



PHARMACOLOGICAL TARGETING OF DRUG-TOLERANT PERSISTENT CELLS TO OVERCOME CANCER TREATMENT RESISTANCE

Dr. Pearl Ifunanya Nwafor-Ezeh^{1*}, Dr. Emmanuel Henry Ezenabor²

^{1*}Department of Biochemistry, Bowen University, Iwo, Nigeria

²Department of Biochemistry, Bowen University, Iwo, Nigeria

**Corresponding Author: dr.pearlifunanyanwaforezeh@gmail.com*

Received: 28/01/2026 Revised: 10/04/2026 Acceptance: 15/05/2026 Published: 30/05/2026

ABSTRACT

The presence of drug-tolerant persister (DTP) cells is a non-genetic reservoir that can be reversibly switched on after treatment with anticancers and is responsible for the residual disease, stable resistance and recurrence. In this review, the authors explore the origins of DTP cells, their mechanisms of survival, microenvironmental regulation, and the pharmacologically targeted vulnerabilities of DTP cells in the context of major cancer types and therapeutic modalities. Epigenetic reprogramming, adaptive oncogenic signalling, mitochondrial and lipid metabolic dependence, autophagy, oxidative-stress regulation, DNA repair, phenotypic plasticity and evasion of apoptosis and ferroptosis all contribute to persister survival. These adaptations provide opportunities for epigenetic inhibitors, metabolic therapies, ferroptosis inducers, apoptosis-restoring agents, pathways-directed combination treatments, and persister-specific targeted therapies. Combinations can be used upfront to avoid DTP formation, or over a period of time (sequential or intermittent) can be used to exploit the weaknesses that develop following initial therapy. Clinical translation is limited due to variability in definitions, differences in models, lack of validated biomarkers, and lack of clarity about the "when" and "how" of treatment, and about treatment toxicity. Combining single-cell and spatial profiling, liquid-biopsy monitoring and adaptive clinical trials may allow for accurate identification and interception of residual persister states. Preventing the development of permanent tolerance may make treatments more durable and decrease the likelihood of cancer recurrence.

Keywords: Drug-tolerant persister cells, cancer resistance, precision pharmacology, ferroptosis, residual disease



1. Introduction

Targeted agents, immune checkpoint inhibitors, endocrine therapy and optimized cytotoxic therapy are used in modern cancer therapy. However, resistance is one of the most significant reasons for poor response, recurrence and cancer mortality. Traditional interpretations focus on picking up new genetic variants or on the emergence of stable resistance mutations. This model cannot account for the fact that after initial effective therapy a small number of malignant cells remain without known changes that confer resistance. These DTP cells are in a reversible adaptive state and enable survival for a lethal dose of the drug. Their resurgence of proliferation puts them in a middle ground, which is between therapeutic response and minimal residual disease and clinically apparent relapse (Lopez-Gonzalez et al., 2026).

DTP cells are not uniform nor do they represent a given molecular type. They can exhibit slow proliferation, dormancy, changed differentiation, stem-like features and a high amount of phenotypic plasticity. In contrast to permanently resistant clones, persister cells can regain drug sensitivity following the removal of the drug, suggesting that tolerance is often achieved in dynamic, non-genetic ways. Their biology parallels the concept of tumour dormancy: when small populations of tumour cells remain clinically undetectable, but are able to be reactivated. The relationship between this type of cancer and targeted therapy may account for the dramatic results of tumour regression but not permanent eradication seen in non-small-cell lung cancer (Lalla et al., 2026). The same phenomenon is seen in haematological malignancies, where cells that survive exploit lineage-specific signalling and protective microenvironments to evade the effects of pharmacology (Ma et al., 2026). The effects of persistence in maintaining residual disease and subsequent resistant evolution (Li et al., 2026 A) underscore the importance of lymphoid malignancies as an example.

The epigenetic, transcriptional, metabolic and stress-response programmes are interconnected and regulate the transition to persistence. Altered metabolism of the mitochondria, autophagy, redox regulation and lipid utilization pathways enable cells to withstand energetic and oxidative stress, while chromatin remodelling pathways can inhibit proliferation and activate survival pathways. Therapeutic inhibition of receptor tyrosine kinases and downstream pathways can be compensated for through adaptive signalling. Metabolic and mitochondrial protection through a telomerase–SUCLG2 signalling axis allows for the preservation of viability of persister cells and the promotion of resistance (Liu et al., 2026). These mechanisms constitute adaptive survival strategies that evolve among cancer types, treatments and environment. In the modern models of resistance, reversible adaptation is now considered together with genetic evolution, drug transport, DNA repair, and pathway reactivation (Cheng et al., 2026).

The tumour microenvironment also helps to reinforce persistence. Protected niches can be formed by cancer-associated fibroblasts, extracellular-matrix components, inflammatory mediators, hypoxia, nutrient limitation and immune-cell interactions which can minimize the damage caused by drugs. Under such circumstances DTP cells can persist until the time of action of the treatment is altered or new resistance mechanisms develop. This adaptative phase provides a reservoir for establishment of stable resistant clones. Research in breast cancer suggests that a pre-adaptive state can influence evolutionary trajectories from a transient state of tolerance to a heritable state of treatment resistance (Choi et al., 2026). There are also persistence programmes shared between treatments and patients in triple-negative breast cancer, indicating a shared vulnerability between heterogeneity of tumour cells and shared vulnerability across treatments (Baudre et al., 2026). Single-cell transcriptomics has now been used to reveal rare persister populations and adaptive responses to treatment at much higher biological resolution (Islam et al., 2026).

In terms of pharmacology, DTP cells are a challenge and an opportunity. They are rare, potentially reversible and highly variable, making them challenging to detect during standard tumour sampling, but reliance on adaptive survival programmes may render them temporarily vulnerable to therapy. Suggested strategies are epigenetic inhibitors, metabolic disruptors, ferroptosis inducers, agents that restore apoptosis, inhibitors of autophagy, and agents that inhibit compensatory signalling. Treatment



scheduling may be comparable as well: combination treatment may be necessary to avoid persistence and sequential treatment may be required to take advantage of vulnerabilities after initial treatment. New models are helping to identify these fragile states and to assess interventions to eradicate them (Zheng et al., 2026). Persister cells can be seen in a wider context that includes the role of drug transporters, senescence, microenvironmental protection, and clonal selection (Nagy et al., 2026).

Although significant advances are being made, there are several clinical translation challenges involving inconsistent definitions, models, biomarkers, and limited longitudinal sampling. True persister cells and quiescent, senescent, stem-like or genetically resistant cells are hard to distinguish. In addition, persister directed treatments need to be sufficiently selective to prevent unacceptable toxicity in normal tissues that are stress adapted. To make progress, standardized language, physiologically relevant models, repeated tumour or liquid-biopsy evaluation, and single-cell, spatial, and functional pharmacologic integration are needed. Therefore, a targeted overview of the DTP biology and vulnerabilities is needed to inform rational drug combinations, and to avoid the generation of transient tolerance to permanent resistance. The objectives of this review are:

1. To explain the biological and pharmacological mechanisms that sustain drug-tolerant persister cells during cancer therapy.
2. To evaluate emerging therapeutic strategies for preventing persister-cell survival, adaptation, and progression toward permanent resistance.
3. To identify translational barriers and research priorities for developing clinically effective persister-directed cancer treatments.

