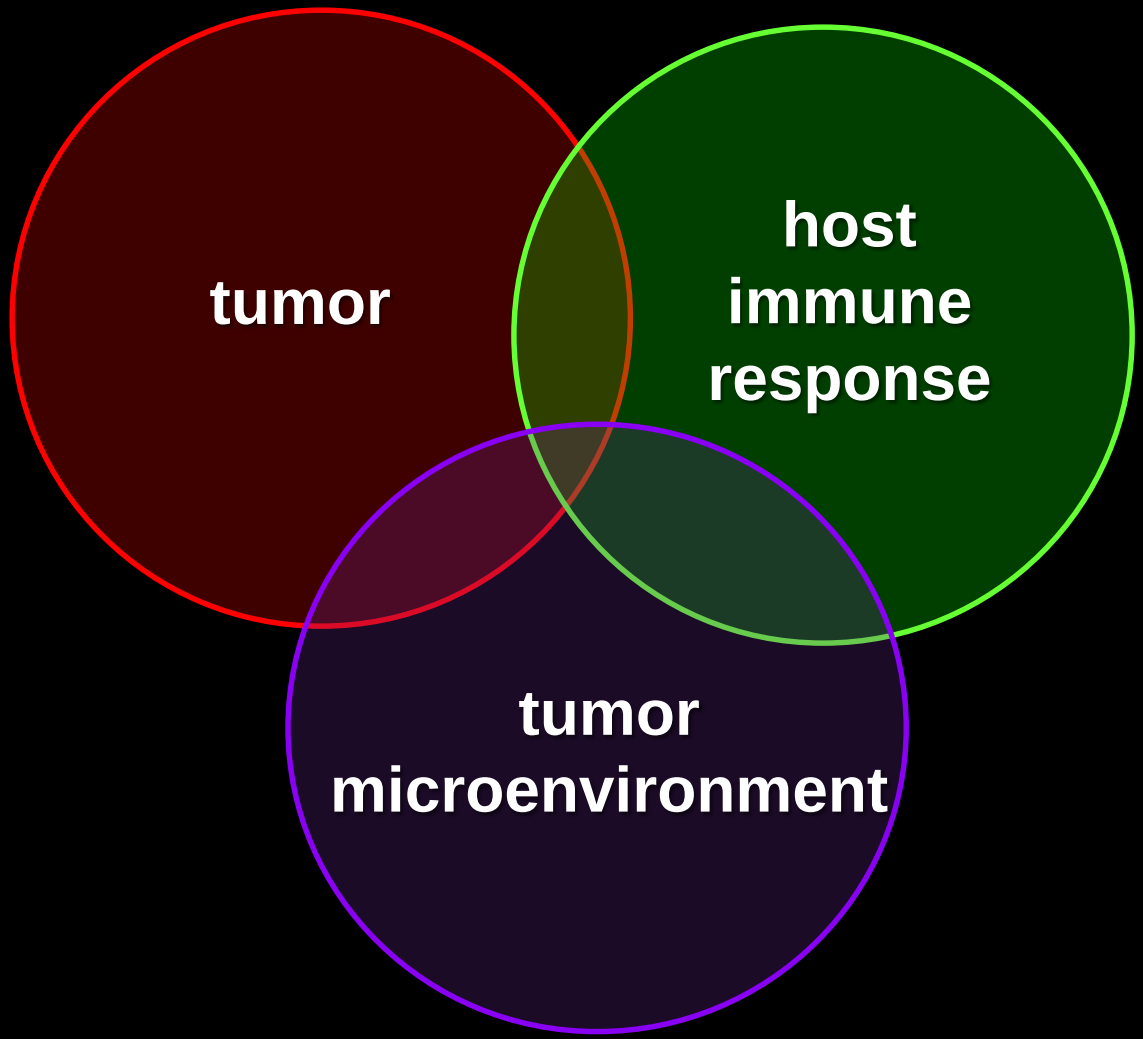




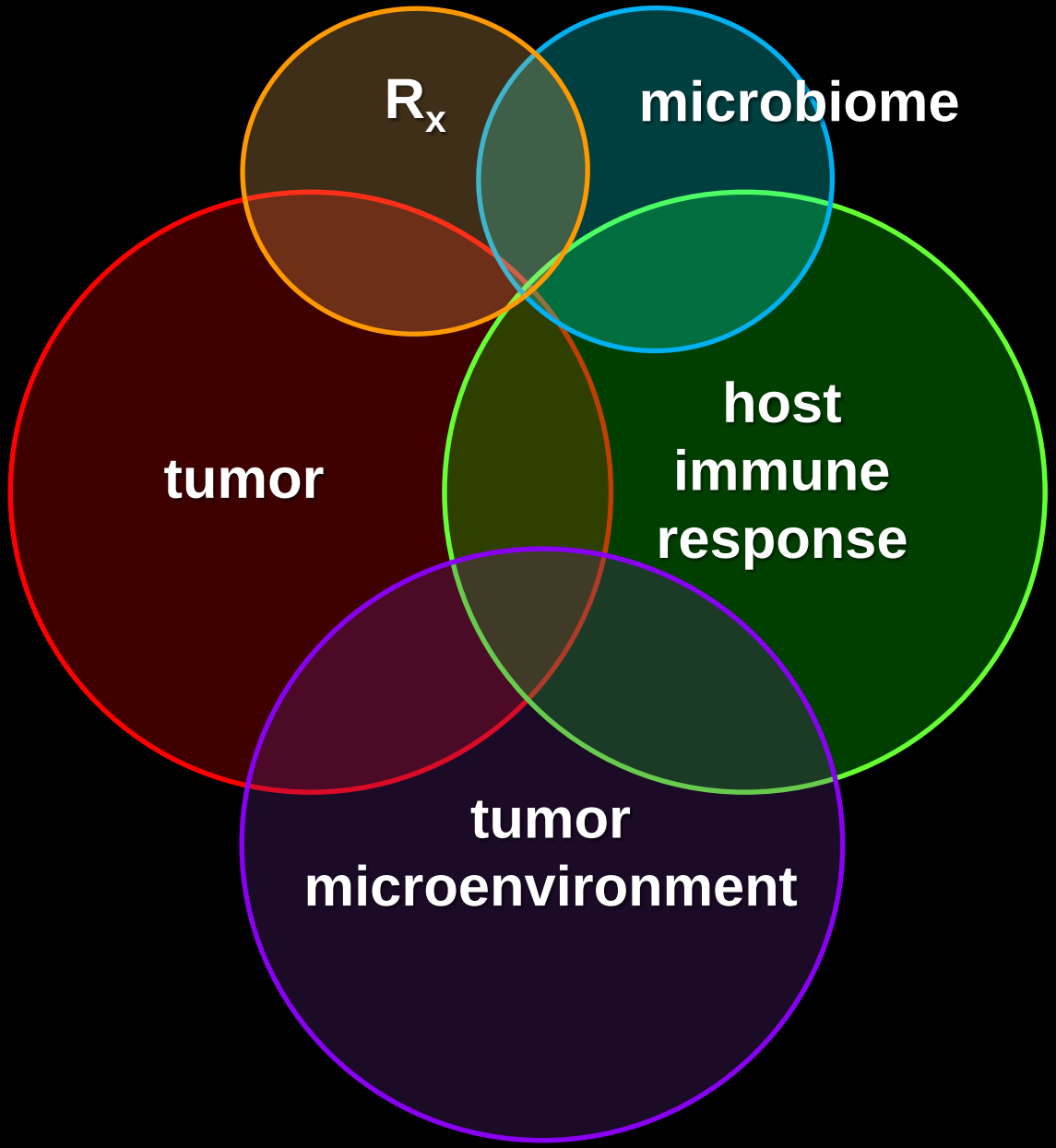




Cancer: A Complex Ecosystem of Tumor and Host Dynamics



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



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

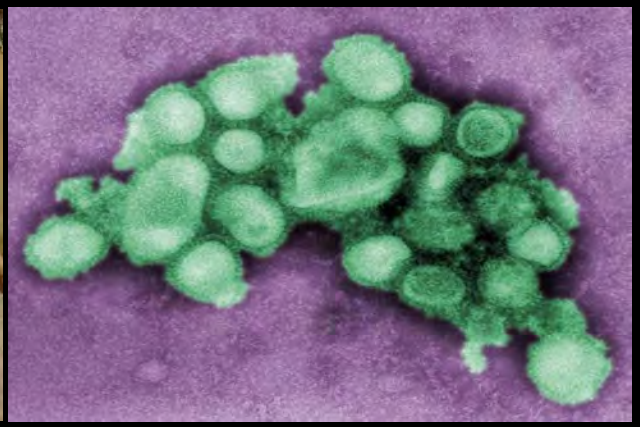
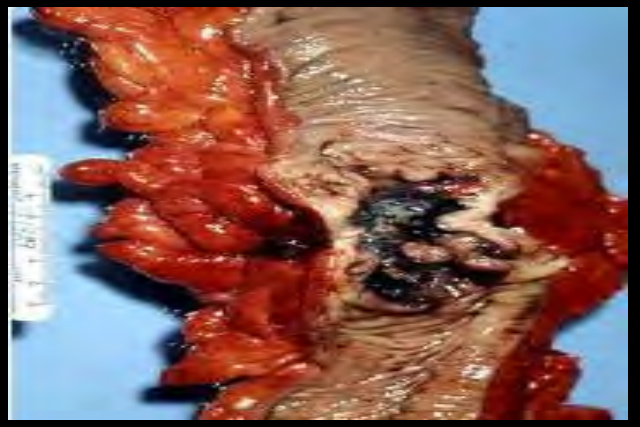







- behavior of components and the assembled whole system is predictable
- proactive awareness of tolerance limits and likely failure points
- performance of the system is fixed and not capable of autonomous evolution

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

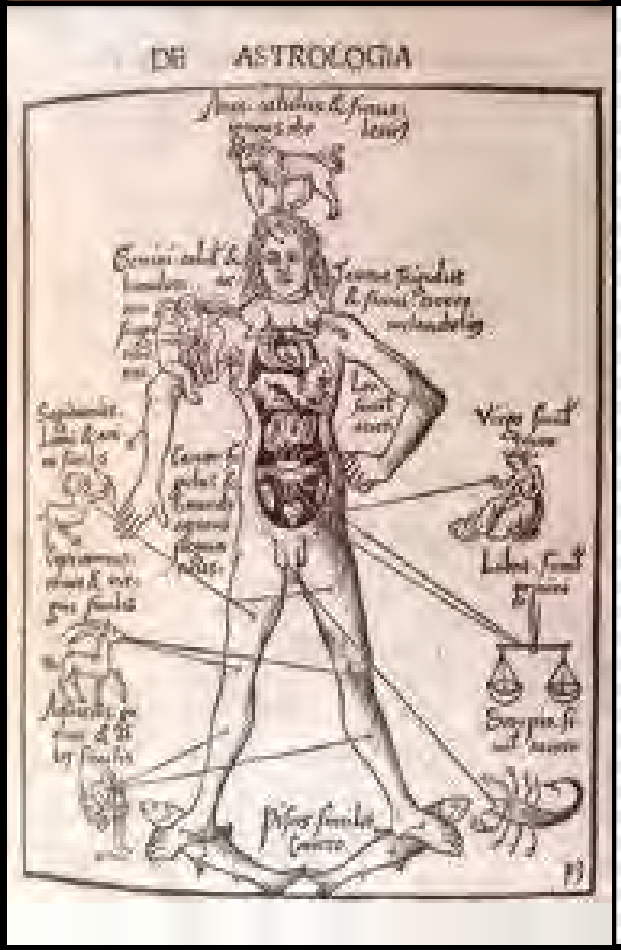
weather/climate	stock markets	geopolitical/ national security
		
		
predator-prey relationships	epidemics/pandemics	disease pathogenesis

Evolvability and Emergence: The Hallmarks of Complex Systems

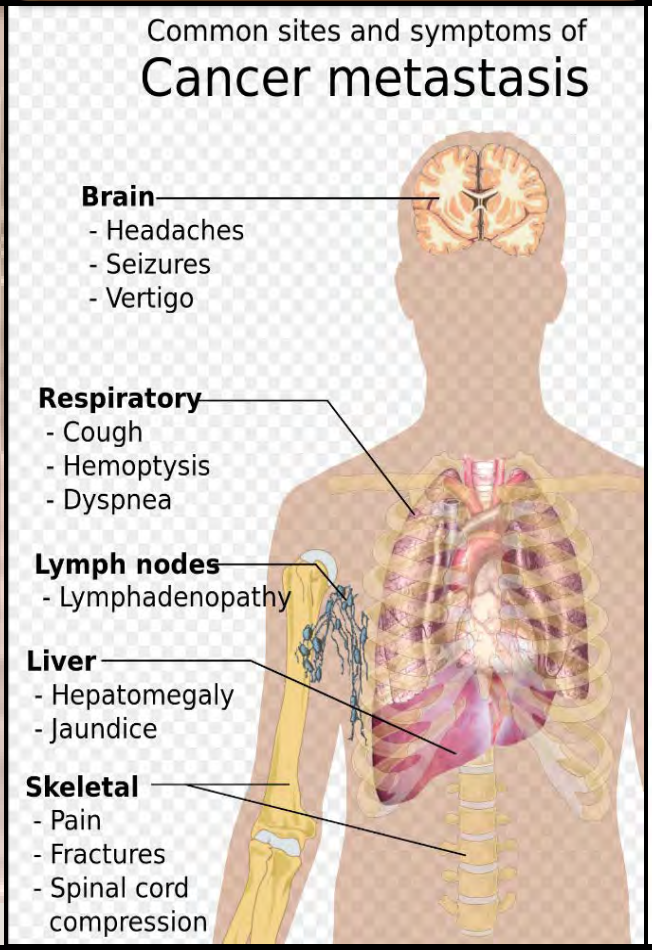
- new properties emerge from the interactions of simpler units (molecules, cells, organs, organisms)
- properties (behavior) of the whole system cannot be reliably predicted from knowledge of the properties of the simpler isolated units
  - "the whole is more than the sum of its parts"
- new and unexpected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

The Path to Precision Oncology:

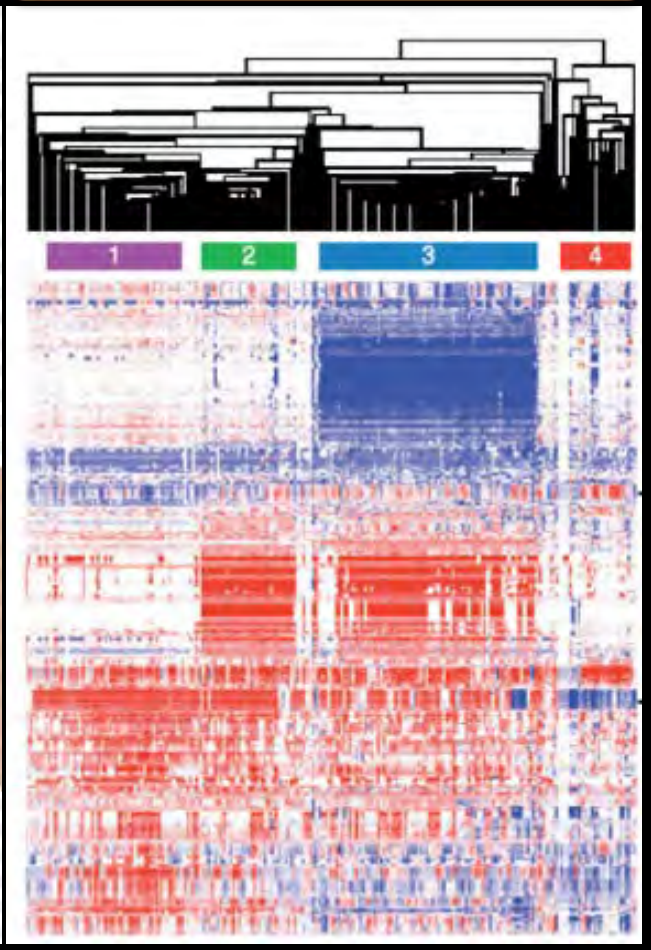
Superstitions



Symptoms

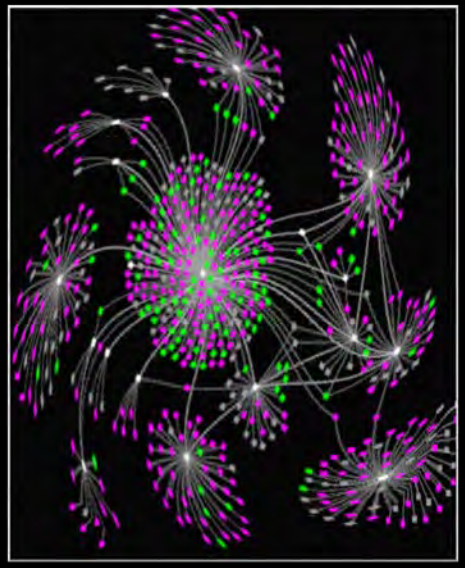


(Molecular) Signatures



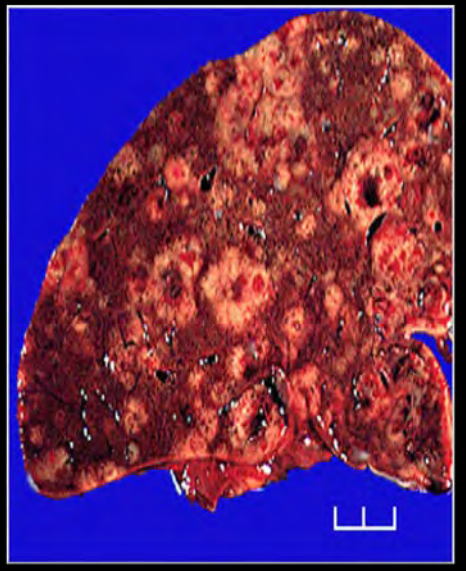
Precision Medicine: Understanding the Disruption of Molecular Information Networks in Disease

encoded information and expression as cell-specific signaling networks



patterns of information flow within signaling networks

stable networks and information fidelity (health)

