An ecosystem framework for understanding and treating disease
Michael Hochberg

To cite this version:
Michael Hochberg. An ecosystem framework for understanding and treating disease. Evolution, Medicine, and Public Health, Oxford: Oxford University Press, 2018, 10.1093/emph/eoy032. hal-02006381

HAL Id: hal-02006381
https://hal.umontpellier.fr/hal-02006381
Submitted on 9 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License
An ecosystem framework for understanding and treating disease

Michael E. Hochberg

1Institut des Sciences de l’Évolution, Université de Montpellier, 34095 Montpellier, France; 2Santa Fe Institute, Santa Fe, NM 87501, USA; and 3Institute for Advanced Study in Toulouse, 31015 Toulouse, France

*Corresponding author. Institut des Sciences de l’Évolution, Université de Montpellier, 34095 Montpellier, France.
E-mail: michael.hochberg@umontpellier.fr

Received 25 September 2018; revised version accepted 2 October 2018

ABSTRACT
Pathogens and cancers are pervasive health risks in the human population. I argue that if we are to better understand disease and its treatment, then we need to take an ecological perspective of disease itself. I generalize and extend an emerging framework that views disease as an ecosystem and many of its components as interacting in a community. I develop the framework for biological etiological agents (BEAs) that multiply within humans—focusing on bacterial pathogens and cancers—but the framework could be extended to include other host and parasite species. I begin by describing why we need an ecosystem framework to understand disease, and the main components and interactions in bacterial and cancer disease ecosystems. Focus is then given to the BEA and how it may proceed through characteristic states, including emergence, growth, spread and regression. The framework is then applied to therapeutic interventions. Central to success is preventing BEA evasion, the best known being antibiotic resistance and chemotherapeutic resistance in cancers. With risks of evasion in mind, I propose six measures that either introduce new components into the disease ecosystem or manipulate existing ones. An ecosystem framework promises to enhance our understanding of disease, BEA and host (co)evolution, and how we can improve therapeutic outcomes.

KEYWORDS: antibiotics; cancer; immune system; resistance; microbiota; pathogens

INTRODUCTION
Despite the pervasiveness of parasites and cancers across animal species and in humans in particular, our knowledge of the ecology and evolution of disease itself is surprisingly limited. When disease is studied in detail, it is often through descriptions of signs and symptoms, or the characterization of the biological etiological agent (BEA) and of diseased tissue ultrastructure. Other study—focusing on population-level interactions—usually abstracts disease into a single variable such as aggressiveness or pathogenicity. Although both approaches produce insights into BEA–host interactions, they oversimplify disease by omitting what may be its single most important driving force—ecology.
I advocate the perspective that when examined through an ecological lens, disease has a characteristic structure. Investigating this structure and variations on it is important not only for understanding ecology and evolution in a fundamental type of habitat—the organism—but also to develop approaches that lessen the burden of BEAs in animal husbandry, wildlife, on endangered and domesticated species, and in human populations—the latter being the focus of this review. The usual approach is to treat BEAs with drugs, but these can fail due to selection for resistance. The two most familiar types in humans are antibiotic resistance and chemotherapeutic resistance in cancers.

Early in the 20th century, Paul Ehrlich encouraged the search for the ‘Magic Bullet’—a single drug that targets and cures a disease with minimal residual toxicity for the patient. Ehrlich [1] also argued for the accepted approach of the day frapper fort et frapper vite (hit hard and without delay), based on the construct that drug dose must be commensurate with the severity of the disease and delaying drug delivery allows BEAs to multiply and cause irreparable damage and possibly death. Ehrlich and his contemporaries knew that some parasites could resist chemotherapy but were unaware of the underlying mechanisms. Despite clear arguments for why attempting to eradicate BEAs risks selecting for resistance [2, 3], frapper vite et frapper fort is still widely regarded as the surest way to cure disease.

The above two challenges—understanding disease and improving therapeutic outcomes—are interrelated because achieving the former will help address the latter, and because both natural, evolved processes that remEDIATE disease and therapeutc interventions have ecology at their foundation. Here, I develop a framework for addressing these challenges. Focus is on humans because of the rich knowledge of some of their diseases and the growing importance of finding solutions to drug resistance and the improvement of therapeutic outcomes. In particular, I describe how disease can be understood as an ecosystem, the components and processes of which can be either manipulated separately or in combination toward a therapeutic objective. The disease ecosystem employs analogies from terrestrial, aquatic and agricultural ecosystems (hereafter ‘classic’ ecosystems), including predators, prey, competitors, detrivores, resources and the environmental surroundings. Thus, like classic ecosystems, disease ecosystems are intrinsically ecological: they are influenced by the environment and composed of feeding relationships (food webs) among ‘species’ in an interactive community.

I begin by justifying the need for an ecosystem framework of disease. I argue that in both healthy and diseased tissues there is a largely undiscovered world of ecosystem-like processes including resource fluxes, inter- and intraspecific competition, predation by immune systems and waste removal. I develop this concept as the central feature of the framework and then focus on how the state of the BEA population and associated disease provide reliable information about disease progression or remediation. Before applying the framework to therapies, I discuss what failures due to resistance typically resemble and present several other routes to therapeutic evasion that have received little attention. Key to applying the framework is how decisions are made about whether a treatment should attempt to eradicate or contain the BEA, or rather simply limit disease, and how strategies and tactics can be either used singly or in combination. Finally, I present some limitations to the framework and concluding thoughts.

The framework is centered on BEAs that replicate in the disease ecosystem such as microparasites and cancers, and not asymptomatic infections or diseases stemming from non-BEAs. The current framework should therefore be viewed as part of a larger picture. I also do not address the important question of how to measure ecological and evolutionary features of disease (see reviews in e.g. [4, 5]). Finally, I do not attempt a systematic overview of the huge diversity of human BEAs. Rather, I refer where appropriate to specific examples in several well-studied BEA groups, principally bacteria and cancers. Comparing and contrasting the basic features of these groups is the first step towards an understanding of disease ecosystems and how they can be used to devise successful therapies.

THE NEED FOR A GENERAL FRAMEWORK

Disease is a complex system of multiple species interacting at multiple biological and spatial scales. Whether and how a disease progresses, what are the implications for the BEA and the host, and how to design therapies can only be answered if we characterize the underlying components, their functions and interrelationships.

The limited accessibility and microscopic nature of disease makes it particularly challenging to study and to measure. As a consequence, in vivo work typically takes physiological and epidemiological approaches, describing signs and symptoms, changes in tissue ultrastructure, and consequences for morbidity and mortality. In contrast, in vitro study usually focuses on the BEA itself and abstracts-out the complexity characteristic of in vivo environments. This is problematic, for example, because in vitro observations can be misleading about in vivo behaviors [6]. The combined situation—the general ignorance of ecological and evolutionary mechanism in vivo, the oversimplification of real environments in vitro—limits our knowledge of how disease-generating processes actually work.

Beyond the importance of how both ecology and evolution influence disease, a general framework needs to have the flexibility to accommodate the effects of therapeutic interventions. Therapy can be viewed as an ecological perturbation intended to reset a disrupted system to its healthy state. As indicated above, the prevailing approach is frapper fort et frapper vite to eliminate BEAs and minimize the chances that (contagious) BEAs are transmitted to other hosts. However, a large body of work indicates that targeted antimicrobial and anticancer chemotherapies select for resistance [3, 7], and there is increasing awareness that drug therapies can
have enduring disruptive effects on the microbiome [8] (but see [9]) and the host itself (e.g. contributing to other diseases, such as secondary cancers).

Despite the large body of evidence that treat-to-cure chemotherapy can lead to resistance and treatment failure, this approach has stood the test of time, largely due to its simplicity and common sense, but also because it often works [10]. Aggressive chemotherapy also continues largely unchallenged because scientific study is still in early days of evaluating alternatives, most of which are centered on preventing or limiting the evolution of resistance. Until relatively recently much of what was known about resistance and its management derived from pesticide use (Box 1). Although the lessons learned are foundational, they often abstract-out ecology, and are sometimes difficult to apply to disease due to differences in biology and ecology, habitat structure and habitat resilience to treatment.

We therefore need a general framework that is firmly rooted in ecology and evolution both as a basis for fundamental understanding and to guide therapies [11]. There are a number of developments and frameworks that integrate ecology and evolution (parasites and pathogens: [12–15]; cancers: [5, 16–20]), but none extend to both infectious and non-infectious BEAs. My aims are to generalize the disease ecosystem concept and to use its insights to suggest several novel therapeutic interventions.

**AN ECOSYSTEM FRAMEWORK OF DISEASE**

The framework for understanding and treating disease (Figs 1 and 2) focuses on how the components and processes in the disease ecosystem interact directly and indirectly with the BEA. The system can be in one of four main states that reflect BEA emergence, population growth, spread and pathogenicity, and regression. Understanding the state of the BEA and associated disease will be the basis for applying the framework to therapeutic interventions, as described below.

