

Evolution and cancer therapy

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NCI
A Comprehensive Cancer
Center Designated by the
National Cancer Institute



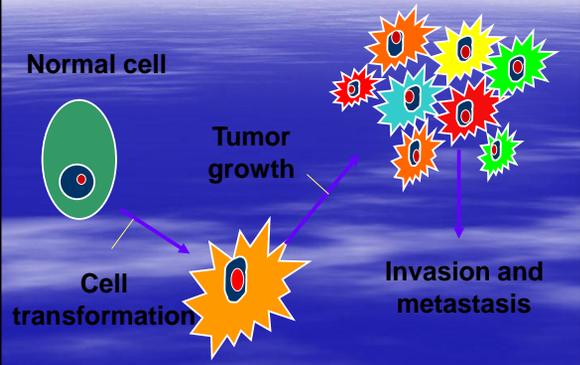
Integrating and Leveraging
the Physical Sciences
to Open a New Frontier
in Oncology



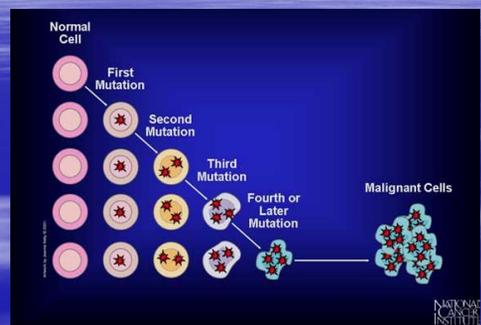
Topics

1. Evolutionary dynamics in cancer
2. Cancer therapy
 - Evolution of resistance
 - Experience in pest management
 - Using evolution to improve tumor control

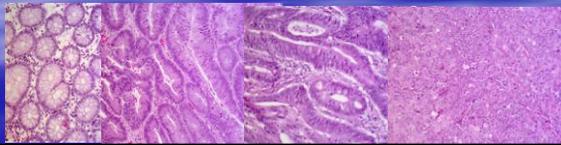
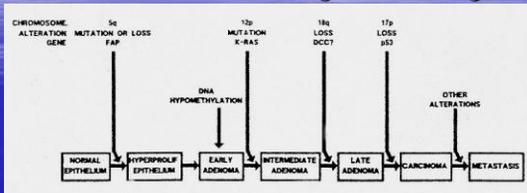
Old medical dogma – a single cell becomes cancerous and then grows clonally.



“Carcinogenesis is somatic evolution”



Conventional view of "somatic evolution" is embodied in Fearon-Vogelstein diagram



There are three necessary and sufficient conditions for natural selection:

- Variation in the population phenotype
- That variation must be heritable
- That variation must affect fitness (reproduction and/or survival)

"Evolution is how life commutes its own death sentence."

What does genetics tell us and not tell us?



Depicting evolution as a sequence of mutations ignores two fundamental questions necessary for understanding carcinogenesis:

How exactly does a mutation confer a proliferative growth advantage?

Evolution selects phenotypes, not genotype. Fitter phenotypes proliferate at the expense of those less fit.

What are the environmental selection forces that control phenotypic evolution?

The fitness of any phenotype is contextual and depends on environmental selection forces

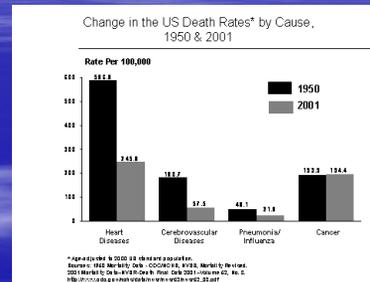
WHICH CAN CHANGE WITH TIME



The 40 Years War

- "I will also ask for an appropriation of an extra \$100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal."
- Richard Nixon. State of the Union Speech, 1970

Who is winning?



Expectations remain that a cure will be found if the medical community is sufficiently diligent, creative, and intelligent

"It (stimulus package) will launch a new effort to conquer a disease that has touched the life of nearly every American by seeking a cure for cancer in our lifetime."

- President Obama

Will today be the day?

Moffitt Cancer Center logo

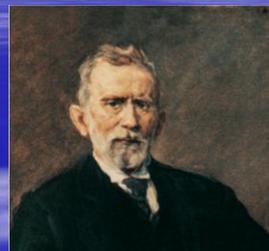
Saudis cure cancer with camel urine

AP news headline

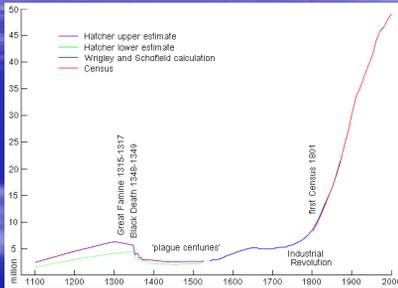
Cannabis linked to 'prostate cancer cure

