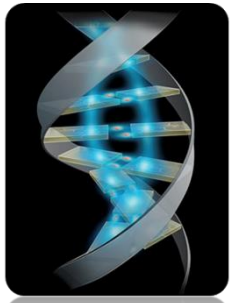

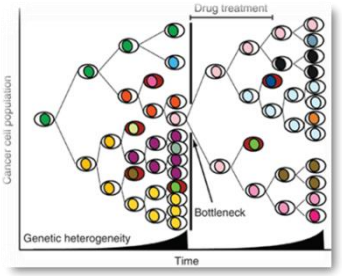

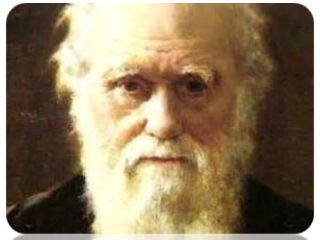

Can the "Cancer Species" be driven to extinction?

William Audeh MD, MS

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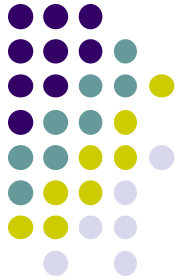
Applying Evolutionary Biology to the problem of Cancer

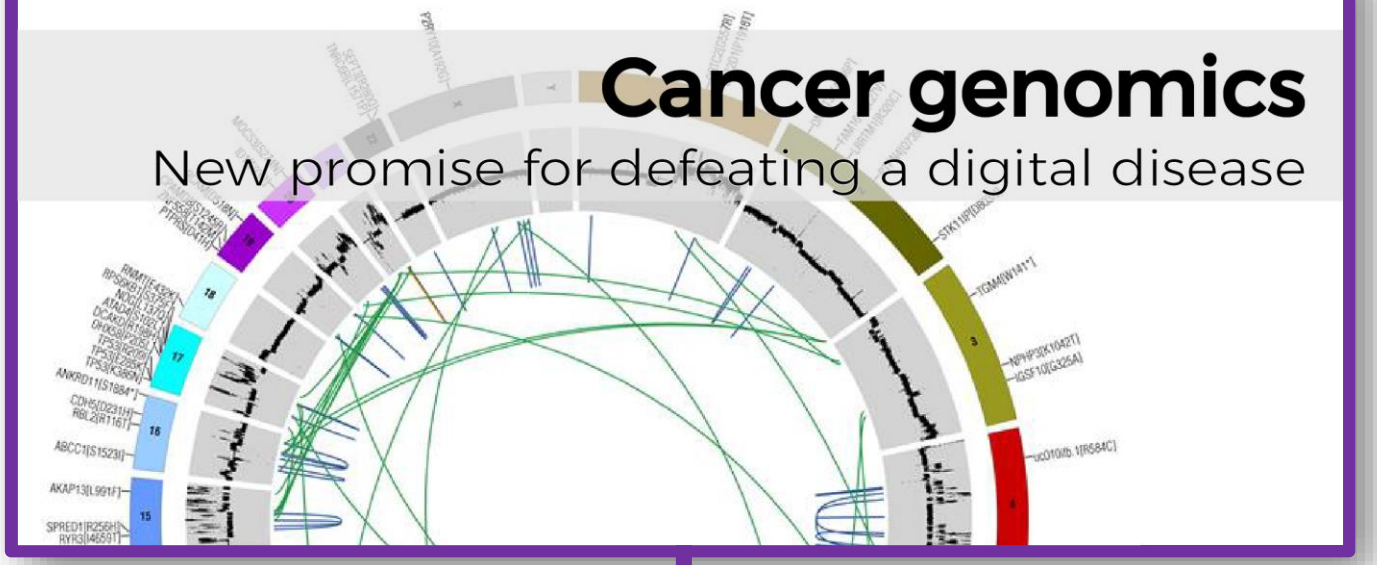


- **To explain why cancer develops**
  - **Intrinsic mutation rates and carcinogenesis**
    - **Mutation necessary for evolution but permits carcinogenesis**
  - **Maladaptation - Mismatch**
    - **Human genome maladapted to modern environment and lifestyle**

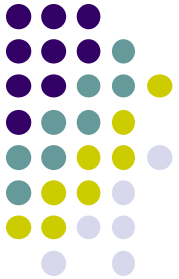
- **To guide therapy of cancer?**
  - **Apply *principles of evolutionary biology* to design and guide the therapeutic strategy?**

Cancer genomics

New promise for defeating a digital disease



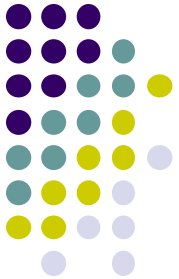
Lack of Progress in Adult Cancers with Chemotherapy



- *DNA damage(mutation)* must be tolerated by cancer cells for their survival
- ***Resistance to Chemotherapy eventually appears in nearly all cases of advanced cancer***
- Chemotherapy ***selects*** for resistant cell population

The “New” Era of Cancer Therapy

- **Molecularly-Targeted Therapy**
  - Generally less toxic than DNA-damaging therapy
  - Therapies targeting
    - hormone-driven pathways- estrogen, androgen
    - growth-promoting pathways
    - cell survival pathways
  - Hundreds of new targets being discovered
  - Over a thousand new cancer drugs in development
- **Immunotherapy**
  - Enhancing immune response against cancer cells
  - Directing immune destruction of cancer cells

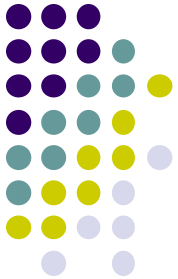


The “New” Era of Cancer Therapies

but still using

The “Old” Strategy for Cancer Therapy

"Resistance" to Targeted Therapy and Immunotherapy inevitably develops….
…as predicted by Evolutionary Biology



- Cancer is a diverse *population* of related cells
- Biological Populations *evolve and adapt*
- Adaptation to <u>any single drug is highly likely</u>
  - Crizotinib in lung cancer (77% respond, all progress)
- *Selection pressure of therapy drives evolution*…
- Adaptation facilitated by *genetic diversity*
- Genetic diversity **= *"tumor heterogeneity"***

Tumor Heterogeneity:

the finding that all cancer cells in the patient are not identical

= Chaos?

