ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
MARCH 4 & 6, 2014

WEEK 8 LECTURE 2:
CANCER AS A COMPLEX ADAPTIVE SYSTEM

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Central Themes in Cancer Biology

- cancer as multi-dimensional ecosystem involving complex interactions between cancer cells and host systems
- genotoxic insult(s), mutations and genomic instability (drivers)
- 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

Central Themes in Cancer Biology

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CANCER:
A COMPLEX ADAPTIVE SYSTEM

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 Versus Complex Systems

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

Ageing Support Structure

Wrong Glide Path

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 an new state with very different properties (emergence)

Anthropogenic Complex Adaptive Systems: Emergence, Unanticipated Consequences and Cascading Shift to New 'State Space'

Internet, Social Media and New Communication Networks

Internet Hacking and Fraud

Financial Systems and Triggered Fragility

Economic Collapse

Transportation and Supply Chain Logistics

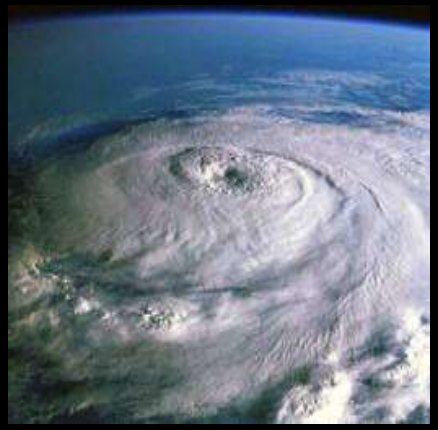
Anti-terror Defenses

Political Instability

Emergence of Antibiotic Resistance

The Ubiquity of Complex Adaptive Systems in Nature: High Degrees of Design Freedom

Earth Systems



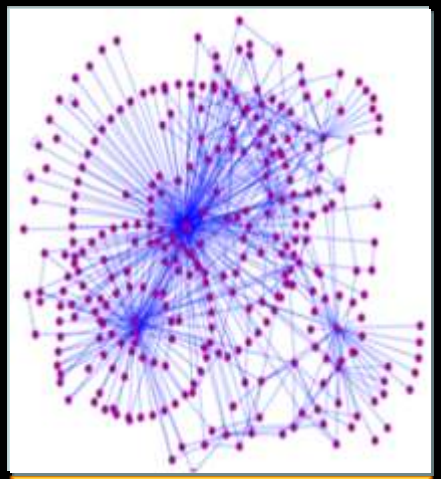
Eco-Systems

Food Webs and Predator: Prey Relationships

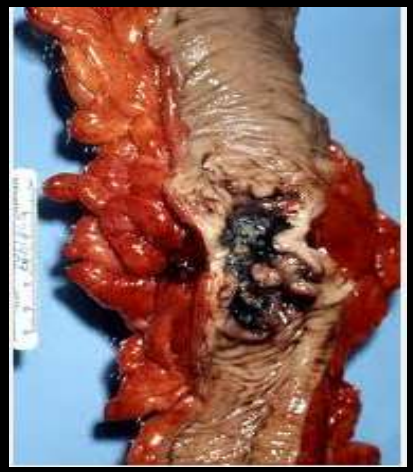
Coordinated Community Behavior

Host-Pathogen Interactions

Physiological Regulatory Networks



Genome Regulatory Networks



Signaling Network Dysregulation in Disease

Cancer as a Complex Adaptive System With Emergent Properties

- the full spectrum of a tumor's behavior in any individual and the accompanying clinical risk cannot be predicted from knowledge of the properties of the multiple components involved in tumor initiation and progression
  - environment and nature of the initiating genotoxic insult
  - tumor progression
  - metastasis
  - host responses
  - treatment outcomes

Cancer as a Complex Adaptive System With Emergent Properties

- the full spectrum of a tumor's behavior and the accompanying clinical risk cannot be predicted from knowledge of the properties of the multiple components involved in tumor progression

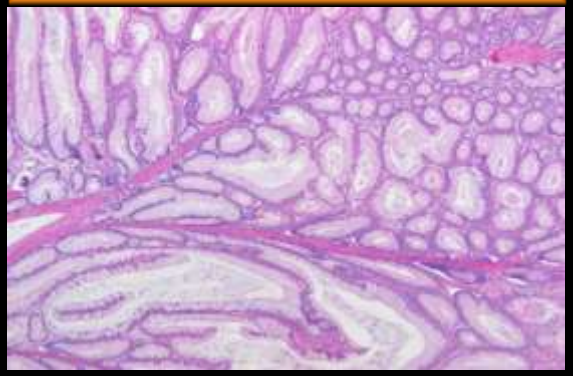
- unknown but likely different patterns of environmental exposure and genotoxic insult as triggers of tumor initiation
  - different individuals
  - different tissues

Cancer as a Complex Adaptive System With Emergent Properties

- emergence of multiple tumor cell clones with different properties in the primary tumor and metastases in same patient and in different patients
- patterns of host cell responses to the primary tumor, metastases in different body organs plus differences between patients
- impact of different treatment regimens on the tumor and host components

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

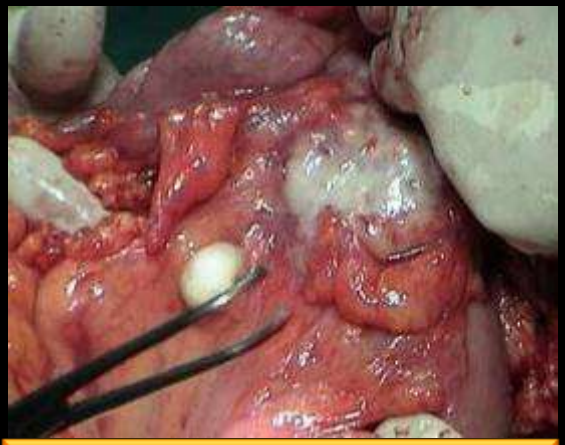
Escape From Controls for Normal Tissue Architecture



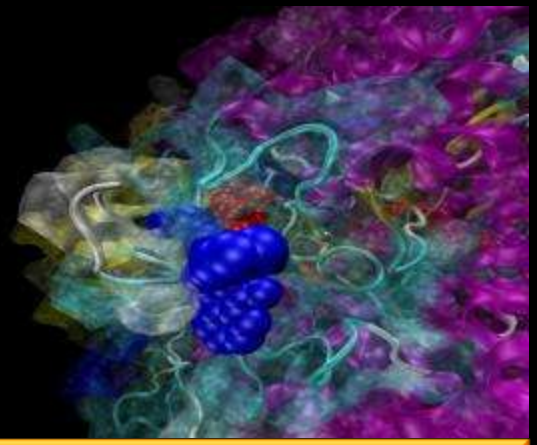
Genome Instability and Emergence of Clonal Variants

Evasion of Detection/Destruction by Host Immune System

Use of Host Systems by the Tumor to Promote Progression

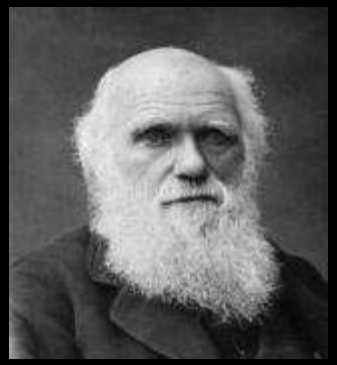


Invasion and Metastasis



Emergence of Drug-Resistant Clones

Microbe: Host Interactions
A Complex Ecosystem and Evolutionary Co-dynamics



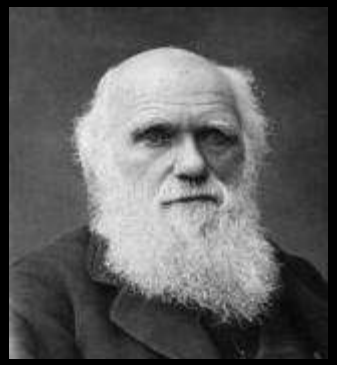
Darwinian Evolution

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

"The future of humanity and microbes will likely evolve as episodes of our wits versus their genes"

Dr. Joshua Lederberg,
Nobel Laureate
Science (2000) 6, 427-30

Microbe: Host Interactions
A Complex Ecosystem and Evolutionary Co-dynamics



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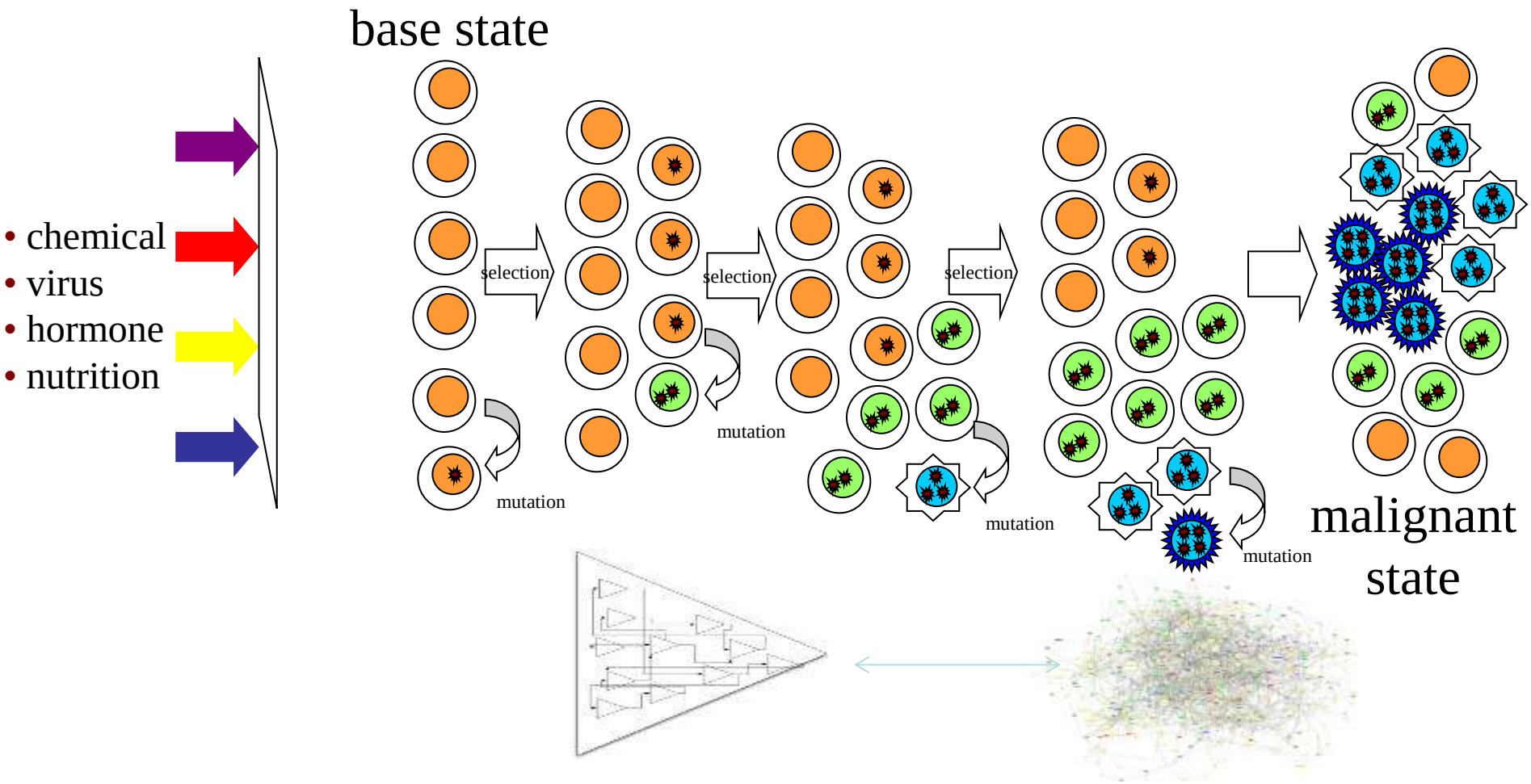
DITTO CANCER

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

Dynamic Heterogeneity

Emergence of Tumor Cell Clones with Different Genotypes and Phenotypes During Tumor Progression