2. Origin and Biological Characteristics of Drug-Tolerant Persister Cells

Drug tolerant persister (DTP) cells are generated when the treatment of cancer kills most of the sensitive tumour cells, and a minority survive in an adaptive mode. Therapeutic pressure is not only able to select for existing resistant mutations, but also can induce transcription, epigenetic, metabolic and phenotypic modifications which temporarily diminish drug susceptibility. Across various malignancies, evidence of a recurrently perturbed 12-gene programme indicates that various types of tumours can potentially have partly shared persistence pathways, despite different lines of origin and exposure to therapy (Arora et al., 2026). One of the hallmarks of DTP cells is that they are usually non-genetic, and the tolerance is often reversible. These cells remain drug resistant for the time being, but can eventually re-sensitize to the drugs following their removal from the system, demonstrating that the cells' state is being altered, not their mutation. Epigenetic remodelling helps in this reversibility by altering the accessibility of the chromatin and the expression of the genes involved and allows rapid adaptation when therapy starts, and proliferation when pressure is reduced (Zhao & Pan, 2026). Persistence is often associated with dormancy, quiescence, or slow cycling that limits sensitivity to agents that target actively dividing cells. These conditions are not the same as total inactivity as DTP cells have essential stress response, repair, redox and metabolic functions. Increased iron regulation might be an ancestral trait shared by microbial and cancer persistence, helping to survive in adverse treatment and setting the sensitivity to oxidative injury and ferroptosis (Rodriguez & Agostinis, 2026). DTP populations are also highly phenotypically plastic with the ability to migrate between epithelial, mesenchymal, stem-like, and differentiated states. In head and neck cancer, RHOJ-induced EMT has been associated with chemotherapy resistance, demonstrating that cells can withstand drugs by undergoing signalling-induced state changes (Ling et al., 2026 A). In a broader sense, the cellular plasticity is responsible for the dynamic regulation of sensitivity to death and for the ability of malignant cells to acquire phenotypes adapted to the changing therapeutic compartments (Malode et al., 2026). These characteristics represent important overlaps between DTP cells and tumour-initiating cells, both of which can display the ability to self-renew and to resist stress, show efficient repair and display tumour-initiating potential. However, the populations cannot be considered as synonymous because stemness may be inherent or acquired, while persistence is mostly defined by survival during otherwise lethal therapy. The DTP cells are therefore a clinically undetectable component of the MRD, and serve as a reservoir for subsequent relapse after apparent



tumour response. In this residual state, further adaptation and genomic evolution of these DTP cells could transform reversible tolerance to stable resistance, emphasising the need for early DTP cell identification and pharmacological elimination to avoid treatment failure (Table 1).

Table 1. Defining Biological Characteristics of Drug-Tolerant Persister Cells

Characteristic	Concise description	Biological significance	References
Therapy-induced emergence	Small populations survive otherwise lethal treatment	Initiates residual disease	(Arora et al., 2026)
Reversible tolerance	Adaptive chromatin states preserve survival without fixed mutations	Allows later resensitization	(Zhao & Pan, 2026)
Dormancy and slow cycling	Reduced proliferation with maintained stress regulation	Avoids cell-cycle-dependent drugs	(Rodriguez & Agostinis, 2026)
Phenotypic plasticity	EMT and state switching increase adaptability	Supports multidrug tolerance	(Ling et al., 2026)
Stemness and residual disease	Self-renewal and death resistance sustain residual populations	Promotes recurrence	(Malode et al., 2026)

3. Molecular Mechanisms Supporting Persister-Cell Survival

3.1 Epigenetic Reprogramming and Chromatin Remodeling

Reversible epigenetic reprogramming can alter chromatin accessibility, without any permanent genetic mutation, and is one of the mechanisms that allow the survival of persister-cells. The epigenetic mechanisms of DNA methylation, chromatin-remodelling complexes and altered enhancement activity can inhibit the expression of growth genes and promote activation of stress-tolerance and survival programmes. These alterations lead to a dynamic (transient) transcriptome in which specific drugs lose their efficiency, but drug resistance can be reversed upon withdrawal of the drug. The concept of tolerance to MAPK-inhibitors is an example of adaptable regulatory states that leave behind surviving cells, identifying targetable vulnerabilities (Shah et al., 2026). Epigenetic inhibitors could thus block the establishment or maintenance of persistence.

3.2 Adaptive Rewiring of Oncogenic Signalling Pathways

In the context of anti-cancer treatment, cells that escape the killing process are not only not eliminated but they also take the information that they were able to carry out via other parallel pathways that allow them to survive even in the presence of blockade of the main pathway. Downstream signalling can be restored by feedback activation, receptor switching, pathway convergence and even by changes in the activity of kinases, to levels that allow persistence. In NSCLC which is exposed to osimertinib, coordinated PLCG1 and RAC1 activities have been linked to adaptive programmes promoting DTP formation (Tiong et al., 2026). This network flexibility is the basis for the temporary control of single-pathway inhibition and why combining multiple pathways is beneficial to blocking both the primary pathway and bypass pathways.

3.3 Metabolic Reprogramming and Mitochondrial Dependence

Metabolic adaptation provides energy and biosynthetic support in a context of constrained proliferative signalling by the pharmaceutical approach. DTP cells could enhance mitochondrial respiration, influence glucose and lipid utilization, boost antioxidant defenses, or rely upon amino-acid pathways. These changes are dependent on context but are often burdening factors that do not occur in an untreated population. CDK4/6 inhibition causes a unique metabolic shift that identifies a therapeutic vulnerability in non-dead breast cancer persister cells in oestrogen-receptor-positive



breast cancer (Yang et al., 2026 A). Treating the tumor in addition to the therapy could kill any surviving cells before they develop stable resistance mechanisms and repopulate the tumor.

3.4 Autophagy, oxidativeresponsive regulation and the repair of DNA damage.

During therapeutic stress, persister cells can recycle macromolecules, eliminate damaged organelles, and supply energy through autophagy. At the same time, antioxidant systems regulate the levels of ROS, thus preventing membrane, protein and mitochondrial damage that can be lethal. Increased sensing and repair of DNA damage allows for survival after chemotherapy or radiation, without compromising the integrity of the genome, which is required to grow and develop again. Bacterial and Malignant Persistent Cell Survival Principles. Stress adaptation is a common theme in drug tolerance (Papaneophytou, 2026). So, simultaneous inhibition of repair mechanisms, redox defenses, and autophagy may then turn cytostatic persistence into irreversible killing of the cell.

3.5 Epithelial–Mesenchymal Plasticity and Stemness

The ability of cancer cells to change their adhesion, movement, differentiation and drug sensitivity in response to drugs is what is called epithelial–mesenchymal plasticity. Pathways of mesenchyme or hybrid activation can trigger survival pathways, and lead to less reliance on the original therapeutic target. These changes are frequently observed in conjunction with stem-like properties such as self-renewal, quiescence, and tumour-reinitiating ability. In non-small-cell lung cancer (NSCLC), it has been observed that a subset of stem-like cells characterized by high plasticity (SP) can be identified and may give rise to TKI-tolerant persisters (Sadeghi et al., 2026). Specificity with regard to the regulation of state transition may limit adaptive flexibility and decrease the relapse reservoir.

