PEQG26
Population, Evolutionary and Quantitative Genetics Conference

#368T

How Cancer Cells Undergoing a Treatment Course Evolve to Survive Multiple Mass Extinctions

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ABSTRACT

The vast diversity of genetic and phenotypic characteristics observed in human cancers, according to Hanahan (2026), can be understood in the context of how cancers arise via multistep pathways of tumorigenesis that lead to the formation of primary tumors, which subsequently evolve and progress due to selective advantage in the face of multifaceted barriers to continuing proliferative expansion, resulting in metastasis and adaptive resistance.

Here we elucidate the adversarial viewpoint: a *press-pulse* framework borrowed from paleobiology (Arens & West, 2008) for modeling therapeutic intervention targeted at the primary tumor, whose microenvironment undergoes *terraforming* and subsequently becomes unfit for cancer cells proliferation, leading to multiple *mass extinctions* over the course of cancer treatment, finally resulting in remission as the residual cancer cells turn quiescent.

The population dynamics driven by tumor growth vs. dose response is captured in our proposed model, as the cancer cells population follows a Gompertzian growth curve after metabolic reprogramming but shrinks in response to drug treatment. In particular, to shrink a tumor over multiple treatment cycles, dose responses are modeled as the outcome of catastrophic events decimating cancer cells as intravenous antibody-drug conjugate (Madhusoodanan, 2024) diffuses across blood vessel walls and penetrates the tumor, driven by concentration gradient according to Fick's laws.

Tumoral evolution within our framework offers mechanistic insights into the structure of a particular fitness landscape characterized by the selective pressure upon residual regrowth. We illustrate how subpopulations of residual cancer cells evolve to survive multiple mass extinctions originated from a prescribed course of antibody-drug conjugate targeting the primary tumor, potentially laying the seeds for future metastasis or adaptive resistance. We propose to construct a simulation testbed to further explore cancer population dynamics to better understand the mechanism of relapse.

INTRODUCTION

Antibody-Drug Conjugates Show Superior Response when Dosed at MTD

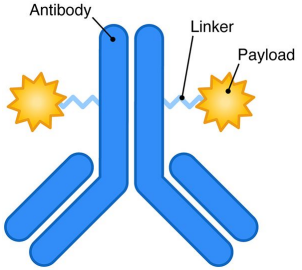


Fig. 1: Antibody-Drug Conjugate (ADC) [4]

Image Credit: Drago & Norton (2021)

Over the last two decades, an increasing number of antibody-drug conjugates (ADCs) have been approved for cancer treatment, broadening therapeutic options for patients beyond traditional small molecule drugs. Through their unique mode of action as *"magic bullets"*, these targeted therapies hold the promise of redressing the poor balance between *safety* and *efficacy* with traditional chemotherapy [4, 6].

The "sweet spot" between the lowest concentration that produces a desired therapeutic effect (minimum effective dose or MED) and the concentration just before toxicity kicks in (maximum tolerated dose or MTD) is called the *therapeutic window*.

When dosed at or near MTD, ADCs display improved efficacy over small molecules in trials. Across the board, ADCs have already achieved greater beneficial outcomes for patients compared with traditional chemotherapy. The *objective response rates* (ORR) of ADC treatments frequently score above 40 percent in breast, gastric, urothelial, and lung cancer trials where small molecules rarely exceed 25 percent [2, 8].

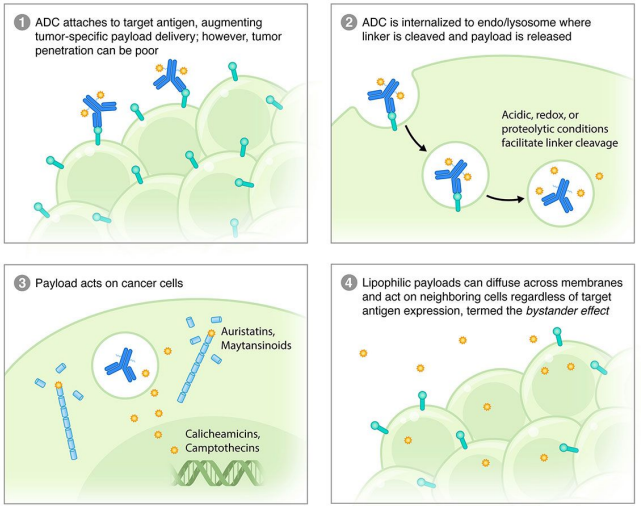


Fig. 2: Mechanism of Action for Antibody-Drug Conjugates [4].

