Recent Advances in Pharmacology: integrating RNA therapeutics, targeted modalities, nano-delivery, artificial intelligence and pharmacogenomics

Rajat Kumar*[1], Sanjay Kumar Verma[1], Priyanka Bisht[1], Sunil Kumar[1]
*[1]*Motherhood University, Roorkee, Uttarakhand*

***Abstract*—Pharmacology is experiencing an era of accelerated innovation, driven by the clinical success of nucleic-acid therapeutics, refinement of targeted modalities such as antibody–drug conjugates (ADCs), breakthroughs in nanodelivery systems, and the rapid incorporation of artificial intelligence (AI) into drug discovery. Coupled with expanding pharmacogenomic knowledge, these advances are moving therapeutics from empirical dosing toward mechanism-informed, personalized strategies. This review synthesizes the latest developments (2023–2025) across these domains, examines translational successes and persistent barriers (delivery specificity, PK/PD complexity, manufacturing, data bias, regulatory adaptation), and proposes integrative pathways to accelerate safe, equitable clinical implementation.**

Keywords*— *RNA therapeutics; antibody–drug conjugates; nanocarriers; lipid nanoparticles; artificial intelligence; pharmacogenomics; precision medicine

I. INTRODUCTION

The last five years have witnessed an unprecedented acceleration in novel therapeutic modalities and enabling technologies. RNA-based therapeutics matured from proof-of-concept vaccines to a broader therapeutic portfolio (mRNA protein-replacement therapies, siRNA, antisense oligonucleotides and base-editing approaches). Parallel advances in targeted biologics — notably antibody–drug conjugates (ADCs) — and sophisticated nanocarriers have improved tissue-selective delivery and therapeutic indices. Meanwhile, AI/ML tools have entered mainstream workflows for target identification, molecular design, and ADMET prediction, while pharmacogenomics increasingly informs patient stratification and dosing. Translating these advances into routine practice requires integrating pharmacology, bioengineering, computational science, and regulatory modernization.[1,2]

II. RNA THERAPEUTICS: SCOPE, PHARMACOLOGY AND DELIVERY ADVANCES

2.1 Modalities and clinical landscape

The portfolio of RNA therapeutics now spans mRNA therapies (vaccines, protein-replacement), siRNA and short-interfering oligonucleotides (for gene silencing), antisense oligonucleotides (ASOs), and RNA-editing systems (base editors, CRISPR–Cas RNA-targeting strategies) under clinical evaluation. The COVID-19 mRNA vaccines validated lipid nanoparticle (LNP) delivery in humans and catalysed broader investment in mRNA therapeutics for inherited diseases, oncology, and protein-replacement therapy. Several siRNA/ASO drugs have reached regulatory approval over the past decade, and the number of clinical-stage mRNA therapies has been expanding rapidly.[2,3]

2.2 Pharmacokinetic and pharmacodynamic considerations

RNA modalities have unique PK/PD behaviours compared with small molecules and biologics. Factors that determine duration and magnitude of effect include stability of the nucleic acid (chemical modifications), efficiency of cellular uptake, endosomal escape, intracellular half-life, and immune recognition. For mRNA therapeutics, protein expression kinetics are governed by mRNA sequence/structure, untranslated regions, and the delivery vehicle; for siRNA/ASO, potency and duration relate to intracellular RISC engagement or RNase H activity and tissue residence time. Quantitative pharmacology frameworks and translational PK/PD modelling (including physiologically based PK) are being developed to predict human dosing and duration of effect. [4,5]

2.3 Delivery innovations

Delivery remains the critical bottleneck for expanding RNA therapeutics beyond the liver. Lipid nanoparticles (LNPs) remain the dominant clinical delivery platform, with innovations in ionizable lipids, PEG-lipids, helper lipids, and surface modifications to improve tissue tropism, reduce immunogenicity, and optimize endosomal escape. Ligand-directed approaches (e.g., GalNAc conjugation for hepatocyte targeting) have enabled robust liver delivery for siRNAs. Emerging strategies include membrane-modified LNPs, targeted polymeric nanocarriers, exosome-mimetic vesicles, and local/implantable delivery systems for tissue-restricted applications. The field is actively pursuing strategies to reach difficult tissues—central nervous system, lung parenchyma, muscle, and tumors—via route-of-administration tailoring and ligand-mediated targeting.[3,27]