The NEW ENGLAND JOURNAL of MEDICINE

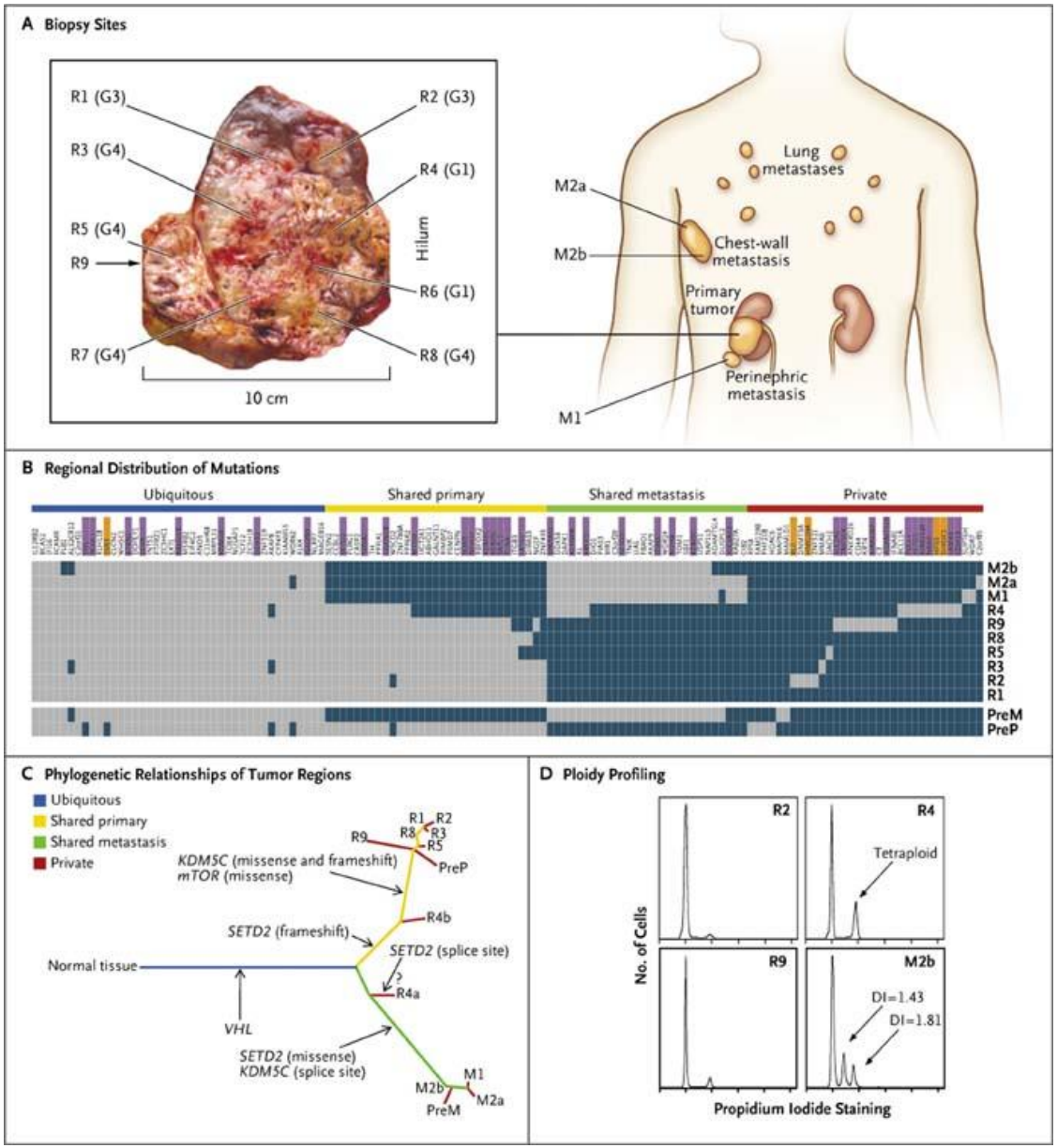
ESTABLISHED IN 1812 MARCH 8, 2012 VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.

- **cancer cell population diversity within a single patient**

Whole Genome Analysis of one Cancer in one Patient.



Multiple mutations

In multiple anatomic sites

Gerlinger M et al. N Engl J Med 2012;366:883-892

The NEW ENGLAND JOURNAL of MEDICINE

“Tumor Heterogeneity” Shakes Up Wall Street…..

THE WALL STREET JOURNAL.
WSJ.com

HEALTH INDUSTRY | Updated March 7, 2012, 6:38 p.m. ET

'Personalized Medicine' Hits a Bump

By RON WINSLOW

A tumor's genetic makeup can vary significantly even within the same tumor sample, researchers said, a finding that poses new challenges to the personalized-medicine movement in cancer.

One big implication of the new research, being published Thursday in the New England Journal of Medicine, is that analyzing only a single sample of a patient's tumor—the current practice—may miss important genetic mutations that affect the course of the disease.

That, in turn, could hinder emerging efforts to match patients with drugs that target the mutations affecting their tumors, a basic strategy of personalized medicine.

