Cancer as Complex Adaptive System

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ASU COMPLEX ADAPTIVE SYSTEMS
ARIZONA STATE UNIVERSITY

Brindley Lecture
UTMB Department of Pathology
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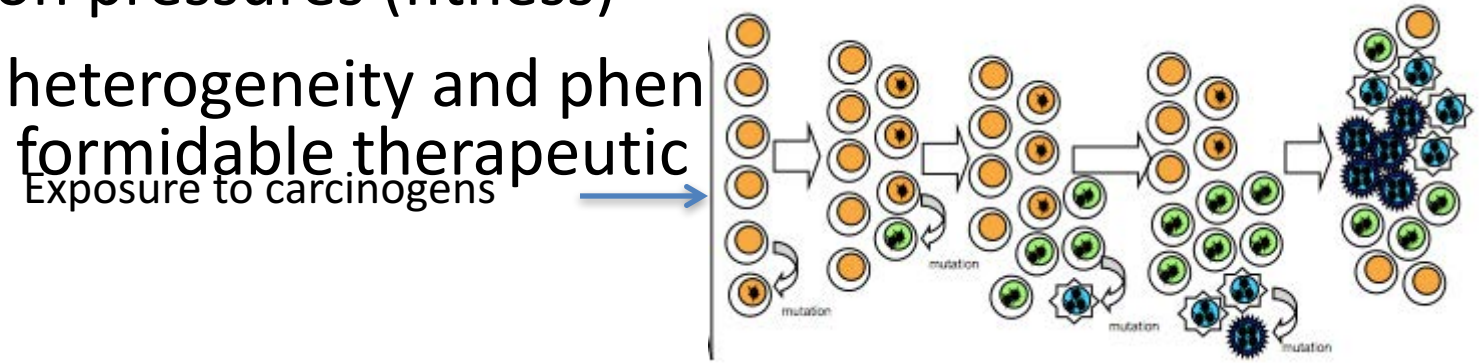
May 15, 2017

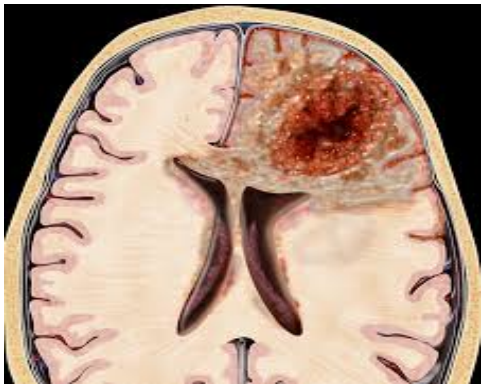
Central Themes in Cancer Biology

- Cancer as a multi-dimensional ecosystem involving complex interactions between cancer cells and host systems
- Genotoxic insults (DNA damage), mutations and genomic instability as drivers of initiation and progression
- Progressive evolution of genomic and phenotypic diversity (tumor subtypes and clonal heterogeneity)
- Tumor-progression as a dynamic process with adaptive evolution of tumor cell clones to diverse selection pressures (fitness)
- Clonal heterogeneity and phen
  posing formidable therapeutic



Invasion and Metastasis: the Deadly properties of cancer

basal cell carcinoma

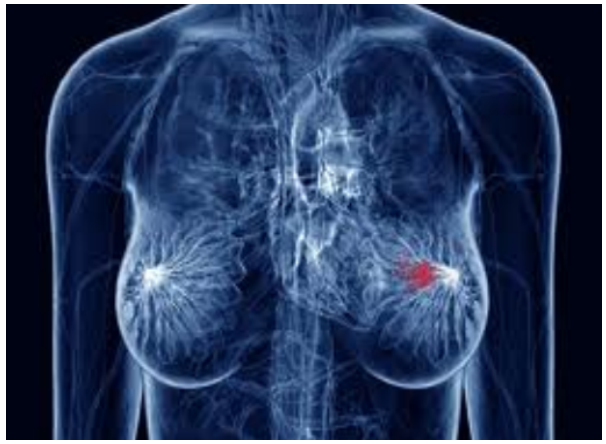


glioblastoma

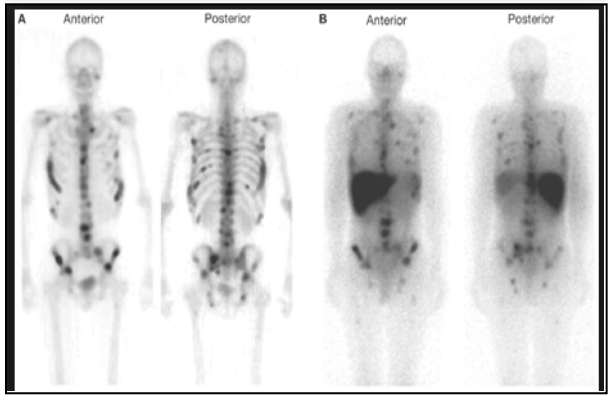
Invasion Without Metastasis

lung

colorectal



breast

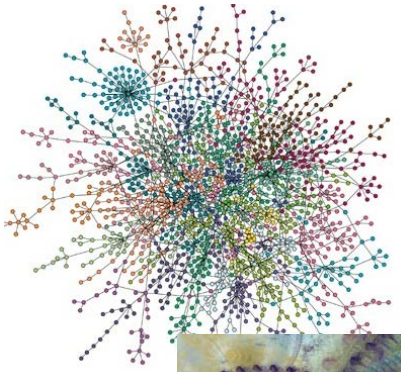


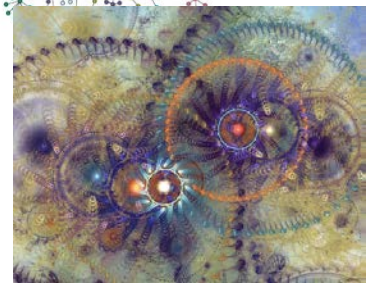
prostate

Invasion and Metastasis

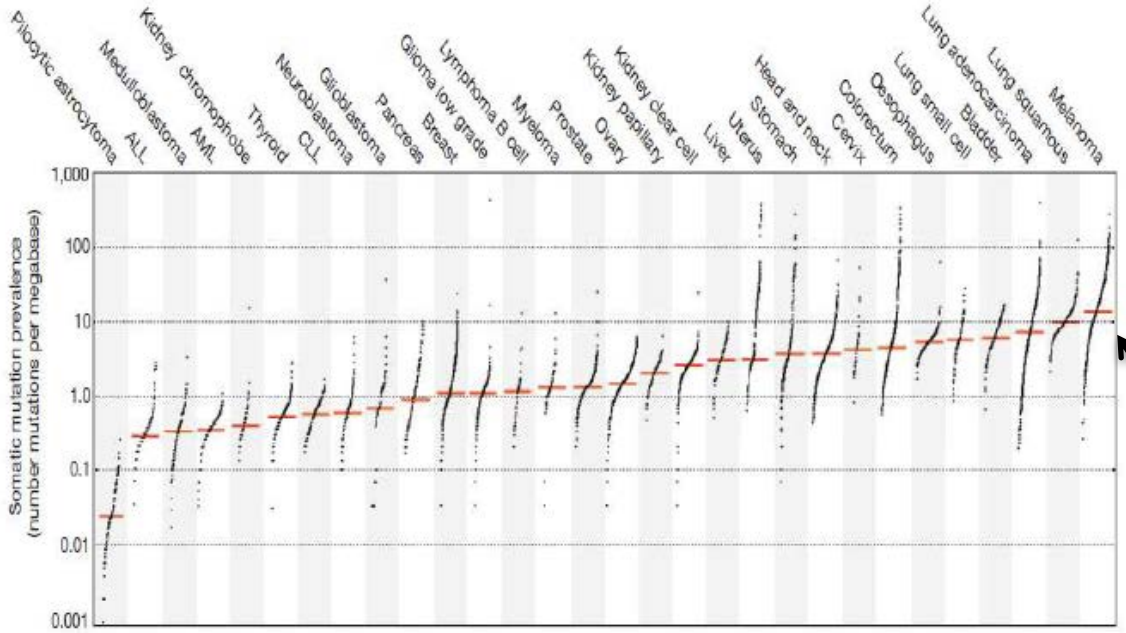
New Biological Insights Enabled by Technology: Quintessential Example Is Cancer Complexity

- **Cancer genome complexity revealed: Formidably complex catalog of genomic changes and molecular network disruptions**
  - **Networks are highly interactive and redundant**
- **Cancer evolution exposed: Continued accumulation of genomic alterations generating numerous clones and sub-clones with different genomic alterations and phenotypes (heterogeneity)**
  - **In a patient**
    - **Within a lesion**
    - **Between lesions**
  - **Between patients**
  - **Treatment-driven evolution (selection and fitness)**





Panorama of Extravagant Genomic Alterations in Cancer

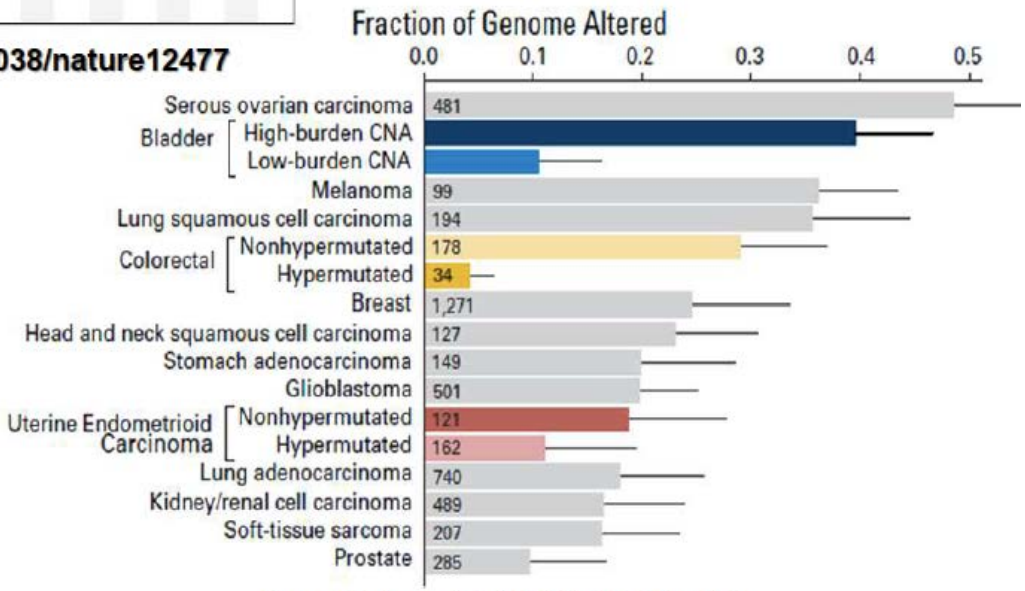


From: L. B. Alexandrove et al. (2013) Nature doi:10.1038/nature12477

Mutations per megabase tumor DNA (3K megabases in human genome)