2.4 Safety and immunogenicity

Innate immune activation (TLR/MDA5 sensing) and complement activation-related pseudo allergy (CARPA) are key safety considerations for nucleic-acid therapeutics and nanoparticle carriers. Chemical modifications to nucleotides, optimization of LNP composition, and refined dosing strategies have reduced reactogenicity, but long-term safety—particularly for repeat-dosing in chronic indications—remains under active study. Regulatory guidance increasingly emphasizes standardized immunotoxicity assays and monitoring in clinical trials.[1,4]

III. ANTIBODY–DRUG CONJUGATES (ADCs): PHARMACOLOGY, DESIGN AND CLINICAL PROGRESS

3.1 From concept to clinic

ADCs combine monoclonal antibodies with potent cytotoxic payloads linked via cleavable or non-cleavable linkers, enabling targeted delivery of chemotherapy to antigen-expressing cells. Over the past decade ADC technologies matured—improved site-specific conjugation, optimized linker chemistries, and novel payload classes—leading to increasing regulatory approvals across oncology indications. Recent reviews (2023–2025) highlight a growing ADC clinical arsenal and an expanding pipeline.[6,7]

3.2 PK/PD complexity

ADCs exhibit multi-modal PK: the intact conjugate, partially deconjugated antibody, free payload, and metabolite profiles all influence efficacy and toxicity. Drug–antibody ratio (DAR) heterogeneity, in vivo linker stability, and target-mediated disposition complicate PK/PD modelling. Model-informed dose selection (including exposure–response analyses) has become a standard tool to rationalize dosing for ADCs. Advances in bioanalytical assays now allow separate quantification of conjugated vs. unconjugated species, improving translational pharmacology.[8,9]

3.3 Resistance and combination strategies

Resistance mechanisms—antigen downregulation, impaired internalization, efflux of payloads—limit ADC durability. Strategies to overcome resistance include bispecific antibodies, dual-payload ADCs, linker optimization for bystander killing, and rational combinations with immunotherapies and small molecules. Clinical trials are increasingly designed to test ADCs in combinations guided by mechanistic pharmacology.[10,21]

IV. NANOTECHNOLOGY AND ADVANCED DRUG-DELIVERY PLATFORMS

4.1 Types and functional design

Nanocarriers encompass lipid nanoparticles, polymeric nanoparticles, inorganic nanoparticles (e.g., gold, silica), dendrimers, and hybrid materials. Design variables (size, surface charge, surface ligands, biodegradability, stimuli-responsiveness) dictate circulation lifetime, biodistribution, cellular uptake, and release kinetics. Stimuli-responsive systems (pH, redox, enzyme-activated) and multi-functional “theranostic” nanoparticles are active research areas. Reviews from 2023–2025 summarize advances and design paradigms. [13,14,25]

4.2 Translational challenges

Despite attractive preclinical data, translation to the clinic faces hurdles: manufacturing scale-up and reproducibility, batch-to-batch quality control, immune interactions (opsonization, complement activation), off-target accumulation (RES organs), and the limited predictive power of animal models for human biodistribution. Standardized characterization methods and regulatory pathways for complex nanomedicines are still evolving. [12,15]

4.3 Clinical successes and case studies

LNP formulations for mRNA vaccines marked a watershed clinical success. Nanomedicines (e.g., liposomal doxorubicin) have earlier market precedents; more recent LNP-based therapeutics (siRNA drugs) and polymer–drug conjugates show that nanodelivery can be clinically viable when target tissue, dosing regimen, and manufacturing are aligned. Integrating quantitative translation frameworks (PBPK, microphysiological systems) improves candidate selection. [1,2,23]

V. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN PHARMACOLOGY

5.1 Roles and milestones

AI/ML contributes across the drug lifecycle: target discovery, de novo molecular design (generative models), virtual screening, ADMET prediction, and trial design optimization. Recent years saw the first AI-designed small molecules enter clinical testing; advances in protein structure prediction and generative chemistry have accelerated hit-to-lead cycles. Reviews and perspective pieces in 2023–2025 document both capabilities and limitations. [17,18]

5.2 Opportunities in pharmacology

AI can optimize PK/PD models, suggest structural modifications to modulate metabolic clearance or permeability, and integrate multi-omics datasets to predict responders vs non-responders. Hybrid human–AI workflows, emphasis on explainability, and prospective validation studies will determine the long-term impact of AI in translational pharmacology. [19,30]

5.3 Risks, biases and governance

Machine learning models depend critically on data quality and representativeness. Bias in training datasets can propagate health disparities in predictions (e.g., pharmacogenomic models trained predominantly on European-ancestry data). Regulatory and ethical frameworks for AI in drug development are evolving; transparent model reporting and prospective, pre-registered validation are emerging best practices. [18,20,22]

VI. PHARMACOGENOMICS, BIOMARKERS AND PRECISION PHARMACOLOGY

Pharmacogenomic discoveries (e.g., CYP variants, HLA associations) and polygenic risk models are increasingly used to guide drug selection and dosing. Multi-omics integration (genomics, transcriptomics, proteomics, metabolomics) and the use of real-world data can refine predictive models for efficacy and adverse events. Implementation challenges include limited clinician familiarity, reimbursement barriers, and the need for diverse genomic databases to ensure equitable predictive performance. [8,24,28]

VII. SAFETY, REGULATORY AND ETHICAL CONSIDERATIONS

New modalities require novel regulatory pathways for complex characterisation (e.g., nanoparticle critical quality attributes, biodistribution assessment for gene-editing agents). Long-term safety surveillance for persistent or cumulative effects (repeat dosing of nucleic-acid therapies, off-target editing) remains essential. AI integration raises issues of traceability, explainability, and liability. Ethical priorities include ensuring global access, preventing exacerbation of health inequities, and safeguarding genomic data privacy. Regulatory agencies are issuing guidance documents but ongoing dialogue between developers, clinicians, and regulators is imperative. [1,11,16]

VIII. INTEGRATIVE TRENDS AND FUTURE DIRECTIONS

1. Convergence of modalities: Combining RNA therapeutics with targeted delivery (ADCs, ligand-directed nanoparticles) could enable tissue-selective gene modulation with reduced systemic exposure. [10]
2. Quantitative translation: Advanced PK/PD and PBPK models for nanoparticles and nucleic acids will improve first-in-human dose prediction and optimize regimens.[5]
3. AI-augmented translational pipelines: Integrating AI for multi-parameter optimization (potency, selectivity, manufacturability, safety) can shorten lead optimization cycles and reduce attrition. [30]
4. Population-inclusive pharmacogenomics: Building diverse genomic cohorts and deploying federated-learning approaches will reduce bias and enhance applicability across ancestries. [18,29]
5. Regulatory science maturation: Standardized assays and real-world evidence frameworks for complex biologicals and nanomaterials are essential to accelerate safe approvals. [26]

IX. CONCLUSION

Pharmacology is transitioning toward an era of modality convergence: RNA therapeutics, ADCs, and nano delivery platforms combined with AI-driven discovery and expanding pharmacogenomic knowledge point to safer, more effective, and individualized therapies. While major translational challenges remain—delivery specificity, PK/PD complexity, manufacturing scalability, data bias, and equitable access—the integrated application of quantitative pharmacology, engineering advances, and rigorous AI validation offers a practical roadmap to realize clinical impact.

