

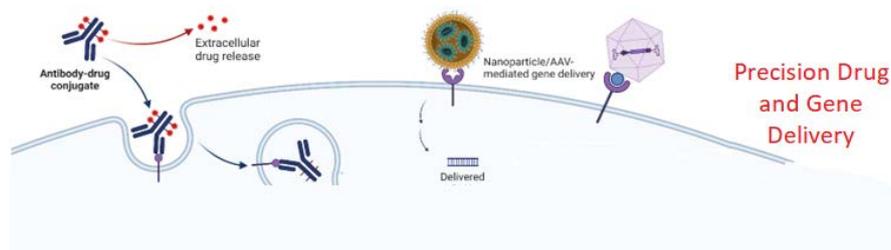
Recent trends in precision drug and gene delivery

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Editorial

ABSTRACT



Delivery is the key to the proper functioning of a system - be it in a social network or a living organism. Imagine your groceries getting delivered to your office or the birthday gift you ordered for your dear ones doesn't reach you on time. Similarly, payload must be timely delivered to the target biological sites for function, prevention, and cure. Thus, precision delivery has been one of the prime focuses of research. Over the decades, researchers have developed many efficient delivery systems for a diverse set of payloads like drug molecules, genes, nutrients, diagnostic probes, engineered cells, or nanorobots. Herein, we have discussed the recent advancement in research towards precision drug and gene delivery for various biological applications.

Keywords: Drug delivery, Gene delivery, Liposomes, Nanoparticles, targeted delivery,

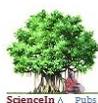
INTRODUCTION

The method of delivering a pharmaceutical compound to produce a therapeutic effect is known as drug delivery.¹ Targeted drug delivery is an optimization technique for increasing the delivered compound's therapeutic index (TI). The directional delivery of the drug guides it to reach the targeted body part of interest (organs, tissues, or cells), enhancing therapeutic efficacy by reducing off-target effects.^{2,3} There is no target selectivity in most conventional drugs used as therapeutic agents, resulting in a low therapeutic index. Peptides, monoclonal antibodies, or vitamins that act as site-specific targeting ligands and interact strongly with the receptor on the cell surface are chemically coupled to the drug delivery system in active targeting. Higher targeting specificity and fewer side effects are made possible by

the targeting ligand attachment. Drug carriers come in various forms, including colloids, polymers, monoclonal antibodies, nanoparticles (NPS), and cells (Figure 1). The type of carrier that will be used depends on the drug, the target, and the disease.⁴

On the other hand, genes regulate both normal biological function and many disease states. Thus, externally controlling gene function has been a long quest for developing therapeutic interventions.^{5,6} Small molecules have shown enormous prospects in modulating all possible cellular events - replication, transcription, translation, posttranslational modifications, or functional activity. However, the intervention of cellular pathways and cellular networks with extracellular nucleic acids remained a significant challenge due to packaging, stability, and cell membrane permeability.⁷ Successful and efficient gene delivery can open the possibility of repair or inactivation of a faulty gene, improvement through the addition of a gene, or even regulation of the cellular network. Researchers have developed numerous gene delivery methods to overcome the challenges using materials like micro-needles, electroporation, lipids, synthetic polymers, peptides, polysaccharides, nanomaterials, and viral vectors.⁸ However, non-specific gene delivery across the body may not be desirable as it may give rise to toxicity. Thus,