**The organism ecosystem**

The ecosystem concept is a general way of representing species interaction networks, non-living organic and inorganic matter pools, and the physical habitat. Key to the concept is the fluxes, balances and stocks in these different compartments, and how events (e.g. environmental disturbance, species invasions) can have consequences for individual compartments or the ecosystem as a whole.

Similar to classic ecosystems, the healthy organism ecosystem is composed of supportive and regulatory structures (Fig. 1A and B). Supportive structures include habitats (tissues), resource replenishment (circulatory system) and waste removal (phagocytosis, circulatory system). Regulatory structures include cooperative interactions (cell–cell signaling, hormonal control), predation (immune systems), and commensalism, competition and parasitism (microbiota). These structures will vary between tissue types [14], suggesting that ecosystem dynamics may contrast as well.

Although it is tempting to perfectly equate different components in organism ecosystems with analogs in classic ecosystems, they do have at least one important difference: whereas Darwinian selection acts on many component species in the latter, it is centered on a single species in the former (but see [21]). Thus, we would expect the core of the organism ecosystem (i.e. host cells) to evolve traits that promote habitat maintenance and remediation, meaning more coordination and less autonomy than species interactions in classic ecosystems. We would nevertheless also expect that similar processes are at work between the two system types, including selection acting on traits ultimately affecting the ecosystem, and co-evolution with mutualists,
commensals and parasites. More research is needed to explore these observations and expectations.

The disease ecosystem

The disease ecosystem results when a healthy ecosystem is disrupted by a BEA and the host organism attempts remediation. This is in some ways analogous to environmental disturbances in classic ecosystems and more specifically to those stemming from invasive species (Box 2). Below I describe some of the main features of the disease ecosystem (Fig. 1C), and briefly review the most understood type—the ‘tumor microenvironment’—in Box 3.

When the BEA enters or emerges from within a healthy host ecosystem it is likely to be confronted by one or more of physical structures [22, 23], oxidative stress, chemical defenses [24] and innate immune responses [25]. Immune systems in particular are central to somatic maintenance, including the host’s ability to either limit the growth and spread of (or eradicate) a BEA [26], and to repair tissue damage [27]. However, some BEAs may evade the immune response, grow, spread and generate disease. BEA and host genotypes, the environment and tissue type are among the many factors influencing these processes and the associated severity and extent of disease [25, 28–31].

Many disease ecosystem interactions involve vying for resources. As the BEA grows it competes for space and/or nutrients and this may result in stressful local conditions (e.g. hypoxia, [32, 33]), and in certain cancers, favor disease progression [34]. Competition for space or nutrients can occur with the same or other BEA types [35–37], host cells [38] or commensal microbiota.
For example, Balmer and Tanner [37] argued that multi-strain infections could have far reaching consequences for the ecological and evolutionary dynamics of disease, including mutualistic interactions and direct and indirect competitive interactions (e.g. apparent competition). Nutrient levels have also been shown to influence BEAs indirectly via the immune system [40]. Despite the multitude of potential indirect interactions suggested by Fig. 1C—particularly with the microbiota—little study to date has investigated these in detail (e.g. [41]).

Although many of the events in disease ecosystems have analogs in classic ecosystems, the detailed functions often contrast. Thus, for example, whereas immune systems and predators ultimately kill their ‘prey’, unlike predators, immune cells do not appear to gain significant energy in the process. Rather, the latter derive energy from nutrients in situ, including in the disease ecosystem (for the tumor microenvironment, see [42]). Moreover, unlike predators, different immune cells cooperate in killing diseased/damaged cells and pathogens. (A notable exception to this in classic communities is cooperative hunting.) Thus, lymphocytes function as precursors for phagocyte activity, either marking or killing target cells, whereas phagocytes engulf and remove target cells and waste. Despite detailed knowledge about immune systems, we know very little about their functional and numerical responses (but see [43]) and how these may contrast with classic species communities.

Figure 2. Four states in BEA and associated disease. This classification is based on growth in a novel and hostile environment (State 1), BEA population size (cumulative number of births) and therefore evolutionary potential (State 2), and spread and colonization of local and distant within-host habitats with correspondingly greater impact of disease on the host (State 3). Therapeutic objectives (eradication, containment, satisficing) change with progression through the three first states (it is assumed that natural remission (State 4) will not be subject to therapeutic intervention). In particular, although optimal protocols are feasible in States 1 and 2, treatment options may be limited to ‘satisficing’ in (late) State 3, for example due to reduced tolerance to drug toxicity. Should the immune response and any corresponding inflammatory response be sufficient, then the BEA and associated disease would regress to the healthy tissue state and homeostasis (State 4). This is shown for remedia- tion from State 3, but it could also occur at States 2 or 1. See main text for further discussion.

States of BEA and associated disease

The BEA is at the center of the disease ecosystem framework. The BEA population is dynamic, yet proceeds through one or more of a characteristic series of states. These states can convey considerable information about the current and future growth of the BEA and disease. Torres et al. [44] proposed a ‘disease map’ that tracks pathogen load and patient health through the course of a disease. Below, I reinterpret this concept emphasizing the growth and evolvability of the BEA population and associated disease (Fig. 2).

State 1. Establishment: small numbers, low evolutionary potential, negligible disease

As described above, during establishment, BEAs confront novel and possibly hostile environments [45, 46]. Establishment will depend on the BEA’s ability to evade immune responses and either already possess or plastically express virulence factors permitting resource acquisition and growth [47]. Should the immune response be sufficient, the BEA enters directly into State 4 (see below) and declines. Even should a small BEA population continue to grow, its total mass and the extent of associated
disease is likely to be minute. State 1 continues until (i) cumulative cell turnover is on the order of the reciprocal of the beneficial mutation rate (entry into State 2), and/or (ii) the intensification of disease due to some combination of direct damage by the BEA and possible chronic inflammation (entry into State 3).

Detailed study of the initial phases of BEA population growth is uncommon. For example, Margolis and Levin [48] considered how commensal *Haemophilus influenzae* could become invasive from the nasal passage to the blood and then evolve. They showed that invasive infections have a significant stochastic component, are typically initiated by a single bacterial cell and found evidence for infrequent within-host evolution. Leggett *et al.* [49] looking across 43 different human pathogens found that lower inoculum numbers were required for infections generating pathogenesis at local as opposed to distant sites. The former tended to be more virulent than the latter. In contrast to parasitic BEAs, tumorigenesis requires key initiating mutations that compromise cooperative cellular functions [50], and together with subsequent tumor progression and metastasis (States 2 and 3), this can take years or even decades to achieve (e.g. [51]).

**State 2. Growth: mutation, adaptation and resistance**

The transition from a relatively slow growing, evolutionarily limited BEA in State 1 to an exponentially growing, evolving BEA in State 2 is associated with both population turnover (total births per unit time) and mutation rate [52, 53]. Population growth will be influenced by the host immune system and nutrient levels [40, 54]. The per-birth mutation rate can be highly variable between different BEA strains and types, with more rapid passage from State 1 to State 2 expected for hypermutating bacteria, RNA viruses such as HIV-1, and genomically unstable tumor cells. For example, Sottoriva *et al.* [55] studied the spatio-temporal dynamics of beneficial mutations in colorectal cancers. They found that the first dominant mutations emerged in tumors containing as few as \(<10^4\) cells, which can be explained in part by mutation rates as high as \(~10^{-5}\) (see also [56]).

BEA population growth and evolutionary potential have two notable consequences. First, growing BEA populations result in alteration of host cell behaviors and for some BEA types, greater tissue damage. Second, higher mutation rate favors anti-immune defenses [57], adaptations in nutrient use [58, 59] and resistance to therapeutic interventions [60, 61].

**State 3. Spread: growth and dispersal magnify disease**

Continued BEA growth eventually results in metabolic competition and—particularly in the tumor microenvironment—waste accumulation. One or both of these factors can promote local colonization and migratory behaviors [62, 63], which lead to increased pathogenicity. Although disease can be significant at low BEA densities (States 1 and 2), all else being equal, it usually worsens with time and as BEA numbers grow (see contrasting scenarios in [64]). Cancers are arguably the best examples of how growth, local tissue invasion and distant tissue colonization—together with chronic inflammation—compromise host condition and increase mortality. Local tissue invasion and metastatic spread are indicative of escape from immune control [65]. Similar patterns are observed in certain microparasites, where disease progression is associated with local tissue invasion and cell entry [23].
State 4: Regression: immune responses abate BEA and disease

Should the combined effects of the innate and adaptive immune systems prevail resulting in BEA population decline, then disease too will eventually regress [44]. Depending on immune and BEA dynamics, State 4 may obtain at any point during States 1 to 3 for infectious BEAs, whereas for cancers State 4 is most likely to obtain during State 1, before the tumor evolves to evade the immune response. BEAs in State 3 that do not enter State 4 either lead to chronic disease or result in host death.