3.6 Apoptosis, Ferroptosis, and Other Cell-Death Pathways Evasion

Persister cells develop resistance to death by elevating the threshold of apoptosis, and strengthening their defense against ferroptosis and other forms of cell death. Weaker apoptotic priming identified as a survival determinant in ALK-rearranged lung-cancer persisters, which suggests how weak priming enables residual cells (Katayama et al., 2026). The disruption of PPP1R15B–ATF4 axis can lead to GPX4-mediated ferroptosis and eliminate the lenvatinib tolerance in hepatocellular carcinoma (Chen et al., 2026). Results corroborate the use of synergistic treatment modalities that induce apoptosis, break antioxidant defenses, and trigger alternative death mechanisms prior to the development of long-term resistance by surviving cells (Figure 1).

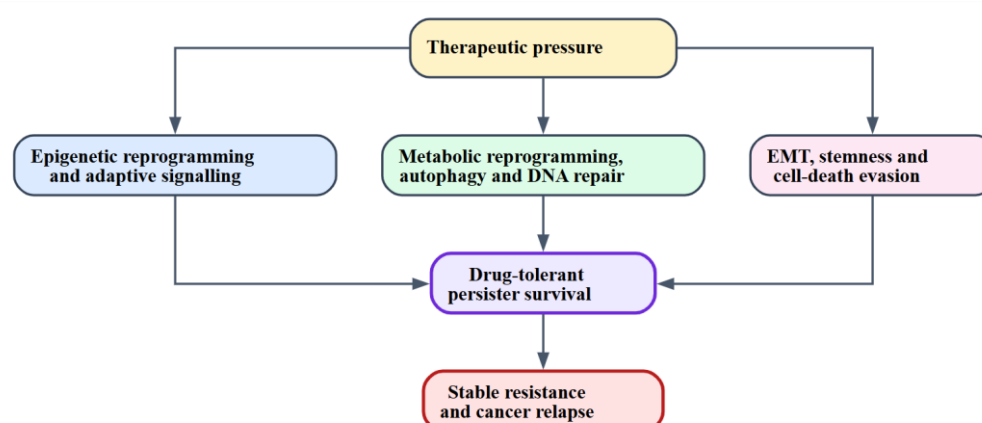


Figure 1. Molecular Mechanisms Supporting Persister-Cell Survival

4. Tumour Microenvironmental Regulation of Drug Tolerance

4.1 Cancer-Associated Fibroblasts and Stromal Signalling

Growth factors, extracellular-matrix deposition, metabolic exchange and contact-dependent signaling



are provided by cancer-associated fibroblasts to protect DTP cells. Fibroblast-derived mediators can restore MAPK, PI3K–AKT and survival pathways following inhibition of tumour-intrinsic oncogenic signaling. Stromal cues also induce epithelial-mesenchymal transition, quiescence and antioxidant defense, which reduce drug-induced apoptosis. Triple-negative breast cancer cells have been identified as sensitive to ferroptosis inducers in a chemotherapy-induced galectin-1 (Shaikh et al., 2026) and an EMT-associated persister state. Disrupting tumour–stroma communication may therefore prevent protective niche formation, and promote persister-cell elimination.

4.2 Hypoxia, Nutrient Deprivation, and Extracellular Acidity

Metabolic stress caused by hypoxia, nutrient deprivation and extracellular acidity kills sensitive tumor cells but can select for populations that can adapt. DTP cells react by adjusting mitochondrial respiration, substrate use, redox state and pH regulation, thus conserving energy and limiting oxidative injury. Acidic conditions can also impair drug uptake and immune-cell activity. Metabolically specialized mitochondrial niches have been linked to residual EGFR-mutant non-small-cell lung cancer, connecting local energetic support with immune-constrained persistence (Liang et al., 2026). Disrupting these adaptations may selectively destabilize persisters in poorly perfused regions of the tumor.

4.3 Extracellular-Matrix Remodeling and Protective Cellular Niches

Remodeling of the extracellular matrix creates physical and biochemical niches that protect persister cells from therapeutic exposure. Increased matrix density may restrict drug penetration, while altered integrin signaling activates focal-adhesion, survival and mechanotransduction pathways. The spatial heterogeneity of the matrix composition may result in unequal concentrations of drug and distinct cellular responses within the same tumor. The emergence of TRAIL tolerant persisters in a dose-dependent continuum of sensitivity demonstrates the role of graded exposure in shaping adaptive cell states (Fiandaca et al., 2026). Targeting matrix-producing cells, adhesion receptors or remodeling enzymes could break down the sanctuaries and improve treatment distribution.

4.4 Inflammatory Cytokines and Paracrine Survival Signals

Inflammatory cytokines and paracrine mediators enable communication between tumour cells, fibroblasts, macrophages, and other components of the microenvironment. Signals involving interleukins, prostaglandins, growth factors, and chemokines can activate STAT3, NF- κ B, MAPK, and metabolic programmes that sustain persister-cell viability. These networks may remain active after direct oncogenic inhibition and provide an external source of rescue signalling. Pharmacological targeting of EP2 has been shown to overcome osimertinib-tolerant persisters through coordinated metabolic and inflammatory reprogramming in non-small-cell lung cancer (Yu et al., 2026). Blocking paracrine feedback may therefore prevent residual-cell recovery.

4.5 Immune Evasion and Suppression of Antitumour Responses

DTP cells can suppress antitumour immunity through decreased antigen presentation, resistance to death-receptor signaling and induction of immunosuppressive myeloid or regulatory-cell activity. Their low abundance and quiescent state may further limit recognition by cytotoxic lymphocytes. Protective niches can thus maintain residual cells even when the tumor burden appears greatly reduced. In EGFR-mutant lung cancer, a four-gene persister signature revealed a susceptibility to ZLN005-induced, GSDME-dependent pyroptosis, indicating that inflammatory cell death can be pharmacologically reinstated (Chang et al., 2026). Combining persister-directed agents with immunotherapy may improve immune recognition and clear otherwise occult residual disease (Table 2) (Figure 2).



Table 2. Microenvironmental Mechanisms Supporting DTP-Cell Survival

Microenvironmental factor	Effect on persister cells	Targeting opportunity	References
Galectin-1 and stromal signalling	Promotes EMT-associated tolerance	Ferroptosis induction	(Shaikh et al., 2026)
Mitochondrial niches	Provide metabolic and immune protection	Disrupt niche metabolism	(Liang et al., 2026)
Drug-exposure gradients	Produce variable tolerance states	Improve delivery and scheduling	(Fiandaca et al., 2026)
EP2 inflammatory signalling	Coordinates metabolic and inflammatory adaptation	EP2 inhibition	(Yu et al., 2026)
Suppressed pyroptosis	Protects residual EGFR-mutant cells	Activate GSDME-mediated death	(Chang et al., 2026)

