Structure-based selection of tumor-antigens for T-cell based immunotherapy

Dinler Amaral Antunes

Postdoctoral Research Associate

Rice University

Kavraki Lab at Rice University
Lizée Lab at UT M.D. Anderson

Houston/TX

RICE

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Focus on structural prediction

- **Our Project:**
  Structure-based selection of tumor-antigens for T-cell based immunotherapy

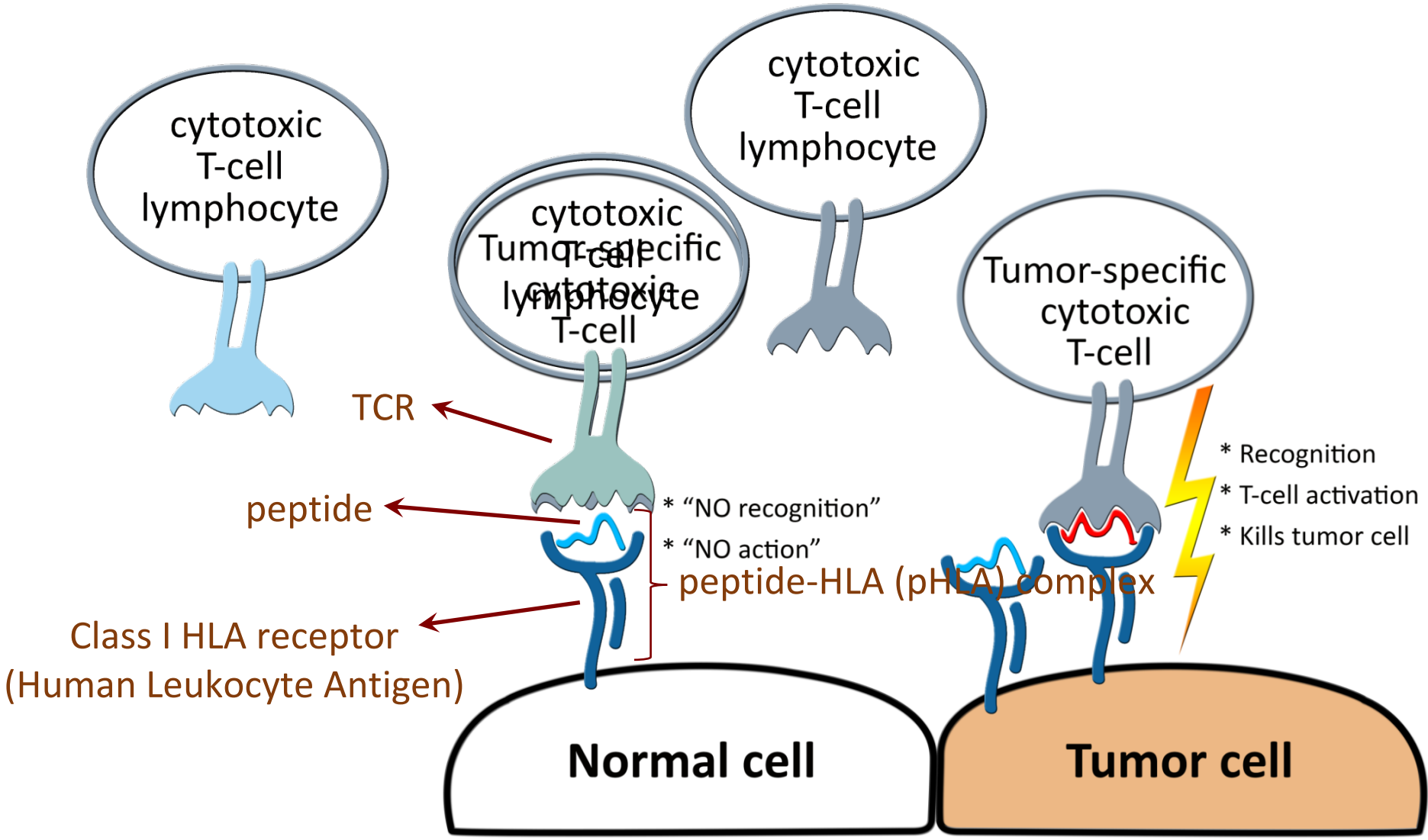
  * Start: Nov. 2016
  * PIs: Lydia Kavraki (Rice University)
    Gregory Lizée (M.D. Anderson)

- **Today's talk:** general structural prediction of peptide-HLA complexes

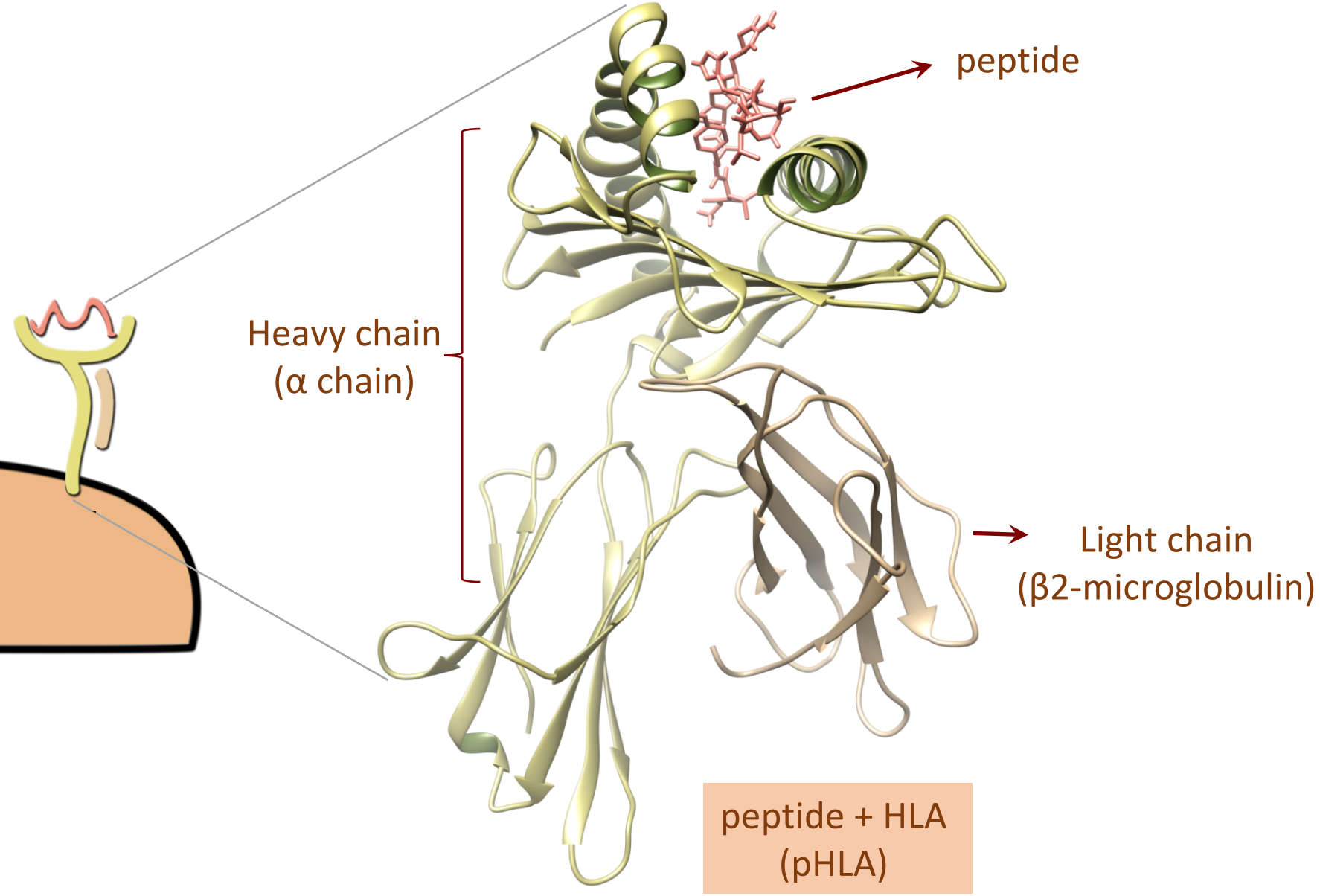
  * Cellular immunity to cancer
  * Proof of concept study
  * Application for immunotherapy
  * Our first contribution: DINC 2.0