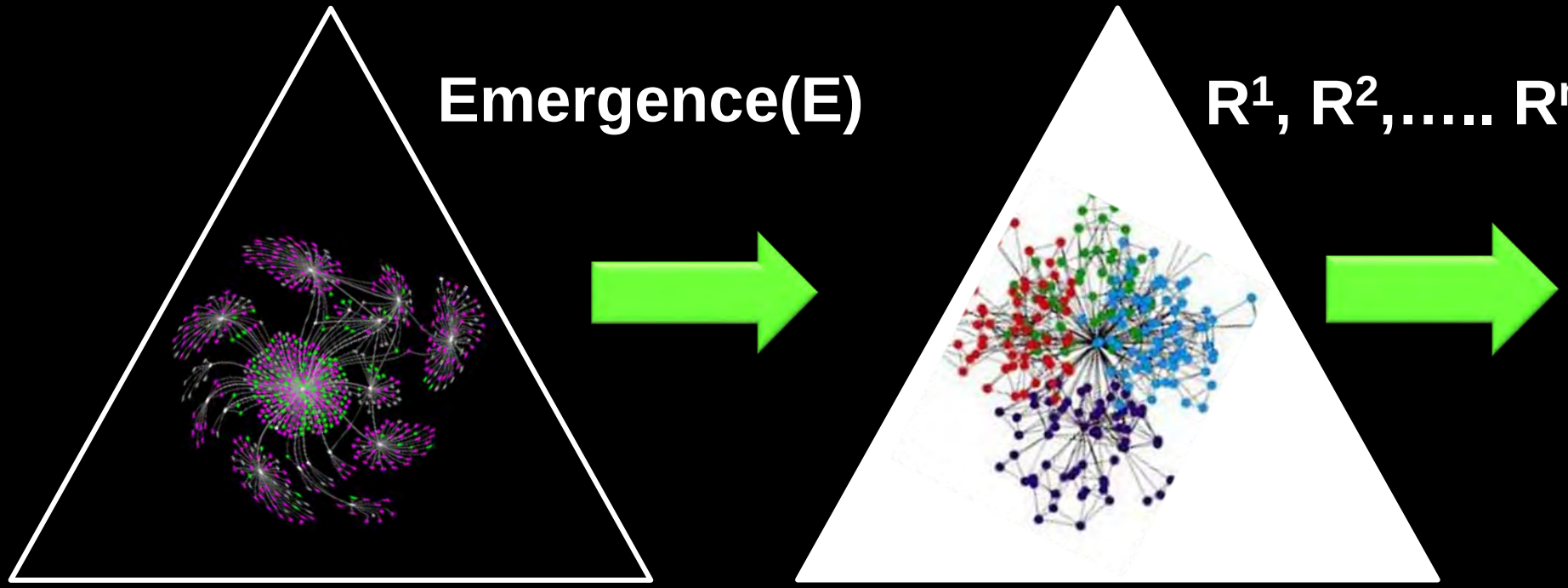


dysregulated networks and altered information patterns (disease)

Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of R_x- Resistance (R)

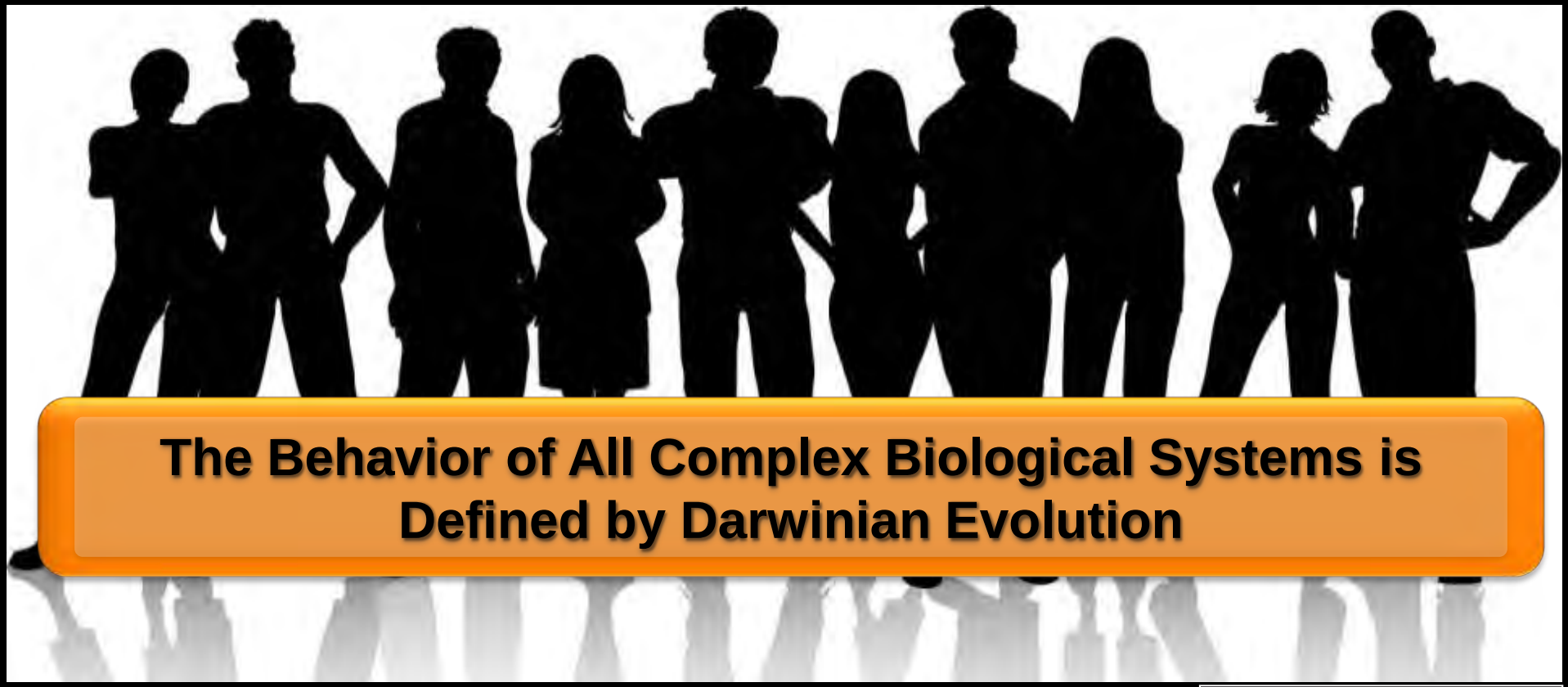
dynamic molecular signaling network topologies

new network topologies to bypass R_x-vulnerable pathways

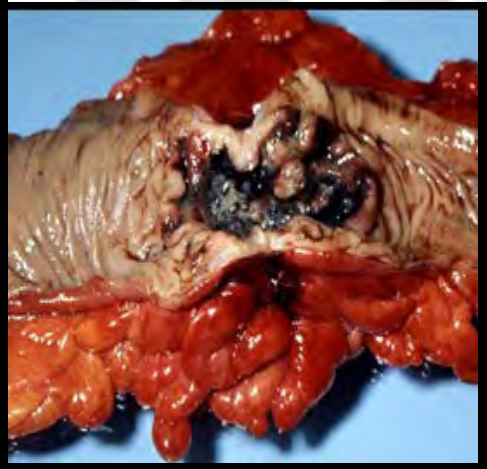


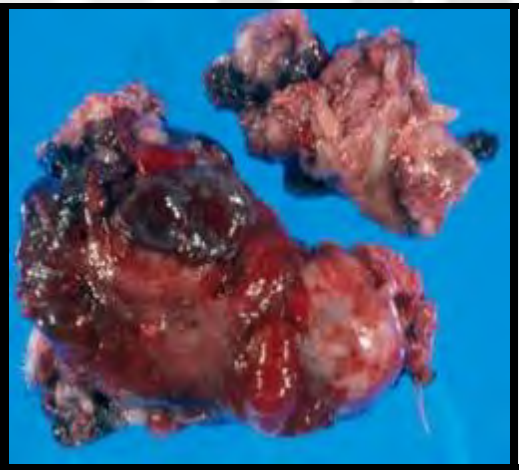
- intrinsic resistance (pre-exist prior to R_x)
- acquired resistance (R_x as selection pressure)

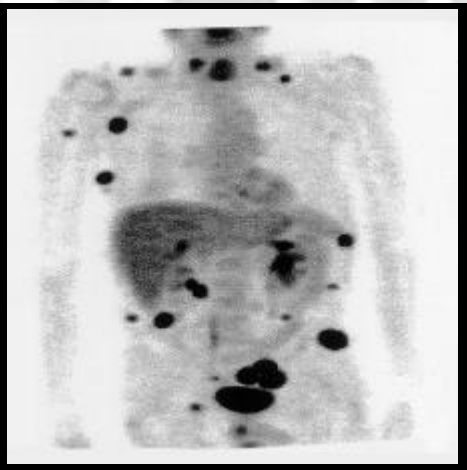
Cancer as a Complex Adaptive System

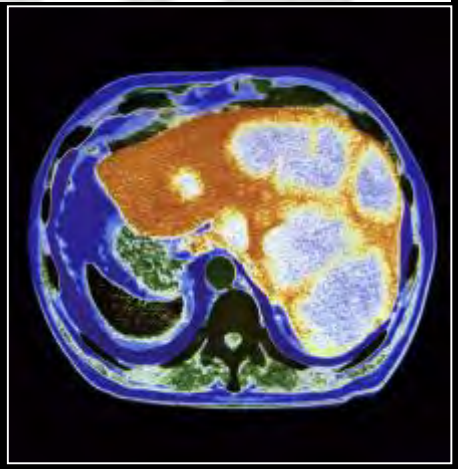


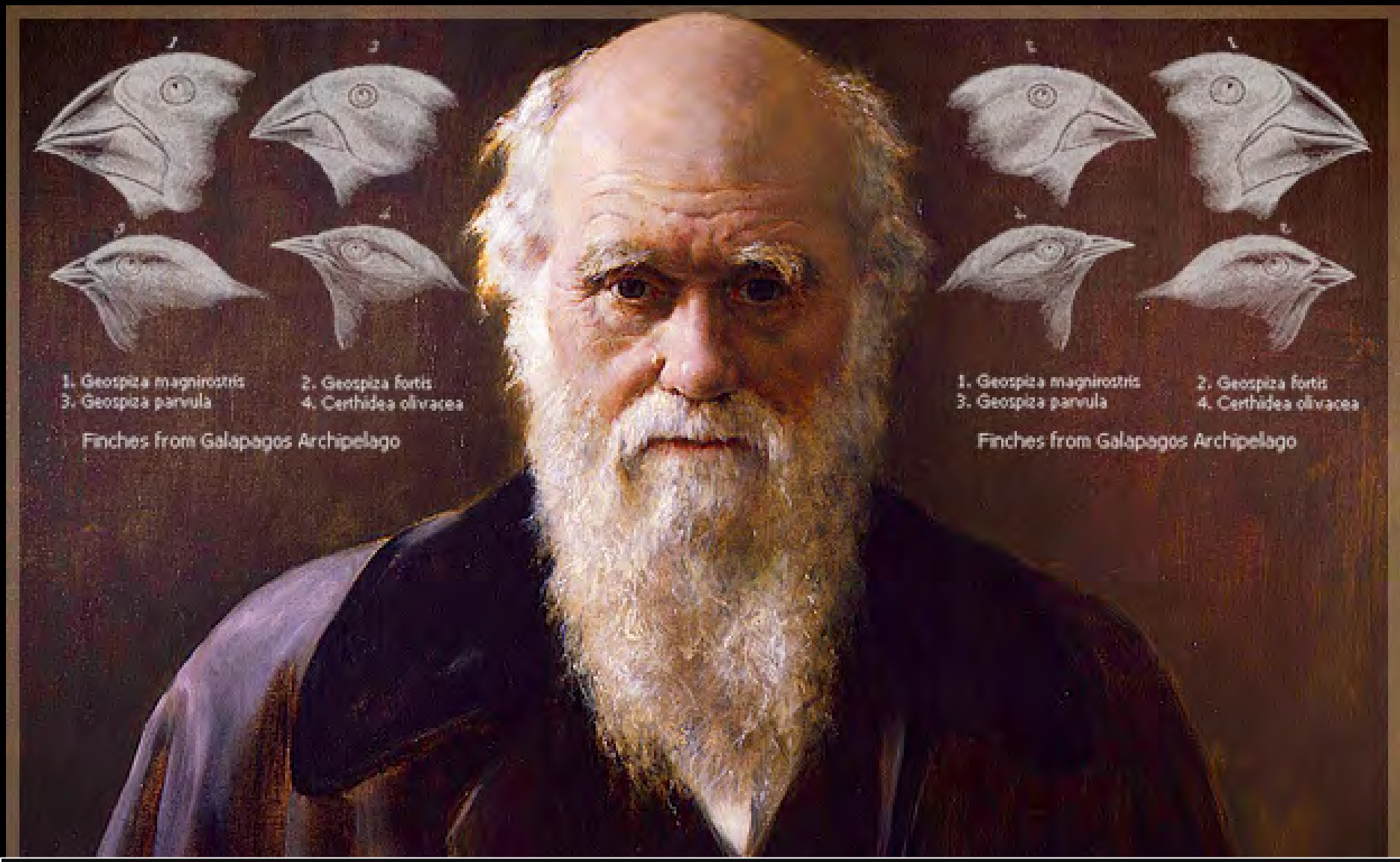
The Behavior of All Complex Biological Systems is Defined by Darwinian Evolution





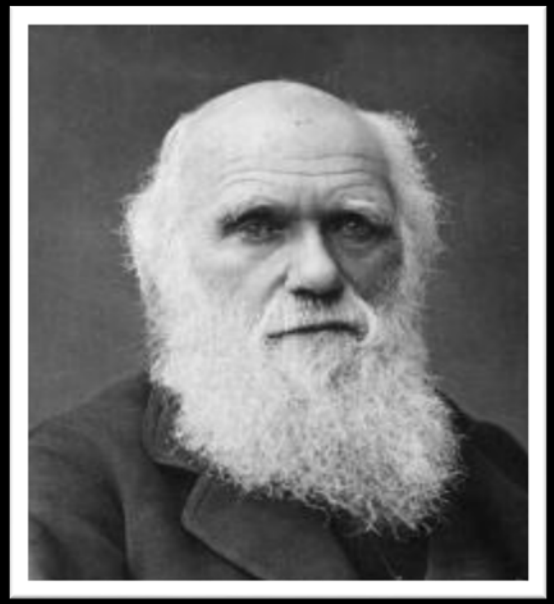






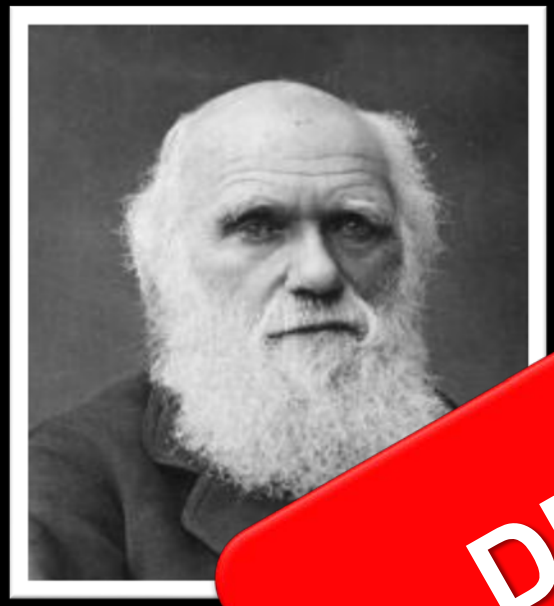
"It is not the strongest of the species that survives, not the most intelligent, but most responsive to *change*."

Darwinian Evolution



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

Darwinian Evolution



- selection by v
- adaptati
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DITTO CANCER

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

- elimination
- equilibrium
- escape

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

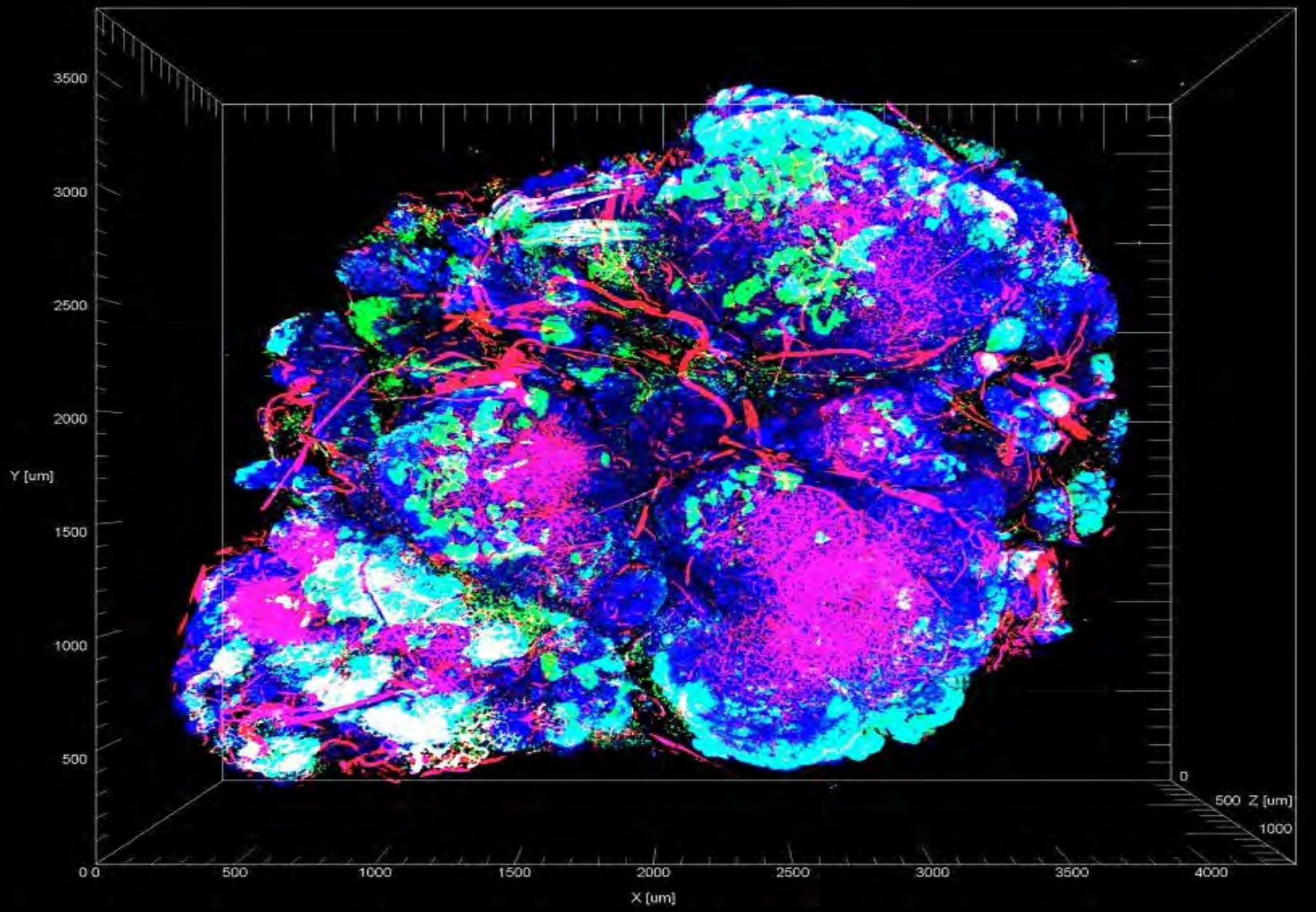
- elimination (detection, surveillance and destruction)
- equilibrium (cancer cells present, but contained)
- escape (breakout and evasion of destruction by body's immune system)

