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Peptide/Antibody–Drug Conjugates for Therapeutic Applications in Inflammatory Disease

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Peptide/antibody–drug conjugates (PADCs) are an emerging class of targeted therapeutics that leverage the specificity of peptide or antibody ligands to deliver potent small-molecule payloads selectively to disease sites via cleavable linkers. This design combines high target affinity with controlled local activation and minimal systemic toxicity. To date, 15 antibody–drug conjugates and 3 peptide–drug conjugates have been approved by the FDA; however, all are indicated exclusively for oncology. Consequently, the development of PADCs has primarily focused on cancer, with relatively few comprehensive reviews addressing their potential in non-oncological applications. In this review, the therapeutic potential of PADCs as a targeted strategy for treating inflammatory diseases—such as inflammatory bowel disease, chronic kidney inflammation, and arthritis—is explored by detailing how engineered peptide or antibody ligands recognize upregulated pathological markers in inflamed microenvironments and enable site-specific drug release through stimuli-responsive linkers. By consolidating recent advances, this review broadens the therapeutic scope of PADCs and highlights their promise as next-generation immunomodulators for targeted treatment of inflammatory diseases.

1. Introduction

Peptide/antibody–drug conjugates (PADCs) represent a promising targeted therapeutic platform that combines the molecular recognition capabilities of peptides or antibodies with the cytotoxic potential of small molecules, offering improved pharmacokinetics and reduced systemic toxicity compared to conventional treatments.[1] Among PADCs, antibody–drug conjugates (ADCs) have been most extensively studied and clinically validated, particularly in oncology.[2] Owing to the high affinity and selectivity of antibodies for tumor-associated receptors, ADCs have enabled targeted delivery of cytotoxic drugs to cancer cells, leading to clinical approval in various malignancies such as breast cancer, lymphoma, and urothelial carcinoma.[3] In contrast, peptide–drug conjugates (PDCs) utilize short, cell-targeting peptides as delivery moieties, offering distinct pharmacological advantages.[4] Their low molecular weight enhances tissue penetration, reduces immunogenicity, and facilitates renal clearance, thereby minimizing off-target accumulation and immune-related adverse effects.[5] In addition, the inherent structural flexibility of peptides—due to their short amino acid sequences—facilitates the incorporation of noncanonical residues, cyclization, and chemical conjugation with diverse functional groups.[6] These features enable advanced molecular engineering, allowing for the development of peptide ligands with enhanced binding affinity, stability, and target specificity.

Recent advances in chemical conjugation techniques and linker chemistries have significantly broadened the design strategies for next-generation PADCs.[7] Notably, innovations in stimuli-responsive linkers—engineered to respond to environmental conditions such as pH, redox status, or protease activity—now allow for enhanced control over drug release, stability, and targeting precision.[8] As a result, multiple PADC candidates are progressing through preclinical and clinical development pipelines, with 15 antibody–drug conjugates and 3 peptide–drug conjugates approved by the FDA to date.[9] However, despite this progress, most PADC research and therapeutic applications have been predominantly focused on oncology. Existing review papers have largely emphasized cancer-targeted platforms, while considerably less attention has been paid to nonmalignant indications,

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particularly inflammatory diseases, where precision drug delivery could offer significant therapeutic advantages.

Inflammatory diseases are characterized by sustained immune activation, elevated levels of pro-inflammatory cytokines (e.g., TNF-α, IL-1β), and tissue-specific pathological changes.[10] Affected microenvironments often exhibit hallmarks such as enhanced vascular permeability, hypoxia, acidic pH, and increased production of reactive oxygen species and proteolytic enzymes (e.g., matrix metalloproteinases).[11] While current anti-inflammatory therapies—including NSAIDs, corticosteroids, and biologic agents such as cytokine inhibitors or monoclonal antibodies—provide symptom relief, they are typically administered systemically and often lead to off-target effects, chronic immunosuppression, and organ toxicity due to the high doses required.[12] PADCs offer a compelling strategy to overcome these limitations by integrating disease-targeting peptides or antibodies with stimuli-sensitive linkers for site-specific drug release. For instance, peptides or antibodies that bind to overexpressed markers on activated immune cells can guide the conjugate to sites of inflammation. Upon localization, environmental triggers such as acidic pH, redox stress, or protease activity can cleave the linker and release the therapeutic payload selectively within diseased tissue. This targeted approach enables higher local drug concentrations at the site of pathology while sparing healthy tissues, potentially allowing for lower therapeutic doses and minimizing systemic side effects.

In this review, we present a comprehensive overview of the design strategies, functional mechanisms, and therapeutic applications of PADCs in inflammatory diseases (**Figure 1**). We highlight recent advances in peptide engineering, linker development, and targeting technologies, and explore how these innovations are being harnessed to address the challenges of immune-mediated pathologies. Finally, we discuss key translational considerations, including manufacturability, peptide stability, and clinical feasibility, that will shape the future of PADC-based therapeutics beyond oncology.

2. PADC Design and Mechanism

PADCs are engineered to enhance therapeutic efficacy by targeting drugs specifically to disease sites while minimizing systemic toxicity. This design is particularly crucial in treating inflammatory diseases, which often involve chronic and systemic immune activation. A modular and rational design strategy underpins the construction of effective PADCs, encompassing three key components: the targeting moiety (peptide or antibody), the therapeutic payload (drug), and the linker that connects them. The interplay between these components determines the pharmacokinetic and pharmacodynamic properties of the conjugate, ultimately influencing its therapeutic efficacy.