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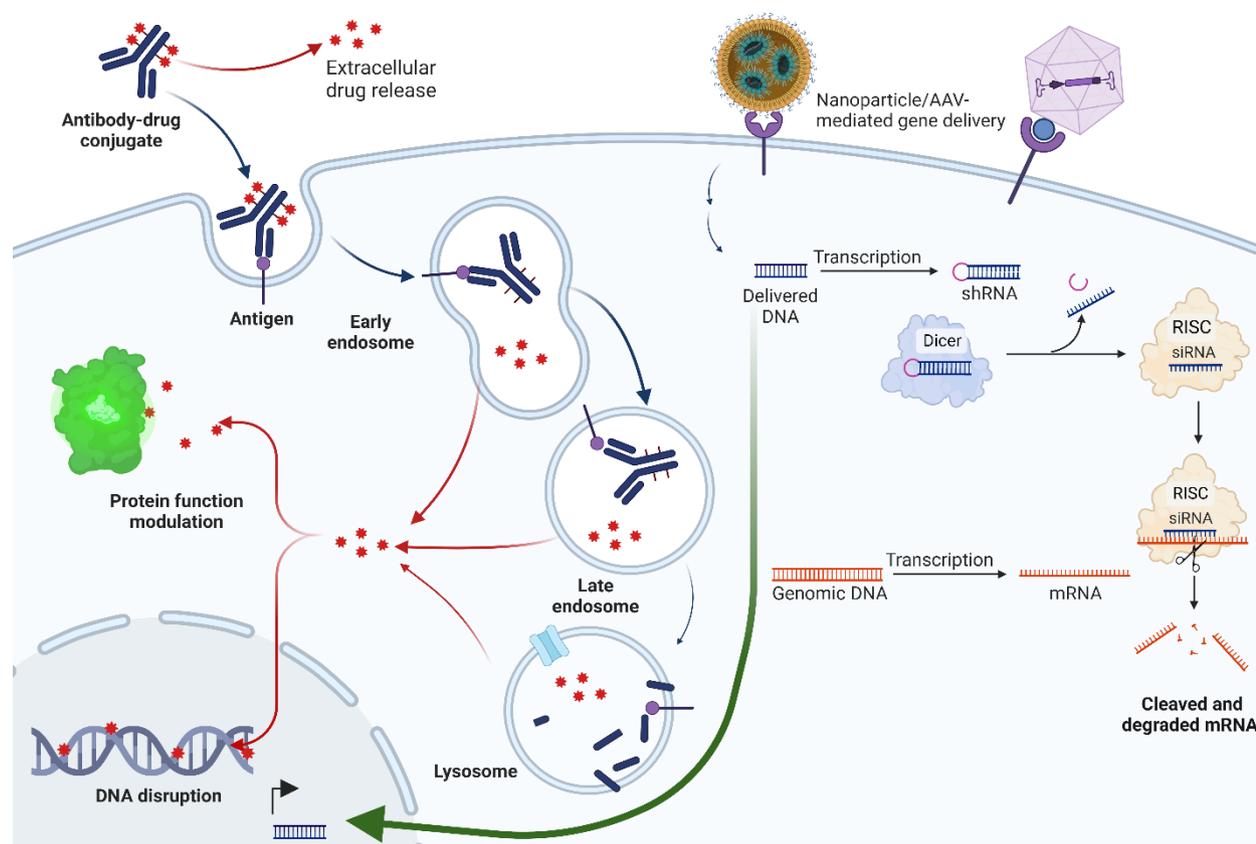


Figure 1. Depiction of receptor-targeted drug and gene delivery methods to the cells of interest. Receptor-mediated endocytosis helps the cargos enter the target cells, followed by the release of the payload via the endosomal pathway. Released drug molecules bind to their target biomolecule, modulating various cellular pathways. Genes are delivered via targeted vehicles, followed by nuclear entry and subsequent interference.

the methods that can deliver genes in a tissue-targeted manner have a higher potential in the therapeutic context. The different methods for targeted delivery of drugs and genes that are developed over the recent years are discussed below (Figure 1).

TARGETED DRUG DELIVERY METHODS

Liposomes

Liposomes are tiny, artificially created vesicles with one or more aqueous compartments and phospholipid bilayers around them. Liposomes can vary in charge, lipid composition, and size (from 20 to 10,000 nm), and these deviations significantly impact how they behave *in vivo*.⁹ Targeted drug delivery (TDD) has also been investigated for liposomes. Without covalent bonding, lipophilic prodrugs can be incorporated into the lipid core.

