



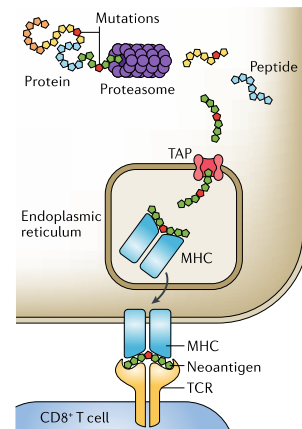
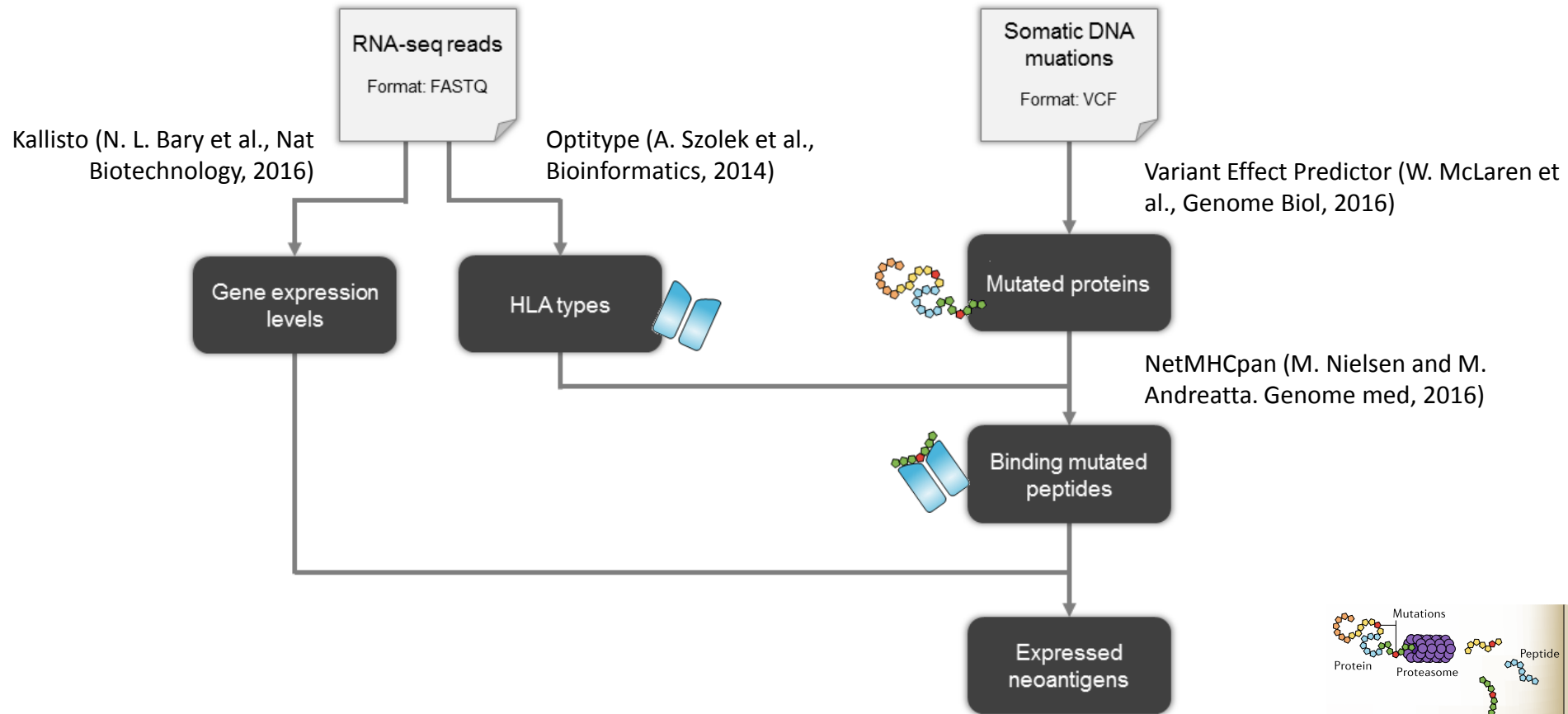
IO17 | Large Scale Bioinformatics for Immuno-Oncology

