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Designing Antibacterial Nanomaterials Under Evolutionary Constraint

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Abstract The rapid expansion of antibacterial nanomaterials has been driven by the assumption that nanoscale antimicrobials are intrinsically resistant to bacterial adaptation, reinforcing a kill-centric view of antimicrobial efficacy. Accumulating evidence now demonstrates that sublethal and chronic exposure to antibacterial nanomaterials under clinically and environmentally relevant conditions can promote bacterial tolerance, persistence, and adaptive survival. In this Review, we synthesize experimental and conceptual studies showing that conventional evaluation frameworks, particularly minimum inhibitory concentration–based metrics, repeatedly fail to capture these adaptive responses. An argument about antibacterial nanomaterials should be reconceptualized as evolutionary interventions whose long-term performance is governed by the selective pressure landscapes they generate. We outline an adaptation-aware design framework linking nanomaterial properties to exposure dynamics and predictable evolutionary outcomes, and discuss how temporal control, multimodal strategies, and biofilm-informed design can mitigate maladaptive trajectories. Recognizing bacterial adaptation as the rule rather than the exception is essential for developing sustainable nano-enabled antimicrobial strategies. Here, we argue that antibacterial nanomaterials should be understood and evaluated primarily as evolutionary pressure–shaping interventions rather than as resistance-proof bactericidal agents.

Keywords: *Antibacterial nanomaterials, Selective pressure, Bacterial tolerance, Adaptive evolution, Evolution-aware design*

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1. Introduction

Literature search and selection strategy

This review will discuss the specific literature that relates to antibacterial nanomaterials during their evolving and adaptive studies. literature surveys are structured and narrative based. it is capturing literature exemplars, conceptual, and translational studies. We conducted literature searches in the primary science databases, PubMed, Web of Science, and Scopus, and in the main publications from the years 2010 to 2025. We combined searches of nanomaterials and related terms with the counter selective terms. The counter selective terms were bacterial adaptation, selective pressure, tolerance, persistence, and evolutionary dynamics.

Studies were included in the review if they described bacterial responses to nanoparticle exposure in the acute/chronic/sub lethal stages, and provided experimental insight, mechanism details, and/or conceptual frameworks. We included laboratory studies, and studies that are clinically/environmentally oriented to enhance translational scope. Articles that dealt solely with short-term bactericidal activity and failed to consider adaptive / evolutionary processes were excluded. Key articles also served to guide the reference search in the identification of studies that were related and relevant to the scope of the review. The focus was to synthesize disciplines that were related to the topic review, rather than conducting formal systematic or meta-analytic reviews.

Section I. The conceptual failure of kill-centric antibacterial nanomaterials

The assumption that solutions at the nanoscale are less likely to be subject to the effects of bacterial resistance has directed the creation of antibacterial nanomaterials. This assumption originates from the belief that due to the multidimensional mechanisms and diverse chemical and physical properties of nanomaterials that lead to membrane damage, formation of oxidative stress, and disturbance with cell division, there are bacterial defense mechanisms that can be overwhelmed, therefore there is no need for adaptation. Antimicrobial success has also been stated as the short-term death of a bacterial cell, which has led to the belief that the most essential factor in the designing of nanomaterials is the emphasis on the killing of the bacteria [1,2]. This belief is overly simplistic and fails to recognize the complexities of measuring the success of responding to the presence of an antimicrobial agent. In response to the presence of nanomaterials that demonstrate antibacterial properties, a number of easily quantifiable, biotechnologically defined, antimicrobial

endpoints are achieved, such as minimal inhibitory concentration (MIC), zone of inhibitory assays, and a reduction in the number of living cells, which lead to an acute bio response event. These endpoints quantify the presence of an antibacterial response; however, the biological response system has not been developed to respond to the presence of an antimicrobial biotechnological product and the response is an adaptive system that accumulates and evolves over time. This is the reason that a great number of nanomaterials designed to have antibacterial properties may, in biological systems, yield poor results.

A central concept that results in a great deal of confusion is the conflation of the concepts of resistance as opposed to tolerance or persistence. Resistance describes genetic changes that are heritable and that increase the concentration of an antimicrobial that will inhibit the growth of a bacterium. Tolerance describes the ability of a bacterial population to survive short term exposure to antimicrobials without changing the threshold of their susceptibility. Tolerance and persistence describe the survival mechanisms that antimicrobial nanomaterials primarily select for. More specifically, bacterial populations survive the absence of shifts in the minimum inhibitory concentration (MIC) because of persistent exposure to antimicrobial nanomaterials, especially the sublethal persistence exposure [3].

The chemical innovations of the antimicrobial agents themselves do not drive the adaptation. The selective pressures of the chemicals give rise to the adaptations. The exposure of the nanomaterials in the sublethal concentration promotes the activation of a stress response, and the adaptation can take the form of phenotypic plasticity changes. While active stress responses and phenotypic plasticity are encouraged, the adaptations can remain dormant until pushed to the forefront. There is a body of literature documenting these dynamics for innumerable antimicrobial formulations [4,5,6]. The inadequate performance of nanomaterials should not simply be attributed to a lack of ingenuity in the design of nanomaterials. There are a mismatch of antimicrobial design and the expectations of the innovation. More often than not, the expectations of the innovations are not aligned to the innovations.

The current strategy in design and evaluation may overestimate therapeutic durability while underestimating long-term adaptive consequences by prioritizing immediate killing and neglecting adaptive and evolutionary outcomes. Considering antibacterial nanomaterials from the viewpoint of eco-evolutionary engagement, where selective pressures are designed, limited, and assessed, allows for sustainable antimicrobial development to be more realistically framed [7].

Section II Mapping antibacterial mechanisms through selective pressure

Antibacterial nanomaterials have unique certain physicochemical properties and ways of inflicting microbial damage, such as disrupting membranes, creating oxidative stress, and interfering with intracellular functions. Despite helping to optimize materials and assess them relative to each other, these classifications have provided little in the way of understanding the long-term biological and evolutionary impacts of the materials. Antibacterial properties of materials do not work independently of one another. Rather, they determine the type of selective pressure, how much of it, and for how long, it will be inflicted on microbial populations. Because of this, it is useful and necessary to consider the range of antibacterial properties as selective pressure in order to forecast evolutionary adaptive and translational reliable potential, [5].

