

Towards personalized cancer treatments using Immunoinformatics

Bjoern Peters

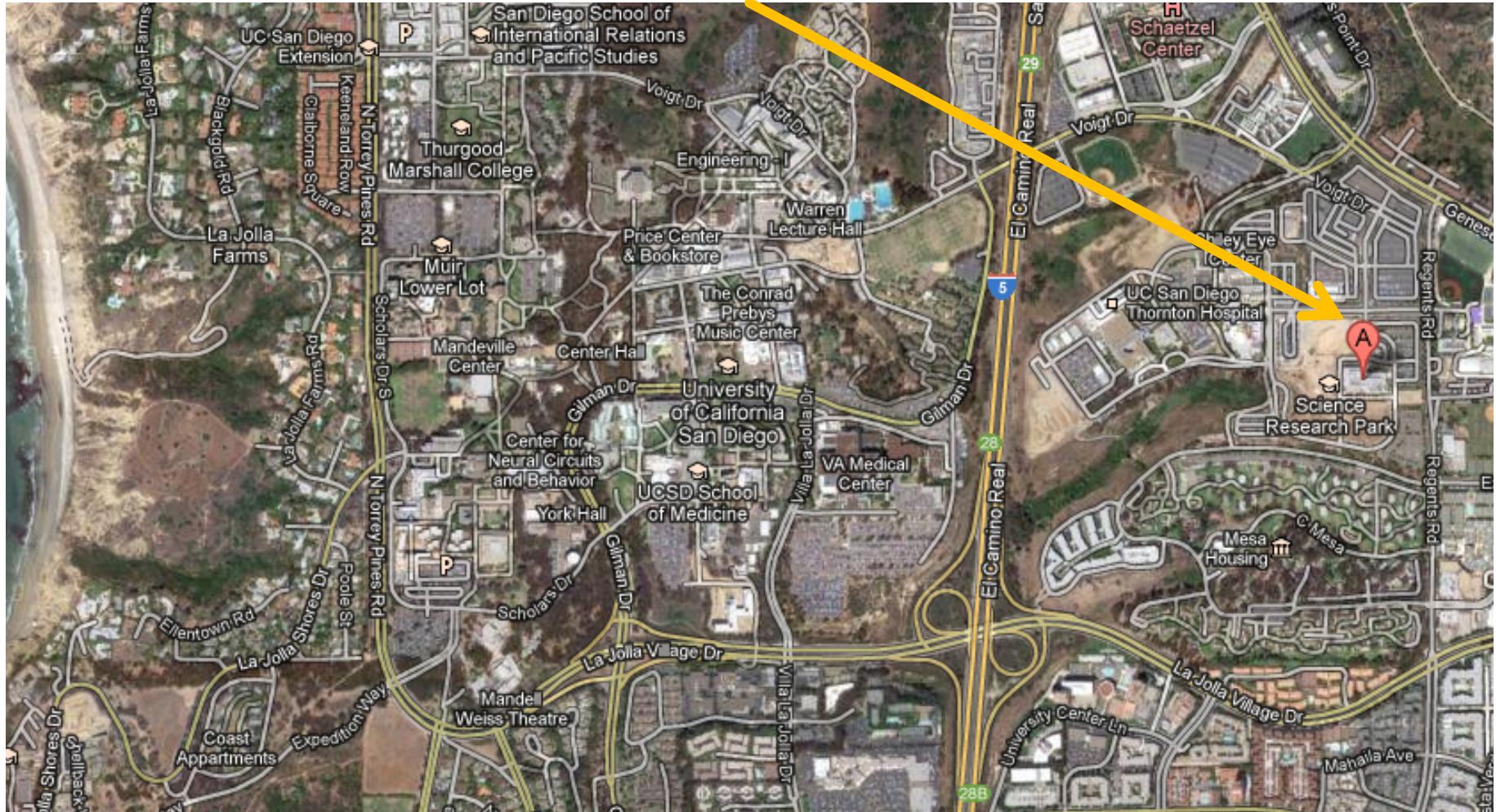
Zeynep Kosaloglu-Yalcin

La Jolla Institute for Immunology

La Jolla
Institute
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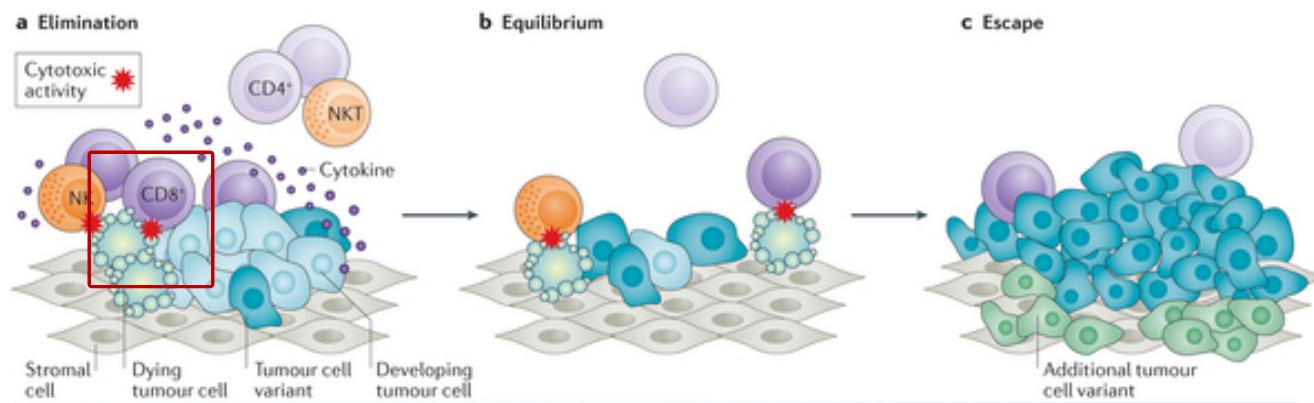


