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Synthetic Lethality as a Conditional Cellular State: A Theoretical Framework Integrating Paralog Buffering, Metabolic Compensation, and Treatment-Induced Plasticity in Molecular Oncology

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Abstract

Synthetic lethality has become an important strategy for exploiting selective vulnerabilities created by cancer-associated molecular alterations. Yet the therapeutic expression of a synthetic-lethal relationship is often less stable than a simple pairwise genetic model implies. Dependency can vary with cellular background, compensatory paralog activity, metabolic configuration, treatment exposure, and the experimental conditions used to measure fitness. This theoretical article develops an evidence-bounded account of synthetic lethality as a conditional cellular state rather than solely a fixed property of two genes or pathways. The analysis distinguishes a candidate synthetic-lethal interaction from the realized vulnerability that emerges when compensatory capacity is insufficient in a particular biological and treatment context. It further separates genuine biological conditionality from variation caused by assay design or model choice. Paralog buffering provides a mechanistically tractable example of how nominally similar lesions can produce different dependencies, while metabolic compensation and treatment-induced plasticity provide temporally dynamic routes through which vulnerability may persist, weaken, or re-emerge. The resulting account generates testable expectations for dependency mapping, biomarker development, pharmacological validation, and resistance research without assuming that all synthetic-lethal interactions are equally plastic or context sensitive.

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Introduction

Synthetic lethality provides a compelling logic for selective cancer therapy because loss or inhibition of one molecular function can create disproportionate dependence on another. Its clinical importance is most clearly demonstrated by therapeutically exploited DNA-repair dependencies, yet contemporary analyses increasingly show that the expression of synthetic lethality can depend on biological context rather than on gene-pair identity alone (Chang *et al.*, 2026). This creates an important interpretive problem for precision oncology. A relationship identified genetically may be robust in one cellular background but attenuated in another, and a dependency detectable by experimental perturbation may not automatically translate into a pharmacologically exploitable therapeutic window (Gonçalves *et al.*, 2026).

The PARP–homologous-recombination paradigm remains the strongest clinical proof that a genetically defined vulnerability can be converted into therapeutic selectivity (Lord *et al.*, 2026). Its success, however, should not be treated as evidence that every candidate synthetic-lethal relationship behaves with comparable stability. Pan-cancer analyses of synthetic-lethality-driven precision oncology instead reveal substantial dependence on molecular stratification, tumor context, and the evidence used to nominate a relationship (Schäffer *et al.*, 2024). The central question therefore extends beyond whether two genes can satisfy a synthetic-lethal definition under some experimental condition. It concerns when that interaction becomes a biologically realized and therapeutically accessible vulnerability.

Large cancer-dependency maps reinforce this distinction. Clinically informed CRISPR analyses show that selective dependencies are distributed unevenly across molecular backgrounds and that prioritization improves when genomic and cellular context is considered explicitly (Pacini *et al.*, 2024). Translational mapping of dependency information onto tumor genomic datasets likewise illustrates both the potential and the limitations of moving from experimental cancer models to patient-relevant predictions (Shi *et al.*, 2024). Dependency is therefore an



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operationally measured phenotype whose interpretation depends on the biological system and on how the perturbation is observed.

This article develops a theoretical account in which a candidate synthetic-lethal interaction and a realized synthetic-lethal vulnerability are analytically distinct. The former refers to a molecular relationship capable of producing selective loss of fitness under defined conditions. The latter refers to the cellular state in which that relationship is expressed strongly enough, and with sufficient selectivity, to constitute a meaningful biological or therapeutic vulnerability. The argument focuses on three mechanisms capable of separating these levels: paralog buffering, metabolic compensation, and treatment-induced plasticity. The framework remains explicitly conditional: some synthetic-lethal relationships may be highly stable, whereas others may depend strongly on background genotype, cellular state, treatment history, or measurement design.

Materials and Methods

Synthetic Lethality beyond Fixed Genetic Dependency

Large-scale functional-genomic studies established that cancer-cell fitness dependencies are not distributed as invariant properties across malignancies. Dependency maps show extensive heterogeneity across cell lines and molecular backgrounds, with only subsets of models exhibiting strong reliance on many individual genes (Tsherniak *et al.*, 2017). Deep RNA-interference screening similarly identified selective dependencies and candidate synthetic-lethal relationships rather than a uniform catalogue of universally essential cancer genes (McDonald *et al.*, 2017). These observations do not weaken the concept of synthetic lethality. They instead indicate that the relevant unit of interpretation is frequently the interaction within a specified cellular context.

Measurement itself can also alter the apparent boundary of a dependency. CRISPR-Cas9 screens demonstrated that copy-number amplification can generate gene-independent cutting toxicity that resembles essentiality unless computational correction is applied (Meyers *et al.*, 2017). Conversely, large-scale CRISPR target-prioritization studies show that appropriately controlled genetic perturbation can identify biologically selective targets across cancer models (Behan *et al.*, 2019). A measured loss-of-fitness phenotype must therefore be separated from the mechanistic claim used to explain it. The same observed phenotype can arise from a genuine conditional dependency, a perturbation-specific artifact, or a combination of biological and technical factors.