2.1. Targeting Moieties: Peptides and Antibodies

2.1.1. Peptide-Based Targeting Moieties

Peptides are short amino acid sequences that can be engineered to bind selectively to receptors overexpressed in inflamed tissues. Due to their small size, peptides can be internalized more efficiently than larger molecules, although this property depends on factors such as amino acid sequence, secondary structure, and hydrophobicity. Their versatility allows for modification to enhance binding affinity, stability, and specificity, making them valuable tools for targeted drug delivery. A key advantage of peptide-based targeting is the ability to direct drugs specifically to inflamed tissues, where certain receptors are upregulated.

Targeting peptides are designed to recognize these receptors, such as integrins or adhesion molecules, which are overexpressed in inflammatory conditions. For instance, the RGD (Arg-Gly-Asp) peptide targets a family of integrins that recognize the RGD motif, including integrin αvβ3, which is commonly expressed on activated endothelial cells and macrophages in inflamed joints. By conjugating RGD peptides with therapeutic agents, such as dexamethasone-loaded nanoparticles, drug accumulation in inflamed tissues is enhanced,[13] thereby improving therapeutic outcomes and minimizing systemic exposure.

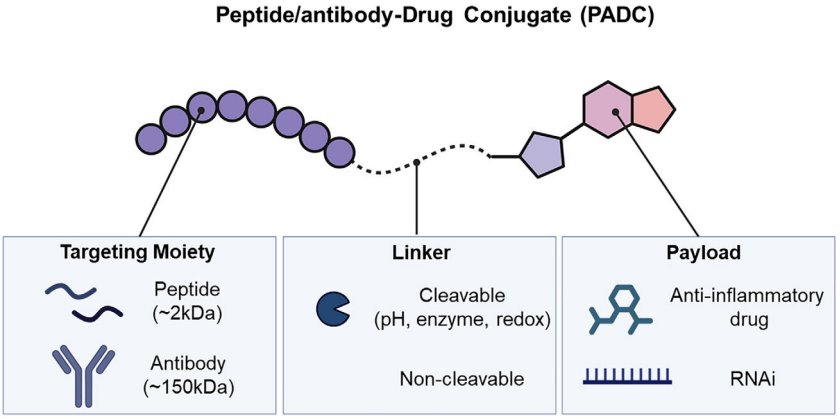


Figure 1. Schematic overview of PADC structure for inflammatory diseases. The PADC is composed of three main components: 1) a targeting moiety, which may be a peptide (≈2 kDa) or an antibody (≈150 kDa), enabling selective delivery to inflamed tissues; 2) a linker, which connects the targeting moiety to the therapeutic payload and can be either cleavable (via pH, enzymatic activity, or redox conditions) or noncleavable; and 3) a payload, typically an anti-inflammatory small molecule drug or RNA interference (RNAi) agent, responsible for the therapeutic effect (created using Biorender).

In addition to targeting peptides, cell-penetrating peptides (CPPs) have become a key strategy in PDC design.[14] CPPs, such as TAT (transactivator of transcription) and penetratin, have the unique ability to cross cellular membranes efficiently, even in the absence of receptor-mediated endocytosis. This capability enables the internalization of the conjugate into the target cell, facilitating intracellular drug delivery. By combining the specificity of targeting peptides with the cell-penetrating capabilities of CPPs, PDCs can effectively deliver drugs both to the right tissue and inside target cells, enhancing the therapeutic efficacy of the treatment. These peptide-based approaches, by providing targeted and efficient drug delivery, represent a promising strategy for the treatment of chronic inflammatory diseases, ensuring that therapeutic agents are precisely delivered to inflamed sites while reducing unwanted side effects.

2.1.2. Antibody-Based Targeting Moieties

Antibodies serve as effective targeting moieties in the design of PADCs and are among the most widely used protein-based ligands. Monoclonal antibodies, in particular, offer high binding affinity and specificity for target antigens, enabling precise localization of therapeutic payloads to inflamed tissues. Although larger in size and slower to penetrate tissue compared to peptides, antibodies benefit from prolonged circulation time and strong molecular interactions with their targets, making them well-suited for sustained and selective drug delivery.

Monoclonal antibodies are commonly used protein targeting ligands that can recognize cell-surface markers selectively upregulated in inflamed tissues. For instance, antibodies against intercellular adhesion molecule-1 (ICAM-1), which is overexpressed on activated endothelial cells, have been conjugated to nanoparticles for targeted drug delivery.[15] In inflammatory disease models, ICAM-1-targeted carriers have shown enhanced uptake by inflamed endothelium and improved therapeutic efficacy. Similarly, tumor necrosis factor (TNF) is a critical proinflammatory cytokine that is highly expressed in various immune-mediated diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD).[16] Anti-TNF monoclonal antibodies have been extensively used as biologic therapies, but systemic administration is associated with immunosuppression and other dose-limiting toxicities. To improve target specificity and reduce systemic side effects, an innovative ADC approach has been developed using anti-TNF antibodies conjugated with anti-inflammatory agents. These ADCs leverage the internalization of anti-TNF antibodies upon binding to transmembrane TNF, enabling lysosomal degradation and intracellular release of the therapeutic payload within immune cells.

While monoclonal antibodies remain the gold standard for protein-based targeting, other protein ligands have been explored as complementary approaches. For instance, cytokines such as interleukin-10 (IL-10) can be engineered as both targeting ligands and biologically active agents. A Stabilized IL-10 dimer has been used to deliver anti-inflammatory effects in a tissue-specific manner, demonstrating effective suppression of immune-mediated inflammation.[17] Additionally, albumin—a naturally abundant and long-circulating plasma protein—has been leveraged as a passive targeting platform due to its ability to accumulate in inflamed tissues via the enhanced permeability and retention (EPR) effect. Dexamethasone-loaded albumin nanoparticles have shown improved therapeutic outcomes and reduced systemic toxicity in preclinical inflammation models.[18]

Despite potential formulation challenges such as instability and immunogenicity, recent advances in protein engineering, PEGylation, and site-specific conjugation have greatly improved the clinical feasibility of antibody-based targeting. Taken together, antibodies targeting inflammation-associated markers represent powerful and selective tools for delivering therapeutics to sites of inflammation, making them essential components in the development of next-generation PADCs for inflammatory diseases.

