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Computational Free Energy Methods for TCR–pHLA Binding Affinity Prediction and their Implications for Cancer Immunotherapy

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Abstract

T cell receptor (TCR)–peptide-human leukocyte antigen (pHLA) interactions are central to adaptive immunity and represent a critical determinant of the efficacy and safety of cancer immunotherapies, including adoptive cell transfer, neoantigen vaccines, and engineered TCR-T cell therapies. Despite decades of structural and biochemical research, the accurate computational prediction of TCR–pHLA binding affinity remains one of the most challenging problems at the intersection of biophysics and immunology. This review surveys the landscape of free energy calculation methods including molecular mechanics Poisson-Boltzmann/Generalized Born Surface Area (MM-PBSA/GBSA), alchemical free energy perturbation (FEP), enhanced sampling molecular dynamics, and emerging machine-learning-augmented approaches as applied to the TCR–pHLA binding problem. We examine what structural and thermodynamic features make this protein–protein interface uniquely difficult to model, assess the accuracy and scalability of current methods against experimental benchmarks, and critically evaluate how TCR cross-reactivity compounds the prediction challenge. Finally, we discuss what advances in computational free energy prediction would unlock for the design of safer and more effective TCR-based therapies and highlight the most productive directions for future methodological development.

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Introduction

The adaptive immune system's ability to distinguish healthy from malignant cells depends critically on the molecular interaction between T cell receptors (TCRs) and peptide-major histocompatibility complex (pMHC) molecules termed pHLA in the human context. When a TCR engages a cognate pHLA complex with sufficient affinity and duration, it triggers a cascade of intracellular signaling events that can lead to cytotoxic killing of the target cell. The selectivity of this interaction has made TCR-based therapies one of the most promising frontiers in cancer immunology: if one can identify or engineer a TCR that binds a tumor-specific pHLA complex with high affinity and specificity, it becomes possible to redirect cytotoxic T cells to selectively destroy cancer cells [1].

The past decade has seen remarkable progress in TCR-based immunotherapies. Adoptive cell transfer using tumor-infiltrating lymphocytes (TILs) has demonstrated durable regressions in melanoma, and engineered TCR-T cell therapies targeting cancer-testis antigens and neoantigens are in active clinical development [2]. Yet the field faces a fundamental bottleneck: identifying and validating a TCR that binds a given tumor antigen with appropriate affinity and specificity is extraordinarily resource-intensive using experimental methods alone. Computational methods offer a potential path through this bottleneck. If one could reliably calculate the binding free energy (ΔG) of a TCR–pHLA interaction from structure, the in silico screening of candidate TCRs would become far more tractable.

However, accurate free energy prediction for TCR–pHLA complexes remains elusive. The TCR–pHLA interface presents a unique combination of challenges: it is a large protein–protein interface rather than a small-molecule binding pocket; the binding affinity is intrinsically weak (Kd typically 1–100 μM); the interaction involves extensive conformational flexibility in the TCR complementarity-determining region (CDR) loops; and TCRs are inherently cross-reactive, capable of recognizing millions of distinct peptide–HLA combinations [3, 4]. This review synthesizes the current state of computational free energy methods as applied to TCR–pHLA binding, evaluating their accuracy, scalability, and clinical relevance.