Table 1. Conceptual distinctions between resistance, tolerance, and persistence under nanoparticle exposure

Concept	Definition	Detectable by MIC?	Dominant under nanomaterials?	Evolutionary risk
Resistance	Heritable genetic increase in MIC	Yes	Occasional	High (genetic fixation)
Tolerance	Survival without MIC shift	No	Predominant	High (selection precursor)
Persistence	Survival of phenotypic subpopulations	No	Frequent	Very high (evolutionary reservoir)

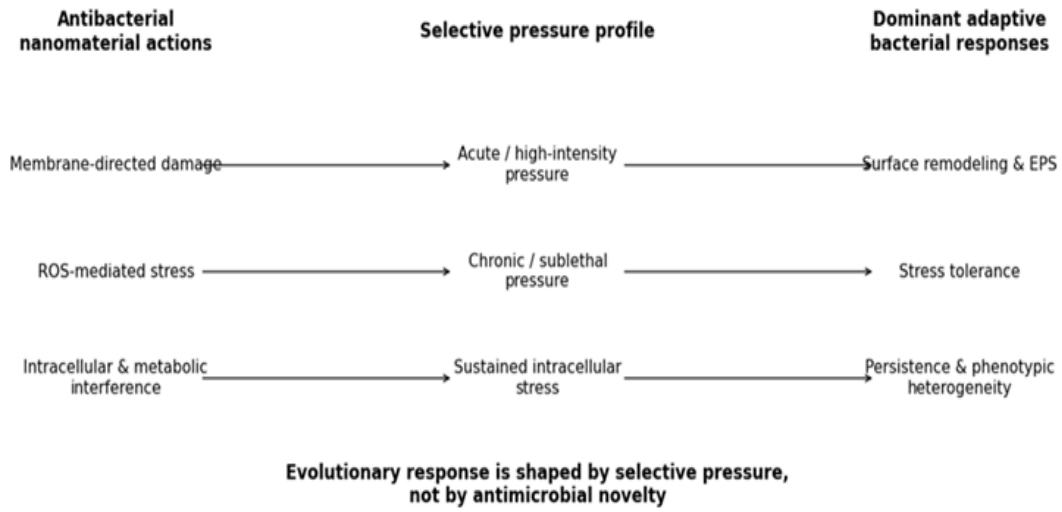


Figure 1. Selective pressure mapping of antibacterial nanomaterial mechanisms

Membrane-directed damage as acute selective pressure

Direct contact with the cell envelope of bacteria is responsible for the antibacterial activity of many kinds of metallic and metal oxide and carbon-based nanomaterials. Membrane rupture, electrostatic destabilization, pore formation, and lipid peroxidation are processes that contribute to a swift loss of membrane integrity. Mechanisms that impact the basal cell wall of bacteria are often viewed as positive because they are likely to circumvent classical resistance pathways that are target specific [2,8]. On the other hand, from the perspective of selective pressure, the destructive effect that the membrane is likely to cause is a high magnitude of stress that is non-specific in nature.

Studies have shown that bacterial phenotypes that are less than optimal are likely to be produced as a result of membrane disruptive nanomaterials. These phenotypes are likely to have altered surface charge, a modified membrane structure, or a greater production of extracellular polymeric substances, which together lower the level of binding of nanomaterials and of damage Panáček et al., (2018); [9,10]. In biofilms and other organized systems, the matrix that is produced externally provides greater resistance to the structural elements of nanomaterials and creates a gradient of exposure to nanomaterials that fosters the biofilm population to use cooperative survival mechanisms [11,12,13]. Thus, while in planktonic phenotypes damage to the membrane causes rapid killing, it also promotes the emergence of surface-protecting phenotypes and community level defensive traits.

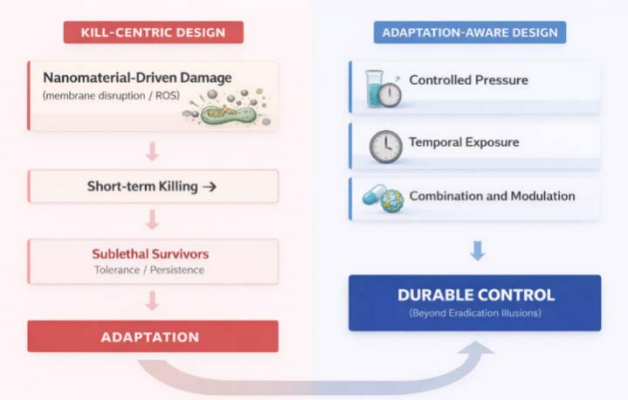


Figure 2. Kill-centric versus adaptation-aware antibacterial nanomaterial design

Oxidative stress–mediated killing as chronic selective pressure

Metal and metal oxide nanoparticles are known for their antibacterial properties, and the production of reactive oxygen species (ROS) is often referred to as one of the main contributors to their antibacterial properties. Nanomaterials, such as zinc oxide and silver, cause macromolecular damage and metabolic disruption by oxidative stress through surface-catalyzed reactions, ion release, and/or intracellular redox imbalance [14] Wahab et al.,(2023). In complex biological surroundings, the impacts of ROS are often sublethal and persistent, as opposed to the immediacy of lethality associated with direct membrane rupture.

Chronic oxidative stress, viewed through a selective-pressure lens, encourages the more rapid activation of antioxidant defenses, stress-response regulons, and metabolic reprogramming, as opposed to rapid cell death. In the absence of measurable shifts in the minimum inhibitory concentration (MIC), repeated-exposure studies have demonstrated increased cross-tolerance, microparticle oxidative sustained stress, and even cross-tolerance to structurally unrelated antimicrobials [3,15,16]. These adaptations create a new set of survival dynamics, and, in the absence of the classical traits of resistance, they erode the long-term therapeutic effectiveness of the antimicrobial agents available.

Intracellular and metabolic interference as sustained selective pressure

As established, certain nanomaterials exhibiting antibacterial behavior penetrate bacterial cells and disrupt intracellular processes such as enzymatic, ribosomal, and metabolic activity. There are also some systems for the delivery of nanoparticles designed to target the intracellular accumulation of antibiotics, particularly those intended for use against multidrug-resistant pathogens [17,18]. Such methods may enhance short-term efficacy, but the phenomenon of incomplete clearance often leads to sustained intracellular selective pressure.

