The Antiviral Nanotechnology Gap in COVID-19: Systematic Barriers to Pandemic-Scale Translation and Deployment

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ABSTRACT

For over two decades, antiviral nanotechnologies have demonstrated robust preclinical efficacy against diverse viral pathogens, including coronaviruses. Yet during the COVID-19 pandemic, these platforms contributed minimally to the global therapeutic response despite unprecedented urgency, regulatory flexibility, and funding availability. This narrative review, structured using the DELIVER framework (Joyce et al., 2024), systematically analyses the translational barriers that constrained deployment across scientific, regulatory, manufacturing, economic, and institutional domains.

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar (January 2000-December 2024), supplemented by ClinicalTrials.gov and regulatory policy documents. Following deduplication and eligibility screening of 2,847 records, 90 peer-reviewed articles were included in the qualitative synthesis (inter-rater agreement: Cohen's kappa = 0.88). Only three systemic antiviral nanotechnology trials were identified during COVID-19, none of which achieved regulatory authorisation. In contrast, mRNA-lipid nanoparticle (LNP) vaccines succeeded because of long-term pre-pandemic platform maturation, established manufacturing partnerships, early regulatory engagement, and coordinated government support through Operation Warp Speed (~$18 billion).

Key barriers included manufacturing complexity, regulatory pathway ambiguity, absent pandemic-ready production capacity, fragmented intellectual property landscapes, and weak cross-sector coordination. Crucially, these barriers did not operate independently but formed mutually reinforcing cascades that rendered single-domain interventions insufficient. Partial successes--including diagnostic nanoparticle platforms and liposomal oncology reformulations--demonstrate that context-specific enabling factors, rather than inherent technological limitations, largely determined translation outcomes. Advancing antiviral nanotechnologies for future pandemics requires proactive, inter-pandemic investment in scalable manufacturing, clearer regulatory frameworks, platform-based development strategies, and coordinated economic instruments. This principally US-focused analysis offers policy insights applicable across high-income country (HIC) and, selectively, lower-middle-income country (LMIC) settings.

Keywords: antiviral nanotechnology; pandemic preparedness; translational barriers; nanomedicine; DELIVER framework; LMIC; implementation science

INTRODUCTION

Well before SARS-CoV-2 emerged, antiviral nanotechnology was positioned as a transformative approach to managing viral infections. Lipid, polymeric, metallic, and carbon-based nanomaterials were developed to target viral entry, enhance drug delivery, and modulate immune responses in ways that conventional small molecules cannot achieve (Chakravarty & Vora, 2021; Hu et al., 2025). By early 2020, thousands of publications had documented nanoparticle efficacy against diverse viruses, including influenza, HIV, herpes simplex, and coronaviruses. The theoretical advantages were compelling: improved drug solubility and stability, cell-specific targeting, sustained release kinetics, and purported "plug-and-play" adaptability for emerging pathogens (Yang et al., 2021).

When COVID-19 created unprecedented therapeutic demand--accompanied by Emergency Use Authorization (EUA) regulatory flexibility, approximately $18 billion in funding through Operation Warp Speed, and advance-purchase market guarantees--antiviral nanotechnology platforms remained conspicuously absent from the clinical response (Afonin et al., 2022). Remdesivir achieved EUA within four months, monoclonal antibodies within eight to nine months, and Paxlovid within 21 months. Systemic antiviral nanotherapeutics contributed negligibly. This paradox was sharpened by the fact that lipid nanoparticles (LNPs)--a nanotechnology platform--enabled the most successful pandemic intervention: mRNA vaccines (Vahedifard & Chakravarthy, 2021).

This discrepancy raises a precise diagnostic question: not whether antiviral nanotechnology is scientifically promising--the evidence confirms that it is--but why it was not deployable when conditions for deployment were uniquely favourable. This review provides that diagnosis.

Scope and Definitions

This review focuses on systemic therapeutic nanomedicines--engineered particles between 1 and 1,000 nm intended to treat or prevent viral infections through human administration (intravenous, oral, inhaled, or intranasal routes). Diagnostic applications, device-based uses, and vaccine adjuvant systems are discussed only where comparative insight is valuable; these categories achieved greater COVID-19 success precisely because they operate under different regulatory frameworks and manufacturing paradigms. The analysis is principally US-centred, examining NIH, BARDA, FDA, and US academic-industry dynamics, with international and LMIC comparisons where they illuminate systemic differences.

Research Questions

This review addresses four specific questions:

1. What was the actual state of antiviral nanotechnology translational readiness in early 2020, beyond publication counts?

2. Why did platforms with strong preclinical data fail to translate during COVID-19 when conditions were unusually favourable?

3. How did barriers interact across domains to create systemic, cascading failure?

4. What distinguishes platforms that succeeded (mRNA vaccines, conventional antivirals) from those that did not, and what are the implications for future preparedness?

Unlike existing nanomedicine reviews that catalogue individual barriers, this review uniquely applies the DELIVER framework systematically to pandemic response; uses COVID-19 as a natural experiment revealing genuine translational readiness; provides detailed case studies illustrating how barriers cascaded in specific platforms; and examines partial successes alongside failures to present a balanced and critical perspective.

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METHODS

Literature Search Strategy

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar from January 2000 through December 2024. Three conceptual clusters were combined: (1) antiviral nanotechnology: ("antiviral" OR "virucidal") AND ("nanotechnology" OR "nanomedicine" OR "nanoparticles" OR "liposomes" OR "dendrimers" OR "polymeric carriers"); (2) translational science: ("clinical translation" OR "scale-up" OR "regulatory approval" OR "GMP" OR "manufacturing" OR "commercialization"); and (3) pandemic: ("pandemic preparedness" OR "SARS-CoV-2" OR "COVID-19"). ClinicalTrials.gov was searched in December 2024 for ("nanoparticle" OR "nanomedicine" OR "liposome" OR "dendrimer") AND ("antiviral" OR "COVID-19" OR "SARS-CoV-2"). Publicly available regulatory and policy documents were also reviewed, including FDA nanotechnology guidance (2014, 2017, 2022), BARDA funding announcements, NIH RePORTER records, and Operation Warp Speed reports.

Study Selection and Eligibility Criteria

Studies were included if they were published in English; focused on therapeutic antiviral applications (not purely diagnostic); discussed translational barriers, clinical development, or COVID-19 application; and constituted primary research, systematic or narrative reviews, or policy analyses. Studies were excluded if they focused primarily on vaccine-delivery systems without comparative discussion of therapeutic nanotechnologies; reported pure efficacy data without translational analysis; or were non-English publications or unreviewed conference abstracts. The initial search yielded 2,847 records. After removal of 897 duplicates, 1,950 titles and abstracts were screened, 412 full-texts were assessed for eligibility, and 90 peer-reviewed articles met inclusion criteria. For clinical trials, 56 pre-pandemic (2000-2019) and three COVID-19-era trials were identified. Two independent reviewers conducted screening; inter-rater agreement was 94% (Cohen's kappa = 0.88). Discrepancies were resolved through consensus discussion. A PRISMA flow diagram is presented in Figure 1 of the original manuscript.

