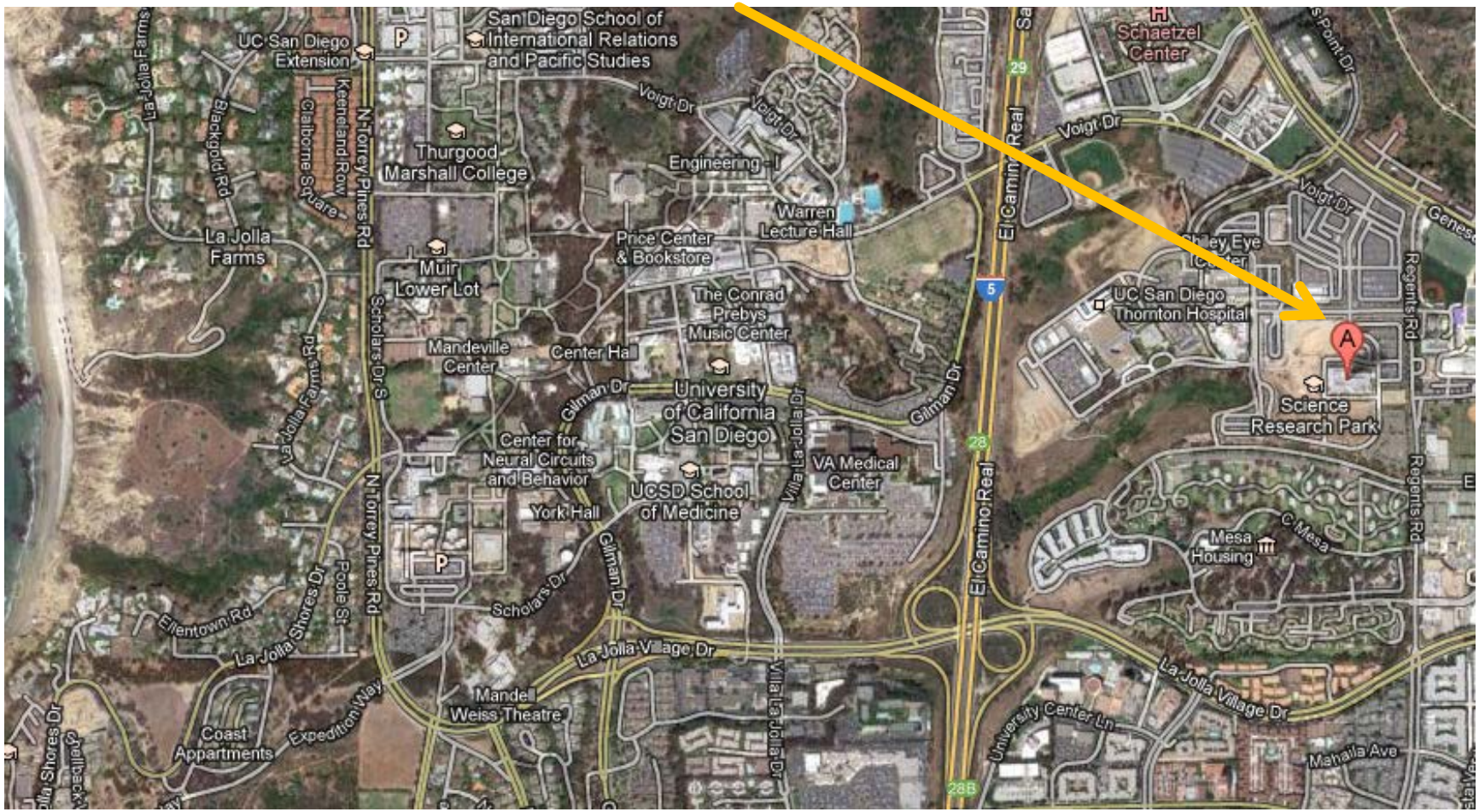
# Towards personalized cancer treatments using Immunoinformatics

**Bjoern Peters**

**Zeynep Kosaloglu-Yalcin**

La Jolla Institute for Immunology

# La Jolla Institute for Immunology (LJI)



# Overview

- Background Biology: The immune system can detect and eliminate mutated cancer cells

- Background Immunoinformatics:
  - Mutations can be detected using patient sequencing data
  - Mutations that can be recognized by T cells can be predicted

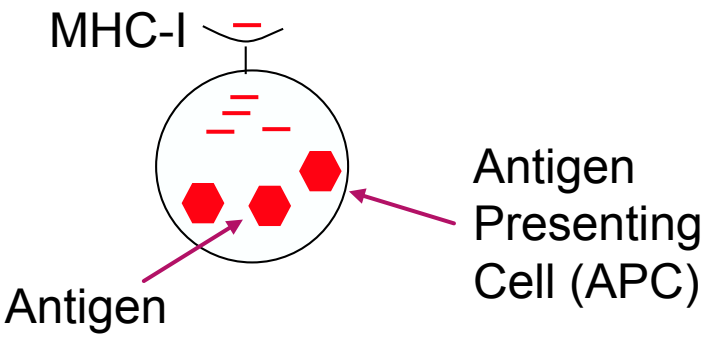
- Hands on: Design a personalized cancer vaccine

# Cancer immune surveillance and escape

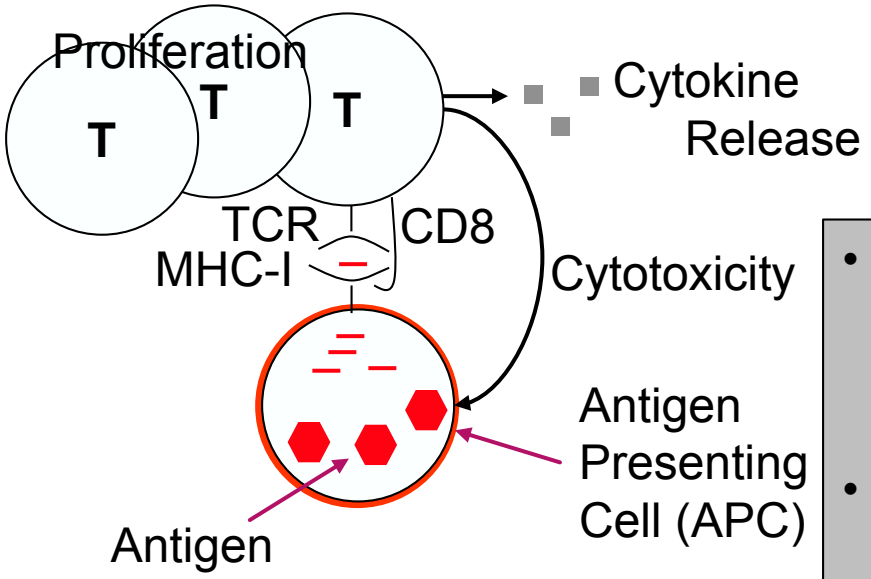
- Mutations in cells occur frequently
- The immune system has the capacity to detect and eliminate such mutated cells, and will do so on a regular basis
- Only when mutated cells find ways to hide from- or suppress an attack by the immune system, they can grow and spread unhindered leading to clinically apparent tumors


Van der Burg et al, Nature Reviews Cancer 16, 219–233 (2016)