2.2. Linker Chemistry

An essential determinant of PADC performance lies in the chemistry of the linker that bridges the targeting moiety and the therapeutic payload. The linker not only stabilizes the conjugate during systemic circulation but also governs the release of the active drug at the desired site, ideally in a controlled and specific manner. Consequently, rational linker design plays a crucial role in balancing stability, specificity, and pharmacological activity. Linkers are broadly categorized into cleavable and noncleavable types, depending on whether they are designed to be broken down under physiological or pathological conditions (**Table 1**). The following subsections outline the key classes of linkers, their mechanisms, and their relevance in inflammatory disease contexts.

2.2.1. pH-Sensitive Linkers

Among cleavable linkers, pH-sensitive types are the most widely applied in inflammatory disease models. These linkers exploit the characteristic acidity of inflamed tissues and intracellular compartments such as endosomes and lysosomes. Common chemical structures used for pH sensitivity include hydrazone and *cis*-aconityl bonds, both of which are stable at physiological pH (≈7.4) but undergo hydrolysis under acidic conditions (pH 5–6). This mechanism has been effectively applied in the design of PADCs for inflammation. For example, a *cis*-aconityl-functionalized conjugate demonstrated efficient doxorubicin release under acidic conditions (pH 5.0), mimicking the microenvironment of inflamed tissues and enhancing therapeutic outcomes while minimizing exposure.[19]

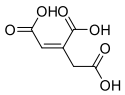
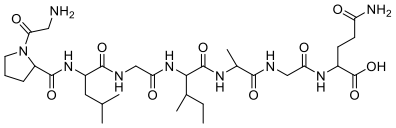
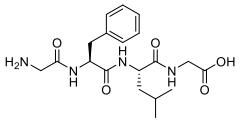
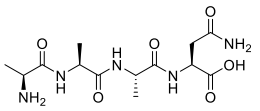
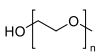
Similarly, in dexamethasone-based PDCs, conjugation via a *cis*-aconityl linker to a joint-targeting peptide resulted in enhanced intracellular release in inflamed joints,[13] leading to superior anti-inflammatory efficacy and reduced systemic toxicity compared to nontargeted or unlinked delivery systems.

The simplicity of pH-triggered hydrolysis makes these linkers attractive for applications where drug release is required within cellular compartments or acidic inflamed environments.

2.2.2. Enzyme-Sensitive Linkers

Enzyme-sensitive linkers provide another layer of specificity by responding to proteolytic activity commonly elevated in inflamed

Table 1. Classification of stimuli-responsive linker types used in PADCs and their mechanism of action in inflammatory microenvironments.

Linker types	Mechanism of action in inflammatory microenvironments	Chemical structure	Reference
pH-sensitive	Acidic environment (pH 5.0–6.5) in inflamed tissue or intracellular compartments	 Hydrazone,	[19,53]
		 Cis-aconityl	[13,19]
Enzyme-sensitive	Proteolytic cleavage by inflammation-associated enzymes	 GPLGIAGQ (MMP-2/9)	[21b,54]
		 GFLG (cathepsin B)	[55]
		 AAAN (elastase)	[20]
Redox-sensitive	High GSH levels in inflamed/ intracellular environments	 Disulfide bond	[22,23]
Non-cleavable	Lysosomal degradation	 Amide bond	[24,25,29]
		 Thioether	[56]
		 PEGylated	[57]

tissues. Inflammatory microenvironments are enriched with enzymes such as matrix metalloproteinases (MMPs), cathepsins, and elastases, which are secreted by activated immune cells, fibroblasts, and endothelial cells.[20] Peptide sequences such as GPLGIAGQ, which are selectively cleaved by MMP-2 or MMP-9, have been incorporated into linker systems to achieve enzyme-triggered drug release. For instance, in models of rheumatoid arthritis and ulcerative colitis, PADCs equipped with MMP-sensitive linkers have enabled localized drug activation, minimizing off-target effects and systemic exposure.[21] This strategy is especially useful in diseases with well-characterized enzymatic profiles, allowing drug release only in the presence of disease-specific protease activity.

2.2.3. Redox-Sensitive Linkers

Redox-sensitive linkers utilize the differential redox environments between healthy tissues and inflamed or intracellular compartments to trigger drug release. Specifically, inflamed tissues and activated immune cells often present elevated levels of glutathione (GSH) and other thiol-reducing agents.[22] Disulfide bonds are widely used redox-sensitive linkers, as they remain stable in the extracellular oxidative milieu but are rapidly cleaved in the reductive intracellular environment. PADCs utilizing disulfide linkers have shown great promise in enhancing the intracellular delivery of anti-inflammatory drugs. For example, in autoimmune disease models, redox-cleavable PADCs have

facilitated efficient cytosolic release of payloads, leading to improved modulation of inflammatory signaling pathways.[23] Because redox gradients are relatively conserved across different types of inflammation, disulfide-based systems offer a broadly applicable release strategy with strong translational potential.