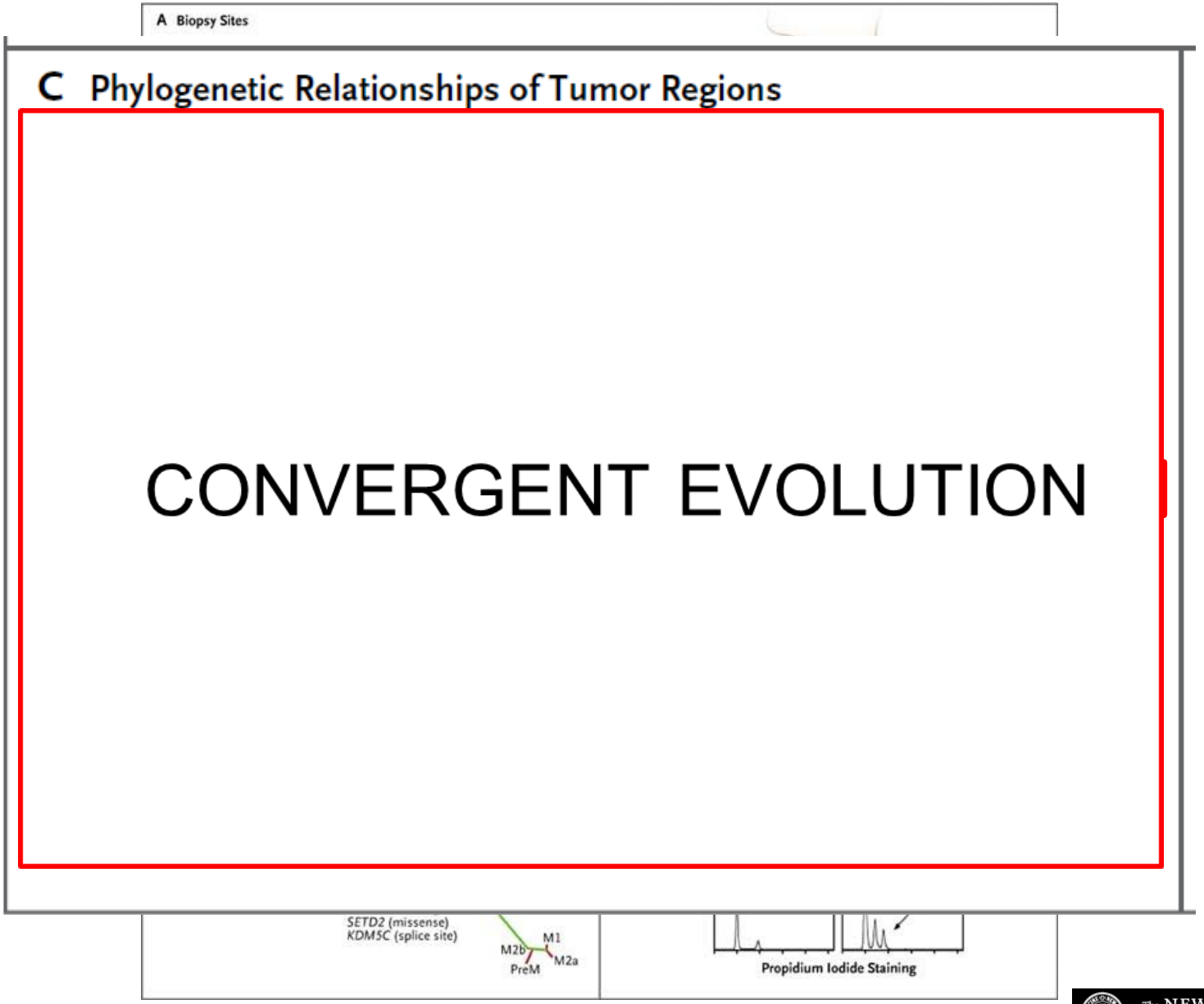
The findings don't diminish enthusiasm for the idea that genetic knowledge about tumors can transform cancer care, the researchers said. But it could make personalized treatment more complex—and more costly.

"It's a sobering finding," said Andrew Futreal, a co-author of the study who until recently was director of cancer genetics and genomics at Wellcome Trust Sanger Institute in London.

In an editorial accompanying the study, Dan L. Longo, an editor at the journal, suggested the varied genetic makeup of tumors described in the study

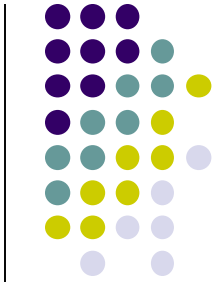
Dashed Hopes for Personalized Medicine With Targeted Therapies?

Whole Genome Analysis of one Cancer in a one Patient.



Gerlinger M et al. N Engl J Med 2012;366:883-892

Applying Evolutionary Biology to Cancer: Concept of Cancer as an "invasive species"

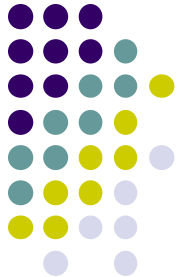


- A diverse population of eukaryotic cells
- Asexually reproducing
- Derived from a complex, multicellular organism
- Access to full "toolbox" of the eukaryotic cell
  - embryonic development, growth, cell migration
- Genomically unstable with high mutation rate
- Extensive adaptive capacity
- Invading the host…

The “Lexicon” of Cancer Medicine:
Clinicians need to “think” differently about Cancer

- ***Words*** lock-in concepts and modes of thinking
- ***Imply*** “operating characteristics” of the system
  - “Response” / “Resistance”
  - “Regression” / “Progression”
  - “Remission” / “Relapse”
- ***Directs*** clinical decision-making and trial design

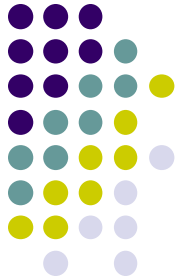
The Evolutionary Biology of Cancer: A *New* Lexicon needed for clinicians...



- *cancer*----------a population of genetically-related cells; “species”
- *tumor heterogeneity*----------genetic diversity within the population of cells
- *genomic instability*-----mutational rate generating diversity and adaptability
- tumor microenvironment--------ecosystem in which the cell population lives
- *cancer therapy*----------selective pressure on the population
- *immunotherapy of cancer*----------introducing “predator” into ecosystem
- *resistance*----------adaptation to selective pressure(s)
- *cure*----------extinction of the species

- ***How are species driven to extinction?***
  - Reduced genetic diversity and population size – “bottleneck”
  - Selective pressures exceed capacity for adaptation in population
    - e.g. insufficient mutational diversity to adapt to multiple targeted therapies