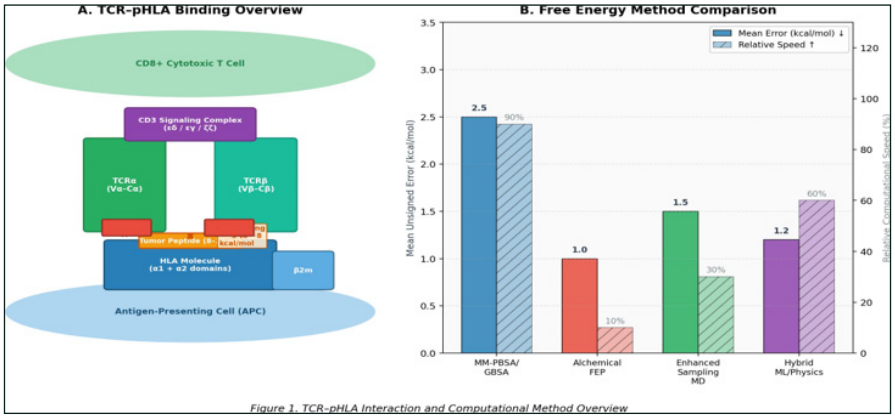

Figure 1. TCR-pHLA Interaction and Computational Method Overview

Figure 1: (A) Schematic of the TCR–pHLA complex showing the TCRα (green) and TCRβ (teal) chains with CDR loops (red) engaging the peptide (orange) in the HLA groove (blue), with the CD3 signaling complex above. (B) Comparison of free energy methods by mean unsigned error (kcal/mol; lower is better) and relative computational speed. MM-PBSA/GBSA offers speed but lower accuracy; FEP is more accurate but computationally expensive; hybrid ML/physics approaches are emerging as a middle ground. Note. Created with Claude 4.5 Sonnet (Anthropic, 2026) using custom visual scripting.

Structural and Thermodynamic Biology of the TCR–pHLA Interface

TCR Architecture and CDR Loops

The T cell receptor is a disulfide-linked heterodimer composed of α and β chains, each containing variable (V) and constant (C) domains. The variable domains present six CDR loops CDR1α, CDR2α, CDR3α and CDR1β, CDR2β, CDR3β that collectively form the binding interface with the pHLA complex [5]. The CDR3 loops are the most

variable, generated by VDJ recombination producing an estimated 10^{15} to 10^{20} distinct TCR sequences in the human repertoire [6]. CDR1 and CDR2 loops make the majority of contacts with the HLA alpha-helices, while CDR3 loops primarily contact the bound peptide. Crystal structures deposited in the Protein Data Bank (PDB) reveal that the interface buries approximately 1,200–2,000 Å² of solvent-accessible surface area and is stabilized by hydrogen bonds, salt bridges, and hydrophobic contacts.

pHLA Presentation and Peptide Diversity

Human leukocyte antigen (HLA) molecules are encoded by the most polymorphic gene loci in the human genome: over 30,000 HLA alleles have been catalogued for class I and class II molecules combined. Class I HLA molecules (HLA-A, -B, -C) present peptides of 8–11 amino acids derived from intracellular proteins and are recognized by CD8+ cytotoxic T cells the primary effectors of anti-tumor immunity. Each HLA allele has a distinct peptide-binding groove geometry that accommodates only a subset of the peptidome, defined by anchor positions at which particular amino acid side chains are preferred. Tumor-specific neoantigens arise from somatic mutations in cancer cells and, being absent from the germline, are not subject to central tolerance, making them attractive targets for T cell-based immunotherapy [7].

Thermodynamic Features of TCR–pHLA Binding

TCR–pHLA binding is characterized by several thermodynamic features that distinguish it from the protein–ligand interactions for which most computational methods were developed. First, affinities are weak: typical Kd values range from approximately 1 to 300 μM, compared to the nanomolar affinities of therapeutic antibodies. This weak affinity prevents constitutive T cell activation but means free energy differences between binding and non-binding interactions can be smaller than the error bars of many simulation methods [8]. Second, TCR–pHLA binding exhibits a characteristic mix of enthalpic and entropic contributions that varies substantially across pairs; many interactions involve enthalpy–entropy compensation that is difficult to capture without extensive sampling [9]. Third, conformational flexibility is computationally challenging: a 2022 study using microsecond-scale MD simulations found that TCR ligation reduced conformational entropy of the peptide-binding groove and altered hydrogen bond networks in ways not apparent from static crystal structures [10].

The Free Energy Prediction Problem

What ΔG Tells Us and Why It Matters

The binding free energy ΔG quantifies thermodynamic favorability of complex formation: $\Delta G = \Delta H - T\Delta S$, where ΔH is the enthalpy change and ΔS is the entropy change upon binding. For TCR–pHLA interactions, ΔG values typically fall in the range −5 to −8 kcal/mol. The relative binding free energy ΔΔG between two variants predicts how an amino acid change affects affinity, enabling computational mutagenesis and rational affinity maturation. The ability to compute ΔΔG accurately is directly actionable for therapeutic TCR engineering.