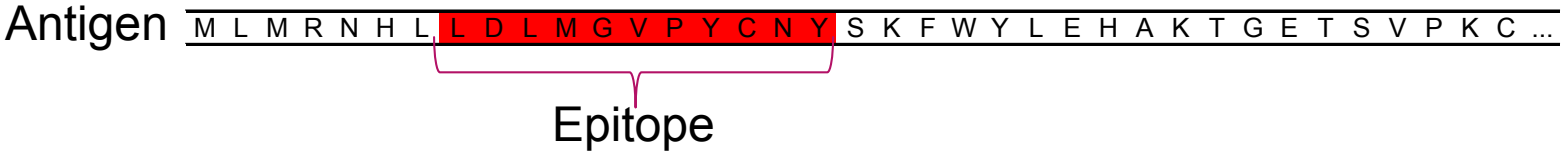
# CD8$^+$ T cell epitope recognition



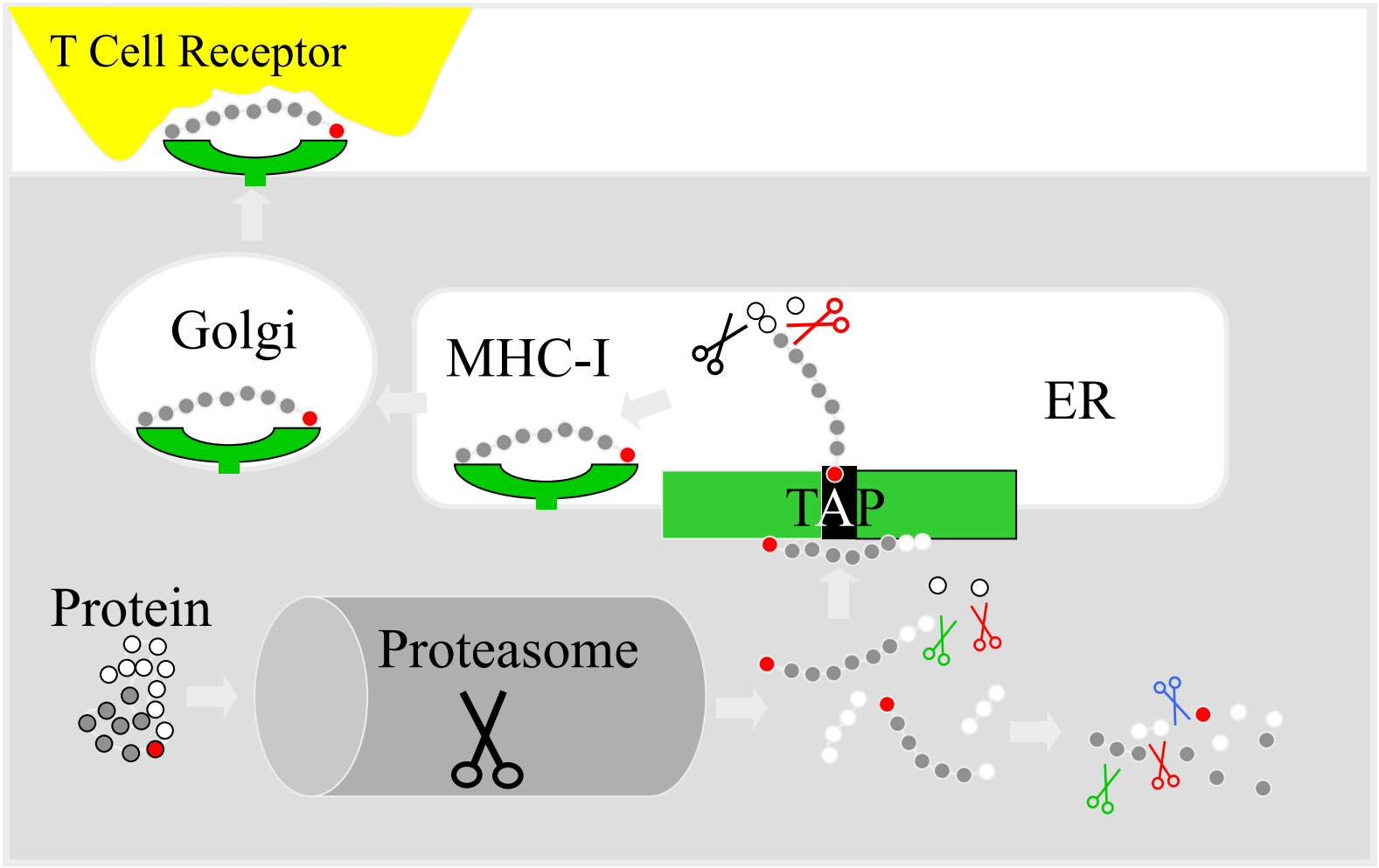
# CD8+ T cell epitope recognition




- What determines what peptides are presented by MHC molecules on the cell surface?
- How do T cells distinguish self- from non-self peptides?

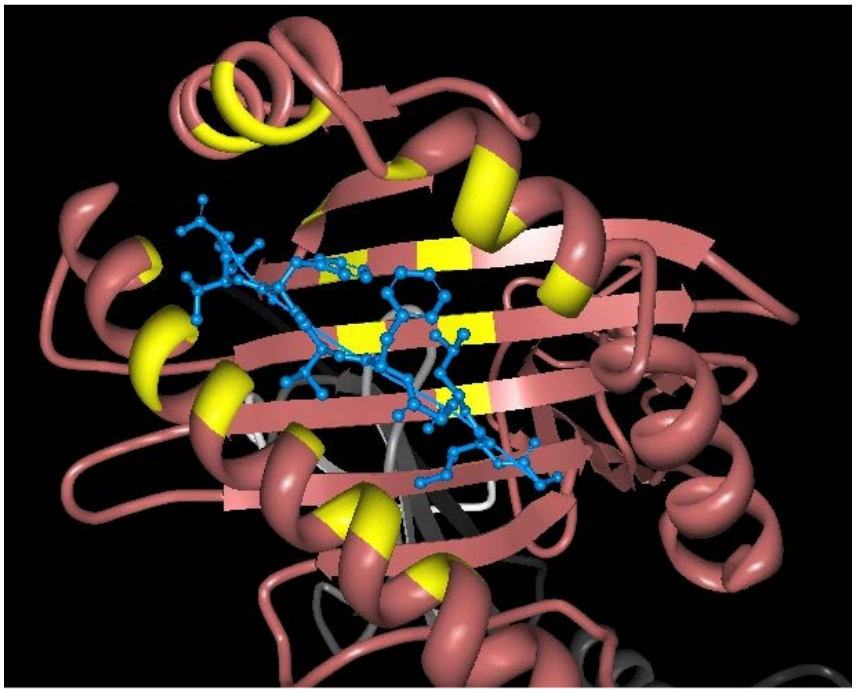


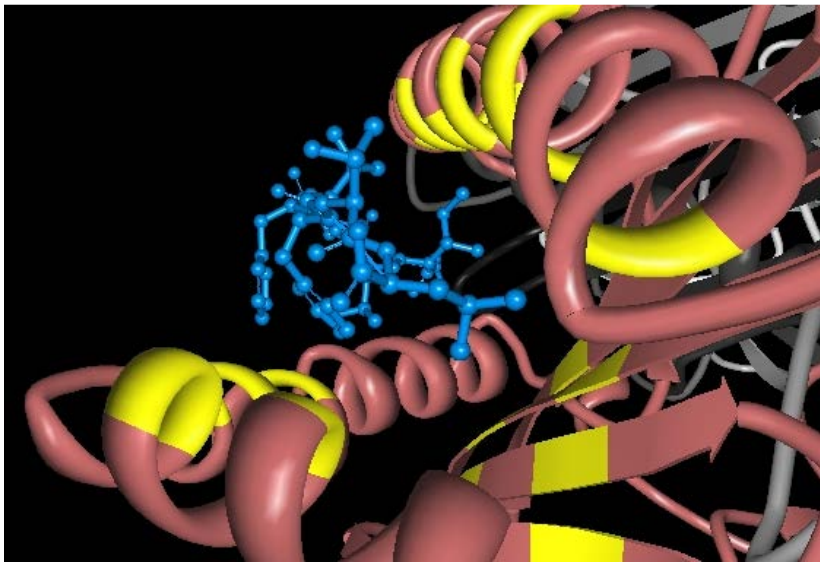
# MHC I - Antigen processing and presentation pathway