Adapted from A. Barker and K. Buetow

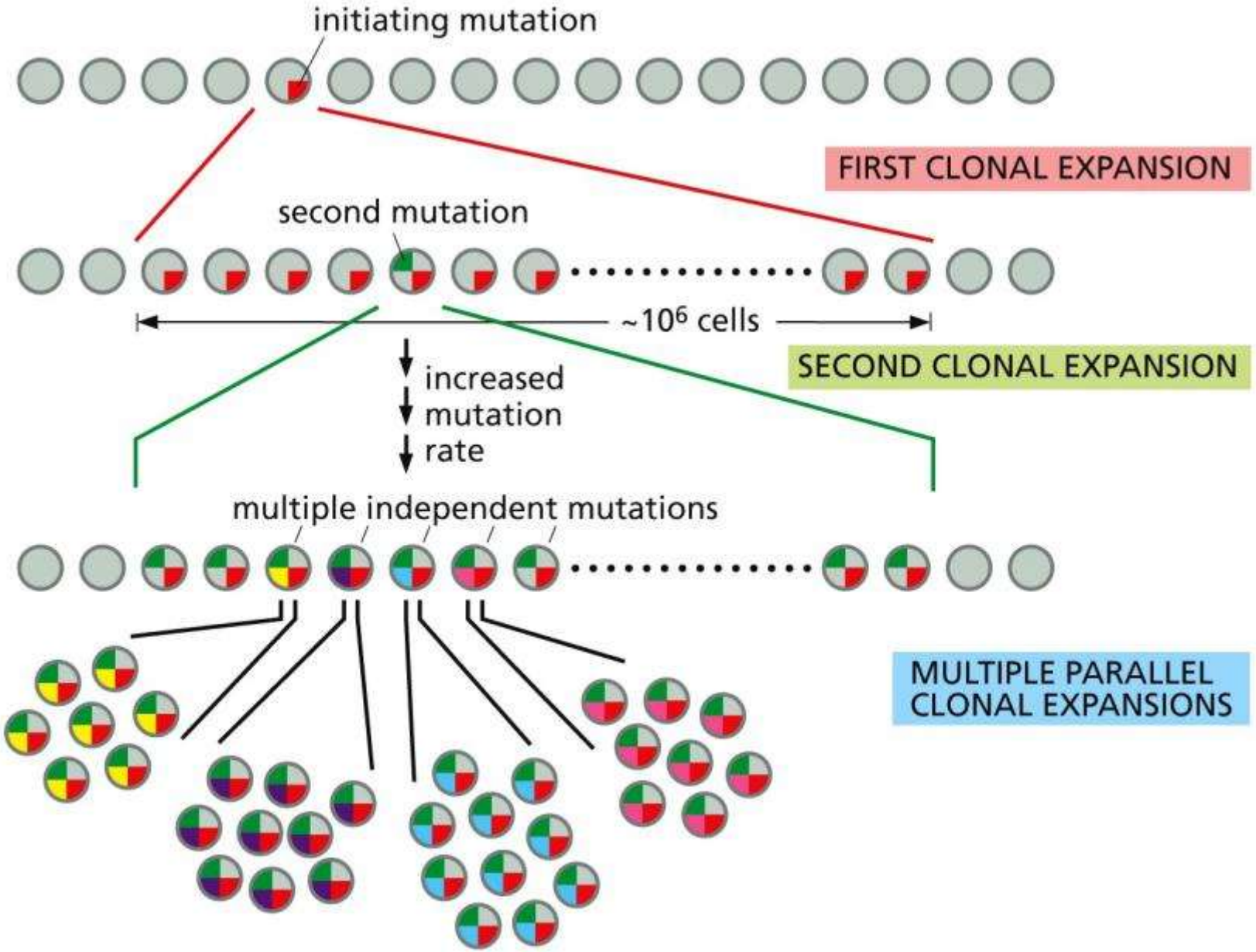
The Quest for Effective Cancer Treatments: Fundamental Challenges

- lengthy time for full progression to metastatic disease after tumor initiation
- general lack of presymptomatic diagnostic methods
- 1 cm^3 lesion (early detection threshold) = 10^9 tumor cells
  - typically asymptomatic at this stage
- highly heterogenous clonal composition even at initial detection

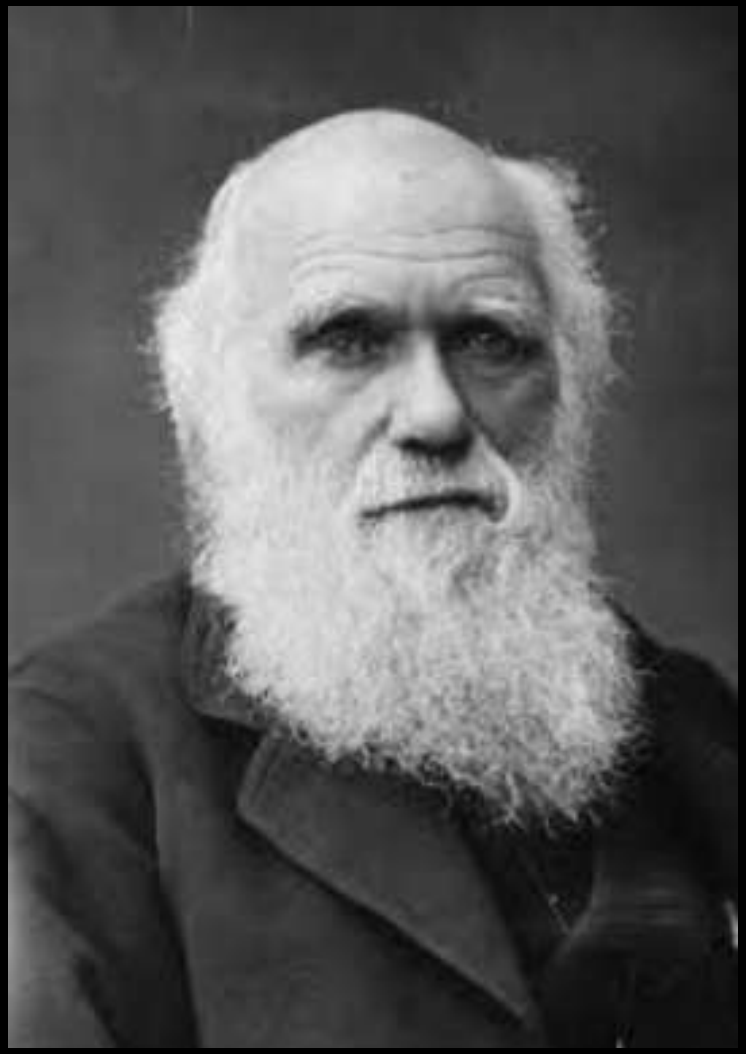
The Highly Heterogenous Clonal Composition of Cancers Even At Initial Detection

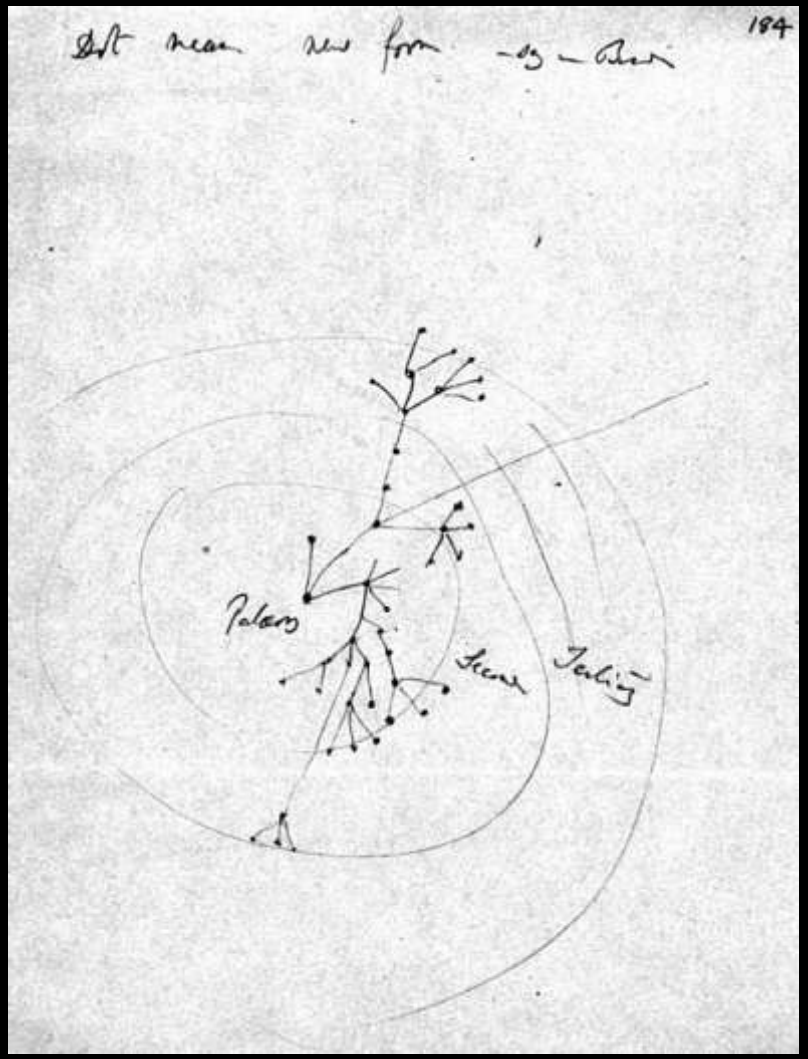
- 1 cm^3 lesion (early detection threshold) = 10^9 tumor cells
  - typically asymptomatic at this stage
- mutation frequency of 10^{-2} /10^{-3} per tumor cell generation= prospect of 10^7 to 10^6 potential variant clones present at first diagnosis
- clones present at initial detection reflect a long (years) interaction between tumor and host and a dynamic process of clonal elimination and emergence of new clones
- ‘fitness’ of surviving clones reflects their evasion of destruction by host immune system and escape from tissue-specific growth controls

Clonal Expansion and Phenotypic Diversification (Heterogeneity) with Tumor Progression



“Dot Means a New Form”
Charles Darwin Sketch of Speciation (Early 1850s)