What Makes Cancer So Dangerous and Difficult to Treat

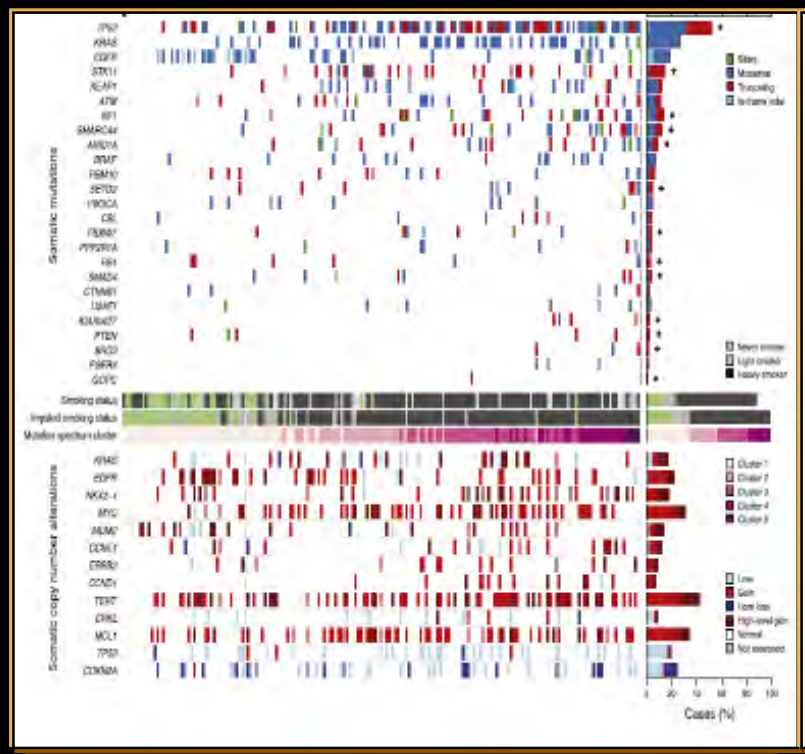
Adaption, Evolvability and Dynamic Heterogeneity

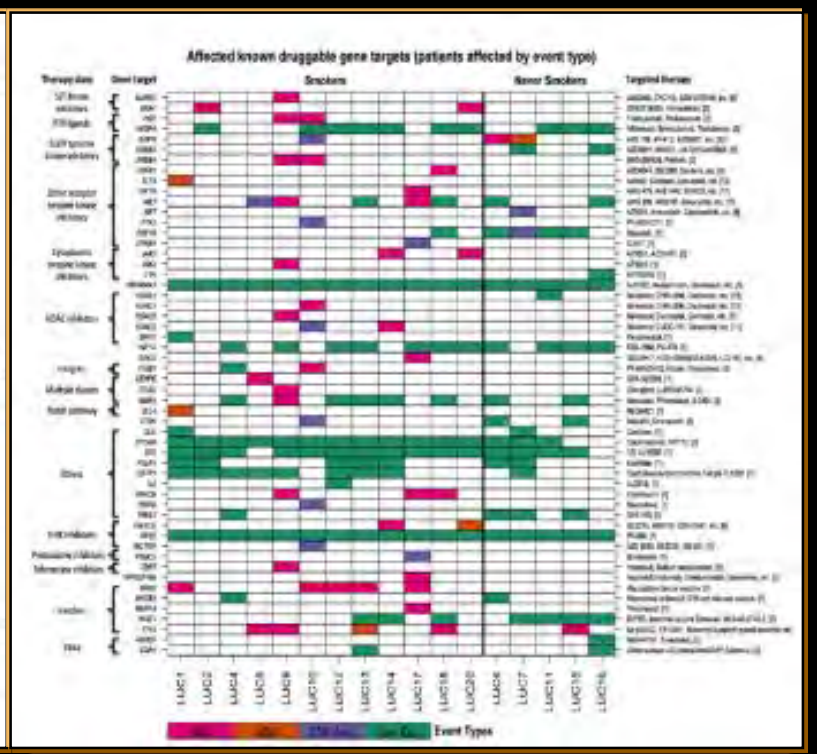
Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression

Mapping Tumor Heterogeneity: Zonal Variation



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



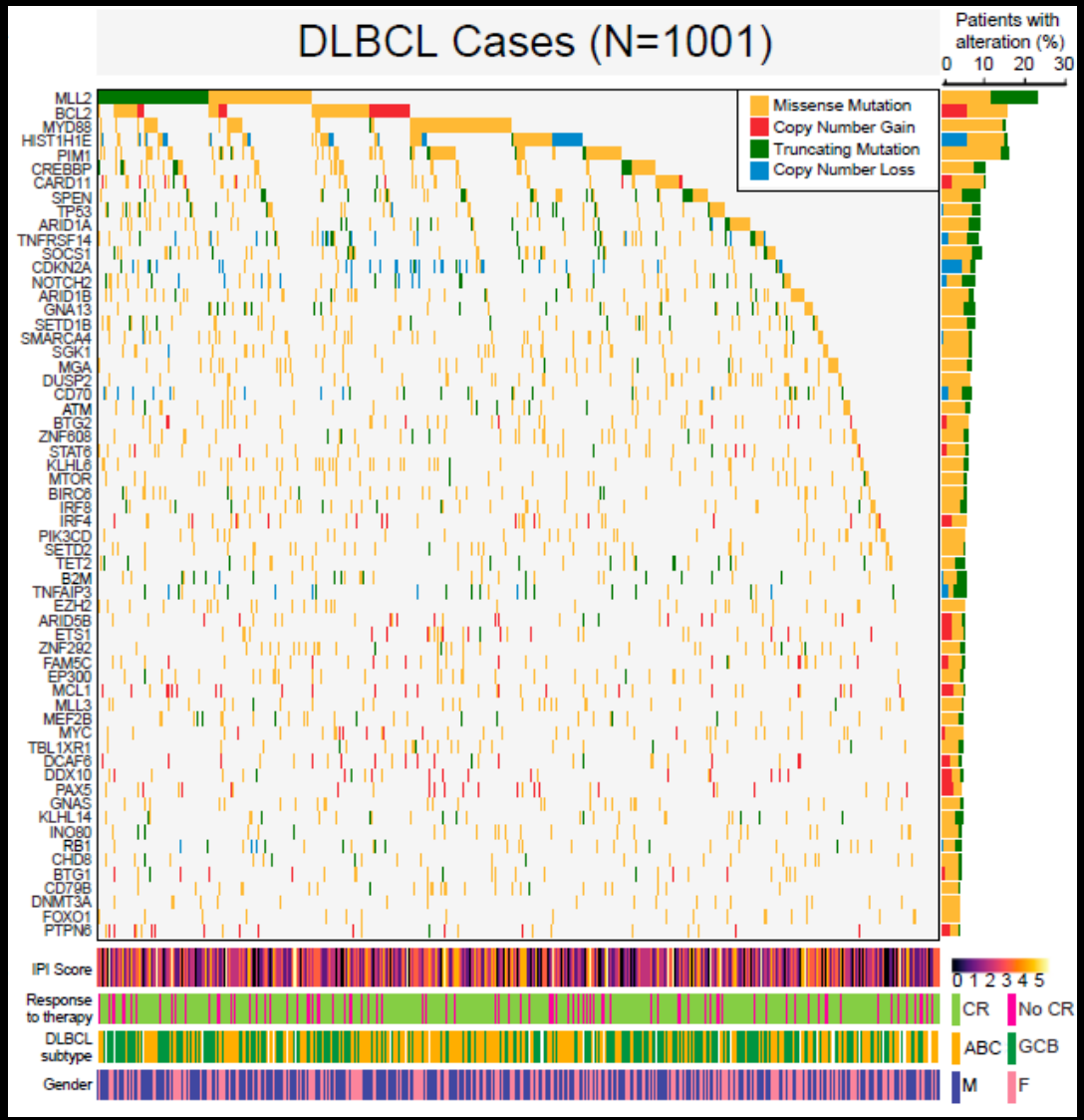


Mutations in Individual Non-small Cell Lung Cancer

Drug Targets in Individual Non-Small Cell Lung Cancers

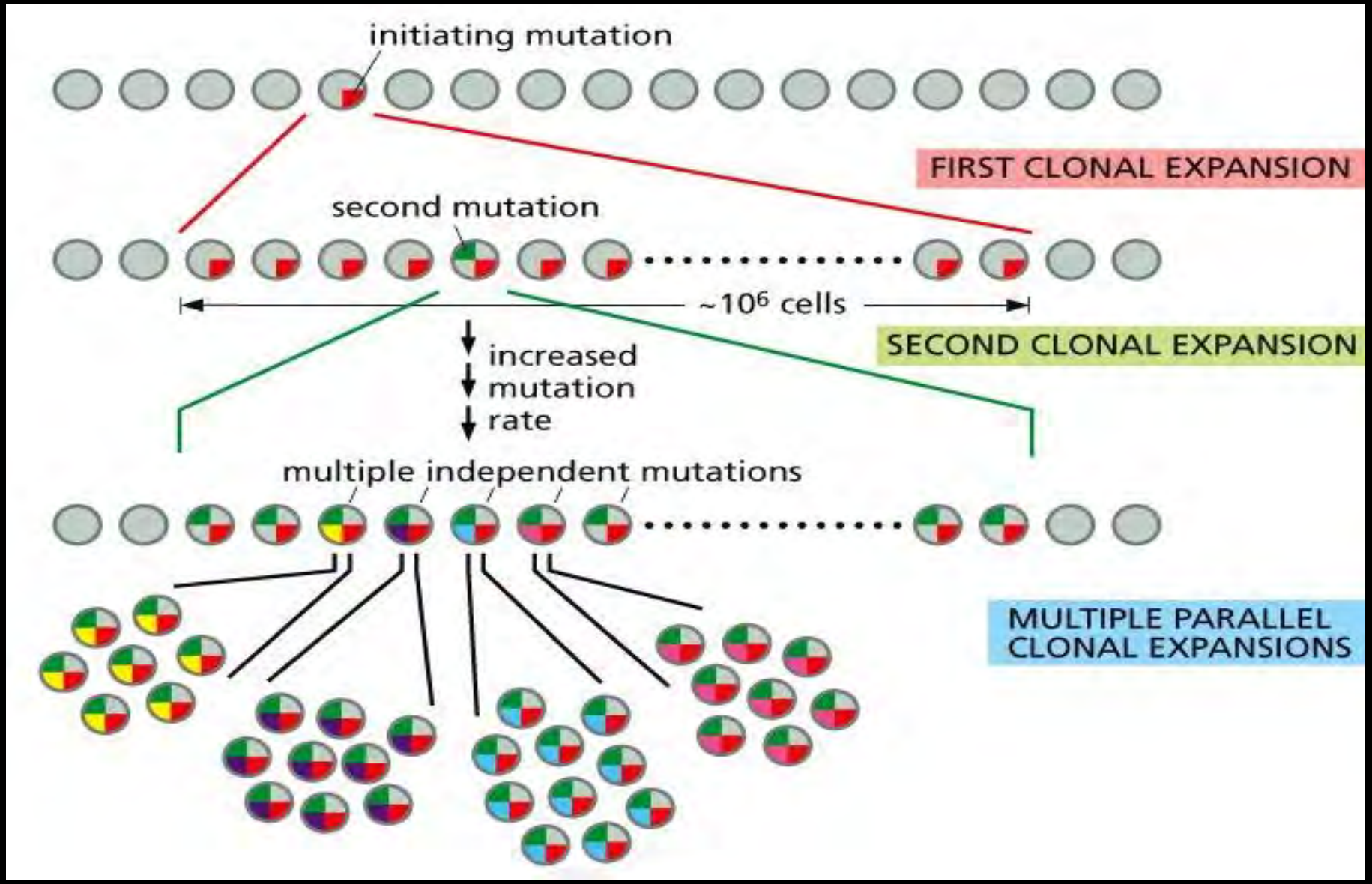
- **“malignant snowflakes”: each cancer carries multiple unique mutations and other genome perturbations**
- **disturbing implications for therapeutic ‘cure’ and development of new R_x**

Genetic and Functional Drivers of Different Large B Cell Lymphomas

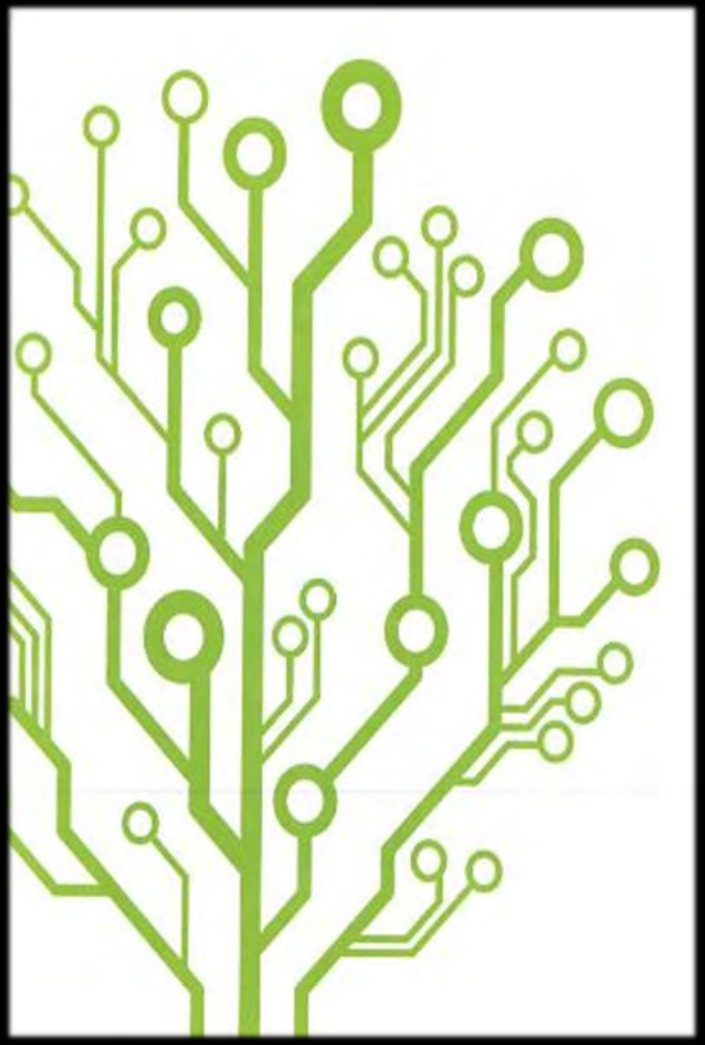


From: A. Reddy et al. (2017) Cell 171, 481

Evolution and Phenotypic Diversification of Tumor Clones and Subclones

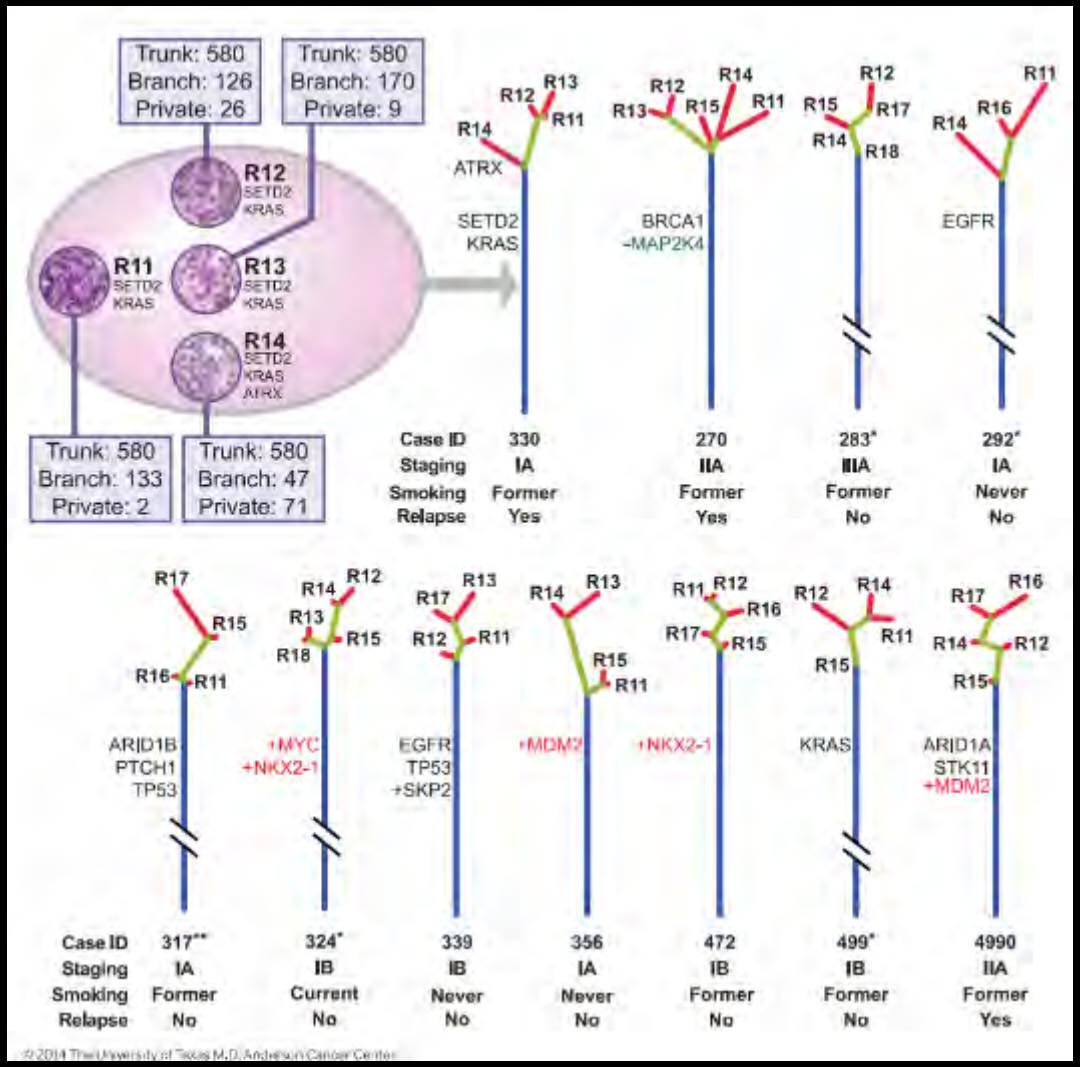


Mapping the Dynamics of Clonal Evolution in the Progression of Malignant Tumors: Clonal Branching