What Makes TCR–pHLA a Hard Case

Several properties of the TCR–pHLA system place it at the difficult end of the spectrum for free energy calculations. The large buried surface area means the system has many degrees of freedom that must be adequately sampled a challenge for methods relying on equilibrium MD, which struggles to sample rare conformational transitions on timescales accessible to conventional simulations. The weak binding affinity means the free energy signal is small relative to sampling noise. The CDR3 loop flexibility means that the unbound TCR adopts an ensemble of conformations in solution, not all of which are competent for pHLA binding, and sampling this ensemble in the unbound state is as important as sampling the bound complex [11]. Force field accuracy is another critical limitation: current biomolecular force fields (AMBER, CHARMM, OPLS) have systematic errors in the treatment of protein backbone and side-chain torsion potentials that accumulate over large interfaces.

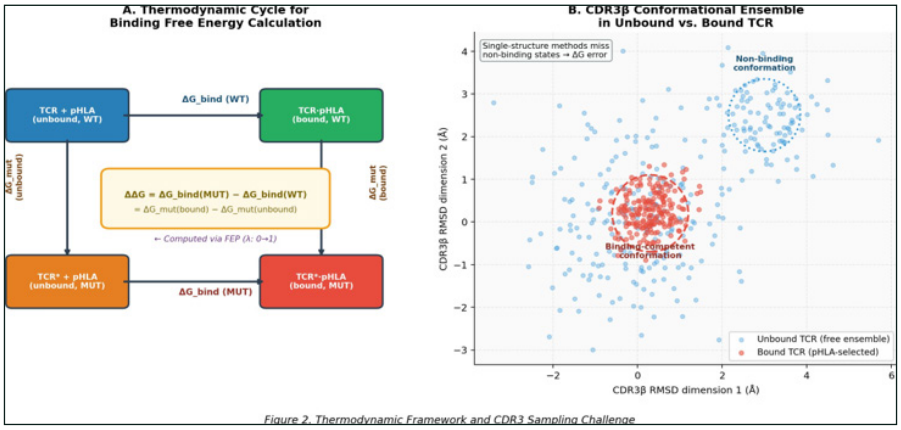

Figure 2: (A) Thermodynamic cycle underlying free energy perturbation (FEP) calculations for TCR variant ranking. ΔΔG is obtained from the difference in alchemical mutation free energies in the bound and unbound states, avoiding the need to directly simulate binding/unbinding. (B) Schematic CDR3β conformational ensemble from MD simulations. The unbound TCR samples a broad landscape including non-binding conformations (blue cluster, right), while the pHLA-bound TCR is restricted to a binding-competent cluster (red). Single-structure methods miss this diversity, leading to systematic ΔG errors. Note. Created with Claude 4.5 Sonnet (Anthropic, 2026) using custom visual scripting based on concepts from Fernández-Quintero et al., 2020, Frontiers in Immunology, and BMC Immunology [11].

MM-PBSA/GBSA: The Workhorse Method

Theoretical Basis

The molecular mechanics Poisson-Boltzmann/Generalized Born Surface Area (MM-PBSA/GBSA) approach is the most widely applied free energy method in biomolecular simulation, owing to its computational efficiency relative to rigorous alchemical methods. The binding free energy is estimated as: ΔG_bind = G_complex − G_receptor − G_ligand, where each term is decomposed into molecular mechanics energy, solvation free energy (electrostatic + nonpolar), and conformational entropy contributions. The electrostatic solvation term is calculated by solving the Poisson-Boltzmann (PB) equation or using the cheaper Generalized Born (GB) approximation; the nonpolar term is estimated from the solvent-accessible surface area (SASA). Conformational entropy is typically approximated via normal mode analysis or the interaction entropy (IE) method, which estimates entropy contributions from the fluctuations of the interaction energy during the MD trajectory [12, 13].

