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AMERICAN CANCER SOCIETY RESEARCH AWARD SPOTLIGHT

Defeating lethal cancer: Interrupting the ecologic and evolutionary basis of death from malignancy

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Abstract

Despite the advances in cancer prevention, early detection, and treatments, all of which have led to improved cancer survival, globally, there is an increased incidence in cancer-related deaths. Although each patient and each tumor is wholly unique, the tipping point to incurable disease is common across all patients: the dual capacity for cancers to metastasize and resist systemic treatment. The discovery of genetic mutations and epigenetic variation that emerges during cancer progression highlights that evolutionary and ecology principles can be used to understand how cancer evolves to a lethal phenotype. By applying such an eco-evolutionary framework, the authors reinterpret our understanding of the metastatic process as one of an ecologic invasion and define the eco-evolutionary paths of evolving therapy resistance. With this understanding, the authors draw from successful strategies optimized in evolutionary ecology to define strategic interventions with the goal of altering the evolutionary trajectory of lethal cancer. Ultimately, studying, understanding, and treating cancer using evolutionary ecology principles provides an opportunity to improve the lives of patients with cancer.

KEYWORDS
cancer ecology, evolutionary ecology, lethal cancer, metastasis, therapy resistance

INTRODUCTION

> "All there is to thinking is seeing something noticeable which makes you see something you weren't noticing which makes you see something that isn't even visible."
>
> Norman Maclean, author, 1976[1]

In 2022, there were almost 20 million new cases of cancer and 9.7 million cancer-related deaths worldwide.[2] Although advances in cancer prevention, early detection, and treatments have led to improvements in cancer survival, the increased incidence of many cancers, coupled with an aging population, continues to lead to increased numbers of cancer cases and cancer-related deaths. By

2040, the number of new cancer cases is expected to rise to 29.9 million per year, and more than one half of these patients (15.3 million) are expected to die of their disease.[3] In the seemingly unending battle to cure cancer, it sometimes appears that we may have exhausted all avenues for a cure. By applying the scientific principles of ecology, we can open up new avenues for understanding—and treating—lethal cancer.

It is widely accepted that a total tumor burden of 1 kilogram within a patient is lethal.[4] On the surface, this is difficult to understand because this burden represents a small percentage (approximately 2%) of an adult's body weight. However, mass is not sufficient to explain this. A person can easily live with a benign tumor, e.g., a lipoma, that is 1 kilogram or greater in size. What separates benign tissue from a lethal tumor? We now appreciate that cancer lethality is the result of several factors, depending on the location of the cancer and its metastases (local effects), treatment resistance, and how it affects the body as a whole (systemic effects). Only a minority of people with cancer, approximately 10%, die because of the direct failure of a local organ from the growth of the primary tumor or its metastases. The most common example of local effects is a brain tumor causing disrupted neural function and increased intracranial pressure, leading to brain herniation. Another example is death caused by liver failure as a result of multiple liver metastases. Primary liver cancer or metastases, however, must destroy greater than 80% of the normal liver to be fatal, which is not a common phenomenon.[5] Most of the remaining cancer deaths are caused by syndromes that are a result of the release of toxins from multiple metastatic sites into the bloodstream.[6] From an ecological perspective, these released toxins are akin to noxious chemicals released into the atmosphere that poison the environment, e.g., the swamp gas methane produced by decaying plant material.[7]

It is important to note that these secreted factors are produced not only by the cancer cells but also by the patient's normal cells responding to the presence of the cancer. Cancer cells and the host cells within the tumor microenvironment produce a myriad of factors, which include cytokines, chemokines, proteases, growth factors, and toxic byproducts, that contribute to tumor growth, immune system suppression, and systemic side effects to the patient (Table 1).

TABLE 1 Factors released by the tumor and their contributions to the lethal toxin syndromes of cancer.

		Thrombosis	Cachexia	Bone metastasis	
Cytokines	Growth differentiation factor 15 (GDF15)		●		A cellular stress factor; promotes cachexia and anorexia
	Interleukin-6 (IL-6)	●	●	●	Promotes tumor growth, angiogenesis, invasion, and metastasis
	Interleukin-1 (IL-1)	●	●	●	Tumor cell growth factor; contributes to angiogenesis, cancer cell invasion, and metastasis
	Interleukin-8 (IL-8)	●	●	●	Promotes tumor growth, angiogenesis, and metastasis
	Tumor Necrosis Factor alpha (TNF-α)	●	●	●	Induces DNA damage and inhibits DNA repair, promotes tumor growth, induces angiogenic factors, promotes EMT and metastasis, and regulates chemokines
	Transforming Growth Factor beta (TGF-β)	●	●	●	Promotes EMT, angiogenesis, and metastasis; has multiple immunosuppressive effects (inhibits T cell proliferation and cytotoxicity, promotes T-reg cell development, and suppresses NK cell function)
	Vascular Endothelial Growth Factor (VEGF)	●			Promotes angiogenesis; has multiple immunosuppressive effects (inhibits dendritic cell maturation, promotes myeloid-derived suppressor cell accumulation, and suppresses T cell responses)
Chemokines	CXCL12 (also known as SDF1)			●	With its receptor CXCR4, promotes cancer cell migration and homing to metastatic sites
	CCL2 (also known as MCP1)			●	Recruits tumor-associated macrophages and promotes metastasis
	CX3CL1			●	Elevated levels are associated with metastasis and has been implicated in bone metastases
	CXCL1			●	Associated with promoting metastasis and is implicated in bone metastases
Proteases	Matrix metalloproteinases (MMPs)	●		●	Degrades the extracellular matrix (ECM) permitting cancer cell invasion and metastasis
	Urokinase plasminogen activator (uPA)	●		●	Facilitates degradation the ECM, permitting cancer cell invasion and metastasis
Coagulation cascade	Thrombin	●			Crucial for metastasis through platelet activation and deposition of fibrin via conversion of fibrinogen
	Tissue Factor (TF)	●			Participates in angiogenesis and correlated with metastatic potential; triggers a hypercoagulable state.
Toxins & Toxic Environment	Lactic Acid		●	●	A metabolic byproduct that promotes tumor growth and invasion, suppresses immune cell function, and enhances metastasis
	Reactive Oxygen Species (ROS)	●	●	●	Causes DNA damage, promotes genetic instability, and induces cell death of normal cells.
	Adenosine	●	●	●	The result of hypoxic conditions in tumors; exerts potent immunosuppressive effects (inhibits T cell activation and function, promotes T-reg cell activity, and suppresses NK cell cytotoxicity)
	Prostaglandin E2 (PGE2)	●	●	●	Produced by stromal tumor microenviornment cells; enhances tumor cell proliferation and survival, promotes angiogenesis, induces metastasis, and suppresses T cell proliferation and activation
	Arginine Depletion	●	●	●	Due to overexpression of arginase; depletion impairs protein synthesis, impairs T cell proliferation and function, suppresses NK cell activity, and compromises endothelial cell function
	Tryptophan Depletion		●	●	Due to overexpression of indoleamine 2,3-dioxygenase (IDO) by cancer cells or myeloid host cells; depletion inhibits T cell proliferation and activation and promotes T-reg cell differentiation

Note: Many secreted factors are released by cancer cells and tumor microenvironment cells that contribute to the lethal toxin syndromes of cancer: cachexia, thrombosis, and bone pain due to bone metastases.

