Check for updates

AI-driven innovation in antibody-drug conjugate design

Heather A. Noriega and Xiang Simon Wang*

Artificial Intelligence and Drug Discovery (AIDD) Core Laboratory for District of Columbia Center for AIDS Research (DC CFAR), Department of Pharmaceutical Sciences, College of Pharmacy, Howard University, Washington, DC, United States

Antibody-drug conjugates (ADCs) represent a mechanistically defined class of targeted therapeutics that combine monoclonal antibodies with cytotoxic payloads to achieve selective delivery to antigen-expressing carcinoma cells. Conventional ADC development has primarily relied on empirical screening and structure-based design, often limited by incomplete structural information, non-systematic linker−payload selection, and constraints in experimental throughput. Computational methods, including artificial intelligence and machine learning (AI/ML) are increasingly being integrated into ADC discovery and optimization workflows (i.e., AI-driven ADC Design) to address these limitations. This review is organized into six sections: (1) the progression from traditional modeling approaches to AI-driven design of individual ADC components; (2) the application of deep learning (DL) to antibody structure prediction and identification of optimal conjugation sites; (3) the use of AI/ML models for forecasting pharmacokinetic properties and toxicity profiles; (4) emerging generative algorithms for antibody sequence diversification and affinity optimization; (5) case studies demonstrating the integration of computational tools with experimental pipelines, including systems that link *in silico* predictions to high-throughput validation; and (6) persistent challenges, including data sparsity, model interpretability, validation complexity, and regulatory considerations. The review concludes with a discussion of future directions, emphasizing the role of multimodal data integration, reinforcement learning (RL), and closed-loop design frameworks to support iterative ADC development.
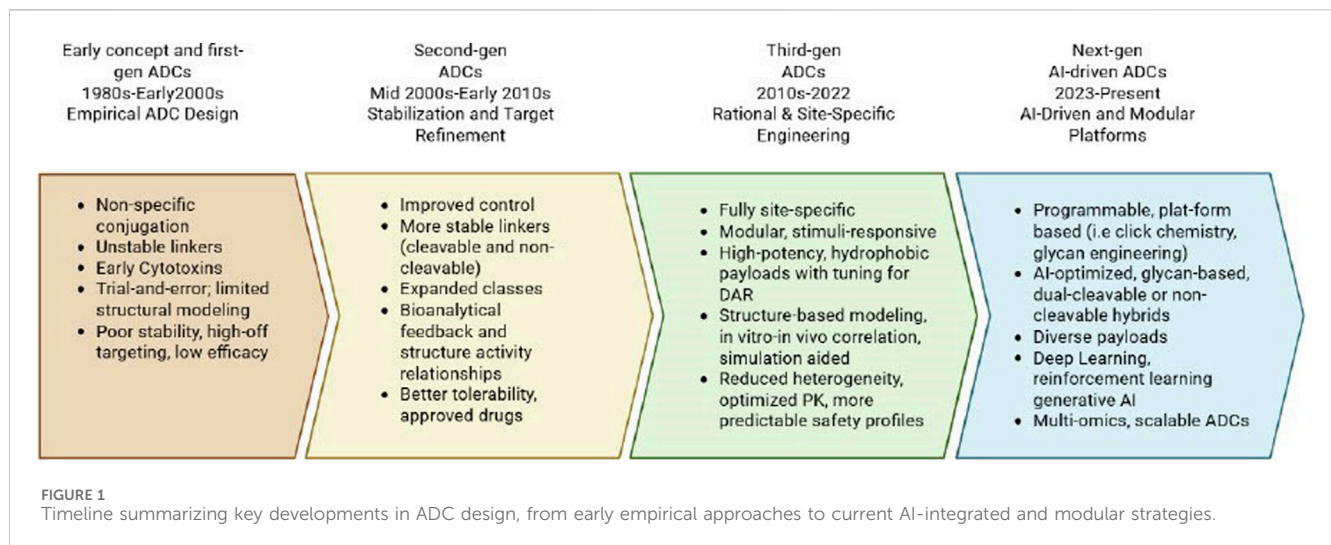
KEYWORDS

AI/ML (artificial intelligence/machine learning), antibody-drug conjugate (ADC), AlphaFold 3, neural ODEs, generative and algorithmic design

Introduction

Antibody-drug conjugates (ADCs) represent a rapidly expanding class of targeted cancer therapeutics that combine the specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule drugs. This dual mechanism enables the selective elimination of cancer cells while minimizing off-target toxicity, offering an enhanced therapeutic indicator compared to traditional therapies. However, despite significant clinical advances, conventional ADC development has been slowed down by empirical approaches, incomplete structural information, and inefficient linker-payload selections, resulting in a time-consuming and costly discovery process (Kim et al., 2023).

Over the past 3 decades, computational methods have steadily evolved to address these limitations, as illustrated in Figure 1. In the early 2000s, *in silico* modeling and basic artificial intelligence/machine learning (AI/ML) algorithms were applied to predict antibody-antigen interactions based on physicochemical features. However, the methods used were limited by

FIGURE 1
Timeline summarizing key developments in ADC design, from early empirical approaches to current AI-integrated and modular strategies.

simple computational resources and the lack of extensive biological datasets. The progress accelerated in the 2010s with the emergence of DL. DL allowed for more complex modeling and high-dimensional relationships critical for predicting antibody structures, binding affinities, and developability parameters (Bai et al., 2023). Today, AI/ML play fundamental roles across the ADC discovery pipeline. ML models have demonstrated efficacy in predicting drug-to-antibody ratios (DAR) and conjugation site preferences with significantly improved accuracy over empirical methods (Angiolini et al., 2025). Another example is DL models capable of learning from three-dimensional structural data, which have enhanced antibody paratope prediction and rational affinity maturation (Dewalker et al., 2025).

The computational revolution has coincided with advances in molecular engineering. Glycan engineering is essential to ADC pharmacology, as it impacts antibody stability and immunogenicity and provides modifiable sites for site-specific conjugation. Recent computational advances have enabled the characterization of glycan microheterogeneity at the glycosylation sites, offering predictive tools to modulate glycan structures for optimal ADC properties (Moore et al., 2024; Cruz and Kayser, 2019). PEGylation, the covalent attachment of polyethylene glycol chains to antibodies, has been extensively used to improve ADC pharmacokinetics. AI-guided modeling optimizes PEG chain length, attachment sites, and structural shielding to prolong circulation while preserving target engagement (Smith, 2015). Small molecule payload optimization is another rapidly advancing area. Traditionally, this was selected via screening; small molecule payloads are now increasingly matched to antibodies using ML models that predict cytotoxic potency, stability, and intracellular trafficking properties (Debnath et al., 2022). ML has enabled the discovery of novel cytotoxic payloads, such as plitidepsin derivatives targeting eEF1A (Antunes et al., 2023). Furthermore, computational simulations of protein-protein interactions (PPIs) have allowed for engineering ADCs with minimized off-target binding and enhanced immune system modulation, including glycan-shielded or albumin-binding formats (Zhong and D'Antona, 2021).

Nanoparticle-enabled ADC systems represent another frontier for precision drug delivery. Antibody-nanoparticle conjugates (ANCs) integrate the targeting specificity of antibodies with the payload versatility and modifiable release kinetics of nanotechnology. Emerging studies demonstrate that ANC platforms can achieve improved pharmacokinetics, enhanced payloads, and better tumor penetration than conventional ADCs (Adhikari and Chen, 2025). AI models are being developed to optimize nanoparticle size, surface chemistry, and antibody orientation to maximize tumor accumulation and minimize off-target effects (Gholap et al., 2024; Chandrika et al., 2024). Most recent examples of antibody-conjugated nanoparticles targeting HEr2 positive breast cancer cells have demonstrated improved binding, enhanced drug release control, and superior therapeutic measures (Juan et al., 2020; Selepe et al., 2024).lipid nanoparticle (LNP) formulations decorated with antibodies are now used for siRNA and therapeutic protein delivery to lymphatic tissues (Sakurai et al., 2022).

Clinically, second-generation ADCs such as Polivy (Polatuzumab vedotin) and Enhertu (trastuzumab deruxtecan) showcase how structure-guided conjugation strategies, linker innovations, and computational payload optimizations are entering real-world practice (Shi and McHugh, 2023). Glycan and PEGylation modifications have refined the pharmacokinetics of investigational ADCs progressing through clinical pipelines (Sakhnini, 2019).

Despite these advances, several challenges remain. Among them are data scarcity for rare conjugation chemistries, interpretability of DL models, experimental validation burdens, and regulatory hurdles (Melo et al., 2018).

This review examines the application of computational approaches in designing and developing antibody-drug conjugates, spanning conventional modeling techniques through recent advances in AI/ML. The discussion is organized into six core areas: (1) the methodological shift from traditional design strategies to AI-enabled modeling of ADC components; (2) DL based approaches for antibody structure prediction and conjugation site identification; (3) ML frameworks for modeling pharmacokinetics and toxicity; (4) generative algorithms for antibody sequence

diversification and affinity engineering; (5) the integration of computational tools with high-throughput experimental systems; and (6) unresolved challenges, validation requirements, and future directions for computational ADC research. Particular attention is given to how these approaches may enable the rational design of next-generation ADCs, including multimeric formats with enhanced modularity, combinatorial targeting capacity, and structural complexity. Together, these developments define a framework for advancing data-driven and mechanism-informed strategies in ADC engineering.

Traditional computational methods

Early ADC development relied on traditional structure-based design methods. X-ray crystallography provided atomic resolution structures of antibodies and target antigens, serving as templates for computational modeling. Structural determination through X-ray diffraction and small-angle X-ray scattering (SAXS) allowed for the initial mapping of epitope-paratope interactions essential for rational design (Chiu et al., 2019; Filntisi et al., 2014). Structural information from these methods informed initial assessments of conjugation sites and antigen binding compatibility. However, structural data were often incomplete. In the Protein Data Bank (PDB) and Electron Microscopy Data Bank (EMDB), only antibody fragments, primarily antigen-binding fragments (Fabs), single-chain variable fragments (scFvs), or isolated VH/VL domains, were typically available. Full-length immunoglobulin G (IgG) structures, encompassing flexible hinge regions and Fc domains, remained scarce due to the inherent difficulty in crystallizing or imaging large, flexible biomolecules (Chaves et al., 2024). This incomplete structural coverage constrained early ADC design efforts, especially in modeling linker attachment sites, steric hindrance, and glycosylation effects. Flexible regions such as the hinge domain, which is important for internalization and payload delivery, were poorly represented in available templates, which resulted in speculation modeling.

Molecular docking emerged as a primary computational tool, which allowed virtual predictions of antibody-antigen poses and assessed the potential effects of conjugation on antigen engagement. However, traditional docking algorithms were often optimized for small molecule ligands and struggled with large, flexible interface characteristics of antibody-antigen interactions. Scoring functions tended to oversimplify binding energetics, leading to overestimating affinities and frequent false positives (Garofalo et al., 2020; Siddiqui et al., 2025). To address these challenges, protein-protein docking platforms such as ClusPro and HADDOCK have been developed to model the flexibility and shape complementarity of larger biological complexes (Kozakov et al., 2017; Dominguez et al., 2003). These tools account for conformational changes and can incorporate experimental data to guide the docking process, making them better suited for simulating antibody-antigen and antibody-linker interactions. Incorporating such methods into ADC modeling has improved our ability to evaluate structural compatibility and binding site accessibility, though challenges still remain in modeling the full ADC assemblies at high resolution. Docking methods have been used to guide *in silico* affinity maturation and

structural optimization of antibody variants during early-stage design.

