REVIEW ARTICLE

Senolytic Clearance of Chemotherapy-Induced Senescence as an Anti-Relapse Strategy: Mechanistic Synthesis, Evidence Timeline, and a Repurposing Framework for Clinical Translation

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Abstract

Genotoxic chemotherapy kills proliferating tumor cells but also drives a substantial fraction of surrounding stromal and normal cells into senescence, a permanently arrested but metabolically active state. Senescent cells secrete a senescence-associated secretory phenotype (SASP), a cocktail of pro-inflammatory cytokines, chemokines, and matrix-remodeling enzymes that actively contributes to chemotherapy side effects and, critically, can reactivate dormant disseminated tumor cells and promote cancer relapse. This paper synthesizes a decade of evidence: from the original identification of senolytic drugs (compounds that selectively clear senescent cells) through direct demonstration that senolytic clearance reduces cancer relapse and metastasis in mice, to a completed first-in-human senolytic trial, and a 2025 mechanistic study directly linking chemotherapy-induced senescence to neutrophil extracellular trap (NET)-mediated reactivation of dormant breast cancer cells. Because the leading senolytic combination (dasatinib plus quercetin) uses two agents already in clinical use—an approved oncology drug and a well-tolerated flavonoid—this represents an unusually mature repurposing opportunity: the missing step is not drug discovery but a dedicated oncology trial testing senolytic administration in the peri-chemotherapy window as a relapse-prevention strategy. We present the mechanistic cascade, tabulate the evidence timeline, and propose a general intervention framework and trial design.

1. Introduction

Cellular senescence is classically understood as a tumor-suppressive mechanism: damaged or oncogene-stressed cells permanently exit the cell cycle rather than risk malignant transformation. Yet this framing, while mechanistically sound, obscures a clinically consequential second fact: senescent cells are not simply inert bystanders. They remain metabolically active and secrete a senescence-associated secretory phenotype (SASP), a complex mixture of pro-inflammatory cytokines (IL-6, TNF-α, IL-8), growth factors (PDGF, FGF), and matrix metalloproteinases that remodel the stromal microenvironment. Genotoxic chemotherapy, which is designed to kill proliferating tumor cells, simultaneously drives large numbers of normal and stromal cells into this senescent, SASP-secreting state as a direct and underappreciated side effect of treatment.

The consequences of therapy-induced senescence (TIS) extend far beyond the well-characterized acute toxicities (fatigue, myelosuppression, cardiac dysfunction). A growing body of evidence, culminating in a direct 2025 mechanistic demonstration, shows that TIS-derived SASP can reactivate dormant disseminated tumor cells and drive the very cancer relapse that chemotherapy was intended to prevent. This paper argues that senolytic drugs—agents that selectively clear senescent cells—represent an unusually well-positioned repurposing opportunity to interrupt this cascade, because the leading senolytic combination is built from two drugs already in clinical use.

1.1. Why This Mechanism Is Repurposing-Ready

Three features make the senolytic strategy distinctive among the mechanisms considered in the broader pre-metastatic niche literature: (i) dasatinib is an FDA-approved tyrosine kinase inhibitor already used in oncology (chronic myeloid leukemia, Philadelphia-chromosome-positive acute lymphoblastic leukemia), so its safety profile in cancer patients is already well characterized; (ii) quercetin is a widely available flavonoid with an established tolerability record; and (iii) a first-in-human senolytic trial using this exact combination has already been completed, albeit for a non-oncology indication, providing a validated dosing and safety template. The step that remains is a dedicated oncology trial testing this combination specifically in the peri-chemotherapy window for relapse prevention.

2. The Mechanistic Cascade

2.1. Overview

The pathway from chemotherapy administration to senescence-driven relapse proceeds through a defined sequence, illustrated in Figure 1 (presented at the end of this article), with senolytic drugs positioned to intercept the cascade at its origin.

2.2. Step 1: Chemotherapy Induces Widespread Senescence in Normal Tissue

Demaria and colleagues (2017, Cancer Discovery) showed, using a transgenic mouse model permitting selective tracking and elimination of senescent cells (p16-3MR), that several genotoxic chemotherapeutic drugs induce senescence broadly in normal murine and human tissue, not only in tumor cells, and that these therapy-induced senescent (TIS) cells persist long after treatment and contribute to local and systemic inflammation [1].

