Advanced Targeting Systems for Tissue-Specific Drug Delivery

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Abstract

More than three decades of research have been necessary to understand the biological barriers that limit tissue-specific drug delivery and possible strategies to overcome them. Designing therapies with desired effectiveness but low toxicities still represents one of the major challenges in medicine. These endeavors have yielded various successes in developing targeting strategies applicable in both preclinical and clinical settings, encompassing small molecule, nucleic acid, peptide, antibody, and cell-based approaches. Most of the notable signs of progress and advancing theories in tissue-specific drug delivery are discussed below.

Keywords

Cell-based approaches · Drug delivery · Small molecule · Targeting systems

1 Introduction

The drug discovery process, intended as the development of therapeutics tailored to specific diseases, has played a crucial role in producing new potential treatment molecules for various medical conditions. While early drug discoveries often occurred by chance, the process has been significantly accelerated by the introduction of innovative tools such as structure-activity correlation, artificial intelligence-aided drug design, high-throughput screening, and combinatorial chemistry (Bhinder et al. 2021; Blay et al. 2020; Ramström and Lehn 2002). Despite the robustness of

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the lead identification process, many drugs encounter challenges in the later stages of their progress, primarily caused by their safety and efficacy. These issues usually stem from either excessive accumulation in unintended organs or in the target ones. This bottleneck has hindered the translation of promising molecules, which inherently show great potential but have failed to reveal significant clinical relevance caused by dose-linked toxicities or constrained effectiveness due to off-target effects.

To overcome these limitations, drug delivery technologies have emerged alongside the drug discovery steps (Zielinski et al. 2021). Throughout the decades, research focusing on drug delivery has presented various strategies for drug targeting, covering topical formulations and hardware (such as Gliadel wafers and drug-eluting stents). While the local approach offers a straightforward means of targeting, it may not be the right one to use when dealing with disease sites that are challenging to access. Targeted drug delivery (TDD) refers to the precise transportation of a therapeutic substance to a specific target. The primary goal is to minimize any unwanted side effects, systemic toxicity, and the necessary dosage. Ligand-based targeted drug delivery, also known as active TDD, entails the utilization of a complex called a ligand-drug conjugate. This complex consists of a targeting ligand that is connected to an active drug component. This active drug can exist either in its free form or be enclosed within a nanocarrier.

To facilitate the delivery of therapies to specific tissues, nanotechnologies have also been developed. For instance, specific physical and chemical features of nanoparticles (NPs) can be modulated, such as size and charge, enhancing their ability to reach the target; however, they encounter biological barriers that can hinder their specific targeting capabilities (Aghebati-Maleki et al. 2020; Blanco et al. 2015; Mitchell et al. 2021; Riley et al. 2019; Wang et al. 2020).

Furthermore, the advent of ligand-based drug carriers, nucleic acid–based therapies, gene therapies, and cell therapies has widened up new possibilities but has also added novel delivery issues and limitations (Kapoor et al. 2019; Khan et al. 2022; Sanjanwala and Patravale 2023).

This chapter presents the broad landscape of the targeting agents used to target specific tissues, emphasizing the unique characteristics of ligand biology, rising concepts, and clinical progresses. In general, the main strategies such as small molecules, aptamers, peptides, antibodies, and cell-based targeting approaches are delved, especially focusing on clinical translation for therapeutics administered intravascularly.

2 Biological Barriers to Biodistribution

All therapeutics that are administered intravascularly, even though their improved drug half-lives or selectivity, encounter several biological borders that severely limit site-specific bioavailability. The intricacy of these obstacles varies based on the characteristics of the therapeutics and how they are formulated (Fig. 1).

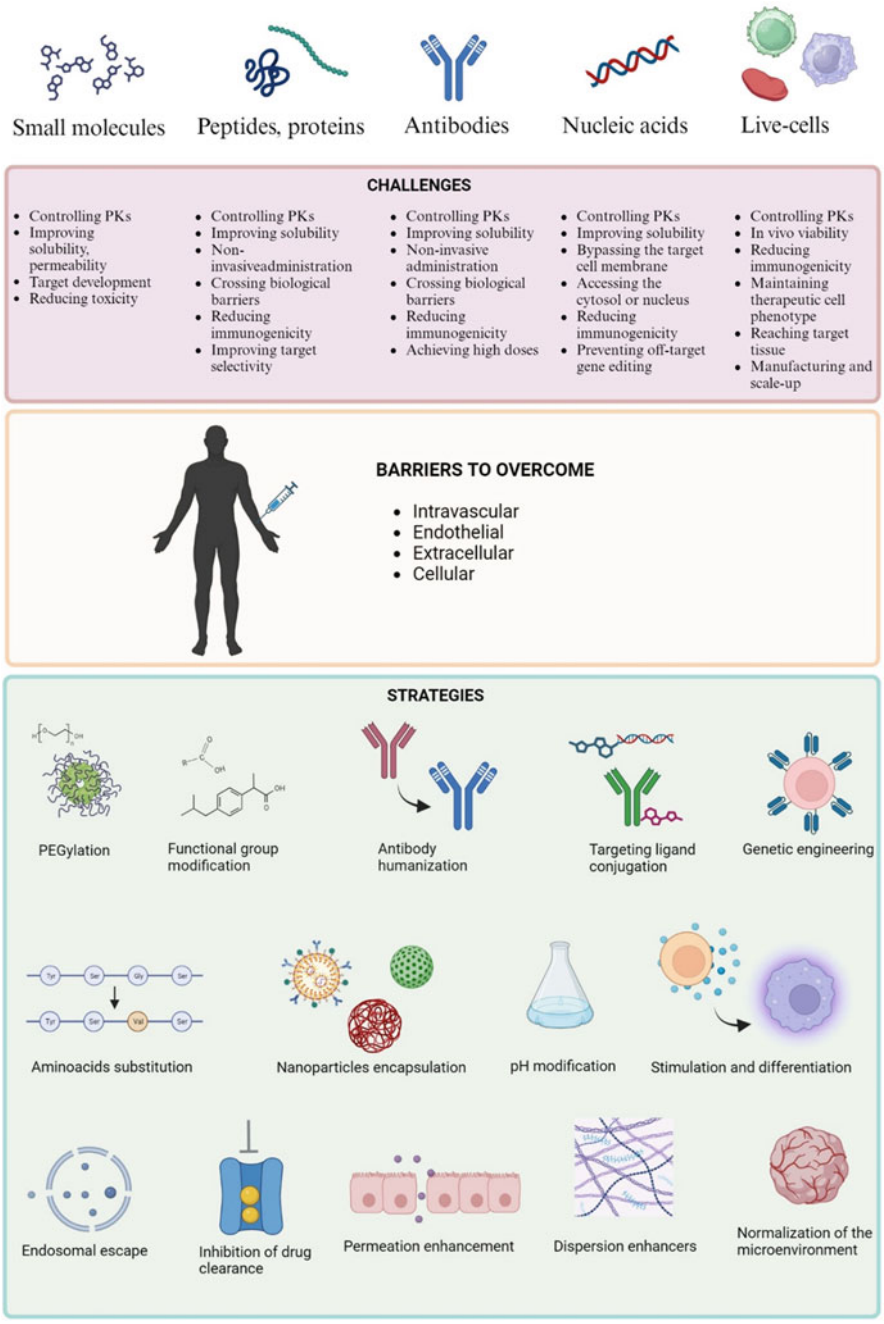

Fig. 1 Classes of therapeutics: challenges, barriers, and solutions. A schematic illustration of all the therapeutics with their unique delivery challenges that have led to the development of new drugs design or modification

In fact, upon their administration, therapeutics encounter the first border represented by the intravascular enzymes (e.g., proteases and nucleases) that degrade the active molecules. In addition, kidneys filter small and large molecule therapeutics of certain size (<6 nm) in the process of clearance (Blanco et al. 2015; Rosenblum et al. 2018).