Cellular immunity to cancer

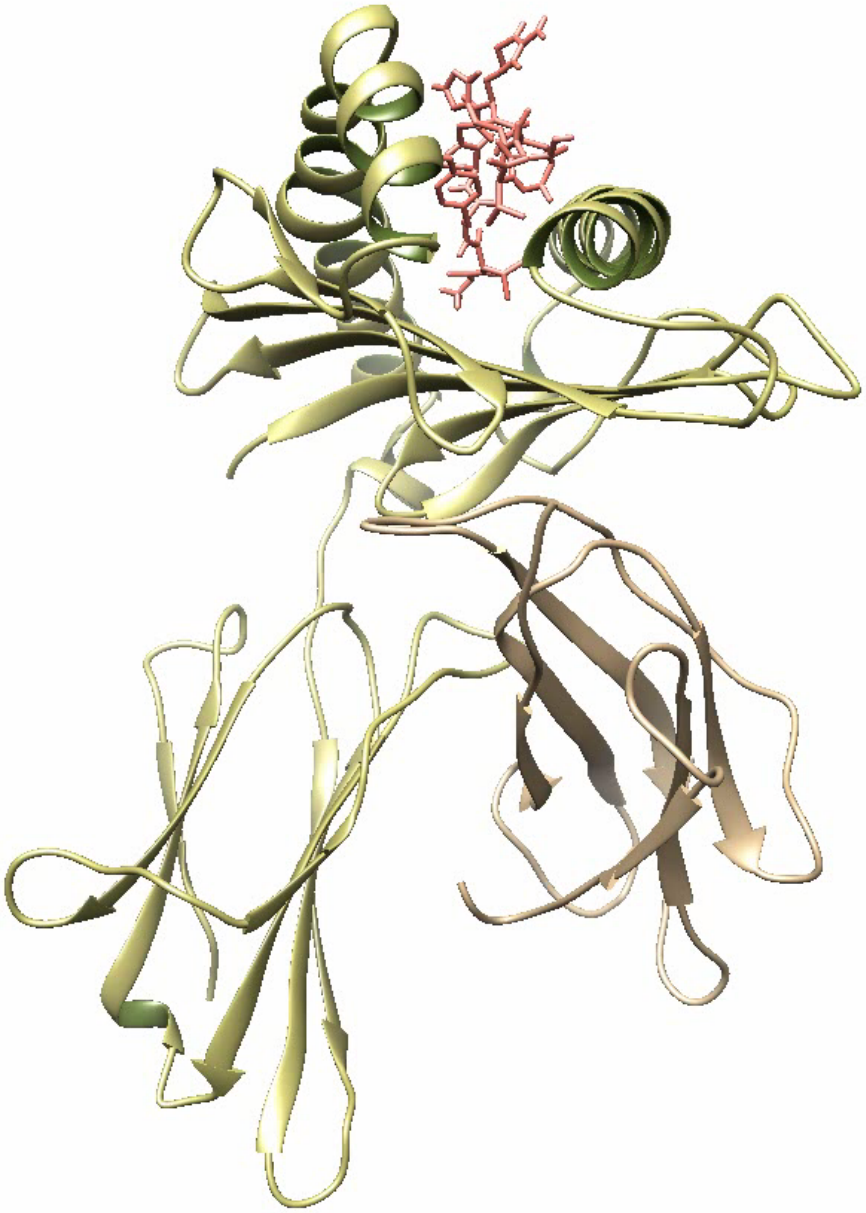
- Intracellular peptides are displayed at the cell surface by HLA receptors



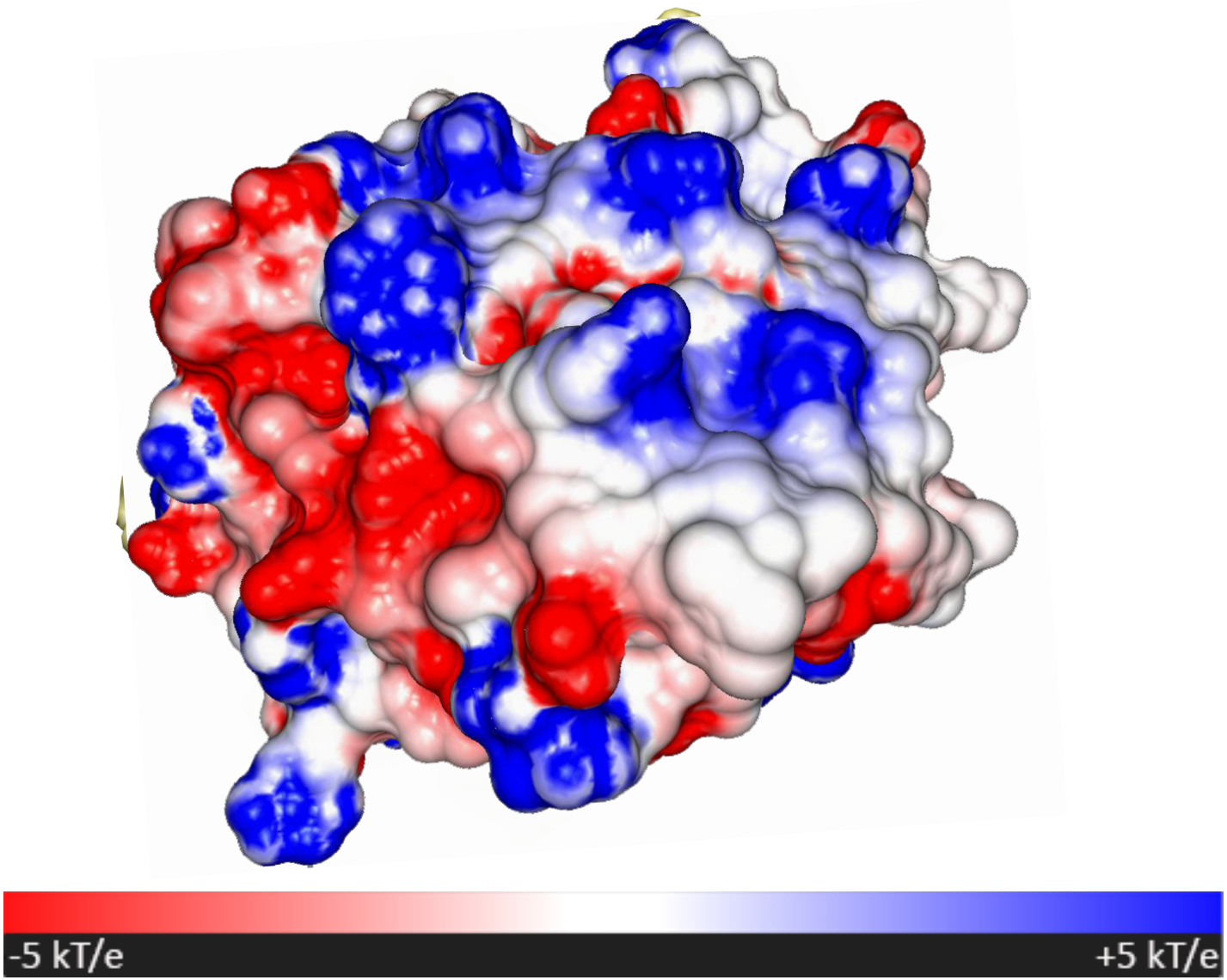
Structure of the pHLA complex (front view)



Structure of the pHLA complex

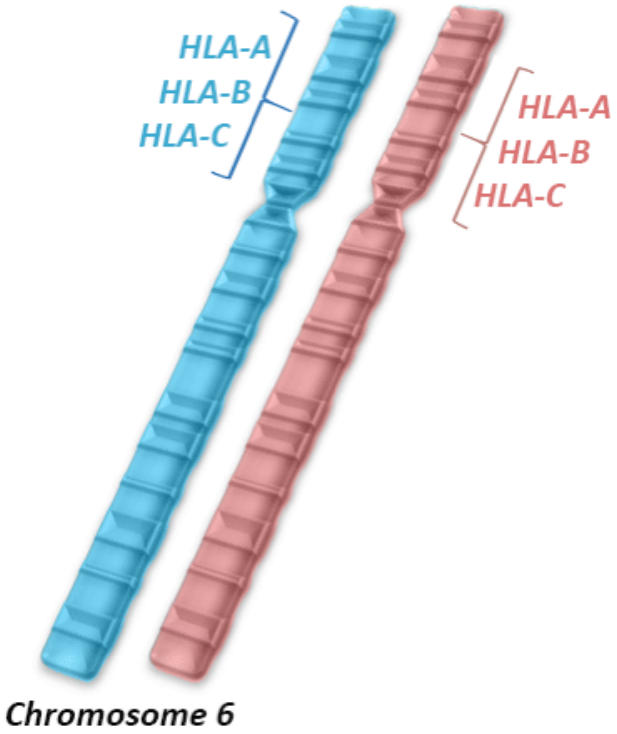


Structure of the pHLA complex (top view)

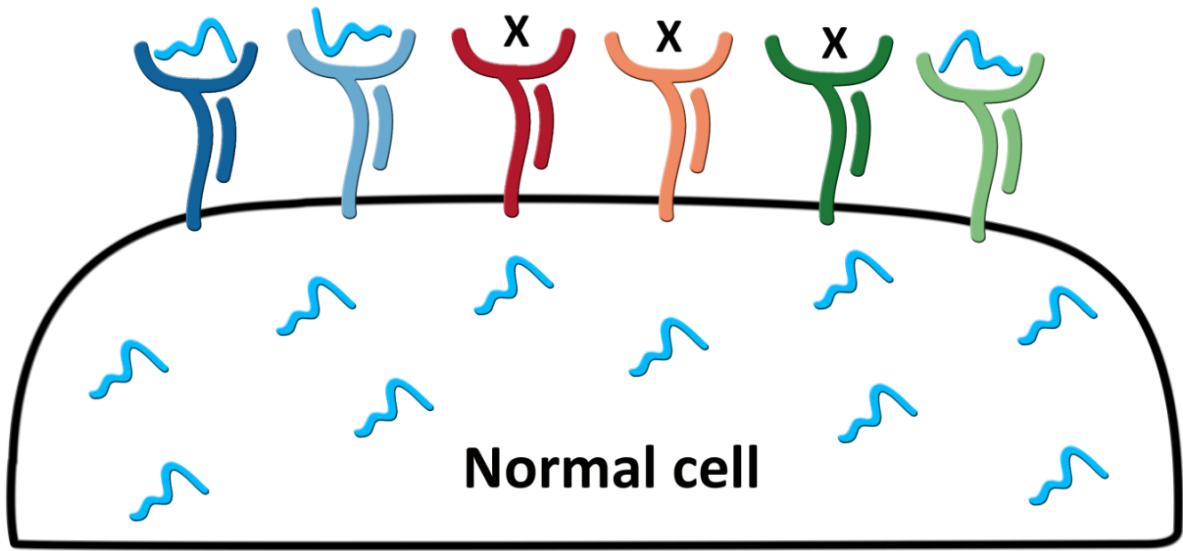


HLA diversity

More than 10,000 known alleles of class I HLAs in the human population!!!