Several liposomal drugs are approved and available on the market. For example, liposomal amphotericin B treats fungal and protozoal infections.⁹ Liposome-PEG doxorubicin for the treatment of HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer, etc. Since Köhler and Milstein first created monoclonal antibodies in 1975, these antibodies have established their superiority over rivals in disease-treating antibody treatments. Even though there are numerous hurdles in developing efficient nanocarriers to treat solid tumors, like both

biological barriers and physiological variables, however, strategically modified liposomes can solve many of these problems.¹⁰ The functionalized liposomes have targeted cancer cell surface receptors. Surface receptors called folic acid receptors are overexpressed on a variety of cancer cells, including the lungs. Low et al. demonstrated that FR-targeted doxorubicin liposomes exhibited more cytotoxicity than straightforward doxorubicin liposomes. Folate-specific liposomes were created employing a PEG spacer to conjugate folate to the liposomes and included PEGylated lipids inside liposomes.¹⁰

Direct functionalization of drug molecules

Drug delivery that targets specific receptors is a developing area in therapeutics. However, it must overcome several obstacles related to carrier systems, targeting ligands, and receptors.¹¹ Nanocarriers can be designed in such a way that they can respond to various biological stimuli like changes in temperature, microenvironmental pH, external light source, ultrasound and magnetic field effect, and redox potential to release the cargo at the target locations.¹² The effectiveness of targeted delivery systems is influenced by competition with endogenous ligands, native and induced immunogenicity, and molecular weight-dependent tissue penetrability. Some of the

popular cell surface marker and their targeting ligands used in the targeted drug delivery are summarized in Table 1.

Table 1: Commonly used targeting ligands for targeted delivery¹²

Name	Targeting ligand	Receptor
Small molecules	Folic acid	Folate
Peptides	RGD	avb3 (integrin receptor)
	ATWLPPR (VEGF peptide)	VEGF receptor
Aptamers	Pegaptanib	VEGF receptor
Proteins Transferrin	Transferrin	Transferrin receptor
Hormone	Luteinizing releasing hormone (LHRH)	LHRH receptor
Antibodies	Herceptin (Trastuzumab)	Her2/neu (Breast cancer)
	Rituxan (Rituximab)	CD20 antigen (B-cell non-Hodgkin)
	CD19 antibody	CD19 antigen (human B-cell lymphoma)

Antibody-drug conjugates

Antibody-drug conjugates (ADC) are the conjugation of a drug with a monoclonal antibody to selectively target tumoral cell masses or lymphomas. The ideal target antigen should be overexpressed with small variation across the tumor microenvironment and low expression in normal tissue. Additionally, there should be little antigen shedding. Finally, the antibody should be efficiently internalized by receptor-mediated endocytosis and the conjugated drug should be able to escape the endosome without modification.¹³ For example, GPNMB is overexpressed in cancer cells, and Glembatumumab vedotin is its target ADC to treat breast cancer and melanoma. Folate receptor- α is the target antigen, and the corresponding ADC is Mirvetuximab soravtansine (IMGN-853). Vintafolide is used for the treatment of Ovarian and endometrial cancer. Few ADCs have been developed for the target of antigens in the tumor vasculature and stroma. Examples include Fibronectin Extradomain B (ED-B), Endothelin receptor ETB, VEGFR2 (CD309), and the corresponding ADCs are Human mAb L19 and F8, RG-7636, Anti-VEGFR-2ScFv-As2O3-stealth.^{14,15}

Synthetic Polymers

There has been exhaustive research into soluble synthetic polymers as functional drug delivery systems (DDS). The regulated drug release at targeted sites is made possible by micro- and nanospheres made from a biodegradable polymer. Polymeric nanocarriers have demonstrated promising pharmacokinetics at both the whole-body and cellular levels, such as poly(D,L-lactide-co-glycolide). The well-known N-(2-hydroxypropyl) methacrylamide (HMPA) polymers have been thoroughly investigated for use in cancer therapy.^{15,16}