2.3. Step 2: SASP Drives Both Chemotherapy Toxicity and Cancer Relapse

In the same study, eliminating TIS cells (either genetically or with the senolytic drug ABT-263/navitoclax) reduced multiple short- and long-term adverse effects of chemotherapy, including bone marrow suppression, cardiac dysfunction, and impaired physical activity. Critically, using a luciferase-labeled murine breast cancer model (MMTV-PyMT) that spreads preferentially to lung and liver, the authors showed that eliminating senescent cells after chemotherapy delayed cancer recurrence and reduced metastatic spread, providing direct causal evidence that senescent cells generated by chemotherapy actively promote relapse rather than merely correlating with it [1]. Consistent with this, senescence markers in circulating T cells before chemotherapy predicted greater risk of chemotherapy-induced fatigue in human patients, indicating the mechanism is not confined to mice [1].

2.4. Step 3: NET Formation as the Proximal Trigger of Dormancy Reactivation

A 2025 Cancer Cell study (He and colleagues) closed the mechanistic loop using a recombinase-based dormancy-tracing system: chemotherapy (doxorubicin, cisplatin) induces senescence specifically in lung fibroblasts, and senescent fibroblasts drive neutrophil extracellular trap (NET) formation, which in turn reactivates dormant breast cancer cells that had been quiescent in the lung. A senolytic cocktail (dasatinib plus quercetin) that cleared the senescent fibroblasts prevented NET formation and blocked chemotherapy-induced metastatic relapse in mice [2]. This provides the direct causal chain linking Step 1 (chemotherapy-induced senescence) to a specific, previously identified pre-metastatic-niche mechanism (NET-mediated dormancy reactivation), rather than a general inflammatory association.

3. Evidence Timeline and Senolytic Pharmacology

The senolytic field has developed along a clear, decade-long trajectory from initial drug discovery to a completed human trial, summarized in Figure 2 (presented at the end of this article).

3.1. Discovery of Dasatinib + Quercetin as Senolytics

Zhu and colleagues (2015, Aging Cell) hypothesized that senescent cells, like cancer cells, depend on anti-apoptotic survival pathways (termed senescent-cell anti-apoptotic pathways, or SCAPs) to resist stress-induced death, and identified dasatinib and quercetin as a combination capable of selectively killing senescent cells at doses insufficient to harm normal proliferating or quiescent cells. Dasatinib inhibits Src-family tyrosine kinases and other survival pathways, while quercetin inhibits PI3K/AKT signaling and BCL-2/BCL-xL, giving the combination complementary and partially non-redundant senolytic mechanisms [3].

3.2. First-in-Human Senolytic Trial

Justice and colleagues (2019, EBioMedicine) conducted the first human senolytic trial, an open-label pilot study of intermittent dasatinib (100 mg) plus quercetin (1,250 mg) dosing over three consecutive days in 14 patients with idiopathic pulmonary fibrosis. The trial demonstrated significant reductions in circulating senescent-cell markers (p16INK4a, p21CIP1) and SASP factors (IL-6, TNF-α, matrix metalloproteinases), along with improvements in physical function (six-minute walk distance, gait speed, chair-standing test) [4]. This established, for the first time in humans, that intermittent senolytic dosing is tolerable and biologically active—a “hit-and-run” mechanism distinguishing senolytics pharmacologically from most chronic cancer therapies.

3.3. Direct Application to Cancer Relapse

The Demaria (2017) and He (2025) studies described in Section 2 provide the cancer-specific causal evidence; the Justice (2019) trial provides the human dosing and safety template. No dedicated human oncology trial testing senolytics for relapse prevention has yet been completed, representing the clearest gap between existing evidence and clinical application.

4. A General Peri-Chemotherapy Senolytic Intervention Framework

4.1. Design Principles

(i) Timing: intermittent senolytic dosing administered after completion of each chemotherapy cycle (once senescent cells have had time to accumulate but before SASP-driven inflammation peaks), rather than concurrent or continuous administration, following the hit-and-run pharmacology validated in Justice et al. [4]. (ii) Drug combination: dasatinib plus quercetin has the strongest combined mechanistic, discovery, and human dosing/safety support of any senolytic regimen; alternative agents (navitoclax/ABT-263, fisetin) have preclinical cancer-relapse data or broader senolytic evidence but lack the same combination of oncology-drug familiarity and completed human trial data. (iii) Patient selection: patients receiving genotoxic, senescence-inducing chemotherapy regimens (anthracyclines, platinum agents) for tumor types with a documented dormancy/late-relapse pattern (e.g., estrogen-receptor-positive breast cancer) are the most mechanistically appropriate population. (iv) Biomarker linkage: circulating senescence markers (p16INK4a, p21CIP1) and SASP factors (IL-6, IL-8) provide direct pharmacodynamic readouts, and NET burden markers (cfDNA-neutrophil elastase complexes, citrullinated histone H3) would test the specific mechanism described in Section 2.4.