Together, these factors mediate the three most common lethal toxin syndromes: cachexia, thrombosis, and pain (Figure 1).[8] In cachexia, which contributes to >20% of all cancer deaths, these factors, among others, promote muscle and fat breakdown, leading to profound weight loss, muscle wasting, and metabolic disturbances.[6,9–13] In thrombosis, these secreted factors contribute to hypercoagulability (an increased tendency of the blood to clot) and endothelial injury (damage to the inner lining of blood vessels), resulting in Virchow's triad of hypercoagulation, stasis, and endothelial cell damage. Clotting syndromes occur in up to 50% of patients and lead to lethal pulmonary emboli in 10%–20% of patients.[14–18] In patients with bone metastases (approximately 30% of all patients with cancer), these secreted factors mediate the activation of osteoblasts and osteoclasts that results in a vicious cycle of bone destruction and increased tumor growth, resulting in pain and skeletal-related complications, including both fractures and spinal cord compression.[19–22] In a significant number of patients, this pain requires higher and higher doses of opioid analgesics, resulting in somnolence, aspirations, respiratory arrest, and/or coma. In at least one autopsy series of patients with prostate cancer, approximately one third of the patients were in an opioid-induced coma at the time of death and had no other discernible cause of death at autopsy.[23] Beyond pain caused by bone metastases, pain can be caused by tumor involvement of nerves, inflammation, and/or organ obstruction. Up to 90% of patients with cancer require pain medication at the end of their lives.[24,25]

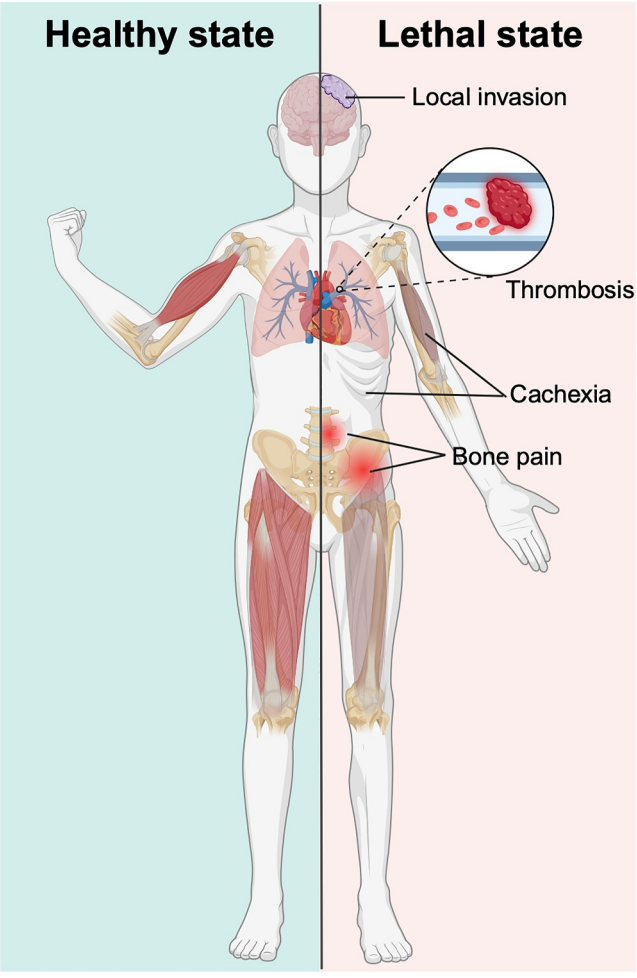

FIGURE 1 Causes of cancer-related death. Approximately 10% of patients die from the direct failure of an organ caused by local tumor invasion. The remaining 90% of patients die because of syndromes resulting from the release of toxins from the tumor, leading to thrombosis, cachexia, and bone pain. Created in BioRender.[8]

Ongoing investigative approaches to mitigate the effects of toxin production

Environmental science is filled with examples of ecologic restoration, from decreasing air pollution from smokestacks, to reducing the leaching of lead into drinking water, to changing strip-mining practices to stop the production of toxic chemicals into the land, water, and air. As delineated in Table 1, the tumor microenvironment creates various toxic substances that promote tumor growth and directly lead to the lethal syndromes.

Cachexia: Currently, there are no US Food and Drug Administration (FDA)-approved treatments specifically for cancer cachexia in the United States, and this remains an urgent unmet need in cancer treatment.[26] Although not yet FDA-approved, ponsegromab is a promising investigational monoclonal antibody targeting the cytokine growth differentiation factor 15 (GDF-15).[27] GDF-15 has been shown to promote anorexia and cachexia in patients with cancer.[28] Ponsegromab treatment has demonstrated significant improvements in body weight, appetite, and physical activity in clinical trials. Multiple other clinical trials are under way to prevent and treat cancer cachexia.[26]

Thrombosis: The FDA has approved several therapies to prevent thrombosis in patients with cancer, focusing on anticoagulants that help manage the risk of venous thromboembolism (VTE). Rivaroxaban (Xarelto; Johnson & Johnson) is approved for the prevention of VTE in acutely ill patients, including those with cancer, who are at risk for thromboembolic complications.[29] Low-molecular-weight heparin (dalteparin) is also approved to prevent VTE.[30]

Bone pain: Although the subject of multiple clinical trials over the years, interrupting the vicious cycle of bone destruction has met with limited success. Bisphosphonates, such as zoledronic acid and pamidronate, as well as the RANK-ligand inhibitor denosumab inhibit osteoclast-mediated bone resorption and reduce the risk of fractures in patients with cancer.[31–33] Their effectiveness in decreasing bone pain is less clear.

Other toxins: There has long been interest in decreasing the production of reactive oxygen species ROS through the ingestion of natural antioxidants, especially to interrupt carcinogenesis.[34] Decreasing prostaglandin E2 production by inhibiting COX-2 continues to be an area of active investigation.[35] Several other strategies are under development to limit the production of toxic byproducts of the tumor ecosystem. Clinical trials against individual chemokines, cytokines, and thrombogenic factors have largely proven to be

ineffective, likely because inhibiting one of the myriad of responsible factors is not sufficient.[13,35–41] Hopefully, continued insight into the molecular events underlying the lethal clinical syndromes that contribute to the morbidity and mortality of cancer and placing them in an ecological framework will continue to suggest avenues of treatment that should be explored.

Whether one dies by local invasion or by systemic effects, there is a tipping point at which cancer becomes incurable. This appears to be caused by the dual capacities of cancer to metastasize and to become treatment-resistant. If cancer never became metastatic, it would be curable by local surgical or radiation therapy. If a cancer never developed therapeutic resistance, even metastatic disease would be curable with systemic therapies.

UNDERSTANDING CANCER LETHALITY IN AN ECO-EVOLUTIONARY FRAMEWORK

> "…nothing in biology makes sense except in the light of evolution…"
>
> Theodosius G. Dobzhansky, evolutionary biologist, 1964[42]

We now understand that cancer remains incurable because it evolves the capacity to metastasize and develop resistance to both host defense systems and systemic therapies.[43] Despite the uniqueness of each patient and each tumor—including different environments, different driver mutations, different organ sites, different treatment regimens, and different medical and personal histories—each of these lethal cancers in different patients independently arise and then evolve the same lethal features in each patient, metastasis and therapeutic resistance, in a process termed *convergent evolution*.[43,44] Convergent evolution describes the independent evolution of a similar feature in different species; for example, wings evolved independently in birds, mammals, and insects. On the surface, that this occurs in cancer across millions of patients with cancer is quite remarkable. How is it possible?

The discovery of the myriad of epigenetic and genetic variation that emerges throughout the course of cancer progression highlights that evolutionary science can be a good tool to understand how cancer evolves and becomes lethal (Table 2). Evolutionary science is the study of the history of life on Earth. It studies how species evolve over time and how genetic variation leads to new observable phenotypes (the physical and functional characteristics of a species). How does this apply to cancer?

When a normal cell breaks its connections to its neighboring cells in a tissue or organ, it dies—this is essential for the survival of a complex multicellular organism like humans.[45] Cancer begins when a once normal cell evolves the ability to break bonds with its neighbors, survives, and proliferates. Once this cell breaks away from the constraints of being a component of a multicellular tissue, it can be thought of as an emerging new species within the patient.[43] Heritable changes in the cancer cells over time lead to alterations in genotypes and resultant phenotypes as the tumor population proliferates. Genetic changes, however, do not happen in a vacuum. Cancer cells are subject to evolution by natural selection in response to forces within their tumor microenvironment ecosystem. This is analogous to how species evolve: for example, how the beak shape of Charles Darwin's finches evolved in response to the various food sources of the different Galapagos Islands.[44,46] Over time, cancer cells that accumulate a heritable variation that is favorable for a particular environment proliferate, become tumors, and grow.

In the ecological sciences, the environment that a species lives in is referred to as an ecosystem (Table 3). An ecosystem describes a biologic community of interacting organisms and their physical environment as a unit (e.g., Yellowstone, the Everglades, New York City) and recognizes that the ecosystem is part of a larger interactive framework that is termed the biosphere (i.e., Earth). In any ecosystem, a species evolves to acquire characteristics or traits that improve the species' chance of survival. If an ecosystem changes, the species must adapt by acquiring new traits that allow it to survive and flourish in the new conditions. If unsuccessful, the species does not survive: for example, the dinosaurs. The cancer ecosystem includes the cancer cell population and its interactions with the many diverse factors of the tumor microenvironment, including other cancer and noncancer cells, the extracellular tissue matrix, and a myriad of circulating factors. The cancer cells, then, are a species in that ecosystem that compete and cooperate with each other and interact with nontumor cells, constantly adapting and evolving.[7,47–53] It has been demonstrated that these interactions can alter the genotype and phenotype of both the host cells and the cancer cells, ultimately influencing the selective environment of the tumor ecosystem and driving further evolution.