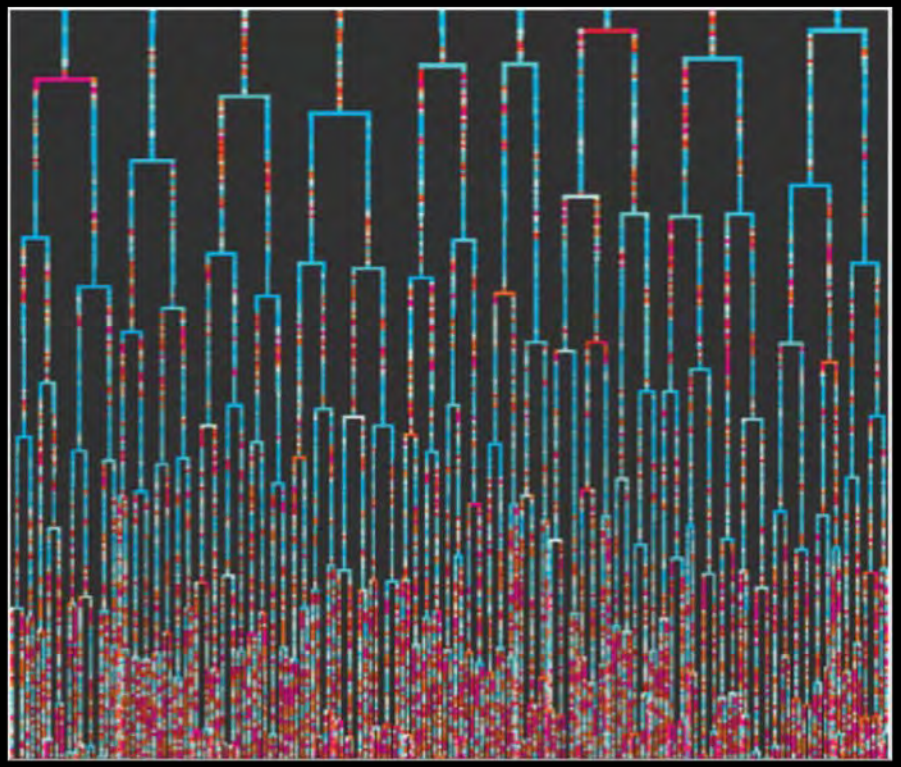
- timing of mutational events
  - ‘early events’ present in clones in both primary tumor and metastases
  - private mutations (unique to individual patients or individual metastatic lesions in same patient) likely have occurred later in progression

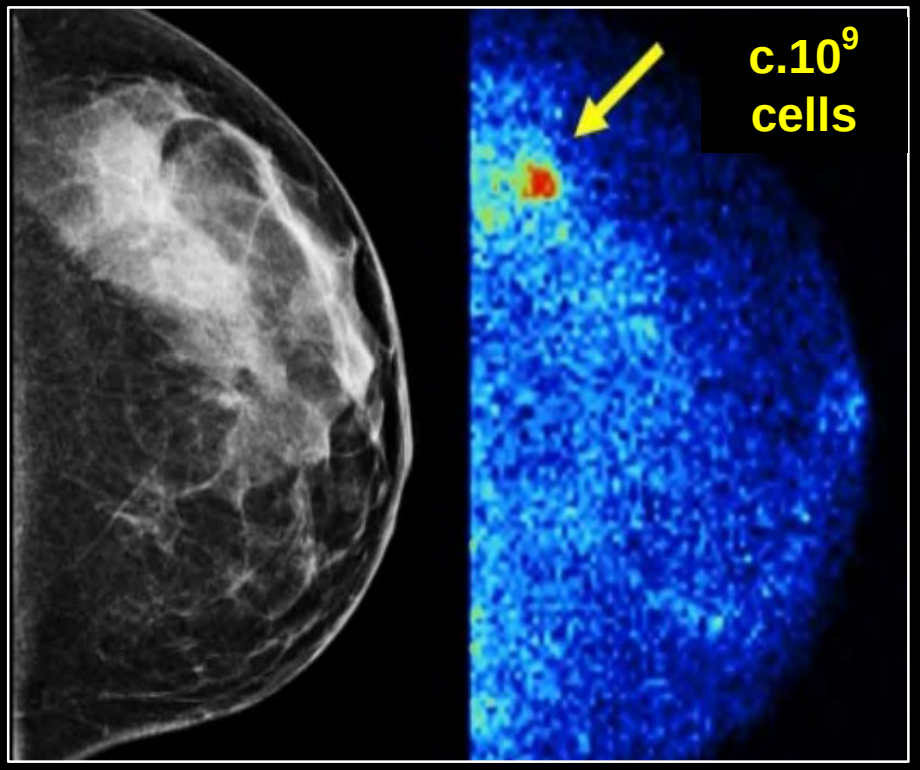
Wagner Parsimony Profiling of Intratumoral Clonal Heterogeneity in 11 Lung Adenocarcinomas and Different Trunk (Blue), Branch (Green) and Private (Red) Branches



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

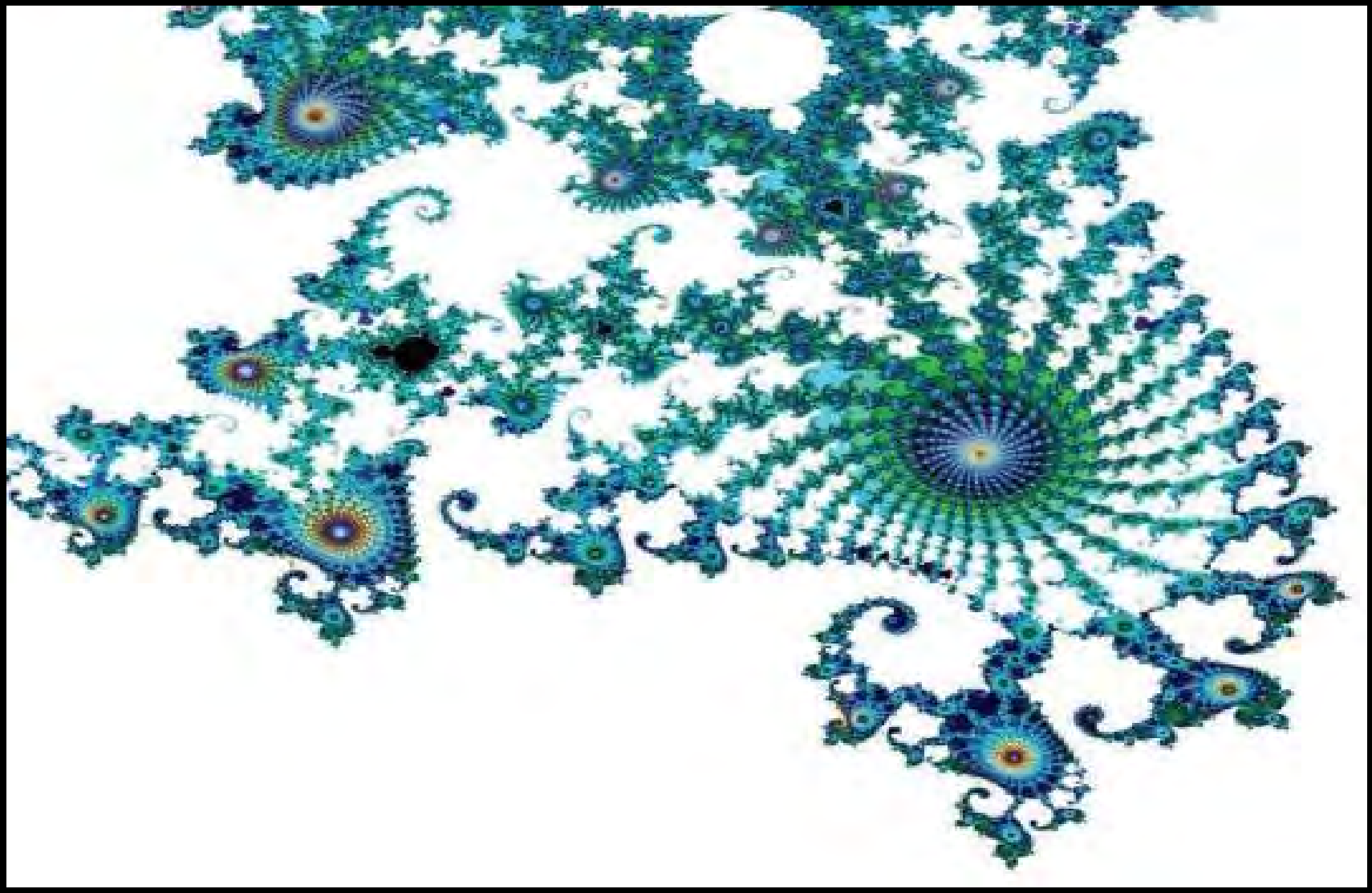
Lineage Trees and Clonal Diversification in Tumor Progression





- normal DNA replication error rates 10^{-6} per cell/generation
- tumor DNA replication error rates 10^{-2} per cell/generation

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



Clonal Heterogeneity:
The Ubiquitous Challenge in Cancer Diagnosis and Treatment

- (epi)genetic and phenotypic changes in tumors arising in different cell types
  - inter-patient heterogeneity
  - intra- and inter-lesional heterogeneity in the same patient
  - effect of R_x on clonal composition

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 one or a few molecular targets/pathways altered in cancer cells
- molecular profiling to ID patients with relevant R_x targets

immunotherapy

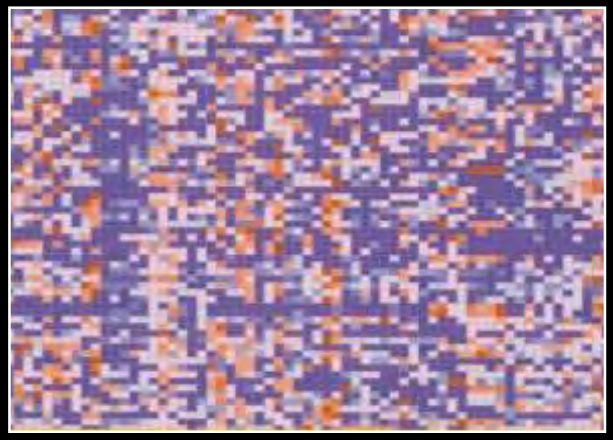
- (re) activation of body's immune defenses to detect and destroy cancel cells

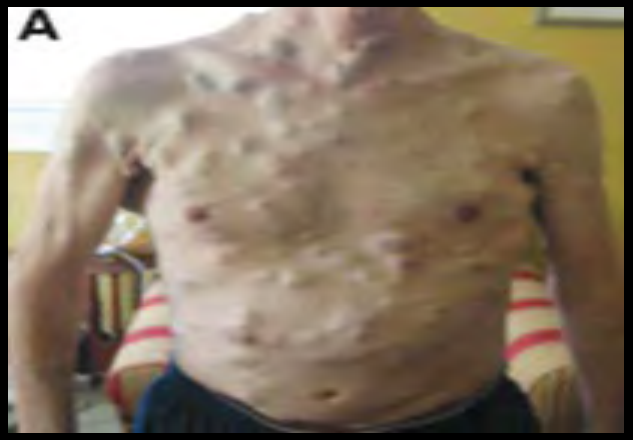
Targeted Therapeutics and the Omnipresent Problem of R_x Failure Due to Emergence of Drug Resistance Clones

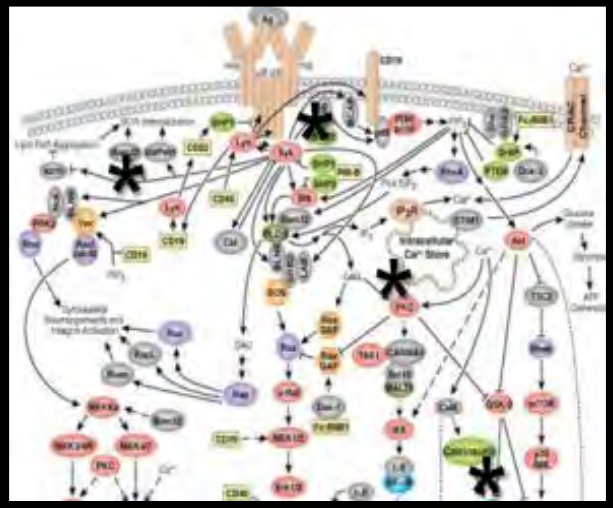
Molecular Subtyping and R_x Targets

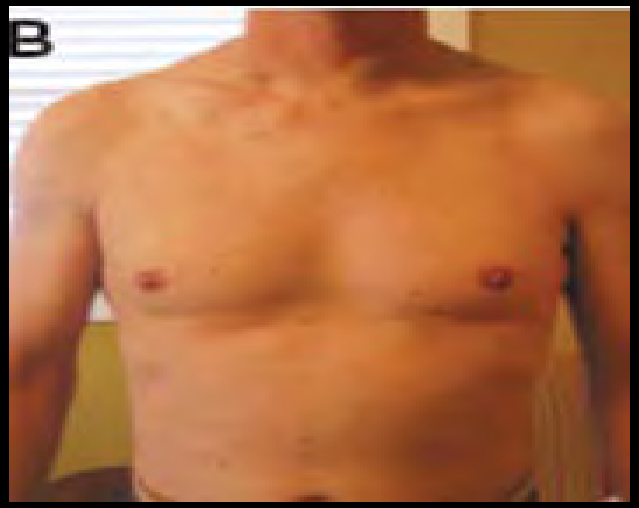
Initial R_x - Response to Targeted R_x

R_x - Resistance via Redundant Molecular Pathways









B = 15 weeks R_x (vemurafenib)

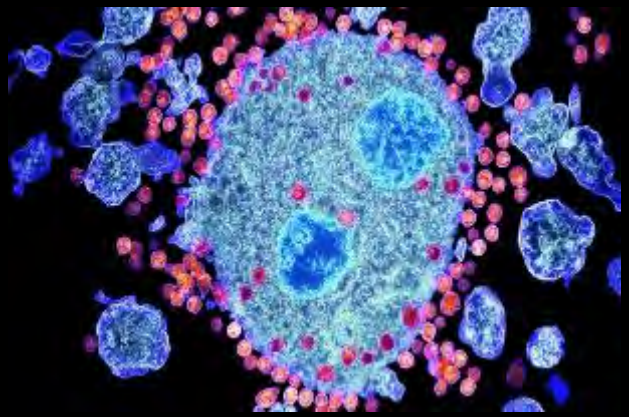
C = 23 weeks R_x and emergence of $MEK1^{C121S}$ mutant

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

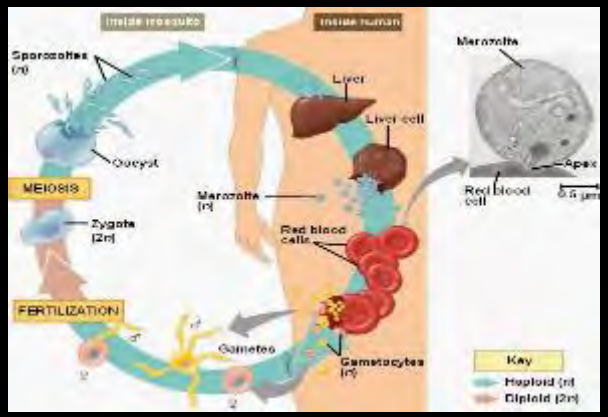
Darwinian Evolution and Selection of Resistant Phenotypes

