Cooperation among cancer cells as a target for intervention

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Outline

1) The problem of acquired drug resistance in cancer
2) The role of cooperation among cancer cells
3) Avoiding drug resistance by disrupting cell cooperation.

1) The problem of acquired drug resistance in cancer

- Targeting cancer cells with cytotoxins is highly effective at "getting a response" (short-term tumor shrinkage).
- It is much less effective at improving patient outcomes.
- The reason for this is now abundantly clear: Darwinian selection and evolution among cells.

Acquired resistance is highly predictable, even for novel cytotoxins.

- To first approximation, every relevant mutation will arise.
  - The number of cancer cells is very large.
  - The number of mitosis events is much larger.
  - Genetic instability is extremely high.
- Any relevant pathway and molecule can be modified to resist a cytotoxin.
- The most effective cytotoxin is also the most effective selective agent.

We need a paradigm shift:

- If our goal is improved survival, developing more cytotoxins is not very promising!
- More promising strategies are available.

2) Cancer cells cooperate through shared 'public goods' molecules

- Angiogenesis factors
- Secreted growth and invasion factors
- Secreted immune suppression factors

From Pepper 2009, *Evolution*.

3) Avoiding drug resistance by disrupting cooperation, instead of killing cancer cells

- Production of effective public goods is not strongly selected.
- Impeding the effect of public goods molecules will not provoke a strong evolutionary response.
- Drugs impeding the effect of public goods molecules will not quickly lose efficacy.

Preferred drug targets

- Preferred targets are those that are more weakly maintained by somatic selection.
- Recent theory tells us what kind of external products to target…

Conditions favoring production of diffusible external goods

$$r > 1 - \frac{uL}{D}\left(\frac{b}{c} - 1\right)$$

r = statistical trait similarity between a focal cell and its neighbors

u = cell uptake rate of external good

L = diffusion length between cells

D = diffusion coefficient

b = fitness benefit of taking up external good

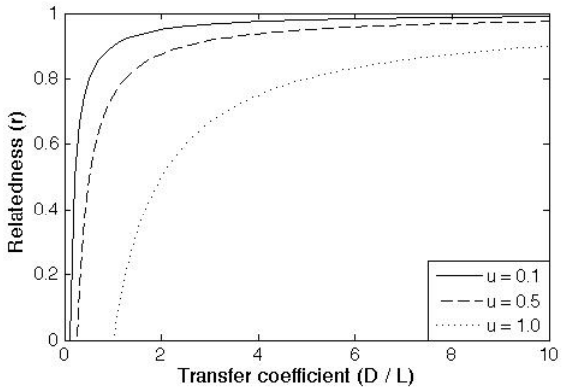
c = cost of producing external good

Driscoll & Pepper 2010, *Evolution*

Evolutionary robustness of diffusible external goods

Production of external goods is favored above the line:

More "private" molecules



More "public" external goods

Driscoll & Pepper 2010, *Evolution*

Preferred drug targets:

- More “private” beneficial molecules are more strongly maintained by somatic selection.
- Preferred targets are external goods that are most “public”: those with high transfer coefficients (large *D* & small *L*)

Limitations of the mathematical model

- Linear analytical math does not allow for complexities such as feedbacks from spatial effects.
- Starting from physics of diffusion does not provide an obvious link to the rest of evolutionary theory.

An agent-based computational model

- Explicitly represents each cell in the population
- Explicitly represents fitness effects on neighbors
- Explicitly represents Darwinian selection and evolution

Pepper & Driscoll, in prep

Basic evolutionary theory

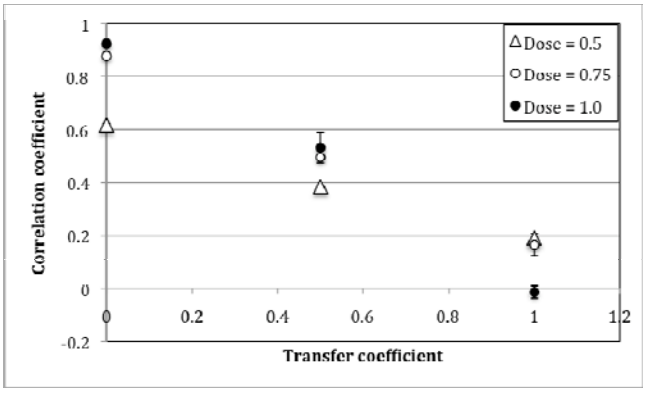
- Adaptive change per generation is a product of three factors:
  1) Population variance in trait value
  2) Population variance in fitness
  3) Correlation between trait value and fitness

Price 1970, Hamilton 1975

How do drugs against public goods compare?

