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Targeted Therapy at the Wrong Biological Level

A Systems Reassessment of Cancer Targeting

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For more than two decades, "targeted cancer therapy" has been defined primarily as mutation-matched pharmaceutical treatment. Drugs directed against EGFR, ALK, BRAF, HER2, and more recently KRAS mutations have represented genuine scientific progress. These advances deserve recognition.

However, an important structural question remains:

Have we defined "targeted therapy" at too narrow a biological level?

Precision Is Not the Same as Breadth

Population-level analyses published in major oncology journals indicate that only a minority of metastatic cancer patients are eligible for genome-driven targeted therapies. Updated estimates suggest that approximately 13-15% of metastatic patients qualify for such treatments, and only a smaller fraction derive measurable clinical benefit.

When structural constraints - including intratumoral heterogeneity and time-limited durability due to acquired resistance - are incorporated, the fraction of the overall metastatic population achieving durable, multi-clonal tumor control may plausibly fall into the low single-digit range. In a semi-quantitative illustrative model presented in the accompanying preprint, compounded estimates suggest an effective coverage on the order of approximately **2-3%** under conservative assumptions. Even under favorable assumptions, mutation-matched targeted therapy remains structurally incapable of delivering durable, multi-clonal control for most metastatic patients.

This figure is conceptual rather than definitive. Its purpose is to highlight the multiplicative structural limits of single-node genomic targeting.

These therapies are precise.

But they are not broadly applicable.

Even among eligible patients, tumor evolution and intratumoral heterogeneity limit durability. Multi-region sequencing studies demonstrate that many mutations are not present in all tumor regions. Acquired resistance is not a failure of targeted therapy - it is an expected evolutionary consequence of selective pressure on a single molecular node.

Precision at one genomic locus does not automatically translate into comprehensive tumor-system control.

This distinction is foundational.

Cancer Is a Systems Disease

Cancer is not sustained solely by discrete mutations. Mutations occur within a broader biological architecture that includes:

- Metabolic reprogramming
- Redox buffering systems
- Replication stress adaptation
- Proteostasis maintenance
- Insulin-IGF signaling dynamics
- Hypoxia and acidic microenvironments

These are not rare molecular subsets.

They are distributed functional programs.

Tumor survival and evolutionary persistence depend on this shared survival infrastructure.

When oncology equates "targeted" exclusively with mutation-matched pharmacology, it implicitly restricts targeting to a narrow biological layer.

The question is not whether genomic targeting works.

The question is whether it is sufficient as a general doctrine.

A Hierarchical View of Targeting

The newly released preprint proposes a layered framework for cancer targeting:

Layer 1 - Genomic Targeting

Mutation-specific drugs directed at defined molecular nodes.

High specificity. Narrow distribution.

Layer 2 - Redox Targeting

Exploiting tumor vulnerability in peroxide detoxification systems.

Pharmacologic ascorbate (high-dose intravenous vitamin C, HDIVC) achieves plasma concentrations in the range of approximately **20-30 mM**, levels not attainable through oral dosing, which is typically limited to peak plasma concentrations in the low hundreds of micromolar range. This several-hundred-fold exposure differential fundamentally changes ascorbate's biological behavior.

At these pharmacologic concentrations, ascorbate can generate extracellular hydrogen peroxide (H_2O_2) in the presence of redox-active metal ions. Tumor cells frequently operate under elevated baseline reactive oxygen species (ROS) and exist near oxidative stress thresholds.

In a comparative multi-cell line analysis (15 tumor vs 10 normal cell lines), Doskey et al. demonstrated that normal cells exhibited approximately **twofold greater hydrogen peroxide clearance capacity** than tumor cells on average. Moreover, ascorbate sensitivity (ED_{50}) correlated inversely with peroxide detoxification rate constants and catalase activity, indicating that differential H_2O_2 metabolism is mechanistically linked to selective cytotoxicity.