Analytical Framework

The DELIVER framework (Joyce et al., 2024) was applied to categorise barriers across five domains: (1) Scientific/Technical--reproducibility, characterisation, stability, and in vivo behaviour; (2) Regulatory--pathway clarity, characterisation requirements, and risk assessment; (3) Manufacturing--scale-up, GMP capability, supply chains, and cost; (4) Economic--funding gaps, investment climate, market dynamics, and IP fragmentation; and (5) Institutional--agency coordination, academia-industry alignment, and preparedness infrastructure. Barrier co-occurrence was coded using NVivo software. Systematic tagging of inter-domain connections (e.g., "manufacturing complexity --> regulatory uncertainty --> reduced investment") yielded a network map showing that 68% of manufacturing barriers co-occurred with regulatory or economic barriers, forming the cascade analysis reported in the Discussion. Qualitative thematic synthesis identified recurring patterns and systemic bottlenecks iteratively across included articles. Monetary values are reported in 2024 US dollars unless otherwise stated.

Methodological Limitations

This review acknowledges several limitations: (i) publication bias may favour successful preclinical studies over null findings; (ii) the US-centric focus limits generalisability, particularly to LMIC contexts; (iii) as a retrospective analysis, causal counterfactual claims cannot be established definitively; (iv) some industry development activities remain confidential; and (v) the inclusion criteria intentionally exclude successful diagnostic nanotechnology applications. These limitations are partially addressed through triangulation across multiple data sources and cautious language regarding causal attribution.

RESULTS

Pre-Pandemic Landscape: Promise and Readiness Assessment

Research Output Trends

Antiviral nanotechnology publication volume grew substantially from dozens annually in the early 2000s to hundreds per year by 2019. Metallic nanoparticles--particularly silver--dominated early research owing to well-established synthesis methods and antimicrobial properties (Begines et al., 2020). Studies documented activity against HIV, HSV, influenza, and hepatitis through viral envelope disruption and reactive oxygen species (ROS) generation (Dung et al., 2020; Ratan et al., 2021). Table 1 classifies major platforms by mechanism, development stage, and representative examples as of 2019.

Table 1. Classification of antiviral nanotechnology platforms by mechanism, pre-2020 development status, and key developers.

Platform Type	Antiviral Mechanism	Dev. Stage Pre-2020	Key Developers	Representative Examples
Metallic Nanoparticles	Direct viral envelope disruption via ion release or ROS generation	Preclinical (in vitro proofs)	NIH, University of Florida	Silver NPs vs. HIV/H1N1 (Chakravarty & Vora, 2021)
Polymeric Nanoparticles	Encapsulation/release of antivirals; endocytosis inhibition	Early clinical (Phase I/II trials)	MIT, Emory University	PLGA NPs for acyclovir delivery vs. HSV
Liposomes	Targeted delivery of siRNA/drugs to infected cells	Advanced (FDA-approved analogs)	Gilead Sciences, Lipid Labs	Liposomal ritonavir for HIV (Yang et al., 2021)
Dendrimers	Multivalent binding to viral glycoproteins; entry blockade	Preclinical (proof-of-concept)	Starpharma, Georgetown University	PAMAM dendrimers vs. Ebola/HIV
Nanofibers	Surface trapping of virions; scaffold for antivirals	Early research (lab prototypes)	Georgia Tech, Nanyang Tech University	Electrospun cellulose nanofibers vs. influenza
Quantum Dots	Photodynamic inactivation; fluorescent tracking	Preclinical (imaging-focused)	Chinese Academy of Sciences	CdSe QDs conjugated for HSV inhibition
Carbon-based (GO/CNTs)	High-affinity adsorption of viral proteins	Exploratory (in vitro studies)	Rice University, Indian Institute of Technology	Graphene oxide sheets vs. DENV/HCV

Despite this output surge, publication volume did not translate into clinical readiness. Most work remained at in vitro proof-of-concept stage; animal studies rarely progressed to IND-enabling data packages (de Souza et al., 2025). The disconnect between publication volume and translational progress was already apparent before COVID-19 (Yang et al., 2021).

Partial Successes and Contextual Advances

A balanced appraisal requires acknowledging partial successes to avoid overgeneralisation of failure. Liposomes represented the most advanced platform in terms of regulatory precedent: multiple liposomal products--including doxorubicin (Doxil(R)), amphotericin B (AmBisome(R)), and morphine (DepoDur(R))--had FDA approval for oncological and other applications, establishing meaningful pathways (Okafor & Nnaji, 2024). Liposomal antiviral formulations (acyclovir, ganciclovir, ritonavir) showed improved pharmacokinetics and reduced toxicity in preclinical models (Javan et al., 2017), though these remained in early clinical stages by 2020.

Dendrimers achieved the furthest clinical progress of any antiviral nanotechnology: Starpharma's VivaGel (SPL7013) reached Phase III trials for HIV and HSV-2 prevention (Filipczak et al., 2021). Polymeric nanoparticles (notably PLGA formulations) demonstrated acceptable safety in several Phase I studies. These partial advances confirm that individual barriers, rather than any categorical impossibility, impeded broader translation. By 2019, however, no antiviral nanoparticle-based therapy had received regulatory approval for systemic human use, and manufacturing at pandemic scale had not been demonstrated (Yang et al., 2021; Pu et al., 2025). COVID-19 did not reveal unexpected barriers--it exposed the consequences of well-documented, longstanding challenges that had not been systematically addressed.

COVID-19 Response: The Natural Experiment

The Opportunity Window

Early 2020 created conditions rarely seen in modern medicine: case fatality rates exceeding 2% overall and approximately 10% in elderly populations, no approved antivirals, regulatory flexibility via EUA, approximately $18 billion in government funding, and advance-purchase market guarantees (Kashte et al., 2021). If antiviral nanotechnologies were approaching translational readiness, this period represented an optimal deployment scenario.

Actual Contribution: Three Trials, No Authorisations

Systematic ClinicalTrials.gov searching identified only three trials evaluating systemic antiviral nanotechnology for COVID-19 (Table 2). None progressed beyond early-phase evaluation, and none achieved regulatory authorisation.

Table 2. Systemic antiviral nanotechnology clinical trials for COVID-19 registered on ClinicalTrials.gov (search conducted December 2024).

Trial ID	Platform	Phase	Enrollment	Sponsor	Status	Outcome
NCT04480333	Remdesivir nanoparticle + liposomal lactoferrin	Phase I	Est. 45	Biomed Industries, Inc.	Unknown	Results not posted
NCT04352465	Methotrexate-loaded Nanoparticles	Phase I/II	Est. 42	Azidus Brasil	Unknown	Results not posted
NCT04894409	Silver Nanoparticles for COVID-19 Prevention	N/A	Actual: 231	Cluster de Bioeconomia de Baja California	Completed	Results not posted

All three trials were small (42-231 participants) and exploratory, representing opportunistic repurposing of diverse agents rather than a coherent antiviral nanomedicine strategy. Two involved repositioning known pharmacological agents (remdesivir, methotrexate) into nanoformulations; one used nanosilver as a largely

empirical prophylactic. None had posted results at the time of searching--itself a signal of limited translational impact. This stands in stark contrast to conventional therapeutics: remdesivir achieved EUA within four months (Eastman et al., 2020), monoclonal antibodies within eight to nine months (Lloyd et al., 2021), and Paxlovid within 21 months including de novo development.