antibiotics

antivirals



antimalarials



insecticides

herbicides

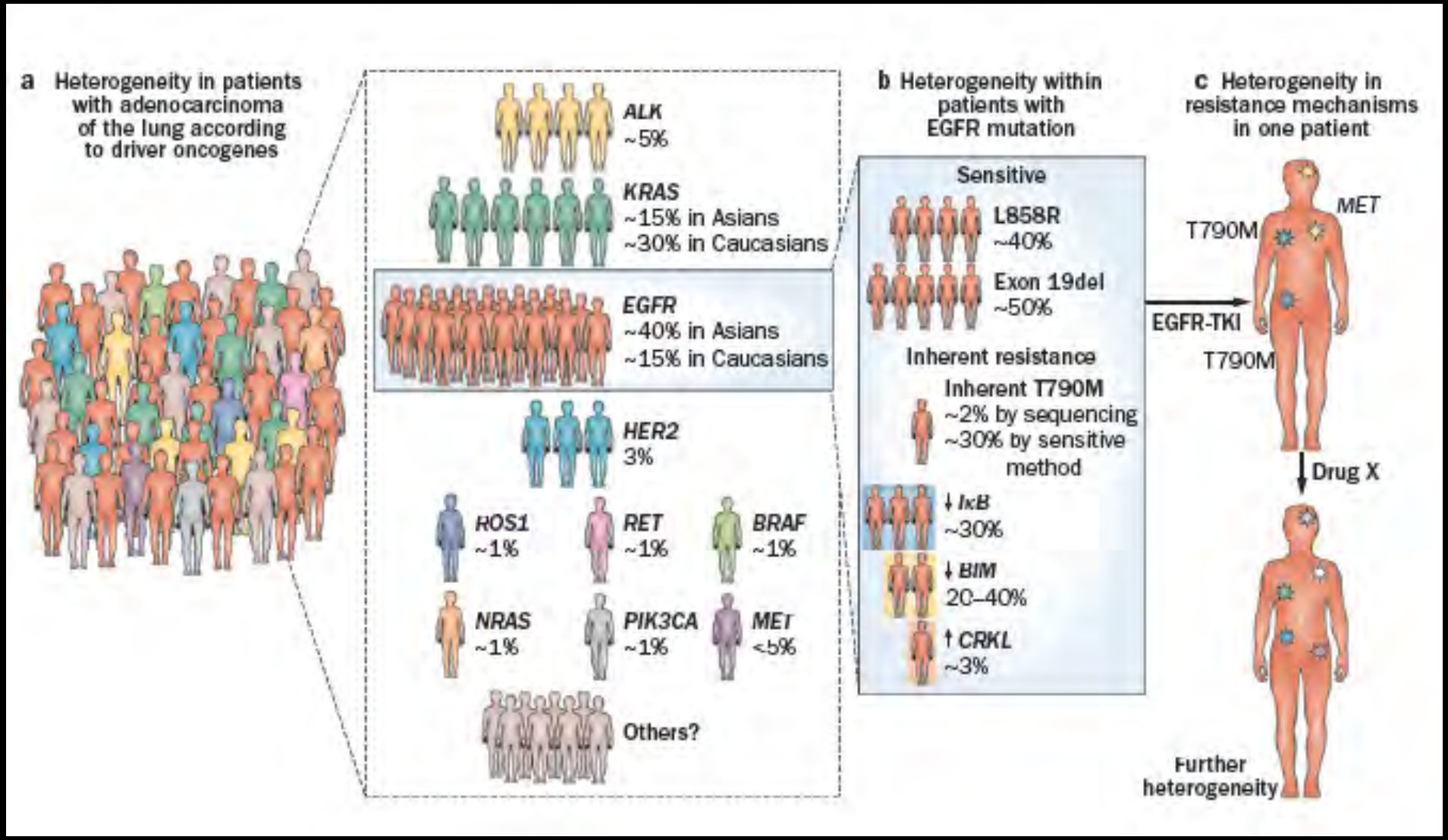
pesticides

The Principal Challenge in Cancer R_x Therapy

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

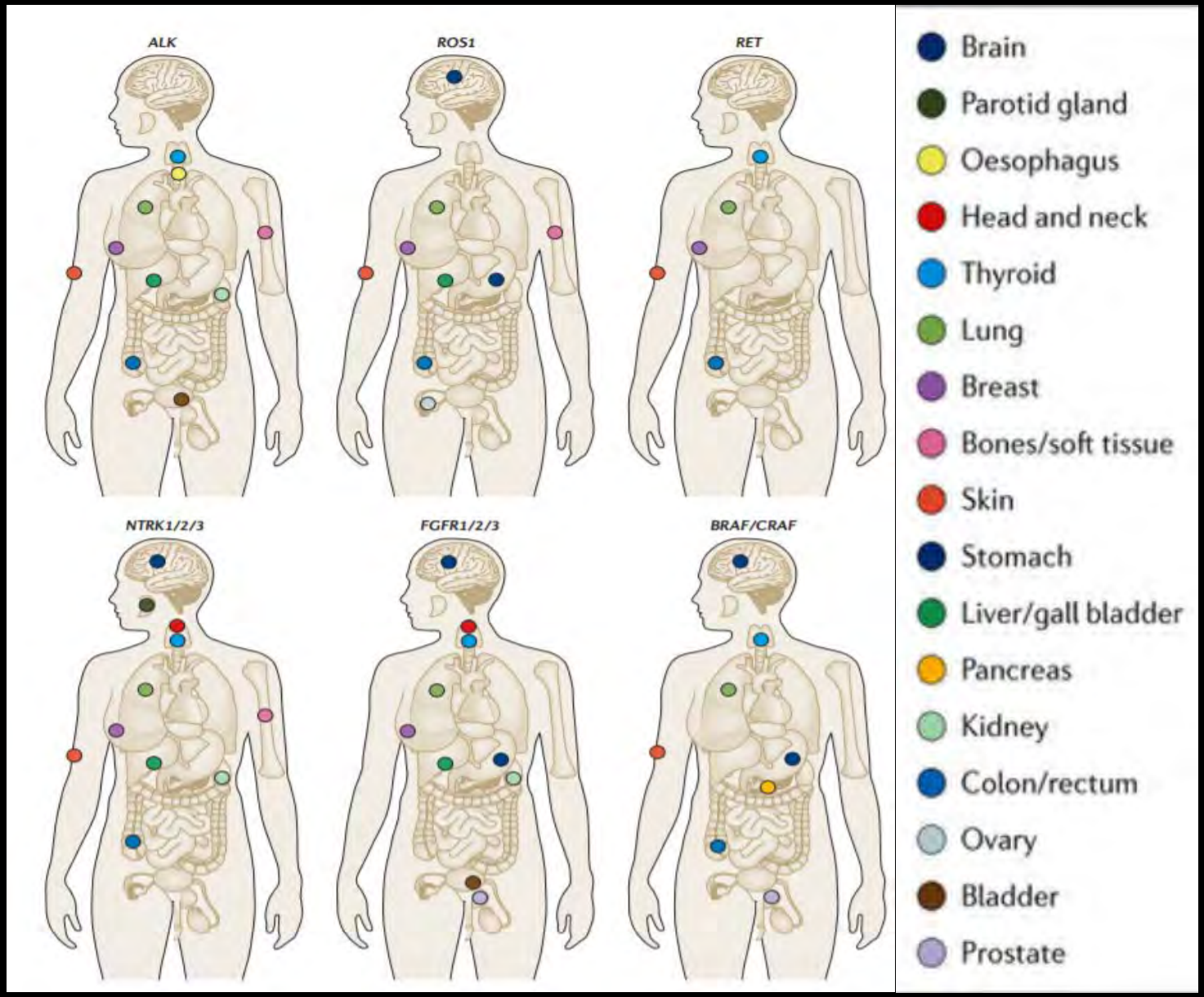
Flying Blind:
Historical "One-Size-Fits All" R_x Approaches to Cancer Therapy

Molecular Profiling and Classification of Subtypes of NSCLC



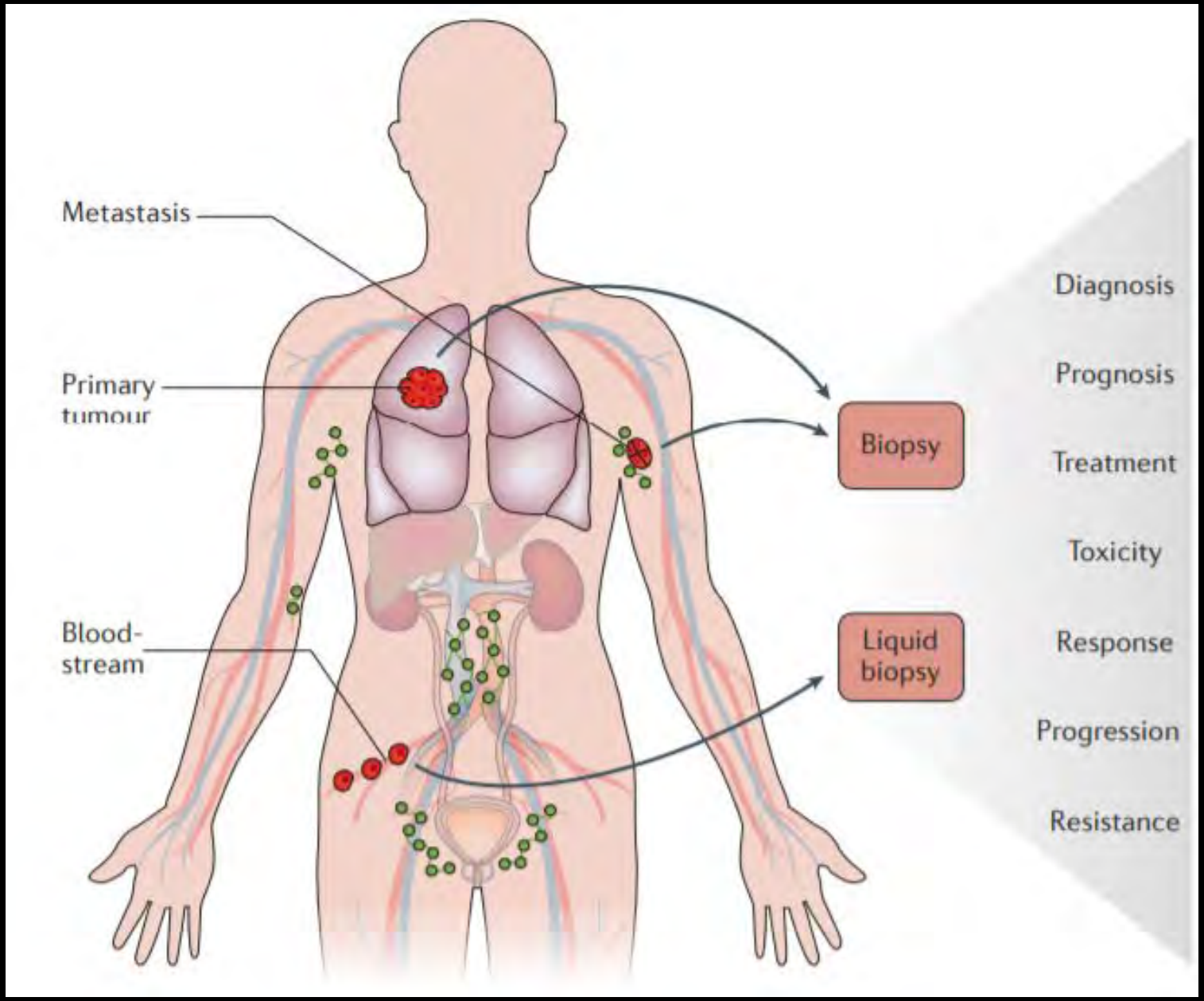
From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

Distribution of Kinase Fusions Across Primary Tumor Sites and Rationale for Use of Mutation Specific R_x in Fusion –Positive Patients



From: A.M. Schram et al. (2017) Nature Reviews Clin Onc. Dec 2017

Molecular Profiling of Cancer

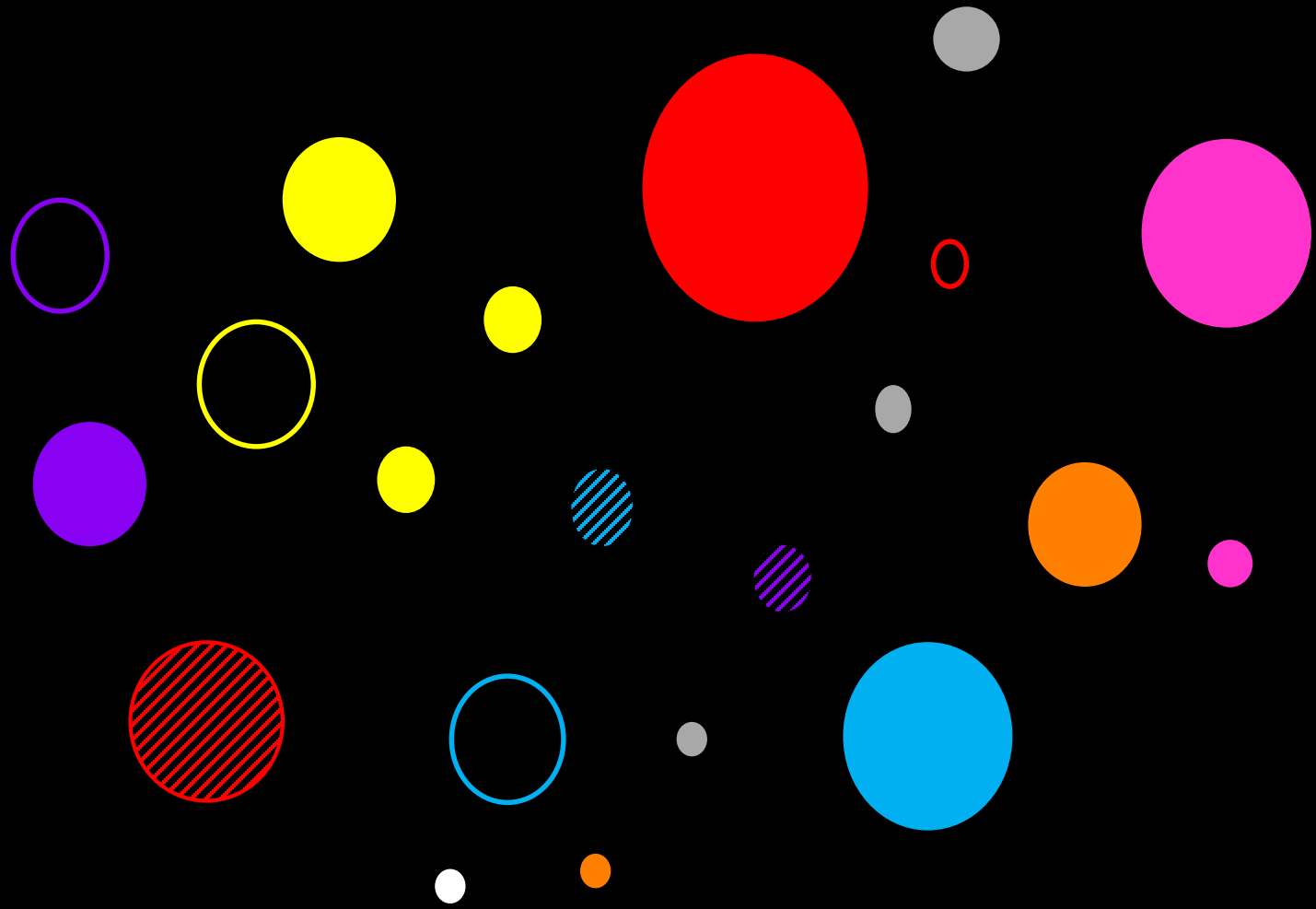


Adapted from : M. Cieślik and A. M. Chinnaiyan (2018) Nature Reviews Genetics 19, 93

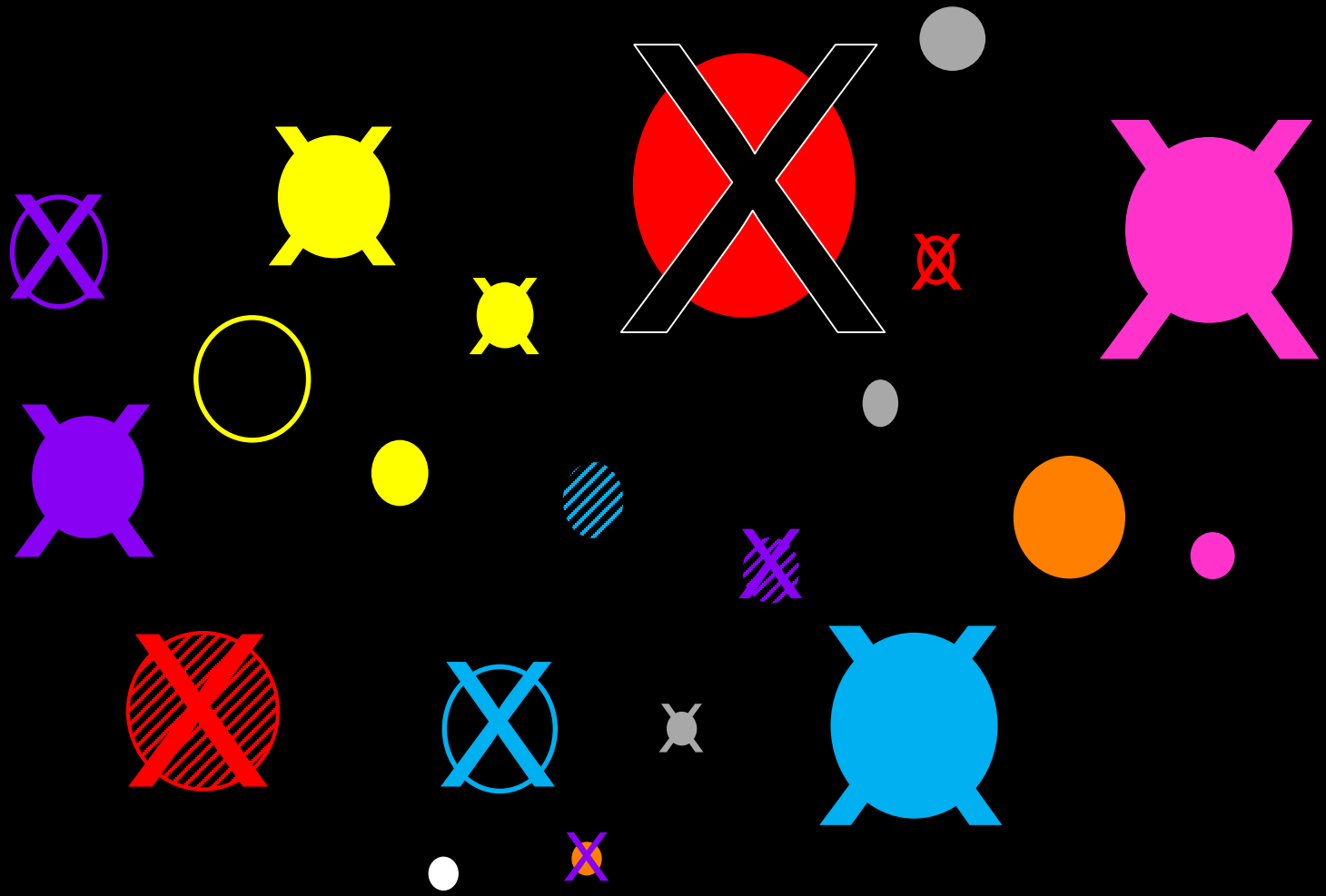
Challenges in Cancer Therapy

- molecular classification of cancer subtypes with defined molecular alterations
  - how to select right R_x for right patient
- alterations in multiple molecular targets and pathways
  - how to design rational combination therapies
- ongoing clonal diversification with tumor progression and effect of R_x on clonal evolution
  - how to destroy multiple clones and/or stop clonal evolvability
- selective targeting of cancer cell multiplication versus protection of cell division and multiplication needed for production of normal cells (gut, bone marrow, hair)
  - how to minimize adverse events on normal cells

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 each new variant clone that may emerge as an escape variant driven by the selection pressure of treatment?