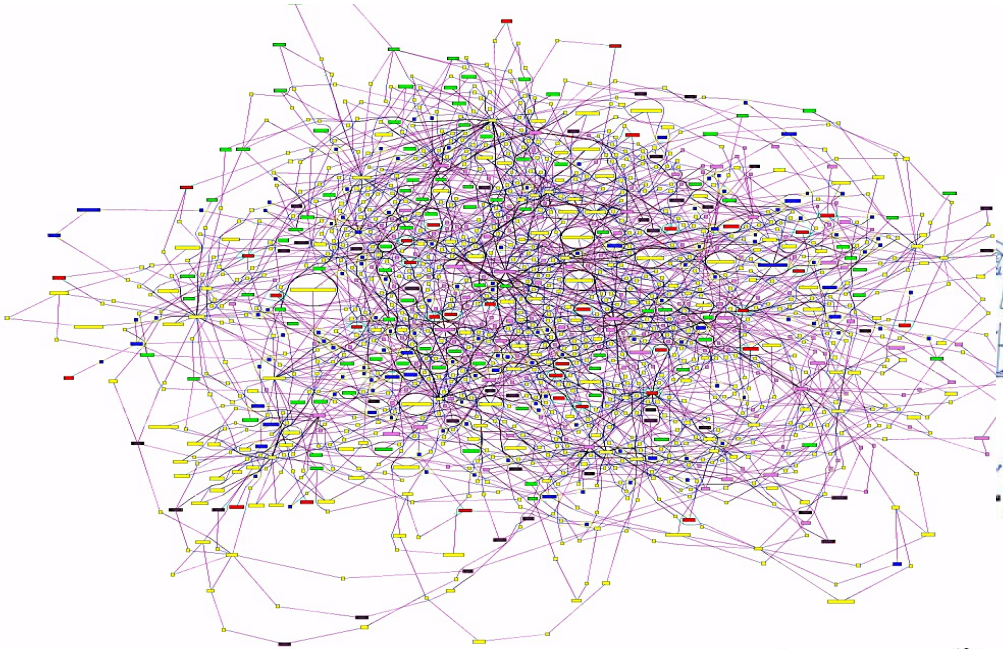
Average 10 per megabase for lung cancer and melanoma

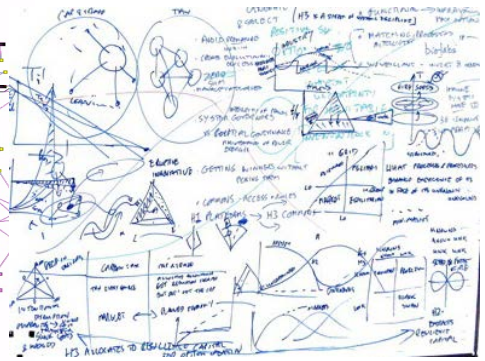
Copy number alterations in solid tumors

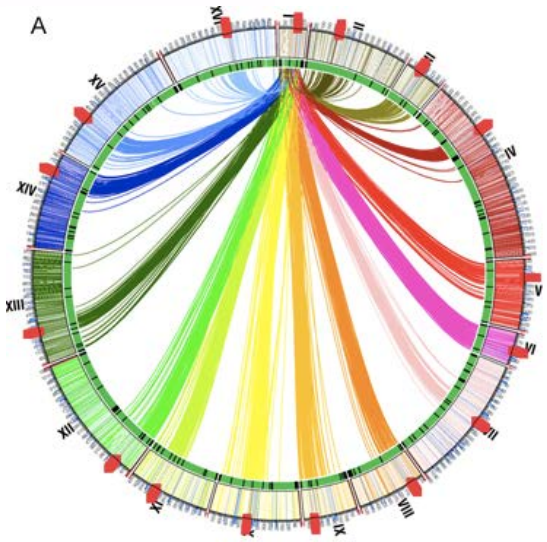


From: G. Iyer et al. (2013) JCO 31, 3133

The Complexity of Gene, Chromosome, and Network Interactions







Complicated Systems
Versus
Complex Systems

The Biological Complexity of Cancer

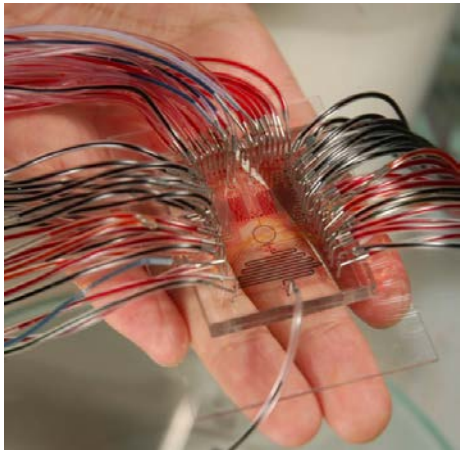
- What is the difference between complicated and complex systems?
- What features of cancer make it a complex system?
- What is meant by “emergence” in complex systems?
- What are the implications of the complex behavior of cancer for diagnosis, treatment and prevention?

Complicated Systems:
Low Degrees of Design Freedom





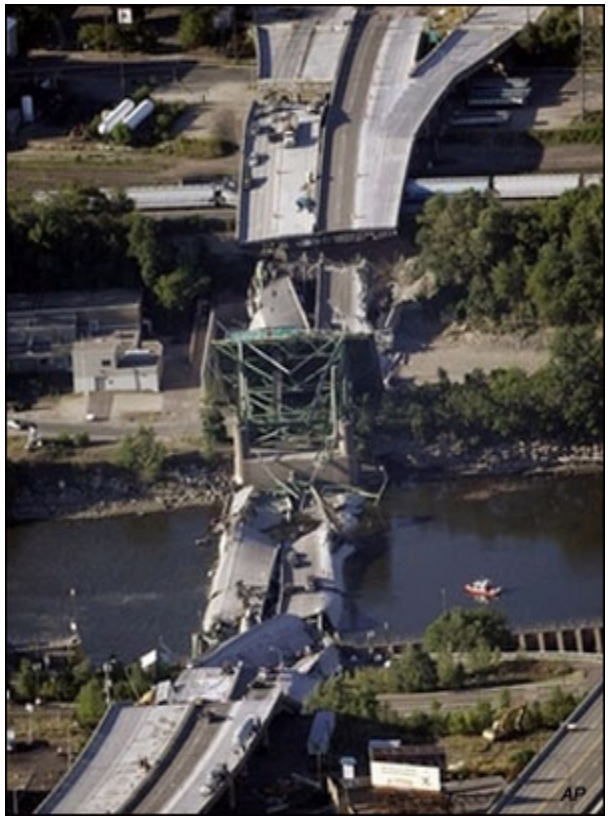


- **Behavior of components and the assembled system is predictable**
- **Knowledge of tolerance limits and likely failure points is possible**
- **Performance of the system is fixed and not capable of autonomous evolution**

Failure Does Occur In Complicated Systems:
When the Source of Failure is Identified, the outcome is predictable

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

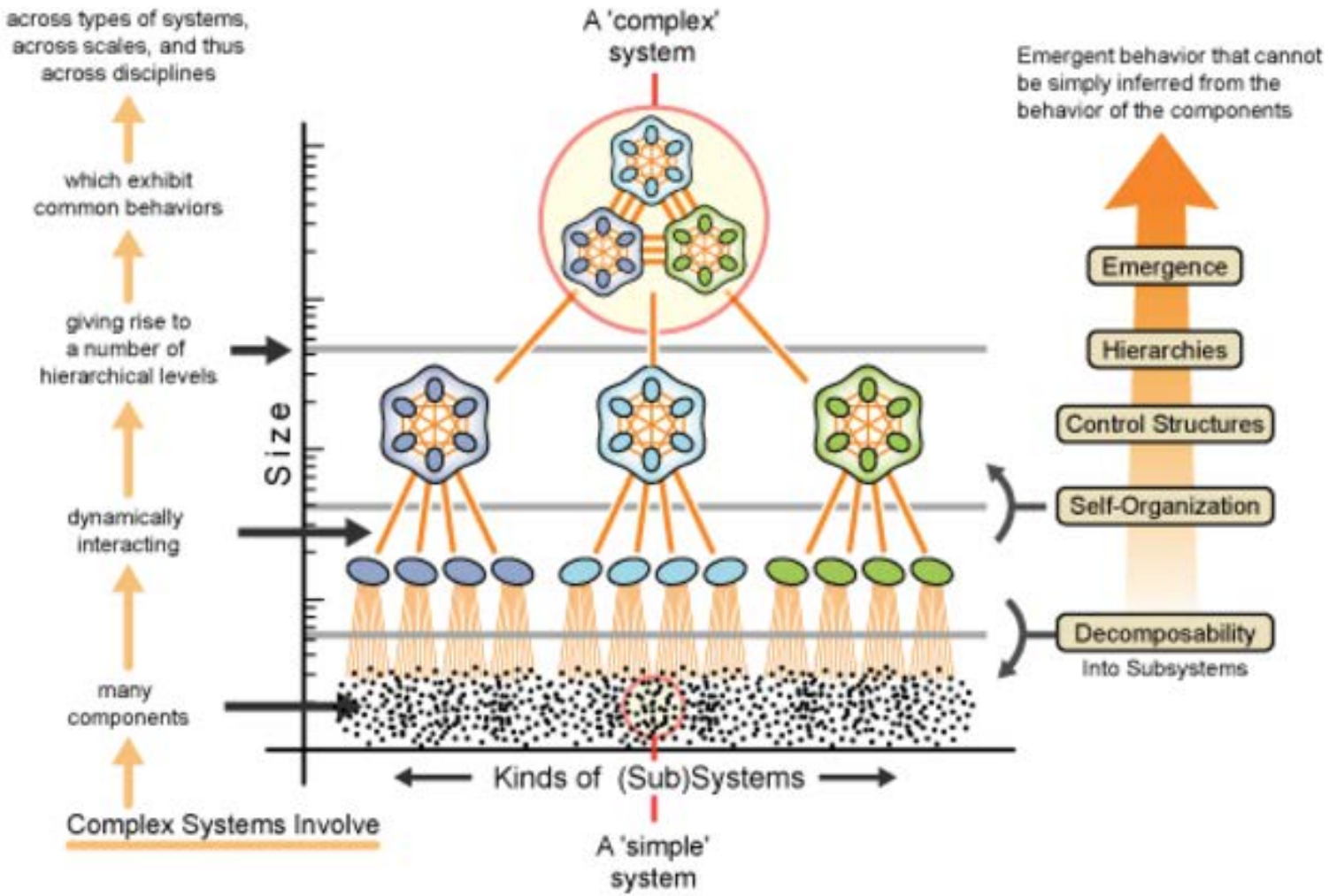


Characteristics Of A Complex Adaptive System (CAS)

