Abstract

Successful therapies to combat microbial diseases and cancers require incorporating ecological and evolutionary principles. Drawing upon the fields of ecology and evolutionary biology, we present a systems-based approach in which host and disease-causing factors are considered as part of a complex network of interactions, analogous to studies of “classical” ecosystems. Centering this approach around empirical examples of disease treatment, we present evidence that successful therapies invariably engage multiple interactions with other components of the host ecosystem. Many of these factors interact nonlinearly to yield synergistic benefits and curative outcomes. We argue that these synergies and nonlinear feedbacks must be leveraged to improve the study of pathogenesis in situ and to develop more effective therapies. An eco-evolutionary systems perspective has surprising and important consequences, and we use it to articulate areas of high research priority for improving treatment strategies.

KEYWORDS
cancer, infectious disease, nonlinear dynamics, resistance, systems approach, therapies
INTRODUCTION

Research efforts to combat cancer, microbial pathogens and viruses tend to operate independently of each other, in part because their underlying genetics and molecular mechanisms are largely distinct. However, when considered together, cancers and infectious agents share key ecological and evolutionary features that may help reveal common principles to improve treatment. Here, we introduce the term—“micros”—to describe this polyphyletic conceptual grouping of microscopic disease agents including viruses, bacteria, protozoans, and cancer. We use the micros concept to discuss how treatment of host illness may be improved through new approaches, in particular an eco-evolutionary systems-based approach (see Glossary) in which host and micro factors are considered as part of a complex, interacting system analogous to classical ecosystems.

A systems-based approach involving micros, human disease, therapeutic strategies, and the host ecosystem is predicated on the following underappreciated observation: essentially all successful therapies engage with multiple factors interacting within a system (Figure 1). Even in traditional “monotherapy,” the target disease agent is ostensibly cleared via synergy with other factors, commonly the host immune system. Synergy may also happen between disease-causing agents themselves, for instance through ecological competition that can suppress resistant or more virulent lineages of bacteria or cancer. This observation also draws attention to the fact that apparently successful therapies may not necessarily contribute directly to a successful recovery, and in these cases a systems-based approach can help reveal the key processes that underlie a therapeutic outcome (Table 1). Together, these examples highlight the utility of eco-evolutionary systems thinking when understanding and combating diseases caused by micros.

We discuss the rationale for a systems approach integrating both ecological and evolutionary processes, and stress the generality of therapeutic synergies and the fundamental ecosystem principles that limit or promote the growth of micros. The resulting framework—which combines conceptual, empirical, and clinical perspectives—helps articulate needed areas of research that will be required to develop a robust systems-based scientific discipline of micro therapy.

THE BODY AS AN ECOSYSTEM

As is well known, complex systems have emergent properties uncharacteristic of their individual components. In this way, a systems approach to medicine is directly analogous to the study of classic ecosystem ecology and evolution: both approaches characterize how a system's individual units interact, including their positive, negative or neutral effects on one another. These effects lead to changes in the individual components as well as the system as a whole. These changes are often the result of nonlinear interactions, meaning that predicting how a system will react cannot be simply extrapolated from data collected at one disease state or condition (Box 1). Complex biological systems also are shaped by evolutionary dynamics, including those from the coevolutionary history of the host and micro, as well as the evolutionary changes occurring within a host during the course of disease. These historical and in situ evolutionary dynamics aid in our understanding of—and can be readily leveraged towards—a systems-based medicine.

The within-host environment as an “ecosystem”