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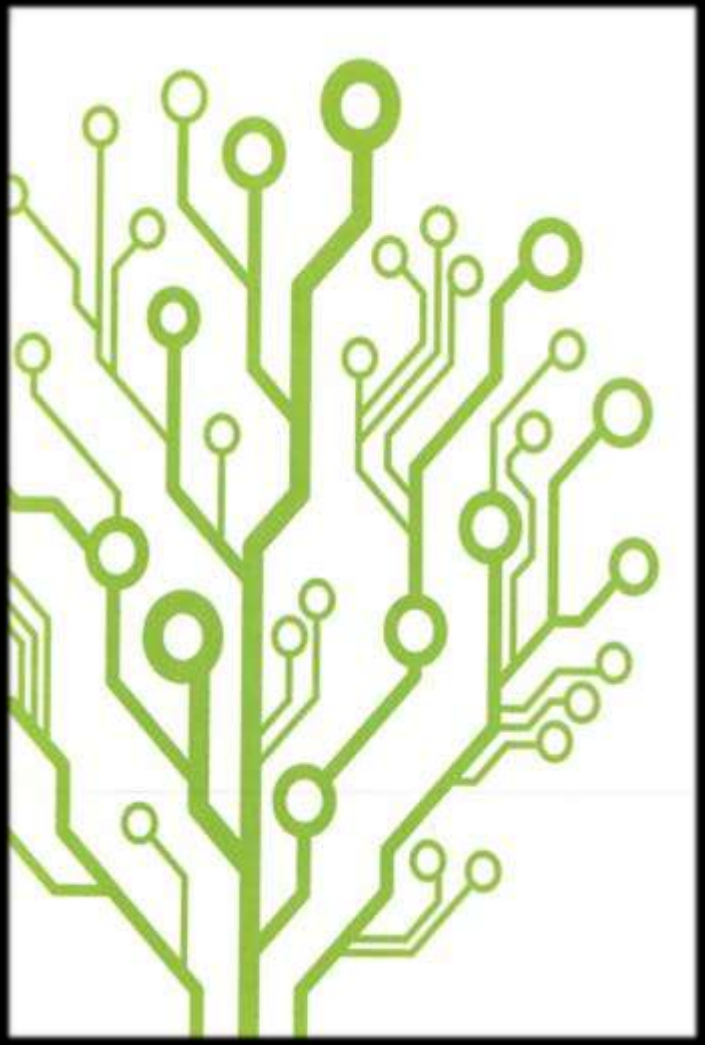
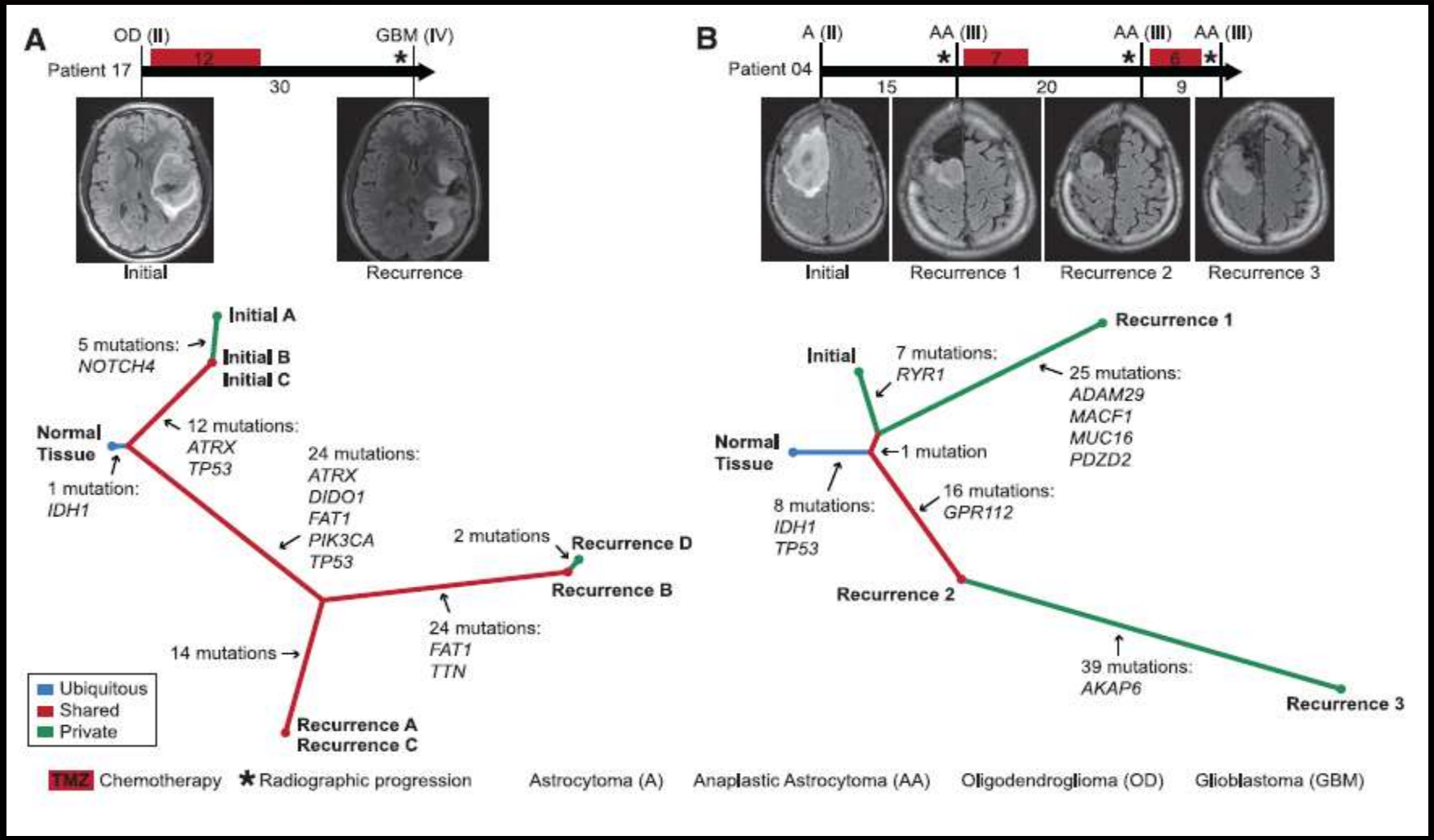
Mapping the Dynamics of Clonal Evolution in Progression of Malignant Tumors: Clonal Branching



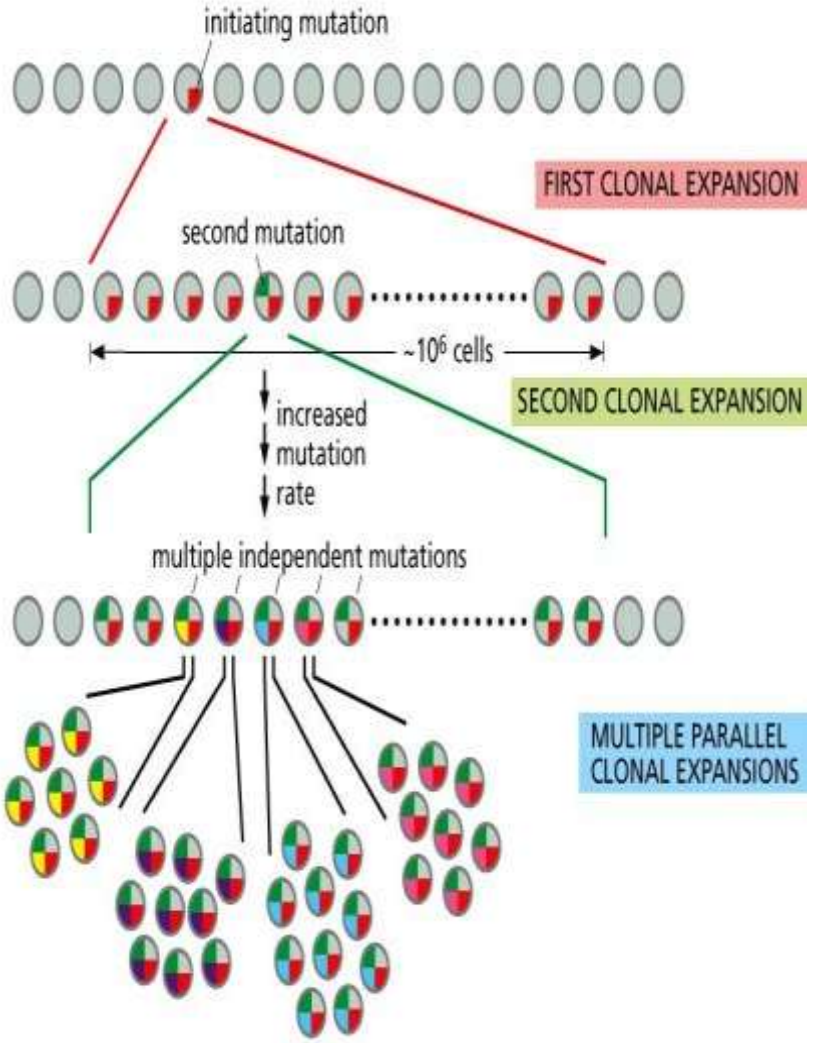
- timing of mutational events
  - ‘early events’ present in clones in both primary tumor and metastases
  - private mutations (unique to individual patients or individual metastatic lesions in same patient) likely have occurred late(r) in progression

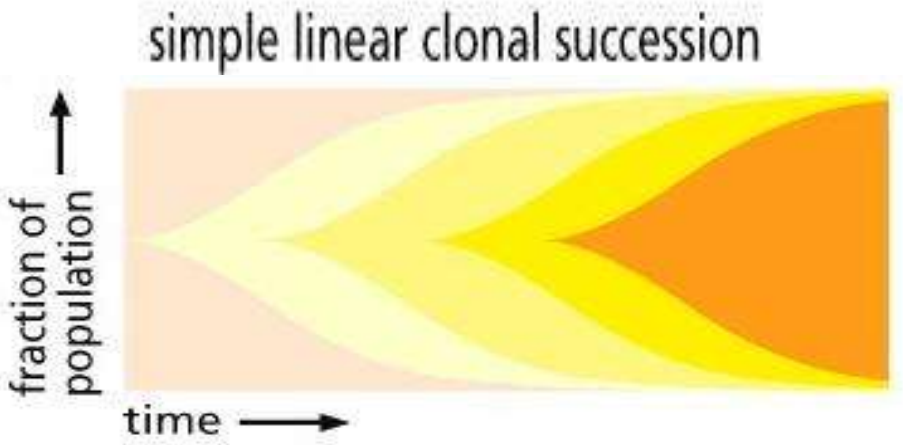
Phylogenetic Tree of Clonal Branching in Two Glioma Patients

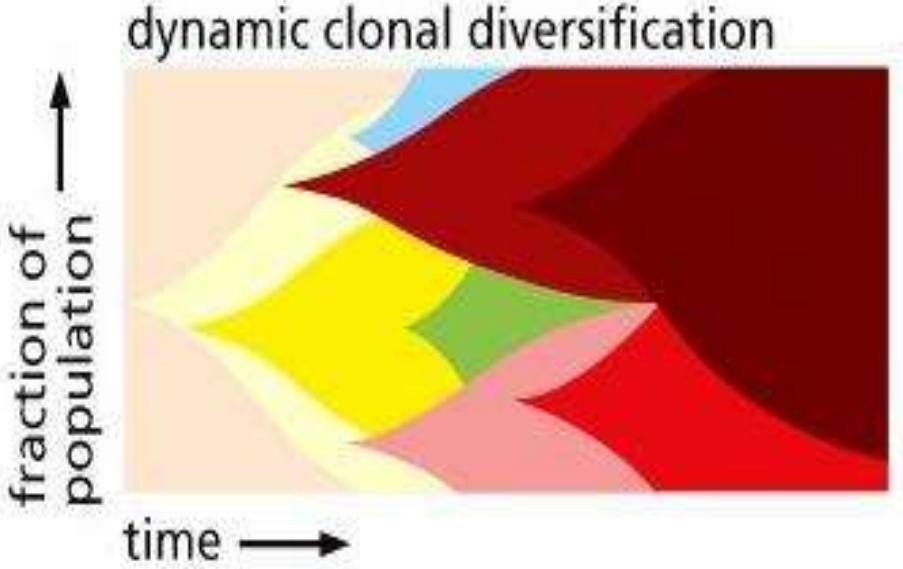


From: B. E. Johnson et al. (2014) Science 343, 189
red= shared between initial and recurrent lesions;
green= not shared between initial and recurrent lesions

Branched Evolution and Phenotypic Diversification of Tumor Clones and Subclones



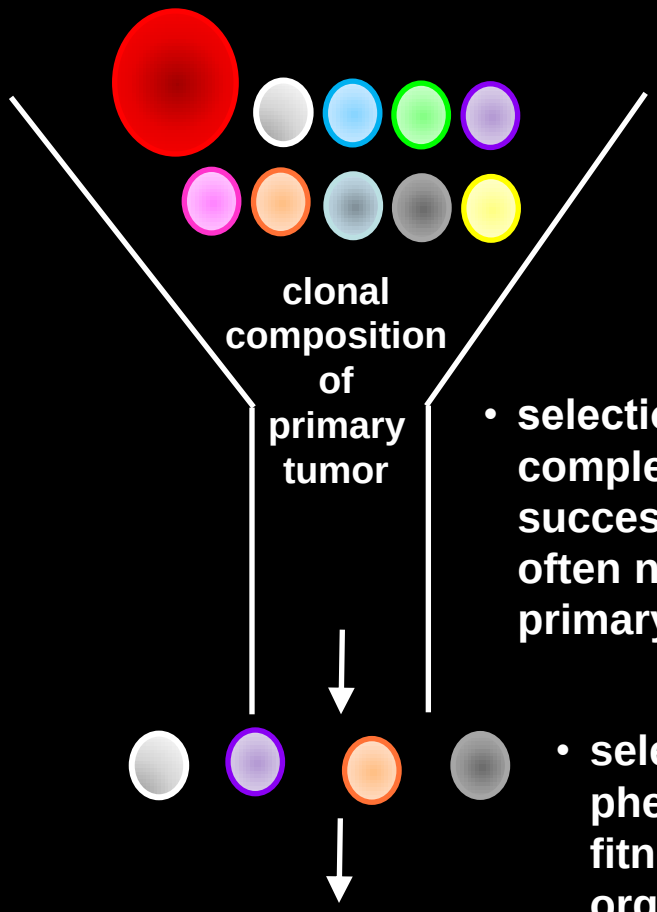




The Clonal Dynamics of Malignant Tumors

- frequent finding of presence of a dominant clone (>50% tumor cells) and multiple subclones at minor frequencies in the primary tumor
- clonal diversity at metastatic sites typically lower than in the primary tumor
  - analogous to an evolutionary bottleneck
  - clonal selection by the ‘fitness’ requirements needed to achieve all steps in the metastatic cascade

The Selection Bottleneck (Selection Sweep) in Metastatic Dissemination



- dominant clone and spectrum of lower frequency clones
- zonal localization of individual clones

- selection bottleneck for 'fitness' to complete multiple steps needed to successfully metastasize (note: often not the dominant clone the primary tumor)

- selection for clonal phenotypes with preferred fitness for growth in specific organs?

