



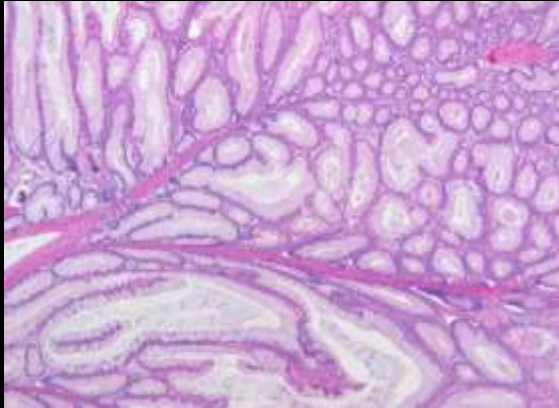
BIO 302: October 26, 2016

**Cancer as a Complex Adaptive System:
cancer progression, evolutionary dynamics
and implications for treatment**

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and Del E. Webb Chair in Health Innovation
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www.casi.asu.edu

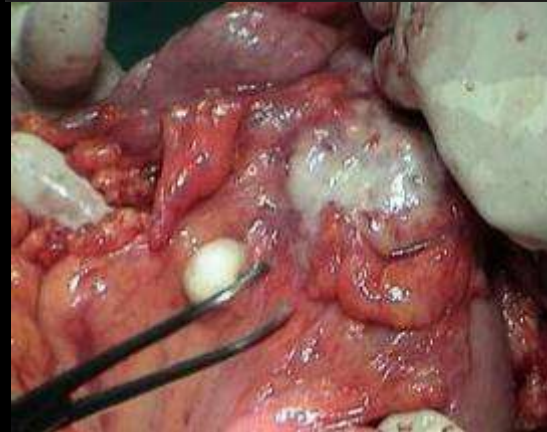
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

**Escape From Controls
for Normal
Tissue Architecture**



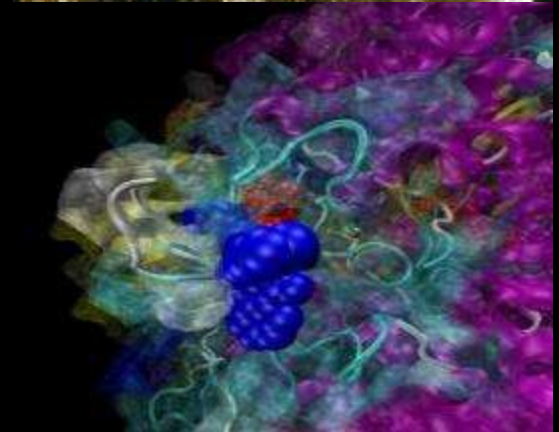
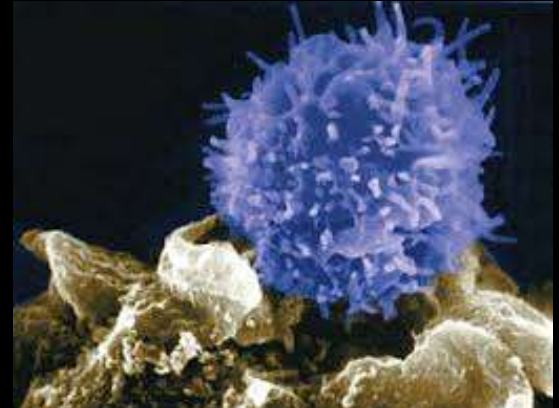
**Use of Host
Systems to
Promote Progression**

**Genome Instability and
Emergence of
Clonal Variants**



**Invasion
and
Metastasis**

**Evasion of
Detection/Destruction by
Host Immune System**



**Emergence
of Drug-Resistant
Clones**

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



**basal cell
carcinoma**



lung



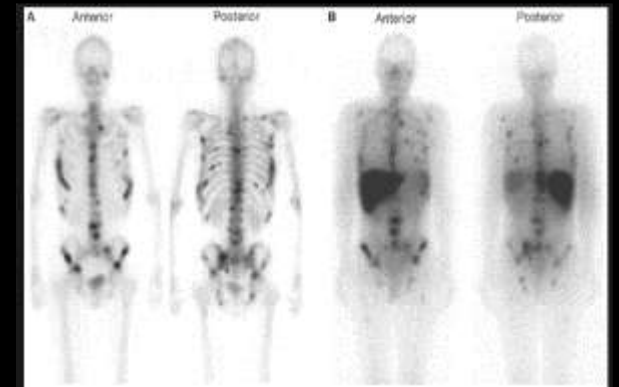
breast



glioblastoma



colorectal



prostate

**Invasion Without
Metastasis**

Invasion and Metastasis

Central Themes in Cancer Biology

- cancer as a multi-dimensional ecosystem involving complex interactions between cancer cells and host systems
- genotoxic insult(s), mutations and genomic instability as drivers of initiation and progression
- progressive evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)
- tumor-progression is a dynamic process with adaptive evolution of tumor cell clones to diverse selection pressures (fitness)
- clonal heterogeneity and phenotypic diversification pose formidable therapeutic challenges

**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?**



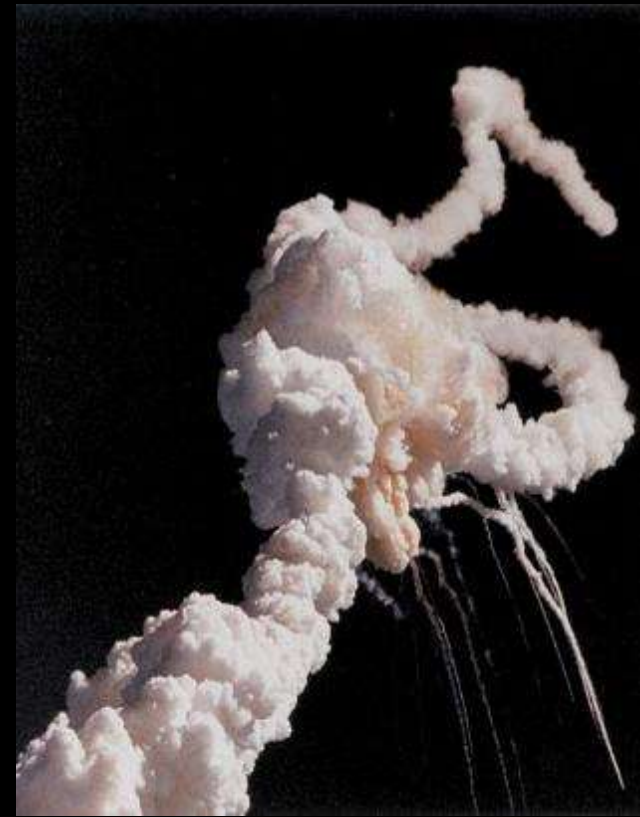
Photo by nobiann/flickr/Getty

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

**Complicated
System**



**Ageing Support
Structure**

**Complicated
System**



Wrong Glide Path

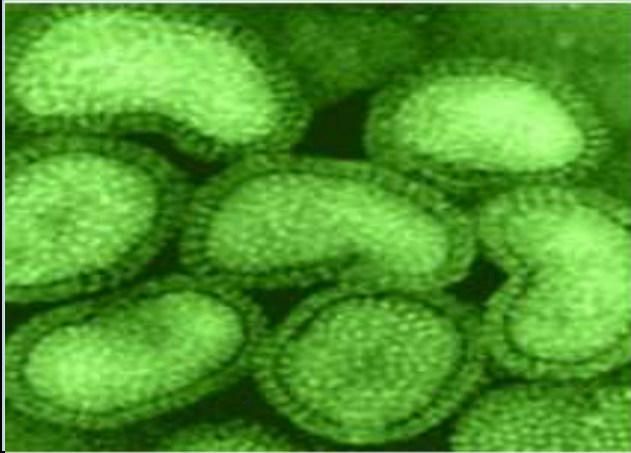
**Complicated System
+ Complexity
(Human Error)**

Emergence: The Hallmark 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)

The Ubiquity of Complex Adaptive Systems in Nature:

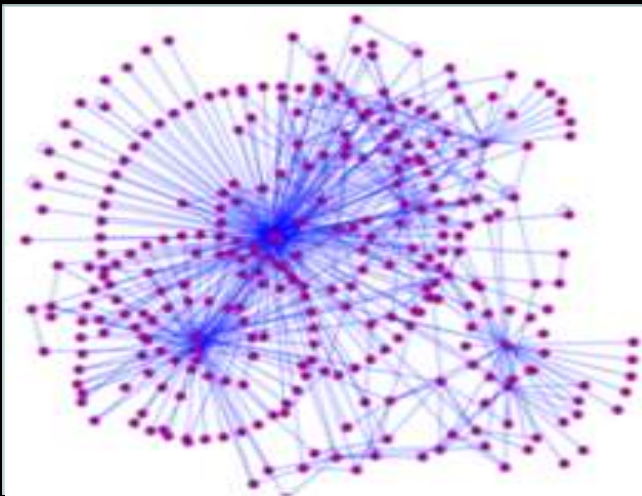
**Host-Pathogen
Interactions**



**Physiological
Regulatory Networks**



**Genome
Regulatory Networks**

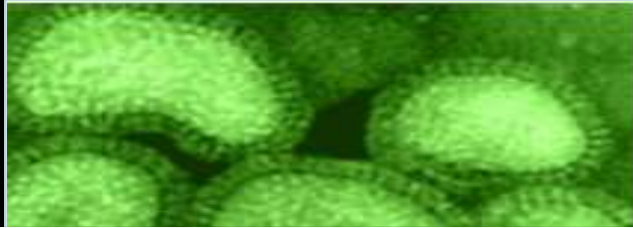


**Signaling Network Dysregulation
in Disease**



The Ubiquity of Complex Adaptive Systems in Nature:

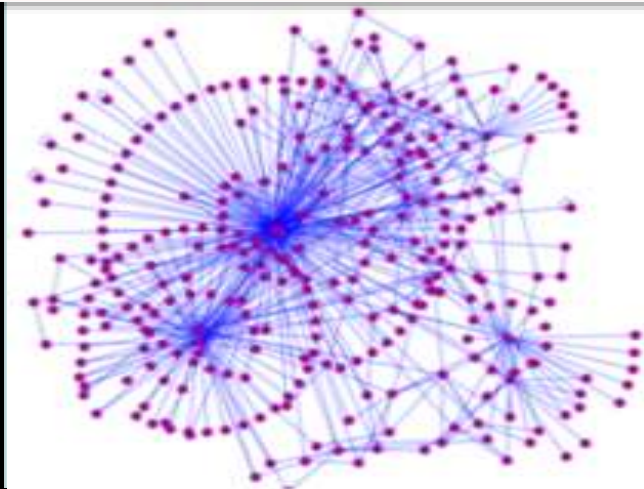
**Host-Pathogen
Interactions**



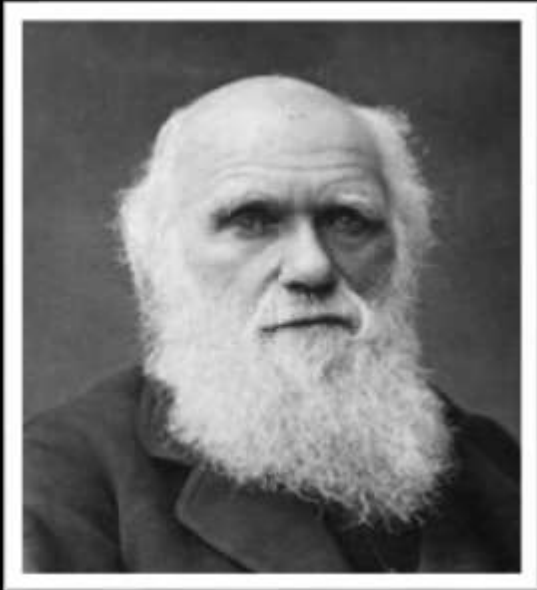
**Physiological
Regulatory Networks**



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

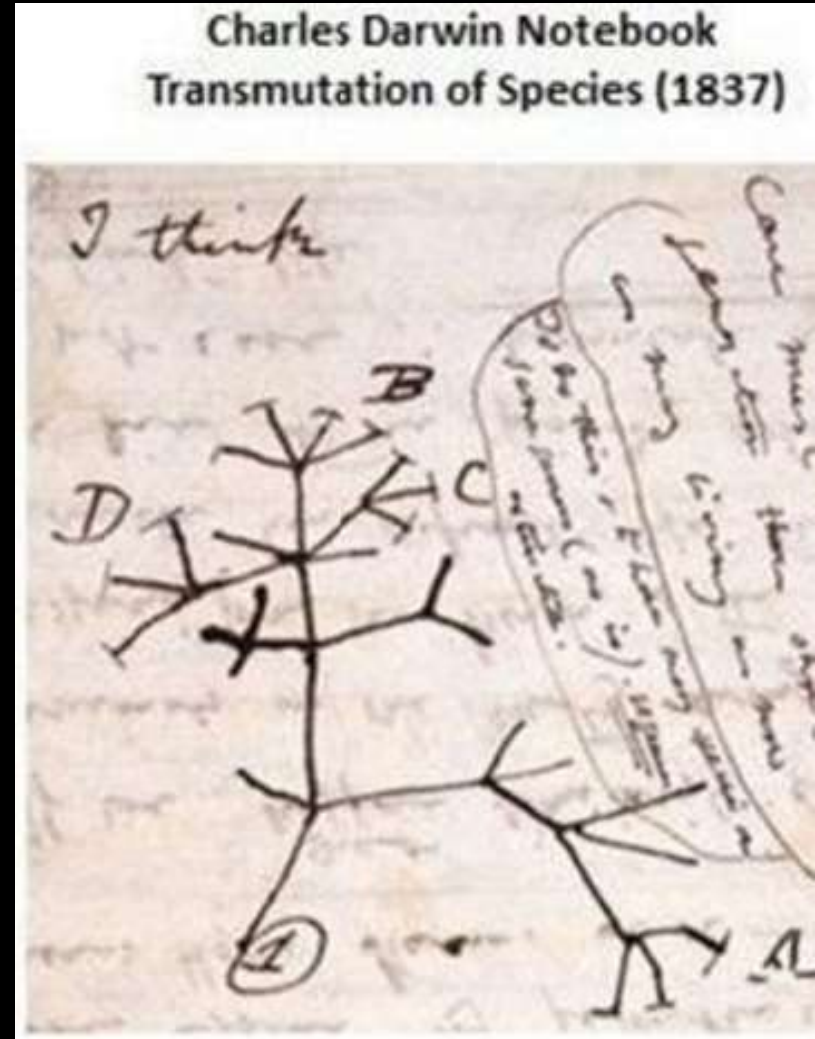
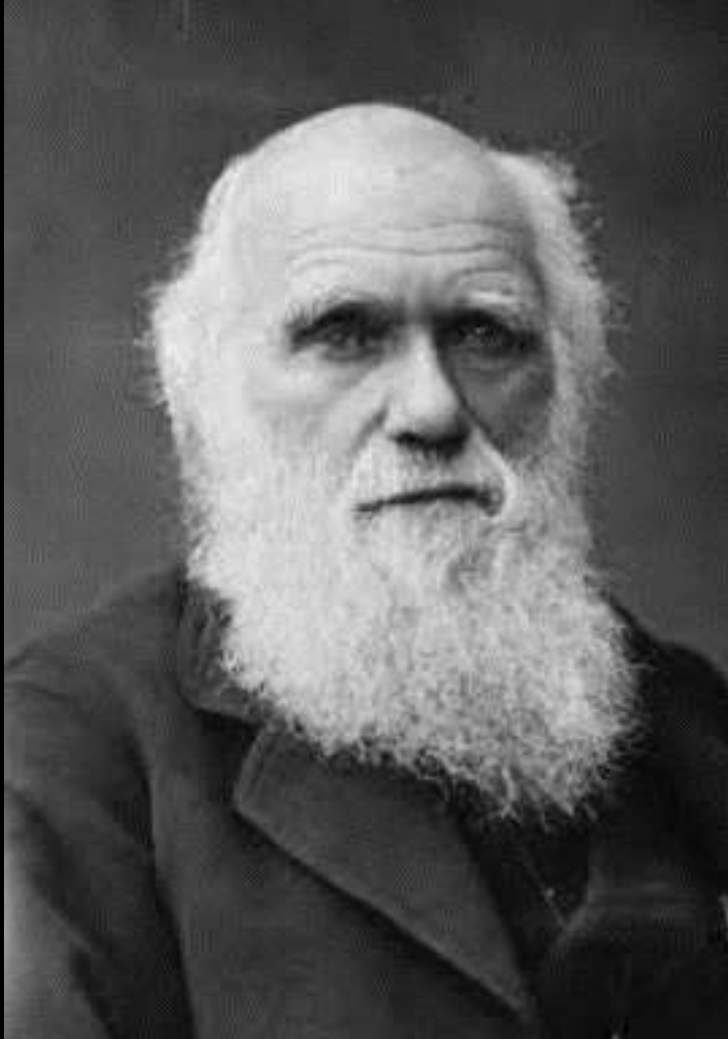


Darwinian Evolution



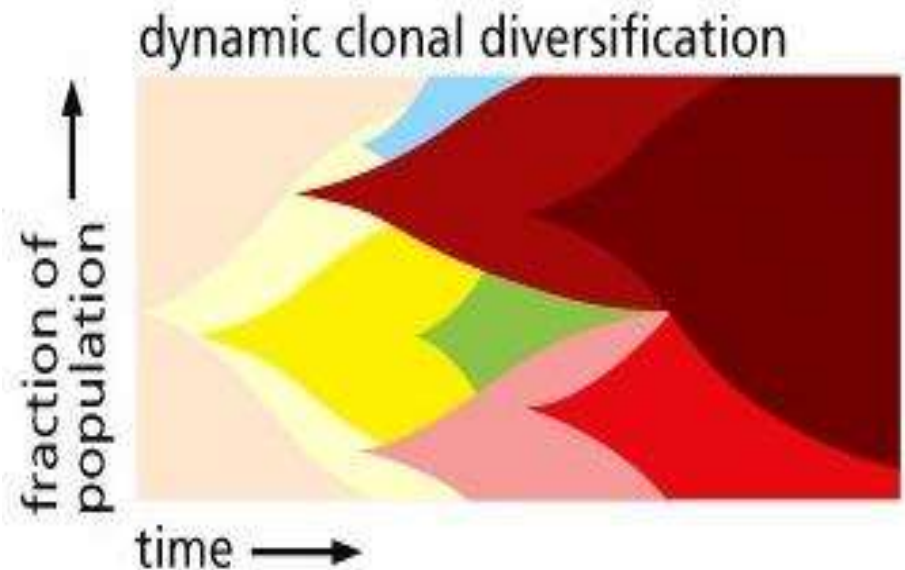
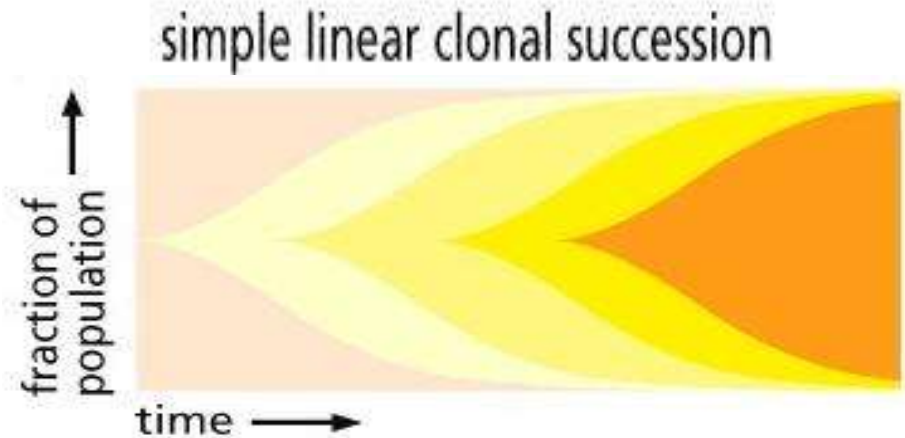
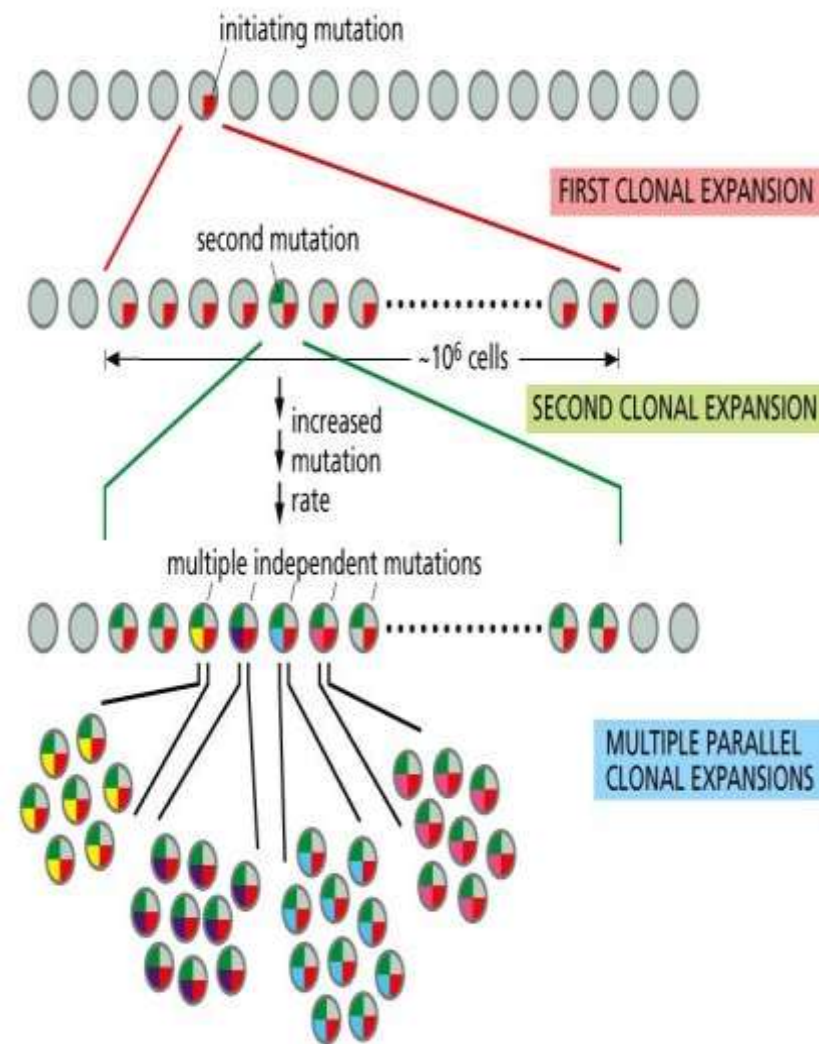
- **selection by variation**
- **adaptation**
- **evolvability**
- **“fitness” for selection pressures operating in a particular environment**

Charles Darwin Sketch of Speciation (Early 1850s)

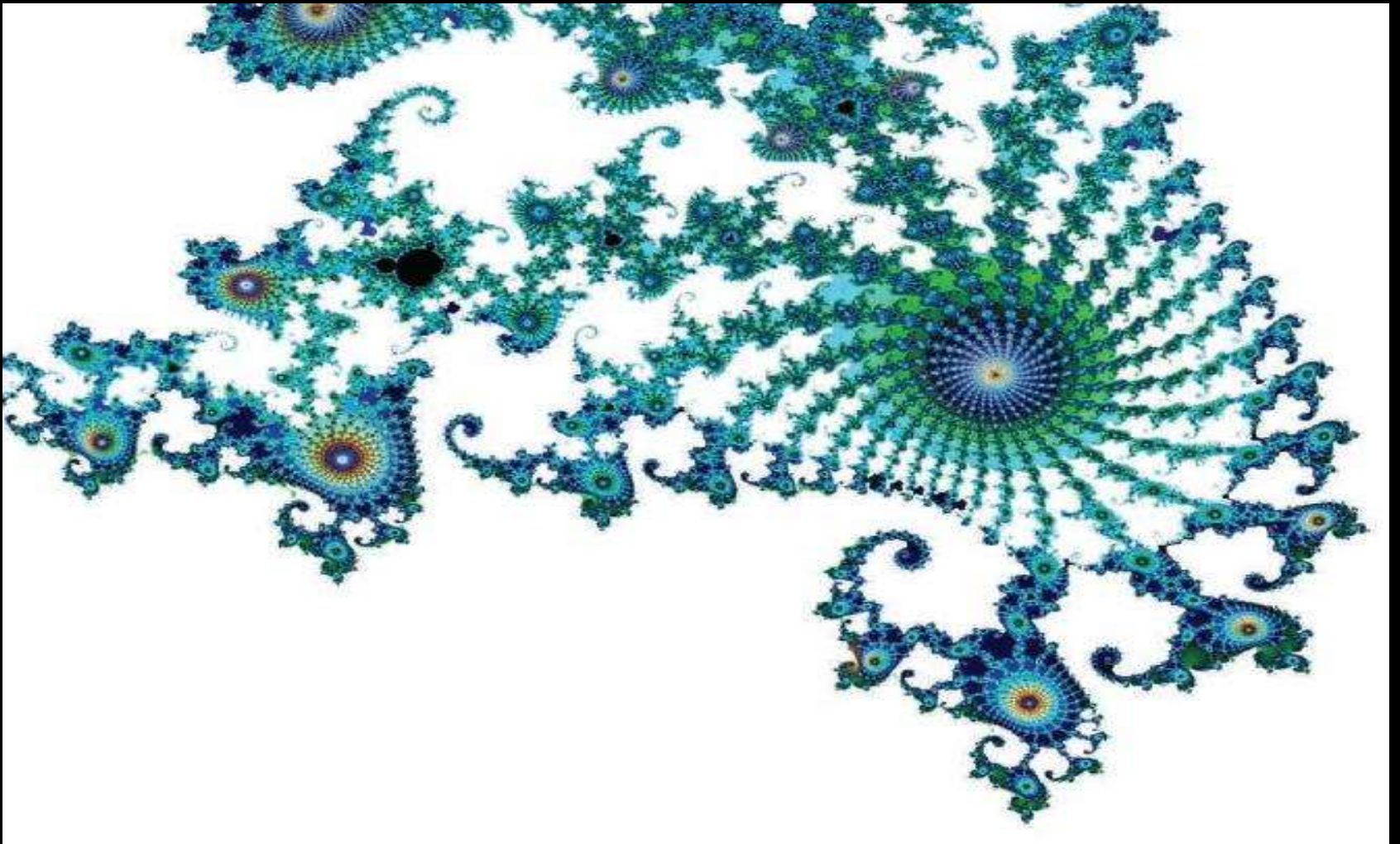


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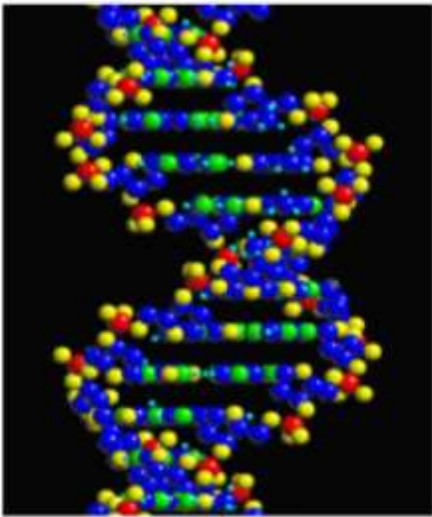
Evolution and Phenotypic Diversification of Tumor Clones and Subclones



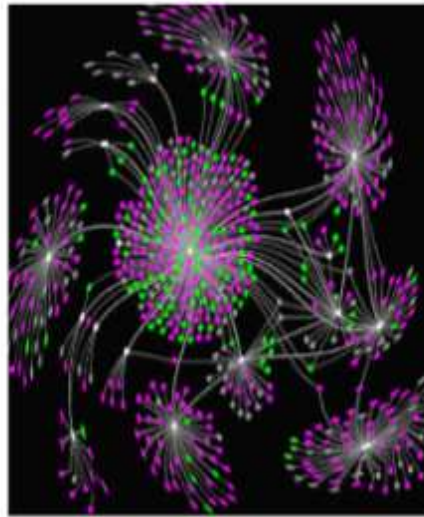
Cancer as a Complex Adaptive System: The Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones During Progression