CAS:

- Innumerable individual parts or agents
- No leader that coordinates the actions of the individual parts
  - System is “self-organizing”
  - System is stochastic (governed by chance)
  - Behavior is non-linear
- Individual parts generate (new) emergent patterns
  - Patterns form even though parts not “directed” to make a pattern
- If the elements of the system are altered, the system adapts or reacts
  - “Adaptive” = “Reactive to Change”

Cancer As A Complex Adaptive System



Emergence:
The Hallmark of Complex Systems

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

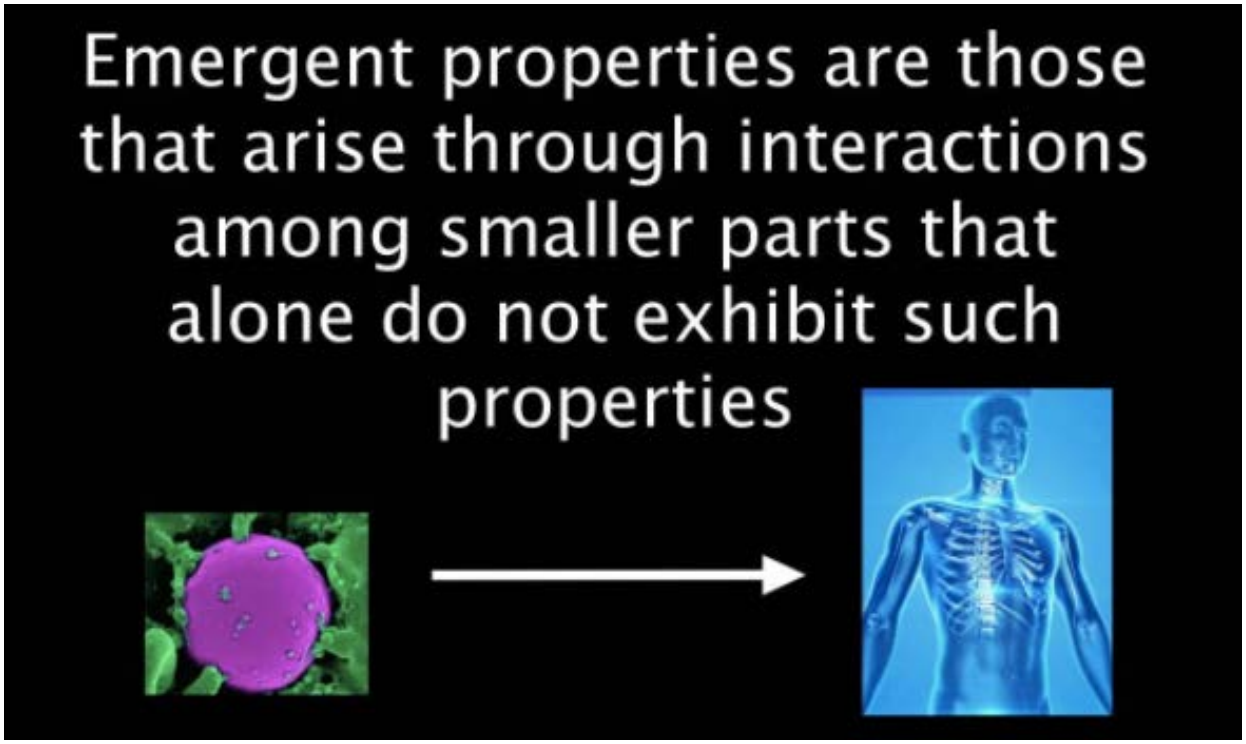
- An emergent property is a property that a complex system has but individual components do not have.

- Properties (behavior) of the whole system cannot be reliably predicted from knowledge of the properties of the simpler units.

  - **"The whole is more than the sum of its parts"**

- New and unexpected patterns of interactions between components can shift the system to an new state with very different properties (emergence).

Cancer As A Complex Adaptive System



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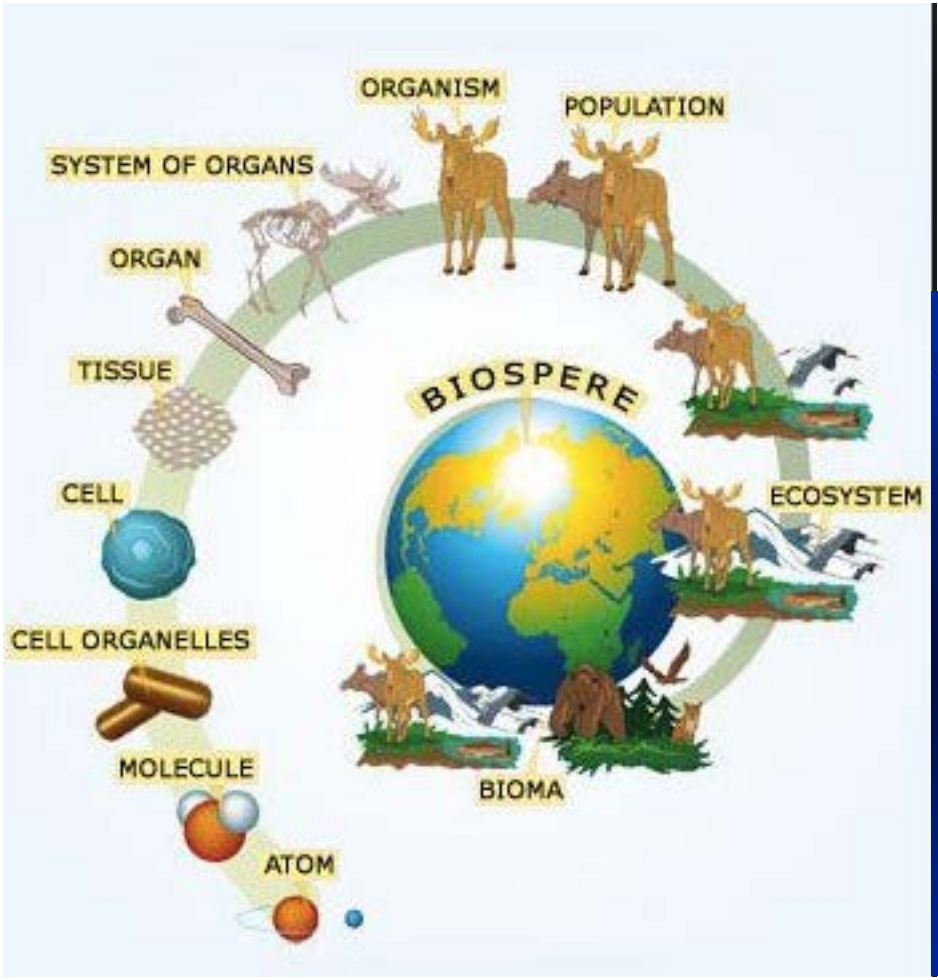


Levels
Hierarchies

Cancer As A Complex Adaptive System

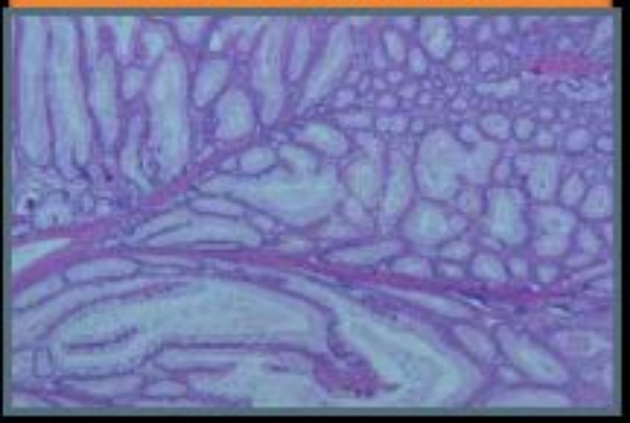
A **complex adaptive system** is a "**complex macroscopic collection**" of relatively "**similar and partially connected micro-structures**" formed in order to adapt to the changing environment **and increase its survivability** as a macro-structure.

Examples:

- **The Global Macroeconomic Network**
- **The Stock Market**
- **Political Parties**
- **Terrorist Networks**
- **War**
- **The Brain**
- **The Immune System**
- **CANCER**

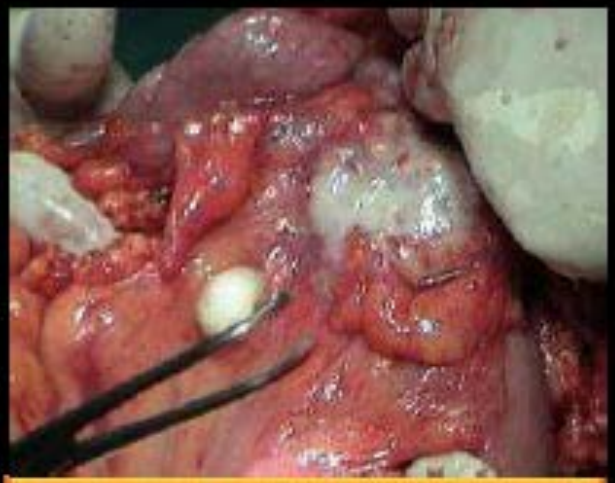
Cancer:
Emergent Properties and System State Shifts

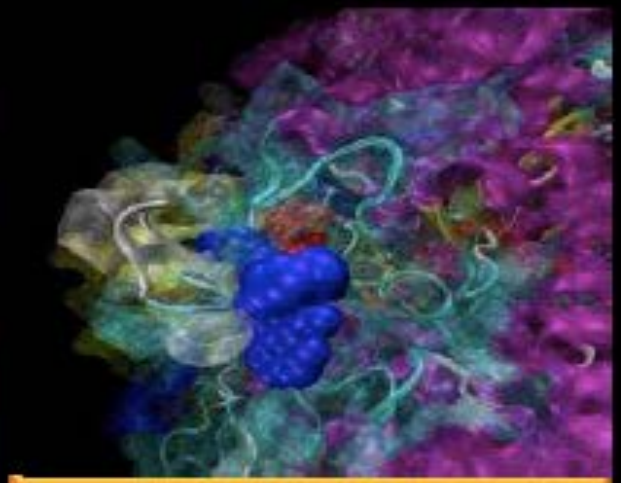
Escape From Controls for Normal Tissue Architecture



