Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302: 13 September 2017

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

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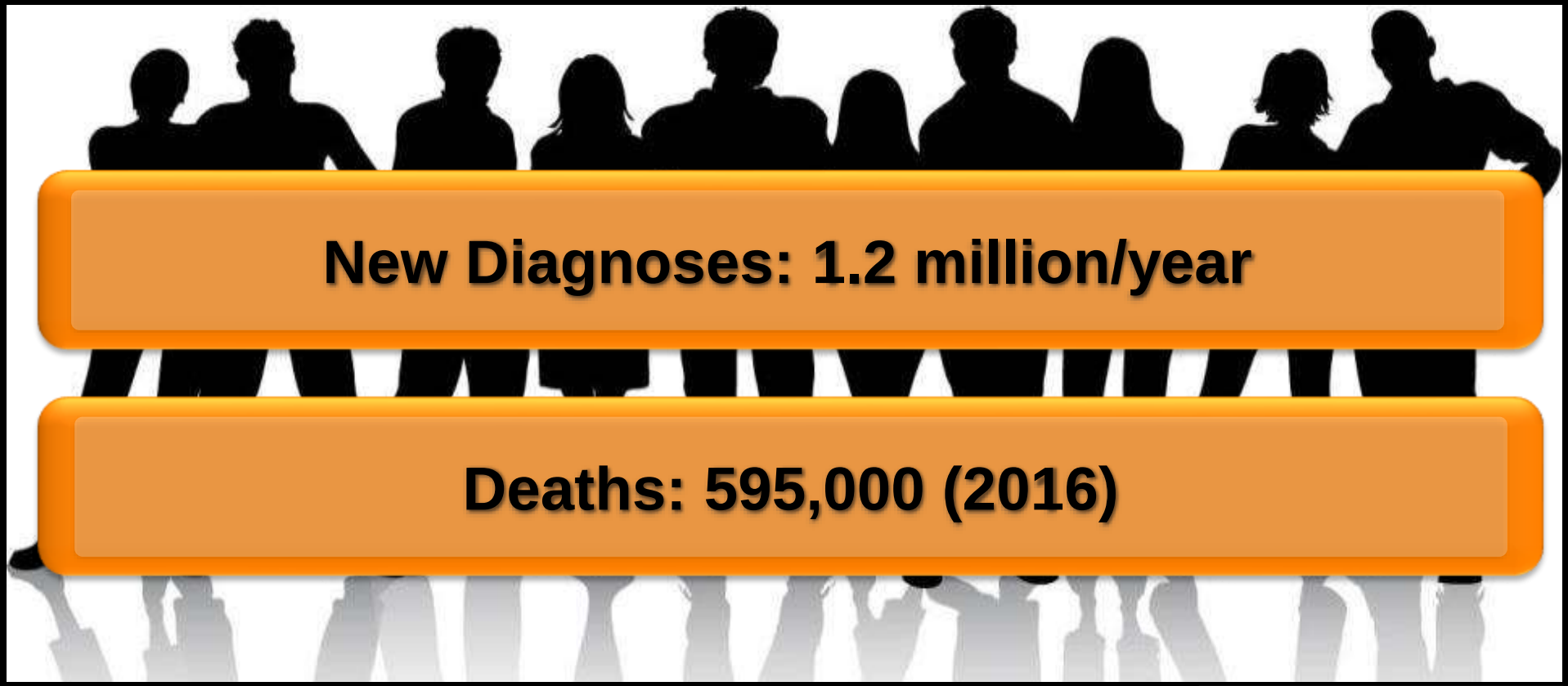
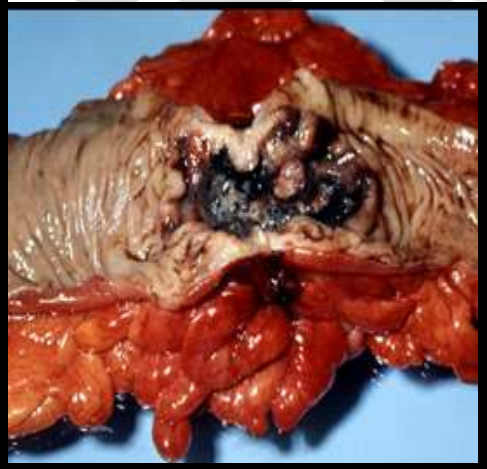
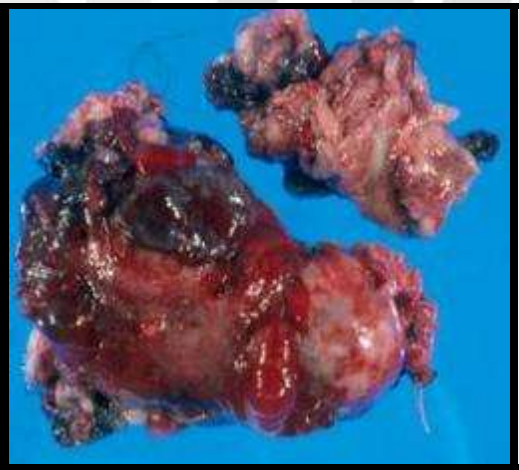
Confronting the Clinical, Economic and Human Toll of Cancer

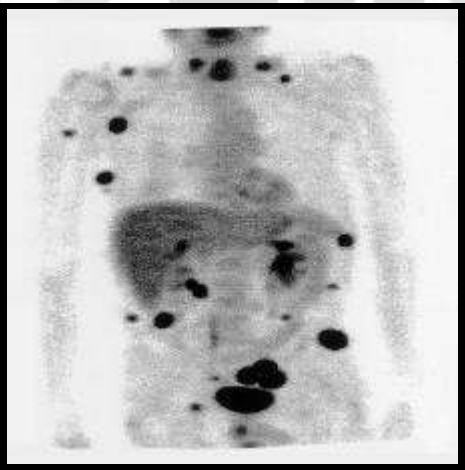


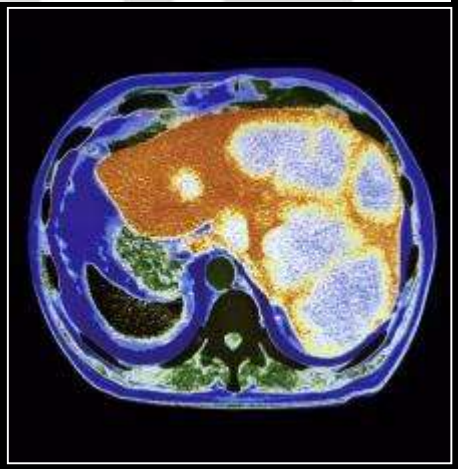
New Diagnoses: 1.2 million/year

Deaths: 595,000 (2016)



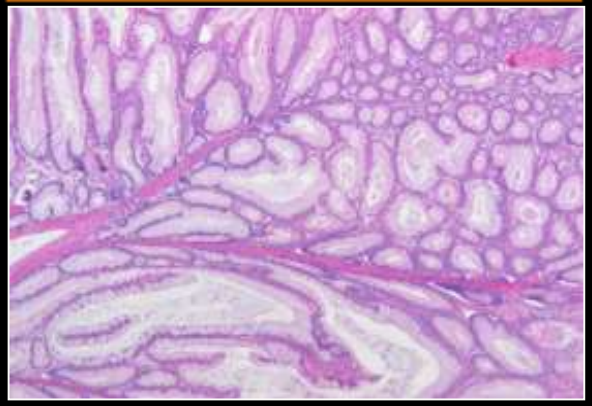






The Complex Biology of Cancer Progression and Treatment Resistance

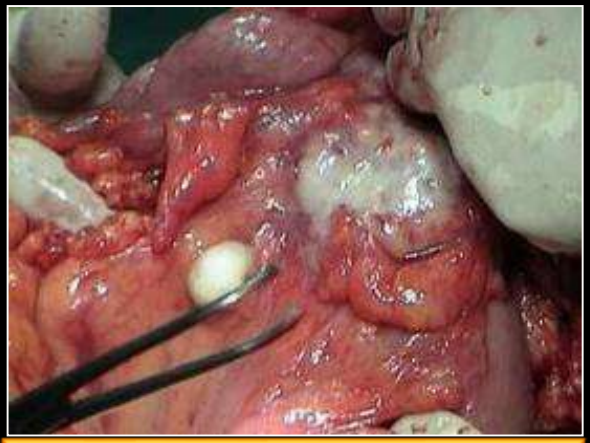
Escape From Controls for Normal Tissue Architecture



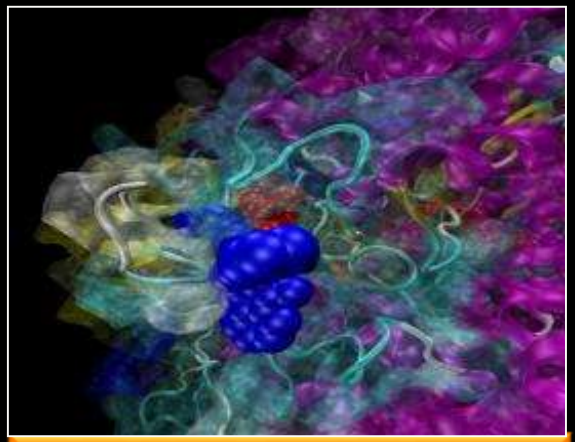
Genome Instability and Emergence of Clonal Variants

Evasion of Detection/ Destruction by Host Immune System

Use of Host Systems to Promote Progression

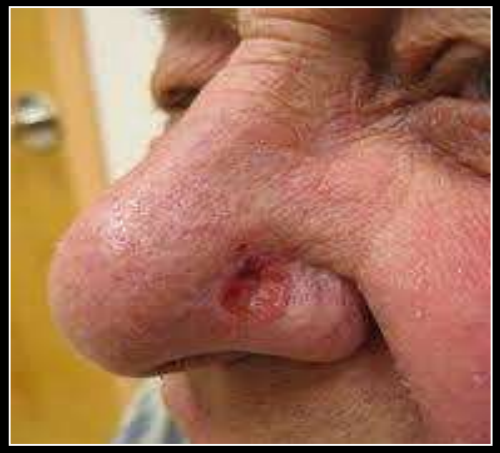


Invasion and Metastasis



Emergence of Drug-Resistant Clones

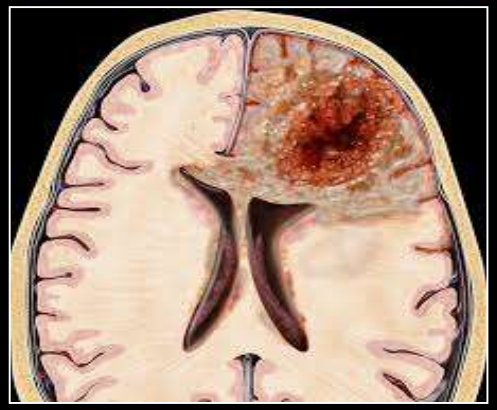
Invasion and Metastasis: The Start of the Deadly Phase of Cancer Progression



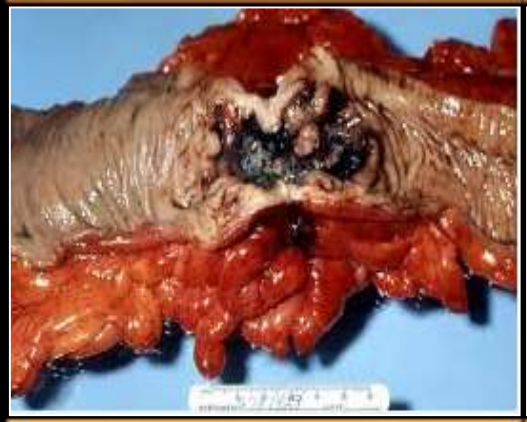
basal cell carcinoma

lung

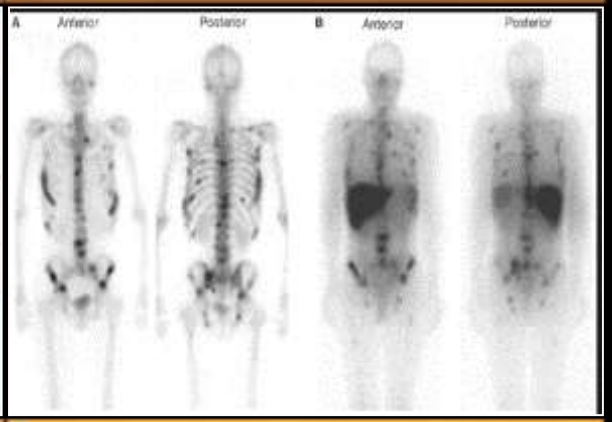
breast



glioblastoma



colorectal

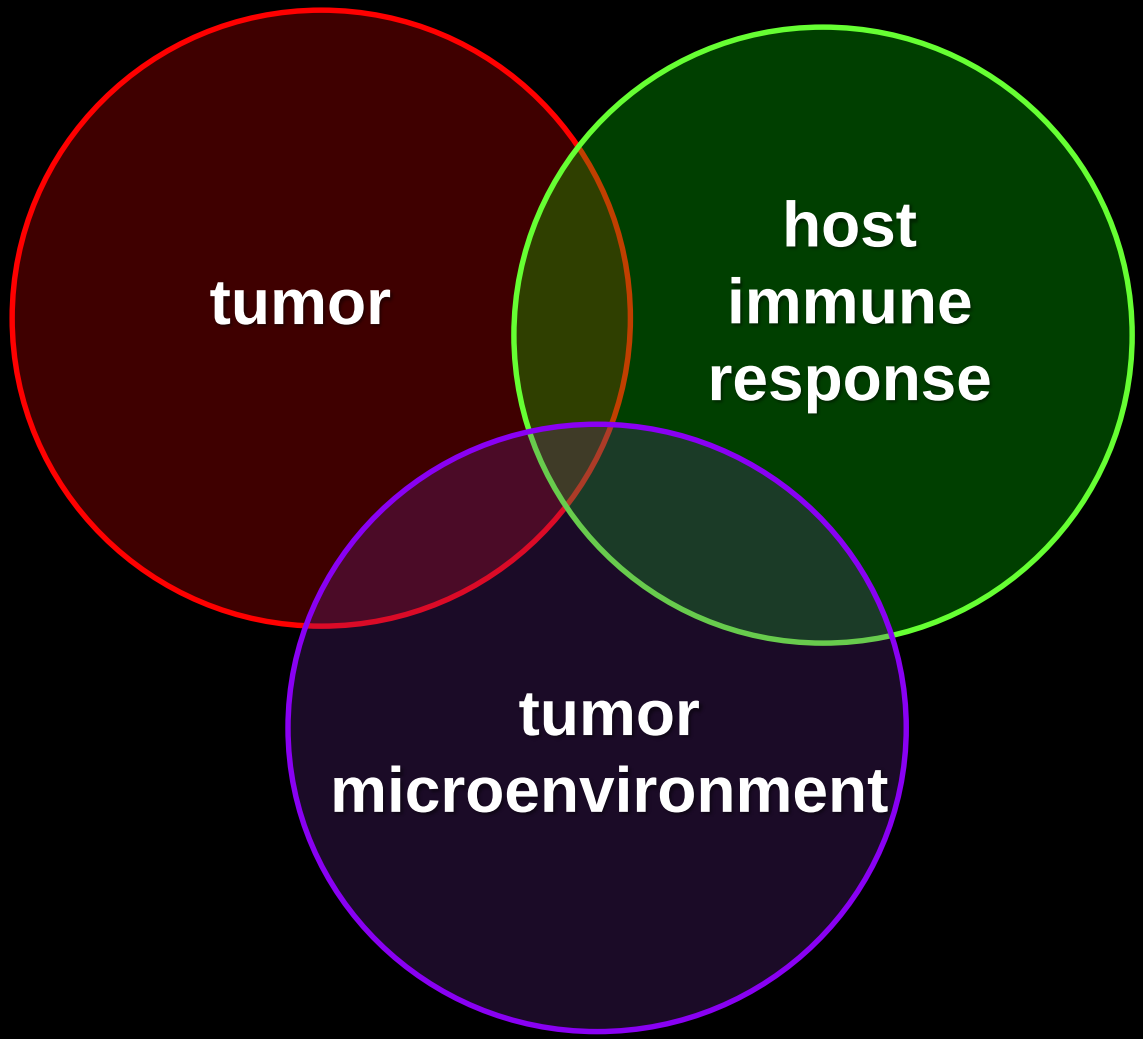


prostate

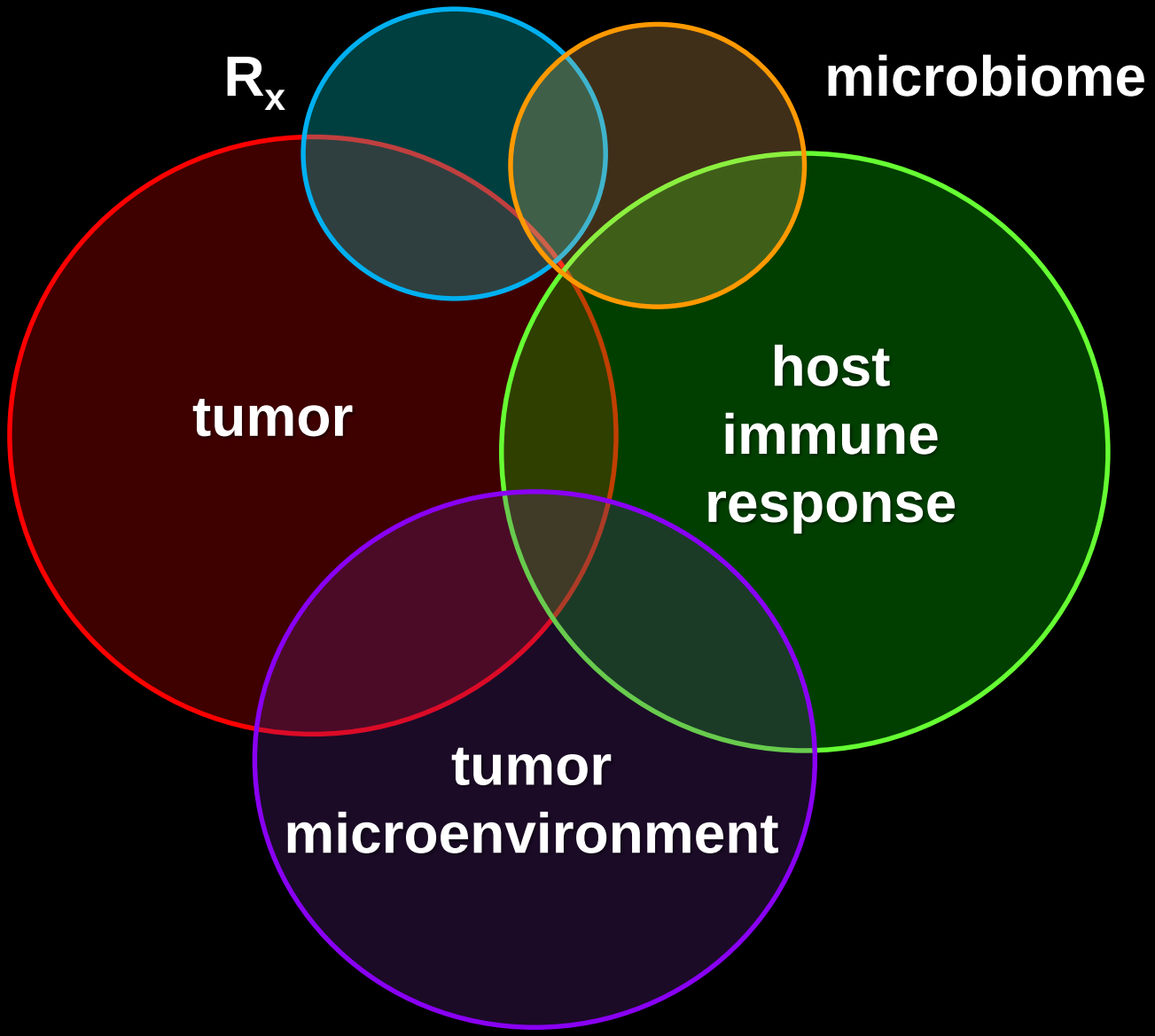
Invasion Without Metastasis

Invasion and Metastasis

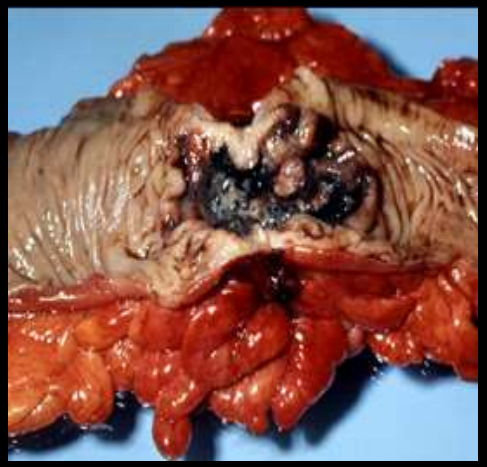
Cancer: A Complex Ecosystem of Tumor and Host Dynamics