Cross-dataset comparison provides a second reason to resist a purely fixed interpretation. Major pan-cancer CRISPR dependency resources show substantial agreement while retaining meaningful differences attributable to libraries, models, analytical procedures, and biological context (Dempster *et al.*, 2019). Environmental composition can be equally consequential. Screening cells in media designed to approximate physiological nutrient concentrations reveals conditionally essential genes that are not equivalently detected under conventional culture conditions (Rossiter *et al.*, 2021). Thus, cellular environment can alter which compensatory routes remain available even when genotype is unchanged.

These findings support an operational distinction between a nominal interaction and an expressed dependency. A synthetic-lethal claim is most informative when it specifies the initiating molecular lesion, the partner perturbation, the biological context in which compensation is available or restricted, and the measurement conditions used to infer loss of fitness. The relevant sources of conditionality are summarized below without assuming that every dependency is controlled by all of them.

Table 1 summarizes biological and measurement conditions that can change the expression of a synthetic-lethal dependency.

Table 1. Biological and measurement conditions that can change the expression of a synthetic-lethal dependency

Conditional dimension	Scientific variable being altered	What is directly observed	Interpretation permitted	Main boundary
Molecular background	Genotype, lineage, co-alterations	Selective change in perturbation fitness	Dependency is background-sensitive	Association alone does not identify mechanism
Gene dosage context	Copy number and locus structure	Altered apparent CRISPR fitness effect	Some essentiality calls require correction	Cutting toxicity can mimic dependency
Perturbation platform	RNAi, CRISPR or related functional assay	Different strength or reproducibility of fitness effects	Measurement method influences detectability	Platform effect is not biological compensation
Nutrient environment	Availability of physiologically relevant metabolites	Gene essentiality changes between media states	Metabolic environment can condition dependency	Culture medium is not equivalent to tumor physiology
Model-to-tumor transfer	Cell-model versus tumor molecular context	Predicted correspondence of dependency with tumor features	Context can improve translational prioritization	Prediction is not patient-level therapeutic validation

The distinction can be visualized as a conditional landscape rather than a fixed pairwise switch. A candidate genetic interaction occupies only one layer; the observed dependency emerges after biological context and measurement conditions determine whether the interaction is actually expressed.

Figure 1 summarizes conditional expression of a synthetic-lethal interaction across biological and measurement contexts.

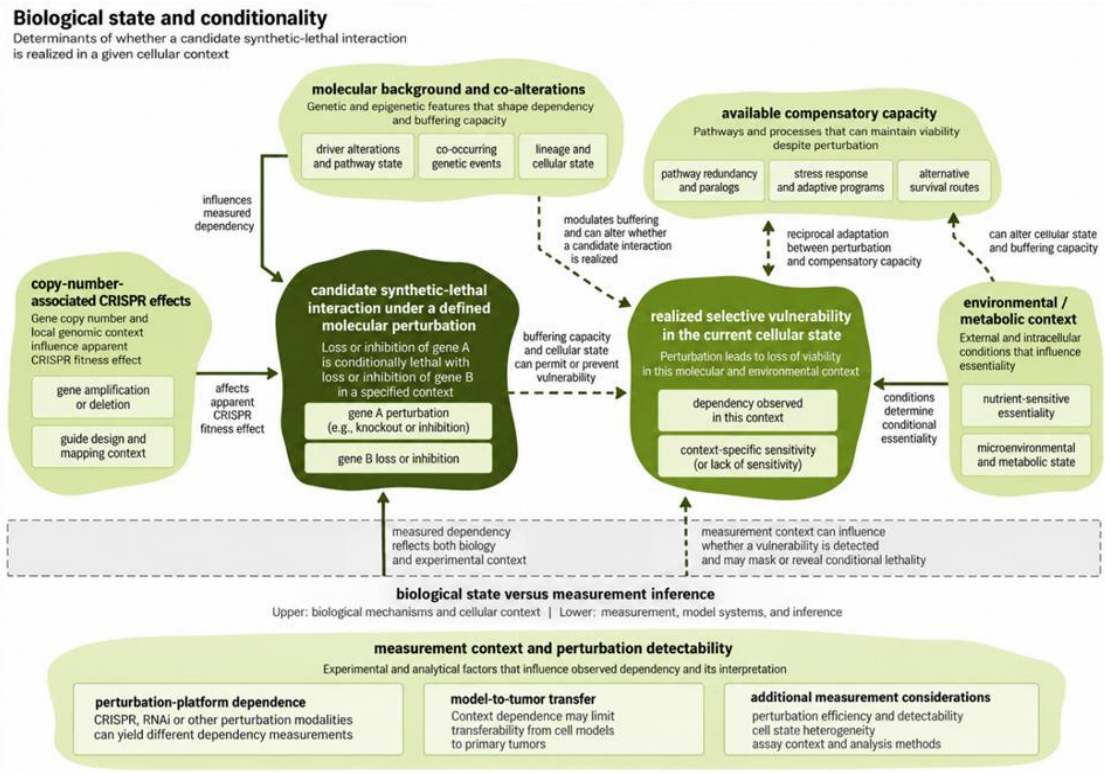


Figure 1. Conditional expression of a synthetic-lethal interaction across biological and measurement contexts