- further clonal diversification within individual metastases

Cancer as a Complex Adaptive System

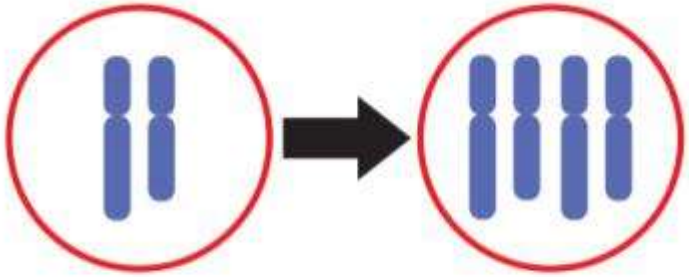
- major gaps in knowledge about the triggers of ‘emergence’ of increasingly dangerous tumor cell phenotypes during cancer progression
  - immune evasion, metastasis, Rx resistance

Genome Instability

- progressive accumulation of mutations and other chromosomal abnormalities
- do major shifts in tumor aggressiveness depend on ‘macromutations’ rather than gradual accumulation of mutations?

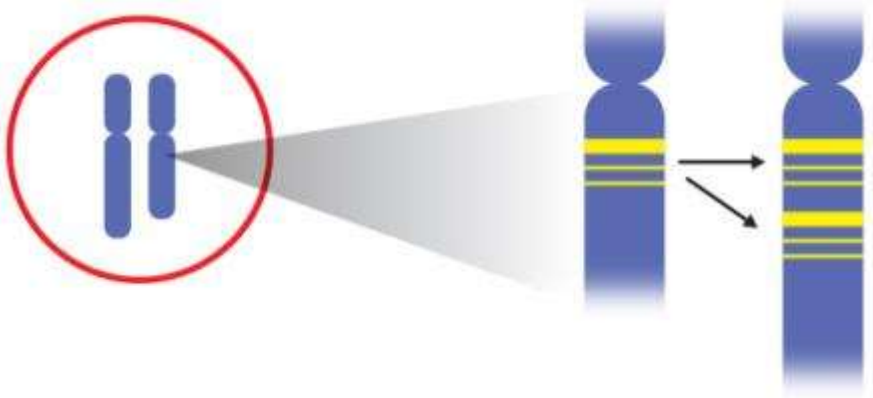
Macromutation in Cancer

Genome Doubling



- faulty cell division

Copy Number Variations



- duplication of chromosome regions (shown)
- deletions and translocations (not shown)

Macromutations in Cancer

- gain and loss of entire chromosomes
- genome doubling due to faulty cell division
- indels (insertions/deletions): copy number variants
  - sections of chromosomes duplicated, deleted or moved (translocated)
- major structural changes but must still be compatible with cell survival
- potential driver for major changes in tumor aggressiveness and clinical risk?
  - metastasis?, recurrence?

Macromutations in Cancer

- genome doubling as a ‘buffer’ to tolerate macromutations
- back up copy of every chromosome
- “healthy” (unaltered) chromosome sustains expression ‘housekeeping genes’
- “aberrant” chromosome drives new behavior created by altered molecular signaling arising from the macromutation
- copy number variants can affect the function of a large set of genes

What is the unit of selection in cancer progression?

Stem Cells and the Growth Dynamics of Normal Tissues

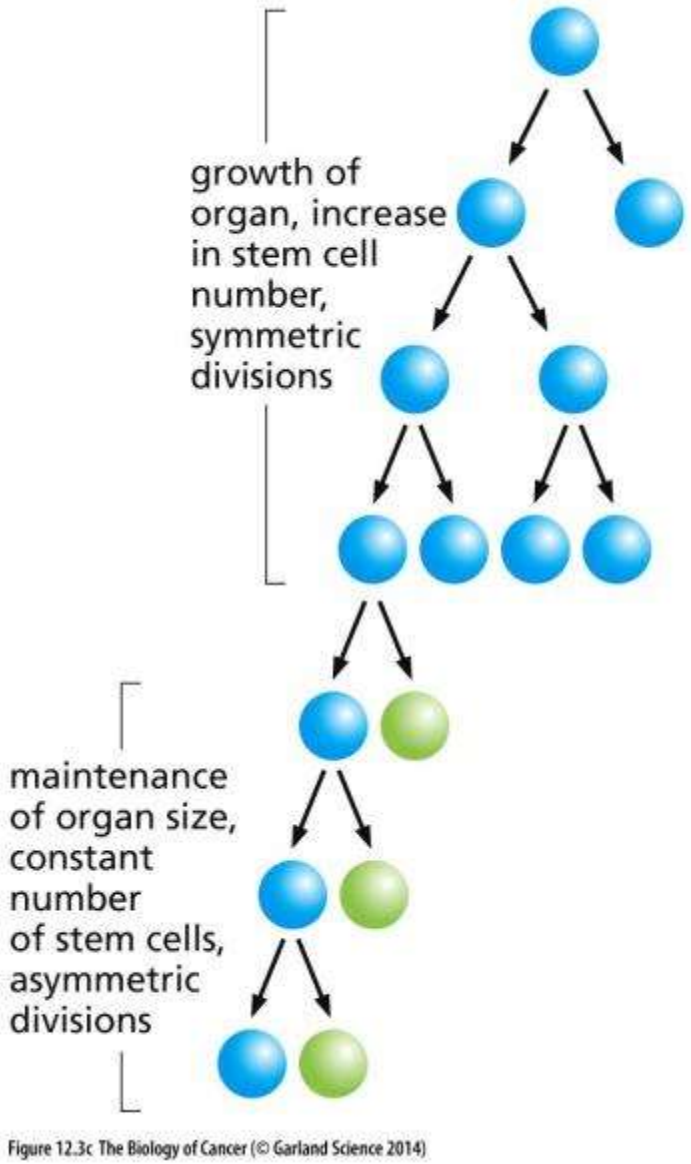
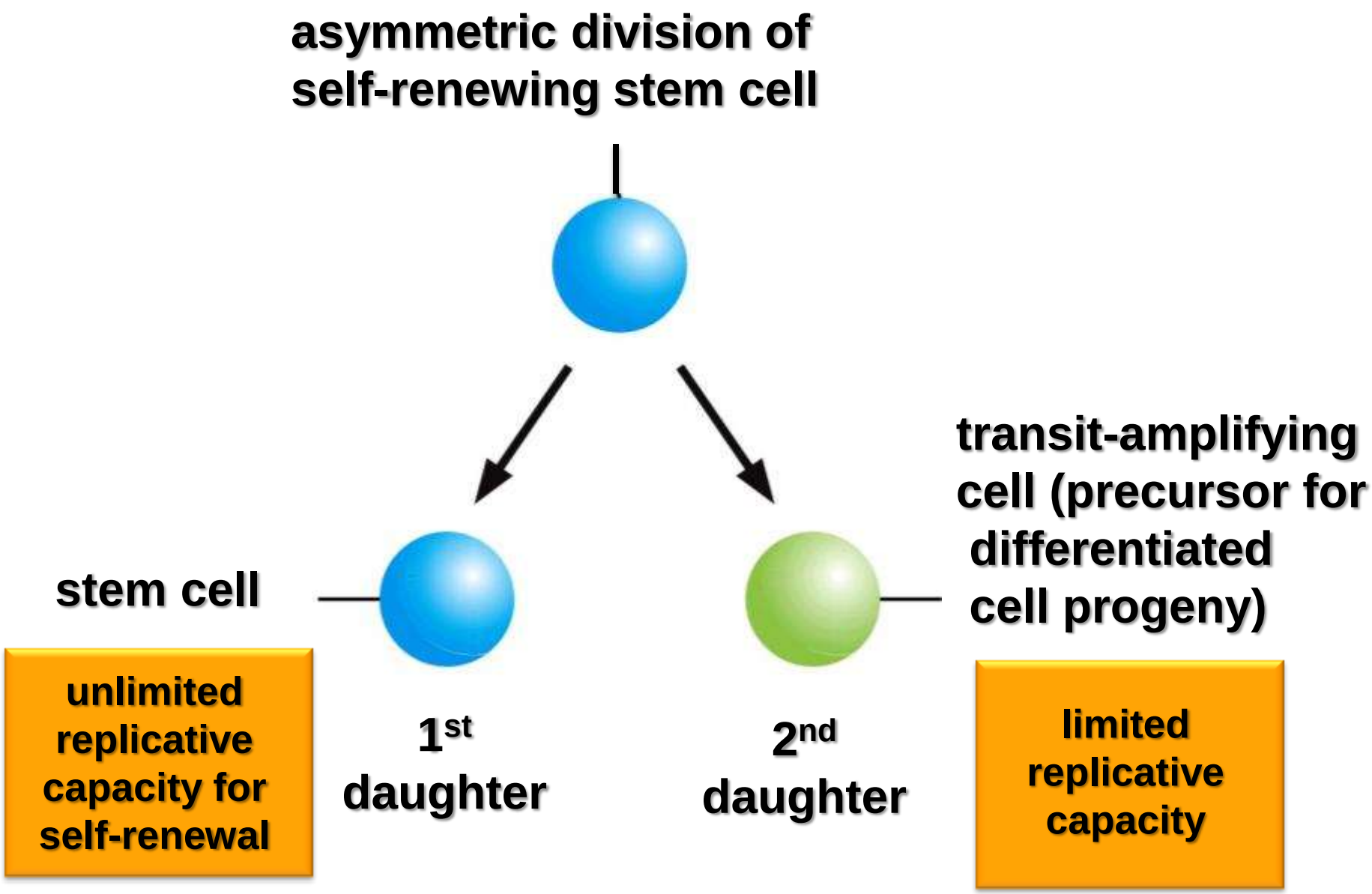
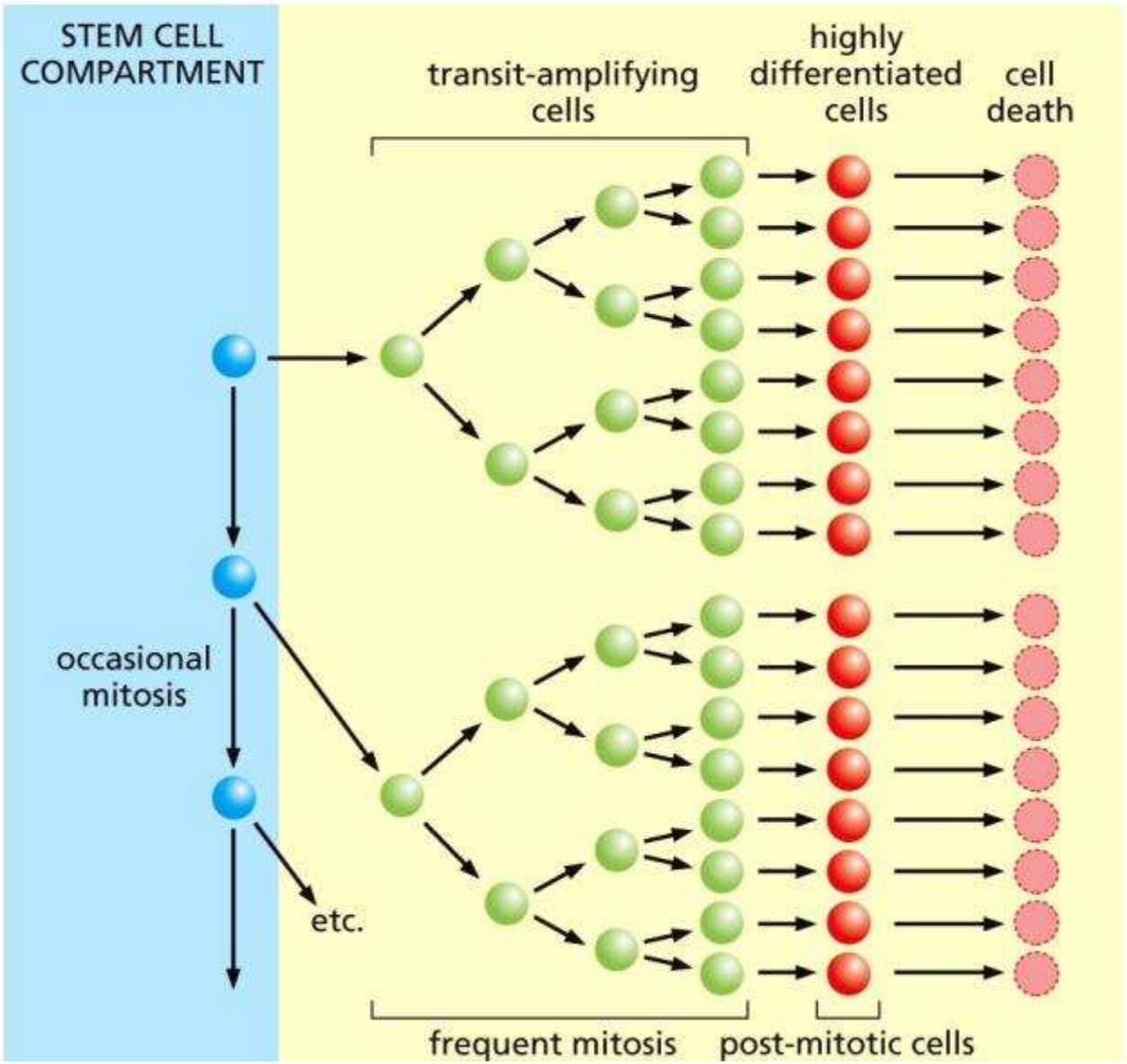