RESEARCH QUESTION

How to Make a Tumor Microenvironment “Most Unfit” Under Press-Pulse?

Four forces that drive cancer cells population dynamics:

(a) **Tumor Growth**: proliferative cancer cells harness aerobic glycolysis to generate energy rapidly to drive tumor growth;

(b) **Pulse Therapy**: dose responses are the outcome of catastrophic events decimating cancer cells as intravenous drug diffusing across blood vessel walls penetrates the tumor;

(c) **Somatic Mutation:** somatic mutation during residual regrowth in between treatment cycles selects for drug-resistant cells that drive future cancer recurrence; and

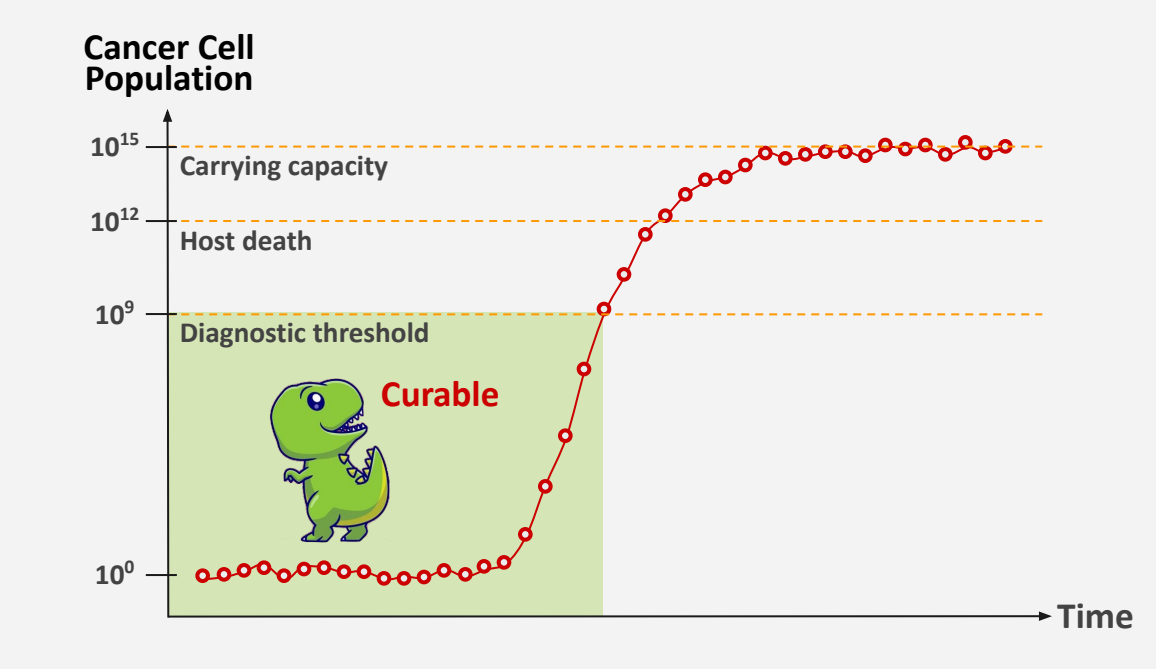
(d) **Press Therapy:** chronic microenvironmental stress (e.g., energy deprivation from starvation of glucose) slows down cell cycles and reduces cancer cells population resistance.

Fig. 3: **Terraforming** a tumor microenvironment under press-pulse.