2.2.4. Noncleavable Linkers

In contrast to cleavable systems, noncleavable linkers are designed to maintain the structural integrity of the PADC throughout systemic circulation and even following cellular uptake.[24] In these systems, drug release is not achieved through environmental triggers such as pH or enzymatic activity. Instead, it relies on complete proteolytic degradation of the entire conjugate within cellular compartments—most commonly lysosomes—after endocytosis. This approach often results in slower and sometimes less efficient drug release compared to cleavable linkers. However, noncleavable linkers offer enhanced plasma stability, a reduced risk of premature payload release, and more predictable pharmacokinetics, making them especially valuable in therapeutic contexts requiring prolonged systemic exposure.[25] These attributes are particularly advantageous for treating systemic or chronic inflammatory diseases, where sustained drug availability is more beneficial than rapid, localized release. Moreover, noncleavable linkers are well suited for therapeutic agents that retain activity in their conjugated form or when the entire PADC functions as the active pharmacological entity. By preventing premature release in circulation, this strategy minimizes off-target toxicity and supports safer long-term administration. Although lacking the environmental responsiveness of cleavable linkers, the simplicity, durability, and stability of noncleavable systems make them an indispensable part of PADC design—particularly in clinical applications where precise control over drug biodistribution and exposure is critical.

2.3. Mechanism of Action

The mechanism of action of PADCs begins with the targeting moiety, which guides the conjugate to the site of action by recognizing specific receptors or biomarkers overexpressed in the target tissues (**Figure 2**). After systemic administration, the PADC circulates through the bloodstream, where the targeting moiety ensures that the conjugate accumulates at the site of inflammation, thereby reducing the likelihood of off-target effects.[26] Following binding to the target receptor, PADCs often enter the target cell via receptor-mediated endocytosis.[27] This process allows the PADC to be internalized and transported within the cell, usually through the endosomal-lysosomal pathway.[28] Once inside the cell, the conjugate is delivered to intracellular compartments such as lysosomes or endosomes, where the conditions are favorable for drug release. For certain types of PADCs, cellular uptake is essential for activating the therapeutic payload—particularly for agents requiring intracellular action, such as corticosteroids, small molecules, or nucleic acids. Drug release is triggered by various factors depending on the chemical design of the linker. In the case of cleavable linkers, release is initiated in response to environmental stimuli such as pH changes, enzymatic activity, or redox conditions specific to the inflammatory microenvironment.[29a,30] For example, inflamed tissues such as arthritic joints or psoriatic lesions exhibit an acidic pH (typically around 6.4–6.8), elevated levels of reactive oxygen species (ROS), and overexpression of proteolytic enzymes like cathepsins or MMPs. These conditions facilitate the cleavage of acid-labile or enzyme-sensitive linkers. A representative example is dexamethasone conjugated via a pH-sensitive hydrazone linker, which is selectively cleaved in the acidic environments of inflamed joints, enhancing localized drug release and reducing systemic exposure. In contrast, noncleavable linkers rely on the complete degradation of the entire conjugate by lysosomal enzymes or proteases after endocytosis. The drug is then released either in its active form or in a

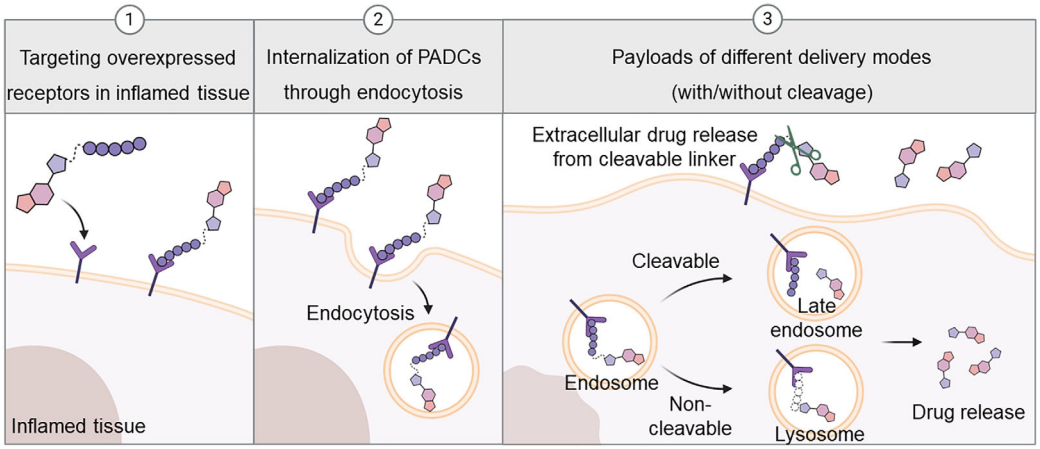


Figure 2. Mechanism of action of PADCs in inflammatory disease therapy. 1) PADCs selectively bind to overexpressed receptors on inflamed tissue via their targeting moiety. 2) After receptor binding, PADCs can undergo internalization into the cell via endocytosis. 3) The therapeutic payload may be released either extracellularly, if the linker is cleaved at the cell surface, or intracellularly, after endocytosis. Intracellular release can occur via cleavable linkers responsive to stimuli such as pH or enzymes within endosomes or lysosomes, or via noncleavable linkers followed by lysosomal degradation. The released drug then exerts its anti-inflammatory effect either within the cell or in the extracellular microenvironment (created using Biorender).

semiactive form following full degradation. This process provides sustained and controlled release, which is especially useful for chronic inflammatory diseases requiring long-term therapy. Once the drug is released, it interacts with intracellular targets to exert its therapeutic effects. For small-molecule drugs like corticosteroids or other anti-inflammatory agents, this often involves modulation of signaling pathways, suppression of proinflammatory cytokine production, or inhibition of immune cell activation.[31] In cases where the payload is a nucleic acid (e.g., siRNA or gene-editing tools), the therapeutic effect may involve gene silencing or regulate immune responses, leading to long-term modulation of disease pathways.