The above classification gives a clear message for therapy. A disease is much more treatable in State 1, but either impossible or difficult to diagnose compared to State 2 and particularly State 3. In States 2 and 3, resistance is a concern, and special measures may be needed to treat the BEA. Finally, drug toxicity becomes an issue as the BEA population grows, disease spreads, and the person’s health is at risk or life is engaged, as would be observed (late) in State 3. Observation that the BEA and associated disease are in State 4 would often preclude a therapeutic intervention.

APPLYING THE FRAMEWORK

The population ecology of BEAs makes them particularly difficult to eradicate. Once disease is detected, BEAs typically will have attained large population sizes and generated mutant strains that result in opportunities for evolutionary responses. There are useful parallels between seeking to cure a disease and attempting to eradicate an invasive species. Perhaps, the most compelling is that eradication becomes more achievable as the population is smaller and more spatially circumscribed (States 1 and 2, Fig. 2). Thus, for example, invasive species are more difficult to eradicate on mainland (or interconnected habitats) than on islands (or isolated habitats) [66]. Both ecological dynamics (e.g. larger population sizes, refugia) and evolutionary dynamics (e.g. greater additive genetic variation) contribute to explaining this observation. The same basic principle applies to treating a BEA, where diversification (State 2) and spread (State 3) make eradication less probable, as is amply demonstrated by relapse due to chemotherapeutic resistance in metastatic cancers.

Below, I first review different ways in which therapies fail. I then present six eco-evolutionary-sensible measures that can be used singly or in combination to achieve therapeutic objectives.

Why do therapies fail?

Excepting technical issues of inappropriate drugs, the main probable cause for treatment failure is BEA resistance [10, 67]. Drug resistance due to high-dose therapy is a textbook example of ‘evolutionary rescue’ [68, 69], where the drug (if it were to be maintained) drives the sensitive population to extinction, but resistant variants already present or emerging during the treatment grow and repopulate the disease ecosystem. The actual sequence of mutational events leading to rescue has rarely been studied [70], and we are only beginning to learn about the underlying ecological processes (see [69] for contrasts between medicine, agriculture and conservation biology). For instance, although the evolution of resistance is often associated with high-dose chemotherapies, lower dosing (e.g. to regulate toxicity, especially in cancer chemotherapies) can also select for resistance [71, 72].

The most discussed mechanism leading to evolutionary rescue is ‘competitive release’, whereby reductions in the population of the sensitive strain open the niche for growth of otherwise competitively suppressed resistant strains [73, 74]. Qualifying all instances of evolutionary rescue as stemming from competitive release is an oversimplification, because there are notable contrasts in the mechanism depending on the absolute and relative fitnesses of sensitive and resistant strains, both in the presence and absence of a drug [74]. Nevertheless, there is some support for the general phenomenon of competitive release [75–77].

Much of what is known about treatment failure comes from studies of the evolution of drug resistance. But barring data actually demonstrating resistance, other less studied, non-mutually exclusive mechanisms may be involved in BEA resurgence or relapse. Competitive release—although sometimes used for inter-strain competitive effects (see above)—is originally an ecological concept [78]. In ecological competitive release, the elimination of the target BEA results in the emergence of one or more otherwise competitively suppressed BEAs [79].

Therapeutic tolerance is the ability of BEAs to withstand the transient effects of a treatment. Examples include reduced receptor sensitivity or density-limited drug impact in cell sub-populations of certain cancers [80], and quiescent or dormant states in cancer stem cells [81] and bacterial persister cells [82]. Other forms of tolerance involve protective structures, such as bacterial biofilms against antibiotics [83], biofilms limiting host immune responses [84], and immune tolerance in the tumor microenvironment [85].

Escape mutants do not have specific resistance or tolerance mechanisms, but rather simply outgrow the suppressive effects of the therapy. This may occur, for example, due to insufficient drug dosing [86, 87]. Spatial and temporal refuges are similar to escape mutants, except that BEA survival is due to heterogeneity in therapeutic exposure. Examples include limited drug diffusion [88–90] and ‘drug holidays’ or patient non-compliance [86].

High mutation rates may favor escape by increasing the chances of resistance emerging in bacteria [91], HIV [92] and certain cancers [93]. Hypoxic stress in leading to higher mutation rates in tumors could explain certain origins of therapeutic resistance [33].

Therapeutic measures

Applying the framework involves first acquiring information about the BEA and disease ecosystem (Figs 1 and 2). A therapeutic
objective is chosen based on this information and on actionable strategies and associated tactics. The choice considers failure risks due to BEA resistance or evasion. Typically, a single strategy and tactic will be deployed to achieve an objective, but as will be explained below, under some circumstances different strategies/tactics may complement one another and become a combination strategy. Below, I refer to strategies and tactics as ‘measures’. A treatment is deemed a success if it achieves its objective (see Supplementary Material for a simple criterion).

Importantly, a chosen measure need not do all the ‘work’ to achieve a therapeutic objective. Rather, it can be employed as an adjuvant either to other measures as part of a combination strategy or to processes already active in the disease ecosystem. For example, amoxicillin is a common antibiotic used for treating type A strep throat associated with *Streptococcal pharyngitis*. The antibiotic interferes with BEA cell wall synthesis and thus targets bacterial replication. Amoxicillin may not be 100% effective on its own (due to limited pharmacokinetics) and different components of the immune system ensure the final stages of the complete clearing of the infection [94].

Below, I present a series of six measures for treating disease (Fig. 3), starting with the most employed—drug-based targeted therapy (Measure 1). Measure 1 has three main variants depending on the objective: eradicate, contain or satisfy. A second approach is to focus on reducing damage, rather than target the BEA *per se* (Measure 2). A third approach is to target other components of the disease ecosystem (Measures 3–6). Finally, I describe the strategy of combining measures into more effective therapies.

**Measure 1: Drugs**

Alexander Fleming expressed a nuanced version of *frapper fort et frapper vite* [95]. His recommendation ‘if you use penicillin, use enough’ was based on the idea that sensitive strains were the origin of *de novo* resistant mutants, and the former needed to be eliminated quickly and decisively. Resistant mutants may however be present even before a therapy commences, either in the pathogen inoculum (or the first cells of an invasive carcinoma) or due to mutations in a growing BEA population (i.e. State 2, Fig. 2). The observation that the Ehrlich–Fleming approach applied to a large enough BEA population risks selecting for resistance has fueled theoretical research aimed at determining the drug doses and scheduling that will either contain or eradicate a BEA (e.g. [96–101]). These studies and others have contributed the following basic insights.

**Eradicate.** If the turnover of the BEA population and/or its genetic diversity are low (State 1), then resistance mutants are unlikely to be present [53] or may fail to emerge even under treatment (see also [102]). Eradication becomes an option. Depending on the information available about possible resistance mutants, the minimal dosing strategy is (in order of decreasing dose) either to apply the maximum tolerated dose (no information), attain the mutant prevention concentration [103] (information about resistance) or apply the dose necessary to clear sensitive strains (no resistance detected).

**Contain.** When the turnover of the BEA population and/or genetic diversity are high (States 2 and 3), then high-dose, targeted therapy is likely to be useless or even counterproductive. Examples where this may occur include clonal expansions [16], and genetically diverse infections [104]. Often the course of action taken when resistance is suspected or identified is to employ particularly aggressive drugs or—for some multi-drug-resistant pathogens—last resort drugs [105]. These treatment strategies, and indeed intermediate dose treatment strategies, are likely to fail [101, 106, 107]. Experimental and theoretical study indicates that the most sensible approach is to aim to contain the BEA through low but sufficient dose chemotherapies (e.g. [101, 108], and references therein). Containment requires that sensitive BEA strains be held in check by the therapy, but maintained at levels so as to competitively limit the populations of any drug-resistant strains when therapy is released. This is most readily achieved through managing the total BEA burden, whereby resistant types express a fitness cost relative to sensitives during periods of relaxed therapeutic selection (recent reviews in e.g. [98, 109]). More nuanced ‘adaptive’ approaches monitor therapeutic performance and eventually adjust drug dose or drug type so as to manage disease burden [110]. Recent experimental demonstrations of tumor containment show some promise (in vitro [111]; in vivo [77]), and the same approach should be applicable to certain microbial pathogens [112]. There are nevertheless situations where containment strategies are unlikely to succeed, such as when fitness-compensatory mutations have emerged in resistant
strains during evolutionary rescue or have been transferred horizontally (e.g. [113–115]).