Note: Cancer cells compete for resources in order to grow rapidly, while evading counterattacks. Mathematical models of tumoral evolution describe how cancer cell populations grow with aerobic glycolysis but shrink under drug treatment, just as Lotka-Volterra equations describe the population dynamics of snowshoe hares and the lynx that feed upon them. New complexity in population dynamics arises when somatic mutation across treatment cycles and metabolic intervention are introduced and added to the model.

METHODS — Tumor Growth

Modeling Tumor Growth with a Gompertzian Curve



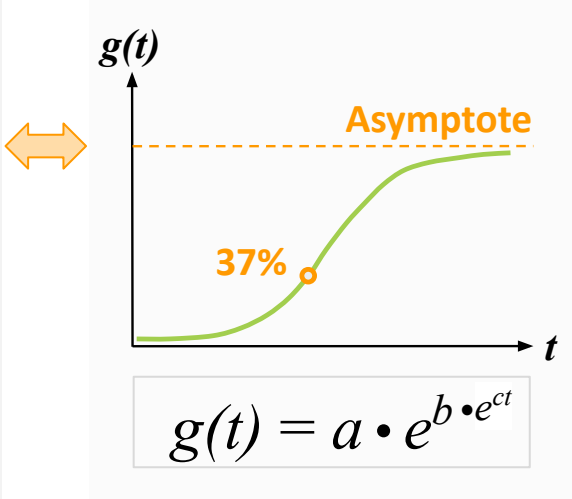


Fig. 4: **Gompertzian tumor growth:** initial growth at the inflection point appeared exponential, before slowing to approach the asymptote (i.e., asymmetric sigmoid curve).

METHODS — Pulse Therapy

1. Dose at Maximal Effective Concentration — Dependent on Size of Tumor

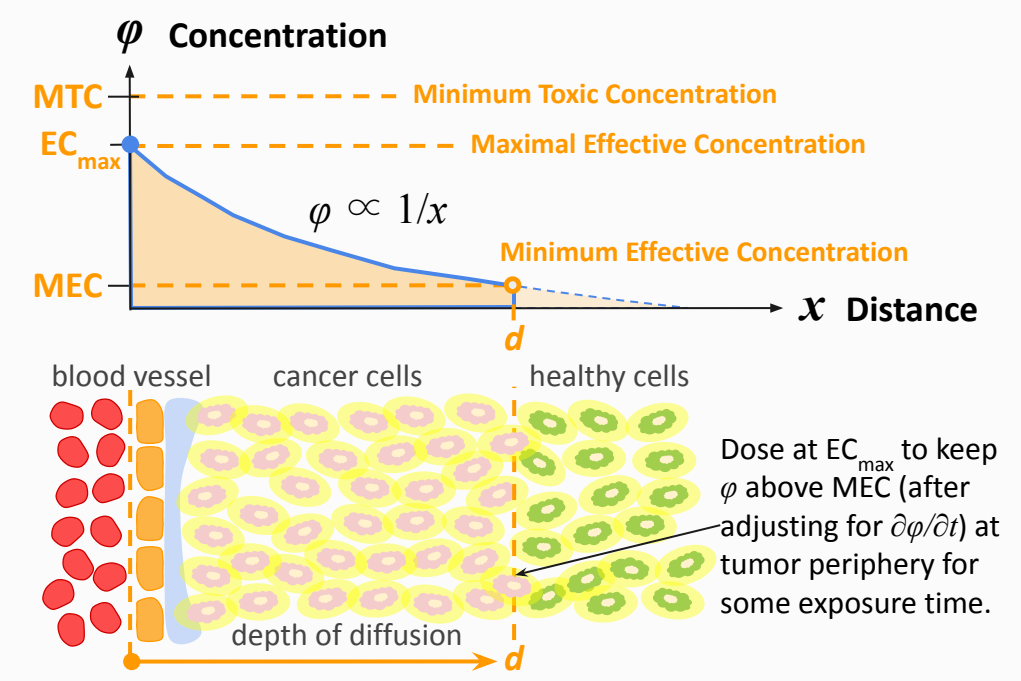


Fig. 5: **Fick's laws** describe diffusion driven by a concentration gradient, from high-concentration intravenous space to low-concentration intercellular space.

