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Review

Artificial Intelligence-Driven Antibody-Drug Conjugate Development for Chronic Neuropathic Pain: From Target Discovery to Clinical Translation

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Abstract: Chronic neuropathic pain affects 7–10% of the global population and imposes a substantial socioeconomic burden, yet existing pharmacological options remain inadequate in efficacy and burdened by systemic toxicity. Antibody-drug conjugates (ADCs) — engineered to deliver neuromodulatory payloads selectively to peripheral nociceptors — represent a compelling but unexplored therapeutic modality; no clinical-stage pain ADC currently exists. To the best of our knowledge based on a structured literature search (January 2000–March 2025) and targeted updates through 6 June 2026, this review provides a systematic and comprehensive conceptual framework mapping AI methodologies validated in oncology ADC development onto the unique challenges of chronic neuropathic pain. The framework spans five pipeline stages: multi-omics integration and graph neural networks for nociceptor-selective target prioritization (Nav1.7, TRPV1, P2X3, TrkA, CGRP receptor, ASIC3); structure prediction and protein language models for antibody engineering against transmembrane pain targets; generative AI for neuromodulatory payload design; deep learning for neural tissue pharmacokinetics and neurotoxicity prediction; and AI-driven patient stratification for precision clinical trial design. A unique three-layer optimization challenge — neural selectivity, analgesic potency, and systemic safety — distinguishes pain ADC AI from oncology ADC AI and defines the core design constraints of this review. Clinical precedent from FDA-approved anti-CGRP pathway antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) and Phase III anti-NGF antibody trials establishes that peripheral nociceptor-targeting biologics are both feasible and clinically active, providing the biological foundation for the pain-ADC concept. Realizing this framework requires curated pain-ADC datasets, interpretable AI, and closed-loop platforms incorporating dorsal root ganglion (DRG) organoids.

Keywords: antibody-drug conjugate; chronic neuropathic pain; artificial intelligence; dorsal root ganglion; Nav1.7; neuromodulation; drug discovery

1. Introduction

1.1 Antibody-Drug Conjugates: Emerging Paradigms in Targeted Pain Therapy

Chronic neuropathic pain, defined as pain arising from a lesion or disease of the somatosensory nervous system, represents one of the most prevalent and

therapeutically refractory conditions in modern medicine [1]. Epidemiological surveys consistently estimate a global prevalence of 7–10%, translating to more than 500 million affected individuals worldwide — though estimates vary substantially depending on diagnostic criteria applied — with an annual economic burden of hundreds of billions of dollars in direct healthcare costs and lost productivity [1,2,3,4]. Despite decades of research, the pharmacological armamentarium for neuropathic pain remains dominated by drugs developed for other indications — anticonvulsants such as gabapentin and pregabalin, antidepressants such as duloxetine, and opioid analgesics — none of which were designed with the molecular architecture of nociceptive pathways in mind [2]. These agents act broadly across the nervous system, producing systemic side effects including sedation, cognitive impairment, dependence, and cardiovascular risk that frequently limit their clinical utility [3].

Antibody-drug conjugates represent a class of targeted therapeutics that combine the exquisite binding specificity of monoclonal antibodies with the pharmacological potency of small-molecule payloads, linked through a chemically engineered linker that controls payload release [5]. In oncology, this architecture had yielded 12 active FDA-approved oncology ADCs by the March 2025 literature-search cutoff (excluding products withdrawn at that time, such as belantamab mafodotin and moxetumomab pasudotox; the regulatory landscape has continued to evolve after the cutoff, including later re-approval of belantamab mafodotin) [6,7,8,9], demonstrating that selective delivery of cytotoxic agents to antigen-expressing cells can dramatically improve the therapeutic index compared to systemic chemotherapy [5,10,11,12]. The conceptual translation of this platform to chronic neuropathic pain is scientifically compelling: the peripheral nervous system, and the dorsal root ganglion (DRG) in particular, harbors a rich repertoire of nociceptor-selective surface proteins that are amenable to antibody targeting and receptor-mediated internalization [13,14].

In the pain context, the ADC architecture requires fundamental reinterpretation. The antibody component targets membrane proteins selectively expressed on DRG neurons and peripheral nociceptors — including voltage-gated sodium channels (Nav1.7), transient receptor potential channels (TRPV1), purinergic receptors (P2X3), and neurotrophin receptors (TrkA) — rather than tumor-associated antigens [15,16]. The neuromodulatory payload is not a cytotoxic agent designed to kill cells, but a neuromodulatory molecule designed to modulate neuronal excitability while preserving cell viability — a fundamentally different pharmacological objective [5]. The linker must release the payload within the neuronal endolysosomal compartment, exploiting the protease environment of DRG neurons rather than tumor cells.

The scientific rationale is supported by clinical precedent: anti-NGF antibodies (tanezumab) demonstrated Phase III analgesic efficacy [17], and anti-CGRP pathway antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab) have received FDA approval for migraine prevention [18], supporting the broader feasibility of peripheral neuron-targeting biologics while underscoring the need for target-specific safety evaluation. These precedents establish the biological plausibility of the pain-ADC concept: ADC-mediated intracellular payload delivery to the same neuronal populations should achieve superior precision. The full AI-driven pain-ADC development pipeline is illustrated in Fig. 1.

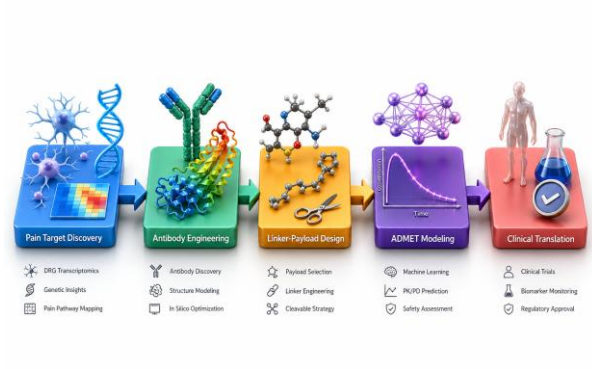

Figure 1. AI-driven antibody-drug conjugate development pipeline for chronic neuropathic pain. The five-stage pipeline integrates multi-omics target discovery (Stage 1), AI-assisted antibody engineering against transmembrane pain targets (Stage 2), generative design of neuromodulatory linker-payload systems (Stage 3), deep learning ADMET prediction with neural tissue pharmacokinetics (Stage 4), and AI-facilitated clinical translation including patient stratification and adaptive trial design (Stage 5). Key AI tools deployed at each stage are indicated. DRG, dorsal root ganglion; GNN, graph neural network; NLP, natural language processing; ADMET, absorption, distribution, metabolism, excretion, and toxicity.

1.2 Persistent Challenges in Pain-ADC Development

Despite the conceptual appeal of pain-directed ADCs, their development faces a constellation of challenges that are distinct from — and in several respects more formidable than — those encountered in oncology ADC development (Table 1). The first challenge concerns target biology. Whereas oncology ADCs typically target single-pass transmembrane or secreted proteins with large extracellular domains (HER2, TROP2, CD30), the most compelling pain targets are multi-pass transmembrane proteins — voltage-gated ion channels and G protein-coupled receptors — with limited extracellular epitope accessibility [15]. Nav1.7, for example, contains 24 transmembrane segments organized across four homologous domains, with accessible extracellular epitopes largely confined to short loops between transmembrane helices — a structural constraint that makes antibody design substantially more challenging than for conventional single-pass tumor antigens [15].

Table 1. Comparison of pain ADC and oncology ADC clinical development.

Dimension	Oncology ADC	Pain ADC	Key Implication
Target biology	Single-pass or secreted tumor antigens (HER2, TROP2, CD30)	Multi-pass transmembrane ion channels/GPCRs (Nav1.7, TRPV1, CGRP-R)	Antibody engineering more challenging; epitope accessibility limited
Payload goal	Cytotoxic cell killing (MMAE, DXd, DM1)	Neuromodulation without cell death (conotoxins, BoNT fragments, siRNA)	Entirely different payload library; potency metrics differ
Critical toxicity	Myelosuppression, ILD (T-DXd class), peripheral neuropathy (MMAE-based), keratopathy (belantamab mafodotin)	Motor neurotoxicity (absolute red line), sensory loss, CNS effects	Neurotoxicity safety studies (ICH S7A/S7B) are mandatory
Delivery barrier	Tumor microenvironment, EPR effect	Blood–nerve barrier (DRG), blood–spinal cord barrier	DRG relatively accessible; CNS targets require special strategies
Primary efficacy endpoint	OS, PFS (objective imaging)	NRS/VAS pain score (subjective), QST (objective)	Subjective endpoints increase trial variability and sample size
Placebo effect	<20%	~30–50% (varies by condition and trial design)	Requires enrichment design and placebo-responder prediction by AI
Patient stratification	Tumor genomics, IHC biomarkers	Pain phenotype (QST), neuroimaging, genomics, serum biomarkers	Multimodal AI stratification essential; no single validated biomarker
Approved products	12 active FDA-approved oncology ADCs by the March 2025 literature-search cutoff, excluding products withdrawn at that time such as belantamab mafodotin and moxetumomab pasudotox; approvals and re-approvals have continued after the cutoff [6,7,8,9]	0 approved; ClinicalTrials.gov and PubMed searches through 6 June 2026 identified no clinical-stage ADC specifically developed for neuropathic pain	Field remains pre-clinical; regulatory pathway not yet defined
Preclinical models	Tumor xenograft, PDX models	CCI/SNI/SNL neuropathic pain models (poor human translation)	AI-assisted translational modeling critical to bridge species gap
Regulatory precedent	Established ADC regulatory framework (FDA, EMA)	No specific guidance; borrows from neurotoxin and biologic frameworks	Early FDA engagement recommended; novel safety endpoints needed

A second challenge is the "double-edged sword" nature of pain targets. Nav1.7 and TRPV1 are not exclusively pathological proteins; they serve essential physiological functions in normal pain sensation, thermal regulation, and protective nociception [16,19]. Complete pharmacological blockade of these targets risks producing dangerous insensitivity to pain — as illustrated by individuals with loss-of-function SCN9A mutations who suffer repeated injuries due to congenital inability to experience pain [19]. This constraint demands that pain ADCs achieve selective modulation rather than complete ablation of target function, a more nuanced pharmacological objective than the cytotoxic endpoint of oncology ADCs.

Delivery barriers represent a third major challenge. The central nervous system is protected by the blood–brain barrier and blood–spinal cord barrier, which are largely impermeable to large-molecule biologics [20]. While the DRG is relatively more accessible due to its fenestrated vasculature and incomplete blood–nerve barrier, achieving sufficient drug concentrations at peripheral nociceptors while avoiding systemic exposure remains a significant pharmacokinetic challenge [13,21]. Motor neurotoxicity constitutes an absolute safety red line: any pain ADC that inadvertently targets motor neurons in the spinal cord anterior horn or peripheral motor nerves would produce unacceptable paralysis, a consequence that is irreversible and potentially life-threatening [22].

