Structure-based modeling of peptide/MHC-I complexes

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Introduction

Figure 1: The antigen processing pathway and an example of a peptide/MHC-I complex (A*24:02 bound to QFKDNVILL)
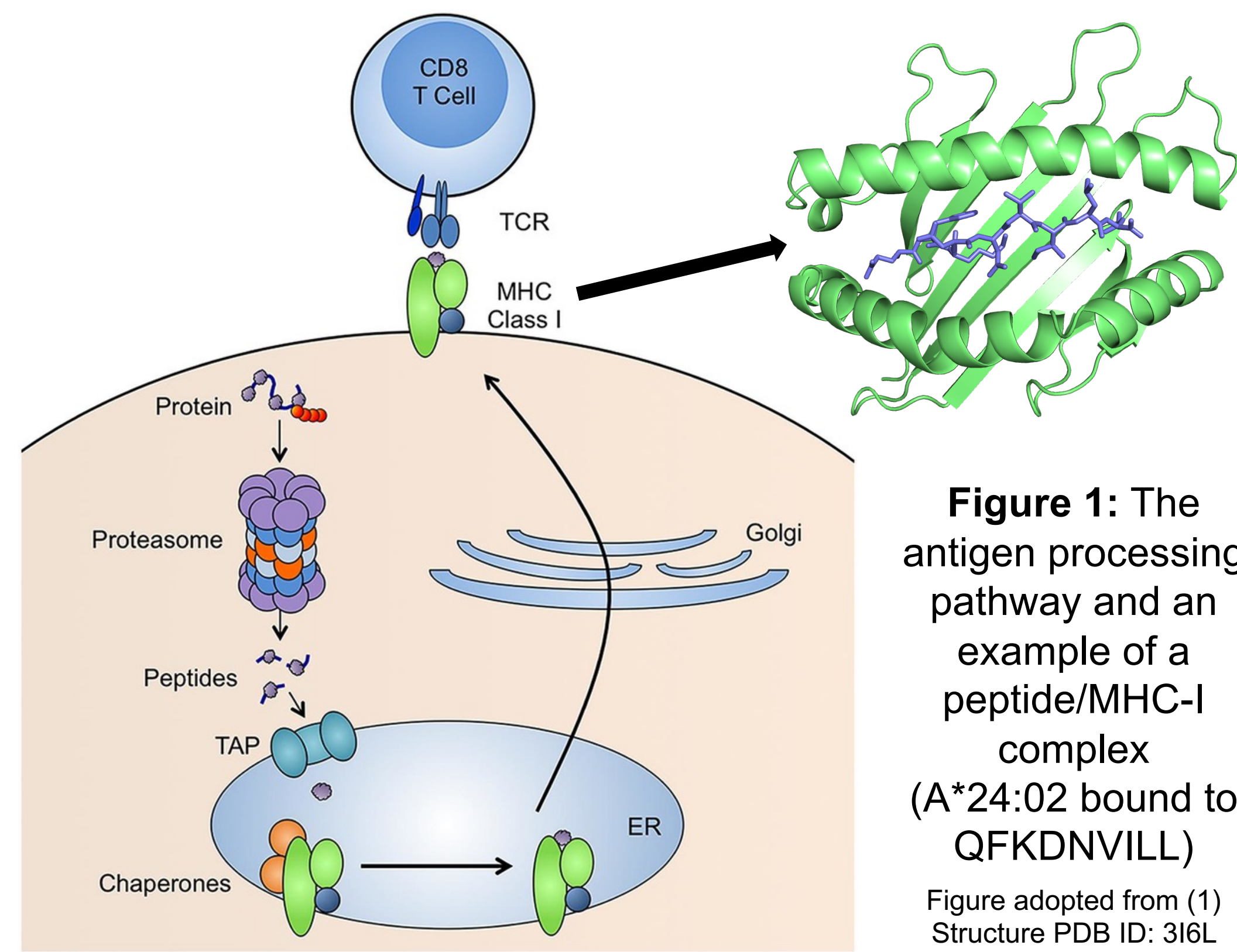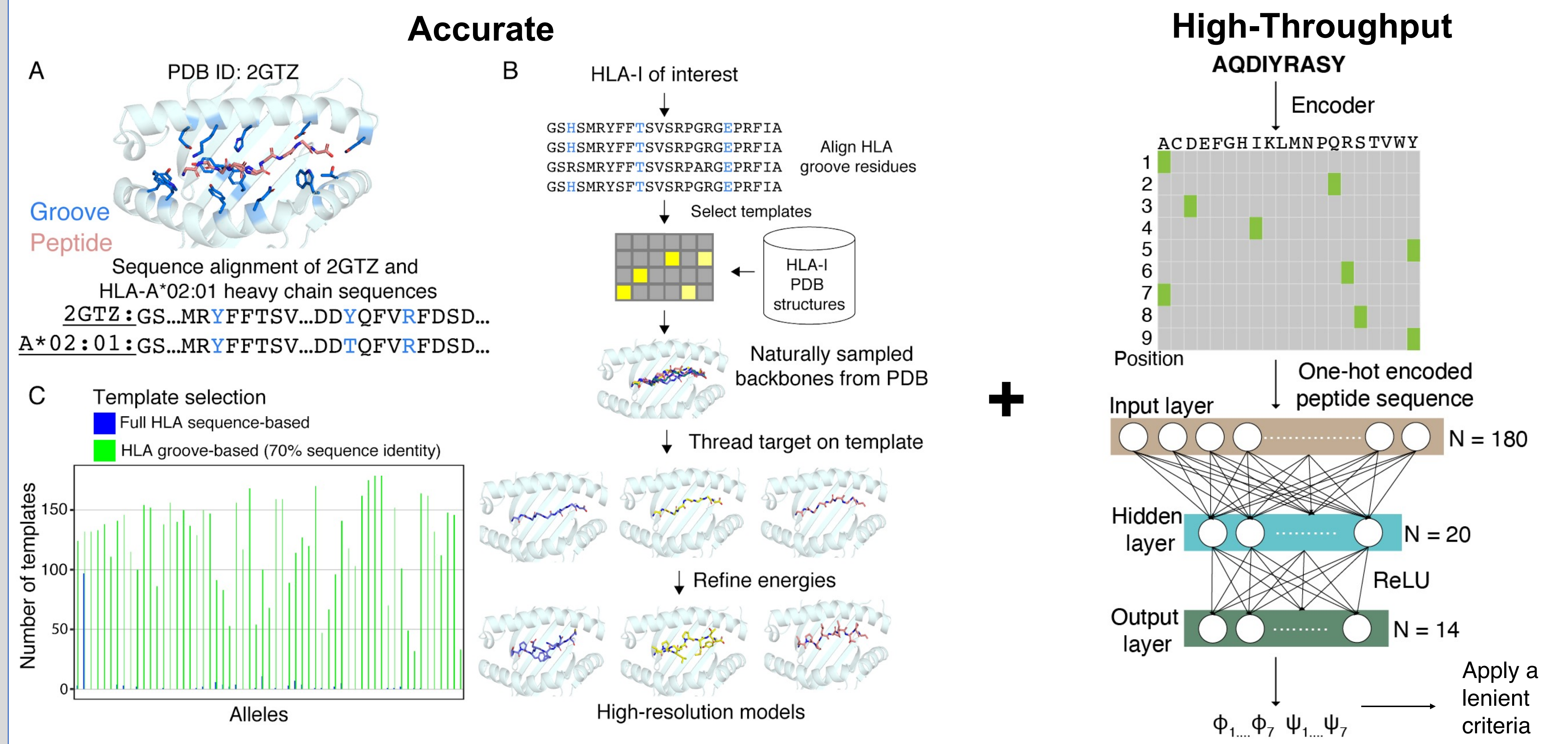
Figure adopted from (1) Structure PDB ID: 3I6L