In some instances, the PADC may act extracellularly, particularly when targeting surface receptors or inflammatory markers that do not require internalization for therapeutic activity.[32] For example, PADCs that target cytokine receptors or cell adhesion molecules on the surface of activated immune cells can release their payload extracellularly, allowing the drug to act directly on cell-surface receptors. This is particularly relevant in diseases such as rheumatoid arthritis or psoriasis, where immune activation in the extracellular matrix plays a central role in disease progression.[33]

3. Applications in Inflammatory Disease

3.1. Autoimmune Disease

PADCs have emerged as a promising therapeutic strategy for autoimmune diseases, offering selective immune modulation and localized drug activity at sites of inflammation. Autoimmune disorders such as multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis are defined by a breakdown in immune tolerance, leading to aberrant activation of autoreactive T and B lymphocytes and sustained immune responses against self-antigens (**Table 2**). This dysregulation drives chronic inflammation and progressive tissue damage across diverse organs—including the central nervous system, joints, skin, and kidneys—and is often characterized by alternating periods of flare and remission. Although recent advances in immunosuppressive therapies have improved disease management, conventional treatments remain limited by systemic toxicity and broad immunosuppression, highlighting the need for more targeted and tissue-specific therapeutic approaches.

In MS, the most common cause of neurological disability in young adults, loss of immune tolerance to myelin sheath proteins such as proteolipid protein (PLP) and myelin basic protein (MBP) is believed to trigger the activation of myelin-reactive CD4+ T cells, resulting in CNS demyelination and progressive neurological symptoms. Traditional therapies, including corticosteroids, can reduce inflammation but often lack specificity, leading to significant adverse effects. To address this, antigen-specific immunotherapies (ASITs) have been explored to restore tolerance to myelin components; however, their clinical efficacy remains limited.

To enhance both specificity and therapeutic potency, antigen–drug conjugates (AgDCs) have been developed by chemically linking myelin-derived peptides (e.g., $PLP_{139–151}$) to immunomodulatory agents such as dexamethasone (DEX) using click chemistry and hydrolyzable ester linkers.[34] This dual-functional design enables antigen-directed delivery of DEX to autoreactive immune cells, allowing for localized immunosuppression while

Table 2. Comprehensive overview of PADCs designed for selective targeting and controlled drug release in inflammatory disease models.

Inflammatory disease		Targeting moiety	Payload	Linker type	Therapeutic effect	References
Autoimmune disease	Multiple sclerosis	Myelin-derived peptides	Dexamethasone	Hydrolyzable ester	Synergistic ASIT–steroid effect via antigen-targeted delivery	[34]
	Rheumatoid arthritis	Synovial-targeting peptide	Sinomenine	6-Aminohexanoic acid	Enhanced joint targeting, improved efficacy	[35]
		Anti-TNF antibody	Glucocorticoid receptor modulator	Dipeptide	Macrophage-selective delivery via TNF targeting	[16]
	Systemic lupus erythematosus	Anti-CD19 antibody	Triptolide	Not specified	Selective B cell depletion, reduced toxicity	[36]
	Psoriasis	SDT7 peptide	6-Paradol	Ester	Selective cytokine suppression through barrier-transcending peptide-guided delivery of PAR	[37]
Kidney disease	Acute kidney injury	G3-C12 peptide	Captopril	Disulfide	Kidney-specific delivery, enhanced ACE inhibition	[38]
	Chronic kidney disease	E-selectin-binding peptide	HPMA copolymer	–	Inhibited leukocyte adhesion (AKI model)	[39]
Inflammatory bowel disease		MAdCAM-1	Dexamethasone	pH-sensitive	Conceptual application in mucosal targeting	[41]
		CD98 peptides	siRNA	Enzyme-sensitive	–	[42a]
Others	Acute lung injury	γ3 peptide	Dexamethasone	ROS-sensitive (boronic ester)	Lung-targeted delivery, reduced cytokine levels	[44]
	Gout	CD44-binding peptide	Colchicine	Glutaryl amide	Macrophage-selective delivery, reduced IL-8/ROS	[45]
	Osteoporosis	$(Asp)_6$ peptide	Acacetin	Acid-sensitive (EMCH)	Bone-specific release, Suppressed osteoclasts	[46]

minimizing systemic exposure. The mechanism involves antigen-mediated targeting of cognate B or T cell receptors, intracellular uptake, and pH-sensitive release of DEX, which subsequently suppresses proinflammatory cytokines and promotes regulatory pathways such as IL-10 upregulation. Preclinical studies using the $PLP_{139–151}$-induced EAE mouse model have confirmed the therapeutic efficacy of this approach both in vitro and in vivo, highlighting the potential of AgDCs to synergize the benefits of ASIT and corticosteroid therapy.

In RA, synovial-targeted peptide–drug conjugates incorporating the anti-inflammatory agent Sinomenine (SIN) have been reported.[35] These conjugates were synthesized using either linear or cyclic forms of the synovial-targeting peptide CKSTHDRLC, coupled via a 6-aminocaproic acid linker. Comparative studies revealed that the cyclic form (conjugate C) exhibited superior stability and targeted drug release, thereby enhancing therapeutic outcomes through optimized tissue-specific delivery. Building on the concept of targeted delivery, a novel anti-TNF ADC, ABBV-3373, was designed to deliver a glucocorticoid receptor modulator (GRM) specifically to activated immune cells in inflammatory conditions such as RA.[16] This ADC employs adalimumab as the targeting moiety, which binds both soluble and transmembrane TNF—the latter enabling receptor-mediated internalization and lysosomal trafficking. The GRM payload is linked via a protease-cleavable Ala-Ala dipeptide linker, which is selectively degraded within lysosomes, triggering intracellular drug release. This dual-action mechanism allows for simultaneous TNF neutralization and targeted intracellular delivery of the anti-inflammatory agent, enhancing therapeutic potency while minimizing systemic glucocorticoid-related side effects.