The pattern--substantial preclinical output without therapeutic impact--implies the constraint was not scientific understanding but translational infrastructure. Technologies capable of generating publications were not capable of generating deployable medicines under crisis conditions.

Where Nanotechnology Succeeded: Contextual Enabling Factors

Nanotechnology did contribute meaningfully to the COVID-19 response, but primarily outside systemic therapeutics. Gold nanoparticle lateral flow assays formed the backbone of rapid antigen testing (hundreds of millions deployed globally) (Tang et al., 2021), succeeding because they used established technologies under device--rather than drug--regulatory frameworks. mRNA-LNP vaccines succeeded because Moderna received more than $1 billion from DARPA/BARDA before 2020, manufacturing partnerships with Lonza and Pfizer existed pre-pandemic, and regulatory engagement had occurred during earlier programmes (Thi et al., 2021; Guerrini et al., 2022). The distinguishing features of both successes were lower or better-defined regulatory hurdles, pre-existing manufacturing infrastructure, prior human safety data, and established market pathways--none of which systemic antiviral nanotherapeutics possessed.

Systematic Barrier Analysis

Table 3 summarises barriers across the five DELIVER domains with corresponding priority recommendations.

Table 3. DELIVER framework: key barriers identified and priority recommendations by domain.

DELIVER Domain	Key Barriers Identified	Priority Recommendations
Scientific/Technical (Platform-Level)	Batch-to-batch variability; reproducibility failures; stability (cold chain); protein corona alteration of in vivo behaviour; lack of standardised characterisation methods	Invest in process analytical technology; standardise characterisation protocols; fund shared nanoparticle testing consortia; support microfluidic continuous manufacturing
Regulatory (Platform + Implementation)	NDA vs. 505(b)(2) pathway ambiguity; extensive characterisation demands; sparse infectious-disease precedent; slow EUA adaptation; pre-IND meeting delays	Issue platform-specific guidance; establish structured pre-IND dialogue programmes; harmonise requirements via ICH mechanisms; create expedited review tracks for pandemic-ready platforms
Manufacturing (Implementation-Level)	Absent GMP-ready capacity; supply-chain fragility; scale-up from grams to tonnes not demonstrated; prohibitive cost-of-goods; limited CMO expertise	Create national GMP nanomedicine centres; invest in dual-use manufacturing; develop continuous-flow GMP processes; build strategic specialty lipid/polymer reserves
Economic (Implementation-Level)	Valley-of-Death funding gap between NIH and BARDA; boom-or-bust pandemic markets; IP fragmentation across universities, SMEs, and pharma; investor risk aversion for 15-year timelines	Introduce advance market commitments; create translational bridging grants ($10-50M); support pre-competitive IP pooling; develop milestone-based public-private financing mechanisms

DELIVER Domain	Key Barriers Identified	Priority Recommendations
Institutional (Implementation-Level)	Agency silos (NIH vs BARDA); weak academia-industry coordination; absent clinical trial networks for nanomedicine in infectious disease; missing preparedness infrastructure	Mandate biennial preparedness assessments; model cross-agency coordination on Operation Warp Speed; build dedicated nanomedicine pandemic trial networks; develop LMIC-accessible platforms

Domain 1: Scientific and Technical Barriers (Platform-Level)

Nanoparticles are exquisitely sensitive to manufacturing conditions; small variations in temperature, pH, or mixing produce substantial changes in particle size, surface properties, and drug loading (Joudeh et al., 2022; Sharifi et al., 2022). Quality control requirements are substantially more complex than for small molecules: particle size distribution, surface charge (zeta potential), morphology, encapsulation efficiency, release kinetics, aggregation behaviour, and long-term stability must all be characterised. Methods are not standardised; dynamic light scattering and nanoparticle tracking analysis frequently yield different size estimates for identical formulations, and regulatory guidance specifies characterisation categories without defining acceptable methods or threshold values (Caputo et al., 2021; FDA, 2017).

Scale-up presents additional fundamental challenges. Laboratory production uses small reactors with magnetic stirring; GMP manufacturing employs large vessels with different mixing regimes that alter nucleation kinetics (Khairnar et al., 2022). Each scale transition requires extensive re-optimisation, potentially taking months without success guarantees--untenable under pandemic timelines. Many formulations require refrigerated or frozen storage, and stability loss (drug leakage, hydrolysis, aggregation) further complicates cold-chain management (Hashiba et al., 2024). Emerging approaches--microfluidic manufacturing, process analytical technology, continuous-flow production--offer partial mitigation. Webb et al. (2020) demonstrated GMP-compatible liposomal scale-up via microfluidics with improved batch consistency, representing an important proof of principle requiring substantial capital investment.

Domain 2: Regulatory Barriers (Platform- and Implementation-Level)

Significant uncertainty surrounded whether nanoparticle formulations constituted new molecular entities (requiring full NDAs) or could proceed via 505(b)(2) pathways when incorporating approved drugs. When nanoparticles substantially altered biodistribution, regulators often treated them as new drugs despite known active ingredients--scientifically defensible but commercially challenging (Csoka et al., 2021). Most approved nanomedicines targeted oncology, leaving sparse infectious-disease precedent; each platform faced case-by-case negotiation rather than established frameworks (Mangla et al., 2025). Extensive characterisation demands--protein corona formation, multi-organ biodistribution, long-term toxicity--while scientifically justified, necessitated prolonged and costly preclinical programmes (Foulkes et al., 2020). EUA reduced evidentiary burdens but still required reasonable safety and efficacy assurance--difficult to establish without prior human data. At the implementation level, FDA workload during the pandemic delayed pre-IND meetings by months, compounding developers' already constrained resources.

Domain 3: Manufacturing and Supply Chain Barriers (Implementation-Level)

In early 2020, no pandemic-ready GMP facilities existed for systemic antiviral nanoparticles (Souto et al., 2020). Treating 100,000 patients at 100 mg/day for five days requires approximately 50 kg of active material; treating millions requires tonnes--yet pre-pandemic production remained at gram scale. Establishing GMP-compliant facilities would have required years and hundreds of millions of dollars (Tureli & Tureli, 2020). Specialty lipids, polymers, and metals were not widely stocked, and suppliers required assured demand before scaling production--a circular dependency (Shegokar & Nakach, 2020). Nanoparticle production costs are substantially higher than small-molecule synthesis, sometimes by orders of magnitude, creating cost-effectiveness barriers pronounced

especially in LMIC settings where per capita healthcare expenditure may be less than $100 annually (Wu et al., 2020; Kirtane et al., 2021).

Domain 4: Economic and Investment Barriers (Implementation-Level*)*

Advancing a candidate to Phase I requires approximately $10-50 million over three to five years. NIH grants support early-stage research but rarely fund IND-enabling studies; BARDA requires IND-ready status before engagement--a catch-22 particularly acute for nanomedicines with 15-year development timelines discouraging investors expecting 7-10-year returns (Thapa & Kim, 2023; Younis et al., 2022). Pandemics create "boom-or-bust" market scenarios--the antithesis of the stable patient populations preferred by pharmaceutical investors. Operation Warp Speed addressed this for vaccines through advance purchase agreements; no comparable commitment existed for antiviral nanotechnologies. IP fragmentation--formulation patents at universities, synthesis methods at small firms, drug patents at large pharma--generated costly licensing negotiations and led to some promising candidates being abandoned for commercial rather than scientific reasons (Afonin et al., 2022).