Applications to TCR–pHLA Systems

MM-PBSA/GBSA has been applied to several TCR–pHLA systems with mixed results. A landmark study by Crean et al. (2022) systematically evaluated MMPB/GBSA protocols for ranking binding affinities of engineered TCR variants targeting cancer-relevant pHLA complexes, including the NY-ESO-1 (1G4 TCR) and HTLV-1 Tax (A6 TCR) antigens. They found that MM-GBSA with entropy corrections outperformed simple MM-GBSA for variant sets with many mutations, achieving Spearman correlations of 0.6–0.7 with experimental affinity measurements using as few as 5–10 replicas of short (4 ns) MD simulations. Critically, performance was sensitive to the simulation protocol and no single approach worked well across all variant sets. A subsequent large-scale study applying MM-PBSA to 130 TCR–pHLA crystal structures found that while the method qualitatively distinguished high-affinity from low-affinity interactions, absolute errors in ΔG were typically 2–4 kcal/mol comparable to or larger than the energetic range of interest for cross-reactivity discrimination [14].

Limitations and Failure Modes

Several systematic limitations of MM-PBSA/GBSA in the TCR–pHLA context are well established. The implicit solvent approximation neglects the specific contributions of interfacial water molecules, which are known to be important for TCR specificity. The entropic term is a major source of uncertainty: for flexible systems like CDR3 loops, the configurational entropy change upon binding cannot be reliably captured by harmonic approximations.

The single-trajectory protocol introduces systematic errors when significant conformational reorganization occurs upon binding, as is common for CDR3 loops. Despite these limitations, MM-PBSA/GBSA remains valuable as a rapid screening tool to rank rather than predict absolute affinities, and best practices have been established in the literature [15].

Alchemical Free Energy Perturbation Methods

Theory and Thermodynamic Framework

Alchemical free energy perturbation (FEP) methods provide a more rigorous thermodynamic framework than MM-PBSA/GBSA at the cost of substantially greater computational expense. In FEP, the free energy difference between two states (e.g., wild-type and mutant TCR bound to pHLA) is computed by introducing a coupling parameter λ that transforms the Hamiltonian of one state into that of the other through a series of non-physical ("alchemical") intermediate states. The free energy difference is obtained by thermodynamic integration (TI) or by reweighting using the Bennett Acceptance Ratio (BAR) or multistate BAR (MBAR). Modern FEP implementations such as FEP+ (Schrödinger) combine these methods with enhanced sampling techniques and improved force fields to achieve sub-kcal/mol accuracy for many protein–small molecule binding problems [16].

Extension to Protein–Protein Interfaces

FEP methods were originally developed for protein–small molecule binding. Extension to protein–protein interfaces including TCR–pHLA introduces additional challenges: the "ligand" (e.g., a mutant TCR CDR3 loop or a variant peptide) is itself a large, flexible polypeptide with many internal degrees of freedom, making the alchemical transformation and sampling of intermediate states substantially more complex. A benchmark study by Sampson et al. (2024) applied FEP+ to 243 protein–protein complex mutations across 19 protein systems, achieving mean unsigned errors (MUEs) of ~1.0 kcal/mol and Pearson correlations of 0.7–0.8 with experimental ΔΔG values significantly better than MM-PBSA on the same dataset [17]. The authors developed an automated protocol for flagging probable outlier cases, particularly for charge-changing mutations, and applying empirical corrections representing a significant step toward reliable prospective use in protein design.

Limitations of FEP for TCR–pHLA

Despite their theoretical rigor, alchemical FEP methods face several limitations specific to the TCR–pHLA problem. The large interface and CDR3 loop flexibility mean that convergence requires very long simulations or sophisticated enhanced sampling methods. A typical relative FEP calculation for a protein–small molecule system might require 10–50 ns per λ window; for a protein–protein interface with flexible loops, 100–500 ns or more may be needed. FEP is also most accurate for small perturbations (e.g., single amino acid mutations between similar residues); large perturbations such as CDR3 loop insertions or deletions cannot be handled by standard protocols. Computational cost remains a practical barrier: a single relative FEP calculation for a protein–protein mutation requires on the order of 1,000–10,000 GPU-hours depending on system size and desired accuracy.