Design of Cancer Treatments to Hit Multiple Targets

- design a single drug that hits multiple clones and multiple signaling pathways
  - pharmacological promiscuity versus specificity
  - very low probability of technical success

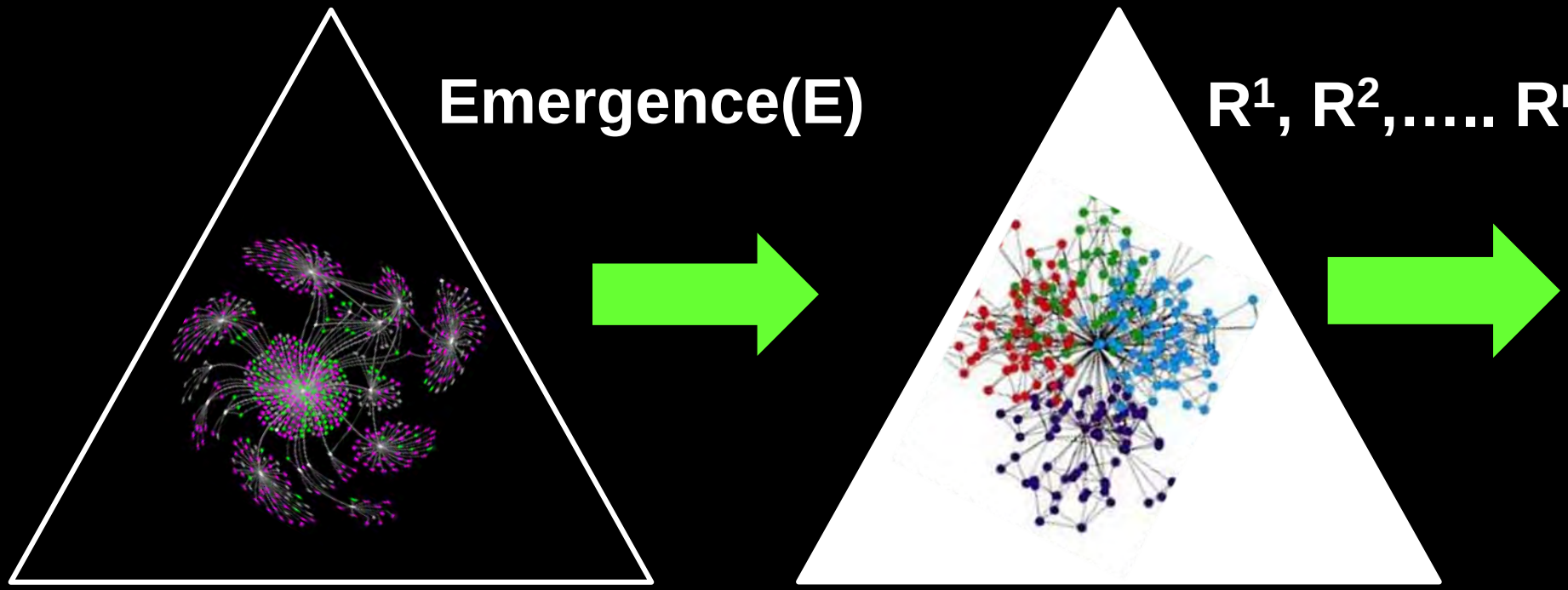
‘Compensatory’ Pathways in Molecular Signaling Networks and Evolution of Drug Resistance

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

Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of R_x- Resistance (R)

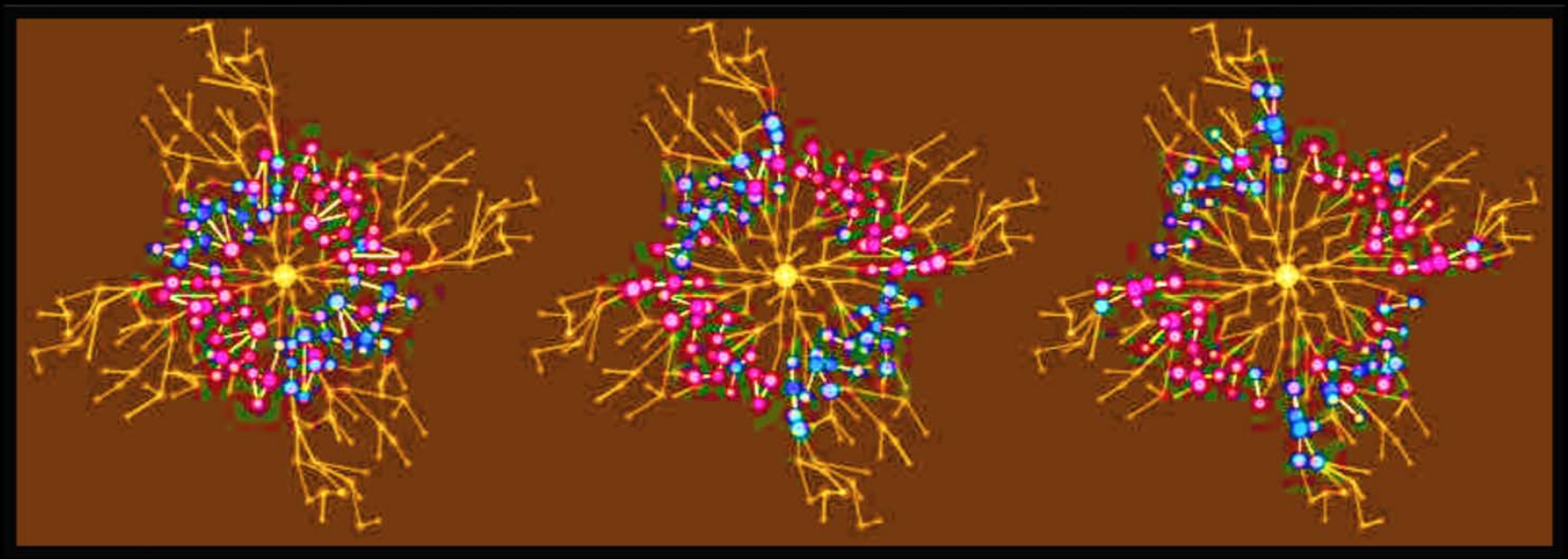
dynamic molecular signaling network topologies

new network topologies to bypass R_x-vulnerable pathways



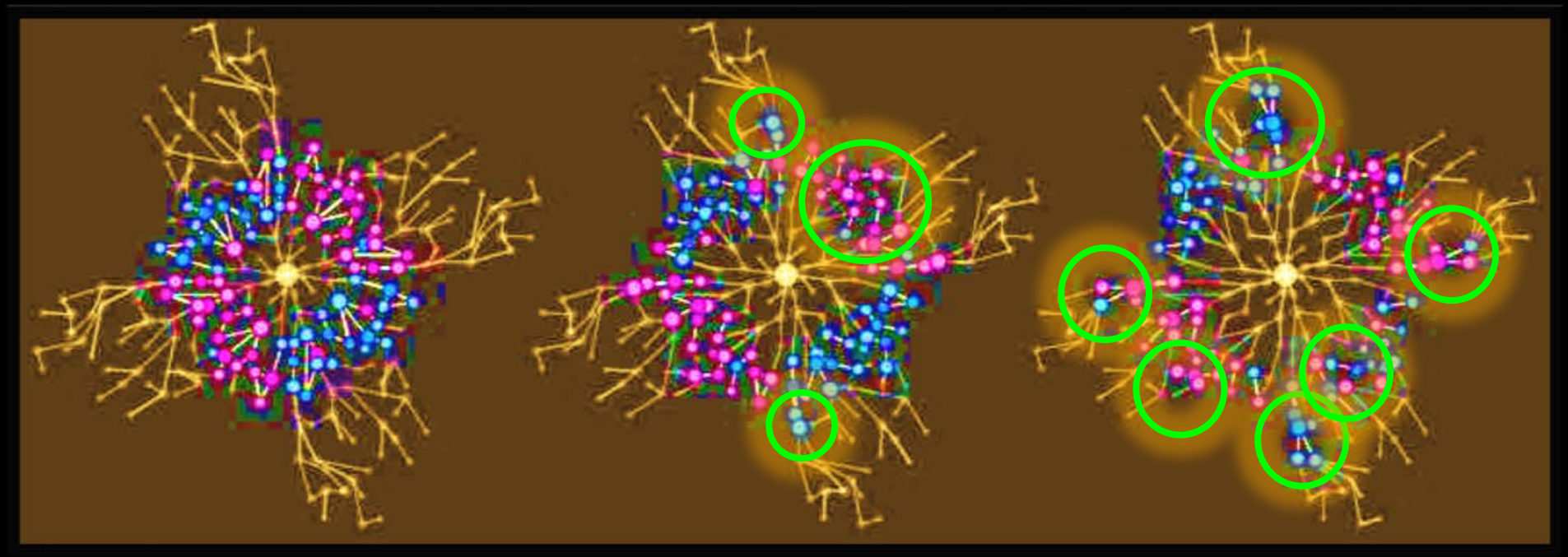
- intrinsic resistance (pre-exist prior to R_x)
- acquired resistance (R_x as selection pressure)

Mapping Molecular Signaling Pathways and Networks in Tumor Progression and Treatment



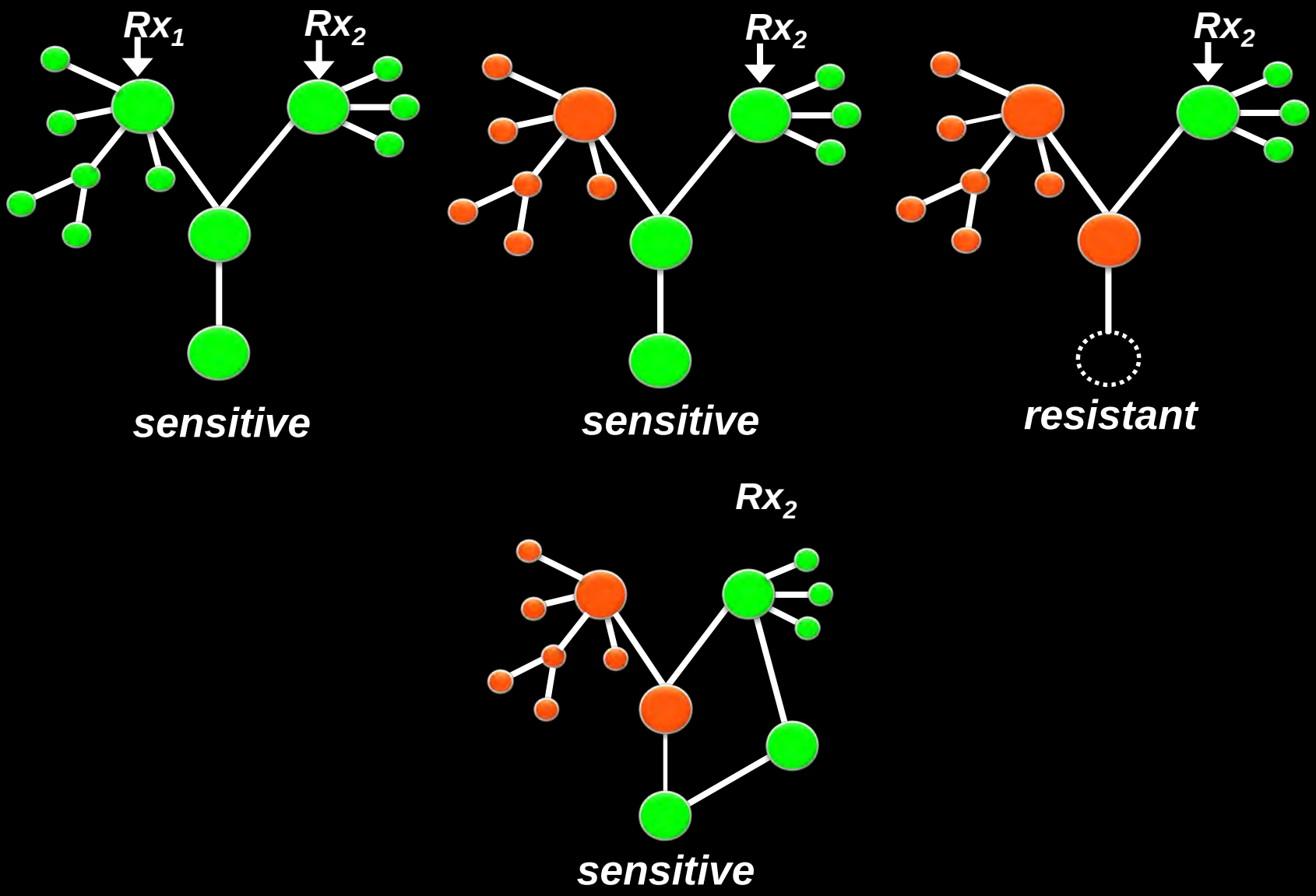
T_1 T_2 T_3

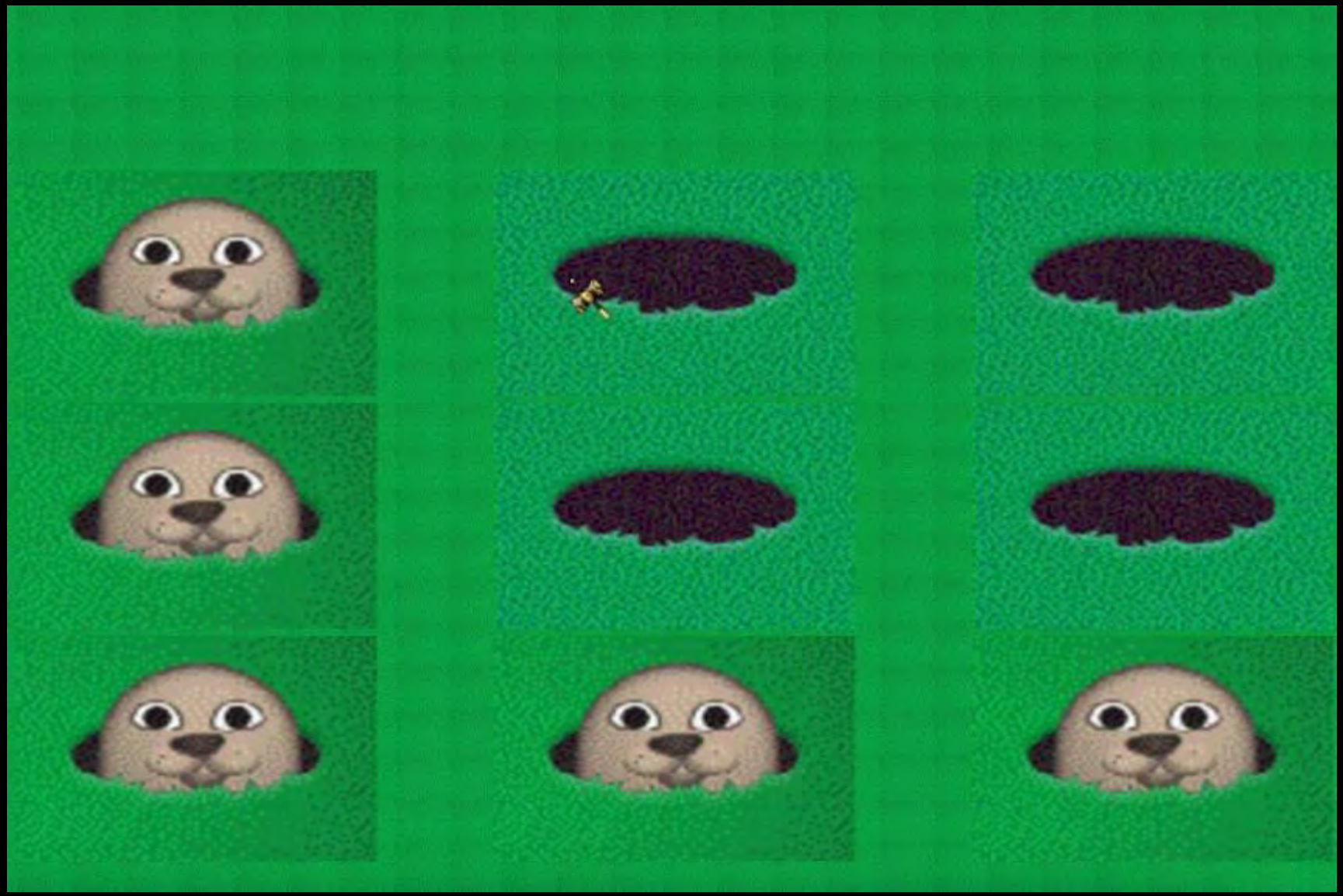
Mapping Molecular Signaling Pathways and Networks in Tumor Progression and Treatment



T_1 T_2 T_3

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

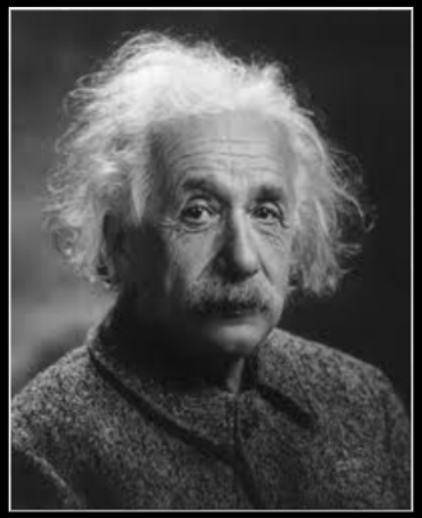




Design of Cancer Treatments to Hit Multiple Targets

- 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
  - direct drug effect to cause mutations and new resistant clones (acquired resistance)
  - R_x elimination of 'dominant' clones allows pre-existing 'minor' clones to prosper (intrinsic resistance)

Knowing When to Stop!



“Insanity is doing the same thing
over and over again
and expecting a different result.”

- Albert Einstein

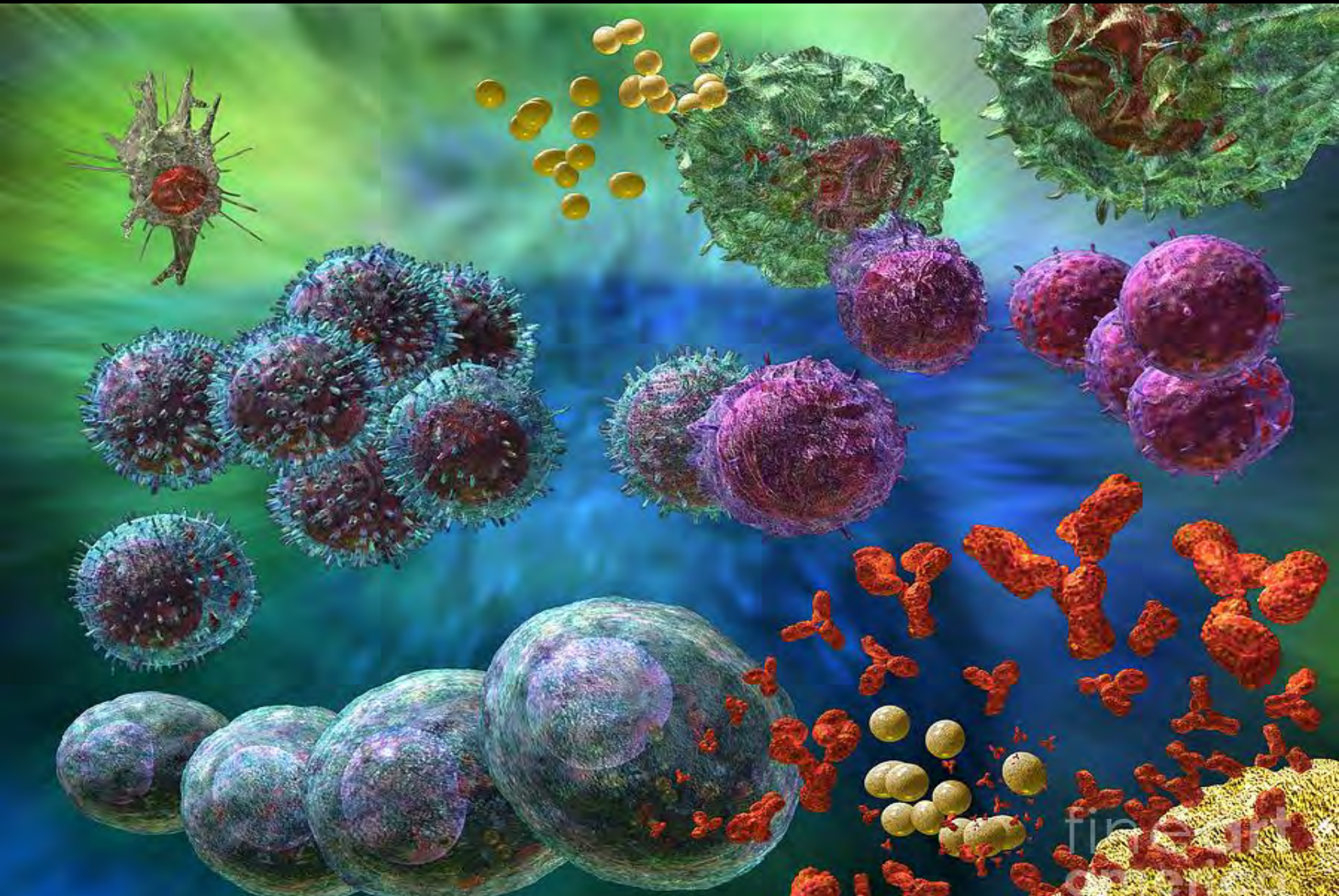
The Therapeutic Challenge of Circumvention of Tumor cell Heterogeneity