$$J = -D\frac{d\varphi}{dx}$$

Fick's 1st law

where

- J is the diffusion flux, which measures the amount of substance flowing through a unit area during a unit time interval,
- D is the diffusion coefficient, or diffusivity, in area per unit time.

$$\frac{d\varphi}{dx} = \frac{1}{x^2}$$

Concentration gradient formula

METHODS — Pulse Therapy

2. Compute Dose Response Curve — for Each Tumor Size and Shape

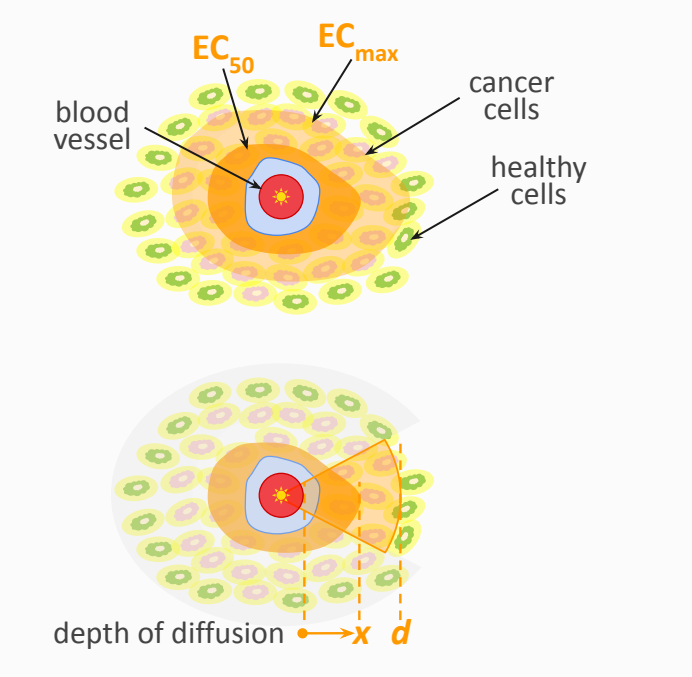


Fig. 6: **Cross-sectional view:** depth of diffusion into a tumor determines effective concentration of dose.

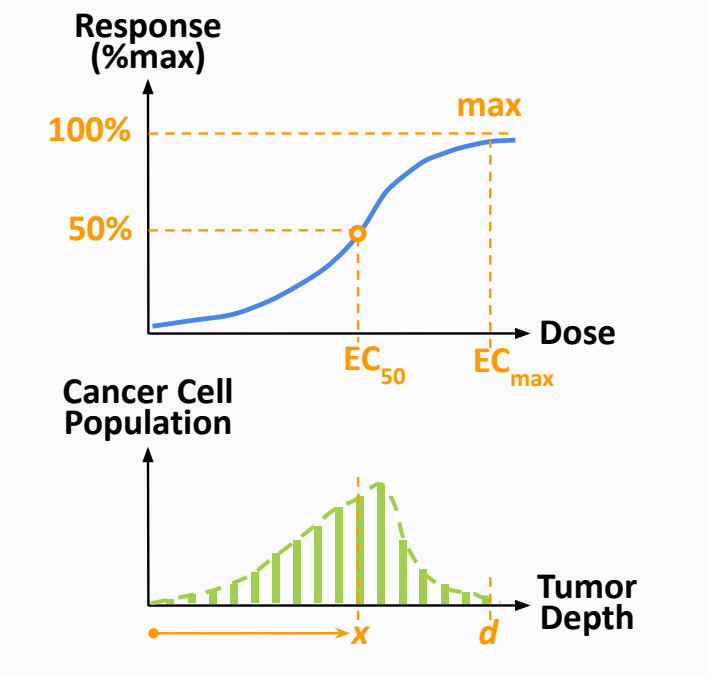


Fig. 7: **Dose response curve** computed based on cancer cell population reachable at each tumor depth.