Molecular dynamics (MD) simulations provided a deeper understanding of antibody flexibility, linker behavior, and payload exposure under dynamic biological conditions. MD simulations enabled the prediction of domain motions, solvent accessibility, and aggregation-prone regions (Codina et al., 2019). These simulations continue to support ADC design efforts by offering atomic-level insight into conformational variability, linker strain, and local solvation effects that influence stability and binding. However, MD was constrained by limitations in simulation timescales, force field inaccuracies, and high computational costs, restricting simulations to relatively short times and small system sizes. Even when used with docking, MD refinements often failed to fully account for flexible loops, glycan motions, or hinge dynamics (Dixit, 2015). Ongoing advances in GPU acceleration, enhanced sampling techniques, and hybrid modeling approaches have improved the feasibility of MD in larger systems, enabling their continued integration alongside AI-driven workflows.

Developability assessments were another primary focus of traditional workflows. The early model evaluated candidate antibodies and ADCs for aggregation susceptibility, chemical stability, and solubility properties. These methods relied on sequence-based descriptors such as hydrophobic patches, charged residues, and coarse-grained structure-based features (Khetan et al., 2022). For example, Evers et al. demonstrated the structure-based *in silico* prediction of aggregation hotspots in biparatopic ADCs targeting c-MET, highlighting the need for early aggregation control to improve manufacturability (Evers et al., 2024). These tools were effective in screening candidates prior to experimental validation and were integrated into early-stage selection protocols to reduce downstream formulation issues.

However, early developability models faced limitations due to small training datasets, narrow antibody diversity coverage, and lack of generalization across different payload-linker combinations. The absence of high-quality 3D structures further compounded these challenges, often forcing researchers to project predictions from fragmentary or homology-modeled structures from software like SWISS-MODEL (Waterhouse et al., 2018). Despite these limitations, sequence-based models provided actionable insights into charge distribution, surface hydrophobicity, and isoelectric point, which remain relevant parameters in manufacturability risk assessment. These tools served as a decision support layer that complemented experimental assays and informed downstream engineering strategies. These traditional computational techniques, covering structure determination, docking, MD, and developability prediction, have established the foundation for modern AI-driven frameworks.

ADC's structural prediction with AlphaFold series and other DL tools

The release of AlphaFold2 introduced a transformative approach to protein structure prediction using novel neural network DL architectures (Jumper et al., 2021; Yang et al., 2023; Skolnick et al., 2021; Marcu et al., 2022). AlphaFold2 achieves near-
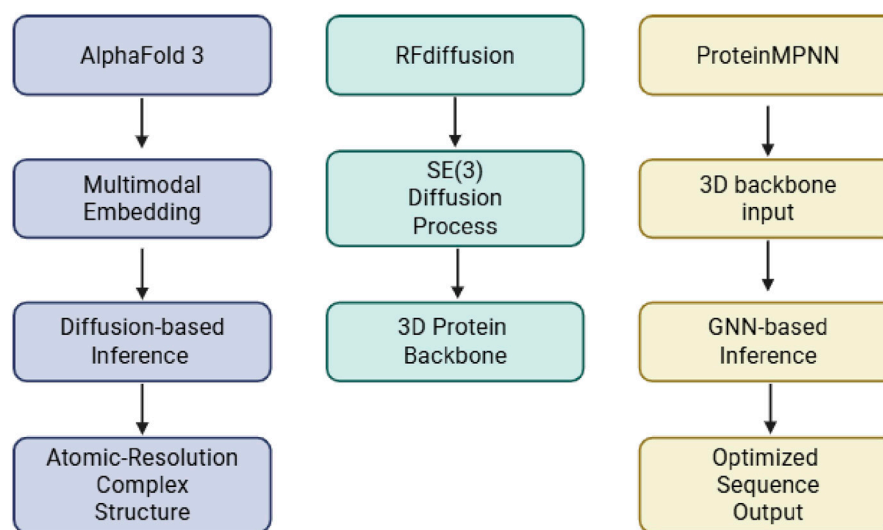
FIGURE 2
Comparison of structural modeling workflows. AlphaFold3 predicts complexes using multimodal diffusion, while RFdiffusion generates 3D protein backbones from structural constraints. ProteinMPNN designs sequences for fixed backbones via graph-based inference.

experimental accuracy for monomeric proteins, and early applications to antibody variable domains demonstrated reliable framework modeling. However, hypervariable complementarity-determining regions (CDRs), particularly CDR-H3 loops, remain challenging to predict accurately due to their intrinsic conformational flexibility (Yin and Pierce, 2023). Studies applying AlphaFold2 to antibodies revealed that while framework regions were modeled with RMSD <2 Å, long antigen-contacting CDR-H3 loops showed structural inaccuracies (Chen et al., 2024). Recognizing the need for complex modeling, DeepMind introduced AlphaFold-Multimer, expanding the system to co-fold protein-protein interactions (Evans et al., 2022). Applications to antibody-antigen complexes, such as CD20-targeted antibodies, demonstrated superior interface prediction compared to traditional docking, although induced-fit interactions remain challenging (Dabkowska et al., 2024; Boross and Leusen, 2012).

While AlphaFold2 and its multimer extension advanced structural modeling of individual proteins and some complexes, they were not designed to predict interactions with small molecules, glycans, or ions. AlphaFold2 primarily focused on monomeric folding and limited protein-protein assemblies, with no support for ligand or post-translational modification modeling. DeepMind recently introduced AlphaFold3 as a next-generation structure prediction system (Abramson et al., 2024; Krokidis et al., 2025; Desai et al., 2024). Compared to other structural modeling approaches such as RFdiffusion and ProteinMPNN, AlphaFold3 employs a diffusion-based generative framework, extending predictive capabilities to complexes involving proteins, nucleic acids, small molecules, ions, and glycans as shown in Figure 2 (Watson et al., 2022; Dauparas et al., 2022). For ADC design, AlphaFold3 offers the potential to predict glycosylated Fc domains, linker-payload interactions, and antigen-binding epitopes in the presence of cofactors (Roy and Al-Hashimi, 2024). However, despite improved static modeling of Fc glycans

and payload-conjugated domains, AlphaFold3 still struggles to fully capture glycan microheterogeneity, dynamic shielding effects, and flexible linker behavior due to the limited availability of data. They also struggle with unusual DNA and RNA structures, such as single mutations (Bergonzo and Grishaev, 2025). Benchmark datasets have demonstrated that AlphaFold3 outperforms traditional methods such as AutoDock Vina as well as deep learning-based RoseTTAFold in analyzing protein-protein interactions, nucleic acid complexes, and glycosylated proteins (Abramson et al., 2024; Eberhardt et al., 2021; Baek et al., 2021). In ligand docking benchmarks, AlphaFold3 exhibited significantly higher success rates than conventional approaches. Evaluations from the 15th Critical Assessment of Structure Prediction (CASP15) further highlighted the advances achieved with AlphaFold3, demonstrating state-of-the-art performance in modeling multimeric protein complexes, protein-small molecule complexes, and protein–glycan assemblies. (Abramson et al., 2024) AlphaFold-Multimer previously achieved interface root-mean-square deviations (iRMSDs) often below 2.5 Å for antibody-antigen complexes (Liu et al., 2023), and AlphaFold3 extended these capabilities further, setting new benchmarks for backbone accuracy, ligand positioning, and covalent modification modeling. Although modeling glycan flexibility and microheterogeneity remains a limitation, AlphaFold3 excels at capturing static glycosylation states, antigenic surfaces, and linker-conjugated domains, making it highly valuable for ADC structural modeling workflows, as shown in Figure 3 using Pertuzumab and HER2 as an example.

Specialized antibody-specific modeling tools have further enhanced precision and contributed to ADC development. DeepAb uses recurrent graph neural networks and recurrent architectures trained on curated antibody datasets to improve the CDR modeling, particularly emphasizing structural diversity in CDR-H3 loops (Ruffolo et al., 2020). DeepAb has performed
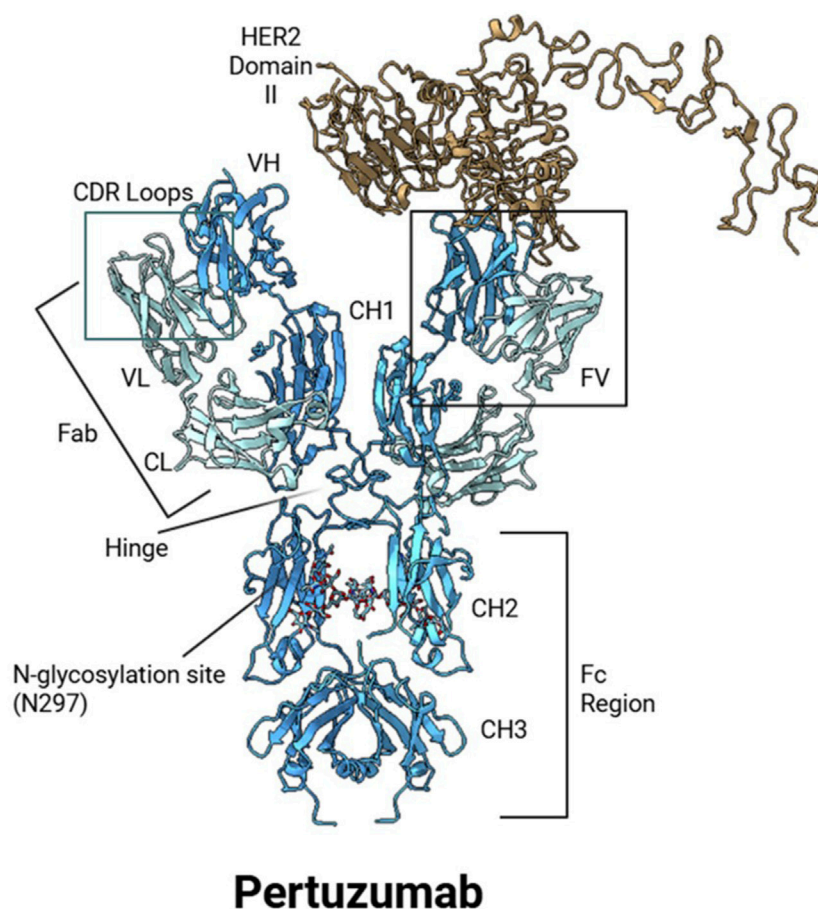
FIGURE 3
AlphaFold3-predicted structure of pertuzumab bound to HER2 Domain II, with modeled N-linked glycans. The model illustrates full antibody architecture, including variable (VH, VL) and constant (CH1, CH2, CH3, CL) domains. The antigen-binding fragment (Fab) regions contain the complementarity-determining regions (CDRs), which mediate interaction with HER2 Domain II. The Fc region includes a glycosylation site at Asn297, with glycans modeled by AlphaFold3. The HER2 epitope is positioned near the FV region, demonstrating structural alignment relevant to ADC targeting and conjugation strategies.

better than Ablang, which was developed by utilizing antibody-specific language modeling to predict and complete missing regions in antibody sequences accurately (Olsen et al., 2022). ABlooper also uses mathematical neural networks, which enables rapid CDR modeling at scale but with reduced accuracy for long or kinked H3 loops (Abanades et al., 2022). SimpleDH3 provides a simple end-to-end DL framework for predicting CDR H3 loop structure. It directly outputs backbone atomic coordinates without relying on post-processing pipelines like Rosetta (Zenkova et al., 2021). Using ELMo embeddings and bi-directional LSTM architectures, SimpleDH3 achieves comparable RMSD performance to state-of-the-art methods such as DeepH3, offering a faster inference speed. It focuses on modeling only the highly variable CDR-H3 loops rather than full Fv domains, enabling efficient large-scale antibody screening for ADC design applications (Chungyoun and Gray, 2024).