Furthermore, nanoscale therapeutics encounter additional obstacles within the bloodstream, one of which involves interaction with the mononuclear phagocyte system (MPS). The latter are made of a network of cells that phagocyte, primarily resident macrophages of the vascular walls in organs such as the liver (Kupffer cells) and spleen (splenic macrophages), as well as monocytes in the bone marrow (Blanco et al. 2015; Ngo et al. 2022). When these NPs enter the bloodstream, plasma proteins swiftly adhere to their surfaces, creating a dense corona in a process named "opsonization." These opsonized NPs are then recognized by the MPS through specific receptor interactions, leading to their subsequent internalization by phagocytes.

The endothelial barrier plays a crucial role in preventing therapeutic agents from exiting the bloodstream and entering target tissues. Endothelial cells form a lining within blood vessels and tightly adhere to the underlying basal membrane and extracellular matrix through integrins; its integrity may vary depending on specific tissues and possible pathological conditions. For instance, the endothelial barrier within the brain, known as the blood-brain barrier (BBB), is exceptionally stringent due to the high quantity of endothelial cells and the tight junctions between them (Karamanos et al. 2021). However, in certain conditions such as tissue injury, cancer, and infections, the vascular endothelium can become dysfunctional, leading to fenestrations and the creation of more permeable vessels. This phenomenon is indicated as the enhanced permeation and retention (EPR) effect, which holds particular relevance in cancer due to its aggressive angiogenic nature (Blanco et al. 2015; Rosenblum et al. 2018). The EPR effect provides a chance to distribute therapeutics, especially via NPs, to tumor sites. In cases of inflammation, the vasculature becomes leaky and facilitates the extravasation, as well the cell-mediated confinement that can support targeted delivery to sites of inflammation (Yuan et al. 2012).

Once successfully traversing the endothelial barrier, treatments must pass through the extracellular matrix (ECM) to access the target tissue cells. While small molecules can easily diffuse through the ECM, larger molecules like NPs encounter resistance. In certain disease conditions, the ECM environment undergoes significant alterations, introducing other biological barriers. For instance, tumors often exhibit scarce lymphatic drainage, a dense ECM, and widespread fibrosis. All together, combined with disrupted vasculature, lead to elevated interstitial fluid pressure within tumors. The passage of small molecules across vessels and the extravasation of large molecules and NPs are significantly hampered by all these factors, impeding them to reach the target (Blanco et al. 2015; Heldin et al. 2004).

While the plasma membrane allows the relatively easy passage of hydrophobic small molecules, the transportation of larger macromolecules and NPs needs an active uptake mechanism. This mechanism relies on effective interactions with the

plasma membrane, followed by subsequent endocytosis processes. These processes encompass phagocytic-, clathrin-, and caveolae-mediated endocytosis (Blanco et al. 2015; Zhao et al. 2019b).

Macromolecules and NPs taken up through endocytosis are transported into intracellular vesicles, such as endosomes, phagosomes, and lysosomes. These ones present are characterized by acidic pH levels and enzymes that promote the breakdown of active therapeutic substances (Zhao et al. 2019b). This situation gives rise to an additional biological obstacle as the entrapped therapeutics must find a means to exit these endosomal compartments in order to reach their intended intracellular targets.

Overall, extravasation results in a nonspecific localization, posing a translational hurdle for applications that demand precise distribution (Blanco et al. 2015).

Enhancing the administration route can optimize biodistribution. The way a drug is administered can influence its fate and effectiveness in vivo, and various studies have investigated the impact of these routes on the destiny of NPs (Battaglia et al. 2018; Zhong et al. 2016). For example, when polymeric NPs, specifically poly (lactic-co-glycolic) acid (PLGA) NPs, are administered intravenously, they tend to gather predominantly in the liver and spleen. In contrast, if these NPs are injected subcutaneously or intranodally, they are more likely to stack in the nearby lymph nodes (Dölen et al. 2020).

These alternative methods of administration provide the opportunity to access the lymphatic system before entering systemic circulation. This particular approach holds potential advantages in specific immunotherapeutic scenarios (Dölen et al. 2020; Sharma et al. 2023). Additionally, an increasingly explored approach to circumvent the need for extravasation in NP delivery involves pulmonary administration, specifically through their inhalation. This delivery route steers clear of systemic circulation before reaching the lungs, thereby sidestepping hepatic first-pass metabolism. Consequently, it enhances the distribution of dendrimer-based NPs to the lungs and lymph nodes rather than intravenously administering them (Zhong et al. 2016).

Nevertheless, despite their enhanced ability to reach lung tissue, inhaled NPs encounter distinctive challenges posed by mucus and pulmonary surfactant, serving as physical barriers to lung delivery. Furthermore, a recent study, which compared three commonly utilized pulmonary administration routes in mouse models—specifically, intratracheal instillation, intratracheal spraying, and intranasal instillation—revealed variations in the deposition rates of polymeric (PLGA) NPs within the lungs. Additionally, these NPs exhibited heterogeneous distributions across the different routes. This emphasizes the crucial need for employing validated and consistent delivery methods when assessing the appropriateness of pulmonary administration routes for NPs (Wu et al. 2020).

From a clinical perspective, approved NP formulations, such as ONPATTRO, VYXEOS, and NBTXR3, are typically either intratumorally or systemically administered. However, there has been limited optimization of alternative administration routes for these formulations (Anselmo and Mitragotri 2019).

In summary, while selecting the most suitable administration route for NPs can improve their distribution, many existing delivery methods still result in widespread dispersion of NPs, falling short of the desired level of precision and specificity. Ultimately, not to forget that, once they reach the target tissue, therapeutics designed for intracellular targets must traverse the plasma membrane to enter the cell's cytosol or nucleus. To address this issue of nonspecific distribution, many NP have incorporated targeting elements onto their surfaces to guide their dispatch. These targeting elements, which encompass various molecules like antibodies, glucose, transferrin, folate, transporters, and integrin ligands, primarily rely on interactions with molecules found on the surface of the target cells. These interactions can include those of ligand-receptor, enzyme-substrate, or antibody-antigen (Nag and Delehanty 2019).

A deeper comprehension of the biological barriers outlined above has greatly spurred the advancement of various successful strategies for attaining targeted drug delivery to specific tissues. In general, achieving close molecular proximity between targeting ligands and their respective receptors relies on nonspecific transport mechanisms such as blood circulation, diffusion, and lymph drainage. The only exception to this rule involves the use of living cells as ligands.

3 Targeting Strategies to Overcome the Borders

3.1 Small Molecules

Targeting ligands with small molecular size refers to entities employed for targeted delivery, possessing an molecular weight below 1 kDa, which corresponds to a Stokes-Einstein radius of 1 nm (Kapoor et al. 2019). Early in the exploration of targeting ligands, small molecules garnered significant attention due to their size that allow a rapid diffusion through biological fluids, across many biological barriers and cell membranes, as well as their straightforward chemistry when conjugated with therapeutic payloads (Absorption Barrier—an overview | ScienceDirect Topics n.d.). To facilitate swift diffusion, small molecules must exhibit solubility in biological fluids, and this characteristic often restricts the therapeutic applicability of molecules with low solubility (Savjani et al. 2012) that represent 90% of drugs candidates. Strategies to overcome this challenge have been developed, for instance, pH modifiers linked to drugs to modulate the microenvironment, such as the link of lactic acid to ciprofloxacin (Sharma et al. 2010), or the improvement of solubility masking ionizable groups for the angiotensin-converting enzyme inhibitors benazepril (Lotensin) and enalapril (Vasotec) (Angiotensin-Converting Enzyme Inhibitors 2012).