Peptide-MHC binding prediction

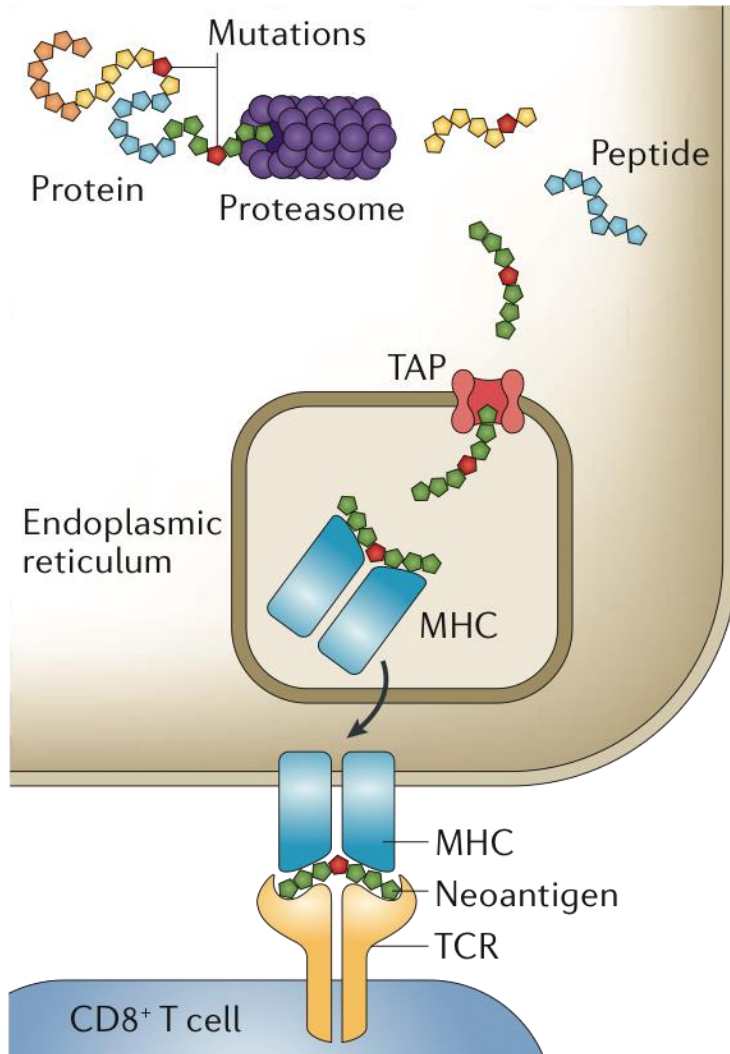
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A pipeline for the prediction of class-I neoantigen



Neoantigen-MHC binding



Not all peptides bind to all MHC molecules (i.e. they can have high or low **binding affinity**)!

Prediction of peptide-MHC binding

Computational methods to predict peptide-MHC binding affinity are:

- Structure-based (3D structures) → threading/docking approaches
- Sequence-based (primary sequence) → more data available for training/validation

Modern sequence-based tools for peptide-MHC binding prediction use **machine learning** algorithms (e.g. neural networks) trained on data-sets of peptide-MHC/HLA with known **primary sequence** and experimentally measured **binding affinity**

Binding affinity is often measured as **half maximal inhibitory concentration (IC₅₀)**

IC₅₀: the concentration of the query peptide which inhibits 50% of a reference peptide binding the MHC (i.e. if a low concentration is required to outcompete the reference peptide, the query peptide has a strong binding affinity for the MHC)