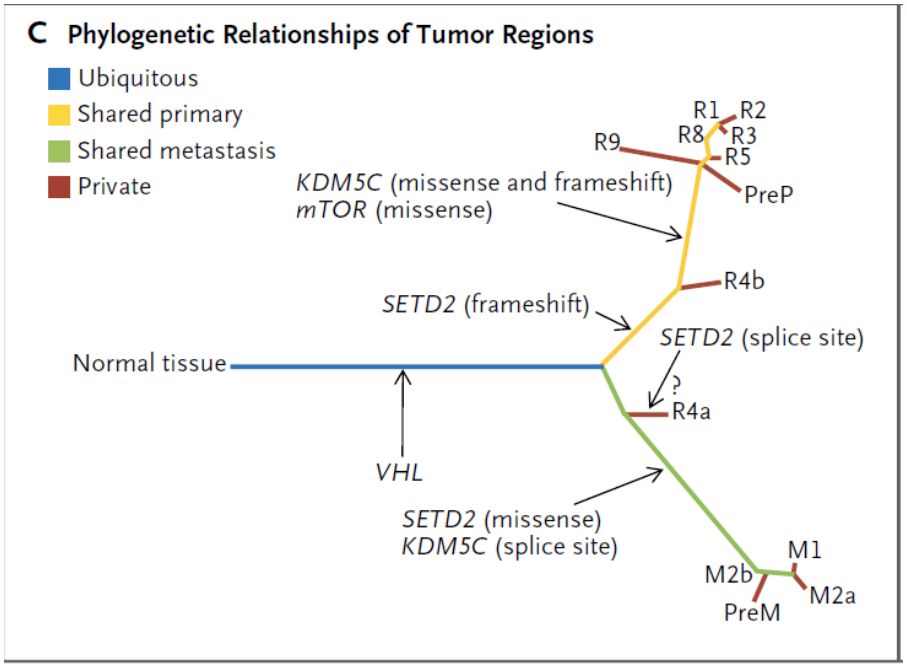
Using *Evolutionary Medicine* to Develop a Strategy for Cancer Therapy



- **Diminishing selection for resistant, aggressive biology**
  - "Adaptive therapy"
    - Intermittent, dose-modified therapy – seek to maintain population in equilibrium
  - Slow attrition, rather than massive (but incomplete) cell death
  - Avoid exerting strong selection pressure for resistance
  - Cancer as a chronic disease co-existing with "host"- not curative
- ***Driving a species to extinction? (i.e. "cure"?)***
  - Genomically characterize cancer cell population
  - Genomically characterize adaptive pathways
  - Strategically apply targeted therapies to direct and limit adaptation
  - Diminish genetic diversity with therapies – create bottleneck
  - Apply therapy to which "bottleneck" population cannot adapt

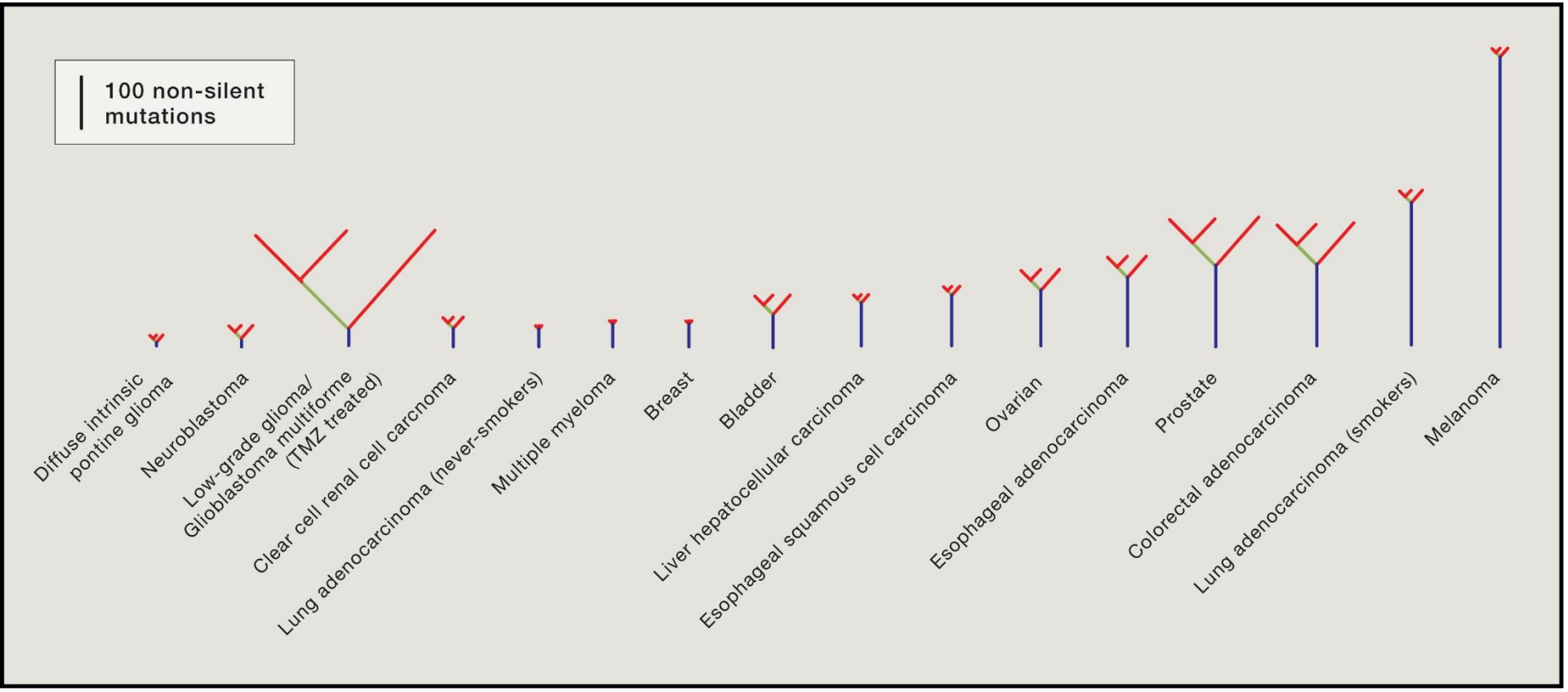
Implications for "Tumor Heterogeneity" from Evolutionary Biology

- Evolutionary contingency / constraint
  - Subsequent mutations contingent upon / constrained by prior mutations



- **Branches**: likely to have predictable, adaptive consequences
  - Not random or infinite, but providing ***survival advantage***
  - ***The clinical "logic" of evolutionary biology***

