Gene delivery is the process of introducing **foreign genetic material (DNA or RNA)** into a cell to alter its function or produce a therapeutic effect. It's a central technique in **gene therapy**, **vaccine development**, **biotechnology**, and **cancer immunotherapy**.

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□ Objectives of Gene Delivery

- **Correct genetic defects** (e.g., cystic fibrosis, muscular dystrophy) - **Deliver therapeutic proteins** (e.g., insulin, clotting factors) - **Reprogram immune cells** (e.g., CAR-T cell therapy) - **Modulate gene expression** (e.g., siRNA or antisense therapies) - **Vaccination** (e.g., mRNA vaccines for COVID-19)

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□ Gene Delivery Methods

1. **Viral Vectors** - **Adenoviruses**, **lentiviruses**, **adeno-associated viruses (AAVs)** - Efficient delivery, especially to dividing and non-dividing cells - Can integrate into host genome (lentivirus) or remain episomal (AAV) - **Limitations**: immunogenicity, limited cargo capacity, potential for insertional mutagenesis

2. **Non-viral Methods** - **Lipid nanoparticles (LNPs)** – used in **mRNA vaccines** - **Electroporation** – electrical pulses to increase membrane permeability - **Gene gun** – shoots DNA-coated particles into cells - **Cell-penetrating peptides (CPPs)** – like the SLE-derived antibody from Chen et al. (2025) - **Polymeric carriers**, dendrimers, or nanocarriers

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□ Barriers to Effective Gene Delivery

- **Cell membrane** – difficult to penetrate without damaging cells - **Endosomal entrapment** – nucleic acids often get degraded in lysosomes - **Immune system** – may neutralize vectors or cause inflammation - **Target specificity** – ensuring delivery to the right cells/tissues - **Genomic integration risks** – unwanted mutations if integrating vectors are used

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□ Emerging Strategies

- **Targeted delivery** using ligands or antibodies (e.g., tumor-specific markers) - **mRNA delivery** for transient expression (no genomic integration) - **CRISPR-Cas systems** for gene editing - **Autoantibody-mediated delivery** (like in the Chen et al. study), which bypasses endosomes

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□ Clinical Applications

- **mRNA vaccines**: e.g., Pfizer/BioNTech and Moderna COVID-19 vaccines - **CAR-T therapy**: gene delivery to T cells to express chimeric antigen receptors - **Zolgensma**: AAV-based therapy for spinal muscular atrophy - **Onpattro (patisiran)**: lipid nanoparticle delivering siRNA to the liver

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⚖ Challenges and Future Directions

- Improving **efficiency and safety** - Reducing **immunogenicity** - Enabling **repeated dosing** - Achieving **precise tissue targeting** - Developing **scalable and cost-effective platforms**

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□ Summary

Gene delivery is the **cornerstone of genetic medicine**, with a wide range of therapeutic and research applications. While viral vectors remain powerful, **non-viral technologies**—especially **lipid nanoparticles** and **novel delivery peptides or antibodies**—are transforming the field by offering safer, more flexible, and more targeted delivery options.

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Would you like a comparison table of delivery methods, or help designing a teaching diagram or research slide on this topic?