Targeting intracellular metal ions

While the uncontrolled proliferation of cells, like in the case of cancer, is one of the profound healthcare challenges across the globe, on the other hand, the limited proliferation of terminally differentiated cells like pancreatic β -cell is a bottleneck in diabetes therapy. Thus, delivering pro-mitotic agents specifically to the cells of our interest could provide efficient therapeutic interventions without detrimental side effects. Based on the discovery of cellular Zn-sensor by the Lippard group,¹⁷ Timothy M. Horton and others demonstrated a zinc-chelating moiety to functionalize a β -cell proliferating molecule for targeted drug delivery.¹⁸ The group discovers that zinc-chelating compounds can preferentially accumulate within β -cell due to the intracellular high zinc content. Additionally, the bioactivity of a non-selective compound that promotes replication is biased toward β -cell when a zinc-chelating moiety is attached to it.¹⁸

Cell-specific peptidases

Targeted cancer therapy frequently employs the prodrug concept. In this strategy, active drug molecules are conjugated with a peptide molecule that can be cleaved off in the presence of cell-specific peptidases. The most common targets are lysosomal proteases like cathepsins and legumain, as well as extracellular matrix (ECM) proteases like the matrix metalloproteases (MMPs) and urokinase-type plasminogen activators (uPA). Targeting is accomplished by including a sequence-specific peptide linker as a "trigger" moiety that prevents the prodrug's free diffusion into cells but releases the cytotoxic agent upon cleavage.¹⁹

Targeted nanomaterial-based carriers

Through cell-specific targeting and molecular transport to particular organelles, nanotechnology could aid in overcoming the limitations of conventional drug delivery, from large-scale problems like biodistribution to smaller-scale barriers like intracellular trafficking.²⁰ Nanoparticles can also be accumulated in the tumor site by tethering with the targeting ligands for endothelial cells, stromal cells, macrophages, or other immune cell types in the tumor microenvironment.²¹ Instead of using drug-ligand conjugates, receptor-targeted carrier systems provide the advantages of enhanced drug loading, biocompatibility, reduced degradation, prolonged release, and site-specific drug targeting.¹¹ Nanospheres are matrix systems in which the drug is physically and evenly dispersed, while Nanocapsules are vesicular systems in which a drug is confined to a cavity and surrounded by a polymer membrane.⁹ For the targeted delivery, encapsulation, and/or for different properties, nanoparticles, nanospheres, or Nanocapsules can be prepared accordingly. Conjugation of a tumor-targeting antibody to fullerene nanoparticles (C60) can help deliver multiple anticancer drug molecules, such as Taxol.

Mesoporous silica nanoparticles (MSNs) like MCM-41 use a physical or chemical adsorption mechanism for drug loading. MSNs are widely used as significant carrier tools in controlled drug delivery systems because of their biocompatibility, ease of functionalization, porous structure framework, and homogeneous composition.^{22,23} The most appealing research strategies currently being used are magnetic nanoparticles, based on their

controllability and cargo distribution at target sites, and polymeric nanoparticles, based on their surface functionalization and biodegradability.

PRECISION GENE DELIVERY METHODS

Lipid nanoparticles

The cationic lipid-based system is one of the earliest methods used in gene delivery. Amphiphilic cationic lipid molecules form liposome structures and can encapsulate negatively charged nucleic acids (DNA and RNA), forming a complex known as lipoplex. The complex can transdeliver nucleic acids across the cell membrane. The composition and structural similarity of membranes among different cell types are responsible for the non-specific behavior of liposomes. However, the presentation of certain ligands from the liposome that can target specific cell-surface receptors can help deliver nucleic acids in a cell-specific manner. For example, peptide ligand GALA presented from liposomes enhances lung-targeted gene delivery.²⁴

Similarly, several other peptide ligands like linear and cyclic RGD, TAT peptide, PR peptide, Transferrin-poly-l-arginine, OX26 MAb, and CTX peptide-modified liposomes are known for different cancer cell-targeted gene delivery.²⁵ Small molecule ligands like folic acid, spironolactone, glucose, mannose, and poly(carboxybetaine) modified liposomes are found to deliver genes in a cell-specific manner like human cervical (KB), human prostate or help to cross the blood-brain barrier.²⁵ Other conjugation like monoclonal antibodies and aptamers also showed promising cell-targeted gene delivery activity to human breast cancer, human prostate cancer, human hepatocellular carcinoma, human leukemia, etc.^{25,26}