The cancer species and its local ecosystem, of course, do not exist in isolation but rather emerge, survive, and grow within the larger biosphere of the individual patient (Table 3). From an ecologic perspective, lethality is caused by the destruction of the local ecosystem, e.g., overwhelming metastases to the liver, or by the release of toxins into the circulation that poisons the patient as the tumor ecosystem's biosphere, e.g., cachexia. Just as the wildfires of Canada in northern North America polluted the air quality of the mid-Atlantic United States and the Eyjafjallajokull volcano in Iceland grounded flights across the globe, so, too, do tumors affect the entire system within which they exist: for cancer cells, the patient is the equivalent of the earth biosphere. Whether on Earth or within one person, once the cumulative contributions of many local ecosystems lead to catastrophic change at the level of the whole system, it is difficult, if not impossible, to intervene successfully. To alter the trajectory of lethal cancer before this final stage, we must understand the underlying mechanisms that lead to lethality: the traits of metastasis and therapy resistance.

TABLE 2 Glossary of evolutionary ecology terms.

Term	Definition	
Disciplines applied in cancer ecology	Ecology	A discipline of biology that deals with the relations of organisms to one another and to their physical surroundings
	Evolutionary biology	A discipline of biology that studies how species evolve over time and how genetic variation leads to new observable phenotypes through processes of evolution, including natural selection, adaptation, and speciation
	Evolutionary ecology	A discipline of biology that explicitly incorporates how interactions among species and their environment shapes evolution over time
	Restoration ecology	The discipline of biology that studies how to intervene to repair damaged or destroyed ecosystems
Adaptation	A heritable phenotypic trait that improves fitness and therefore has evolved through natural selection	
Adaptive	Characteristic of a heritable trait that improves fitness; the opposite is maladaptive, a heritable trait that reduces fitness: Traits that are adaptive in one environment may be neutral or maladaptive in another (and vice versa).	
Epigenetic plasticity	The capacity for altering phenotype (e.g., pigmentation or protein expression) in response to environmental factors without altering heritable genotype	
Evolution	Change in heritable characteristics over generations	
Evolutionary double bind	A situation in which an organism adopts a particular adaptive trait in response to a particular selective pressure that renders it vulnerable to another environmental pressure; also known as evolutionary trap	
Evolutionary rescue	A process by which a population that would have gone extinct persists because of a selective or adaptive process	
Evolutionary triage	Describes how the frequency of heritable change and magnitude of phenotype can be influenced by the selective environment: Individuals with more adaptive traits are selected over those with a less fit (although not absent) trait value.	
Fitness	The ability of organisms to survive and reproduce in the environment in which they find themselves	
Natural selection	A mechanism of evolution; the differential fitness (survival and reproduction) of individuals because of differences in phenotype, resulting in the representation of heritable traits in the population over time	
Phenotype	An individual's observable traits, such as height, eye color, and blood type: A person's phenotype is determined by both genetic and epigenetic factors.	
Selective pressure	Factors that cause a particular phenotype to be more favorable in the particular circumstance	
Trade-off	A process by which increasing fitness of one trait decreases the fitness of another trait	
Trait	A distinguishing quality or characteristic: In terms of fitness and cancer, it refers to a characteristic that contributes to survival.	

Why does cancer spread? Adaptive phenotypes that result in metastasis

> "When a plant goes to seed, its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil.... While many researchers have been studying "the seeds," the properties of "the soils" may reveal valuable insights into the metastatic peculiarities of cancer cases."
>
> Stephen Paget, surgeon, 1889[54]

The ability to metastasize to other organs is a fundamental hallmark of lethal cancer.[55] One of the great mysteries of cancer, however, is why cancer cells metastasize at all. Most cancer cells in the primary tumor never leave. Why do some cancer cells move? Even if a cancer cell acquires the ability to move, it does not mean that it must. Is the metastatic process merely caused by chance sloughing of cells into a lymphatic vessel, or are there forces that actively drive a cancer cell to leave a tumor?

The process of cancer metastasis to a secondary site is directly analogous to how species invades an ecosystem[56–60] (Figure 2; Table 3). The metastatic cascade has been well described. Cancer cells must acquire the ability to move, exit the tumor and extravasate into the lymphatics or bloodstream, survive in the circulation, and intravasate into a secondary organ site. Upon colonizing this secondary site, the metastasizing cells often undergo a period of dormancy—sometimes for years or decades—before reengaging proliferation to form a clinically meaningful metastatic tumor.[54,61–65] Similarly, in the ecological setting, an invasive species must first have the capacity to leave its native ecosystem, survive transit, and then establish itself in a new ecosystem. Upon arrival in this new *secondary site* ecosystem, the invasive species will undergo a lag period during which it becomes used to its new environment before regaining high reproduction levels, when it then exerts an impact on the invaded

TABLE 3 Ecological characteristics of cancer.

Term	Definition	Ecology	Cancer biology
Ecosystem	A biological community of interacting organisms and their physical environment as a unit	All animals, trees, soil, streams, etc. in a forest	All of the cells, secreted factors, etc. of an organ or tumor
Invasive species	A nonnative species that harms its new ecosystem, causing damage to habitats and other species living in the ecosystem	Beavers, lantern flies	Metastasizing cancer cells
Species	Individuals with a shared lineage and similar functional traits	Wolves, butterflies	Cancer cells
Biosphere	All ecosystems contained on the planet.	Earth	Patient
Dormancy	A transient, nonreproductive state; a lag period is a phase in which an invading species has low or absent reproduction	Hibernating bear	Nonproliferating cancer cell
Habitat	The physical features in which an organism lives	Physical features of a forest or lake, etc.	The physical features of a tissue or tumor
Convergent evolution	The independent evolution of a similar feature in different species	Wings (present in mammals, birds, and insects)	Metastasis and therapy resistance (present in 10 M patients who die of cancer annually)
Habitat selection	The ability of organisms to move to and establish in a habitat, influenced by resources, hazard avoidance, and competition	Salmon select specific streams to spawn	Organotrophism; metastasizing cells grow in nonrandom sites

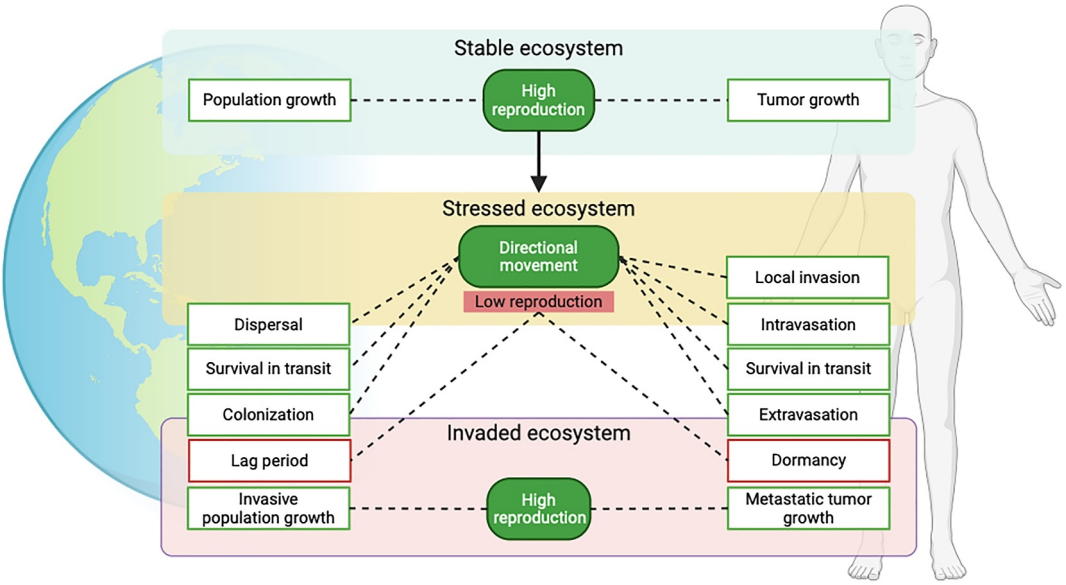

FIGURE 2 Invasion ecology of metastasis. Successful invasive species undergo the same observable stages as successful metastasis. Traits that are selected for and optimized in a particular ecosystem may also provide an advantage when engaged for metastatic—or invasive species—success. The observable phenotypes of metastasis or invasion (e.g., intravasation, survival in transit, dormancy, or metastatic tumor growth) are a result of adaptive traits selected for in the primary tumor ecosystem. There are several steps to ecologic invasion. First, individuals leave their native ecosystem. The traits that enable adaptive directional movement in a stressed ecosystem (e.g., overcrowding caused by high reproduction/proliferation, poor resources) simultaneously enable the observable phenotypes of metastasis and invasion, e.g., intravasation and survival in transit. The trade-off to this adaptive directional movement is low reproduction; this is observed in an ecologic invasion as a lag period and is recognized in the metastatic cascade as a period of dormancy. Eventually, individuals exit the lag period and re-engage high reproduction/proliferation in the invaded ecosystem of the secondary site. Created in BioRender.[8]

ecosystem. As discussed in below, while in this dormant state, cancer cells are inherently resistant to most anticancer therapies designed to eliminate highly proliferative cells. By recognizing the process of metastasis as one of invasive species invasion, it is possible to identify the particular adaptive traits that are selected for and then engaged for metastatic (that is, invasion) success (Figure 2).