Enhanced Sampling Methods and AI-Augmented Approaches

Enhanced Sampling Molecular Dynamics

The convergence problem in TCR–pHLA free energy calculations has motivated the application of enhanced sampling methods. Replica exchange molecular dynamics (REMD) runs multiple copies (replicas) of the system at different temperatures, periodically swapping configurations between replicas to allow thermally activated barrier crossing. Metadynamics adds a history-dependent bias to the potential energy surface along collective variables (CVs) to discourage revisiting previously explored configurations, effectively flattening energy barriers. REST2 applies temperature-like scaling to a subset of the system (e.g., the CDR3 loops) rather than the entire system, reducing computational cost while focusing enhanced sampling where it is most needed.

These methods have been applied to characterize CDR3 loop conformational ensembles in the unbound state, which is a necessary prerequisite for accurate binding free energy calculations. A landmark 2025 study in Nature Communications demonstrated that dynamic allostery within the HLA peptide-binding groove motions that vary with peptide identity and are not apparent from static crystal structures can gate TCR binding through a conformational selection mechanism [18]. In this study, TCR discrimination between the PI3Kα neoantigen and its wild-type counterpart emerged from distinct motions

within the HLA-A3 groove that created a dynamic gate impeding TCR binding in the WT complex but not the neoantigen complex. This finding, accessible only through long-timescale or enhanced sampling MD, underscores that methods relying on a single crystal structure may systematically miss the contribution of dynamic gating to the binding free energy.

Machine Learning and AI Integration

The past five years have seen an explosion of ML approaches to TCR–pHLA binding prediction. Methods such as NetTCR-2.0, ERGO, and PanPep have demonstrated impressive performance, achieving AUC values of 0.8–0.9 for predicting whether a given TCR–peptide pair will bind [19]. However, these methods primarily predict binary binding or relative rank rather than absolute free energies, limiting their utility for quantitative affinity engineering. A more promising integration is the combination of ML-predicted structures with physics-based free energy calculations. AlphaFold3 (2024) made it feasible to generate structural models of TCR–pHLA complexes without experimental crystallography, and recent work combining AlphaFold3-generated structures with GROMACS MD simulations and MM-PBSA/GBSA has demonstrated that predicted structures can serve as viable inputs for free energy calculations [14]. ML approaches face a fundamental generalizability problem: training data is sparse and biased toward a small number of well-studied HLA alleles and peptide sequences, limiting reliability for novel TCR–pHLA pairs of clinical interest.

Cross-Reactivity as a Compounding Challenge

The Scope and Mechanics of TCR Cross-Reactivity

TCR cross-reactivity the ability of a single TCR to recognize multiple distinct pHLA complexes is an intrinsic property of the adaptive immune system, arising from the need for a fixed repertoire of ~10^7 to 10^8 clonotypes to protect against a virtually unlimited universe of pathogens. Early estimates suggested each TCR must recognize at least 10^6 distinct peptide–HLA combinations to provide adequate immune coverage, supported by experimental analyses [3, 4]. From the perspective of immunotherapy, cross-reactivity is a double-edged sword: it enables T cells to recognize related neoantigens across tumor heterogeneity, but it creates the risk of off-target toxicity if a therapeutic TCR cross-reacts with self-peptides presented in normal tissue.

Structural studies have revealed that TCR cross-reactivity operates through multiple mechanisms. In some cases, cross-reactive peptides share key anchor residues and present chemically similar molecular surfaces. In others, cross-reactivity is mediated by a "register shift"a binding-induced reorientation of the peptide within the HLA groove that creates a superficially similar interface from a chemically distinct peptide sequence [20]. More recently, Ma et al. (2025) demonstrated that dynamic allostery in the pHLA complex itself can enable neoantigen selectivity, with the TCR discriminating between a neoantigen and its wild-type counterpart through groove dynamics rather than direct contact differences illustrating that cross-reactivity and specificity are not always determined by static structural complementarity.