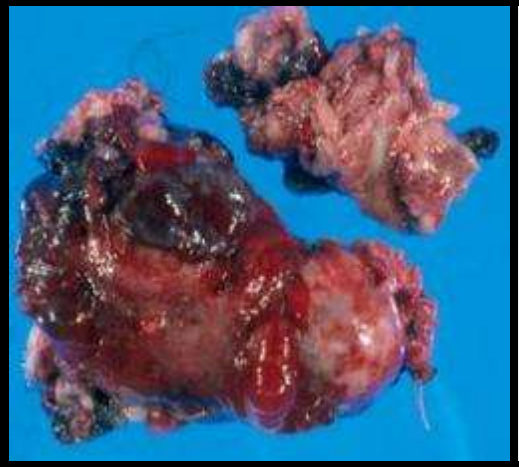


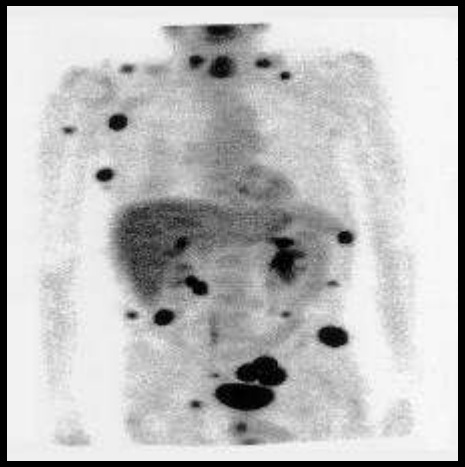
Cancer: A Complex Ecosystem of Tumor and Host Dynamics

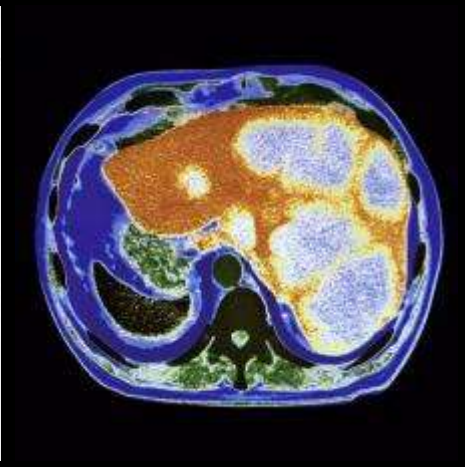


Cancer as a Complex Adaptive System









Complicated Systems
Versus
Complex Systems

The Biological Complexity of Cancer

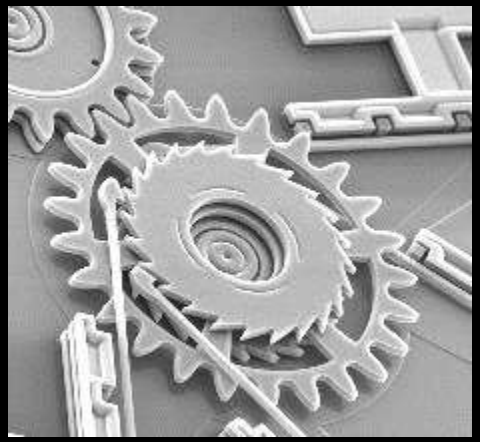
- what is the difference between complicated and complex systems?
- what features of cancer make it a complex system?
- what is meant by “emergence” in complex systems?
- what are the implications of the complex behavior of cancer for diagnosis, treatment and prevention?

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

Failure Does Occur In Complicated Systems But Was a Predictable Outcome Once the Source of Failure Was Identified

Faulty O-Ring	Aging Support Structure	Wrong Glide Path
Complicated System	Complicated System	Complicated System + Introduced Complexity (Human Error)

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

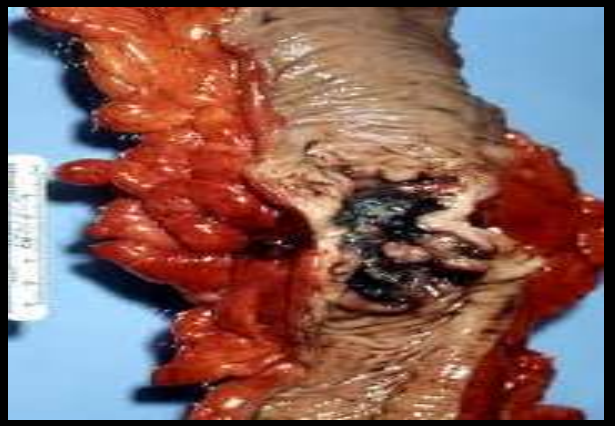
weather/climate

stock markets

internet DOSA/hacks

geopolitical/ national security

epidemics/pandemics

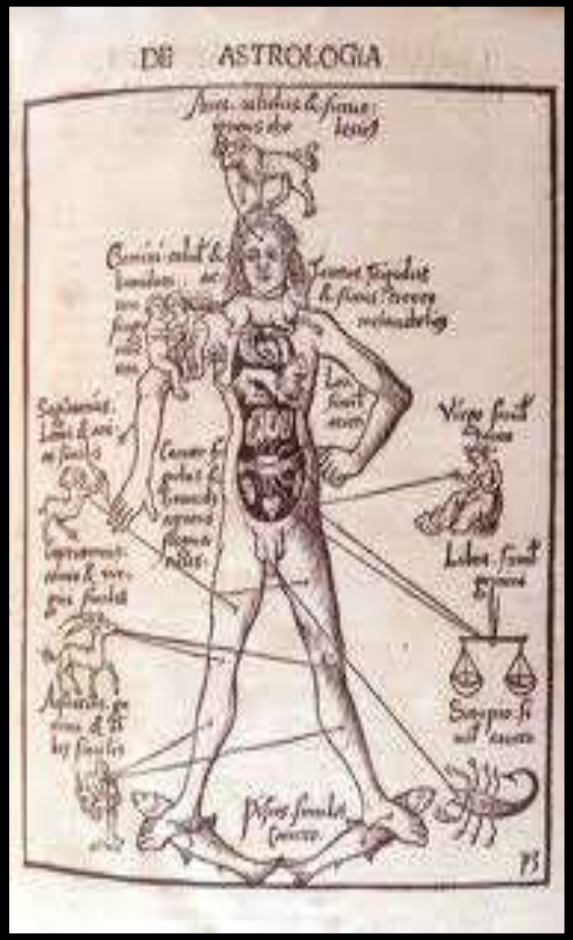


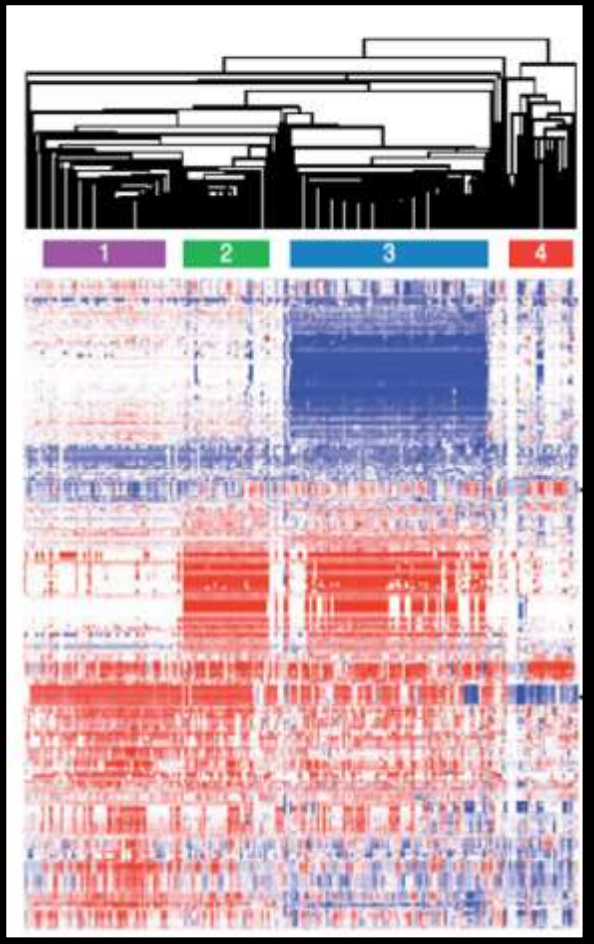
disease pathogenesis

Evolvability and Emergence: The Hallmarks of Complex Systems

- new properties emerge from the interactions of simpler units (molecules, cells, agents, people)
- 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)

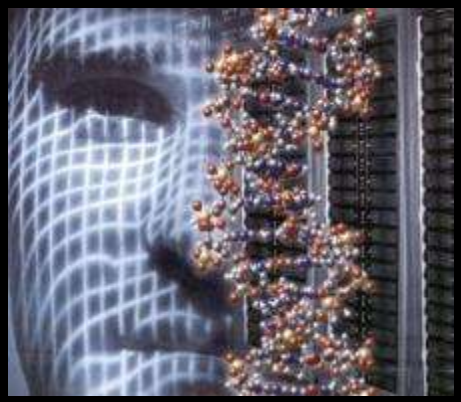
Medical Progress:
From Superstitions to Symptoms to Signatures



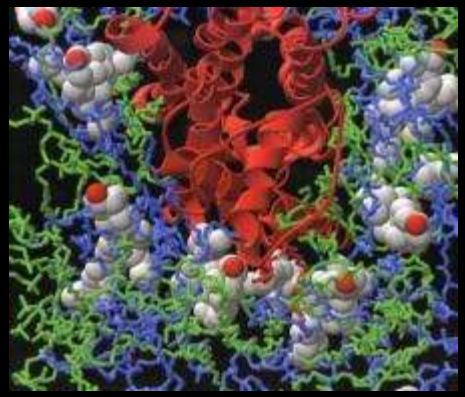


Precision Medicine and Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

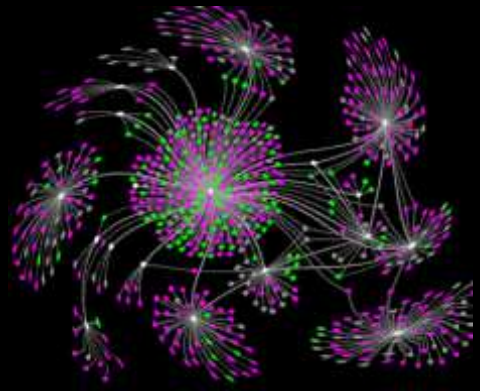
(Epi)Genomics



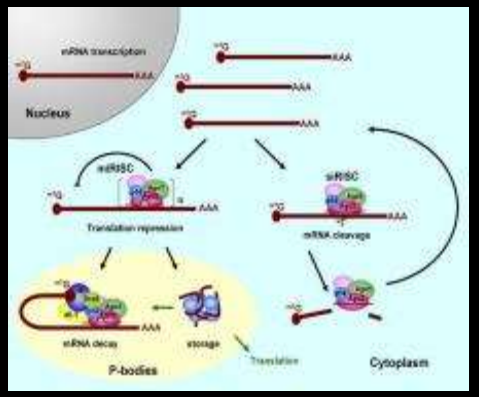
Proteomics

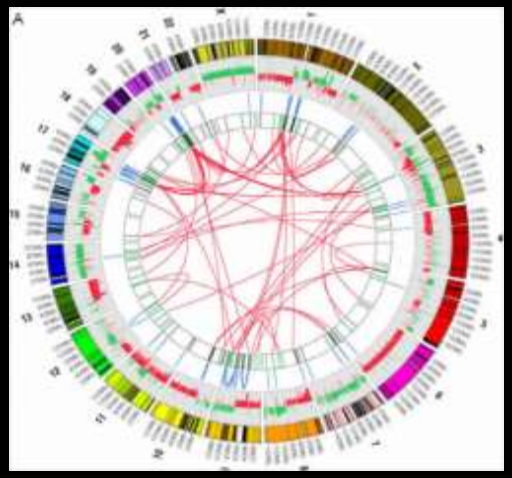


Molecular Pathways and Networks



Network Regulatory Mechanisms

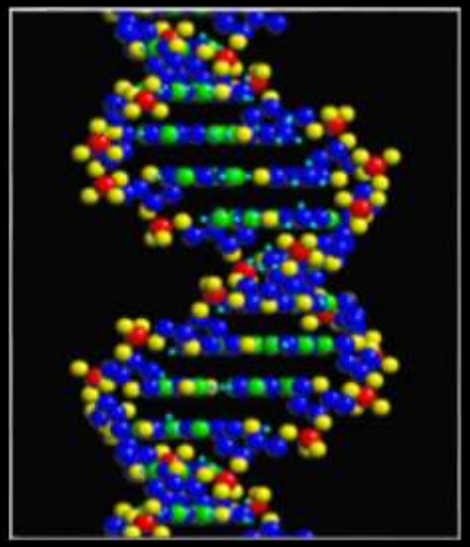




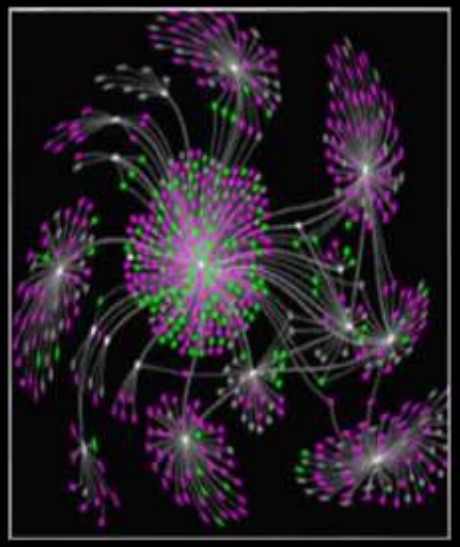
ID of Causal Relationships Between Molecular Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease

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

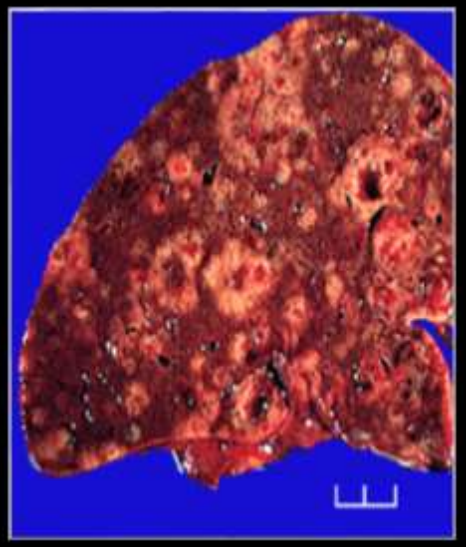


encoded information and expression as cell-specific signaling networks



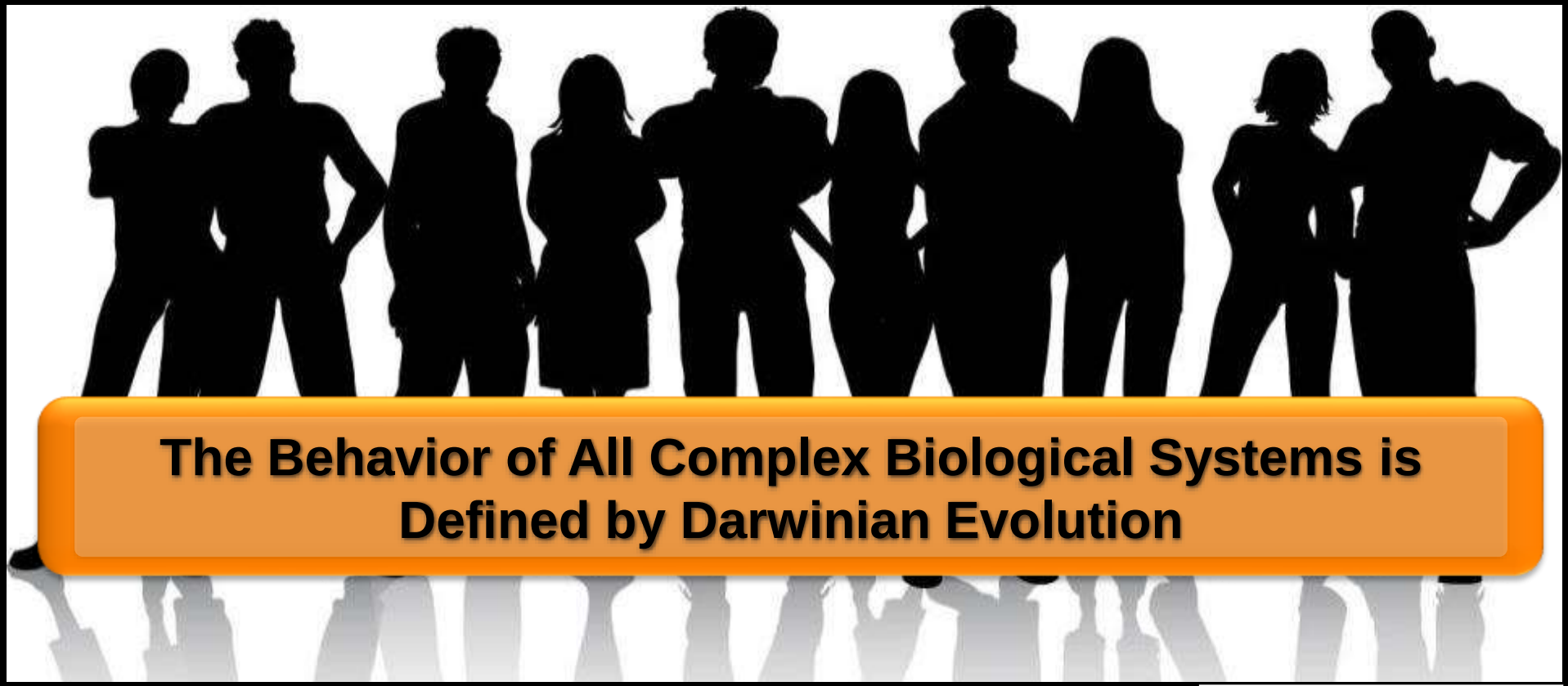
patterns of information flow within signaling networks

stable networks and information fidelity (health)