Cells exist in an ecosystem that is highly dynamic in both space and time. To survive, these cells must be able to sense their

environment, moving from one that does not allow for their growth to one that does. It is well established in the evolutionary ecology field that directional movement is adaptive under stress, i.e., it increases the likelihood of survival and increases fitness by moving away from a poor environment.[66–68] However, there are trade-offs to moving. For example, migrating species are exposed to the dangers of changing habitats, e.g., crossing rapidly flowing rivers and exposure to predators. Migration is also inherently metabolically costly, so offspring are generally born before or after migrations. To move, cancer cells use epigenetic switches to adopt a mesenchymal phenotype that allows movement across changing habitats, e.g., the bloodstream, while simultaneously inhibiting cell division.[61,69] Thus cancer cells physically leave the primary tumor as a result of adopting a prosurvival adaptation to escape hostile local microenvironment conditions that likely include lack of nutrients, hypoxia, and anti-tumor immune cells.[61,63,65,70–72]

Once a cell successfully emigrates from the primary tumor, it must survive transit through the lymphatics and bloodstream to immigrate to a new organ site. For distant metastasis, regardless of the route of dissemination from the primary tumor, metastasizing cancer cells ultimately arrive in the arterial blood supply and will be spread to all parts of the body subject to blood perfusion rates (Table 4).[6,73,76] Paradoxically, as first documented in 1889 in patients with breast cancer, specific tumor types exhibit organotropism.[54] Rather than tropism in the classical sense (i.e., directional movement in response to a stimulus), tumor organotropism describes the propensity for individual cancer types to establish clinically meaningful tumors in particular secondary sites.[77–81] The mechanisms underlying organotropism still largely remain a mystery. It is worth emphasizing that blood flow is unidirectional and that cancer cells must enter the venous blood, go through the heart to the lungs, and then leave the heart through the arterial blood supply (Figure 3).[8] This means that there is no direct gradient of chemokine attractants from the primary organ to the new metastatic site. For example, prostate cancer has a clear propensity to establish metastases in bone. One explanation for this stems from the finding that prostate cancer cells express a receptor on their cell surface for stromal-derived factor 1 (SDF-1), which is a chemokine secreted into blood by cells in the bone marrow.[82,83] Because of arterial–venous blood flow and the structure of the vascular system, with many organs set up in parallel, there is no direct gradient of SDF-1 from the bone vasculature (high SDF-1) to the prostate vasculature (low SDF-1). Indeed, there is no direct blood flow from the bone to the prostate. A prostate cancer cell that has migrated out of the prostate into the venous blood and then travels through the lungs and heart into the arterial system that is then delivered to the bone (a likelihood determined by the percentage of cardiac output to that tissue [for bone, it is 5%]; Table 4) can sense the local gradient of SDF-1 in the bone vasculature and intravasate into the bone marrow to establish a metastatic colony.

Paget's seed and soil hypothesis, widely accepted as dogma in metastasis biology, states that successful metastasis requires both an appropriately primed *seed* and a *congenial soil* of a secondary site.[54] Although the mechanisms underlying organotropism remain poorly understood, the observed pattern of metastases from different primary sites has a direct effect on the lethal syndrome of different cancers. Prostate and breast cancers, for example, have a predilection to form metastases in bone, leading to fractures and pain. Lung and colon cancers tend to form metastases in the liver, leading to liver failure and changes in coagulation. Each organ inherently offers a unique ecosystem milieu and selective pressures, both for the cancer cells that initially emerge in the primary tumor site and for would-be metastatic cells invading a new ecosystem. Each cancer type expresses phenotypic traits that confer different fitness advantages within a particular ecosystem, and thus the suitability of a secondary site will vary, depending on the origin and adaptive strategies of the cancer cell. If a metastasizing cancer cell senses a resource-rich tissue environment, it will extravasate out of the blood vessel and into the surrounding tissue, moving up the resource gradient (e.g., a local concentration of a chemokine) to invade the secondary ecosystem. In ecological terms, this constitutes adaptive habitat selection[69,84–86] (Table 3). Again, the capacity to undergo

TABLE 4 Paradox of cardiac output versus observed frequency of metastasis of common solid tumor types.[a]

		Site of metastasis				
		Liver	Muscle	Brain	Lung	Bone
Cardiac output, %		26.0	15.0	12.0	2.5	5.0
		Frequency of metastasis, %				
Primary site	Breast	62.0	1.0	22.0	71.0	71.0
	Prostate	25.0	1.0	1.6	46.0	90.0
	Lung	21.0	1.0	39.0	--	34.0
	Colon	70.0	1.0	5.0	32.0	8.0

[a]The organotrophism, i.e., the nonrandom frequency of metastasis of particular tumor types (indicated by the frequency of metastasis) is not explained and, in some cases, is inverse to the percentage cardiac output delivered to common sites of metastasis.[73–75]

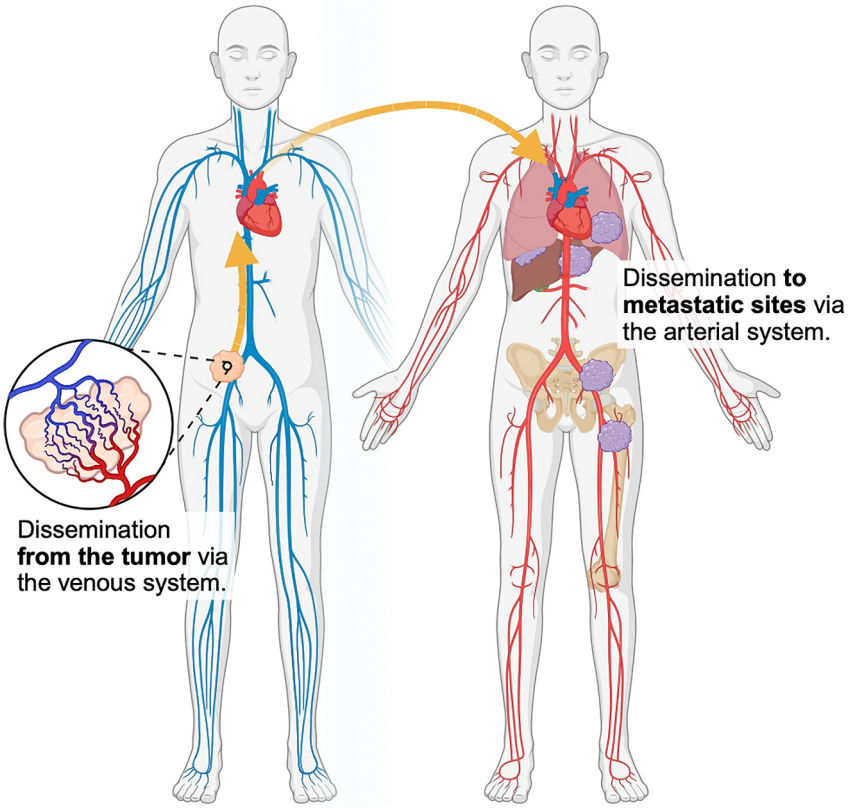

FIGURE 3 Path of a metastasizing cancer cell. Cancer cells disseminate from the primary tumor through a number of routes, including in the lymphatics, along a nerve, or directly in a venous capillary. Eventually, all disseminating cancer cells enter the venous blood supply and are subject to the well characterized blood flow of the vascular system. That is, disseminating cancer cells pass through the heart and the lungs to enter the arterial blood system and are carried with the blood to all organs of the body, subject to the cardiac output percentages outlined in Table 2. Upon entering a distant-site capillary bed, cells then may extravasate to invade the metastatic site. Created in BioRender.[8]

habitat selection—in this case, to sense and respond to local chemical cues and invade a secondary site—is an adaptive trait that will increase the fitness of the metastasizing cancer cell while simultaneously and unwittingly resulting in the unintended consequence of metastatic seeding. These features of both the invading cancer cell and the invaded ecosystem may be leveraged to control metastatic recurrence (Figure 2).