Overview

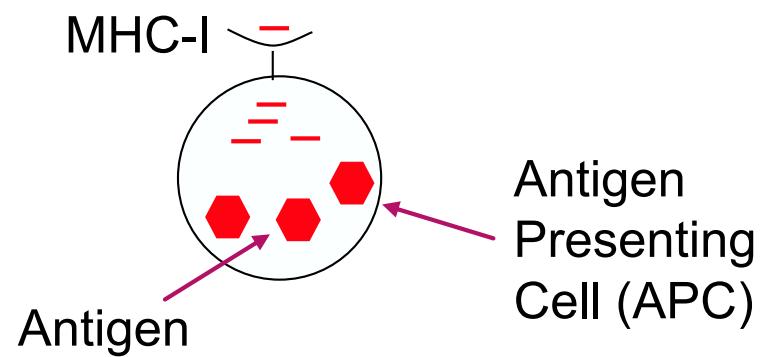
- 
- Background Biology: The immune system can detect and eliminate mutated cancer cells
 - Background Immunoinformatics:
 - Mutations can be detected using patient sequencing data
 - Mutations that can be recognized by T cells can be predicted
 - Hands on: Design a personalized cancer vaccine

Cancer immune surveillance and escape

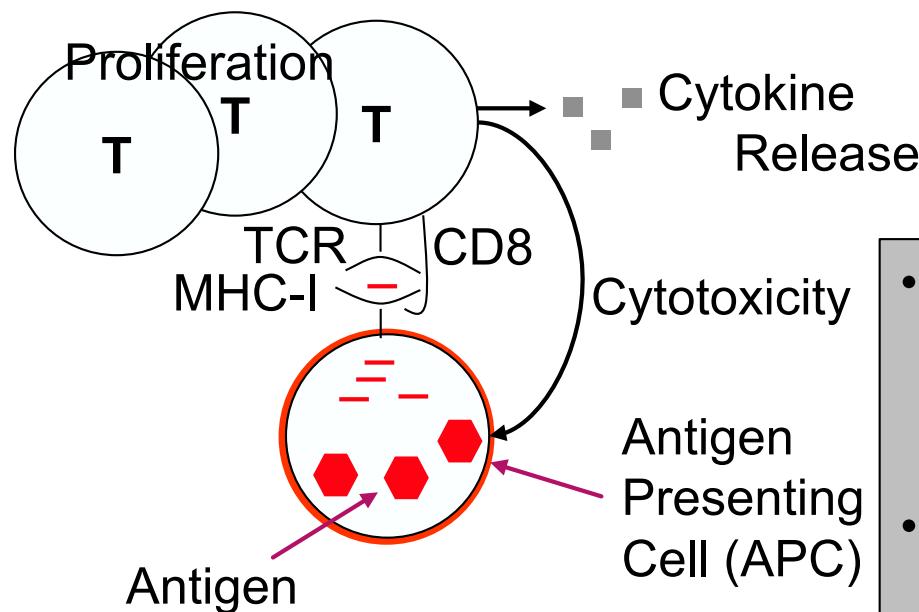
- Mutations in cells occur frequently
- The immune system has the capacity to detect and eliminate such mutated cells, and will do so on a regular basis
- Only when mutated cells find ways to hide from- or suppress an attack by the immune system, they can grow and spread unhindered leading to clinically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



CD8⁺ T cell epitope recognition



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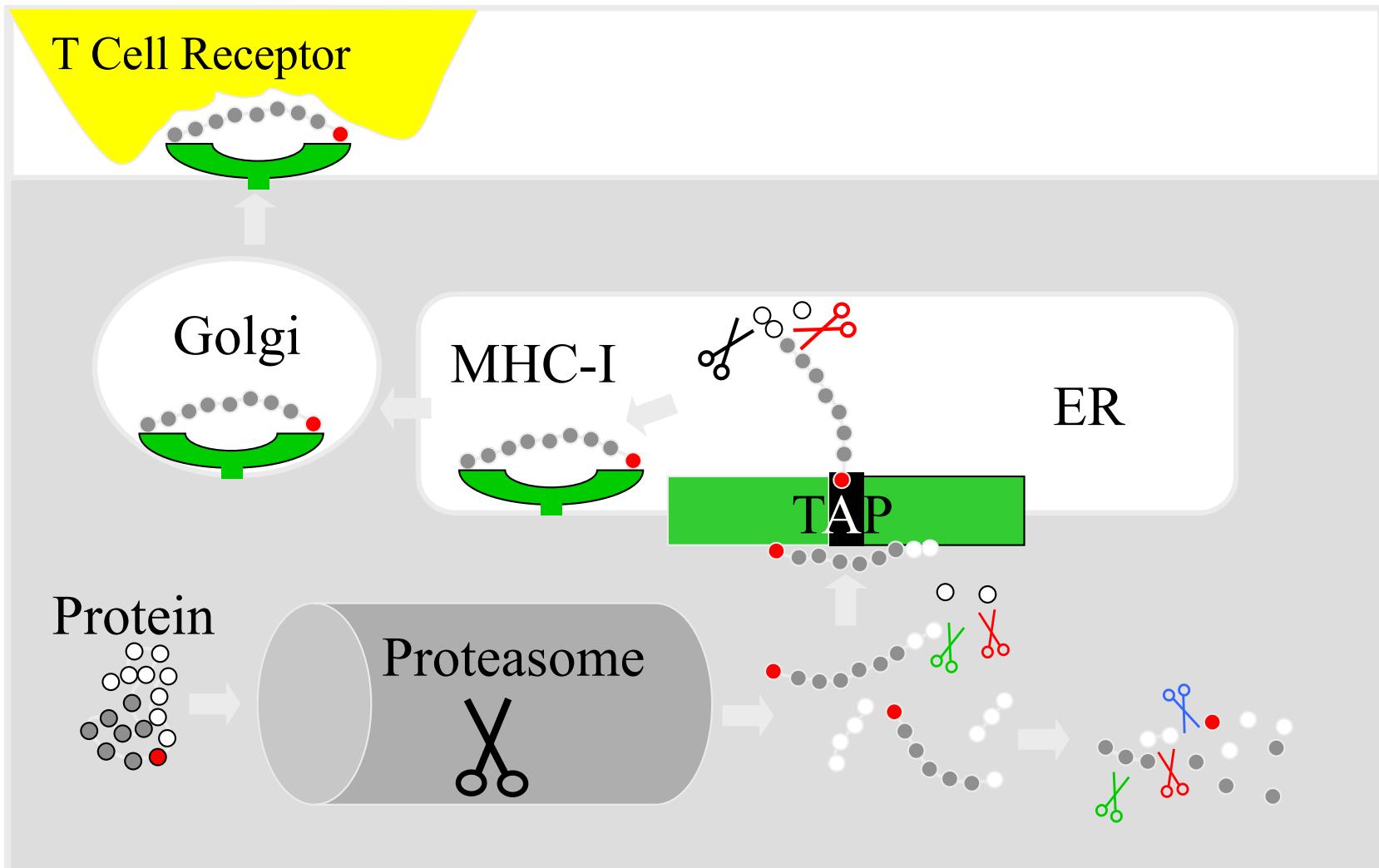