SLE is a complex autoimmune disease characterized by multisystem involvement and chronic inflammation, with pathogenic B cells playing a central role in disease progression. To enhance therapeutic efficacy and reduce systemic toxicity, CD19-targeting antibody–drug conjugates have emerged as a compelling strategy.[36] One example, ADC-TP, links triptolide (TP)—a potent but highly toxic compound derived from *Tripterygium wilfordii*—to anti-CD19 monoclonal antibodies via a cleavable linker. Triptolide exerts immunosuppressive effects by inhibiting proinflammatory signaling pathways (e.g., NF-κB, JAK/STAT) and inducing immune cell apoptosis; however, its clinical utility has been limited by severe off-target toxicities. Conjugation to anti-CD19 mAb enables targeted delivery of TP to CD19+ B cells, improving specificity and reducing systemic exposure. In lupus mouse models, ADC-TP specifically depleted pathogenic B cells, ameliorated clinical symptoms, and significantly reduced triptolide-associated toxicity, representing advance in B cell-directed immunotherapy.

In the context of psoriasis—a chronic autoimmune skin disease characterized by abnormal keratinocyte proliferation, epidermal thickening, and immune-mediated inflammation—a novel transcellular PDC, TM5, was developed to overcome skin limitations.[37] TM5 was created by coupling the transcellular peptide SDT7 with 6-paradol (PAR), a natural phosphodiesterase 4 (PDE4) inhibitor identified via docking analysis. SDT7, derived by mining CPP-like antimicrobial peptides, exhibits strong cell and skin permeability through direct membrane translocation. The components were conjugated via an ester bond linker, allowing for hydrolysis-triggered payload release in the local tissue environment. In a psoriasis-like mouse model, TM5 significantly reduced skin thickness, plaque severity, and proinflammatory cytokine levels, demonstrating robust local anti-inflammatory activity. The mechanism involves SDT7-facilitated transdermal transport and site-specific enzymatic cleavage of the ester bond, enabling intracellular delivery of PAR. These results highlight the potential of ester-linked transcellular PDCs to enhance topical drug efficacy in inflammatory skin disorders.

3.2. Acute Kidney Injury and Chronic Kidney Disease

Renal inflammatory diseases such as acute kidney injury (AKI) and chronic kidney disease (CKD) are typified by localized immune activation, cellular infiltration, and fibrotic remodeling. Despite differing pathologies, both conditions offer opportunities for localized therapeutic strategies via PADCs.

One representative strategy utilizes a disulfide-linked conjugate comprising the G3-C12 peptide (ANTPCGPYTHDCPVKR), which exhibits selective accumulation in the kidney following systemic administration.[38] This peptide was chemically conjugated to the angiotensin-converting enzyme (ACE) inhibitor captopril via a glutathione-cleavable disulfide linker. In murine studies, this G3-C12–captopril conjugate demonstrated rapid renal uptake, mediated by reabsorption in proximal tubular epithelial cells, and significantly enhanced local drug concentration compared to free drug. Importantly, complete release of captopril occurred within minutes in the renal microenvironment, leading to greater in vivo ACE inhibition. These results indicate that G3-C12 is a promising carrier for kidney-targeted drug delivery.

Another approach involves polymer–peptide conjugates designed to target cell adhesion molecules implicated in leukocyte recruitment during kidney inflammation.[39] In a dual-model study involving ischemia–reperfusion injury (AKI) and adenine-induced nephropathy (CKD), an HPMA copolymer was conjugated with a multivalent E-selectin binding peptide (*P*-Esbp). This construct blocked E-selectin-mediated leukocyte adhesion and attenuated inflammation in the AKI model. Although efficacy was limited in CKD due to compensatory upregulation of *P*-selectin and VCAM-1, the study highlights the therapeutic potential of multivalent CAM-targeting conjugates in reducing leukocyte infiltration during acute inflammatory responses.

Recent work has also leveraged AI-driven peptide discovery pipelines to identify novel targeting moieties for injured kidney tissue.[40] A virtual peptide library of over 1,800 candidates was designed based on predicted binding to the Ig V domain of kidney injury molecule-1 (KIM-1). Through in vitro and in vivo screening, a lead peptide (TKP4) was selected for liposomal delivery of the anti-apoptotic agent nystatin. The KIM-1-targeting liposome achieved selective renal accumulation, reduced DR5 activation, and suppressed tubular cell apoptosis in an AKI mouse model. This study exemplifies how integrating computational design with experimental validation can accelerate the development of antibody-based targeting systems for renal drug delivery.

Collectively, these findings emphasize the translational potential of PADC-based strategies in nephrology. By integrating kidney-specific ligands and cleavable linkers responsive to renal biochemistry, PADCs offer a precision platform for addressing unmet needs in AKI and CKD.

3.3. Inflammatory Bowel Disease

IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of the gastrointestinal tract characterized by persistent mucosal inflammation, disruption of the epithelial barrier, and dysregulated immune activity. These processes lead to progressive tissue damage and compromised intestinal function. While current treatments—including biologics and small molecule drugs—have improved disease management, they are often associated with systemic side effects, diminished efficacy over time, and substantial patient-to-patient variability.