Additionally, small molecules are typically easy to manufacture, which enhances their practicality; they tend to form relatively feeble bonds with their target receptors (Srinivasarao and Low 2017); thus, consequently, these ligands require receptors with substantial surface features to ensure effective target engagement.

Folic acid (FA) is a vitamin that plays a crucial role in nucleotide synthesis, essential for all cells and stands out as the most extensively employed small molecule targeting agent (Ledermann et al. 2015; Low et al. 2007). Folic acid receptors (FRs) are present in various cell types, offering the opportunity for selective targeting; for example, over 40% of human cancers express FR alpha (FR α), including central nervous system (CNS) and ovarian cancers (Ledermann et al. 2015; Scaranti et al. 2020), whereas FR beta (FR β) is found on activated macrophages (Salazar and Ratnam 2007). FR α receptors are well suited for applications in oncology and FR β for autoimmune disorders. Folic acid exhibits a notably strong affinity for FR (with a dissociation constant, Kd of 10^{-7} mM), making it a flexible targeting method applicable to various medical approaches (Ledermann et al. 2015; Srinivasarao and Low 2017). Crucially, FA also enhances effective intracellular delivery via FR-mediated endocytosis, given that the utilized linker can facilitate escape from the endosomes (Zheng et al. 2019).

Monosaccharides, including glucose, mannose, and galactose, belong to another category of highly effective targeting ligands. In fact, glucose has the ability to target the GLUT1 receptor, which is notably upregulated at the BBB. In the context of treating glioma, research has explored therapeutic approaches using nanocarriers modified with glucose and its derivatives (Jiang et al. 2014; Liu et al. 2022).

In the context of using glycolysis inhibitors as therapeutic agents, ensuring their targeted delivery to cancer cells is crucial to avoid adverse effects. Hence, the investigation of the potential anticancer properties of a glycolysis inhibitor, specifically 2-deoxy-D-glucose (2DG) encapsulated within PLGA NPs (referred to as 2DG-PLGA-NPs), has been conducted in mouse models of hepatocellular carcinoma. The research has yielded positive results, demonstrating cytotoxic effects as well as the stimulation of antitumor immune responses through improved T cell migration (Sasaki et al. 2021).

It is important to note that glucose serves as a primary energy source for all cells. One instance is the chemotherapeutic agent glufosfamide, which has been modified using D-glucose and capitalizes on the Warburg effect to selectively target cells engaged in aerobic glycolysis. Unfortunately, phase II clinical trials showed severe off-target toxicities in glioblastoma multiforme, pancreatic cancer, and soft tissue sarcoma (Clinical-Trials.gov: NCT00099294, NCT00014300, NCT00005053, and NCT00441467) (van den Bent et al. 2003) but got forward in phase III clinical trials for metastatic pancreatic cancer with gentamicine failing efficacy (NCT00099294) (Ciuleanu et al. 2009).

Likewise, the mannose-6-phosphate receptor serves as a glycoprotein target present on the cell membrane in various tissues, including the lung and brain, and is particularly prevalent on immune cells (Irache et al. 2008). In preclinical models, the utilization of nanocarriers with mannosylation has been demonstrated to showcase effective targeting, leading to improved efficacy observed in rodent models for both tumors and inflammation (Gupta and Gupta 2022; Sahu et al. 2015).

Protein receptors in the category of lectin-like receptors, including the mannose-6-phosphate receptor, are responsive to carbohydrate interactions. Specifically, C-type lectin receptors are frequently employed as targets for therapeutic modalities

with glycosylation (Kapoor et al. 2019). Additionally, in preclinical models, delivery systems modified with galactose have been used to target galectin-3, especially in the context of applications related to colorectal cancer (Minko 2004).

Moreover, a synthetic agent designed for carbohydrate binding (CBA) has been developed. This agent effectively targets mannosidic residues found on the surfaces of various cancer cell lines, particularly those with overexpressed high-mannose-type glycans. The structure of the mannose receptor has undergone modification to produce a stable amphiphilic analog, making it suitable for the functionalization of doxorubicin-based niosomes (Burrini et al. 2023).

Galactose has found applications in both preclinical models and clinical scenarios related to hepatocellular carcinoma. This is primarily attributed to its capacity to target asialoglycoprotein (ASGP) receptors. Significantly, a recent advancement includes the approval by the Food and Drug Administration (FDA) of galactosamine-modified small interfering RNA (siRNA) for the medication Givlaari, employed in the treatment of acute hepatic porphyria (Chen and Huang 2019).

Urea derivatives have been a subject of investigation for their potential to target the prostate-specific membrane antigen (PSMA). PSMA, as a receptor, is recognized for its internalization process through clathrin-mediated endocytosis, wherein it takes up the attached ligand and promptly returns to the cell surface. In the context of targeting PSMA, natural ligands such as glutamate urea have been employed; in particular, (2-[3-(1,3-dicarboxypropyl)-ureido] pentanedioic acid (DUPA) is notable for its exceptionally high affinity for PSMA, with a binding constant of 14 nM approximately (Lv et al. 2018).

Apart from the previously mentioned compounds, a variety of additional small molecules have been employed for targeting specific tissues. To illustrate, pharmaceuticals modified with derivatives of glycyrrhetinic acid (GA) have found utility in several preclinical applications focused on hepatocellular targeting. This choice is based on the presence of GA receptors and the observed variabilities and immunogenicity linked to therapies targeting folate receptors and epidermal growth factor receptors (EGFR) (Singh et al. 2018).

Sulfonamide derivatives offer an alternative strategy for selectively targeting solid tumors that express carbonic anhydrase IX (Krall et al. 2014). Benzamides, exemplified by anisamide, exhibit a specific affinity for sigma-1 receptors (Huo et al. 2017). Additionally, phenyl boronic acid (PBA) has proven efficacy in targeting components that contain sialic acid (Deshayes et al. 2013).

Furthermore, hyaluronic acid has been established as having an affinity toward CD44 receptors (Kim et al. 2018), and bisphosphonates have proven effective for targeting bone tissue (Farrell et al. 2018; Xing et al. 2020), while biotin-mediated drug delivery has potential applications in tumor targeting through interactions with biotin receptors (Maiti and Paira 2018; Ren et al. 2015).

Overall, despite numerous reports of small molecule-based targeting strategies, only Givlaari has successfully obtained FDA approval. The limitations of small molecule targeting ligands in clinical settings arise from their challenges in engaging with targets and demonstrating clinical specificity. Nevertheless, as new therapeutic approaches and potential targets emerge, ongoing research persists in exploring the

possibilities of utilizing small molecule targeting ligands for groundbreaking targeted therapies.

The key challenges faced by small molecule targeting ligands include their notable mobility, leading to potential off-target effects, and their compact size, which requires molecular interactions for achieving tissue specificity. For instance, small molecules such as urea, glucose, and folic acid exhibit rapid diffusion rates in tissues and efficient membrane transport, raising the possibility of unintended distribution to other organs unless the cargo itself is sufficiently large to impede diffusion. In this context, targeting primarily relies on enhancing drug retention at the target site rather than actively guiding the cargo to the intended tissue. The main drawback of this approach is that a substantial portion of the ligand may not initially reach the target, which becomes especially problematic when the targeting ligand has a short half-life and/or undergoes metabolism in highly perfused organs like the liver.

Due to their dimension, small molecule ligands typically exhibit lower binding affinity, with exceptions being possible. Nevertheless, their compact size, simplicity of chemical synthesis, and lack of immunogenicity make small molecules an appealing choice for targeting applications. Although the advent of biologics has somewhat diminished the importance of small molecule targeting ligands, their historical significance and contributions to clinical advancements remain undeniable. As therapeutic approaches transition from tissue-specific to more cellular- and subcellular-specific methods, targeting ligands play a crucial role in providing an additional layer of selectivity. Notably, the use of proteolysis targeting chimeras (PROTACs) has emerged as a powerful technique for destabilizing proteins of interest. While the initial generation of PROTACs relied on peptides, there is now a growing presence of small molecule ligands, such as thalidomides, which have recently been employed to demonstrate their efficacy in reducing protein levels in a primate model (Sun et al. 2019).