REFERENCE

[1] Ezike TC, Pang Z, et al. Advances in drug delivery systems, challenges and future perspectives. *Pharmacol Rev.* 2023. PMC

[2] Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater.* 2021;6:1078–1094. Nature

[3] Ma Y, et al. A perspective of lipid nanoparticles for RNA delivery. *Exp Ther Med.* 2024. Wiley Online Library

[4] Pozdniakova N. RNA Therapeutics: Delivery Problems and Solutions—A Critical Review. *Pharmaceutics.* 2025. MDPI

[5] Zhang M, et al. Pharmacometric modeling of lipid nanoparticle-encapsulated modalities: A review. *Clin Pharmacol Ther.* 2025. PMC

[6] Wang R, et al. Antibody–Drug Conjugates (ADCs): current and future directions. *J Hematol Oncol.* 2025. BioMed Central

[7] Zhou M, et al. The next frontier in antibody-drug conjugates. *Nat Rev Clin Oncol.* 2025. PMC

[8] Géraud A, et al. Pharmacology and pharmacokinetics of antibody–drug conjugates. *Cancer Treat Rev.* 2025. cancertreatmentreviews.com

[9] Hu Q, et al. Review of dose justifications for ADCs: exposure–response considerations. *J Pharm Sci.* 2024. ScienceDirect

[10] Grairi M, et al. Antibody–drug conjugates: prospects for the next generation. *Drug Discov Today.* 2024. ScienceDirect

[11] Liu T, et al. Efficacy and safety of ADCs in the clinic: systematic review. *Front Pharmacol.* 2025. Frontiers

[12] Younis MA, et al. Clinical translation of nanomedicines: challenges and opportunities. *Adv Drug Deliv Rev.* 2022. ScienceDirect

[13] Islam S, et al. Advances in nanoparticles in targeted drug delivery: A 2025 review. *Curr Opin Chem Eng.* 2025. ScienceDirect

[14] ResearchGate. A comprehensive review on nanoparticles: from drug delivery systems to successful clinical translation. 2024. ResearchGate

[15] Abbas T, et al. Nanoparticles in Drug Delivery Systems: Challenges and Innovations. *Int J Biomed Res.* 2025. IJBR

[16] Das U, et al. Generative AI for drug discovery and protein design. *Trends Biotechnol.* 2025. ScienceDirect

[17] Tang X, et al. Survey of generative AI for de novo drug design. *Brief Bioinform.* 2024. OUP Academic

[18] Niazi SK, et al. Artificial intelligence in small-molecule drug discovery — review. *Pharmacol Res Perspect.* 2025. PMC

[19] Khater T, et al. Generative AI-based molecular optimization. *J Cheminform.* 2025. BioMed Central

[20] Bassey GE, et al. Transformative role of AI in drug development. *Drug Dev Res.* 2025. PMC

[21] Reuters. US FDA approves AstraZeneca's Datroway (datopotamab deruxtecan) for breast cancer. 2025 Jan 17. Reuters

[22] Verywell Health. Datroway approval summary. 2025. Verywell Health

[23] BiochemPEG. Industry coverage of ADC approvals and pipeline (news). 2024. ScienceDirect

[24] Ezike TC, et al. Multi-omics and pharmacogenomics in clinical practice: recent perspectives. *Clin Pharmacol Ther.* 2024. PMC

[25] Sadee W, et al. Pharmacogenomics: driving personalized medicine. *Clin Pharmacol Ther.* 2023. (review) PMC

[26] Ma Y, et al. Membrane modifications and LNP tropism strategies. *Exp Ther Med.* 2024. Wiley Online Library

[27] Chowdhury CR, et al. Membrane-modified lipid nanoparticles for RNA delivery—methods review. *Mol Ther Methods Clin Dev.* 2025. Cell

[28] Zhang M, et al. PBPK considerations for LNPs—perspective. *Clin Pharmacol Ther.* 2025. PMC

[29] Tang X, et al. Data-driven de novo design: impact of chemical libraries and AI. *Brief Bioinform.* 2024. OUP Academic

[30] ACS Omega. AI-driven drug discovery: comprehensive review (2025). ACS Publications