Figure 12.3c The Biology of Cancer (© Garland Science 2014)

- **embryogenesis**
- **organ regeneration (limited in mammals)**

- **post-natal cell turnover in different body tissues/ organs**
- **tissue repair**


asymmetric division of self-renewing stem cell
stem cell
transit-amplifying cell (precursor for differentiated cell progeny)
unlimited replicative capacity for self-renewal
1st daughter
2nd daughter
limited replicative capacity


STEM CELL COMPARTMENT
transit-amplifying cells
highly differentiated cells
cell death
occasional mitosis
etc.
frequent mitosis
post-mitotic cells

Replicative Self-Renewal

normal tissues

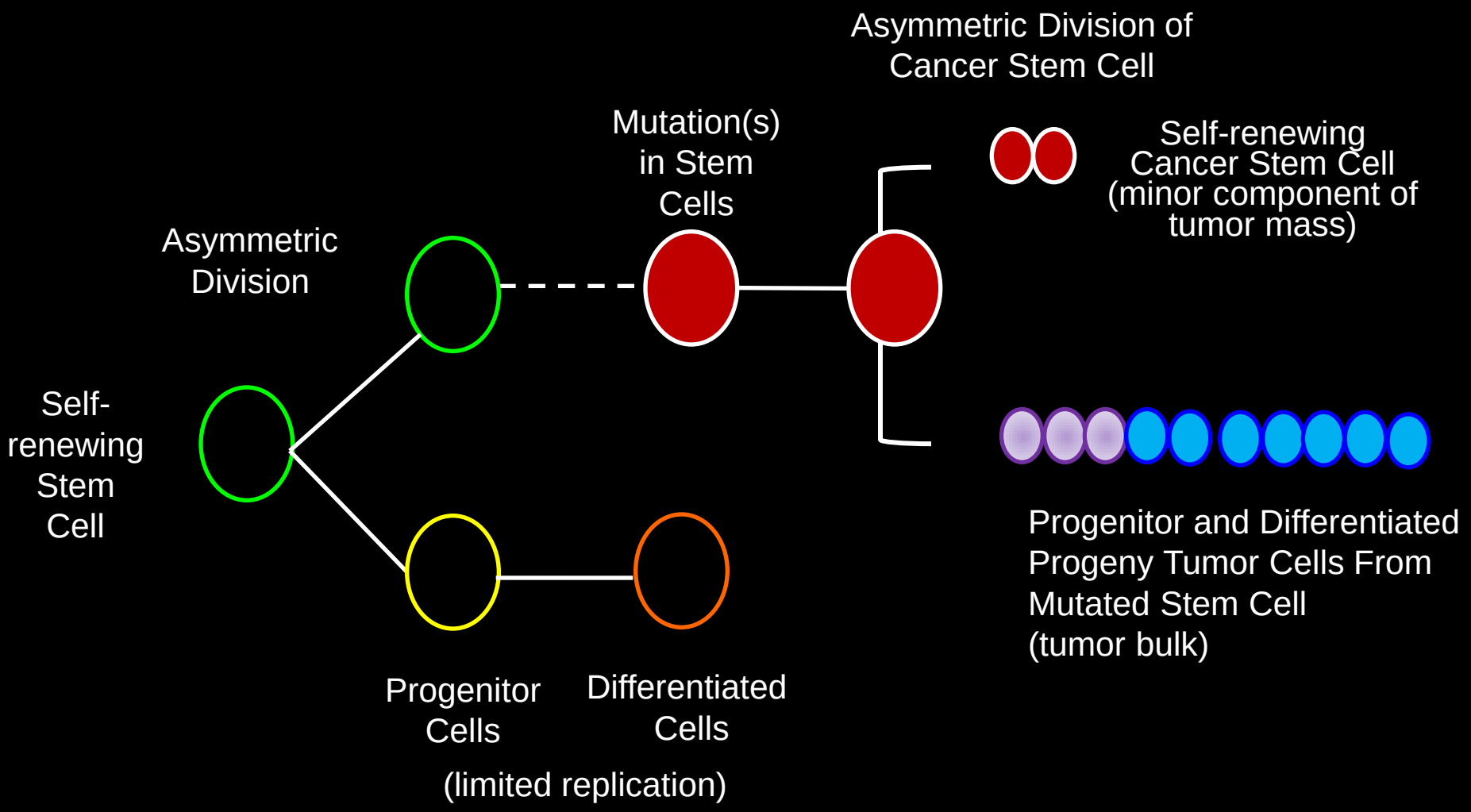
- **stem cells: unlimited but highly controlled division potential**
- **asymmetric division sustains stem cell population and pool of progenitor and differentiation committed cells with limited number of cell divisions (terminal differentiation)**

Replicative Self-Renewal

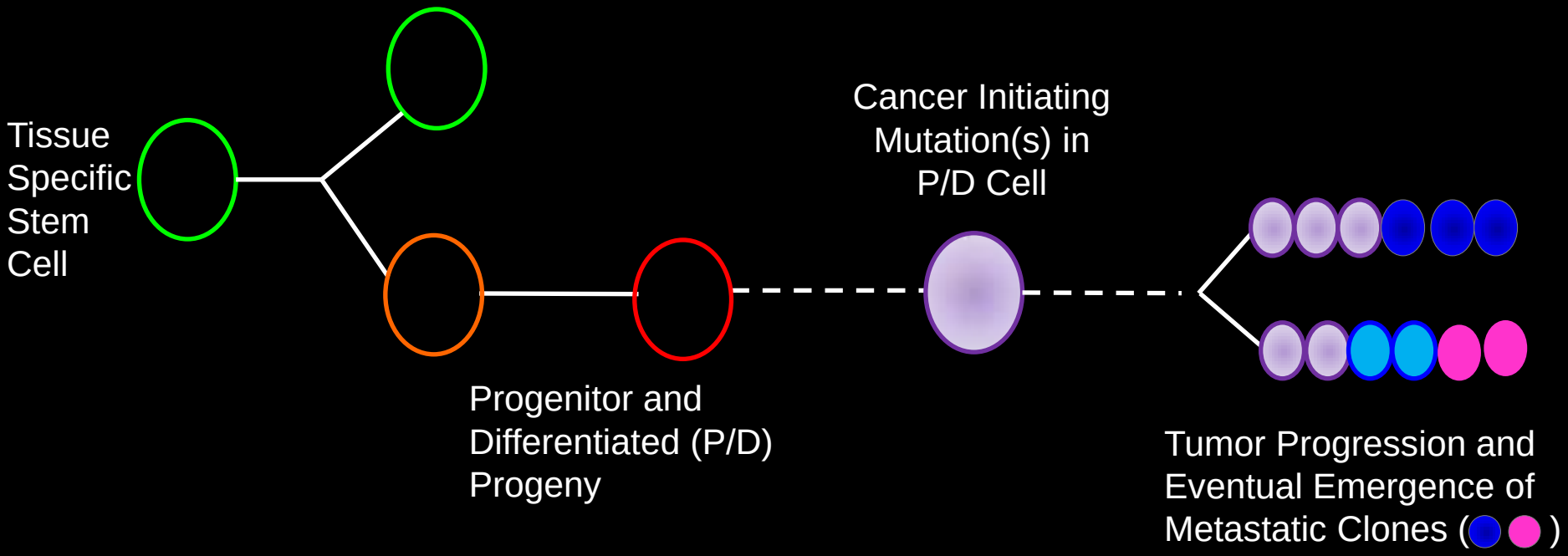
cancer

- loss of control circuits that limit the number of cell divisions as hallmark feature of cancer
- does every cancer cell have potential to generate clones with metastatic ability and unlimited replicative capacity or are only a specific population of stem-like cancer cells (CSCs) endowed with this capability?