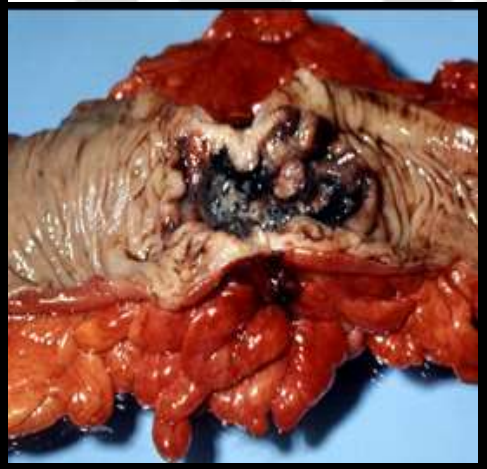


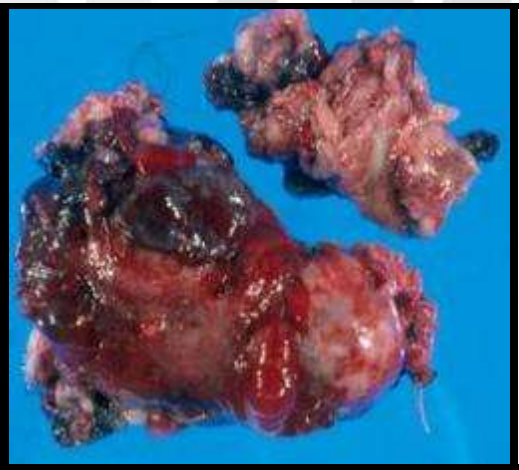
dysregulated networks and altered information patterns (disease)

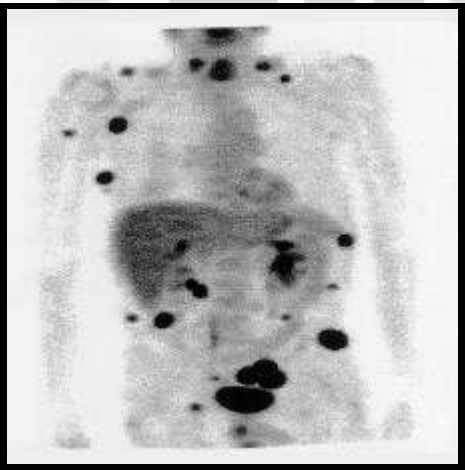
Cancer as a Complex Adaptive System

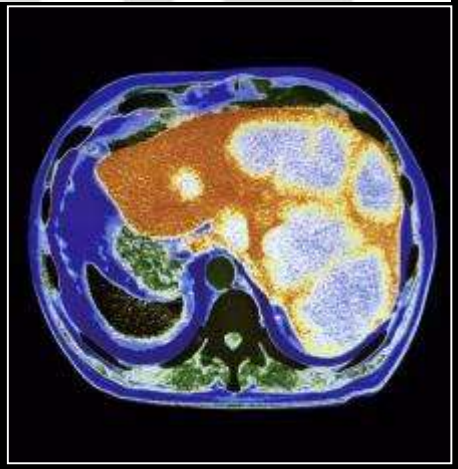


The Behavior of All Complex Biological Systems is Defined by Darwinian Evolution

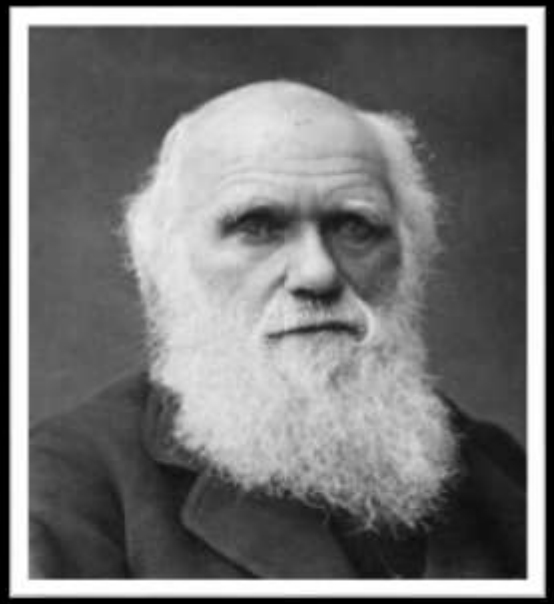






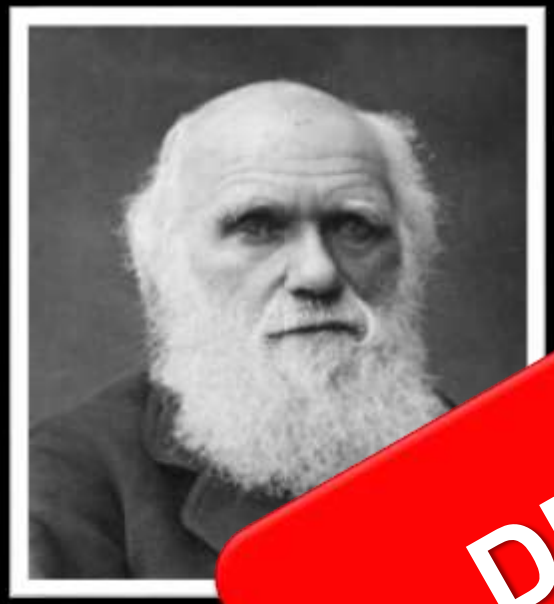


Darwinian Evolution



- 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

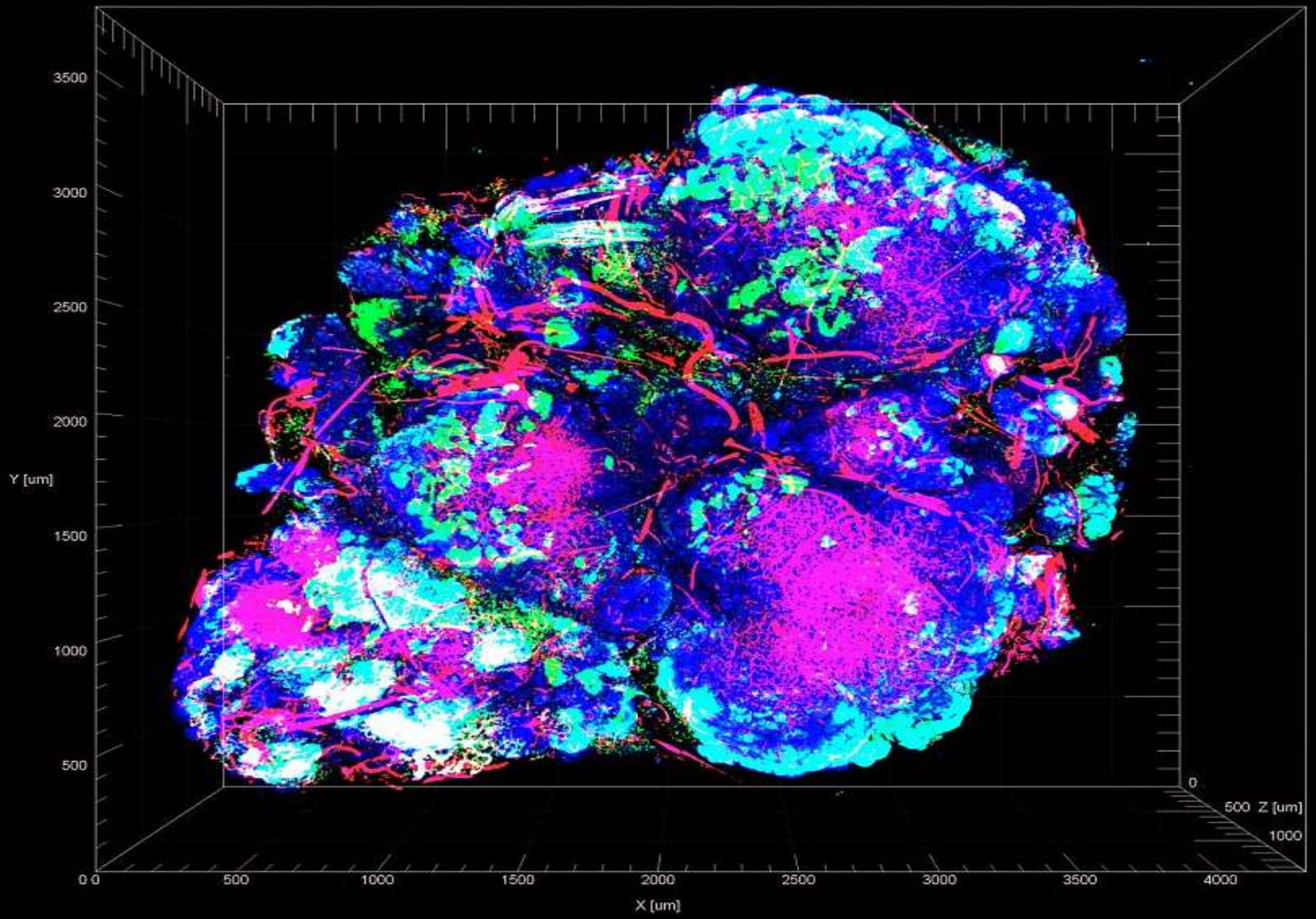
3E's: The Interplay Between Cancer and the Body's Defense Mechanisms

- elimination
- equilibrium
- escape

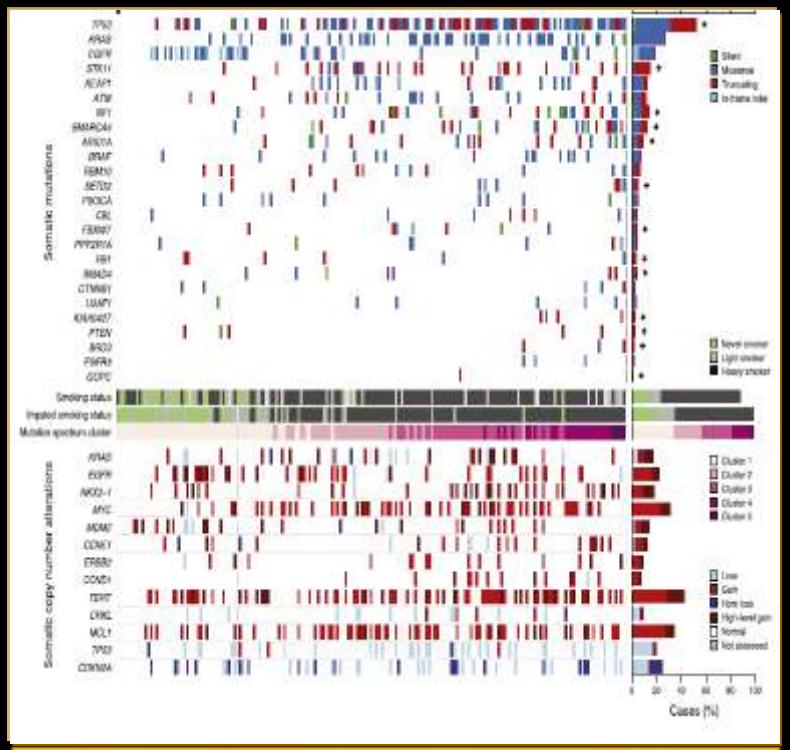
3E's: The Interplay Between Cancer and the Body's Defense Mechanisms

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

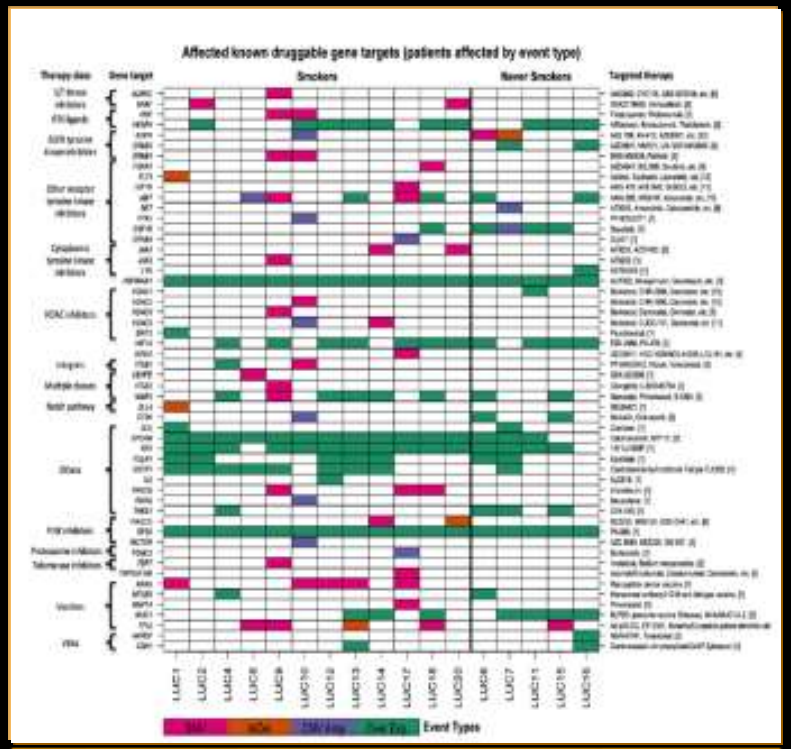
Mapping Tumor Heterogeneity: Zonal Variation



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



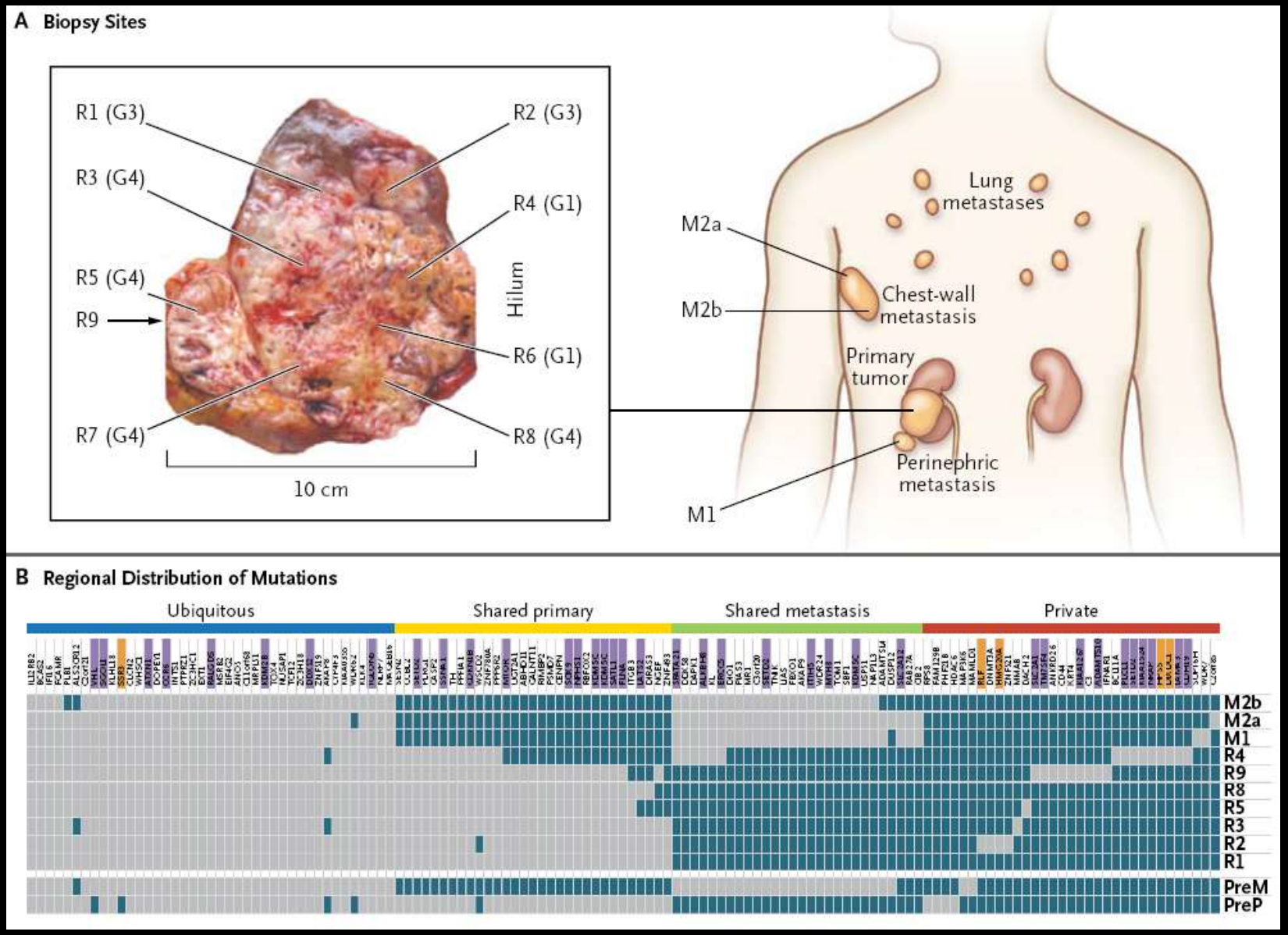
Mutations in Individual Non-small Cell Lung Cancer



Drug Targets in Individual Non-Small Cell Lung Cancers

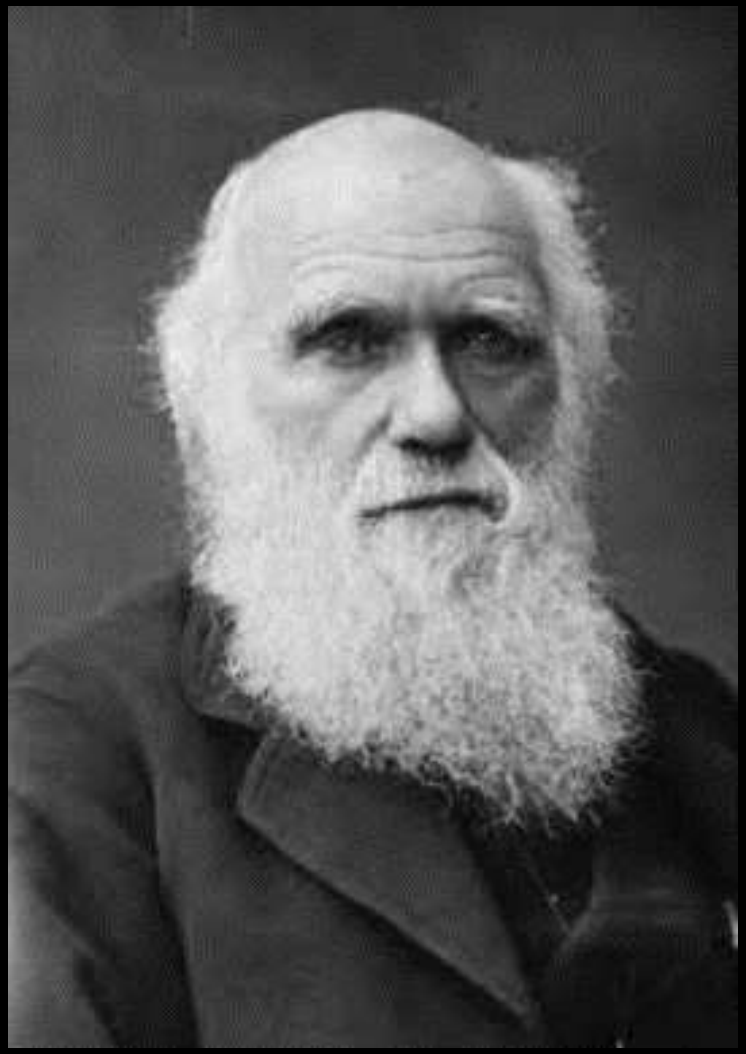
- "malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations
- disturbing implications for therapeutic 'cure' and development of new R_x