Adaptations to intracellular persistence such as the activation of efflux, metabolic downregulation, and the shift to tolerant or persistent states [19,20]. Responses of this kind are often pleiotropic, acting beyond the immediate stressor, and creating a wider tolerance ‘hold’ that further impacts and diminishes explicit antimicrobial activity.

From mechanistic action to evolutionary consequence

The differing mechanisms of antibacterials operate at different cellular targets and different levels of selection pressure that they impose. Acute, high, and intense selective pressure result in rapid population bottlenecks and the selection of traits that protect the surface, while chronic, sustained, and sublethal pressures lead to flexible, and stress tolerant, and diversely phenotypically differentiated populations. The inability to distinguish between these selective pressures has resulted in the overestimation of the robustness of nanomaterials and the underestimation of the adaptive risk [7,21].

The antibacterial mechanisms in the context of selective pressure opens up a pathway that integrates the three disparate fields of material science, microbial response, and the intended/ unintended evolutionary impact of the engineered materials. This approach does not overlook the importance of mechanistic understanding, but rather places it in an adaptive framework, which allows for it to be optimized in the design of antibacterial nanomaterials to limit microbial evolution rather than just extending short-term killing.

Section III Bacterial adaptation to nanoparticles: evidence, trajectories, and recurring patterns

Many initial hypotheses believed that the antibacterial nanomaterials have antimicrobial activity that is impossible to evolve around. More recent experimental studies have shown that vast populations of bacteria can stress, adapt, and reproduce, in some situations even quickly, to the effects of nanoparticles. Most importantly, these adaptive responses have been documented outside of lab-based studies. They have been noted in many different

bacterial populations, various classes of nanoparticles, and different exposure situations. These studies, in totality, address the basic premise of assuming nanoscale antimicrobials are immune to selective pressure. Rather, most of these adaptive responses can be attributed to the chronic exposure to the specific nanoparticles.

Experimental evidence for adaptive responses to metallic nanoparticles

Silver nanoparticles are among the first and most widely researched antibacterial nanomaterials. An important example is the study by Graves et al. [22]. These researchers exposed Escherichia coli populations to silver nanoparticles and noted rapid evolution of the bacteria leading to the development of decreased susceptibility. This was done through successive transfer experiments and the resultant phenotypic changes were both stable and heritable. Notably, these changes remained after the exposure to silver nanoparticles ended. This study provides proof of the evolutionary changes, as opposed to the physiological responses that are generally temporary, which are possible due to the stresses associated with silver nanoparticles.

McNeilly et al. [9] encountered similar adaptive responses in Acinetobacter baumannii after repeated exposures to the silver nanoparticles. The authors noted the adaptive responses during their study and raised a valid concern on the extensive use of silver-based nanomaterials in hospitals. Likewise, Panáček et al., (2018) found both phenotypic and genetic factors to reduced susceptibility during exposure to nanoparticles. This study contradicts the belief that there is antimicrobial activity that is resistant to counteraction.

Other than adaptive responses, the use of nanoparticles has also raised concern due to adaptive responses other than silver-based systems. Zinc oxide nanoparticles caused physiological and regulatory changes in Bacillus cereus which induced changes in survival; however, these changes did not result in elevated MIC value increases [15]. Similar adaptive behavior has been documented with titanium dioxide and other metal oxide nanoparticles suggesting that adaptive potential is a cross-nanomaterial phenomenon driven by selective pressure, and not chemistry [3,23].

Sublethal exposure and tolerance-dominated adaptation

Adaptation studies have noted the importance of sublethal exposure. Failure to select for classical resistance occurs due to prolonged exposure at low or sub-inhibitory levels of nanoparticles. Exposure to hyperosmotic stress generated by Zhang et al. [16] nanoparticles activated some previously described conserved pathways of tolerance. This activated some pathways of tolerance that permitted the bacterial populations to survive successive antimicrobial stressors without a change in the minimal inhibitory concentration (MIC).

Stressing of surviving bacterial populations is consistent within the field of evolutionary biology. This is an example of surviving and subsequently enabling the fixation of a resistive. Importantly, there is a disconnect between standard antimicrobial susceptibility testing (AST) and the long-duration antimicrobial treatment outcomes. This disconnect is due to tolerance and persistence. Even in the absence of true resistance, Zenel et al., (2016) highlight the importance of tolerance, especially for environmental nanoparticles, in low, clinically realistic concentrations.

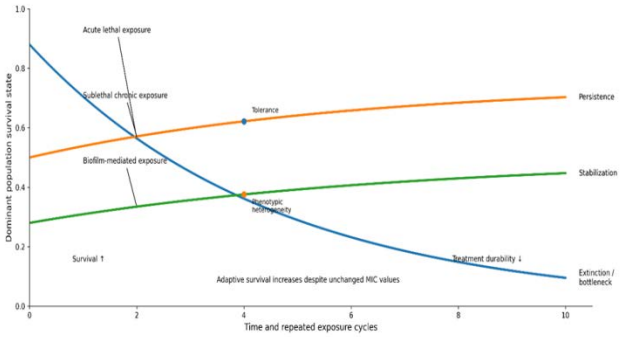


Figure 3. Adaptive trajectories under nanoparticle exposure

The exposure to nanoparticles typically spurs a sequence of phenomena: from an initial stress response to tolerance, followed by persistence, with resistance developing only in certain instances. Conventional MIC-based assays overlook adaptive stages that are essential for the long-term trajectory of the response.

Biofilms as amplifiers of adaptive pressure

The communities found within biofilms present optimal environments for the adaptation of driven nanoparticles. Diversity in the chemical and structural components of biofilms creates concentration gradients of nanoparticles. In turn, this situates different subpopulations of biofilm bacteria in environments which expose them to a continuum of sublethal stresses. ikuma et al. [11] showed that, due to the limitations of matrix diffusion and binding, the interaction of nanoparticles and biofilms can be managed to prolong exposure while reducing the acute toxicity.

The biofilm communicates adaptive responses amongst the various bacterial subpopulations within the biofilm through collective defense, metabolic cooperation, and horizontal gene transfer. Truu et al. [24] showed that, even in environmental and engineered systems, biofilms exposed to driven nanoparticles change their community composition and enrich genes of resistance. This consistent evidence shows that biofilm analyses characterize the strength of tolerance, phenotypic, collective, and heterogenic as the most dominant survival strategies in antimicrobial pressure [12,13,25].

