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Letter to Editor

OXFORD

Re: Qi et al. "A roadmap for T cell receptor–peptide–MHC binding prediction by machine learning: glimpse and foresight" (*Briefings in Bioinformatics*, 2025)

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The authors are interested in developing and applying experimental and dry lab prediction tools to identify unknown ligands of any T cell receptor (TCR).

Dear Editors,

We read the roadmap article by Qi *et al.* with great interest [1]. The authors provide a broad overview of the relevant biological principles, data modalities, and machine learning approaches for TCR-pMHC binding prediction. Their discussion of data quality, encoding strategies, and model generalization challenges, as illustrated in their conceptual figures and methodological summaries, offers a helpful entry point for researchers entering this rapidly expanding field. We appreciate the considerable effort required to compile and synthesize such diverse material.

After carefully studying the review, we would like to provide more context to expand the scope of the article. Many of the limitations outlined by Qi *et al.*, including data imbalance, peptide overlap, heterogeneous assay conditions, and challenges in generalizing to unseen peptides, have been demonstrated in previous systematic benchmarking studies. Studying this earlier body of work can help readers understand the consistency with which these limitations have been identified in independent analyses. For instance, Grazioli *et al.* demonstrated that state-of-the-art deep learning models struggle to generalize to unseen peptides despite their strong performance on overlapping datasets [2]. This study demonstrated that performance is often driven by dataset structure rather than biological features. Similarly, Tippalagama *et al.* reviewed antigen-specificity measurement techniques and highlighted substantial assay-dependent variability and noise as factors that directly influence the downstream reliability of prediction models [3]. Most directly relevant to the roadmap proposed by Qi *et al.*, our work by Deng and Ly *et al.* conducted a large-scale benchmarking study of multiple modern prediction models and dataset variants [4]. We observed that all models experienced severe performance degradation under strict, unseen peptide evaluation, and that predictive behavior depended strongly on dataset composition, probably mainly driven by a few abundant peptides. We also addressed two general biases in the data used for predicting TCR-pMHC binding: First, the abundance of a few peptides, and second, the imbalance of peptide origin. More than half of all peptides in the dataset originated from studies about the common flu or SARS-CoV-2. These findings parallel the generalization challenges described qualitatively in the review. Finally, in complementary considerations to those raised by Qi *et al.*, McMaster *et al.* provided a structural perspective on why predicting TCR specificity remains inherently difficult, emphasizing $\alpha\beta$-pairing, conformational dynamics, and cross-reactivity [5].

Additionally, we would like to provide clearer direction for future progress. Recent benchmarking work has revealed several consistent themes: the necessity of well-controlled, balanced datasets; improved strategies to mitigate donor and peptide biases; the explicit modeling of $\alpha\beta$ chain pairing and HLA context; the multimodal integration of structural and sequence information; and the development of more interpretable modeling frameworks capable of distinguishing biological determinants from data artifacts. Elaborating further on such actionable directions would increase the roadmap's practical value for the community. We offer these comments respectfully and in a constructive spirit. Qi *et al.* provide a timely and informative synthesis. Acknowledging earlier benchmarking literature should strengthen the continuity of the field's conceptual development, in our view. We hope these remarks contribute to a clearer understanding of the challenges and opportunities inherent in TCR–pMHC predictive modeling.

Sincerely,

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Key Points

- Earlier benchmarking studies have highlighted the main limitations of current TCR–pMHC prediction approaches.
- Evidence from independent analyses shows that current model performance is strongly shaped by underlying dataset biases, underscoring the need for high-quality, balanced training data.
- Further elaboration on actionable next steps, including improved data curation, bias mitigation, and multimodal modeling, should enhance the current roadmap's practical utility for the field.

Conflict of interest

None declared.

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None declared.

Data availability

None declared.

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