Towards personalized cancer treatments using Immunoinformatics

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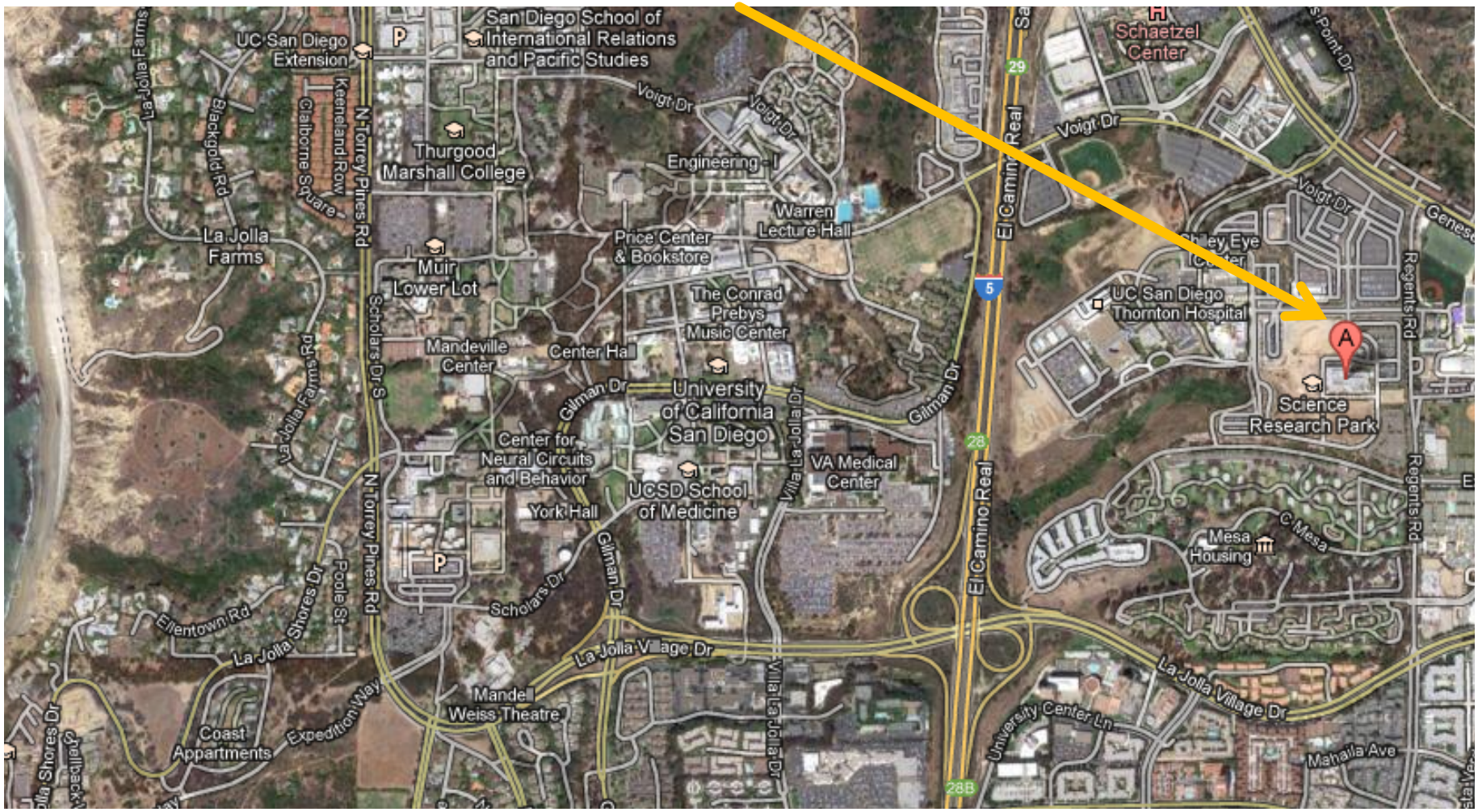
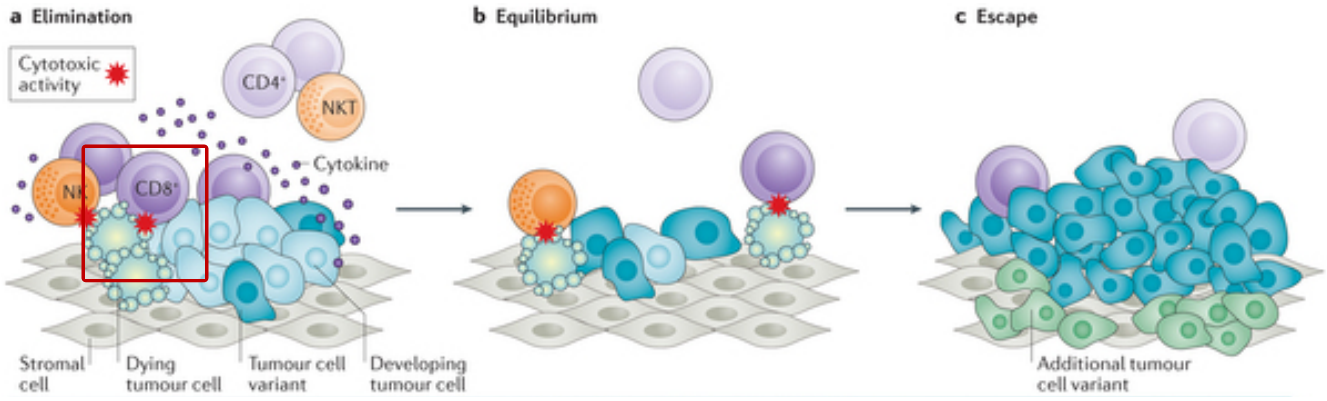


