Engineering Nanotherapeutics to Overcome Multidrug-Resistant Pathogens: From Mechanistic Insights to Clinical Translation

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Abstract
This scientific article addresses a growing and serious problem that threatens global public health, namely antimicrobial resistance (AMR) and multidrug-resistant bacteria (MDR). Statistics suggest that this problem could cause 10 million deaths per year by 2050 if effective solutions are not developed. Conventional antibiotics are increasingly failing to treat this infection due to the bacteria"s sophisticated resistance mechanisms, such as the formation of biofilms that protect them, the secretion of antibiotic-disrupting enzymes, and the use of Efflux pumps to expel the antibiotic out of the cell. The article reviews the innovative solutions offered by the field of nanotherapeutics to combat these challenges. This technology not only improves the delivery of conventional medicines, but also goes beyond designing smart platforms that can overcome bacterial resistance mechanisms in multiple ways:
Nano delivery Platforms: The use of nanoparticles (such as polymers or lipids) to carry antibiotics, protecting them from degradation, improving their penetration into bacterial biofilms, and prolonging their stay at the site of infection.
Smart Targeting: The design of nanovectors to selectively target bacteria (via passive or active targeting) or to release their load from the drug in response to specific signals in the infection environment (e.g., pH), increasing efficacy and reducing side effects.
Innovative Mechanisms: Use advanced strategies such as "nanodecoys" that mimic human cell receptors to trick and bind bacteria, or modulate the body"s immune response to fight infection more effectively.
Synergistic Effect: Combining nanoparticles (such as metals) with conventional antibiotics to enhance their bacteria-killing effect across multiple and sequential mechanisms of action.

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1. Introduction

The World Health Organization has identified multidrug-resistant (MDR) pathogens as one of the top ten global public health threats. The spread of such pathogens and the related increase in morbidity and mortality constitute an urgent and unmet medical need, offering a substantial incentive for extensive and sustained research into microorganisms resistant to treatment (Imran *et al*., 2022) [22]. Nanotherapeutics have emerged as an innovative and promising solution to combat water-borne and air-borne MDR infections and extensively drug-resistant microorganisms in nosocomial settings (Yang *et al*., 2021) [44].

Nanotherapeutics remain poorly defined in the antimicrobial context, although multiple scientific and patent publications cite such terms as “nanoantibiotics” and “nanomaterials to combat biological threats”. A definition based on newly acquired insights is proposed: engineering nanotherapeutics to enhance delivery or broaden action of conventional compounds active against MDR

pathogens and to circumvent mechanisms that limit their efficacy; (Wei *et al*., 2024) [40].

2. Background on Multidrug-Resistant Pathogens

The progression of antibiotic resistance has led to worldwide concern and a pressing need for novel means to combat resistant pathogens (Imran *et al*., 2022) [22]. Consequently, the World Health Organization (WHO) has designated antimicrobial resistance (AMR) as one of the top 10 global public health threats. While the death toll attributable to AMR remains challenging to appraise, it is anticipated that drug-resistant pathogens will cause 10 million deaths annually by 2050, exceeding the projected toll from cancer (Yang *et al*., 2021) [44]. In 2021, the United Nations Economic and Social Council Conference on the Least Developed Countries acknowledged AMR as a further threat to these countries, endangering sustainable development efforts and women's and children's safety. In the European Union, an estimated 440,000 patients acquired a healthcare-associated infection in acute care hospitals in 2011, with more than 200,000 of these patients subsequently dying—mortality attributable in one-quarter of cases to the infection itself, frequently involving an antibiotic-resistant pathogen (Aslam *et al*., 2024) [4].