- moving from classical ‘chemo’ and “targeted” agents to devise new ways to attack every clone

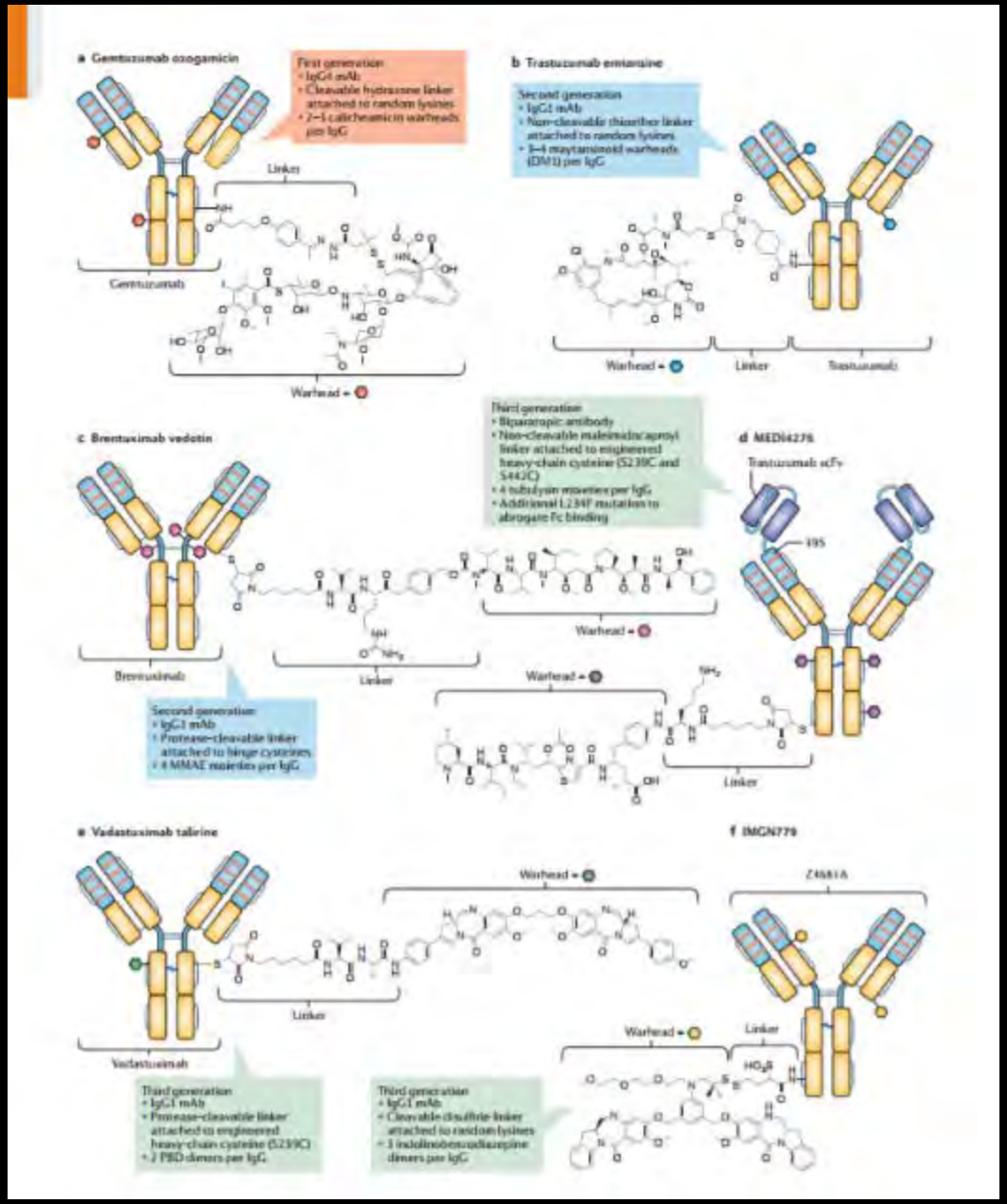
- harnessing the cognate (detection) and destruction (killing) capabilities of the body’s immune system

- therapeutic targeting of neoantigens expressed on tumor cells
  - passive immunotherapy (designer antibodies)
  - active immunotherapy (activation of immune functions)

Passive Immunotherapy With Antibodies



Antibody-Drug Conjugates for Cancer Therapy



A. Beck et al. (2017) Nature Reviews 16, 315

Monoclonal Antibodies (Mabs) and Cancer Immunotherapy

- direct destruction of tumor cells with or without "R_x warhead"
- tagging tumor cells for destruction by immune cells
- blocking tumor cell signaling pathways to halt proliferation (anti-EGFR Mabs)
- blocking host tissue stroma signaling pathways that promote tumor proliferation (anti-angiogenesis Mabs) or suppress anti-tumor immune defenses (immune checkpoint inhibitors)

Antibody Therapy in Cancer by Targeting Tumor-Specific Neoantigens

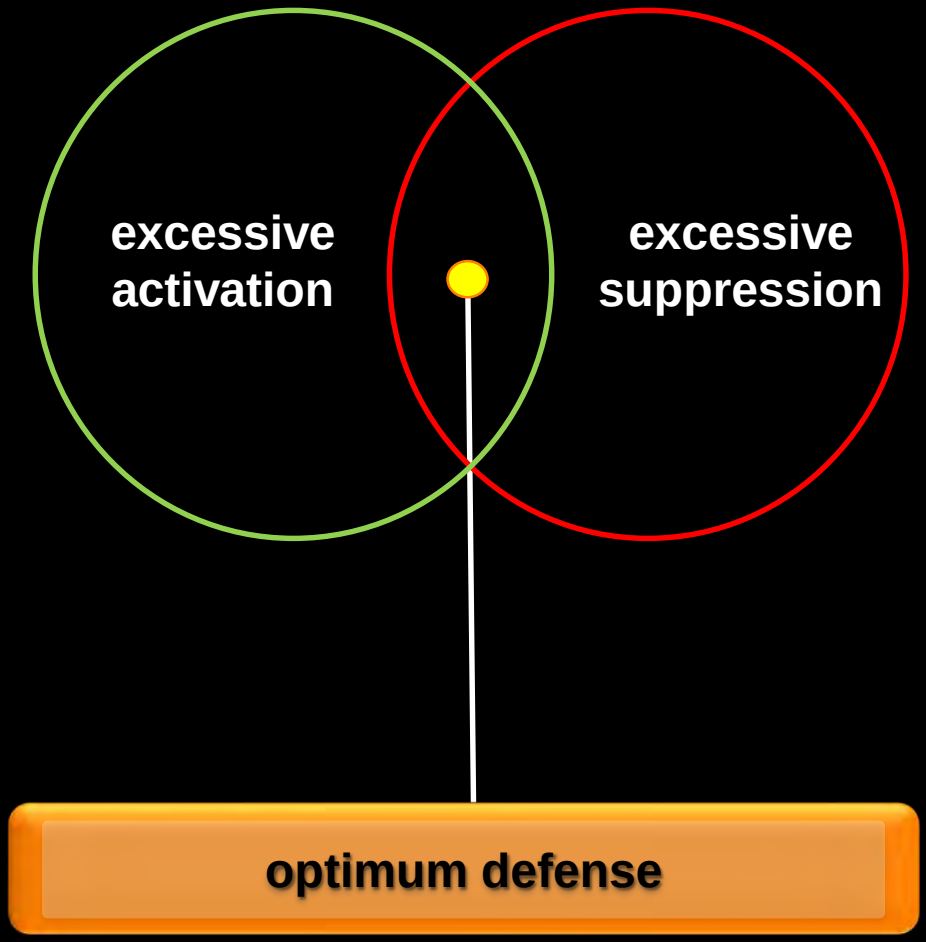
- intrinsic limitations
- Mab or bi-specific Mabs target only one of the many neoantigens expressed by different clones
- high probability of neoantigen-negative Mab-resistant clones emerging in similar fashion to resistance to targeted anti-cancer drugs

Cancer Immunotherapy

Vaccines

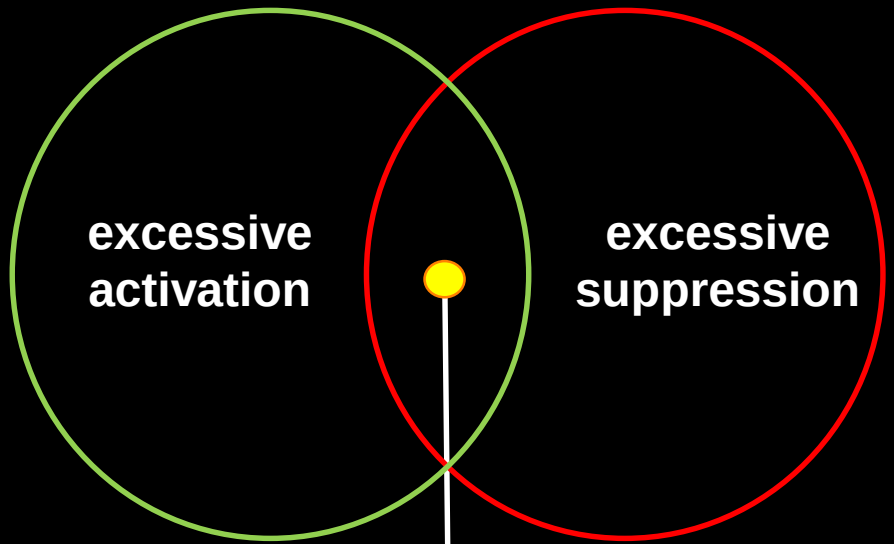
- greater technical challenge than most antimicrobial vaccines
- antigenic variation in different tumor cell clones plus inter-patient variation
- how to identify the best combination of antigens as vaccine candidates
- high probability of antigen-negative/deletion variants and tumor relapse
- analogy with the still unsuccessful quest for a HIV vaccine
  - same problem: massive antigenic heterogeneity due to rapid evolution of new viral quasispecies

Balancing The Body's Immune Response



Balancing The Body's Immune Response

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



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

optimum defense

The Immune System and Host Defense

- recognition of diverse ‘non-self entities
  - infectious agents, parasites, cancer
- ‘rapid on’ (and memory of past encounters)
- ‘switch off’ when the threat is eliminated
- without efficient down-regulation (“off”) unchecked activation of immune system is dangerous
  - acute overdrive: sepsis and shock
  - chronic overdrive: inflammation, autoimmunity, increased cancer risk, neurodegeneration

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

Immunoevasion by Tumor Cells

- avoiding detection
  - loss or masking of abnormal tumor cell surface proteins recognized by antibodies, NK cells and/or killer T lymphocytes
- suppression of the host immune system
  - tumor signaling to activate regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) that suppress action of anti-tumor killer T cells

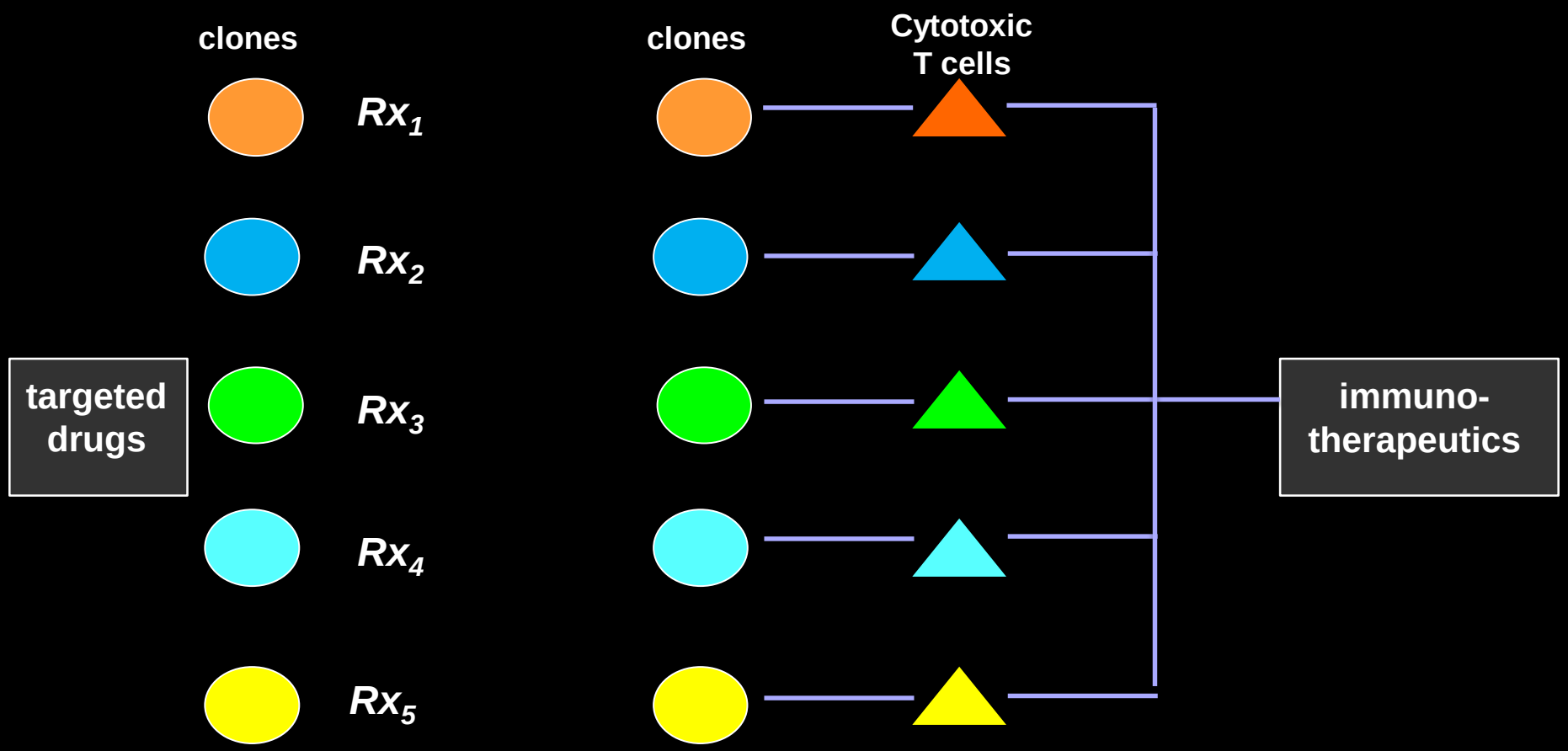
Setting the Immune System Free To Combat Cancer

Host Immune-Tumor Interactions

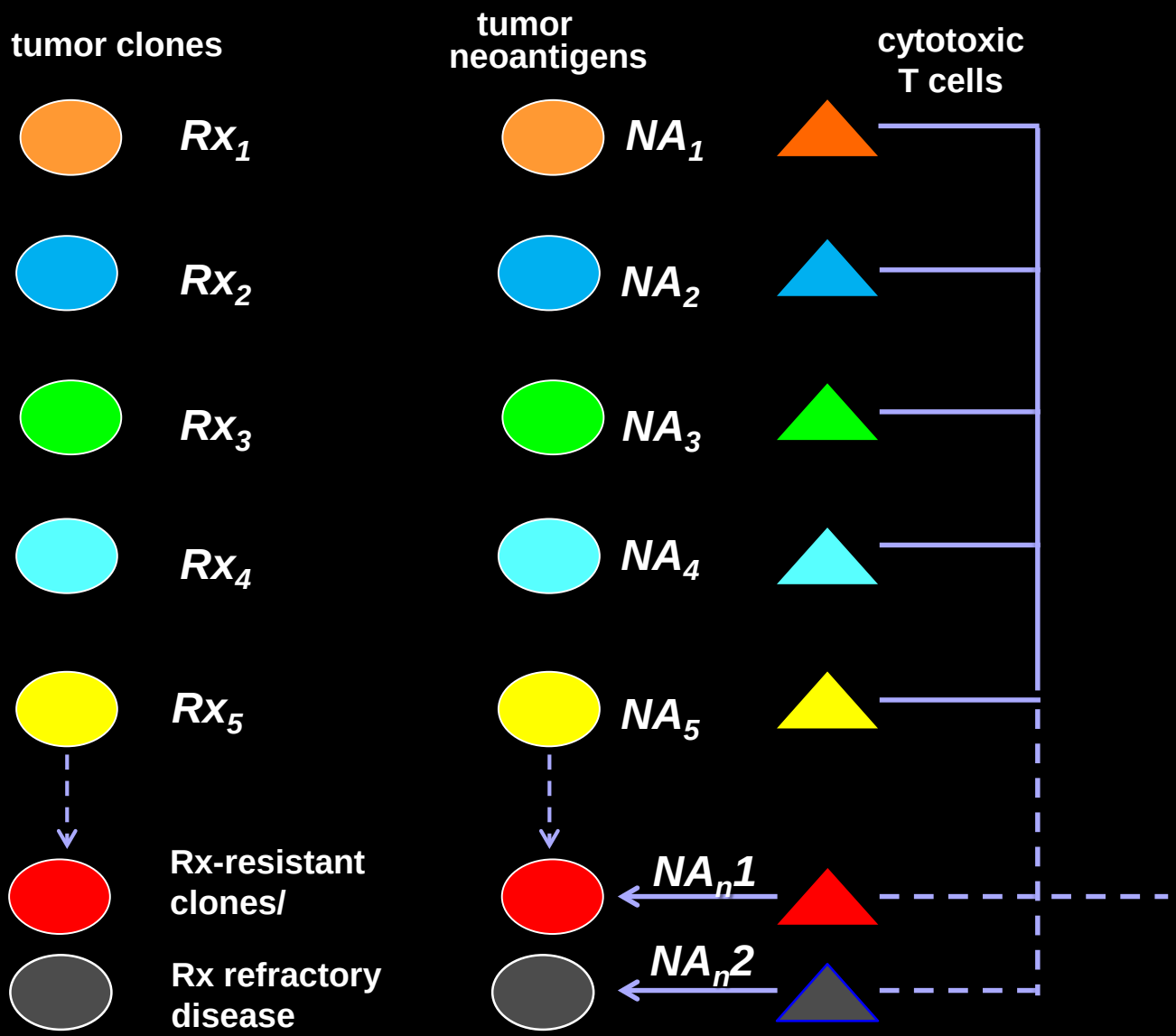
Clone Wars

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)