Different HLAs display different pools of peptides



Need for personalized approaches

More than 10,000 known alleles of class I HLAs in the human population!!!

tumor-derived peptide

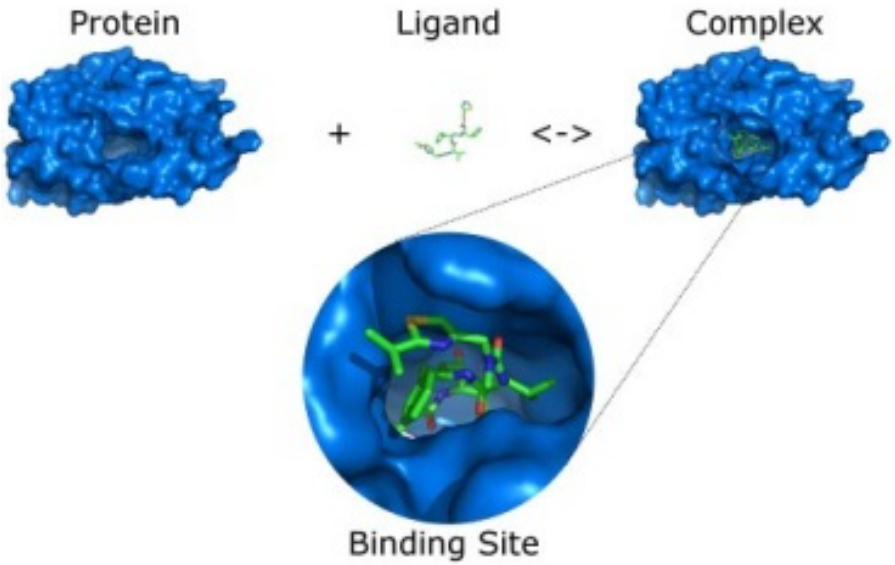
patient-specific HLA

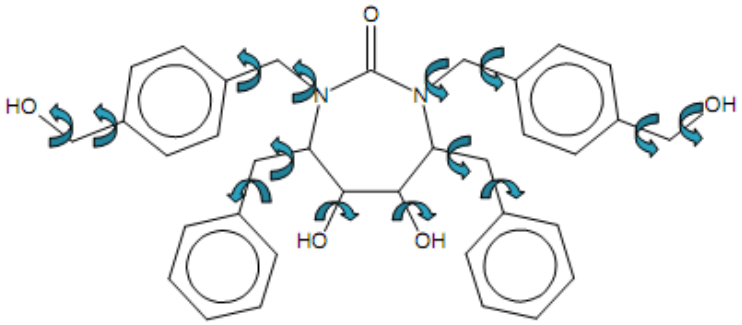
T-cell-based Immunotherapy requires
personalized analyses of peptide-HLA complexes

The Problem

Perform accurate structural prediction of the binding modes of tumor-derived peptides to patient-specific HLA molecules, using computational methods

Molecular Docking





- Rotation & Translation
- Internal Degrees of Freedom (DoFs)

- Molecular Docking Applications:
  * Binding mode prediction/**geometry Optimization**
  * Structure-based **virtual screening** of potential binders

Drug-like ligands

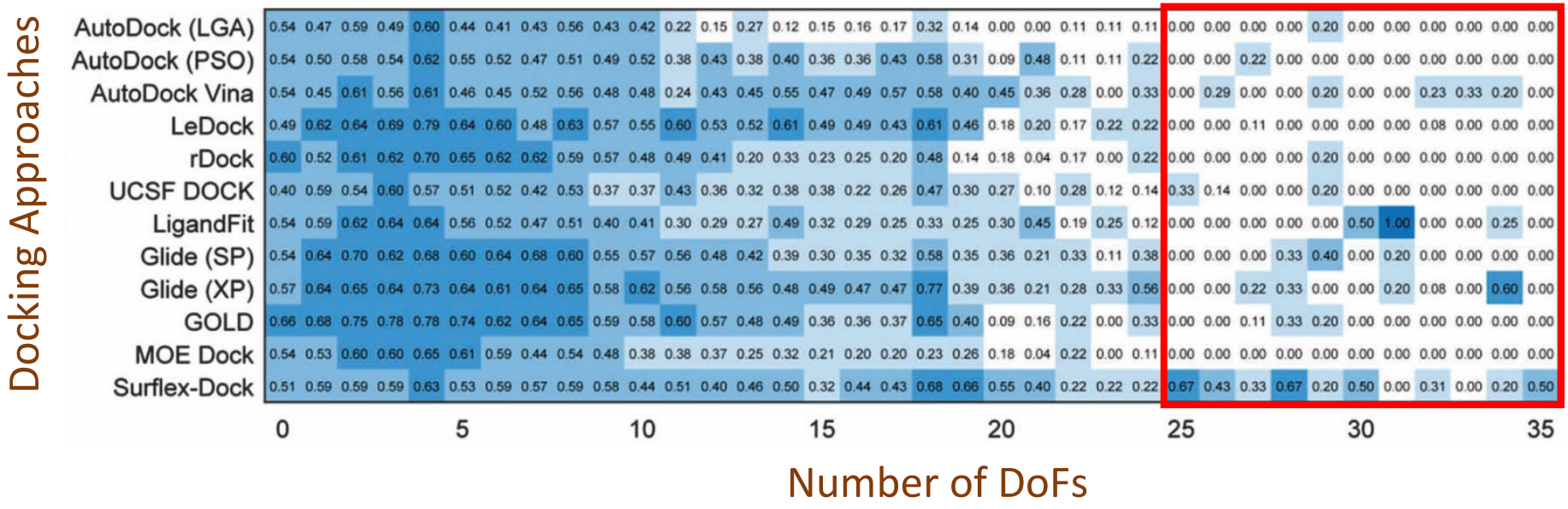
DoFs.: Up to 10 DoFs

The open challenge of docking large ligands

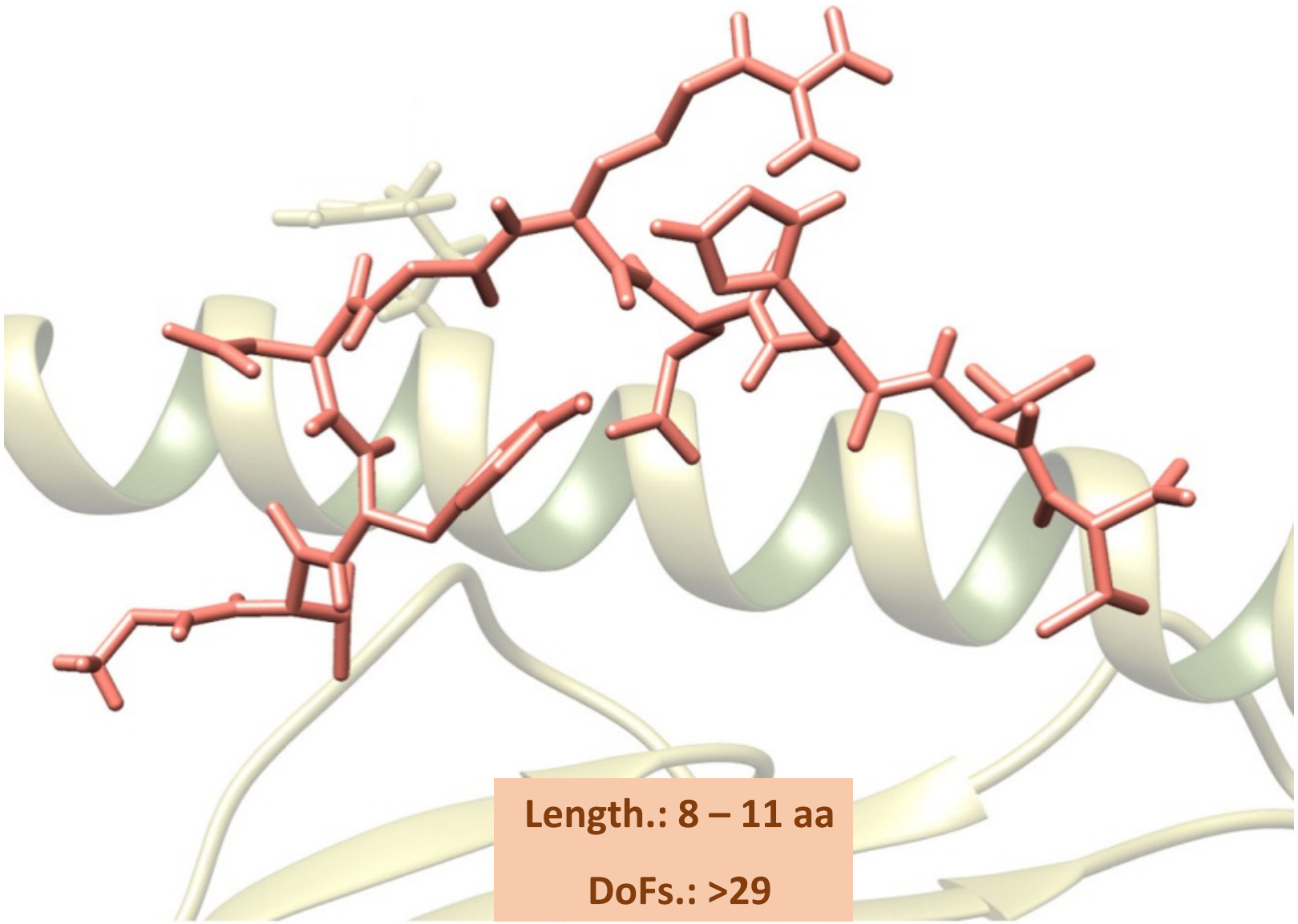
Comprehensive evaluation of ten docking programs on a diverse set of protein–ligand complexes: the prediction accuracy of sampling power and scoring power†