Satisfice. Simple dosing rules can be misleading when toxicity is an issue (late State 3 and no indication of entering State 4), as is often encountered in metastatic cancers. This is because the doses needed to optimally treat the (advanced) BEA are too toxic for the weakened patient. This situation becomes particularly acute when the patient’s life is engaged and rapid decisions need to be made [116]. In such scenarios aiming for ‘optimality’ is better replaced by ‘satisficing’, where success is equated with an acceptable improvement in signs and/or symptoms [117]. Much of what is known about containing a BEA while managing toxicity through scheduled dosing comes from theoretical study. For example, Foo et al. [118] examined pharmacokinetic models of the emergence of drug resistance in patients with epidermal growth factor receptor lung cancers. They found that the pulsed dosing (to control toxicity) could limit tumor growth, but long intervals risked the emergence of new drug-resistant clones.

Drug therapies are not ‘stand-alone’—particularly when targeting a microparasitic infection. Unless a patient is immunosuppressed, the immune system will act in conjunction with the treatment. This means that optimal dosing may depend on host condition (drug tolerance, ability to mount an immune response) and the disease ecosystem (the BEA population state). For example, Ankomah and Levin [119] studied a model of how the innate and adaptive immune systems could complement the effects of a drug to clear a bacterial infection. They showed that high drug doses led to the most successful outcomes (but see contrasting findings in [101]).

Despite empirical work showing that drug dose can influence treatment outcomes (for literature survey, see [101]), the necessary information required to make strategic decisions is often lacking. This could in part explain why eco-evolutionary reasoning is not being used to its full potential in deciding whether and how to employ aggressive treatment or containment strategies [98, 104, 107].

Measure 2: Virulence factors

The severity of disease will be influenced by the expression of ‘virulence factors’ that enable the BEA to construct its niche. Virulence factors may promote resource extraction, protect from host defenses, or attach to cell or tissue surfaces. They are most documented for microparasitic BEAs and include adhesive structures, motility enhancers such as Type IV pili, and toxins [120, 121]). Virulence may also have a social component, for example via quorum sensing in certain bacteria [122, 123].

Anti-virulence drugs have gained attention as possibly being ‘evolution proof’, because the traits actually targeted have little influence on fitness [120, 124]. Examples of drug targets include rendering bacteria more susceptible to immune clearance and increasing antibiotic efficacy [125], and cytostatic drugs that stall cancer cell division rather than targeting cell survival [126]. Other approaches seek to change BEA behaviors, such as increasing pH in cancer microenvironments that reduces tumor growth and metastasis [127]. Although in vitro studies of anti-virulence strategies appear promising (e.g. [128]), resistance is a concern, and there may be limitations in their efficacy in vivo [117, 120, 121].

Measure 3: Immune system

The immune system is the single most important mechanism responsible for preventing disease and limiting its spread. Immune systems can be remarkably complex, and their detailed description is beyond the scope of this review. Broadly speaking, immune responses may involve specialized molecules and/or cell types. Introducing molecules from the innate immune response—notably antimicrobial peptides—shows great therapeutic potential by both their stunning diversity and the lower likelihood of resistance evolution compared to antibiotics [129]. Immunotherapies that stimulate the production of specific immune cell motifs show promise in treating certain cancers [130] and bacterial diseases [131], but their use is still controversial due to risks of immunotoxicity and autoimmune disorders [132]. Related to this, Smyth et al. [133] recently argued for using information about components of the tumor microenvironment in decisions about immunotherapies, particularly as adjuvants to other therapies.

Measure 4: Resources—competition

BEAs need resources to grow and multiply. Resources include hospitable space and nutrients such as glucose, oxygen, carbon, nitrogen and phosphorus. Glucose use in particular differs fundamentally between healthy cells and tumor cells (with the latter consuming up to 18 times the former; [134]), as does phosphorus [135], and leveraging these may contribute to a strategy for tumor control. Resource deprivation by curtailing angiogenesis has proved successful in certain cancer treatments, but can come at a cost of limiting drug diffusion through the tumor [136]. In Plasmodium, Wale et al. [137] recently showed how resource limitation could differentially impact sensitive and resistant strains. Other tactics either limiting or excluding BEAs include boosting the competitiveness of healthy cells [138], or of commensals in the microbiome [139].

Measure 5: Microbiome

The microbiome is increasingly recognized as foundational to organism biology and condition. Some analogies are likely to apply between the functions of microbes in classic ecosystems and in healthy and diseased ecosystems [15]. For example, dysbiosis may be associated with certain BEA infections [121] and cancers [140], and there is accumulating evidence that the gut microbiota modulates the effectiveness of cancer therapies and associated toxic effects [141].
That microbiome disruption can influence disease suggests that re-normalizing it could prevent or ameliorate certain diseases. For example, lifestyle changes (e.g. avoiding high caloric intake and excessive hygiene) may indirectly prevent disease via their impacts on the microbiome, and more active interventions such as microbiome transplants could either be used preventively or therapeutically [140, 141].

**Measure 6: Aliens**

‘Living drugs’ such as bacteriophages (or ‘phages’) are akin to introducing a predator to control an agricultural pest. Phages self-amplify and adapt to their bacterial hosts, meaning that they can continually counter bacterial resistance [142]. In addition to their use as self-propagating, evolving antimicrobials, bacteriophage can be applied prophylactically to prevent bacterial pathogens from emerging [143], or engineered and introduced to disrupt antibiotic resistance [144]. Although less studied, replicating oncolytic viruses have clinical potential similar to baculoviruses [145], but with the added twist that under some circumstances they can induce anti-tumor immunity [146].

Similar to drug therapies, when submitted to phage predation, sufficiently large and diverse bacterial populations evolve resistance. Although a phage population will typically respond by evolving countermeasures, a more proactive, promising strategy is to evolutionarily ‘train’ phage before they are actually employed [147, 148]. Training involves selecting phage in *vitro* for traits that impact current bacteria at the infection site and prevent the future emergence of resistant strains. *In vitro* study indicates that passaging phage achieves the former objective, whereas coevolving them with the bacterium achieves the latter [148–150]. Training oncolytic viruses on tumor cells *in vitro* remains unexplored.

**Combining measures**

An important principle from integrated pest management is that attaining a control objective is more likely as multiple, complementary practices are put into place. This same idea—combining two or more variations of the same measure or two or more measures—is therapeutically sensible both ecologically and evolutionarily [151]. Combination therapies are most likely to succeed when each measure (i) reduces BEA numbers or turnover, thereby removing existing resistance mutations and lowering the probability of such mutations emerging *de novo* to other measures (e.g. therapy A kills single mutants with resistance to therapy B, and vice versa) and (ii) acts through a different, non-antagonistic mechanism in targeting the BEA. Both of these effects imply that different genes are involved in resisting different measures. Crucially, because in sufficiently small populations it is unlikely that multiple resistance factors will occur in the same BEA individual, combinations are less likely than single measures to select for resistance [86, 152, 153] (see [60, 154] for possible exceptions in tumors).

Combination therapies have become a mainstay for treating HIV, malaria and tuberculosis and are particularly relevant to cancers [133, 145, 155]. They are also effective against bacterial pathogens, for example, the use of phage cocktails [156, 157], multiple antibiotics [158, 159], certain aminoglycosides and metabolites against persister bacteria [160], antimicrobial peptide cocktails [161], phage–antibiotic combinations [157], and phage to select for increased sensitivity to antibiotics [162]. Like phage–antibiotic combinations, antibiotic combinations that target different critical bacterial functions may not only increase the chances of therapeautic success but also limit the evolution and spread of antibiotic resistance [163]. Due in part to their great diversity, combinations involving natural host-derived antimicrobial peptides are particularly promising in this regard [164].

Depending on the nature of their interactions, measures can be combined either simultaneously or sequentially. For instance, Roemhild *et al.* [165] demonstrated how the order of sub-lethal doses of antibiotics could have substantial effects on bacterial population sizes and resistance (see also [96]). Torres-Barceló *et al.* [166] showed how intermediate delays between phage and antibiotic application not only minimized numbers of *Pseudomonas aeruginosa* but also minimized resistance to both antibiotics and phage. Sequential applications have also shown promise in combinations of chemotherapy and immunotherapy [167], and polyADP ribose polymerase inhibitors capitalizing on synthetic lethality in certain breast and ovarian cancers [168]. Other more information-based combination strategies such as evolutionary steering [169] and resistance reversal [170] have shown proof of concept.