Understanding the Disruption of Molecular Information Networks in Disease



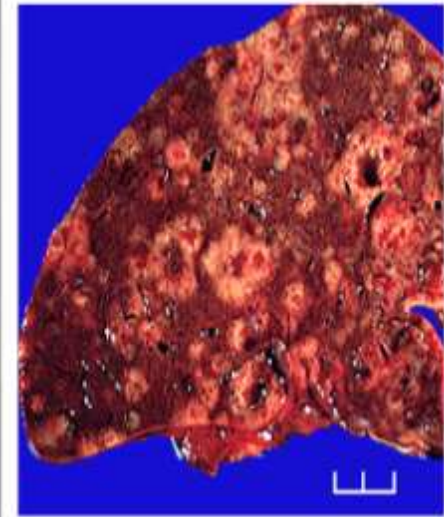
**encoded information
and expression as
cell-specific
signaling networks**



**patterns of
information flow
within signaling
networks**

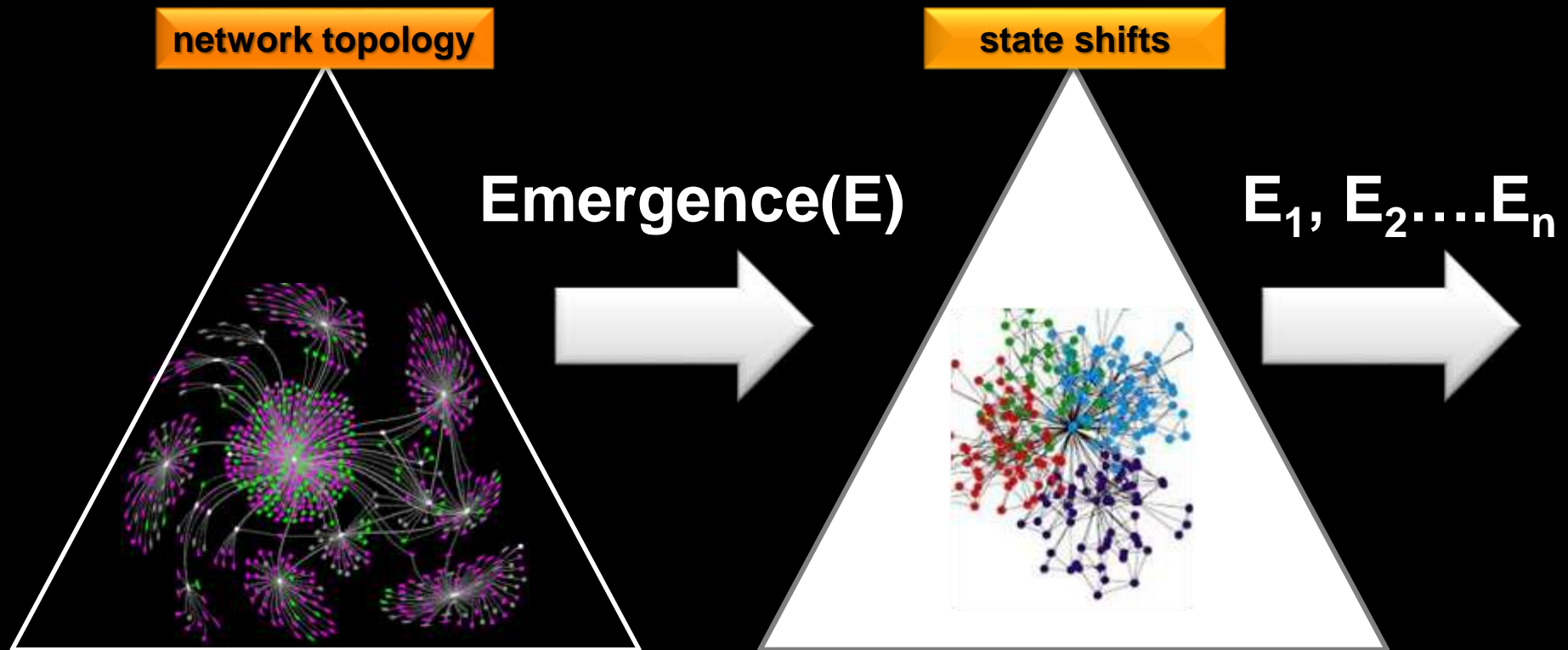


**stable
networks and
information fidelity
(health)**



**dysregulated
networks and
altered information
patterns (disease)**

Understanding State Shifts in Complex Adaptive Systems and Identification of Triggers of Emergence

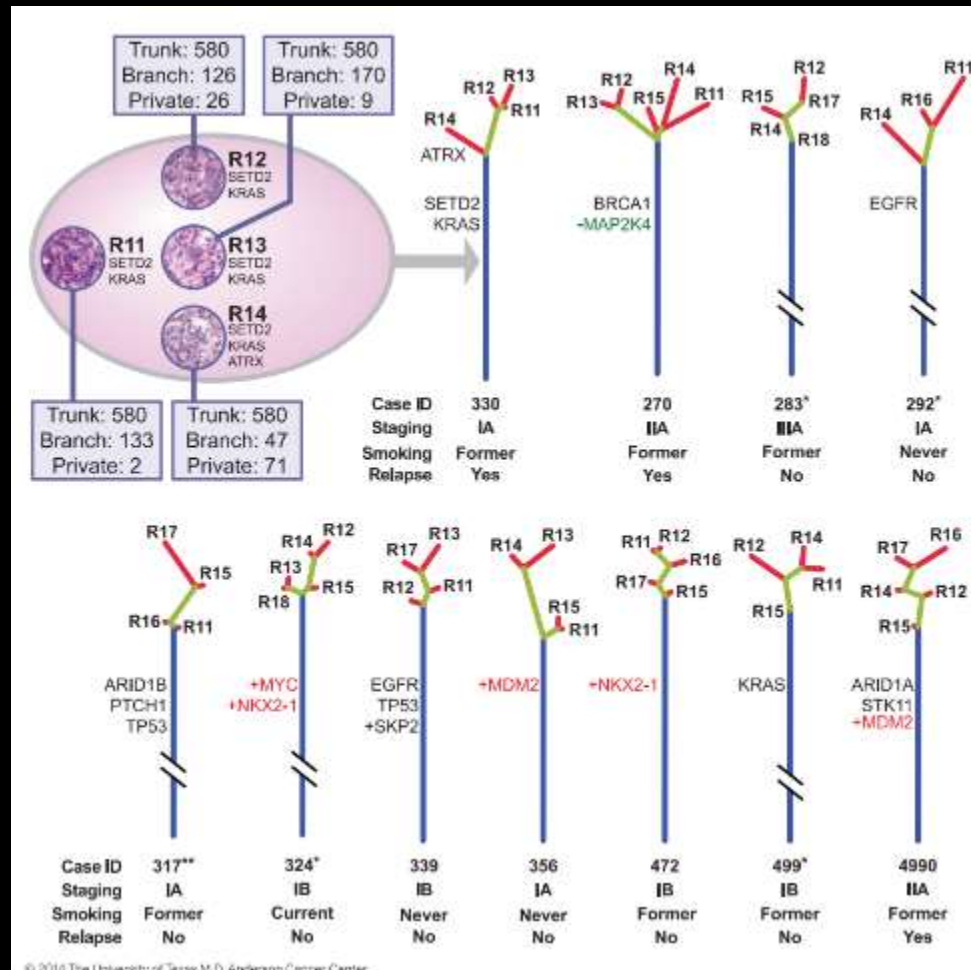


- Black Swans
- dislocations
- tipping points
- irreversible cascades

- phase shifts
- perturbations
- inflection points
- unintended consequences

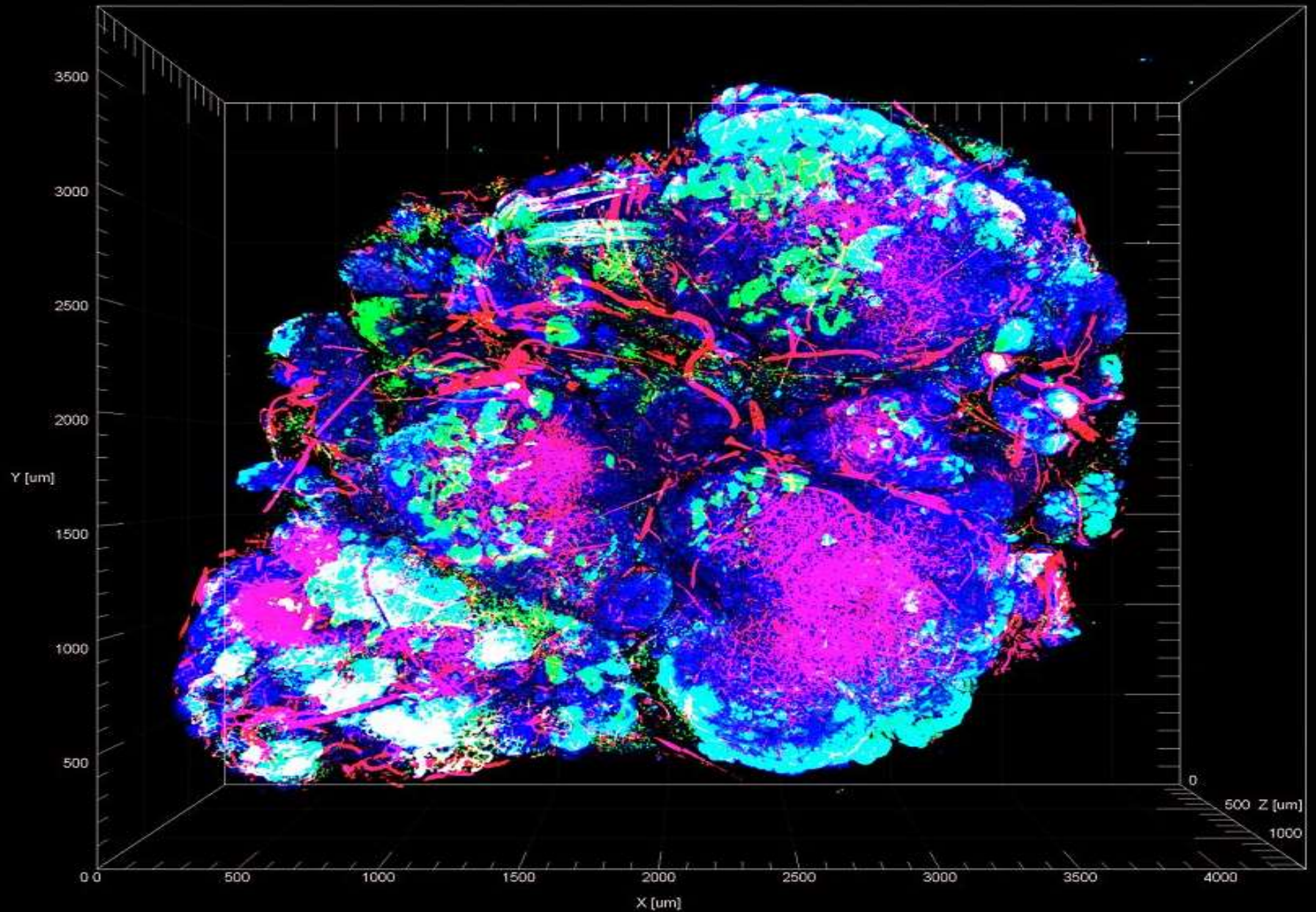
- critical thresholds
- bifurcations
- trigger points

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



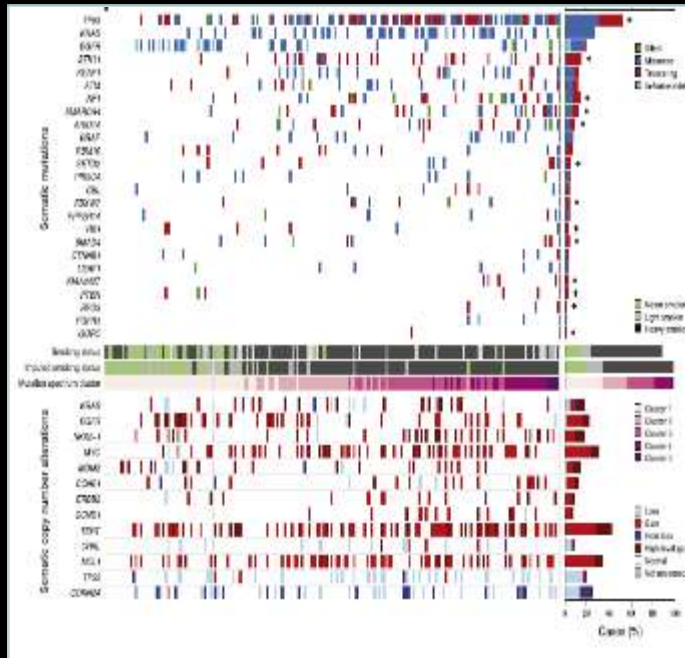
From: J. Zhang et al. (2014) Science 346, 256