Finally, the clinical development of pain ADCs faces the challenge of subjective endpoints. Unlike oncology trials, where tumor response can be objectively measured by imaging, pain trials rely primarily on patient-reported numerical rating scales (NRS) and visual analogue scales (VAS), which are inherently variable and subject to a placebo effect that ranges from approximately 30–50% in neuropathic pain trials, varying by condition and trial design [23,24]. This high placebo response rate substantially increases the sample sizes required to demonstrate efficacy and demands sophisticated patient stratification strategies.

1.3 The Emergence of AI: Accelerating Pain-ADC Innovation

Artificial intelligence has emerged as a transformative force across the drug discovery and development continuum, offering computational capabilities that address many of the challenges outlined above [5]. Graph neural networks (GNNs) can integrate heterogeneous multi-omics data — single-cell transcriptomics, genome-wide association studies, proteomics — to identify and prioritize target proteins with the selectivity profiles required for pain ADC development [5]. Transformer-based protein language models, including ESM-2 and ProtT5, enable rapid in silico screening of antibody sequence space for affinity, stability, and developability [5]. Generative molecular models can design novel neuromodulatory payloads with optimized selectivity profiles. Deep learning ADMET frameworks predict neurotoxicity, pharmacokinetics, and neural tissue distribution with increasing mechanistic clarity [5].

The AI applications described throughout this review span a spectrum of validation maturity: methods such as AlphaFold2 structure prediction and protein language model-based antibody optimization are already validated in oncology ADC development and adjacent domains, while applications such as pain-specific GNN target prioritization, neuromodulatory payload generative design, and AI-driven pain patient stratification are prospective — methodologically grounded but not yet experimentally validated in the pain ADC context. We explicitly distinguish these two categories throughout the review.

The application of AI to pain ADC development presents a unique three-layer optimization challenge that has no direct counterpart in oncology: simultaneously maximizing neural selectivity (sensory over motor neurons), analgesic potency (sufficient neuromodulation at the target site), and systemic safety (minimal off-target neural effects). This multi-objective optimization problem, spanning molecular design, pharmacokinetics, and clinical response prediction, is precisely the domain where AI-driven approaches offer the greatest advantage over traditional empirical methods.

The remainder of this paper is organized as follows: Section 2 establishes the scientific rationale for pain ADCs; Sections 3–7 address AI applications at each pipeline stage; Section 8 covers clinical development; and Section 9 discusses challenges and future perspectives.

2. Scientific Rationale for ADC-Based Pain

Therapy

The ADC approach to chronic neuropathic pain must be justified on three grounds: the inadequacy of existing therapies, the clinical validation of peripheral neuron-targeting antibodies, and the unique anatomical properties of the DRG that make it a tractable ADC delivery target. As detailed in Section 1, current analgesics — opioids, anticonvulsants, antidepressants, and NSAIDs — share a fundamental limitation: they lack molecular selectivity for the specific neuronal populations and ion channels that drive neuropathic pain, producing systemic effects that limit their therapeutic utility [2,3,25].

The clinical validation of peripheral neuron-targeting antibodies provides the most compelling scientific rationale for pain ADCs. Tanezumab (anti-NGF mAb) demonstrated Phase III analgesic efficacy in osteoarthritis [17] and chronic low back pain [26], establishing that antibody-mediated blockade of peripheral neurotrophin signaling can produce durable analgesia; however, an FDA advisory committee voted 19-to-1 in March 2021 that its REMS was insufficient to justify the risk of rapidly progressive osteoarthritis (RPOA), leading to discontinuation of global development [27]. The anti-CGRP antibody class — erenumab, fremanezumab, galcanezumab, and eptinezumab — has achieved FDA approval for migraine prevention, establishing regulatory and biological precedent for large-molecule biologics targeting peripheral nociceptive signaling [18]. These approvals represent a paradigm shift: the peripheral nervous system is a tractable target for antibody-based therapeutics, and the blood–nerve barrier does not preclude meaningful drug exposure at peripheral nociceptors. Anti-CGRP efficacy is primarily attributed to peripheral actions at the trigeminal ganglion and meningeal vasculature — analogous to the DRG blood–nerve barrier — rather than CNS penetration [18].

The logical extension to ADCs is straightforward: ADC-mediated intracellular payload delivery bypasses extracellular receptor blockade, enabling modulation of intracellular targets (ion channel trafficking machinery, siRNA gene silencing) inaccessible to conventional antibodies, and sustained intracellular release providing longer-lasting analgesia than receptor-blocking antibodies subject to competitive displacement by endogenous ligands.

The DRG is anatomically well-positioned for ADC delivery [13,21]. Located in the intervertebral foramen, the DRG is supplied by capillaries with relatively permeable endothelium and an incomplete blood–nerve barrier, allowing greater macromolecular access than the CNS [13]. Radiolabeled antibody biodistribution studies confirm that large-molecule biologics achieve meaningful DRG concentrations following systemic administration [21], and nanoparticle delivery systems targeting DRG surface proteins (e.g., ADAM8) further demonstrate the feasibility of selective peripheral nervous system drug delivery [28]. DRG neurons internalize antibody-receptor complexes via clathrin-mediated endocytosis and other routes [29], though internalization kinetics in primary human DRG neurons require direct validation. FcRn is expressed in peripheral endothelial cells [30], and if expressed in DRG neurons, could extend intraneuronal ADC half-life — a hypothesis requiring experimental confirmation.

Pain ADCs occupy a unique therapeutic niche relative to competing modalities. Versus small-molecule Nav1.7 inhibitors — which have repeatedly failed clinically, likely due to insufficient Nav1.4/Nav1.5 selectivity and compensatory sodium channel upregulation [22,31] — pain ADCs provide target cell selectivity (DRG neurons over motor neurons) independently of payload channel selectivity. Versus gene therapy (AAV-mediated Nav1.7 knockdown) [32], pain ADCs offer reversibility without viral vector delivery. Versus neuromodulation devices [33], pain ADCs enable systemic administration without surgery, though they lack real-time adjustability. Pain ADCs are thus molecularly targeted, reversible, systemically administered, and capable of addressing the specific molecular pathology of individual pain subtypes.

Early proof-of-concept studies for neurotoxin-antibody conjugates provide direct experimental support for the pain ADC concept. Targeted delivery of botulinum toxin fragments using antibodies directed against peripheral nociceptor markers has been explored as a strategy to achieve localized, long-lasting inhibition of neurotransmitter release at pain-relevant synapses [34]. Conotoxin-antibody fusion proteins targeting Nav1.7 have been conceptually proposed as a means to achieve selective peripheral sodium channel blockade without the systemic cardiovascular and CNS effects that have limited the clinical development of small-molecule Nav1.7 inhibitors [22], though experimental demonstration of this specific approach in

primary sensory neurons remains limited. These early studies, while largely at the conceptual or early preclinical stage, establish the feasibility of the pain ADC approach and provide a foundation for the AI-driven development framework described in the subsequent sections.

2.1 Neuroimmune Mechanisms of Neuropathic Pain: Immunological Rationale for Pain ADCs

A critical dimension of the scientific rationale for pain ADCs — and one that is directly relevant to the immunological scope of this review — is the neuroimmune basis of neuropathic pain. Neuropathic pain is not a purely neuronal phenomenon; it is fundamentally a neuroimmune disease in which bidirectional communication between the nervous system and the immune system drives and sustains the chronic pain state [25,28,35]. Understanding these neuroimmune mechanisms is essential for designing pain ADCs that are both effective and immunologically safe.

Following peripheral nerve injury, a coordinated immune response is initiated at the site of injury and within the DRG itself. Resident macrophages in the DRG — which constitute approximately 9–10% of DRG cells under homeostatic conditions — undergo rapid activation and adopt a pro-inflammatory phenotype, releasing tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) that directly sensitize adjacent nociceptors by lowering their activation thresholds [28,30,36]. Circulating monocytes are recruited to the injured nerve and DRG, differentiating into macrophages that amplify this inflammatory cascade [36]. T lymphocytes — both CD4+ helper T cells and CD8+ cytotoxic T cells — infiltrate the DRG and dorsal horn following nerve injury, with distinct T cell subsets playing opposing roles: pro-nociceptive Th1 and Th17 cells promote pain sensitization through interferon-γ and IL-17 release, while regulatory T cells (Tregs) and Th2 cells contribute to pain resolution through IL-10 and IL-4 signaling [25,28]. Mast cells, which reside in peripheral nerves and DRG connective tissue, degranulate in response to nerve injury and release histamine, serotonin, and tryptase that activate nociceptors and increase vascular permeability — the latter potentially facilitating ADC access to the DRG [36]. Neutrophils are among the earliest immune cells recruited to the injury site, releasing reactive oxygen species and proteases that contribute to the initial sensitization phase [36].

This neuroimmune landscape has three direct implications for pain ADC design. First, TNF-α and IL-1β upregulate Nav1.7, TRPV1, and TrkA in the injured DRG [28,30], potentially providing a built-in selectivity advantage: pain ADCs may achieve higher effective concentrations at sensitized nociceptors than at normal sensory neurons. Second, activated macrophages and T cells in the DRG express Fc receptors, making Fc effector silencing (LALA/LALAPG mutations) a practical necessity to prevent ADCC against DRG neurons and avoid amplifying neuroinflammation [28]. Third, neuroinflammation-associated vascular permeability may enhance macromolecular DRG access, improving ADC delivery efficiency in the pathological state.

Immunological safety considerations for pain ADCs. Beyond the neuroimmune mechanisms of pain, the immunological properties of pain ADCs themselves require careful consideration. Anti-drug antibody (ADA) formation is a well-recognized risk for all biologic therapeutics, and pain ADCs face particular ADA challenges due to the immunogenic nature of their neuromodulatory payloads — conotoxin derivatives and botulinum toxin fragments are foreign proteins that may elicit robust humoral immune responses upon repeated dosing [28]. ADA formation can neutralize ADC efficacy, alter pharmacokinetics, and in severe cases trigger hypersensitivity reactions. AI-driven immunogenicity prediction tools — including T-cell epitope prediction algorithms (EpiVax, Optitope) and B-cell epitope mapping models — can identify immunogenic hotspots in both the antibody and payload components, enabling rational sequence modifications to reduce ADA risk before clinical testing. Complement activation represents a second immunological safety concern: IgG antibodies with intact Fc regions can activate the classical complement pathway through C1q binding, potentially triggering complement-mediated neuroinflammation in the DRG. The LALA/LALAPG Fc silencing mutations that eliminate FcγR binding also substantially reduce C1q binding and complement activation, providing dual protection against Fc-mediated immune toxicity in neural tissue [28]. Cytokine release syndrome (CRS), which can occur when high-affinity antibodies engage targets expressed on immune cells in addition to the intended cellular target, is a third consideration: if Nav1.7 or TRPV1 are expressed on DRG-resident immune cells (macrophages, mast cells),

rapid ADC binding could trigger cytokine release. AI models trained on CRS risk data from existing biologic therapies may support early CRS risk stratification from antibody sequence and target expression profiles, but such predictions would require pain-ADC-specific validation.