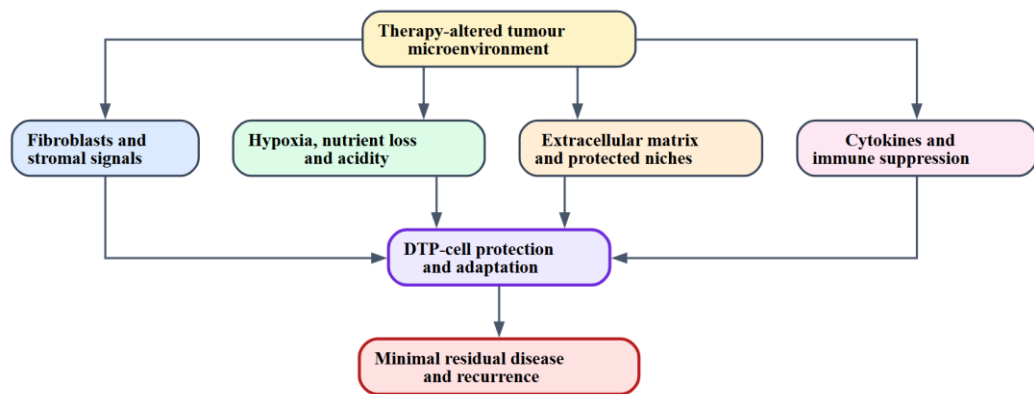


Figure 2. Tumour Microenvironmental Regulation of Drug Tolerance

5. Pharmacologically Actionable Vulnerabilities of Persister Cells

Not all drug-tolerant persisters are drug resistant; rather, drug tolerant persisters have become an adaptive state and thus dependencies that can be pharmacologically exploited. Epigenetic enzymes and chromatin regulators are a significant vulnerability since persister survival is not solely dependent on fixed mutations, but also on reversible transcription programmes. Epigenetic states that are inherited can be stable over multiple generations of cells and can help to developmentally prime the cells to become permanently resistant (Liang & Lei, 2026). Histone deacetylase, methyltransferase, demethylase and bromodomain inhibitors may interfere with these programmes, reinstalling the sensitivity of the residual cells, and limiting adaptive plasticity (Yang et al., 2026 B). Another dependency that can be acted upon is mitochondrial metabolism, because DTP cells are often dependent on the ability to use oxidative phosphorylation, redox buffering, efficient substrate utilization and stay alive during treatment-induced stress. Inhibition of respiratory complexes, mitochondrial translation or antioxidant systems therefore may selectively kill persisters while leaving less metabolically active populations. Lipid metabolism also plays a crucial role as fatty acid oxidation provides energy, while glutathione and lipid-peroxide protect cells against ferroptosis. The inhibition of GPX4 activity, uptake of cystine or lipid-remodelling enzymes may overdrive persisters. The metabolic flexibility and self-renewal/regulated cell death dependency of DTP cells and stem-like cancer populations further underscore the interaction between these two processes (Martellucci, 2026). Anti-apoptotic proteins and integrated stress-response regulators also protect against cell death after drugs by inhibiting mitochondrial apoptosis, protein homeostasis, and by regulating autophagy. Death competence could be restored by pharmacological inhibition of BCL-2-family proteins, heat-shock proteins, or stress-adaptive transcription factors. Alternative receptors, downstream kinases and



paracrine feedback can be activated upon pathway inhibition, providing other targets, including receptor tyrosine kinases and adaptive signalling networks. In EGFR-mutated lung adenocarcinoma, secreted signals of adaptive survival can disrupt immunotherapy via CCL20, which is a DTP-derived signal (Kwok et al., 2026). The inhibition of such signalling could have a dual effect of reducing the persisters while enhancing antitumour immunity. Persister-specific surface markers are especially appealing as they can be directly targeted using antibodies, antibody–drug conjugates, bispecific molecules or cellular therapies. The interest in TROP family antigens exemplifies the prospect of turning a persister associated surface marker into a therapy-relevant liability (Izumi et al., 2026). But there is a need to validate marker heterogeneity and expression in normal tissues. Sequential treatment and microenvironment-responsive delivery could be useful to enhance selectivity by eradicating bulk tumour cells first and the vulnerabilities of the persisters later. Analogous approaches used against bacterial persisters highlight the pharmacologic potential of using combinations of staged eradication and locally activated delivery systems (Bai et al., 2026) (Table 3) (Figure 3).

Table 3. Pharmacologically Actionable Vulnerabilities of Persister Cells

Vulnerability	Persister dependency	Potential intervention	References
Epigenetic inheritance	Maintains tolerance across cell generations	Chromatin-modifying inhibitors	(Liang & Lei, 2026)
Epigenetic enzymes	Sustain reversible resistance programmes	HDAC, BET, or methyltransferase inhibitors	(Yang et al., 2026)
Stem-like survival	Supports self-renewal and repair	Stemness-pathway inhibition	(Martellucci, 2026)
CCL20 signalling	Weakens immunotherapy responses	CCL20–CCR6 blockade	(Kwok et al., 2026)
TROP-family antigens	Provide accessible surface targets	Antibody–drug conjugates	(Izumi et al., 2026)
Protected drug delivery	Limits exposure of residual cells	Responsive sequential delivery	(Bai et al., 2026)

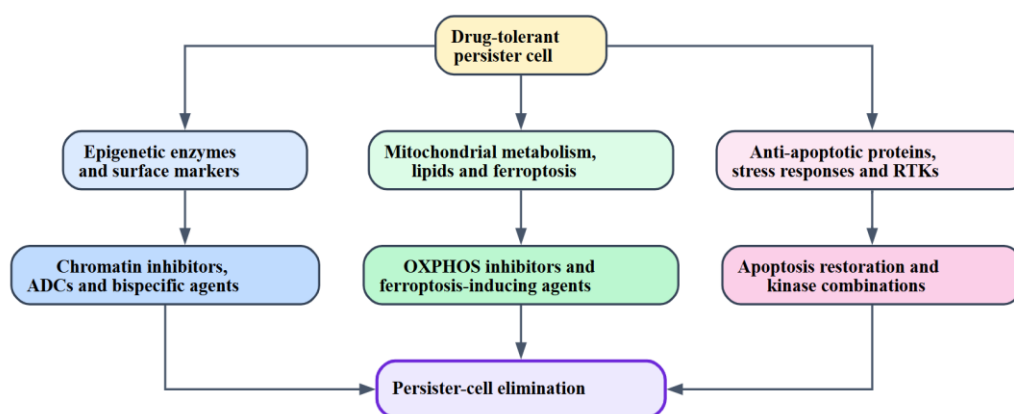


Figure 3. Pharmacologically Actionable Vulnerabilities of Persister Cells

6. Pharmacological Strategies for Preventing and Eliminating Persister Cells

6.1 Upfront Combination Treatments

The upfront combination approach aims to prevent DTP formation by simultaneously targeting the dominant oncogenic driver and the expected adaptive escape mechanisms. This can diminish the residual population available for subsequent evolution, but combinations need to be selected mechanistically to avoid unnecessary toxicity. In EGFR-mutant lung cancer, treatment-induced



adaptation could be intercepted by the addition of an agent, as the AhR antagonist DA-4505 inhibited persisters generated by exposure to amivantamab–lazertinib (Shim et al., 2026). Biomarker-guided combinations should therefore target complementary survival pathways while maintaining tolerability and sufficient dose intensity.