4.2. Proposed Trial Design

A Phase 1b/2a design is proposed: patients receiving standard-of-care anthracycline- or platinum-based chemotherapy for solid tumors with documented dormancy biology are randomized 1:1 to add intermittent dasatinib+quercetin (100 mg dasatinib + 1,250 mg quercetin orally once daily for 3 consecutive days following each chemotherapy cycle) or placebo, synchronized to the Justice et al. protocol [4]. Enrollment target: 60–80 patients across 2–3 sites. Primary efficacy endpoint: change in circulating senescence biomarkers (p16INK4a, p21CIP1) and SASP factors (IL-6, TNF-α, IL-8) from baseline through final chemotherapy cycle. Secondary endpoints: NET burden markers, chemotherapy-related toxicity grading, and—in a planned long-term extension—distant-metastasis-free survival at 2 and 5 years. Stratification: hormone-receptor status, age (≤50 vs. >50), and chemotherapy regimen.

4.3. Relationship to the Broader Niche-Stratification Framework

This senolytic strategy is the most directly evidence-linked of the systemic adjuncts in the pre-metastatic niche literature, since the He et al. [2] mechanism was the original basis for classifying PAD4 inhibition as a Tier-1 intervention for NET-dominant niches. Senolytic clearance and PAD4 inhibition act on the same causal pathway at two different points—senescent-cell source versus NET-formation itself—and are natural candidates for combination in patients with both elevated senescence burden and elevated NET markers following chemotherapy.

5. Discussion

5.1. Strength of Evidence

Two independent, mechanistically detailed studies using genetic and pharmacological senescent-cell elimination in mouse models of breast cancer support the causal chain from chemotherapy to senescence to SASP/NET-driven relapse, with a directly analogous human dosing and safety trial already completed for the same drug combination in a different disease. This is a more direct and complete evidentiary chain (mechanistic → animal → human dose/safety → proposed mechanism in target population) than exists for most systemic adjuncts in the pre-metastatic niche literature, and represents an unusual opportunity to translate well-characterized basic biology directly into a falsifiable clinical hypothesis.

5.2. What Remains Unproven

No study has yet administered dasatinib plus quercetin to cancer patients specifically to test relapse prevention; the mouse cancer-relapse data (Demaria [1], He [2]) and the human dosing/safety data (Justice [4]) come from different studies in different contexts. It is not yet established whether intermittent D+Q dosing in the peri-chemotherapy window achieves sufficient senescent-cell clearance in human tumors and stroma to reproduce the mouse relapse-reduction effect, nor whether senolytic clearance could interfere with any beneficial, tissue-repair-related functions of transient senescence. Dasatinib carries its own toxicity profile (pleural effusion, myelosuppression, QT prolongation) that would need careful management in a non-leukemia population receiving it as an adjunct rather than as primary cancer therapy.

5.3. Limitations

The direct cancer-relapse mechanism has been demonstrated conclusively in only one genetic mouse model (MMTV-PyMT breast cancer) and validated using a different chemotherapy exposure; generalization to other tumor types (ovarian, lung, colorectal) with different dormancy niches remains plausible but untested, and may require dose or schedule adjustments. The human trial data (Justice et al. [4]) come from a non-cancer, fibrotic-disease population and cannot be assumed to transfer directly to oncology patients who may have different baseline senescent-cell burden, organ function, and concurrent treatment exposures.

6. Conclusion

Chemotherapy's therapeutic benefit and its contribution to relapse may share a common, underappreciated origin: the senescent cells it leaves behind. Senolytic clearance of these cells, using a drug combination already validated for safety and biological activity in humans, and already shown to reduce cancer relapse and metastasis when tested causally in mice, represents arguably the most mechanistically direct and immediately translatable senescence-targeting intervention yet identified in oncology. The critical next step is a dedicated oncology trial testing intermittent dasatinib-plus-quercetin dosing in the peri-chemotherapy window, using the biomarker and dosing framework proposed here, ideally in combination with the NET-directed strategies described in our companion framework.