This neuroimmune framework positions pain ADC development at the intersection of pain neurobiology, immunology, and ADC chemistry. AI tools described in subsequent sections must be evaluated not only for pharmacological efficacy optimization but for their capacity to predict and mitigate immunological risks inherent to biologic therapy in an inflamed neural tissue environment.

3. Literature Search and Selection Strategy

A structured literature search was conducted across PubMed/MEDLINE, Web of Science, and Scopus (January 2000 – March 2025) using three Boolean domain clusters: (1) pain biology — ("neuropathic pain" OR "chronic pain" OR "dorsal root ganglion" OR "nociceptor") AND ("Nav1.7" OR "TRPV1" OR "P2X3" OR "CGRP" OR "NGF" OR "TrkA" OR "ASIC3"); (2) ADC technology — ("antibody-drug conjugate" OR "ADC") AND ("linker-payload" OR "neuromodulatory payload" OR "neurotoxin conjugate" OR "pain"); and (3) artificial intelligence — ("machine learning" OR "deep learning" OR "graph neural network" OR "generative model" OR "NLP") AND ("drug discovery" OR "ADC" OR "pain" OR "ADMET"). Inclusion criteria: peer-reviewed original research, reviews, and clinical trial reports relevant to at least one domain; exclusion criteria: conference abstracts without full-text data, non-English publications, and CNS-only studies without peripheral nociceptor relevance. Reference lists were manually screened for additional sources. Given the interdisciplinary scope, a formal PRISMA diagram was not generated; the three-domain search strategy and methodology transfer framework serve as the transparency mechanism. Database searches were last updated on 6 June 2026 for the specific question of whether any clinical-stage ADC had been developed for neuropathic pain. Given the absence of clinical-stage pain ADC data, this review employs a methodology transfer strategy: AI methods validated in oncology ADC development are mapped onto the biological and clinical requirements of pain ADC development, drawing evidence from oncology ADC AI (methodological foundation), pain neurobiology (target biology and clinical precedent), and AI in pain medicine (clinical development framework). All claims regarding pain ADC efficacy or safety are framed as hypotheses to be tested in future studies.

3.1 Research Gap: What This Review Uniquely Addresses

To the best of our knowledge based on a structured literature search (January 2000–March 2025) and targeted updates through 6 June 2026, no prior review has integrated AI in oncology ADC development [5,10,11,12], pain neurobiology [13,14,15,16], and AI in pain medicine [37,38,39] into a unified framework. This review fills that gap by: (1) mapping validated oncology ADC AI methodologies onto neuropathic pain biology; (2) proposing the first AI-driven patient stratification framework for pain ADC clinical trials; (3) identifying the unique three-layer optimization challenge (neural selectivity × analgesic potency × systemic safety); and (4) proposing the Pain-ADC Commons data infrastructure as a field prerequisite.

4. AI for Target Identification in Pain ADCs

4.1 AI-Driven Platforms for High-Throughput Pain Target Discovery

Optimal pain ADC targets must satisfy four simultaneous criteria: (1) selective expression on DRG nociceptors relative to motor neurons and CNS cells; (2) efficient receptor-mediated internalization; (3) robust genetic and pharmacological evidence linking the target to neuropathic pain; and (4) accessible extracellular epitopes for antibody binding [14,15,40,41]. No single database or platform evaluates all four criteria simultaneously, making AI-driven multi-source data integration essential.

Graph neural networks (GNNs) have emerged as the most powerful architecture for integrating heterogeneous data types relevant to pain target discovery [5]. Validated in oncology (e.g., PandaOmics for tumor target prioritization), their application to pain ADC target discovery is prospective. By representing proteins, genes, diseases, and phenotypes as nodes — with edges encoding protein-protein interactions, gene-disease associations, and pharmacological relationships — GNNs identify proteins centrally positioned in nociceptive signaling networks. Applied to DRG single-cell atlases integrated with UK Biobank pain GWAS data, GNN platforms could rank candidate targets by selectivity, internalization potential, and genetic validation scores — though this specific

application remains to be implemented and validated [5].

The resulting target landscape for pain ADCs centers on six high-priority candidates, summarized in Table 2 and illustrated in Fig. 2. Nav1.7 (SCN9A) is expressed in DRG neurons and sympathetic ganglia; the key selectivity challenge is discrimination from Nav1.4 (skeletal muscle) and Nav1.5 (cardiac), and its causal role in pain is established by gain-of-function mutations causing erythromelalgia and loss-of-function mutations causing congenital inability to experience pain [15,19,22,31,42,43,44]. TRPV1, expressed in peptidergic C-fibers, is efficiently internalized and validated by TRPV1 knockout mouse studies; TRPV1-targeted small molecules have failed clinically due to hyperthermia, underscoring the need for targeted delivery [16,45,46,47,48,49]. P2X3, expressed in non-peptidergic C-fibers in rodents — with broader distribution in human sensory neurons [14,50] — is pharmacologically validated by the Phase III P2X3 antagonist gefapixant in chronic cough; pain-specific validation remains limited [35,51,52,53]. TrkA, the high-affinity NGF receptor on peptidergic DRG neurons, is a receptor tyrosine kinase with efficient internalization kinetics validated by Phase III anti-NGF antibody efficacy [17,21,26]. The CGRP receptor complex (CALCRL/RAMP1) is validated by FDA-approved anti-CGRP antibodies for migraine prevention [3,18]. ASIC3, expressed on peripheral nociceptors, contributes to inflammatory and ischemic pain and presents accessible extracellular domains [14].

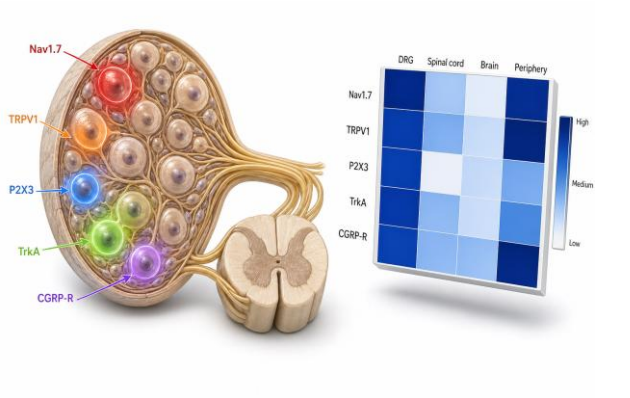

Figure 2. Dorsal root ganglion target atlas for pain ADC development. (A) Anatomical cross-section of the DRG illustrating the major nociceptor subtypes and their surface expression of candidate ADC targets. Peptidergic C-fibers (CGRP+) express TRPV1, TrkA, and CGRP receptor; non-peptidergic C-fibers (IB4+) express P2X3 and ASIC3; all nociceptor subtypes express Nav1.7. (B) Expression heatmap showing relative expression levels of the six candidate targets across DRG neuronal subtypes, motor neurons, and cardiac tissue, illustrating the selectivity profiles relevant to pain ADC safety. GoF, gain-of-function; LoF, loss-of-function; RTK, receptor tyrosine kinase.

Table 2. Candidate targets for pain-directed antibody-drug conjugates.

Target	Gene	Expression Pattern	Pain Genetic Evidence	ADC Feasibility	Target Validation (non-ADC)	ADC-Specific Stage
Nav1.7	SCN9A	DRG >> sympathetic ganglia >> motor neurons	GoF mutations → erythromelalgia; LoF → congenital inability to experience pain	High: accessible extracellular loops; humanized antibodies available	Human genetics (SCN9A); small-molecule clinical failures	Preclinical concept (no ADC)
TRPV1	TRPV1	Peptidergic C-fibers (DRG)	TRPV1 KO mice: reduced thermal hyperalgesia; human variant studies show altered thermal sensitivity	High: efficient internalization; cryo-EM structure resolved	Rodent KO studies; small-molecule clinical failures (hyperthermia)	Preclinical concept (no ADC)
P2X3	P2RX3	Predominantly non-peptidergic C-fibers (rodents);	P2X3 antagonist gefapixant: Phase	Moderate: extracellular ATP-binding domain	Small-molecule Phase III (cough); pain	Preclinical concept (no ADC)

		broader in humans	III refractory chronic cough (pain indication early-stage)	accessible	indication early-stage	
TrkA	NTRK1	Peptidergic DRG neurons	Anti-NGF/TrkA antibody tanezumab: Phase III OA pain efficacy	High: RTK with efficient internalization; clinical antibody precedent	Anti-NGF antibody Phase III (tanezumab; discontinued)	Preclinical concept (no TrkA-ADC)
CGRP Receptor	CALCRL/RAMP1	DRG + trigeminal ganglia	Anti-CGRP pathway mAbs: erenumab (CGRP receptor), fremanezumab, galcanezumab, and eptinezumab (CGRP ligand): all FDA-approved for migraine prevention	Moderate: GPCR complex; bispecific design may be needed	Anti-CGRP antibody FDA-approved (migraine)	Preclinical concept (no CGRP-R ADC)
ASIC3	ASIC3	Peripheral nociceptors	ASIC3 KO mice: reduced acid-evoked pain; inflammatory pain model	Moderate: extracellular domain accessible; limited clinical antibody data	Rodent KO studies; no clinical antibody	Early concept (no ADC)

AI platforms analogous to PandaOmics, developed by Insilico Medicine for oncology target discovery, can be adapted to pain neurobiology by substituting tumor transcriptomic databases with DRG single-cell atlases and pain GWAS datasets [5,54,55]. Natural language processing tools including BioGPT and PubMedBERT can systematically mine the pain neurobiology literature to extract and score target-pain associations, providing a complementary evidence layer to the quantitative multi-omics analysis [5]. The AI target discovery workflow is illustrated in Fig. 3.

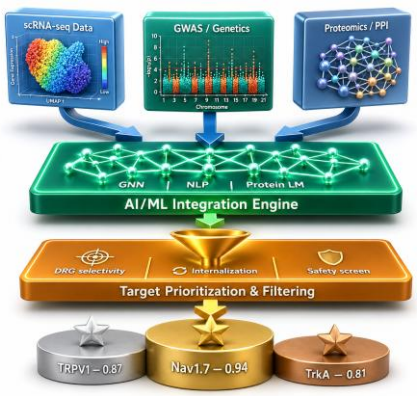

Figure 3. AI-driven target discovery workflow for pain ADCs. Multi-omics data inputs (single-cell RNA-sequencing, GWAS, proteomics, and literature mining) are integrated by graph neural networks and natural language processing algorithms to generate a ranked list of candidate pain ADC targets. Each candidate is scored across five criteria: nociceptor expression selectivity, internalization efficiency, genetic validation strength, extracellular epitope accessibility, and pharmacological precedent. The top-ranked targets advance to antibody engineering. GWAS, genome-wide association study; scRNA-seq, single-cell RNA sequencing.