- What determines what peptides are presented by MHC molecules on the cell surface?
- How do T cells distinguish self- from non-self peptides?

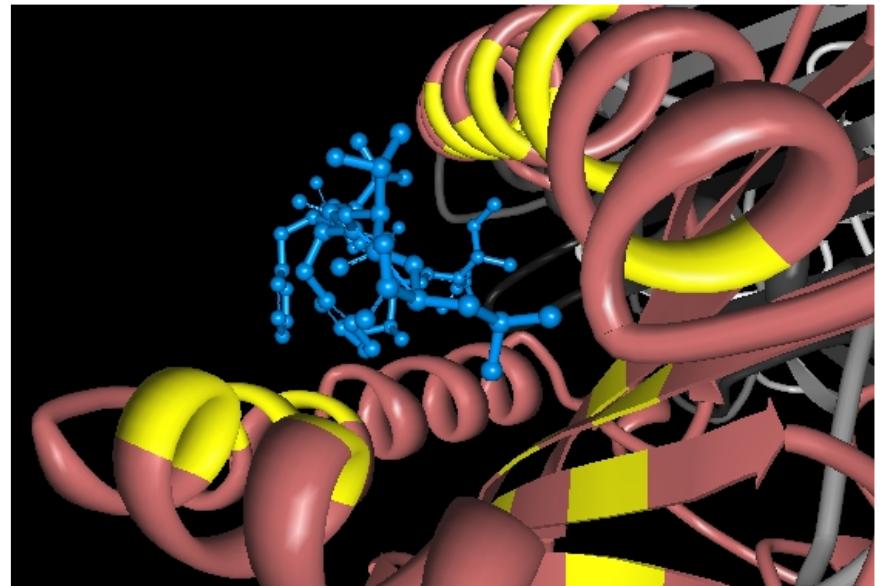
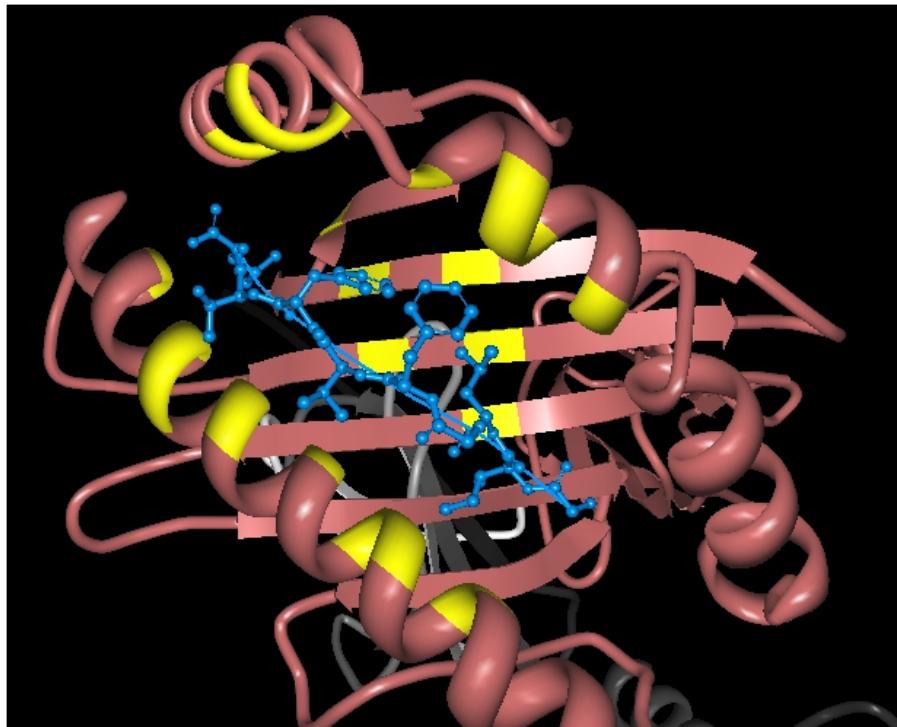
Antigen M L M R N H L L D L M G V P Y C N Y S K F W Y L E H A K T G E T S V P K C ...