While AlphaFold3 and related deep learning models represent significant progress in structural prediction, particularly for complex and multicomponent assemblies, they do not fully resolve the longstanding challenges associated with structure-based design. These model remain limited in their ability to capture dynamic behaviors, glycan heterogeneity, induced fit effects, and other context-dependent molecular phenomena critical to ADC functionality. As such, their outputs should be interpreted as static approximations within broader design frameworks that still require empirical testing, molecular simulation, and domain-specific validation. The increasing accuracy of predicted structures enhances the utility of *in silico* workflows but does not eliminate the need for mechanistic interpretation or experimental confirmation.

Integration of AI/ML in ADC ADMET prediction and linker design

AI/ML plays a significant role in designing linker architectures for ADCs, moving beyond static structure prediction to proactive optimization of linker flexibility, stability, and payload compatibility. Recent studies have demonstrated that DL models integrated with molecular simulations can efficiently propose linker sequences optimized for specific mechanical properties and conformational flexibility, influencing ADC internalization and payload release (Su and Zhang, 2021). By learning from

structural ensembles, these AI-driven methods can anticipate steric clashes, predict linker degradation pathways, generate linker-payload combinations made to diverse intracellular environments, and enhance ADC efficacy and pharmacokinetics.

Transcending static structure optimization, ML, and DL models have become implementations in predicting key developability properties in early ADC discovery. Computational platforms now routinely evaluate solubility, aggregation propensity, chemical stability, and expression titer using ensemble ML methods trained on large antibody engineering datasets (Prihoda et al., 2022; Raybould et al., 2019). Aggregation-prone regions can be computationally mapped using support vector machine (SVM) classifiers and recurrent neural networks, while solubility predictors such as CamSol and SoluProt provide additional developability screening (Ghomi et al., 2020; Oeller et al., 2023). These approaches have reduced attrition rates and accelerated the selection of viable ADC lead candidates.

AI/ML have also been fundamental in linker and payload optimization, critical parameters that govern ADC stability, efficacy, and pharmacokinetics. Machine learning-based predictive models are trained to match linker properties to payload hydrophobicity, steric constraints, and chemical reactivity, ensuring optimal intracellular release profiles (Shen et al., 2023; Xiong et al., 2024). Novel informatics platforms now curate large libraries of ADC chemical structures and employ AI to identify linker–payload–antibody compatibility rulesets, streamlining rational ADC design (Shen et al., 2023).

To evaluate the outcomes of linker optimization, several metrics are employed. These include predictions of plasma stability, cleavage rate in lysosomal conditions, linker exposure under solvent-accessible surface area (SASA) analysis, and simulated steric compatibility with antibody and payload components. Additionally, docking scores, binding energy (ΔG), and RMSD across conformational ensembles are employed to assess spatial fit and flexibility. ML models often use predicted ADMET properties, such as half-life, cell permeability, and intracellular release kinetics as surrogate endpoints. For example, Su and Zhang demonstrated a model that predicted intracellular release profiles based on linker-payload hydrophobicity and steric load, validated against *in vitro* lysosomal degradation assays. (Su and Zhang, 2021) In glycan-based linker studies, the Woods Group used MD simulations to analyze hydrogen bond occupancy and glycosidic torsion angle variability, providing insight into stability and solvent exposure (Woods Group, 2025) More broadly, benchmarking efforts described by Bhatt and Shea have highlighted the use of hybrid ML-mechanistic evaluation pipelines, supported by publicly available ADC performance datasets (Bhatt and Shea, 2025).
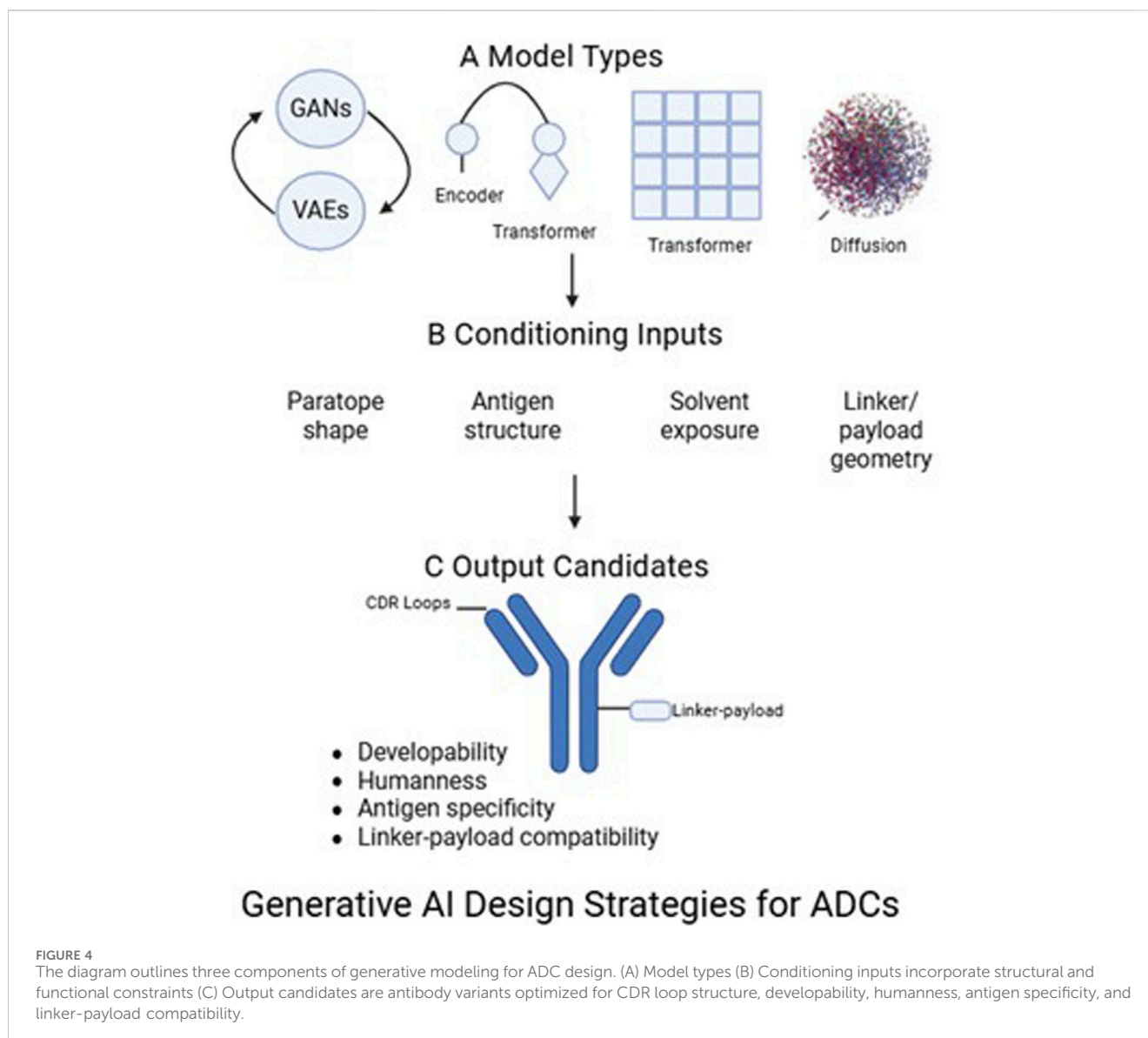
Efficient, flexible linker modeling and design are further augmented by combining DL and MD simulations. Models trained on simulated ensembles can predict linker dynamics, steric hindrance, and degradation pathways, tailoring linker structures for optimal tumor penetration and cytotoxic payload release (Imrie et al., 2020). These advances allow ADC developers to model static conjugates and dynamic, physiologically relevant states critical for *in vivo* efficacy.

Glycan-based linkers represent a modular and biocompatible strategy for next-generation ADCs. These linkers are engineered to incorporate site-specific conjugation, enzymatically cleavable motifs, or sterically protective elements that modulate payload exposure and tumor microenvironment responsiveness. Using MD simulations with the GLYCAM force field, glycan linkers can be modeled at atomic resolution to evaluate conformational flexibility, hydrogen bonding patterns, and solvent accessibility under physiologically relevant conditions. Such simulations enable the rational design of glycan linkers with controlled degradation profiles and enhanced plasma stability (Woods Group, 2025).

State-of-the-art AI pipelines built on NVIDIA GPU architecture have been increasingly adopted. These platforms offer scalable, parallelized computing that supports large-scale simulation and high-throughput docking workflows. Tools like DiffDock, a diffusion-based structure prediction and docking algorithm (Corso et al., 2022), can leverage these GPU-accelerated environments to model glycan–antibody and glycan–payload interactions with high spatial accuracy and computational efficiency. DiffDock's ability to integrate conformational sampling and ligand flexibility makes it particularly suited for evaluating the dynamic behavior of glycan-containing conjugates. When deployed on NVIDIA's optimized inference engines and CUDA-based infrastructure, these pipelines enable rapid screening and prioritization of glycan linker candidates across diverse structural and chemical configurations (St. John et al., 2024). This integration of DL-based docking, MD simulation, and high-performance computing provides a framework for the rational design of ADC–glycan conjugates that meet structural and functional constraints, supporting the development of next-generation modular linkers with tunable therapeutic properties.

Reinforcement learning (RL) methods represent an unexplored territory for *de novo* ADC design. Recent studies have demonstrated that RL frameworks can simulate iterative mutation and optimization cycles across antibody sequences, linker chemistries, and payload combinations. (Schneider, 2021). These algorithms allow the system to learn from each design iteration, refining candidates based on developability scores, predicted cytotoxicity, and pharmacokinetic parameters. Integrating RL into closed-loop experimental workflows offers the potential for fully autonomous ADC engineering platforms capable of continuous improvement and optimization.

Recent computational reviews have emphasized the growing sophistication of AI-driven ADC design strategies. For instance, Bhatt D and Shea J. summarized advances in computational lead optimization for antibody–linker–payload systems (Bhatt and Shea, 2025), while Lodge et al. described emerging technologies for quantifying antibody binding properties and their downstream implications for ADC design (Lodge et al., 2025). Together, these innovations show how AI/ML are no longer supplementary to ADC development but are becoming essential at every stage, from early antigen selection and antibody optimization to chemical linker matching and payload stability prediction. As datasets expand and DL algorithms grow, the integration of AI/ML holds great promise, and this is only the beginning.