6.2 Sequential and Intermittent Drug Administration

Sequential and intermittent schedules exploit the shifting dependencies of cancer cells during treatment. The first drug can shrink sensitive tumor populations, while a second can target vulnerabilities specifically induced in surviving persisters. Intermittent dosing may also avoid continuous selection and normal tissues may recover. Mathematical modeling of ribosome competition has generated experimentally testable scheduling strategies for DTP populations, exemplifying how quantitative frameworks can guide treatment timing (Tang et al., 2026). Effective scheduling requires pharmacodynamic monitoring, because untimely withdrawal may allow for reactivation of persisters, their expansion and the acquisition of stable resistance.

6.3 Epigenetic and Transcriptional Inhibitors

Epigenetic and transcriptional inhibitors may interfere with reversible programs that maintain persistence without directly targeting the oncogenic target. Shared regulatory dependencies may remain targetable across tumor types and therapies, indicated by conserved adaptive transcriptional programs across DTP populations (Chen & Robertson, 2026). Hence, histone-modifying enzymes, bromodomain proteins, transcription factors and enhancer-associated complexes are potential targets for intervention. Functional screening also found that the YAP–TEAD axis mediates drug tolerance in EGFR-mutant lung cancer (Yusuf, 2026). Such inhibitors combined with driver-directed therapy may prevent establishment of adaptive states or resensitize existing persisters.

6.4 Metabolic and Mitochondrial Therapies

Metabolic therapies take advantage of the observation that persister cells rely on energy production, redox control, and flexible substrate utilization. Preclinical studies have shown that DTP cells are able to redirect carbon sources to antioxidant metabolism to counteract treatment-induced oxidative stress (Li et al., 2026 B). Other persisters utilize FABP1–PPAR γ signaling to promote peroxisomal fatty-acid oxidation and maintain cetuximab resistance in head and neck cancer (Ling et al., 2026 B). Inhibiting oxidative phosphorylation, fatty-acid oxidation, antioxidant synthesis or mitochondrial quality control may therefore collapse survival capacity, particularly when treatment is timed to emerging metabolic dependence.

6.5 Ferroptosis-Inducing and Apoptosis-Restoring Agents

Induction of ferroptosis and restoration of apoptosis directly target the enhanced death resistance of persister cells. Ferroptosis can be induced by lipid peroxidation increase, cystine-derived glutathione limitation, or inhibition of GPX4 and related antioxidant systems; however, the metabolic context has a strong impact on the therapeutic response (Liu, 2026). Targeting the FSP1–ACSL4 axis induced ferroptosis and reversed cisplatin resistance in drug-tolerant papillary thyroid carcinoma (Yang et al., 2026 C). Simultaneous inhibition of antiapoptotic BCL-2-family proteins may restore mitochondrial priming. Combining complementary death mechanisms would reduce escape by pathway redundancy, but would require careful protection of normal tissues.

6.6 Drug Repurposing and Multi-Target Pharmacology

Drug repurposing could speed up persister-directed therapy by using drugs with known safety profiles against newly found adaptive targets. Potential candidates might include metabolic drugs, anti-inflammatory compounds, autophagy inhibitors and approved kinase inhibitors active against compensatory signaling. Multi-target pharmacology is especially pertinent because DTP survival rarely relies on a single pathway. Yusuf (2026) showed how a CRISPR screen that identifies the



YAP–TEAD signaling pathway can connect persister biology with current and emerging classes of inhibitors. However, repurposed combinations require mechanistic validation, exposure assessment, and testing in clinically relevant models prior to translation.

6.7 Immunotherapy and Persister-Directed Combination Approaches

Combinations of immunotherapy aim to expose or kill persister cells that are resistant to targeted and cytotoxic therapies. Potential strategies include checkpoint blockade, bispecific antibodies, antibody-drug conjugates, adoptive cellular therapy, and agents restoring antigen presentation or immunogenic cell death. The emergence of DTP cells during amivantamab–lazertinib therapy suggests that even antibody-directed targeted combinations may require additional pharmacologic intervention (Shim et al., 2026). Agents against persisters might facilitate immune recognition by enhancing tumor cell death or dampening suppressive signaling. The clinical development should be based on biomarkers, treatment sequence and toxicity since immune activation could affect normal tissues (Table 4) (Figure 4).

Table 4. Strategies for Preventing and Eliminating Persister Cells

Strategy	Main target or timing	Intended outcome	References
Upfront combination	Driver pathway plus AhR adaptation	Prevent DTP formation	(Shim et al., 2026)
Sequential treatment	Therapy-induced vulnerabilities	Eliminate residual cells	(Tang et al., 2026)
Transcriptional inhibition	Conserved adaptive programmes	Reverse tolerance	(Chen & Robertson, 2026)
Metabolic therapy	Carbon allocation and antioxidant metabolism	Exhaust survival capacity	(Li et al., 2026)
Ferroptosis induction	Lipid-peroxide defence systems	Restore regulated cell death	(Yang et al., 2026)
Multi-target pharmacology	YAP–TEAD and compensatory pathways	Restrict adaptive escape	(Yusuf, 2026)
Immunotherapy combinations	Persister-mediated immune suppression	Improve immune clearance	(Kwok et al., 2026)