Domain 5: Institutional and Coordination Barriers (Implementation-Level)

Research, industry, and government operated largely in parallel rather than concert (Joyce et al., 2024), contrasting sharply with mRNA vaccines where substantial pre-pandemic coordination existed among DARPA, BARDA, NIH, and companies such as Moderna. NIH's emphasis on basic science and BARDA's focus on IND-ready candidates left the intermediate phase--advanced preclinical development and IND-enabling studies--inadequately supported, precisely where antiviral nanotechnologies resided. Robust preparedness systems (trial networks, regulatory pathways, stockpiling, distribution) existed for conventional vaccines and small-molecule drugs; comparable systems for nanotechnology therapeutics were largely absent and could not be established within pandemic timescales.

Case Studies: Barriers in Cascade

Case Study 1: Dendrimer Microbicide Platform (VivaGel/SPL7013)

Starpharma's VivaGel (SPL7013) reached Phase III trials for HIV and HSV-2 prevention by 2019, the most clinically advanced antiviral nanotechnology globally (Falanga et al., 2021). In March 2020, Starpharma announced in vitro SARS-CoV-2 activity, and the platform theoretically offered rapid adaptation. However, a cascade of interdependent barriers prevented deployment: systemic use required substantially different formulation from the approved topical gel (requiring 12-18 months of reformulation and stability testing); FDA required comprehensive new biodistribution and toxicity studies for the new route, effectively restarting the regulatory pathway; Starpharma lacked capital for rapid systemic reformulation; and pharmaceutical partnership negotiations operated on 6-12-month due diligence timelines incompatible with pandemic urgency (Stanberry, 2007). By mid-to-late 2020, remdesivir, dexamethasone, and monoclonal antibodies had demonstrated efficacy; the therapeutic opportunity window had closed. Even the most clinically advanced antiviral nanotechnology could not translate within pandemic timelines without pre-positioned infrastructure.

Case Study 2: Liposomal Antiviral Platforms

Multiple academic groups developed liposomal antiviral formulations showing improved pharmacokinetics and reduced toxicity in preclinical models (Mastrangelo et al., 2014; Croci et al., 2016; Jbara-Agbaria et al., 2022). Liposomes had the strongest regulatory precedent of any nanoparticle class, with multiple FDA-approved products. When remdesivir showed modest efficacy, liposomal reformulations offering enhanced lung delivery appeared potentially valuable (Lamb, 2020). Nevertheless, none reached clinical trials during the acute pandemic phase. Academic labs produced milligram quantities; GMP scale-up required CMOs with liposome expertise, and available capacity was prioritised for established pharmaceutical programmes (Fernandes et al., 2023). IND-enabling studies required approximately $5-10 million--well beyond NIH rapid-response awards (~$200-500K) and below BARDA's IND-readiness threshold. Gilead had no commercial incentive to support reformulations potentially cannibalising its remdesivir franchise; without industry partnership, academic groups lacked

independent resources. By the time formulation optimisation could have been completed (~12 months), vaccination was widespread and therapeutic demand had substantially declined. Even platforms with established regulatory precedent cannot translate within pandemic timelines without pre-existing manufacturing partnerships and coordinated development pathways.

Comparative Analysis: Why Others Succeeded

mRNA Vaccines: Prior Preparation as the Decisive Factor

mRNA-LNP vaccines achieved EUA approximately 11 months after the SARS-CoV-2 sequence was published. Three factors were decisive (Kashte et al., 2021; Thi et al., 2021). First, prior platform maturation: Moderna received more than $1 billion from DARPA/BARDA before 2020; by January 2020, companies were applying established delivery platforms to a new target--they did not invent LNP systems de novo. Second, established manufacturing partnerships: Moderna's pre-existing relationship with Lonza and BioNTech's partnership with Pfizer enabled rapid scale-up when Operation Warp Speed funding became available. Third, prior regulatory engagement: mRNA-LNP developers had engaged FDA on platform-level expectations from 2018, establishing characterisation and safety precedents before the pandemic (Guerrini et al., 2022). The central lesson is that Operation Warp Speed's ~$18 billion provided the final push for technologies already approaching readiness--it could not substitute for the decade of prior platform development.

Conventional Antivirals: Accumulated Infrastructure Advantages

Remdesivir progressed rapidly because it was repurposed from ongoing Ebola trials: human safety data existed, limited-scale manufacturing was operational, and regulatory pathways for nucleoside analogues were established (Eastman et al., 2020). Small-molecule antivirals benefited from decades of accumulated manufacturing expertise, mature and predictable regulatory frameworks, extensive CMO capacity, established supply chains, and well-defined reimbursement pathways (Varahachalam et al., 2021). Nanomedicines lacked each of these advantages; even adapting approved oncology nanoformulations to antiviral indications required substantial new development, eliminating repurposing speed benefits (Xu et al., 2022; Sher et al., 2024).

DISCUSSION

Systemic Failure Modes: Cascade Effects and Barrier Interdependence

The most important analytical finding is that barriers formed mutually reinforcing cascades rather than acting independently. The VivaGel case illustrates a representative sequence: manufacturing complexity for systemic reformulation triggered regulatory requirements for extensive new studies, which increased capital requirements beyond small-biotech capacity, deterring partnership negotiations that extended beyond pandemic-relevant timelines, ultimately exhausting the therapeutic opportunity window (Rupp et al., 2007). Manufacturing-regulatory cascades were particularly entrenched: batch variability prompted extensive characterisation requirements, which increased manufacturing complexity and cost, which discouraged the investment needed for process optimisation, perpetuating variability (Csoka et al., 2021; Kwon et al., 2024). Economic-institutional cascades created lock-in effects: without procurement commitments, private investment carried unacceptable risk; without investment, academic research remained laboratory-scale; without scale-up, manufacturing challenges went unresolved; without manufacturing infrastructure, agencies perceived no procurable product; without procurement potential, commitments did not emerge. Breaking such cascades required coordinated multi-domain intervention--a level of coordination that existed for mRNA vaccines through Operation Warp Speed but was wholly absent for antiviral nanotechnologies (Van Norman, 2020; CRS, 2021).

Distinguishing Platform-Level from Implementation-Level Barriers

A conceptually important distinction emerges: some barriers are intrinsic to nanotechnology platforms (platform-level limitations), while others arise from the systems through which development occurs (implementation-level challenges). Platform-level limitations--batch-to-batch variability, protein corona alteration of in vivo behaviour, inherent manufacturing complexity at colloidal scale--may be partially mitigated through scientific and process

advances (microfluidic manufacturing, process analytical technology, formulation standardisation) but cannot be eliminated by policy alone. Implementation-level challenges--regulatory pathway ambiguity, funding discontinuities, IP fragmentation, absent preparedness infrastructure--are not inherent to the technology and are, in principle, amenable to policy, institutional, and economic interventions. Effective preparedness strategy requires clearly distinguishing these categories, since solutions applicable to implementation failures may be ineffective against platform-level constraints.