The within-host environment should be viewed as an ecosystem in order to better understand how the introduction of a new
| Clinical approach | Therapeutic strategy from a systems perspective | Considerations for personalized medicine and risks | Example references |
|-------------------|-----------------------------------------------|---------------------------------------------------|--------------------|
| Leveraging defenses | Harness or complement weakened immune systems | Vaccinate vulnerable individuals | Bacteria\(^1,2\) Cancer\(^3,4\) Plasmodium\(^5\) HIV\(^6,7\) |
| Prevention and early treatment | Relative ease at containing or extinguishing (a smaller) micro population | Vaccinate vulnerable individuals | Bacteria\(^8\) Cancer\(^9\) Plasmodium\(^10\) |
| Drug dose and/or treatment schedule | Prevent emergence of resistant mutants | Determine doses and administration schedule based on micro type, and presence of resistant variants | Bacteria\(^13\) Cancer\(^14,15\) Plasmodium\(^16\) HIV\(^17\) |
| Broad spectrum monotherapies | Target multiple genes, multiple micro variants or types (species) | Use when micro is not known with certainty, or when a known micro is likely to have multiple vulnerabilities exploitable by a treatment | Bacteria\(^18,19\) Cancer\(^20\) |
| Combination therapy directly targeting micro | Increase impact on micro | Use drug combinations or viruses (as cocktails) with or without drugs to target a wider spectrum of micros. Use drug combinations and cocktails to reduce the spectrum of micro escape variants (e.g., resistance, biofilms, persisters, spatial refuges) Use when micro target is not known with certainty | Bacteria\(^21–24\) Cancer\(^25–27\) Plasmodium\(^28\) |
| Combinations including components indirectly impacting micro (e.g., adjuvant therapy) | Increase impact on micro | Determine whether harnessing other system components, such as the immune system or modulating vascularization (angiogenesis), contributes to controlling or eliminating an indolent micro | Bacteria\(^29\) Cancer\(^30–36\) Plasmodium\(^37\) HIV\(^38\) |
| Modify or interrupt signaling or communication | Reduce growth or virulence factors, increase death signals | Use although largely untested and unlikely as stand-alone therapy Quench cell-cell signaling, such as quorum sensing molecules in “social” bacteria Use tumor exosomes to increase angiogenesis, apoptosis, and immune function | Bacteria\(^39\) Cancer\(^40,41\) |
| Evolutionary trade-offs | Directly impact micro and select for residual microbes, the latter of which are either less virulent, or more vulnerable to other therapeutic agents Preemptively treat known resistance mechanisms | Use for drug resistant microbes Leverage known trade-off mechanisms Risks: Chronic disease if selection for less virulence; Micros that evade the tradeoff | Bacteria\(^42–44\) Cancer\(^45–47\) Plasmodium\(^48\) |
BOX 1. Immunophage synergy

Bacteriophages are obligate intracellular parasites; that is, they can only replicate inside of bacterial cells. However, the replication and lysis (death) of individual cells by lytic phages need not translate into population-level elimination. Instead, bacteriophages coexist and coevolve with their bacterial hosts in natural systems, raising questions on when and how phage therapy works. In a disease context, microbial pathogens are targeted both by a therapeutic (e.g., phages, antibiotics, and/or a combination of factors) and by components of the human disease ecosystem including immune cells. In systems with phages and bacteria alone, theory, experiments, and environmental field work suggests that phages and bacteria should coexist. To investigate how the immune system would impact coexistence, a model of “immunophage synergy” was developed that examined tripartite interactions between phages, bacteria, and immune effector cells.\(^{49}\) In this model, phages infect and lyse bacteria, immune responses increase in response to bacterial proliferation, and immune cells directly target and eliminate bacteria (at least at low densities). Analysis of this model revealed key outcomes arising from systems thinking. First, phage therapy is not expected to eliminate bacteria in the absence of a sufficient immune response. Second, bacterial infections may not be controllable by an immune system alone if the pathogen density exceeds a critical “tipping point.” However, together phages and the immune response can eliminate a microbial pathogen. In doing so, phage lysis reduces bacterial densities to levels controllable by an activated immune response. This control is possible even if phage-resistant bacterial mutants are present. This model of immunophage synergy was also verified experimentally in a murine model of acute respiratory infections, such that phage therapy was effective in immunocompetent animals but not in those animals that were neutropenic or had immune signaling deficiencies.\(^{50}\) Hence, the system (and not just the therapeutic) is critical to the elimination of pathogens.

Within the host ecosystem, the immune response—analogous in some ways to predation—is of central importance in disease control. For example, host-cell mimics are analogous to prey camouflaging in natural ecosystems; micros invading certain tissues that are inaccessi-ble to the host immune response is analogous to hiding behavior in prey; and bacterial biofilms are analogous to herd protection. One of the immune system’s major roles is preventing a micro from becoming established in the first place.\(^{54}\) For example, in HIV patients immunosuppression increases the risk of infection by oncogenic viruses and the emergence of associated cancers.\(^{55}\) In immuno-competent systems, microbes that do persist are often either host-cell mimics undetectable by the immune system, occupants of spaces not reachable by appropriate immune cells, or capable of outgrowing the innate immune response.\(^{56}\) In other cases, the invading micro may successfully establish if the host immune system is too slow to respond, in particular due to the time-lags required for full activation of the adaptive immune response. However, given sufficient time, the immune response may control or eliminate the micro either on its own\(^{57,58}\) or together with treatments.\(^{49,50,59}\)