Paralog Buffering and Compensatory Molecular Interactions

Paralog relationships provide a particularly clear setting in which a fixed-pair interpretation becomes inadequate. Large combinatorial analyses show that synthetic lethality among paralog pairs is heterogeneous across cancer backgrounds, with interaction penetrance influenced by additional molecular features rather than by paralog identity alone (Flister *et al.*, 2025). Genome-scale discovery studies likewise identify specific paralog pairs in which loss of one gene exposes dependence on the other, while many apparently redundant pairs do not produce equivalent synthetic-lethal behavior (Parrish *et al.*, 2021). The relevant variable is therefore not duplication by itself but the amount and form of function that remains available after one paralog is lost.

Predictive analyses reinforce this conclusion. Some paralog pairs exhibit robust synthetic lethality across many cellular contexts, whereas others require particular genomic or transcriptional backgrounds (De Kegel *et al.*, 2021). Broader dependency analyses show that paralog buffering contributes to the variable essentiality of human genes, reducing the phenotypic consequence of perturbation when overlapping function remains accessible (De Kegel & Ryan, 2019). Network-level analyses further indicate that paralogs can support robustness indirectly through their placement in molecular interaction systems rather than through simple one-for-one replacement (Dandage & Landry, 2019). Functional redundancy should consequently be treated as a graded property embedded in a cellular network.

Direct experimental evidence shows how this grading can become mechanistically decisive. In cancer cells dependent on TRA2A, the paralog TRA2B can compensate when expressed at sufficient levels, demonstrating that paralog buffering can depend on dosage and molecular state rather than merely on sequence similarity (Lee *et al.*, 2025). Proteomic analysis of gene-loss contexts provides a complementary mechanism: loss of one paralog can increase the abundance of another and thereby preserve parts of a protein-interaction network (Venkatesh *et al.*, 2025). Importantly, such compensation is not the dominant outcome for every paralog pair. Its selective occurrence is precisely what makes it relevant to conditional synthetic lethality.

The translational consequences are visible in defined cancer genotypes. SMARCA4 loss can create selective reliance on SMARCA2, enabling pharmacological degradation of SMARCA2 to exploit a paralog vulnerability in appropriately selected cancers (Hulse *et al.*, 2026). At the same time, reviews of paralog-based synthetic lethality emphasize that identifying a genetic dependency is only one step; achieving paralog-selective pharmacology and an adequate therapeutic window can remain difficult (Ryan *et al.*, 2023). Other chromatin-regulatory systems provide similarly restricted examples. SMARCB1-deficient cancers can acquire specific dependencies involving CBP/p300-associated regulatory biology rather than a universal dependence shared by all tumors (Sasaki *et al.*, 2024).

Conditional molecular interactions also extend beyond the simplest duplicate-gene model. Mesenchymal-like cancer states can expose dependence on CDS2, illustrating how a cellular phenotype can delimit the population in which a candidate synthetic-lethal mechanism operates (Arnoldus *et al.*, 2025). In glioblastoma, VRK2 deficiency creates selective vulnerability to VRK1 disruption, again showing that the loss of a related function can uncover partner dependence in a defined molecular setting (Shields *et al.*, 2022). These cases converge on one conclusion: paralog buffering and compensatory interaction are mechanisms that determine whether a candidate dependency is expressed, not merely background annotations applied after a synthetic-lethal pair has already been defined.

The distinctions required for the later conditional-state model are summarized below.

Table 2 summarizes mechanistically distinct routes through which compensation modifies synthetic-lethal vulnerability.

Table 2. Mechanistically distinct routes through which compensation modifies synthetic-lethal vulnerability

Compensatory route	Relevant molecular condition	What remains available after primary loss	Expected effect on vulnerability	Key interpretation boundary
Direct paralog redundancy	Overlapping biochemical or regulatory function	Partner paralog activity	Can weaken dependence when residual function is sufficient	Similarity does not guarantee functional rescue
Dosage-sensitive buffering	Compensating paralog expressed above a functional requirement	Increased partner dosage or activity	Vulnerability varies with expression state	Expression is not equivalent to complete functional substitution
Proteomic compensation	Gene loss changes abundance or stability of related proteins	Preserved protein-interaction capacity	Can maintain network function despite gene loss	Compensation is selective, not a universal response
Network-mediated robustness	Multiple connected proteins preserve pathway output	Distributed functional support	Can reduce the phenotypic effect of single-gene perturbation	Network association alone does not establish causal rescue
Genotype-restricted partner dependence	Loss of one paralog or regulator removes alternative function	Remaining partner becomes disproportionately necessary	Can create a strong selective dependency	Dependency remains genotype and disease-context specific
Phenotypic-state dependence	A defined cellular state restricts alternative routes	Limited pathway or metabolic alternatives	Can expose vulnerability only in selected states	State association must be separated from direct mechanism

Together, these observations supply the first mechanistic component of the conditional-state account. A synthetic-lethal relationship can remain latent when alternative molecular capacity is sufficient and become strongly expressed when that capacity falls below what the cell requires. The relevant compensatory capacity may be supplied by a direct paralog, by altered protein abundance, or by a wider interaction network. Because these mechanisms operate differently across backgrounds, the same nominal genetic relationship need not generate the same cellular consequence. Sections that follow extend this logic beyond relatively local molecular buffering to metabolic compensation and treatment-induced changes in cellular state.