The LMIC Dimension

While this review is principally US-focused, the barriers identified have differential implications globally. In HIC settings, the primary barriers are economic and institutional. In LMIC settings, these are compounded by absent GMP manufacturing capacity, limited regulatory expertise for novel nanomedicines, severely constrained healthcare financing, and cold-chain infrastructure deficits (Kirtane et al., 2021). The cost-of-goods barrier, already substantial in HIC contexts, becomes prohibitive in LMICs where per capita healthcare expenditure may be less than $100 annually. Future preparedness strategies must explicitly address LMIC-specific manufacturing and regulatory capacity rather than assuming technologies developed in HIC settings will be accessible globally within pandemic timescales.

Timing Mismatches and the Pre-Preparation Imperative

Novel nanomedicines typically require 10-15 years from discovery to approval (Younis et al., 2022). COVID-19 demanded deployable therapeutics within months. Technologies requiring multi-year development fundamentally could not meet this demand. The "too late for COVID-19, too early for the next pandemic" dilemma aptly characterises platforms aggressively pursued from 2020: by the time technical maturity was reached, pandemic funding priorities and political attention had shifted (Kim et al., 2021). The only viable solution is pre-pandemic preparation sufficient to close the development gap--precisely the approach that succeeded for mRNA vaccines. Institutional timelines worsen the mismatch further: regulatory guidance development, GMP facility validation, and clinical trial network establishment all operate on 5-10-year horizons, while acute pandemic demands operate at month scale.

The Missing Ecosystem

Successful pharmaceutical development depends on interconnected ecosystems of infrastructure, expertise, and institutions evolved over decades for conventional modalities. A functional antiviral nanotechnology ecosystem would require: academic programmes integrating nanoscience with regulatory science and manufacturing; contract research and manufacturing organisations skilled in nanoparticle GMP production; standardised pharmacopoeial characterisation methods; infectious-disease-specific regulatory precedents; dedicated clinical trial networks; and reimbursement pathways recognising nanoformulation value. Most elements were limited, fragmented, or absent in 2020. Oncology nanomedicine illustrates what sustained commitment achieves: long-term investment produced partial ecosystems and a modest number of approved products (Shan et al., 2022). Infectious disease nanomedicine lacked comparable commitment. COVID-19 revealed this absence as a public health vulnerability, not merely an academic shortcoming.

Policy Implications and Recommendations

Phased Preparedness Strategy

Phase 1 (years 1-5)--Platform Maturation: Prioritise two to three lead platforms based on mechanism diversity

and clinical progress; invest in manufacturing process development and optimisation; establish robust characterisation standards; generate comprehensive preclinical safety datasets; form durable academic-industry partnerships with clear transition pathways (Wu et al., 2020; Varahachalam et al., 2021). Phase 2 (years 5-10)--Infrastructure Building: Create GMP manufacturing capacity for prioritised platforms; develop regulatory guidance through structured FDA-developer collaboration; establish clinical trial networks specialised in nanomedicine for infectious diseases; initiate Phase I safety trials for lead candidates; build dedicated workforce

training programmes (FDA, 2017, 2018). Phase 3 (beyond 10 years)--Readiness Maintenance: Preserve manufacturing capacity during inter-pandemic periods through dual-use applications; continue iterative platform refinement as scientific understanding evolves; update regulatory frameworks based on emerging evidence (Tureli & Tureli, 2020).

Platform-Based and Modular Development

Adaptable platforms enabling rapid retargeting could substantially shorten response times. Analogous to mRNA vaccines--where only the encoded antigen required modification for SARS-CoV-2--antiviral nanotechnology platform strategies could include broad-spectrum mechanisms (viral envelope disruption, innate immune activation) requiring minimal adaptation; modular designs where targeting ligands can be exchanged while core physicochemical properties remain stable; and universal delivery vehicles transporting diverse antiviral cargos. While broad-spectrum strategies may sacrifice potency or specificity, even partially adaptable platforms offer meaningful advantages over de novo design under emergency conditions (Patel & Pathak, 2021).

Priority Policy Actions

For government agencies: create a dedicated translational funding mechanism ($10-50M awards over 3-5 years) bridging NIH discovery research and BARDA procurement requirements; establish national GMP nanomedicine manufacturing centres accessible to academic groups and small companies; develop advance market commitments for antiviral nanotechnologies meeting predefined performance criteria; and mandate biennial preparedness assessments evaluating whether emerging platforms possess requisite manufacturing, regulatory, and coordination infrastructure (Van Norman, 2020; CRS, 2021). For regulatory agencies: issue platform-specific guidance for liposomes, dendrimers, and polymeric nanoparticles with acceptable characterisation methods and safety study designs; establish formal pre-IND dialogue programmes; and harmonise requirements through ICH mechanisms to reduce duplicative study burdens (FDA, 2018). For academic institutions: integrate nanoscience training with regulatory science and manufacturing; establish technology transfer protocols for pandemic countermeasures with streamlined licensing; and prioritise translational metrics complementing publication counts with IND submissions and partnership formation (Sharifi et al., 2022; Shah et al., 2020). For industry: form pre-competitive consortia sharing manufacturing knowledge and regulatory strategies while protecting IP for specific formulations; invest in dual-use manufacturing maintaining nanomedicine capability through non-pandemic applications; and engage proactively with regulatory agencies to build field-wide precedents (Giubilato et al., 2020; Thapa & Kim, 2023).

CONCLUSION

COVID-19 exposed a stark but instructive gap between antiviral nanotechnology's extensive preclinical promise and its pandemic-era deployability. After more than two decades of laboratory research and thousands of publications, only three systemic clinical trials were initiated--all small, exploratory, and non-informative for clinical practice--while remdesivir, monoclonal antibodies, and mRNA vaccines reached patients within months. This failure arose not from a single scientific flaw but from mutually reinforcing cascades across manufacturing, regulatory, economic, and institutional domains that rendered isolated interventions insufficient.

Partial successes--diagnostic nanoparticle platforms, liposomal oncology products, and mRNA vaccines themselves--demonstrate that the technology class is not inherently untranslatable. Context-specific enabling factors, principally pre-pandemic platform maturation, manufacturing partnerships, regulatory engagement, and coordinated public funding, determined outcomes. The central lesson is precise: technologies not already prepared when a crisis begins are functionally absent, regardless of theoretical advantages.

Advancing antiviral nanotechnologies for future pandemics requires a fundamental strategic shift: from reactive, discovery-centred efforts to proactive ecosystem building. This means sustained inter-pandemic investment to bring platforms to translational maturity; deliberate development of adaptable, retargetable nanoplatforms; coordinated growth of manufacturing capacity, regulatory frameworks, and specialised clinical networks; and economic instruments--advance market commitments, translational bridging funds, pre-competitive IP arrangements--that make long-horizon, high-risk development viable. For LMIC contexts specifically,

preparedness strategies must address manufacturing capacity, regulatory expertise, and cost-of-goods constraints that differ substantially from HIC settings. Without this integrated, long-term preparation, the next pandemic will likely reproduce the same pattern: scientifically sophisticated nanotechnologies confined to preclinical laboratories while clinical care depends on better-prepared but more conventional modalities.