Treating the ecosystem, not just the target micro

A systems-based approach to therapeutic interventions must integrate both knowledge of system dynamics as well as current conventional approaches. One common conventional approach is empiric therapy, which typically aims to directly eliminate the micro and alleviate symptoms. This strategy is then often credited to any successful outcome, for example when an antibiotic is given during the early stages of sepsis before the underlying bacteria can be screened for antibiotic sensitivity, or when cancer chemotherapy successfully brings a patient

component (e.g., a therapy) will impact overall system health. Ecol-

ical interactions such as predation, competition and mutualism are of central importance to population dynamics, species coexistence and evolutionary change in terrestrial and aquatic (classic) ecosystems. The ecosystem concept has proved a general way to classify different species in a given habitat by their interrelationships (e.g., predators and prey, hosts and parasites), as well as to define the processes that generate resources such as decomposition and nutrient recycling. Like the body during disease, ecosystems are dynamic entities that are ulti-
mately regulated by the direct and indirect ecological interactions and evolution of the component species.

Individual host organisms have many parallels with classic ecosys-
tems. These similarities include fluctuations in glucose and oxygen that echo ecosystem resource flows; they involve interactions among cells, tissues and organ systems that are reminiscent of population and community interactions; and they include production of metabolic wastes analogous to the byproducts produced by ecosystem members. A healthy host ecosystem can be disrupted by invasion by a micro (e.g., an infecting bacterial pathogen) or emergence of a micro from within the system (e.g., an evolved tumor). These disruptions create a diseased host ecosystem, somewhat akin to the spread of an invasive species in a classical ecosystem\(^{51}\) or the spread of native invading species.\(^{52}\) The disease ecosystem contains many of the same components of the healthy host ecosystem, but it is centered around how the growth, spread and evolution of the micro is influenced by and affects interac-
tions with the host. Considering disease as a system and more specifically an ecosystem, lends itself to a more general and integrated view on treatment. However, there are also some differences between nat-
ural ecosystems and the host ecosystem.\(^{51}\) For instance, organisms have evolved homeostasis mechanisms as a means of habitat mainte-
nance, unlike classical ecosystems (but see\(^{52}\)).
FIGURE 2  Major routes of micro escape and systems-based therapeutic approaches to address each. (A) Evolution of resistance: Through population-level genetic changes, the evolution of resistance provides a means of therapeutic escape in all microbes. Therapeutic approaches involve leveraging in situ evolution and the ongoing development of new therapies. (B) Phenotypic Shielding: Through changes due to phenotypic plasticity, nature of the micro, or the habitat, therapeutic approaches involve development of drugs that can permeate the micro’s phenotypic barriers. (C) Dormancy: Through transient changes to the micro’s phenotype, the micro is temporarily resistant to treatment. Therapeutic approaches include a variety of methods to keep the dormant population size low or inactive.

Empiric therapy may also fail, either because the micro and its associated disease are untreatable (e.g., multi-resistant bacterial pathogens, inoperable cancers, and weakened patient conditions), or because the therapy did not sufficiently consider elements and processes in the disease ecosystem. Systems-based thinking aids in understanding these outcomes, and it forms the basis of treating multiple parts of the host ecosystem and not just the micro itself. For example, a systems perspective is a way to mitigate the risk of therapeutic failure when resistance (Figure 2) is a real concern and complete elimination of the micro is unlikely. Systems thinking could also facilitate the development of drug dosing regimens that leverage host immunity to clear the infection. The immune system is oft-neglected and little understood in explaining actual therapeutic outcomes, but it plays a central role in the disease ecosystem of a host undergoing medical treatment. For targeted therapies to be effective, they must not only expose the micro to sufficient treatment concentrations for long enough periods, but also act in concert with the body’s immunocompetence. In the total absence of immune responses in vitro, single agents are most likely to eliminate bacteria when the latter are at low numbers and/or low diversity.
Theoretical models suggest that immune systems can be central in reducing the emergence of drug resistance during, for example, antibiotic treatment.\textsuperscript{64} With the possible exception of mitigated successes of combination therapies on immunosuppressed patients (Table 1), we are unaware of in vivo assessments of whether introduced therapies alone explain therapeutic success.