Metabolic Compensation and Treatment-Induced Cellular Plasticity

Paralog buffering explains one route by which a candidate synthetic-lethal relationship can remain incompletely expressed, but compensatory capacity is not confined to related genes. Metabolic state can alter which pathways remain available after a perturbation and thereby change the fitness consequence of the same nominal molecular lesion. Multivariate analyses across cancer contexts demonstrate that metabolic configurations are associated with different vulnerability patterns, including combinations consistent with context-selective synthetic lethality (Abecunas *et al.*, 2024). Metabolic and epigenetic remodeling also interact during treatment adaptation, allowing cancer cells to redistribute pathway dependence rather than preserving a single pre-treatment state (Gantner *et al.*, 2024). Such observations place cellular metabolism within the causal environment in which a synthetic-lethal interaction is expressed.

Treatment history introduces a temporal dimension. Drug-tolerant persister populations can survive otherwise effective therapy through reversible or semi-stable cellular states that differ from both untreated cells and genetically fixed resistant clones (Russo *et al.*, 2024). These populations are heterogeneous, and their trajectories need not reflect a single molecular program. Reviews of persister plasticity nevertheless show that therapy can change transcriptional, signaling, metabolic, and phenotypic states sufficiently to alter subsequent drug sensitivity (He *et al.*, 2024). The resulting liabilities may themselves become targetable, although no universal persister vulnerability has been established (Liu *et al.*, 2025). Consequently, a synthetic-lethal dependency measured before treatment cannot be assumed to retain identical penetrance after sustained exposure or during recovery.

Direct metabolic synthetic-lethal examples support the same principle at a more restricted mechanistic level. PI3K-driven cancer can display metabolic dependencies that become selectively exploitable in the presence of defined oncogenic signaling states (Andrieu *et al.*, 2025). Broader analyses of cancer metabolism

similarly show that metabolic rewiring generates dependencies whose therapeutic importance depends on tissue environment, nutrient availability, pathway configuration, and competing routes of energy or biosynthetic support (Xue *et al.*, 2025). These data justify treating metabolism as a conditioning mechanism while resisting the stronger claim that every metabolic adaptation modifies synthetic lethality.

Resistance can further reorganize the cellular state in which a dependency is evaluated. Therapy-resistant cancer cells may alter glycolytic, mitochondrial, and biosynthetic programs as part of adaptation (Tzeng *et al.*, 2026). In colorectal cancer models, resistance-associated metabolic dependencies have been experimentally exploited to restore treatment sensitivity in defined settings (Hellkamp *et al.*, 2026). Such evidence does not establish a universal cycle of vulnerability, compensation, and re-sensitization. It does, however, support the proposition that therapeutic pressure can move a cell population into a state in which previously weak dependencies strengthen, previously strong dependencies weaken, or new liabilities become accessible.

The resulting distinctions are summarized without assigning numerical transition probabilities or assuming a fixed sequence.

Table 3 summarizes conditions under which synthetic-lethal vulnerability may persist, weaken, or become re-exposed.

Table 3. Conditions under which synthetic-lethal vulnerability may persist, weaken, or become re-exposed

Cellular condition	Compensatory capacity	Treatment-state feature	Expected implication for synthetic-lethal vulnerability	Interpretation limit
Stable vulnerable state	Insufficient alternative function	No major adaptive restructuring	Dependency may remain strongly expressed	Persistence must be demonstrated in the relevant system
Metabolically compensated state	Alternative metabolic or biosynthetic routes available	Adaptive pathway redistribution	Dependency may weaken despite unchanged initiating genotype	Metabolic association does not prove causal rescue
Drug-tolerant state	Stress-survival programs remain accessible	Reversible or semi-stable persistence	Original dependency may weaken or coexist with new liabilities	Persister states are heterogeneous
Resistant remodeled state	Durable compensatory circuitry or clonal adaptation	Continued treatment selection	Dependency profile may differ substantially from baseline	Genetic resistance and plastic adaptation must be distinguished
Re-sensitized state	Compensatory support becomes restricted or disrupted	Withdrawal, combination treatment, or state transition	A previously attenuated vulnerability may become detectable again	Re-sensitization is interaction-specific, not inevitable

These states are best interpreted as mechanistic possibilities rather than stages through which every tumor must pass.

Figure 2 summarizes treatment-dependent remodeling of synthetic-lethal vulnerability across compensated and re-sensitized cellular states.