 *Peters et al, J Mol Biol 2002, Bioinformatics 2003, J Immunol.2003; CMLS 2005 ; Assarson, J Immunol 2007*

# MHC:peptide binding mode



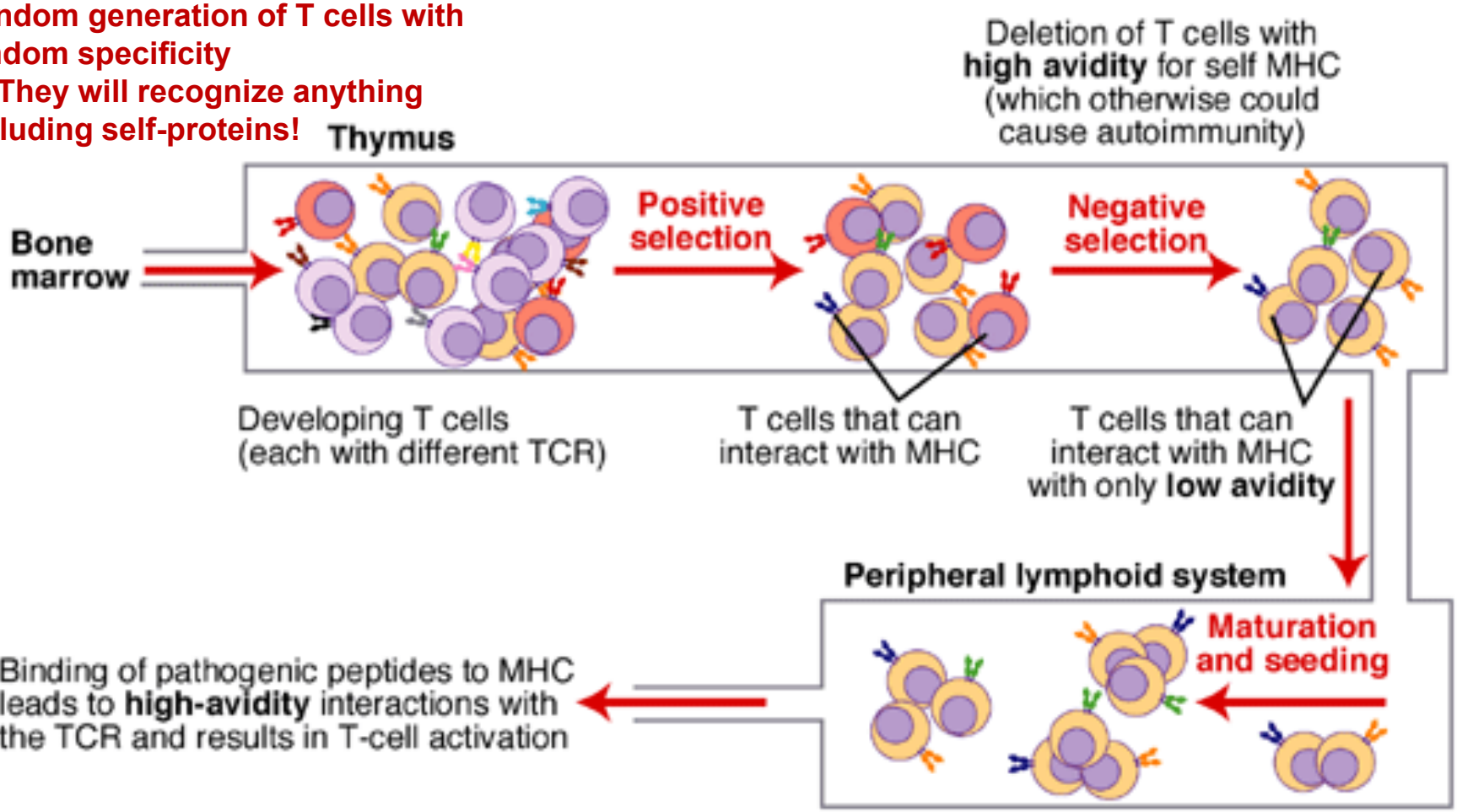


- Each human expresses up to 6 different MHC-I molecules in every cell
- >3000 MHC variants are known
- Distinct binding specificities → individual epitope repertoire

*Viewer: Beaver and Ponomarenko, Immunome Research, 2007*

# Self –reactive T cells are deleted during maturation

**Random generation of T cells with random specificity**
**➔ They will recognize anything including self-proteins!**




The repertoire of T cells is shaped by both positive and negative selection

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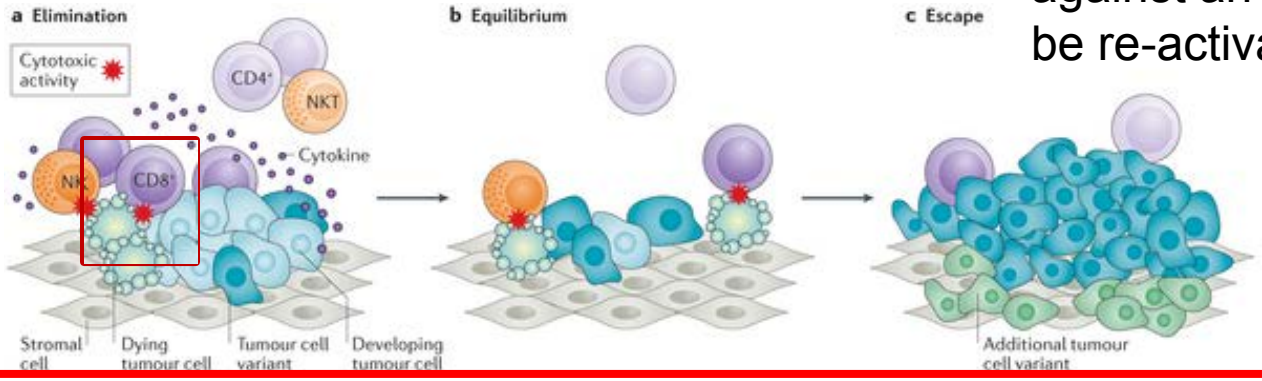
Can the immune response against an 'escaped' cancer be re-activated?



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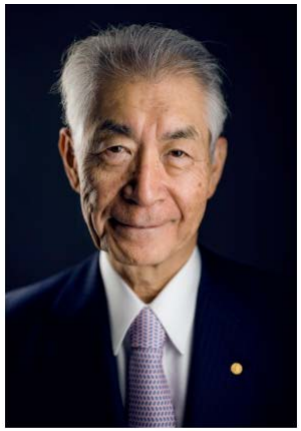
# Nobel Prize 2018 in Medicine

- Identification of the molecules PD-1 and CTLA-4 that function as 'T cell brakes' (immune checkpoints)
- Blockade of PD-1 and CTLA-4 results in activation of T cells which has "*fundamentally changed the outcome for certain groups of patients with advanced cancer*"
- *"Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions […]"*

© Nobel Media AB. Photo: A. Mahmoud

James P. Allison



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Tasuku Honjo

***"for their discovery of cancer therapy by inhibition of negative immune regulation"***



https://www.nobelprize.org/uploads/2018/10/press-medicine2018.pdf

# Rationale for Personalized Cancer Immunotherapy

- Vaccination: Introduce or boost an immune response against a specific target (antigen)
- Cancer cells contain non-self antigens that *could* be recognized by T cells, but presence of cancer means this mechanism has failed, typically by the tumor suppressing immune responses
- Checkpoint blockade treatments: Block immune suppressive mechanisms to boost T cell immune responses against cancer cells.
- Problem: Checkpoint blockade is unspecific, and will also boost unwanted autoimmune responses
- Personalized Cancer Immunotherapy: Boost anti-tumor response with vaccine containing peptides corresponding to cancer mutations that can be recognized by T cells.