Computational tools for peptide-MHC binding prediction

| | | |
|-------------|---|---|
| CONSENSUS | Consensus approach for prediction of pMHC-I and pMHC-II binding affinity hosted on the IEDB website | http://tools.immuneepitope.org/mhcii |
| netMHC | Machine-learning-based prediction of pMHC binding affinity to human and non-human MHC-I molecules | http://www.cbs.dtu.dk/services/NetMHC |
| netMHCcons | Consensus-based prediction of pMHC-I binding affinity integrating the predictions of NetMHC, NetMHCpan and PickPocket | http://www.cbs.dtu.dk/services/NetMHCcons |
| netMHCpan | Pan-specific version of netMHC | http://www.cbs.dtu.dk/services/NetMHCpan |
| netMHCstab | Machine-learning-based prediction of the stability of binding of small peptides to HLA-A and HLA-B molecules | http://www.cbs.dtu.dk/services/NetMHCstab-1.0 |
| netMHCII | Machine-learning-based prediction of binding affinity to human and mouse class-II MHC molecules | http://www.cbs.dtu.dk/services/NetMHCII |
| netMHCIIpan | Pan-specific version of netMHCII | http://www.cbs.dtu.dk/services/NetMHCIIpan |
| PickPocket | Pan-specific predictor of pMHC-I binding affinity based on PSSM of peptides and MHC pockets | http://www.cbs.dtu.dk/services/PickPocket |

Experimental data on peptide-MHC binding is lacking for the large majority of HLA alleles

Development of **pan-specific** methods, like NetMHCpan, which predict peptide binding to any class-I HLA molecules of known protein sequence

NetMHCpan represents HLA as pseudo-sequences (HLA residues in contact with bound peptides) and trains a neural network to output the affinity of a given HLA-peptide pair

NetMHCpan scored amongst the best performers, even compared to allele-specific methods

NetMHCpan 3.0 is used by TIminer for peptide-HLA binding prediction and is available as web-based and standalone tool: <http://www.cbs.dtu.dk/services/NetMHCpan/>

```
from TIminer import TIminerAPI  
TIminerAPI.executeNetmhspan(...)
```

From TIminer documentation

<http://icbi.i-med.ac.at/software/timiner/doc/index.html>

`TIminer.TIminerAPI.executeNetmhspan(inputFile, mutatedProteinsInputFile, hlaInputFile, outputFile, threadCount=1, minPeptideLength=8, maxPeptideLength=11, affinityThresh=500, rankThresh=None)`

This function considers, a file of annotated mutations, a corresponding FASTA file with the sequence of the mutated proteins, and a list of class-I HLA types. It extracts short mutated peptides (default: 8-11 amino acids) and predicts their binding affinity to HLA types using NetMHCpan. Only mutated peptides with a binding affinity < 500 nM are reported in the output file.

Parameters:

- **inputFile** (*str*) – Path to the `input file` of annotated DNA somatic mutations generated by the Variant Effect Predictor (see the `output files` section for details).
- **mutatedProteinsInputFile** (*str*) – Path to the `FASTA file` with the sequences of the mutated proteins generated by the Variant Effect Predictor (see the `output files` section for details).
- **hlaInputFile** (*str*) – Path to the `file` containing the HLA types, that can be generated with `Optitype` or provided by the user (for details see the `output files` section).
- **outputFile** (*str*) – The path to the column based `output file` (see the `output files` section for details).
- **threadCount** (*int*) – Number of threads to be used (optional, default = 2).
- **minPeptideLength** (*int*) – Minimal peptide length to test (optional, default = 8).
- **maxPeptideLength** (*int*) – Maximal peptide length to test (optional, default = 11).
- **affinityThresh** (*int*) – binding affinity threshold (optional, default = 500. If set the rank threshold needs to be None).
- **rankThresh** (*int*) – ranking based binding threshold (optional, default = None. If set the binding affinity threshold needs to be None).

IC₅₀ →

Tab-delimited text file with the information about all mutated peptides passing the binding-affinity threshold. Format:

#SubjectID: subject ID

Pos: genomic position of the mutation

GeneID: Ensemble gene ID

TranscriptID: Ensemble transcript ID

GeneSymbol: HGNC gene symbol

Protein: Ensemble protein ID

ProteinPos: position of the mutated amino acid in the protein sequence

Mut: amino acid change

VariantType: type of variant

HLA: HLA type

MutPeptide: sequence of the mutated peptide

MutAFF: IC50 affinity of the mutated peptide in nM

MutRank: rank of the mutated peptide affinity compared to a set of 400.000 random peptides

RefPeptide: sequence of the wild-type (i.e. non-mutated) peptide

RefAFF: IC50 affinity of the unmutated peptide in nM

RefRank: rank of the wild-type peptide affinity compared to a set of 400.000 random peptides