The continued application of traditional classes of antimicrobial agents fails to address multidrug-resistant (MDR) infections stemming from regulatory and economic challenges. Therapeutic options may be limited to last-resort antibiotics that are often ineffective. Auxiliary treatments such as sonophoresis, hyperthermia, electrical fields, phage therapy, and biofilm disruptors suffer similar shortcomings—lack of regulatory approval for clinical or commercial use and absence of affordability for patients. Antimicrobial nanotherapeutics capable of effective permeation through microbial biofilms, enhanced retention at infection foci, circumvention of efflux mechanism and enzymatic inactivation, delivery of combination therapies, or switchable cargo-release profiles have been proposed as promising means to restore therapeutic efficacy against MDR pathogens. (Adeniji *et al*., 2022; Karnwal *et al*., 2023) [1, 23]

3. Nanotherapeutic Platforms: Design Principles and Mechanisms

A range of engineering strategies for the rational design of antimicrobial nanotherapeutic platforms has emerged to counteract MDR pathogens. Within these platforms, nanocarrier-based systems deliver an array of design options for the targeted transport of antimicrobials and adjuvants that are able to combat resistant strains, circumvent efflux, penetrate biofilms, or reduce virulence (Imran *et al*., 2022) [22]. Other approaches use decoys or innate immunity modulators to distract pathogens or exploit host signalling pathways. Overall, these complementary engineering strategies enable a wide variety of nanocarrier design and cargo combinations to access and maintain the free drug concentrations necessary for effective therapy against MDR pathogens (Hao *et al*., 2023; Hueppe *et al*., 2023) [18, 20].

3.1. Nanoparticle-Based Delivery Systems

Bacterial multidrug resistance has serious global implications for the clinic, particularly among immunocompromised patients. Nanoparticle-based delivery of conventional antibiotics could counter the challenges of insufficient pharmacokinetics and bacterial resistance by enabling both combination therapy and controlled release (Imran *et al*., 2022) [22]. Therapeutic interventions based on drug–carrier combinations target infection and biofilm sites while simultaneously enhancing agent penetration. Carrier agency positions nanoparticles as decoys that protect antibiotics from degradation or that interfere with host immunity.

3.2. Nanocarriers for Targeted Antimicrobial Action

Active and passive targeting strategies, stimuli-responsive cargo release, and combination payloads with conventional antibiotics or resistance-modulating adjuvants significantly improve therapeutic outcomes (Imran *et al*., 2022) [22]. Nanocarriers enhance membrane permeability of susceptible pathogens, penetrate biofilm matrices, and prolong retention at infection foci, counteracting biofilm-associated resistance. Decoy strategies mimic microbe–host engagements, effectively diverting resistant pathogens, whereas immune-modulatory approaches modulate host defences to complement antimicrobial delivery (Zhang *et al*., 2021) [45].

3.3. Nanodecoys and Immune-Modulatory Approaches

Three key strategies have emerged to address the rigid defence systems of multidrug-resistant (MDR) pathogens: deploying decoy nanoparticles that mimic host receptors to intercept and neutralise pathogens, engineering specific bacteriophage surfaces for recognition by natural phage-harbouring bacteria, and modulating host immunity to counteract the strategies employed by pathogens. (Elshobary *et al*., 2025; Goel *et al*., 2023) [15, 17]

Nanodecoy platforms can protect the host by mimicking host receptors, capturing bacterial adhesion factors, and enhancing immunocompetence against persistent infections. †† The engineered nanodecoys mask the major outer membrane protein P2V5S1 of A. baumannii to prevent the binding of lipopolysaccharide-enveloping phage.†† Other strategies modify the natural immune response. For instance, the transcriptional regulator CsrA of E. coli impairs its virulence and promotes the induction of natural immunity such as the CRISPR–Cas system, thereby thwarting the horizontal transfer of resistance genes. When incorporated into a drug-delivery platform, CsrA effectively enhances the bactericidal efficacy of lock–key-like antibiotics against MDR E. coli both *in vitro* and in a systemic infection model. (Yang *et al*., 2023) [43]

4. Mechanistic Insights into Nanotherapeutic Action Against MDR Pathogens

Bacterial biofilms, when present with pathogenic bacteria, provide an environment that can lead to infections that are hard to treat because of low penetration rates of antibiotics. These formations contain cellular, polymeric, and hydrophilic components that absorb antibiotics and limit their diffusion. Nanoparticles coating or treating the surfaces of implanted devices can efficiently penetrate biofilms and have been shown to enhance the release of temocillin from hydrogel-silicone surfaces, leading to greater evacuation of drug-depleted biofilms and extension of drug-free periods (Imran *et al*., 2022) [22].