Several trials for personalized cancer vaccines are currently ongoing

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## Is the Next Big Step in Cancer Therapy Personalized Vaccines?

*UC San Diego Health and La Jolla Institute launch clinical trial harnessing an individual's immune system in a syringe*

October 12, 2018 | Yadira Galindo

Ezra Cohen, MD, UC San Diego Health physician scientist, administered the first-of-its-kind personalized cancer vaccine to Tamara Strauss, while Aaron Miller, MD, PhD, UC San Diego Health physician scientist, Tamara's mother, Iris Strauss, and Stephen Schoenberger, PhD, La Jolla Institute for Allergy and Immunology professor of immunology, look on.

After sequencing Tamara's tumor and normal tissue, the team identified mutations expressed solely by cancer cells in her body. Schoenberger and LJI's Bjoern Peters, PhD, developed a novel algorithm to select mutations that are recognized by the immune system. This algorithm was deployed to recognize the neoantigens that generated the strongest T cell response from Tamara's tissue samples. These neoantigens were then presented to Tamara's own T cells and cultured over a two-week period using 50 milliliters of her blood to develop a personalized vaccine.

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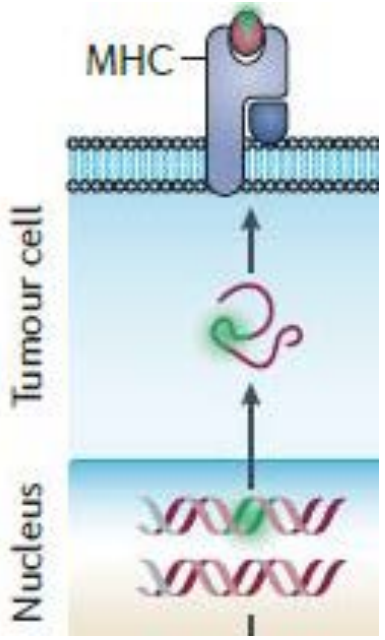
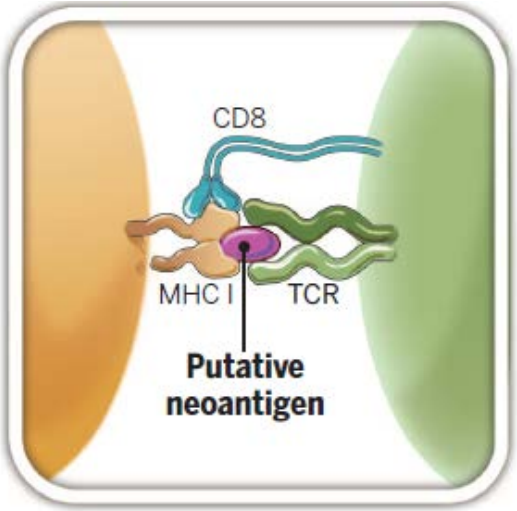
# Neoepitopes (Neoantigens)




- Cancers genomes accumulate mutations
- Mutations in coding regions are translated in mutated protein sequences
- Mutated peptides can be presented as epitopes on MHC to T cells

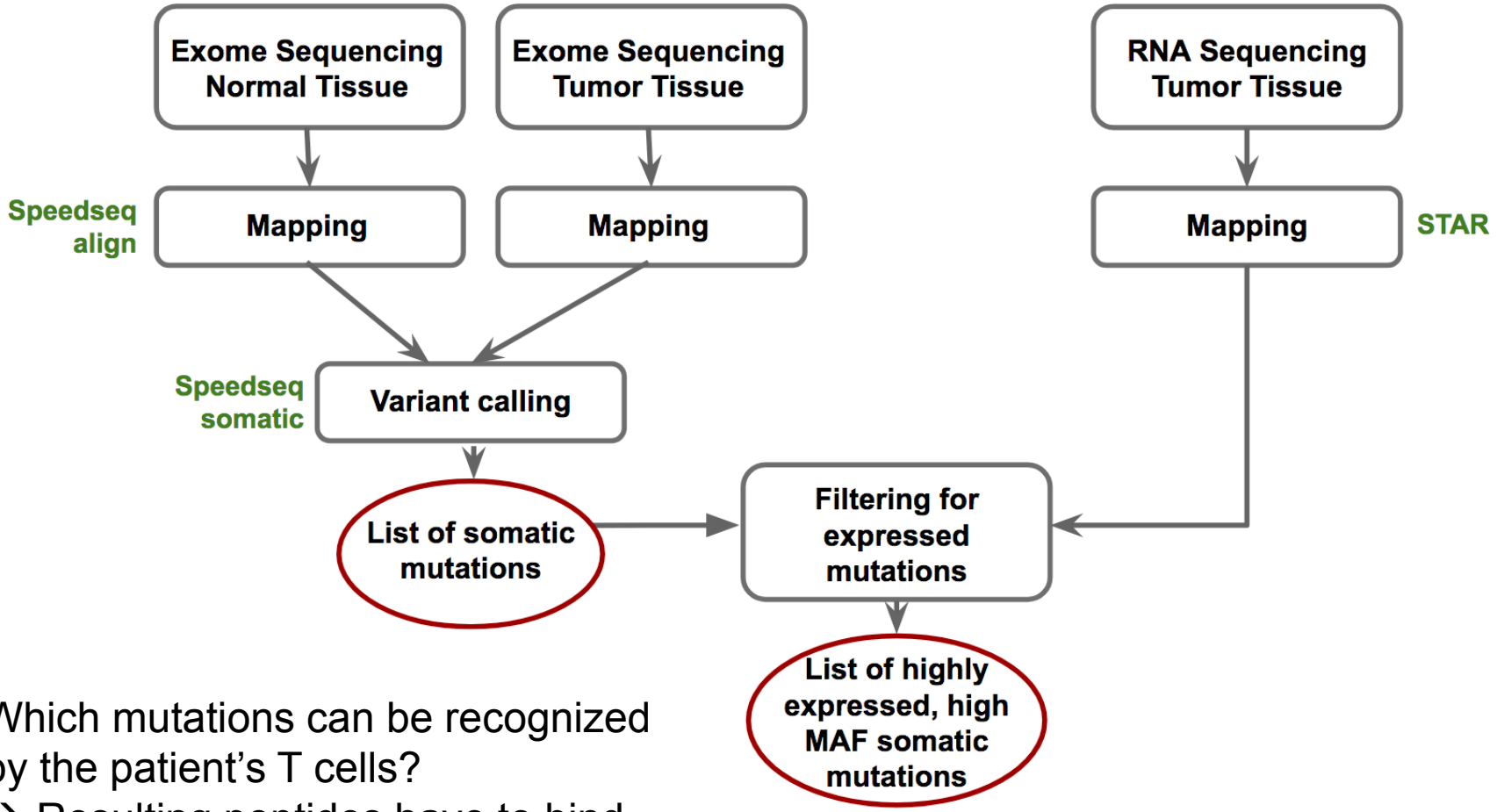
**Neoepitopes** can be recognized by tumor-infiltrating lymphocytes **(TILs)**