Epitope

MHC I - Antigen processing and presentation pathway



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

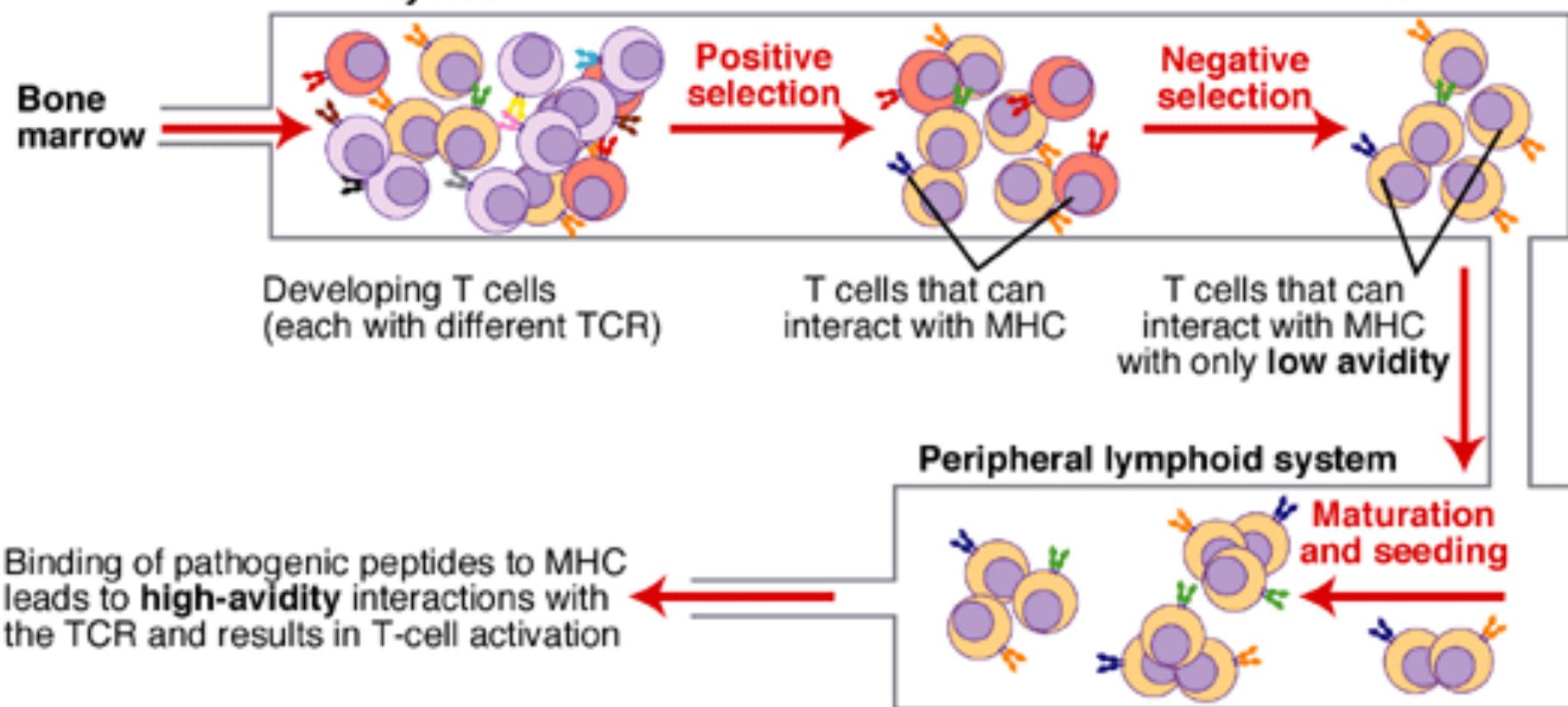
Viewer: Beaver and Ponomarenko, Immunome Research, 2007

Self-reactive T cells are deleted during maturation

Random generation of T cells with random specificity

→ They will recognize anything including self-proteins!

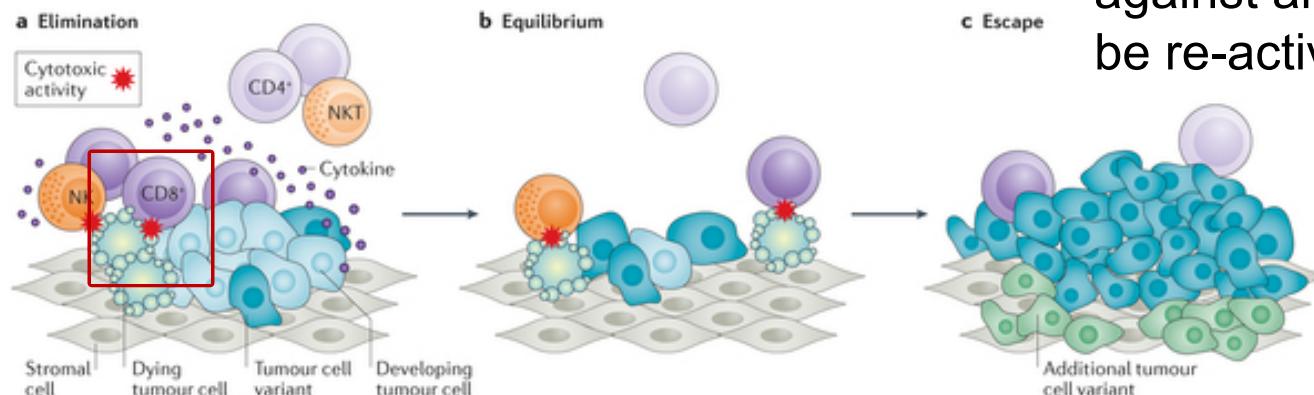
Thymus



The repertoire of T cells is shaped by both positive and negative selection
Expert Reviews in Molecular Medicine © 1999 Cambridge University Press

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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 [...]”



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Mahmoud
James P. Allison



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Mahmoud
Tasaku Honjo

“for their discovery of cancer therapy by inhibition of negative immune regulation”

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.

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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.

Personalized Cancer Immunotherapy



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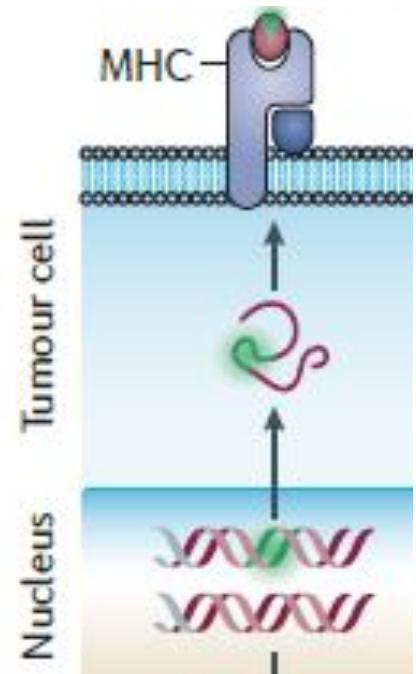
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Overview