Zhe Wang,[a] Huiyong Sun,[a] Xiaojun Yao,[b] Dan Li,[a] Lei Xu,[c] Youyong Li,[d] Sheng Tian[d] and Tingjun Hou*[ae]

Cite this: *Phys. Chem. Chem. Phys.*, 2016, **18**, 12964



HLA receptors bind large peptide ligands



Docking-based prediction of pHLA complexes

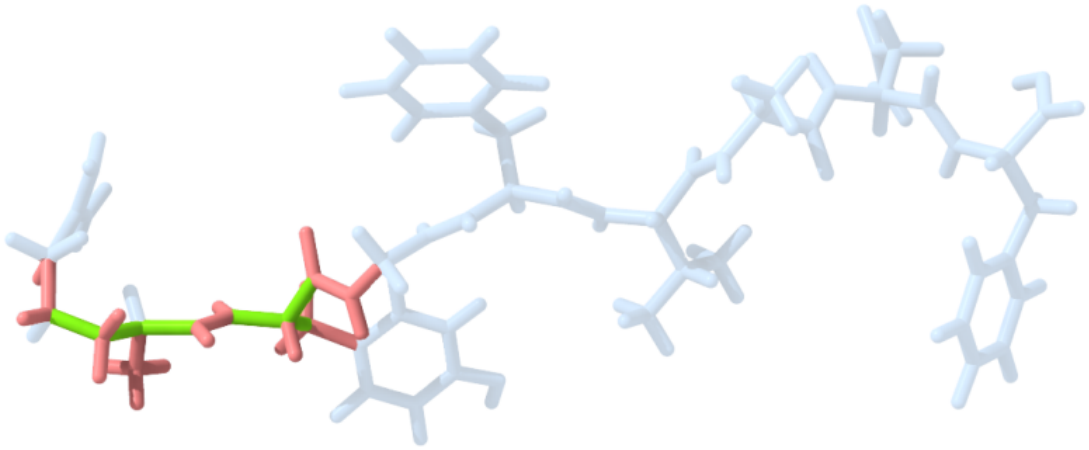
* Tong *et al.*, 2004.	ICM + loop closure
* Antes *et al.*, 2004.	*DynaPred*
* Bordner *et al.*, 2006.	ICM + monte carlo
* Todman *et al.*, 2007.	*MHCSim* (*crystal template*)
* Antunes *et al.*, 2010.	*D1-EM-D2* (*crystal template*)
* Bordner *et al.*, 2010.	ICM + monte carlo + machine learning
* Khan *et al.*, 2010.	ICM + monte carlo + homology modeling
* Liu *et al.*, 2014.	*FlexPepDock* (*crystal template*)
* Rigo *et al.*, 2015.	*DockTope* (*crystal template*)

Ways to reduce dimensionality:

- Use of Ad hoc approaches
- Use of crystal templates
- Use of HLA-specific constraints

Limited to specific HLAs and requiring expert guided constraints

Docking INCrementally (DINC)



Atoms: 28

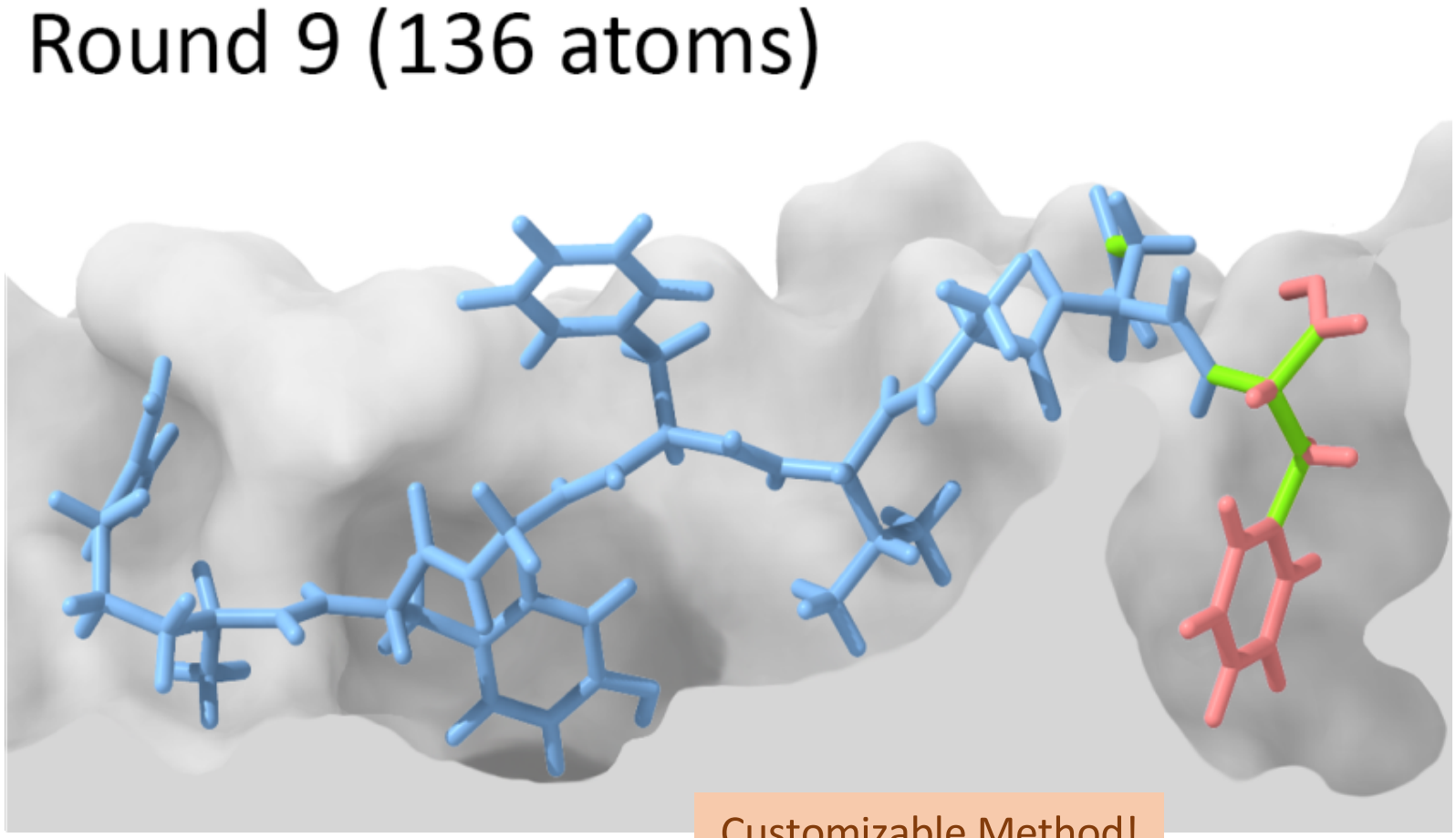
DoFs: 6

Length: 8 aa

Atoms: 136

DoFs: 30

Incremental docking of an 8-mer peptide



Customizable Method!