Environmental and translational relevance of adaptation

Not even the more controlled aspects of laboratory environments can contain the stress tolerance adaptations of bacteria to nanoparticles. Consider the environmental exposure scenarios that contribute to coatings of medical devices, consumer products, and even certain elements of wastewater treatment systems. Encountering nanoparticles for the first time can alter the composition of microbial communities during low, chronic exposures and even wastewater systems [24,26]. In particular, the study demonstrated that silver nanoparticles in hybrid wastewater systems could alter microbial community compositions and increase the incidence of certain resistance genes.

The more practical aspects of these findings also make clear that how antibacterial nanomaterials are assessed and how they are actually used in practice are misaligned. For

antibacterial nanomaterials to continuously perform antibacterial functions, it is assumed that the adaptive responses of the target microbes are, or will be, limited. In fact, more and more studies are producing evidence to support the opposite [2,21,27]. In the absence of adaptive responses, the long-term efficacy of antibacterial nano technologies is overstated.

Converging patterns across studies

Regardless of the experimental design, the composition of the nanomaterials, or which organisms are targeted, studies on adaptation show a number of converging patterns. The first is that, irrespective of the parameters of the study, the chronic/sublethal exposures give rise to a tolerance dominated survival strategy. The second is that early adaptive responses are primarily regulatory / physiological with little or no genetic changes. The third is that biofilms and other complex microbial systems are reservoirs that reinforce and accentuate adaptive responses. The fourth is that the use of antimicrobial activity assessment techniques hides all these adaptive processes and leads to an over-simplified assumption of the microbial communities in question, which, in turn, gives the impression of a larger adaptive capacity than is present.

The adaptive capacity of all the microbial communities/agents exposed to nanomaterials is, in fact, demonstrated by the patterns above. Since chronic exposure to antimicrobial nanomaterials will undoubtedly give rise to microbial adaptation, we must take this fact into consideration in redesigning the systems antimicrobial nanomaterials are deployed in, and in determining what the objectives of the antimicrobial nanomaterials are.

Section IV Why current evaluation models mislead translation

The existing evaluation criteria in the field of antibacterial nanomaterials continue to be rooted in short-term, inhibition-centric criteria that ignore biological realities and the phenomena of evolvability of the given biological systems. The existing criteria serve as standard metrics, allowing comparison of different systems, but fail to incorporate the various types of adaptive responses that can occur under continuous or sublethal selective pressure. This results in the models fundamentally underestimating the therapeutic timescales and mischaracterizing the long-term antimicrobial activities of the technologies being evaluated.

MIC-centric limitations

The minimum inhibitory concentration, or MIC, reflects the antimicrobial activity of a given treatment as the lowest concentration capable of inhibiting visible bacterial growth, under defined laboratory conditions. While the comparison of different technologies using MIC values can be helpful, MIC values alone oversimplify the phenomena of antimicrobial action and subsequently provide a severe scope of information, or lack thereof. They do not distinguish the extent of cell killing (if any), nor do they assess the presence or absence of subpopulations within the cell population and the phenomena of recovery, which can occur even after the exposure of the population to a therapeutic agent, nor do they assess the adaptive responses which may occur during repeat or prolonged exposure to the treatment. Most notably, MIC assays fail to assess the phenomena of tolerance and persistence which are increasingly recognized as dominant survival strategies under nanoparticle-mediated stress [19].

Consequently, MIC values alone provide a poor standard for assessing antimicrobial activity and can lead to mischaracterizations of the antimicrobial activity of the treatment being evaluated. In the near term, new nanoparticle formulations that appear effective based on MIC may primarily promote the selection of tolerant, or slowly growing, subpopulations, fostering sustained effectiveness illusions while posing long-term adaptive risks. Antimicrobial agents with the same MIC values produce different time-kill profiles, adaptive trajectories, and therapeutic outcomes. This phenomenon has been documented [28]. This phenomenon is particularly documented in the field of antibacterial nanomaterials evidence where the patterns of exposure, persistence, and the physicochemical alterations of nanomaterials led to the microbial response of the materials [7].

Clinical Misinterpretation and Translational Bias

MIC-centered evaluations even in the design of the experiments have some limitations for the clinical interpretations. MIC values are often viewed as black and white definitions of susceptibility or resistance at the expense of the complexities embedded in the pharmacodynamics of the materials, the varying levels of exposure, and the atypical intertwined antimicrobial mechanisms. Some clinical pathways recognize that the MIC must not be used in isolation to steer effective therapy [29]; nonetheless, the overreliance on the MIC is the most prominent source of translational bias, especially in situations characterized by temporal concentration gradients of the drug, patterned microbial populations, or infection structures, such as in biofilms (Tamura et al., 2025).

Furthermore, antibacterial nanomaterials are still evaluated experimentally in simplified in vitro models where, for example, static cultures, short exposure times, and artificial media formulations dominate. These explanations focus on the simplistic integration of antimicrobial sensitivity. They also neglect the integration of biological and biochemical phenomena such as the binding of proteins, extracellular matrices, and resorption and elution gradients. Thus, these types of models are functionally incapable of predicting the in vivo behavior and adaptability of the systems in question.

The disconnect between *in vitro* and *in vivo* and realism of exposure

The differences between the in vitro efficacies and the *in vivo* outcomes are among the more significant challenges of the field of nanomedicine. The formation of a protein corona around the surface of the nanoparticles, which has been shown to change the cellular uptake, toxicity, and antimicrobial effectiveness of the nanoparticles, is one of the more documented phenomena that is often overlooked in standard susceptibility testing [30]. Moreover, along with biodegradation, nanomaterials will encounter a host of physicochemical changes that will alter their environmental exposure and change the selective pressure that they will exert [31].

Environmental exposure also complicates the assessment of the effectiveness of nanomedicine. Medical devices, consumer products, and wastewater treatment systems are all sources of nanoparticles that pose

potentially hazardous exposure, but are often experienced at low and variable concentrations over long periods of time. Under these conditions, the selective pressure that is exerted is more adaptive survival than rapid lethality.