METHODS — Pulse Therapy

3. Adjust Dose Response Model — as Concentration Decreases Over Time

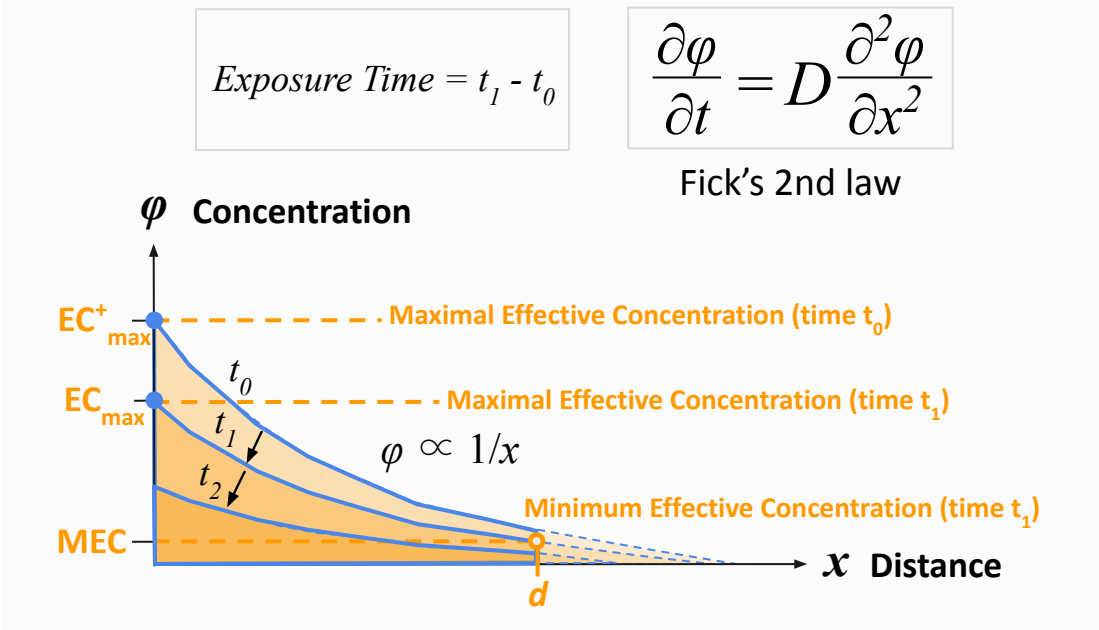


Fig. 8: **Changing concentration:** ensure tumor periphery at *d* has enough exposure time (t_1 - t_0) by working backwards to set maximal effective concentration at EC^+_{max}.

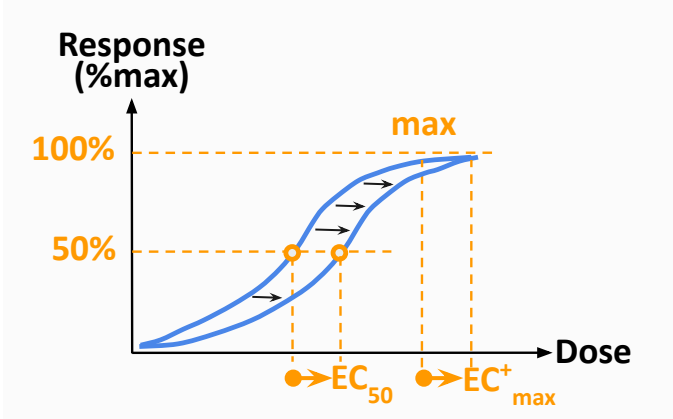


Fig. 9: Dose response model adjusted for maximal effective concentration (at EC^+_{max}).