Polypeptides

Peptides are mostly used to make gene delivery vehicles cell-targeted by targeting various cell surface receptors. Another class of peptides, cell-penetrating peptide (CPP), can deliver payload across the cell membrane. However, specific peptides can form self-assembly and be used as non-viral vectors for gene delivery. The polarity distribution defines the key feature that promotes such peptides to form nanostructures. Based on the nature of hydrophobic and hydrophilic components, peptides are categorized as amphiphilic peptides (APs) and peptide amphiphiles (PAs).²⁷ APs are composed of hydrophobic and hydrophilic amino acid chains. The hydrophobic residues (A, I, L, M, V) and aromatic amino acids (F, W, and Y) constitute the hydrophobic region. On the other hand, charged residues (H, K, R, D, and E) and polar amino acids (S, Q, and N) provide hydrophilicity.²⁸ Based on such a principle, a peptide KHV-LHRH (K12H6V8SSQHWYSYKLRP) was designed, which showed cancer cell-specific gene delivery.²⁹ K residues provide hydrophilic properties, H residues help endosomal escape, and V residues provide a hydrophobic nature. The luteinizing hormone-releasing hormone (LHRH) helped the peptide-DNA particles target cancer cells, explicitly expressing LHRH receptors.²⁹

On the other hand, PAs are peptides functionalized by hydrophobic lipid molecules, alkyl chains, or hydrophobic organic molecules. For example, palmitoyl-GGGAAKRRK is an amphiphilic peptide conjugate that can form a peptide nanofibril

structure with siRNA and deliver it to the brain.³⁰ Palmitoyl chain and beta-sheet forming hydrophobic hexapeptide GGGAAA form the core peptide nanostructure, whereas the cationic amino acid residues KRR bind to siRNA.

Nanoparticle

Both organic and inorganic nanoparticles have been widely explored in gene delivery applications. Organic nanoparticles made of organic polymers like cationic chitosan, cationic gelatin, cationic dextrose, cationic cellulose, cationic pullulan, cationic cyclodextrin, cationic polyetherimide, poly(amidoamine) dendrimers, poly(dimethylaminoethyl methacrylate), etc showed promising gene delivery activity. Some of these nanoparticles have been functionalized for targeted gene delivery. For example, bio-reducible poly(amido amine)s-based nanoparticles showed excellent plasmid gene delivery to tonsil-derived mesenchymal stem cells (TMSCs) *in vitro* and *in vivo*.³¹ Gold nanoparticles are well known among inorganic nanoparticles due to their stability, biocompatibility, and ease of conjugation. PEGylation of cell-penetrating peptide conjugated GNPs showed efficient tumor-targeted gene delivery activity.³² Interestingly, combining organic and inorganic nanoparticles has also shown efficient gene delivery properties. For example, conjugating folic acid to PEI-carbon-dot (CD) generated nanoparticles capable of cell-targeted lung cancer gene silencing.³³ Apart from conventional material-based nanoparticles, another emerging field is DNA-based nanoparticle. Programmable DNA-sequences can be assembled into nanostructures for targeted drug delivery *in vivo*.³⁴

AAVs

The versatile viral vector technology known as adeno-associated virus (AAV) can be designed for very specific functionality in gene therapy applications. AAV has so far proven to be secure and efficient in both preclinical and clinical settings. It is extremely difficult to deliver the genes to the desired tissue. AAV vectors have received attention in the field of gene therapy in recent years due to their non-pathogenicity, distinct biological, and biophysical characteristics in humans, and their sustained and long-lasting expression after delivery. The intrinsic tissue-tropism properties of different AAV serotypes have helped delivering genes in a tissue-specific manner.^{35,36} The tissue tropism properties and their applications in targeted gene delivery have been summarized in the table 2.