Genome Instability and Emergence of Clonal Variants

Evasion of Detection/Destruction by Host Immune System





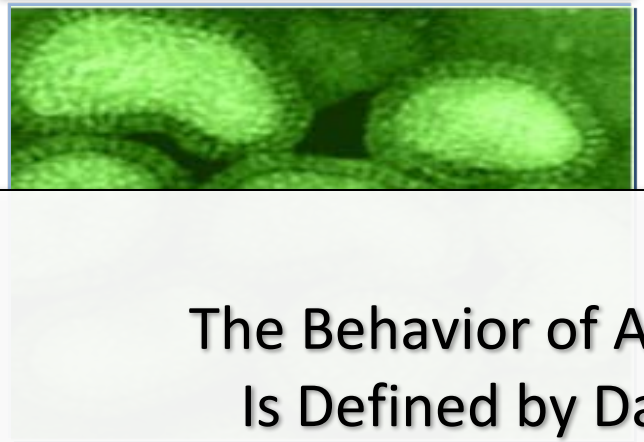
Use of Host Systems by the Tumor to Promote Progression

Invasion and Metastasis

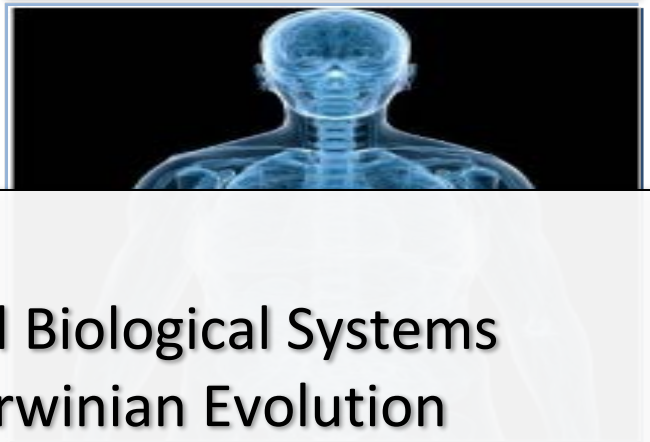
Emergence of Drug-Resistant Clones

Complex Adaptive Systems Are Ubiquitous in Nature

Host-Pathogen Interactions

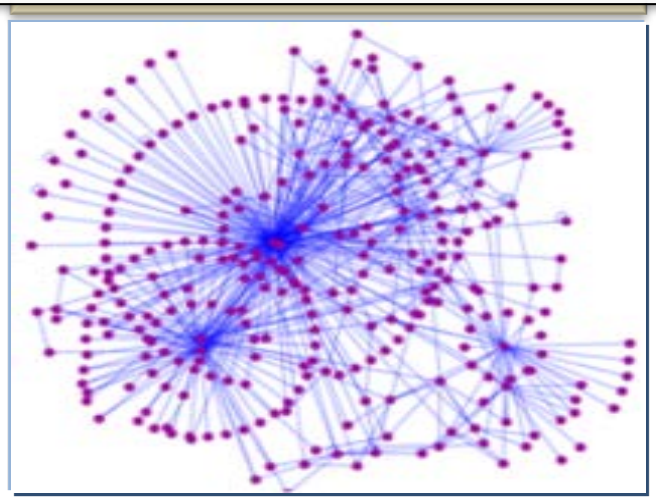


Physiological Regulatory Networks



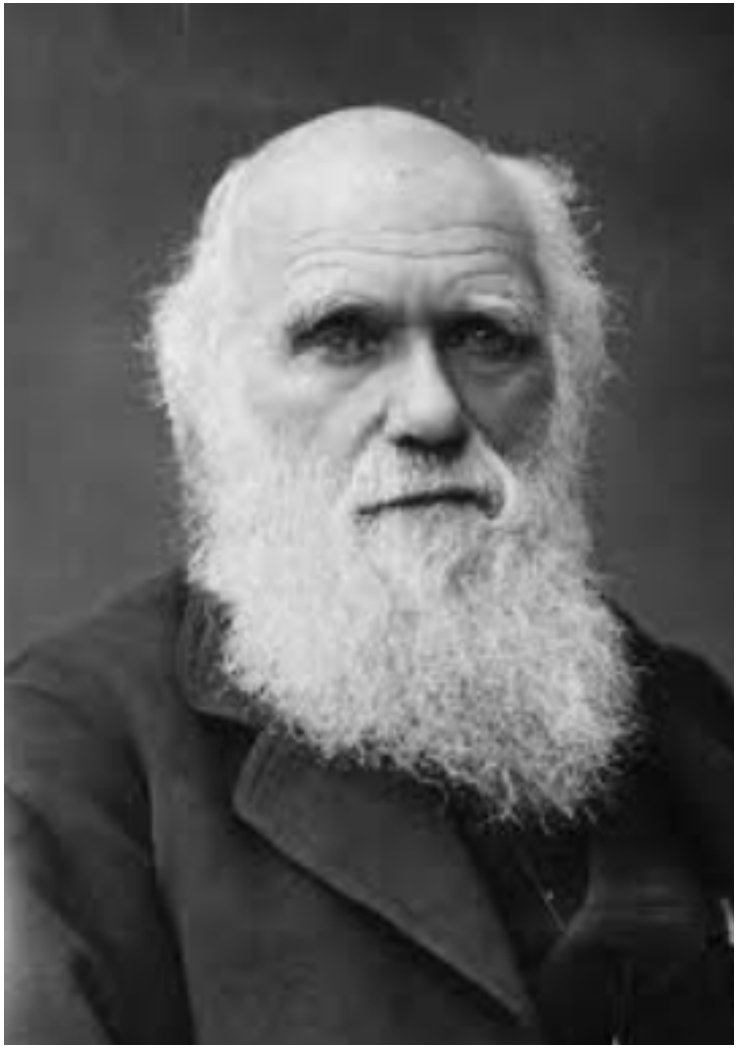
The Behavior of All Biological Systems Is Defined by Darwinian Evolution

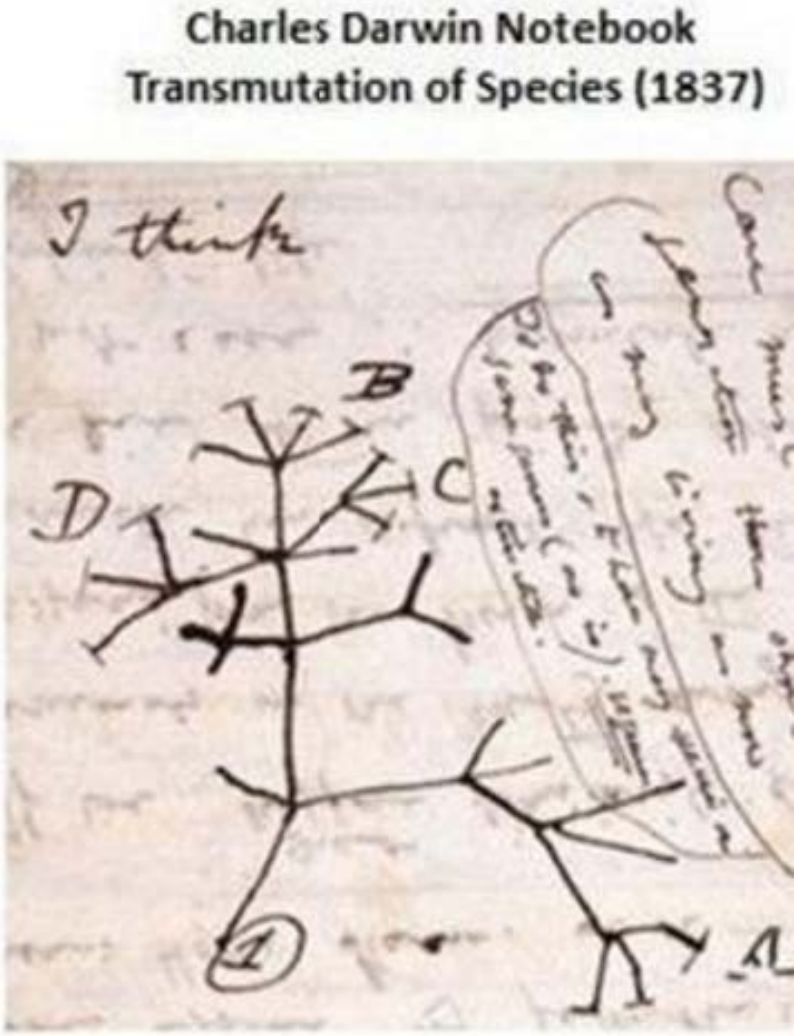
Genome Regulatory Networks



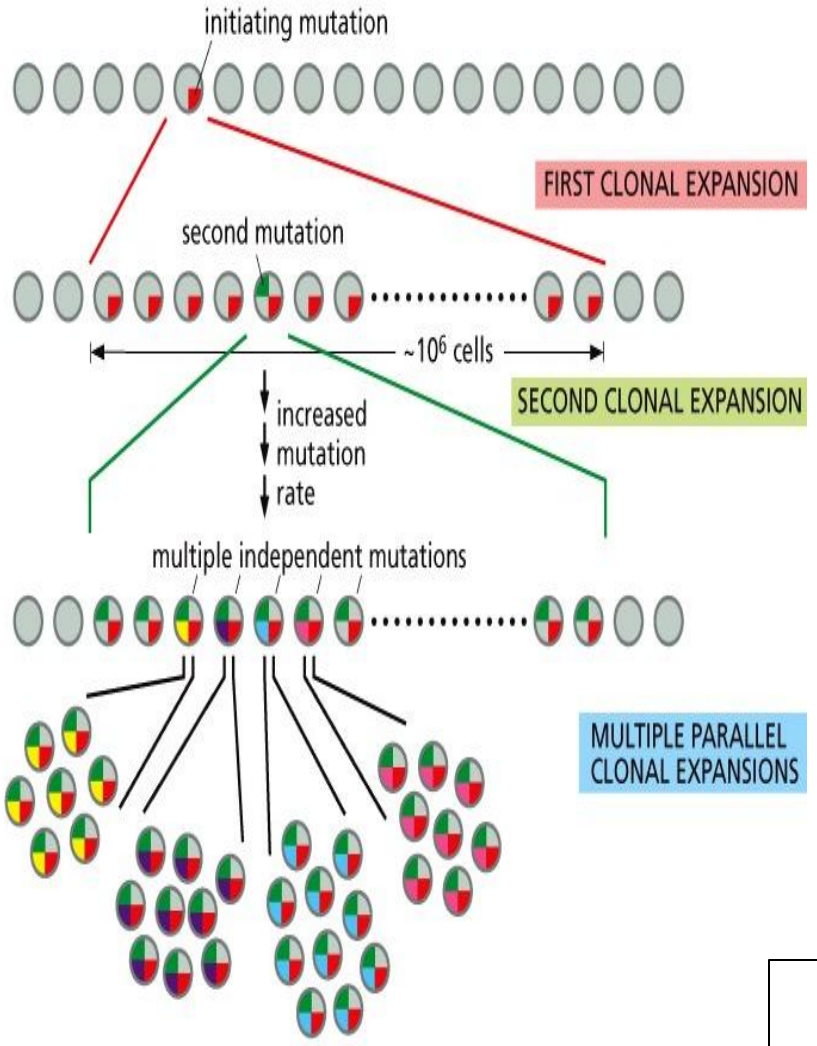
Signaling Network Dysregulation in Disease