Evaluation against known crystal structures

Diverse dataset of 25 high resolution crystal structures of peptide-HLA complexes

Receptors:

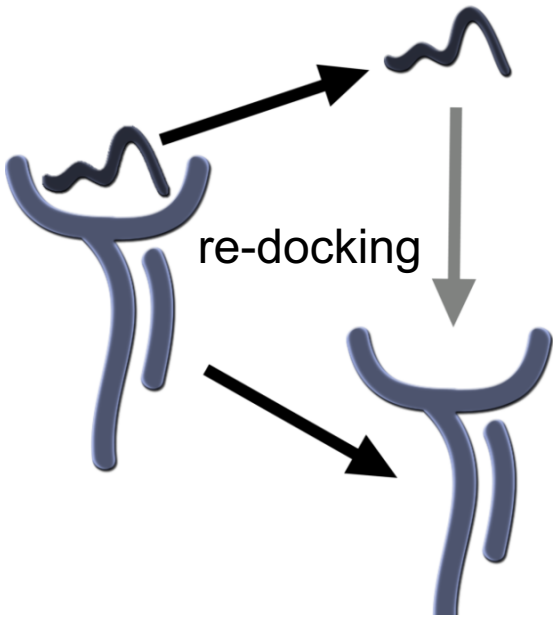
- HLA-A*01:01
- HLA-A*02:01
- HLA-A*11:01
- HLA-A*24:02
- HLA-B*35:01
- HLA-B*44:03
- HLA-B*51:01
- HLA-B*57:01
- HLA-B*57:03
- HLA-C*08:01

Peptide Lengths:

- 8-mers
- 9-mers
- 10-mers

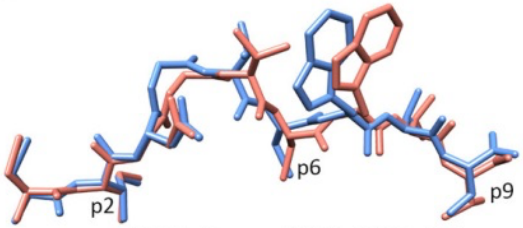
Peptide Sources:

- self
- virus
- tumor



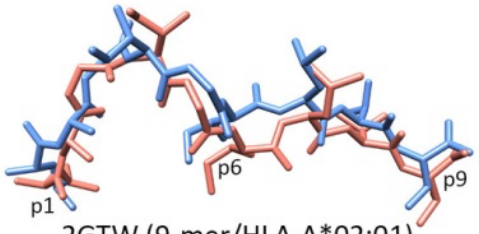
Reproduction of different binding modes

A



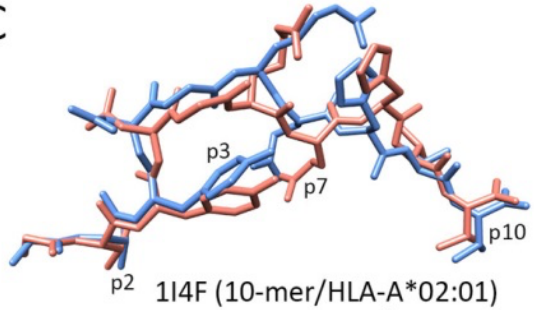
3MRG (9-mer/HLA-A*02:01)
LRMSD (Cα): 0.72 Å
RMSD (all): 1.38 Å

B



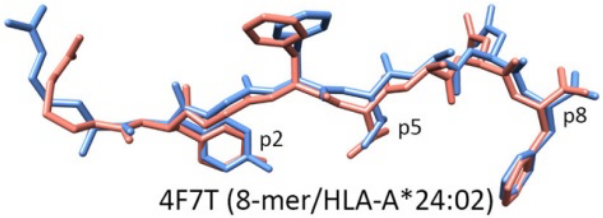
2GTW (9-mer/HLA-A*02:01)
LRMSD (Cα): 1 Å
RMSD (all): 1.84 Å

C



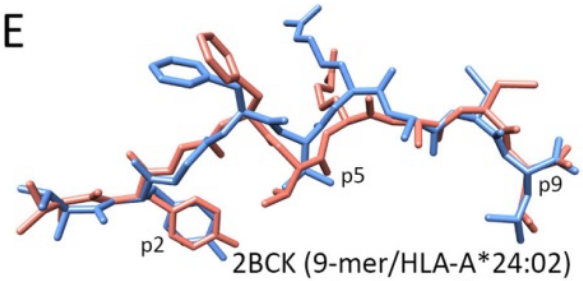
1I4F (10-mer/HLA-A*02:01)
LRMSD (Cα): 1.11 Å
RMSD (all): 2.01 Å

D



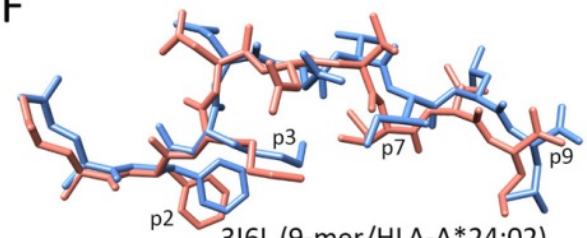
4F7T (8-mer/HLA-A*24:02)
LRMSD (Cα): 0.36 Å
RMSD (all): 1.37 Å

E



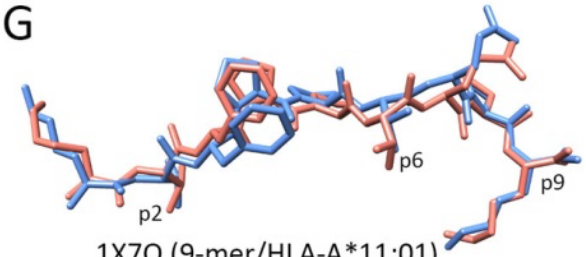
2BCK (9-mer/HLA-A*24:02)
LRMSD (Cα): 0.99 Å
RMSD (all): 1.98 Å

F



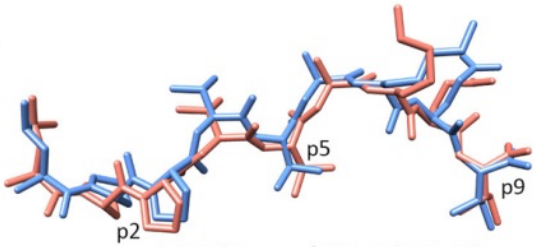
3I6L (9-mer/HLA-A*24:02)
LRMSD (Cα): 1.23 Å
RMSD (all): 2.5 Å

G



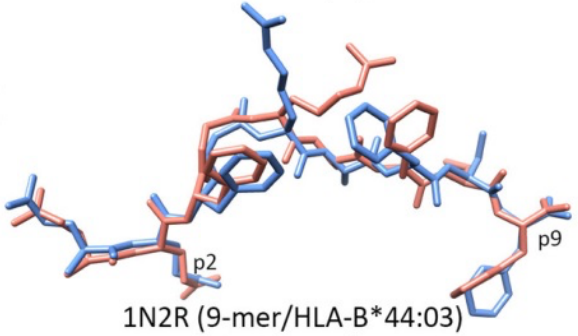
1X7Q (9-mer/HLA-A*11:01)
LRMSD (Cα): 0.72 Å
RMSD (all): 1.3 Å

H



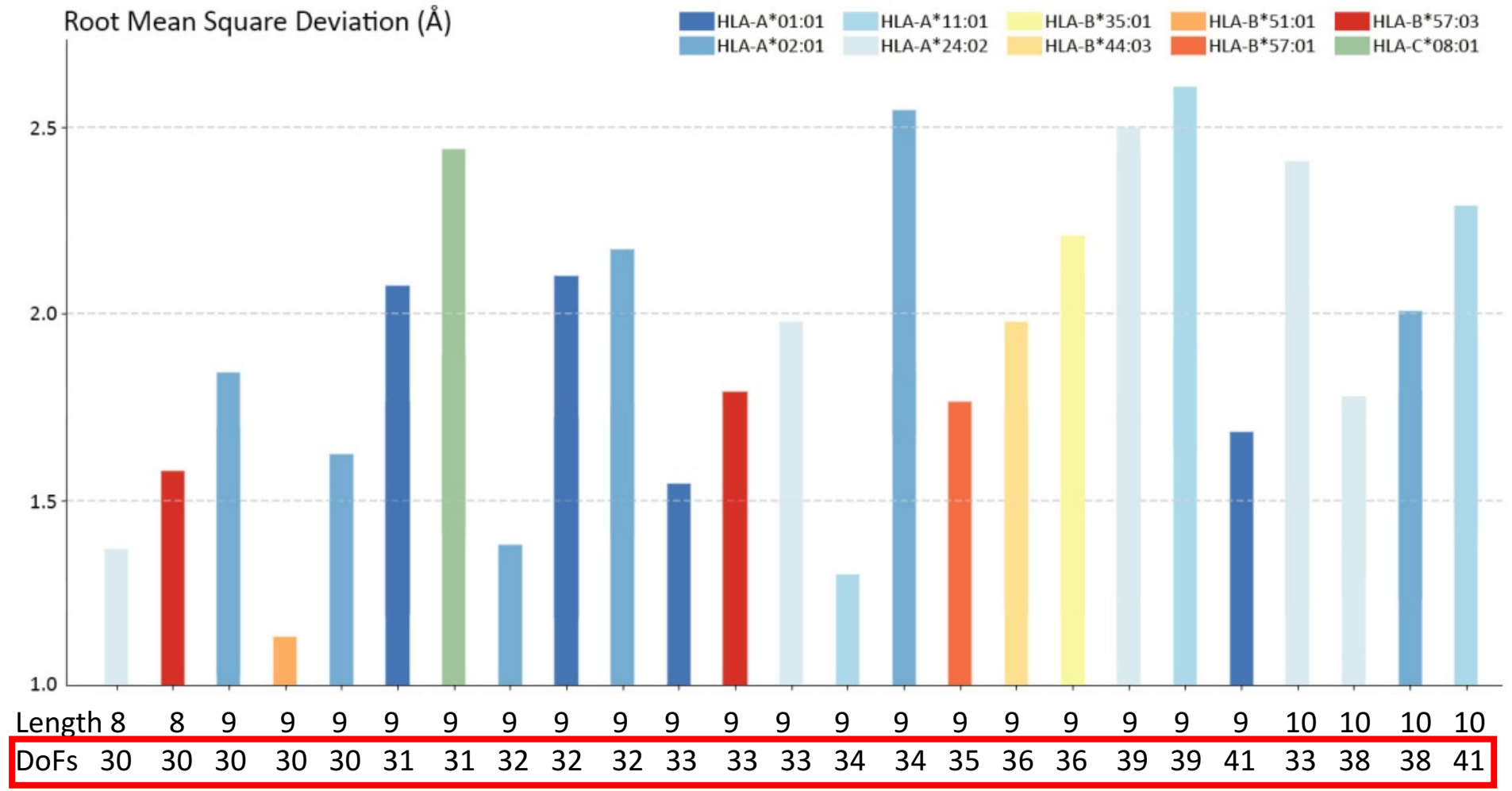
1E27 (9-mer/HLA-B*51:01)
LRMSD (Cα): 0.61 Å
RMSD (all): 1.14 Å