Cancer Originates and is Maintained by Mutations in Tissue Stem Cells

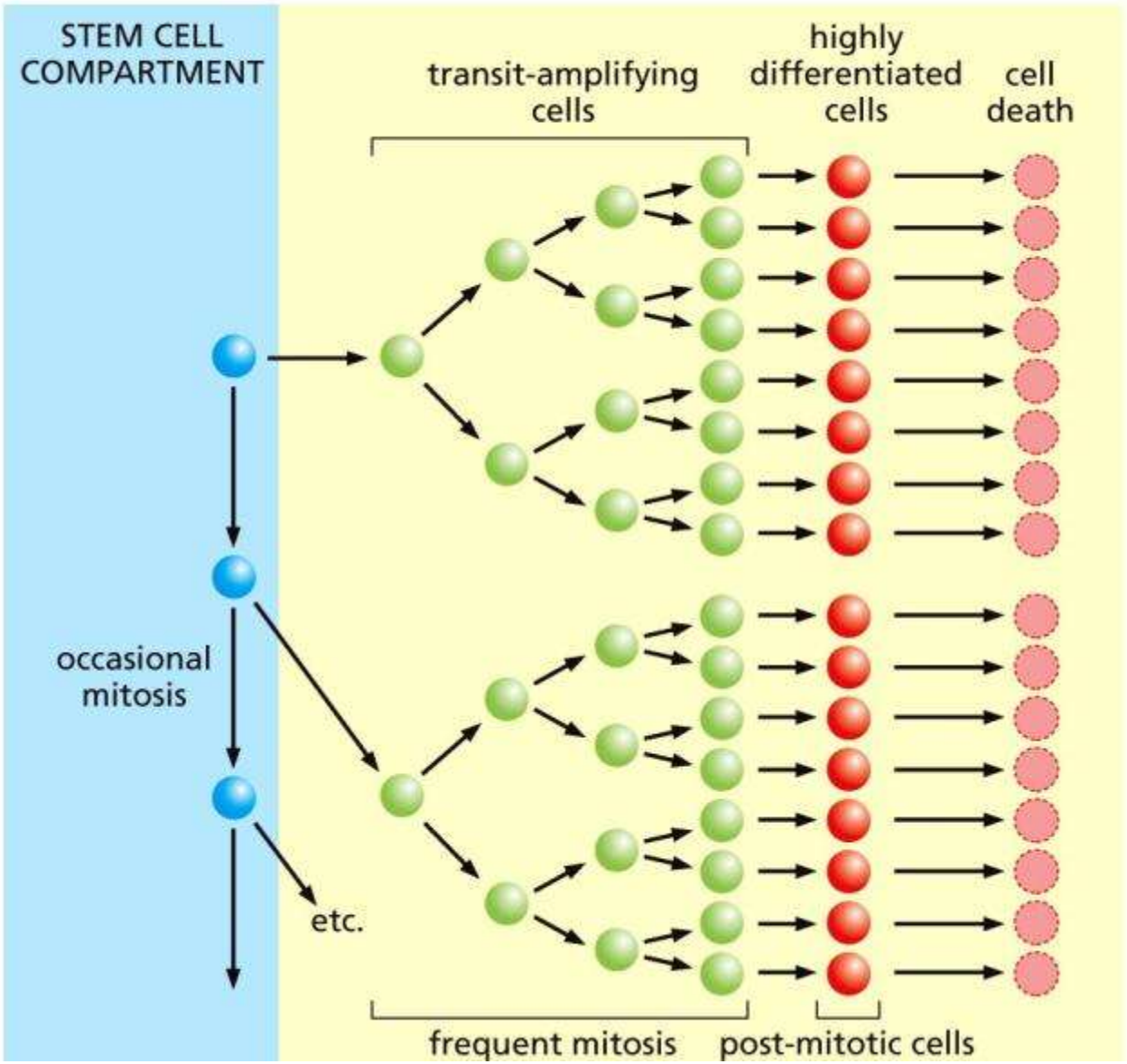


All Initiated Cells Have Potential for Unchecked Replication and Progression to Malignancy



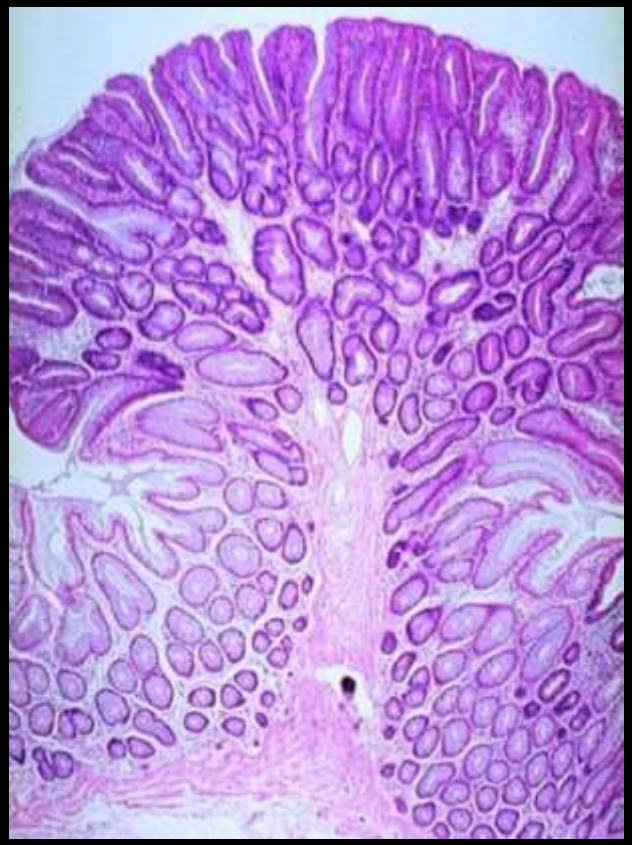
The Cell-of-Origin in Cancer

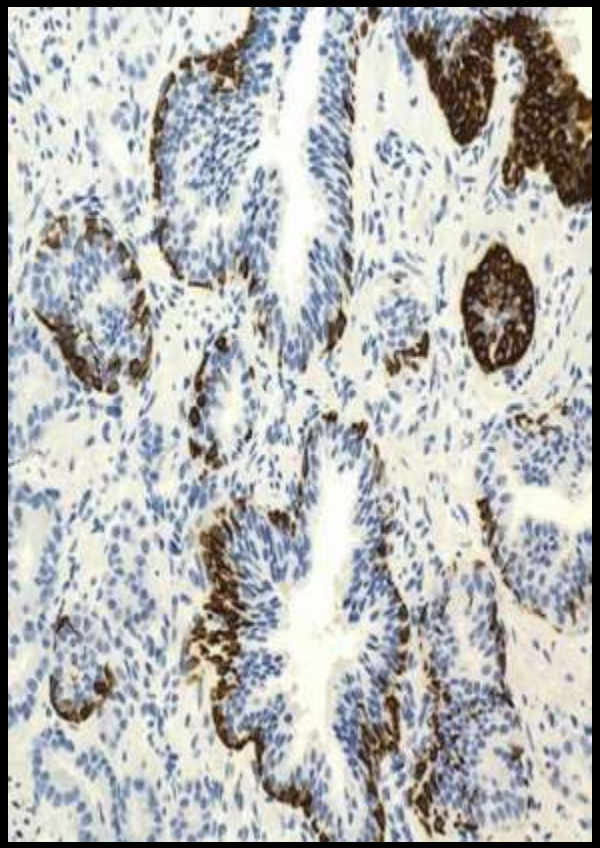
- balance of evidence shifting to cancer stem cell (CSC) model

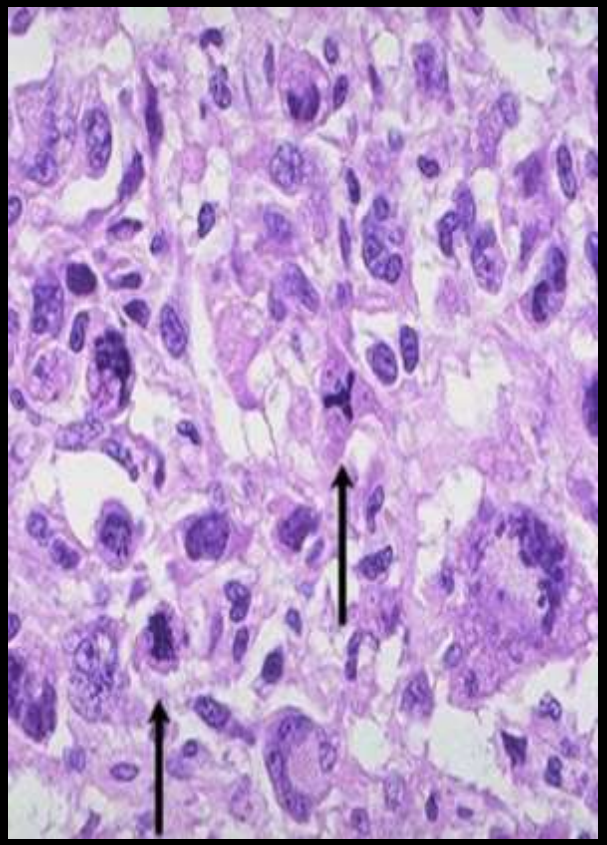

STEM CELL COMPARTMENT
transit-amplifying cells
highly differentiated cells
cell death
occasional mitosis
etc.
frequent mitosis
post-mitotic cells

Expression of ‘Differentiated Features’ in Tumors

Benign Tumors	Malignant Tumors	
	Low Grade/ High Differentiation	High Grade/ Anaplastic Features







CSCs and Therapy

- normal SCs and CSCs appear to exhibit greater radio-and chemo-resistance
  - slower reproductive cycling versus progenitor/differentiated lineages
  - faster DNA repair and suppression of apoptotic pathways
  - higher expression of free radical scavenging pathways to limit damage by reactive oxygen species (ROS)
  - greater hypoxic survival via activation of HIF1α and HIF2α pathways and shift to glycolytic metabolism (versus oxidative phosophorylation via Krebs cycle)

The Dynamics of Self-Renewal, Proliferation and Differentiation in Tumor Progression

- what determines the proportional fractions of self-renewing stem cells and progenitor and differentiated lineages?
  - in different tumor types?
  - in different patients with same tumor subtype?
  - in metastases versus the primary tumor?
  - in response to Rx?

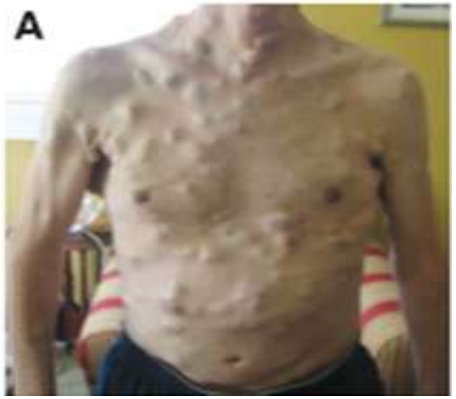
Cancer Stem Cells (CSCs) Markers

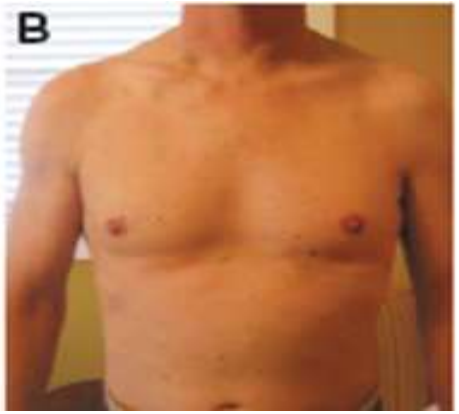
- CD 133+
  - glioma, colon cancer
- CD444, CD24
  - breast cancer
- ALDH+
  - pancreatic cancer cells
- suggested role for activation of Hedgehog and Hippo pathways

Why Understanding the Altered Patterns of Molecular Signaling Networks and Clonal Diversification in Different Cancers and Cancer Subtypes is Fundamental to More Rational Approaches to Diagnosis and Treatment

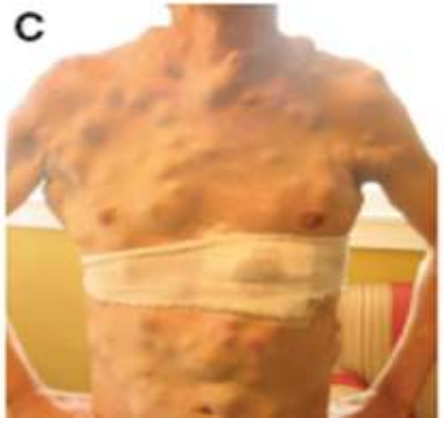
Emergence of Drug Resistance to Targeted Therapy in Melanoma

Initial Rx-Response to Targeted Rx



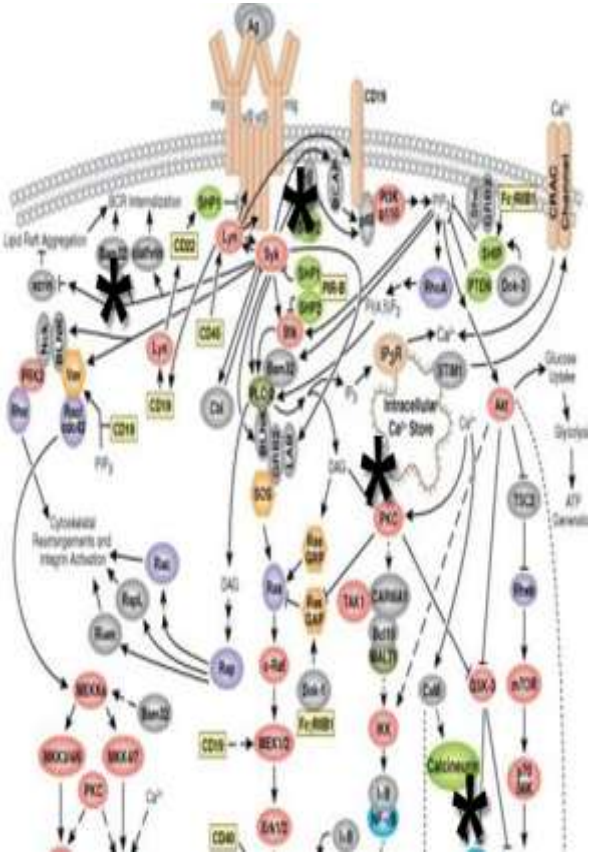


Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)