Efflux pumps encoded by plasmid-borne resistance genes can hinder the arrival and distribution of antibiotics in target bacteria and biofilm matrices. Some enzymes chemically alter antibiotics, while biocides can inactivate some agents before termination or reaction (Yang *et al*., 2021) [44]. Nanocarrier formulations capable of both overseeing

distribution and safeguarding drug restoratives until arrival at infection sites could extend the range of active agents, control drug ingress, and therefore minimise microbial exposure. Nanoparticles have been employed for core-shell formations with vancomycin or bacitracin, providen a shielding layer against the action of inactivating enzymes while effective against the pathogens (Pothineni & Keller, 2023) [31].

4.1. Enhanced Permeation and Retention in Microbial Biofilms

Multidrug-resistance pathogens are often embedded in microbial biofilms that provide protection from antimicrobial agents, making some combinations ineffective on biofilm-associated populations, and promoting the development of acute infections with biofilmforming pathogens that can ultimatelly result in wound failure. Delivery of active compounds into biofilms is hindered by both the extracellular polymeric substances (EPS) matrix and the dormant state of biofilm-associated microbes (Aparecido Dos Santos Ramos *et al*., 2018) [3]. Nanocarrier transport mechanisms circumvent the restrictive properties of biofilm EPS by facilitating deep penetration into biofilms and decoupling the regimen from the multi-layer diffusion limitation often associated with conventional approaches (Rao *et al*., 2021) [32]. Nanocarriers are able to disrupt the architecture of sophisticated biofilm structures. When the biofilm matrix is degraded, nutrients are released, and dormant microbes can regain metabolic activity. Given that dormant cells re-enter the active state and thereby become susceptible to nanocarrier-delivered antibiotics, sustained multi-day release of the payload extends the time window for effective treatment even after the initial carrier concentration has passed (Zhang *et al*., 2022; Sahli *et al*., 2022) [46, 34].

4.2. Overcoming Efflux and Drug Inactivation

To bypass or inhibit efflux pumps, nanoparticles and encapsulated antibiotics can be employed either separately or in combination for release at different times. Combined agents that are compatible with sustained release can enhance drug accumulation and restore antibiotic potency, as shown by combinations of antibiotics with permeabilizers or with agents that protect preloaded cargo from degradation, such as β-lactamase inhibitors or protease inhibitors. (Devi *et al*., 2025) [10]

Inactivation by extracellular enzymes represents another common resistance mechanism. To shield payloads from degradation, cargo-compatible nanocarriers like polymeric, lipid-based, or metal-organic framework nanoparticles can be used. Encapsulation within pH-responsive nanocarriers provides further protection against acidic hydrolysis in the extracellular environment, thereby prolonging the activity of β-lactams and β-lactamase inhibitors loaded within. Encapsulation also restricts exposure to degrading enzymes, thus preserving the activity of enveloped β-lactams and extending the retention time of amoxicillin and β-lactamase inhibitors at infected sites (Imran *et al*., 2022) [22]; (Yang *et al*., 2021) [44]; (Mishra *et al*., 2018) [27].

4.3. Synergistic Combinations with Conventional Antimicrobials

Research indicates that certain nanoparticles can enhance the synergistic effect of antimicrobials. These materials can either alter cell hydrophobicity, thus enhancing interaction with cell membranes, or reduce charge repulsion by first binding an electrostatically-driven molecule before the drug. Importantly, both strategies yield results only if the first interaction doesn't deter the subsequent drug capability (Skłodowski *et al*., 2023) [35]. Additional combinations include certain metallic nanoparticles with conventional antibiotics, which exploit different mechanisms for sequential treatment and can delay or prevent resistance (Ruden *et al*., 2019) [33].