Charles Darwin and Species Evolution

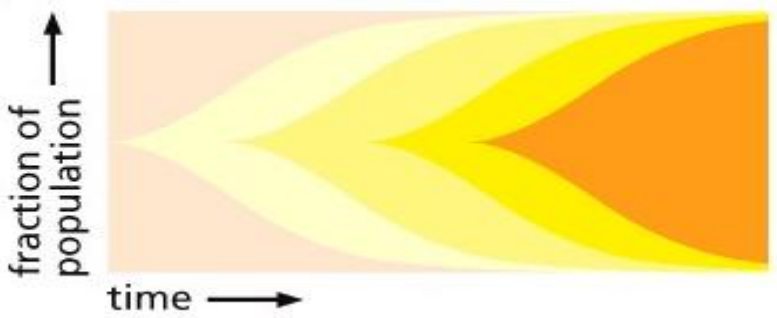


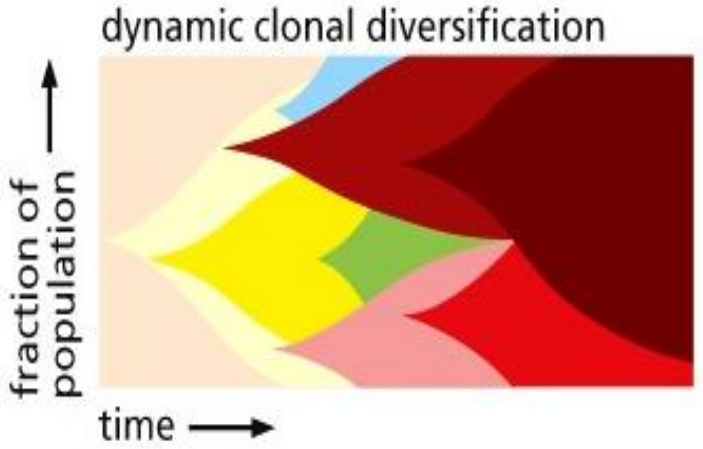


Evolution and Diversification of Tumor Clones and Subclones



One beneficial mutation at a time (simple linear clonal succession)





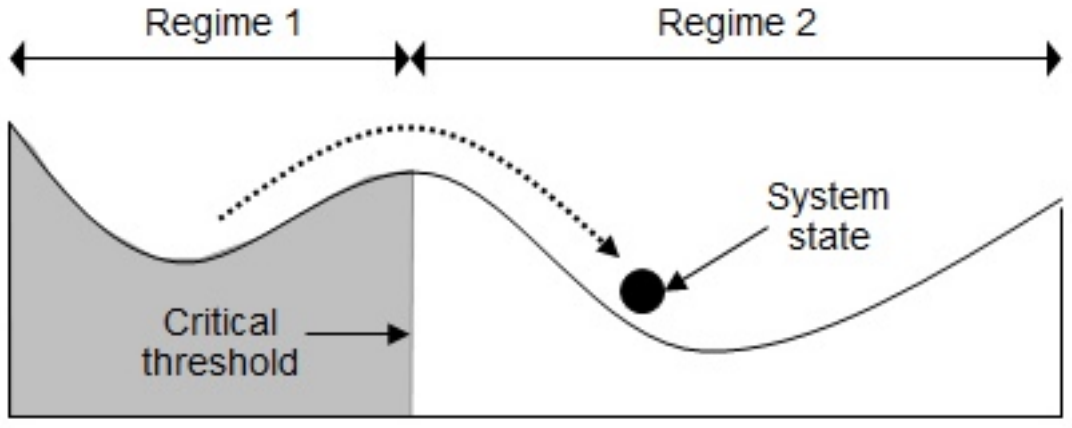
Multiple beneficial mutations simultaneously (compete with one another or co-exist)

Understanding State Shifts a
nd Triggers of Emergence in Complex Adaptive Systems

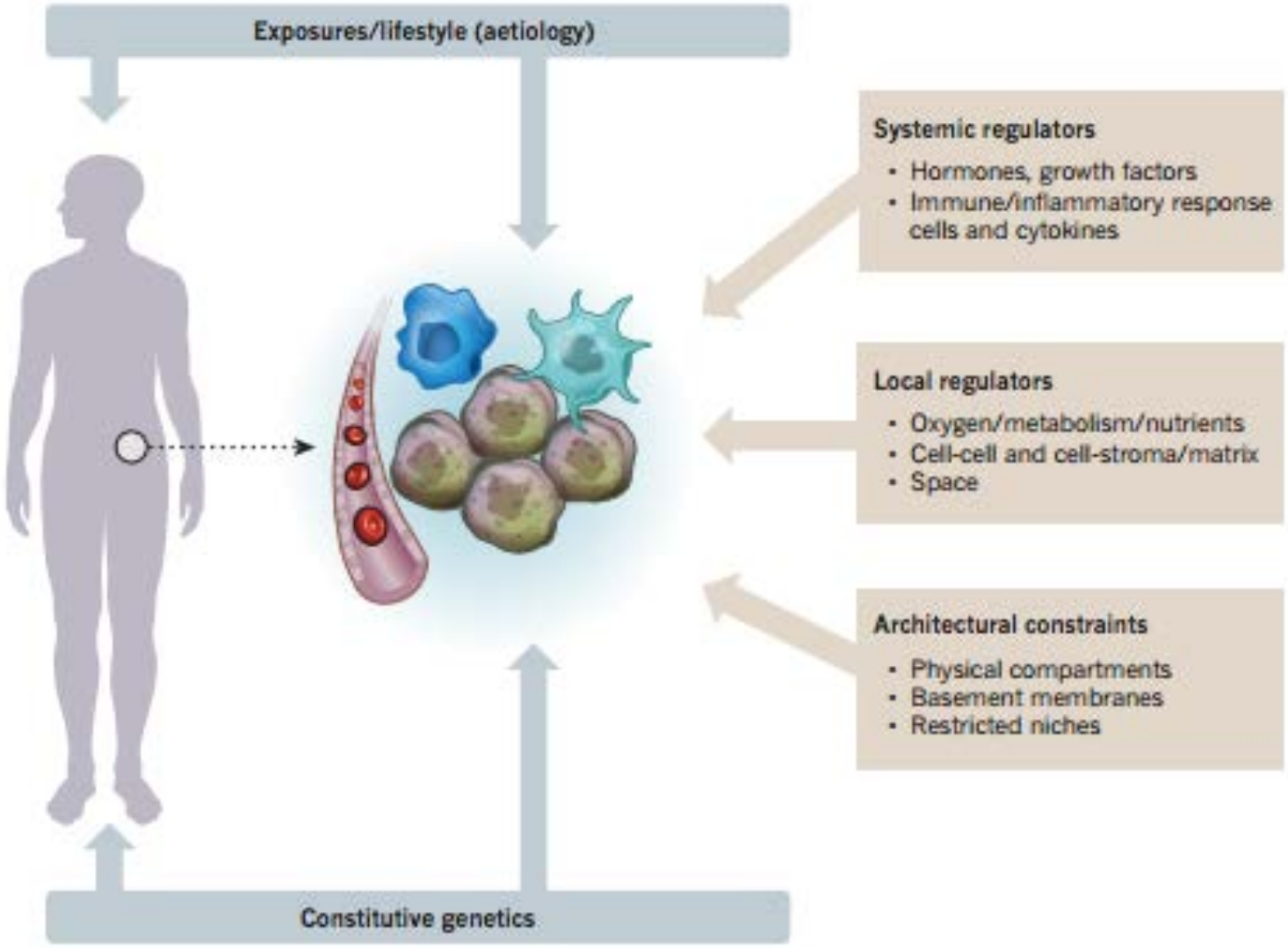
Localized ecological systems are known to **shift** abruptly and irreversibly from one **state** to another when they are forced across critical thresholds.

A change in ecosystem conditions can result in an abrupt shift in the state of the ecosystem, such as a change in population or community composition.

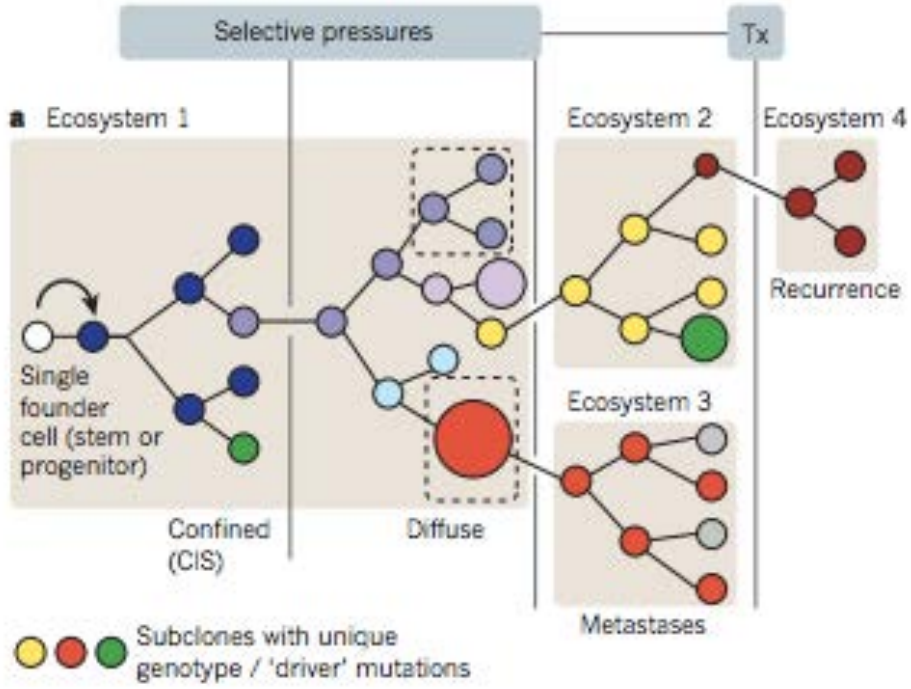
In cancer it may be hypoxia-induced or therapy-induced metabolic state shifts.