I



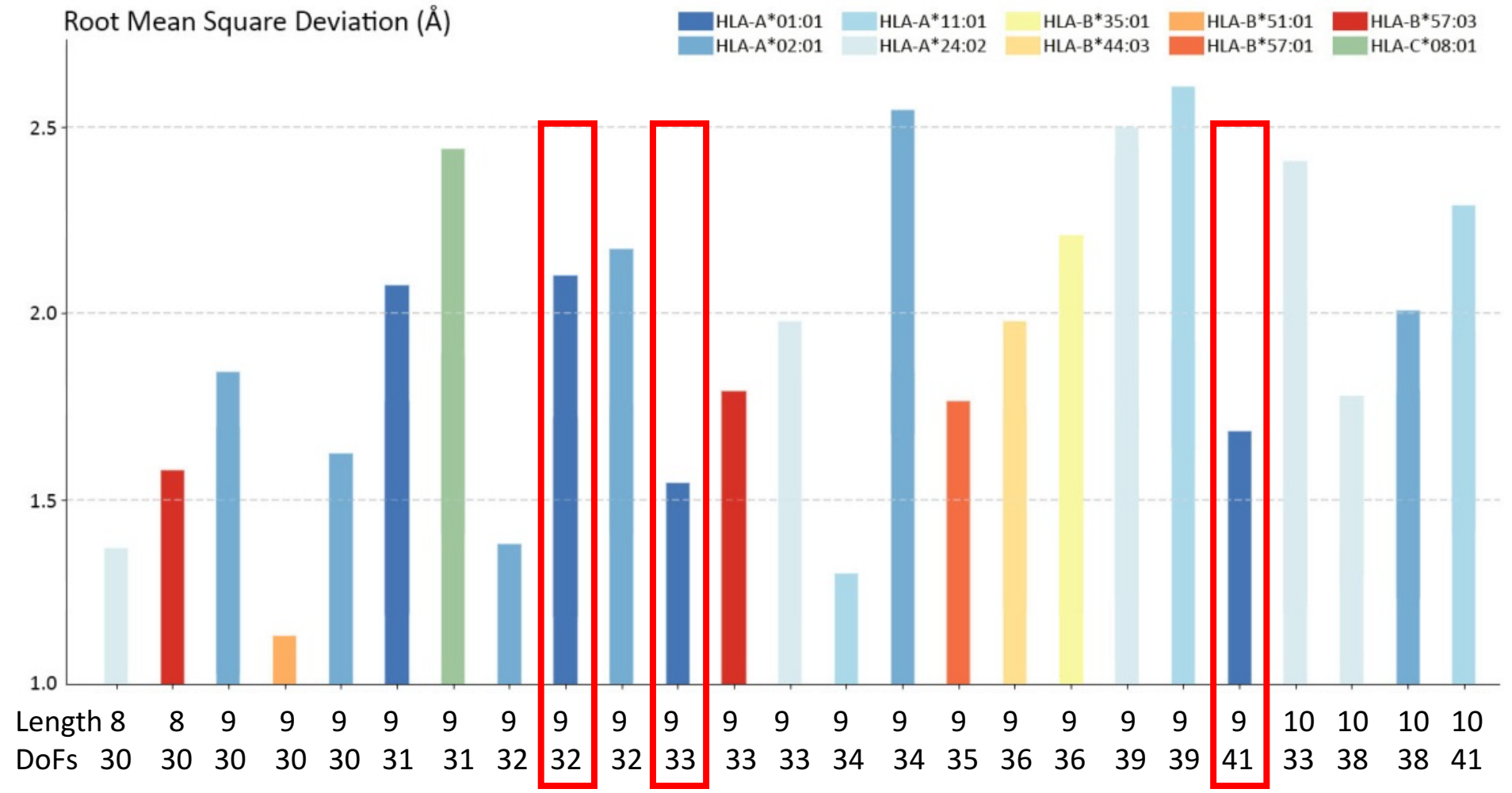
1N2R (9-mer/HLA-B*44:03)
LRMSD (Cα): 0.64 Å
RMSD (all): 1.98 Å

Proof of concept study using re-docking



Average RMSD of models: 1.92 Å

Proof of concept study using re-docking

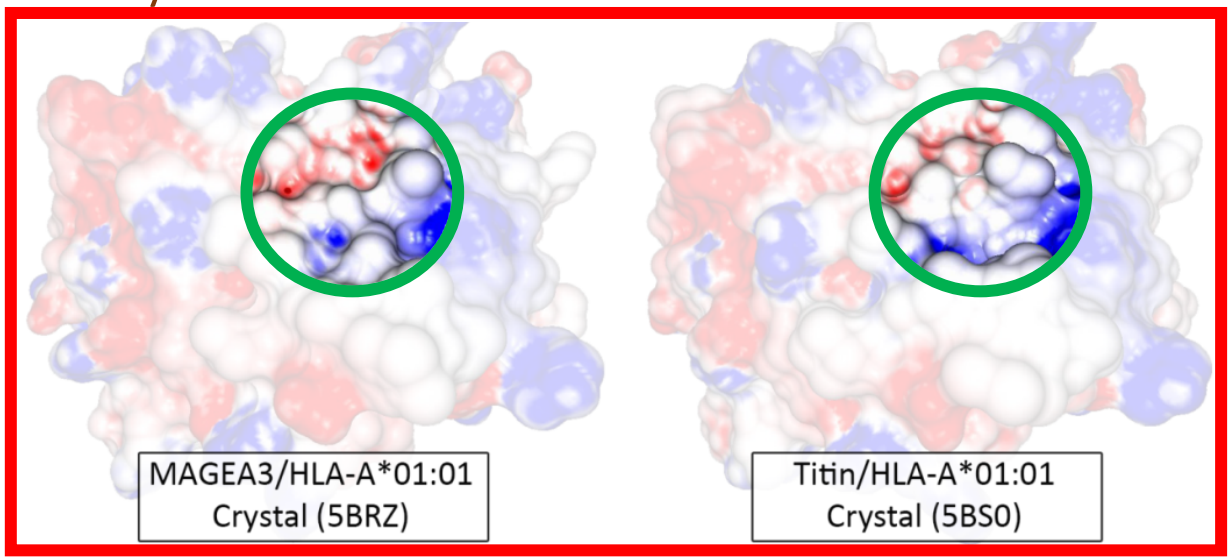


Some complexes are more challenging than others

Some parameters work better than others

pHLA structural similarity and T-cell cross-reactivity

- Crystal structures:



- TUMOR-derived peptide (EVDPIGHLY) lockin SELF-derived peptide (ESDPIVAQY)