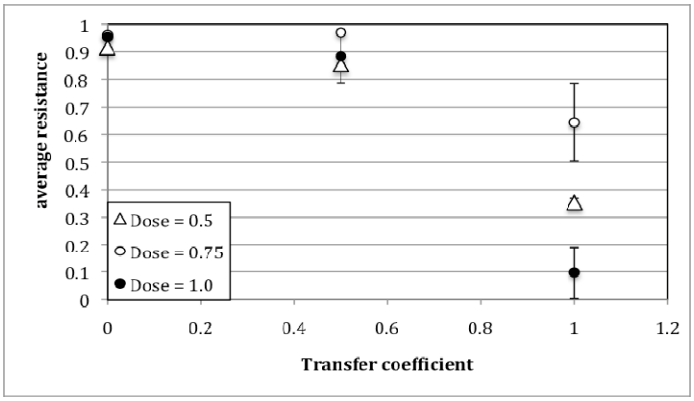
1) Population variance in trait value:
   No difference
2) Population variance in fitness:
   No difference
3) Correlation between trait value and fitness:
   - Significantly lower

Drugs targeting public goods reduce correlation of resistance with cell fitness



Pepper & Driscoll, in prep

Drugs targeting public goods reduce evolution of acquired resistance



Pepper & Driscoll, in prep

Blocking cancer public goods is effective:

- Angiogenesis
- Matrix metalloproteinases
- Local acidification (Gatenby)

Theory predicts this will be <u>both</u> effective and sustainable.

This is demonstrated for angiogenesis blockers, and should be tested for others ASAP.

Collaborators

- William Driscoll, *University of Arizona*
- Athena Aktipis, *University of Arizona*
- Carlo Maley, *Wistar Institute*
- Evolution in Cancer Working Group, *Santa Fe Institute*
- *PSOC center, USC*

Funders

- Vital Spark Foundation
- National Cancer Institute

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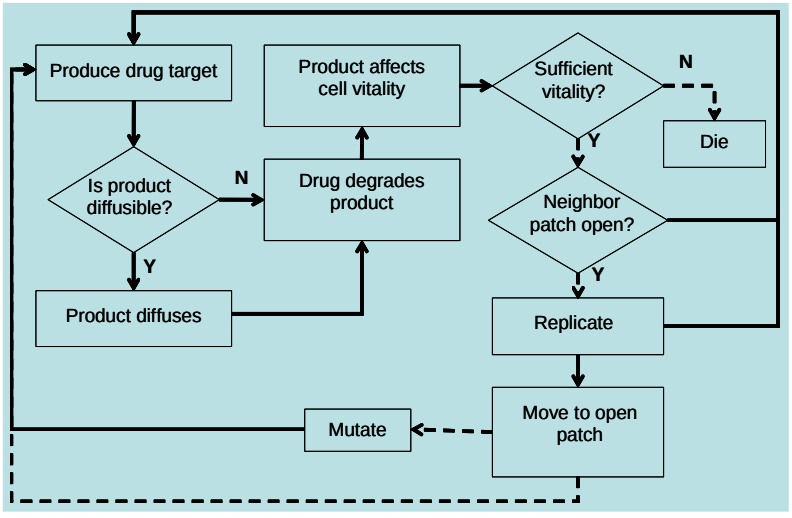
Questions, please!

(The following slides were skipped in talk to save time.)

2) The role of cooperation among cancer cells

- Like many pathogens, cancer cells thrive by modifying their micro-environment with shared, secreted, “public goods” molecules that increase the fitness of both the producer, and their neighboring cancer cells.
- These cooperative traits entail a cost to producer and a benefit to other cells, and thus require special conditions to be positively selected.
- They are less evolutionarily robust than the usual drug targets: cell-intrinsic traits effecting cell fitness.

Flow of events in agent-based model



What about targeted agents?

"Under the selective pressure of a toxic therapy, the genetic diversity within most human tumors leads to rapid outgrowth of drug-resistant cells.

"A vast array of resistance mechanisms… can defeat single agents, no matter how well designed and targeted."

- Chabner & Roberts (2005), *Nat. Rev. Cancer*

1) The problem of acquired drug resistance in cancer

- In the clinic, patients often respond to the initial application of a therapy but are prone to relapse, at which point repeating the same therapy is rarely effective. (Pepper et al, 2009, *Evol. Appl.*)
- Cancer therapies often cause the somatic evolution of resistance, which is the central problem in cancer therapy.(Merlo, Pepper, et al. (2006, *Nat. Rev. Cancer*)

The source of acquired drug resistance in cancer

- Most cancer drugs are designed to reduce the fitness (survival and proliferation) of the targeted cancer cells.
- This exerts a strong somatic selective pressure on the diverse individual cells, evoking rapid somatic evolution of drug resistance.

Diverse molecular mechanisms of resistance all arise through the same process: somatic evolution

- Cancer cells generate vast genetic diversity, affecting many pathways and properties.
- Cytotoxins act as powerful selective agents, eliminating drug-sensitive cells, and leaving only the most drug-resistant cells to flourish with reduced competition.
- Each cell generation repeats this process, generating numerous mechanisms of resistance

What is our real goal?

- "Melanoma Drug Vindicates Targeted Approach"
  K. Garber, 2009, *Science*
  - 70% response rate to PLX4032 described as "an astounding leap"
  - patients relapsed after about 9 months, and no survival benefit was demonstrated