Therapies and immune systems may have complementary effects on the micro, the former eliminating the most exposed and least resistant microbes, and the latter clearing remaining segments of the micro population.\textsuperscript{50,51,65} Moreover, their effects may be synergistic, as for example "immune storms" induced by certain oncolytic viruses.\textsuperscript{66} Evidence also suggests that drugs and immune responses may interact in complex ways, potentially either augmenting or weakening their independent actions. For example, prior work\textsuperscript{67} showed how antibiotics and pathogenic bacteria may metabolically alter the disease ecosystem, resulting in lowered antibiotic activity and either the enhancement or impairment of immune responses. Although immune responses can contribute to successful therapeutic outcomes, they can also result in failure or unintended side effects, such as immunooediting, autoimmunity, and cytokine release syndromes associated with certain immunotherapies.\textsuperscript{68–70}

Despite the immune system's central importance in the disease ecosystem, other underappreciated host features can influence therapeutic impacts. These include tissue heterogeneities that result in spatial refuges for microbes,\textsuperscript{71–73} differences in organ system habitats,\textsuperscript{74} the commensal microbiome,\textsuperscript{75} and resource replenishment.\textsuperscript{51} For example, the disorganized and often leaky vasculature within the tumor microenvironment not only compromises drug delivery to many areas of the tumor but also results in stress, such as hypoxia, acidity, and limited nutrient supply, all of which mediate metabolic changes that influence drug sensitivity.\textsuperscript{76} Moreover, when treated with chemotherapeutics, the tumor microenvironment itself can engage in tissue repair responses that indirectly promote tumor growth and invasion.\textsuperscript{77}

Not only do these host features have the capacity to influence the effectiveness of traditional micro-targeted therapies, they also present opportunities to modify the host ecosystem in beneficial ways (Figure 1). Indeed, there is already precedent for treating micro disease by modulating other features of the host ecosystem. For example, bacteriotherapy (i.e., fecal transplantation) is a recommended treatment for recurrent Clostridium difficile infections.\textsuperscript{78,79} There is also evidence that iron-chelators used in combination with antibiotics could be an effective treatment for biofilms, although further development of this approach is required before it will be regularly used in the clinic.\textsuperscript{80–82}

Integrating nonlinearity and networks is essential to a systems approach

Ecosystems are often thought of as having characteristic features that persist well beyond the typical lifetime of constituent organisms. Yet counterintuitively, ecosystems can suddenly shift from one seemingly stable state to another, for example when nutrient influx stabilizes the system as a whole.

Ecosystems are often composed of networks of interacting organisms, and these networks have important implications on the stability of ecosystems and their nonlinear dynamics. A network is a simplification of the heterogeneous (and often sparse) interactions between system components. For example, predators consume a subset of potential prey, parasites infect a subset of potential hosts, and cell types interact with a subset of each other. Defining the structure of networked interactions—whether for predator-prey, host-parasite, or cell-cell systems—is a critical first step to understanding how networks shape dynamics, often in surprising ways. For example, despite early claims that large complex systems are inherently unstable,\textsuperscript{84} we now understand that in many instances networked interactions can actually stabilize the system as a whole.\textsuperscript{85–87} Hence, large complex systems may be "resilient" to small perturbations, such that the characteristic features of a system (e.g., nutrient uptake rate and population diversity) are not fundamentally altered by small changes in environmental drivers or endogenous fluctuations.