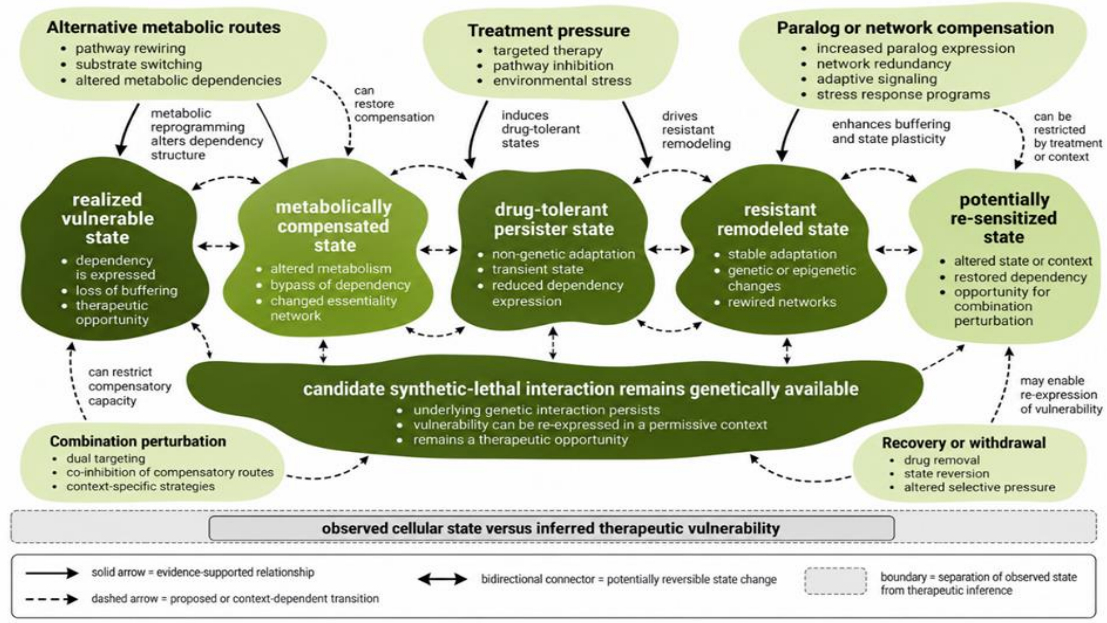


Figure 2. Treatment-dependent remodeling of synthetic-lethal vulnerability across compensated and re-sensitized cellular states

A Conditional-State Framework for Synthetic Lethal Vulnerability

The evidence considered above supports a distinction between the existence of a candidate synthetic-lethal interaction and the realization of that interaction as a selective cellular vulnerability. Contemporary analyses increasingly incorporate context, resistance, and translational constraints into synthetic-lethal target discovery (Li *et al.*, 2026). The present framework extends that logic by treating realized vulnerability as a state produced when an initiating molecular lesion coincides with insufficient compensatory capacity under the relevant cellular and treatment conditions.

This distinction has two consequences. First, a gene pair can remain biologically capable of synthetic lethality while its phenotypic expression varies. Resistance-focused analyses show that therapeutic pressure can expose new vulnerabilities or attenuate previously useful ones, depending on the adaptive state that emerges (Xiong *et al.*, 2025). Paralog buffering, protein-level compensation, metabolic rewiring, and drug-induced plasticity are therefore not interchangeable mechanisms; they are separate routes by which available functional capacity can change.

Second, measurement context should influence confidence in the inference without being mistaken for part of the biological state itself. Context-selective DNA-damage-response dependencies illustrate why genetic vulnerability and pharmacological exploitation must be evaluated separately (Jo *et al.*, 2026). The same principle applies beyond DNA repair. A dependency detectable by knockout may fail to translate to partial pharmacological inhibition, and a drug can fail despite a valid genetic interaction because exposure, selectivity, target engagement, or therapeutic index is inadequate.

The framework therefore generates a limited set of discriminating expectations. If compensatory capacity is reduced, a conditional interaction should become more penetrant under otherwise comparable conditions. If adaptation restores sufficient pathway function, the dependency should weaken. If treatment subsequently constrains the compensatory route, vulnerability may become detectable again. These are theoretical predictions, not reported outcomes. They can be tested only in interaction-specific systems using perturbations that distinguish causal compensation from coincident cell-state change.

Results and Discussion

Therapeutic Implications, Model Predictions, and Contextual Limitations

For precision oncology, the principal implication is that the biomarker defining a synthetic-lethal target may sometimes need to describe more than the initiating lesion. Dependency maps already show that molecular background improves interpretation of selective cancer vulnerabilities (Pacini *et al.*, 2024), while genotype-restricted paralog targeting demonstrates how loss of one component can create druggable reliance on another (Hulse *et al.*, 2026). Where compensation is variable, a clinically useful biomarker may therefore require information about expression, pathway activity, cellular state, or treatment history in addition to genotype. This remains a prediction of the framework rather than a recommendation that every synthetic-lethal program adopt multivariable biomarker panels.

Genetic validation and pharmacological validation also require separate evidentiary standards. Synthetic-lethal target discovery can fail during translation because a genetically precise dependency is not matched by an equally precise drug (Gonçalves *et al.*, 2026). Paralog systems make the problem especially clear: inhibition must often distinguish closely related proteins while achieving sufficient target suppression in the vulnerable cells. Context-selective DNA-damage-response programs likewise show that biological vulnerability does not guarantee pharmacological exploitability (Jo *et al.*, 2026). A rigorous development strategy should therefore ask independently whether the dependency exists, whether the proposed mechanism explains it, and whether a feasible intervention reproduces the necessary perturbation.