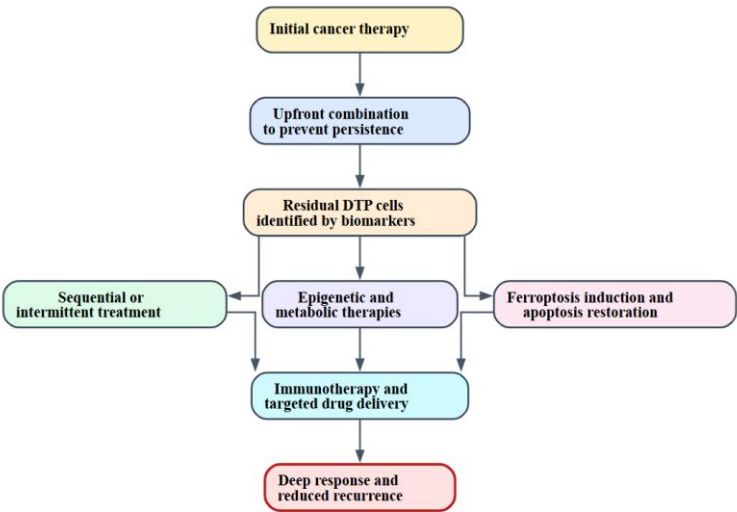


Figure 4. Strategies for Preventing and Eliminating Persister Cells

7. Evidence Across Cancer Types and Treatment Modalities



The known examples of DTP-mediated resistance now cover a range of cancer types and treatment approaches, with the depth of the mechanisms involved and their validation in the clinic varying. One of the best-defined settings is that of non-small-cell lung cancer cells that harbor mutations in the EGFR, in which targeted therapy leaves behind resistant cells that reprogram signal transduction, metabolism, and interactions with the immune microenvironment. Single-cell and spatial-omics technologies are now starting to capture these rare states and where they reside in tumour-immune ecosystems, which is aiding more precise pharmacological targeting (Lian et al., 2026). However, the role of persisting is not limited to kinase inhibition; epigenetic repression of TP53 transcription is linked to carboplatin resistance in lung cancer cells (Ha & Kim, 2026). In melanoma, BRAF and MEK inhibition generates different persister states that drive different resistances, suggesting that residual cells should not be considered as a homogenous subpopulation (Li et al., 2026 C). Similarly, in breast and prostate cancers, therapy targeting hormones and other slow-cycling cells or cells with lineage plasticity that can become hormone independent are targeted. The transitions are readily explained by cellular plasticity and epigenetic instability, and CRISPR-based epigenome editing can be used to functionally test candidate regulators (Fatima, 2026). Gastrointestinal and pancreatic cancers are other challenges as chemotherapy persistence may overlap KRAS signalling, stromal protection, autophagy and metabolic flexibility. Targeting complementary survival processes (Furukawa et al., 2026) has been shown to be effective at eliminating drug-tolerant KRAS-mutant cancer cells, highlighting the value of targeting complementary survival processes. In all of these diseases, metabolic plasticity allows for transitions between glycolytic and mitochondrial energy production, which allows residual cells to adjust to treatment and nutrient availability (Tzeng et al., 2026). Immune-mediated elimination after immunotherapy, unlike targeted drugs, is less precisely defined but available evidence indicates that there are various mechanisms which can restrict elimination, including reduction in antigen presentation, quiescence, production of anti-inflammatory cytokines, and metabolically protected niches. They will be detected by sampling over time – using molecular profiling in conjunction with functional evidence of reversible tolerance. The majority of persister-directed interventions are still pre-clinical, using cell lines, organoids, xenografts and genetically engineered models. Proposed biomarkers should be evaluated in the clinical setting to establish whether these markers detect residual DTP cells from patients and whether combination or sequential therapy is effective in achieving durable response, but without undue toxicity. This approach could be particularly advantageous as adaptive states may be genetically unstable at early stages of tumour transition that can be treated (Al-Ewaidat & Naffaa, 2026). The need for biomarker-guided trials, repeated review of residual disease and treatment regimens tailored to the changing biological fate of each tumour means that translation is crucial (Table 5) (Figure 5).

Table 5. Evidence Across Cancer Types and Treatments

Cancer setting	Treatment context	Principal persister evidence	References
EGFR-mutant NSCLC	EGFR-targeted therapy	Metabolic and immune ecosystem adaptation	(Lian et al., 2026)
NSCLC	Carboplatin	Epigenetic repression of TP53	(Ha & Kim, 2026)
Melanoma	BRAF and MEK inhibition	Diverse DTP states shape clonal resistance	(Li et al., 2026)
Breast and prostate cancers	Endocrine and targeted therapy	Epigenetic and lineage plasticity	(Fatima, 2026)
KRAS-mutant cancers	Chemotherapy and targeted therapy	Glutamine and lysosomal dependence	(Furukawa et al., 2026)
Multiple cancer types	Different treatment modalities	Glycolytic-mitochondrial switching	(Tzeng et al., 2026)
Translational development	Emerging interventions	Targetable transition windows	(Al-Ewaidat & Naffaa, 2026)

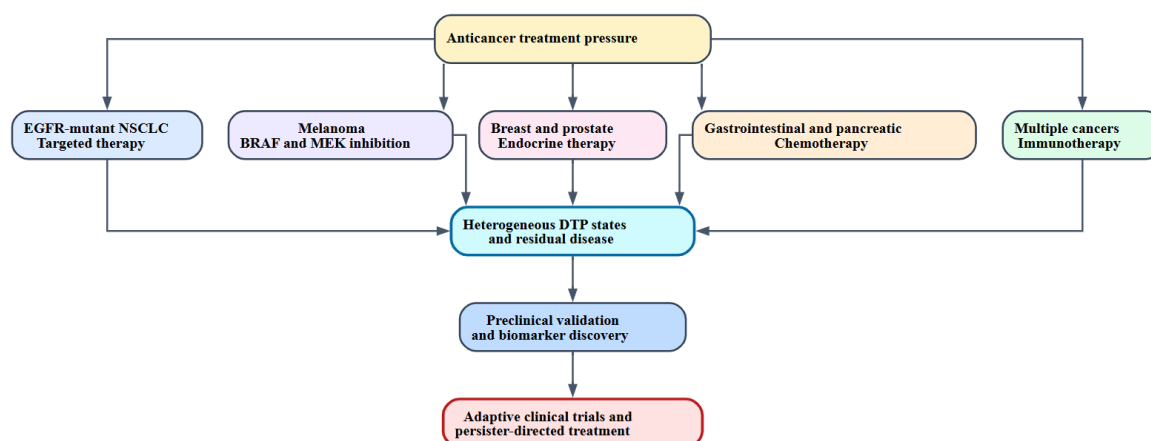


Figure 5. Evidence Across Cancer Types and Treatment Modalities

8. Translational Challenges, Research Gaps, and Future Directions

Definitions of reversible tolerance and dormancy, senescence, stemness and permanent genetic resistance are not standardized between research groups in DTP. There is also variability in the amount of drug exposure, recovery time, and survival thresholds for these experimental models. Criteria of consensus and reproducible assays are needed for comparison. There is no cancer and therapy common biomarker that identifies persister cells. Transcriptional, metabolic and surface markers are frequently contextual or common to stress adapted cells. Development of biomarkers should include a molecular signature and evidence of survivability, reversibility and relapse potential. Intra-tumoural heterogeneity enables multiple persister states to coexist within a single tumour and changes in the vulnerabilities of these states over time as a result of treatment. Longitudinal models need to reflect the shifts from adaptation to stable resistance and the ability to distinguish pre-existing tolerant groups from therapy induced. Many persister dependencies are also critical in normal tissues, posing toxicities. Timing of treatment is critical; vulnerabilities may be only present during specific adaptive windows. Selectivity could be enhanced with pharmacodynamic markers, rational sequencing, and interruptive schedules. Residual populations and their niches can be detected by single-cell sequencing, spatial transcriptomics, proteomics, and metabolic imaging. Combining these strategies with lineage tracing and functional drug testing will aid in understanding which cellular states survive treatment and that will later regenerate tumours. Liquid biopsies can assist in monitoring with circulating tumour DNA, RNA, proteins, or extracellular vesicles and circulating cells. Adaptive trials should involve measurements to adjust therapy as the residual states change, and prospective testing of whether intervention on the basis of the biomarkers leads to better clinical outcomes. These are elements that should be brought together in future persister-directed precision pharmacology: genotype, state of the cell, metabolic dependence, immune context and treatment history. Combinations, sequential regimens, or locally delivered agents can be identified using predictive models when and how to target persisters. Standardised endpoints, shared datasets and trials based on residual disease will be necessary to achieve progress.