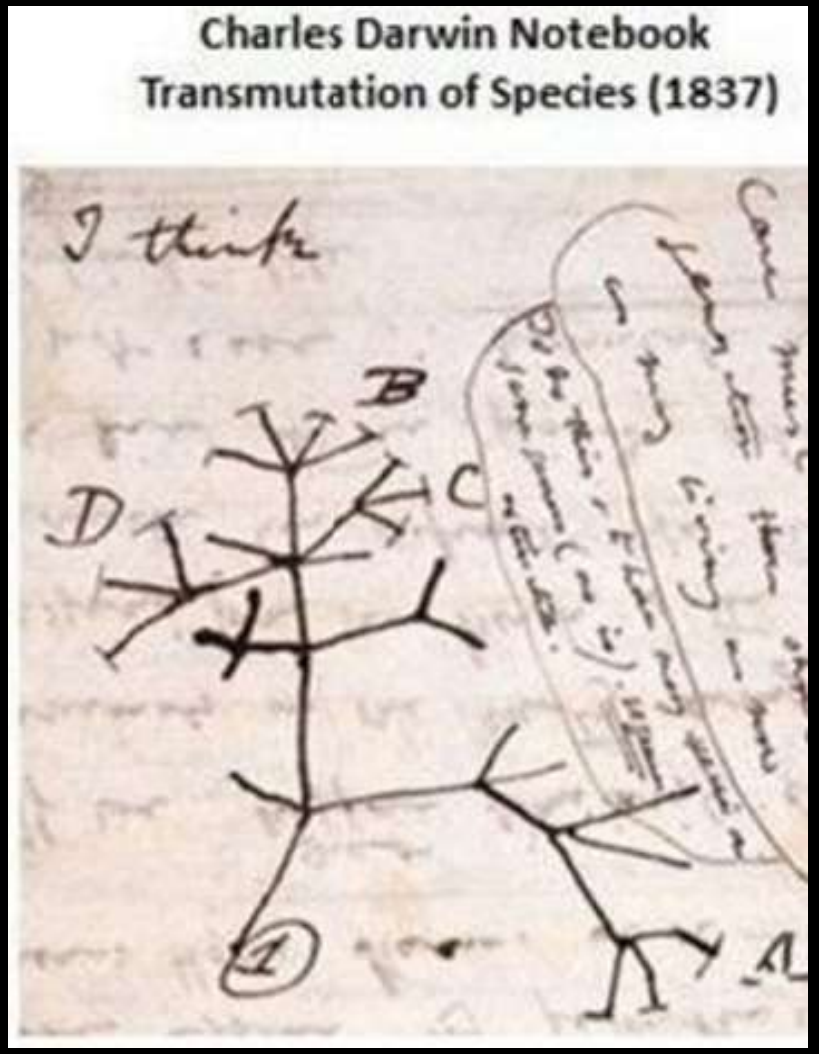
Intratumor Genetic Heterogeneity in Multiple Regions of Primary Clear Cell Tumor and Three Metastases (Perinephric and Chest Wall) in RCC



From: M. Gerlinger et al. (2012) NEJM 366, 883

Charles Darwin's Sketch of Speciation (1837)





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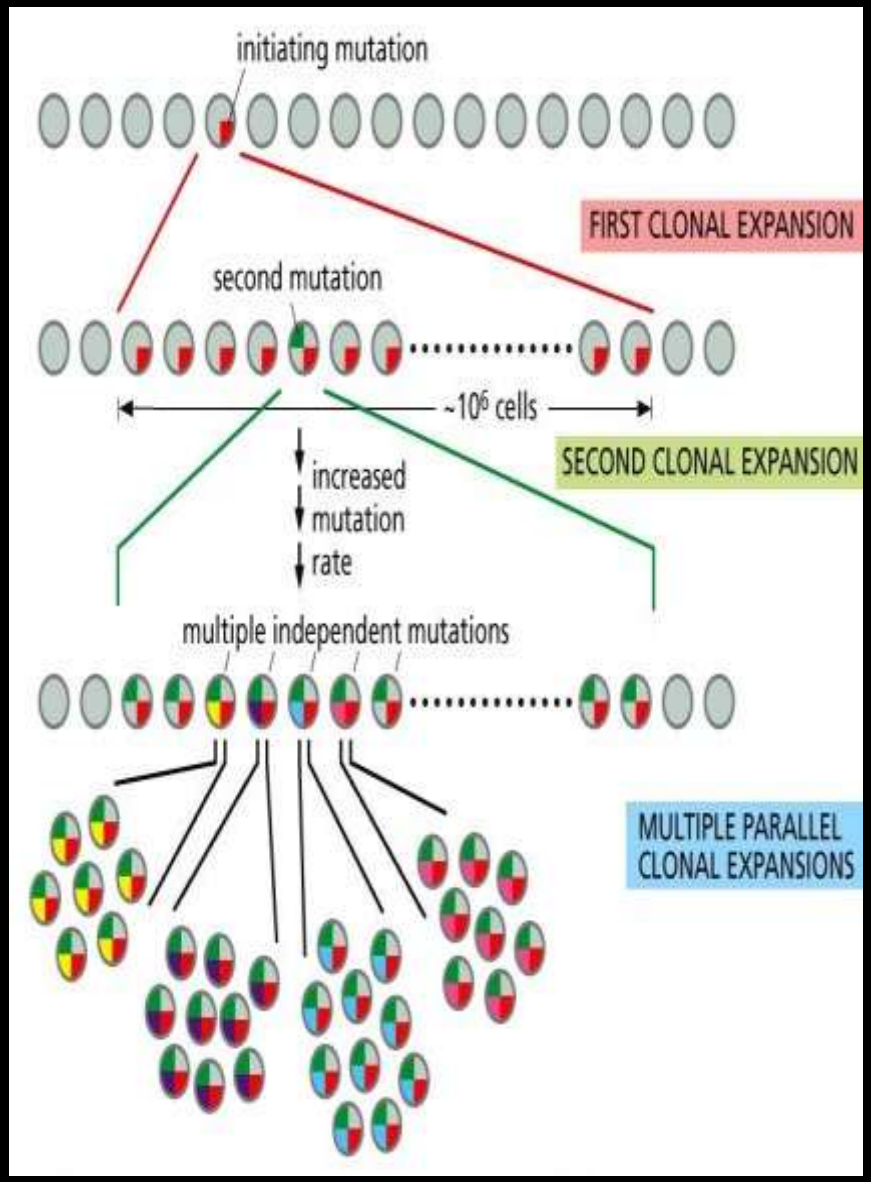
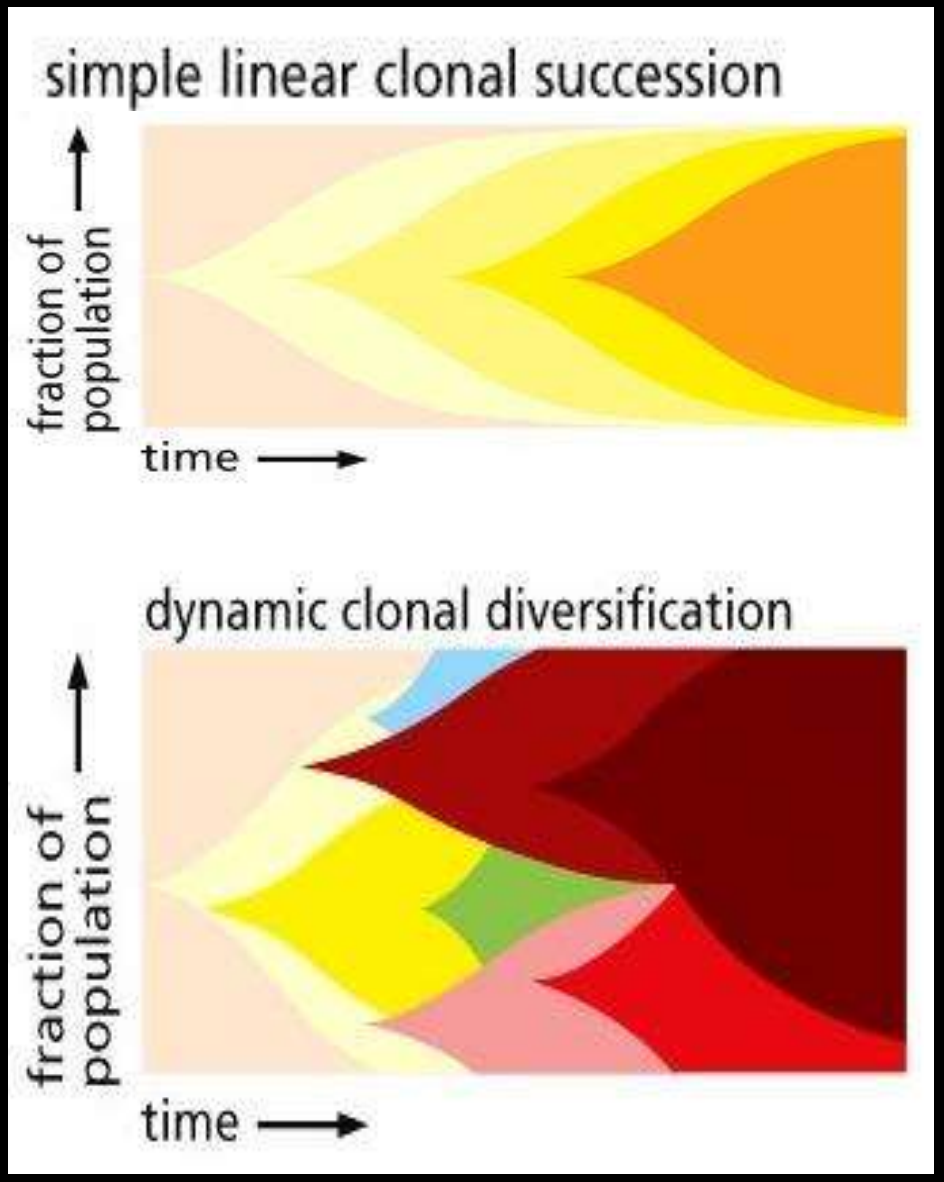
What Makes Cancer So Dangerous and Difficult to Treat

Dynamic Heterogeneity

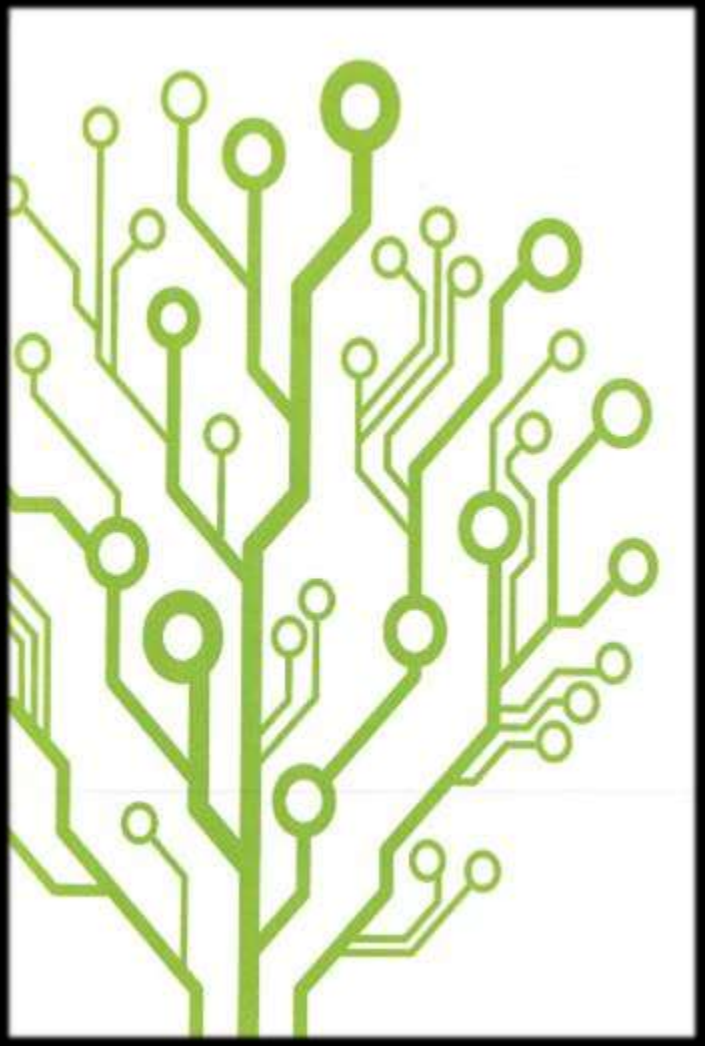
Emergence and Adaptive Evolution of Tumor Clones With Different Properties During Tumor Progression

Evolution and Phenotypic Diversification of Tumor Clones and Subclones



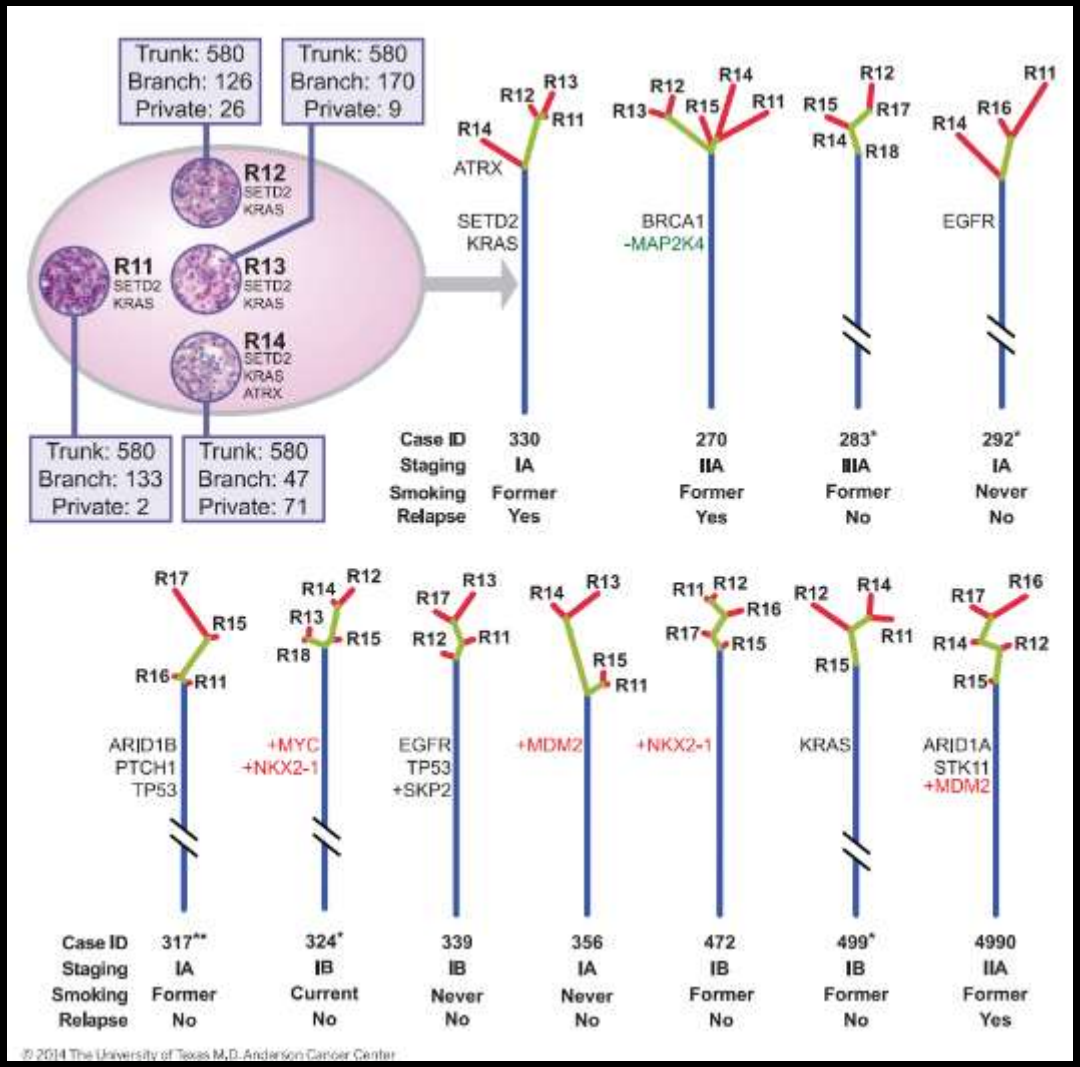


Mapping the Dynamics of Clonal Evolution in the Progression of Malignant Tumors: Clonal Branching



- 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 late(r) 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

Cancer as a Complex Adaptive System With Emergent Properties

- unknown but different patterns of environmental exposure and genotoxic insults as triggers of tumor initiation and progression
  - different individuals
  - different tissues
  - different patterns of mutations generate different clonal phenotypes (heterogeneity)

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
- profiling heterogeneity
  - clinical presentation and progression
  - response to R_x
  - cellular heterogeneity (multiple clones)
  - molecular network heterogeneity (different signaling circuits in different clones)

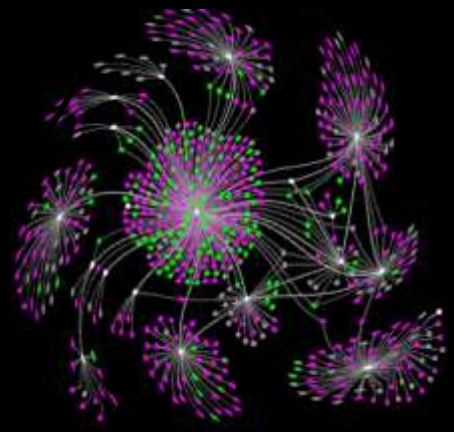
Understanding Emergent State Shifts in Molecular Signaling Networks and Identification of Triggers of R_x- Resistance (R)

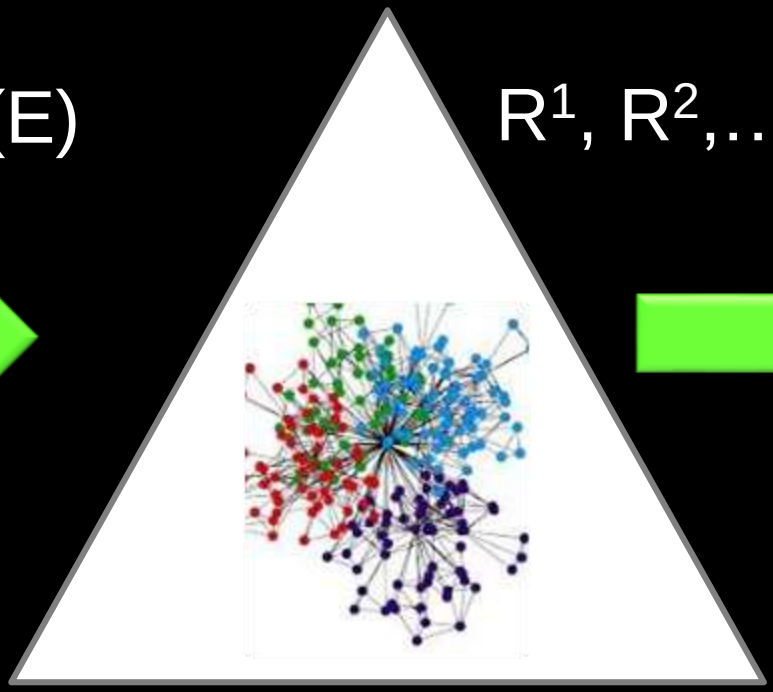
dynamic molecular signaling network topologies

new network topologies to bypass R_x-vulnerable pathways

Emergence(E)

R^1, R^2,..... R^n





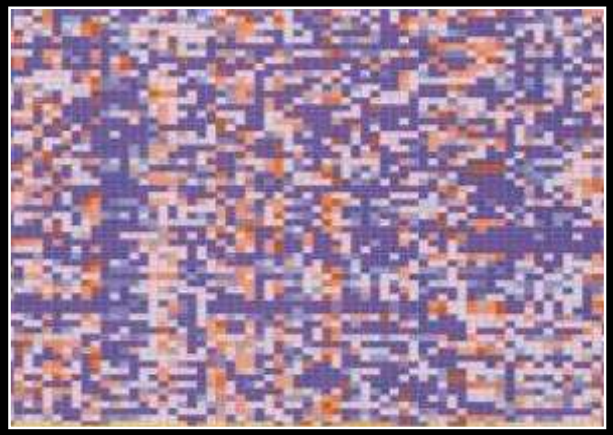
- **intrinsic resistance (pre-exist prior to R_x)**
- **acquired resistance (R_x as selection pressure)**