Implications for Free Energy Calculations

Cross-reactivity poses a specific and severe challenge for computational free energy methods. The energetic differences between a cognate and a cross-reactive pHLA are often small 1–2 kcal/mol or less—well within the error bars of most current methods. A method accurate to ±1.5 kcal/mol in absolute terms (a reasonable estimate for MM-PBSA on favorable systems) may simply be unable to distinguish a cross-reactive from a non-reactive interaction. For clinical applications where off-target cross-reactivity could cause serious toxicity as occurred in the MAGE-A3 trial where three patients experienced severe neurological toxicities attributed to TCR cross-reactivity with MAGE-A12 expressed in brain tissue, resulting in two deaths of this level of accuracy is insufficient [21].

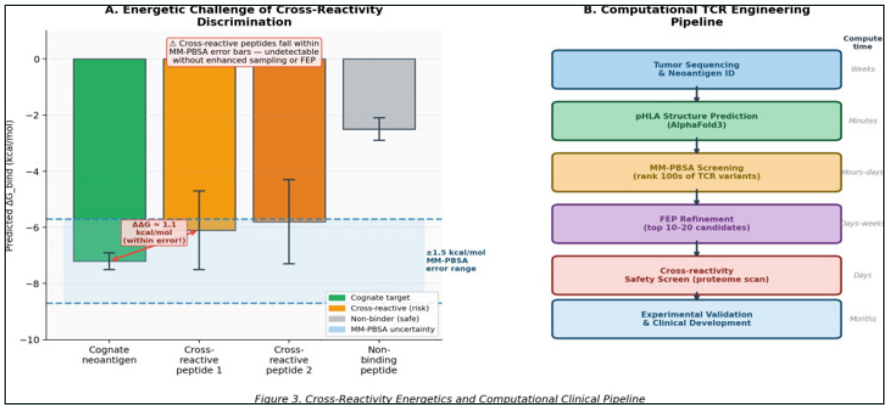

Figure 3. Cross-Reactivity Energetics and Computational Clinical Pipeline

Figure 3: (A) Energetic challenge of cross-reactivity discrimination. The cognate neoantigen (green) and two cross-reactive peptides (orange) differ in predicted ΔG by only 1–2 kcal/mol, falling within the ±1.5 kcal/mol uncertainty band of MM-PBSA (blue shading). Enhanced sampling or FEP methods are required to resolve such differences reliably. (B) Computational pipeline for therapeutic TCR engineering, from tumor sequencing and neoantigen identification through MM-PBSA screening, FEP refinement, cross-reactivity safety screening, and experimental validation. Note. Created with Claude 4.5 Sonnet (Anthropic, 2026) using custom visual scripting.

Clinical Implications and the Stakes of Better Prediction

The clinical motivation for accurate TCR–pHLA binding free energy prediction is compelling. The process of identifying a patient-specific neoantigen, screening T cell repertoires for reactive clones, sequencing and expressing the cognate TCR, and validating its specificity and safety profile currently requires months of laboratory work and significant cost [2]. Three specific clinical applications would be most directly enabled by improved prediction accuracy. First, TCR affinity maturation: engineering TCRs with higher affinity for a target pHLA complex would improve T cell avidity and therapeutic potency. Computational ΔΔG calculations that accurately predict the affinity effects of single amino acid mutations in CDR3 loops would allow rational, structure-guided mutagenesis rather than costly random mutagenesis and high-throughput screening. Second, cross-reactivity prediction and safety screening: reliable identification of potential off-target pHLA complexes that a candidate therapeutic TCR might recognize is critical for patient safety and cannot be adequately achieved with current methods for near-cognate peptides. Third, neoantigen prioritization: free energy-based descriptors derived from MD simulations may add discriminative power beyond what is captured by sequence-based machine learning models alone [7].