The framework is also falsifiable. Environmental conditioning provides one direct strategy: if a dependency attributed to metabolic compensation remains unchanged after relevant environmental conditions are altered, the proposed metabolic explanation becomes weaker (Rossiter *et al.*, 2021). Paralog systems provide another. If experimentally changing the compensating paralog fails to modify the penetrance of an interaction predicted to depend on buffering, that mechanism is not supported (Flister *et al.*, 2025). Direct rescue experiments such as those demonstrated in dosage-sensitive paralog systems offer stronger discrimination because they manipulate the proposed compensatory variable itself (Lee *et al.*, 2025). Metabolic-state studies can similarly test whether vulnerability changes when the implicated metabolic configuration is perturbed rather than merely correlated with outcome (Abecunas *et al.*, 2024).

Measurement artifacts must be excluded before such negative or positive findings are interpreted mechanistically. Copy-number-related CRISPR toxicity can produce false dependency signals (Meyers *et al.*, 2017), while incomplete agreement between large screening resources demonstrates that technical and analytical choices remain relevant even in mature functional-genomic platforms (Dempster *et al.*, 2019). Apparent conditionality should therefore not be attributed to cellular plasticity until perturbation quality, model composition, and measurement context have been examined.

The framework has important limits. It does not claim that synthetic lethality is inherently unstable, that every compensatory mechanism is reversible, or that every resistant state produces collateral vulnerability. Some interactions may remain robust across broad biological conditions. Others may be so dependent on lineage, genotype, or treatment state that their therapeutic value is restricted to narrowly defined populations. Current reviews of resistance-directed synthetic lethality support substantial opportunity but also considerable mechanistic heterogeneity (Xiong *et al.*, 2025). The strongest use of the conditional-state concept is therefore as a discipline for specifying when a vulnerability is expected to exist and what evidence would show that it has changed.

Conclusion

Synthetic lethality is most informative when a candidate molecular interaction is distinguished from the cellular state in which that interaction becomes an expressed therapeutic vulnerability. Paralog buffering, metabolic compensation, and treatment-induced plasticity provide mechanistically different means by which compensatory capacity can alter that expression. The resulting conditional-state account does not replace conventional genetic definitions; it adds the biological and temporal conditions needed to interpret their penetrance. Its value lies in generating testable distinctions between stable dependency, compensation, adaptive attenuation, and possible re-sensitization while preserving the possibility that some synthetic-lethal relationships remain highly robust. Therapeutic translation should therefore establish not only that a candidate interaction exists, but also when the relevant vulnerability is biologically present and pharmacologically accessible.

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References

Abecunas, C., Kidd, A. D., Jiang, Y., Zong, H., & Fallahi-Sichani, M. (2024). Multivariate analysis of metabolic state vulnerabilities across diverse cancer contexts reveals synthetically lethal associations. *Cell Reports*, *43*(10), 114775. doi:10.1016/j.celrep.2024.114775

Andrieu, G. P., Simonin, M., Cabannes-Hamy, A., Lengliné, E., Marçais, A., Théron, A., Huré, G., Doss, J., Nemazanyy, I., Dourthe, M. É., et al. (2025). A metabolic synthetic lethality of phosphoinositide 3-kinase-driven cancer. *Nature Communications*, *16*(1), 2191. doi:10.1038/s41467-025-57225-7

Arnoldus, T., van Vliet, A., Bleijerveld, O. B., de Groot, A. F. H., Piao, Q., Blomberg, N., Schatton, D., Dong, J., van Hal-van Veen, S. E., Harkes, R., et al. (2025). Cytidine diphosphate diacylglycerol synthase 2 is a synthetic lethal target in mesenchymal-like cancers. *Nature Genetics*, *57*(7), 1659-1671. doi:10.1038/s41588-025-02221-2

Behan, F. M., Iorio, F., Picco, G., Gonçalves, E., Beaver, C. M., Migliardi, G., Santos, R., Rao, Y., Sassi, F., Pinnelli, M., et al. (2019). Prioritization of cancer therapeutic targets using CRISPR-Cas9 screens. *Nature*, *568*(7753), 511-516. doi:10.1038/s41586-019-1103-9

Chang, L., Shaw, K., Vazquez, F., & Sellers, W. R. (2026). Context-dependent synthetic lethality—an emerging precision therapeutic approach. *Nature Reviews Cancer*, *26*(7), 534-554. doi:10.1038/s41568-026-00929-9

Dandage, R., & Landry, C. R. (2019). Paralog dependency indirectly affects the robustness of human cells. *Molecular Systems Biology*, *15*(9), e8871. doi:10.15252/msb.20198871

De Kegel, B., Quinn, N., Thompson, N. A., Adams, D. J., & Ryan, C. J. (2021). Comprehensive prediction of robust synthetic lethality between paralog pairs in cancer cell lines. *Cell Systems*, *12*(12), 1144-1159.e6. doi:10.1016/j.cels.2021.08.006