Mapping Tumor Heterogeneity



**Tumor Cell Heterogeneity:
The Greatest Obstacle
to Curative Cancer Therapy**

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



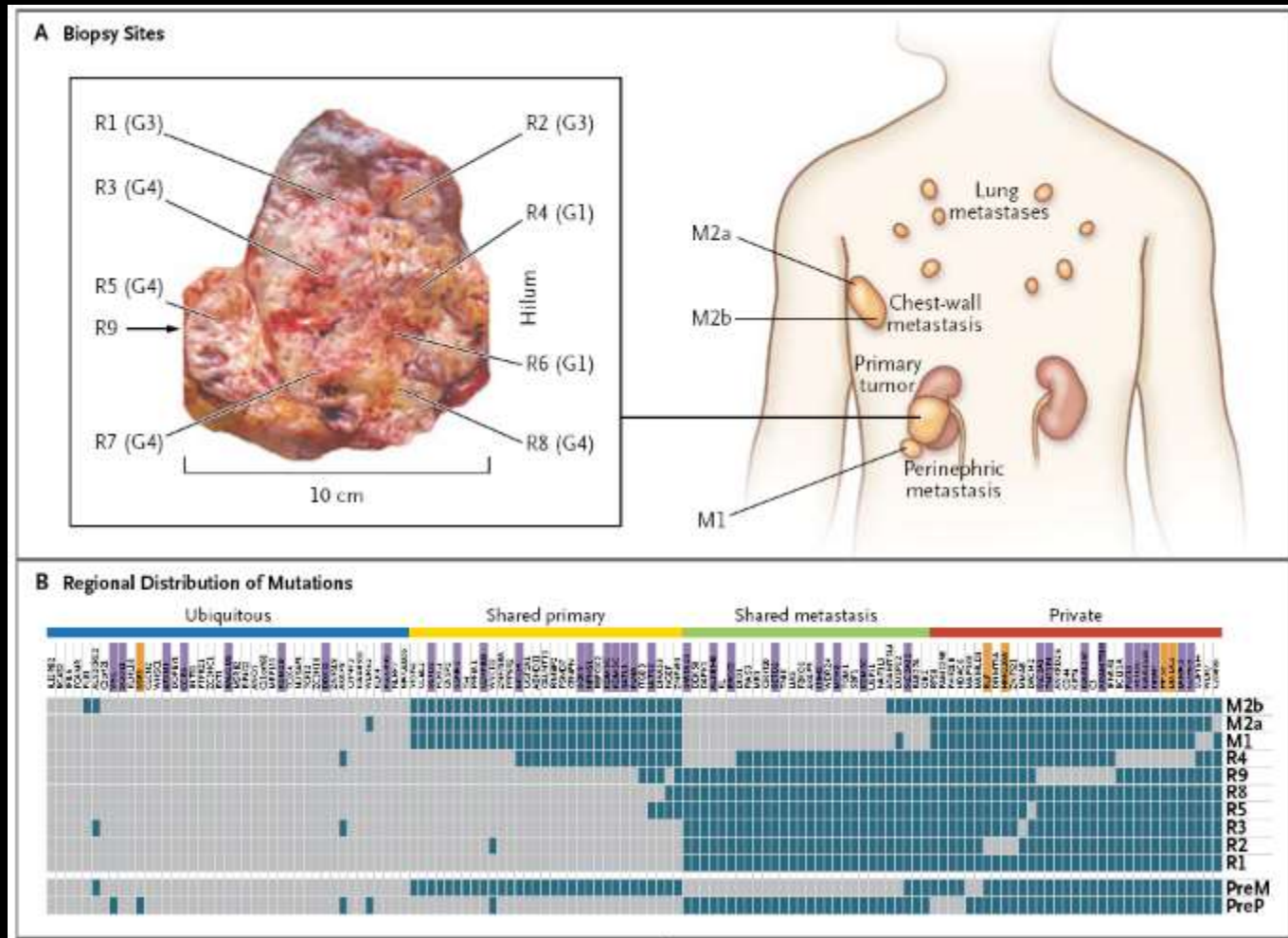
**Mutations in Individual
Non-small Cell Lung Cancer**



**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 Rx

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

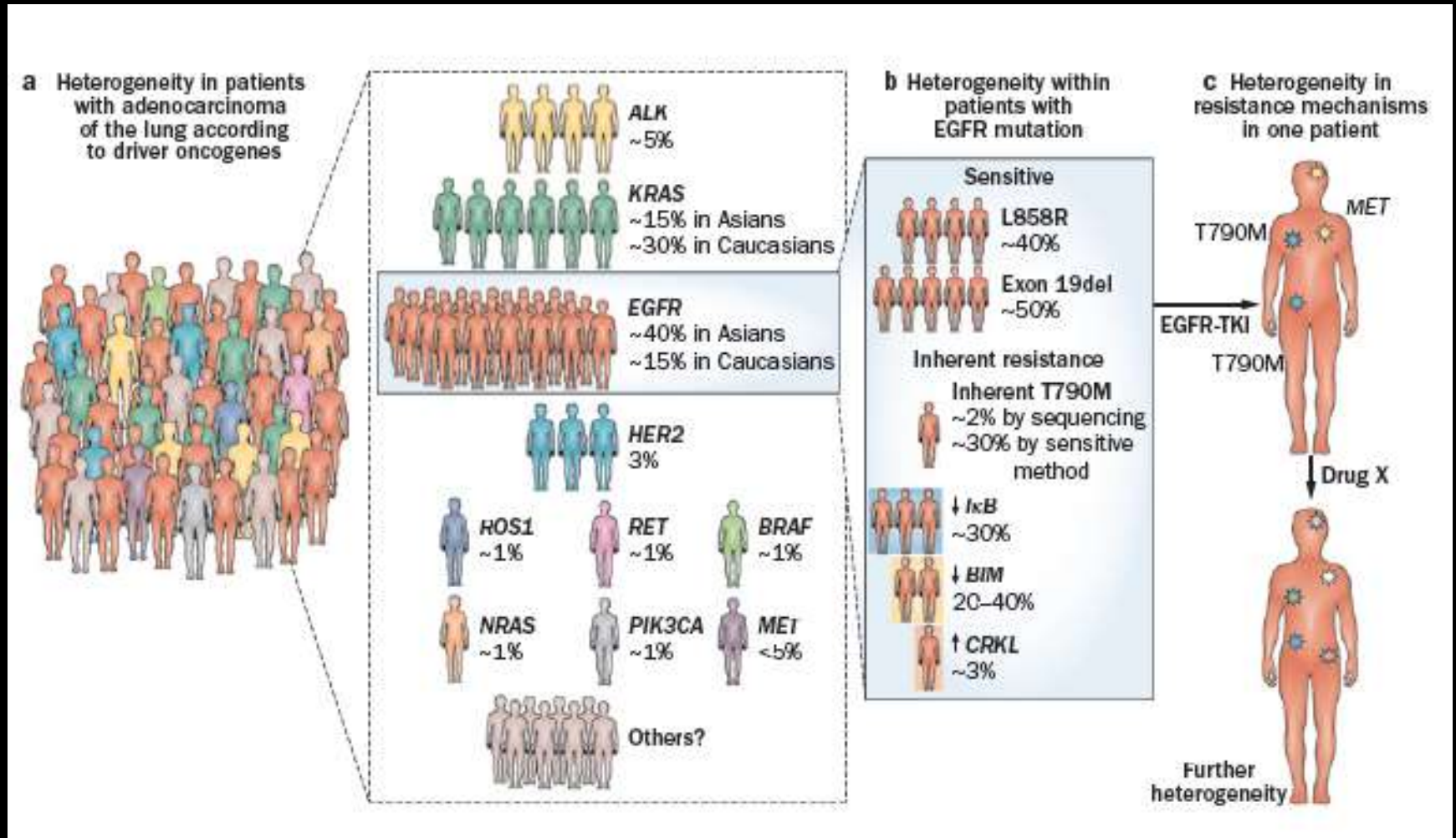


From: M. Gerlinger et al. (2012) NEJM 366, 883

The Principal Challenge in Cancer Rx Therapy

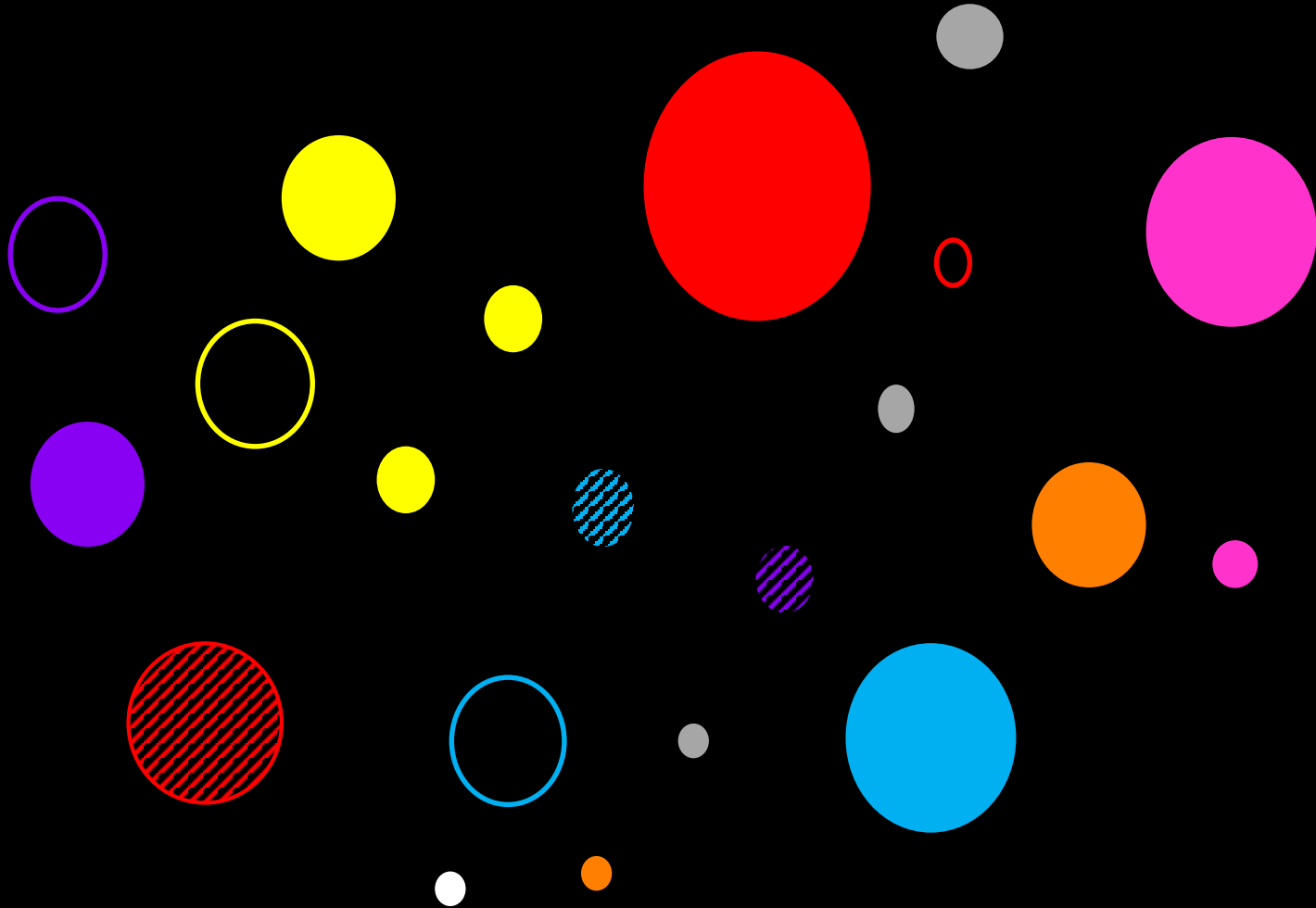
**The Co-existence of Multiple Tumor Cell Clones with
Varied Susceptibility to Different-Rx**

Molecular Profiling and Classification of Subtypes of NSCLC

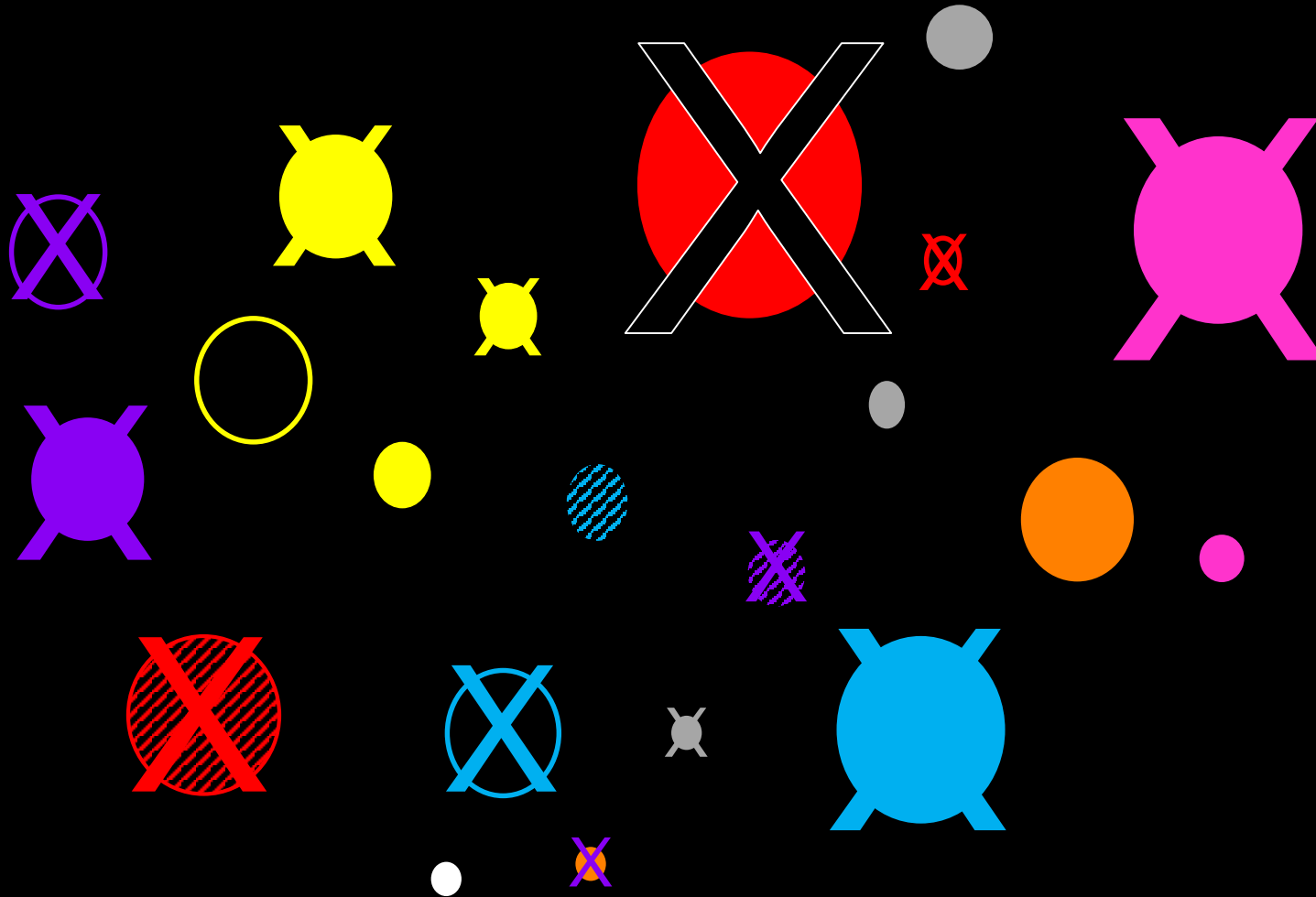


From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

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

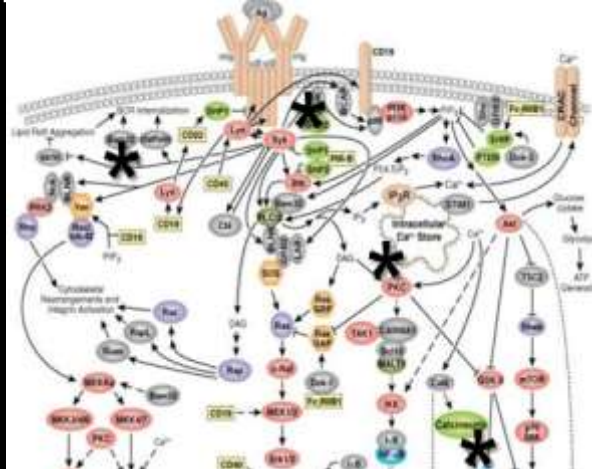
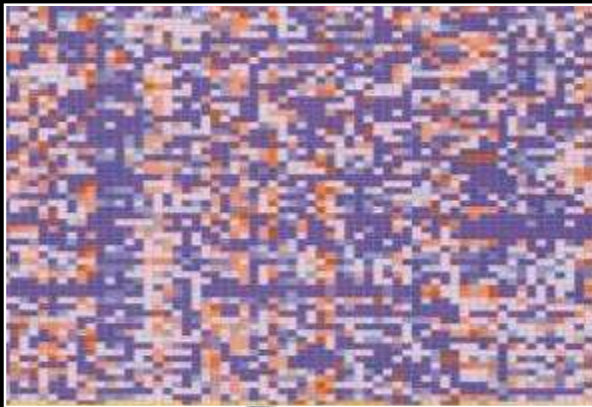
- **design a single drug that hits multiple clones and multiple signaling pathways**
 - **pharmacological promiscuity**
 - **very low probability of technical success**