Additional preclinical work has shown that pharmacologic ascorbate disrupts tumor iron metabolism and increases oxidative stress selectively in certain KRAS- and BRAF-mutant contexts, further supporting a biologically coherent redox vulnerability axis.

This is not mutation-targeting.

It is phenotype-targeting - exploiting a distributed functional vulnerability (peroxide detoxification capacity) rather than a rare genomic alteration.

Layer 3 - Metabolic/Systemic Targeting

Addressing insulin-IGF signaling, substrate restriction, and metabolic inflexibility through ketogenic metabolic therapy and host-level modulation.

Cancer metabolism is heterogeneous but widely distributed across tumor types. A pan-cancer TCGA analysis encompassing **9,668 patients across 33 tumor types** identified glycolysis- and oxidative phosphorylation-dominant metabolic phenotypes using transcriptomic scoring frameworks, demonstrating that metabolic reprogramming is not confined to rare molecular subsets but represents a cross-tumor organizational axis.

Insulin and IGF signaling activate PI3K-AKT-mTOR pathways across multiple malignancies. Hyperinsulinemia has been associated epidemiologically with increased cancer progression risk, and insulin receptor/IGF signaling components are expressed across a broad spectrum of tumor types. Unlike mutation-restricted targets, insulin signaling is a systemic growth-regulatory axis affecting both tumor cells and the tumor microenvironment.

Ketogenic metabolic therapy reduces circulating insulin levels - often by **30-50% or more** in insulin-resistant individuals - and lowers glucose availability while increasing ketone bodies. Many tumor cells demonstrate relative metabolic inflexibility and impaired ketone utilization compared with normal tissues, creating a potential host-mediated energetic differential.

This is not clone-specific targeting.

It is host-ecosystem targeting - modulating growth signaling and substrate availability at the systemic level rather than inhibiting a single genomic node.

Each layer operates at a different level of biological organization. Each exploits a different form of vulnerability.

Together, they form a hierarchy of intervention breadth.

Semi-Quantitative Perspective: Effective Target Coverage

The preprint introduces a conceptual metric termed "Genomic Effective Target Coverage" (GETC), which considers:

- Population eligibility
- Response among eligible patients
- Tumor-cell coverage within heterogeneous tumors
- Durability of response

When these factors are compounded multiplicatively, the resulting effective coverage can shrink substantially - even when each individual parameter appears clinically meaningful.

This is not a criticism of precision oncology.

It is a reminder that structural constraints compound.

High molecular precision does not necessarily translate into broad tumor-system impact.

Redefining "Targeted"

In this context, "targeted" should be understood as referring to molecular specificity - not population-wide effectiveness.

If targeting is defined instead by the biological level at which vulnerability is exploited, then redox and metabolic interventions qualify as legitimate targeting modalities.

They target:

- Hydrogen peroxide detoxification limits
- Catalase capacity
- Insulin-IGF growth signaling
- Metabolic substrate dependence

These are not nonspecific approaches.

They are biologically coherent.

They simply operate at broader levels of tumor architecture.

Not Replacement - Expansion

This framework does not reject genomic therapy.

It rejects reductionism as a monopoly.

Genomic, redox, and metabolic targeting are not competitors. They are interoperable layers.

Cancer biology is hierarchical. Therapeutic strategy should be as well.

The future of oncology may not lie in choosing between precision drugs and metabolic or redox strategies, but in integrating them within a systems doctrine that expands effective target coverage across heterogeneous tumor ecosystems.

Precision remains essential.

But precision without breadth is incomplete.

The full manuscript, *"Targeted Therapy Has Been Operationalized at a Narrow Biological Level,"* is available at:

Cheng, R. Targeted Cancer Therapy Has Been Defined at a Narrow Biological Level-A Hierarchical and Semi-Quantitative Reassessment of Genomic, Redox, and Metabolic Targeting. Preprints 2026, 2026021555. https://doi.org/10.20944/preprints202602.1555.v1