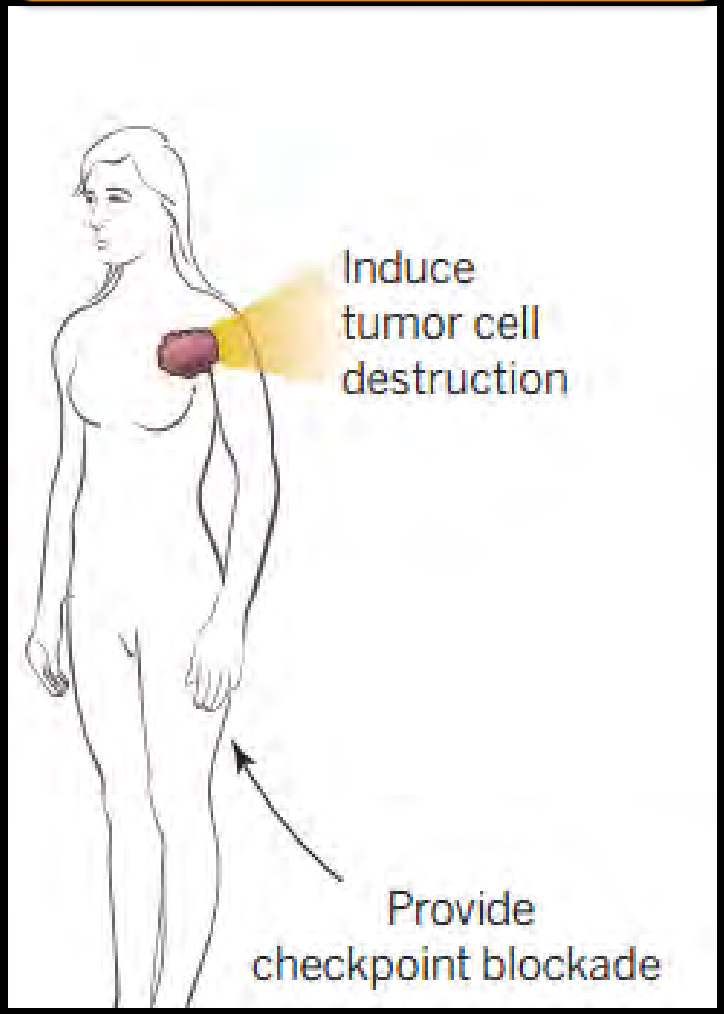
Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance



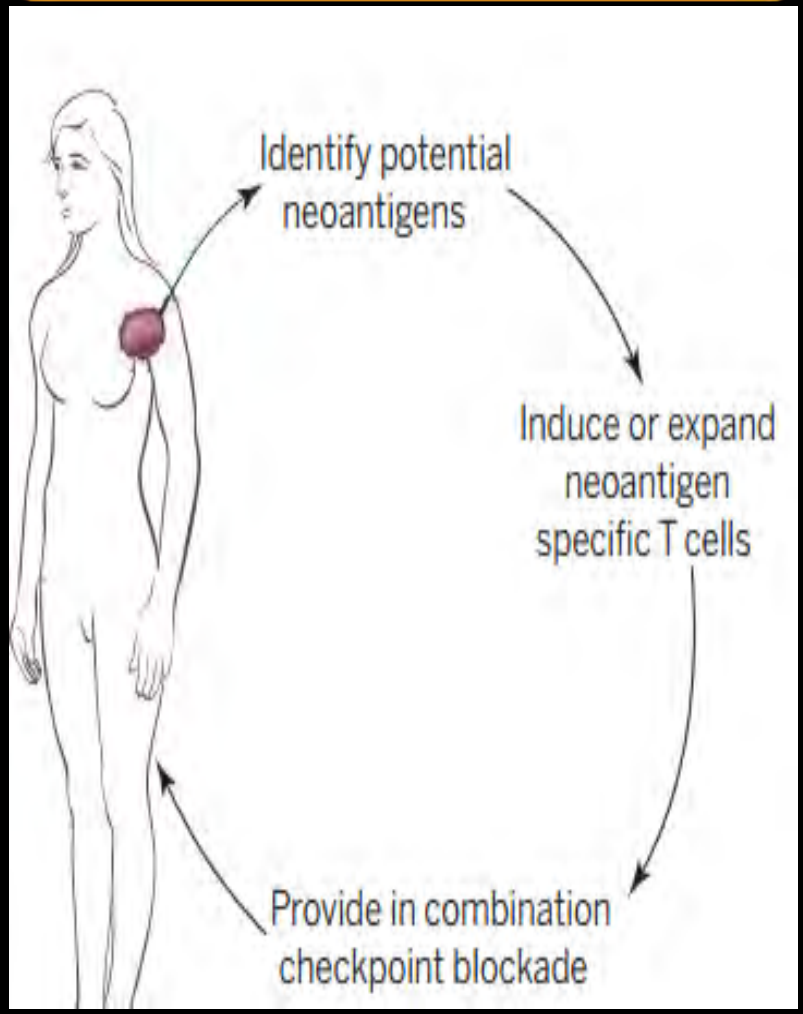
adaptive evolution of immune response and expanded cytotoxic T cell responses

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

Immune Checkpoint Modulation



Adoptive Cell Therapy TILs, TCRs, CARs

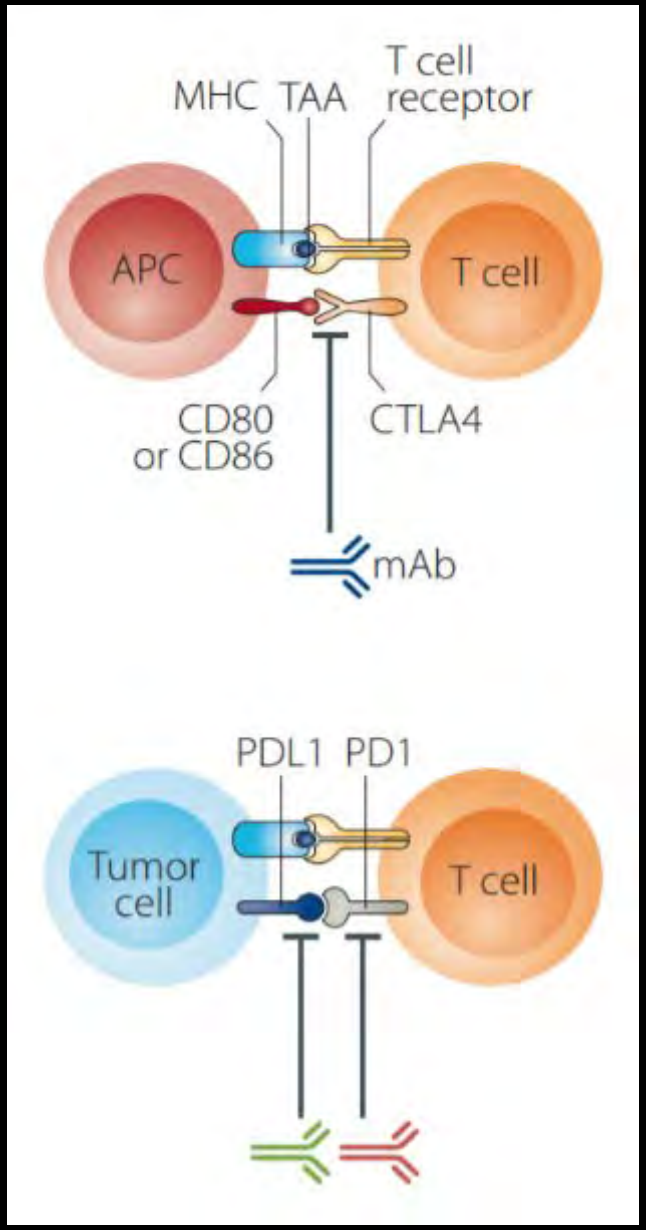


Adapted From: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69

MERCK

Bristol-Myers Squibb

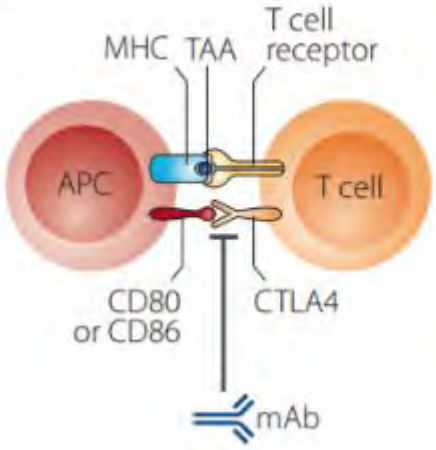
Immune Checkpoint Inhibitors in Cancer Treatment

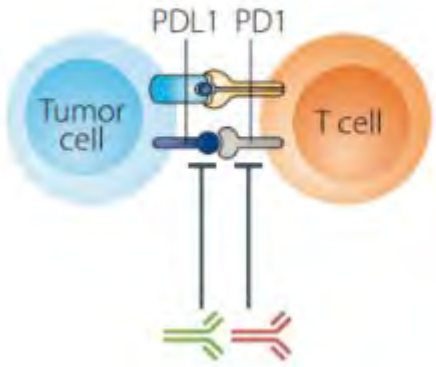


Antibodies to CTLA4

Antibody to PDL-1 or PD-1

Immune Checkpoint Inhibitors in Cancer Treatment





CTLA4 inhibitors

Ipilimumab
Brand name: Yervoy
Developing company: Bristol-Myers Squibb
FDA-approved indications: unresectable or metastatic melanoma; adjuvant therapy for stage 3 melanoma

Tremelimumab
Brand name: N/A
Developing company: MedImmune, the biologics arm of AstraZeneca
FDA-approved indications: none yet; in phase 3 trials

PD1 inhibitors

Nivolumab
Brand name: Opdivo
Developing company: Bristol-Myers Squibb
FDA-approved indications: unresectable or metastatic melanoma, metastatic NSCLC, advanced RCC, Hodgkin lymphoma

Pembrolizumab
Brand name: Keytruda
Developing company: Merck & Co.*
FDA-approved indications: unresectable or metastatic melanoma, metastatic NSCLC, recurrent or metastatic HNSCC

PDL1 inhibitors

Atezolizumab
Brand name: Tecentriq
Developing company: Genentech/Roche
FDA-approved indications: urothelial carcinoma

Durvalumab
Brand name: N/A
Developing company: MedImmune, the biologics arm of AstraZeneca
FDA-approved indications: none yet; in phase 3 trials

Avelumab
Brand name: N/A
Developing companies: Merck KGaA and Pfizer
FDA-approved indications: none yet; in phase 3 trials

Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

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

Less Responsive

- pancreatic
- colorectal (MSI-low)
- ovarian

Immunogenic Versus Non-Immunogenic Tumor Microenvironments

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

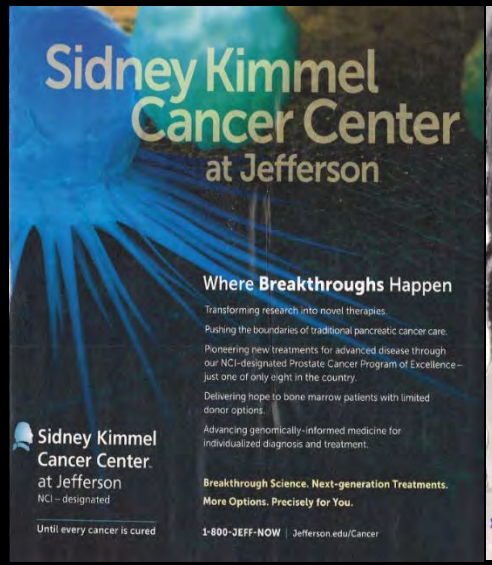
Engineering Killer T Cells for Cancer Therapy

- 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

Realizing The Promise of Cancer Immunotherapy

- 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

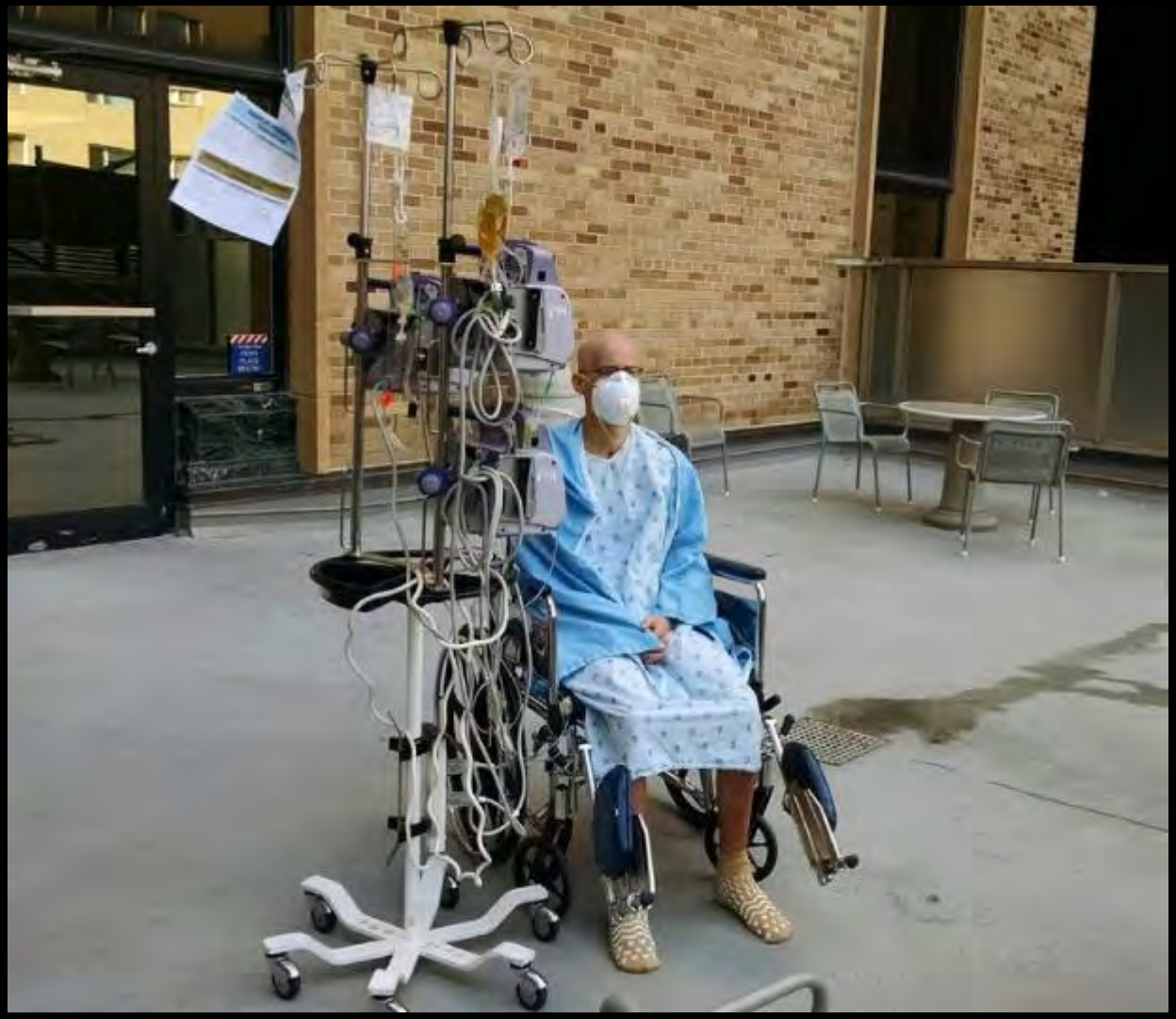
The Ethics of Hype and Hope



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

Cancer Treatment's New Direction: Genetic Testing and Tailored Treatments



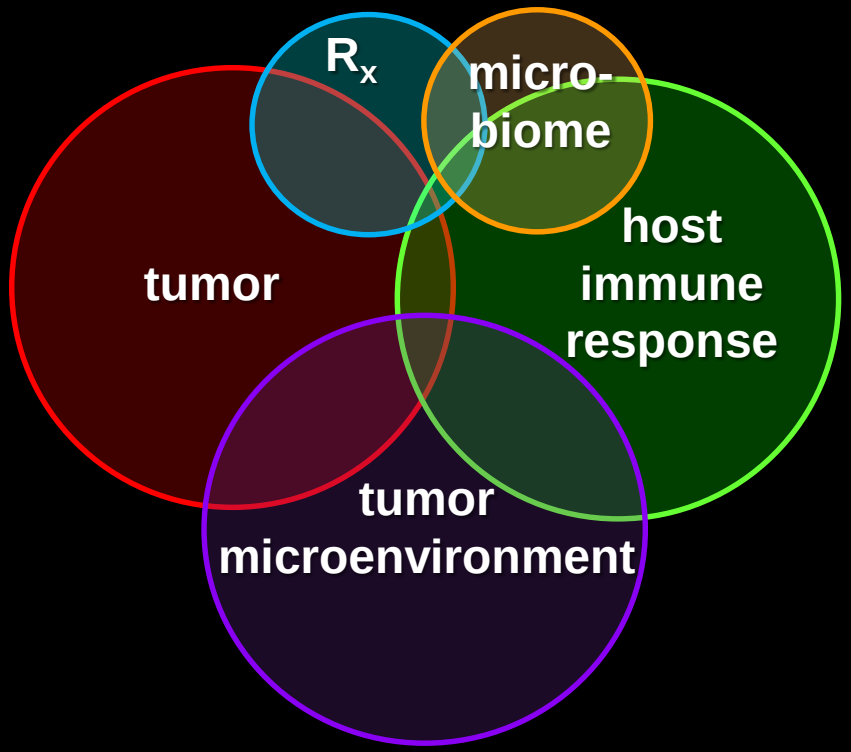
- AML
- an 18 month journey to remission
- 3 approved drugs, 2 investigational drugs
- 2 stem cell transplants
- $ 4 million dollars

From: Winslow, R. (2016) Cancer Treatment's New Direction. WSJ

Summary and Key Points

Understanding the Complex Ecosystem of Constantly Changing Tumor and Host Interactions

- lineage and subtype
- clonal heterogeneity
- mutagen burden
- neoantigen profile



balance of stimulatory and suppressive factors

- localization of immune cells/soluble mediators and impact of R_x

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 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

Aspirations for Improved Cancer Treatment

- how to maximize the efficacy and safety of therapeutic interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected R_x regimen (overcoming the heterogeneity problem)
  - dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones and more agile, anticipatory shifts in R_x regimen
  - mobilization (reactivation) of body's immune defenses to detect and destroy all clones

Realizing The Promise of Cancer Immunotherapy

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  - 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

The Future Landscape for Cancer Care

BIO 302: 23 April 2018

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

Complex Clinical, Scientific, Economic, Ethical and Legal Issues