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Journal of Nanomedicine & Biotherapeutic Discovery

Opinion Article

Nanoparticle-Based Delivery of Antisense Oligonucleotides

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DESCRIPTION

Nanoparticle-Based delivery of antisense oligonucleotides represents an important area of investigation because it addresses several limitations that can restrict the clinical performance of biological medicines. In conventional formulations, therapeutic molecules may undergo rapid degradation, limited tissue distribution, short systemic exposure, or inefficient access to intracellular targets. Nanomedicine provides a means of altering these limitations by placing a therapeutic payload within a defined physicochemical environment. The carrier can influence circulation, tissue interaction, cellular uptake, intracellular trafficking, and release. This is particularly relevant for biotherapeutics because proteins, peptides, antibodies, and nucleic acids are sensitive to enzymatic degradation and changes in their surrounding environment. A useful formulation must therefore be considered as an integrated therapeutic system rather than simply as a drug enclosed within a nanoscale material.

The principal formulation is protecting oligonucleotides from nuclease degradation and supporting intracellular hybridization with Ribonucleic Acid (RNA). After administration, a nanocarrier encounters proteins, immune cells, endothelial barriers, extracellular matrices, and cellular membranes before the payload reaches its intended site of action. Particle size, surface charge, morphology, composition, and colloidal stability can influence each of these stages. A formulation that performs well in a simplified laboratory medium may behave differently in blood or diseased tissue. For this reason, formulation development should combine physicochemical characterization with biological testing. Encapsulation efficiency, payload integrity, release kinetics, particle-size distribution, surface properties, and stability are useful measurements, but they become more informative when linked to cellular uptake, pharmacodynamic activity, and tissue distribution.

Targeting is another major consideration. Passive accumulation may occur in tissues with altered vascular permeability, but this effect is variable and should not be assumed to occur equally across diseases or patients. Active targeting can involve antibodies, peptides, carbohydrates, aptamers, receptor ligands, or cell-derived components that promote interaction with selected cells. However, attachment of a targeting ligand does not automatically produce selective therapeutic delivery. Receptor abundance, ligand accessibility, protein-corona formation, endocytosis, receptor recycling, and tissue penetration can all modify performance. For many biotherapeutics, intracellular localization is as important as tissue localization. Demonstrating productive delivery therefore requires evidence that the payload reaches the biological compartment where it can exert its intended effect.

Safety and pharmacokinetics are central to translation. Nanocarriers can change the distribution and elimination of their associated payloads and may consequently alter both efficacy and toxicity. Interaction with complement proteins, macrophages, endothelial cells, and other immune components can influence circulation and organ accumulation. Repeated administration introduces additional considerations because immune recognition, clearance, or tissue retention may change over time. Safety assessment should therefore extend beyond simple cell viability assays and include appropriate evaluation of inflammatory responses, complement activation, hemocompatibility, organ distribution, degradation products, and dose-related effects. The relationship between carrier exposure and therapeutic activity should also be examined because a formulation that increases tissue concentration is not necessarily beneficial if the increase is accompanied by unacceptable toxicity.

Clinical translation presents a separate set of challenges. Laboratory formulations can be difficult to reproduce at manufacturing scale, and apparently minor changes in mixing, purification, raw materials, storage, or sterilization may influence particle characteristics. Biological payloads add another layer of complexity because their structural integrity and activity must be maintained throughout processing. Critical quality attributes should therefore be defined early, with analytical methods capable of detecting meaningful changes in the final product. Translational studies are strongest when formulation characteristics, exposure measurements, pharmacodynamic markers, and clinically relevant outcomes are evaluated together.

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Received: 01-Jul-2025, Manuscript No. JNBD-25-44301; **Editor assigned:** 03-Jul-2025, PreQC No. JNBD-25- 44301 (PQ); **Reviewed:** 16-Jul-2025, QC No. JNBD-25-44301; **Revised:** 23-Jul-2025, Manuscript No. JNBD-25-44301 (R); **Published:** 30-Jul-2025, DOI: 10.35248/2155-983X-25.15.326.

Citation: Warren O (2025). Nanoparticle-Based Delivery of Antisense Oligonucleotides. J Nanomedicine Biotherapeutic Discov. 15:326.

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The development in nanoparticle-based delivery of antisense oligonucleotides is likely to depend on closer integration of nanomaterial engineering with molecular pharmacology, bioanalytics, toxicology, and clinically relevant disease models. Greater emphasis on quantitative biodistribution and intracellular delivery should help distinguish simple tissue accumulation from therapeutically productive delivery. Manufacturing and regulatory strategies must advance alongside discovery so that promising formulations can be produced reproducibly and evaluated against clearly defined quality criteria. Patient heterogeneity is also important because receptor expression, immune status, disease stage, tissue barriers, and prior treatment can influence nanomedicine performance. The most useful advances will therefore be those that connect formulation design with measurable biological mechanisms and clinically meaningful endpoints. Such an approach can strengthen the evidence required to move biotherapeutic nanomedicines from experimental platforms toward dependable therapeutic applications.