**Neoepitopes** are highly tumor-specific!




Coulie et al, Nat Rev Cancer. 2014 Feb;14(2):135-46
Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74

# DNA and RNA sequencing identifies tumor specific somatic mutations




Which mutations can be recognized by the patient's T cells?
→ Resulting peptides have to bind HLA molecules of the patient

# Hands On Part 2.1

- Identify mutated sites in the provided p53 protein sequences
- Identify sequence regions that contain all 9-mer peptides that are only found in the tumor (that contain a mutation)

# Input data from patient:

**>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGP
DEAPRMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

**>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMLDLMLSPDDIEQWFTEDPGP
DEAPWMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFVHSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLEV

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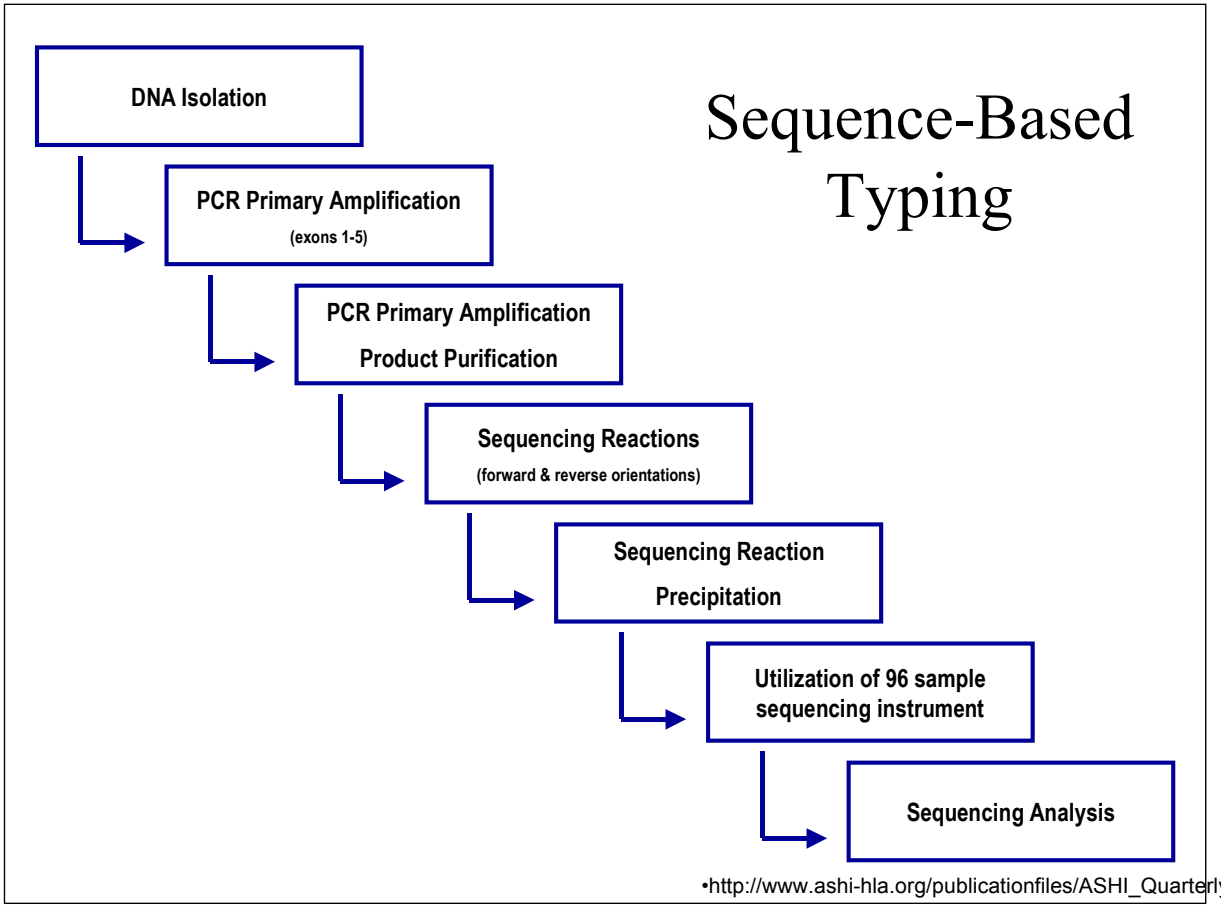
# HLA Typing: Targeted sequencing of HLA locus



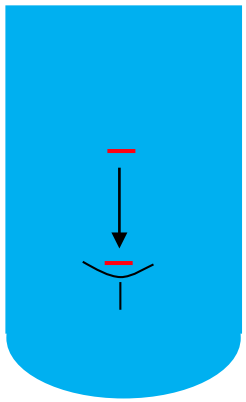

•http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/25_2_2001/highthrusbt3.htm

HLA genotype of patient can be determined in the hospital/lab or can also be determined with immunoinformatics tools using the sequencing data

# Measuring and predicting MHC:peptide binding

**Experimental Basis: MHC Binding Assay**

List of peptides with allele specific binding affinity



| Sequence | $IC_{50}$ |
|---|---|
| QIVTMFEAL | 3.6 |
| LKGPDIYKG | 308 |
| NFCNLTSAF | 50,000 |
| AQSQCRTFR | 38,000 |
| CTYAGPFGM | 143 |
| CFGNTAVAK | 50,000 |
| . . . | |

$\log(IC_{50})$ ~ Binding free Energy

low $IC_{50}$ → high affinity

**Impossible to measure all peptides**

→ Predict binding peptides using machine learning

Find function $F_i$ in $F_1, F_2, F_3, \ldots$

$F_i$ (Sequence) ≈ Affinity

Many different approaches (ANN, SVM, HMM, LP, ... )

T cell epitope mapping

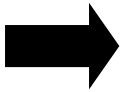
| | |
|---|---|
| ORF 1 | M G Q I V T M F E A L P H I I D E V I N I V I I V L I V I T G I K A V Y N ... |
| ORF 2 | M G L K G P D I Y K G V Y Q F K S V E F D M S H L N L T M P N A C S A N N ... |
| ORF 3 | M H N F C N L T S A F N K K T F D H T L M S I V S S L H L S I D G N S N Y ... |
| ORF 4 | M S A Q S Q C R T F R G R V L D M F R T A F G G K Y M R S G W G W T G S D ... |
| ORF 5 | M H C T Y A G P F G M S R I L L S Q E K T K F F T R R L A G T F T W T L S ... |
| ORF 6 | M K C F G N T A V A K C N V N H D A E F C D M L R L I D Y N K A A L S K F ... |
| ORF 7 | M L M R N H L L D L M G V P Y C N Y S K F W Y L E H A K T G E T S V P K C ... |

# Calculate scoring matrix from affinities

Machine learning PSSM = Minimize the difference between predicted and measured binding affinities by varying the matrix values