Design of Cancer Treatments to Hit Multiple Targets

- **multi-drug combinations**
 - **patient tolerance**
 - **cost**
- **high probability that Rx-resistant variants will eventually emerge**
- **Rx as selection pressure to generate Rx-resistant 'escape' clones**

Targeted Therapeutics and Cancer

**Molecular Subtyping
and
RX Targets**



**Initial Rx-Response
to
Targeted Rx**



**Rx-Resistance
via
Redundant
Molecular Pathways**

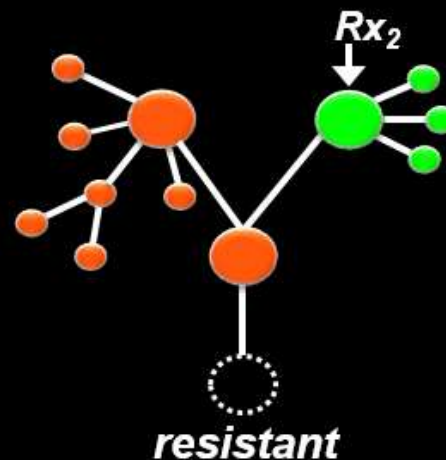
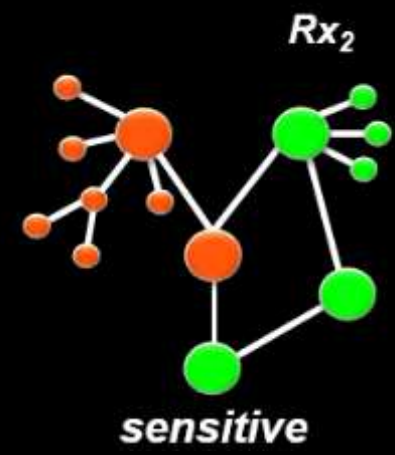
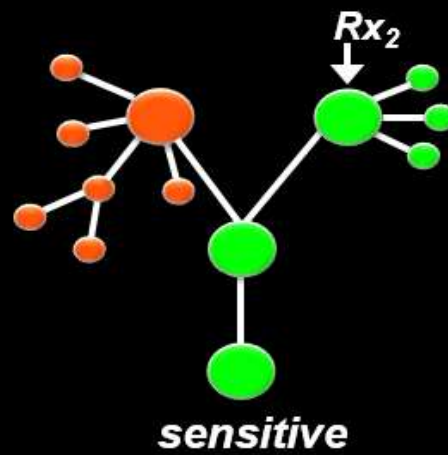
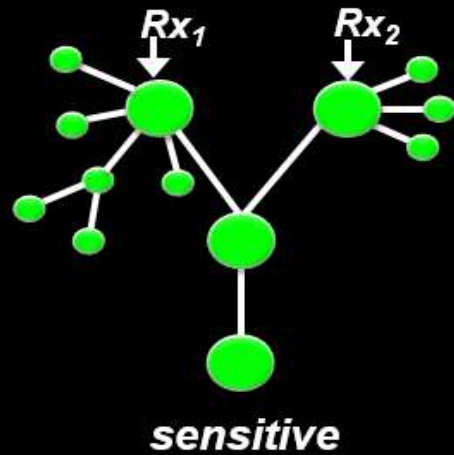


**B = 15 weeks Rx
(Zelboraf®)
C = 23 weeks Rx
and emergence of
MEK1C1215 mutant
(Wagle et al. (2011)
JCO 29, 3085)**

‘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 Rx Resistance

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



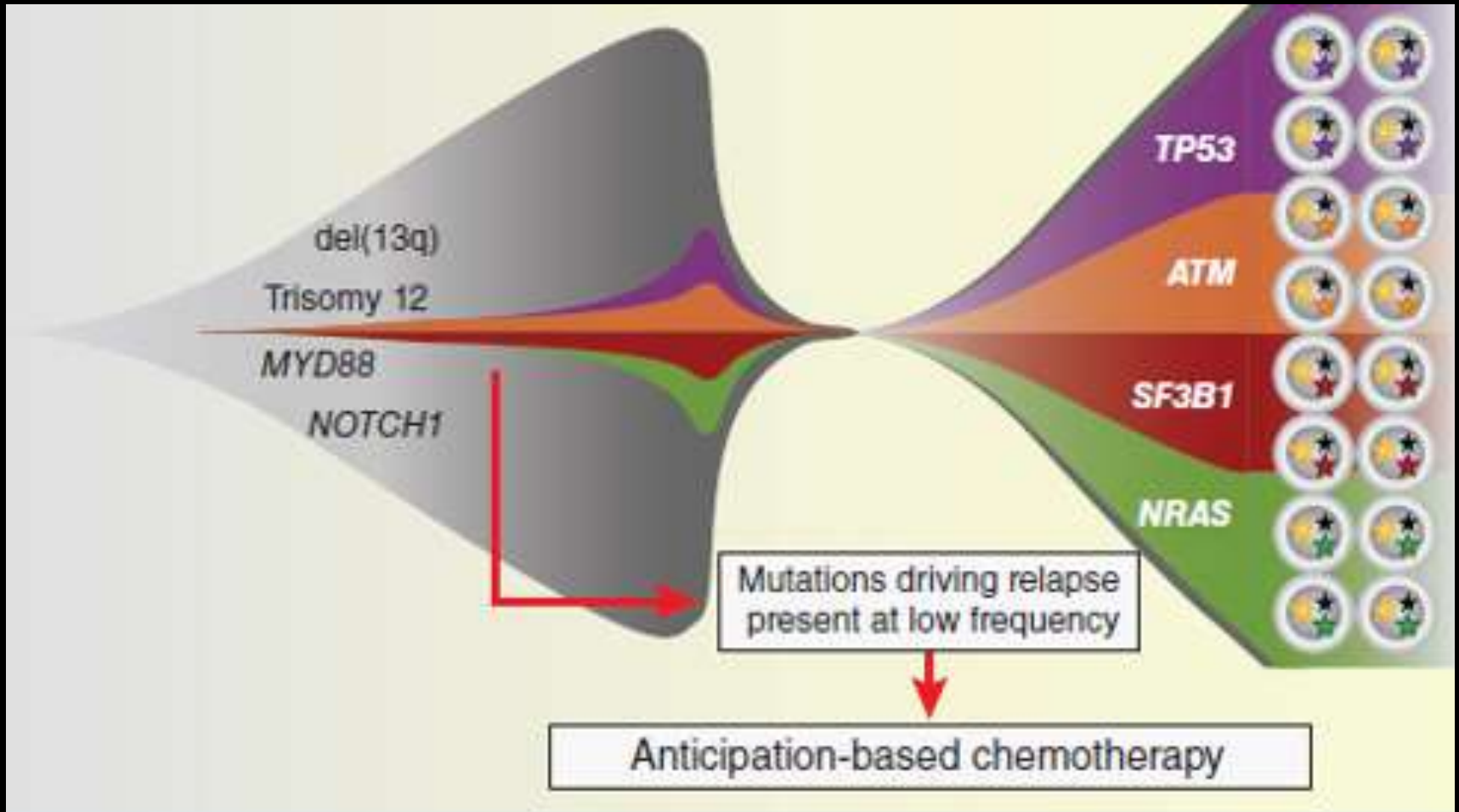
**The Urgent Need for New Diagnostic Tests
and Molecular Profiling Tools
for Improved Monitoring of Tumor Progression**

**From 'Static Snap Shot' at Initial Diagnosis to
Dynamic Monitoring of Clonal Population Changes**

Tumor Profiling and Adjustment of Treatment Selection to Reflect Changes in Clonal Composition

- **initial diagnosis ('static snapshot')**
- **longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones**
- **more agile shifts in Rx regiment to reflect changing clonal dynamics driven by Rx selection pressure(s)**

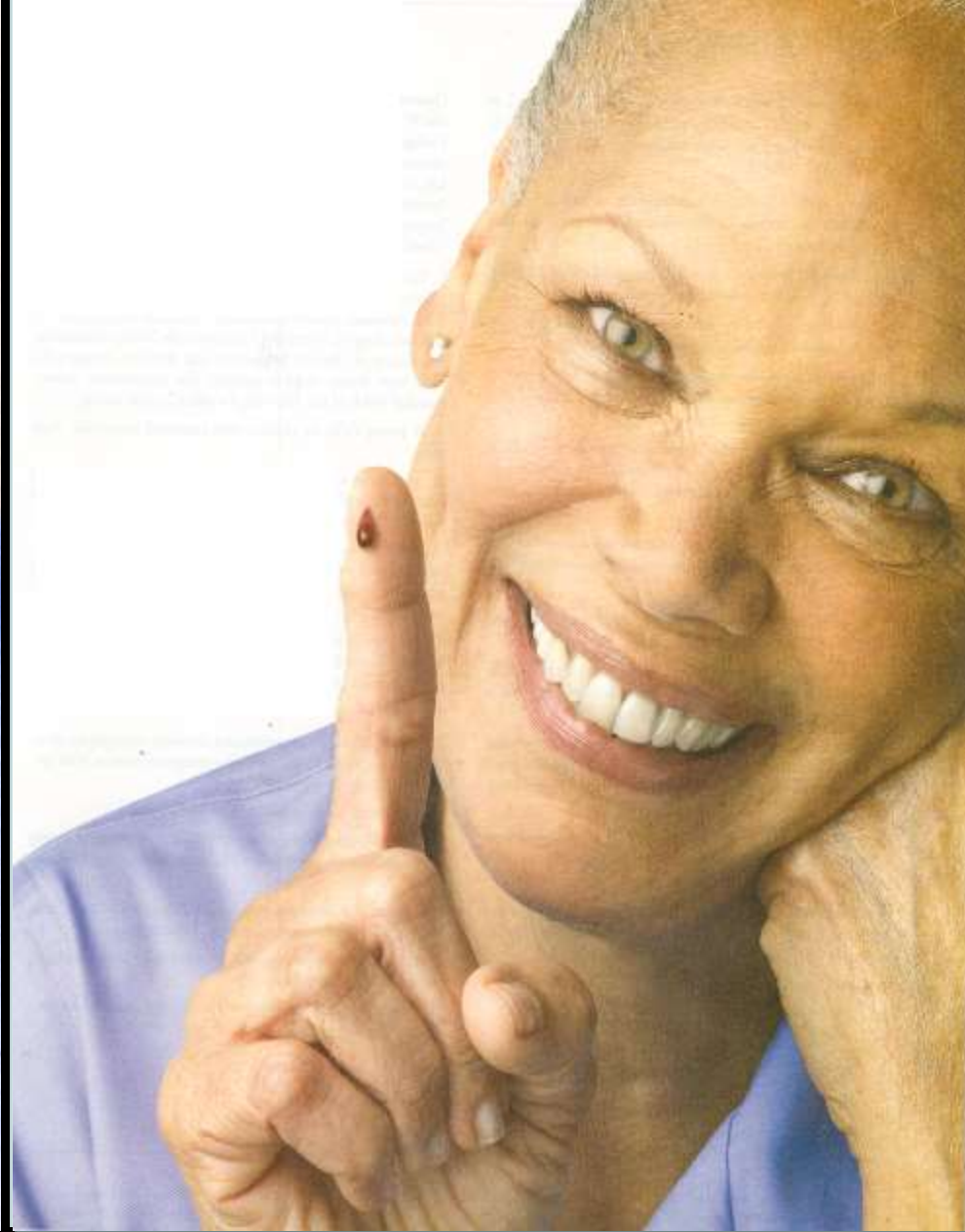
Anticipation-Based Chemotherapy in CLL



From: X. S. Puente and C. López-Otín (2013) Nature Genetics 45, 230



Fine Needle Aspiration (FNA) Biopsy



**Minimally-Invasive Profiling
(Blood/Other Body Fluids)**

Detection of Tumor-Associated Biomarkers in Blood: ‘The Liquid Biopsy’

- **cell-free tumor nucleic acids**
 - **DNA, miRNAs**
- **circulating tumor cells(CTC)**
- **exosomes**

**Flying Blind:
“One-Size-Fits All” Rx-Guidelines Ignore New Knowledge
of Cancer Subtypes and Clonal Dynamics in Tumor Progression**