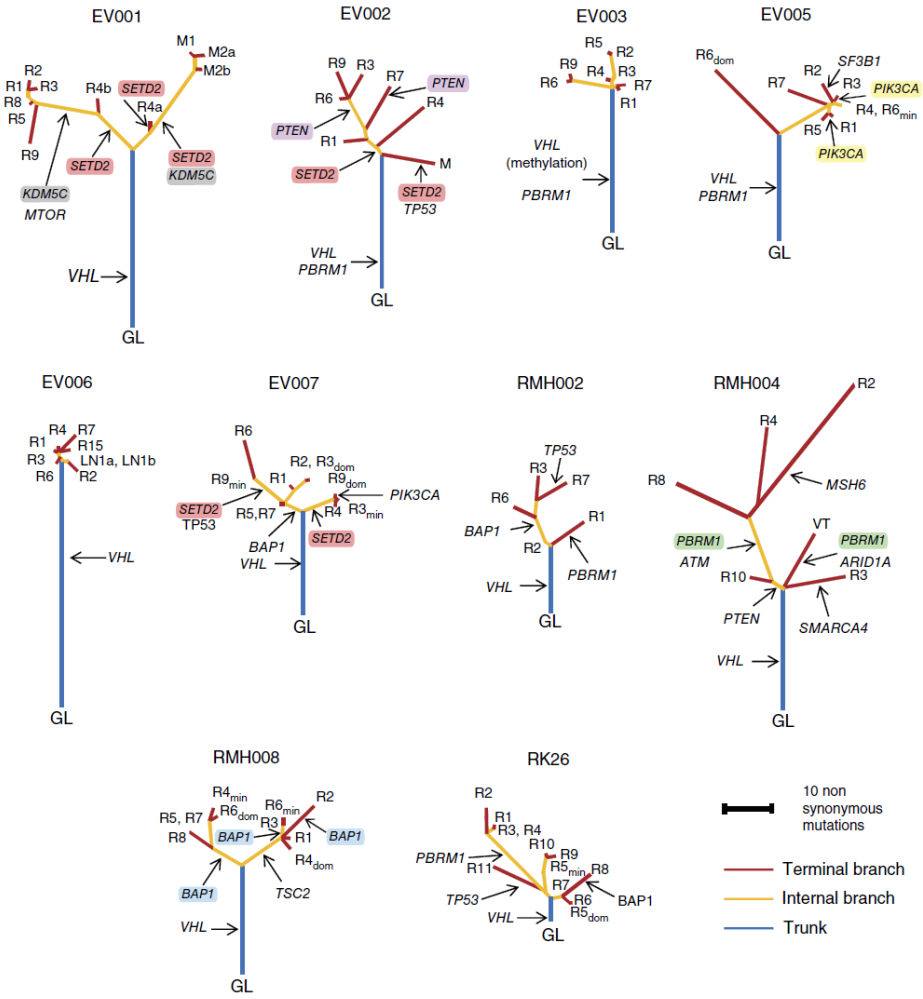
Evolutionary Trees Illustrating Intratumor Heterogeneity across Cancer Types



Cell 2017 168, 613-628DOI: (10.1016/j.cell.2017.01.018)

Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing

Marco Gerlinger[1,12], Stuart Horswell[2,12], James Larkin[3,12], Andrew J Rowan[1,12], Max P Salm[2,12], Ignacio Varela[4],