Why does therapy fail patients? Mapping the evolutionary paths of therapeutic resistance

> "One general law, leading to the advancement of all organic beings, namely, multiply, vary, let the strongest live and the weakest die."
>
> Charles Darwin, naturalist, 1959[46]

All lethal cancers develop resistant to systemic therapies—*even before* initial exposure of any given treatment. How is this possible?

During the course of cancer progression, the tumor ecosystem is rarely stable. Cancer cells are subject to repeated extreme changes in their ecosystem, rapidly and fundamentally altering the tumor environment and the cancer cells within it, immediately influencing the fitness advantage of a phenotypic trait, and selecting for individuals with that adaptive trait. These catastrophic events are inherent to the growth of the tumor itself (e.g., loss of oxygenation caused by tumor growth away from the vasculature or collapse of the disorganized neovasculature).[7,62,63,87] Such a catastrophic shift in the tumor ecosystem can also be externally applied in the form of anticancer therapy. Although the specific features and impact of these catastrophes are unique, in each instance, they will lead to the extinction of the cancer species unless it evolves rapidly to suit this new environment. This is referred to as evolutionary rescue.[88–90]

There are innumerable examples of how cancer cells are resistant to systemic therapy; some are specific to a particular tumor type or drug class; others are more general to any external stressor. What is common among each of these mechanisms is that the individual resistant cellular phenotype ultimately results in higher fitness after treatment, resulting in evolutionary rescue and subsequent survival and proliferation of the cancer species and cancer recurrence in the patient.[91–93] With this understanding, we can classify each of these specific resistance mechanisms into four major paths to evolutionary rescue, providing a greater understanding of the eco-evolutionary forces at play and how they intersect: phenotypic heterogeneity,

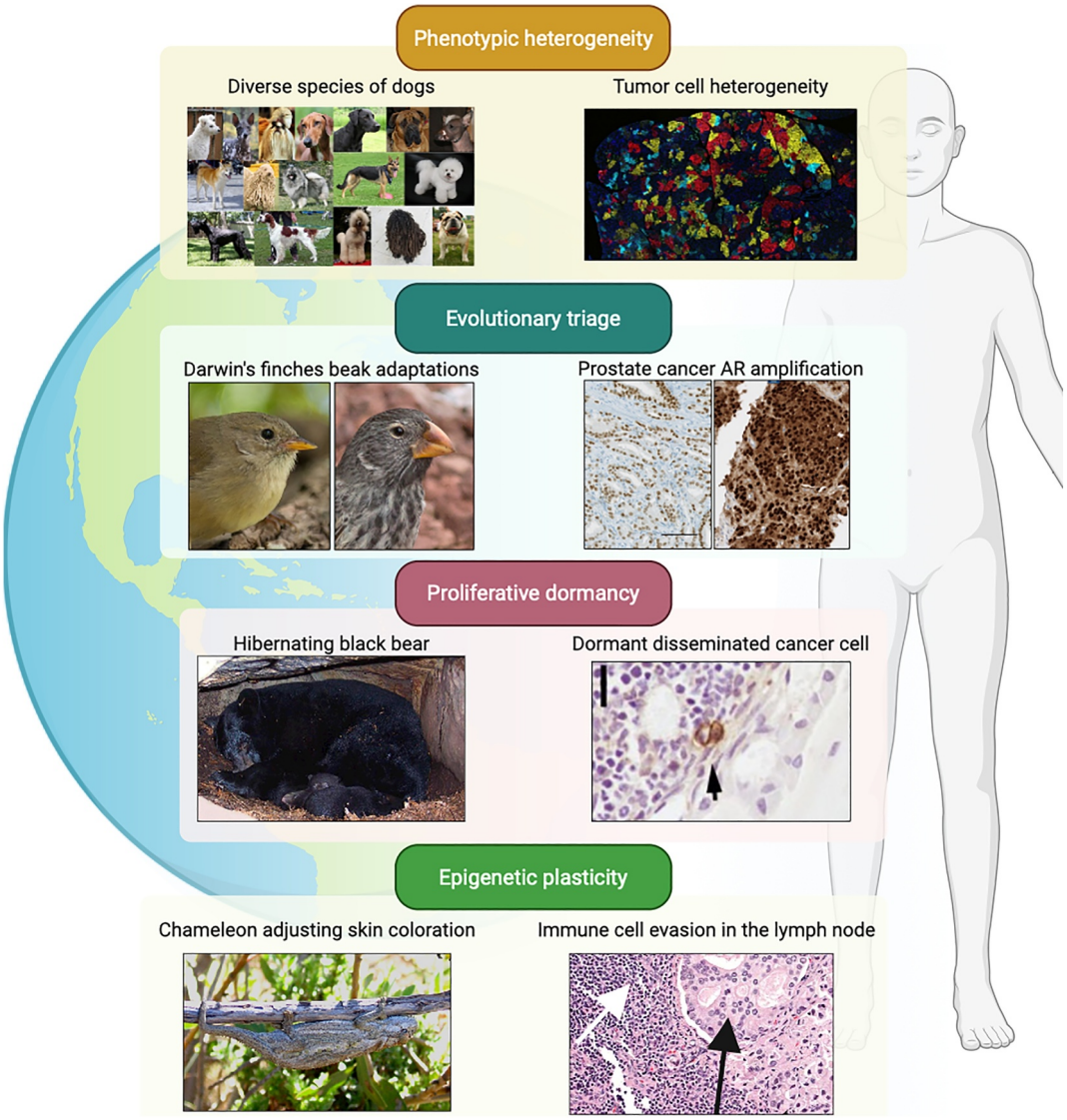

FIGURE 4 Eco-evolutionary paths to resistance. There are four major eco-evolutionary paths to evolutionary rescue that are readily observed in the natural world and the evolution of cancer resistance: phenotypic heterogeneity, evolutionary triage, proliferative dormancy, and epigenetic plasticity. Differential survival of different breeds of dogs[94,95] or different clones of cancer cells (image from Maddipati 2015[96]) are examples of *phenotypic heterogeneity*. Beak shape adaptation because of food type availability (e.g., seeds vs. insects) in Darwin's finches[97,98] and cancer cell amplification of the androgen receptor (AR) caused by hormone therapy exposure (image courtesy of Angelo De Marzo) are examples of *evolutionary triage*. Examples of *proliferative dormancy* include hibernation of black bears during harsh seasons[99] and a solitary, nonproliferative, disseminated cancer cell in bone[100] (image from Lawson et al. 2015[101]). A chameleon adjusting skin pigmentation, shown here for camouflage[102] (image from Stuart-Fox & Moussalli 2008[103]), and the altered expression of immune recognition molecules (e.g., downregulation of MHCI and increased expression of PD-L1) in cancer cells (black arrow) in the lymph node (white arrow; image courtesy of Angelo De Marzo) are examples of *epigenetic plasticity*. MCHI indicates major histocompatibility complex class 1; PD-L1, programmed death-ligand 1. Created in BioRender. Amend SR, 2024; https://BioRender.com/u71g448.[8]

evolutionary triage, epigenetic plasticity, and dormancy (Table 3, Figure 4).

Phenotypic heterogeneity: Under this scenario, commonly defined as tumor cell heterogeneity (TCH) among the billions of genetically and phenotypically heterogeneous cancer cells in the population of a tumor, there *already existed* at least one cell that expressed a trait or set of traits that conferred the ability to survive and repopulate the tumor with resistant cells.[104–107] An eco-evolutionary example of such interspecies heterogeneity is the myriad of dog breeds that exist in the same environment (Figure 4). If that environment suddenly becomes cold rapidly, the Husky and the St Bernard are equipped to survive while the others perish. If it becomes hot, the Afghan Hound and the Australian Cattle Dog have the right phenotype to survive while the others perish. In the cancer setting, upon treatment, the cancer cell expressing that phenotypic trait will survive (will be selected for) while all others will die. An example of this mechanism is a cell that has a drug efflux pump that removes the toxic therapy from the cell so that there is limited DNA damage.[108–110] Another

example is a cancer cell that has an inactivating mutation of p53, the *guardian of the genome*.[111–113] The role of p53 is to shunt unrepaired cells to apoptosis. If p53 is mutated, the damaged cells may still transit through mitosis, propagating the population despite the chemotherapy-damaged DNA.