4.2 AI-Powered Characterization of Nociceptor Heterogeneity

A critical insight from single-cell transcriptomics is that the DRG is not a homogeneous structure but a collection of functionally distinct neuronal subtypes with markedly different target expression profiles [14]. Human and mouse DRG atlases have identified at least ten distinct neuronal populations, including peptidergic

C-fibers (CGRP+/substance P+), non-peptidergic C-fibers (IB4+), Aδ mechanonociceptors, Aβ low-threshold mechanoreceptors, and proprioceptors [14]. These subtypes differ not only in their molecular markers but in their contributions to specific pain modalities: thermal hyperalgesia is primarily mediated by TRPV1-expressing peptidergic C-fibers, mechanical allodynia involves sensitized Aβ fibers, and spontaneous neuropathic pain is driven by ectopic discharge in Nav1.7-expressing C-fibers [14].

Dimensionality reduction methods (UMAP, deep learning autoencoders) combined with graph-based clustering algorithms (Leiden community detection) applied to DRG single-cell RNA-sequencing data can resolve the precise cellular distribution of candidate ADC targets across neuronal subtypes [5]. This resolution is clinically important: an ADC targeting TRPV1 will primarily reach peptidergic C-fibers, making it most appropriate for thermal hyperalgesia, while a Nav1.7-targeting ADC will have broader coverage across nociceptive subtypes, potentially addressing multiple pain modalities simultaneously. The target expression atlas generated by AI analysis of DRG single-cell data directly informs the patient stratification strategy described in Section 8, enabling the matching of ADC target selection to individual pain phenotypes (Fig. 2).

Beyond expression profiling, AI-powered high-content imaging systems can quantify the internalization kinetics of candidate antibodies in neuronal cell models, including SH-SY5Y neuroblastoma cells and human iPSC-derived sensory neurons [29]. This approach has been demonstrated in neuroblastoma cell lines [29]; its extension to primary human DRG neurons and to ADC-specific internalization assays is prospective and requires experimental validation. Convolutional neural networks trained on fluorescence microscopy images can measure the rate and extent of antibody-receptor complex internalization, the intracellular trafficking route (early endosome → late endosome → lysosome), and the efficiency of payload release — all critical parameters for ADC efficacy that differ substantially between neuronal and tumor cell models [29]. Spatial transcriptomics applied to spinal cord tissue can further map the expression of potential central targets in the dorsal horn, informing decisions about peripheral versus central ADC targeting strategies.

4.3 Leveraging Real-World Data and Literature Mining

The pain neurobiology literature contains a wealth of target-disease association evidence that is not captured in structured databases, making natural language processing an essential tool for comprehensive target discovery [5]. BioGPT and PubMedBERT, pre-trained on biomedical text corpora, can extract structured relationships between gene names, pain phenotypes, experimental models, and clinical outcomes from millions of publications, generating quantitative target-pain association scores that complement the multi-omics analysis [5]. Applied to the pain genetics literature, NLP tools can systematically identify genes implicated in neuropathic pain by Mendelian randomization studies, rare variant analyses, and pharmacogenomic studies, providing genetic validation evidence for candidate ADC targets.

Real-world data sources offer additional validation layers. The UK Biobank, with pain phenotype data and genome-wide genotyping from more than 500,000 participants, provides the largest available resource for identifying genetic variants associated with chronic pain susceptibility and severity [56]. AI analysis of UK Biobank data has already identified novel pain biomarkers and genetic risk factors that were not detectable in smaller cohorts [56]. The OPPERA (Orofacial Pain: Prospective Evaluation and Risk Assessment) cohort provides longitudinal multi-omics data for temporomandibular joint pain, offering a model for the kind of prospective pain biomarker study that will be needed to validate pain ADC targets in human populations. The FDA Adverse Event Reporting System (FAERS) can be mined by NLP tools to extract safety signals from existing neurologically active drugs, providing negative evidence that informs the safety boundaries for pain ADC target selection.

The AI target prioritization framework integrates these diverse evidence streams into a composite scoring system that ranks candidate targets by their combined genetic association strength, expression selectivity index (DRG/motor neuron expression ratio), internalization efficiency score, pharmacological validation level, and structural druggability assessment (Table 3). This multi-criteria scoring approach, analogous to the target prioritization frameworks used in oncology drug discovery, provides a rational basis for selecting the lead targets that will advance into antibody engineering and ADC development programs.

A summary of AI/ML methods applied to pain ADC

target identification — including GNN, NLP, multi-omics integration, single-cell clustering, and transfer learning approaches — is provided in Supplementary Table S1.

4.4 Overcoming Hurdles in AI-Driven Pain Target Discovery

The most distinctive challenge in pain ADC target discovery is the "double-edged sword" problem: the most compelling pain targets are also essential for normal physiological functions that must be preserved [16,19]. Nav1.7 is required for normal protective pain sensation — individuals with complete Nav1.7 loss of function suffer repeated injuries because they cannot detect tissue damage [19]. TRPV1 mediates normal thermal sensation and body temperature regulation — complete TRPV1 blockade would impair the ability to detect dangerously hot surfaces [16]. This constraint means that pain ADCs cannot simply maximize target blockade; they must achieve selective modulation within a therapeutic window that reduces pathological pain signaling while preserving physiological nociception.

AI can address this challenge in two complementary ways. First, generative models can design payloads that act as partial agonists or state-dependent blockers — molecules that preferentially inhibit the hyperactivated, high-frequency firing characteristic of neuropathic pain while sparing the lower-frequency activity associated with normal nociception [22]. Second, the ADC format itself provides a selectivity advantage: by concentrating payload delivery at the site of antibody binding (the DRG neuron surface), the ADC achieves local intracellular concentrations that are orders of magnitude higher than systemic concentrations, potentially enabling effective neuromodulation at doses that produce negligible systemic effects [5].

Data scarcity represents a second major challenge. Human DRG tissue is difficult to obtain — it requires surgical access to the intervertebral foramen or post-mortem collection — and existing human DRG single-cell datasets are substantially smaller than the tumor transcriptomic databases that underpin oncology ADC target discovery [13]. Transfer learning approaches, which adapt models trained on large mouse DRG datasets to human data using smaller human datasets, offer a practical solution to this limitation [5]. Synthetic data augmentation using variational autoencoders trained on existing DRG transcriptomic data can further expand the effective training dataset size. However, the species differences in Nav1.7 sequence and pharmacology between mice and humans — which have contributed to the failure of several Nav1.7-targeted analgesics in clinical translation — must be explicitly modeled in any AI system that relies on cross-species transfer [15].

5. AI in Antibody Engineering for Pain ADCs

5.1 AI Accelerates Structure Prediction and Affinity Optimization

The antibody engineering challenge for pain ADCs differs fundamentally from oncology, where targets such as HER2 and TROP2 present large, accessible extracellular domains [5]. The primary pain ADC targets — Nav1.7, TRPV1, P2X3, and the CGRP receptor — are multi-pass transmembrane proteins with extracellular epitopes confined to short inter-helical loops, severely constraining the antibody binding surface [15]. Nav1.7's 24 transmembrane segments require antibodies with exceptional CDR geometry for high-affinity binding [15]. TRPV1's cryo-EM structure (resolved 2013) reveals antibody-accessible epitopes primarily at the outer pore region, while the capsaicin-binding site is intracellular and inaccessible to extracellular antibodies — complicating structure-based antibody design [57,58,59].

AlphaFold2 and RoseTTAFold have transformed structure-based antibody design by enabling accurate prediction of protein structures without experimental crystallography [5,60,61]. For pain ADC targets, these tools must be applied in their multimer configurations to model the antibody-target complex, accounting for the membrane-embedded context of the target protein. Molecular dynamics simulations, increasingly guided by AI-based force field optimization, can sample the conformational ensemble of transmembrane targets in a lipid bilayer environment, identifying transient epitope-accessible states that are not apparent in static crystal structures [5]. The combination of AlphaFold2-Multimer predictions with molecular dynamics sampling provides a computational framework for rational epitope selection on transmembrane pain targets that was not feasible with traditional structure-based methods.

DeepAb and related deep learning antibody design tools can optimize CDR sequences for affinity, specificity, and developability simultaneously, screening millions of virtual CDR variants in silico before committing to experimental synthesis [5,62,63,64,65]. For pain ADC antibodies, the optimization objective must include not only affinity for the target epitope but also selectivity

against closely related ion channel subtypes — particularly Nav1.4 (skeletal muscle) and Nav1.5 (cardiac), which share significant sequence homology with Nav1.7 in their extracellular loops [15]. AI models trained on available Nav-channel antibody and epitope data may guide CDR optimization toward sequences that discriminate between these closely related subtypes, although the scarcity of such data remains a major limitation.

Bispecific antibody designs offer an additional engineering strategy for pain ADCs. One arm of the bispecific antibody can target a highly efficient DRG internalization receptor — such as TrkA, which undergoes rapid receptor-mediated endocytosis upon NGF or antibody binding — while the second arm carries the neuromodulatory function or serves as the payload attachment site. AI-based bispecific antibody design tools can optimize the geometry of the two binding arms to ensure simultaneous engagement of both targets without steric interference, and can predict the impact of bispecific format on antibody stability and manufacturability. Single-domain antibodies (nanobodies) targeting Nav1.7 offer an alternative format with superior tissue penetration and epitope accessibility on transmembrane targets [66,67,68,69].

5.2 AI Supports Fc Engineering and Developability Assessment

The Fc region of pain ADC antibodies requires engineering considerations that differ from those in oncology ADCs, reflecting the unique biology of the neural tissue target environment [5]. FcRn is expressed in peripheral tissues including endothelial cells [30], and if expressed in DRG neurons, could extend the intraneuronal half-life of ADC antibody components — a hypothesis that requires direct experimental validation. AI models trained on FcRn binding data can predict the impact of Fc mutations on FcRn affinity in the neural tissue context, enabling optimization of ADC half-life in DRG neurons independently of systemic pharmacokinetics.

Fc effector function silencing is a critical design requirement for pain ADCs that has no direct counterpart in most oncology ADC programs [5]. Fc-mediated effector functions — antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) — are desirable in oncology ADCs because they contribute to tumor cell killing. In the pain context, however, Fc effector activation in neural tissue would trigger neuroinflammation, potentially exacerbating rather than alleviating neuropathic pain [34]. Pain ADC antibodies therefore require Fc silencing mutations — such as the LALA (L234A/L235A) substitution, which substantially reduces FcγR binding, or the more complete LALAPG (L234A/L235A/P329G) substitution, which more fully abolishes FcγR binding — while preserving FcRn-mediated recycling [5]. AI models can predict the impact of these mutations on the full Fc interaction profile, ensuring that effector silencing is complete without compromising other desirable Fc properties.

