Rosetta-based modeling of peptide-MHC I complexes

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Adoptive T-cell therapy
Neoantigens in cancer immunotherapy

Precision immuno pipeline (in brief), Arjun Rao

- Matched tumor/normal sequencing: exome, RNASeq
- Haplotyping (phlat)
- Variant calling: mutations/indels (mutect, radia, somaticseq,..)
- Map to AA changes and epitopes
- MHC-binding predictions (netMHCpan, Rosetta?)
Knowledge-based vs. knowledge-based:

- **NetMHCpan**: neural-network classifier trained on 186,684 peptide-MHC affinity measurements from IEDB
- **FlexPepDock**: MCMC search over fragment database built from current* PDB database; detailed/realistic all-atom energy function
Test case: allele HLA-A*01:01

<table>
<thead>
<tr>
<th></th>
<th>Peptide</th>
<th>PDB Code</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>CTELKLNNDY</td>
<td>4NQX</td>
<td>flu (H7N9)</td>
</tr>
<tr>
<td>P2</td>
<td>CTELKSNDY</td>
<td>4NQV</td>
<td>flu (H7N9)</td>
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<tr>
<td>P3</td>
<td>EVDPIGHLY</td>
<td>5BRZ</td>
<td>MAGE-A3</td>
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<tr>
<td>P4</td>
<td>ESDPIVAQY</td>
<td>5BS0</td>
<td>Titin</td>
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<tr>
<td>P5</td>
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<td>MAGE-A1</td>
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<td>P6</td>
<td>EADPTGHSY</td>
<td>1W72</td>
<td>MAGE-A1</td>
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</tbody>
</table>

**IEDB binding data:**

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Overview: peptide-MHC-I binding in 5BRZ
Sequence-independent peptide-MHC-I binding in 5BRZ
Peptide P1: “near” native vs. extended, 100 decoys
Superimposed MHC receptors: 4NQX and 5BRZ
Peptides P1 and P3, extended, 100 decoys
5BRZ: Contacts to C-terminal Tyr 9

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Native and Modified P3 (Y9A), extended, 100 decoys

- Density distribution
- RMS to native
- Rosetta All-atom Energy Score
Next steps:

- Scale up to productions runs.
- Investigate existing FlexPepDock alternative score terms.
- Correlate IEDB training database with FlexPepDock score terms.
- Model water binding?