FUTURE PROSPECTS

The development of active drug molecule and genetic interferons are only half on the story in the novel therapeutic approach. Many of the active drug molecules do not make it to the clinic due to their inefficient bio-availability, unintended side effects, etc. The toxicities, pharmacokinetics, and biodistribution of the drug are the main areas that need improvement for the currently available medications. In an organismal context, side effects could be due to two different mechanisms - off-target toxicity and on-target toxicity. Off-target toxicity may arise due to non-specific activities whereas on-target toxicity could be due to on-target activity but in healthy cells. While off-target toxicity can be improved by fine-tuning the drug molecules but the on-

Table 2. Summary of the tissue tropism properties and their applications in targeted gene delivery

Stereotype	Origin	Primary Receptor	Secondary receptor	Natural Tropism	Disease	Gene	Target tissue
AAV1	Non-human primate (NHP)	Sialic acid	AAV	CNS, heart, liver, and lungs.	AAT deficiency LGMDT2C Familial LPL deficiency Heart failure	AAT αSG and YSG LPL SERCA2a	Muscle Heart
AAV2	Human	heparin sulfate proteoglycan (HSPG),	integrin fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (HGFR), and laminin receptor (LamR).	CNS, heart, liver, lungs, and retina.	Cystic fibrosis Parkinson's disease AAT deficiency Hemophilia AADC deficiency Alzheimer's Disease Batten Disease Aged macular degeneration Leber congenitamaurosis	CFTR GAD, AADC, NRTN or GDNF AAT Factor IX AADC NGF CLN2 sFLT1 RPE65	Airway Brain Muscle Liver Brain Eye
AAV3	NHP	HSPG	LamR, FGFR, and AAVR	Liver	human liver diseases in general, hemophilia in particular	_____	_____
AAV4	NHP	sialic acid	Unknown	retina, lungs, and kidneys.	Leber congenital amaurosis	RPE65	Eye
AAV5	Human	sialic acid	Platelet-derived growth factor receptor (PDGFR), AAVR.	retina, CNS, liver	Hemophilia B Acute intermittent porphyria	Factor IX PBGD	Liver
AAV6		sialic acid		for heart, liver, muscle, retina	hemophilia and mucopolysaccharides	_____	_____
AAV7	NHP	Unknown	Unknown	Liver	Hemophilia Liver Diseases	_____	_____
AAV8	NHP	Unknown	LamR, AAVR	muscle, heart CNS, and Liver	Hemophilia B	Factor IX	Liver
AAV9	Human	galactose	LamR, AAVR.	heart, CNS, and Liver	Sanfilippo type B Spinal muscular atrophy 1 Pompe disease	NAGLU SMN GAA	Brain CNS Muscle
AAV10	NHP	Unknown	Unknown	muscle, myoblast tissue	Batten disease MLD Sanfilippo type A	CLN2 ARSA SGSH and SUMF1	Brain
AAV11	NHP	Unknown	Unknown	muscle, myoblast tissue	Gene therapy Vaccination testing	A-NP gene	Nasal tissue
AAV12	NHP	Unknown	Unknown	Salivary gland Muscle	Immunological properties Neutralization of resistance	_____	_____

precision medicine. The by developing efficient on-target specific delivery system. Drug nanocrystals, solid lipid-drug particles, and polymeric nanoparticles are some of the new approaches and delivery systems being researched to improve loading efficiency. In preclinical research, there have been comparatively few attempts application of nanomedicine in the emerging field of medical nanorobotics will be a promising advancement in the design, manufacture, and therapeutic deployment of pharmacocytes. Employment of engineered viruses and functionalized nano-vehicles might help us in developing precision chemotherapy and gene therapy in the near future. The intrinsic tissue-tropism properties of different AAV serotypes have helped deliver genes in a tissue-specific manner. The tissue tropism properties and their applications in targeted gene delivery have been summarized in the table 2.^{35,36}

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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