The resilience to small perturbations can also underlie a different phenomenon in which complex, networked ecosystems exhibit threshold effects or tipping points given suitably large perturbations.\textsuperscript{88} A tipping point represents the critical system state that, when perturbed, undergoes a cascade of events that shifts the system to another stable state. In addition to understanding the tipping points themselves, it is also important to understand the processes that tip a system from one state to another. For example, a shift that moves a disease ecosystem to a healthy ecosystem may be caused by a drug's specific mechanism, its dosing, and/or its scheduling. In terms of disease onset, tipping points are often revealed by a minimal infectious dose (the lowest number of micro units required to establish disease). For example, \(~10^5\) cells of Staphylococcus aureus are estimated to robustly establish infection.\textsuperscript{89} Below this point, the infection tends to fail, while above this point, the infection is expected to proliferate. Similarly, cancer emergence may also depend on immune system dynamics during tumor growth.\textsuperscript{90} For example, in multiple myeloma, patients that never progress from the preneoplastic gammopathy phase possess a significant number of rapid effector T cells that react to antigens of the preneoplastic cells. This T cell response is not found in patients that have progressed to malignant multiple myeloma, suggesting that the immune system can successfully prevent the progression of some early cancers.\textsuperscript{91} The quantitative
aspects of this apparent tipping point in multiple myeloma are not yet well understood and will likely vary between cancer types and patients. The development of novel therapeutics that are not focused on cell death, but instead on shifting the disease ecosystem to promote equilibrium or elimination of cancerous cells could prove extremely useful in systems-based oncology. Furthermore, manipulating these tipping points could increase the effectiveness of currently available drugs due to the altered disease state.

**Host-micro interactions have been molded by species evolution**

Multicellular host organisms are constantly subject to challenges from micros. These challenges come from diverse sources, including transmissible infections, pathogens emerging from within the microbiome, and host cells carrying mutations leading to malignancy.Unchecked, these threats can result in damage or destruction at different levels, ranging from subcellular modification, to cellular lysis, tissue damage, organ failure and death. The pervasiveness and diversity of such dangers throughout the course of evolution have constituted important selection pressures for a range of diverse defense systems—most notably the immune system—to limit micro establishment and growth.[92,93]

As mentioned in the previous section, hosts have a considerable repertoire of evolved systems that contribute to preventing, controlling and eliminating micros. The immune system is central, deploying a range of tactics, including a rapid, general response (innate immunity and inflammation), delayed responses to uncontrolled and evolving threats (adaptive immunity), intra-cellular (humoral) and extra-cellular (antibody) responses, and diverse immune cell types associated with each of these responses. But a wide array of systems either redundant or complementary to the immune system also contribute to micro control. Some of these constitute barriers to micro invasion and emergence. Examples include the host cell membrane, cell behaviors such as apoptosis and senescence, and larger-scale protection through tissue architecture.[94,95] Some provide general protection against many micro types, such as enhanced stem cell protection in tissues exposed to the outer environment. Others are more specific, including tumor suppressor genes that initiate cellular apoptosis in reaction to danger signals, and in particular those indicating the threat of malignant transformation.[96] Finally, rather than only resist micros, hosts may also have co-evolved with their microbiota to tolerate them.[75] For example, commensal microbiota can contribute to remediating certain pathologies due to micros, including tissue repair, toxin neutralization, inflammation and metabolic homeostasis.[75]

Natural selection shapes host-micro interactions, providing an evolutionary basis for systems thinking and new therapeutic strategies. These strategies may replace limited or defective defenses, or add new, complementary defenses. The complementary and adaptive nature of the immune response is the basis for why combination therapies, immunotherapy and viral therapies, which might not succeed on their own, are so promising (Table 1). It also makes the immune response a model for how existing defenses could be augmented or supplemented. In particular, the use of self-amplifying viruses as therapeutics offers the potential to seed the host ecosystem with a small founding population that then grows as it targets the pathogenic micro.[97,98] For bacterial infections, these include lytic bacteriophages (Boxes 1 and 2) that target specific bacterial strains. Similarly, oncolytic viruses target specific tumor-associated cells. Using natural micro-defense systems leverages deep host-micro evolutionary histories to create new synergies in therapeutic design.

**Evolution also occurs within the host**

While evolutionary responses are often thought of as long-term changes within populations, micros can evolve rapidly during the course of disease in an individual patient. These evolutionary changes influence disease ecosystem dynamics and therapeutic outcomes, including ways that within-host evolution can both hinder and help micros during infection. During within-host evolution, micro population dynamics and therapeutic outcomes are determined by the within-host population size, growth rate, and diversity of the micro. A very large micro population can have considerable adaptive potential, including the emergence of resistance mutations (Figure 2). This adaptive potential suggests that monotherapies themselves are unlikely to fully explain therapeutic success in sufficiently advanced disease, as monotherapies can act in synergy with other factors, such as the immune system. However, it is important to note that proliferation of resistance within an individual host is not inevitable and is probabilistic based on the micro’s mutation rate, population size, and the dose and time period of treatment. Controlling or eliminating resistant variants will either mean strategically employing combinations, such as multi-drug combinations[100] or phage-antibiotic combinations for bacterial infections (Box 1),[21] or engaging mono- or combination therapies that act in conjunction with host-based processes, such as the immune response.[101] Moreover, within-host evolution also occurs within components of the host ecosystem. For example, B cell populations of the host immune system are both amplifying as well as adaptive, changing genetically in a within-host evolutionary process that improves immune recognition of micro antigens.[102]

