Evolutionary Dynamics in Cancer Control and Cure

Bob Gatenby, MD
Department of Integrated Mathematical Biology
Department of Radiology
Moffitt Cancer Center
Personalized oncology focuses on matching treatment to molecular targets. But, …

General principle: Resistant phenotypes are inevitable but clinical resistance requires the population to proliferate, which is governed by Darwinian forces.
Second principle: Treatment as a game between the oncologist (treatment) and cancer (adaptation)

The oncologist has 2 large game theoretic advantages:
1. He/she plays first (Stackelberg dynamics – i.e. white pieces in chess)
2. He/she is sentient and can play dynamically while an evolving cancer population can never anticipate the future.

By “playing” the same treatment continuously until progression, oncologists lose both advantages
Combining personalized medicine and game theory models: MTD kills maximum numbers of cancer cells but selects for resistance and eliminates competitors – “competitive release”
Adaptive therapy - exploiting the cost of resistance in clinical cancer treatment

- Limited administration of therapy to maintain sensitive cell population
- Sensitive cells, without the phenotypic cost of resistance, suppress resistant cells during no treatment. Treatment is a forcing function that, when applied at the correct time, induces oscillating near steady state
First clinical application: Abiraterone blocks androgen synthesis in mCRPC. In large trials 62% of men with mCRPC respond (radiographic TTP 8 to 16 months).
Evolution-based mathematical models to design trial

Define mCRPC subpopulations based on androgen dynamics:

- **T+ cells** require exogenous testosterone (sensitive to ADT)
- **TP cells** produce testosterone (sensitive to Abi) and promote T+ cells
- **T- cells** proliferate independent of testosterone (bad guys!)

The oncologist-tumor “game” is modeled as a payoff matrix:

<table>
<thead>
<tr>
<th></th>
<th>T+</th>
<th>TP</th>
<th>T-</th>
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</thead>
<tbody>
<tr>
<td>T+</td>
<td>0</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>TP</td>
<td>c</td>
<td>0</td>
<td>d</td>
</tr>
<tr>
<td>T-</td>
<td>e</td>
<td>f</td>
<td>0</td>
</tr>
</tbody>
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ADT Inequalities

- c > e
- a > b
- a > f
- c > d
- b < d
- e > f

Evolution mathematical models define intratumoral Darwinian dynamics during therapy.

The fitness function is set up as follows:

\[ G_i = r_i \left( \frac{K_i - (1 - E_i) \sum x_j}{K_i} \right) \]

where \( \sum x_j = x_1 + x_2 + x_3 \).

The population dynamics are a simple difference equation.

\[ \Delta x_i = x_i G_i \]

The PSA dynamics are shown below.

\[ \frac{d\text{PSA}}{dt} = f_1 x_1 + f_2 x_2 + f_3 x_3 - \sigma_{\text{PSA}} \cdot \text{PSA} \]

where \( \sigma_{\text{PSA}} = 0.3 \) and

where \( f_i \) is the PSA production per cell based on the frequency of TP cells.
Integrating adaptive therapy mathematical model into clinical oncology practice

- Initial administration of abiraterone
- When PSA is <50% of pretreatment value, discontinue abiraterone
- Tumor grows but treatment sensitive cells (TP and cheater T+) suppress growth of the resistant T- cells in the absence of treatment
- Resume abiraterone when PSA returns to the pretreatment level and start the cycle over
- Simulations predict control for 2 to 20 cycles

Jingsong Zhang, MD PhD
Accrual goals met: Cycle length 4 to 14 months. Earliest recurrence at 2 cycles. Some patients still on treatment at 14 cycles.

About 1 in 4 patients had long delay in upcycle after decline suggesting achievement of new steady state.

The novel eco-evolutionary dynamics of small populations.
Current status

Adaptive therapy patients received 41% (22-66%) of SOC

Average cost reduction: $50,00 per patient per year

Kaplan-Meier Estimate of Radiographic Progression

Control
Adaptive

$p<0.001$, Mantel's Log Rank

Median=14.3
Median=30.35

Estimated survival function

Time

0  10  20  30  40  50

0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1

Treatment sensitive cells have a positive (and probably $>1$) competition coefficient ($\alpha_{SR}$) for resistant cells in the absence of treatment.

Total suppression is function of $\alpha_{SR}N_S$, where $N_S$ is the number of resistant cells.
Subject 1010 progressed after 6 cycles (30 months). Inverse problem approach: Run the model backward from outcome to initial conditions followed by computational exploration of treatment parameter space to improve outcomes (West et al. Clin. Cancer Res. 2019).

Modeling recommendation: Stop abiraterone at 80% of pre-treatment value. Cycle time shorter but control maintained for 58 cycles ~ 63 months.

Mathematical analysis of evolution dynamics suggests future trial strategies and can investigate outcomes when other agents are added.
Extinction caused by application of massive evolutionary force also destroyed 60% of other land animal species.

In the popular imagination, extinction = KT impact caused by the extinction of the mighty dinosaurs.

Extinction caused by application of massive evolutionary force also destroyed 60% of other land animal species.

Brute force as an extinction strategy is limited by indiscriminate effects.

Current MTD treatment arguably mimics the dinosaur extinction – curing cancer by application of maximum force. But limited by toxicity to normal cells.

Pediatric oncologists: “Adaptive therapy is ok, but we only want cures”

Adult oncologists: “This is bullshit, just give me better drugs … ”

Back to the drawing board: Cancer Cure as Extinction of large, diverse, spatially-dispersed, asexually-reproducing clades.

Is there an alternative?
In the Anthropocene era, extinction dynamics have been revisited.

Key principle: Background and anthropogenic extinctions are multi-step, multi-cause. None of perturbations that cause the extinctions can, as a single agent, eradicate the species.

Intentional Anthropogenic extinction: The Galapagos Goat

First Strike
Reducing population size and heterogeneity

Second Strike
Dynamics of small populations
Once a population begins to decline, it is vulnerable to stochastic and Allee effects, which become synergistic and self-reinforcing.

**Hypothesis:** Small population dynamics in cancer treatment are relevant to eradication of microscopic metastases (adjuvant/neoadjuvant therapy) and following initial response in non-curative treatment.

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**Metastatic Pediatric Rhabdomyosarcoma**

Reed et al. *Cancer*, 2020
Highly effective therapies that reduce metastatic cancers to NED (e.g. ADT in mCSPC, platinum in pediatric sarcomas) are excellent first strikes but usually result in evolutionary rescue. Extinction vulnerability is maximum when the surviving populations is smallest and homogeneous.

Key Principle

*Time is of the essence*

Continued application of first strike therapy allows the surviving population to proliferate, occupy additional niches, and increase diversity.

*The opportunity to cause extinction is lost!*
Cancer therapy at MTD until progression

“Measurable” tumor >2 cm probably >1 billion cells.

Lessons from simulations
Waiting for measurable disease after first strike is too late
The ideal second strike is a sequence of different demographic and ecological perturbations. Continuous application of second-strike agent(s) until progression is evolutionarily unwise
Lessons from Anthropogenic extinctions

1. Kick them when they are down!

2. The final nail in the extinction decline is virtually never the first strike agent

Androgen Deprivation Therapy (ADT) is an effective first strike but never curative. When do you add second line therapies?
This theoretical strategy is virtually identical to treatment for curative treatment pediatric developed through decades of trial and error.

Lacking *magic bullets*, cure may be achievable through strategic combinations of regular bullets.
Integrating evolution and mathematics into routine clinical oncology
The Moffitt Evolution Tumor Board
Thank you

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