3.2 Nucleic Acid Fragments

Nucleic acids provide a means for exact regulation of gene expression and can be employed to rectify or suppress aberrant genes, as well as to induce the expression of therapeutically significant genes (Opalinska and Gewirtz 2002). The evident potential of nucleic acids was proved by the approval of formivirsen (Vitravene), an antisense oligonucleotide (ASO) therapy used for the treatment of immunocompromised patients carrying cytomegalovirus rhinitis (Rinaldi and Wood 2018).

Despite their potential, nucleic acids, in their original state, are prone to degradation by nucleases, restricting their lifespan; in addition, the immune system is able to detect them and trigger their removal as foreign molecules of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) (Nastasi et al. 2020). Moreover, to be effective, messenger RNA (mRNA) and small interfering RNA (siRNA) need to be delivered to the cytoplasm while ASO, DNA, and CRISP into nucleus, thus requiring cell

internalization and endosomal escape (Coutinho et al. 2019). These challenges have led to innovative chemical modifications to the nucleobases, the sugar rings, and the 3′ and 5′ ends of nucleic acids. This allows resistance against nuclease, reduced immunogenicity, and improved interactions with target cells (Kormann et al. 2011). As such, a next-generation ASO, nusinersen (Spinraza) was approved for spinal muscular atrophy (Khvorova and Watts 2017).

Aptamers, single-stranded DNA or RNA molecules, achieve binding to protein targets by adopting a three-dimensional conformation, akin to antibodies. Aptamers can identify specific binding domains on receptors and show a distinct low molecular weight targeting approach, typically weighing between 5 and 15 kDa (Kapoor et al. 2019; Nimjee et al. 2017; Srinivasarao and Low 2017).

Aptamers achieve binding to their intended targets by adopting a particular three-dimensional structure primarily influenced by their nucleic acid sequence. Nucleic acid aptamers exhibit strong affinity in binding to their targets comparable to antibodies, showcasing dissociation constants (Kd) typically falling within the nano and picomolar range. Besides their high-affinity binding, aptamers also display remarkable specificity, akin to small molecules. They can discern and differentiate between target proteins that possess similar structural epitopes.

Overall, aptamers present a versatile and flexible three-dimensional structure that allows for conjugation with a wide array of chemotherapeutic drugs and nanocarriers. This conjugation facilitates the efficient transport of drugs deep into target tissues and cells. Moreover, aptamers are easy to produce and exhibit low batch-to-batch variation, making them a promising choice for tissue-specific drug delivery. Nonetheless, aptamer-targeted systems face inherent challenges. Being nucleic acid based, they are susceptible to degradation in biological media, posing a significant obstacle.

To tackle this concern, one approach involves modifying nucleotide bases. Moreover, aptamers linked to small molecule drugs might undergo renal filtration because of their small size (<5 nm). Strategies such as polyethylene glycol ligation (PEGylation) can alleviate this excretion concern. Additionally, despite their specificity, an aptamer may still display some degree of cross-reactivity. Therefore, implementing rigorous selection protocols and precise synthesis methods can help overcome this challenge.

In contrast to small molecules, which usually necessitate complex topographies to achieve efficient engagements, aptamers can effectively interact with receptor surfaces that are relatively flat, owing to their distinctive three-dimensional structures (Kim et al. 2021; Nimjee et al. 2017). Noteworthy is the fact that aptamers demonstrate heightened interactions with receptors known for high glycosylation, such as MUC1 (Srinivasarao and Low 2017). In fact, several aptamers have already made their way to clinical use, with an aptamer targeting VEGF approved by the FDA for treating age-related macular degeneration (Mullard 2023; Zhu et al. 2015).

Regarding targeted drug delivery, numerous aptamers are currently undergoing preclinical trials; however, as of now, no aptamer-conjugated product has been

commercialized. For a detailed understanding of aptamer-mediated drug delivery, comprehensive reviews are available elsewhere (Nimjee et al. 2017; Zhu et al. 2015).

3.3 Proteins, Peptides, and Antibodies

The need for alternative therapeutic options started when small molecules were considered limited in aiming a wide range of molecules, since those targets are encoded by 2–5% of the human genome. Thus, peptides (ranging from 2 to 50 amino acids) and proteins (consisting of 50 or more amino acids) have naturally developed within the human body to exhibit remarkable selectivity for specific targets. Due to their substantial size and varied three-dimensional structures, peptides and proteins possess multiple interaction points with specific protein-binding sites. This characteristic grants them increased potency and reduced toxicity compared to numerous small molecules, but a unique set of challenges related to their delivery has emerged (Moncalvo et al. 2020; Pisal et al. 2010).

While the intricate architecture of peptides and proteins enhances their effectiveness and specificity when compared to small molecules, it also makes them susceptible with poor stability. In fact, they are easily broken down under typical storage conditions and are sensitive to various factors, including common proteases, changes in temperature, and fluctuations in pH levels within the body. This vulnerability is further exacerbated by their swift spread of stabilizing additives in bodily fluids (Schuster et al. 2020).

Moreover, peptides and proteins have the potential to trigger immune responses due to the presence of antigens within their structure or as a result of their degradation, aggregation, or posttranslational modifications. This often results in swift elimination of the drug from the body and can give rise to undesirable immune-driven side effects (Dingman and Balu-Iyer 2019). To address the issues stemming from their inherent structure, synthetic or humanized peptide analogs are engineered with not natural amino acids or are linked to chemical components known to enhance their half-life, stability, receptor binding, or safety profile. These modifications collectively contribute to what is known as the drug-like properties of peptides and proteins; for example, desmopressin (1-deamino-8-D-arginine vasopressin), a synthetic analog of vasopressin, represents a clinical success for the treatment of a wide variety of medical conditions due to the improved half-life and stability compared to its natural peptide vasopressin (Lau and Dunn 2018).

PEGylation can serve to protect immunogenic epitopes and enlarge the hydrodynamic size of the therapeutic compound. This shielding effect results in a decrease in the drug's renal clearance and an extension of its half-life in circulation. Another approach entails altering the local environment by introducing protease inhibitors that disrupt the breakdown of the peptide or protein in bodily fluids (Brown et al. 2020).

The penetration of biological barriers by peptides and proteins is constrained by their dimensions. Therefore, there is a need for enhancers that either modulate the local pH or actively enhance the transcellular absorption of the protein or peptide. A

notable success in this regard is semaglutide (Rybelsus), the first orally administered glucagon-like peptide GLP-1 (Suzuki et al. 2020).

Complications linked to noninvasive routes of administration (such as oral, transdermal, inhalation, and mucosal delivery) for the delivery of peptides and proteins have stimulated innovation in drug delivery systems. Notable examples include the improvement in solubility and bioavailability of cyclosporine through its oral administration in a self-emulsifying formulation (Neoral), the utilization of enhancers and pH modulators to enhance the absorption of Rybelsus, and the formulation of insulin with the small excipient fumaryl diketopiperazine suitable for inhaled delivery (Afrezza) (Pfützner et al. 2002; Ritschel 1996).

Comparable technologies for regulating therapeutic release have been employed for peptides, as exemplified by the release of the peptide hormone leuprolide from a microparticle depot. This approach has resulted in a decreased frequency of injections, minimized side effects, and the successful market release of Lupron Depot (Dlugi et al. 1990).