N peptides with measured binding affinities

| log (IC50) | Peptide |
|---|---|
| 0.50 | FQPQNGSFI |
| 0.72 | ISVANKIYM |
| 2.37 | RVYEALYYV |
| 3.42 | FQPQSGQFI |
| 3.46 | LYEKVKSQL |
| 4.07 | FKSVEFDMS |
| 4.18 | FQPQNGQFH |
| 4.24 | VLMLPVWFL |
| 4.39 | YMTLGQVVF |
| 4.40 | EDVKNAVGV |
| 4.90 | VFYEQMKRF |
| | ... |



| | HLA A*0201 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| A | -0.3 | 0.8 | -0.3 | -0.3 | -0.2 | -0.3 | 0.0 | 0.0 | -0.9 |
| C | 0.2 | 0.9 | 0.0 | 0.3 | -0.5 | -0.1 | 0.1 | 0.2 | 0.4 |
| D | 0.8 | 0.9 | -0.4 | -0.3 | 0.3 | 0.2 | 0.4 | 0.3 | 0.6 |
| E | 0.6 | -0.4 | 0.7 | -0.2 | 0.1 | -0.4 | -0.2 | -0.2 | -0.5 |
| F | -1.3 | 0.5 | -0.5 | 0.1 | -0.1 | 0.0 | -0.3 | -0.4 | -0.8 |
| G | -0.2 | 0.1 | 0.3 | -0.1 | 0.0 | 0.4 | 0.3 | -0.1 | 0.2 |
| H | 1.1 | 0.9 | -0.1 | 0.4 | 0.1 | 0.2 | 0.0 | 0.2 | 0.8 |
| I | -0.4 | -0.7 | -0.4 | 0.1 | -0.1 | -0.4 | -0.5 | 0.5 | -1.4 |
| K | -0.3 | 0.0 | 1.1 | 0.1 | 0.1 | 0.6 | 0.9 | 0.2 | 0.9 |
| L | 0.0 | -1.9 | -0.4 | -0.2 | 0.0 | -0.2 | 0.0 | -0.1 | -1.1 |
| M | -0.7 | -1.2 | -0.7 | 0.2 | -0.6 | 0.0 | 0.0 | 0.0 | -0.8 |
| N | -0.1 | 0.3 | 0.1 | -0.3 | -0.1 | -0.3 | 0.0 | 0.2 | 0.7 |
| P | 1.2 | 0.5 | 0.6 | -0.3 | 0.4 | 0.0 | -0.4 | -0.5 | 0.7 |
| Q | 0.4 | -1.1 | 0.0 | -0.1 | 0.4 | -0.2 | -0.3 | 0.2 | 0.7 |
| R | -0.2 | 0.9 | 1.0 | 0.3 | 0.1 | 0.4 | 0.7 | 0.0 | 0.9 |
| S | -0.3 | 0.1 | 0.1 | -0.4 | 0.1 | 0.3 | -0.2 | -0.1 | 0.2 |
| T | -0.2 | -0.5 | 0.1 | 0.4 | 0.1 | -0.5 | 0.2 | 0.0 | -0.1 |
| V | -0.1 | -0.9 | -0.1 | 0.2 | 0.0 | -0.3 | 0.1 | 0.1 | -1.9 |
| W | 0.0 | 0.7 | -0.5 | -0.2 | -0.1 | 0.2 | -0.3 | -0.1 | 0.4 |
| Y | -0.3 | 0.2 | -0.6 | 0.2 | 0.0 | 0.4 | -0.4 | -0.3 | 0.8 |

Offset: 4.3

# Predictions available as webserver

- Immune Epitope Database (IEDB) Analysis resource
- http://tools.iedb.org/mhci/

# MHC-I Binding Predictions

| | |
|---|---|
| Prediction Method Version | 2013-02-22 [Older versions] |
| **Specify Sequence(s)** | |
| Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI) | |
| Or select file containing sequence(s) | Choose File No file chosen |
| Choose sequence format | auto detect format |
| **Choose a Prediction Method** | |
| Prediction Method | IEDB recommended Help on prediction method selections |
| **Specify what to make binding predictions for** | |
| MHC source species | human |
| *Show only frequently occuring alleles:* Select MHC allele(s) Select HLA allele reference set: | Allele Length Upload allele file |
| **Specify Output** | |
| Sort peptides by | Percentile Rank |
| Show | All predictions |
| Output format | XHTML table |
| Email address (optional) | |
| | Submit Reset |

| | |
|---|---|
| Prediction Method Version | 2013-02-22 [Older versions] |
| **Specify Sequence(s)** | |
| Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI) | >Region 1<br>SPLPSQAMLDLMLSPDD<br>>Region 2<br>DPGPDEAPWMPEAAPPV |
| Or select file containing sequence(s) | Choose File No file chosen |
| Choose sequence format | auto detect format |
| **Choose a Prediction Method** | |
| Prediction Method | IEDB recommended Help on prediction method selections |
| **Specify what to make binding predictions for** | |
| MHC source species | human |
| *Show only frequently occuring alleles:* Select MHC allele(s)<br>Select HLA allele reference set: | Allele Length<br>Upload allele file |
| **Specify Output** | |
| Sort peptides by | Percentile Rank |
| Show | All predictions |
| Output format | XHTML table |
| Email address (optional) | |
| | Submit Reset |

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| | |
|---|---|
| Prediction Method Version | 2013-02-22 [Older versions] |

**Specify Sequence(s)**

| | |
|---|---|
| Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI) | >Region 1<br>SPLPSQAMLDLMLSPDD<br>>Region 2<br>DPGPDEAPWMPEAAPPV |
| Or select file containing sequence(s) | Choose File No file chosen |
| Choose sequence format | auto detect format |

**Choose a Prediction Method**

| | |
|---|---|
| Prediction Method | IEDB recommended — Help on prediction method selections |

**Specify what to make binding predictions for**

| | |
|---|---|
| MHC source species | human |
| *Show only frequently occuring alleles:* Select MHC allele(s)<br>Select HLA allele reference set: | Allele: HLA-A*01:01, HLA-A*02:01, HLA-A*02:06, HLA-A*03:01, HLA-A*11:01, HLA-A*23:01, HLA-A*24:02, HLA-A*25:01, HLA-A*26:01, HLA-A*29:02, HLA-A*30:01, HLA-A*30:02, HLA-A*31:01, HLA-A*32:01 — Length — *Upload allele file* |

**ecify Output**

| | |
|---|---|
| Sort peptides by | |
| Show | |
| Output format | |
| Email address (optional) | |

Submit Reset

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| | |
|---|---|
| Prediction Method Version | 2013-02-22 [Older versions] |

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| | |
|---|---|
| Enter protein sequence(s) in FASTA format or as whitespace-separated sequences. (Browse for sequences in NCBI) | >Region 1<br>SPLPSQAMLDLMLSPDD<br>>Region 2<br>DPGPDEAPWMPEAAPPV |
| Or select file containing sequence(s) | Choose File No file chosen |
| Choose sequence format | auto detect format |

**Choose a Prediction Method**

| | |
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| Prediction Method | IEDB recommended — Help on prediction method selections |

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|---|---|
| MHC source species | human |
| *Show only frequently occuring alleles:* Select MHC allele(s)<br>Select HLA allele reference set: | Allele: HLA-A*02:01 — Length: 9 — *Upload allele file* |

**Sp**

| | |
|---|---|
| Sort peptides by | Percentile Rank |
| Show | All predictions |
| Output format | XHTML table |
| Email address (optional) | |

Length options: 8, 9, 10, 11, 12, 13, 14, All lengths

Submit Reset

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| | |
|---|---|
| Prediction Method Version | 2013-02-22 [Older versions] |

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| | |
|---|---|
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| Or select file containing sequence(s) | Choose File No file chosen |
| Choose sequence format | auto detect format |

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| | |
|---|---|
| Prediction Method | IEDB recommended — Help on prediction method selections |

**Specify what to make binding predictions for**

| | |
|---|---|
| MHC source species | human |
| *Show only frequently occuring alleles:* Select MHC allele(s)<br>Select HLA allele reference set: | Allele: HLA-A*02:01 — Length: 9<br>Upload allele file |

**Specify Output**

| | |
|---|---|
| Sort peptides by | Percentile Rank |
| Show | All predictions |
| Output format | XHTML table |
| Email address (optional) | |

Submit Reset

# MHC-I Binding Predictions

*Loading... please wait.*

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# MHC-I Binding Prediction Results