Studies have shown that even when there is no evident toxicity, persistent exposure to nanoparticles can cause changes in the composition of microbial communities and increase the number of resistance-related genes. This shows the need to reevaluate the long-term risks of nanoparticle exposure, as current evaluations rely on acute toxicity [24,32].

Towards evaluation frameworks that incorporate adaptive awareness

These issues point out an evident gap in the evaluation frameworks and the adaptive feedback system that modulates the response of microbial community to the use of antibacterial nano materials. Most frameworks that incorporate the concept of growth inhibition ignore the fact that the system displays tolerance, persistence, and evolutionary change in the long run. As a result, they falsely conflate adaptive survival as success from a therapeutic point of view.

Closing this gap involves the use of evaluation frameworks that factor in the possibility of biofilm formation and sustained selective pressure. Time-resolved killing assays, laboratory evolution or passaging experiments, and systems that incorporate biofilms and repeated exposures provide a better understanding of selective microbe systems. These models are more representative of the real-world exposures and provide better predictive frameworks for behavioral and adaptive changes [6].

It is critical to clarify that evaluating adaptive outcomes does not undermine the importance of traditional susceptibility testing. Rather, it incorporates an evolutionary perspective on these methodologies, thus elucidating their limitations and contextualizing the domains of their appropriate application. Without this shift in perspective, the advancements in the development of antibacterial nanomaterials are likely to result in the same failures that have historically plagued the development of novel antimicrobials.

Section V Design principles for adaptation-aware antibacterial nanomaterials

Understanding bacterial adaptation as a reasonable response to continued selective pressure requires a deep change in the conceptual approach to the design of antibacterial nanomaterials. Instead of focusing on the short-term lethality of antibacterial nanomaterials and placing an emphasis on the pressure (i.e. lethality) in a short time, an adaptation aware approach suggests modulation of selective pressure (i.e. biological targeting) to promote and sustain susceptibility (or lack of responsive adaptation) in microbes over time. This also reframes the perspective of nanomaterials so that they are not viewed as 'kill all' agents that are impervious to resistance, but rather as facilitators of evolutionary control in microbes.

Conventional kill-centric designs focus on speed for the bactericidal mechanisms and MIC-based readouts while ignoring the selective pressure landscapes formed by sublethal exposure, extended timeframes, biofilm buffering, and environmental persistence. On the other hand, the adaptation-aware frameworks combine pressure modulation, temporal control, multifaceted approaches, and biofilm-inclusive consideration to evolutionary pressure to harmonize nanomaterial design with evolutionary principles.

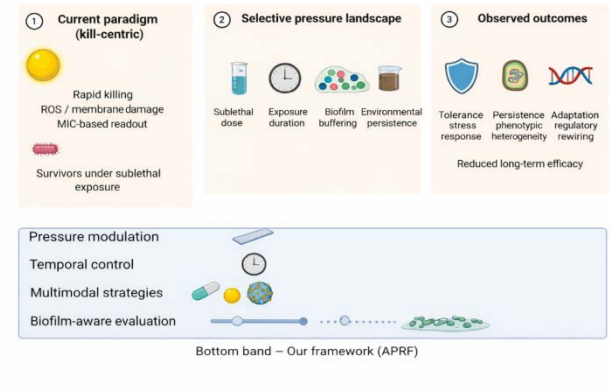


Figure 4. From kill-centric evaluation to adaptation-aware pressure regulation

Multimodal and combination strategies to diffuse selective pressure

Perhaps one of the best ways to limit adaptive escape is the use of multimodal systems that target different forms of biological mechanisms. Nano-antimicrobial combinations, such as the co-delivery of nanoparticles with antibiotics, enzymes, or adjuvants, will most likely reduce the chances of one adaptive response achieving the survival advantage Ribeiro et al.,(2022); Leon-Buitimea et al., (2022). Because of the involvement of multiple cell mechanisms, the response to selection is likely to be evolutionary and dominant to tolerance adaptation.

Combination systems also limit the extent of chronic sublethal exposure. Nanoparticles that serve as temporary delivery systems can create a localized and time-limited antimicrobial effect that promotes rapid clearance and stress, which is most aligned with a short-term evolutionary containment [18,17,33]. Stand-alone nanoparticle formulations, however, with a longer persistence in the tissue or the environment, are at a higher risk of sustaining little tissue damage selective pressure that promotes adaptive remodeling over time.

Dynamic and stimuli-responsive delivery systems

Static exposure profiling is the primary cause of tolerance and persistence. The latest developments in the field of stimuli-responsive nanomaterials may be able to temporally coordinate the antimicrobial functions of nanomaterials with the specific infection markers. These markers may include pH, specific degradative enzymes, or pathogen-related by-products [1,8]. These types of systems will remain functionally inactive under non-infected condition and will only be activated in the presence of bacteria. This case is especially applicable to infections with intermitting and uneven bacterial distribution in the microenvironment. From every evolutionary angle, staying in continuous in contact with an infection is redundant and counterproductive. Responding systems effectively reduce and avoid the circumstances leading to migratory bacterial infection. Although lethally effective, the systems may prolong the period of adaptive response development [5].

Targeting collective and structural defenses

Tolerance, phenotypic diversification, and evolutionary experimentation act as defense mechanisms of biofilms that must also be handled by adaptation-aware design. When engineered to remove and alter biofilm structures and polymeric substances, as well as to disrupt quorum sensing, nanomaterials may reduce structural protection and also rely less on increased chemical stress [11,12,34].

The latest hybrid approaches are the first to address the interleaving of evolution, structural, and selective pressure with nanomaterials. Along with antibiofilm properties, the bacteriophages and nanoparticles act as selective pressure for the surrounding microbes. The phage-nanoparticle system has been shown to provide effective biofilm penetration and reduce biofilm, with specificity and marginal selective pressure on surrounding microbes Szymczak et al., (2024).

Integrating evolutionary and environmental considerations into design

Adaptation-aware nanomaterials need to consider the broadest possible implications of the nanomaterials they design. The nanoparticles will, without fail, interact with nontarget microbial communities when they enter clinical, industrial, or environmental applications. Exposure, even at low levels, creates a selective pressure. Microbial community structure is altered through chronic exposure to nanoparticles. Microbial communities can be enriched for genes associated with resistance. This is critical for the design of nanoparticles to have the least possible impact [24,26,32].