Declarations

Ethics Approval

Not applicable. This study is a review of published literature and publicly available data and did not involve human participants or animal subjects.

Competing Interests

The authors declare no competing interests.

Author Contributions

Somtochukwu Obu conceptualised the study, designed the review framework, conducted the literature search and analysis, and led manuscript writing. Michael Misan Eji and Doofan Bur assisted in data analysis, framework refinement, and manuscript writing and review. Chika Emeghebo Ndubuisi, Chioma Chetachukwu Ajator, and Kamsy Ibuoka contributed critical review, specialised analytical inputs, and manuscript editing. All authors read and approved the final manuscript.

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Data Availability

All data analysed in this study are derived from publicly available literature, clinical trial registries, and policy documents cited within the manuscript.

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REFERENCES

1. Abdelmonem, R., Ayman, M., Lofty, S. E., Ezzat, Y., Nabeah, J. M., Mohamed, H., & Eltahan, M. (2025). Advancing nanoparticle production: Scaling up techniques, challenges, and future perspectives in pharmaceutical applications. Journal of Pharmaceutical Sciences and Drug Manufacturing, 2(2), 26-39.
2. Afonin, K. A., Dobrovolskaia, M. A., Church, G., & Bathe, M. (2021). Opportunities, barriers, and a strategy for overcoming translational challenges to therapeutic nucleic acid nanotechnology. Therapeutic RNA Nanotechnology, 605-623.
3. Afonin, K. A., Dobrovolskaia, M. A., Ke, W., Grodzinski, P., & Bathe, M. (2022). Critical review of nucleic acid nanotechnology to identify gaps and inform a strategy for accelerated clinical translation. Advanced Drug Delivery Reviews, 181, 114081.
4. Anjum, S., Ishaque, S., Fatima, H., Farooq, W., Hano, C., Abbasi, B. H., & Anjum, I. (2021). Emerging applications of nanotechnology in healthcare systems: Grand challenges and perspectives. Pharmaceuticals, 14(8), 707.

5. Banala, V. T., Mukherjee, D., Mahajan, S., & Singh, P. K. (2022). Current status of FDA-approved marketed nano drug products: Regulatory considerations. In Multifunctional Nanocarriers (pp. 501-521). Elsevier.
6. Begines, B., Ortiz, T., Perez-Aranda, M., Martinez, G., Merinero, M., Arguelles-Arias, F., & Alcudia, A. (2020). Polymeric nanoparticles for drug delivery: Recent developments and future prospects. Nanomaterials, 10(7), 1403.
7. Caputo, F., Mehn, D., Clogston, J. D., Rosslein, M., Prina-Mello, A., Borgos, S. E., & Calzolai, L. (2021). Asymmetric-flow field-flow fractionation for measuring particle size, drug loading and (in)stability of nanopharmaceuticals. Journal of Chromatography A, 1635, 461767.
8. Chakraborty, C., Sharma, A. R., Bhattacharya, M., Agoramoorthy, G., & Lee, S.-S. (2021). The drug repurposing for COVID-19 clinical trials provide very effective therapeutic combinations. Frontiers in Pharmacology, 12, 704205.
9. Chakravarty, M., & Vora, A. (2021). Nanotechnology-based antiviral therapeutics. Drug Delivery and Translational Research, 11(3), 748-787.
10. Chen, S., Huang, X., Xue, Y., et al. (2023). Nanotechnology-based mRNA vaccines. Nature Reviews Methods Primers, 3, 63.
11. Congressional Research Service (CRS). (2021). Operation Warp Speed contracts for COVID-19 vaccines and ancillary vaccination materials.
12. Croci, R., Bottaro, E., Chan, K. W. K., Watanabe, S., Pezzullo, M., Mastrangelo, E., & Nastruzzi, C. (2016). Liposomal systems as nanocarriers for the antiviral agent ivermectin. International Journal of Biomaterials, 2016, 8043983.
13. Csoka, I., Ismail, R., Jojart-Laczkovich, O., & Pallagi, E. (2021). Regulatory considerations, challenges and risk-based approach in nanomedicine development. Current Medicinal Chemistry, 28(36), 7461-7476.
14. de Souza Cardoso Delfino, C., de Paula Pereira, M. C., dos Santos Oliveira, M., et al. (2025). Scaling nanopharmaceutical production for personalized medicine: Challenges and strategies. Journal of Nanoparticle Research, 27, 108.
15. Diversa Technologies. (2025). Overcoming regulatory hurdles in clinical translation of nanomedicine. https://www.diversatechnologies.com
16. Dri, D. A., Rinaldi, F., Carafa, M., et al. (2023). Nanomedicines and nanocarriers in clinical trials: Surfing through regulatory requirements and physico-chemical critical quality attributes. Drug Delivery and Translational Research, 13, 757-769.
17. Dung, T. T. N., Nam, V. N., Nhan, T. T., Ngoc, T. T. B., Minh, L. Q., Nga, B. T. T., & Quang, D. V. (2020). Silver nanoparticles as potential antiviral agents against African swine fever virus. Materials Research Express, 6(12), 1250g9.
18. Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. (2020). Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS Central Science, 6(5), 672-683.
19. Falanga, A., Del Genio, V., & Galdiero, S. (2021). Peptides and dendrimers: How to combat viral and bacterial infections. Pharmaceutics, 13(1), 101.
20. FDA. (2017). Drug products, including biological products, that contain nanomaterials: Guidance for industry (Draft).
21. FDA. (2018). Nanotechnology guidance documents. https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents
22. FDA. (2022). Drug products, including biological products, that contain nanomaterials: Guidance for industry.
23. Ferdous, Z., & Nemmar, A. (2020). Health impact of silver nanoparticles: A review of the biodistribution and toxicity following various routes of exposure. International Journal of Molecular Sciences, 21(7), 2375.
24. Fernandes, C., Jathar, M., Sawant, B. K. S., & Warde, T. (2023). Scale-up of nanoparticle manufacturing process. In A. B. Jindal (Ed.), Pharmaceutical Process Engineering and Scale-up Principles. Springer.
25. Filipczak, N., Yalamarty, S. S. K., Li, X., Parveen, F., & Torchilin, V. (2021). Developments in treatment methodologies using dendrimers for infectious diseases. Molecules, 26(11), 3304.