FIGURE 4
The diagram outlines three components of generative modeling for ADC design. (A) Model types (B) Conditioning inputs incorporate structural and functional constraints (C) Output candidates are antibody variants optimized for CDR loop structure, developability, humanness, antigen specificity, and linker-payload compatibility.

Emerging generative AI models for ADCs

A notable advancement in this field is the emergence of generative AI frameworks specifically adapted for antibody engineering, which contributes to ADC development, as illustrated in Figure 4. Generative adversarial networks (GANs) and variational autoencoders (VAEs) have generated diversified CDR loop libraries with enhanced antigen-binding potential. For example, PALM-H3, a recent GAN-based generative framework, was created for SARS-CoV-2 antibody studies, which enables the design of the CDR-H3 sequences conditioned on antibody structural context by learning potential representations that preserve loop geometry and canonical structural motif while also introducing functional diversity for antigen recognition (He et al., 2024). Similarly, the Ig-VAE model efficiently learns potential representations of the antibody Fv domains, which allows the conditional generation of variant antibodies with user-friendly and user-defined properties (Eguchi et al., 2022).

Transformer-based architecture has further expanded the landscape of antibody sequence generation for mutations. Pretrained models like AntiBERTa and AbLang influence antibody sequence databases to learn language-like patterns (Gao et al., 2024). These models enable the generation of synthetic antibody libraries, the prediction of structural features from sequences, and the scoring of sequences for humanness, which is essential to the ADC developmental pipeline. For example, Hu-mAB is designed using ML classifiers that can discriminate between human and non-human antibody variable domain sequences using the larger available repertoire data (Marks et al., 2021). As discussed earlier, recent extensions of these models incorporate paratope conditioning and allow for targeted CDR diversity, which is aimed at antigens and optimizes workflows (Peng and Yang, 2022).

In silico affinity maturation and humanness, scoring have also been transformed by integrating experimental deep mutational scanning (DMS) datasets with computational optimization strategies. Early work demonstrated that mutation libraries

coupled with binding assays could map affinity and excel in this area (Barderas et al., 2008). Building on these computational frameworks, such as computational affinity maturation (CAM) models, has led to the development of models that predict point mutations that enhance antigen-binding affinity without compromising solubility or how it works (Koenig et al., 2015). These approaches allow ADC developers to simulate mutations *in silico*, guiding rational design for affinity and developability improvements.

Introducing diffusion-based generative models into antibody engineering has been a paradigm-shifting development. For example, EvoDiff, a diffusion-based model developed for protein generation, has recently been adapted for antibody design tasks, enabling the controllable generation of novel binders with desired paratope features (Alamdari et al., 2023). Similarly, DiffAb, a diffusion model trained specifically on antibody structural ensembles, allows users to sample structurally diverse yet functionally plausible antibody variants, providing new avenues for ADC diversification (Luo et al., 2022). These emerging models offer a path toward more integrated structure-function co-design, enabling the simultaneous optimization of sequence and structural properties. Traditional antibody modeling workflows often separate sequence optimization from structural validation. Diffusion models can generate sequences directly constrained by desired structural outcomes, such as loop angles, epitope curvature, or solvent accessibility parameters relevant to ADC linker engineering and payload accessibility.

Case applications and platforms

Case applications further showed the impact of AI-driven ADC design. In human epidermal growth factor receptor 2 (HER2) targeted ADCs, machine learning predicts optimal conjugation sites that maintain receptor affinity while maximizing internalization and endosomal escape efficiency. DL frameworks trained on antibody-antigen complex structures have guided the selection of paratope configurations that preserve epitope accessibility after conjugation, improving both binding and cytotoxicity (Sobhani et al., 2024; Dewalker et al., 2025). For the cluster of differentiation 30 (CD30) targeted ADCs, AI-based classification models have aided in predicting trafficking behavior and lysosomal delivery, leading to improved cytotoxic payload delivery in hematologic malignancies (Goeij et al., 2016). Another example is the epidermal growth factor receptor (EGFR) targeted ADCs, convolutional neural networks (CNNs) and graph-based models have been applied to forecast receptor expression heterogeneity across tumor subtypes, guiding rational selection and payload tuning to avoid off-target toxicity (Zhang et al., 2024).

Tools such as the ADCdb provide a curated repository of structural, functional, and clinical metadata for over 200 ADCs, which serves as a valuable foundation for multi-tasking learning models that integrate linker chemistry, payload class, and efficacy metrics (Shen et al., 2023).

Recent studies have demonstrated the efficacy of Neural Ordinary Differential Equations (Neural-ODEs) with an example of ADCnet, a deep neural network of the model, in capturing the dynamic behavior of ADCs, including intracellular trafficking, linker cleavage kinetics and payload release over time (Ahmed et al., 2022;

Losada and Terranova, 2024; Bram et al., 2023).These continuous-time models are well suited for simulating the nonlinear kinetics observed in lysosomal degradation and drug activation. They provide valuable insights into structure-activity relationships relevant to payload potency and release (Jin et al., 2023), while IgFold, DeepAb, and DiffAb support rapid antibody structure prediction and paratope design specific for stable conjugation (Luo et al., 2022; Ruffolo et al., 2023; Ruffolo et al., 2022). Generative tools such as EvoDesign facilitate the structure-guided design of the antibody variant compatible with linkers and drug loading, while Mabtope aids in identifying conjugation-tolerant epitopes and evaluating developability and immunogenicity (Pearce et al., 2019; Bourquard et al., 2018; Tahir et al., 2021). Prihoda et al. (2022) This is to name a few, but we have provided Table 1 with a more in-depth explanation to others in the Antibody and ADC pipeline that are accessible as open source and through the industry.

Challenges and future directions in AI-Driven ADC design

Integrating AI/ML into ADC design faces several challenges despite growing enthusiasm for their potential to accelerate discovery (Visan and Negut, 2024). One of the issues is the scarcity of high-quality, publicly available data. Much of the experimental information surrounding ADCs, such as conjugation chemistry, drug-to-antibody ratio (DAR), linker stability, pharmacokinetics, and toxicity, is either proprietary or inconsistently reported, limiting the development of generalizable models (Mckertish and Kayser, 2021). Even when data is available, the inherent complexity of ADCs poses unique modeling difficulties. Unlike traditional small molecules or monoclonal antibodies, ADCs comprise three interdependent components: the antibody, the chemical linker, and the cytotoxic payload, which can influence efficacy, stability, and safety in nonlinear and context-dependent ways (Dewalker et al., 2025). Current models often struggle to capture these multimodal interactions, especially when detailed 3D structural information of the complete ADC is lacking (Sapoval et al., 2022). Additionally, AI models developed for small molecule or biologic therapeutics frequently fail to translate to ADCs, as they inadequately predict developability factors such as aggregation, solubility, and clearance (Chen et al., 2023). Off-target effects and antigen heterogeneity complicate predictive modeling, particularly when simulating tumor selectivity or toxicity across diverse patient populations (Zhang and Liu, 2025). The reliance on black-box neural networks also introduces interpretability and regulatory acceptance issues, particularly in safety-critical environments (Hassija et al., 2023).

Future progress in AI-driven ADC development will rely on integrated, multi-scale modeling approaches that bridge protein structure prediction, systems pharmacology, and real-world clinical and omics data. Recent advancements such as AlphaFold3 enable structural inference of antibody–ligand complexes, including glycan and payload binding, which can support atomic-level modeling of full ADCs. (Abramson et al., 2024) These structural insights offer a path toward more predictive therapeutic design when coupled with system-level

TABLE 1 Antibody and ADC design tools.

No	Tools/Model	Year	Function/Role	References
Structural Prediction of CDRs				
1	AlphaFold3	2024	Structure prediction and modeling in complexes	Abramson et al. (2024)
2	AbFlex	2024	CDR design method with a given antibody-antigen complex	Jeon and Kim (2024)
3	ESMFold	2023	predicts protein structures directly from sequence using a language model without relying on alignments	Lin et al. (2023)
4	AlphaFold-Multimer	2023	Models antibody-antigen complexes and multi-protein assemblies to assess conjugation impact	Liu et al. (2020)
5	AbDiffuser	2023	Generation of antibody 3D structures and sequences	Martinkus et al. (2023)
6	ImmuneBuilder/ABodyBuilder2/NanoBodyBuilder2/TCRBuilder2	2023	Fv modeling, antibody structure modeling, TCR structure modeling, nanobody structure modeling	Abanades et al. (2022)
7	IgFold	2023	Accurate antibody structure prediction	Ruffolo et al. (2023)
8	tFold-Ab	2022	predicts antibody structures using ProtXLNet embeddings and a simplified Evoformer, with attention to CDR loops and side-chain conformations	Wu et al. (2022)
9	xTrimoABFold	2022	Uses ProtXLNet embeddings and streamlined architecture to predict antibody structures with improved CDR and side-chain accuracy	Wang et al. (2022)
10	DiffAb	2022	Diffusion model for generating structurally diverse antibody variants to support ADC design	Luo et al. (2022)
11	ABLooper	2022	Antibody CDR loop structure prediction	Abanades et al. (2023)
12	DeepSCAb	2022	Prediction of antibody backbone and side-chain conformations	Akpinaroglu et al. (2022)
13	DeepAb	2022	Antibody structure prediction	Ruffolo et al. (2022)
14	SMCDiff	2022	Protein backbones and motif-scaffolding	Trippe et al. (2023)
15	DeepH3	2020	Prediction of CDR H3 loop	Ruffolo et al. (2020)
16	RosettaAntibody	2018	Antibody modelling	Adolf-Bryfogle et al. (2018)
Optimization and Affinity improvement				
17	IgDiff	2024	*De novo* antibody design	Cutting et al. (2025)
18	AbGAN-LMG	2023	Higher-quality antibody library generation and optimization	Zhao et al. (2023)
19	Ens-Grad	2020	CDR design	Liu et al. (2023)
20	OptMAVEn2.0	2018	*De novo* Design of Antibody Variable Region	Chowdhury et al. (2018)
21	OptCDR	2010	CDR designing	Pantazes and Maranas (2010)
22	MEAN	2023	Antibody design	Kong et al. (2023)
Generating CDR Libraries				
23	IgLM	2023	Generates full-length antibody sequences and Infilled CDR H3 loop libraries generated	Shuai et al. (2023)
Optimizing CDR Immunogenicity				
24	reportBERT	N/A	Optimizing CDR Immunogenicity	Dewalker et al. (2025)
Binding site prediction and interaction				
25	EquiPocket	2023	Binding site prediction	Zhang et al. (2023)
26	AbAgIntPre	2022	Predict antibody-antigen interactions	Huang et al. (2022)
27	DLAB	2022		Schneider et al. (2022)

(Continued on following page)

TABLE 1 (*Continued*) Antibody and ADC design tools.