Chronic exposure is closely associated with adaptive risks and incorporates the evolutionary design parameter. From a design perspective, controllable persistence, degradability, and targeted delivery should be regarded as primary design features. In the context of evolutionary risk management, these features align the duration of the material with its therapeutic purpose and mitigate prolonged exposure [31].

From killing efficiency to evolutionary stewardship

These principles collectively represent a shift in policy from the maximization of bactericidal efficacy towards evolutionary stewardship of human-associated microbial ecosystems. Receptive to adaptation, durable control requires more, not less, antimicrobial ambition, focused as it must be on selective pressure. Addressing this gap, we discuss how an appropriate combination of strategic multimodality, dynamic responsiveness, anatomical targeting, and contextual realism among antibacterial nanomaterials would harmonize short-term therapeutic advantage with long-term sustainability.

Nanotechnology is not free from evolutionary constraints but a distinctive tool for bringing those constraints to bear. Longevity of nano-antimicrobials will no longer rely on rate of kill as much as it will on the precision of driving microbial evolution to human-beneficial, enduring fates.

Operational and regulatory implications of adaptation-aware frameworks

There is a need for a change in antibacterial nanomaterials evaluation when translating adaptive-aware design principles to practice. Preclinical and regulatory assessments need to be adapted. Current evaluations which are based on a single measure of potency, e.g., MIC, can be supplemented by evaluations which take adaptive criteria into account considering exposure to repeated, prolonged, and sublethal levels. More accurate assessments may be obtained through the addition of time-resolved killing kinetics, repeated exposure, biofilm testing, and tolerance assessments.

Table 2. Design features of antibacterial nanomaterials and their associated adaptive outcomes

Design feature	Exposure profile	Selective pressure	Associated adaptive outcome
Persistent metallic nanoparticles	Chronic	Sustained	Tolerance-dominated survival
Stimuli-responsive nanoparticles	Transient	Pulsed	Rapid clearance (limited adaptation)
Combination-based systems	Distributed	Diffuse	Diffuse adaptive pressure
Biofilm-disruptive nanoparticles	Structural	Collective	Enhanced susceptibility

From a regulatory point of view, these assessments may not need to be framed as the abandonment of the current testing standards, but rather standards framed in an evolutionary context. Adaptive-aware testing means that for certain nanomaterials and in specified applications, diminishing use and ephemeral exposure tests may provide added value. With adaptive-aware criteria, regulatory assessments may become more descriptive and aligned to anticipate the testing conditions, thereby reducing the bias attributed to the laboratory conditions and the adaptive responses. In adaptation-aware evaluations, the focus rather than bacterial suppression, is on biofilm and bacterial persistence, leading to more durable infections. More adaptive, sustainable use of antibacterial nanomaterials is achieved under these frameworks.

Section VI Future applications under adaptation-aware constraints

Antibacterial nanomaterials may have future applications, but these too must be assessed and deployed with the full understanding that, given sustained selective pressure, bacteria will adapt. Instead of discarding nano-enabled approaches, an adaptation-aware framework sharpens their use domain by identifying situations where nanomaterials provide a distinct advantage and the evolutionary costs are low. Such a perspective retains the benefits of nanotechnology, while confining its application to a biophysically realistic realm of potential application.

Biofilm-associated infections as conditional targets

Infectious diseases related to biofilms are characterized by a unique set of challenges. These challenges stem from the biofilms' intrinsic tolerance, spatial heterogeneity, and mechanisms of collective defense. Nanomaterials are widely perceived to address these challenges, but overcoming these challenges using nanomaterials requires a careful and contextual alignment of mechanisms and intended outcomes. Within this scenario, nanomaterials are most suitably positioned as structural or ecological modifiers, rather than primary bactericidal agents.

In the disruption of biofilm organization by the weakening of collective defense mechanisms, no uniform selective pressure is imposed across the population [11,12]. Strategies such as disruption of extracellular polymeric

substances, interference with adhesion, and enhancement of antimicrobial penetration, serve as biofilm-architecture weakening. These strategies are not substitutes but, rather, are sensitizers. There is less of a need for prolonged exposure to nanoparticles with such an approach, and as a result the risk of adaptive escalation is limited [25,35]. In this case, nanomaterials serve as discrete temporary enablers rather than continuous selective agents.

Combination and adjunctive therapies

The supplementary use of nanomaterials and traditional or biological antimicrobials is an evolutionarily defensible application. With nanomaterials, drug entrapment, and intracellular delivery can be combined with the disruption of protective niches which promote re-sensitization to agents compromised by resistance [17,18]. When used together, multiple antagonistic mechanisms diminish selective pressure and with that the possibility of convergent adaptation.

Constructs of phages and nanomaterials illustrate this ideal. Phage-nanoparticle constructs integrate biological selectivity and the capacity of nano materials to penetrate the cell to achieve selective pressure of varying mechanisms and pos from position. This is ideal in the case of chronic or persistent infections where the use of repeated cycles of monotherapy has failed Szymczak et al., (2024).

Diagnostics, sensing, and non-lethal interventions

Applications that separate therapeutic benefit from microbial killing have great evolutionary potential. Nano-enabled biosensors and diagnostics are able to detect pathogens, profile resistance, and monitor treatment in real time without being a selective pressure on microbes [36] Daramola et al., (2022); [37]. The reduction of antimicrobial misuses through increased diagnostic technology improves antimicrobial resistance. Misuse of antimicrobials is a principal factor in resistance development [6].

The same is true with non-lethal strategies, whether quorum sensing interference, immune modulation, or CRISPR-based soft killing of resistance and virulence factors—these all are within the adaptation-aware constraints as they lose pathological function but not survive. While many of these strategies are still in the developmental phases, they focus therapeutic goals not on eradication but on evolutionary containment, thus being a valuable adjunct to traditional antimicrobial strategies Saffari Natanzi et al., (2025).

Environmental and infrastructure-related applications

Even though many have been proposed for clinical use, the non-clinical use of nanomaterials in surfaces, coatings, and infrastructural development would associate the highest adaptive risk due to the potentially chronic and low-level exposure they would create in microbial environments. Further, environmental studies show that the release of nanoparticles into wastewater and natural systems can alter the community structure and load the genes associated with resistance even in the absence of visible toxicity [24,26,32].