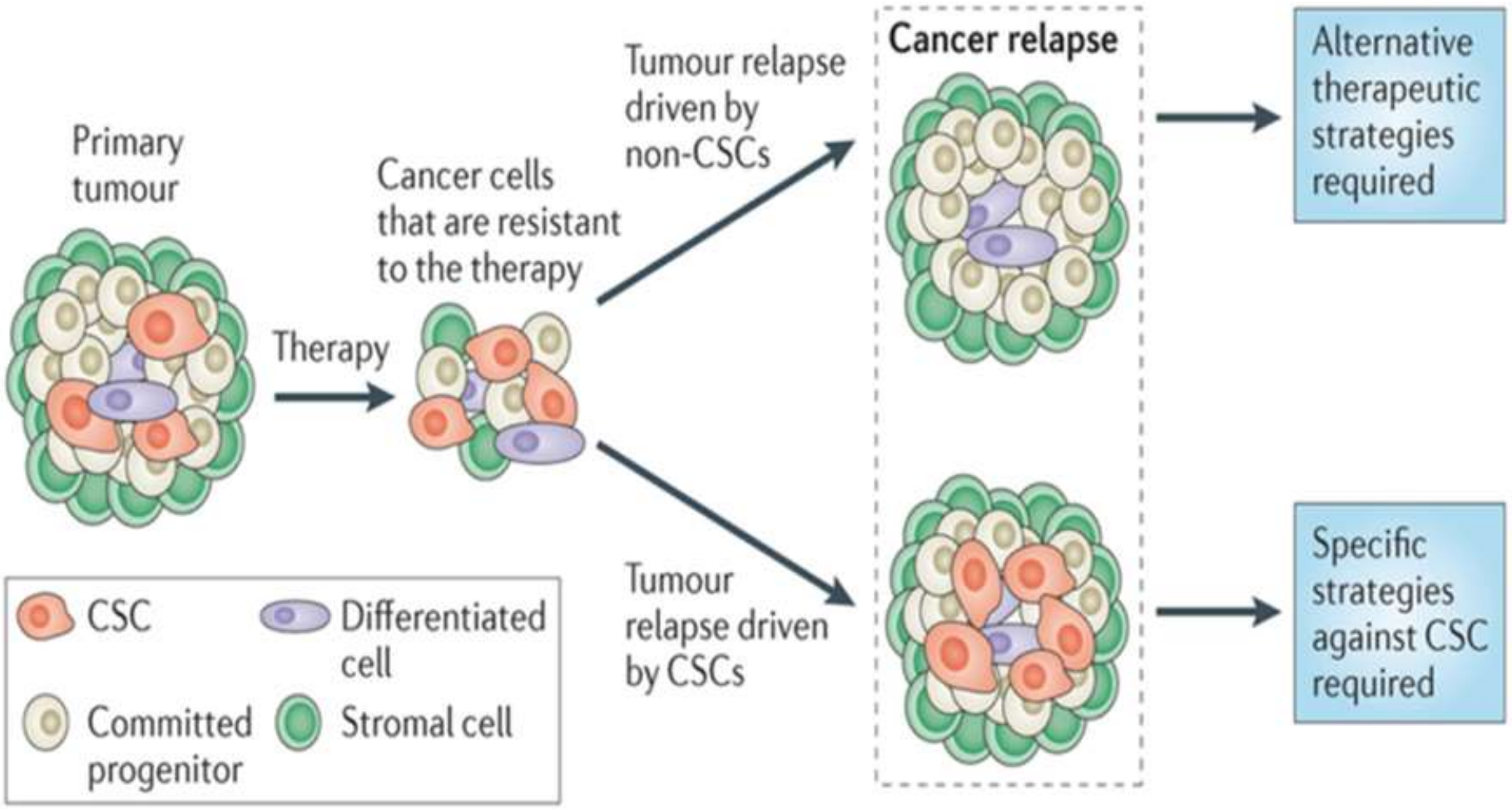


B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)

Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways



Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies

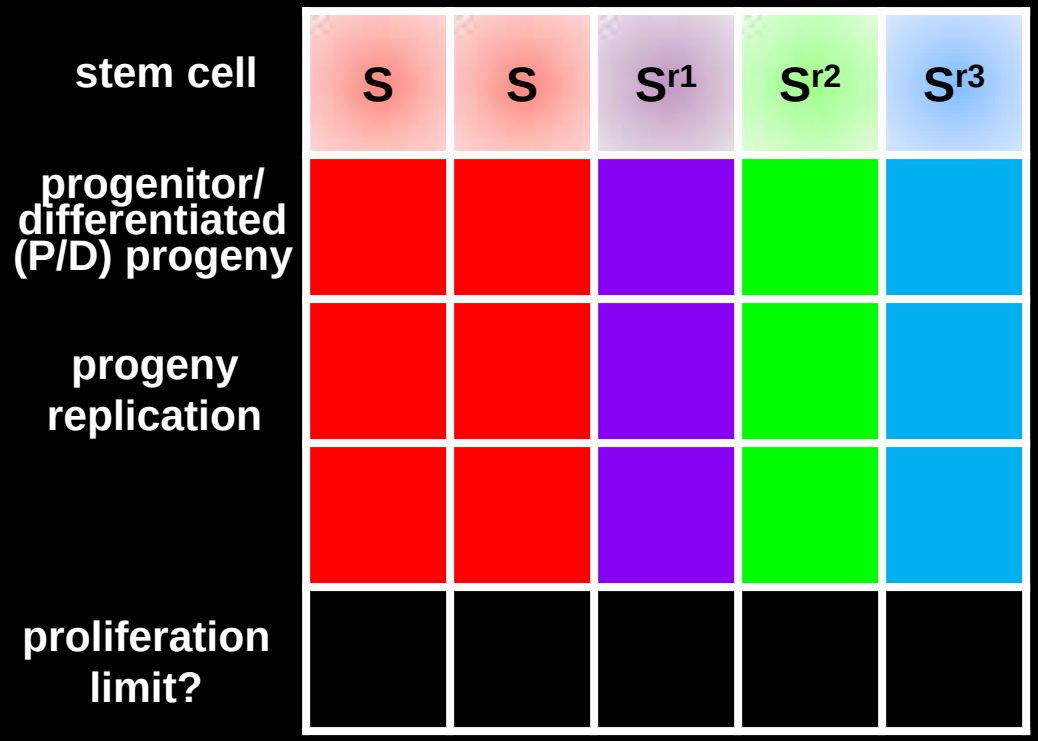


Adapted From: B. Beck and C. Blanpain (2013) Nature Rev. Cancer 13, 734

Unknown But Crucial Issues in the Evolution of Drug-Resistance (D^r) Phenotypes in Cancer

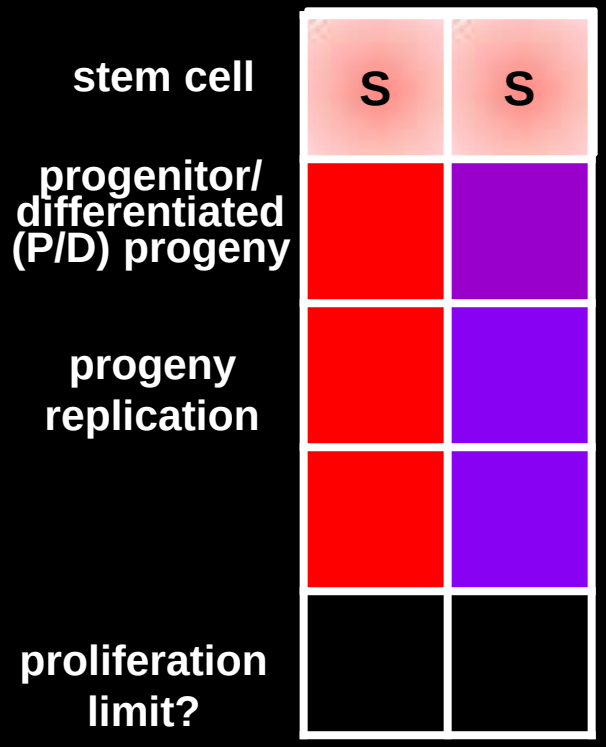
- can only stem cells seed metastases with subsequent expansion of the tumor cell population in metastases by proliferation of their P/D progeny?
- do all drug-resistance (D^r) phenotypes arise in stem cells and subsequent expression in their P/D progeny?

Evolution of Drug-Resistant Phenotypes (r1, r2, r3) in Cancer Stem Cells and Sustained Expression in Their Progenitor/Differentiated Progeny



mixture of stem cells and P/D progeny with Rx susceptibility and stem cells with different Rx resistance mutations and expression of same resistance phenotypes in their P/D progeny

Evolution of Drug-Resistance (D^r) Phenotypes in P/D Cell Compartment Independent of Stem Cell Phenotype

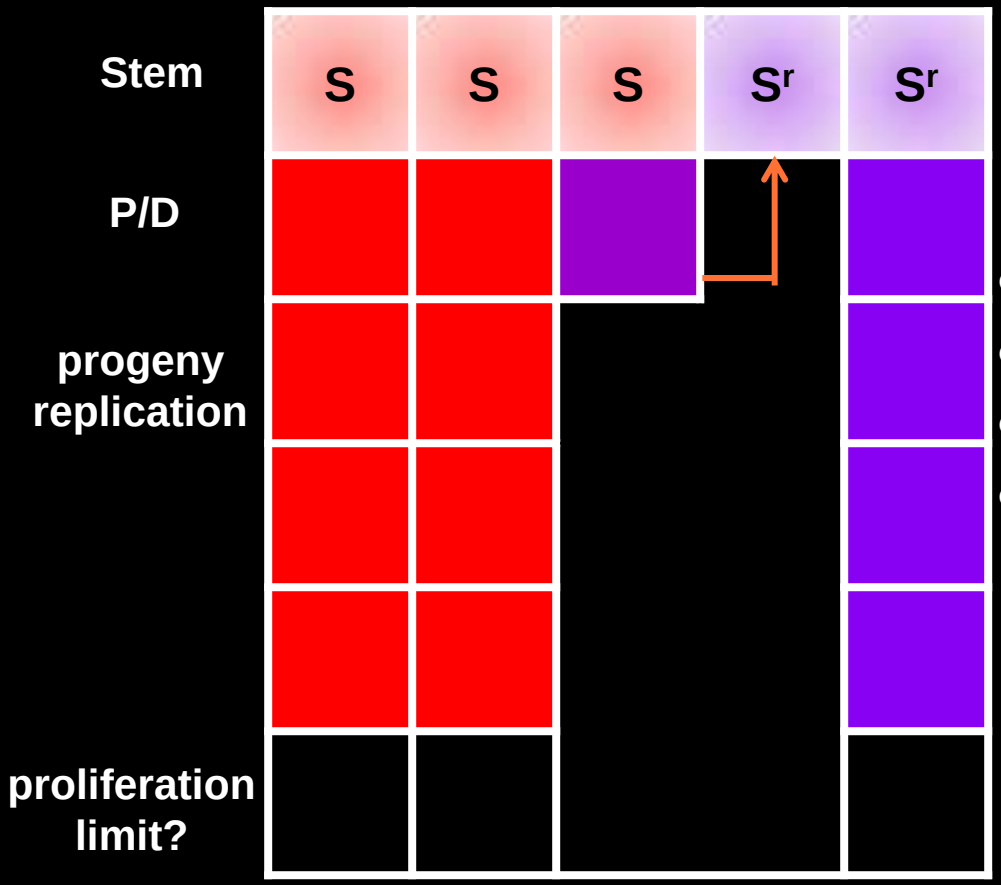


- evolution of resistance phenotype to Rx
- D^r P/D Cells will continue to generate tumor bulk for the lifetime of their proliferation limit

The Stem Cell to Progenitor/Differentiated Fate Pathway is Not One Way

- drug-resistant (D^r) progenitor (P) cells reacquire stem cell like properties with result that next wave of P/D progeny will carry same D^r phenotype
- does Rx selection pressure increase the prospect of reacquisition of stem cell properties by P/D cells?