Evolutionary triage: In the setting of evolutionary triage, cells with *better* (i.e., more adaptive) phenotypic traits are selected over those with a *less fit* (although not necessarily absent) adaptive trait. A classic example of evolutionary triage is Darwin's finches (Figure 4). As the birds were exposed to different environments, the finches adapted and eventually specialized. The finches' beaks and bodies changed, allowing them to eat certain types of foods, such as nuts, fruits, or insects. In a patient who has cancer, as the tumor experiences multiple cycles of chemotherapy over time, the cells that express a more fit adaptive trait will increase in frequency, whereas those that are less fit will die off.[114–116] The cancer cells in this scenario adapt to the changing environment until they maximize the fitness advantage of the resistant trait. An example of this in tumors treated with DNA-damaging chemotherapy is that, in regions of the tumor with suboptimal drug delivery, cells that are equipped to survive the therapy through adequate upregulated DNA damage-repair pathways will survive and proliferate, whereas those that do not have an adequate resistance trait perish.[117–119] Over time, the cancer cells will optimize this adaptive trait to eventually have sufficient DNA damage repair without too great a metabolic cost. Another example of evolutionary triage in cancer is observed in prostate cancer treated with antiandrogen therapy that deprives the cancer cells of a major growth factor.[120–122] Eventually, this therapy fails because, among other mechanisms, cancer cells upregulate the number of androgen receptors, allowing them to better bind the limited supply of testosterone available. Importantly, evolutionary triage as a mechanism underlying the emergence of drug resistance is most likely in regions of the tumor with smaller perturbations to the local tumor ecosystem, i.e., those with suboptimal drug delivery because of disorganized vasculature, etc., providing an opportunity for a range of adaptations to result in sufficient fitness. Those phenotypic traits that emerge because of evolutionary triage may be selected for later in a TCH scenario.

Epigenetic plasticity: In this scenario, the adaptive trait that is selected for is the capacity of a cell to alter its phenotype in response to its environment.[123–126] As a cell responds to stress, it can access a myriad of phenotypes by engaging otherwise epigenetically silenced programs that promote survival in that environment. A prototypical example of epigenetic plasticity is the chameleon that uses a combination of pigment manipulation and structural changes in skin cells to alter its color as needed for camouflage (Figure 4). A continued cancer mystery is how cancer cells can survive in lymph nodes, given the high numbers of immune cells. Cancer cells downregulate antigen-presenting major histocompatibility complexes and upregulate checkpoint molecules, e.g., Programmed death-ligand 1, effectively hiding them from the immune system effector cells.[127–129] Another example of epigenetic plasticity is the accession of a stem cell state, which enables the cancer cell access to multiple programs that promote survival.[130–133] Again, this mechanism for resistance does not sit in isolation: epigenetic plasticity itself may be the trait that is selected for in the setting of TCH, and the capacity to enter and exit a proliferatively dormant state, as described below, is another example of epigenetic plasticity.

Dormancy: Cancer cells are only susceptible to most systemic therapies if they are actively proliferating, i.e., progressing through a complete cell division. If a cell is not progressing through a complete mitotic cell division, it cannot be shunted to an apoptotic pathway at the DNA repair checkpoint after suffering damage from chemotherapy. Similarly, if they are addicted to a growth factor, targeted therapy is most effective when the cells are driven to divide in response to that growth factor. Finally, it is very difficult for the immune system to recognize a cancer cell as foreign if it is residing in a tissue without dividing because it is unlikely to be recognized by an immune cell. Dormancy as a resistance mechanism does not require a history of mutations that lead to TCH or adaptive mutations over time. Many examples of dormancy exist in nature, but perhaps none is more familiar than the hibernating bear (Figure 4). Hibernation is a state an animal enters to conserve energy when food is scarce and to minimize exposure to harsh winter conditions. As conditions become more favorable, the bears reemerge and resume activity, including procreation. The cellular mechanisms that lead to cancer cell dormancy remain poorly understood, with cancer cells described as being paused in or exited from the cell cycle. Explanations include the cancer cell entering a classical G0 quiescent state, accessing a reversible senescent state, or accessing a nonproliferative endocycle, among other mechanisms.[134–138] In addition, as discussed above, it is thought that dormancy plays a major role in metastasis. It is observed clinically that many patients relapse in a distant organ months or years after treatment to their primary site. The only explanation for this is that a cancer cell metastasized from the primary tumor before surgical removal or definitive radiation treatment.[139–142] Indeed, most current research on cancer cell dormancy specifically focuses on the nonproliferative disseminated tumor cells (DTCs) that seed distant metastases. Thus any strategies to target cells that survive therapy through dormancy may also be effective against metastatic recurrence.

Understanding which eco-evolutionary mechanism(s) cancer cells use to adapt and evolve resistance and how each of these mechanisms interplays together across the trajectory of the evolution of lethal cancer is critical to developing new approaches to cancer treatment that move beyond single-gene or pathway-targeted approaches.

DEFEATING LETHAL CANCER: PRACTICAL APPLICATIONS OF ECO-EVOLUTIONARY MEDICINE

> "Discovery consists of seeing what everybody has seen and thinking what nobody has thought."
>
> Attributed to Albert Szent-Györgyi, biochemist[143]

There are approximately 25,000 clinical trials currently recruiting participants to improve cancer outcomes.[144] The majority of these trials developing therapies are simply *plug-and-play* designs, testing a single new agent where others have failed, adding a new agent to existing therapies, or trying an agent that works in one cancer in another indication. These trials echo the traditional approach for treating people with cancer, which is to treat with a single class of drug or combination of drugs until it fails and the tumor recurs, and then treat with a second set of drugs, and a third, continuing until the cancer is nonresponsive to all therapies. As noted above, virtually all systemic therapies rely on targeting cells that are actively proliferating. This paradigm directly interrupts the fitness of highly proliferative cancer cells with antiproliferative agents with little regard to the adaptive traits the cancer cells use to realize evolutionary rescue, which is observed in the patient as a resistant recurrence. When resistance occurs, the cancer field has spent the most energy looking for new mutations in resistant patients in the hope of finding a new therapeutic target.

From an evolutionary ecology perspective, defeating therapy resistance can be achieved by creating an extinction event while avoiding evolutionary rescue (Table 2). By appreciating the underlying eco-evolutionary paths to therapy resistance that a cancer may take, rational approaches may be deployed to directly influence and direct the evolutionary trajectory of the cancer. Alternatively—or concurrently—we can also influence the *ecology* of the tumor to bend the evolutionary path of a cancer cell using restoration ecology approaches. The aim of restoration ecologists is to restore damaged ecosystems through systematic intervention to remove invading species (e.g., mussels in Lake Erie), restore nutrient balance (e.g., fertilizer run-off into lakes), and decrease toxic byproduct production (e.g., air pollution from smokestacks), thereby improving the quality of the habitat for native species. The successes of restoration ecology, such as the restoration of Lake Erie by decreasing the population of invading zebra mussels and decreasing fertilizer runoff, cleanup efforts after oil spills, and community watershed and beach management, suggest points of therapeutic intervention for patients with cancer. Fortunately, we are starting to see new therapeutic strategies develop that focus on intercepting the ecologic and evolutionary mechanisms by which resistance arises (Table 5).

Strategy: Evolutionary double bind to prevent evolutionary rescue

Type: Evolutionary strategy

Targets: Phenotypic heterogeneity—epigenetic plasticity

Multiagent chemotherapies are standard in virtually all solid and liquid tumors and have led to cures in highly proliferative cancers, e.g., acute leukemias. Another strategy used to enact an extinction event and limit evolutionary rescue in ecology is an evolutionary double-bind approach. An example of an evolutionary double bind in ecology is the interaction between gerbils, owls, and snakes in desert environments.[145] To avoid owl predation, gerbils seek refuge in bushes scattered across the desert. Snakes also lurk in bushes. By hiding in bushes to avoid owls, gerbils inadvertently increase their risk of encountering snakes—the gerbils' adaptive strategy to one predator (owls) makes them more vulnerable to another predator (snakes). This creates an evolutionary pressure that makes it difficult for gerbils to develop a single, effective defense strategy against both predators.

The key principle is to strategically sequence or combine therapies so that the evolutionary adaptations cancer cells make to survive one treatment end up making them more vulnerable to another.[89,146,147] For example, the first strike could be a standard antiproliferative agent, e.g., chemotherapy, to select for particular adaptive traits. The second strike to eliminate the surviving cells requires a therapy that specifically targets the unique adaptations of the surviving cells.[147,148] To be successful, this will require understanding which resistance mechanism(s) the survivors are using. Antiproliferative agents that have been previously used in a nondiscriminant fashion as antitumor agents and have failed to produce a treatment effect may have activity if used at the appropriate time in the appropriate sequence. This general principle has been used successfully in synthetic lethality approaches, such as the use of poly(adenosine diphosphate–ribose) polymerase (PARP)

TABLE 5 Eco-evolutionary strategies to treat cancer.