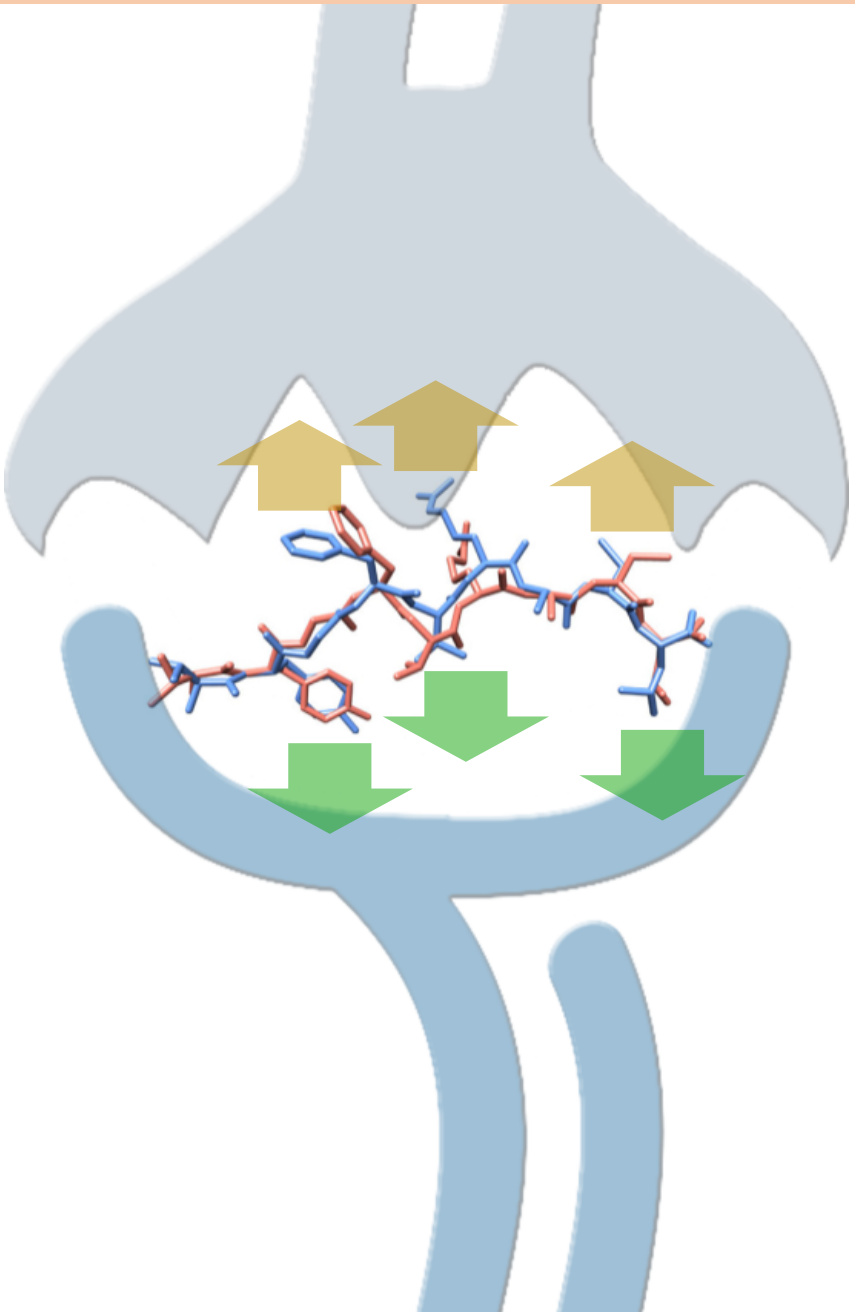
VIRUS-derived peptide (CTELKLNDY)

IMMUNOTHERAPY

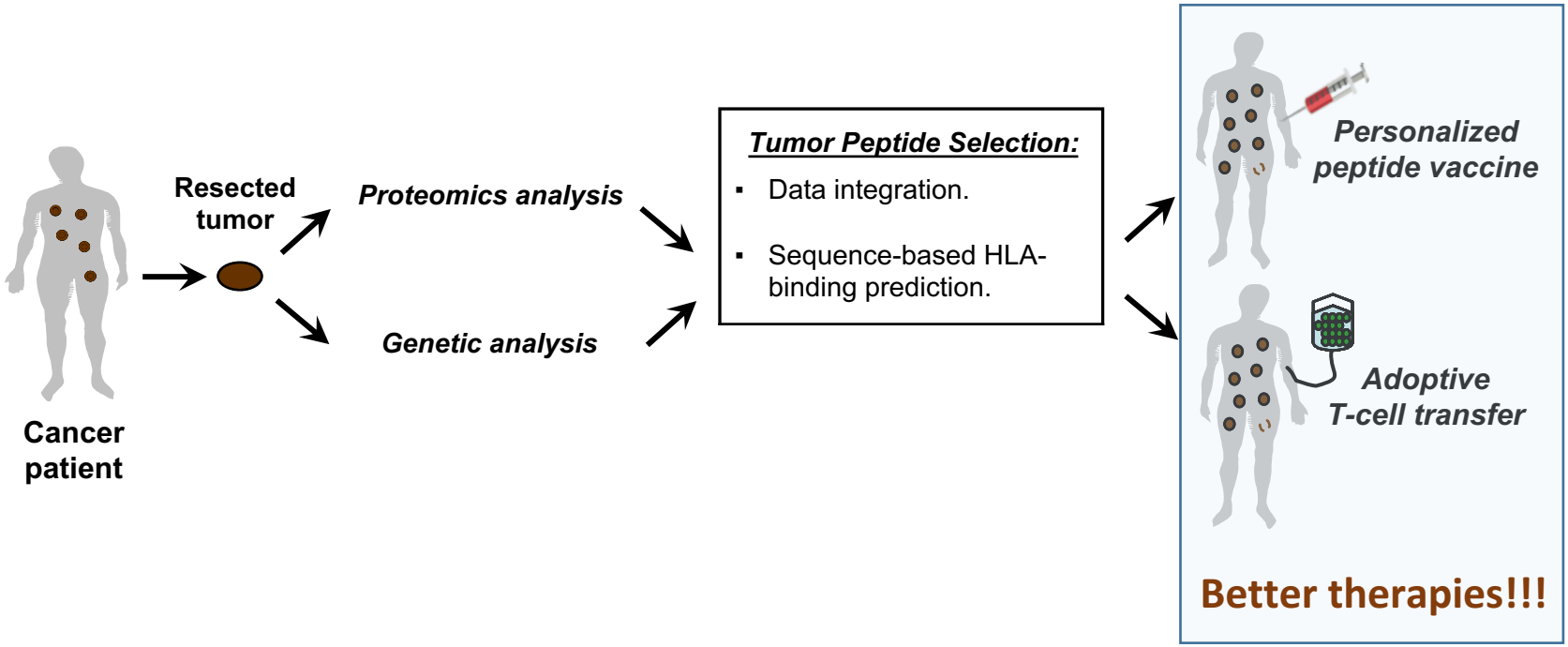
Identification of a Titin-Derived HLA-A1–Presented Peptide as a Cross-Reactive Target for Engineered MAGE A3–Directed T Cells

Cameron et al., 2013.
Science Translational Medicine 07 Aug 2013:
Vol. 5, Issue 197, pp. 197ra103
DOI: 10.1126/scitranslmed.3006034

Implications of the peptide structure

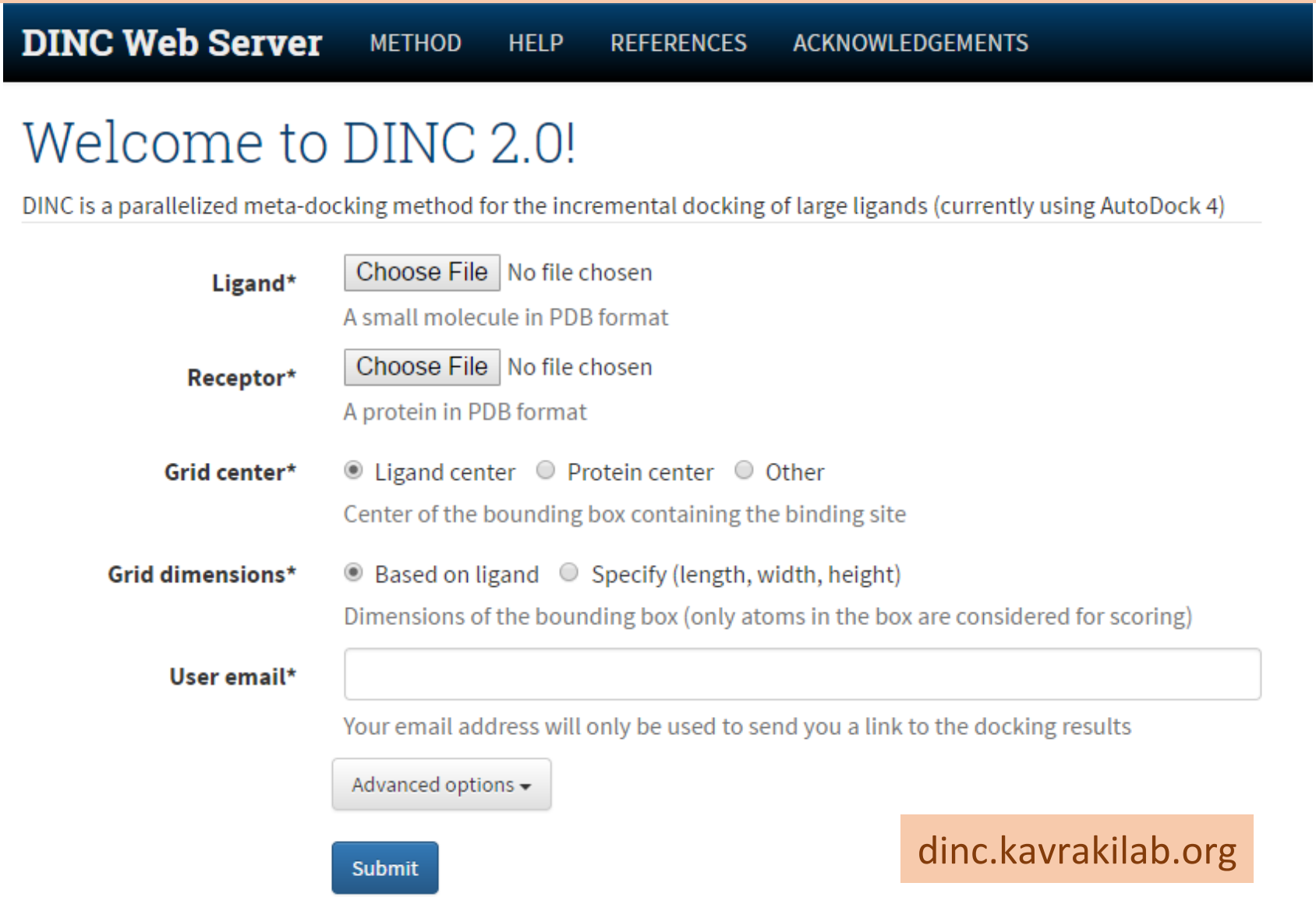


Application for immunotherapy



- Pipeline applied to >140 human tumors (M.D. Anderson Cancer Center)
- **Strength:** Allows for patient-specific identification of tumor peptides
- **Weakness:** Does not provide accurate ranking or cross-reactivity prediction