The consequences of insufficient cross-reactivity screening are well-documented. In the MAGE-A3 TCR-T cell trial, unexpected cardiac and neurological toxicities occurred in three patients, later attributed to TCR cross-reactivity with MAGE-A12 expressed in brain tissue, resulting in two patient deaths [21]. Better computational tools would not have eliminated the need for experimental safety testing but could have flagged this cross-reactive interaction at an earlier stage, potentially preventing patient harm. This example underscores that the stakes of improved prediction are not merely academic.

Future Directions and Methodological Recommendations

Based on this review, we identify the following as the most productive directions for future methodological development.

Force Field Improvement. Systematic errors in biomolecular force fields particularly in the treatment of protein backbone torsion potentials and charged amino acid interactions are a root cause of inaccuracy across all physics-based methods. Ongoing efforts to develop polarizable force fields and to use quantum mechanical calculations to re-parameterize classical force fields for challenging interface chemistries are directly relevant to the TCR–pHLA problem and merit continued investment.

Enhanced Sampling as Standard Practice. The conformational flexibility of TCR CDR3 loops means that conventional MD starting from a single crystal structure will systematically underestimate the conformational ensemble relevant to binding. Methods such as REST2 or metadynamics applied to CDR3 loops should be incorporated as standard components of TCR–pHLA free energy pipelines [11]. The additional computational cost is justifiable given the qualitative improvement in sampling accuracy.

Integration of AlphaFold3 Predictions with Free Energy Calculations. The availability of high-quality structural models from AlphaFold3 eliminates the crystallographic bottleneck for free energy calculations of TCR–pHLA pairs without solved structures. Rigorous benchmarking of AF3-seeded versus crystal structure-seeded free energy calculations across a diverse set of TCR–pHLA systems would establish the reliability of this approach and identify its failure modes.

Curated Benchmark Datasets. The field currently lacks a comprehensive, curated benchmark dataset of experimentally measured TCR–pHLA binding affinities spanning diverse HLA alleles, peptide sequences, and TCR frameworks. Such a dataset analogous to FEP benchmark sets used in drug discovery would enable rigorous, reproducible evaluation of new computational methods and accelerate identification of best practices.

Hybrid Physics/ML Approaches. The complementary strengths of physics-based and machine learning methods suggest that hybrid approaches in which ML models correct systematic errors in physics-based calculations or prioritize candidates for more expensive free energy calculations will outperform either approach in isolation. Developing and benchmarking such hybrid architectures for TCR–pHLA applications is a high-priority research direction, particularly as equivariant neural networks and protein language models continue to mature.

Conclusion

The accurate computational prediction of TCR–pHLA binding free energies remains one of the most challenging unsolved problems at the interface of computational biophysics and cancer immunology. The TCR–pHLA system combines a large, flexible protein–protein interface with intrinsically weak binding affinities, conformational dynamics essential to specificity, and a pervasive cross-reactivity that makes small energetic differences clinically significant. Current free energy methods—MM-PBSA/GBSA, alchemical FEP, and enhanced sampling MD each capture important aspects of the problem but none yet achieves the combination of accuracy, scalability, and generalizability required for routine clinical application.

Progress is tangible. Recent benchmark studies have demonstrated that FEP methods can achieve ~1.0 kcal/mol accuracy for protein–protein mutations under favorable conditions enhanced sampling methods have revealed dynamic binding mechanisms invisible to static structure-based approaches and integration with AlphaFold3-predicted structures is beginning to eliminate the crystallographic bottleneck [17, 18]. The clinical stakes are high and well-defined: better free energy prediction would accelerate TCR affinity maturation, improve neoantigen prioritization, and provide earlier warning of potential off-target cross-reactivity each addressing a current rate-limiting step in TCR-based cancer immunotherapy. Achieving this goal will require coordinated investment in force field development, enhanced sampling methods, benchmark dataset generation, and hybrid physics/ML architectures. The convergence of increasing computational power, improving structural prediction tools, and maturing free energy algorithms suggests that meaningful advances are achievable within the near term advances that could improve the safety and efficacy of the next generation of cellular cancer therapies.

Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work the author used Claude (Anthropic) to assist with manuscript drafting, structural organization, and language refinement. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published work.

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