Despite overcoming numerous challenges, there is still a remarkable opportunity to mimic the naturally regulated processes of peptide and protein secretion using stimuli-responsive delivery systems. For instance, emulating the insulin-glucagon balance in response to glucose fluctuations or achieving pulsatile hormone release throughout the day would be noteworthy achievements.

Antibodies, in particular, are extensively utilized as targeting agents in various drug delivery systems. The unique structure of antibodies, differing significantly from other biologic classes, facilitates specific interactions with therapeutic targets and the immune system by binding to cellular targets.

Antibody-drug conjugates (ADCs) represent a recent category of anticancer treatments engineered to combine the precision of monoclonal antibodies (mAbs) with the cell-destructive attributes of chemotherapy. Often dubbed the "Trojan Horses" of the therapeutic toolkit, they possess the unique ability to transport cytotoxic drugs (payloads) directly into the tumor area, effectively converting chemotherapy into a targeted therapeutic approach (Shastry et al. 2023).

Recombinant mAbs are instrumental in the development of ADCs or immunoconjugates as they possess a natural affinity for their corresponding antigens, displaying strong and highly specific binding with dissociation coefficients (Kd) typically in the sub-nanomolar range (Pini et al. 1998; Vaughan et al. 1996).

These configurations include the antibody, which targets an overexpressed antigen or receptor on the cell surface, an active therapeutic agent referred to as the warhead, and a chemical linker connecting the two components. Most IgG antibodies exhibit prolonged circulation times, often lasting from days to weeks. This extended circulation results from their uptake and recycling by endothelial cells, facilitated by surface receptors. This mechanism enhances the exposure of associated therapeutics to the targeted tissues. However, this distinctive feature of antibodies is specific to their natural state. For example, nanoparticles modified with antibodies are cleared from the system much more rapidly than free antibodies (Mamot et al. 2012; Wang et al. 2023). Nevertheless, ADCs still benefit from an

extended circulation period, as small molecules do not significantly alter the antibody's circulation dynamics.

The primary clinical objective for ADCs has predominantly revolved around oncological treatment. This is substantiated by the approval of four ADCs by the FDA and the extensive clinical and preclinical research concerning the application of ADCs against both hematological and solid cancers.

Recently, a number of ADCs have undergone trials in breast cancer (BC), primarily aimed at targeting either the human epidermal growth factor receptor-2 (HER2), an overexpressed tyrosine kinase receptor in BC that triggers downstream signaling pathways through autophosphorylation upon activation, or Trophoblast cell surface antigen 2 (Trop2), or Nectin4. The FDA approved the first ADC for the treatment of HER2-positive metastatic BC (mBC) in 2013, known as trastuzumab emtansine (T-DM1, Kadcyla), combining the humanized mAb trastuzumab (a human HER2-targeted treatment for breast and stomach cancer) with the cytotoxic DM1 (mertansine).

After several highly successful clinical trials, this compound was introduced in 2019 for the treatment of early-stage breast cancer (BC). In the same year, a second anti-HER2 ADC, trastuzumab deruxtecan (T-DXd), gained approval for the treatment of HER2-positive mBC. Furthermore, its application was expanded to HER2-low advanced BC in 2022. Currently, the only available anti-Trop2 ADC is sacituzumab govitecan (SG), approved by the FDA for the treatment of both triple-negative BC (TNBC) in 2021 and hormone receptor (HR)-positive BC in 2023. Additionally, several ADCs are currently undergoing advanced stages of investigation, including trastuzumab duocarmazine (SYD985), datopotamab deruxtecan (Dato-DXd), and patritumab deruxtecan (HER3-DXd) (Criscitiello et al. 2021; D'Arienzo et al. 2023).

Despite being meticulously designed for high selectivity toward their targets in order to minimize toxicity, ADCs have been linked with reported treatment-related adverse events (TRAEs) (D'Arienzo et al. 2023; Zhu et al. 2023b).

Presently, substantial endeavors are being undertaken in clinical trials to diminish adverse effects, refine dosage and treatment timetables, adjust individual components of each ADC, identify indicative biomarkers for adverse reactions, and create inventive diagnostic instruments for individuals with solid tumors (Tarantino et al. 2023).

Through an examination of co-crystal structures involving idiotypic antibodies and their corresponding antibodies, it becomes evident that anti-idiotypic antibodies typically attach themselves to the complementarity-determining regions (CDR) of idiotypic antibodies. Certain sequence and structural characteristics, like the cavity volume within the CDR region and the hydrophobicity of the CDR-H3 loop region, have been pinpointed as factors that can distinguish between immunogenic and non-immunogenic antibodies. These attributes have been integrated into a machine learning platform called PITHA, which serves to predict the immunogenicity of therapeutic antibodies that are humanized or fully human (Liang and Zhang 2023).

Yet, the utilization of ADCs has broadened further than the scope of cancer treatments, encompassing a range of autoimmune conditions like systemic disorders

such as systemic sclerosis, graft versus host disease, and lupus erythematosus (NCT03198689, NCT03222492, NCT01596218, NCT02533570).

Furthermore, ADCs that focus on antigens present on bacterial or viral surfaces are also currently under active exploration as potential treatments for bacterial and viral infections. This exploration spans both clinical trials and preclinical research (Peck et al. 2019; Pincus et al. 2017; Surur and Sun 2021).

Despite the advantages observed with these commercialized ADCs, their efficacy has been dampened by dose-restricted toxicity due to a narrow therapeutic window. One significant limitation of ADCs lies in the selection of drugs suitable for conjugation to antibodies. Taken the substantial dimension of antibodies, the coupling of a few small molecules results in a poor loading capability. Consequently, this strategy is constrained to highly potent drugs. Consequently, numerous preclinical investigations have been conducted to enhance the translation of this technology into clinical settings.

The present generation of ADCs incorporates several strategies, such as identifying novel tumor-specific antigens and associated targets for antibodies (Damelin et al. 2017; Sano et al. 2019); employing a warhead with a sub-nanomolar IC50 value and optimal physicochemical properties for effective conjugation (Lerchen et al. 2018); refining conjugation techniques to elevate the drug-to-antibody ratio (DAR) and facilitate a uniform ADC product (Nanna et al. 2017); and engineering either a non-cleavable or cleavable linker to release the warhead at the intended extracellular or intracellular site (Anami et al. 2018; Rossin et al. 2018).

The critical determinant in enhancing the tissue-targeting effectiveness of ADCs is the selection of the target antigen. The chosen antigen should possess both specificity and sensitivity to the target cells within the diseased tissue. A high level of antigen expression on the target cells, coupled with minimal to no expression in normal tissues, is pivotal in constructing efficacious ADCs. This, in turn, augments the precision of ADC targeting by minimizing off-target interactions and accumulation.

In instances where the antigen is present on both cancerous and normal cells, like the human HER2 receptor, it becomes crucial to attain an elevated expression level of the antigen localized specifically to the surface of the target cell (Yuan et al., Yuan et al. 2012). This increases the likelihood of successful ADC-antigen binding to the cells of interest and augments the precision of ADC accumulation. The required level of antigen expression may vary depending on the particular ADC. In a phase I clinical trial involving an ADC with an anti-CD33 antibody, it was revealed that a minimum of 10^4 antigens per cell is essential for adequate ADC activity (Lapusan et al. 2012). Moreover, targeting antigens expressed on stromal cells associated with tumor tissue, such as the endothelial cells of tumor vasculature, is also undertaken. A recent study exemplified that an anticancer drug, internalized by tumor stromal cells as part of an ADC, was subsequently released into the extracellular space, eliminating neighboring cancer cells through a bystander mechanism (McCann et al. 2018).

Simultaneously, biological molecules based on shorter amino acid have been studied as alternative targeting ligands for drug delivery and diagnostic imaging,

particularly synthetic peptides, which, on the whole, exhibit heightened selectivity compared to traditional small molecules.