No	Tools/Model	Year	Function/Role	References
			Predict antibody-antigen binding for antigens/binder/Virtual screening/ non-binder classifier	
28	PECAN	2020	Predict binding interfaces on both antibodies and antigens	Pittala and Bailey-Kellog (2020)
Epitope and Paratope Prediction				
29	Paragraph	2023	Antibody paratope prediction	Chinery et al. (2023)
30	SEMA	2022	B-cell conformational epitope prediction	Shashkova et al. (2022)
31	EPMP	2021	Joint epitope-paratope prediction	Del Vecchio et al. (2021)
32	EvoDesign	2019	Epitope-guided sequence design optimizing paratopes for conjugation compatibility	Pearce et al. (2019)
33	MabTope	2018	Structure-based epitope prediction supporting ADC-compatible conjugation strategies	Bourquard et al. (2018)
Other Antibody/ADC Tools				
34	AbSciBio	2024	*De novo* antibody design	Shanehsazzadeh et al. (2024)
35	ADCdb	2024	Aggregates structural, functional, and clinical data for over 200 ADCs to enable modeling of design trends and outcomes	Shen et al. (2023)
36	ProGen2	2023	Modeling evolutionary sequence distributions, creating novel sequences, and predicting protein fitness	Nijkamp et al. (2023)
37	Protpardelle	2023	Generative model for protein design	Chu et al. (2024)
38	ADC-net (Neural-ODEs)	2022	DL framework integrating protein and small-molecule representations to predict ADC activity	Ahmed et al. (2022)
39	AbLang	2022	Restores the missing residues of antibody sequences	Olsen et al. (2022)
40	AbBERT-HMPN	2022	Generation of sequences and structures, focusing on the design of antigen-binding CDR-H3 regions	Gao et al. (2022)
41	AntiBERTa	2022	Tracing B cell origins, quantifying immunogenicity, and predicting antibody binding sites	Leem et al. (2022)
42	HERN	2022	Antibody docking and design	Jin et al. (2022)
43	RFdiffusion	2022	Enables the creation of complex, functional proteins from basic molecular conditions	Watson et al. (2022)
44	PROTAC-DB/PROTAC-Builder	2022	Originally for PROTACs, linker design tools adapted for ADC applications	Li et al. (2022)
45	DiffDock	2022	Predicts how small molecules bind to proteins by generating binding poses using a diffusion generative model	Corso et al. (2022)
46	AntiBERTy	2021	Understanding of immune repertoires/and affinity maturation/insights into antigen binding	Ruffolo et al. (2021)
47	RefineGNN	2021	Optimization guided by specific properties to design new antibodies with enhanced neutralization capabilities	Jin et al. (2022)
48	LSTM based study	2021	Antibody design and affinity maturation/Antibody Binding site prediction	Sata et al. (2021)
49	Fold2Seq	2021	Designing protein sequences tailored to a specific target fold	Cao et al. (2021)
50	UniRep	2019	Protein engineering and informatics	Alley et al. (2019)
51	PEP-FOLD3	2016	*De novo* modeling of peptide linkers for spatially compatible conjugation with antibody regions	Lamiable et al. (2016)
52	Glycam Builders/Glycoprotein/Carbohydrate	2005-now	Provides tools for building and modeling 3D structures of carbohydrates and glycoproteins linkers	Woods Group (2025)
AI/ML ADC Design Platforms/Pipelines				
53	VERISIM Life	2025		VERISIMLife (2025)

TABLE 1 *(Continued)* Antibody and ADC design tools.

No	Tools/Model	Year	Function/Role	References
			Virtual clinical trial platform integrating PK/PD models, population variability, and tumor-specific parameters	
54	RADR (Lantern Pharma)	2025	AI platform identifying ADC targets and payloads using ML, aiding novel ADC development	LanternPharma (2025)
55	BigHat Biosciences	2025	ML with high-throughput wet lab for iterative antibody optimization, including ADCs	Biosciences (2025)
56	MabSilico	2025	AI-driven antibody discovery for accelerated ADC candidate optimization	MAbSilico (2025)
57	Generate: Biomedicines	2025	ML-based protein design, including antibodies for therapeutic ADCs	Generate: Biomedicines (2025)

models incorporating tumor heterogeneity, immune microenvironment data, and patient-specific expression profiles. Generative models based on diffusion processes and variational inference are increasingly capable of proposing novel antibody scaffolds, conjugation sites, and payload chemistries that conform to structural and functional constraints (Corso et al., 2022). Transfer learning from related biologic modalities, including multimeric, bispecific antibodies, and nanoparticle conjugates, can further improve predictive accuracy when direct ADC training data is limited. Several methodological strategies have been introduced to address constraints related to the limited availability of training data and the narrow diversity of antibody sequences. Transfer learning allows models trained on large-scale protein datasets to be adapted to smaller, task-specific datasets through fine-tuning. Data augmentation techniques, including *in silico* mutagenesis and synthetic sequence generation, increase the number of training examples while preserving biologically grounded features. Self-supervised learning methods, such as masked language modeling and contrastive representation learning, are used to extract structural and sequence-level patterns without requiring labeled outputs. These approaches are designed to improve model performance under limited data conditions and reduce overfitting by enhancing feature extraction and sampling variability. Techniques such as federated learning enable the development of multi-institutional models without compromising data privacy, while active learning frameworks prioritize the experimental validation of high-uncertainty predictions to refine model performance iteratively. Interpretability methods, including attention-based attribution and saliency mapping, can help identify biologically relevant features driving model outputs, facilitating mechanistic understanding and regulatory transparency. Addressing these challenges systematically will be essential to establish AI-augmented workflows for the rational engineering multimeric and next-generation ADCs.

Conclusion

AI/ML have begun to redefine the field of ADC design by introducing advanced capabilities for prediction, optimization, and iterative refinement across the development pipeline. Unlike traditional trial-and-error approaches, AI/ML models can extract subtle structure-activity relationships from complex, high-dimensional data and identify candidate designs that might be overlooked. These tools have already demonstrated utility in predicting antigen-antibody interactions, optimizing conjugation sites, forecasting pharmacokinetics and off-target liabilities, and selecting linker–payload combinations with improved stability and therapeutic index. As a result, researchers are shifting toward a rational, data-driven paradigm for ADC discovery, minimizing the need for resource-intensive empirical screening.

With the emergence of next-generation ADCs, including multimeric constructs, bispecific formats, and modular payload systems, there is an urgent need for more advanced computational frameworks capable of modeling their increased structural and functional complexity. Multimeric ADCs, which incorporate multiple antigen-binding domains or payload units, hold the potential for enhanced avidity, dual-target engagement, and improved tumor selectivity, particularly in heterogeneous or resistant cancers. However, the design of these molecules requires a detailed understanding of inter-domain spatial orientation, linker flexibility, steric constraints, and payload-release kinetics, all of which are challenging to assess experimentally. AI-driven platforms, particularly those employing graph neural networks, transformer-based architectures, and multimodal representation learning, are well-positioned to address these needs.

Recent breakthroughs such as AlphaFold3 offer unprecedented accuracy in predicting antibody structures and multicomponent protein complexes with bound ligands, glycans, and small molecules. This capability enables the structural modeling of full ADCs, including multimeric variants, at atomic resolution, facilitating *in silico* evaluation of conjugation strategies, epitope accessibility, and linker spatial compatibility. Complementing these efforts, diffusion-based generative models have emerged as powerful tools for the *de novo* design of antibody scaffolds, linkers, and payload-functional groups. These models operate by iteratively denoising latent molecular representations, allowing for the exploration of chemical and structural design spaces while maintaining biologically relevant constraints. Generative approaches, active learning, and experimental feedback transform the ADC design process from an enumeration-based approach to an intelligent, hypothesis-driven synthesis.

Continued investment is required in standardized data infrastructures, experimentally verified datasets, and regulatory frameworks that support algorithmic validation and model interpretability. However, increases in model complexity and dataset size do not resolve fundamental limitations in statistical learning. The performance of AI/ML models is influenced by data quality, including annotation accuracy, measurement consistency, and the completeness of molecular descriptors. Limitations in training set diversity, class imbalance, and non-independent sampling introduce bias, while improper separation of training and validation sets, as well as test sets, reduces reliability and inflate performance estimates. Without systematic evaluation protocols and benchmarking against external datasets, model generalizability remains constrained.

As AI/ML methods are incorporated into experimental and preclinical workflows, their utility depends on the alignment between the model structure, biological context, and the design of the training and validation processes. Establishing iterative feedback between *in silico* prediction and empirical testing, alongside coordination across computational, chemical, and clinical disciplines, become essential to enable the reliable application of these technologies. Ultimately, AI/ML approaches are positioned to transform the design and development of ADCs, including multimeric and next-generation formats, by enabling scalable and mechanistically grounded strategies. Approaches such as transfer learning, data augmentation, and representation learning can improve model performance in data-constrained settings and be incorporated into AI workflows without relying on large, labeled datasets. Their impact, however, will depend on the integration of these tools with high-quality datasets, validated model architecture, and coordinated experimental feedback to ensure biological relevance and translational applicability.

Author contributions

HN: Writing – original draft, Writing – review and editing. XW: Writing – review and editing.

References

Abanades, B., Georges, G., Bujotez, A., and Deane, C. M. (2022). "ABlooper: fast accurate antibody CDR loop structure prediction with accuracy estimation." *Bioinformatics* 38.7. doi:10.1093/bioinformatics/btac016

Abanades, B., Wong, W. K., Boyles, F., Georges, G., Bujotzek, A., and Deane, C. M. (2023). "ImmuneBuilder: deep-Learning models for predicting the structures of immune proteins." *Nat. Commun. Biol.* 6, 575. doi:10.1038/s42003-023-04927-7

Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., et al. (2024). "Accurate structure prediction of biomolecular interactions with AlphaFold 3." *Nature* 630: 493–500. doi:10.1038/s41586-024-07487-w

Adhikari, A., and Chen, I. A. (2025). "Antibody-Nanoparticle Conjugates Ther. Comb. Best Two Worlds." Wiley 21.15: 2409635. doi:10.1002/smll.202409635

Adolf-Bryfogle, J., Kalyuzhniy, O., Kubitz, M., Weitzner, B. D., Hu, X., Adachi, Y., et al. (2018). "RosettaAntibodyDesign (RAbD): a general framework for computational antibody design." *PLOS Comput. Biol.* 14, e1006112. doi:10.1371/journal.pcbi.1006112

Ahmed, S., Le, D., Son, T., Adejumo, T., Ma, G., and Yao, X. (2022). "ADC-net: an open-source deep learning network for automated dispersion compensation in optical coherence tomography." *Front. Med.* 9, 864879. doi:10.3389/fmed.2022.864879

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. Generative AI tools were used during the early stages of manuscript preparation to assist in organizing the outline and drafting portions of the introduction. All generated content was reviewed, assessed, and rewritten in the authors' own words to ensure accuracy, originality, and alignment with scholarly standards.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fddsv.2025.1628789/full#supplementary-material

Akpinaroglu, D., Ruffolo, J. A., Mahajan, S. P., and Gray, J. J. (2022). "Simultaneous prediction of antibody backbone and side-chain conformations with deep learning." *PLOS one* 17, e0258173. doi:10.1371/journal.pone.0258173

Alamdari, S., Thakkar, N., van den Berg, R., Lu, A. X., Fusi, N., Amini, A. P., et al. (2023). "Protein generation with evolutionary diffusion: sequence is all you need." *bioRxiv*. doi:10.1101/2023.09.11.556673