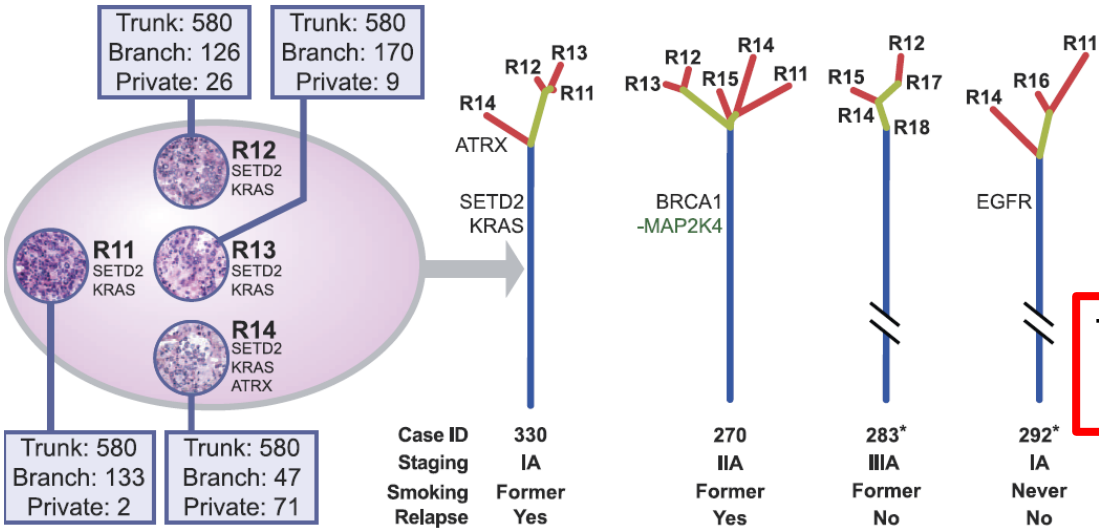


Trunk mutation: VHL

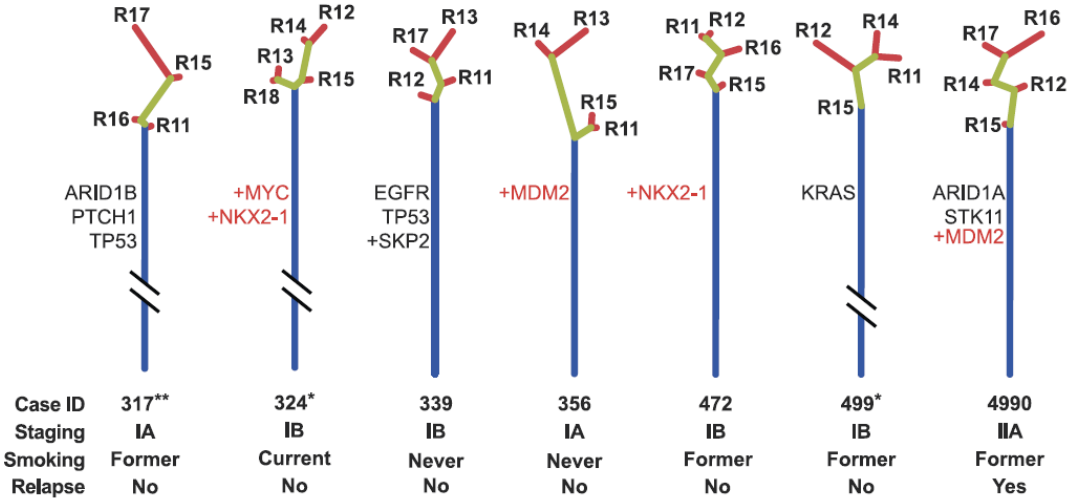
LUNG CANCER EVOLUTION

Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing

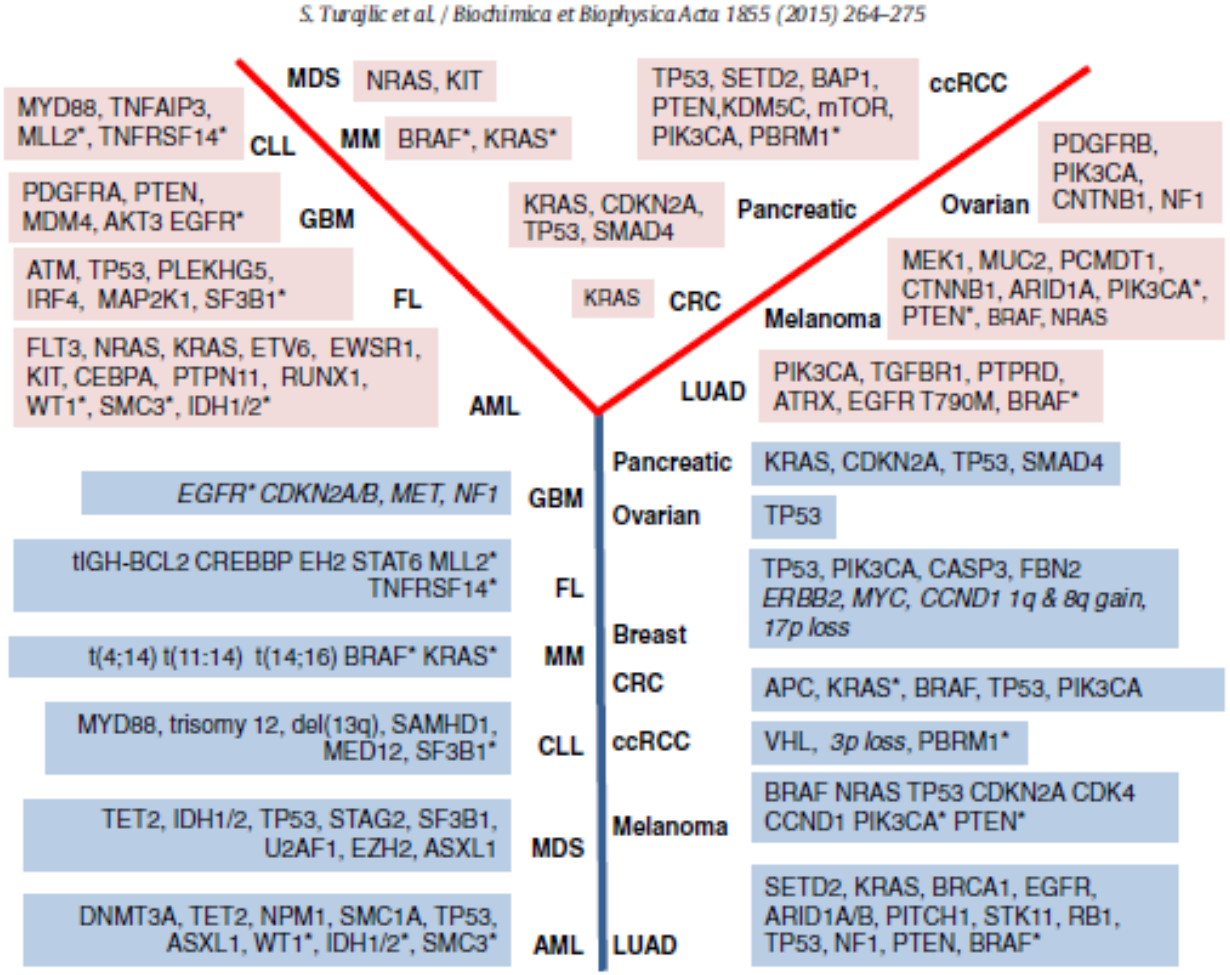
Jianjun Zhang,[1,2] Junya Fujimoto,[3] Jianhua Zhang,[4] David C. Wedge,[5] Xingzhi Song,[4]