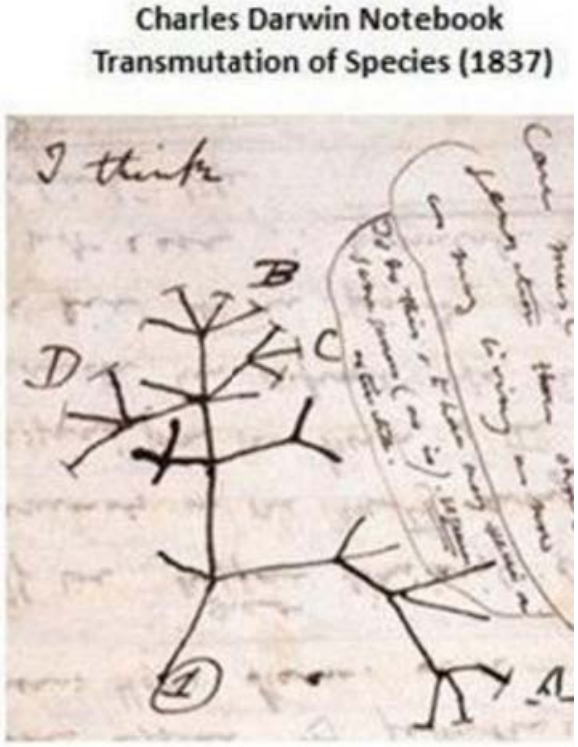


Evolution and Selection Pressures



Evolution and Diversification of Tumor Clones and Subclones

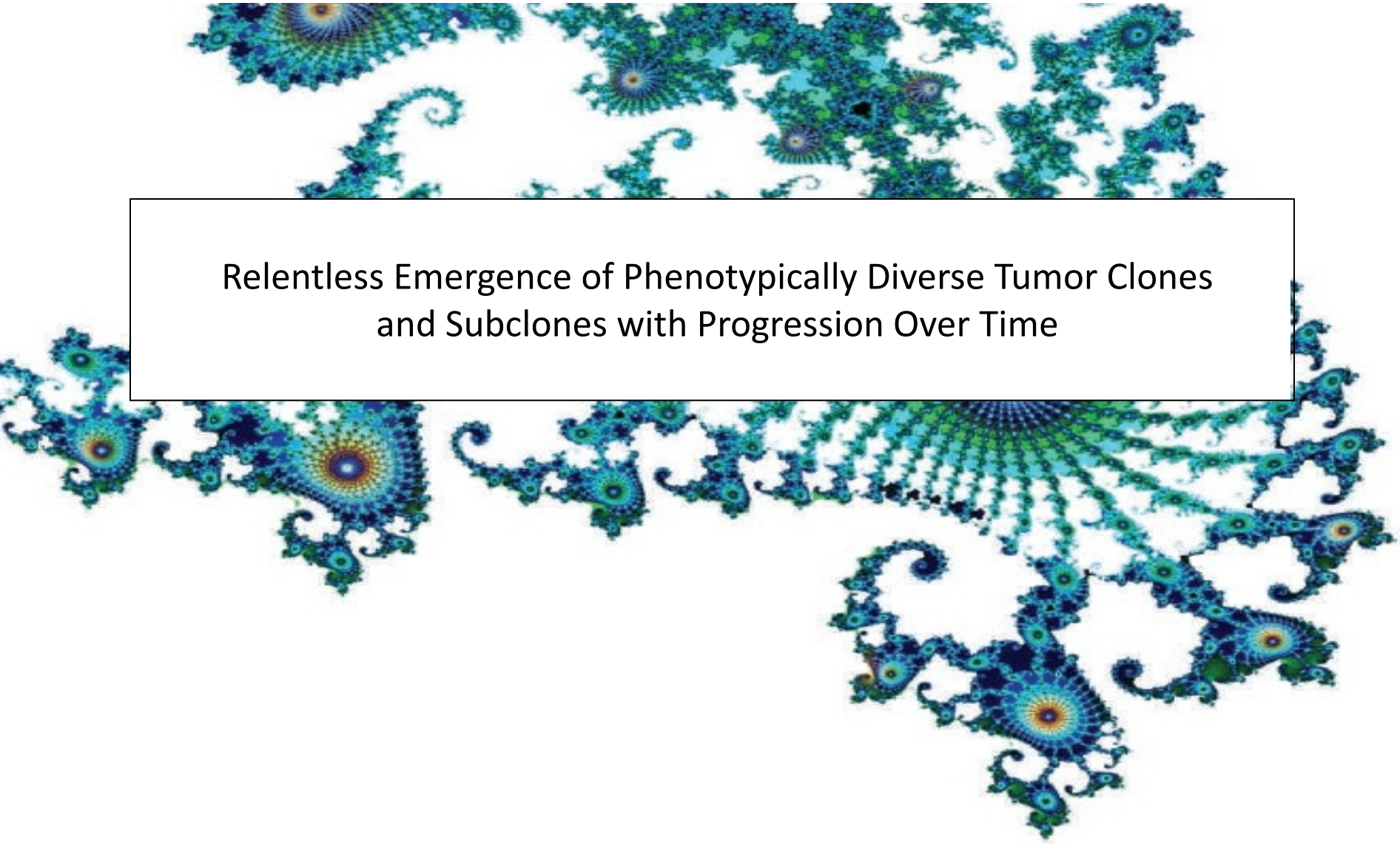




Selective pressures (vertical lines) allow some mutant clones to to expand but pushes others to become extinct or dormant

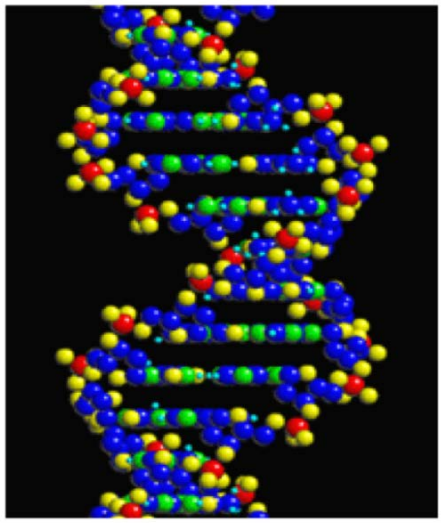
- Shaded boxes = tissue ecosystems
- Smaller boxes (dotted lines) = niches within an ecosystem
- Rx = Therapy (a powerful selective pressure)

Cancer As A Complex Adaptive System

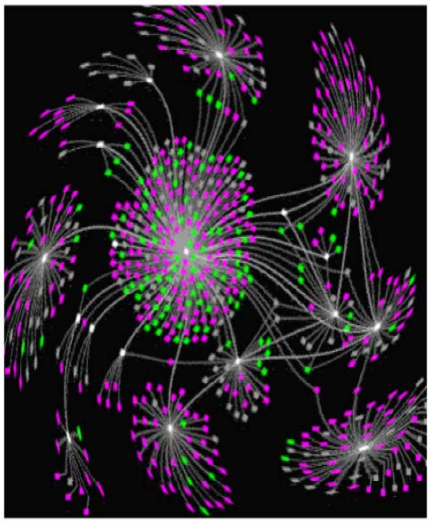


Relentless Emergence of Phenotypically Diverse Tumor Clones and Subclones with Progression Over Time

Understanding the Disruption of Molecular Information Networks in Disease

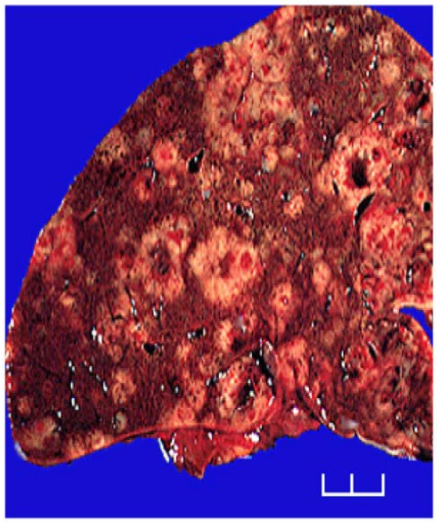


Encoded information and expression



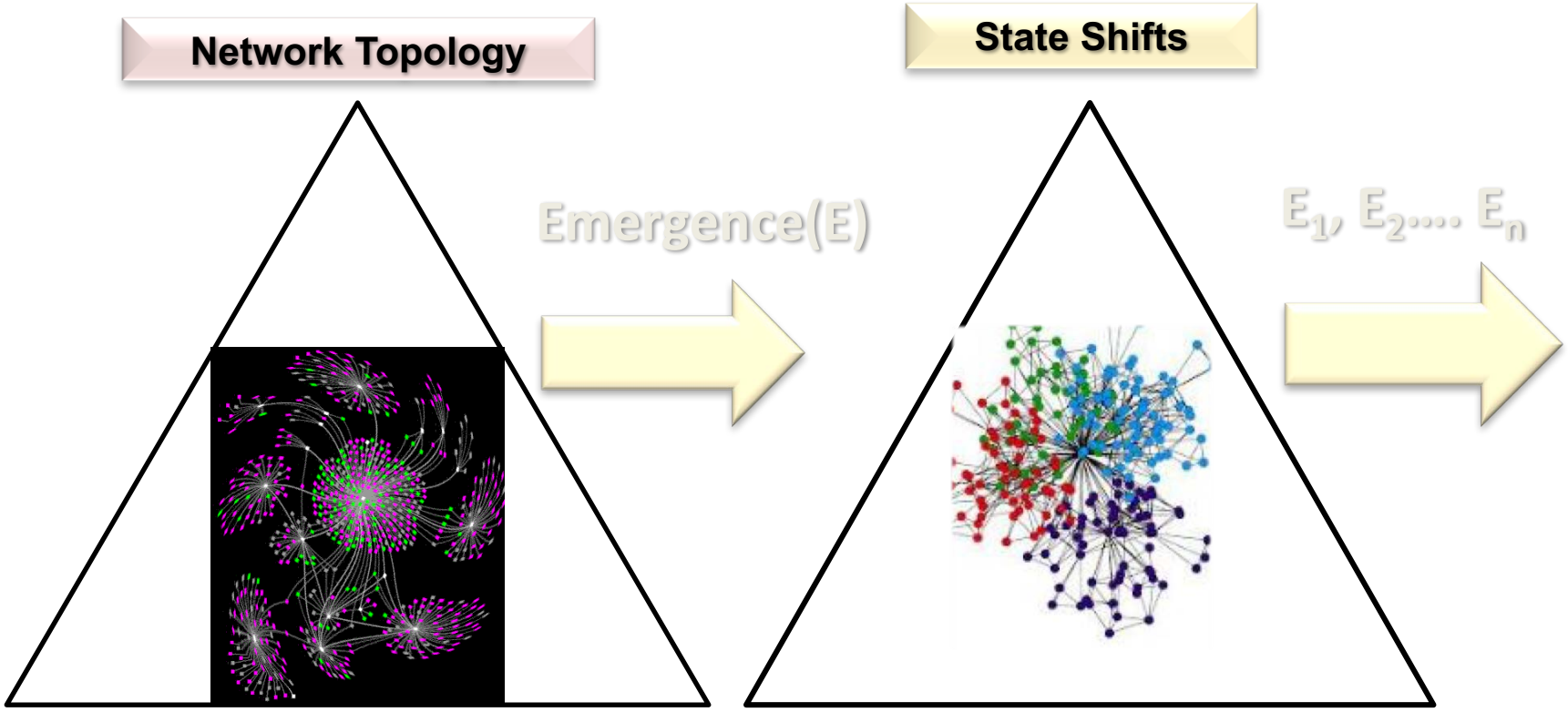
Patterns of information flow within signaling networks