Alley, E. C., Khimulya, G., Biswas, S., alQuraishi, M., and Church, G. M. (2019). "Unified rational protein engineering with sequence-based deep representation learning." *Nat. Methods* 16, 1315, 1322. doi:10.1038/s41592-019-0598-1

Angiolini, L., Manelli, F., Spiga, O. A., Tafi, A., Visibelli, A., Petricci, E., et al. (2025). "Machine learning for predicting the drug-to-antibody ratio (DAR) in the synthesis of antibody-drug conjugates (ADCs)." *Am. Chem. J. Chem. Inf. Model.* doi:10.1021/acs.jcim.5c00037

Antunes, E. M., Beukes, D. R., Caro-Diaz, E. J. E., Narchi, N. E., Tan, L. T., and Gerwick, W. H. (2023). "Chapter 5 - medicines from the sea," in *Oceans and human health* 2nd edn. Editors L. E. Fleming, L. B. A. Creencia, W. H. Gerwick, H. C. Goh, M. O. Gribble, and B. Maycock, et al. (Cambridge, MA: Academic Press), 103–148. doi:10.1016/B978-0-323-95227-9.00009-9

Baek, M., Dinaio, F., Anishchenko, I., Dauparas, J., Ovchiinnikov, S., Lee, G. R., et al. (2021). "Accurate prediction of protein structures and interactions using a three-track neural network." *Science* 373: 871–876. doi:10.1126/science.abj8754

Bai, G., Sun, C., Guo, Z., Wang, Y., Zeng, X., Su, Y., et al. (2023). "Accelerating antibody discovery and design with artificial intelligence: recent advances and prospects." *Seminars Cancer Biol.* 95: 13–24. doi:10.1016/j.semcancer.2023.06.005

Barderas, R., Desmet, J., Timmerman, P., Casai, J. I., and Casal, J. I. (2008). "Affinity maturation of antibodies assisted by *in silico* modeling." *PNAS* 105: 9029–9034. doi:10.1073/pnas.0801221105

Bergonzo, C., and Grishaev, A. (2025). "Critical assessment of RNA and DNA structure predictions via artificial intelligence: the imitation game." *J. Chem. Inf. Model.* 65, 3544, 3554. doi:10.1021/acs.jcim.5c00245

Bhatt, D., and Shea, J. (2025). VERISIMLife. 9 1 2025. Available online at: https://www.verisimlife.com/publications-blog/knowledge-enhanced-ai-to-supercharge-adc-development-for-treatment-of-cancer#:~:text=Given%20the%20combinatorial%20nature%20of,ADC%20that%20may%20be%20concerning.2842025.

Biosciences, B. H. (2025). Better biologics faster through ML-guided design. Available online at: https://www.bighatbio.com/May 1, 2025).

Boross, P., and Leusen, J. H. W. (2012). Mechanisms of action of CD20 antibodies. *Am. J. Cancer Res.* 2 (6), 676–90.

Bourquard, T., Musnier, A., Puard, V., Tahir, S., Ayoub, M. A., Jullian, Y., et al. (2018). "MAbTope: a method for improved epitope mapping." *J. Immunol.* 201: 3096–3105. doi:10.4049/jimmunol.1701722

Bram, D. S., Nahum, U., Schropp, J., Pfister, M., and Koch, G. (2023). "*Low-dimensional neural ODEs and their application in pharmacokinetics.*" Springer: 123–140. doi:10.1007/s10928-023-09886-4

Cao, Y., Das, P., Chenthamarakshan, V., Chen, P. Y., Melnyk, I., and Shen, Y. (2021). Fold2Seq: a joint sequence(1D)-Fold(3D) embedding-based generative model for protein design. *Proc. Mach. Learn Res.* 139, 1261–1271.

Chandrika, S., Rani, A. P., Meghana, K., Jyothsna, K., Yamini, S., and Kumar, V. K. (2024). AI: THE Revolutionary impact on drug delivery systems– a new era in medicine. *World J. Pharm. Res.*, 109–130. doi:10.20959/wjpr202424-34871

Chaves, E. J. F., Coelho, D. F., Cruz, C. H. B., Moreira, E. G., Simoes, J. C. M., Nascimento-Filho, M. J., et al. (2024). "Structure-based computational design of antibody mimetics: challenges and perspectives." *FEBS Open Bio* 15: 223–235. doi:10.1002/2211-5463.13855

Chen, H., Fan, X., Zhu, S., Pei, Y., Zhang, X., Zhang, X., et al. "Accurate prediction of CDR-H3 loop structures of antibodies with deep learning." *eLife* 12(2024). doi:10.7554/eLife.91512

Chen, Z., Wang, X., Chen, X., Huang, J., Wnag, C., Wang, J., et al. (2023). Accelerating therapeutic protein design with computational approaches toward the clinical stage. *Comput. Struct. Biotechnol. J.* 21, 2909–2926. doi:10.1016/j.csbj.2023.04.027

Chinery, L., Wahome, N., Moal, I., and Deane, C. M. (2023). "Paragraph-antibody paratope prediction using graph neural networks with minimal feature vectors." *Bioinformatics* 39, btac732. doi:10.1093/bioinformatics/btac732

Chiu, M. L., Goulet, D. R., Teplyakov, A., and Gilliland, G. L. (2019). "Antibody structure and function: the basis for engineering therapeutics." *MDPI* 8.4: 55. doi:10.3390/antib8040055

Chowdhury, R., Allan, M. F., and Maranas, C. D. (2018). "OptMAVEn-2.0: *de novo* design of variable antibody regions against targeted antigen epitopes." *Antibodies* 7, 23. doi:10.3390/antib7030023

Chu, A. E., Kim, J., Cheng, L., Nesr, G. E., Xui, M., Shuai, R. W., et al. (2024). "An all-atom protein generative model." *PNAS* 121, e2311500121. doi:10.1073/pnas.2311500121

Chungyoun, M., and Gray, J. J. (2024). AI models for protein design are driving antibody engineering. *Curr. Opin. Biomed. Eng.* 28, 100473. doi:10.1016/j.cobme.2023.100473

Codina, N., Zhang, C., Chakroun, N., and Dalby, P. A. (2019). "Insights into the stability of a therapeutic antibody Fab fragment by molecular dynamics and its stabilization by computational design." *bioRxiv.* doi:10.1101/644369

Corso, G., Stark, H., Jing, B., Barzilay, R., and Jaakkola, T. (2022). DiffDock: diffusion steps, twists, and turns for molecular docking. *arXiv.* doi:10.48550/arXiv.2210.01776

Cruz, E., and Kayser, V. (2019). Monoclonal antibody therapy of solid tumors: Clinical limitations and novel strategies to enhance treatment efficacy. Biol.: Targets Ther. 13, 33–51. doi:10.2147/BTT.S166310

Cutting, D., Dreyer, F. A., Errington, D., Schneider, C., and Deane, C. M. (2025). De novo antibody design with SE(3) diffusion. *J. Comput. Biol.* 32 (4). doi:10.1089/cmb.2024.0768

Dauparas, J., Anishchenko, I., Bennett, N., Bai, H., Ragotte, R. J., Milles, L. F., et al. (2022). Robust deep learning–based protein sequence design using ProteinMPNN. *Science.* 378 (6615), 49–56. doi:10.1126/science.add2187

Dabkowska, A., Domka, K., and Firczul, M. (2024). "Advancements in cancer immunotherapies targeting CD20: from pioneering monoclonal antibodies to

chimeric antigen receptor-modified T cells." *Front. Immunol.* 15 1363102. doi:10.3389/fimmu.2024.1363102

Debnath, U., Verma, S. J., Patra, J., and Mandal, S. K. (2022). "A review on recent synthetic routes and computational approaches for antibody drug conjugation developments used in anti-cancer therapy." *J. Mol. Struct.* 1256: 132524. doi:10.1016/j.molstruc.2022.132524

Del Vecchio, A., Deac, A., Lio, P., and Velckovic, P. (2021). "Neural message passing for joint paratope-epitope prediction." *arXiv.* doi:10.48550/arXiv.2106.00757

Desai, D., Kantliwala, S., Vybhavi, J., Ravi, R., Patel, H., and Patel, J. (2024). "Review of AlphaFold 3: transformative advances in drug design and therapeutics." *Cureus* 16: e63646. doi:10.7759/cureus.63646

Dewalker, V., Morya, V. K., Kim, Y. H., Park, S. T., Kim, H. S., and Koh, Y. H. (2025). "Revolutionizing oncology: the role of Artificial Intelligence (AI) as an antibody design, and optimization tools." *Biomark. Res.* doi:10.1186/s40364-025-00764-4

Dixit, S. B. (2015). "Computational methods in the optimization of biologic modalities," in *Developability of biotherapeutics: computational approaches*, Editors S. K. Singh and S. Kumar. CRC Press, 35–54.

Dominguez, C., Boelens, R., and Bonvin, AMJJ (2003). HADDOCK: a protein–protein docking approach based on biochemical or biophysical information. *J. Am. Chem. Soc.* 125 (7), 1731–1737. doi:10.1021/ja026939x

Eberhardt, J., Santos-Martins, D., Tillack, A. F., and Forli, S. (2021). "AutoDock Vina 1.2.0: new docking methods, expanded force field, and Python bindings." *J. Chem. Inf. Model.* 61, 3891, 3898. doi:10.1021/acs.jcim.1c00203

Eguchi, R. R., Choe, C. A., and Huang, P. S. (2022). "Ig-VAE: generative modeling of protein structure by direct 3D coordinate generation." *PLOS Comput. Biol.* 18.6: e1010271. doi:10.1371/journal.pcbi.1010271

Evans, R., O'Neill, M., Pritzel, A., Antropova, N., Senior, A., Green, T., et al. (2022). "Protein complex prediction with AlphaFold-Multimer." *bioRxiv.* doi:10.1101/2021.10.04.463034

Evers, A., Krah, S., Demir, D., Gaa, R., Elter, D., Schroeter, C., et al. (2024). "Engineering hydrophobicity and manufacturability for optimized biparatopic antibody-drug conjugates targeting c-MET." *mABs* 16: 2302386. doi:10.1080/19420862.2024.2302386

Filntisi, A., Vlachakis, D., Matsopoulos, G. K., and Kossida, S. (2014). "*Computational construction of antibody–drug conjugates using surface lysines as the antibody conjugation site and a non-cleavable linker.*" Cancer Inform. 13, 1–12. doi:10.4137/CIN.S19222

Gao, K., Wu, L., Zhu, J., Peng, T., Xia, Y., He, L., et al. (2022). "Incorporating pre-training paradigm for antibody sequence-structure Co-design." *arXiv.* doi:10.48550/arXiv.2211.08406

Gao, X., Cao, C., He, C., and Lai, L. (2024). "Pre-training with a rational approach for antibody sequence representation." *Front. Immunol.* 15 1468599. doi:10.3389/fimmu.2024.1468599

Garofalo, M., Grazioso, G., Cavalli, A., and Sgrignani, J. (2020). "How computational chemistry and drug delivery techniques can support the development of new anticancer drugs." *Molecules* 25.7: 1756. doi:10.3390/molecules25071756

Generate: Biomedicines (2025). *Gener. Biomed.* Available online at: https://generatebiomedicines.com/ (May 1, 2025).