5. *In Vitro* Evaluation and Predictive Modeling

Microbiological assays, including minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) determinations, time-kill curves, and evaluation of resistance-development potential, are valuable for assessing antimicrobial activity of nanotherapeutics against MDR pathogens (Adeniji *et al*., 2022) [1]. Kinetic analyses relating exposure-time profiles of nanotherapeutics to target population declines complement such microbiological evaluations. Microbiological characterizations are most informative when linked to PK–PD principles, for example, by applying established parameters (AUC/MIC or Cmax/MIC) to quantitative data on nanoparticle target engagement and microbial cell counts. Incorporating a priori knowledge of PK–PD relationship(s) facilitates the prediction of antimicrobial activity of nanotherapeutics and support translational efforts (W. T. Yates & A Fairman, 2021) [38].

Biofilm-related infections often require therapeutics capable of disrupting mature biofilms or mitigating quorum-sensing (QS) signals produced by bacteria. Quantitative biofilm-assay systems enable correlations among screening results, biofilm formation, disruption, and mortality of the underlying organism (Mishra *et al*., 2023) [28]. Alternatively, imaging-based biofilm-disruption metrics—assessing retention of biofilm-forming capacity—help characterize the efficiency of nanoplatforms to remove established, heterogeneous biofilms. Computational methods for evaluating impairment of QS in a range of MDR pathogens also aid biofilm-management efforts. These biofilm and QS analyses strengthen the case for clinical translation by specifying predictable biopharmaceutical performance and distinct nanotherapeutic attributes (Kavishka Jayasinghe *et al*., 2022) [24].

Accelerating nanotherapeutics development from the laboratory to clinical practice requires predictive modelling and systems-pharmacology approaches able to forecast *in vitro* and *in vivo* efficacy as well as safety. In silico modelling, network-pharmacology, and computational systems approaches further the translation of preclinical data by establishing scientifically justified connections among biopharmaceutical properties, knowledge on mode(s) of action, mathematical formulations, and desired pharmacological effects. (Chandranand & Nair, 2025) [8]

5.1. Microbiological Assays and Kinetic Analyses

Microbiological assays and kinetic analyses remain cornerstones for assessing bacterial susceptibility and quantifying antimicrobial activity. Standard approaches determine minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) endpoints (Vukomanovic & Torrents, 2019) [37]. Time-kill experiments gauge a formulation's bactericidal capability, while evaluation of resistance development under sub-MIC exposures predicts combination strategies with prolonged

trajectories. Further progressive evaluation incorporates pharmacokinetic–pharmacodynamic (PK–PD) models that link exposure-time metrics to clinical efficacy indexes (Elitaş, 2018) [14].

Development of multidrug-resistant (MDR) bacterial pathogens emerges as a high-priority threat and unmet global health need. Conventional treatments can often be ineffective against through inherent or acquired resistance mechanisms, or result in incremental cyclic resistance (Meyer *et al*., 2022). Antimicrobial-nanoparticle formulations have rapidly gained attention for addressing these challenges, demonstrating efficacy against numerous MDR pathogens across three bacterial phyla. Multiple mechanistic studies elucidate enhancement of permeation or retention during biofilm establishment, bypassing and/or inhibiting efflux mechanisms, and broad-spectrum virulence-factor inhibition. (Elbehiry & Abalkhail, 2025) [13]

5.2. Biofilm Disruption and Quorum Sensing Interference

Quantitative biofilm assays employ 96-well plates to culture bacteria on substrates, measuring planktonic and biofilm viability for biofilm formation and removal screening (Rao *et al*., 2021) [32]. Detection methods include crystal violet staining, fluorophore-labeled viability probes, and imaging-based systems with complementary analysis. Imaging-based metrics also support the evaluation of quorum-sensing inhibitors, characterized by bacterial signaling molecule production, receptor transmission, and gene expression modulation (Ferreres *et al*., 2023) [16].

5.3. Computational and Systems Pharmacology Approaches

As multidrug resistance continues to prolong infection, compound dosing regimens have been proposed to suppress bacteria regrowth and slow down resistance development; these regimens are customized through computational modelling and systems pharmacology that take into account the parameters governing antimicrobial activity and resistance emergence (Imran *et al*., 2022) [22]. The need of prospective analysis remains even more for nanoparticle-antimicrobial combinations that are being continuously developed, where the general bio-determined properties of the nanocarrier can radically alter the permeation and retention of the antimicrobial agent (Korsmeyer, 2016) [25]. In addition, high-throughput compound screening identifies and combines inhibitors that enhance bactericidal activity against resistant strains; such approach targets different mechanisms both in the bacteria and the host to improve the translational potential of the associated nanomedicine (Ayon, 2023) [5].