9. Conclusion

Cancer returns frequently do not occur as a complete therapeutic failure, but as the survival of a small population of adaptable cells. Drug-tolerant persisters resist the effects of anti-cancer drugs through an integrated epigenetic reprogramming, compensatory signaling metabolism, mitochondrial adaptation, autophagy, oxidative-stress control, DNA repair, phenotypic plasticity and protection from the tumor microenvironment. These mechanisms also establish pharmacological vulnerabilities in chromatin regulators, oxidative phosphorylation, lipid metabolism, anti-apoptotic proteins, ferroptosis defenses, receptor tyrosine kinases and persister-associated surface targets. Taking action



when drug tolerance is still reversible is of great value because it can kill cells that are still susceptible to the drug before they are further selected and genetically evolved into permanent resistance. Combinations that will work in the clinic will involve combinations of biomarkers that are able to inhibit both dominant oncogenic drivers and treatment induced survival pathways. Conventional (sequential or intermittent) regimens may additionally take advantage of vulnerabilities that happen only following initial treatment, but with lowered cumulative toxicity. But to be able to translate into the clinic, persister-specific biomarkers must be validated, monitoring should be done longitudinally, models must be physiologically representative, and therapeutic windows must be carefully chosen. Single-cell profiling, spatial analysis, liquid-biopsy surveillance, and functional drug testing could all be integrated to allow treatment to be personalized as residual disease evolves. Pharmacology that targets persisters has the potential then to enhance therapeutic effect, slow the emergence of resistance and prevent recurrence. Ultimately, its clinical utility will rely on translating the biological vulnerabilities that are observed as acute conditions into accurate, well-tolerated and sustainable therapies.

References

1. Al-Ewaidat, O. A., & Naffaa, M. M. (2026). Targeting tumor transition windows. *Exploration of Targeted Anti-tumor Therapy*, 7, 1002390.
2. Arora, I., Adam, A. M., Aljaylani, A. O., Alzuhayri, J. Z., Ali, E. M., Alzahrani, F. A., ... & Yaqinuddin, A. (2026). A recurrently perturbed 12-gene program marks drug-tolerant persister states across cancer types. *Frontiers in Bioinformatics*, 6, 1882238.
3. Bai, J., Han, L., Cheng, X., Fu, H., Zhang, X., He, H., & Wang, J. (2026). Sequential eradication of bacterial persisters: integrating phytochemical pharmacology with microenvironment-responsive delivery strategies. *Frontiers in Microbiology*, 17, 1842301.
4. Baudre, L., Jouault, G., Prompsy, P., Saichi, M., Gastineau, S., Huret, C., ... & Vallot, C. (2026). Characterization of drug-tolerant persister cells in triple-negative breast cancer identifies a shared persistence program across treatments and patients. *Cancer research*, 86(3), 802-817.
5. Chang, W., Yuan, J., Zhang, H., Yu, Y., Ma, Y., Li, M., ... & Sun, Y. (2026). A four-gene signature identifies TKI-induced persister cells and uncovers a ZLN005-induced pyroptotic vulnerability via the GSDME pathway in EGFR-mutant lung cancer. *Molecular Medicine Reports*, 34(5), 1-28.
6. Chen, M. Y., Lai, S. W., Cheng, Y. C., Yadav, V. K., Fong, I. H., Kuo, K. T., ... & Cherng, Y. G. (2026). Targeting PPP1R15B and ATF4 axis in hepatocellular carcinoma: a novel strategy for overcoming lenvatinib-tolerant persister cells through GPX4-mediated ferroptosis induction. *European Journal of Pharmaceutical Sciences*, 107434.
7. Chen, Y. C., & Robertson, G. P. (2026). Drug-tolerant persister cells use conserved adaptive transcriptional programs. *Translational Cancer Research*, 15(8), 662.
8. Cheng, X., Xu, M., Wei, J., & Cao, C. (2026). Cancer drug response and resistance: molecular mechanisms and combating strategies. *Signal Transduction and Targeted Therapy*, 11(1), 307.
9. Choi, H. Y., Park, M. J., Lee, S. J., Hwang, J., Choi, H. C., & Hah, Y. S. (2026). Pre-Adaptive States and Evolutionary Trajectories in Breast Cancer Drug Resistance: From Drug-Tolerant Persisters to Clonal Evolution. *Cells*, 15(9), 756.
10. Fatima, S. W. (2026). Cellular plasticity and epigenetic instability in cancer: Mechanistic insights and functional dissection with CRISPR-based epigenome editing. *Cancer Letters*, 218679.
11. Fiandaca, G., Péré, M., Bonhomme, K., Chaves, M., & Roux, J. (2026). Drug-tolerant persisters to TRAIL emerge from a dose-dependent surface in a cell-state continuum of sensitivity. *npj Systems Biology and Applications*.
12. Furukawa, H., Umezawa, K., Sun, Y., Chiba, H., Kubonishi, M., Naito, H., ... & Aoki, S. (2026). Dual targeting of glutamine metabolism and lysosomal function in eliminating drug-tolerant KRAS-mutant cancer cells. *Communications Biology*.



13. Ha, S., & Kim, W. Y. (2026). Epigenetic Repression of TP53 Transcription Underlies Cancer Cell Persistence for Carboplatin Resistance in Non-Small Cell Lung Cancer. *Biomolecules & Therapeutics*, 34(5), 1221.
14. Islam, M. N., Suja, M. K. I. S., Takbir, A. A., & Kibria, M. K. (2026). Single-Cell Transcriptomic Identification of Drug-Tolerant Persister Mechanisms in Capecitabine-Treated Triple-Negative Breast Cancer. *Computational and Systems Oncology*, 6(1), e70025.
15. Izumi, M., Kobayashi, S. S., & Halmos, B. (2026). Targeting drug-tolerant persister cells: Let's bring on the TROPs!. *Cancer Cell*, 44(7), 1333-1335.
16. Katayama, R., Utsumi, T., Uchibori, K., & Nishio, M. (2026). CRISPR screening identifies BMF loss as a drug-tolerant persister cell survival factor in ALK-rearranged lung cancer. *Cancer Research*, 86(7_Supplement), 1852-1852.
17. Kwok, H. H., Yang, J., Lee, N. C. M., Deng, J., & Lam, D. C. L. (2026). CCL20 Released by Drug-Tolerant Persisters Impairs Immunotherapy in EGFR-Mutant Lung Adenocarcinoma. *MedComm*, 7(8), e70888.
18. Lalla, M., Ratnani, A., Yang, J., Wang, M., & Cheng, H. (2026). Drug-tolerant persister cells and tumor dormancy in NSCLC: a new frontier in overcoming therapeutic resistance. *Cancers*, 18(5), 779.
19. Li, H., Chen, Y., Kaster, J., Dunne, M., Xiao, M., Li, L., ... & Herlyn, M. (2026 A). Clonal dynamics shaped by diverse drug-tolerant persister states in melanoma resistance. *Molecular Cancer*, 25(1), 127.
20. Li, M., Priem, B., Loftus, L. V., Betenbaugh, M. J., Pienta, K. J., & Amend, S. R. (2026 B). Drug-tolerant persister cells reallocate carbon sources to fuel antioxidant metabolism for survival. *bioRxiv*.
21. Li, M., Tang, S., Yang, P., & Zhou, H. (2026 C). Drug-tolerant persister cells in lymphoid malignancies: from mechanisms to therapeutic opportunities. *Frontiers in Oncology*, 16, 1713277.
22. Lian, Z., Wu, X. J., Zhou, Y., Tang, P., & Ge, H. (2026). Single-cell and spatial omics in non-small cell lung cancer: dissecting metabolic reprogramming and tumor-immune ecosystems for precision pharmacology. *Frontiers in Immunology*, 17, 1865367.
23. Liang, X., & Lei, J. (2026). Epigenetic state inheritance drivers drug-tolerant persister-induced resistance in solid tumors: A stochastic agent-based model. *arXiv preprint arXiv:2601.22619*.
24. Liang, Z., Zhao, X., Jiang, M., Zhou, M., Cheng, M., Liu, S., & Zhao, Y. (2026). Mitochondrial niches of residual disease in EGFR-mutant NSCLC: immune-constrained persistence and therapeutic interception. *Frontiers in Immunology*, 17, 1908826.
25. Ling, H. H., Huang, C. M., Hsieh, M. S., Yadav, V. K., Fong, I. H., Kuo, K. T., ... & Tsai, J. T. (2026 A). RHOJ-induced chemotherapy resistance through epithelial-mesenchymal transition in drug-tolerant persister cells of head and neck cancer. *Translational Oncology*, 65, 102673.
26. Ling, H. H., Huang, C. S., Hsieh, M. S., Yadav, V. K., Fong, I. H., Kuo, K. T., ... & Tsai, J. T. (2026 B). Redox-driven FABP1/PPAR γ signaling fuels peroxisomal fatty acid oxidation and confers cetuximab resistance in drug-tolerant head and neck cancer cells. *Free Radical Biology and Medicine*.
27. Liu, Y. (2026). Metabolic regulation of ferroptosis in cancer: mechanisms, pharmacological inducers, and translational challenges. *Apoptosis*, 31(6), 160.
28. Liu, Y., Zhao, K., Hu, B., Tan, J., Yang, Z., Vasilopoulos, T., ... & Zhang, G. (2026). A telomerase-SUCLG2 signaling axis drives drug resistance by protecting persister cells. *Cell Reports*, 45(7).
29. Lopez-Gonzalez, J. S., Perez-Medina, M., Galicia-Velasco, M., & Aguilar-Cazares, D. (2026). Drug-tolerant persister cells in cancer: a scoping review of definitions, models, and molecular mechanisms. *Frontiers in Oncology*, 16, 1771061.
30. Ma, Q., Cao, T., Zhou, L., Cheng, J., & Zhao, L. (2026). Drug-tolerant persister cells: the deadly survivors in hematological malignancies. *Frontiers in Pharmacology*, 17, 1740281.



