Journal of Nanomedicine & Biotherapeutic Discovery

OPEN ACCESS Freely available online

Opinion Article

Smart Nanomaterials for the Co-Delivery of Gene and Protein Therapeutics

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DESCRIPTION

The convergence of nanomedicine and biotherapy has opened up new opportunities in the treatment of complex diseases. Among them, the co-delivery of gene and protein therapies represents an innovative approach to treat multidimensional disease pathways. Smart nanomaterials, with their programmable properties and multifunctional capabilities, offer a promising platform for integrating gene and protein delivery, thereby improving therapeutic efficacy and minimizing off-target effects. Gene and protein therapies each bring distinct advantages in disease management. Gene therapies, such as those using plasmid DNA (pDNA), small interfering RNA (siRNA), or messenger RNA (mRNA), can modulate gene expression to correct genetic defects or to block disease pathways. Protein therapies, on the other hand, provide immediate biological activity by delivering enzymes, antibodies, or cytokines directly to the target site. Co-administration of these modalities utilizes complementary mechanisms of action, providing both immediate and long-term therapeutic benefits.

Despite their potential, the simultaneous administration of genes and proteins faces significant obstacles. These include changes in physicochemical properties, stability requirements, and cellular uptake pathways. Gene therapies require protection against nucleases and efficient intracellular delivery to the nucleus or cytoplasm, while protein therapies often require stabilization against enzymatic degradation and precise targeting of functional sites. Furthermore, the different sizes, charges, and solubility profiles of these biomolecules complicate their encapsulation and release from a single delivery platform. Smart nanomaterials have emerged as versatile carriers capable of meeting the challenges of co-administration. These materials are designed with tunable properties such as pH reactivity, enzymatic degradability, and temperature sensitivity, which allow precise control of the release of the therapeutic payload. Lipid-based Nanoparticles (LNPs) are widely used for nucleic acid delivery and can be engineered to bind proteins. Their biocompatibility and ability to bind to cell membranes improve intracellular delivery. Polymers such as Poly Lactic-co-Glycolic Acid (PLGA) or Polyethyleneimine (PEI) can form nanoparticles that protect nucleic acids and proteins while providing sustained release. Hydrogels and dendrimers offer high loading capacities and customizable architectures, allowing simultaneous encapsulation and controlled release.

To improve therapeutic impact, smart nanomaterials can be functionalized with ligands, peptides, or antibodies that target specific cell types or tissues. For example, nanoparticles conjugated with transferrin or folic acid can exploit receptor-mediated endocytosis to selectively deliver therapy to cancer cells. Similarly, PEGylation improves circulation time by reducing opsonization and clearance from the Reticuloendothelial System (RES). Utility of smart nanomaterials in co-administration is illustrated by several preclinical and clinical studies. For example, lipid nanoparticles used in mRNA-based COVID-19 vaccines demonstrate the potential for efficient nucleic acid delivery. Co-delivery systems that combine siRNA with therapeutic proteins, such as Vascular Endothelial Growth Factor (VEGF), have shown promise in regenerative medicine to promote angiogenesis while silencing inhibitory genes. Nanoparticles that co-deliver the tumour suppressor gene p53 in cancer treatment and chemotherapeutic proteins have shown synergistic effects, effectively halting tumor progression in animal models. Similarly, in neurodegenerative diseases, nanocarriers that deliver neuroprotective proteins together with gene editing tools hold promise for treating complex pathological cascades.

The development of smart nanomaterials for co-delivery is still in its infancy, with many challenges ahead. Achieving precise control of the release kinetics of gene and protein therapy remains a technical hurdle. In addition, the scalability, reproducibility and regulatory approval of these systems need to be further improved. Despite these challenges, continued advances in nanotechnology, along with interdisciplinary collaborations, are expected to accelerate the translation of co-delivery systems into clinical practice. The bridge between nanomedicine and biotherapy, smart nanomaterials have the potential to revolutionize the treatment of complex diseases, ushering in a new era of precision medicine. The integration of gene and protein therapies through smart nanomaterials

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Received: 23-Oct-2024, Manuscript No. JNBD-24-36214; **Editor assigned:** 25-Oct-2024, PreQC No. JNBD-24-36214 (PQ); **Reviewed:** 08-Nov-2024, QC No. JNBD-24-36214; **Revised:** 15-Nov-2024, Manuscript No. JNBD-24-36214 (R); **Published:** 22-Nov-2024, DOI: 10.35248/2155-983X.24.14.285

Citation: Clark E (2024). Smart Nanomaterials for the Co-Delivery of Gene and Protein Therapeutics. J Nanomedicine Biotherapeutic Discov. 14:285.

represents a transformative approach to disease treatment. By overcoming current limitations and improving therapeutic precision, these innovations promise to unlock unprecedented opportunities in healthcare.