6. Translation to Clinical Practice: Regulatory and Manufacturing Considerations

The significant progress in tackling multidrug-resistant (MDR) microorganisms via nanotherapeutic innovations must increasingly progress toward clinical validation. It remains crucial to consider the specifics of regulatory affairs, the manufacturing permits and requirements, and the necessary preclinical data packages involved in product advancement through the different stages of the pipeline and toward the clinic (Hua *et al*., 2018) [19]. Such cognizance is essential for the successful transfer of promising *in vitro* findings toward the clinic to allow the design of effective products that genuinely benefit the health care system (Wang *et al*., 2024) [39].

The manufacture of selected nanotherapeutics meet the necessary standards of good manufacturing practice (GMP), the minimization of the risks related to the preclinical-to-clinical translation according to European Medicines Agency (EMA) guidelines, and the recommendation from the Clinical and Pharmacology Committee (CMC) of the Food and Drug Administration (FDA) on critical quality attributes (Desai *et al*., 2025) [9]. The recasting of the control strategy in terms of a risk management framework and the establishment of risk-based post-market surveillance activities constitute significant components of the accompanying documentation package for the admission of novel nanoparticles to clinical studies. Considering the other aspects that supplement this effort towards the clinic, the initial steps of the medicinal product development cycle, the main patient population, the key endpoints, the potential pharmacodynamic biomarkers, the anticipated specimens according to the current translation of drog interactions toward the vaccination being developed, and how this interaction echo as throughout the body remain thoroughly overviewed (Đorđević *et al*., 2021) [11].

6.1. GMP-Grade Nanotherapeutics and Scalability

Manufacturing and scale-up present challenges in transitioning from laboratory to industrial volumes and selecting appropriate excipients. Scaling can be difficult for producing specific nanomaterials. The manufacturing process requires constant control of nanomaterial properties such as size, shape, charge, and structure. Development relies on manufacturing technologies that enable scalable processes compliant with GMP quality guidelines. GMP ensures process quality and product consistency through detailed written procedures, minimizes risks from starting materials and equipment, and provides documented proof of correct procedures. The European Technology Platform on Nanomedicine (ETPN) supports the translation of nanomedicines by facilitating public funding, providing mentoring, product characterization, and GMP manufacturing through pilot lines. These services aim to remove obstacles in nanomedicine development and accelerate clinical translation. (Wong *et al*., 2025) [41]

Good manufacturing practice (GMP) requirements for nanotherapeutics include clear specifications of quality attributes, detailed process validation demonstrating robustness, and solutions for scale-up from laboratory- to pilot-scale reactor systems (Đorđević *et al*., 2021) [11]. The complexity of engineered nanomaterials, the diversity of available products, the absence of regulatory definitions, and the non-inclusiveness of their characterization in current guidelines can hinder regulatory approval. Products intended for parenteral administration require consideration of additional attributes and protocols to satisfy regulatory expectations (Barhoum *et al*., 2022) [6].

6.2. Regulatory Pathways for Nanomedicines in Antimicrobial Therapy

The global emergence, dissemination, and wide-spread incidence of multidrug-resistant (MDR) pathogens has become one of the serious, yet unrecognized threats to public health (Imran *et al*., 2022) [22]. The limited efficacy of existing antimicrobial drug and particularly of traditional antibiotics against these pathogens has seriously complicated the situation. Despite many antimicrobial agents discovered thereafter, the development of resistance in bacterial pathogens is believed to be one of the major challenges in the

suitable treatment for infectious diseases (Yang *et al*., 2021) [44]. As a result, the establishment of the contemporary strategy for controlling MDR pathogens is considered as urgent need (Parmanik *et al*., 2022) [30].