De Kegel, B., & Ryan, C. J. (2019). Paralog buffering contributes to the variable essentiality of genes in cancer cell lines. *PLOS Genetics*, *15*(10), e1008466. doi:10.1371/journal.pgen.1008466

Dempster, J. M., Pacini, C., Pantel, S., Behan, F. M., Green, T., Krill-Burger, J., Beaver, C. M., Younger, S. T., Zhivich, V., Najgebauer, H., et al. (2019). Agreement between two large pan-cancer CRISPR-Cas9 gene dependency data sets. *Nature Communications*, *10*(1), 5817. doi:10.1038/s41467-019-13805-y

Flister, M. J., Verduzco, D., Petiwala, S., Carneiro-Lobo, T. C., Gekas, C., Shi, X., Lu, C., & Dezso, Z. (2025). Genetic mapping and predictive modeling of paralog synthetic lethality. *Cell Reports*, *44*(11), 116512. doi:10.1016/j.celrep.2025.116512

Gantner, B. N., Palma, F. R., Pandkar, M. R., Sakiyama, M. J., Arango, D., DeNicola, G. M., Gomes, A. P., & Bonini, M. G. (2024). Metabolism and epigenetics: Drivers of tumor cell plasticity and treatment outcomes. *Trends in Cancer*, *10*(11), 992-1008. doi:10.1016/j.trecan.2024.08.005

Gonçalves, E., Ryan, C. J., & Adams, D. J. (2026). Synthetic lethality in cancer drug discovery: Challenges and opportunities. *Nature Reviews Drug Discovery*, *25*(1), 22-38. doi:10.1038/s41573-025-01273-7

He, J., Qiu, Z., Fan, J., Xie, X., Sheng, Q., & Sui, X. (2024). Drug tolerant persister cell plasticity in cancer: A revolutionary strategy for more effective anticancer therapies. *Signal Transduction and Targeted Therapy*, *9*(1), 209. doi:10.1038/s41392-024-01891-4

Hellkamp, M., Gertken, S., Buchloh, J., Hellwig, J.-L., Kowitzke, L. B., Duan, N., Gaspardo, I., Küffer, S., Linnebacher, M., Ströbel, P., et al. (2026). Targeting metabolic dependencies to reverse chemoradiotherapy resistance in colorectal cancer. *Journal of Experimental & Clinical Cancer Research*, *45*(1), 143. doi:10.1186/s13046-026-03755-x

Hulse, M., Wang, M., Xu, C., Carter, J., Agarwal, A., Lu, L., Pitis, P., Bhagwat, N., Rager, J., Kurian, J., et al. (2026). PRT3789 is a first-in-human SMARCA2-selective degrader that induces synthetic lethality in SMARCA4-mutated cancers. *Cancer Research*, *86*(1), 213-235. doi:10.1158/0008-5472.CAN-25-1141

Jo, N., Kang, S.-J., Kim, J., Lee, K. H., & Jang, S. (2026). Synthetic lethality and context-selective DNA-damage response dependencies: From genetic vulnerability to pharmacological translation. *Drug Discovery Today*, *31*(6), 104803. doi:10.1016/j.drudis.2026.104803

Lee, A. R., Tangiyan, A., Singh, I., & Choi, P. S. (2025). Incomplete paralog compensation generates selective dependency on TRA2A in cancer. *PLOS Genetics*, *21*(5), e1011685. doi:10.1371/journal.pgen.1011685

Li, J., Zhang, L., Shang, Y., Liu, J., & Zhao, H. (2026). Synthetic lethality in cancer therapy: Mechanisms, models and

clinical translation for overcoming therapeutic resistance. *Clinical and Translational Medicine, 16*(1), e70586. doi:10.1002/ctm2.70586

Liu, S., Jiang, A., Tang, F., Duan, M., & Li, B. (2025). Drug-induced tolerant persisters in tumor: Mechanism, vulnerability and perspective implication for clinical treatment. *Molecular Cancer, 24*(1), 150. doi:10.1186/s12943-025-02323-9

Lord, C. J., Tutt, A. N. J., & Ashworth, A. (2026). Two decades of PARP inhibitor synthetic lethality in cancer. *Nature, 653*(8113), 41-51. doi:10.1038/s41586-026-10404-y

McDonald, E. R., de Weck, A., Schlabach, M. R., Billy, E., Mavrakis, K. J., Hoffman, G. R., Belur, D., Castelletti, D., Frias, E., Gampa, K., et al. (2017). Project DRIVE: A compendium of cancer dependencies and synthetic lethal relationships uncovered by large-scale, deep RNAi screening. *Cell, 170*(3), 577-592.e10. doi:10.1016/j.cell.2017.07.005

Meyers, R. M., Bryan, J. G., McFarland, J. M., Weir, B. A., Sizemore, A. E., Xu, H., Dharia, N. V., Montgomery, P. G., Cowley, G. S., Pantel, S., et al. (2017). Computational correction of copy number effect improves specificity of CRISPR-Cas9 essentiality screens in cancer cells. *Nature Genetics, 49*(12), 1779-1784. doi:10.1038/ng.3984