Our first contribution: DINC 2.0



dinc.kavrakilab.org

Submitted to a special feature in Cancer Research

DINC 2.0 (Results Page)

DINC Web Server METHOD HELP REFERENCES ACKNOWLEDGEMENTS

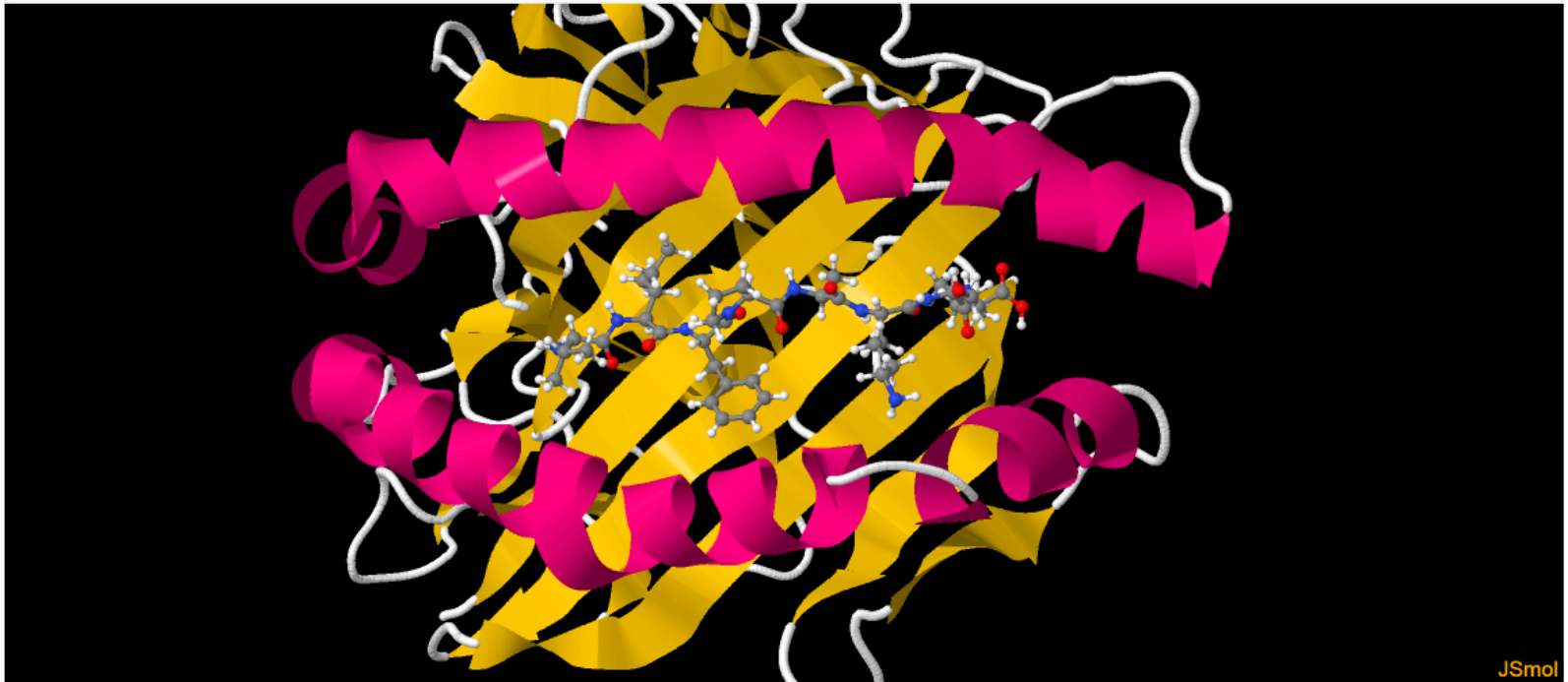
Thank you for using DINC!

You can visualize your results below. You can also download them for offline analysis.

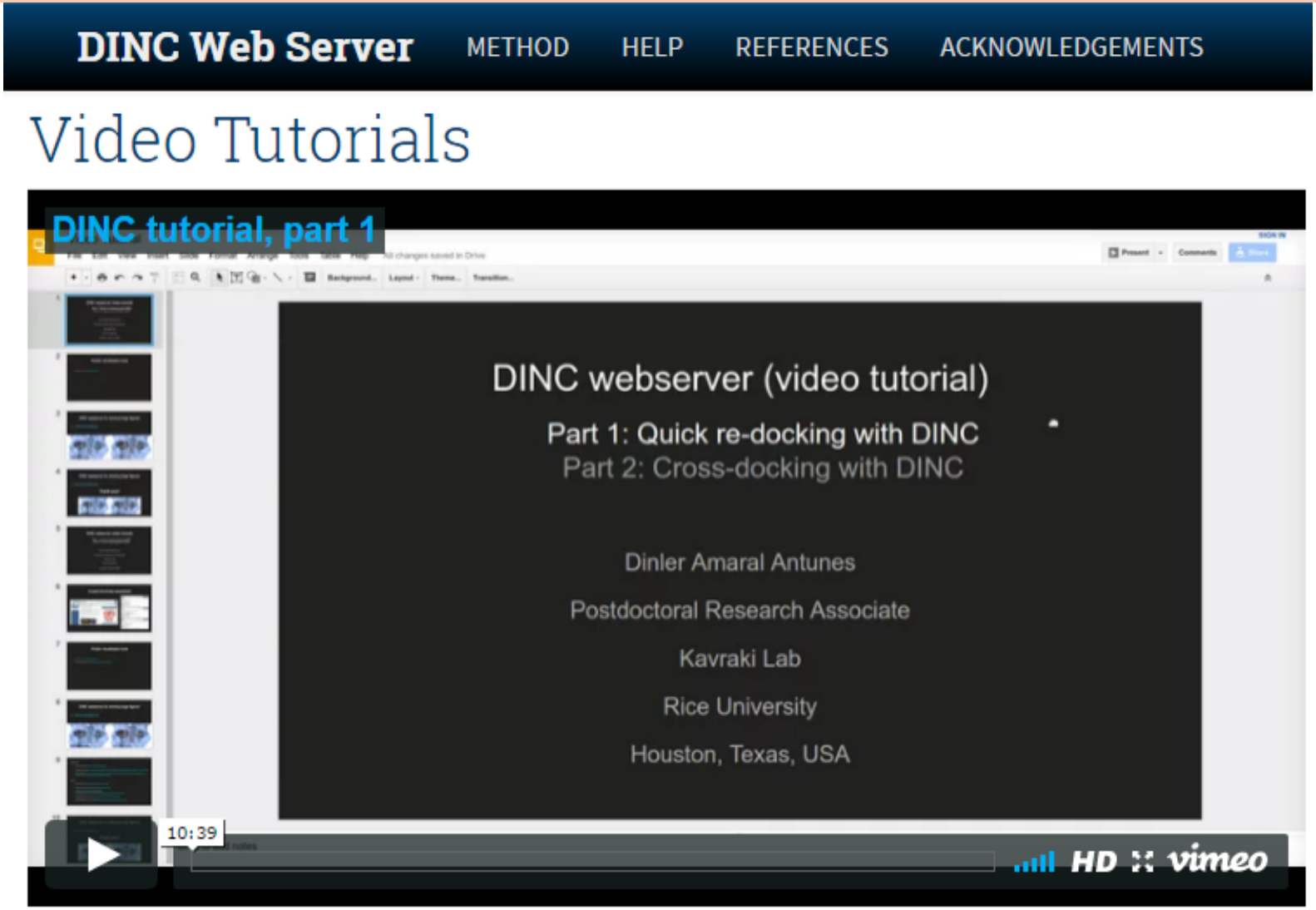
Ligand:	4d0d_ligand.pdb
Receptor:	4d0d_receptor.pdb
Grid center:	Ligand Center
Center coordinates:	(-12.258000000000001, -27.6245, 77.779)
Grid dimensions:	(109, 72, 61)

For each ligand conformation, the AutoDock score is reported in kcal/mol, and the distance to the original ligand conformation is reported in Å.

Ligand conformation: 1. -13.46 kcal/mol, 1.61Å | Save image | Download results | Visualization | Advanced



DINC 2.0 (Help)



http://dinc.kavrakilab.org/

Acknowledgements

- **Rice University (TX, US)**
  - Lydia Kavraki
  - Mark Moll
  - Didier Devaurs
- **UT M.D. Anderson (TX, US)**
  - Gregory Lizée
  - Cassian Yee
  - Kyle Jackson
- **UMASS (MA, US)**
  - Liisa Selin
  - Lawrence Stern
  - Inyoung Song
- **UFRGS (RS, Brazil)**
  - Gustavo Vieira
  - Maurício Rigo
  - Marialva Sinigaglia