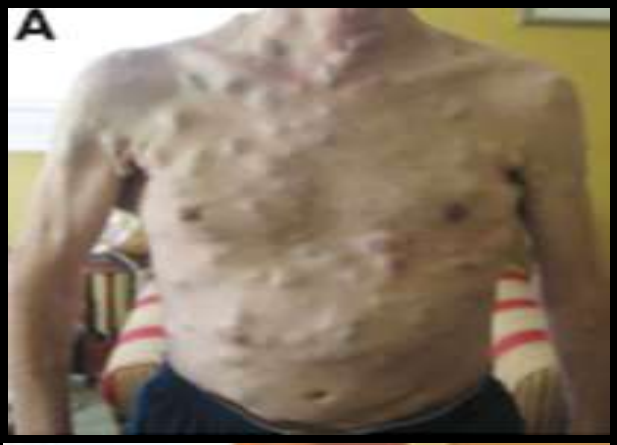
Targeted Therapeutics and the Omnipresent Problem of R_x Failure Due to Emergence of Drug Resistance Clones

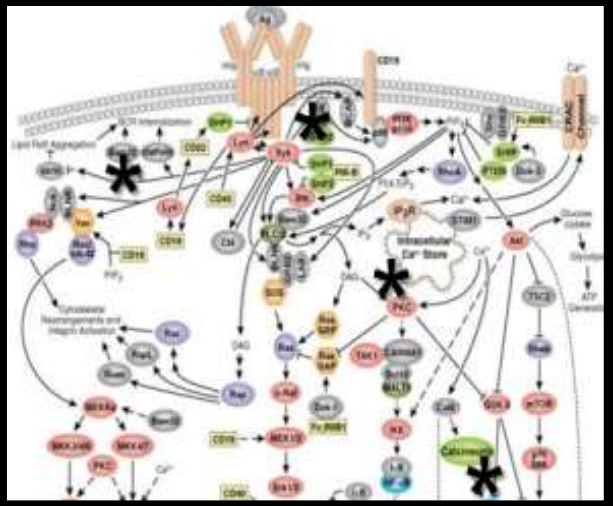
Molecular Subtyping and R_x Targets

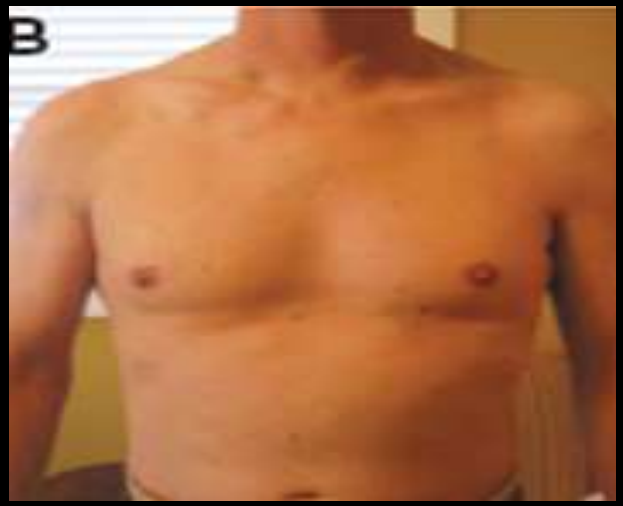
Initial R_x - Response to Targeted R_x

R_x - Resistance via Redundant Molecular Pathways





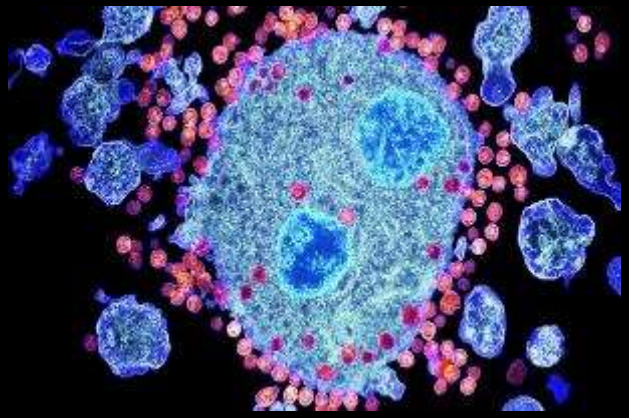
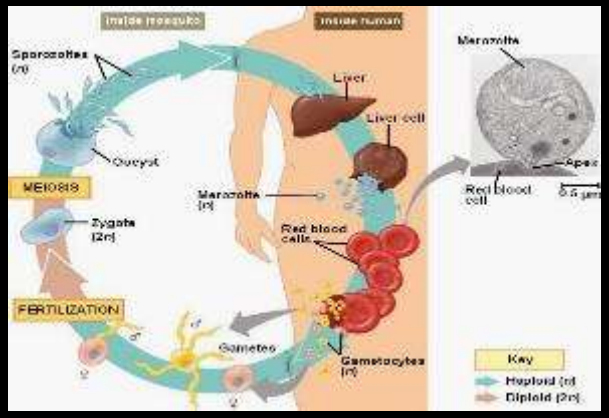




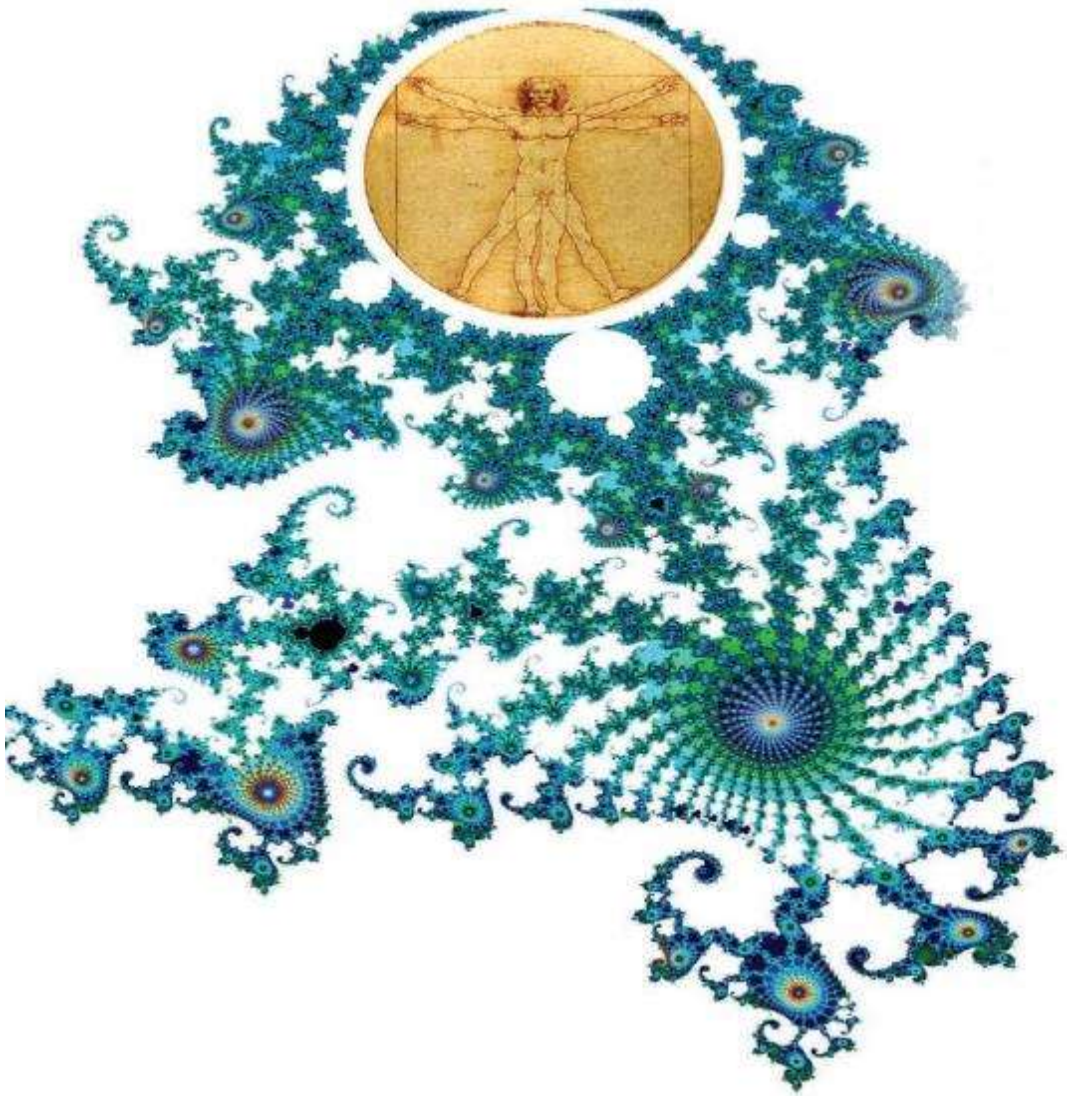
B = 15 weeks R_x (vemurafenib)

C = 23 weeks R_x and emergence of $MEK1^{C121S}$ mutant[1]

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

antibiotics	antivirals	antimalarials
		
		
insecticides	**herbicides**	**pesticides**

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



The Principal Challenge in Cancer R_x Therapy

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

The Biological Complexity of Cancer and the Design of Treatment Strategies

- successful surgical removal of primary tumor assumed (except brain tumors)
- targeting metastatic disease and circumventing R_x resistance
  - subclinical disease with evidence 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

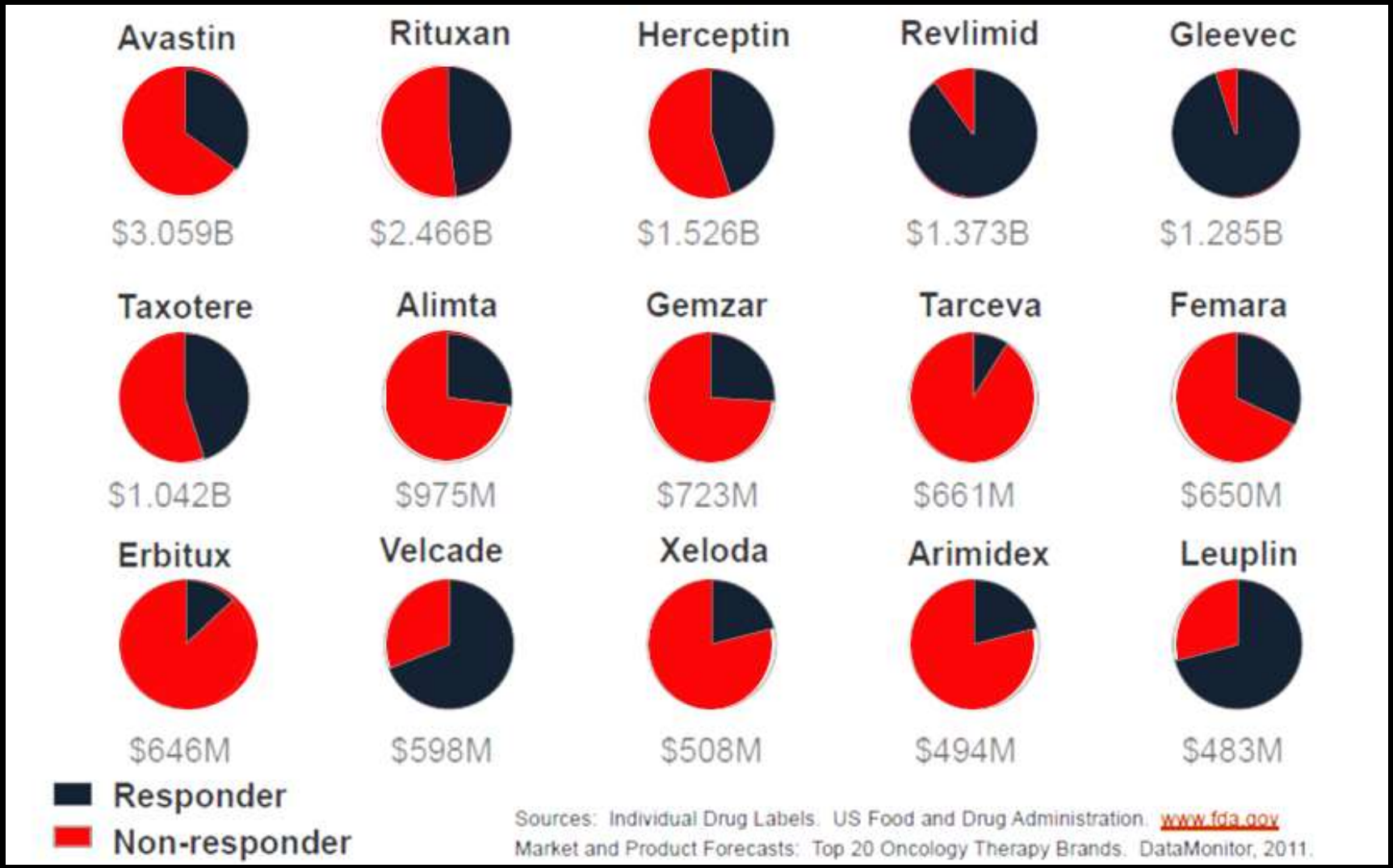
- R_x designed to inhibit one or a few molecular targets/pathways altered in cancer cells
- molecular profiling to ID patients with relevant R_x targets

immunotherapy

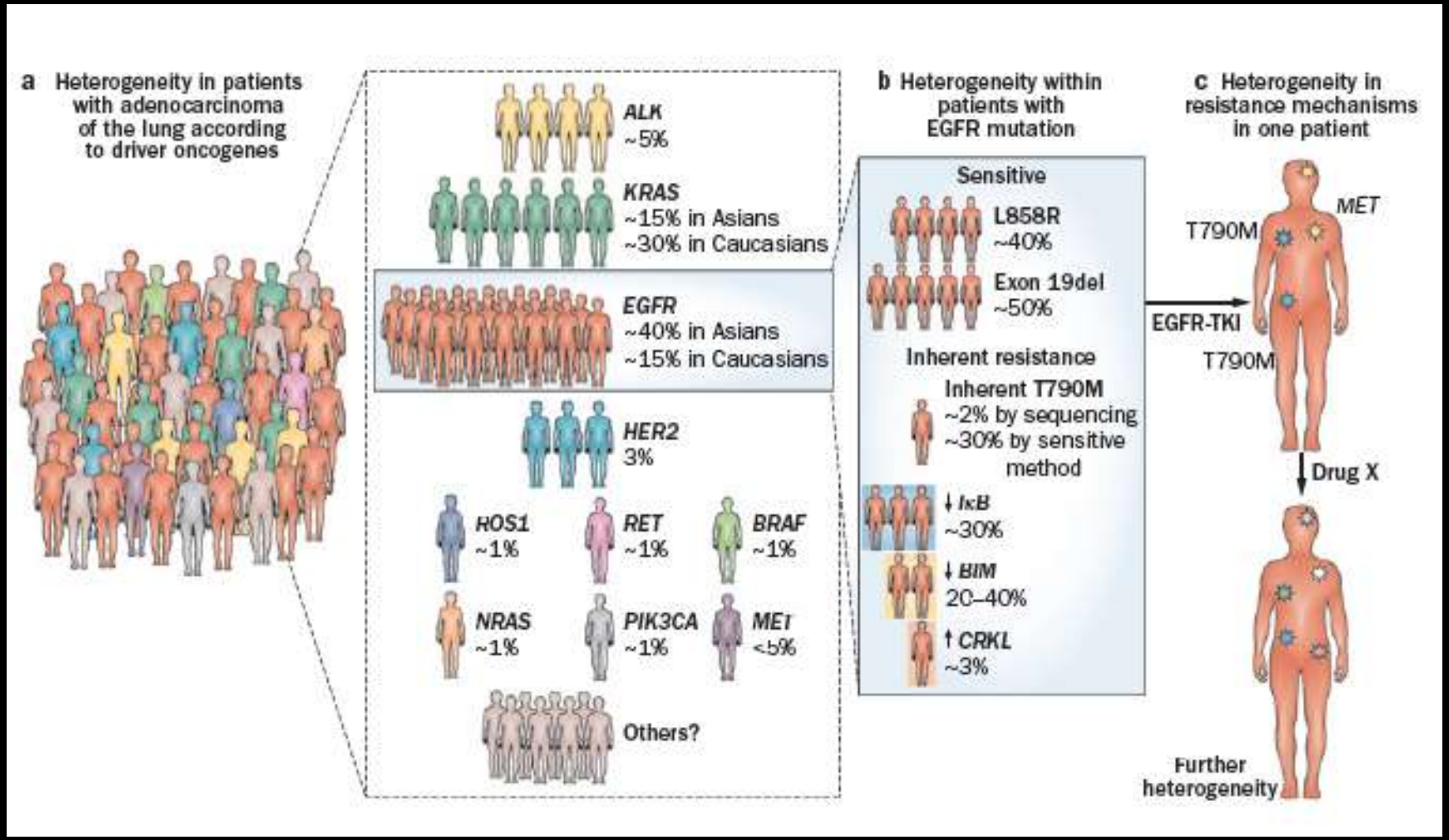
- (re) activation of body's immune defenses to detect and destroy cancel cells