Polyreactivity screening is particularly important for pain ADC antibodies, given the risk of cross-reactivity with myelin-associated proteins [5]. Antibodies that bind non-specifically to myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG) could trigger demyelinating reactions in peripheral nerves, producing a toxicity profile that would be catastrophic for a pain therapeutic. AI models trained on polyreactivity data from large antibody libraries can predict the risk of myelin protein cross-reactivity from antibody sequence features alone, enabling early elimination of high-risk candidates before experimental testing (Table 4).

A detailed summary of AI applications in antibody engineering for pain ADCs — covering structure prediction, affinity maturation, developability screening, Fc engineering, and immunogenicity prediction — is provided in Supplementary Table S2.

5.3 Scalable Antibody Optimization Workflows

Protein language models — including ESM-2, ProtT5, and the antibody-specific AbLang — have been trained on hundreds of millions of protein sequences and can generate meaningful representations of antibody sequence space that capture the relationship between sequence, structure, and function [5]. These representations enable rapid in silico screening of CDR variant libraries containing millions of sequences, identifying candidates with predicted improvements in affinity, stability, and selectivity before any experimental synthesis is required [5]. The computational throughput of protein language model-based screening — millions of sequences per hour on modern GPU hardware — far exceeds the capacity of experimental high-throughput screening, enabling a much more comprehensive exploration of antibody sequence space.

Immunogenicity prediction is a critical component of the pain ADC antibody optimization workflow, given that

neuromodulatory payloads such as conotoxin derivatives and botulinum toxin fragments are themselves potentially immunogenic [5]. Multi-task neural networks trained on T-cell epitope databases can predict the immunogenic potential of antibody sequences, enabling the identification and elimination of T-cell epitope hotspots through targeted sequence humanization [5]. The integration of immunogenicity prediction with affinity optimization and developability assessment in a unified AI workflow — analogous to the DBTL (design-build-test-learn) cycle used in synthetic biology — enables iterative antibody optimization that converges on candidates with the optimal combination of properties for pain ADC development.

6. AI for Linker-Payload Optimization in Pain ADCs

6.1 Neuromodulatory Payload Design with Generative AI

The payload design challenge for pain ADCs represents the most fundamental departure from oncology ADC development. Oncology ADC payloads are cytotoxic agents — microtubule inhibitors (MMAE, DM1), topoisomerase I inhibitors (DXd), and DNA-damaging agents (calicheamicin) — designed to kill cells at sub-nanomolar concentrations [5,70,71,72]. Pain ADC payloads must achieve the opposite: they must modulate neuronal function without killing neurons, maintaining cell viability while durably altering the electrophysiological properties of nociceptors. This distinction demands an entirely different payload library, different potency metrics, and different release kinetics [5,73,74].

Four classes of neuromodulatory payloads are primary candidates for pain ADC development (Fig. 4); comparative assessments are based on qualitative synthesis of published preclinical literature, not direct head-to-head comparisons. **(1) Conotoxin derivatives** — sub-nanomolar ion channel modulators with clinical proof-of-concept (ziconotide/Prialt, FDA-approved 2004 for intrathecal pain) — face ADC-specific challenges including disulfide bond instability, proteolytic susceptibility, and conjugation complexity [22]. **(2) BoNT/A light chain fragments**, which cleave SNAP-25 to block neurotransmitter release, offer weeks-to-months duration in preclinical models, though ADC-mediated DRG delivery duration has not yet been established [34]. **(3) Small-molecule Nav1.7-selective blockers** (aryl/acyl sulfonamide series) offer superior chemical stability and conjugation feasibility, but achieving Nav1.7/Nav1.4/Nav1.5 selectivity >100-fold remains a medicinal chemistry challenge [22]. **(4) siRNA** targeting SCN9A or TRPV1 mRNA is the least mature class: endosomal escape efficiency is typically ⩽1%, meaning >99% of internalized siRNA is trapped in the endolysosomal compartment rather than reaching the cytoplasmic RNAi machinery [75,76,77,78,79,80]. No siRNA-ADC has entered clinical development in any indication. Despite this barrier, successful siRNA delivery would offer durable gene-level silencing from a single dose — a compelling theoretical advantage that justifies continued research into endosomal escape strategies.

Drug-to-Antibody Ratio Considerations for Pain ADCs. The drug-to-antibody ratio (DAR) profoundly affects ADC efficacy, pharmacokinetics, and safety. Oncology ADCs typically have DARs of 3–4 (brentuximab vedotin ~4, T-DM1 ~3.5), with newer agents such as trastuzumab deruxtecan employing higher DARs (~8). For pain ADCs, the optimal DAR is likely lower (estimated 2–4): neuromodulatory payloads are biologically active at low concentrations, and high DARs increase non-specific neuronal uptake and off-target neuromodulation risk — particularly concerning given the irreversibility of potential motor neurotoxicity. Site-specific conjugation (engineered cysteine, unnatural amino acid, enzymatic) is preferred over stochastic lysine conjugation to produce homogeneous DAR distributions enabling precise payload dose control per DRG neuron.

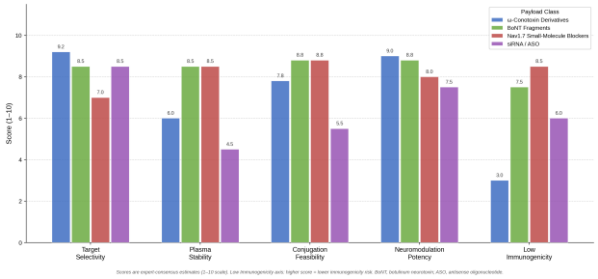

Figure 4. Comparative analysis of neuromodulatory payload classes for pain ADCs. Grouped bar chart comparing four payload categories — ω-conotoxin derivatives, botulinum toxin A (BoNT) fragments, Nav1.7 small-molecule blockers, and siRNA/ASO — across five performance dimensions: target selectivity, plasma stability, conjugation feasibility, neuromodulation potency, and low immunogenicity (higher score = lower immunogenicity risk). ω-Conotoxin derivatives and BoNT fragments show the highest target selectivity and neuromodulation potency; siRNA/ASO offers durable

gene-level silencing but faces the lowest plasma stability and conjugation feasibility scores. BoNT, botulinum neurotoxin; ASO, antisense oligonucleotide; Nav, voltage-gated sodium channel. *Note: Scores shown are illustrative expert consensus estimates (1–10 scale) based on published preclinical literature and are not derived from direct head-to-head experimental comparisons; they are intended to convey relative conceptual rankings only.*

Generative AI models are well-suited to the design of novel neuromodulatory payloads with optimized properties for ADC conjugation [5]. MolGPT and ChemBERTa, trained on chemical databases including ChEMBL and the ConoServer conotoxin database, can generate novel molecular structures with predicted Nav1.7 selectivity profiles, optimized for the physicochemical properties required for stable ADC conjugation — including appropriate molecular weight, aqueous solubility, and the presence of a reactive handle for site-specific conjugation [5]. For peptide payloads, recurrent neural network and transformer-based peptide generative models can design conotoxin analogs with reduced disulfide bond count (improving stability), modified immunogenic epitopes (reducing immunogenicity), and optimized conjugation sites that do not interfere with the pharmacophore [22]. Graph neural networks trained on structure-activity relationship data from ion channel pharmacology databases can predict the potency and selectivity of novel payload candidates, enabling rapid virtual screening before experimental synthesis.

6.2 Predictive Modeling of Neuronal Intracellular Dynamics

The intracellular fate of ADC payloads in neurons differs substantially from their fate in tumor cells, with important implications for linker design and payload release kinetics [29]. Tumor cells typically have abundant lysosomes with high cathepsin B and cathepsin L activity, enabling efficient cleavage of valine-citrulline and other protease-sensitive linkers [5,70,73,81]. DRG neurons may have a different lysosomal protease profile from tumor cells — with potentially higher cathepsin D relative to cathepsin B activity based on neuronal cell line data — though direct quantitative protease profiling of primary human DRG neurons remains limited [29]. This distinction, if confirmed in primary neurons, may require linker chemistry optimization to achieve efficient payload release in the neuronal intracellular environment. AI models trained on protease cleavage data from neuronal cell lines can provide initial predictions of linker cleavage efficiency, but validation in primary DRG neurons will be essential before these predictions can be relied upon for clinical candidate selection.

A unique feature of neuronal ADC pharmacology is axonal transport. DRG neurons have among the longest axons of any cell type in the body, extending up to one meter from the cell body to peripheral nerve terminals [14]. Following internalization at the DRG soma, ADC-payload complexes may be transported along the axon by retrograde or anterograde transport mechanisms, potentially delivering payload to nerve terminals at the site of peripheral sensitization [21]. AI modeling of axonal transport kinetics — based on the biophysical parameters of motor protein-driven vesicle transport and the dimensions of the DRG neuron — could help generate testable predictions about payload distribution along the axon, but ADC-specific neuronal transport remains to be experimentally characterized.

The release kinetics requirements for pain ADC payloads also differ from those in oncology. Cytotoxic oncology payloads require rapid, complete release to achieve the intracellular concentrations needed for cell killing. Neuromodulatory pain payloads, by contrast, may benefit from sustained, controlled release that maintains a steady-state level of ion channel modulation over days to weeks, analogous to the sustained-release formulations used for small-molecule analgesics [5]. AI-based pharmacokinetic/pharmacodynamic (PK/PD) modeling can optimize linker cleavage kinetics to achieve the desired payload release profile, integrating the neuronal lysosomal protease environment, axonal transport dynamics, and the dose-response relationship of the neuromodulatory payload.

6.3 Multi-Objective Optimization for Neural Selectivity

The multi-objective optimization of pain ADC linker-payload systems presents a higher-dimensional challenge than the analogous problem in oncology, requiring simultaneous optimization across six distinct objectives: nociceptor analgesic potency, sensory/motor neuron selectivity, plasma stability, antibody developability, CNS penetration minimization, and payload immunogenicity minimization [5]. Reinforcement learning (RL) algorithms, which learn to navigate complex multi-objective optimization

landscapes through iterative trial-and-error, are well-suited to this problem [5]. An RL agent trained on a reward function that combines all six objectives can explore the chemical space of linker-payload combinations and converge on Pareto-optimal solutions that represent the best achievable trade-offs between competing objectives.

The sensory/motor selectivity objective deserves particular emphasis, as it represents the most critical safety constraint for pain ADC development. Nav1.7 is expressed at high levels in DRG sensory neurons but at low levels in motor neurons of the spinal cord anterior horn [15]. However, the closely related Nav1.4 channel, which is essential for skeletal muscle function, shares significant sequence homology with Nav1.7 in the extracellular loops targeted by antibodies [15]. An RL-based optimization framework that explicitly penalizes predicted Nav1.4 activity — using a multi-task neural network trained on Nav channel pharmacology data — can guide payload design toward molecules with the selectivity profile required to avoid motor toxicity.