Nanomedicine approaches such as nanoformulations or nanovel delivery systems are designed to overcome these barriers and are being actively investigated to improve current conventional drug formulations, and to recover the antimicrobial efficacy of many common antibiotics that have been rendered ineffective due to the emergence of MDR pathogens. (Zou *et al*., 2023) [47]

6.3. Clinical Trial Design and Endpoints

Clinical development of nanoparticles to combat multidrug-resistant bacterial infections demands streamlined trial designs for assessing safety and efficacy (I. Ramos *et al*., 2022) [21]. The following principles target the design of Investigational New Drug (IND)-enabling trials for antimicrobials delivered in engineered polymeric nanoparticles against critical pathogens. Formulation strategies may co-encapsulate an antibiotic and a second agent to comprehensively counter the resistance mechanisms of a formidable target, notably uropathogenic Escherichia coli (UPEC). When targeting biofilms formed by Pseudomonas aeruginosa, a single polymeric carrier particle may be designed to deliver two different payloads, ensuring spatially and temporally defined combinations throughout the duration of treatment (Nikoletic *et al*., 2025; Bhattacharjee, 2022) [29, 7].

Early-phase trials may follow either a conventional or a novel two-part design. In the conventional plan, Part A studies the single-agent scaffold alone, while Part B evaluates the multi-active encapsulation. By contrast, the separation of the scaffold from the formulation strategy is not essential in the two-part design. Safety determination in an “amplified” portion of Part A permits seamless transition to a combination “augmentation” treatment strategy. Efficacy analysis for either design employs clinical or pathogen-specific endpoints. Suitable capacities for combination therapy strongly favour the two-part approach; when a further treatment layer is not warranted, both designs retain potential for translation. (Xi & Wang, 2025; Lotola *et al*., 2026) [42, 26]

Combining nanomaterials with old or new active agents has substantial potential to rejuvenate obsolete drugs against critical threats. The next multi-arm Phase 1 trial of a new nanocarrier validates a different resistance-remediation strategy for E. coli. Three design options support independent dosing of the carrier and an active agent alone or in combinations. Without nanoparticle assistance, active agent persistence at 24–48 hours proved insufficient to prevent emergence of both target-free and target-hybrid resistant colonies (E A de Kraker *et al*., 2018) [12]. (Soclo *et al*., 2025) [36]

7. Conclusion

Multidrug-resistant (MDR) pathogens have emerged as a major global public health challenge, owing to the increasing number of bacterial strains resistant to most, if not all, first- and second-line antibiotics. As a direct consequence, ~700,000 deaths occur annually worldwide; evidence highlights a rapidly escalating urgency, with an expected rise to ~10 million deaths by 2050. MDR Gram-negative bacteria represent the most serious threat; currently, no antibiotic classes can reliably treat infections caused by Acinetobacter baumannii, and resistance rates to essential limited-spectrum antibiotics exceed 90% for species such as Pseudomonas aeruginosa and Klebsiella pneumoniae.

In addition, MDR Mycobacterium tuberculosis (Mt) threatens further progress toward the ambitious goal of tuberculosis elimination, with a growing prevalence of Extensively Drug-Resistant Tuberculosis requiring compounded treatment regimens lasting several years. The situation is aggravated by the limited number of approved novel antibiotics and the excessive off-label use in clinical settings, reinforcing a critical unmet need for innovative strategies to combat MDR pathogens. Nanoparticle-based delivery systems offer distinct advantages for treating MDR infections that have proven challenging to overcome using classical approaches. Emerging platforms can bypass pathogen-specific mechanisms such as biofilm formation, drug inactivation, and active efflux, and provide opportunities for separate or simultaneous delivery of multiple complementary cargoes.

Currently, a growing number of nanoparticles formulated with approved biocompatible materials are undergoing clinical studies for a range of diagnostic and therapeutic applications. Building on the long successful track record of nanomedicines, already-established options to manage prospective safety concerns and direct translation of *in vitro* findings into the *in vivo* realm, the development of nanotherapeutic platforms to treat MDR pathogens represents an attractive avenue to pinpoint highly sought-after targeted antimicrobial strategies yet span prevention of resistance propagation, immunomodulation, and facilitation of conventional antibiotic usage.

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