Pacini, C., Duncan, E., Gonçalves, E., Gilbert, J., Bhosle, S., Horswell, S., Karakoc, E., Lightfoot, H., Curry, E., Muyas, F., et al. (2024). A comprehensive clinically informed map of dependencies in cancer cells and framework for target prioritization. *Cancer Cell, 42*(2), 301-316.e9. doi:10.1016/j.ccell.2023.12.016

Parrish, P. C. R., Thomas, J. D., Gabel, A. M., Kamlapurkar, S., Bradley, R. K., & Berger, A. H. (2021). Discovery of synthetic lethal and tumor suppressor paralog pairs in the human genome. *Cell Reports, 36*(9), 109597. doi:10.1016/j.celrep.2021.109597

Rossiter, N. J., Huggler, K. S., Adelmann, C. H., Keys, H. R., Soens, R. W., Sabatini, D. M., & Cantor, J. R. (2021). CRISPR screens in physiologic medium reveal conditionally essential genes in human cells. *Cell Metabolism, 33*(6), 1248-1263.e9. doi:10.1016/j.cmet.2021.02.005

Russo, M., Chen, M., Mariella, E., Peng, H., Rehman, S. K., Sancho, E., Sogari, A., Toh, T. S., Balaban, N. Q., Batlle, E., et al. (2024). Cancer drug-tolerant persister cells: From biological questions to clinical opportunities. *Nature Reviews Cancer, 24*(10), 694-717. doi:10.1038/s41568-024-00737-z

Ryan, C. J., Mehta, I., Kebabci, N., & Adams, D. J. (2023). Targeting synthetic lethal paralogs in cancer. *Trends in Cancer, 9*(5), 397-409. doi:10.1016/j.trecan.2023.02.002

Sasaki, M., Kato, D., Murakami, K., Yoshida, H., Takase, S., Otsubo, T., & Ogiwara, H. (2024). Targeting dependency on a paralog pair of CBP/p300 against de-repression of KREMEN2 in SMARCB1-deficient cancers. *Nature Communications, 15*(1), 4770. doi:10.1038/s41467-024-49063-w

Schäffer, A. A., Chung, Y., Kammula, A. V., Ruppin, E., & Lee, J. S. (2024). A systematic analysis of the landscape of synthetic lethality-driven precision oncology. *Med, 5*(1), 73-89.e9. doi:10.1016/j.medj.2023.12.009

Shi, X., Gekas, C., Verduzco, D., Petiwala, S., Jeffries, C., Lu, C., Murphy, E., Anton, T., Vo, A. H., Xiao, Z., et al. (2024). Building a translational cancer dependency map for The Cancer Genome Atlas. *Nature Cancer, 5*(8), 1176-1194. doi:10.1038/s43018-024-00789-y

Shields, J. A., Meier, S. R., Bandi, M., Mulkearns-Hubert, E. E., Hajdari, N., Ferdinez, M. D., Engel, J. L., Silver, D. J., Shen, B., Zhang, W., et al. (2022). VRK1 is a synthetic-lethal target in VRK2-deficient glioblastoma. *Cancer Research, 82*(21), 4044-4057. doi:10.1158/0008-5472.CAN-21-4443

Tsherniak, A., Vazquez, F., Montgomery, P. G., Weir, B. A., Kryukov, G., Cowley, G. S., Gill, S., Harrington, W. F., Pantel, S., Krill-Burger, J. M., et al. (2017). Defining a cancer dependency map. *Cell, 170*(3), 564-576.e16. doi:10.1016/j.cell.2017.06.010

Tzeng, Y.-D. T., Raj, E. N., Cheng, S.-H., Yong, S.-B., Lin, S.-C., Peng, R.-W., & Li, C.-J. (2026). Tumor metabolic plasticity in therapy resistance: From the Warburg effect to mitochondrial hijacking. *Theranostics, 16*(9), 4865-4882. doi:10.7150/thno.131708

Venkatesh, A., Quinn, N., Upadhya, S. R., De Kegel, B., Bolado Carrancio, A., Lefeivre, T., Dennler, O., Wynne, K., von Kriegsheim, A., & Ryan, C. J. (2025). Proteomic compensation by paralogs preserves protein interaction networks after gene loss in cancer. *Molecular Systems Biology, 21*(8), 1090-1118. doi:10.1038/s44320-025-00122-4

Xiong, Q., Jin, J., Lin, J., Zhang, B., Jiang, Y., Sun, Z., Zhang, L., Wu, Y., Zhao, G., Qin, J.-J., et al. (2025). The role of synthetic lethality in overcoming cancer therapy resistance: Emerging paradigm and recent advances. *Drug Resistance Updates, 83*, 101290. doi:10.1016/j.drup.2025.101290

Xue, Z.-R., Xin, Y.-Y., & Jin, W.-L. (2025). Exploiting metabolic vulnerabilities in cancer: From mechanisms to therapeutic opportunities. *Cancer Letters, 634*, 218067. doi:10.1016/j.canlet.2025.218067