Gholap, A. D., Uddin, M. J., Faiyazuddin, M., Omri, A., Gowri, S., and Khalid, M. (2024). "Advances in artificial intelligence for drug delivery and development: a comprehensive review." *Comput. Biol. Med.* 178: 108702. doi:10.1016/j.compbiomed.2024.108702

Ghomi, F. A., Kittila, T., and Welner, D. H. (2020). "A benchmark of protein solubility prediction methods on UDP-dependent glycosyltransferases." *bioRxiv.* doi:10.1101/2020.02.28.962894

Goeij, B. F., Vink, T., Napel, H. T., Breij, E. C. W., Satijn, D., Wubbolts, R. W., et al. (2016). "Efficient payload delivery by a bispecific antibody-drug conjugate targeting HER2 and CD63." *Mol. Cancer Ther.* 15, 2688, 2697. doi:10.1158/1535-7163.MCT-16-0364

Hassija, V., Chamola, V., Mahapatra, A., Singal, A., Goel, D., Huang, K., et al. (2023). "Interpreting black-box models: a review on explainable artificial intelligence." *Springer Nat. Link.* 16: 45–74. doi:10.1007/s12559-023-10179-8

He, H., He, B., Guan, L., Zhao, Y., Jiang, F., Chen, G., et al. (2024). "De novo generation of SARS-CoV-2 antibody CDRH3 with a pre-trained generative large language model." *Nat. Commun.* 15 6867. doi:10.1038/s41467-024-50903-y

Huang, Y., Zhang, Z., and Zhou, Y. (2022). "AbAgIntPre: a deep learning method for predicting antibody-antigen interactions based on sequence information." *Front. Immunol.* 13, 1053617. doi:10.3389/fimmu.2022.1053617

Imrie, f, Bradley, A. R., Van der Schaar, M., and Deane, C. M. (2020). "Deep generative models for 3D linker design." *J. Chem. Inf. Model.* 60, 1983, 1995. doi:10.1021/acs.jcim.9b01120

Jeon, W., and Kim, D. (2024). "AbFlex: designing antibody complementarity determining regions with flexible CDR definition." *Bioinformatics* 40.btae122. doi:10.1093/bioinformatics/btae122

Jin, W., Barzilay, R., and Jaakkola, T. (2022). "Antibody-antigen docking and design via hierarchical equivariant refinement." *arXiv*. doi:10.48550/arXiv.2207.06616

Jin, W., Wohlwend, J., Barzilay, R., and Jaakkola, T. (2022). "Iterative refinement graph neural network for antibody sequence-structure Co-design." *arXiv*. doi:10.48550/arXiv.211

Jin, Y., Schladetsch, M. A., Huang, X., Balunas, M. J., and Wiemer, A. J. (2023). "Stepping forward in antibody-drug conjugate development." *Pharmacol. Ther.* 229: 107917. doi:10.1016/j.pharmthera.2021.107917

Juan, A., Cimas, F. J., Bravo, I., Pandiella, A., Ocana, A., and Alonso-Moreno, C. (2020). "Antibody conjugation of nanoparticles as therapeutics for breast cancer treatment." *MDPI* 21.6018. doi:10.3390/ijms21176018

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., et al. (2021). "Highly accurate protein structure prediction with AlphaFold." *Nature* 596: 583–589. doi:10.1038/s41586-021-03819-2

Khetan, R., Curtis, R., Deane, Cm, Hadsund, J. T., Kar, U., Krawczyk, K., et al. (2022). "Current advances in biopharmaceutical informatics: guidelines, impact and challenges in the computational developability assessment of antibody therapeutics." *mABs* 14.1: 2020082. doi:10.1080/19420862.2021.2020082

Kim, J., McFee, M., Fang, Q., Abdin, O., and Kim, P. M. (2023). "Computational and artificial intelligence-based methods for antibody development." *Trends Pharmacol. Sci.* 44.3: 175–189. doi:10.1016/j.tips.2022.12.005

Koenig, P., Lee, C. V., Sanowar, S., Wu, P., Stinson, J., Harris, S. F., et al. (2015). "Deep sequencing-guided design of a high affinity dual specificity antibody to target two angiogenic factors in neovascular age-related macular degeneration." *J. Biol. Chem.* 290: 21773–21786. doi:10.1074/jbc.M115.662783

Kong, X., Huang, W., and Liu, Y. (2022). End-to-End full-atom antibody design. *In Proceedings of the 40th International Conference on Machine Learning* 202, 17526–17544. doi:10.48550/arXiv.2302.00203

Kozakov, D., Hall, D. R., Xia, B., Porter, K. A., Padhorny, D., Yueh, C., et al. (2017). The ClusPro web server for protein–protein docking. *Nat. Protoc.* 12 (2), 255–278. doi:10.1038/nprot.2016.169

Krokidis, M. G., Koumadorakis, D. E., Lazaros, K., Ivantsik, O., Exarchos, T., Vrahatis, A., et al. (2025). "AlphaFold3: an overview of applications and performance insights." *Mol. Sci.* 26, 3671. doi:10.3390/ijms26083671

Lamiable, A., Thevenet, P., Rey, J., Vavrusa, M., Derreumaux, P., and Tuffery, P. (2016). PEP-FOLD3: faster *de novo* structure prediction for linear peptides in solution and in complex. *Nucleic Acids Res.* 44, W449–W454. doi:10.1093/nar/gkw329

LanternPharma (2025). RADR® AI Platform: Transforming the pace and precision of oncology drug discovery. *Lantern Pharma*. Available online at: https://www.lanternpharma.com/ai-platform

Leem, J., Mitchell, L. S., Farmery, J. H. R., Barton, J., and Galson, J. D. (2022). "Deciphering the language of antibodies using self-supervised learning." *Patterns* 3, 100513. doi:10.1016/j.patter.2022.100513

Li, F., Hu, O., Zhang, X., Liu, Z., Wu, S., Tian, S., et al. (2022). DeepPROTACs is a deep learning-based targeted degradation predictor for PROTACs. *Nat. Commun.* 13, 7133. doi:10.1038/s41467-022-34807-3

Lin, Z., Akin, H., Rao, R., Hie, B., Zhu, Z., Lu, W., et al. (2023). Evolutionary-scale prediction of atomic-level protein structure with a language model. *Science* 379, 1123–1130. doi:10.1126/science.ade2574

Liu, G., Zeng, H., Mueller, J., Carter, B., Wang, Z., Schilz, J., et al. (2020). "Antibody complementarity determining region design using high-capacity machine learning." *Bioinformatics* 36, 2126, 2133. doi:10.1093/bioinformatics/btz895

Liu, J., Guo, Z., Wu, T., Roy, R. S., Quadir, F., Chen, C., et al. (2023). "Enhancing alphafold-multimer-based protein complex structure prediction with MULTICOM in CASP15." *Nature* 6, 1140. doi:10.1038/s42003-023-05525-3

Lodge, J., Kaitar, L., Duxbury, R., Hall, D., Burley, G. A., Cordy, J., et al. (2025). "Quantifying antibody binding: techniques and therapeutic implications." *mABs* 17, 2459795. doi:10.1080/19420862.2025.2459795

Losada, I. B., and Terranova, N. (2024). "Bridging pharmacology and neural networks: a deep dive into neural ordinary differential equations." *CPT Pharmacometrics and Syst. Pharmacol.* 13: 1289–1296. doi:10.1002/psp4.13149

Luo, S., Su, Y., Peng, X., Wang, S., Peng, J., and Ma, J. (2022). "Antigen-specific antibody design and optimization with diffusion-based generative models for protein structures." *bioRxiv*. doi:10.1101/2022.07.10.499510

MAbSilico (2025). 21 days to design the best antibody candidates. Available online at: https://www.mabsilico.com/May 1, 2025).

Marcu, S. B., Tabirca, S., and Tangney, M. (2022). "An overview of alphafold's breakthrough." *Front. Artif. Intell.* 5, 875587. doi:10.3389/frai.2022.875587

Marks, C., Hummer, A. M., Chin, M., and Deane, C. M. (2021). "Humanization of antibodies using a machine learning approach on large-scale repertoire data." *Bioinformatics* 37.22: 4041–4047. doi:10.1093/bioinformatics/btab434

Martinkus, K., Ludwiczak, J., Cho, K., Liang, W. C., Lafrance-Vanasse, J., Hotzel, I., et al. (2023). AbDiffuser: full-atom generation of in vitro functioning antibodies. *arXiv*. doi:10.48550/arXiv.2308.05027

Mckertish, C. M., and Kayser, V. (2021). Advances and limitations of antibody drug conjugates for cancer. *Biomedicines* 9, 872. doi:10.3390/biomedicines9080872

Melo, R., Agostinho, L., Preto, A., Almeida, J. G., Correia, J. D. G., Ozge, S., et al. (2018). "Computational approaches in antibody-drug conjugate optimizationin for targeted cancer therapy." *Curr. Top. Med. Chem.* 18: 1091–1109. doi:10.2174/1568026618666180731165222

Moore, E. J., Rice, M., Roy, G., Zhang, W., and Marelli, M. (2024). "Emerging conjugation strategies and protein engineering technologies aim to improve ADCs in the fight against cancer." *Xenobiotica* 54. 469. 491. doi:10.1080/00498254.2024.2339993

Nijkamp, E., Ruffolo, J. A., Weinstein, E. N., Nikhil, N., Madani, A., Nijkamp, E., et al. (2023). ProGen2: exploring the boundaries of protein language models. *Cell Syst.* 14, 968–978.e3. doi:10.1016/j.cels.2023.10.002

Oeller, M., Kang, R., Bell, R., Ausserwoger, H., Sormanni, P., and Vendruscolo, M. (2023). "Sequence-based prediction of pH-dependent protein solubility using CamSol." *Brief. Bioinform.* 24, bbad004. doi:10.1093/bib/bbad004

Olsen, T. H., Moal, I. H., and Deane, C. M. (2022). "AbLang: an antibody language model for completing antibody sequences." *Bioinform Adv.* 2.1: vbac046. doi:10.1093/bioadv/vbac046

Pantazes, R. J., and Maranas, C. D. (2010). "OptCDR: a general computational method for the design of antibody complementarity determining regions for targeted epitope binding." *Protein Eng. Des. and Sel.* 23, 849, 858. doi:10.1093/protein/gzq061

Pearce, R., Huang, X., Setiawan, D., and Zhang, Y. (2019). "EvoDesign: designing protein-protein binding interactions using evolutionary interface profiles in conjunction with an optimized physical energy function." *J. Mol. Biol.* 431: 2467–2476. doi:10.1016/j.jmb.2019.02.028

Peng, H. P., and Yang, A. S. (2022). "Computational analysis of antibody paratopes for antibody sequences in antibody libraries." *Methods Mol. Biol.* 2552. 437–445. doi:10.1007/978-1-0716-2609-2_24

Pittala, S., and Bailey-Kellog, C. (2020). "Learning context-aware structural representations to predict antigen and antibody binding interfaces." *Bioinformatics* 36: 3996–4003. doi:10.1093/bioinformatics/btaa263

Prihoda, D., Maamary, J., Waight, A., Juan, V., Fayadat-Dilman, L., Svozil, D., et al. (2022). "BioPhi: a platform for antibody design, humanization, and humanness evaluation based on natural antibody repertoires and deep learning." *mABs* 14, 2020203. doi:10.1080/19420862.2021.2020203