While the requisites for target receptors of peptide ligands align with those of target antigens for antibodies, the utilization of peptides as a class of targeting agents presents both unique advantages and disadvantages. Manipulating the length of the peptide provides an opportunity to optimize the balance between size and selectivity. Small peptides typically induce minimal immune response, enhancing safety, and are more efficient in terms of manufacturing costs (Harding et al. 2010).

Nevertheless, similar to small molecules, peptides must establish molecular interactions with the target for successful targeting, relying on natural physiological transport mechanisms to bring the peptide-cargo complex in close proximity to the target for optimal effectiveness. This makes peptides vulnerable to comparable constraints as small molecules. Additionally, further complications may arise, particularly related to protease degradation when using peptide-based targeting ligands.

The existence of exploration tools offers the potential to expand the range of peptide ligands directed at specific targets. To navigate the complexities and potential toxicity associated with receptor-specific proteins, highly conserved motifs and minimal protein sequences crucial for precise binding to target receptors are scrutinized. These biomimetic peptides are identified through a combination of bioinformatics and biomolecular tools emphasizing structural and sequence homology, ultimately resulting in binding activity (Apostolopoulos et al. 2021; Vanhee et al. 2011). Recent preclinical investigations have demonstrated a focused effort to identify biomimetic peptides from emerging protein candidates, such as rabies virus glycoprotein-29 (Lee et al. 2017) and apamin venom (Oller-Salvia et al. 2016), which target the CNS and BBB, respectively.

Through in vitro or in vivo phage display, a method involving the screening of random peptide sequences presented on a viral surface for their interaction with known or unknown receptors on target cells; the pool of peptide ligands has been significantly broadened. This technique has proven to be potent in identifying peptides with high affinity and selectivity (Pung et al. 2023; Saw and Song 2019). Peptides designed for tumor targeting show encouraging outcomes in molecular imaging, although their application is currently confined to animal models. In 1997, a linear tripeptide with the sequence RGD was identified, demonstrating binding to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors (Pasqualini et al. 1997). Subsequent refinements of this ligand include cyclic RGD, bicyclic RGD, and the more recent iRGD. The iRGD variant serves a dual purpose by binding to integrin receptors overexpressed in tumor vasculature and facilitating extravasation via the neuropilin-1 receptor after site-specific cleavage (Teesalu et al. 2009).

In comparison to ADCs, the utilization of targeting peptides as drug carriers in clinical trials or under development is notably limited. Several factors contribute to this disparity, including diminished stability due to peptidase-driven degradation, a restricted capacity for drug conjugation with peptides, and a reliance on natural physiological transport mechanisms to facilitate molecular interaction between a peptide ligand and its intended target. These aspects collectively impede the effective delivery and sustained presence of peptide-conjugated therapeutics within the therapeutic range. This scarcity of drug carriers may elucidate the prevalent

emphasis on peptide-targeted diagnostic tools over therapeutic applications, as the use of specific imaging agents or detection tools significantly amplifies sensitivity. Over the last decade, the emergence of cell-penetrating peptides (CPPs) has bolstered the efficacy of peptides by enabling both targeting and intracellular delivery of conjugated therapeutics (Rohira et al. 2023).

One significant drawback of current peptide- or antibody-based systems is their inadequate accumulation in the intended target tissue. This limitation hampers the effectiveness of the treatment and leads to unintended toxicity in off-target areas. The shortfall can be partially attributed to a better understanding of the variability in the clinical pathology of diseased tissues among different patients. Indeed, a more comprehensive patient diagnosis considering the molecular target expression levels and careful selection of the patient cohort for a specific therapy could enhance the therapeutic outcomes of existing treatments. Moreover, integrating dual targeting capabilities could increase the chances of the investigational drugs accumulating at the intended site.

3.4 Cell-Coupled Approach

Numerous intrinsic mechanisms for precise targeting operate within the human body. For instance, as an initial defense mechanism, immune cells like neutrophils swiftly migrate toward infected tissues upon invasion by pathogens (Russo and Nastasi 2022). This phenomenon has sparked interest among researchers in utilizing either naturally occurring or genetically modified cells as a strategy for highly specific targeting at particular sites. Although still in its early stages, cell-based targeting offers distinct advantages over conventional approaches, notably in terms of precision and adaptability. Therapeutic agents can be affixed to the surfaces of cells or enclosed within them, according to the characteristics of the medicine and their intended uses (Stephan et al. 2010; Zhang et al. 2018). Diverse cell types, such as red blood cells (RBCs), immune cells, stem cells, platelets, dendritic cells, and even bacteria, have been utilized to transport small molecules, large molecules, and NPs to particular tissues (Fliervoet and Mastrobattista 2016).

Cell-based targeting approaches primarily hinge the following biological principles: camouflaged immune recognition and inherent affinity for target tissues. Due to being perceived as "self," cells loaded with therapeutic substances typically avoid swift clearance. However, certain cell types possess the inherent ability to sense biological signals arising from alterations in the pathological microenvironment at target sites through receptor-ligand interactions. These cells can then migrate to these specific locations. Therapeutics loaded onto or within these cells have the capability to co-migrate with the carrier cells, thereby accomplishing precise and localized delivery to the intended site.

Therapies based on cells capitalize on the intrinsic therapeutic capabilities of certain types of cell to modulate or facilitate crucial biological processes. For instance, pluripotent stem cells possess the ability to rejuvenate and repair tissues (Liu et al. 2020), reprogrammed immune cells can harness the immune system for

immunization and cancer treatment (June et al. 2018; Palucka and Banchereau 2013), and microbes can engage with the microbiome to regulate mucosal immunity, metabolic functions, and chronic inflammatory processes (Sorbara and Pamer 2022; Zhao et al. 2023).

A wide array of therapeutic agents, spanning from minute to substantial molecules, has been either linked to the surfaces of red blood cells (RBCs) or encapsulated within them. This approach aims to address a broad spectrum of ailments, such as cancer, inflammatory conditions, and enzyme-deficient disorders (Brenner et al. 2021).

In detail, RBCs have garnered the most attention in the exploration to target specific tissues. As the most abundant category of blood cells in humans, RBCs feature numerous self-identifying markers (like CD47) which serve to shield them from macrophage clearance, resulting in an extended lifespan in circulation (approximately 120 days in humans) (Wang et al. 2022). These advantageous attributes have predominantly made RBCs a preferred choice for targeting blood tissues, facilitating the prolonged release and continued presence of therapeutic agents within the bloodstream.

A wide range of therapeutic agents, spanning from small to substantial molecules, have been attached to the surfaces of RBCs or encapsulated within these cells. This approach aims to address a diverse array of conditions, encompassing cancer, inflammatory ailments, and disorders related to enzyme deficiencies.

For example, dexamethasone sodium phosphate encapsulated in RBCs, named EryDex, led to a sustained release of dexamethasone for up to a month after dosing; it showed good safety and tolerability profile in phase I clinical trials (NCT01925859 and NCT02380924) (Coker et al. 2018) and excellent efficacy in the treatment of ataxia telangiectasia (AT) patients in phase II study (NCT01255358) (Chessa et al. 2014).

Likewise, RBCs loaded with long-acting enzymes are currently studied; for instance, Eryaspase is carrying asparaginase and currently tested in phase II/III clinical trials for several types of cancers (NCT04292743, NCT03674242, NCT01910428, NCT03267030, NCT03665441, NCT01810705, and NCT02195180).