Combination therapies nevertheless have several notable drawbacks. First, they can fail if not carefully devised. Hegreness *et al.* [171] showed how synergistic antibiotic combinations could accelerate the evolution of resistance compared to *(a priori*, less preferred) antagonistic combinations (see also [96]). Second and similarly, the use of multiple tactics could mean that lower intensities of each are employed to limit toxicity; these lower doses are more likely to fall within the ‘mutant selection window’ should such resistant strains be present, and result in resistance evolution [101, 172]. Third, it is logistically more challenging to administer combinations than monotherapies. This extends both to the willingness of medical practitioners to employ unfamiliar novel therapies and for patients to follow protocols.

**POTENTIAL LIMITATIONS**

The disease ecosystem framework focuses on a well-studied host (humans) and a small number of their well-studied BEAs (most examples from bacteria and cancer). The remarkable diversity of
host species and BEAs and their intra-population variation—but also the fact that many BEAs are associated with multiple disease ecosystems within the same host individual, or exploit multiple host species, or have complex life cycles with intermediate hosts—mean that the framework presented here is only an initial step towards a more refined general framework and more taxon-specific versions. This situation is no different from the challenges of understanding classic ecosystems, and much of the progress in identifying process and pattern in the latter should be useful in instructing approaches to understanding disease ecosystems.

Second and similarly, many BEA taxa do not replicate in all hosts (particularly for complex life-cycle parasites, such as helminth worms), meaning that in situ mutation is not a factor. These species are confronted with some of the same basic constraints as are parasites that can replicate and evolve within their host (resource levels, competition, immune responses), and consequently have evolved mechanisms to plasticly adapt to the host ecosystem and in particular, regulate host immunity [173]. The present framework could be extended to accommodate these BEAs.

Third, the ecosystem framework notably ignores host-to-host transmission of BEAs and the spread of resistance between hosts. This concern is evidently not relevant to cancers but is an important factor for infectious diseases, where there is a potential conflict between the immediate interests of individual patients and future interests of the greater population (e.g. [7, 108, 163, 174, 175]).

A fourth limitation is the need for sufficiently rich information to employ certain therapeutic measures, particularly those aiming to contain the BEA. Some BEAs can be quantified either directly or through correlations with measurable signs of disease (e.g. biomarkers, scans). Quantifying ecosystem components such as the immune system (e.g. [176]) could show promise as performance indicators of natural or therapeutically influenced BEA control.

**CONCLUDING REMARKS**

The immense body of knowledge on classic ecosystems can contribute to our understanding of disease ecosystems. We will however need more than these analogies to achieve a predictive theory of disease ecosystem dynamics. The principal reason is their underlying complexity. Healthy organism ecosystems and their responses to disease have evolved to maintain homeostasis/performance and remediation to homeostasis, respectively. Although the former should be fairly predictable, the latter will be dynamic, context dependent and more challenging to forecast. The disease ecosystem framework represents an initial step toward understanding disease, predicting its course and designing eco-evolutionarily sensible therapies.

Disease ecosystems are complex and dynamic and have no a priori spatial limits. The ecosystem framework focuses on proximal interactions at the host cellular and tissue levels. These interactions will interlock with other tissue and organ systems in the host individual, and ultimately influence and be influenced by population and external environmental-scale systems. Maintaining generality even at the cellular and tissue scales necessarily means omitting considerable realistic detail (see e.g. Table 2 in [177]). Moreover, at aggregate levels, ecological and evolutionary dynamics are likely to be complex given the feedback structures of homeostatic regulation [27], interaction networks [14], and stochasticity in the mutation process and the host’s immune response [178, 179]. Despite this complexity, it is encouraging that across two pervasive BEA types in humans (bacteria and cancer) there is broad similarity in the basic interactions of the disease ecosystem (this study), and with regard to therapies, correspondences in drug resistance evolution [115]. This suggests generality in the framework presented here.

The ecosystem framework is a scaffolding. To be fully operative, it needs to be supplemented with quantitative descriptions of each component process. Although the framework on its own can advise specific types of therapeutic decisions (either ones where resistance is not an issue or satisfying is the only option—i.e. State 1 and late State 3), it will be limited without parameterized models to guide finer containment approaches such as adaptive therapies (States 2 and 3; see e.g. [111]). Such a model would link the most important components of the ecosystem to the variables of interest, typically BEA population size, frequency of resistance, virulence factors or aggressiveness, and disease signs. The model would then be used to evaluate how different candidate therapeutic interventions affect the likelihood that an objective will be achieved. Usually but not always, preventing or limiting BEA evasion (e.g. resistance) will be an integral part of which measure(s) is (are) finally employed.

We are only beginning to scratch the surface of how the disease ecosystem functions and its relevance as part of a larger network, including other ecosystems in the individual, the population and as part of wider (classic) ecosystems [180]. Understanding these processes, their interactions, and importance in creating pattern at different scales will be considerable challenges (Box 4), but promise to lead to novel insights about the ecology and evolution of symbioses, and new breakthroughs in conceptualizing and treating disease.

**GLOSSARY**

(1) **Disease.** Changes to the structure and function of host cells, tissues or organ systems associated with interactions between the BEA and the host.

(2) **Signs.** Objective observations of disease, typically of macroscopic features, such as swollen tonsils consistent with strep throat.

(3) **Symptoms.** Subjective assessments of disease, such as pain or discomfort.

(4) **Pathogenicity.** The propensity for disease to result in tissue damage, morbidity and mortality. Like
disease, pathogenicity is a property of the interaction between the BEA and host.

(5) **Resistance.** A BEA phenotype that protects from specific antagonisms such as immune responses or therapies.

(6) **Cure.** Disease remediation to no detectable signs and symptoms.

(7) **Chemotherapy.** The use of chemicals to treat disease, usually focused at killing the etiological agent, either microparasites or tumor cells.

(8) **Eradication.** The complete elimination of the BEA.

(9) **Containment.** Maintaining disease below an acceptable maximum threshold.

(10) **Microparasites.** Microbial parasites that replicate within their host, including viruses, bacteria, fungi and protozoa.

(11) **Virulence factors.** BEA traits that increase BEA fitness (growth, survival and reproduction) and intensification of disease (i.e. pathogenicity).

(12) **Inflammation.** Alteration of the disease ecosystem that promotes the intensification of the immune response and remediation of disease damage. Chronic inflammation can result in tissue damage.

(13) **Satisficing.** An acceptable improvement in disease signs and symptoms.

**ACKNOWLEDGEMENTS**

The author acknowledges participants of the ‘Aging and Adaptation in Infectious Diseases’ workshop at the Santa Fe Institute, three anonymous reviewers, and Sebastian Bonhoeffer, Troy Day, Andrea Graham, Andrew Read, Roland Regoes and Jens Rolff for discussions.

**FUNDING**

I acknowledge financial support from the McDonnell Foundation (Studying Complex Systems Research Award No. 22002094), ITMO Cancer AVIESAN (Program ‘HetColi’) and the Institut National du Cancer (2014-1-PL-BIO-12-IGR-1) for funding.

**SUPPLEMENTARY DATA**

Supplementary data is available at EMPH online.

**Conflict of interest:** None declared.

**REFERENCES**

1. Ehrlich P. Address in pathology on chemotherapeutics: methods, and results. *Lancet* 1913; **182**(445–51).

2. Read AF, Day T, Huijben S. The evolution of drug resistance and the curious orthodoxy of aggressive chemotherapy. *Proc Natl Acad Sci U S A* 2011; **108**(10871–7).

3. Gillies RJ, Verduzzo D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. *Nat Rev Cancer* 2012; **12**(487–93).

4. Haegeman B, Hamelin J, Moriarty J et al. Robust estimation of microbial diversity in theory and in practice. *ISME J* 2013; **7**(1092–101).

5. Maley CC, Akhtiasis A, Graham TA et al. Classifying the evolutionary and ecological features of neoplasms. *Nat Rev Cancer* 2017; **17**(605–19).

6. Cornforth DM, Dees JL, Ibberson CB et al. Pseudomonas aeruginosa transcriptome during human infection. *Proc Natl Acad Sci U S A* 2018; **115**(ES125–34).

7. Lipsitch M, Samore MH. Antimicrobial use and antimicrobial resistance: a population perspective. *Emerg Infect Dis* 2002; **8**(347–54).

8. Becattini S, Taur Y, Pamer EG. Antibiotic-induced changes in the intestinal microbiota and disease. *Trends Mol Med* 2016; **22**(458–78).

9. Estrella S, Brown SP. Community interactions and spatial structure shape selection on antibiotic resistant lineages. *PLoS Comput Biol* 2018; **14**(e1006179).