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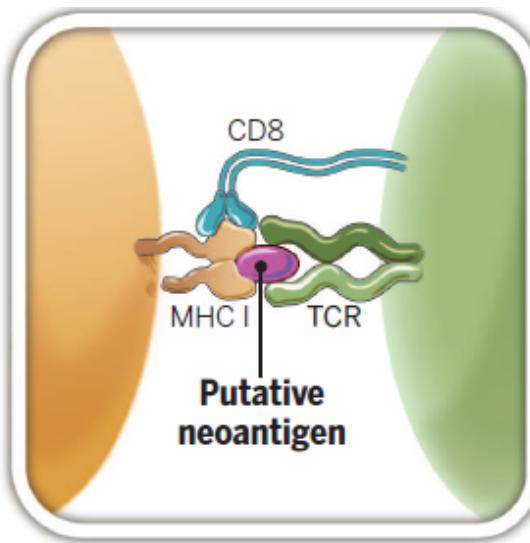
Neoepitopes (Neoantigens)

- 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

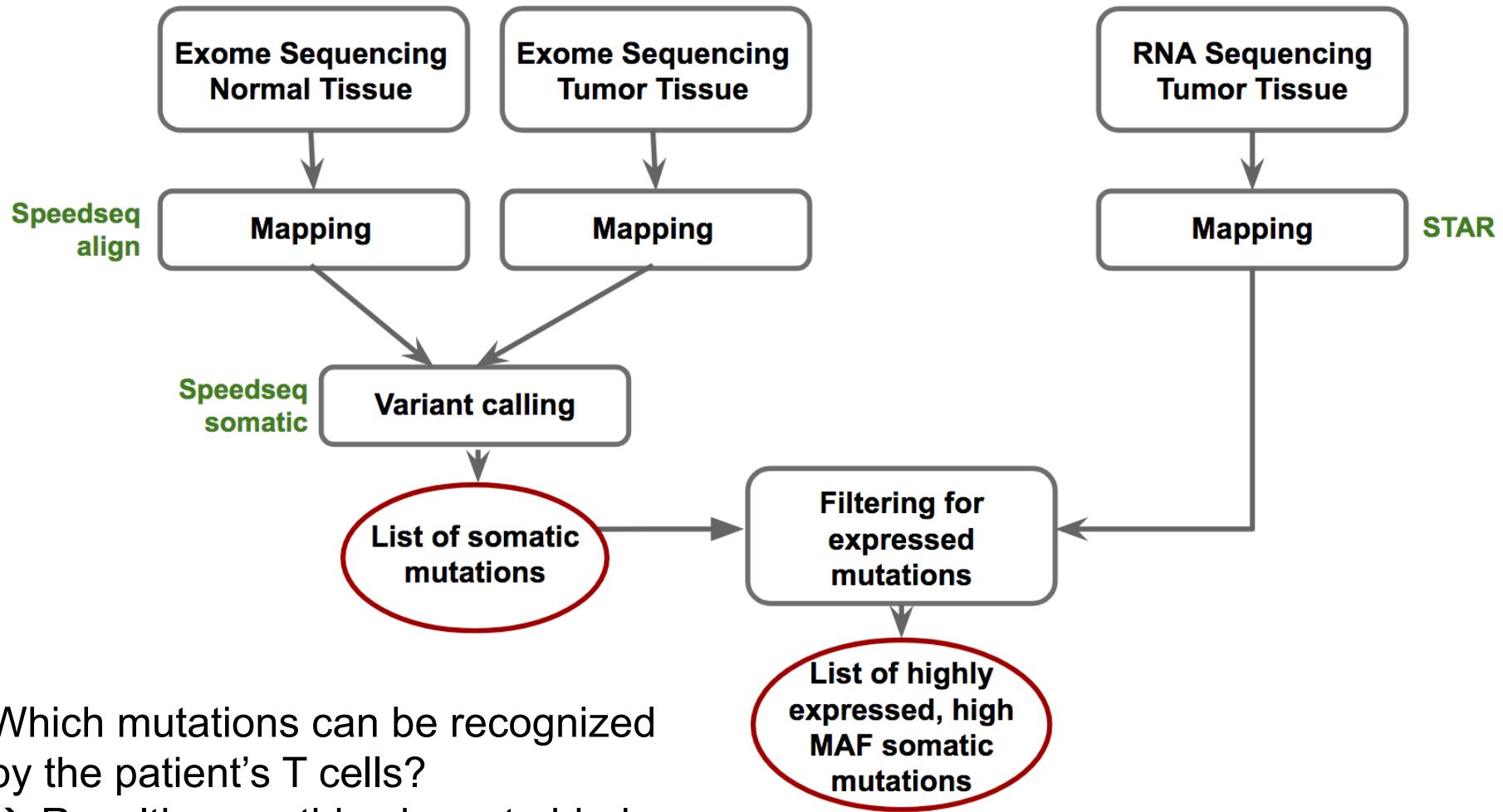


Neoepitopes are presumably recognized by tumor-infiltrating lymphocytes (**TILs**)

Neoepitopes are highly tumor-specific!



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

```
MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPSQAMDDLMLSPDDIEQWFTEDPGP  
DEAPRMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK  
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIIYKQSQHMTEVVRCPHHE  
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFRHSVVVPYEPPEVGSDCTTIHYNYMCNS  
SCMGGMNRRPILTITLEDSSGNLLGRNSFEVRVCACPGDRRTEEENLRKKGEPHHELP  
PGSTKRALPNNTSSSPQPKKPQLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG  
GSRAHSSHLSKSKKGQSTSRRHKKLMFKTEGPDS
```

>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue

```
MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPSQAMDDLMLSPDDIEQWFTEDPGP  
DEAPWMPEAAPPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSYGFRLGFLHSGTAK  
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIIYKQSQHMTEVVRCPHHE  
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTFVHSVVVPYEPPEVGSDCTTIHYNYMCNS  
SCMGGMNRRPILTITLEV
```

Mutated sites

>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPSQAM**D**DLMLSPDDIEQWFTEDPGP
DEAP**R**MPEAAPVAPAPAAPTPAAPAPAPS**W**PLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMA**I**YKQSQHMTEVVRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**R**HVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**D**SSGNLLGRNSFEVRVCACPGDRRTEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKP**L**DGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLSKKQSTS**R**HKKLMFKTEGPDSD