Trunk mutation: variable



Trunks and Branches of Common Malignancies

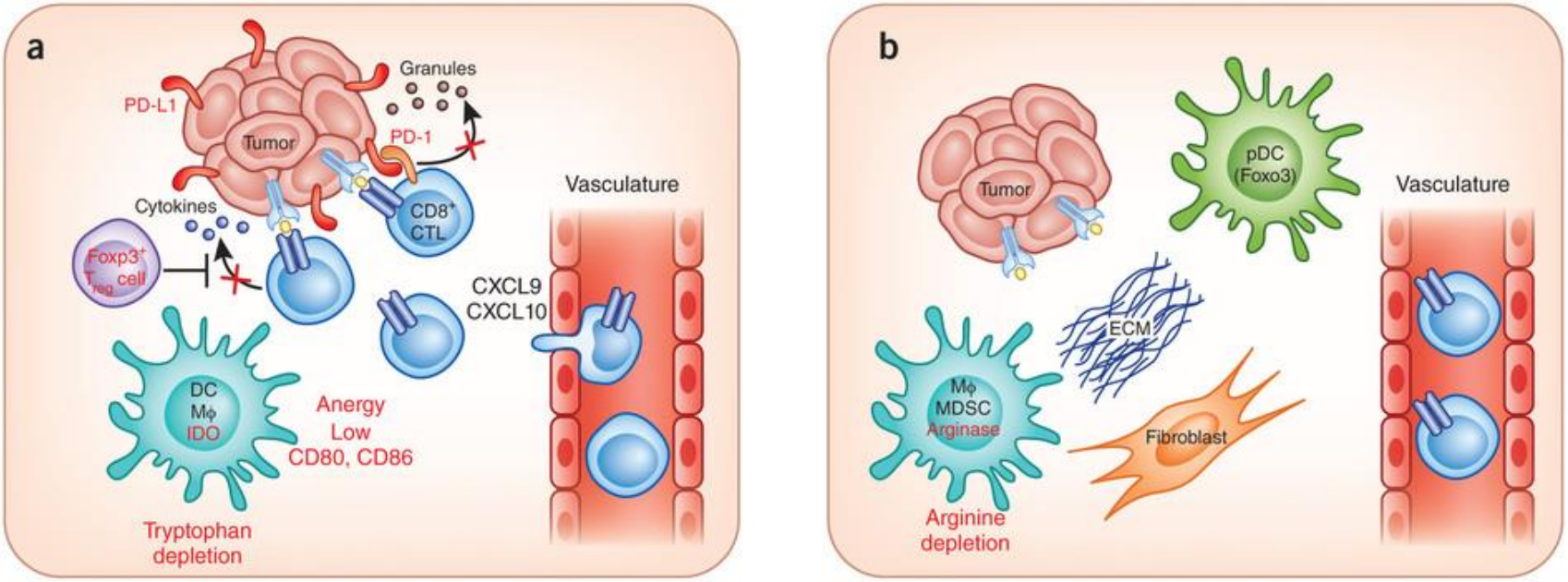


Evolutionary Strategic Therapy

- Predict adaptive responses to targeted therapy
  - Catalogue recurring mutations, convergent evolution
- Anticipate resistance pathways
  - Apply therapy while resistant population subclinical
- ***Role of the Immune System as "Predator"?***
  - ***Mechanisms of evolutionary escape from predation***

Immune Microenvironment: Adaptive Escape from Predation

(high mutational load and neoantigen expression)



Nature Immunology 14, 1014–1022 (2013)

- **Evolutionary Adaptation to Predation:**
  - "Camouflage" through escape from recognition
  - Anti PD(L)1 Immunotherapy "removes" the camouflage

“Hyperprogression” after Immunotherapy

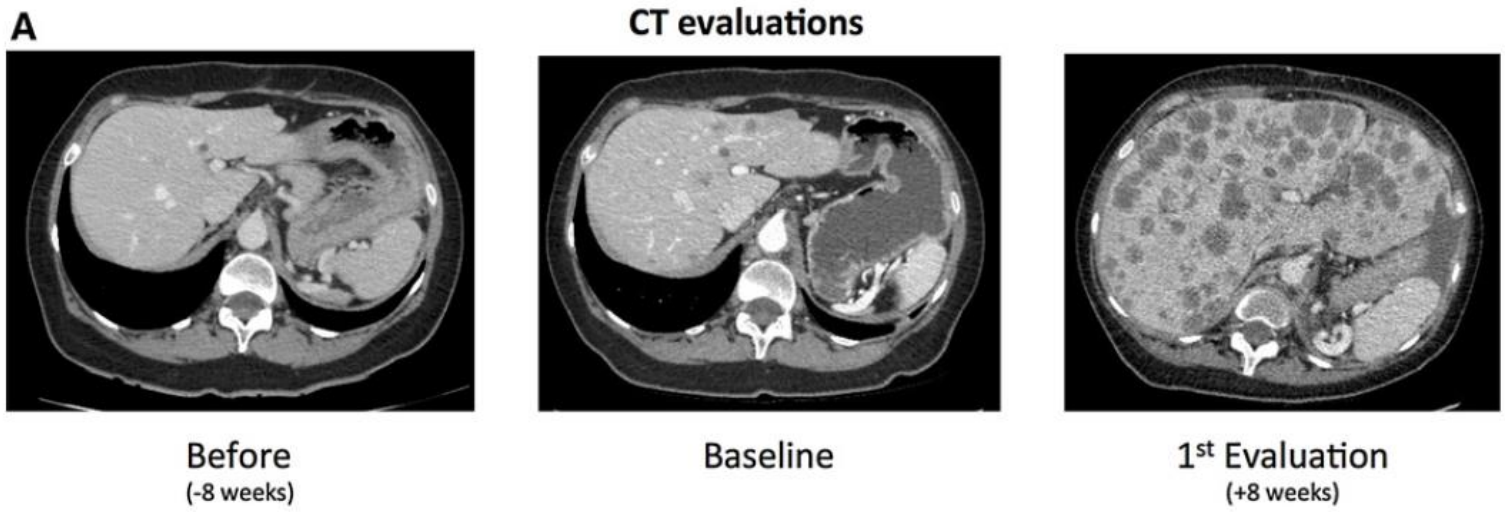
Published OnlineFirst November 8, 2016; DOI: 10.1158/1078-0432.CCR-16-1741

Cancer Therapy: Clinical

Clinical Cancer Research

Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat[1,2], Laurent Dercle[3], Samy Ammari[4], Christophe Massard[1], Antoine Hollebecque[1], Sophie Postel-Vinay[1,2], Nathalie Chaput[5,6,7,8], Alexander Eggermont[9], Aurélien Marabelle[1,10], Jean-Charles Soria[1,2], and Charles Ferté[1,11,12]



frontiers in Oncology

REVIEW
published: 06 August 2020

Mechanisms of Cancer Resistance to Immunotherapy

*Rilan Bai, Naifei Chen, Lingyu Li, Nawen Du, Ling Bai, Zheng Lv, Huimin Tian and Jiuwei Cui**

Trends in Cancer

CellPress REVIEWS

Trends in Cancer, March 2020, Vol. 6, No. 3

Opinion

Hyperprogression and Immunotherapy: Fact, Fiction, or Alternative Fact?