10. Currie CJ, Berni E, Jenkins-Jones S et al. Antibiotic treatment failure in four common infections in UK primary care 1991-2012: longitudinal analysis. *BMJ* 2014; **349**(g5493).
11. Courchamp F, Dunne JA, Le Maho Y et al. Fundamental ecology is fundamental. *Trends Ecol Evol* 2015; 30:1–8.
12. Conrad D, Haynes M, Salamon P et al. Cystic fibrosis therapy: a community ecology perspective. *Am J Respir Cell Mol Biol* 2013; 48:150–6.
13. McNally L, Brown SP. Building the microbiome in health and disease: niche construction and social conflict in bacteria. *Philos Trans R Soc Lond B Biol Sci* 2015; 370:20140298.
14. Rynkiewicz EC, Pedersen AB, Fenton A. An ecosystem approach to understanding and managing within-host parasite community dynamics. *Trends Parasitol* 2015; 31:1–10.
15. Robinson CJ, Bohannan BJM, Young VB. From structure to function: the ecology of host-associated microbial communities. *Microbial Mol Biol Rev* 2010; 74:453–76.
16. Merlo LMF, Pepper JW, Reid BJ et al. Cancer as an evolutionary and ecological process. *Nat Rev Cancer* 2006; 6:924–35.
17. Pienta KJ, McGregor N, Axelrod R et al. Ecological therapy for cancer: defining tumors using an ecosystem paradigm suggests new opportunities for novel cancer treatments. *Transl Oncol* 2008; 1:158–64.
18. Basanta D, Anderson ARA. Exploiting ecological principles to better understand cancer progression and treatment. *Interface Focus* 2013; 3:20130020.
19. Amend SR, Roy S, Brown JS et al. Ecological paradigms to understand the dynamics of metastasis. *Cancer Lett* 2016; 380:237–42.
20. Alfarouk KO, Ibrahim ME, Gatenby RA et al. RIParian ecosystems in human cancers. *Evol Appl* 2013; 6:46–53.
21. Free A, Barton NH. Do evolution and ecology need the Gaia hypothesis? *Trends Ecol Evol* 2007; 22:611–9.
22. Doran KS, Banerjee A, Disson O et al. Concepts and mechanisms: crossing host barriers. *Cold Spring Harb Perspect Med* 2013; 3:a010090.
23. Ribet D, Cossart P. How bacterial pathogens colonize their hosts and invade deeper tissues. *Microbes Infect* 2015; 17:173–83.
24. Levin BR, Antia R. Why we don’t get sick: the within-host population dynamics of bacterial infections. *Science* 2001; 292:1112–5.
25. Schmid-Hempel P. Immune defence, parasite evasion strategies and their relevance for “macroscopic phenomena” such as virulence. *Philos Trans R Soc Lond B Biol Sci* 2009; 364:85–98.
26. Brown EM, Sadarangani M, Finlay BB. The role of the immune system in governing host-microbe interactions in the intestine. *Nat Immunol* 2013; 14:660–7.
27. Rankin LC, Artis D. Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. *Cell* 2018; 173:554–67.
28. McDade TW, Georgiev AV, Kuzawa CW. Trade-offs between acquired and innate immune defenses in humans. *Evol Med Public Health* 2016; 2016:1–16.
29. Hochberg ME, Noble RJ. A framework for how environment contributes to cancer risk. *Ecol Lett* 2017; 20:117–24.
30. Schmid-Hempel P. Parasite immune evasion: a momentous molecular war. *Trends Ecol Evol* 2008; 23:318–26.
31. Noble R, Kalz O, Hochberg ME. Petó’s paradox and human cancers. *Philos Trans R Soc Lond B Biol Sci* 2015; 370:20150104.
32. Schaffer K, Taylor CT. The impact of hypoxia on bacterial infection. *FEBS J* 2015; 282:2260–6.
33. Verduzco D, Lloyd M, Xu L et al. Intermittent hypoxia selects for genotypes and phenotypes that increase survival, invasion, and infection resistance. *PLoS One* 2015; 10:e0120958.
34. Chang C-H, Qiu J, O’Sullivan D et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* 2015; 162:1229–41.
35. Read AF, Taylor LH. The ecology of genetically diverse infections. *Science* 2001; 292:1099–102.
36. Mideo N. Parasite adaptations to within-host competition. *Trends Parasitol* 2009; 25:261–8.
37. Balmer O, Tanner M. Prevalence and implications of multiple-strain infections. *Lancet Infect Dis* 2011; 11:688–78.
38. Smith VH, Holt RD. Resource competition and within-host disease dynamics. *Trends Ecol Evol* 1996; 11:386–9.
39. Bämmler AJ, Sperando V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* 2016; 535:85–93.
40. Cressler CE, Nelson WA, Day T et al. Disentangling the interaction among host resources, the immune system and pathogens. *Ecol Lett* 2014; 17:284–93.
41. Cobey S, Lipsitch M. Pathogen diversity and hidden regimes of apparent competition. *Am Nat* 2013; 181:12–24.
42. Buck MD, Sowell RT, Kaech SM et al. Metabolic instruction of immunity. *Cell* 2017; 169:570–86.
43. Fenton A, Perkins SE. Applying predator-prey theory to modelling immune-mediated, within-host interspecific parasite interactions. *Parasitology* 2010; 137:1027–38.
44. Torres BY, Oliveira JHM, Thomas Tate A et al. Tracking resilience to infections by mapping disease space. *PLoS Biol* 2016; 14:e1002436.
45. Rolfe MD, Rice CJ, Lucchini S et al. Lag phase is a distinct growth phase that prepares bacteria for exponential growth and involves transient metal accumulation. *J Bacteriol* 2012; 194:686–701.
46. Gillies RJ, Gatenby RA. Metabolism and its sequelae in cancer evolution and therapy. *Cancer J* 2015; 21:88–96.
47. Brown SP, Cornforth DM, Mideo N. Evolution of virulence in opportunistic pathogens: generalism, plasticity, and control. *Trends Microbiol* 2012; 20:336–42.
48. Margolis E, Levin BR. Within-host evolution for the invasiveness of commensal bacteria: an experimental study of bacteremias resulting from *Haemophilus influenzae* nasal carriage. *J Infect Dis* 2007; 196:1068–75.
49. Leggett HC, Cornwallis CK, West SA. Mechanisms of pathogenesis, infective dose and virulence in human parasites. *PLoS Pathog* 2012; 8:e1002512.
50. Aktipsis CA, Boddy AM, Jansen G et al. Cancer across the tree of life: cooperation and cheating in multicellularity. *Philos Trans R Soc Lond B Biol Sci* 2015; 370:20140219.
51. Iwasa Y, Nowak MA, Michor F. Evolution of resistance during clonal expansion. *Philos Trans R Soc Lond B Biol Sci* 2015; 370:20140219.
52. Wodarz D, Komarova N. Can loss of apoptosis protect against cancer? *Nat Genet* 2006; 37:9–10.
53. Sottoriva A, Kang H, Ma Z et al. A Big Bang model of human colorectal cancer evolution: a comparison. *Philos Trans R Soc Lond B Biol Sci* 2015; 370:20140219.
54. Yachida S, Jones S, Bozic I et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; 467:1114–7.
55. Wodarz D, Komarova N. Can loss of apoptosis protect against cancer? *Trends Genet* 2007; 23:232–7.
56. Iwasa Y, Nowak MA, Michor F. Evolution of resistance during clonal expansion. *Genetics* 2006; 172:2557–66.
57. De Boer RJ, Perelson AS. Target cell limited and immune control models of HIV infection: a comparison. *J Theor Biol* 1998; 190:201–14.
58. Sottoriva A, Kang H, Ma Z et al. A Big Bang model of human colorectal tumor growth. *Nat Genet* 2015; 47:209–16.
59. Williams MJ, Werner B, Barnes CP et al. Identification of neutral tumor evolution across cancer types. *Nat Genet* 2016; 48:1–9.
The disease ecosystem

57. Caswell DR, Swanton C. The role of tumour heterogeneity and clonal cooperativity in metastasis, immune evasion and clinical outcome. BMC Med 2017; 15:133.

58. Olive AJ, Sassetti CM. Metabolic crosstalk between host and pathogen: sensing, adapting and competing. Nat Rev Microbiol 2016; 14:221–34.

59. Rohmer L, Hoquet D, Miller SI. Are pathogenic bacteria just looking for food? Metabolism and microbial pathogenesis. Trends Microbiol 2011; 19:341–8.

60. Komarova NL, Wodarz D. Drug resistance in cancer: principles of emergence and prevention. Proc Natl Acad Sci U S A 2005; 102:9714–9.

61. Bozic I, Nowak MA. Timing and heterogeneity of mutations associated with drug resistance in metastatic cancers. Proc Natl Acad Sci U S A 2014; 111:15964–8.

62. Hibbing ME, Fuqua C, Parsek MR et al. Bacterial competition: surviving and thriving in the microbial jungle. Nat Rev Microbiol 2010; 8:15–25.