DISCUSSION — Somatic Mutation

Cancer Cells Evolve in Between Treatment Cycles to Survive Mass Extinctions

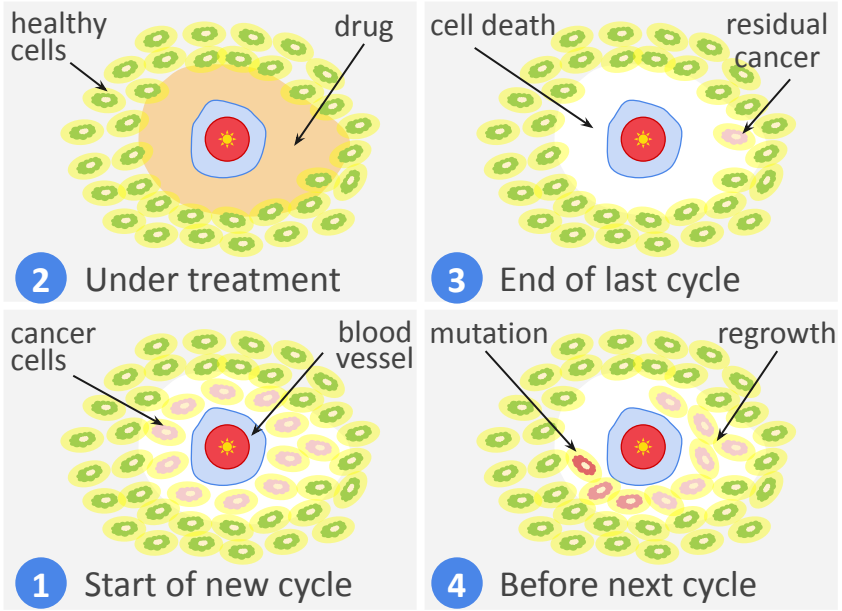


Fig. 10: **Residual regrowth** in between treatment cycles selects for drug-resistant cells that drive future cancer recurrence.

Would starving *proliferative* cancer cells of glucose improve dose response for cancer patients?

Could one switch to a *reduced dose* regimen without compromising dose response by going on a calorie-restricted diet to bring down the glucose level, which slows down the cell cycle and makes proliferative cancer cells more vulnerable?

It follows that one could then apply a *denser* dose schedule to suppress residual regrowth while also shortening treatment cycles.

Reduced heterogeneity in the tumor would then make relapse less likely, thus maximizing disease-free survival (DFS) for cancer patients.

DISCUSSION — Press Therapy

Making Proliferative Cancer Cells Vulnerable Through Bioenergetic Intervention

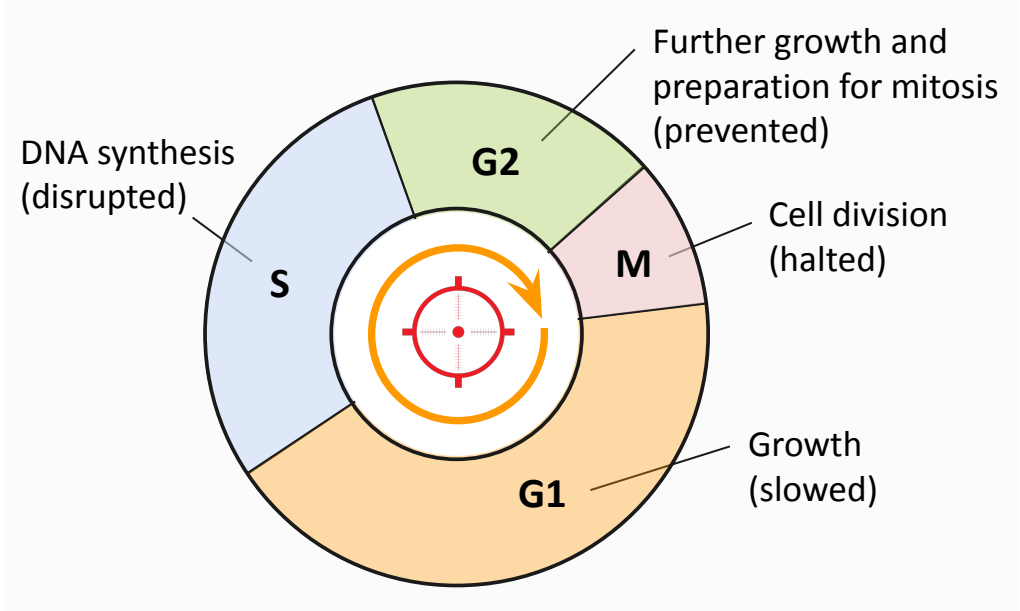


Fig. 11: **Proliferative cancer cell cycle:** glucose restriction can cause cancer cells to stay in G1 phase longer (or become quiescent), so cell-cycle (S/G2/M) targeting drug has ample time to enter cancer cells before the start of its targeted phase (e.g., to disrupt DNA synthesis), thus improving dose response.