	Goal	Approach	Clinical application	Invasive sp. lag period	Phenotypic heterogeneity	Evolutionary triage	Epigenetic plasticity	Dormancy
Evolutionary strategies	Prevent evolutionary rescue	Evolutionary double bind	Targeted synthetic lethal approaches		✕	✕		
	Manage the evolution of resistance	Adaptive therapy	PSA-guided therapy			✕		
Ecological restoration	Remove invading species	Kill-on-sight order	Ablation of oligometastases, eliminate dormant DTCs	✕				✕
	Prolong lag period	Block disseminated tumor cell "awakening"	Activate TME factors to reinforce dormancy	✕				✕
	Destroy pro-tumor ecosystem	Prescribed burn for land management	Bone marrow transplant	✕	✕	✕	✕	✕
	Shift the selective pressure of the tumor ecosystem	Promote recruitment anti-tumor host cells	Immunotherapy, induce immunogenic cancer cell death			✕	✕	
		Restore nutient balance	Angiogenesis inhibitors			✕	✕	✕

PSA: prostate specific antigen; DTC: disseminated tumor cell; TME: tumor microenvironment; Invasive sp.: Invasive species

Abbreviations: DTCs, disseminated tumor cells; PSA, prostate-specific antigen; TME, tumor microenvironment.

inhibitors to treat BRCA-defective cancers.[149,150] DNA damage repair is achieved through multiple, partially redundant DNA damage-repair pathways. BRCA mutation leads to defective DNA damage repair and enhanced genetic instability that is adaptive in tumor growth. However, this genetic defect renders the cells reliant upon a second DNA damage pathway that requires the protein PARP. Thus, in the presence of a BRCA mutation, inhibition of this requisite DNA damage-repair pathway through PARP inhibitors leads to cell death. The majority of data using the PARP inhibitors have been generated in the adjuvant setting, in which, in studies like OlympiAD (ClinicalTrials.gov identifier NCT02000622) and EMBRACA (ClinicalTrials.gov identifier NCT19455775), olaparib and talazoparib reduced the risk of disease progression by 42% and 46%, respectively, compared with chemotherapy.[151–153] Ongoing phase 2/3 studies include PARP inhibitors combined with chemotherapy and with immune checkpoint inhibitors are now directly addressing the evolutionary double bind/synthetic lethal approach.[151]

Strategy: Adaptive therapy to slow the evolution of resistance

Type: Evolutionary strategy

Targets: Evolutionary triage

Cancer cell adaptation through evolutionary triage as a result of selective environmental pressure can be disrupted by decreasing that selective environmental pressure. Adaptive therapy is an innovative approach to cancer treatment that aims to manage drug resistance and prolong patient survival by strategically modulating treatment intensity.[154–157] Adaptive therapy is based on two main evolutionary principles: somatic selection (that tumors contain diverse cell populations that evolve over time in response to treatment pressures) and trade-offs (that drug-resistant cancer cells have fitness costs in the absence of treatment, making them less competitive than sensitive cells). The primary objective of adaptive therapy is to maintain a stable tumor burden rather than eradication of all cancer cells. This is achieved by preserving a population of treatment-sensitive cells to competitively suppress resistant cells, ultimately delaying the emergence of drug resistance and lethal recurrence. Practically, adaptive therapy uses a dynamic treatment protocol that adjusts drug dosing and timing based on the tumor's response, alternating between periods of treatment and treatment holidays. This strategy uses lower cumulative drug doses compared with standard maximum-tolerated-dose approaches. To be successful, adaptive therapy requires continuous monitoring of tumor burden using biomarkers or imaging, mathematical modeling to guide treatment decisions, and patient-specific treatment adjustments based on individual tumor dynamics. The first application of successful adaptive therapy was observed in metastatic castrate-resistant prostate cancer.[157] Abiraterone acetate interrupts the synthesis of testosterone and is an effective treatment for metastatic castrate-resistant prostate cancer. Unfortunately, evolution of resistance inevitably leads to progression. In a pilot study, abiraterone was stopped when the prostate-specific antigen (PSA) value was <50% of pretreatment value and resumed when PSA returned to baseline. Results were compared with a contemporaneous cohort who had a >50% PSA decline after initial abiraterone administration and met trial eligibility requirements but chose standard-of-care (SOC) dosing. The adaptive therapy cohort had a significantly improved median time to progression (33.5 months) and median overall survival (OS; 58.5 months; hazard ratio, 0.41; 95% confidence interval [CI], 0.20%–0.83%; $p < .001$) compared with 14.3 and 31.3 months, respectively, in the SOC cohort. Patients who undergoing adaptive therapy did not receive abiraterone during approximately 50% of their time on trial. Adaptive therapy has shown promise in metastatic castrate-resistant prostate cancer trials, and trials are ongoing for melanoma, sarcoma, prostate, and ovarian cancers.[156–158] Although still in early stages of clinical implementation, it shows promise for improving outcomes in metastatic cancers.

Strategy: Remove invading species

Type: Ecologic restoration

Targets: Invasive species lag period—dormancy

As noted above, invasive species, like metastatic deposits, disrupt their new environment, usually to the detriment of the native species or cells. There are multiple ecologic examples of how removal of an invasive species restores ecosystems, allowing the rehabilitation of the native species.[159–161] One key strategy to remove or manage invasive species that is encouraged by the US Department of Agriculture is *early detection and rapid response*. The goal of early detection and rapid response is to identify and control—or, ideally, eradicate—invading species during their lag period or dormancy phase, when they are in low numbers before they can have negative effects on the ecosystem. Multiple approaches may be deployed simultaneously, directed both to the invasive species itself and to the supportive ecosystem, including fencing, deployment of ecologic traps, and hunting. Pest-management principles have become an important underpinning of farming as well as the management of our national parks.[162] Early intervention to eliminate invasive species, such as the kill-on-sight order for the Spotted Lanternfly across the mid-Atlantic in the United States, is often key to success.

Remove invasive species before uncontrolled population growth: Oligometastasis is an intermediate state between a localized primary tumor and systemic metastatic disease.[163–165] Ablation of these small metastatic sites is becoming more widespread in clinical practice and has demonstrated a survival benefit in patients with a variety of solid tumor types.[165] The traditional strategy for treating metastatic cancer has been to use only systemic therapy and not to intervene with local treatment unless to treat pain, e.g., targeted radiation for painful bone metastases. More recently, there has been growing recognition that oligometastatic (OM) disease is a separate clinical disease space that may be amenable to invasive species-eradication strategies. OM disease describes patients who clinically have less than five metastases.[166] Theoretically, eradicating OM disease not only reduces tumor burden but also eliminates the possibility of further seeding of new

metastases from these sites. Recent studies have demonstrated that treatment of OM with stereotactic ablative radiotherapy (RT) in multiple cancer types can lead to substantial increases in patient survival.[167,168] The SABR-COMET phase 2 randomized trial (ClinicalTrials.gov identifier NCT10446744) randomized patients who had a controlled primary malignancy and from one to five metastatic lesions amenable to either stereotactic ablative RT, palliative SOC, or SOC plus stereotactic ablative RT. The 5-year OS rate was 17.7% (95% CI, 6%–34%) versus 42.3% (95% CI, 28%–56%).[167] The SINDAS trial (ClinicalTrials.gov identifier NCT02893332) evaluated first-line tyrosine kinase inhibitor (TKI) therapy for EGFR-mutated, synchronous, OM nonsmall cell lung carcinoma and randomized patients to upfront RT versus no RT. The median OS was 17.4 versus 25.5 months ($p < .001$) for TKI only versus TKI with RT. Multiple other studies are ongoing, reflecting that the treatment of OM disease is undergoing a paradigm shift for cancer treatment.[168]

Eliminate dormant, invading cancer cells: To date, there are no strategies that can identify the presence of dormant cancer cells or therapeutically target them. The surrogate for dormant tumor cells has been to identify DTCs and to target these cells. Improved detection of DTCs, combined with better molecular markers of dormancy, should lead to improved therapeutic strategies for targeting these cellular reservoirs of therapeutic resistance and metastatic recurrence.