Two particularly promising therapeutic strategies that capitalize on within-host evolution are to contain or eliminate micros using evolutionary trade-offs and/or competitive effects (Table 1).[42,103–105] For instance, “phage steering” leverages trade-offs through within-host evolution to restore antibiotic sensitive genotypes (Box 2). Leveraging competitive effects has also shown promising results both in vitro[14,106] and in vivo.[15] For example, drug-dosing protocols designed to maximize competition between sensitive and resistant strains can (under certain circumstances) more effectively manage in vitro populations of *Escherichia coli* than attempting to eliminate them.[14,106] It is also possible to simultaneously leverage both evolutionary trade-offs and competition to contain (and possibly eliminate) resistance by changing resource levels available to resistant variants.
BOX 2. Phage Steering

Phage therapy typically utilizes strictly-lytic (bactericidal) phages to kill target pathogenic bacteria within a host organism, and this approach predates the discovery and subsequent therapeutic use of chemical antibiotics.[97] However, a long-recognized limitation is that phages impose strong selection for evolution of resistance in the bacteria, a seemingly inevitable outcome that permits treatment failure. One modern approach to phage therapy is to both acknowledge and capitalize on this certainty, leveraging the evolution of phage resistance as a strength rather than a weakness. In particular, if the proximate binding of a lytic phage is known to associate with a mechanism for antibiotic resistance in the target bacteria, this should exert strong selection for the bacteria to mutate or down-regulate the phage-binding target(s), likely compromising their ability to maintain resistance to chemical antibiotics. This phenotypic concession of gaining greater phage resistance at the expense of drug re-sensitivity would exemplify an evolutionary trade-off in the bacterial pathogen. Thus, this “steering” approach to phage therapy should be doubly effective; success is achieved when phages lyse the target bacteria, but also when evolution of phage resistance causes the bacteria to suffer greater antibiotic sensitivity. Mechanistically, this prediction was demonstrated via interactions between lytic phages and bacterial efflux pumps: protein complexes whose functions include active removal of chemical antibiotics that enter the cell, thus contributing to the widespread ability for some bacterial pathogens to resist antibiotics of various drug classes. In particular, the use of a lytic phage to bind the outermost protein of the TolC efflux-pumps in E. coli selects for evolution of phage resistance that can coincide with antibiotic re-sensitivity.[42,43] Based on this logic of predictable phage/antibiotic synergy observed in vitro,[42] a lytic phage plus ceftazidime antibiotic was successfully administered to treat a chronic P. aeruginosa-biofilm infected aortic-arch graft.[99] Although highly encouraging, it is important to note that some mutations for phage resistance would not necessarily cause this useful trade-off; rather, the possibility exists for bacteria to evolve phage escape while remaining unchanged in their antibiotic resistance, or to even increase growth in presence of the drug (i.e., an evolutionary “trade-up.”[43]) Further research will show whether useful trade-off-generating mutations occur reliably within the “black box” of the human disease ecosystem. If so, phage/antibiotic synergies would constitute a reliable approach to phage therapy. This approach would re-invigorate our waning antibacterial arsenal and address the widespread failure of standalone chemical antibiotics.

Translating systems thinking into new therapies

Conventional therapeutic interventions aim to remedy disease by direct elimination of targeted microbes. A systems approach expands conventional therapies by emphasizing that there are (i) many ways to effect change (e.g., interventions may directly or indirectly target the micro) and (ii) many types of desirable change (e.g., interventions do not need to eliminate the micro to be successful) (Table 1). For example, rather than trying to avoid resistance (Figure 2), a novel approach leverages trade-offs to steer bacterial evolution towards re-sensitization of antibiotics (Box 2). Below, we present three general approaches that will help integrate eco-evolutionary systems thinking into existing paradigms, ultimately leading to new therapies.