The success of PADCs in IBD relies heavily on identifying and exploiting molecular targets selectively overexpressed in inflamed intestinal mucosa. Notable targets include mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is upregulated in the colonic mucosa of UC patients and correlates with mucosal inflammation and relapse risk.[41] CD98, a cell-surface amino acid transporter, is also implicated in IBD pathogenesis, with studies demonstrating its overexpression in intestinal epithelial cells during inflammation.[42] Additionally, the integrin α4β7 is highly expressed on gut-homing lymphocytes and plays a key role in trafficking to the intestinal mucosa, making it a viable target for PADC-based strategies.[43] These molecules serve as entry points for designing peptide-guided delivery systems.

Although direct applications of PADCs in IBD remain limited, their potential as targeted delivery platforms for intestinal inflammation is increasingly recognized. For example, conjugating anti-inflammatory agents—such as dexamethasone or siRNA—to peptides that bind disease-specific targets like MAdCAM-1 or CD98 via pH-sensitive or enzyme-cleavable linkers could enable controlled release in the acidic or protease-rich environment of inflamed gut tissue.

In summary, while PADC-based therapies for IBD remain at a conceptual stage, the identification of inflammation-specific surface markers provides a strong foundation for future development. Advances in linker chemistry and peptide engineering will be essential to translating these concepts into effective therapies for patients with UC and CD.

3.4. Others

In addition to autoimmune, renal, and gastrointestinal diseases, PADCs have demonstrated therapeutic potential across a range of localized and systemic inflammatory disorders, including pulmonary inflammation, joint inflammation, and skeletal pathologies. These applications often leverage the modular design of PADCs—comprising a targeting moiety, cleavable linker, and anti-inflammatory payload—to achieve site-specific drug delivery under disease-relevant microenvironmental cues.

In acute lung injury (ALI), a highly inflammatory condition driven by infection or trauma-induced cytokine storms, targeted drug localization remains a major challenge. To address this, a ROS-responsive nanoparticle-based PADC system was developed, in which dexamethasone was encapsulated within phenylboronic ester-based polymeric nanoparticles and surface-functionalized with a γ3 peptide. The γ3 peptide functions as a lung-homing moiety that enhances accumulation in inflamed pulmonary tissues, while the phenylboronic ester linker is cleaved in response to elevated ROS levels, enabling drug release specifically in oxidatively stressed environments.[44] This dual-targeted system minimized off-target toxicity and significantly reduced pulmonary edema and cytokine production in ALI mouse models.

Gout, an inflammatory arthritis characterized by monosodium urate crystal deposition and macrophage-driven inflammation, has prompted the development of a CD44-targeted ADC to improve treatment specificity and minimize systemic toxicity. Colchicine, a conventional antigout agent known for its narrow therapeutic window, was conjugated to the CD44-binding P6 peptide via a glutaryl amide linker.[45] CD44 is highly expressed on activated macrophages in inflamed joints, allowing targeted uptake of the P6–colchicine conjugate. The linker design conferred stability during circulation and enabled intracellular release following macrophage internalization. Compared to free colchicine, the conjugate reduced IL-8 secretion and ROS production while exhibiting lower cytotoxicity, demonstrating an improved therapeutic index through selective delivery.

In skeletal inflammation, particularly osteoporotic bone loss, a bone-targeted PADC was developed using acacetin, a natural flavonoid with antiresorptive and anti-inflammatory properties. Acacetin was conjugated to a bone-homing hexapeptide ($(Asp)_6$) via an acid-sensitive EMCH (N-ε-maleimidocaproic acid hydrazide) linker, forming the construct Acacetin–EMCH–D6.[46] The $(Asp)_6$ peptide binds preferentially to mineralized bone surfaces, especially at osteoclastic resorption sites, where acidic conditions trigger EMCH linker cleavage and drug release. In an ovariectomy-induced osteoporosis model, the conjugate selectively accumulated in bone tissue, reduced osteoclast activity, and preserved trabecular bone mass. Mechanistic studies revealed that therapeutic efficacy was linked to autophagy inhibition via the PI3K/AKT/mTOR pathway.

Expanding beyond conventional drug delivery, lysosome-targeting chimeras (LYTACs) represent a novel PADC strategy that promotes degradation of extracellular and membrane-bound inflammatory proteins.[47] In a recent study, bis–mannose-6-phosphate (bisM6P) was conjugated to Fc-engineered antibodies using site-specific glycan-conjugation. The bisM6P motif engages the cation-independent mannose-6-phosphate receptor (CI-MPR), facilitating receptor-mediated internalization and lysosomal degradation of targets such as soluble TNF. This system operated without chemical glycan modification and reflects a shift from payload release to event-driven pharmacology, expanding the therapeutic scope of PADCs.

Collectively, these studies highlight the structural versatility and mechanistic diversity of PADCs in the treatment of inflammatory disease. By carefully selecting targeting peptides (e.g., γ3 for lungs, P6 for joints, $(Asp)_6$ for bone); designing linkers responsive to oxidative stress, acidity, or enzymatic activity; and incorporating potent anti-inflammatory agents (e.g., dexamethasone, colchicine, acacetin), PADCs enable precision delivery that improves therapeutic outcomes while limiting systemic burden. The integration of receptor-targeted uptake, environment-sensitive release, and immune modulation positions PADCs as a next-generation platform for localized control of complex inflammatory pathologies.

4. Challenges and Future Perspectives

The application of PADCs in inflammatory diseases has demonstrated impressive therapeutic potential through improved targeting, localized delivery, and enhanced efficacy. However, translating these promising preclinical outcomes into clinical success remains a complex endeavor. The following sections outline the key challenges in PADC development and highlight future directions that are actively shaping the field.