Transfer learning addresses the data scarcity challenge in pain ADC payload optimization. The ConoServer database contains sequence data for approximately 3,000 conotoxin sequences, a dataset that is orders of magnitude smaller than the chemical databases used to train oncology payload optimization models [22]. Transfer learning approaches — which adapt models pre-trained on large general pharmacology datasets to the specific task of conotoxin optimization using the smaller ConoServer dataset — can substantially improve prediction accuracy compared to models trained on ConoServer data alone [5]. This approach has been validated in analogous data-scarce domains in drug discovery and represents a practical strategy for accelerating pain ADC payload optimization in the absence of large pain-specific training datasets.

7. AI in ADMET Modeling for Pain ADCs

7.1 Deep Learning for Neural Tissue Disposition

The pharmacokinetic modeling of pain ADCs requires a neural tissue compartment model that has no direct counterpart in oncology ADC pharmacokinetics. Whereas oncology ADC PK models focus on tumor tissue distribution, plasma half-life, and systemic clearance, pain ADC PK models must explicitly represent the sequential tissue compartments relevant to nociceptor targeting: systemic circulation → DRG (relatively accessible, fenestrated vasculature) → peripheral nerve axons (axonal transport) → spinal cord dorsal horn (blood–spinal cord barrier) → brain (blood–brain barrier) [13,20]. The permeability of each barrier to the ADC depends on the antibody's physicochemical properties — molecular weight, isoelectric point, FcRn affinity, and glycosylation pattern — as well as the specific barrier characteristics at each anatomical level.

Deep learning-based physiologically-based pharmacokinetic (PBPK) models, trained on biodistribution data from radiolabeled antibodies and ADCs in preclinical species, can predict the tissue distribution of pain ADC candidates based on their molecular properties [5,54,55]. For DRG targeting specifically, AI models can be trained on the growing body of data from anti-NGF and anti-CGRP antibody biodistribution studies, which demonstrate that IgG antibodies achieve measurable DRG concentrations following systemic administration [21]. The FcRn-mediated recycling mechanism in DRG neurons — if FcRn is expressed there, which remains to be confirmed — could extend the intraneuronal half-life of IgG antibodies substantially beyond their plasma half-life and should be incorporated into these models as a testable hypothesis [30].

Axonal transport kinetics represent a unique pharmacokinetic feature of neuronal ADC distribution. Anterograde transport in DRG axons occurs at 250–400 mm/day (fast) and 0.1–8 mm/day (slow), though ADC transport — if it occurs — would likely involve distinct mechanisms from endogenous vesicular cargo and remains to be experimentally characterized [14]. AI models trained on axonal transport data could support hypotheses about ADC distribution from DRG soma to peripheral terminals, informing experiments that test the relationship between systemic dosing and payload concentration at the site of peripheral sensitization. PET/SPECT imaging with radiolabeled ADC candidates can provide in vivo validation in preclinical models [5].

7.2 Multimodal AI for Neurotoxicity Prediction

Neurotoxicity prediction is the most critical ADMET challenge for pain ADC development, and the one where the consequences of prediction failure are most severe. Unlike the reversible toxicities associated with oncology ADCs — keratopathy (belantamab mafodotin), interstitial lung disease (T-DXd class), myelosuppression — neurological damage can be permanent and profoundly disabling [5]. Motor neurotoxicity, which would manifest as muscle weakness or paralysis,

represents an absolute safety red line that must be predicted and excluded with high confidence before any pain ADC candidate advances to clinical testing. The deep learning ADMET prediction framework for pain ADCs is illustrated in Fig. 5.

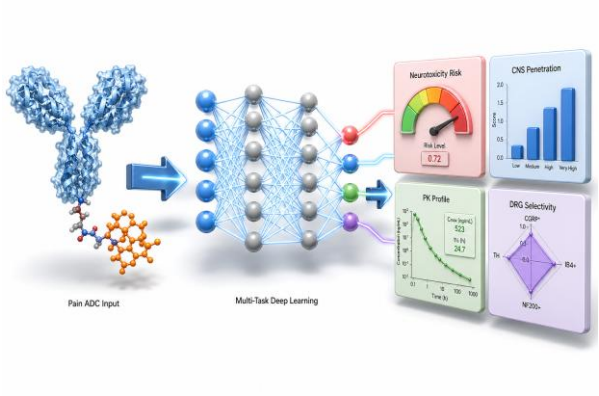

Figure 5. Deep learning framework for ADMET prediction in pain ADC development. The multimodal input layer accepts antibody sequence features, linker chemical descriptors, and payload molecular fingerprints. A multi-task neural network simultaneously predicts neurotoxicity risk (motor vs. sensory selectivity), neural tissue pharmacokinetics (DRG C_{max}, $t_{1/2}$), blood–nerve barrier penetration, and systemic safety endpoints. Explainability modules (SHAP values, attention maps) identify the molecular features driving each prediction, enabling rational optimization. SHAP, SHapley Additive exPlanations; DRG, dorsal root ganglion; PK, pharmacokinetics.

Multi-task deep neural networks, trained on the full spectrum of neural adverse event data from FAERS and clinical trial safety databases, can simultaneously predict five distinct neurotoxicity endpoints: motor neurotoxicity (the primary safety concern), sensory function loss (thermal or mechanical hypoesthesia), CNS toxicity (cognitive impairment, seizures), neuroinflammation (demyelination, glial activation), and autonomic dysfunction (cardiovascular, gastrointestinal) [5]. The multi-task architecture enables the model to leverage shared representations across related toxicity endpoints, improving prediction accuracy for each individual endpoint compared to single-task models trained on the same data.

The Nav channel subtype selectivity prediction is a particularly important component of the neurotoxicity assessment. Nav1.7 is the primary pain target, but Nav1.4 (skeletal muscle) and Nav1.5 (cardiac) are closely related subtypes whose inhibition would produce motor weakness and cardiac arrhythmia, respectively [15]. AI models trained on patch-clamp electrophysiology data from all Nav channel subtypes can predict the selectivity profile of candidate payloads across the Nav channel family, providing a quantitative selectivity index that directly informs the motor toxicity risk assessment. The regulatory requirements for safety pharmacology studies under ICH S7A and S7B guidelines — which mandate assessment of cardiovascular, CNS, and respiratory effects — can be partially addressed by AI-predicted safety profiles, potentially reducing the number of in vivo safety studies required in early development [5].

The irreversibility of neural damage distinguishes pain ADC neurotoxicity from the reversible toxicities of oncology ADCs and demands a more conservative approach to safety prediction. SHAP (SHapley Additive exPlanations) analysis of neurotoxicity prediction models can identify the specific structural features of antibody sequences and payload molecules that drive neurotoxicity risk, enabling rational structural modification to eliminate high-risk features while preserving pharmacological activity [5]. This interpretable AI approach provides mechanistic insight into the structural determinants of neural safety that is valuable both for compound optimization and for regulatory submissions.

7.3 Interpretability and Regulatory Compliance

The regulatory landscape for AI-assisted drug development is evolving rapidly, with the FDA's 2023 discussion paper on AI/ML in drug and biological product development establishing a framework for the use of AI-generated evidence in regulatory submissions [5]. For pain ADC development, where the safety stakes are particularly high due to the irreversibility of potential neurotoxicity, the interpretability of AI predictions is not merely a scientific preference but a regulatory necessity. Regulators will require not only accurate predictions but mechanistic explanations of why a particular compound is predicted to be safe or toxic.

GNN attention mechanisms and SHAP-based feature attribution provide two complementary approaches to interpretable neurotoxicity prediction [5]. GNN attention weights identify the specific molecular substructures — functional groups, ring systems, stereochemical features — that the model associates with neurotoxicity risk, providing a structural basis for medicinal chemistry optimization. SHAP values quantify the contribution of each input feature (antibody sequence position, payload

structural descriptor, linker chemistry) to the overall toxicity prediction, enabling a transparent audit trail from molecular structure to predicted safety outcome. The integration of these interpretability tools into the regulatory submission package — alongside traditional in vitro and in vivo safety data — represents a novel but increasingly accepted approach to demonstrating the scientific rigor of AI-assisted safety assessment.

8. AI in Preclinical and Clinical Development

> **Lessons from Clinical Failures: What AI Cannot Solve Alone**

>

> Two cautionary precedents must guide pain ADC development. Tanezumab (anti-NGF mAb) demonstrated Phase III analgesic efficacy but was discontinued after an FDA advisory committee voted 19-to-1 that its REMS was insufficient to justify the risk of rapidly progressive osteoarthritis (RPOA) [27] — an adverse event mechanistically linked to NGF's role in joint homeostasis that was not predicted by preclinical models. Nav1.7 small-molecule blockers, despite compelling human genetic validation, have repeatedly failed in clinical trials, likely due to compensatory sodium channel upregulation in acquired neuropathic pain [31]. AI models trained on preclinical data cannot fully anticipate these translational gaps. For pain ADCs, this underscores the necessity of: (1) prospective safety monitoring for off-target tissue effects; (2) human DRG organoid validation before IND filing; and (3) explicit AI uncertainty quantification so that high-confidence predictions are not mistaken for clinical guarantees.

8.1 AI for Pain Biomarker Discovery and Patient Stratification

The clinical development of pain ADCs faces a fundamental challenge that has no counterpart in oncology: the absence of validated, objective biomarkers that can identify the patient subpopulations most likely to respond to a specific ADC target. In oncology, tumor biomarkers such as HER2 amplification or TROP2 expression directly identify the patient population for which the ADC was designed. In neuropathic pain, the relationship between molecular target expression and clinical pain phenotype is far more complex, mediated by central sensitization, psychological factors, and the dynamic plasticity of the nervous system [24,25,82].

AI-driven multimodal biomarker integration offers a path toward pain patient stratification analogous to — but more complex than — oncology genomic stratification (Fig. 6) [83,84,85]. Machine learning applied to multimodal neuroimaging can predict clinical pain intensity with meaningful accuracy [56,86,87]. Relevant biomarker modalities include: quantitative sensory testing (QST) identifying sensory phenotypes (thermal hyperalgesia, mechanical allodynia) that map onto specific ADC targets; functional MRI connectivity analysis revealing central sensitization; intraepidermal nerve fiber density (IENFD) from skin biopsy quantifying small fiber neuropathy; genomic data (SCN9A, COMT, OPRM1 variants); serum CGRP and NGF levels; and nerve conduction studies [37,38,39].