31. Malode, S., Desai, S., Mhatre, D., Patel, V., Chhajed, F., & Surade, S. (2026). CELLULAR PLASTICITY AS A DYNAMIC REGULATOR OF DEATH SENSITIVITY AND DRUG RESISTANCE IN CANCER. *Cell Death*, 100016.
32. Martellucci, S. (2026). Unlocking cancer's secrets: overcoming drug resistance in cancer stem cells. *Frontiers in Pharmacology*, 17, 1913266.
33. Nagy, P., Kis, A. K., Bajtai, E., Haffaressas, I. L., Gombos, B., Bereczki, D., ... & Füredi, A. (2026). Reframing cancer drug resistance: transporters, persister cells, senescence, and emerging therapeutic strategies. *Magyar Onkologia*, 70(2), 8134.
34. Papanephytou, C. (2026). Two Worlds, One Battle: How Bacteria and Malignancies Converge on Drug Resistance. *International Journal of Molecular Sciences*, 27(10), 4239.
35. Rodriguez, R., & Agostinis, P. (2026). An iron logic unites bacterial and cancer persister cells. *Nature Reviews Molecular Cell Biology*, 1-3.
36. Sadeghi, M., Salama, M., Choudhury, S., Huang, A., Yang, J., & Hannun, Y. A. (2026). TKI-Tolerant Persisters Emerge from a PKC α -Dependent and Highly Plastic Subpopulation of Stem-Like Cells in NSCLC. *bioRxiv*, 2026-05.
37. Shah, B., Mayhew, M. M., Sellers, J., & Witt, R. G. (2026). MAPK Inhibitor-Tolerant Persister Cells in Melanoma: Mechanisms and Therapeutic Vulnerabilities. *Cancer Science*.
38. Shaikh, S. A., Sharma, K., Bhattacharya, D., Kothari, V., Jadhav, S., & Verma, N. (2026). Chemotherapy-induced galectin-1 derives drug-tolerant persister state associated EMT in triple negative breast cancer with targetable vulnerability to ferroptosis inducers. *Cancer Research*, 86(7_Supplement), 5663-5663.
39. Shim, J. S. G., Cho, B. C., Lim, S. M., & Hong, M. H. (2026). 143RO AhR antagonist DA-4505 suppresses the generation of amivantamab-lazertinib-induced drug-tolerant persisters in EGFR-mutant lung cancer. *ESMO Open*, 11.
40. Tang, X., Wang, Y., Pu, Y., Li, K., Ding, Z., Wang, M., ... & Shen, S. (2026). Mathematical modeling of ribosome competition informs testable treatment strategies for drug-tolerant cancer persister cells. *Iscience*, 29(4).
41. Tiong, T. Y., Wang, C. Y., Chen, Y., Lin, Y. H., Changchien, C. Y., Chian, C. F., & Tsai, C. L. (2026). PLCG1 and RAC1 Orchestrate Adaptive Cellular Programs Driving Osimertinib-Tolerant Persister Cell Formation in Malignant Pleural Effusion-Associated Non-Small Cell Lung Cancer. *European Journal of Pharmaceutical Sciences*, 107608.
42. 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.
43. Yang, C. Y., Huang, C. M., Yasir, M., Ko, C. C., Yadav, V. K., & Liu, S. C. (2026). Therapeutic targeting of the FSP1-ACSL4 axis reverses cisplatin resistance via ferroptosis induction in drug-tolerant papillary thyroid carcinoma. *European Archives of Oto-Rhino-Laryngology*, 283(3), 1771-1785.
44. Yang, H., Tau, S., McCray, A. D., Roberts, A. M., Marotti, J. D., Muller, K., ... & Miller, T. W. (2026). Metabolic Response to CDK4/6 Inhibition in ER+ Breast Cancer Creates a Therapeutic Vulnerability in Drug-Tolerant Persister Cells. *The FASEB Journal*, 40(7), e71746.
45. Yang, J., Zhang, M., Zhong, Y., Sun, C., & Zhuang, J. (2026). Epigenetic modifications in cancer drug resistance: Molecular mechanisms and therapeutic interventions. *Molecular Biomedicine*, 7(1), 60.
46. Yu, H., Lu, L., Hu, X., Wang, Q., Wei, J., Wu, Y., ... & Pan, Y. (2026). Targeting EP2 overcomes osimertinib-tolerant persisters through metabolic and inflammatory reprogramming in non-small cell lung cancer. *International Immunopharmacology*, 188, 117313.
47. Yusuf, M. (2026). CRISPR screens reveal YAP/TEAD axis as a mediator of drug-tolerant cells in EGFR-mutant NSCLC. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 399(4), 5761-5776.
48. Zhao, W., & Pan, J. X. (2026). Epigenetic plasticity in cancer drug resistance: mechanistic



- insights and strategies for therapeutic intervention. *Acta Pharmacologica Sinica*, 1-16.
49. Zheng, Y., Deng, X., Su, Y., Chien, J. R., & Liang, M. (2026). Targeting Drug-Tolerant Persister Cells in Cancer: Progress From Modeling to Targeting Fragility Studies. *Frontiers in Bioscience-Landmark*, 31(9).