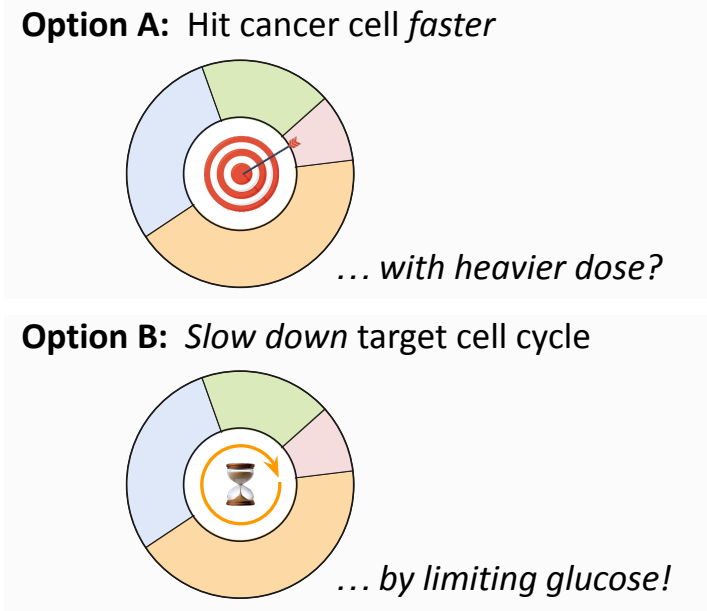


Fig. 12: **Epiphany:** either: (A) magic bullet moves *faster* to hit cancer cells with heavier dose of ADC at a higher concentration gradient; or (B) we *slow down* target cell cycle awaiting magic bullet arrival.