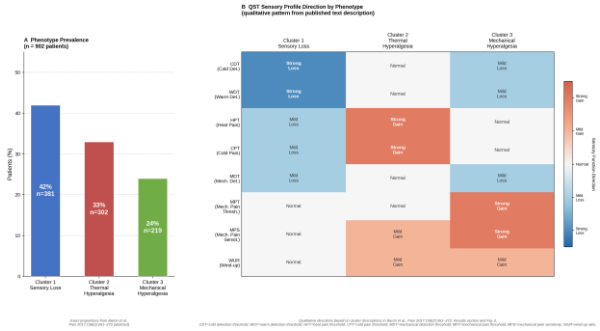

Figure 6. QST-based sensory phenotype stratification in peripheral neuropathic pain. **Panel A**: Prevalence of three distinct sensory phenotypes identified by hypothesis-free cluster analysis of 13 quantitative sensory testing (QST) parameters in 902 patients with peripheral neuropathic pain across multiple etiologies (diabetic polyneuropathy, peripheral nerve injury, postherpetic neuralgia, radiculopathy). Cluster 1 (Sensory Loss, 42%, n=381), Cluster 2 (Thermal Hyperalgesia, 33%, n=302), and Cluster 3 (Mechanical Hyperalgesia, 24%, n=219). Proportions are exact values reported in the abstract of Baron et al. [88]. **Panel B**: Qualitative sensory function direction for each phenotype across eight key QST parameters, based on the cluster descriptions reported in Baron et al. [88] (Results section and Fig. 2). Cluster 1 is characterized by loss of small and large fiber function; Cluster 2 by preserved sensory detection with heat and cold hyperalgesia; Cluster 3 by thermal detection loss combined with mechanical hyperalgesia and dynamic mechanical allodynia. This phenotype framework illustrates how QST-based patient stratification could guide ADC target selection: Cluster 2 patients (peripheral sensitization, Nav1.7/TRPV1 gain-of-function) are candidates for Nav1.7- or TRPV1-targeted ADCs, while Cluster 3 patients (central sensitization signature) may benefit from TrkA-targeted ADCs that

modulate NGF-driven central sensitization. CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio. Data source: Baron et al., *Pain* 2017;158(2):261–272 [88].

Machine learning algorithms — including k-means clustering, hierarchical clustering, and deep learning autoencoders — applied to this multimodal biomarker dataset can identify distinct pain subtypes that correspond to different underlying mechanisms and, by extension, different optimal ADC targets. A large-scale demonstration of this approach was provided by Fillingim M et al. [56], who applied machine learning to pain phenotype data from over 523,000 participants across multiple datasets and identified robust pain biomarker clusters that predicted chronic pain risk and severity. The pain subtypes identified by AI clustering directly inform ADC target selection: patients with thermal hyperalgesia and elevated TRPV1 expression in skin biopsies are candidates for TRPV1-targeting ADCs; patients with spontaneous pain and SCN9A gain-of-function variants are candidates for Nav1.7-targeting ADCs; patients with elevated serum NGF and TrkA-expressing DRG neurons are candidates for TrkA-targeting ADCs.

[Prospective concept — not yet validated in any ADC or pain clinical context] Digital twin models — computational representations of individual patients that integrate PK/PD models with patient-specific biomarker profiles — represent a highly speculative but conceptually compelling future direction for personalized pain ADC dosing [5]. While digital twin approaches have been explored in cardiovascular and metabolic disease modeling, their application to neurological ADC development remains entirely prospective and will require substantial validation before clinical implementation. By simulating the expected analgesic response and toxicity profile for a specific patient based on their biomarker data, digital twin models can guide dose selection and treatment duration decisions before the first dose is administered. The development of validated digital twin models for pain ADC clinical development will require large, well-characterized patient cohorts with longitudinal biomarker data — a data infrastructure that does not yet exist but that should be a priority for the field.

8.2 AI-Assisted Clinical Trial Design

The design of pain ADC clinical trials presents challenges that are substantially more complex than those encountered in oncology ADC trials, primarily due to the high placebo response rate and the subjective nature of pain endpoints. Placebo response rates of 30–50% in neuropathic pain trials [24] mean that a substantial proportion of patients in the control arm will report meaningful pain relief, dramatically reducing the detectable treatment effect and requiring larger sample sizes to achieve adequate statistical power [39]. AI models trained on historical pain trial data may estimate individual placebo-response probability based on patient characteristics — including psychological factors, prior treatment history, pain duration, and baseline pain scores — supporting enrichment or stratification strategies that must be prospectively justified and ethically reviewed.

[Prospective concept — no RL-based dose escalation algorithm has yet been validated in any ADC clinical trial] Reinforcement learning-based adaptive dose escalation represents a promising future direction for pain ADC development, given the narrow therapeutic window imposed by the motor neurotoxicity constraint [5]. The approach described here is prospective, drawing on RL methodology developed in adjacent domains. Traditional 3+3 dose escalation designs are inefficient and may expose patients to subtherapeutic doses for extended periods. RL-based dose escalation algorithms, which learn from accumulating safety and efficacy data in real time, can identify the optimal biological dose more efficiently while maintaining rigorous safety monitoring for motor function — the primary safety endpoint for pain ADC trials [5]. Bayesian adaptive designs can incorporate early biomarker data (QST changes, serum CGRP levels) as surrogate endpoints to inform dose selection decisions before the primary pain score endpoint is evaluable.

Patient-reported outcome (PRO) data quality control is a critical but often overlooked aspect of pain trial design. The subjective nature of NRS and VAS pain scores means that data quality varies substantially across patients and sites, with some patients providing inconsistent or implausible response patterns that introduce noise into the efficacy analysis. AI algorithms trained on historical PRO data can identify anomalous response patterns in real time, flagging patients for

additional clinical assessment and enabling data quality interventions before the trial database is locked. The integration of electronic PRO platforms with AI-based quality monitoring represents a practical near-term application of AI in pain ADC clinical development that can be implemented without waiting for the broader AI infrastructure described in this review.

8.3 Transferable Lessons from Neurology and Pain Drug Development

The clinical development of pain ADCs can draw on a growing body of AI experience from adjacent therapeutic areas in neurology and pain medicine. The anti-CGRP antibody development programs provide the most directly relevant precedent: Clinical analyses of migraine patient data have identified baseline migraine frequency, CGRP pathway sensitivity, and prior preventive treatment history as factors associated with anti-CGRP antibody response [18], providing a patient stratification framework that can be adapted for CGRP receptor-targeting pain ADCs. The lessons from these programs inform the biomarker strategy for CGRP-R-targeting ADC development, although predictive biomarkers for individual anti-CGRP response remain incompletely validated.

Synthetic control arms, generated by matching historical control data to the characteristics of the current trial population, are an emerging strategy in rare neurological disease development; their use in pain ADC trials would require careful regulatory discussion and indication-specific validation [5]. For rare neuropathic pain indications such as hereditary erythromelalgia (caused by SCN9A gain-of-function mutations), where the patient population is too small for conventional randomized controlled trials, AI-generated synthetic control arms could enable rigorous efficacy assessment with substantially smaller trial sizes. Gopal et al. [89] demonstrated that machine learning models trained on intraoperative neural recording data could predict spinal cord stimulation outcomes in chronic pain patients with high accuracy, establishing a precedent for AI-based patient selection in interventional pain therapies that is directly applicable to pain ADC development.

The model-informed precision dosing (MIPD) framework, which uses Bayesian PK/PD modeling to individualize drug doses based on patient-specific pharmacokinetic parameters, has been applied to several oncology ADCs and is directly transferable to pain ADC development [5]. For pain ADCs, MIPD models would integrate patient body weight, renal and hepatic function, FcRn genotype, and target expression levels to predict the optimal dose for each individual patient — maximizing analgesic efficacy while maintaining the motor safety margin that is the primary constraint on pain ADC dosing.

9. Challenges and Future Perspectives

9.1 Data, Algorithms, and Validation Challenges

The most fundamental challenge facing AI-driven pain ADC development is the near-total absence of the training data that AI models require. In oncology ADC development, AI models can be trained on the ADCdb database (containing data on hundreds of ADC candidates), the TCGA multi-omics database (containing genomic and transcriptomic data from approximately 11,000 tumor samples across 33 cancer types), and the clinical trial databases of approved ADCs (containing pharmacokinetic, efficacy, and safety data from thousands of patients) [5]. No equivalent data infrastructure exists for pain ADCs: there are no approved pain ADCs, no clinical-stage pain ADC candidates, and no curated database of pain ADC structure-activity relationships.

The scarcity of human DRG tissue compounds this data challenge. Unlike tumor tissue, which is routinely obtained by biopsy or surgical resection, human DRG tissue is accessible only through surgical procedures (laminectomy, foraminotomy, or other spinal surgeries that expose the intervertebral foramen) or post-mortem collection, and the resulting datasets are typically small (tens to hundreds of samples) compared to the thousands of samples available in tumor transcriptomic databases [13]. This data scarcity limits the accuracy of AI models trained on human DRG data and necessitates the transfer learning and synthetic data augmentation approaches described in Section 4.4 [40,41].

The poor translational fidelity of animal models of neuropathic pain represents a third data challenge [31]. The most widely used preclinical models — chronic constriction injury (CCI), spared nerve injury (SNI), and spinal nerve ligation (SNL) — produce behavioral pain phenotypes in rodents that do not reliably predict clinical efficacy in human neuropathic pain [2]. AI models trained on preclinical pain ADC data from these models may therefore generate predictions that are accurate for the animal model but not for the human disease. Addressing this translational gap will require AI models that explicitly incorporate species differences in target

pharmacology, pain behavior, and immune response — a challenging but tractable computational problem.

We propose the establishment of a "Pain-ADC Commons" — an open, FAIR-compliant data consortium that would aggregate DRG single-cell atlases, pain genomics data, neuromodulatory compound activity data, and clinical pain biomarker datasets from academic and industry sources. Modeled on the Cancer Genome Atlas and the ADCdb, the Pain-ADC Commons would provide the training data infrastructure needed to develop and validate the AI models described in this review, and would accelerate the entire pain ADC field by making high-quality data accessible to all researchers.

9.2 Translational and Regulatory Challenges

The regulatory pathway for pain ADCs has not yet been defined, and early engagement with regulatory agencies will be essential to establish the safety and efficacy standards that pain ADC developers must meet. The FDA's existing guidance for pain drug development (2014) emphasizes the importance of objective functional endpoints alongside subjective pain scores, and requires demonstration that analgesic efficacy is not achieved at the cost of sensory or motor function impairment [22]. For pain ADCs, this guidance implies that motor function assessment — including electromyography, nerve conduction studies, and functional motor testing — must be incorporated as mandatory safety endpoints in all clinical trials, from Phase I dose escalation through Phase III efficacy studies.

The irreversibility of potential neurotoxicity creates a regulatory risk profile that is substantially more challenging than that of oncology ADCs, where most toxicities are reversible upon dose reduction or treatment discontinuation [5]. Regulatory agencies may require more extensive preclinical neurotoxicity characterization — including chronic toxicity studies in non-human primates with comprehensive neurological assessment — before approving first-in-human studies of pain ADCs. AI-predicted neurotoxicity profiles, while not a substitute for in vivo safety studies, can inform the design of these studies and provide mechanistic context for observed toxicities.

Patient acceptance of injectable biologics for pain management represents a practical barrier to pain ADC adoption that is distinct from the scientific and regulatory challenges. Chronic pain patients are accustomed to oral medications and may be reluctant to accept subcutaneous or intravenous injections, particularly for a novel therapeutic modality with no established clinical track record. AI-assisted patient education tools that provide personalized risk-benefit analyses — based on the patient's specific pain phenotype, biomarker profile, and treatment history — could help bridge this acceptance gap by demonstrating the individualized value proposition of pain ADC therapy.