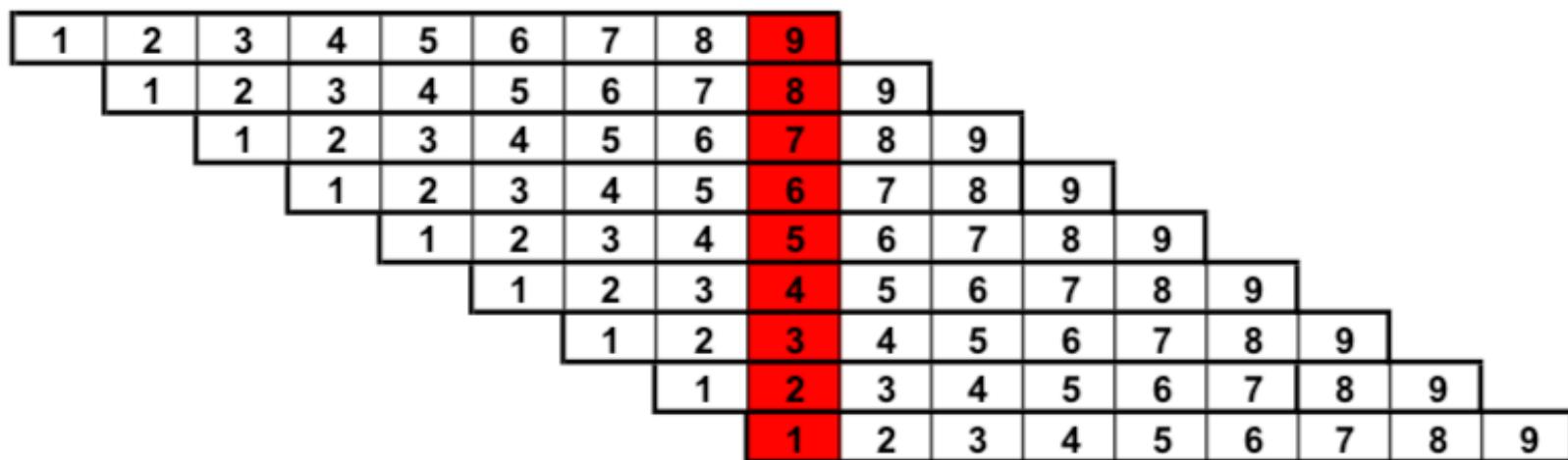
>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPSQAM**L**DLMLSPDDIEQWFTEDPGP
DEAP**W**MPEAAPVAPAPAAPTPAAPAPAPS**W**PLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMA**I**YKQSQHMTEVVRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**V**HVVVPYEPPEVGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**V**

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

Mutation

-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	X	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
-----	----	----	----	----	----	----	----	----	----	---	----	----	----	----	----	----	----	----	----	-----



1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----

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

Mutated regions

>P53_HUMAN Cellular tumor antigen p53 - Healthy Tissue

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPSQAM**D**DLMLSPDDIEQWFTEDPGP
DEAP**R**MPEAAPPVAPAPAAPTPAAPAPAPS**W**PLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**R**HHSVVPYEPP**E**VGSDCTTIHYNYMCNS
SCMGGMNRRPILTIITLE**D**SSGNLLGRNSFEVRVCACPGDRRTEENLRKKGEPHHELP
PGSTKRALPNNTSSSPQPKKPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPG
GSRAHSSHLKSKGQSTSRHKKLMFKTEGPDSD

>P53_HUMAN Cellular tumor antigen p53 - Tumor Tissue

MEEPQSDPSVEPPLSQETFSDLWKLLPENNVL**SPLPSQAMLDLMLSPDDIEQWFTEDPGP**
DEAPWMPEAAPPVAPAPAAPTPAAPAPAPS**W**PLSSSVPSQKTYQGSYGFRLGFLHSGTAK
SVTCTYSPALNKMFCQLAKTCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTEVVRRCPHHE
RCSDSDGLAPPQHLIRVEGNLRVEYLDDRNTF**V**HHSVVPYEPP**E**VGSDCTTIHYNYMCNS
SCMGGMNRRP**ILTIITLEV**