63. Renner K, Singer K, Koehl GE et al. Metabolic hallmarks of tumor and immune cells in the tumor microenvironment. Front Immunol 2017; 8:248.

64. Casadevall A, Pirofski L-A. The damage-response framework of microbial pathogenesis. Nat Rev Microbiol 2003; 1:17–24.

65. Khong HT, Restifo NP. Natural selection of tumor variants in the generation of “tumor escape” phenotypes. Nat Immunol 2002; 3:999–1005.

66. Veitch CR, Clout MN, Towns DR. Island Invasions: Eradication and management. Gland, Switzerland: IUCN, 2011.

67. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol 2005; 205:279–92.

68. Gonzalez A, Ronco O, Ferriere R et al. Evolutionary rescue: an emerging focus at the intersection between ecology and evolution. Philos Trans R Soc Lond B Biol Sci 2013; 368:20120150.

69. Bell G. Evolutionary rescue. Annu Rev Ecol Evol Syst 2017; 48:605–27.

70. Mwangi MM, Wu SW, Zhou Y et al. Tracking the in vivo evolution of multidrug resistance in Staphylococcus aureus by whole-genome sequencing. Proc Natl Acad Sci U S A 2007; 104:9451–6.

71. Gullberg E, Cao S, Berg OG et al. Mechanisms of antibiotic resistance in bacterial biofilms. Trends Microbiol 2016; 24:466–74.

72. Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. Nat Rev Microbiol 2004; 2:15964–8.

73. de Roode JC, Culleton R, Bell AS et al. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007; 99:1441–54.

74. Negri MC, Lipsitch M, Blázquez J et al. Concentration-dependent selection of small phenotypic differences in TEM beta-lactamase-mediated antibiotic resistance. Antimicrob Agents Chemother 2000; 44:2485–91.

75. Fu F, Nowak MA, Bonhoeffer S. Spatial heterogeneity in drug concentrations can facilitate the emergence of resistance to cancer therapy. PLoS Comput Biol 2015; 11:e1004142.

76. Oliver A, Levin BR, Juan C et al. Hypermutation and the preexistence of antibiotic-resistant Pseudomonas aeruginosa mutants: implications for susceptibility testing and treatment of chronic infections. Antimicrob Agents Chemother 2004; 48:4226–33.

77. Cuevas JM, Geller R, Garijo R et al. Extreme high mutation rate of HIV-1 in vivo. PLoS Biol 2015; 13:e1002251.

78. Martinezcorena I, Campbell PJ. Somatic mutation in cancer and normal cells. Science 2015; 349:1483–9.

79. Soderholm AT, Barnett TC, Sweet MJ et al. Group A streptococcal pharyngitis: immune responses involved in bacterial clearance and GAS-associated immunopathologies. J Leukoc Biol 2018; 103:193–213.

80. Sharma SV, Lee DY, Li B et al. A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations. Cell 2010; 141:69–80.

81. Cleviers H. The cancer stem cell: premises, promises and challenges. Nat Med 2011; 17:313–9.

82. Balaban NQ, Merrin J, Chait R et al. Bacterial persistence as a phenotypic switch. Science 2004; 305:1622–5.

83. Stewart PS. Mechanisms of antibiotic resistance in bacterial biofilms. Int J Med Microbiol 2002; 292:107–13.

84. Bjarngadottir T, Alhede M, Alhede M et al. The in vivo biofilm. Trends Microbiol 2013; 21:466–74.

85. Vinay DS, Ryan EP, Pawelec G et al. Natural selection of tumor variants in the generation of “tumor escape” phenotypes. Nat Immunol 2002; 3:999–1005.

86. Veitch CR, Clout MN, Towns DR. Island Invasions: Eradication and Management. Gland, Switzerland: IUCN, 2011.

87. Akhmetzhanov AR, Hochberg ME. Dynamics of preventive vs post-diagnostic cancer control using low-impact measures. Elife 2015; 4:e06266.

88. Trédan O, Galmarini CM, Patel K et al. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007; 99:1441–54.

89. Negri MC, Lipsitch M, Blázquez J et al. Concentration-dependent selection of small phenotypic differences in TEM beta-lactamase-mediated antibiotic resistance. Antimicrob Agents Chemother 2000; 44:2485–91.

90. Fu F, Nowak MA, Bonhoeffer S. Spatial heterogeneity in drug concentrations can facilitate the emergence of resistance to cancer therapy. PLoS Comput Biol 2015; 11:e1004142.

91. Oliver A, Levin BR, Juan C et al. Hypermutation and the preexistence of antibiotic-resistant Pseudomonas aeruginosa mutants: implications for susceptibility testing and treatment of chronic infections. Antimicrob Agents Chemother 2004; 48:4226–33.

92. Cuevas JM, Geller R, Garijo R et al. Extreme high mutation rate of HIV-1 in vivo. PLoS Biol 2015; 13:e1002251.

93. Martinezcorena I, Campbell PJ. Somatic mutation in cancer and normal cells. Science 2015; 349:1483–9.

94. Soderholm AT, Barnett TC, Sweet MJ et al. Group A streptococcal pharyngitis: immune responses involved in bacterial clearance and GAS-associated immunopathologies. J Leukoc Biol 2018; 103:193–213.

95. Fleming A. Penicillin. Nobel Lectures, Physiology or Medicine 1942–1962. Amsterdam, NL: Elsevier Publishing Company, 1964.

96. Pena-Miller R, Laehnemann D, Jansen G et al. From resistance to antibiotic resistance. Nat Rev Microbiol 2004; 2:15964–8.

97. de Roode JC, Culleton R, Bell AS et al. Competitive release of drug resistance following drug treatment of mixed Plasmodium chabaudi infections. Molalar 2004; 3:33.

98. Day T, Huijsken S, Read AF. Is selection relevant in the evolutionary emergence of drug resistance? Trends Microbiol 2015; 23:126–33.

99. Nordström A, Petterson I. Resistance to antibiotics. J Theor Biol 2004; 228:195–208.

100. Hansen E, Woods RJ, Read AF. How to use a chemotherapeutic agent when resistance to it threatens the patient. PLoS Biol 2017; 15:e2001110.

101. Slaten HC, Okell LC, Gharib AN. Mathematical modelling to guide drug development for malaria elimination. Trends Parasitol 2017; 33:175–84.

102. Gelri P, Laxminarayan R, Dunne M et al. “One-size-fits-all”? Optimizing treatment duration for bacterial infections. PLoS One 2012; 7:e29838.

103. Day T, Read AF. Does high-dose antimicrobial chemotherapy prevent the evolution of resistance? PLoS Comput Biol 2016; 12:e1004689.

104. Hartfield M, Alizon S. Within-host stochastic emergence dynamics of immune-escape mutants. PLoS Comput Biol 2015; 11:e1004149.
103. Drlica K, Zhao X. Mutant selection window hypothesis updated. Clin Infect Dis 2007; 44:881–8.

104. Zur Wiesch PA, Kouyos R, Engelstädter J et al. Population biological principles of drug-resistance evolution in infectious diseases. Lancet Infect Dis 2011; 11:236–47.

105. Weiss E, Zahar J-R, Lesprit P et al. Elaboration of a consensus definition of de-escalation allowing a ranking of β-lactams. Clin Microbiol Infect 2015; 21:649.e1–10.

106. Tam VH, Louie A, Deziel MR et al. The relationship between quinolone exposures and resistance amplification is characterized by an inverted U: a new paradigm for optimizing pharmacodynamics to counterselect resistance. Antimicrob Agents Chemother 2007; 51:744–7.

107. Kouyos RD, Metcalf CJE, Birger R et al. The path of least resistance: aggressive or moderate treatment. Proc R Soc B Biol Sci 2014; 281:20140566.

108. Huijben S, Bell AS, Sim DG et al. The population genetics of antibiotic resistance mutations. Antimicrob Agents Chemother 2011; 55:2799–807.

109. MacLean RC, Hall AR, Perron GG et al. The effects of spatial competition constrains resistance to targeted cancer therapy. Nat Commun 2020; 11:3261.

108. Weiss E, Zahar J-R, Lesprit P et al. Elaboration of a consensus definition of de-escalation allowing a ranking of β-lactams. Clin Microbiol Infect 2015; 21:649.e1–10.

111. Bacevic K, Noble R, Soffar A et al. Spatial competition constrains resistance to targeted cancer therapy. Nat Commun 2020; 11:3261.

112. Ternent L, Dyson RJ, Krachler A-M et al. Bacterial fitness shapes the population dynamics of antibiotic-resistant and -susceptible bacteria in a model of combined antibiotic and anti-virulence treatment. J Theor Biol 2015; 372:1–11.

113. Johnson BK, Abramovitch RB. Small molecules that sabotage bacterial virulence. Trends Pharmacol Sci 2017; 38:339–62.