Therefore, these non-clinical applications in the future should focus on persistence control, reduced bioavailability and ecological footprint. Design paradigms that focus on degradability, confinement, and target specificity are crucial to avoiding diffuse selective landscapes that would undermine antimicrobial stewardship [31].

Defining appropriate use boundaries

Thus, an underlying premise of adaptable frameworks is that not all antimicrobial challenges merit a nano-enabled solution. Short-term intervention with nanomaterials may be advantageous for the treatment of more acute, localized infections with clear-cut clearance endpoints, and chronic, low-grade infections and diffuse environmental exposures would require a different strategy. Setting these kinds of limits is vital to maintaining the value of antibacterial nano materials in the long run.

Aligned with an evolutionary realistic perspective, nanotechnology and antimicrobial stewardship need not be mutually exclusive. The case of antibacterial nanomaterials shows that the future of these materials will be crucially dependent on the mode of administration as well as their design — namely, selectively and ethically employed.

Section VIII A research agenda for adaptation-aware antibacterial nanomaterials

The compiled data in this document leads to a singular conclusion: After a period of consistent selective pressure, bacterial adaptation to antibacterial nanomaterials will happen, and is an expected biological response. Future advancements in antibacterial nanotechnology will not be characterized by the pursuit of materials that do not allow bacterial resistance. Rather, future advancements will be dictated by the intentional creation of antibacterial nanotechnology that will respond to, and limit, the bacterial adaptive response. To accomplish this, evolutionary principles need to be incorporated into the design of antibacterial nanomaterials. Evolutionary principles need to be integrated at the crossroads of materials science, microbiology, evolutionary biology, and regulatory science.

Integrating evolution into early-stage design

Integrating principles of evolution after the failure of an antimicrobial is not only inefficient, it is poor design thinking. Evolutionary dynamics need to be incorporated into nanomaterials design from the very beginning. Preclinical frameworks should be designed to incorporate controlled lab evolution experiments, models that simulate repeated bacterial exposure, and tolerant bacterial population assessments to mitigate adaptive risk and downstream translational failure [5,6,19]. This change enables the evaluation of antibacterial nanomaterials to shift towards an understanding of bacterial populations that are heterogeneous and capable of adaptive change.

There remain definitions to complete in regard to systems that describe the interaction of the physiology of the microbes and the physicochemical characteristics of the nanomaterials, although selective landscapes in such systems have begun to be defined Suchánková et al., (2026), more documentation warranted.

Moving Beyond Lethal Paradigms

A second priority involves moving beyond kill-centric paradigms in antibacterial research. Strategies aimed at modulating virulence, biofilm disassembling, metabolic state alteration, or host–pathogen interplay could be therapeutically beneficial while exerting less selective pressure than complete elimination [25,35]. Because of its spatio-temporal control of mechanisms, nanotechnology

can be used to implement such approaches.

The evaluation of these more sophisticated approaches will require a change in metrics, concentrating on the clinically relevant parameters in the infection rather than on less important, short-term bacterial load declines in order to achieve infection resolution and infection control. This change is in alignment with the principles of antimicrobial stewardship and addresses the clinically persistent disconnect between success and efficacy in the laboratory.

Convergence of nanotechnology and biological control

The fusion of nanomaterials and biological control agents is one of the most rapidly developing fields of study. Szymczak et al. (2024) and Saffari Natanzi et al. (2025) discuss hybrid systems with biologicals (e.g., bacteriophages, biological control agents, modulators of the immune system, CRISPR, etc.), which utilize biological specificity and are less likely to experience adaptive escape. Progress in this field will not stem solely from increasing levels of technological sophistication, but rather from the understanding of which complementing mechanisms interact to the constrain adaptive escape. The empirical evidence that remains in the field will likely be one of the more compelling explanations for the irrational barrier that remains to be overcome in the field within the material-biological systems Xie et al., (2025).

Long-term perspective and stewardship-driven research

Lastly, adaptive research must consider a longer time horizon in which antimicrobial durability is prioritized, and this must be within the context of stewardship whereby the frameworks begin to merge design, evaluation, governance, and deployment. If research is to be effective, the principles of stewardship must be incorporated, and in addition to the therapeutic end-point, the duration of exposure, the persistence of the materials in the environment, and the ecological impact (intended or otherwise) must be monitored [26].

When integrating evolutionary realism into research agendas, one may develop approaches that move beyond reactive responses to resistance toward proactive management of selective pressure. Within this context, antibacterial nanomaterials are not placed as definitive solutions to antimicrobial resistance, but as powerful means, whose long-term efficacy will be determined by the design, testing, and application, in all its dimensions, of these nanomaterials.

2. Conclusion

Antibacterial nanomaterials can promote tolerance and persistence in bacteria and, survival adaptations, particularly in cases of sub-lethal or chronic exposure, where changes in bacteria themselves can promote survival. To conventionally attribute an antimicrobial or persistent action to these nanomaterials is a mischaracterization considering their broad and corrective potential. If antibacterials of nanoscale are reframed to serve in the primary function to politically, and socially, alter the evolution of resistances to antimicrobial agents, that is, from injustices of killing to control the resistance from sub-lethal exposure, they then gain a function that is far broader than control of death at levels that are unacceptable in social justice terms. Moving away from short-term lethal targets to alter the selective pressures enabling the evolution of resistance is the paradigmatic shift needed to achieve real, world sustainable antimicrobial control. The recognition of targeted selective pressures and the biological context is of vital importance. Predicting bacterial adaptation and applying resistance to justify lethal targets are paradigmatic shifts needed to achieve world sustainable control. Failure to account for adaptation is not a technical oversight but a conceptual error that has shaped an entire generation of antibacterial nanomaterial research. Without reframing design and evaluation around evolutionary dynamics, improvements in material chemistry alone will not translate into durable antimicrobial control.

References

[1] Huh, A. J. & Kwon, Y. J. (2011). Nanoantibiotics: A new paradigm for infectious disease treatment. *Journal of Controlled Release* **156**, 128–145.

[2] Gupta, A. *et al.* (2019). Combatting antibiotic-resistant bacteria using nanomaterials. *Chemical Society Reviews* **48**, 415–427.

[3] Kamat, S. & Kumari, M. (2023). Emergence of microbial resistance against nanoparticles: Mechanisms and strategies. *Frontiers in Microbiology* **14**, 1102615.