LA Times

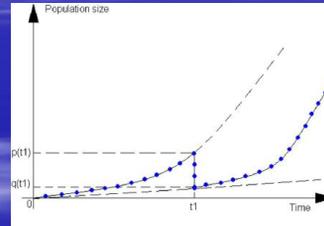
The concept of a cancer cure stems from Paul Ehrlich's magic bullet which proved prophetic in treating infectious diseases



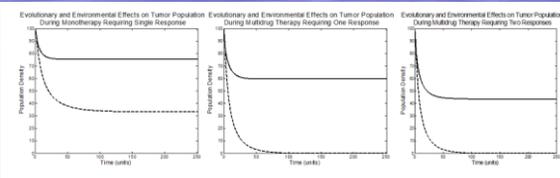
The human population decreased but returned to pre-disease levels



If resistance cells due to environmental or phenotypic are present prior to therapy, recurrence is inevitable



What if we give multiple drugs like HIV?



Cancer cells have access to the full complexity of the human genome to develop adaptive strategies

Despite the critical role of evolution therapy failure, evolutionary dynamics virtually never enter clinical design

Overlooking evolution: A systematic analysis of cancer relapse and therapeutic resistance research

C. Adeno Altgiers^{1,2}, Virginia S. Y. Kwai¹, Kathryn A. Johnson¹, Steven L. Neuberg¹, Carlo C. Maley¹

- Cancer therapy selects for cancer cells resistant to treatment, a process that is fundamentally evolutionary. To what extent, however, is the evolutionary perspective employed in research on therapeutic resistance and relapse? We analyzed 6,228 papers about therapeutic resistance and/or relapse in cancers and found that the use of evolution terms in abstracts has remained at about 1% since the 1980s. However, detailed coding of 22 recent papers revealed a higher proportion of papers using evolutionary methods or evolutionary theory, although this number is still less than 10%. Despite the fact that relapse and therapeutic resistance is essentially an evolutionary process, it appears that this framework has not permeated research. This represents an unrealized opportunity for advances in research on therapeutic resistance.

Consider the diamondback moth (*Plutella xylostella*)



- Probably of European origin - first observed in North America in 1854 in Illinois . Eats cabbage
- The moth has been treated with a wide range of chemicals with transient success
- It has now spread throughout North America causing serious damage to cabbage crops
- In 1988 the moth was reported to be resistant to all known insecticides
- A moth infestation is incurable. Current treatments limit pesticide application to reduce crop damage

Consider the Rhinoceros Beetle (*Oryctes rhinoceros*)



- Significant pest of the coconut palm in islands in the south Pacific
- Rhinoceros beetles are also the strongest animals on the planet in relation to their size
- Rhinoceros beetle larvae are sometimes fried and eaten as a delicacy
- Male beetles are also used for gambling fights since they naturally compete for female beetles with the winner knocking the other off a log
- Pesticides unsuccessful

A biological solution proved effective



- A baculovirus that attacks both the larval and adult stages was discovered in Malaysia
- Introduction of the baculovirus has resulted in successful control of the beetle population for over 20 years
- Despite the fact that a number of beetle phenotypes resistant to infection have been discovered

Invasive pests are now managed using principles of Integrated Pest Management (IPM): lessons from the alfalfa weevil



- "The presence of alfalfa weevils in an alfalfa field does not in itself justify pesticide application."
- "Chemical control should not be used unless weevil damage approaches the level that will reduce net profit by at least the cost of a pesticide application"
- Several species of wasps and a parasite of the adult weevil (*Microctonus aethiopoidea*), have been introduced. In most cases, these natural enemies will help keep infestations below economically damaging levels

Lessons from Integrated Pest Management – Strategic Therapy

1. Eradication of a disseminated invasive pest is virtually never successful
2. Heterogeneity in pest phenotype and environmental conditions will result in resistance to virtually any therapy.
3. Control is possible but requires treatment strategies explicitly designed for that purpose
4. Kill not the maximum number of pests but the minimum necessary
5. “Biological controls” are more effective than chemical

Cancer therapy is an environmental selection force in the cancer adaptive landscape

The collage consists of three overlapping article thumbnails:

- Top Left:** "Mathematical Oncology: Adaptive Therapy" by Robert A. Gatenby, Aronsohn S. Nika, Robert J. Gillies, and R. Roy Vaidya. It includes a small diagram of a cell population.
- Top Right:** "ESSAY: A change of strategy in the war on cancer" featuring a cartoon illustration of a person in a lab coat standing next to a large, branching tree structure labeled "CANCER".
- Bottom:** "Lessons from Applied Ecology: Cancer Control Using an Evolutionary Double Bind" by Robert A. Gatenby, Joel Brown, and Thomas Vincent. It includes a small diagram of a cell population.