Understanding how therapeutic strategies relate to “natural” processes

Cellular maintenance, tissue architecture, and the immune system have been subjected to selection by microbes throughout the course of metazoan evolution. The immune system employs a multi-pronged approach that kills or immobilizes microbes, continually adapts to novel microbial variants and cordons-off and remediates the diseased area. Conventional micro-targeted monotherapies are analogous to single components of the innate immune response that kill or immobilize a micro. Drug combinations are then analogous to the immune system’s diverse collection of cell types.[107] Some therapies are even more similar to the adaptive immune system in that they self-amplify (e.g., lytic bacteriophages and oncolytic viruses), analogous to how B- and T-cell specific to micro variants replicate during infection.

Redesigning in-vitro platforms to screen for synergy

Anti-micro drugs are generally evaluated in terms of their ability to eliminate microbes in vitro and then in animal models before being applied in a clinical context. Elimination is often predicated on the ability of the therapeutic to kill a micro or halt micro growth in the in vitro environment. However, if therapeutic efficacy is driven by synergistic interactions with other factors, including but not limited to the host immune system, then efforts to develop a translation pipeline will need to revisit those synergies during initial screening for new therapeutics. Moving from in vitro to in vivo work within the next decade will require addressing the “lack of reality” usually inherent to lab studies. Improved assessments would need to involve the factors not typically replicated in the lab: large population sizes, environmental complexity, immune-cell populations, diversity of the microbiome, and horizontal gene transfer.
From a system perspective, we advocate for considering therapeutics through the lens of synergistic properties, that is, the extent to which they stimulate the ecosystem to respond to a micro, thereby enabling disease remediation. Ecosystem effects may include activating immune cells, leveraging resident members of the commensal microbiome to outcompete the micro, or other combinations of effects that elicit a host response. For instance, if a therapeutic agent works by tipping the system to clear a bacterial pathogen, virus, or cancer, then pre-clinical development should emphasize synergistic interactions, combination use, or other properties rather than strictly through direct killing assays. Such an approach requires development of disease model systems that replicate interactions with host features. An example, a study in small-cell lung cancer showed that while the use of the a p53 vaccine for ovarian cancer provided little benefit as a monotherapy, subsequent use of chemotherapy resulted in a significantly increased rate of clinical response. If this connection had not been found, the p53 vaccine likely would have been discontinued due to lack of efficacy. In-vitro screening and in-vivo trials that explicitly test for these kinds of synergies will greatly increase the number of drugs in the cancer therapy arsenal. Screening for synergy might also yield “ecophillic” therapeutics, that is, those that are selected for their interactions with components of the host ecosystem.

Considering management over elimination

A systems approach emphasizes that micro elimination is not the only acceptable therapeutic outcome. Focusing on elimination artificially limits therapeutic options, may hasten treatment failure by promoting resistance and increasing toxic side effects for the patient. The motivating principle behind micro management is that there are situations where treatment should be used to manipulate the size of the micro population in beneficial ways as opposed to attempting to eliminate the micro population entirely. In practice, micro management can take many different forms (e.g., adaptive and bipolar androgen therapies for prostate cancer). One of its key benefits is reducing toxic and other side effects of some therapies on the host. Management may also better address the risk of resistance than elimination (e.g., competition between drug-sensitive and drug-resistant microbes and drug-addiction of resistant microbes). Successfully employing management will require identifying situations where it will be beneficial and then personalizing the treatment approach to capitalize on feedback mechanisms.

CONCLUSIONS AND OUTLOOK

The scientific disciplines of ecology and evolutionary biology have much to contribute to our understanding of disease development and treatment. There is considerable potential in developing an eco-evolutionary systems-based framework by evaluating analogies with better understood terrestrial and aquatic ecosystems. Identifying the system components and quantifying their interactions in both healthy host ecosystems and disease ecosystems can contribute to designing improved therapies, given the realistic constraints likely to occur in actual treatment situations. To do this will require combining the knowledge and technical expertise of theoreticians who work at the most abstract level, basic empirical researchers who work in vitro and in vivo, and clinical researchers and clinicians who can translate this knowledge in situ to patients.