114. Lorz A, Pertheame B, Lorenzi T et al. Population adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies. Esaim Math Model Numér Anal 2013; 47:2013–5.

115. Hughes D, Andersson DI. Evolutionary consequences of drug resistance: a proof of concept. Proc Natl Acad Sci U S A 2015; 112:2059–64.

116. Woods RJ, Read AF. Clinical management of resistance evolution in a bacterial infection. Curr Opin Infect Dis 2016; 29:681–8.

117. Libberton B, Horsburgh MJ, Brockhurst MA. The effects of spatial structure, frequency dependence and resistance evolution on the dynamics of toxin-mediated microbial invasions. Evol Appl 2015; 8:738–50.

118. Bhatt AP, Redinbo MR, Bultman SJ. The role of the microbiome in cancer development and therapy. CA Cancer J Clin 2017; 67:326–44.

119. Roy S, Trinchieri G. Microbiota: a key orchestrator of cancer therapy. Nat Rev Clin Oncol 2014; 11:13774–9.

120. Pirnay J-P, Verbeken G, Rose T et al. Introducing yesterday’s phage therapy in today’s medicine. Future Virol 2012; 7:379–90.

121. Levin BR, Bull JJ. Phage therapy revisited: the population biology of a bacterial infection and its treatment with bacteriophage and antibiotics. Annu Rev Med 1996; 47:881–98.
The disease ecosystem

144. Yosef I, Manor M, Kiro R et al. Temperate and lytic bacteriophages programmed to sensitize and kill antibiotic-resistant bacteria. Proc Natl Acad Sci U S A 2015; 112:7267–72.

145. Twumasi-Boateng K, Pettigrew JL, Kwok YYE et al. Oncolytic viruses as engineering platforms for combination immunotherapy. Nat Rev Cancer 2018; 18:419–32.

146. Kaufman HL, Kohlhapp FJ, Zloza A. Oncolytic viruses: a new class of immunotherapy drugs. Nat Rev Drug Discov 2015; 14:642–62.

147. Pirnay JP, De Vos D, Verbeken G et al. The phage therapy paradigm: prêt-à-porter or sur-mesure? Pharm Res 2011; 28:934–7.

148. Betts A, Kaltz O et al. Back to the future: evolving bacteriophages to increase their effectiveness against the pathogen Pseudomonas aeruginosa PA01. Evol Appl 2013; 6:1054–63.

149. Poullain V, Gandon S, Brockhurst MA et al. The evolution of specificity in evolving and coevolving antagonistic interactions between a bacteria and its phage. Evolution 2008; 62:1–11.

150. Betts A, Kaltz O, Hochberg ME. Contrasted coevolutionary dynamics between a bacterial pathogen and its bacteriophages. Proc Natl Acad Sci U S A 2014; 111:11109–14.

151. Fitzgerald JB, Schoeberl B, Nielsen UB et al. Systems biology and combination therapy in the quest for clinical efficacy. Nat Chem Biol 2006; 2:458–66.

152. Torres-Barceló C, Fransen B, Vasse M et al. Long-term effects of single and combined introductions of antibiotics and bacteriophages on populations of Pseudomonas aeruginosa. Evol Appl 2016; 9:583–95.

153. Goldie JH, Coldman AJ. The genetic origin of drug resistance in neoplasms: implications for systemic therapy. Cancer Res 1984; 44:3643–53.

154. Bozic I, Reiter JG, Allen B et al. Evolutionary dynamics of cancer in response to targeted combination therapy. Elife 2013; 2:e00747.

155. Vanneman M, Dranoff G. Combining immunotherapy and targeted plasms: implications for systemic therapy. Clin Cancer Res 2013; 19:458–68.

156. Elife 2013; 2:e00747.

157. Torres-Barceló C, Arias-Sánchez FI, Vasse M et al. Temporal variation in antibiotic environments slows down resistance evolution in pathogenic Pseudomonas aeruginosa. Evol Appl 2015; 8:945–55.

158. Torres-Barceló C, Arias-Sánchez FI, Vasse M et al. A window of opportunity to control the bacterial pathogen Pseudomonas aeruginosa combining antibiotics and phages. PLoS One 2014; 9:e106628.

159. Barbosa C, Beardmore RE et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res 2006; 12:878–87.

160. Antonia SJ, Mirza N, Fricke I et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Proc Natl Acad Sci U S A 2008; 105:17079–84.

161. Nichol D, Jeavons P, Fletcher AG et al. Steering evolution with sequential therapy to prevent the emergence of bacterial antibiotic resistance. PLoS Comput Biol 2015; 11:e1004493.

162. Chan BK, Sistrom M, Wertz JE et al. Modelling the spatial configuration of heterogeneous environments slows down resistance evolution in pathogenic Pseudomonas aeruginosa. Proc Natl Acad Sci U S A 2015; 112:7267–72.

163. Baym M, Stone LK, Kishony R. Multidrug evolutionary strategies to reverse antibiotic resistance. Science 2016; 351:eaad3529.

164. Rex Consortium. Heterogeneity of selection and the evolution of resistance management. PLoS Comput Biol 2012; 8:e1005745.

165. Roemhild R, Jaspers JE, Kersbergen A et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A 2008; 105:13977–81.

166. Hegreness M, Shores N, Damjan D et al. Accelerated evolution of resistance in multidrug environments. Proc Natl Acad Sci U S A 2008; 105:13977–81.

167. Andersson DI, Hughes D. Evolution of antibiotic resistance at non-lethal drug concentrations. Drug Resist Update 2012; 15:162–72.

168. Rottenberg S, Jaspers JE, Kersbergen A et al. Steering evolution with sequential therapy to prevent the emergence of bacterial antibiotic resistance. PLoS Comput Biol 2015; 11:e1004493.
186. Costello EK, Stagaman K, Dethlefsen L et al. The application of ecological theory toward an understanding of the human microbiome. *Science* 2012; 336:1255–62.

187. Lloyd MC, Cunningham JJ, Bui MM et al. Darwinian dynamics of intratumoral heterogeneity: not solely random mutations but also variable environmental selection forces. *Cancer Res* 2016; 76:3136–44.

188. Vila` M, Espinar JL, Hejda M et al. Ecological impacts of invasive alien plants: a meta-analysis of their effects on species, communities and ecosystems. *Ecol Lett* 2011; 14:702–8.

189. Jacqueline C, Abbate JL, Sorci G et al. The macroecology of cancer incidences in humans is associated with large-scale assemblages of endemic infections. *Infect Genet Evol* 2011; 61:189–96.

190. Dillon SM, Frank DN, Wilson CC. The gut microbiome and HIV-1 pathogenesis: a two-way street. *AIDS* 2016; 30:2737–51.

191. Thomas RM, Jobin C. The microbiome and cancer: is the “oncobiome” mirage real? *Trends Cancer Res* 2015; 1:24–35.

192. Amend SR, Pienta KJ. Ecology meets cancer biology: the cancer swamp promotes the lethal cancer phenotype. *Oncotarget* 2015; 6:9669–78.

193. Waclaw B, Bozic I, Pittman ME et al. A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity. *Nature* 2015; 525:261–4.

194. Anderson ARA, Weaver AM, Cummings PT et al. Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. *Cell* 2006; 127:905–15.

195. Axelrod R, Axelrod DE, Pienta KJ. Evolution of cooperation among tumor cells. *Proc Natl Acad Sci U S A* 2006; 103:13474–9.

196. Lyssiotis CA, Kimmelman AC. Metabolic interactions in the tumor microenvironment. *Trends Cell Biol* 2017; 27:863–75.

197. Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? *Trends Biochem Sci* 2016; 41:211–8.

198. Smallbone K, Gatenby RA, Gillies RJ et al. Metabolic changes during carcinogenesis: potential impact on invasiveness. *J Theor Biol* 2007; 244:703–13.

199. Folkman J. Angiogenesis. *Annu Rev Med* 2006; 57:1–18.

200. Carmona-Fontaine C, Bucci V, Akkari L et al. Emergence of spatial structure in the tumor microenvironment due to the Warburg effect. *Proc Natl Acad Sci U S A* 2013; 110:19402–7.

201. Castillo SPP, Rebolledo R, Arim M et al. The Network Structure of Cancer Ecosystems 2017. *BioRxiv* DOI: 10.1101/240796.

202. Aktipis CA, Boddy AM, Gatenby RA et al. Life history trade-offs in cancer evolution. *Nat Rev Cancer* 2013; 13:883–92.

203. David P, The´bault E, Anneville O et al. Impacts of invasive species on food webs. In: Bohan DA, Dumbrell AJ, Massol F (eds). *Networks of Invasion: A Synthesis of Concepts*, London: Academic Press, 2017, 1–60.