Raybould, M. J., Marks, C., Krawczyk, K., Deane, C. M., Nowak, J., Lewis, A. P., et al. (2019). "Five computational developability guidelines for therapeutic antibody profiling." *PNAS* 116: 4025–4030. doi:10.1073/pnas.1810576116

Roy, R., and Al-Hashimi, H. M. (2024). AlphaFold3 takes a step toward decoding molecular behavior and biological computation. *Nat. Struct. and Mol. Biol.* 31, 997–1000. doi:10.1038/s41594-024-01350-2

Ruffolo, J. A., Chu, L. S., Mahajan, S. P., and Gray, J. J. (2023). "Fast, accurate antibody structure prediction from deep learning on massive set of natural antibodies." *Nat. Commun.* 14: 2389. doi:10.1038/s41467-023-38063-x

Ruffolo, J. A., Gray, J. J., and Sulam, J. (2021). "Deciphering antibody affinity maturation with language models and weakly supervised learning." *arXiv*. doi:10.48550/arXiv.2112.07782

Ruffolo, J. A., Guerra, C., Mahajan, S. P., Sulam, J., and Gray, J. J. (2020). "Geometric potentials from deep learning improve prediction of CDR H3 loop structures." *Bioinformatics* 36: i268–i275. doi:10.1093/bioinformatics/btaa457

Ruffolo, J. A., Sulam, J., and Gray, J. J. (2022). "Antibody structure prediction using interpretable deep learning." *Patterns* 3, 100406.2. doi:10.1016/j.patter.2021.100406

Sakhnini, L. I., Greisen, P. J., Wiberg, C., Bozoky, Z., Lund, S., Wolf Perez, A.-M., et al. (2019). Improving the developability of an antigen binding fragment by aspartate substitutions. *Biochemistry* 58 (24), 2750–2759. doi:10.1021/acs.biochem.9b00251

Sakurai, Y., Abe, N., Yoshikawa, K., Oyama, R., Ogasawara, S., Murata, T., et al. (2022). "Targeted delivery of lipid nanoparticle to lymphatic endothelial cells via anti-podoplanin antibody." *J. Control. Release* 349: 379–387. doi:10.1016/j.jconrel.2022.06.052

Sapoval, N., Aghazadeh, A., Nute, M. G., Antunes, D. A., Balaji, A., Baraniuk, R., et al. (2022). Current progress and open challenges for applying deep learning across the biosciences. *Nat. Commun.* 13, 1728. doi:10.1038/s41467-022-29268-7

Sata, K., Kakuzaki, T., Metsugi, S., Kashiwagi, D., Yoshida, K., Wada, M., et al. (2021). "Antibody design using LSTM based deep generative model from phage display library for affinity maturation." *Nature*. doi:10.1038/s41598-021-85274-7

Schneider, C. (2021). *Deep learning algorithms for predicting association between antibody sequence, structure, and antibody properties (Doctoral dissertation)*. Ann Arbor, MI: ProQuest LLC. Available online at: https://www.proquest.com/openview/b38e647d7547fbd481d257a4291b5c0f/1?cbl=2026366&diss=y&pq-origsite=gscholar.

Schneider, C., Buchanan, A., Taddese, B., and Deane, C. M. (2022). "DLAB: deep learning methods for structure-based virtual screening of antibodies." *Bioinformatics* 38, 377, 383. doi:10.1093/bioinformatics/btab660

Selepe, C. T., Dhlamini, K. S., Tshweu, L., Moralo, M., Kwezi, L., Ray, S. S., et al. (2024). "Trastuzumab-based nanomedicines for breast cancer therapy: recent advances and future opportunities." *Wiley* 5.5: 2300191. doi:10.1002/nano.202300191

Shanehsazzadeh, A., McPartlon, M., Kasun, G., Steiger, A. K., Sutton, J. M., Yassine, E., et al. (2024). "Unlocking *de novo* antibody design with generative artificial intelligence." *bioRxiv*. doi:10.1101/2023.01.08.523187

Shashkova, T. I., Umerenkov, D., Salnikov, M., Strashnov, P. V., Konstantinova, A. V., Lebed, I., et al. (2022). "SEMA: antigen B-cell conformational epitope prediction using deep transfer learning." *Front. Immunol.* 13, 960985. doi:10.3389/fimmu.2022.960985

Shen, L., Sun, X., Chen, Z., Guo, Y., Shen, Z., Song, Y., et al. (2023). "ADCdb: the database of antibody-drug conjugates." *Nucleic Acid Res.* 52: D1097–D1109. doi:10.1093/nar/gkad831

Shi, M., and McHugh, K. J. (2023). "Strategies for overcoming protein and peptide instability in biodegradable drug delivery systems." *Adv. Drug Deliv. Rev.* 199: 114904. doi:10.1016/j.addr.2023.114904

Shuai, R. W., Ruffolo, J. A., and Gray, J. J. (2023). "IgLM: infilling language modeling for antibody sequence design." *Cell Syst.* 14, 979, 989.e4. doi:10.1016/j.cels.2023.10.001

Siddiqui, B., Yadav, C. H., Akil, M., Faiyyaz, M., Khan, A. R., Ahmad, N., et al. (2025). "Artificial intelligence in computer-aided drug design (CADD) tools for the finding of potent biologically active small molecules: traditional to modern approach." *Combinatorial chemistry and high throughput screening*. doi:10.2174/0113862073334062241015043343

Skolnick, J., Gao, M., Zhou, H., and Singh, S. (2021). "AlphaFold 2: why it works and its implications for understanding the relationships of protein sequence, structure, and function." *J. Chem. Inf. Model* 61: 4827–4831. doi:10.1021/acs.jcim.1c01114

Smith, A. J. (2015). "New horizons in therapeutic antibody discovery: opportunities and challenges versus small-molecule therapeutics." *SLAS Discov.* 20.4: 437–453. doi:10.1177/1087057114562544

Sobhani, N., D'Angelo, A., Pittacolo, M., Mondani, G., and Generali, D. (2024). "Future AI will Most likely predict antibody-drug conjugate response in oncology: a review and expert opinion." *Cancers (Baseline)* 16: 3089. doi:10.3390/cancers16173089

St. John, P., Lin, D., Binder, P., Greaves, M., Shah, V., St.John, J., et al. (2024). "BioNeMo framework: a modular, high-performance library for AI model development in drug discovery." *arXiv*. Available online at: https://arxiv.org/abs/2411.10548.

Su, D., and Zhang, D. (2021). "Linker design impacts antibody-drug conjugate pharmacokinetics and efficacy via modulating the stability and payload release efficiency." *Front. Pharmacol.* 12: 687926. doi:10.3389/fphar.2021.687926

Tahir, S., Bourquard, T., Musiner, A., Jullian, Y., Corde, Y., Omahdi, Z., et al. (2021). "Accurate determination of epitope for antibodies with unknown 3D structures." *MAbs* 13: 1961349. doi:10.1080/19420862.2021.1961349

Trippe, B. L., Yim, J., Tischer, D., Baker, D., Broderick, T., Barzilay, R., et al. (2023). "Diffusion probabilistic modeling of protein backbones in 3D for the motif-scaffolding problem." *Biomolecules*. doi:10.48550/arXiv.2206.04119

VERISIMLife (2025). Available online at: https://www.verisimlife.com/May 1, 2025).

Visan, A. I., and Negut, I. (2024). Integrating artificial intelligence for drug discovery in the context of revolutionizing drug delivery. *Life* 14, 233. doi:10.3390/life14020233

Wang, Y., Gong, X., Li, S., Yang, B., Sun, Y., Shi, C., et al. (2022). xTrimoABFold: *de novo* antibody structure prediction without MSA. *arXiv*. doi:10.48550/arXiv.2212.00735

Waterhouse, A., Bertoni, M., Bienert, S., Studer, G., Tauriello, G., Gumienny, R., et al. (2018). "SWISS-MODEL: homology modelling of protein structures and complexes." *Nucleic Acid Res.* 46: W296–W303. doi:10.1093/nar/gky427

Watson, J. L., Juergens, D., Bennett, N. R., Trippe, B. L., Yim, J., Eisenach, H. E., et al. (2022). "Broadly applicable and accurate protein design by integrating structure prediction networks and diffusion generative models." *bioRxiv*. doi:10.1101/2022.12.09.519842

Woods Group (2025). "GLYCAM web," in *Carbohydrate research center*. Athens, GA: University of Georgia. Available online at: http://glycam.org.

Wu, J., Wu, F., Jiang, B., Liu, W., and Zhao, P. (2022). tFold-ab: fast and accurate antibody structure prediction without sequence homologs. *bioRxiv*. doi:10.1101/2022.11.10.515918

Xiong, Z., Liu, K., Liu, S., Feng, J., Wang, J., Feng, Z., et al. (2024). "Precision HER2: a comprehensive AI system for accurate and consistent evaluation of HER2 expression in invasive breast Cancer." *BMC Cancer* 24, 1204. doi:10.1186/s12885-024-12980-6

Yang, Z., Zeng, X., Zhao, Y., and Chen, R. (2023). "AlphaFold2 and its applications in the fields of biology and medicine." *Signal Transduct. Target. Ther.* 8, 115. doi:10.1038/s41392-023-01381-z

Yin, R., and Pierce, B. G. (2023). Evaluation of AlphaFold antibody-antigen modeling with implications for improving predictive accuracy. *bioRxiv*, 2023.07.05.547832. doi:10.1101/2023.07.05.547832

Zenkova, N., Sedykh, E., Shugaeva, T., Strashko, V., Ermak, T., and Shpilman, A. (2021). Simple end-to-end deep learning model for CDR-H3Loop structure prediction. *Mach. Learn. arXiv*. doi:10.48550/arXiv.2111.10656

Zhang, C., and Liu, H. (2025). Advancements and future directions of dual-target chimeric antigen receptor T-cell therapy in preclinical and clinical studies. *J. Immunol. Res.* 2025, 5845167. doi:10.1155/jimr/5845167

Zhang, G., Shang, L., Cao, Y., Zhang, J., Li, S., Qian, R., et al. (2024). "Prediction of epidermal growth factor receptor (EGFR) mutation status in lung adenocarcinoma patients on computed tomography (CT) images using 3-dimensional (3D) convolutional neural network." *Quant. Imaging Med. Surg.* 14.8: 6048–6059. doi:10.21037/qims-24-33

Zhang, Y., Huang, W., Wei, Z., Yuan, Y., and Ding, Z. (2023). "EquiPocket: an E(3)-equivariant geometric graph neural network for ligand binding site prediction." *arXiv*. doi:10.48550/arXiv.2302.12177

Zhao, W., Luo, X., Tong, F., Zheng, X., Li, J., Zhao, G., et al. (2023). "Improving antibody optimization ability of generative adversarial network through large language model." *Comput. Struct. Biotechnol. J.* 21, 5839, 5850. doi:10.1016/j.csbj.2023.11.041

Zhong, X., and D'Antona, A. M. (2021). "Recent advances in the molecular design and applications of multispecific biotherapeutics." *MDPI* 10.2. doi:10.3390/antib10020013>