Nevertheless, aged RBCs exhibit heightened levels of aging indicators, like phosphatidylserine, making them naturally identifiable and eliminated by immune cells present in the spleen. This presents an opportunity to employ aged RBCs as a targeting method specifically directed toward the spleen. This targeting approach has been investigated for delivering self- and tumor-specific antigens to the spleen, triggering antigen-specific immune responses essential for treating autoimmune diseases and cancer (Lorentz et al. 2015; Pishesha et al. 2017). Autoantigens associated with diseases, chemically linked to engineered RBCs, were observed to be directed to the spleen, instigating immunotolerance that mitigated disease manifestations in conditions such as multiple sclerosis and type I diabetes (Pishesha et al. 2017). Similarly, it was also demonstrated to significantly abrogate the development of antibodies against immunogenic protein drugs such as *Escherichia coli* L-asparaginase (Lorentz et al. 2015). Furthermore, this method of utilizing RBCs for drug delivery was also shown to effectively direct drug nanoparticles to

specific disease sites, including lung metastasis nodules, resulting in encouraging therapeutic outcomes (Zhao et al. 2019a).

Leukocytes naturally migrate toward areas of tissue damage, infection, and inflammation. In these locations, resident macrophages release chemokines and inflammatory cytokines that establish a gradient that draws circulating leukocytes toward the sites of inflammation. Simultaneously, the release of inflammatory cytokines prompts the endothelium near these inflammatory areas to overexpress cellular adhesion molecules, facilitating leukocyte rolling, adhesion, and transmigration, inspiring scientists to employ leukocytes as a potential strategy for precise drug delivery to specific sites.

In fact, monocytes/macrophages have been studied in order to target specific tissues as they are professional phagocytes that preferentially internalize nano/micro-sized pathogens, thus potentially used for delivering micro- or nanotherapeutics (Fliervoet and Mastrobattista 2016). Macrophages are also able to pass the BBB and have been employed as driver for directing nanoparticle-based drugs to the brain. For instance, antiretroviral drug (indinavir) NPs enclosed within macrophages were successfully directed to the brain (Dou et al. 2009). Similarly, strategies centered on macrophages have been applied aiming to mitigate inflammation and alleviate conditions like Parkinson's disease (Biju et al. 2010; Brynskikh et al. 2010) and inhibit the spread of cancer to the brain (Choi et al. 2012; Kannan and Cheng 2023).

Monocytes/macrophages have also been extensively studied for targeting tumors, both for therapeutic and diagnostic purposes as they tend to home in on tumor sites and can even penetrate deep into hypoxic regions that exhibit heightened expression of chemokines (Bai et al. 2022). Remarkably, a recent investigation demonstrated that a modified macrophage sensor identified tumors as tiny as 25–50 mm^3, even in the presence of concurrent inflammation, and exhibited greater sensitivity than cancer biomarkers derived from clinically employed proteins and nucleic acids (Aalipour et al. 2019).

Additional white blood cells, including neutrophils and T cells, have been considered as potential carriers, selectively transporting cRGD liposomes. This strategy effectively promoted transmigration across the BBB, penetration into the cerebral parenchyma, and conveyance of therapeutic compounds to the injured sites and target cells (Hou et al. 2019). Monocyte-, macrophage-, and neutrophil-based targeting strategies are currently only in preclinical studies but have not entered the clinic.

Interestingly, therapeutics loaded inside leukocytes possibly degrade, especially if located in endosome/lysosomes, and for this reason the concept of "backpack" particles seems to be rather preferred, allowing the maintenance of the physicochemical properties of therapeutics that remains stable on the surface of cells that migrate to the target sites (Anselmo et al. 2015; Lu et al. 2023). For example, cell surface–conjugated nanogels were designed to carry an interleukin-15 super-agonist complex that, systemically administered, selectively expanded T cells 16-fold in tumors; the improved therapeutic window enabled substantially increased tumor clearance by mouse T cell and human chimeric antigen receptor (CAR) T cell therapy in vivo (Tang et al. 2018).

Much like leukocytes, stem cells also possess chemokine receptors and the capacity to navigate toward areas of injury, inflammation, and tumors (Fliervoet and Mastrobattista 2016; Wu et al. 2019). Stem cells, with a particular focus on mesenchymal stem cells (MSCs), have thus been employed as a method for precisely directing them to sites of injury or tumors in virtually all organs (Wu et al. 2019).

However, naturally cultured and expanded stem cells may show suboptimal targeting efficacy due to their limited expression of adhesion ligands and chemokine receptors. To address this limitation, various strategies have been developed to enhance the targeting capabilities of stem cells, such as genetic engineering to induce the expression of chemokine receptors and essential homing ligands (Sackstein et al. 2008; Takayama et al. 2023; Zhu et al. 2023a).

Stem cells serve not only as a targeting vehicle but also as a "cellular factory" capable of expressing therapeutic proteins at designated sites. For instance, MSCs engineered with mRNA encoding IL-10 could efficiently home in on local inflamed sites, resulting in an enhanced anti-inflammatory effect through the secretion of IL-10 (Levy et al. 2013).

Platelets, which are nucleus-free cells that circulate in the bloodstream, are primarily recognized for their essential role in managing blood clotting and thrombosis. This aspect of platelet biology has sparked interest in utilizing them toward sites of vascular injury and thrombosis (Lu et al. 2019).

In particular, researchers have begun exploring platelets to specifically target and treat residual tumors following surgical procedures, capitalizing on the innate affinity of platelets for surgical wounds (Wang et al. 2017). Furthermore, with mounting evidence indicating that platelets attach to circulating tumor cells in the bloodstream, investigations are underway to employ platelets as a potential strategy for targeting tumor metastases (Papa et al. 2019).

In addition to considering the use of living cells, there is ongoing research into the utilization of cell membranes and extracellular vesicles derived from cells as vehicles for precise targeting (Fang et al. 2018; Herrmann et al. 2021).

Furthermore, living cells can undergo genetic modification. An exemplar of this is the chimeric antigen receptor (CAR) T cells, a prominent case in point. These cells, clinically approved in 2017, are cytotoxic T cells that have been genetically engineered to target specific cancer-associated antigens (Prasad 2018). Indeed, CAR T cell therapies underscore the functionalities and benefits of cell therapies, including their inherent capability to pinpoint disease sites, exert potent effects at the targeted location, directly interact with the immune system, and proliferate within the organism (Jackson et al. 2016). Additional FDA-approved adoptive cell therapies include sipuleucel-T (Provenge) utilized in the treatment of prostate cancer (Cheever and Higano 2011), and stem cells derived from cord blood (Research 2023).

Cells can also be genetically modified to produce drugs or facilitate critical biological reactions, effectively functioning as depots for drug production. These engineered depots that secrete drugs are now being tested in clinical trials, serving to safeguard delicate biologics during transport and replicate natural, pulsatile, or stimuli-responsive delivery patterns. However, delivering live cells presents distinct

challenges. Cells are considerably larger than other therapeutic classes, making them prone to rapid entrapment in lung capillaries and subsequent elimination. In the case of adoptive cell therapies, particularly immunotherapies, the size of live cells, combined with the hostile tumor microenvironment, leads to limited cell penetration in solid tumors. Consequently, their clinical application is currently restricted primarily to hematological malignancies (Newick et al. 2017).

Cell-based targeting strategies have demonstrated promising effectiveness in preclinical investigations, yet they remain in their early developmental stages. To progress toward clinical implementation, several critical issues must be addressed.

First, a more profound comprehension of the biology of carriers and the different diseases is imperative for the judicious selection of targeting cells. This foundational knowledge will enable more precise and effective targeting. Furthermore, immunogenicity is a significant concern in these strategies. Autologous cells are theoretically less likely to provoke an immune response, but their availability can be limited in certain situations, particularly for non-proliferative cell types. On the other hand, allogeneic cells are generally more readily available but may pose challenges related to rejection by the recipient's immune system. Overcoming these issues will necessitate tailored solutions on a case-by-case basis in future studies.

