Disclosure

- I do not have any relevant financial relationships to disclose at this time.
Growth Kinetics Dissects the Complexity of Cancer

1. The Enigma
2. Implications of "Gompertzian" Growth
3. "Biology is Destiny"

Implications of "Gompertzian" Growth

Resistance is Mobile

The Enigma: Breast cancers are distinguishable by RNA expression patterns

(A Few More) Therapeutic Implications

Courtesy of Charles Perou, PhD
RNA patterns are thought to map to DNA mutations

DNA mutations are thought to underlie biology

Furthermore, many of the aberrations are targetable

The Enigma: So why is the cure of cancer so elusive?
Precise targeting is appropriate only when the target is solitary and not complicated.

A sharpshooter can help you here.

...but not here!

Is combination precision therapy the solution?

The Log-Kill Model predicts that proportional killing is multiplicative.

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Skipper HE, Schabel FM Jr, Wilcox WS.
Experimental Evaluation of Potential Anticancer Agents. XIII.
On the Criteria and Kinetics Associated with “Curability” of Experimental Leukemia.
Cancer Chemotherapy Reports, 35:1-111, 1964

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No Therapy One Drug

90% cell kill per administration

17

No Therapy One Drug Two Drugs

90% + 90% × 10% = 99% cell kill per administration of doublet

18

No Therapy One Drug Two Drugs Three Drugs

The Log-Kill Model predicts that proportional killing is multiplicative

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So why does this not always work?

Skipper HE, Schabel FM Jr, Wilcox WS.
Experimental Evaluation of Potential Anticancer Agents. XIII.
On the Criteria and Kinetics Associated with “Curability” of Experimental Leukemia.
Cancer Chemotherapy Reports, 35:1-111, 1964
Point #1: Having several sharpshooters is good, but only if they know where to aim

Point #2: The Skipper-Schabel Model is based on exponential growth, but cancers grow by Gompertzian kinetics

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The rate of regression of a Gompertzian tumor is proportional to its rate of growth
Hence, dose-dense sequential therapy should maximize the curative impact of cytotoxic chemotherapy.
OK, Gompertzian growth kinetics is true and it can be used to improve cancer therapy.

But what is the etiology of Gompertzian growth?
Tumor growth and cancer cell metastases are linked

**Minn et al., Nature, 2005**

![Graph showing growth in mammary fat pad](image)

- S-Phase Fraction (Ki67) Not Different

**Norton and Massague, Nature Med, 2006**

![Diagram of tumor growth and metastasis](image)

Tumor growth and cancer cell metastases are linked

**Kim et al., Cell, 2009**

![Diagram showing cancer cells prefer to go home](image)

Cancer cells prefer to go home

**Kim et al., Cell, 2009**
Cancer cells prefer to go home

Kim et al., Cell, 2009

Seeding from outside in explains the Gompertzian pattern of growth since as objects get larger their surface area to volume ratio decreases

\[
dN(t)/dt = (k_1-k_2)^*N^{d/3} - (k_3-k_4)^*(N - N^{d/3})
\]

Self-seeded growth explains cancer anatomy
Effective PI3Kα inhibition can be thwarted by different mutations that all lead to PTEN loss

But four separate metastatic sites had the same mutation

Breast cancer seeds create their own microenvironment by recruitment
Breast cancer seeds create their own microenvironment by recruitment

Kim MY et al., Cell, 2009

Blood vessels and leukocytes support the survival of the cancer cells exposed to chemotherapy

S. Acharyya et al., Cell 2012

Disrupting the leukocyte-cancer interaction augments the effects of chemotherapy

S. Acharyya et al., Cell 2012

Two more points of interest:

1. This might apply to checkpoint inhibition as well. (Chris Klebanoff)
2. The tumor infiltrating leukocytes are often (>50%) mutant with known oncogenic mutations. (M. Kleppe, E. Comen, R. Levine, J. Reis Filho)
In conclusion:

**Signaling is complex**

but results in predictable kinetics

and has many therapeutic implications.

**Thank You!**