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

Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



Molecular Profiling and Classification of Subtypes of NSCLC

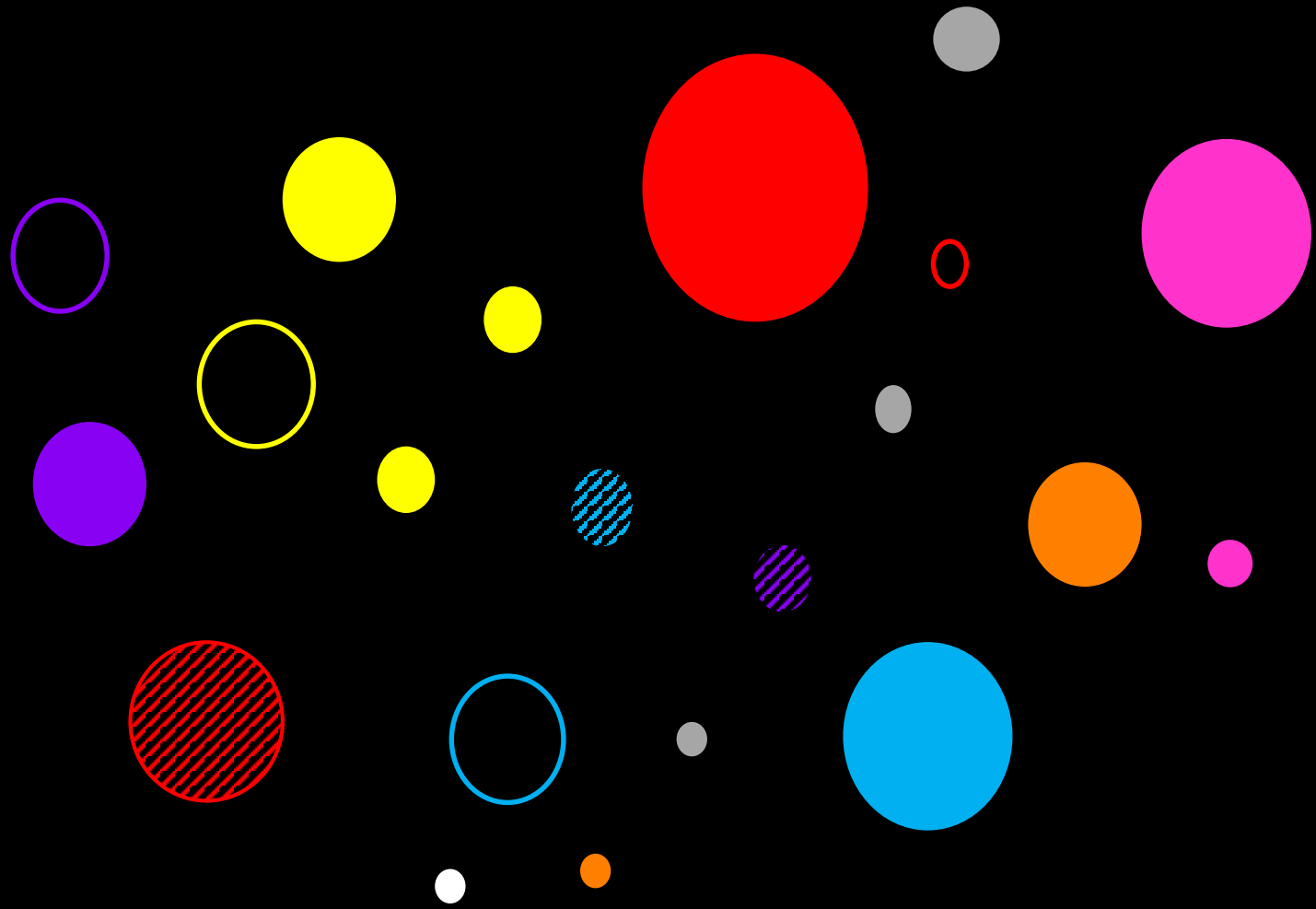


From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

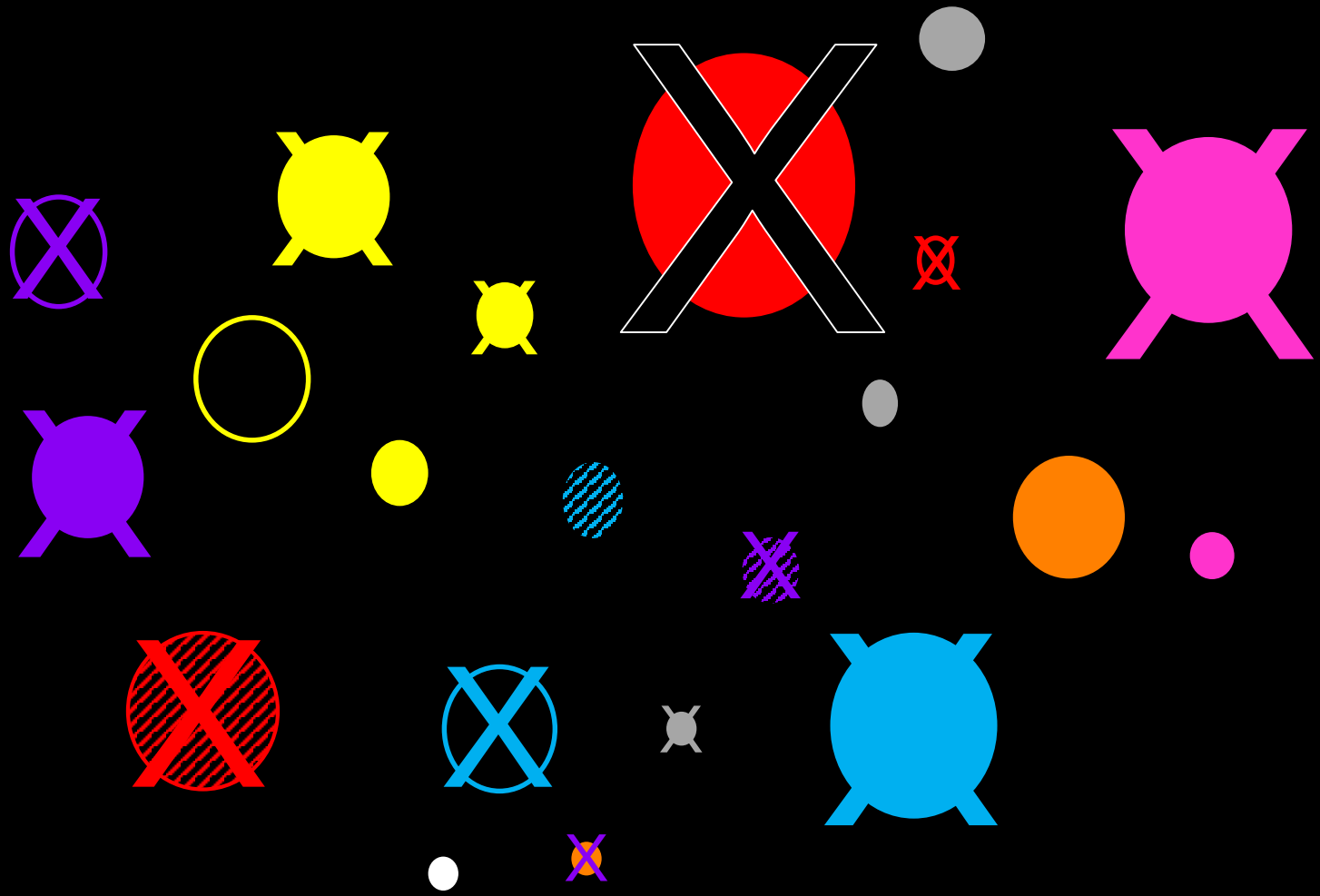
Challenges in Cancer Therapy

- 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
  - very low probability of technical success

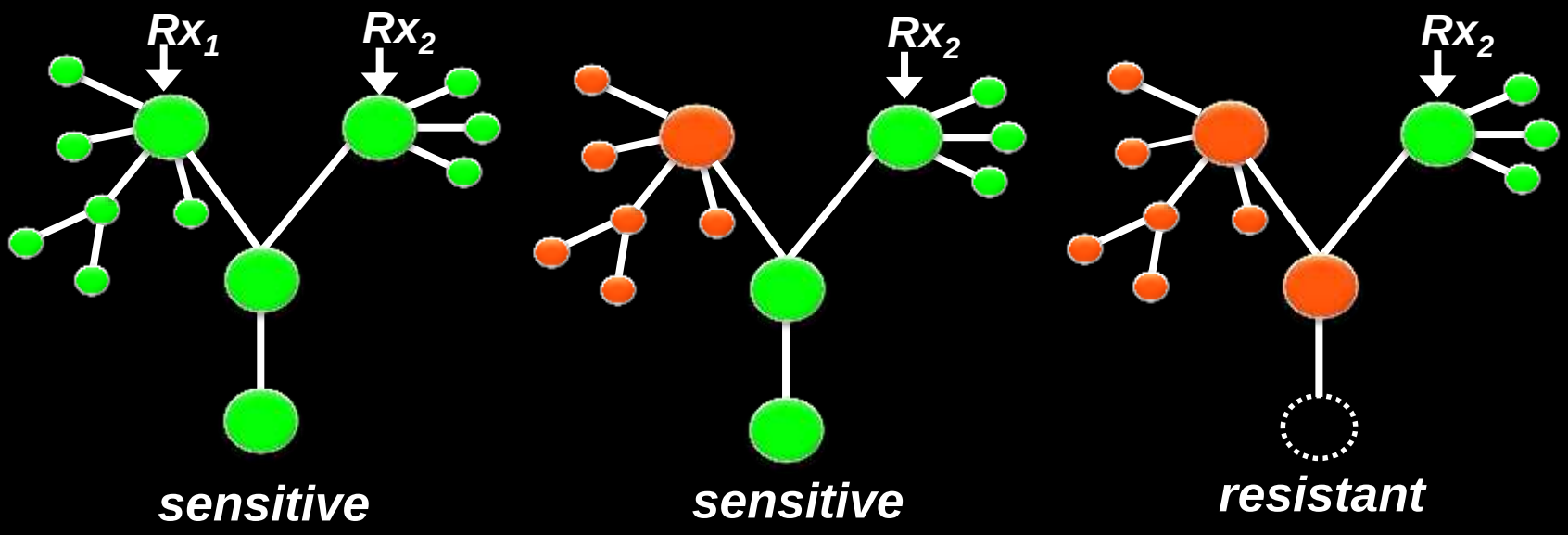
Design of Cancer Treatments to Hit Multiple Targets

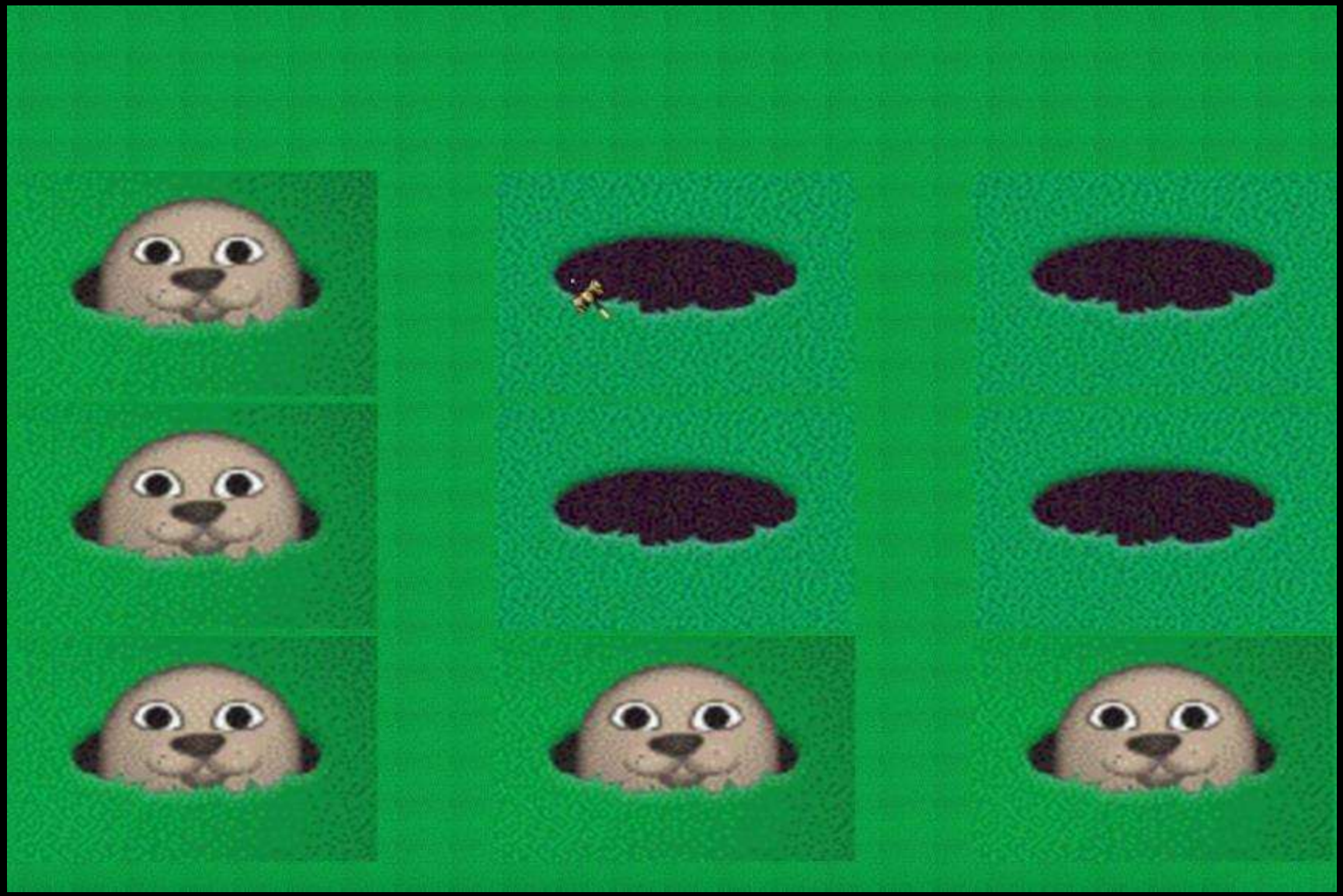
- multi-drug combinations
  - patient tolerance
  - cost
- high probability that R_x-resistant variants will eventually emerge
- R_x as selection pressure to generate R_x-resistant 'escape' clones
  - direct drug effect to cause mutations and new resistant clones
  - R_x elimination of 'dominate' clones allows pre-existing 'minor' clones to prosper

‘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

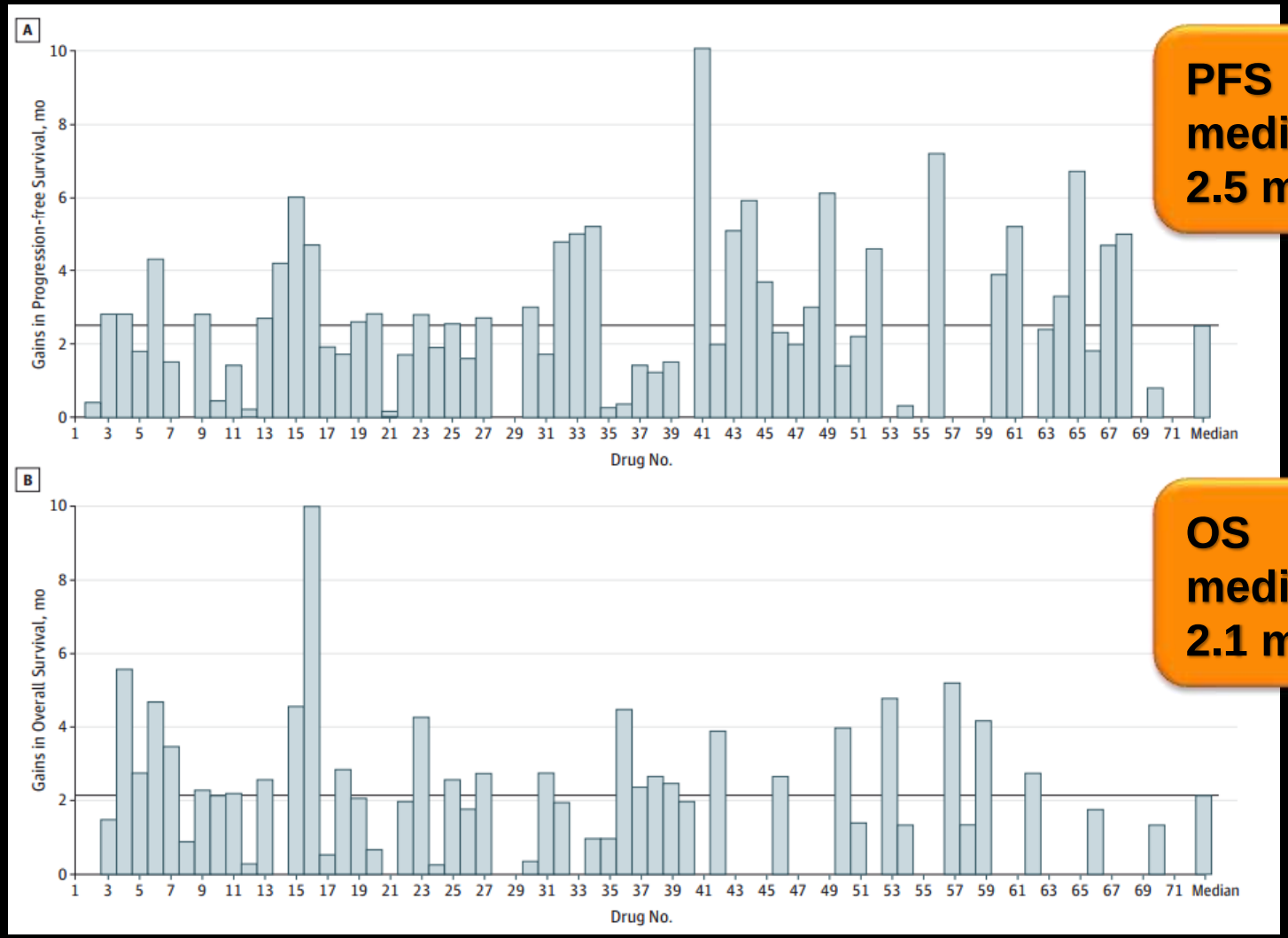
Redundancy and Robustness in Molecular Signaling Networks: The Biological Foundation of R_x Resistance





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

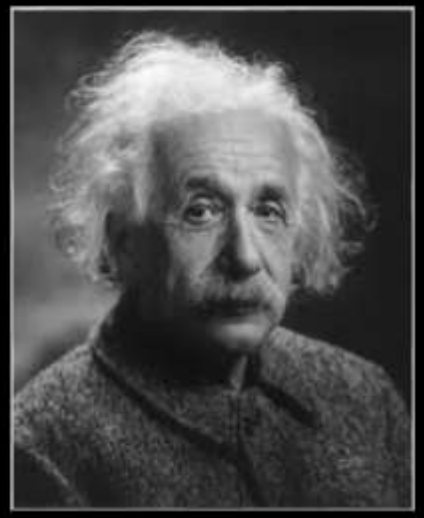


PFS median 2.5 months

OS median 2.1 months

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

Knowing When to Stop!



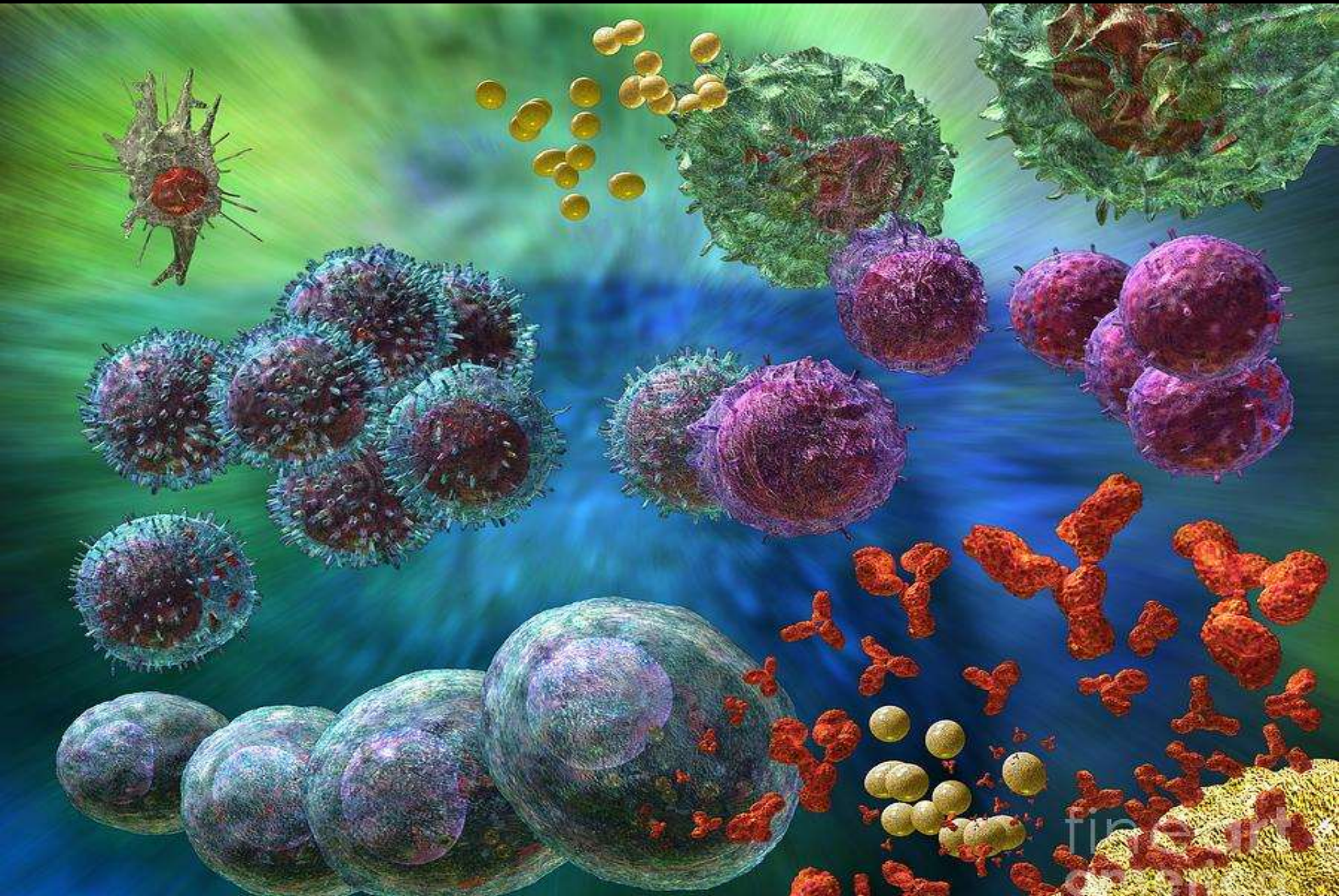
“Insanity is doing the same thing
over and over again
and expecting a different result.”