Jacob J. Adashek,[1] Ishwaria M. Subbiah,[2] Ignacio Matos,[3] Elena Garralda,[3] Arjun K. Menta,[4] Dhakshina Moorthy Ganeshan,[2] and Vivek Subbiah [2,*]

- Observed across multiple patient and tumor types
- No consistent genomic or immune features
  - EGFR and MDM2 amplification (↑proliferation ,↓apoptosis)
- ***No mention of Evolutionary Biology to explain***

Displaying the Clinical Relevance of Evolutionary Biology for Cancer Management Strategy?

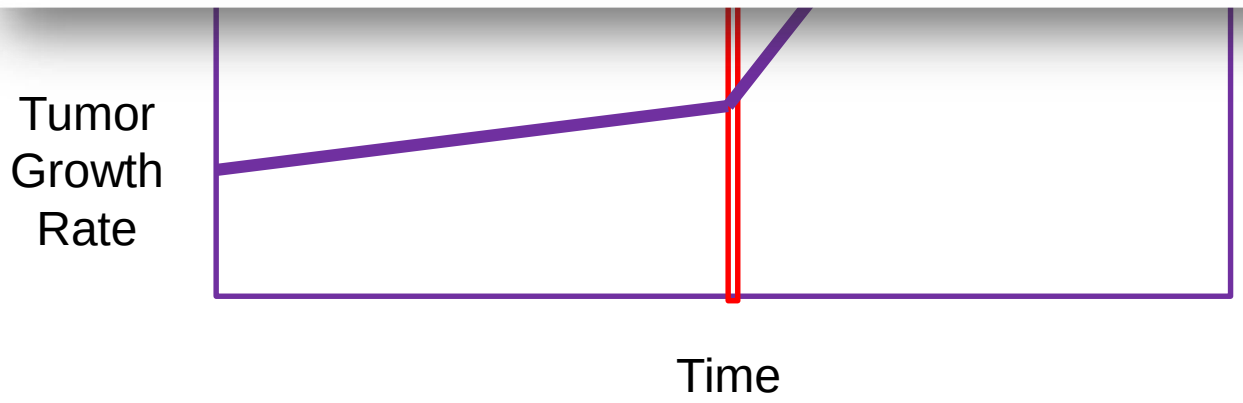
NATURE REVIEWS | CANCER

OPINION

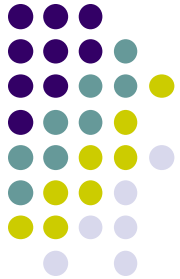
VOLUME 13 | DECEMBER 2013 | 883

Life history trade-offs in cancer evolution

C. Athena Aktipis, Amy M. Boddy, Robert A. Gatenby, Joel S. Brown and Carlo C. Maley

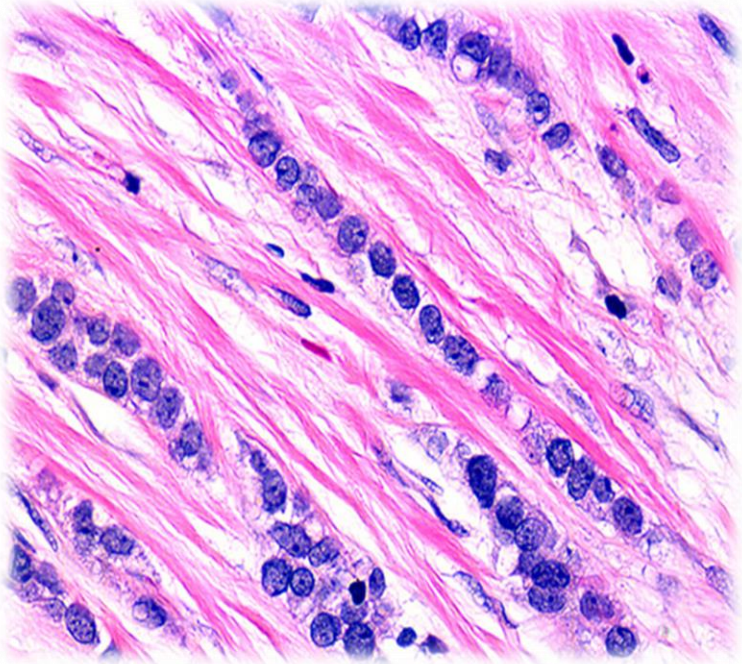


Using Evolutionary Medicine to Develop an "Extinction" Strategy for Cancer Therapy

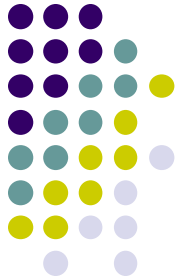


- **Driving a species to extinction:**
  - ***Genomically characterize cancer cell population***
  - ***Genomically characterize adaptive pathways***
  - Strategically apply targeted therapies to direct and limit adaptation
  - Diminish genetic diversity with therapies – create bottleneck
  - Apply therapy to which "bottleneck" population cannot adapt
    - Immunotherapy?
    - Specific targeting?

Clinicians need to think of Cancer as...
...an evolving population
...following principles of evolutionary biology

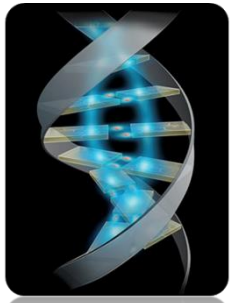


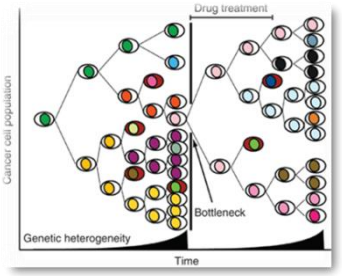
Driving Cancer to Extinction?

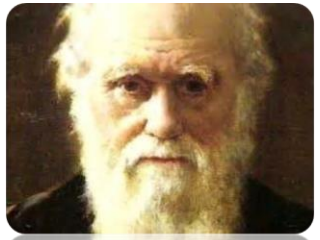


No force of nature, apart from an extraterrestrial asteroid, has been more efficient at driving species to extinction than *Homo sapiens…*

...surely, we can apply this unique skill to conquering cancer…







Can the "Cancer Species" be driven to extinction?

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