Stable networks and information fidelity (health)



Dysregulated networks and altered information patterns (disease)

Understanding State Shifts and Triggers of Emergence in Complex Adaptive Systems

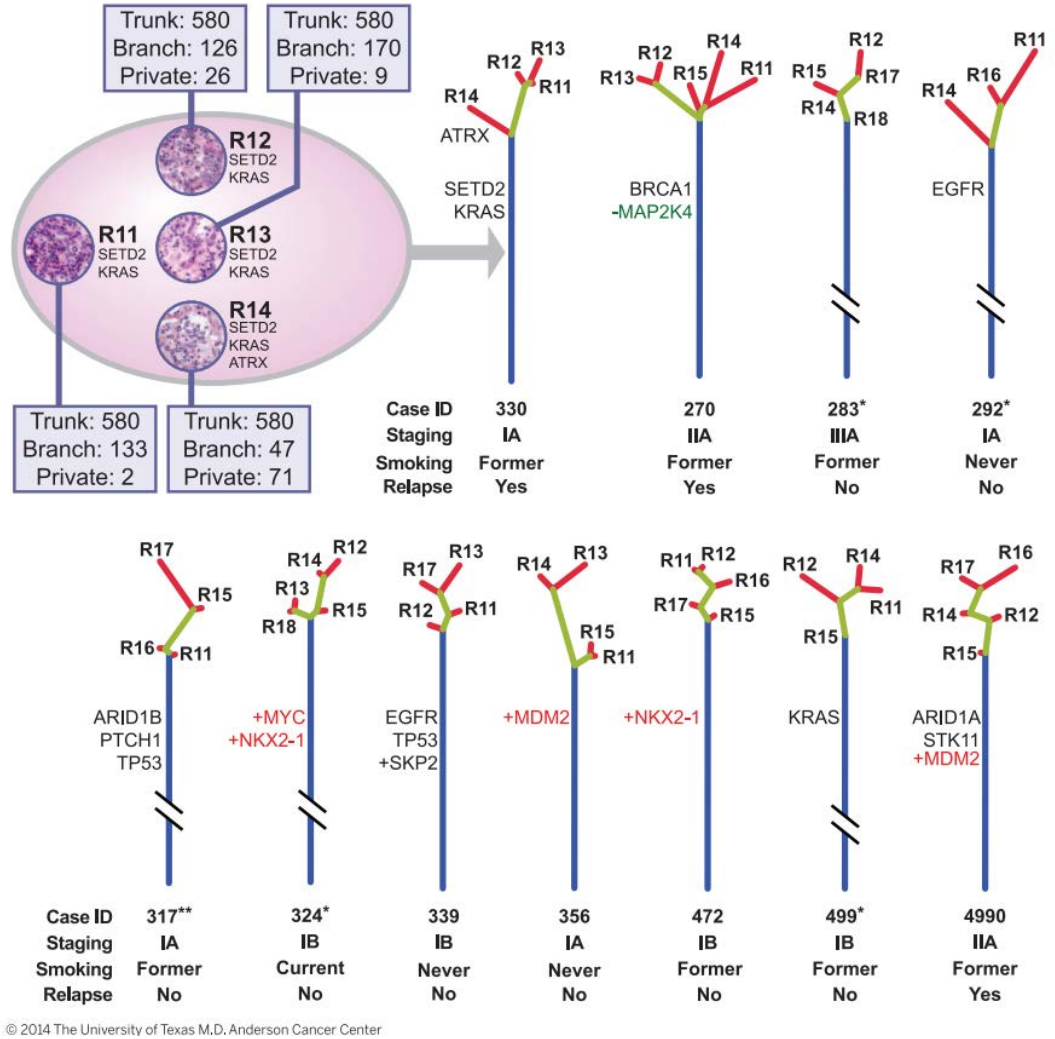


- black swans
- dislocations
- tipping points
- irreversible cascades

- phase shifts
- perturbations
- inflection points
- unintended consequences

- critical thresholds
- bifurcations
- trigger points

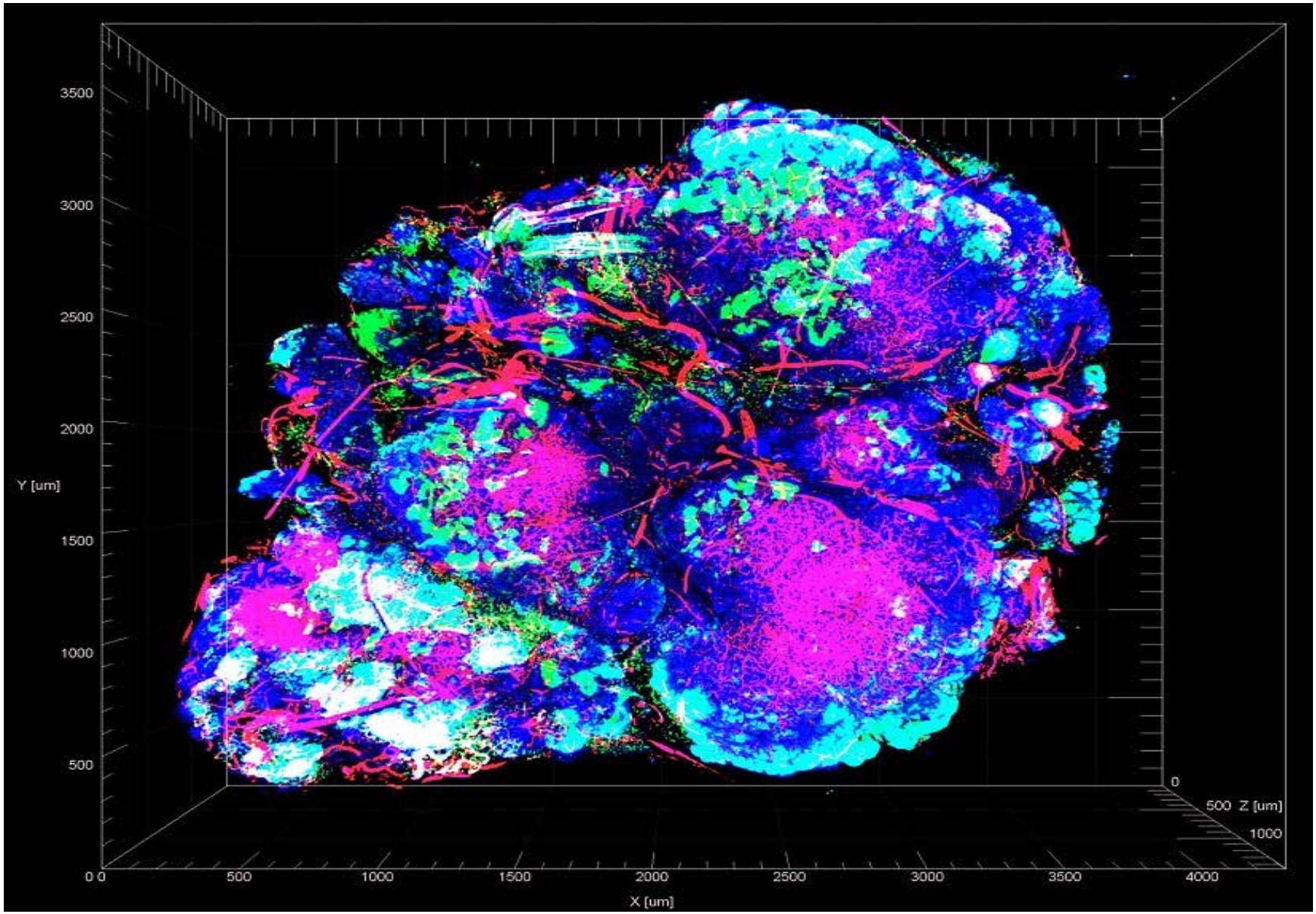
Phylogenetics Profiles of Intratumoral Clonal Heterogeneity in 11 Lung Cancers:



DIFFERENT CLONES

- **Trunk (Blue)**
- **Branch (Green)**
- **Private (Red)**

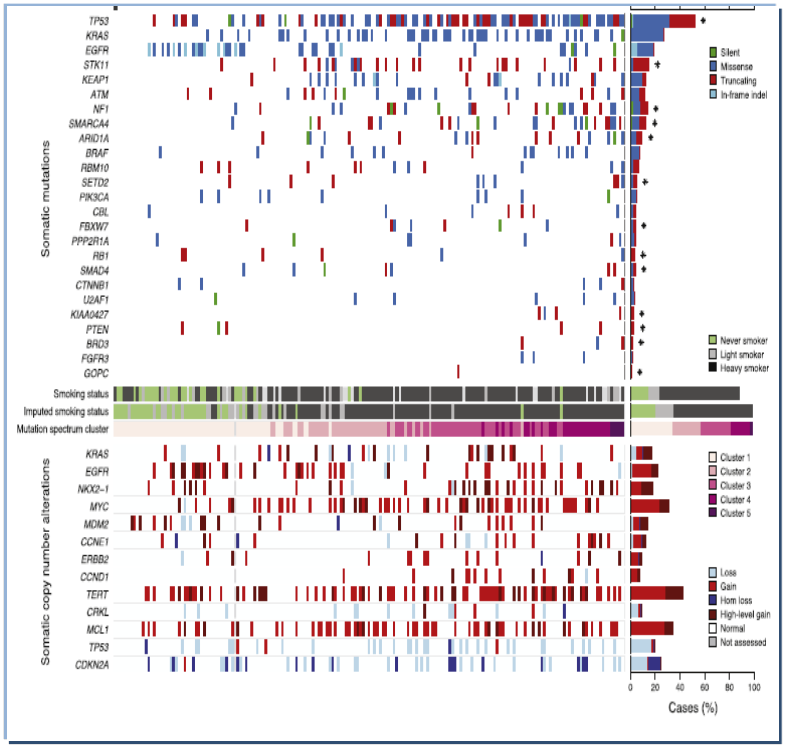
Mapping Tumor Heterogeneity



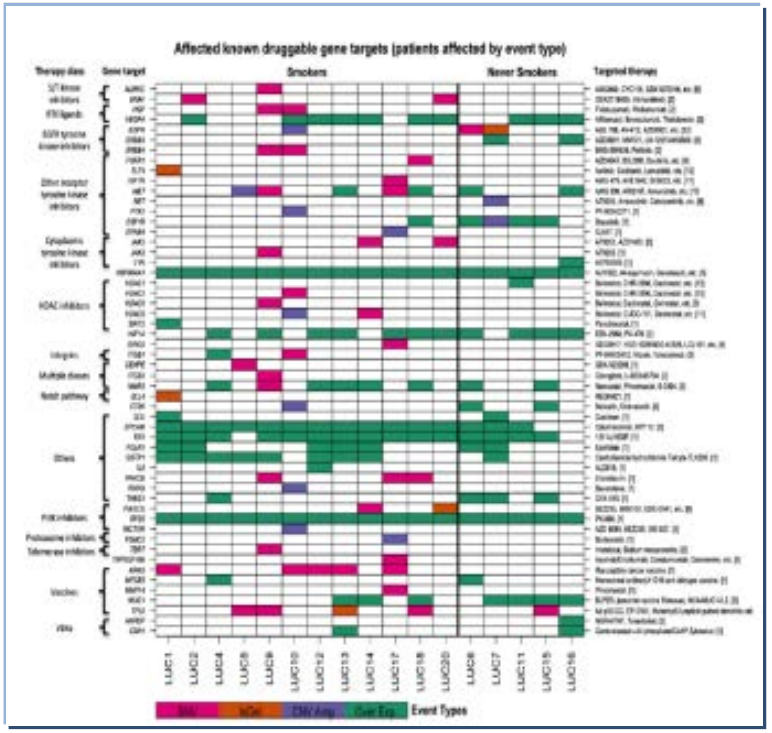
Tumor Cell Heterogeneity: The Greatest Obstacle to Curative Cancer Therapy

Landscape of The Extravagant Genomic Alterations in lung Cancer

Each column is a separate cancer



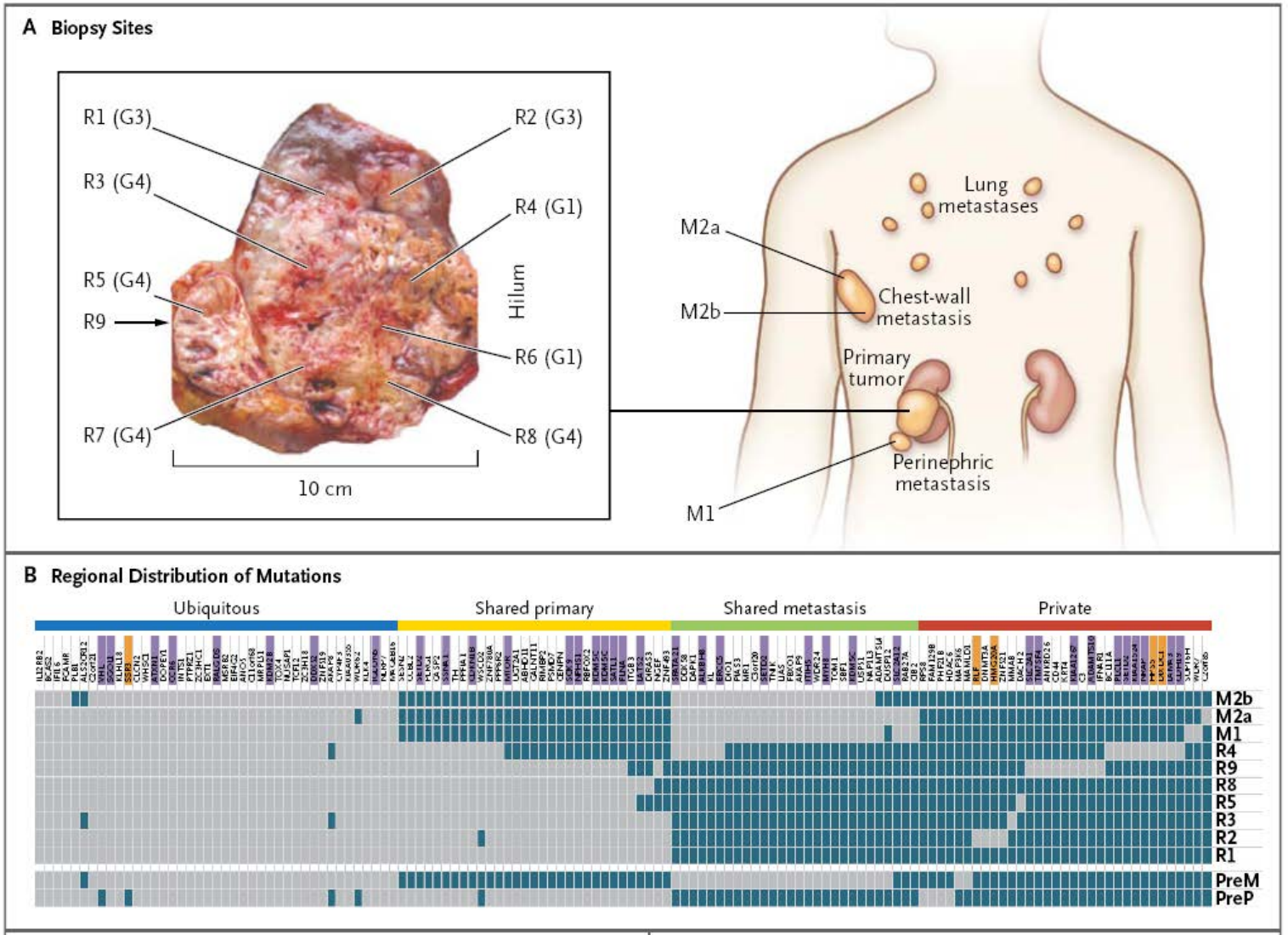
Mutations in Individual Non-small Cell Lung Cancer



Drug Targets in Individual Non-Small Cell Lung Cancers

- "Malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations (such as epigenomic changes)
- Disturbing implications for therapeutic 'cure' and development of new Rx

Intra-tumoral Genetic Heterogeneity: Multiple Regions of Primary Kidney Cancer and 3 Different Metastases



Malignant Snowflakes

Review

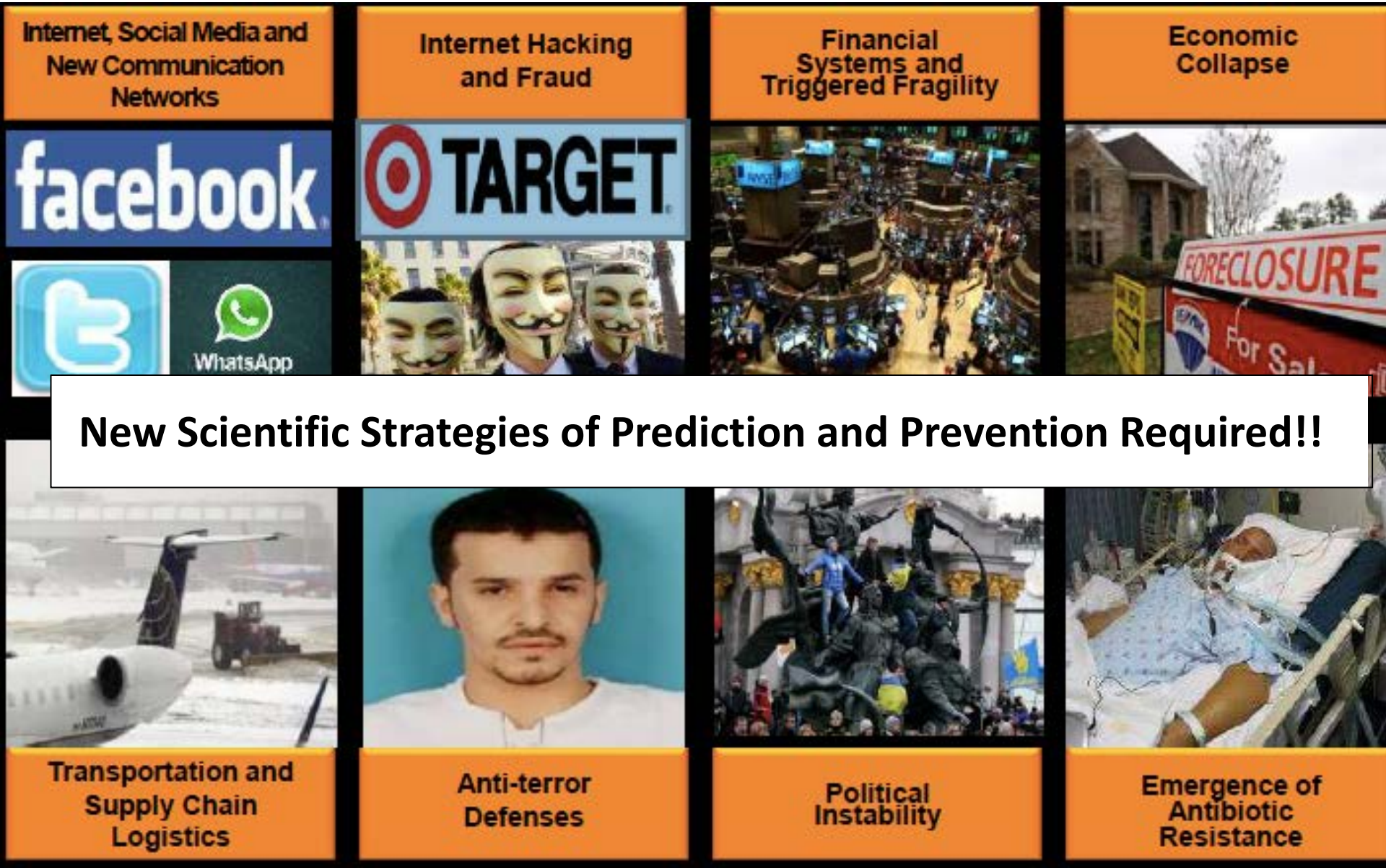
How many molecular subtypes? Implications of the unique tumor principle in personalized medicine

Shuji Ogino, Charles S Fuchs & Edward Giovannucci

Pages 621-628 | Published online: 09 Jan 2014

Essentially, each tumor possesses its own unique characteristics in terms of molecular make-up, tumor microenvironment and interactomes within and between neoplastic and host cells. Starting from the

Complex Systems in a Complex World



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