- Albert Einstein

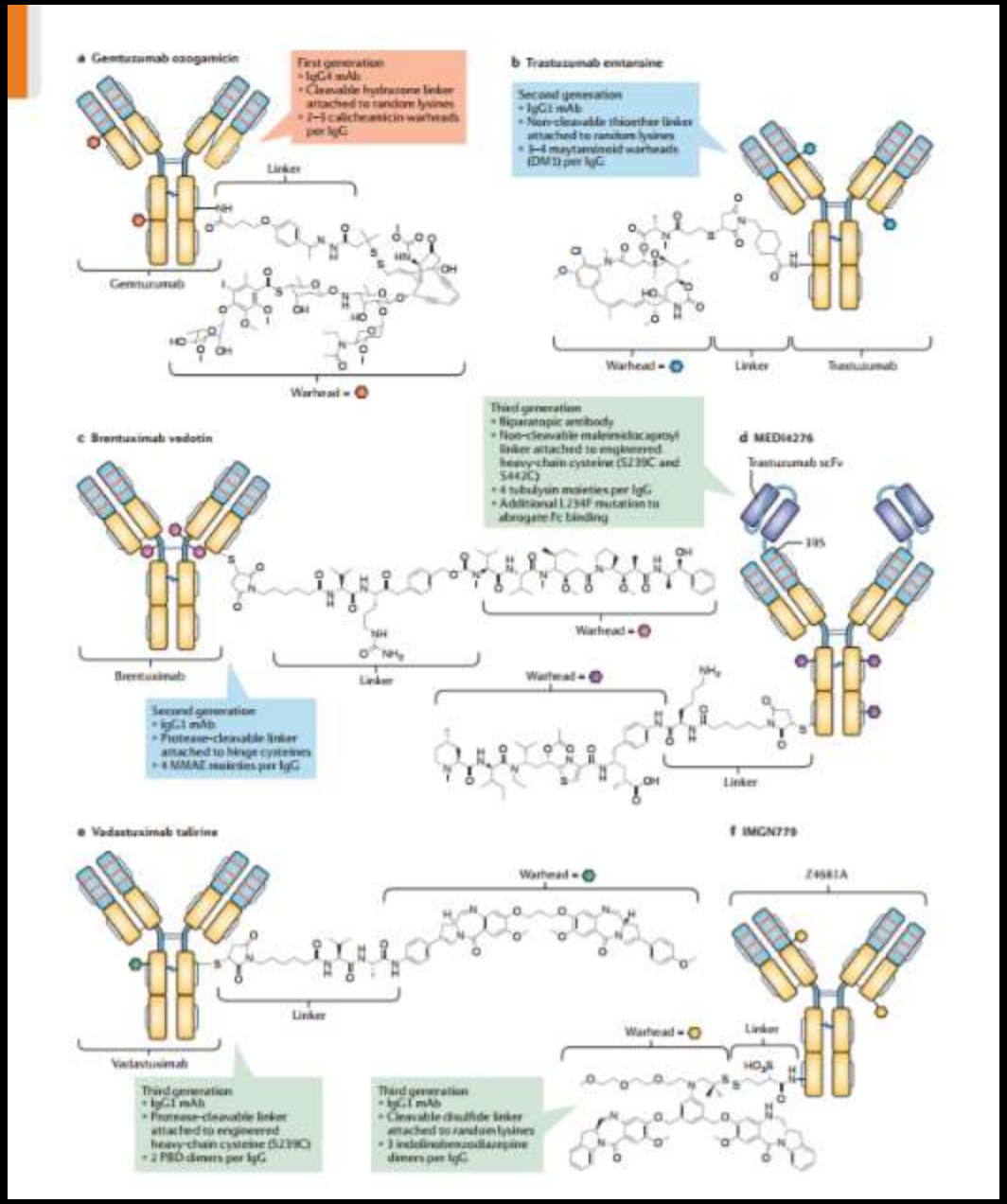
The Therapeutic Challenge of Circumvention of Tumor cell Heterogeneity

- moving from classical ‘chemo’ and newer 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) Immunotherapy for Cancer

- 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)

Antibody Therapy in Cancer

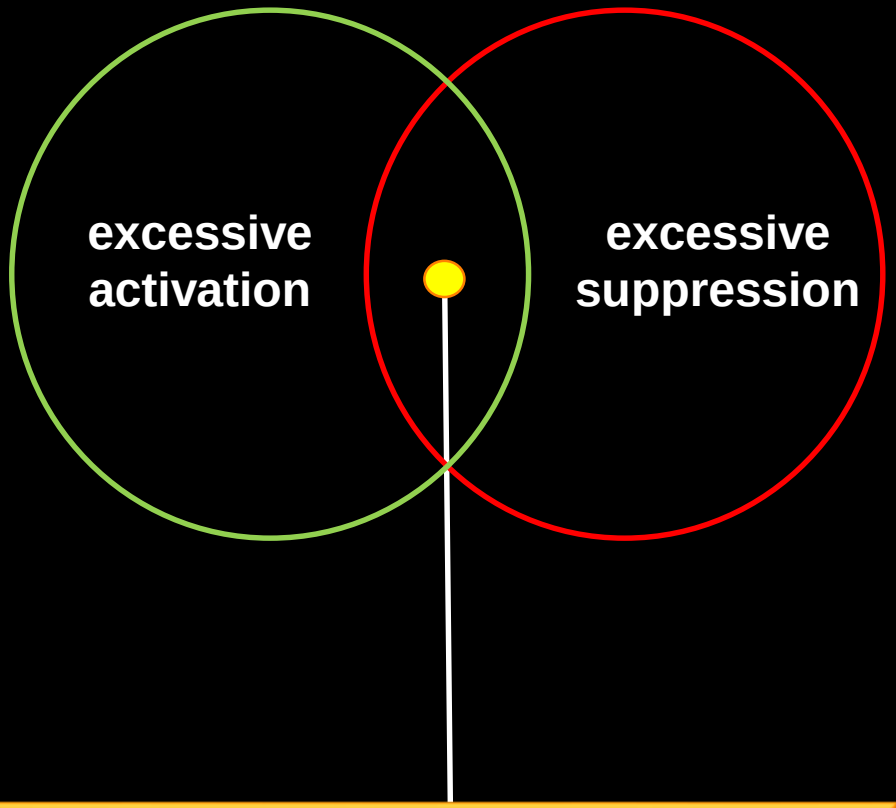
- intrinsic limitations
- Mab or bi-specific Mabs target only one of the many neoantigens expressed by different clones
- high probability or Mab-resistant clones emerging in similar fashion to resistance to targeted anti-cancer drugs

Immunoevasion by Tumor Cells

- "stealthy" tumor cell strategies
  - reduce detection and/or killing by body's immune defenses
- 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

Balancing The Body's Immune Response

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



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

Setting the Immune System Free to Combat Cancer

Host Immune-Tumor Interactions

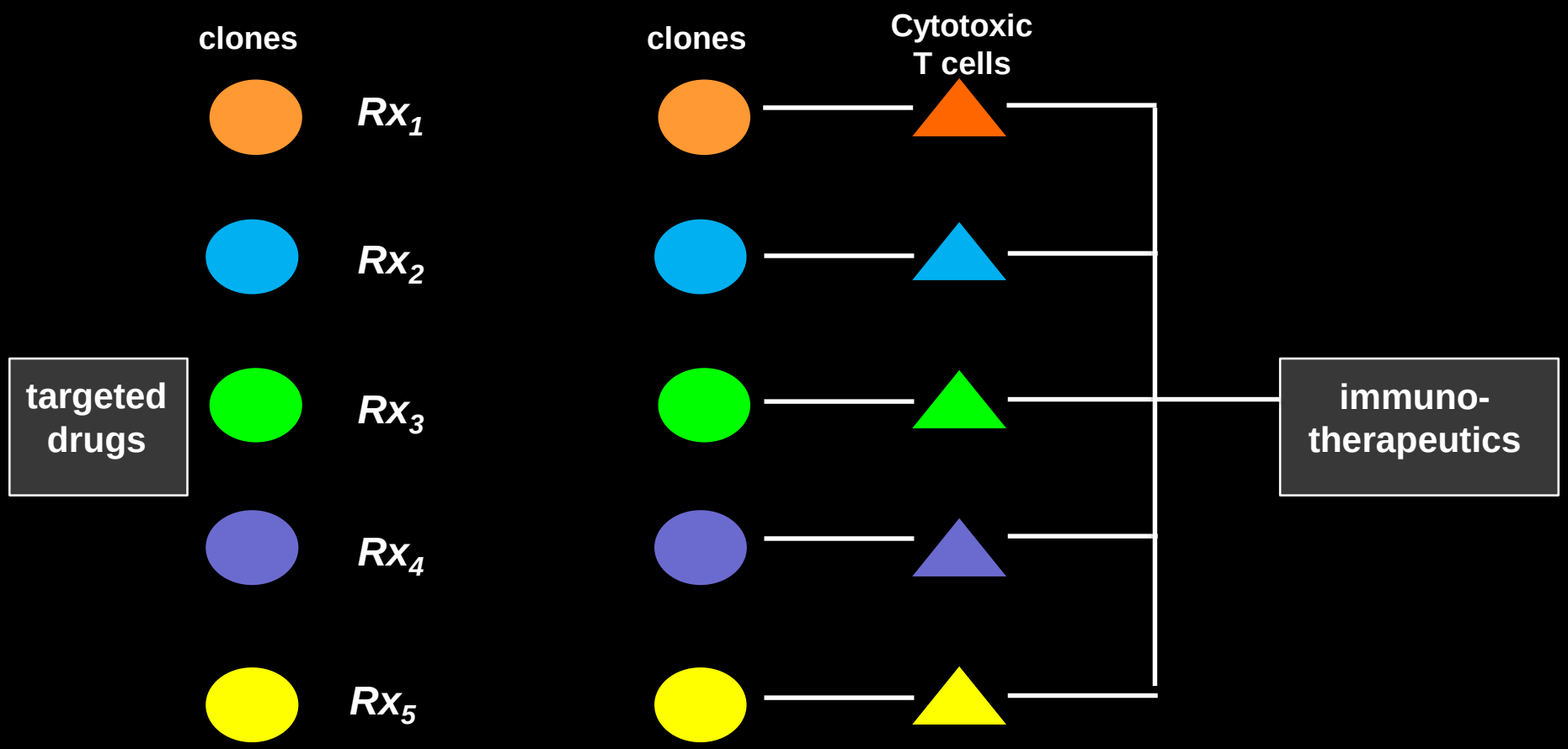
Clone Wars

Relentless Emergence of New Tumor Cell Clones During Tumor Progression and Immune Evasion

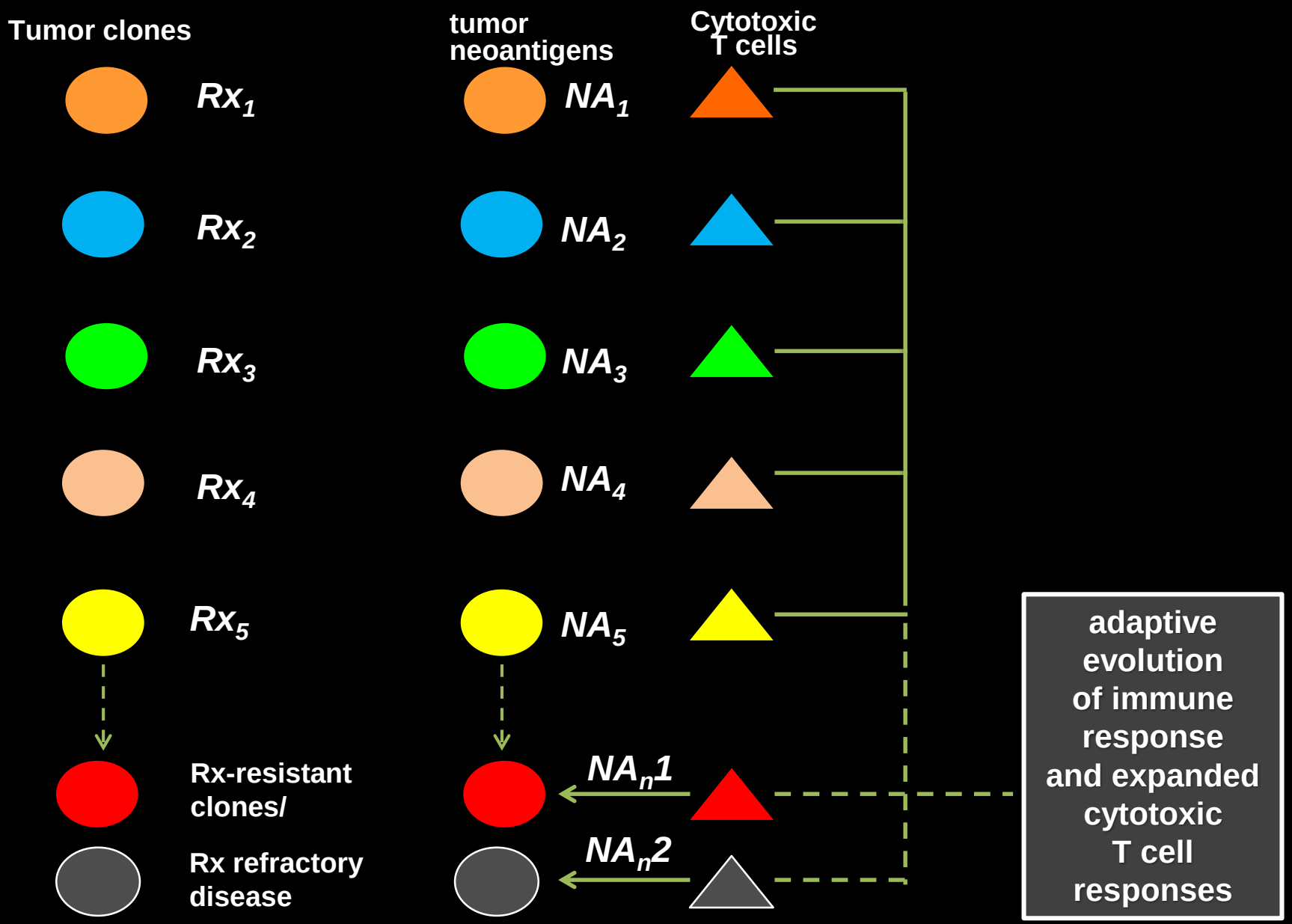
versus

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)

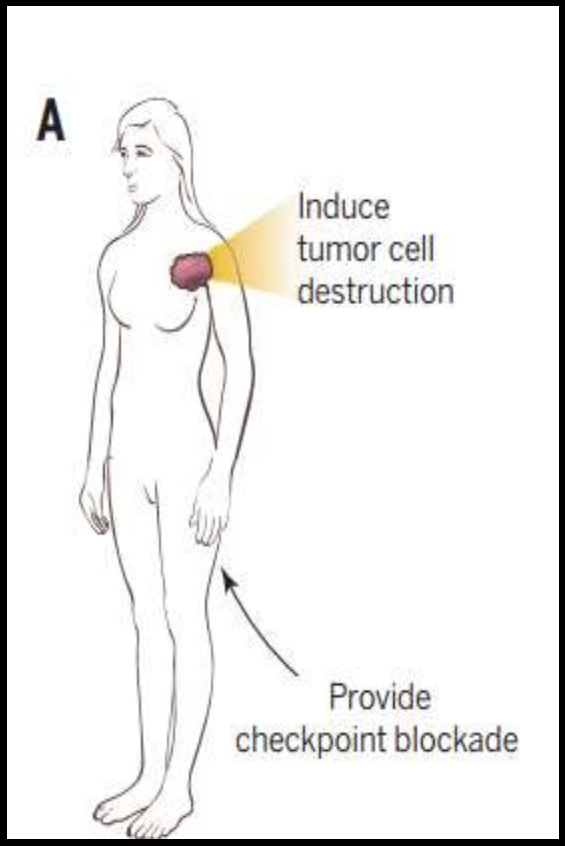


Circumventing the Inevitable Drug Resistance Problem in Targeted Rx Therapy versus Restoration of Effective Immune Surveillance

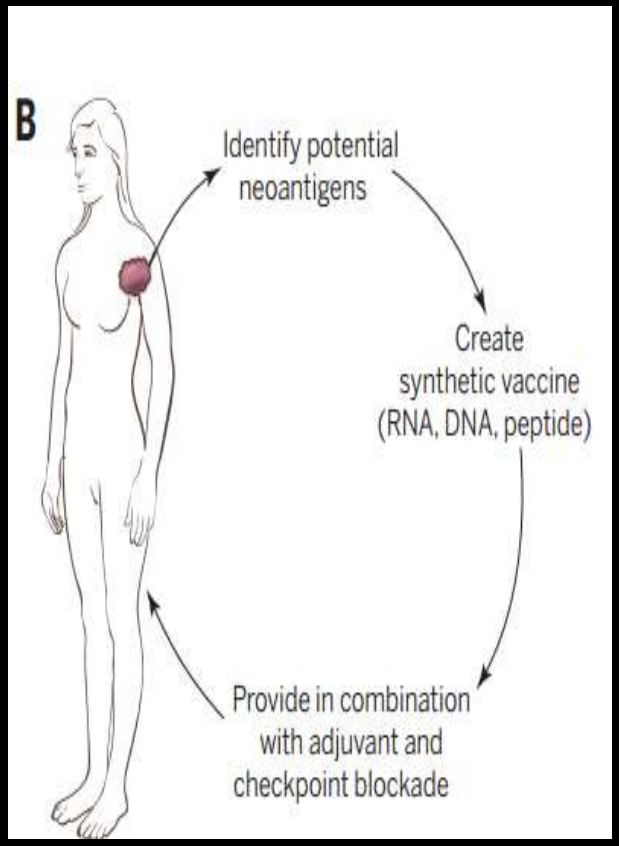


Immunotherapeutic Strategies to Enhance Immune Responses to Patient-Specific Tumor Neoantigens