References

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FIGURES

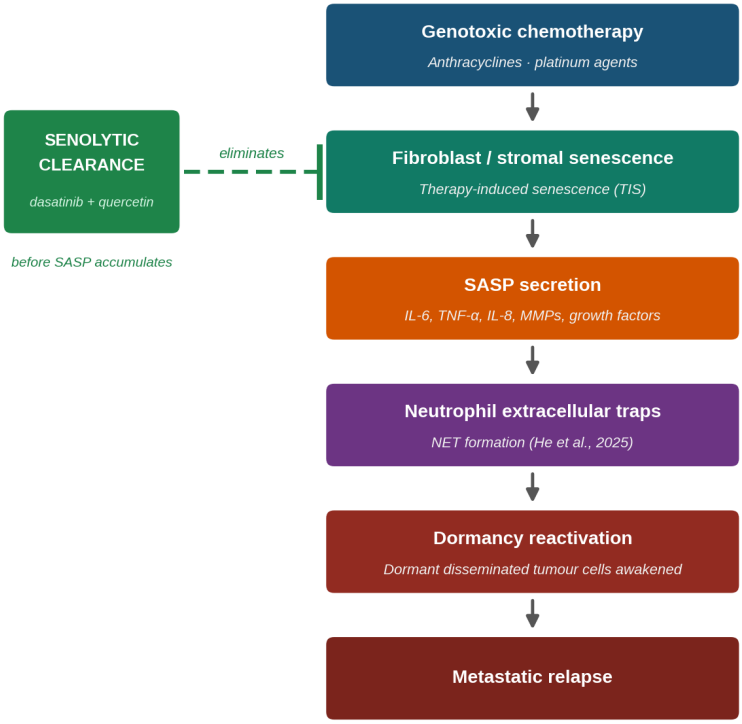


Figure 1. *Mechanistic cascade from chemotherapy-induced senescence to metastatic relapse, showing the senolytic intervention point. Genotoxic agents induce senescence in fibroblasts and stromal cells; senescent cells secrete a SASP that drives neutrophil extracellular trap (NET) formation; NETs reactivate dormant cancer cells. Senolytic clearance (dasatinib + quercetin) intercepts this cascade by eliminating senescent cells before SASP accumulation.*

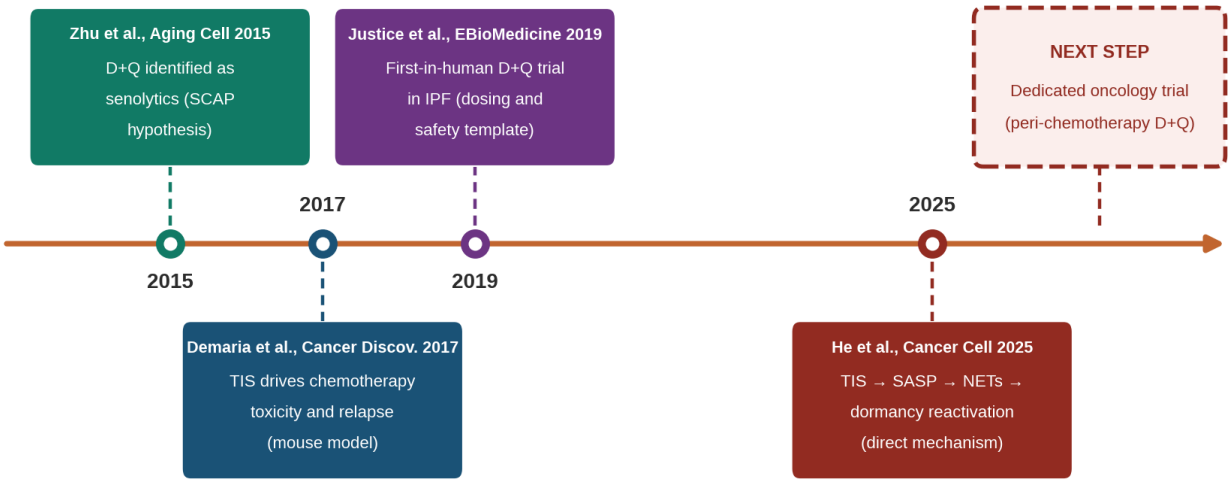


Figure 2. *Decade-long evidence trajectory from senolytic drug discovery (Zhu et al., 2015) through preclinical cancer-relapse demonstration (Demaria et al., 2017; He et al., 2025) and human dosing validation (Justice et al., 2019), illustrating the rare convergence of causal mechanism, animal efficacy, and human safety data supporting clinical translation.*