CONCLUSIONS

The Dose Makes the Poison: “Pulse Train” Designed to Suppress Regrowth

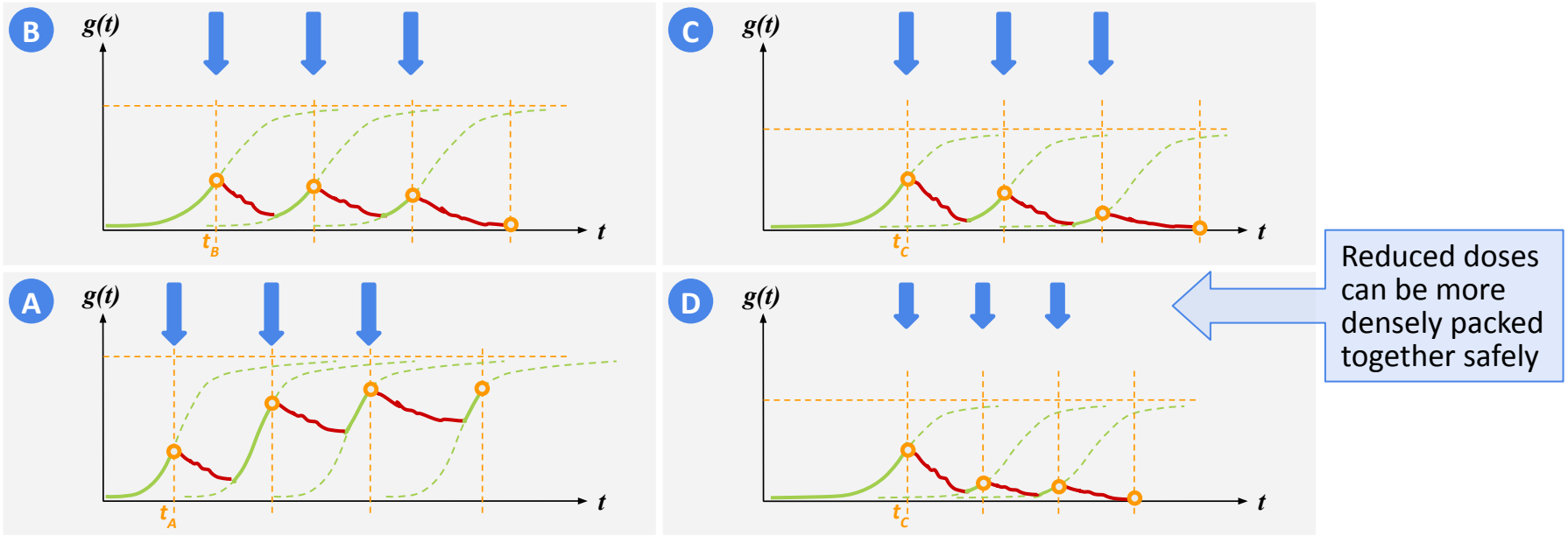


Fig. 13: Residual regrowth between treatment cycles drives somatic mutation: (A) high residual regrowth fails to shrink primary tumor, (B) baseline residual regrowth shrinks primary tumor but neglects somatic mutation, (C) low residual regrowth under press therapy reduces somatic mutation, and (D) least residual regrowth under press therapy minimizes somatic mutation with a *denser* dose schedule.

FUTURE WORK

Safer ADC Regimens That Also Maximize Disease-Free Survival?

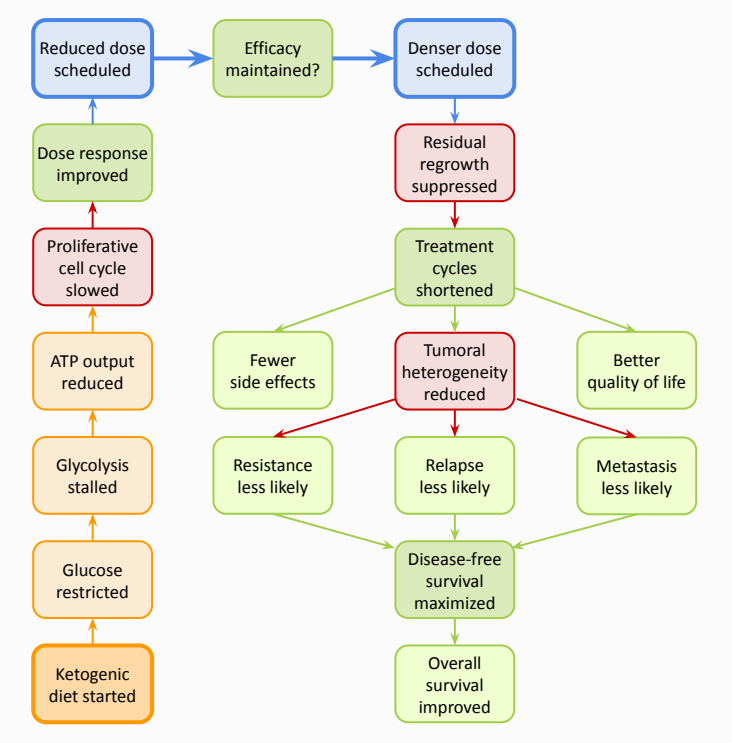


Fig. 14: *Chain-of-thought reasoning* for our research design.

We illustrated how tumor size and bioenergetics together determine dose response, which we see as multifaceted and not simply a static curve as commonly believed. Importantly, a cancer patient can improve dose response when combined with bioenergetic intervention.

Our ongoing research has therapeutic implications: a *safer* ADC regimen realized through improved dose response modeling benefits not just late-stage cancer patients considering palliative care, but also early-stage cancer patients seeking alternative treatment paths that maximize long-term *disease-free survival* [3].

By taking a longer view of DFS as an alternate endpoint, we hope to optimize *safety* and *efficacy* together by limiting residual regrowth during treatment — unlike traditional chemotherapy preoccupied with maximizing cell kill in the primary tumor, sacrificing safety.

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