>D41L

SPLPSQAM**L**DLMLSPDD

>R65W

DPGPDEAP**W**MPEAAPPV

>R213V

YLDDRNTF**V**HHSVVPYE

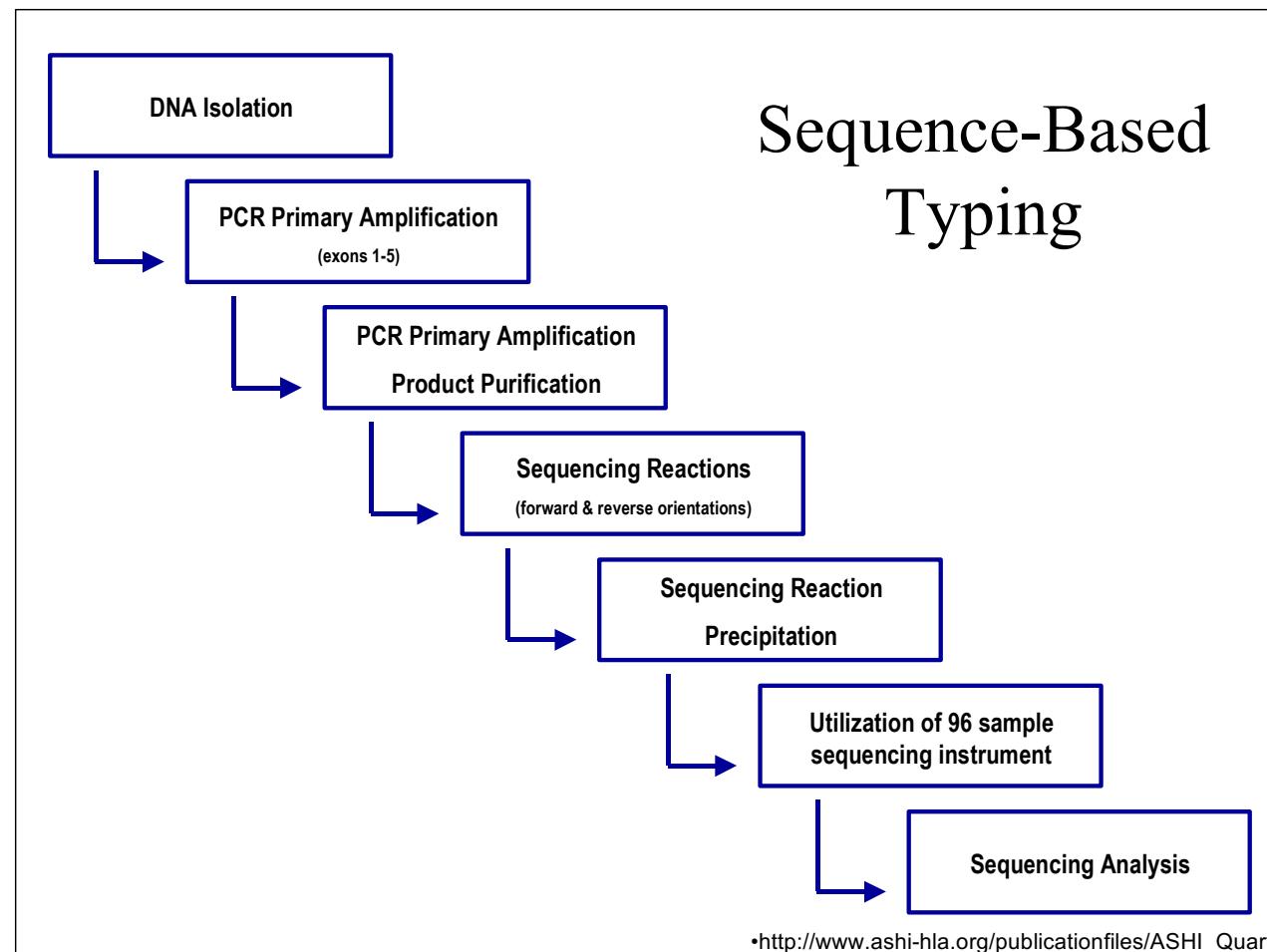
>D259V

ILTIITLE**V**

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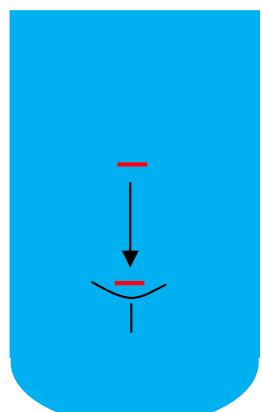
HLA Typing: Targeted sequencing of HLA locus



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
LKGPDIFYKG	308
NFCNLTSAF	50,000
AQSQCRTFR	38,000
CTYAGPFGM	143
CFGNTAVAK	50,000
...	

$\log(\text{IC}_{50}) \sim \text{Binding free Energy}$

low IC₅₀ → high affinity

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 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 ...

Impossible to measure all peptides

→ Predict binding peptides using machine learning

Find function F_i in F_1, F_2, F_3, \dots
 $F_i(\text{Sequence}) \approx \text{Affinity}$

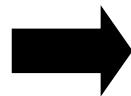
Many different approaches
(ANN, SVM, HMM, LP, ...)

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

<u>log (IC50)</u>	Peptide
0.50	FQPQNGSFI
0.72	ISVANKIYM
2.37	RVYEALYYV
3.42	FQPQSGQFII
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)

 No file chosen

Choose sequence format

Choose a Prediction Method

Prediction Method

Specify what to make binding predictions for

MHC source species

Show only frequently occurring alleles: [?](#)
Select MHC allele(s)

Select HLA allele reference set: [?](#)

 [?](#)

Specify Output

Sort peptides by

Show

Output format

Email address (optional)

Specify Sequence(s)

Enter protein sequence(s) in FASTA format or as whitespace-separated sequences.
[\(Browse for sequences in NCBI\)](#)

```
>Region 1
SPLPSQAMLDLMLSPDD
>Region 2
DPGPDEAPWMPEAAPPV
```

Or select file containing sequence(s)

No file chosen

Choose sequence format

Choose a Prediction Method

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[Select HLA allele reference set:](#) [?](#)

[?](#)

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

Sort peptides by

Show

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Email address (optional)

Specify Sequence(s)

Enter protein sequence(s) in FASTA format or as whitespace-separated sequences.
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```
>Region 1
SPLPSQAMLDLMLSPDD
>Region 2
DPGPDEAPWMPEAAPV
```

Or select file containing sequence(s)

No file chosen

Choose sequence format

Choose a Prediction Method

Prediction Method

Specify what to make binding predictions for

MHC source species

Show only frequently occurring alleles: [?](#)
Select MHC allele(s)

[Select HLA allele reference set:](#) [?](#)

Allele	Length
HLA-A*02:01	8
	9
	10
	11
	12
	13
	14

[Upload allele file](#) [?](#)

Sort peptides by

Show

Output format

[All lengths](#)

Email address (optional)

Specify Sequence(s)

Enter protein sequence(s) in FASTA format or as whitespace-separated sequences.
[\(Browse for sequences in NCBI\)](#)