[4] Harada, K. & Asai, T. (2010). Selective pressure and antimicrobial resistance prevalence. *Journal of Biomedicine and Biotechnology* **2010**, 180682.

[5] Maeda, T. & Furusawa, C. (2024). Laboratory evolution of antimicrobial resistance in bacteria to develop rational treatment strategies. *Antibiotics* **13**, 94.

[6] Souque, C., González Ojeda, I. & Baym, M. (2024). Evolutionary mechanisms driving antimicrobial resistance. *Annual Review of Microbiology* **78**, 361–382.

[7] Duval, R. E., Gouyau, J. & Lamouroux, E. (2019). Limitations of recent studies dealing with the antibacterial properties of silver nanoparticles: Fact and opinion. *Nanomaterials* **9**, 1775.

[8] Wang, L., Hu, C. & Shao, L. (2017). Antimicrobial activity of nanoparticles. *International Journal of Nanomedicine* **12**, 1227–1249.

[9] McNeilly, O. *et al.* (2021). Emerging concern for silver nanoparticle resistance. *Frontiers in Microbiology* **12**, 652863.

[10] Modi, S. K. *et al.* (2023). Mechanistic insights into nanoparticle surface–bacterial membrane interactions in overcoming antibiotic resistance. *Frontiers in Microbiology* **14**, 1135579.

[11] Ikuma, K., Decho, A. W. & Lau, B. L. T. (2015). Nanoparticle–biofilm interactions governing environmental fate. *Frontiers in Microbiology* **6**, 591.

[12] Sindeldecker, D. & Stoodley, P. (2021). Antibiotic resistance and tolerance strategies. *Biofilm* **3**, 100056.

[13] Mohanta, Y. K. *et al.* (2023). Nanotechnology in combating biofilm: A smart and promising therapeutic strategy. *Frontiers in Microbiology* **13**, 1028086.

[14] Alfei, S. *et al.* (2024). ROS-mediated antibacterial oxidative therapies: Mechanisms and emerging strategies. *International Journal of Molecular Sciences* **25**, 7182.

[15] Krzepiłko, A. *et al.* (2023). Sublethal zinc oxide nanoparticle exposure induces bacterial adaptation. *Pathogens* **12**, 485.

[16] Zhang, P. *et al.* (2022). Nanoparticles promote bacterial antibiotic tolerance via osmotic stress. *Small* **18**, 2105525.

[17] Alabresma, A. *et al.* (2020). Nanoparticles as antibiotic-delivery vehicles overcome multidrug resistance: The grenade hypothesis. *Journal of Global Antimicrobial Resistance* **22**, 811–817.

[18] Baptista, P. V. *et al.* (2018). Nano-strategies to fight multidrug-resistant bacteria. *Frontiers in Microbiology* **9**, 1441.

[19] Brauner, A., Fridman, O., Gefen, O. & Balaban, N. Q. (2016). Distinguishing resistance, tolerance and persistence to antimicrobial treatment. *Nature Reviews Microbiology* **14**, 320–330.

[20] Sulaiman, J. E. & Lam, H. (2021). Evolution of bacterial tolerance under antimicrobial pressure. *Frontiers in Microbiology* **12**, 617412.

[21] Mouzakis, A. *et al.* (2025). A comprehensive review of nanoparticles in the fight against antimicrobial resistance. *Pathogens* **14**, 1090.

[22] Graves, J. L. *et al.* (2015). Rapid evolution of silver nanoparticle resistance in *Escherichia coli*. *Frontiers in Genetics* **6**, 42.

[23] Ammendolia, M. G. & De Berardis, B. (2022). Nanoparticle-driven bacterial adaptation: Focus on nano-titania. *Nanomaterials* **12**, 3616.

[24] Truu, M. *et al.* (2022). Impact of silver nanoparticles on biofilm communities and resistance genes. *Journal of Hazardous Materials* **440**, 129721.

[25] Ciofu, O. & Tolker-Nielsen, T. (2019). Tolerance and resistance of *Pseudomonas aeruginosa* biofilms to antimicrobial agents. *Frontiers in Microbiology* **10**, 913.

[26] Ngoepe, M. P., Schoeman, S. & Roux, S. (2025). Challenges associated with the use of metal and metal oxide nanoparticles as antimicrobial agents: Resistance mechanisms and environmental implications. *Biotechnology Journal* **20**, e70066.

[27] Hochvaldová, L. *et al.* (2022). Antibacterial nanomaterials as tools against antimicrobial resistance. *Nanotechnology Reviews* **11**, 1115–1142.

[28] Wen, X. *et al.* (2016). Limitations of MIC as a sole metric of antimicrobial response. *Scientific Reports* **6**, 37907.

[29] Magréault, S. *et al.* (2022). When and how to use MIC in clinical practice. *Antibiotics* **11**, 1748.

[30] Lynch, I., Salvati, A. & Dawson, K. A. (2009). Protein corona formation at the bio–nano interface. *Nature Nanotechnology* **4**, 546–547.

[31] Fadeel, B. *et al.* (2018). Advanced tools for the safety assessment of nanomaterials. *Nature Nanotechnology* **13**, 537–543.

[32] Lekamge, S. *et al.* (2018). Ecotoxicological impacts of silver nanoparticles. *Frontiers in Environmental Science* **6**, 152.

[33] Pachghare, P. *et al.* (2025). Combating multidrug resistance with silver nanoparticles: A systematic review. *The Microbe* **9**, 100608.

[34] Iaconis, A. *et al.* (2024). Anti-biofilm strategies: A focused review on innovative approaches. *Microorganisms* **12**, 639.

[35] Afrasiabi, S. & Partoazar, A. (2024). Targeting bacterial biofilm-related genes using nanoparticle-based strategies. *Frontiers in Microbiology* **15**, 1387114.

[36] Abdelhamied, N., Abdelrahman, F., El-Shibiny, A. & Hassan, R. Y. A. (2023). Bacteriophage-based nano-biosensors for fast impedimetric pathogen detection in food samples. *Scientific Reports* **13**, 3498.

[37] Xia, Q. *et al.* (2024). Advances in engineered nano-biosensors for bacteria diagnosis and multidrug-resistance inhibition. *Biosensors* **14**, 59.



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