Traditional high dose density

- Norton-Simon model of high dose density
 Maximum tolerable dose in shortest period of time
 Minimize probability of mutation conferring resistance.
- Three critical assumptions:
1. Resistant populations are not present prior to therapy
 2. Resistance is acquired as a step-wise mutation
 3. The resistant phenotype rapidly proliferates and results in patient death.

Why does therapy fail? Consider the sources of resistance

1. Reaction norm – individual cells can change their phenotype
2. Multiple subpopulations with different phenotype
3. Environmental factors confer resistance to phenotypically sensitive populations

KEY POINT: Cancer therapy is typically applied with a fixed strategy while cancer adapts and evolves with the first dose

Is there any hope? Lessons from IMP: Key parameter is cost of resistance

- Any resistance mechanisms requires resources
- Resources diverted to resistance are not available for proliferation
- In the absence of therapy, the resistant populations will generally be less fit
- The cost of resistance manifests in various ways depending on the therapy

Alternative approach from pest management experience – think strategically

i.e. beyond the first move

- Resistant populations are present prior to therapy as part of the "normal" range of phenotypic diversity and microenvironmental heterogeneity
- Resistant phenotype are, in the absence of therapy, less fit than the sensitive phenotype
- Removing sensitive cells permits unopposed growth of less fit resistant phenotypes

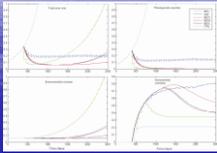
Adaptive therapy

- Explicitly abandon the concept of high dose density for cure or control
- The goal is to maintain tolerable tumor burden
- Assume resistant cells are less fit, in the absence of therapy, and are present prior to treatment
- Apply chemotherapy judiciously to maintain a stable population of sensitive cancer cells to suppress proliferation of resistant phenotypes
- Basic principle – retain a cell population that you can control and get them to suppress growth of the population you cannot control

Kill not the maximum possible number of cells, just the minimum necessary

- Low dose chemotherapy
 - Less toxicity? Limit sensitive cell death
- Attempt to maintain stable tumor burden
- Chemotherapy sensitive cells suppress resistant cell growth
- Induce near steady state of patient-tumor interaction

Adaptive therapy



Mathematical Models

High dose density results in shortest patient survival – killing sensitive cells leaves adaptive landscape open to rapid proliferation by resistant phenotype

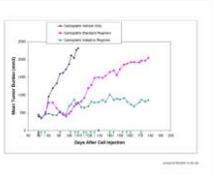
Adaptive therapy – abandon curative intent - limit therapy to stabilizing sensitive population which then suppresses growth of resistant clones

Experiments:

Adaptive therapy achieves long term survival with decreasing dose of carboplatin

Caveat:

If the resistant phenotype is fitter than the resistant phenotype, you are screwed.



Why are biological controls more effective?

- Hypothesis: the key to pest control is phenotypic cost of resistance
- Adaptation to drugs (like pesticides) usually requires upregulation of extant cellular machinery – relatively inexpensive
- Adaptation to predator may require more extensive phenotypic changes at greater cost.
- The evolutionary double bind – the cost of adaptation reduces fitness such that proliferation of the resistant population is limited

Cancer therapy requires dynamical thinking

Introduce a cat



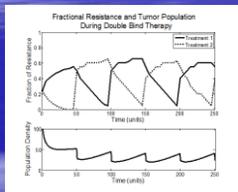
The squirrel adapts



Answer: add a snake

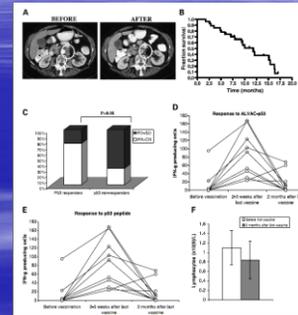


Double bind therapy uses cats and snakes



- Initial therapy kills tumor cell and selects for resistant populations with a known strategy
- Follow with a therapy focused on the adaptation
- Repeat as necessary

Moffitt study: 2nd and 3rd line therapy in small cell lung cancer with vaccine against mutant p53. Results: strong immune response elicited but only one partial clinical response in 29 subjects



Fortuitously, the patients were followed after exiting the trial. 21 received 2nd or 3rd line chemotherapy. Historical experience predicts a response rate of <5%

Table 3. Response to second-line chemotherapy in vaccinated patients

All patients who received chemotherapy after vaccine (n = 21)		Platinum-resistant patients who received chemotherapy after vaccine (n = 13)	
Response	n (%)	Response	n (%)
CR	3 (14.3)	CR	1 (8)
PR	10 (47.6)	PR	7 (54)
SD	4 (19.05)	SD	3 (23)
PD	4 (19.05)	PD	2 (15)
CR + PR	13 (61.9)	CR + PR	8 (61.5)

Abbreviations: PD progressive disease; SD, stable disease; PR, partial response; CR, complete response (all according to Response Evaluation Criteria in Solid Tumors).