**Input Sequences**

| # | Name | Sequence |
|---|---|---|
| 1 | Reg 1 | SPLPSQAMLDLMLSPDD |
| 2 | Reg 2 | DPGPDEAPWMPEAAPPV |

**Prediction method: IEDB recommended | Low percentile_rank = good binders**

Download result

Citations

Check to expand the result:

| Allele | # | Start | End | Length | Peptide | Method used | Percentile_rank |
|---|---|---|---|---|---|---|---|
| HLA-A*02:01 | 2 | 9 | 17 | 9 | WMPEAAPPV | Consensus (ann/comblib_sidney2008/smm) | 0.4 |
| HLA-A*02:01 | 1 | 8 | 16 | 9 | MLDLMLSPD | Consensus (ann/comblib_sidney2008/smm) | 2.9 |
| HLA-A*02:01 | 1 | 7 | 15 | 9 | AMLDLMLSP | Consensus (ann/comblib_sidney2008/smm) | 4.0 |
| HLA-A*02:01 | 1 | 5 | 13 | 9 | SQAMLDLML | Consensus (ann/comblib_sidney2008/smm) | 7.7 |
| HLA-A*02:01 | 1 | 6 | 14 | 9 | QAMLDLMLS | Consensus (ann/comblib_sidney2008/smm) | 26.0 |
| HLA-A*02:01 | 2 | 5 | 13 | 9 | DEAPWMPEA | Consensus (ann/comblib_sidney2008/smm) | 32.0 |
| HLA-A*02:01 | 1 | 1 | 9 | 9 | SPLPSQAML | Consensus (ann/comblib_sidney2008/smm) | 33.0 |
| HLA-A*02:01 | 1 | 3 | 11 | 9 | LPSQAMLDL | Consensus (ann/comblib_sidney2008/smm) | 39.0 |
| HLA-A*02:01 | 1 | 4 | 12 | 9 | PSQAMLDLM | Consensus (ann/comblib_sidney2008/smm) | 43.0 |

# Evaluating binding predictions

- Percentile rank < 0.5% = high affinity binder
- Percentile rank 0.5%-1% = intermediate binder
- Percentile rank 1% - 2% = low affinity binder
- Percentile rank 2% - 5% = borderline
- Percentile rank >5% is a non-binder

# Overview

- Background Biology: The immune system can detect and eliminate mutated cancer cells
- Background Immunoinformatics: Mutations that can be recognized by T cells can be predicted
- Hands on: Design a personalized cancer vaccine

# Hands On Part 2.2

- Step 1: Identify sequence regions that contain all 9-mer peptides that are only found in the tumor
- Step 2: Run HLA binding prediction to identify 9-mer peptides in the sequence regions unique to the tumor to select peptides that can be presented to T cells in this patient
- Step 3: Determine if the identified peptides are specific for the tumor
- Final question: Which peptide would you choose?

Bonus problem: Start with DNA sequencing data

# HLA binding Prediction on IEDB

**Peptides:**

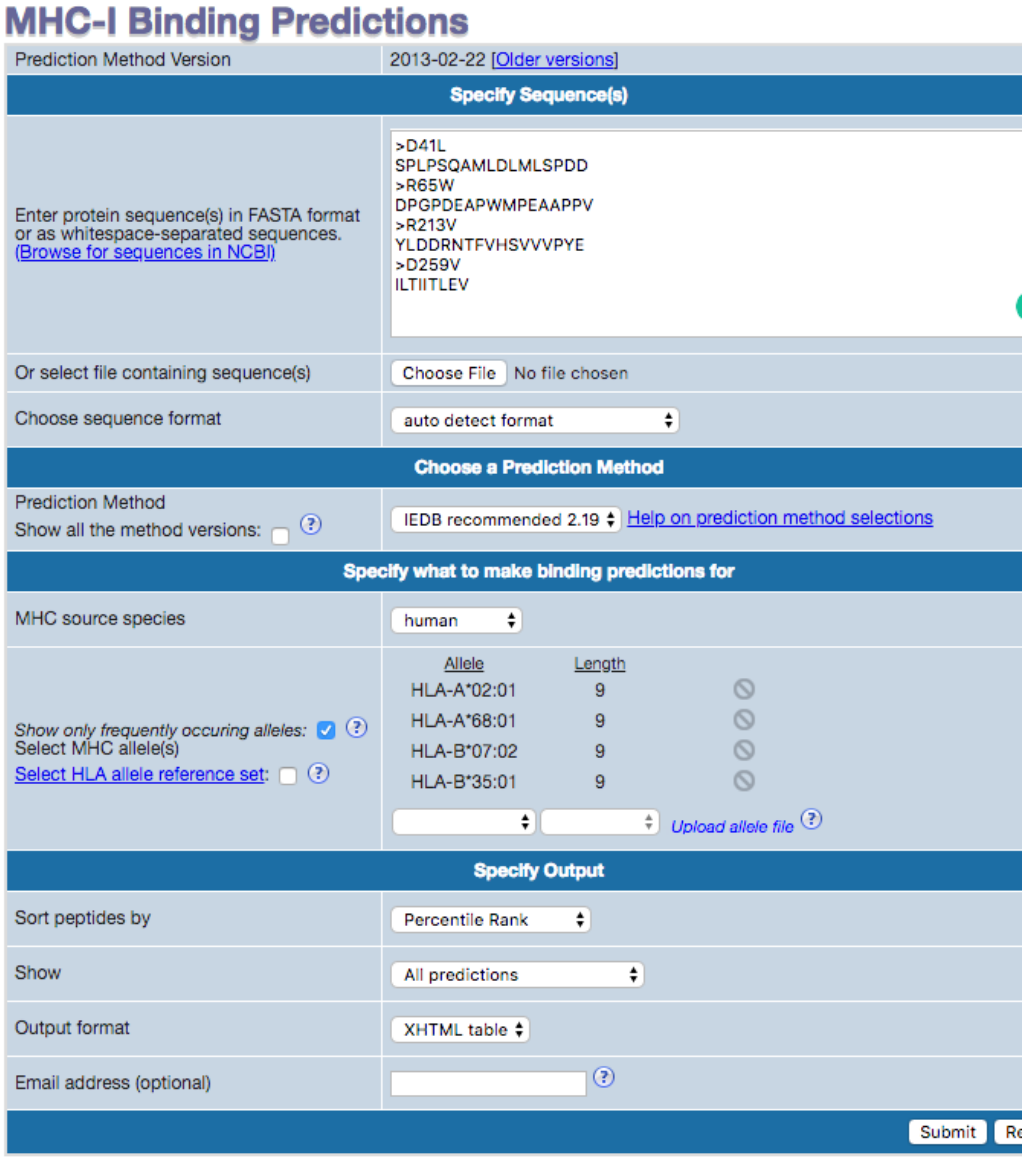
```
>D41L
SPLPSQAMLDLMLSPDD
>R65W
DPGPDEAPWMPEAAPPV
>R213V
YLDDRNTFVHSVVVPYE
>D259V
ILTIITLEV
```