4.1. Clinical Translation Challenges

The heterogeneity of inflammatory diseases presents a major obstacle to the clinical translation of PADCs.[48] Unlike oncology, where well-characterized tumor antigens enable precise molecular targeting, inflammatory conditions are marked by dynamic and patient-specific expression of surface markers such as ICAM-1, integrins, or cytokine receptors. This biological variability complicates the selection of universal targets and increases the risk of off-target effects. Moreover, the complex and evolving pathophysiology of inflamed tissues can significantly alter the biodistribution, pharmacokinetics, and metabolic fate of PADCs, ultimately impacting their therapeutic performance. The immunomodulatory nature of many PADCs introduces additional concerns, particularly in chronic diseases requiring long-term administration. Achieving sustained efficacy without inducing immunosuppression or tolerance remains a delicate balance, compounded by interindividual variability in immune responsiveness. Addressing these challenges requires a deeper understanding of immune phenotypes across different disease stages, which is essential for informing rational PADC design, target selection, and personalized dosing strategies.

The instability of peptides and antibodies in protease-rich inflammatory environments often limits the systemic half-life and therapeutic persistence of PADCs. While strategies such as cyclization, incorporation of non-natural amino acids, and PEGylation have been employed to reduce degradation, these modifications may inadvertently affect target binding or pharmacodynamics.

Pharmacokinetic limitations, particularly the rapid renal clearance of low-molecular-weight conjugates, further restrict therapeutic utility. Approaches such as conjugation to albumin-binding domains, polymer shielding, or formulation into nanoparticle systems have demonstrated improved systemic retention. However, optimizing these platforms to balance stability, bioavailability, and controlled release remains an ongoing challenge.

Manufacturing considerations also constrain PADC development. Achieving site-specific and reproducible conjugation at scale is essential to ensure batch consistency and functional integrity. Techniques including sortase-mediated ligation, click chemistry, and oxime formation are under active investigation, yet standardized protocols suitable for industrial-scale production remain limited. Additionally, comprehensive analytical characterization of complex conjugates is required to meet regulatory standards, including assessments of purity, potency, and structural heterogeneity.

4.2. Emerging Trends and Technological Innovation

Recent advances in computational biology have introduced new opportunities in PADC discovery and design. Artificial intelligence (AI)-based methods now support rational peptide design, enabling prediction of binding affinities, metabolic stability, and immunogenic risk.[29b,49] Deep learning architectures, including transformer models and graph-based neural networks, are being applied to identify bioactive motifs with high selectivity for inflammation-associated targets such as IL-6R, TNF-α, or integrin subtypes.[50] In parallel, high-throughput screening technologies—such as phage display, mRNA display, and peptide arrays—enable rapid experimental validation of computationally derived candidates.[51] Together, these platforms accelerate the generation of optimized peptides suitable for conjugation and targeted delivery. Advances in linker chemistry and nanomaterial engineering are facilitating the development of multifunctional PADCs with environment-responsive behavior. The integration of cleavable linkers responsive to pH, redox state, or enzyme activity enables site-specific payload release, improving therapeutic precision and minimizing systemic effects.

Additionally, recent studies have introduced carrier-free nanoassembly strategies based on PADC platforms for the treatment of inflammatory diseases such as sepsis, acute liver failure, and IBD.[11a,52] These systems rely solely on the intrinsic properties of the peptide and drug components to drive spontaneous nanoassembly through intermolecular interactions in aqueous environments. In inflamed tissues, where vascular permeability is increased and lymphatic drainage is impaired, such assemblies exploit the EPR effect to achieve passive targeting and selective accumulation at disease sites. Furthermore, the absence of additional carriers simplifies the formulation process, offering significant advantages in large-scale manufacturing and clinical translation. Their passive accumulation and scalable production profile position them as promising candidates for further development in inflammation-targeted therapy.

Overall, while PADCs face notable translational challenges, ongoing innovation in peptide chemistry, drug formulation, and computational tools are steadily addressing these limitations. With continued refinement, PADC-based therapeutics hold significant promise for the effective and safe management of complex inflammatory diseases.

5. Summary

PADCs have emerged as a versatile therapeutic platform for targeted therapy, offering highly selective delivery of payload to diseased sites. However, their clinical application has thus far been largely confined to oncology. In this review, we explored the therapeutic potential of PADCs as a targeted strategy for treating inflammatory diseases. In particular, the advent of sophisticated stimuli-responsive linkers, combined with peptides or antibodies engineered for improved pharmacokinetics, has significantly expanded the therapeutic repertoire of PADCs, providing a robust platform for next-generation immunomodulation with enhanced safety and efficacy. Collectively, this review highlights the promise of PADCs as a modular and clinically adaptable platform for precise immunomodulation in inflammatory diseases,

laying the groundwork for the next generation of inflammation-targeted therapeutics.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Yeongji Jang: writing—review and editing, data curation, and investigation. **Jiwoong Choi**: writing—review and editing, data curation, and investigation. **Youngri Ryu**: data curation and investigation. **Hyun Kyu Song**: validation. **Man Kyu Shim**: writing—review and editing, funding acquisition, data curation, and conceptualization. **Yoosoo Yang**: writing—review and editing, supervision and project administration, funding acquisition, data curation, and conceptualization. All authors have read and approved the final version of the manuscript for submission. **Yeongji Jan** and **Jiwoong Choi** contributed equally to this work.

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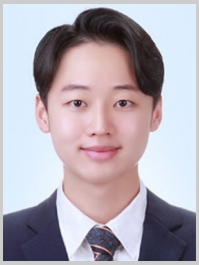

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