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

Avastin



\$3.059B

Rituxan



\$2.466B

Herceptin



\$1.526B

Revlimid



\$1.373B

Gleevec



\$1.285B

Taxotere



\$1.042B

Alimta



\$975M

Gemzar



\$723M

Tarceva



\$661M

Femara



\$650M

Erbitux



\$646M

Velcade



\$598M

Xeloda



\$508M

Arimidex



\$494M

Leuplin

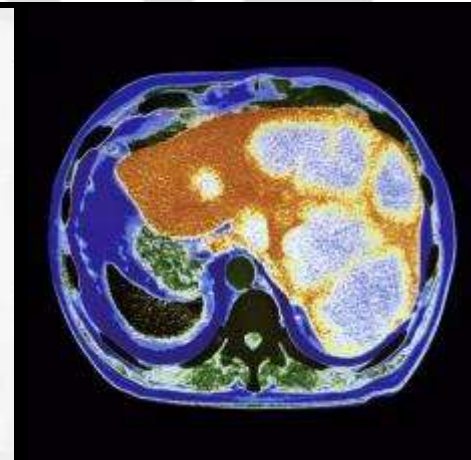
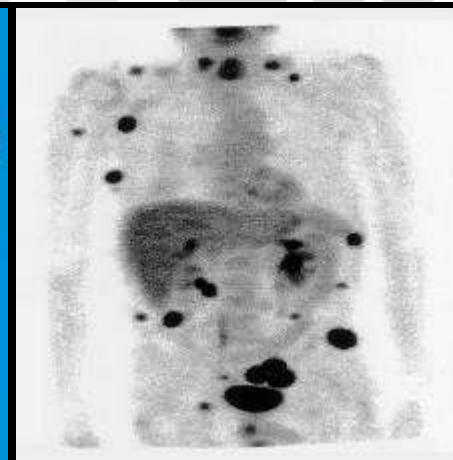
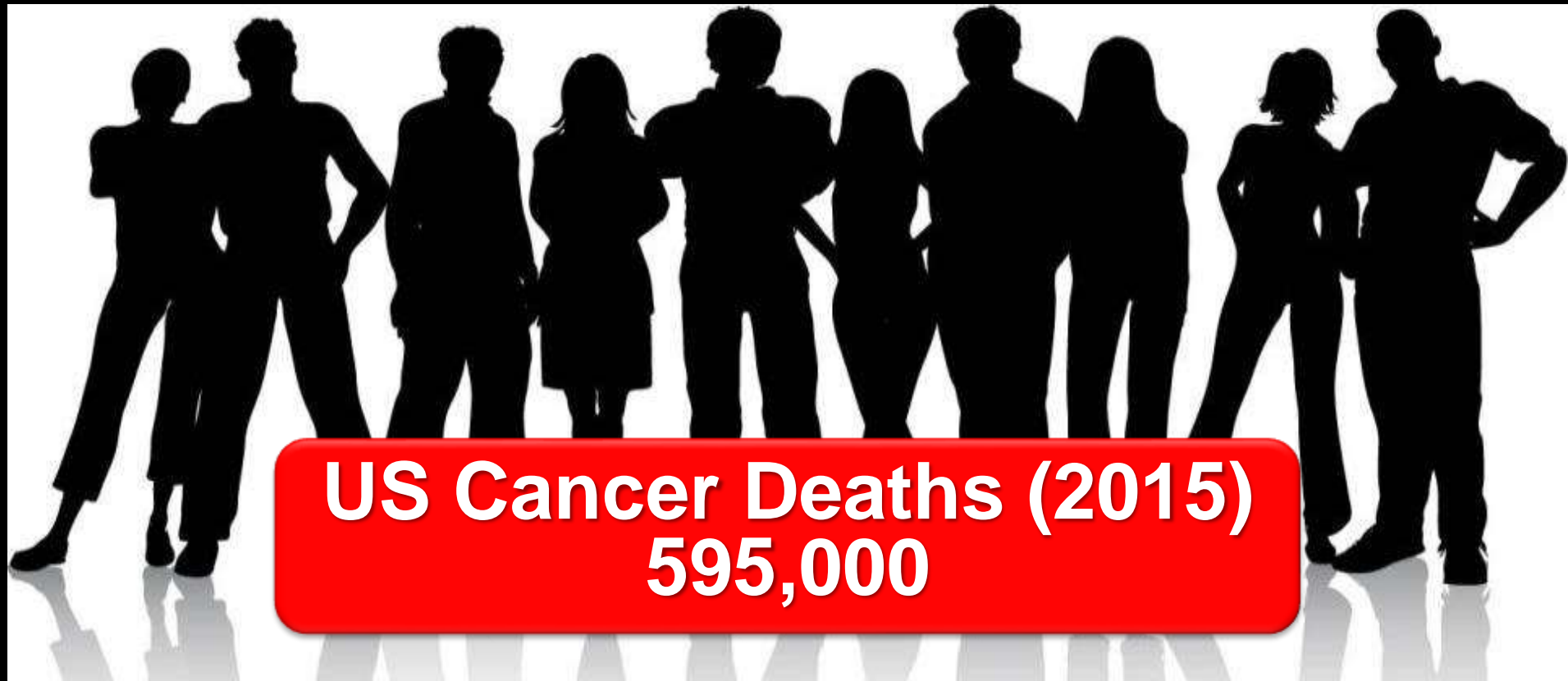


\$483M

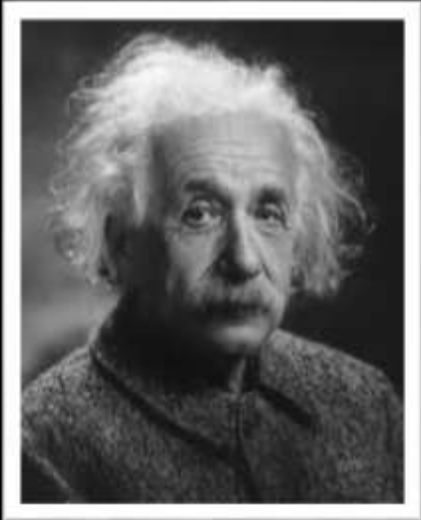
■ Responder
■ Non-responder

Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

Confronting the Clinical, Economic and Human Toll of Cancer



Knowing When to Stop!

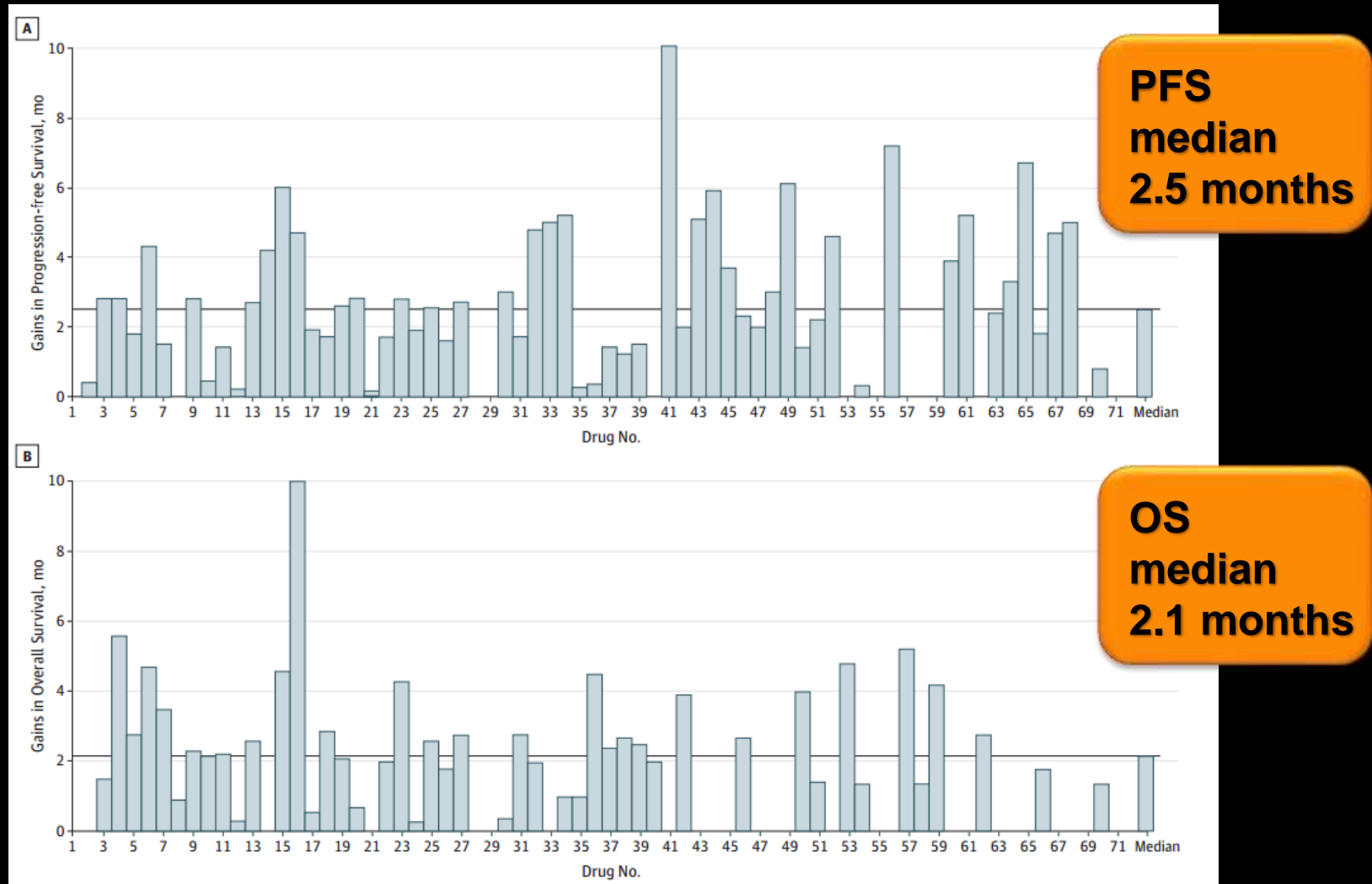


**“Insanity is doing the same thing
over and over again
and expecting a different result.”**

Albert Einstein

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

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



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

Recognition of the Need for New Approaches to Cancer Treatment

- **current clinical strategies for treatment have not kept pace with advances in understanding the biology of cancer**
- **cancer is a complex adaptive system with dynamic properties shaped by Darwinian Evolution**
 - **variation (clonal diversity)**
 - **adaptation and evolvability (selection pressures)**
 - **immuno-evasion and Rx-resistance (fitness)**

Cancer Treatment Challenges

Chemotherapy

- lack of specificity
- impact on replicating normal cells (gut, b. marrow, hair follicles)

Targeted Agents

- highly specific for altered molecular targets in cancer cells
- lack of efficacy against target-negative clones

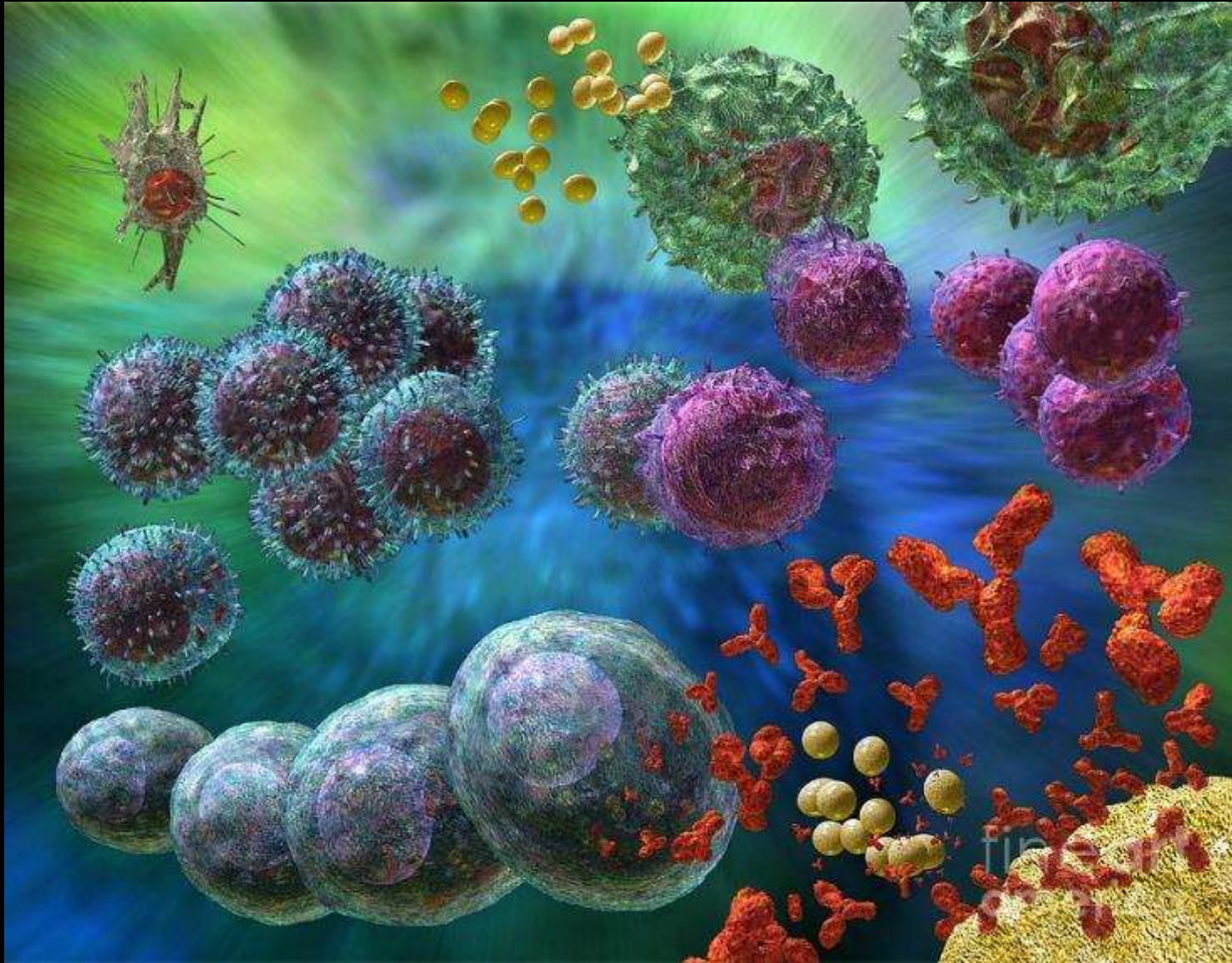
Drug Resistance

- intrinsic (pre-existing before Rx begins)
- acquired (resistant clones selected by Rx regimen)

The Urgent Imperative to Develop New Treatments to Circumvent Clonal Heterogeneity