The Stem Cell to Progenitor/Differentiation Fate Pathway is Not One Way: Implications for Drug-Resistance



- acquired D^r in P/D (most likely P) cell ( )
- reacquisition of S phenotype by D^r-P cell
- new S cell now carries D^r phenotype ( )
- D^r phenotype now expressed in all P/D progeny from this S^r cell

The Need for a Better Conceptual Understanding of the Fundamental Differences in the Behavior and Clinical Risk Posed by Different Tumors and Tumor Subtypes

The Need for a Better Conceptual Understanding of the Biology of Cancer Progression and Clinical Risk

- indolent disease likely to cause little to no harm
- consequential tumors with major clinical risk (metastasis) if not treated
- drivers of progressive metastatic disease (macrometastatic disease)
- mechanisms of tumor dormancy (micrometastatic disease) and recurrent disease

The Need for a Better Conceptual Understanding of the Biology of Cancer Progression

- cancer still perceived (and treated) as a diagnosis with lethal consequences if left untreated
- clear evidence of indolent tumors and use of screening programs has resulted in increased incidence
  - certain breast and prostate subtypes as prototype examples
- emerging view that the term ‘cancer’ should be reserved for tumor subtypes with reasonable likelihood of lethal progression if untreated
  - “consequential tumors”
  - mitigate the “over diagnosis-over treatment” dilemma

Intrinsic Differences in Tumor Biology and Risk
L. J. Esserman et al. (2013) JAMA 310, 797

diagnostic separation of indolent and consequential tumor subtypes arising in the same organ

- breast, prostate, lung and bronchus
- screening increases overall incidence of tumor detection (all subtypes)
- earlier detection reduces mortality from consequential lesions
- increased detection of indolent lesions predisposes to overtreatment
- need for new biomarkers and diagnostic tests to reliably distinguish indolent (watchful waiting) from consequential lesions with metastatic potential (require Rx intervention)

Intrinsic Differences in Tumor Biology and Risk

consequential cancers but largely slow growing

- colon, cervix
- screening reduces incidence of lethal tumors due to early detection and removal of precursor lesions

consequential cancers characterized by a fraction of highly aggressive tumors and difficulty of identification by screening

- thyroid
- melanoma

Change in Incidence and Mortality of Cancers (1975-2010) (Surveillance, Epidemiology and End Results Data)

	Incidence per 100K			Mortality per 100K		
	1975	2010	% change	1975	2010	% change
Breast[c]	105.07	126.02	20	31.45	21.92	−30
Prostate	94	145.12	54	30.97	21.81	−30
Lung and bronchus[d]	52.26	56.68	8	42.56	47.42	11
Colon	41.35	28.72	−31	28.09	15.51	−45
Cervical	14.79	6.71	−55	5.55	2.26	−59
Thyroid	4.85	13.83	185	0.55	0.51	−7
Melanoma	7.89	23.57	199	2.07	2.74	32

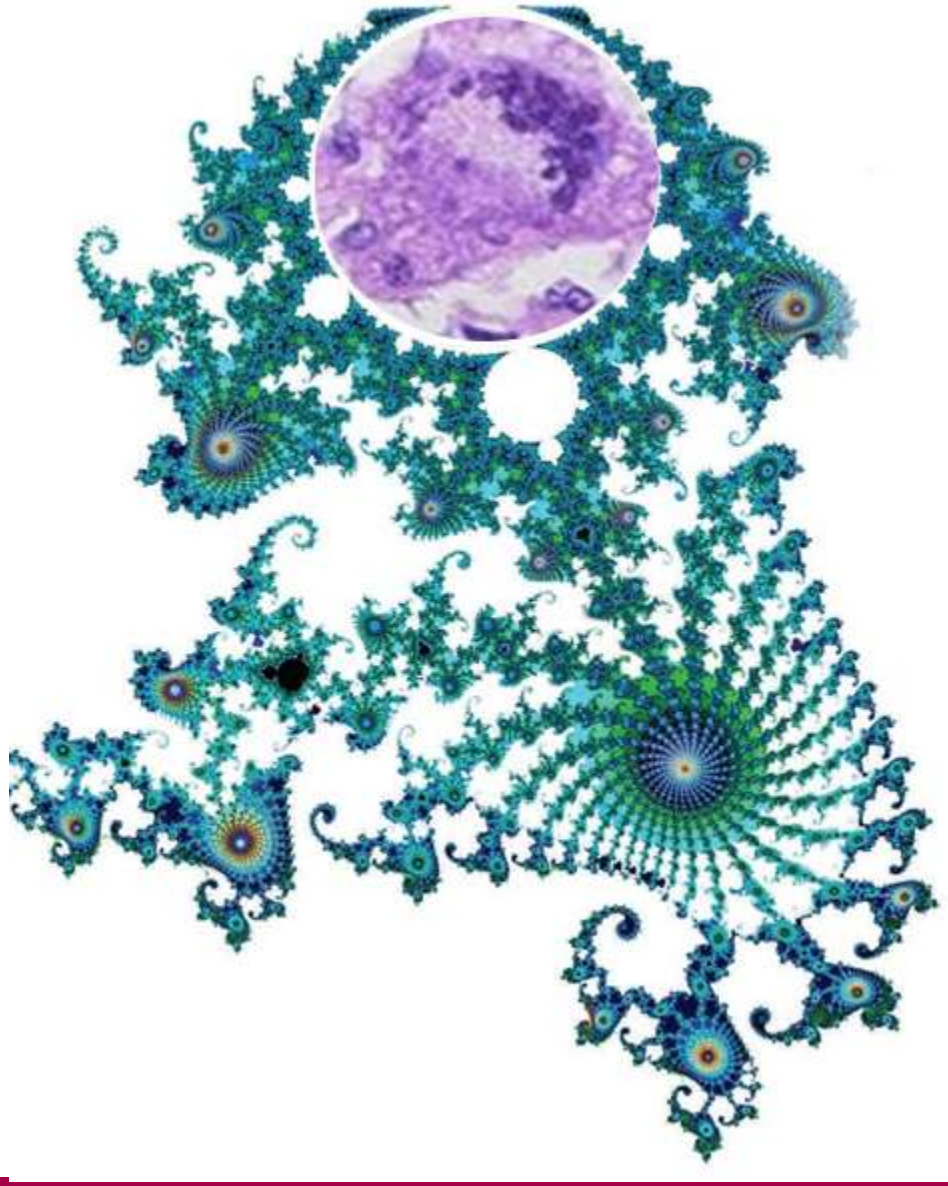
over-diagnosis/ over treatment of indolent lesions

consequential slow growing tumors: screening reduces morbidity/ mortality via removal of precursor lesions

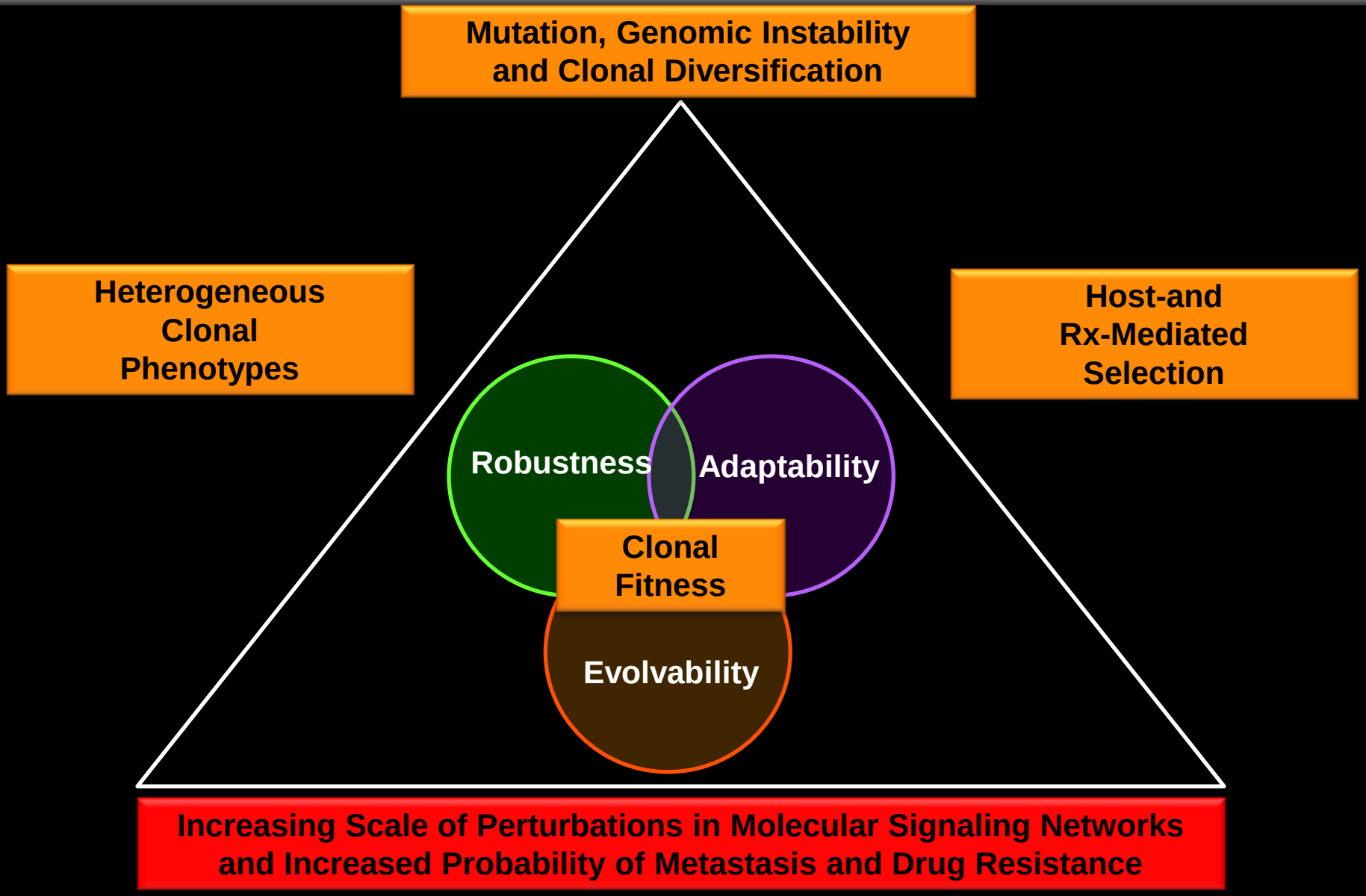
screening expands incidence of indolent lesions but limited impact on aggressive subset of tumors

Adapted From: L. Esserman et a. (2013) JAMA 310, 798

Genomic and Phenotypic Diversification of Tumor Cell Clones in Tumor Progression and Metastasis



Cancer as a Complex Adaptive System



Tumor Cell Heterogeneity and Core Challenges in Cancer Diagnosis and Treatment

confronting the complexity of clonal heterogeneity and metastatic disease

- improved prediction of how molecular signaling networks are altered and most likely “escape” pathways that would confer drug resistance/immune evasion
- new minimally invasive methods for longitudinal monitoring of clonal dynamics with tumor progression
- more agile therapeutic regimens to reflect changing clonal dynamics and earlier detection of emergence of drug-resistant clones

Implications of Cancer as a Complex Adaptive System for the Development of More Effective Diagnostics and Treatment

Weeks 11 and 14

- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies and the particular promise of immunotherapy
- the time, cost and complexity of development of new diagnostics and therapies to achieve FDA approval and marketing