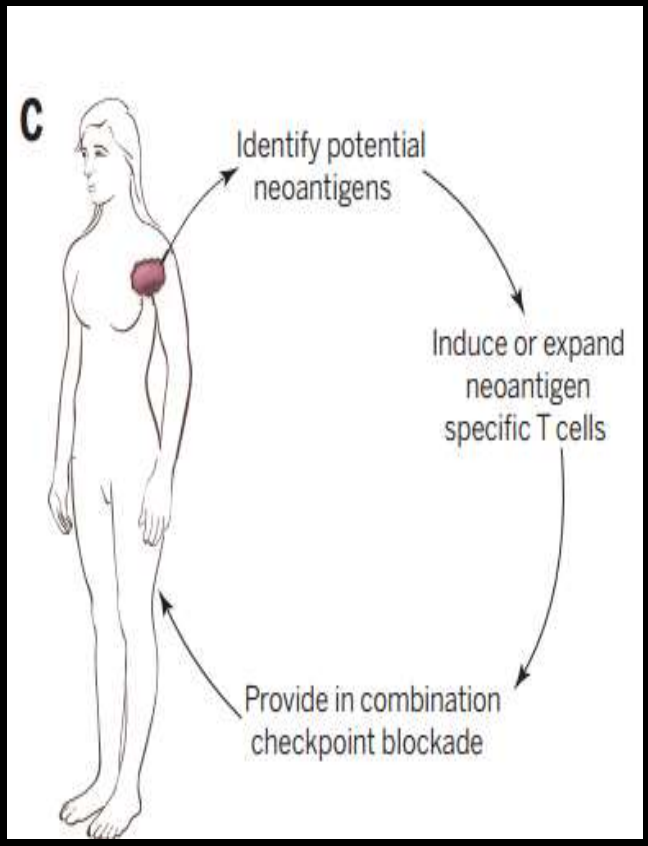
Immune Checkpoint Modulation



Cancer Neoantigen Vaccines

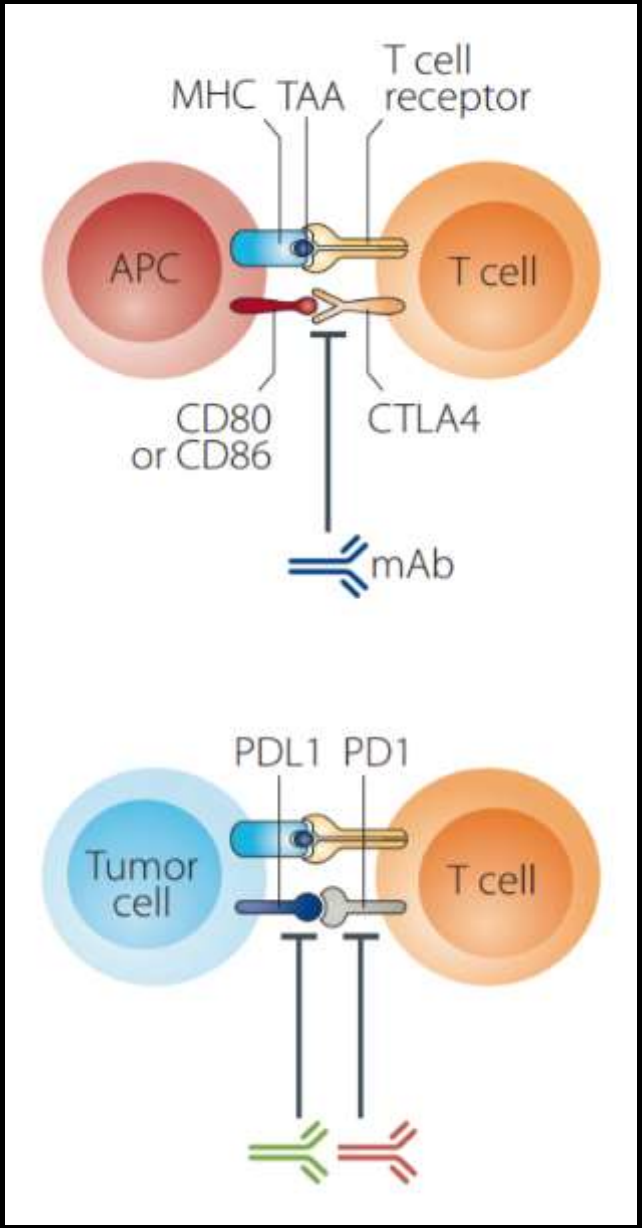


Adoptive Cell Therapy TILs, TCRs, CARs



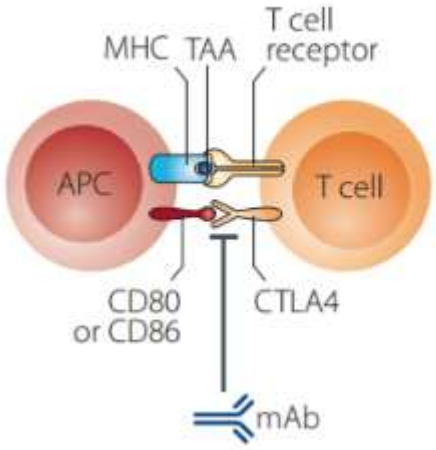
Adapted From: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69

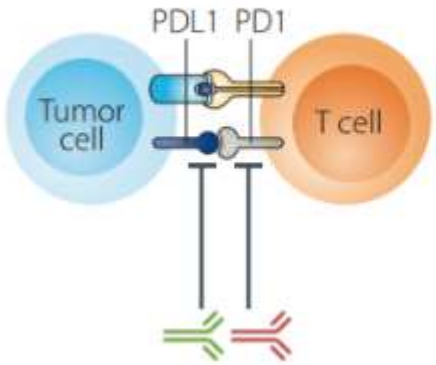
Immune Checkpoint Inhibitors in Cancer Treatment



From: September 2016 biopharmadealmakers.nature.com

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

From: September 2016 biopharmadealmakers.nature.com

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

Immunotherapy for Cancer

Vaccines

- far 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

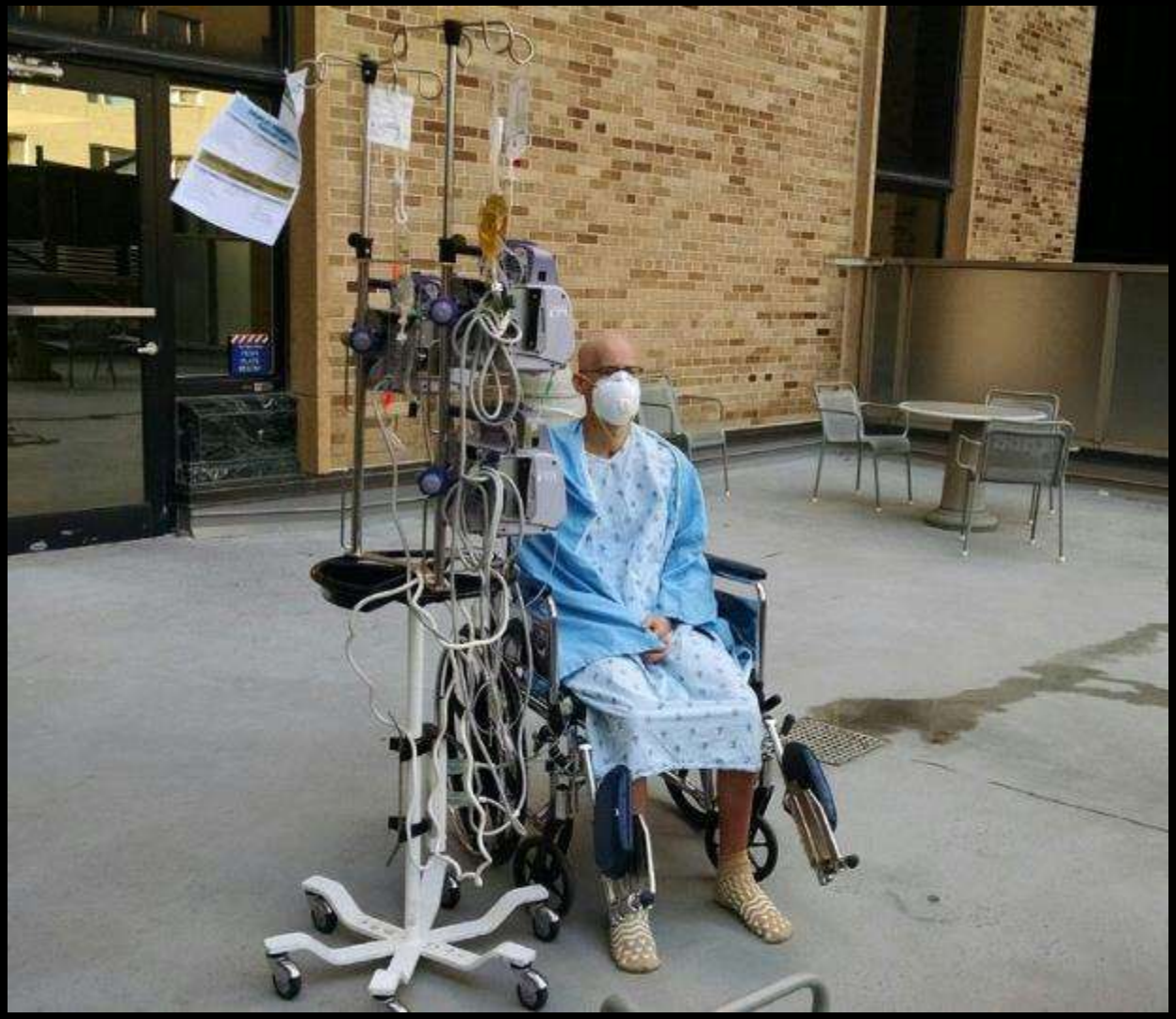
Engineering Killer T Cells for Cancer Therapy

- 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

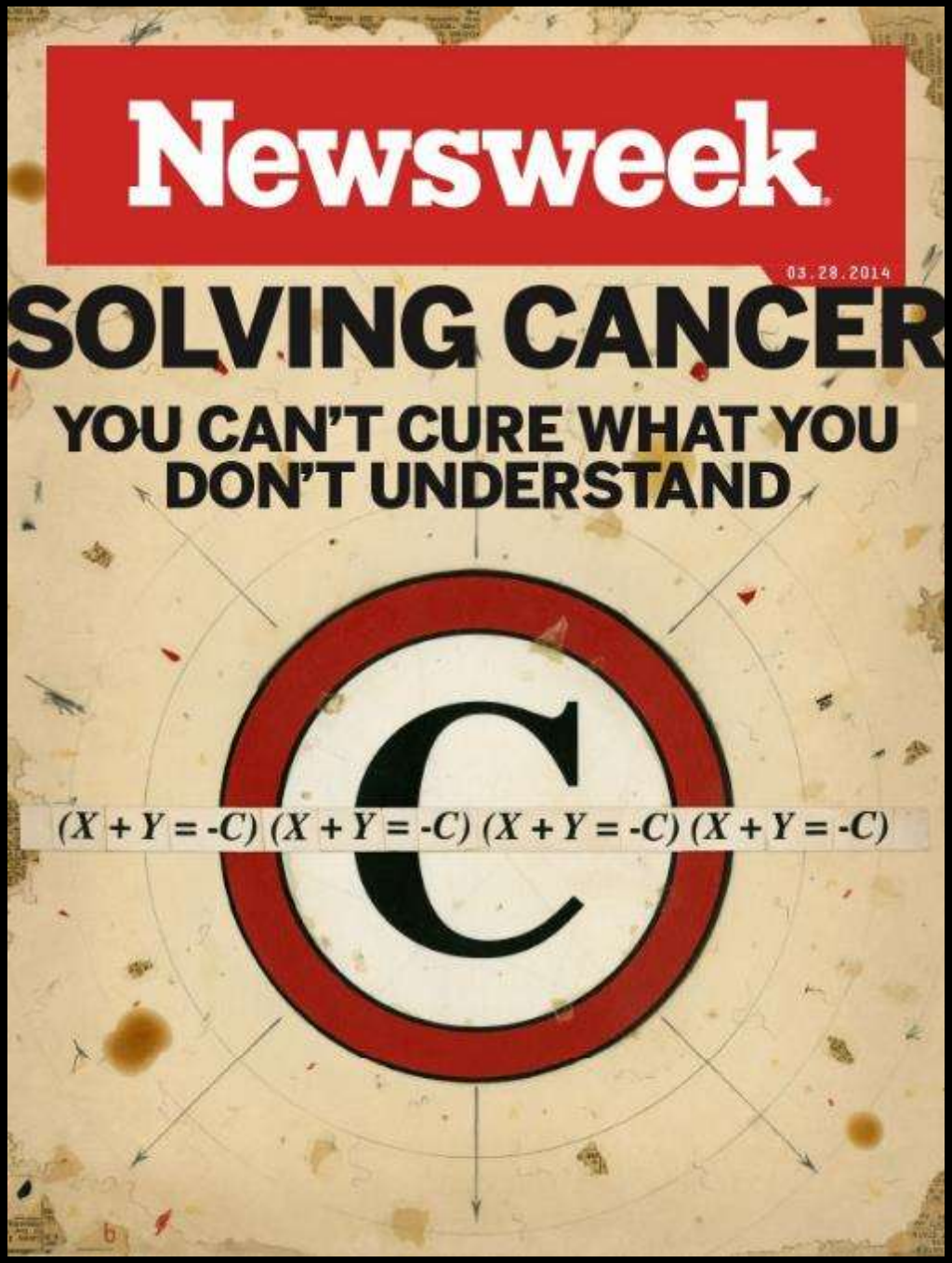
Cancer Treatment's New Direction: Genetic Testing and Tailored Treatments



- 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

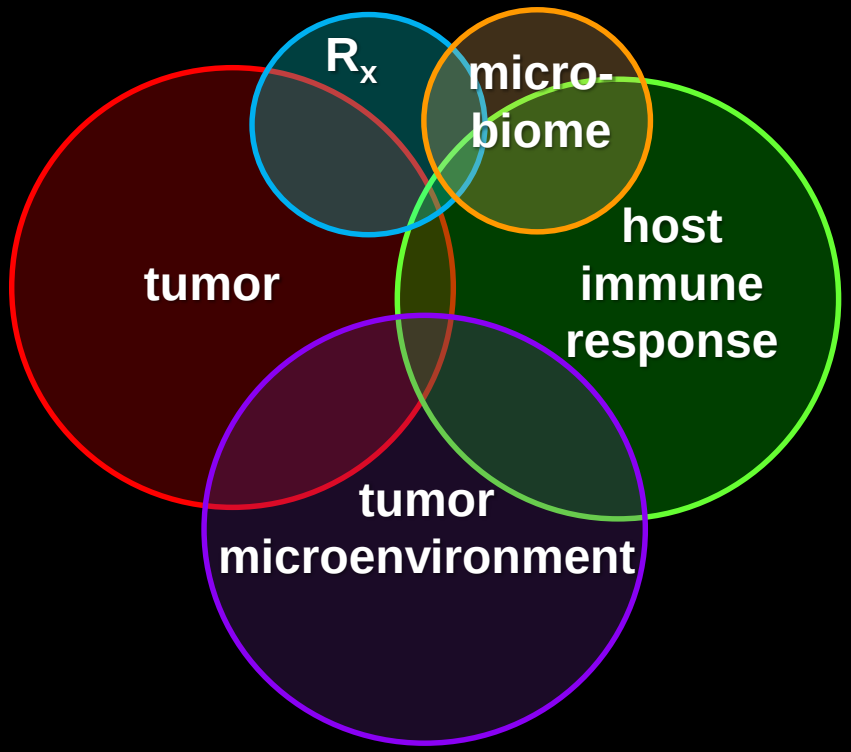
Summary and Key Points



- cancer as a complex adaptive system
- understanding clonal evolution during tumor progression and treatment
- clonal evolutionary dynamics as a complex interplay between tumor (evasion) and host (detection/ destruction) activities
- the evolution of clonal heterogeneity is the core problem in effective therapy

Understanding the Complex Ecosystem of Constantly Growing Tumor and Host Interactions

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



balance of stimulatory and suppressive factors

- complex non-immune cell contributions to suppressive environment
- localization of immune cells/soluble mediators and impact of R_x

Cancer As a Complex Adaptive System

- cancer as multi-component, multi-dimensional 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)
- clonal heterogeneity and phenotypic diversification pose formidable therapeutic challenges

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 as de novo mutations conferring selective survival 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

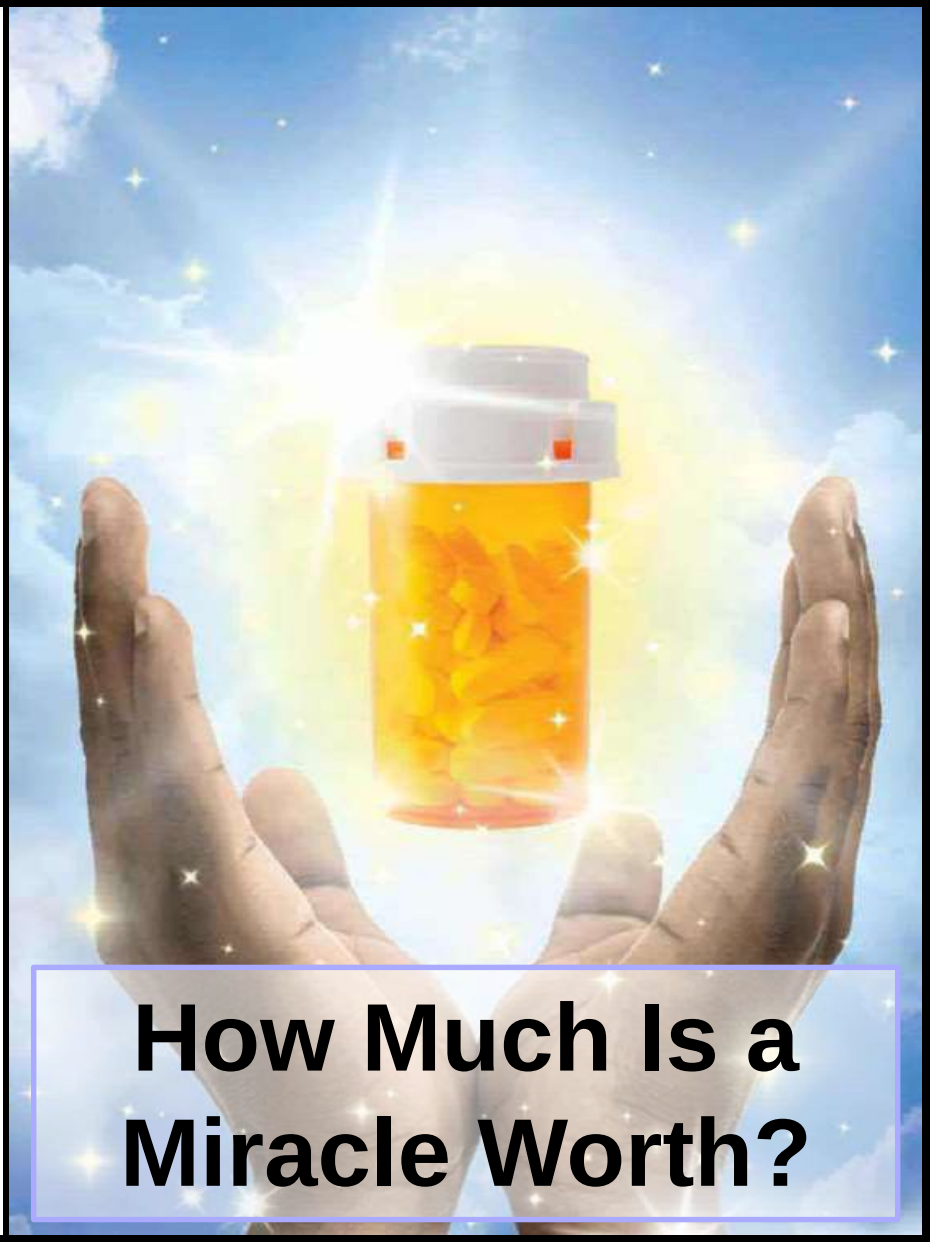
Cancer Treatment

- how to design new strategies to hit multiple clones and every new clonal variant that emerges
- the promise of immunotherapy
  - leveraging the detection and destruction capabilities of the host immune system
  - reactivation of immune system following suppression by tumor
  - highly promising early results but long term evaluation needed to assess risk of relapse due to immunoevasion clones
  - value of new combinations of drug and immunotherapies?
  - affordability ?

Cancer Action Network
American Cancer Society

The Costs of Cancer

Addressing Patient Costs



How Much Is a Miracle Worth?

The Future Landscape for Cancer Care

BIO 302: 27 November 2017

Demographics of an Aging Society and A Major Expansion in Cancer Cases

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

Complex Clinical, Scientific, Economic, Ethical and Legal Issues