- **harnessing the cognate (detection) and destruction (killing) capabilities of the body's immune system**
- **therapeutic targeting of neoantigens expressed on tumor cells**
 - **passive immunotherapy (designed antibodies)**
 - **active immunotherapy (activation of immune functions)**

Passive Immunotherapy With Anti-tumor Antibodies



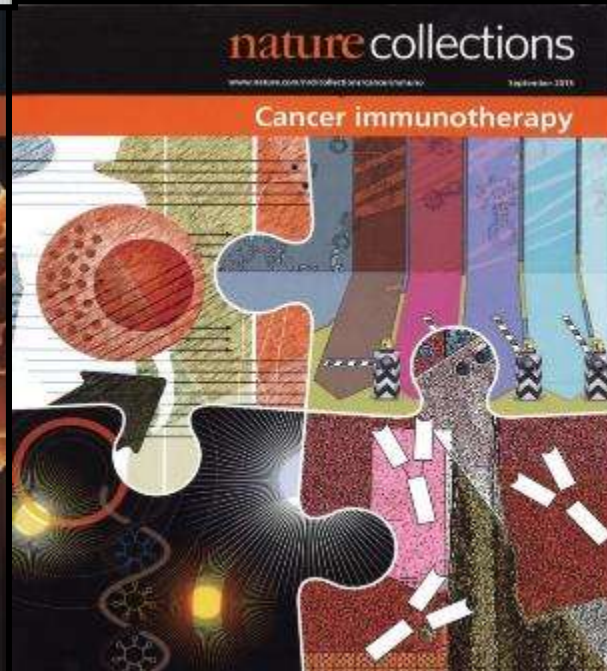
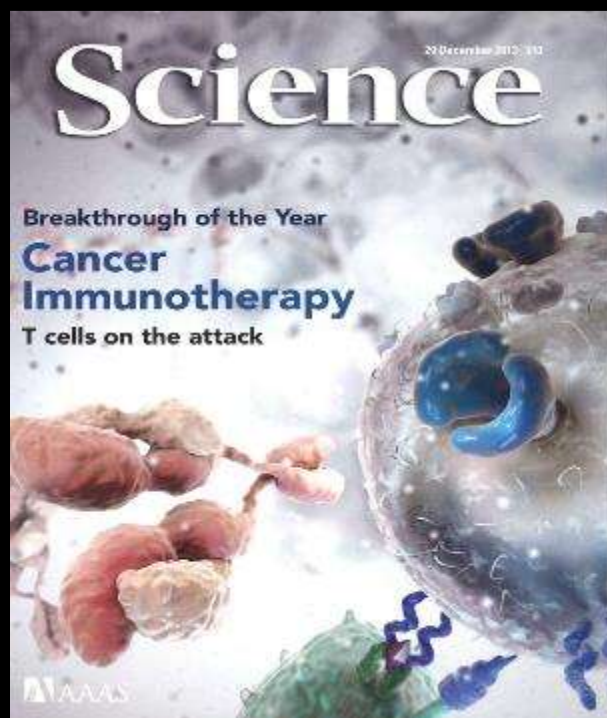
Passive Immunotherapy With Anti-tumor Antibodies

- **direct destruction of tumor cells with or without “Rx warhead”**
- **tag tumor cells for destruction by immune cells**
- **block host tissue stroma signaling pathways that promote tumor proliferation (anti-angiogenesis Mabs)**
- **restricted physical access to target tumor cells**
- **antigen-deletion clones escape destruction**
- **how to develop Mabs against the diverse neoantigens expressed by tumor cells (heterogeneity)**

Immunoavoidance by Tumor Cells

- **“stealthy” tumor cell strategies that 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**

Setting the Immune System Free to Combat Cancer



The Promise of Immune Checkpoint Modulator Therapy in Cancer Therapy

Pembrolizumab and
Therapy of Metastatic Melanoma
in President J. Carter



Saturation TV Advertising

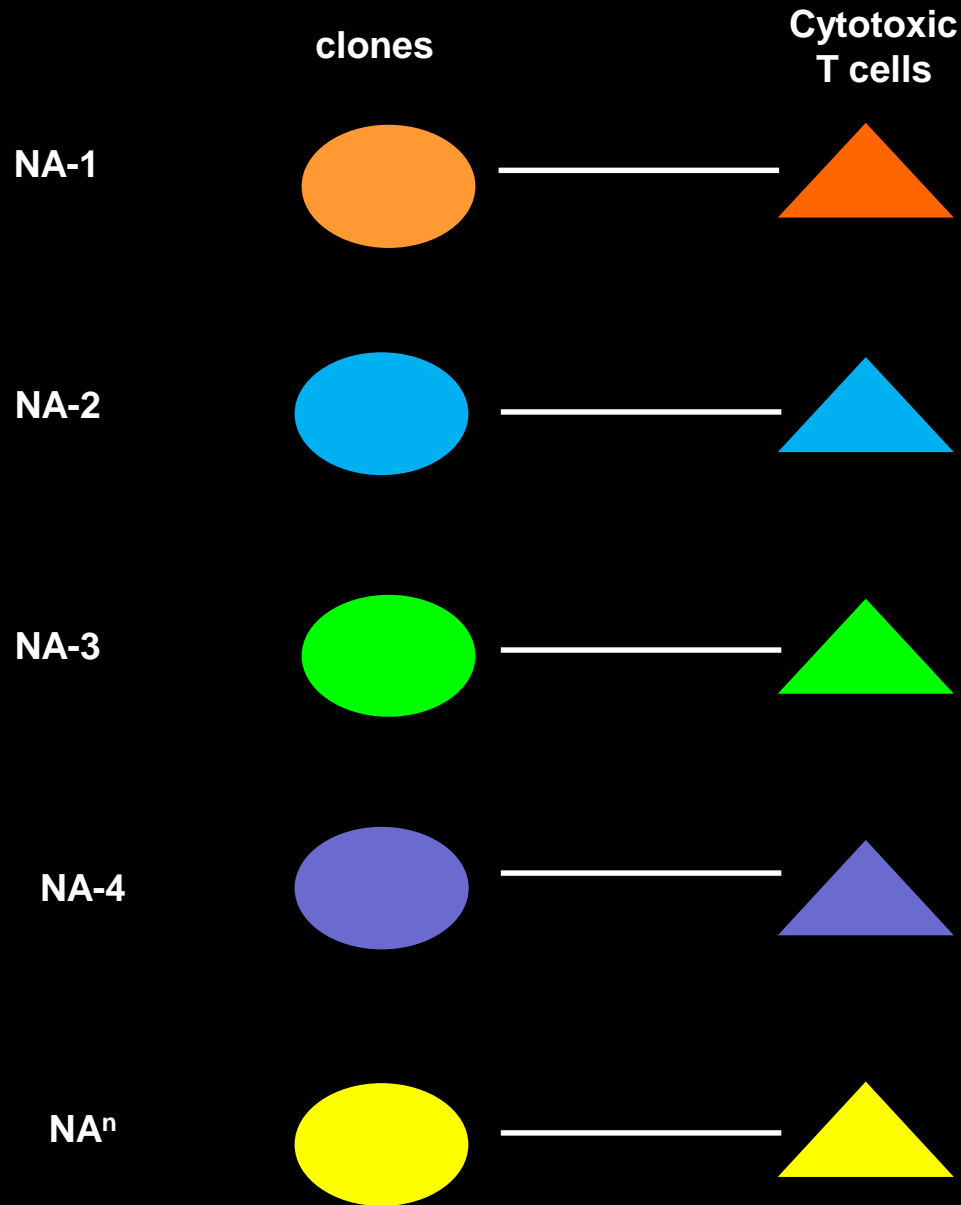


Activation of Anti-tumor Immune Functions

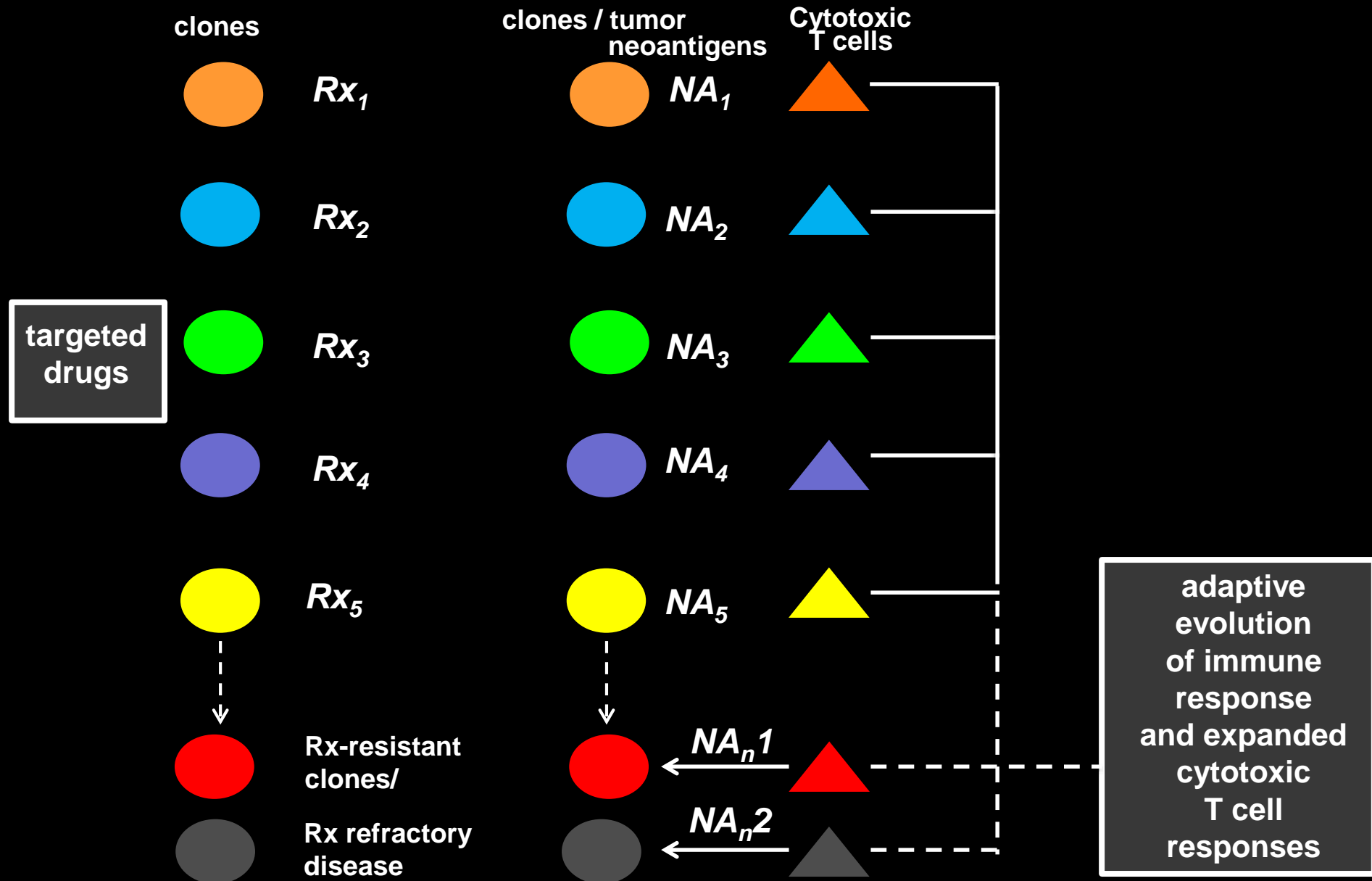
**Relentless Emergence of New Tumor Cell Clones
During Tumor Progression and Immune Evasion
versus
Activation of Host T Lymphocyte Clones to
Kill (Neo)Antigen-Specific Tumor Clones**

Clone Wars

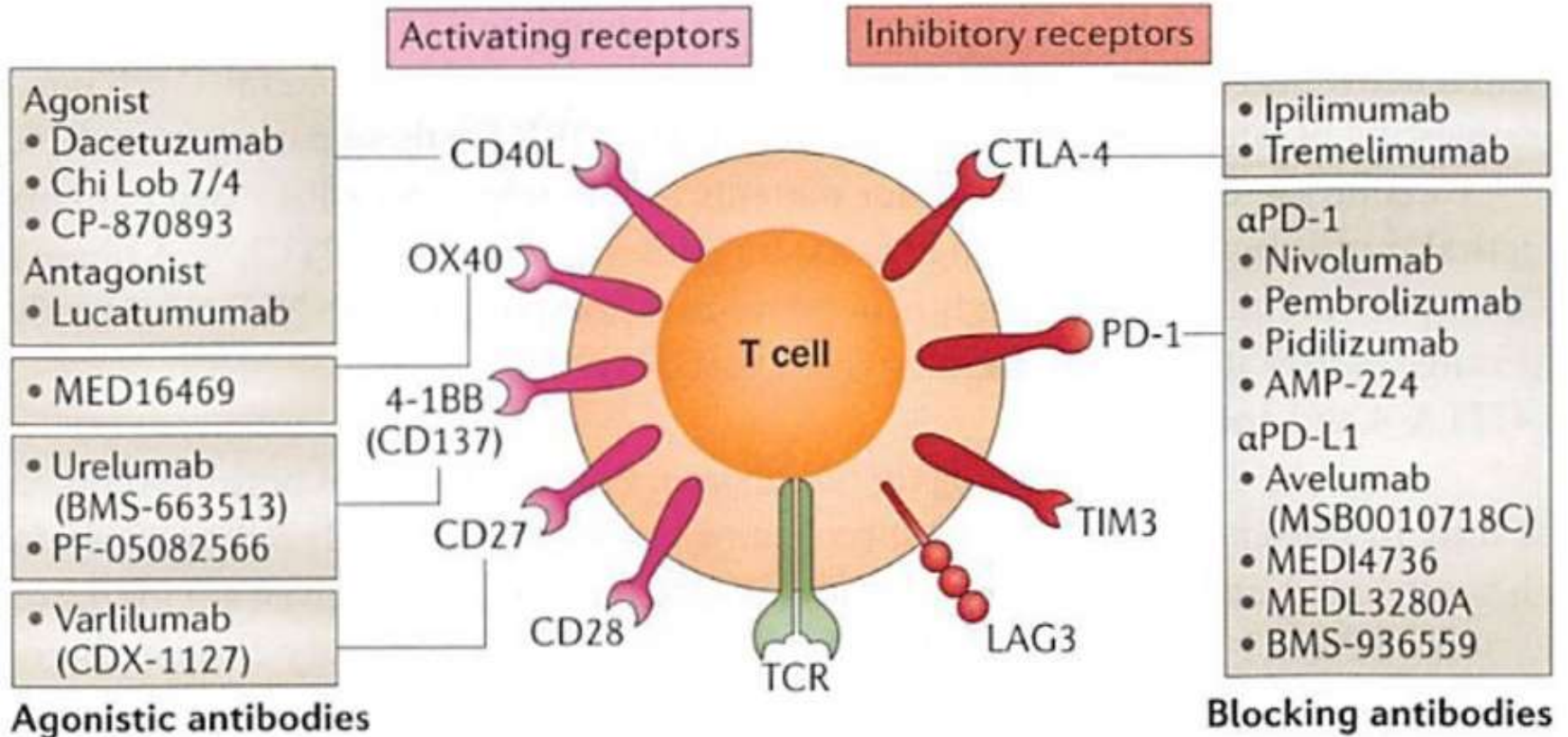
Recognition of Neoantigens (NA) by Cytotoxic (Killer) T Cells



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



Cancer Immunotherapy



Why Are Some Cancer Types More Responsive to Immunotherapy?