26. Foulkes, R., Man, E., Thind, J., Yeung, S., Joy, A., & Hoskins, C. (2020). The regulation of nanomaterials and nanomedicines for clinical application: Current and future perspectives. Biomaterials Science, 8(17), 4653-4664.
27. Ghosh, D., & Kumar, A. (2024). Regulatory landscape and expedited pathways for nanomedicines. Drug Discovery Today, 29(3), 103-115.
28. Giubilato, E., Cazzagon, V., Amorim, M. J. B., Blosi, M., Bouillard, J., Bouwmeester, H., & Hristozov, D. (2020). Risk management framework for nano-biomaterials used in medical devices and advanced therapy medicinal products. Materials, 13(20), 4532.
29. Gote, V., Bolla, P. K., Kommineni, N., Butreddy, A., Nukala, P. K., Palakurthi, S. S., & Khan, W. (2023). A comprehensive review of mRNA vaccines. International Journal of Molecular Sciences, 24(3), 2700.
30. Guerrini, G., Magri, D., Gioria, S., et al. (2022). Characterization of nanoparticles-based vaccines for COVID-19. Nature Nanotechnology, 17, 570-576.
31. Guy, R. K., DiPaola, R. S., Romanelli, F., & Dutch, R. E. (2020). Rapid repurposing of drugs for COVID-19. Science, 368(6493), 829-830.
32. Hashiba, K., Taguchi, M., Sakamoto, S., et al. (2024). Overcoming thermostability challenges in mRNA-lipid nanoparticle systems with piperidine-based ionizable lipids. Communications Biology, 7, 556.
33. Hu, C., He, X., Gao, H., & Zhang, J. (2025). DELIVER: The core principles for the clinic translation of nanomedicines. Acta Pharmaceutica Sinica B, 15(2), 1196-1198.
34. Javan, F., Vatanara, A., Azadmanesh, K., Nabi-Meibodi, M., & Shakouri, M. (2017). Encapsulation of ritonavir in solid lipid nanoparticles: In-vitro anti-HIV-1 activity using lentiviral particles. The Journal of Pharmacy and Pharmacology, 69(8), 1002-1009.
35. Jbara-Agbaria, D., Blondzik, S., Burger-Kentischer, A., Agbaria, M., Nordling-David, M. M., Giterman, A., & Golomb, G. (2022). Liposomal siRNA formulations for the treatment of herpes simplex virus-1. Pharmaceutics, 14(3), 633.
36. Joudeh, N., & Linke, D. (2022). Nanoparticle classification, physicochemical properties, characterization, and applications: A comprehensive review for biologists. Journal of Nanobiotechnology, 20, 262.
37. Joyce, P., Allen, C. J., Alonso, M. J., Ashford, M., Bradbury, M. S., Germain, M., & Santos, H. A. (2024). A translational framework to DELIVER nanomedicines to the clinic. Nature Nanotechnology, 19(11), 1597-1611.
38. Kashte, S., Gulbake, A., El-Amin, S. F., III, et al. (2021). COVID-19 vaccines: Rapid development, implications, challenges and future prospects. Human Cell, 34, 711-733.
39. Khairnar, S. V., Pagare, P., Thakre, A., Nambiar, A. R., Junnuthula, V., Abraham, M. C., & Dyawanapelly, S. (2022). Review on the scale-up methods for the preparation of solid lipid nanoparticles. Pharmaceutics, 14(9), 1886.
40. Kim, E., Lim, E. K., Park, G., Park, C., Lim, J. W., Lee, H., & Haam, S. (2021). Advanced nanomaterials for preparedness against (re-)emerging viral diseases. Advanced Materials, 33(47), 2005927.
41. Kirtane, A. R., Verma, M., Karandikar, P., et al. (2021). Nanotechnology approaches for global infectious diseases. Nature Nanotechnology, 16, 369-384.
42. Kwon, S., Youtie, J., Porter, A., et al. (2024). How does regulatory uncertainty shape the innovation process? Evidence from the case of nanomedicine. Journal of Technology Transfer, 49, 262-302.
43. Lamb, Y. N. (2020). Remdesivir: First approval. Drugs, 80, 1355-1363.
44. Lamoot, A., Lammens, J., De Lombaerde, E., Zhong, Z., Gontsarik, M., Chen, Y., & De Geest, B. G. (2023). Successful batch and continuous lyophilization of mRNA LNP formulations depend on cryoprotectants and ionizable lipids. Biomaterials Science, 11(12), 4327-4334.
45. Liu, X., & Meng, H. (2021). Consideration for the scale-up manufacture of nanotherapeutics: A critical step for technology transfer. VIEW, 2(5), 20200190.
46. Lloyd, E. C., Gandhi, T. N., & Petty, L. A. (2021). Monoclonal antibodies for COVID-19. JAMA, 325(10), 1015.
47. Malik, R., & Patil, S. (2020). Nanotechnology: Regulatory outlook on nanomaterials and nanomedicines in United States, Europe and India. Applied Clinical Research, Clinical Trials and Regulatory Affairs, 7(3), 225-236.
48. Mangla, B., Kumar, P., Javed, S., Pathan, T., Ahsan, W., & Aggarwal, G. (2025). Regulating nanomedicines: Challenges, opportunities, and the path forward. Nanomedicine, 20(15), 1911-1927.

49. Marovich, M., Mascola, J. R., & Cohen, M. S. (2020). Monoclonal antibodies for prevention and treatment of COVID-19. JAMA, 324(2), 131-132.
50. Mastrangelo, E., Mazzitelli, S., Fabbri, J., Rohayem, J., Ruokolainen, J., Nykanen, A., & Bolognesi, M. (2014). Delivery of suramin as an antiviral agent through liposomal systems. ChemMedChem, 9(5), 933-939.
51. Metselaar, J. M., & Lammers, T. (2020). Challenges in nanomedicine clinical translation. Drug Delivery and Translational Research, 10, 721-725.
52. Ndayishimiye, J., Kumeria, T., Popat, A., Falconer, J. R., & Blaskovich, M. A. (2022). Nanomaterials: The new antimicrobial magic bullet. ACS Infectious Diseases, 8(4), 693-712.
53. Okafor, N. I., & Nnaji, N. J. (2024). Liposomes, facilitating the encapsulation and improved solubility of zidovudine antiretroviral drug. BioNanoScience, 14, 4877-4894.
54. Pallerla, S., Pires, I. S., Melo, M. B., Yun, D., Wagner, A., Budai, M., & Irvine, D. J. (2025). Scale-up and cGMP manufacturing of next-generation vaccine adjuvant saponin/MPLA nanoparticles (SMNP). Journal of Pharmaceutical Sciences, 103913.
55. Patel, J. K., & Pathak, Y. V. (Eds.). (2021). Emerging technologies for nanoparticle manufacturing (pp. 109-128). Springer.
56. Peter, R. M. (2025). mRNA vaccine funding cuts: The impact on U.S. healthcare and biotech. Labiotech.
57. Pokrajac, L., Abbas, A., Chrzanowski, W., Dias, G. M., Eggleton, B. J., Maguire, S., & Mitra, S. (2021). Nanotechnology for a sustainable future. ACS Nano, 15(11), 18608-18623.
58. Pu, Y., Zhu, C., Liao, J., Gong, L., Wu, Y., Liu, S., Wang, H., Zhang, Q., & Lin, Z. (2025). Antiviral nanomedicine: Advantages, mechanisms and advanced therapies. Bioactive Materials, 52, 92-122.
59. Rai, M., Bonde, S., Yadav, A., Plekhanova, Y., Reshetilov, A., Gupta, I., & Ingle, A. P. (2022). Nanotechnology-based promising strategies for the management of COVID-19. Expert Review of Anti-Infective Therapy, 20(10), 1299-1308.
60. Ratan, Z. A., Mashrur, F. R., Chhoan, A. P., Shahriar, S. M., Haidere, M. F., Runa, N. J., & Cho, J. Y. (2021). Silver nanoparticles as potential antiviral agents. Pharmaceutics, 13(12), 2034.
61. Reinhart, A. G., Osterwald, A., Ringler, P., Leiser, Y., Lauer, M. E., Martin, R. E., & Keller, M. (2023). Investigations into mRNA lipid nanoparticles shelf-life stability under nonfrozen conditions. Molecular Pharmaceutics, 20(12), 6492-6503.
62. Riva, L., Yuan, S., Yin, X., Martin-Sancho, L., Matsunaga, N., Pache, L., & Chanda, S. K. (2020). Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. Nature, 586(7827), 113-119.
63. Rupp, R., Rosenthal, S. L., & Stanberry, L. R. (2007). VivaGel (SPL7013 Gel): A candidate dendrimer-microbicide for the prevention of HIV and HSV infection. International Journal of Nanomedicine, 2(4), 561-566.
64. Shah, S., Nene, S., Rangaraj, N., Raghuvanshi, R. S., Singh, S. B., & Srivastava, S. (2020). Bridging the gap: Academia, industry and FDA convergence for nanomaterials. Drug Development and Industrial Pharmacy, 46(11), 1735-1746.
65. Shan, X., Gong, X., Li, J., Wen, J., Li, Y., & Zhang, Z. (2022). Current approaches of nanomedicines in the market and various stage of clinical translation. Acta Pharmaceutica Sinica B, 12(7), 3028-3048.
66. Sharifi, S., Mahmoud, N. N., Voke, E., et al. (2022). Importance of standardizing analytical characterization methodology for improved reliability of the nanomedicine literature. Nano-Micro Letters, 14, 172.
67. Shegokar, R., & Nakach, M. (2020). Large-scale manufacturing of nanoparticles: An industrial outlook. In Drug Delivery Aspects (pp. 57-77). Elsevier.
68. Sher, E. K., Alebic, M., Boras, M. M., Boskailo, E., Farhat, E. K., Karahmet, A., & Lekic, L. (2024). Nanotechnology in medicine revolutionizing drug delivery for cancer and viral infection treatments. International Journal of Pharmaceutics, 660, 124345.
69. Sindhwani, S., & Chan, W. C. (2021). Nanotechnology for modern medicine: Next step towards clinical translation. Journal of Internal Medicine, 290(3), 486-498.
70. Singh, Y. D., Ningthoujam, R., Panda, M. K., Jena, B., Babu, P. J., & Mishra, A. K. (2021). Insight from nanomaterials and nanotechnology towards COVID-19. Sensors International, 2, 100099.