Is this a double bind?

- Mutant p53 is known to confer drug resistance. Adaptation to vaccine resulted in lower p53 expression and increased drug sensitivity
- Chemotherapy reduces immuno-suppressive intratumoral T lymphocytes enhancing the immune response
- Proposals: 1. Same study, repeat vaccine after chemo. 2. Give chemo prior to vaccine

How can we apply this? Consider Multiple Myeloma

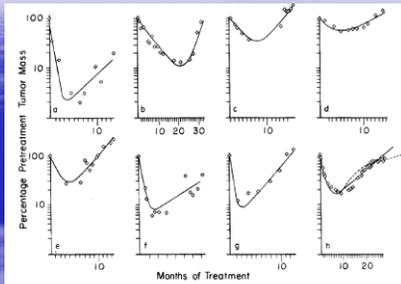


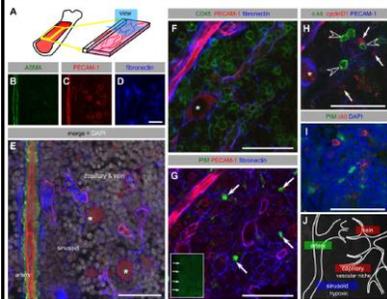
FIG. 2. Curves calculated from serial measurements of tumor mass in eight patients using the double exponential model. Fig. 2b (dotted line) illustrates the curve calculated for one patient using the exponential-Gompertzian model. Abscissa indicates months of treatment and ordinate is percentage of pretreatment tumor mass.

TUMOR GROWTH PATTERNS IN MULTIPLE MYELOMA *Cancer* 39:1077-1084, 1977
 JAMES A. HIGGANS, PhD,* BARRY W. BROWN, PhD,* JAMES R. THOMPSON, PhD,
 BENJAMIN DZIBICKO, MD, PhD,† AND RAYMOND ALEXANDER, MD*

Goal of this project

- Understand the cellular and micro-environmental dynamics that govern the rate of evolution of drug resistance.
- The long term goal is developing strategies to control Myeloma cell growth for a period longer than the expected lifespan

Environmentally mediated disease is a critical source of de novo resistance in MM



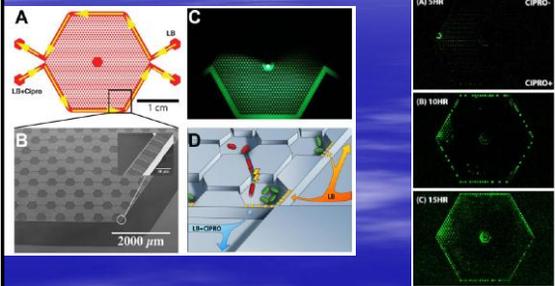
Gradients
 - Cytokines
 - Hypoxia

Bone Marrow microenvironment
 •ECM
 - Bone Marrow
 - Mesenchy

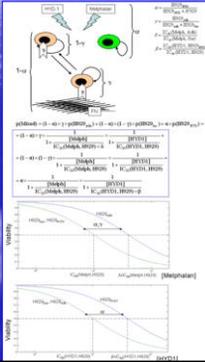
Cell types at different differentiation stages

* Kubota et al. | *Biochemical and Biophysical Research Communications* 366 (2008) 333-339

Drug and oxygen gradients to examine evolution of resistance in MM cells aspirated from patients



The double bind for Multiple Myeloma



- Melphalan resistance is conferred by MM binding to mesenchyma or ECM (fibrinogen)
- New drug HYD-1 targets cell binding. Selectively kills cells highly bound to ECM or mesenchyma
- Each therapy selectively drives adaptive strategies that increase sensitivity to the other therapy

Approach Proposed

- Culture human Multiple Myeloma cell lines (HMCL) and patient samples in gradients of hypoxia and DNA-damaging chemotherapeutics (Doxorubicin and Melphalan);
- (Also include co-culture with stromal cell lines)
- Study the evolution of drug resistance and the possible existence of Goldilocks in this hematologic malignancy;

Conclusions

- Evolutionary dynamics provide novel insights in tumor adaptation to therapy.
- Lessons from applied ecology and treatment of invasive pests may be relevant.
- Cancer therapy should be more strategic – anticipating mechanisms and costs of adaptation and designing strategies to prevent or exploit those adaptations.
- Adaptive therapy and evolutionary double bind therapy are possible “evolutionarily enlightened” strategies
- While we need to pursue new drugs, we also have to use current drugs better.