Additionally, the vitality, endurance, and preservation of effective cellular characteristics heavily rely on the surroundings and recipient's system in which the administered live cells are placed (Fraietta et al. 2018). There are also practical considerations linked to the mass production of therapeutic live cells. Autologous therapies, though possessing more favorable safety profiles, necessitate several steps such as the collection, processing, and reintroduction into the same patient, thus restricting the scalability of the treatment. Conversely, allogeneic therapies offer more straightforward scalability but require cold-chain storage and transportation, along with strict demands for biocompatibility and sterility (Hourd et al. 2014; Levine et al. 2017).

4 Conclusions and Remarks

Over the course of therapeutic development, drug delivery techniques have progressed in tandem with the emergence of various types of therapeutics, from small molecules to proteins, peptides, nucleic acids, and most recently, live-cell therapies. Each class of therapeutics has faced its own set of delivery challenges, which have been effectively addressed through a combination of drug modifications and alterations to the surrounding microenvironment. Modifications applied to both the drug itself and its surrounding microenvironment offer the means to fine-tune and optimize the drug's effectiveness.

Notably, the development of multifunctional delivery systems has significantly enhanced the delivery of all therapeutic classes. These advanced systems often achieve superior control over drug actions by integrating both drug modifications and environmental adjustments. In the evolution of drug delivery, established delivery approaches have been utilized to boost the implementation of emerging

therapeutic techniques. This includes the application of controlled-release and sustained-release systems (initially developed for small molecules) across a diverse range of therapeutic applications. Contrarily, approaches and methods for drug delivery developed to accommodate new therapeutic modalities have, in turn, been modified and applied to enhance the delivery of older therapeutic agents (Fig. 1).

The early years of modern drug delivery research unveiled the significant impact of altering a drug's release rate within the body on its pharmacokinetic (PK) parameters. This influence encompasses factors such as the drug's biodistribution, half-life, cumulative exposure over time, and peak concentration in the bloodstream (Glassman and Muzykantov 2019). The development of controlled-release delivery systems represents a notable advancement, providing a greater degree of control, while modifications to dosage, dosing frequency, and infusion rates can impact these parameters (Blanco et al. 2015). These systems included hydrogels and polymeric implants, based on the four essential mechanisms of controlled release—namely, dissolution, diffusion, osmosis, and ion exchange. Moreover, micro and NPs enabled surface modifications to prolong drug half-life and improve tissue targeting by tailored interactions with the microenvironment (Kamaly et al. 2016; Park et al. 2022).

The establishment of controlled-release technologies originally designed for small molecules has played a pivotal role in laying the groundwork for delivery approaches tailored to therapeutic peptides and proteins. These biologics often have brief drug half-lives, necessitating frequent and invasive injections for sustained effectiveness. Within this framework, the effectiveness of peptide therapeutics was significantly enhanced by the introduction of sustained-release systems, which represent a specific category of controlled-release systems designed to uphold therapeutic drug concentrations over prolonged periods (Awwad and Angkawinitwong 2018; Elgundi et al. 2017; Ezike et al. 2023; Malta et al. 2023; Park et al. 2022; Schwendeman et al. 2014).

Nucleic acids have benefitted from drug delivery systems such as lipid-based nanoparticles, whose surface can be modified to improve drug loading, cell uptake, and endosomal escape in vivo (Blanco et al. 2015). Nevertheless, the challenges of toxicity, complement activation, and inadequate distribution prompted the creation of lipid NPs explicitly tailored for siRNA, incorporating PEGylated, neutral, and ionizable cationic lipids as stable carriers (Semple et al. 2001).

Modifications to drugs have been instrumental in progressing the development of noninvasive controlled-release delivery systems for therapeutics based on proteins, peptides, and live cells. Intentional design alterations have been applied to peptides and proteins to manage their solubility, as demonstrated in the case of insulin, and improve their stability, as observed with desmopressin. These deliberate modifications aim to optimize their pharmacokinetics (PKs), exemplified by the enhanced enzymatic stability of the GLP-1 analog semiglutide compared to other agonists (Suzuki et al. 2020).

Additionally, environmental modifiers have found application across various classes of therapeutics.

For small-molecule medications, a specific set of adjuvants has been formulated to enhance drug absorption within the small intestine. This is achieved by either prolonging the transit time through the intestinal tract or ameliorating their

bioavailability in the bloodstream through the active inhibition of certain metabolic processes (Breda et al. 2009; Taniguchi et al. 2014). When it comes to proteins and peptides, pH-modifying agents like citric acid have been addressed as solubilizers for small molecules. Currently, their application extends to restraining proteolysis and fortifying the stability of proteins and peptides within physiological fluids (Welling et al. 2014). Furthermore, the systemic introduction of steroids has been utilized to modulate the immune milieu and forestall undesirable reactions to protein therapeutics and nucleic acid–based therapies (Chen et al. 2018).

Moreover, alterations in the gene expression profile of cells, directly impacting their characteristics or phenotypic appearance, can occur in response to environmental signals. In the clinical realm, strategies focusing on the microenvironment have been implemented in CAR T cell therapy to address the complexities associated with solid tumors. This includes addressing challenges like the existence of an antagonistic microenvironment marked by heightened interstitial pressure, abnormal vasculature, and immune signaling suppression (Elahi et al. 2018). In the early stages of clinical trials for CAR T cells, cytokines were initially delivered systemically with the aim of modifying the immunosuppressive tumor microenvironment and fostering the expansion of T cells (Shum et al. 2017). However, this approach was associated with significant toxicity and, consequently, cells were subsequently engineered becoming themselves cytokine-producing CAR T cells. Later advancements led to the development of inducible "armored" CAR T cells capable of selectively releasing cytokines only within the tumor microenvironment, often referred to as "safety switches" (Jaspers and Brentjens 2017; Yeku and Brentjens 2016). This strategy successfully reduced the toxicity associated with cytokine administration while retaining the capability to reshape the tumor microenvironment at the designated site, fostering T cell expansion (Ma et al. 2020).

Furthermore, progress made in one category of therapeutics has laid the groundwork for the clinical application of therapeutics in other categories. A case in point is the utilization of therapeutic antibodies as modifiers for small molecules, manifested in the form of ADCs. These leverage the specificity of antibodies to facilitate precise site-specific delivery, allowing for the clinical use of cytotoxic compounds with levels of toxicity that would be otherwise challenging to manage, such as monomethyl auristatin E, a synthetic anticancer small molecule (Best et al. 2021); additionally, ADCs linked to immunostimulant drugs elicit the activation of antitumoral immunity and sustain durable memory (Ackerman et al. 2020).

An assessment of the current portfolio of therapeutics and supply techniques, encompassing drug modifications and microenvironmental adjustments, reveals three key challenges. The difficulties at hand are centered on accomplishing precise delivery that targets individual cells or cellular compartments. Overcoming biological barriers that impede the delivery of intricate therapeutic molecules is crucial, as is the development of drug delivery systems capable of promptly releasing biomolecules within specific tissues at designated times and concentrations, responding to environmental signals.

Though these challenges may not hinder the application of most therapeutics, we suggest that cell therapies have the capability to tackle them at the same time and

usher efficient single-dose drug delivery systems. Cell therapies excel in delivering a sustained provision of intricate biologics, passing biological barriers, and responding to host cues in a manner that emulates natural biological processes. As a result, cell therapies can serve as both dynamic delivery systems and therapeutic agents. They are especially suitable for addressing rare blood disorders, inadequately responsive cancers, and metabolic genetic disorders, such as hemophilia and sickle cell disease. By emulating crucial biological processes, like host-responsive insulin secretion, advanced cell therapies have the potential to reduce the frequency of dosing and the necessity for certain medical interventions. Cell therapies will build upon established methods to alter drugs and their microenvironments in order to modulate drug efficacy and toxicity. Ultimately, enhancements made to these strategies will benefit other categories of therapeutics.

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