In animal models, it has been suggested that dormant DTCs often reside in protective niches within the bone: e.g., the perivascular niche. Theoretically, by disrupting the interactions between tumor cells and endothelial cells in these niches using antibodies to target integrins, dormant cells could be sensitized to chemotherapy.[169] One intriguing therapeutic approach to disrupting dormant cancer cells is the use of hydroxychloroquine, which may disrupt autophagy, an important regulator of metabolism in dormant tumor cells.[170] Hydroxychloroquine is being combined in clinical trials with multiple agents in patients who have breast cancer with no evidence of clinical disease but with bone marrow DTCs present after definitive treatment, including the mTOR inhibitor everolimus (to disrupt dormant cell metabolism) and the CDK4/6 inhibitors abemaciclib and palbociclib (to prevent DTC reactivation).[171,172]

Strategy: Prolong lag period and block exit from dormancy

Type: Ecologic restoration

Targets: Invasive species lag period—dormancy

If a would-be destructive, invading species fails to exit its lag period of low reproduction, it will not have a negative effect on the invaded ecosystem. Likewise, if a dormant cancer cell does not reengage proliferation, it will not go on to form a clinically meaningful metastatic recurrence. It has been proposed that it might be possible to develop therapeutic agents that promote maintenance of dormancy in DTCs, especially in the bone marrow.[173] Tumor microenvironment factors that promote DTC dormancy include osteonectin, thrombospondin-1, and transforming growth factor beta 2. In preclinical studies, reactivation of these molecules by demethylating agents maintained cellular dormancy. Proving that these strategies would be effective in patients is difficult, however, given the difficulty in identifying which patient has DTCs present as well as the inability to measure success in the clinic.[142]

Strategy: Destroy the protumor ecosystem

Type: Ecologic restoration

Targets: All—eliminate cancer cells directly

Comprehensive land-management strategies often include prescribed burns of forest and prairie ecosystems. This approach rapidly and fundamentally alters the invaded and degraded ecosystem, making it inhospitable to or eradicating invading species and facilitating the growth and re-establishment of native species. The parallel strategy in hematologic cancers is total body irradiation or high-dose chemotherapy followed by bone marrow transplantation (BMT), leading to effective cures in patients with leukemia and multiple myeloma.[174] BMT not only eradicates cancerous cells in the ecosystem, but it essentially is also a prescribed burn of the bone marrow habitat, allowing for the reintroduction of *native* hematopoietic stem cells.[175] BMT has been less successful for solid tumors; this is likely at least in part because the bone marrow is not the primary ecosystem of tumors originating in other organs. The success of BMT in repopulating the bone marrow habitat is reflected in the growing use of BMT in nonmalignant diseases, including multiple systemic sclerosis, various anemias, Crohn disease, and systemic lupus erythematosus.[175]

Strategy: Shift the selective pressure of the tumor ecosystem

Type: Ecologic restoration

Targets: Epigenetic plasticity, evolutionary triage, dormancy

Tumor cells have the ability to respond to environmental changes by accessing phenotypic programs that enhance their survival advantage. Altering the selective environment of the tumor ecosystem, therefore, has the potential to decrease selective pressure and/or make the environment so inhospitable that the tumor cells cannot survive. The tumor ecosystem is complex, and there are multiple orthogonal approaches that may be effective in influencing the ecosystem.

Influence the cell types occupying the tumor ecosystem: Perhaps the best example of this is using immunotherapy to shift the tumor ecosystem from a protumorigenic environment to an anticancer ecosystem.[176–181] Immunotherapies have revolutionized cancer treatment, for example, by the reactivation of immune checkpoints, which are often downregulated on cancer cells.[127–129,182] This allows the recruitment of cytotoxic host cells, e.g., T cells, macrophages, and dendritic cells, that create an inhospitable and, in some cases, even lethal environment for the cancer cells.[183–185] Although effective in prolonging life, current immunotherapy strategies still rarely cure metastatic disease. Thousands of studies are being conducted to

develop next-generation immunotherapeutics, including the development of improved T-cell modulators, adoptive cell therapies against multiple microenvironment cell types, chimeric antigen receptor T cells, and T-cell receptor therapies.[186–190]

New cancer-eradication paradigms to alter the tumor ecosystem: Classical cancer therapeutics (e.g., chemotherapy, growth factor inhibitors, radiation) most often target the machinery that a cell uses to proliferate, i.e., seeks to intervene directly to reduce fitness, regardless of the adaptive traits that underlie that fitness level. Virtually all of these therapeutics rely on intact cell cycle checkpoints that are triggered after recognition of DNA damage, resulting in cell death through apoptosis.[191] By evolutionary design, apoptosis enables an organism to eliminate a cell with minimal perturbation of the surrounding tissue and is programmed to proceed without activating adaptive immune cells.[191–193] Therefore, the majority of cancer therapies do not activate the immune system to help eliminate the cancer.[194] There are other mechanisms of regulated cell death that specialize in eliminating cells in various contexts. Although there is substantial knowledge of the molecular mechanisms of regulated immunogenic death pathways, their relationship to cancer and cancer therapy is just beginning to be explored. New cancer therapies are being investigated that independently activate the host immune system to prompt effector cell recruitment through the death of individual cells or damaged tissue. Immune activation after cell death is mainly achieved through a loss of cell membrane integrity and cellular contents released into the extracellular space, including ferroptosis and necrosis.[195–197] Agents that activate ferroptosis cell death as a direct cytotoxic pathway that also results in activation of the immune system are under active development.[198–200]

Modulate the environment of the tumor ecosystem: Altering nutrient flow also can affect the selective pressures of an ecosystem. It is now well recognized that excess fertilizer run-off can feed algae, causing overgrowth and destruction of the native habitat. As a tumor expands, it relies on new blood vessel growth to have access to an abundance of nutrients and oxygen, creating an imbalance with surrounding normal tissue. Inhibitors of vascular endothelial growth factor to disrupt this supply are now part of the cancer therapeutic armamentarium.[201] Another recent approach is to block the activation of hypoxia-inducible factors 1α and 2α, which are activated in response to a lack of oxygen as cancer cells grow away from existing blood vessels. Hypoxia-inducible factor 2α inhibitors have entered clinical use and have demonstrated activity in multiple tumor types.[202] Other strategies are focused on directly restoring nutrient balance.[203] Olecumab, for example, is an antibody that binds to CD73 and decreases the amount of tumor microenvironment adenosine by preventing the conversion of adenosine monophosphate to adenosine,[204] and indoleamine 2,3-dioxygenase inhibitors prevent depletion of the vital immune system nutrient tryptophan.[205]

CONCLUSION

> "Cancer is no more a disease of cells than a traffic jam is a disease of cars. A lifetime of study of the internal-combustion engine would not help anyone understand our traffic problems."
>
> David W. Smithers, cancer biologist and radiotherapist, 1962[206]

Viewed through the lens of classic cancer biology, cancer is a disease of uncontrolled growth caused by an accumulation of mutations to the genome. Viewed through the lens of evolutionary ecology, cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection.[44] Viewed through an ecologic science lens, however, cancer is a disease that is the result of a complex interplay between the growing tumor cells and the local and systemic responses by the patient to the presence of malignancy. What are the implications of this? As Dr Smithers pointed out, understanding mutations is not enough. Traditional cancer therapy has focused on cytotoxic agents to kill the proliferating cancer cells themselves rather than strategies taking a multifaceted approach that understand the evolution of the resistance mechanisms that allow evolutionary rescue as well as ameliorate the effects of byproducts of the cancer cells or the proinflammatory host response to their presence.[13,36–41,87–93,207] Continued insight into the eco-evolutionary events that contribute to the morbidity and mortality of patients with cancer will continue to suggest avenues of treatment that should be explored. Specifically, we believe it is critical, where possible, to identify which mechanisms of resistance are in play in a particular patient at a given time in their treatment course. No amount of antiproliferative chemotherapy, for example, will eradicate a dormant cancer cell or a cell that is modulating its phenotype through epigenetic plasticity. In the research setting, true collaborative research across disparate clinical, biomedical, and basic biology disciplines and beyond—such as molecular and cell biology, evolutionary ecology, phylogenetics, mathematical modeling, medical oncology, pathology, clinical trial design, and others—will be critical to address the mechanistic underpinnings of cancer lethality. In the clinic, as we have seen the advent of *molecular tumor boards* over the last decade to help clinicians decide how to target specific mutations, we expect that we will see the adoption of *evolutionary tumor boards* to guide clinicians as they treat patients.[208,209]

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CONFLICT OF INTEREST STATEMENT

Kenneth J. Pienta is a two-time American Cancer Society clincial research professor award recipient. He reports personal/consulting

fees from Cue Biopharma, Inc. outside the submitted work; has equity in PEEL Therapeutics; and is a founder and equity holder and Kreftect Inc. Sarah R. Amend reports support for professional activities from Springer Science and Business Media LLC outside the submitted work. Patrick L. Goodin disclosed no conflicts of interest.

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