```
>Region 1
SPLPSQAMLDLMLSPDD
>Region 2
DPGPDEAPWMPEAAPV
```

Or select file containing sequence(s)

No file chosen

Choose sequence format

Choose a Prediction Method

Prediction Method

Specify what to make binding predictions for

MHC source species

Show only frequently occurring alleles: [?](#)
Select MHC allele(s)

[Select HLA allele reference set:](#) [?](#)

Allele	Length
HLA-A*02:01	9

[Upload allele file](#) [?](#)

Specify Output

Sort peptides by

Show

Output format

Email address (optional)

[?](#)

MHC-I Binding Predictions

 Loading... please wait.

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Supported by a contract from the [National Institute of Allergy and Infectious Diseases](#), a component of the National Institutes of Health in the Department of Health and Human Services

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/complib_sidney2008/smm)	0.4
HLA-A*02:01	1	8	16	9	MLDMLMLSPD	Consensus (ann/complib_sidney2008/smm)	2.9
HLA-A*02:01	1	7	15	9	AMLDLMLSP	Consensus (ann/complib_sidney2008/smm)	4.0
HLA-A*02:01	1	5	13	9	SQAMLDLML	Consensus (ann/complib_sidney2008/smm)	7.7
HLA-A*02:01	1	6	14	9	QAMLDLMLS	Consensus (ann/complib_sidney2008/smm)	26.0
HLA-A*02:01	2	5	13	9	DEAPWMPEA	Consensus (ann/complib_sidney2008/smm)	32.0
HLA-A*02:01	1	1	9	9	SPLPSQAML	Consensus (ann/complib_sidney2008/smm)	33.0
HLA-A*02:01	1	3	11	9	LPSQAMLDL	Consensus (ann/complib_sidney2008/smm)	39.0
HLA-A*02:01	1	4	12	9	PSQAMLDLM	Consensus (ann/complib_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?

HLA binding Prediction on IEDB

Peptides:

>D41L
SPLPSQAMLD**L**MLSPDD
>R65W
DPGPDEAP**W**MPEAAPPV
>R213V
YLDDRNTF**V**HSVVVPYE
>D259V
ILT**I**TLEV

HLA Alleles:

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

Length:

9

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](#))

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

Or select file containing sequence(s) No file chosen

Choose sequence format

Choose a Prediction Method

Prediction Method Show all the method versions: ? IEDB recommended 2.19

Specify what to make binding predictions for

MHC source species

Show only frequently occurring alleles: ? Select MHC allele(s) ? Select HLA allele reference set: ? ?

Allele	Length	
HLA-A*02:01	9	<input type="checkbox"/>
HLA-A*68:01	9	<input type="checkbox"/>
HLA-B*07:02	9	<input type="checkbox"/>
HLA-B*35:01	9	<input type="checkbox"/>

Specify Output

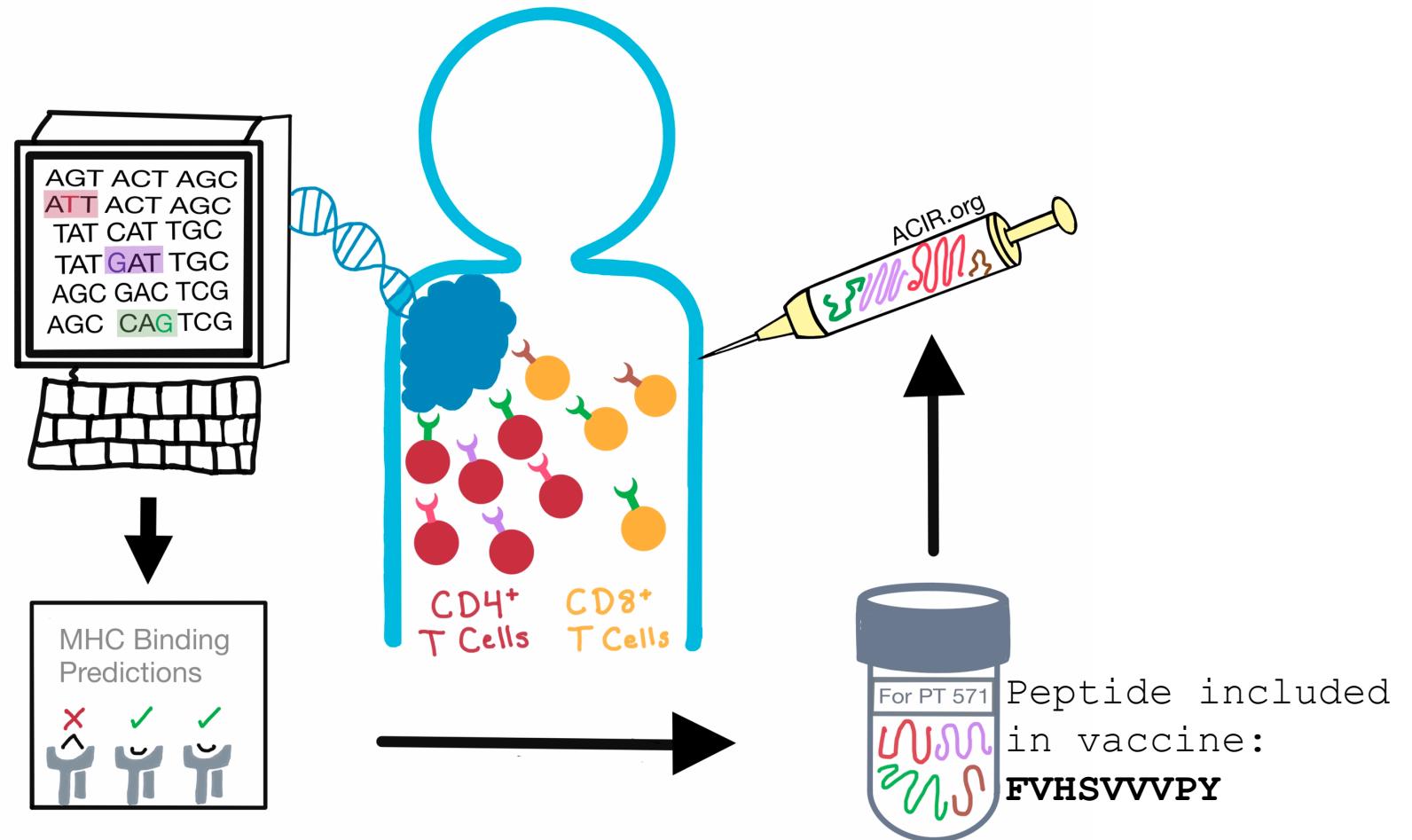
Sort peptides by

Show

Output format

Email address (optional)

Personalized Vaccines for Cancer Immunotherapy



Contact & Feedback

Bjoern Peters

bpeters@lji.org

Zeynep Kosaloglu Yalcin

zeynep@lji.org

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