- In this work, we present *RosettaMHC*, a peptide/MHC-I homology modeling tool which utilizes structural templates derived from the PDB using MHC groove sequence identity and peptide dihedral angle similarity

Method

### Accurate

High-Throughput

Results

Discussion

- Multi-template modeling allows for sampling of natural and diverse peptide backbones for underrepresented alleles in the PDB
- A feed forward neural network was used as a coarse-grain classifier which reduced a number of incorrect templates for multi-template modeling.
- On average, the number of templates decreases by 56% across 41 alleles displaying 214 peptides in the PDB while maintaining sub-angstrom accuracy among the top five best scoring structures for 89% and top scoring models for 68% of the peptides.
- *RosettaMHC* modeled sub-angstrom structures for 6 out of 7 SARS-CoV-2 peptides in the top five best scoring templates

Conclusions

- *RosettaMHC* is a pan-allelic comparative modeling method that can predict structures of pMHC complexes with sub-angstrom accuracy
- As more pMHC crystal structures become available, the accuracy of our method is expected to increase
- Since *RosettaMHC* is accurate and high-throughput, it is highly applicable for research of peptide-mediated immune response
- In the future, we can use HLAs from other vertebrates to train the neural network and expand the template set
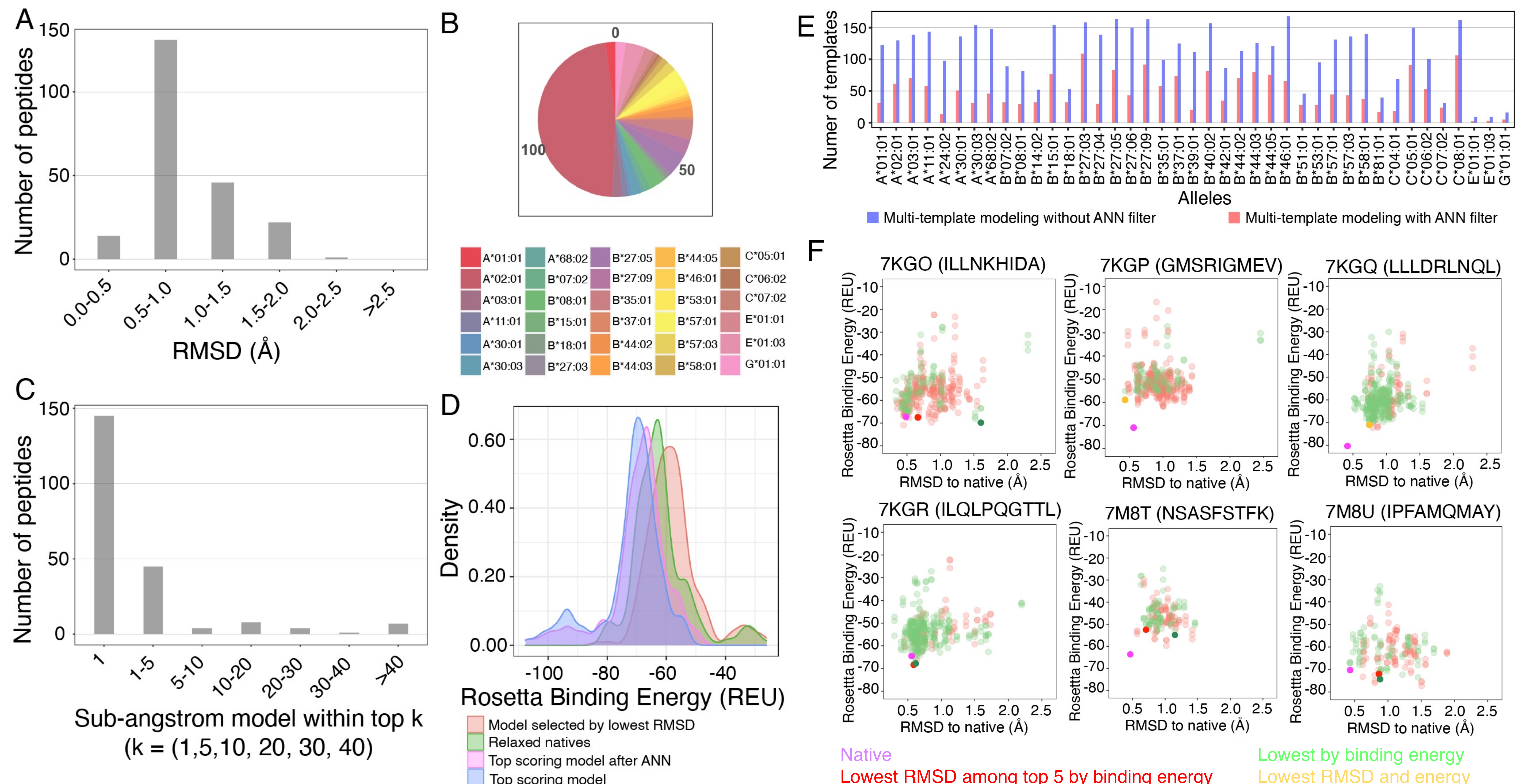
Acknowledgements

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