9.3 Future Perspectives: The Intelligent Pain-ADC Ecosystem

The long-term vision for AI-driven pain ADC development is an integrated, closed-loop discovery ecosystem that continuously learns from experimental data and iteratively improves the design of pain ADC candidates (Fig. 7). This ecosystem rests on three strategic pillars.

Figure 7. Closed-loop intelligent pain ADC development ecosystem. A circular closed-loop system integrating six interconnected components: (1) AI-driven molecular design (target prioritization, antibody engineering, payload optimization); (2) robotic synthesis and conjugation; (3) DRG organoid testing (human iPSC-derived sensory neurons); (4) pain-on-a-chip electrophysiological validation; (5) data integration and AI model refinement from experimental results; and (6) AI learning and iterative design improvement, feeding back into the next design cycle [90]. Each cycle of the loop generates data that improves the AI models, accelerating convergence toward optimal pain ADC candidates. iPSC, induced pluripotent stem cell; DRG, dorsal root ganglion.

The first pillar is open data infrastructure. The Pain-ADC Commons described above would serve as the data foundation for the entire ecosystem, providing standardized, curated datasets that enable AI model training, validation, and benchmarking. Beyond the Pain-ADC Commons, integration with existing resources — the Allen Brain Atlas for neural gene expression, the UK Biobank for pain genomics, ConoServer for

conotoxin pharmacology, and ChEMBL for ion channel pharmacology — would create a comprehensive knowledge graph of pain-relevant biology that AI models can query to generate and evaluate pain ADC hypotheses.

The second pillar is pain neurobiology-specific AI architectures. The general-purpose AI tools currently used in drug discovery — GNNs, transformers, generative models — were not designed with the specific challenges of pain neurobiology in mind. The next generation of pain ADC AI tools will need to incorporate domain-specific knowledge: physics-informed neural networks that embed the Hodgkin-Huxley equations for ion channel dynamics, enabling mechanistic prediction of how payload molecules alter neuronal firing patterns; graph-transformer hybrid architectures that represent the topology of nociceptive neural circuits, enabling prediction of how DRG-targeted ADCs affect spinal cord pain processing; and multimodal foundation models trained on the full spectrum of pain biology data — genomics, transcriptomics, electrophysiology, imaging, and clinical outcomes — that can generate unified representations of pain pathophysiology.

The third pillar is closed-loop experimental platforms. Human iPSC-derived DRG organoids, which recapitulate the cellular diversity and electrophysiological properties of native DRG tissue, provide a human-relevant experimental system for pain ADC screening that is not subject to the species translation problems of rodent models [40,41]. Coupled with multi-electrode array (MEA) electrophysiology systems and AI-based spike sorting and network analysis algorithms, DRG organoids enable real-time, quantitative assessment of pain ADC effects on nociceptor activity — the most direct measure of analgesic efficacy available in a preclinical system. Pain-on-a-chip microfluidic platforms, which model the DRG-spinal cord neural circuit in a miniaturized format, extend this capability to include the synaptic transmission and central sensitization components of neuropathic pain. The integration of these experimental platforms with AI-driven design algorithms and robotic synthesis systems creates a fully automated DBTL cycle that can iterate through pain ADC design-test cycles at a speed and scale that is impossible with conventional experimental approaches.

9.4 Key Open Questions for the Field

Ten critical open questions in AI-driven pain ADC development are summarized in Table 6.

Table 6. Key open questions in AI-driven pain ADC development.

#	Domain	Open Question
1	Target validation	Which candidate target (Nav1.7, TRPV1, P2X3, TrkA, CGRP-R, ASIC3) demonstrates sufficient internalization efficiency in primary human DRG neurons?
2	Antibody engineering	Can AI-designed antibodies achieve Nav1.7/Nav1.4/Nav1.5 selectivity >100-fold to avoid motor and cardiac toxicity?
3	Payload design	What minimum intracellular payload concentration achieves durable analgesia without neuronal cytotoxicity?
4	DAR optimization	What is the optimal DAR range for pain ADCs, and how does it interact with neuronal uptake kinetics and motor safety margins?
5	Linker chemistry	Which cleavage mechanism (cathepsin-sensitive, pH-sensitive, disulfide) achieves most efficient payload release in DRG lysosomes?
6	Axonal transport	Do pain ADCs undergo meaningful axonal transport from DRG soma to peripheral terminals, and does this enhance or reduce efficacy?

7	Blood-nerve barrier	What is the quantitative dose–DRG concentration relationship, and how does it vary across patient populations?
8	Patient stratification	Which biomarker combination (QST, genomics, neuroimaging, serum markers) best predicts pain ADC response?
9	Placebo response	Can AI models trained on historical pain trial data reduce effective placebo response below 20%?
10	Regulatory pathway	What preclinical neurotoxicity data package will regulators require before approving first-in-human pain ADC studies?

10. Discussion and Conclusions

10.1 Discussion

This review has proposed a systematic framework for applying AI methodologies validated in oncology ADC development to the distinct biological and clinical challenges of chronic neuropathic pain. Several aspects of this framework merit broader discussion.

First, the neuroimmune dimension of pain ADC development distinguishes this field from oncology ADC development in ways that extend beyond the pharmacological differences discussed in earlier sections. Neuropathic pain is not merely a neuronal phenomenon — it is fundamentally a neuroimmune disease. Peripheral nerve injury triggers a cascade of immune cell infiltration into the DRG and peripheral nerve, with macrophages, T cells, and mast cells releasing cytokines that sensitize nociceptors and sustain the chronic pain state [25,28,35]. Pain ADCs must therefore be designed not only to modulate nociceptor activity but to do so within an inflamed, immune-activated tissue environment that may alter antibody pharmacokinetics, trigger Fc-mediated immune responses, and generate anti-drug antibodies (ADAs) that neutralize therapeutic efficacy. The immunological properties of pain ADCs — Fc effector silencing, ADA risk, complement activation potential — are therefore not secondary engineering considerations but primary determinants of therapeutic success.

Second, the comparison of pain ADC development with the historical trajectory of anti-CGRP antibody development is instructive. The anti-CGRP antibody class required approximately 15 years from initial target validation to FDA approval, with multiple failed small-molecule attempts preceding the successful biologic approach. Pain ADC development is likely to follow a similarly extended timeline, with the additional complexity of ADC chemistry, neuromodulatory payload design, and the absence of any clinical precedent for ADC-based analgesia. The AI framework proposed here is intended to compress this timeline by enabling more rational target selection, more efficient antibody optimization, and more predictive preclinical models — but it cannot eliminate the fundamental biological uncertainties that make pain drug development challenging.

Third, the scope of this review is explicitly limited to peripheral neuropathic pain with DRG-accessible targets. Central sensitization, which contributes substantially to the maintenance of chronic neuropathic pain, is not directly addressable by peripherally targeted ADCs. Future work should explore whether ADC-mediated modulation of peripheral sensitization is sufficient to reverse central sensitization, or whether combination approaches targeting both peripheral and central mechanisms will be required.

10.2 Conclusions

The convergence of ADC platform maturation, AI capability advances, and deepening understanding of neuropathic pain molecular architecture creates a unique opportunity that this review has sought to map systematically. The AI methodologies validated in oncology ADC development — graph neural networks for target discovery, protein language models for antibody engineering, generative models for payload design, deep learning for ADMET prediction, and machine learning for patient stratification — can be systematically adapted to the unique biological, pharmacological, and clinical challenges of the pain

domain.

The key opportunities identified at each pipeline stage are substantial. AI-driven multi-omics integration can identify and prioritize nociceptor-selective ADC targets with the genetic validation and internalization efficiency required for effective pain ADC development. Structure prediction tools can address the formidable challenge of engineering antibodies against multi-pass transmembrane pain targets. Generative AI can design novel neuromodulatory payloads — conotoxin derivatives, BoNT fragments, Nav1.7-selective blockers, siRNA — with the selectivity profiles required to achieve analgesia without motor toxicity. Deep learning ADMET models may help prioritize pain ADC candidates for neural tissue distribution and neurotoxicity testing, but regulatory acceptance would require interpretable models validated against experimental and clinical data. And AI-driven patient stratification can identify the pain phenotype subgroups most likely to respond to specific ADC targets, enabling the precision medicine approach that is essential for demonstrating efficacy against the high placebo response background of neuropathic pain trials.

The critical caveats of this framework must be clearly stated: pain ADCs are a conceptual modality with no approved products and no clinical-stage candidates. The AI applications described here are largely prospective, and their translation into validated pain ADC development tools will require substantial investment in data infrastructure, experimental platforms, and interdisciplinary collaboration. The path from this conceptual framework to a clinical pain ADC will be long and uncertain, and many of the specific AI approaches described here will require adaptation and validation in the pain context before they can be reliably applied.

Nevertheless, the convergence of three enabling trends — the maturation of the ADC platform in oncology, the rapid advancement of AI capabilities in drug discovery, and the growing understanding of the molecular architecture of neuropathic pain — creates a unique opportunity to develop a new class of precision analgesics that could transform the treatment of one of medicine's most challenging conditions. Realizing this opportunity will require the concerted effort of pain neurobiologists, ADC chemists, AI/ML scientists, and clinical pain medicine specialists working in close collaboration — an interdisciplinary partnership that this review aims to catalyze.

Abbreviations

ADC, antibody-drug conjugate; ADA, anti-drug antibody; ADCC, antibody-dependent cellular cytotoxicity; ADMET, absorption, distribution, metabolism, excretion, and toxicity; AI, artificial intelligence; ASIC3, acid-sensing ion channel 3; BoNT/A, botulinum toxin A; CGRP, calcitonin gene-related peptide; CRS, cytokine release syndrome; DAR, drug-to-antibody ratio; DRG, dorsal root ganglion; ESM-2, Evolutionary Scale Modeling 2; FDA, US Food and Drug Administration; FcRn, neonatal Fc receptor; GNN, graph neural network; GWAS, genome-wide association study; IgG, immunoglobulin G; IL-1β, interleukin-1β; IL-6, interleukin-6; LALA, L234A/L235A Fc mutation; mAb, monoclonal antibody; ML, machine learning; Nav1.7, voltage-gated sodium channel 1.7 (encoded by SCN9A); NGF, nerve growth factor; NLP, natural language processing; NRS, numerical rating scale; PBPK, physiologically-based pharmacokinetic; P2X3, purinergic receptor P2X3; QST, quantitative sensory testing; RL, reinforcement learning; REMS, Risk Evaluation and Mitigation Strategy; RPOA, rapidly progressive osteoarthritis; siRNA, small interfering RNA; SNARE, soluble NSF attachment protein receptor; TNF-α, tumor necrosis factor-α; TrkA, tropomyosin receptor kinase A; TRPV1, transient receptor potential vanilloid 1; VAS, visual analogue scale.

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Author Contributions

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