We believe that an eco-evolutionary systems-based approach will lead to new options and better patient outcomes in the form of personalized medicine. This approach will integrate tested systems models with patient data to produce treatment options that account for risks such as the evolution of resistant variants. Systems approaches to personalized medicine will be well suited to confront specificities and idiosyncrasies of the disease (e.g., bacterial strain and tissue or organ affected) and the patient (e.g., condition, age, genetics), given the knowledge of the ecological interactions between a treatment and the systems-level feedbacks of the host. Similar to pest management systems, given the complexity of even the simplest treatment scenarios, a future personalized medicine will require focusing on a small number of salient interactions, while being attentive to other factors that could intervene as well. Nevertheless, we cannot ignore the fact that the use of traditional empiric therapy and targeted monotherapy often works. Insights from empiric therapy should be integrated into the systems approach for risk assessment and therapeutic objectives.

Glossary

**Combination therapy**: Any therapeutic approach that involves more than one introduced agent or pre-existing component of the disease ecosystem.

**Disease ecosystem**: The host ecosystem when disrupted by a micro and characterized by interactions involving micro growth, evolution and spread, and host ecosystem responses to limit the micro and remediate associated damage.

**Empiric therapy**: Also referred to as “heuristics,” involves the use of experience to select a treatment for presented symptoms, especially when data are not readily available.

**Host ecosystem**: A conceptual model that views the host as harboring processes and ecological interactions analogous to those found in classical ecosystems.

**Nonlinear dynamics/interactions**: A change in one part of a system that results in a disproportionate change in another part.

**Synergy**: When two or more processes — be they part of the host ecosystem (e.g., immune response), therapies, or both — contribute to improved outcomes compared to fewer acting processes.

**Systems-based approach**: The view that a system’s behavior cannot be represented as the sum of identifiable, discrete parts; instead identifying direct and indirect interactions between components are required to explain emergent phenomena.

**Targeted therapy**: A therapy aimed at a single element in the disease ecosystem, usually the micro itself.
BOX 3. Towards an in situ science

A future science of micro therapy will identify and measure disease ecosystem dynamics, and then relate these to the efficacy of various therapies. Achieving this and moving beyond single-action target-drug paradigms will require that we address several conceptual and logistic challenges. First, the complexity of disease ecosystems needs to be categorized in an actionable way. Factors that determine these categories must not only include micro and host properties (micro type, host age and condition), but also the current state of progression of the disease.[115] For example, a recent proposal for an “eco-evo” classification of cancers[116] partitioned ecological (“eco”) parameters into hazards (e.g., immune system, toxins, waste), and resource levels (e.g., oxygen, glucose). Parameterizing the host ecosystem in such a way may foster prediction of how system components and processes will interact. Despite the promise of this and simpler (e.g.,[51]) frameworks, significant challenges remain in measuring parameters directly or via indicators, and evaluating their significance in improving treatment strategies. Second, improved therapies will require consideration of the possible roles played by the innate and adaptive components of the immune system. Such considerations will need to include accurate assessments of immunocompetence relative to the disease in question, as well as options for increasing competence.[117] For example, immunity-boosting immunotherapies combined with conventional chemotherapy are most effective early in tumor progression, as for patients with BRAF-mutant metastatic melanoma.[118]

Likewise, targeted immunotherapy is also an opportunity to treat bacterial sepsis in combination with antibiotics.[119] Third, we need a deeper understanding of the synergies among drugs and existing components of the host ecosystem. This will notably help address the major and growing problem of multi-drug resistance in infectious diseases[120] and cancer. Conventional high-dose, monotherapeutic drug-based strategies are unlikely to succeed as standalone options to treat multidrug resistant bacteria, and indeed, such strategies may even select for their more rapid emergence. Rather, drug combinations and/or combinations of other ecosystem components such as the immune system, microbiome, nutrients and introduced control agents such as viruses will need to be seriously considered (Table 1, Figure 1).

Tumor microenvironment: The disease ecosystem associated with cancer that focuses on the activity of healthy and diseased cells, tissues and vasculature in the proximity of a tumor.

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CONFLICT OF INTEREST

P.E.T. is a co-founder of Felix Biotechnology Inc., and declares a financial interest in this company that seeks to commercially develop phages for use as therapeutics. A.R.B. and P.E.T. disclose two provisional patent applications involving phage therapy. JSW discloses a provisional patent application related to bacteriophage therapy.

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