More Responsive

- melanoma
- NSCLC
- bladder
- renal
- head and neck

Less Responsive

- pancreatic
- colorectal
- ovarian

Immunogenic Versus Non-Immunogenic Tumor Microenvironments

Immunogenic

- 'hot'
- 'inflamed'
- 'stimulatory'

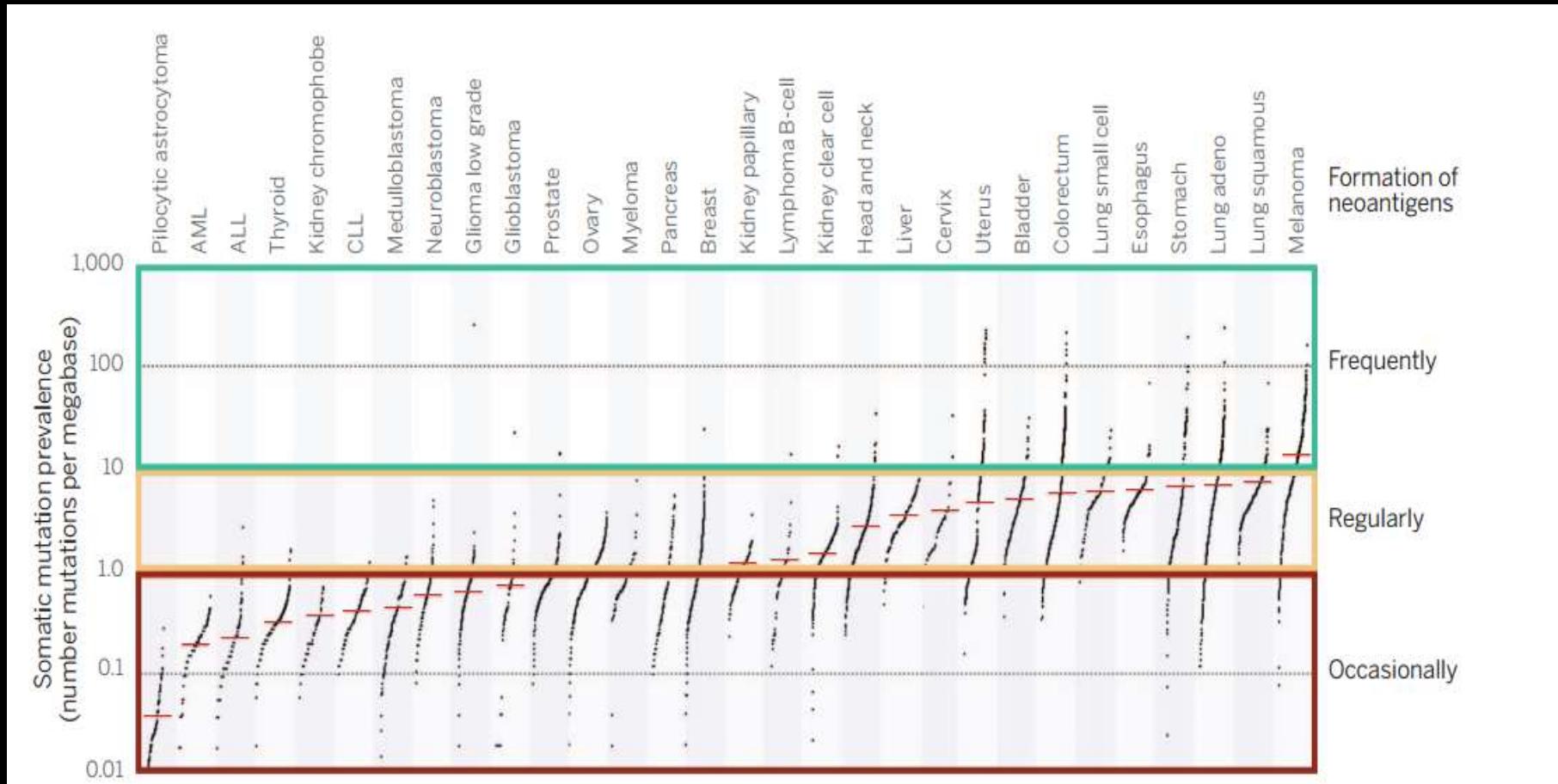
Non-Immunogenic

- 'cold'
- 'non-inflamed'
- 'silent'

- high mutagenic burden
- high tumor neoantigen expression

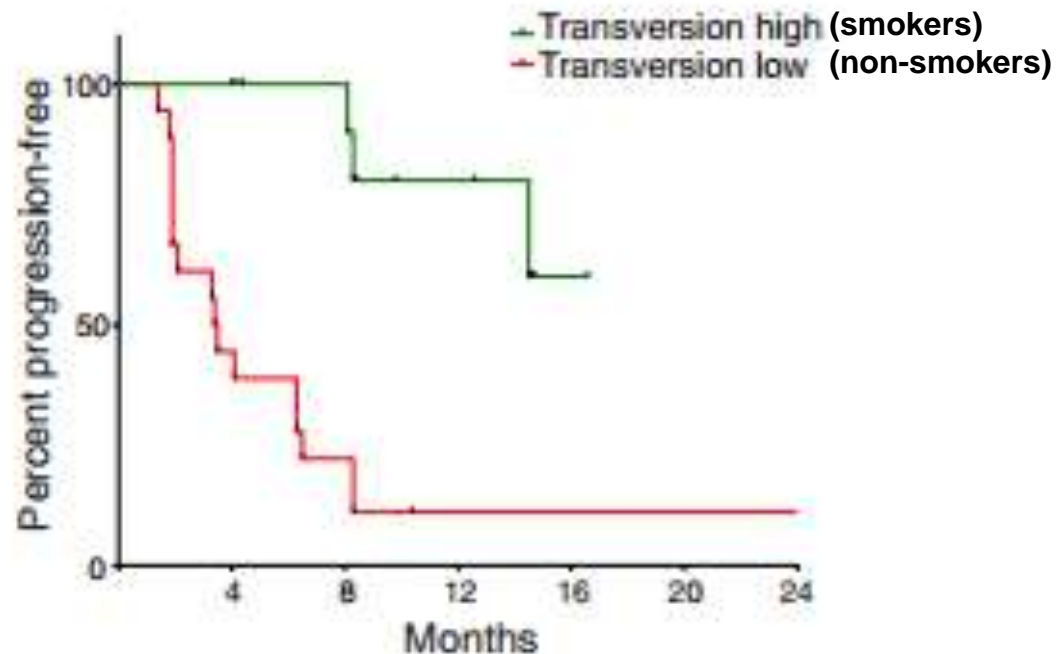
- low mutagenic burden
- low tumor neoantigen expression

Estimates of Likelihood of Neoantigen Expression Based on Somatic Mutation Prevalence in Different Tumor Types



Adapted from: T. N. Schumacher and R. D. Schreiber (2015) Science 348, 69
and L. B. Alexandrov et al. (2013) Nature 500, 415

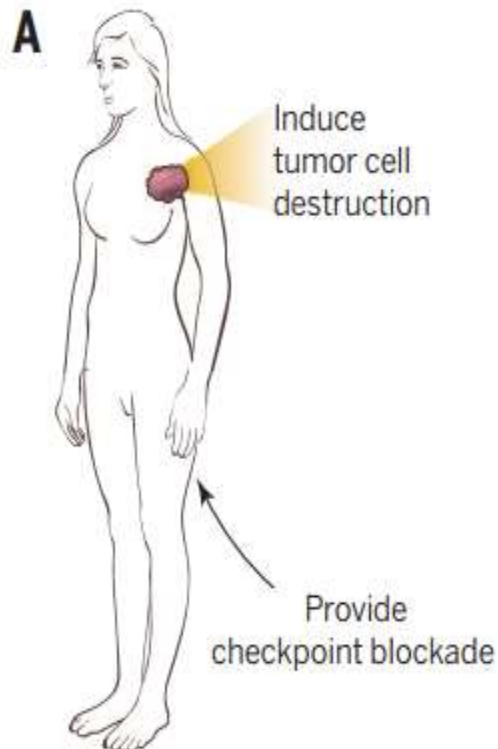
Molecular 'Smoking Signature' in NSCLC and PFS in Patients Treated with Pembrolizumab



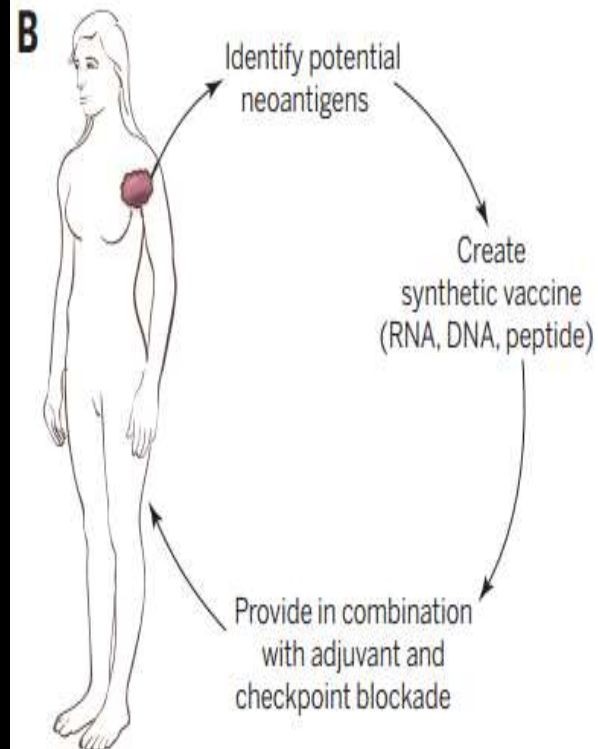
From: N.A. Rizvi et al. (2016) Science 348, 124

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

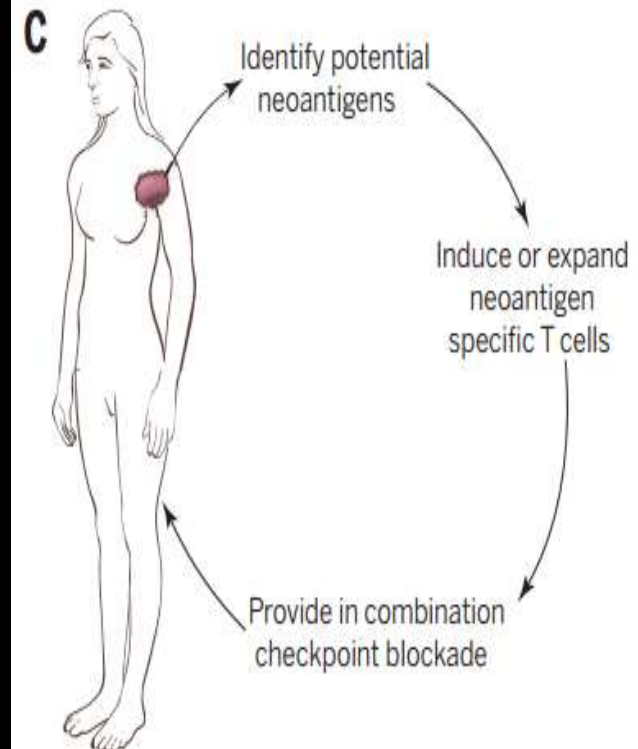
Immune Checkpoint Modulation



Cancer Neoantigen Vaccines



Adoptive Cell Therapy TILs, TCRs, CARs



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

Cancer Vaccines

- far greater technical challenge than most antimicrobial vaccines
- antigenic variation in different tumor cell clones plus inter-patient variation (personalized vaccines)
- 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 quasi-species

Activated (Immune) Cell Therapy (ACT) for Cancer

- capture, expand and re-infuse unmodified tumor-infiltrating lymphocytes (TIL)
- genetic engineering of killer lymphocytes with new T cell receptors (TCRs) to enhance tumor cell detection and killing

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 Rx 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

The Future Debate on Cancer

**Demographics of an Aging Society and
Increased Cancer Incidence**

Cost of Care

**Complex Clinical, Scientific, Economic,
Ethical and Legal Issues**

Cancer Treatment's New Direction

Genetic Testing Helps Oncologists Target Tumors and Tailor Treatments



Evan Johnson sits on a terrace at the Mayo Clinic Hospital, Methodist Campus in Rochester, Minn. during the summer of 2014.

- **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

Newsweek

03.28.2014

SOLVING CANCER

YOU CAN'T CURE WHAT YOU
DON'T UNDERSTAND



$(X + Y = -C)$ $(X + Y = -C)$ $(X + Y = -C)$ $(X + Y = -C)$

- cancer as a complex adaptive system
- 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 curative cancer therapy

Aspirations for Improved Cancer Diagnosis and Treatment

- **maximize the efficacy and safety of Rx interventions against advanced (metastatic) disease**
 - **circumventing variability in tumor cell clones to the selected Rx 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 Rx regimen**

Cancer Rx: Ugly Realities

- in the majority of cancers the efficacy of single therapies is either short-lived or completely ineffective
- mutations that confer Rx resistance may pre-exist prior to treatment (intrinsic resistance) or arise as de novo mutations conferring selective survival during treatment (acquired resistance)

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 immuno-evasive clones**
 - **value of new combinations of drug and immunotherapies?**