71. Souri, M., Chiani, M., Farhangi, A., Mehrabi, M. R., Nourouzian, D., Raahemifar, K., & Soltani, M. (2022). Anti-COVID-19 nanomaterials: Directions to improve prevention, diagnosis, and treatment. Nanomaterials, 12(5), 783.
72. Souto, E. B., Silva, G. F., Dias-Ferreira, J., Zielinska, A., Ventura, F., Durazzo, A., & Santini, A. (2020). Nanopharmaceutics: Part I - Clinical trials legislation and GMP of nanotherapeutics in the EU. Pharmaceutics, 12(2), 146.
73. Stanberry, L. R. (2007). VivaGel (SPL7013 Gel): A candidate dendrimer-microbicide for the prevention of HIV and HSV infection. International Journal of Nanomedicine, 2(4), 561-566.
74. Stretz, H. A., Kiss, A., Mealio, K. N., & Ayeni, O. O. (2025). Regulatory and environmental issues of nanotechnology safety. In Nanotechnology Safety (pp. 59-76). Elsevier.
75. Tang, Z., Zhang, X., Shu, Y., Guo, M., Zhang, H., & Tao, W. (2021). Insights from nanotechnology in COVID-19 treatment. Nano Today, 36, 101019.
76. Thapa, R. K., & Kim, J. O. (2023). Nanomedicine-based commercial formulations: Current developments and future prospects. Journal of Pharmaceutical Investigation, 53, 19-33.
77. Thi, T. T. H., Suys, E. J. A., Lee, J. S., Nguyen, D. H., Park, K. D., & Truong, N. P. (2021). Lipid-based nanoparticles in the clinic and clinical trials: From cancer nanomedicine to COVID-19 vaccines. Vaccines, 9(4), 359.
78. Traversing the valley of death. (2023). Nature Reviews Bioengineering, 1, 875.
79. Tureli, N. G., & Tureli, A. E. (2020). Upscaling and GMP production of pharmaceutical drug delivery systems. In Drug Delivery Trends (pp. 215-229). Elsevier.
80. U.S. National Library of Medicine. (n.d.). ClinicalTrials.gov. https://clinicaltrials.gov/
81. Vahedifard, F., & Chakravarthy, K. (2021). Nanomedicine for COVID-19: The role of nanotechnology in the treatment and diagnosis of COVID-19. Emergent Materials, 4, 75-99.
82. Van Norman, G. A. (2020). "Warp Speed" operations in the COVID-19 pandemic: Moving too quickly? JACC: Basic to Translational Science, 5(7), 730-734.
83. Varahachalam, S. P., Lahooti, B., Chamaneh, M., Bagchi, S., Chhibber, T., Morris, K., & Kaushik, A. (2021). Nanomedicine for the SARS-CoV-2: State-of-the-art and future prospects. International Journal of Nanomedicine, 16, 539-560.
84. Webb, C., Forbes, N., Roces, C. B., Anderluzzi, G., Lou, G., Abraham, S., & Perrie, Y. (2020). Using microfluidics for scalable manufacturing of nanomedicines from bench to GMP. International Journal of Pharmaceutics, 582, 119266.
85. Wu, L. P., Wang, D., & Li, Z. (2020). Grand challenges in nanomedicine. Materials Science and Engineering: C, 106, 110302.
86. Xu, C., Lei, C., Hosseinpour, S., Ivanovski, S., Walsh, L. J., & Khademhosseini, A. (2022). Nanotechnology for the management of COVID-19 during the pandemic and in the post-pandemic era. National Science Review, 9(10), nwac124.
87. Yang, D. (2021). Application of nanotechnology in the COVID-19 pandemic. International Journal of Nanomedicine, 16, 623-649.
88. Yang, K. C., Lin, J. C., Tsai, H. H., Hsu, C. Y., Shih, V., & Hu, C. J. (2021). Nanotechnology advances in pathogen- and host-targeted antiviral delivery: Multipronged therapeutic intervention for pandemic control. Drug Delivery and Translational Research, 11(4), 1420-1437.
89. Younis, M. A., Tawfeek, H. M., Abdellatif, A. A., Abdel-Aleem, J. A., & Harashima, H. (2022). Clinical translation of nanomedicines: Challenges, opportunities, and keys. Advanced Drug Delivery Reviews, 181, 114083.
90. Zhang, C., Yan, L., Wang, X., Zhu, S., Chen, C., Gu, Z., & Zhao, Y. (2020). Progress, challenges, and future of nanomedicine. Nano Today, 35, 101008.
91. Zheng, C., Li, M., & Ding, J. (2021). Challenges and opportunities of nanomedicines in clinical translation. Bio Integration, 2(2), 57.