**HLA Alleles:**

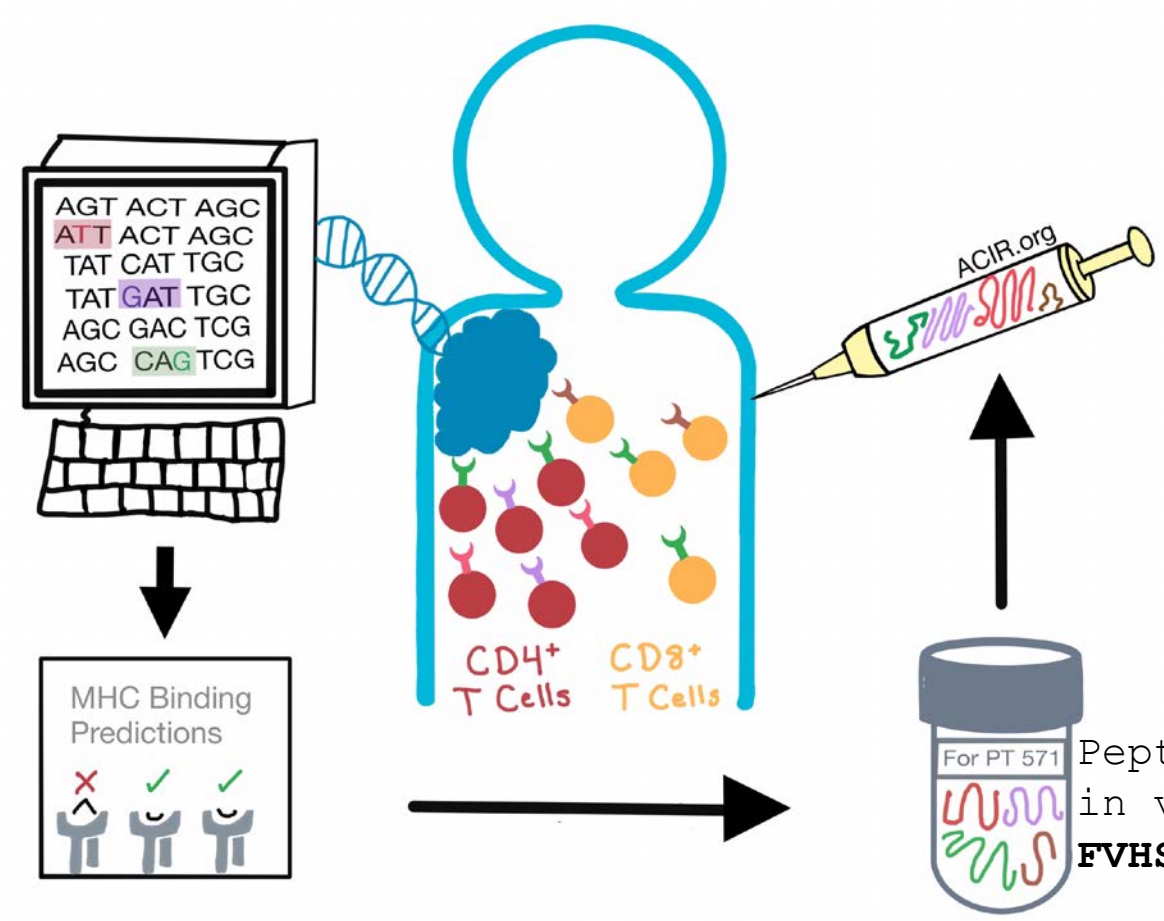
```
HLA-A*02:01
HLA-A*68:01
HLA-B*07:02
HLA-B*35:01
```

**Length:**

9



# Personalized Vaccines for Cancer Immunotherapy




Peptide included in vaccine:
**FVHSVVVPY**

# Contact & Feedback

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Zeynep Kosaloglu Yalcin
zeynep@lji.org

**Feedback link** < https://goo.gl/forms/jfrqJHVq0SzCF4JC3 >

# Input data from patient:

**>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGP
DEAPRMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

**>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMLDLMLSPDDIEQWFTEDPGP
DEAPWMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFVHSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLEV

# Mutated sites

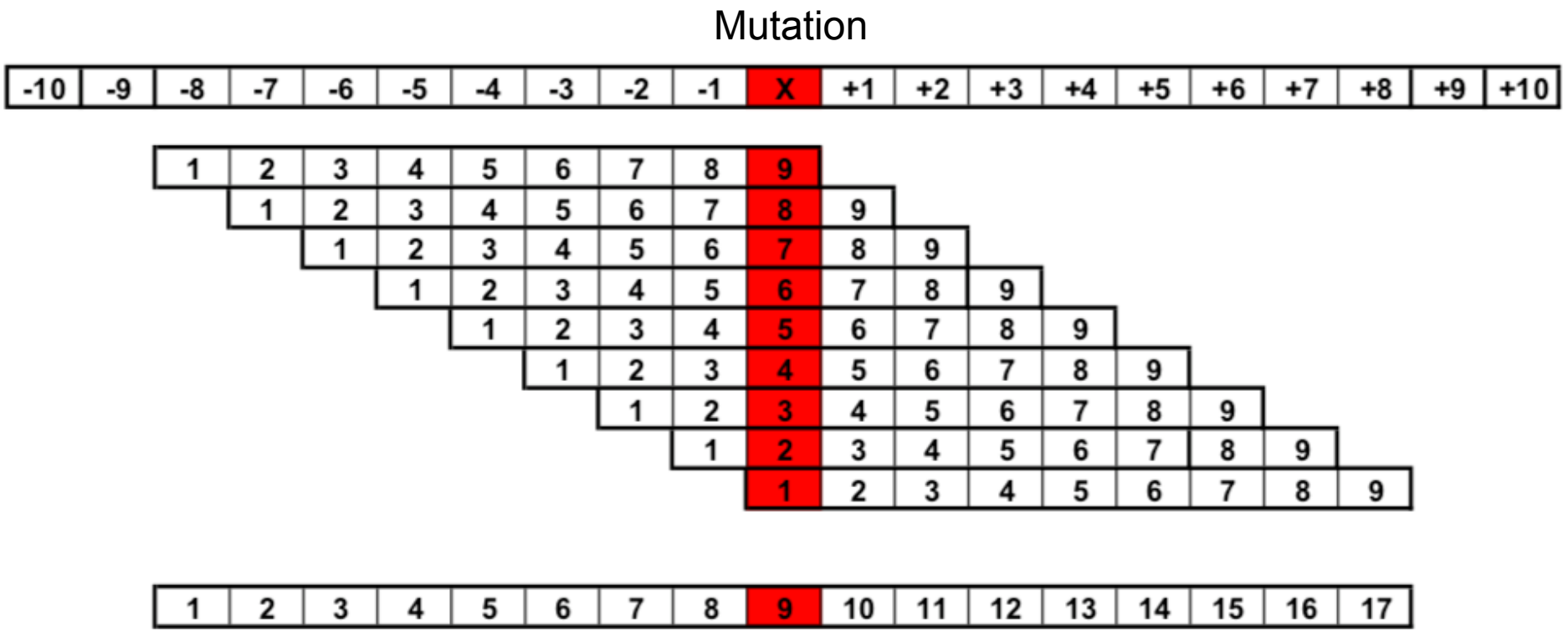
**>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAM**D**DLMLSPDDIEQWFTEDPGP
DEAP**R**MPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**R**HSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**D**SSGNLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

**>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAM**L**DLMLSPDDIEQWFTEDPGP
DEAP**W**MPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**V**HSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**V**

# How long do the sequence regions that contain all 9-mer peptides with the mutation need to be?




➔ 17-mer peptide will cover all 9-mers that contain the mutation

# Mutated regions

**>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAM**D**DLMLSPDDIEQWFTEDPGP
DEAP**R**MPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**R**HSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**D**SSGNLLGRNSFEVRVCACPGRDRRTEEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD

**>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue**

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAM**L**DLMLSPDDIEQWFTEDPGP
DEAP**W**MPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**V**HSVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**V**

**>D41L**

SPLPSQAMLD**L**MLSPDD

**>R65W**

DPGPDEAP**W**MPEAAPPV

**>R213V**

YLDDRNTF**V**HSVVVPYE

**>D259V**

ILTIITLE**V**