Overview

- 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

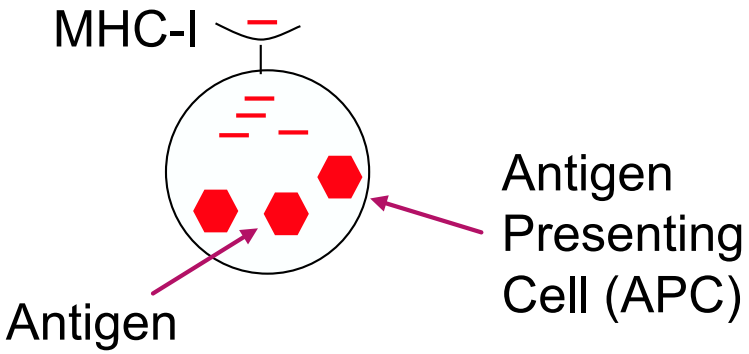
Cancer immune surveillance and escape

- 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

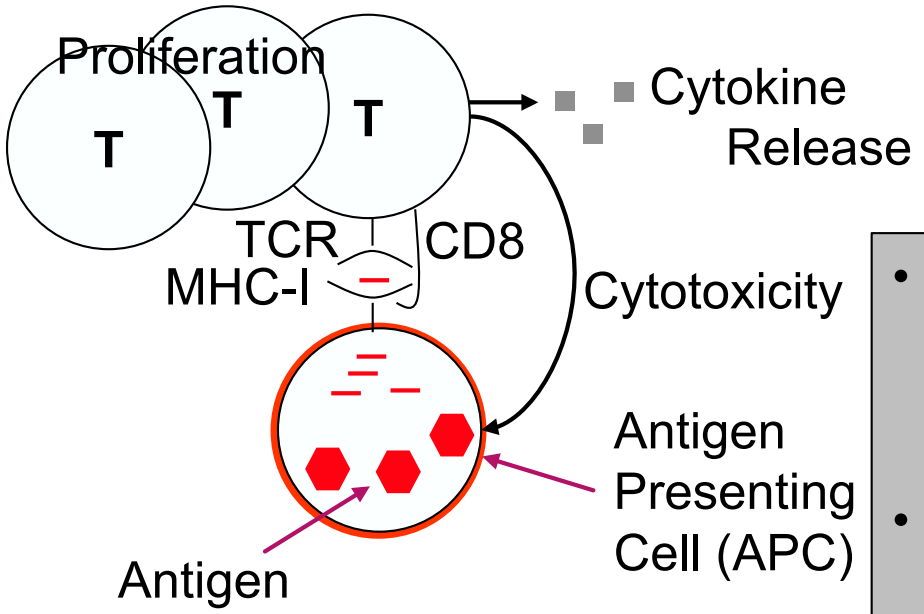


Van der Burg et al, Nature Reviews Cancer 16, 219–233 (2016)

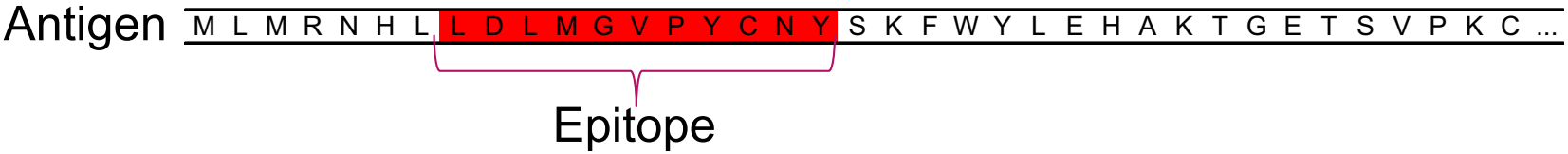
CD8$^+$ T cell epitope recognition



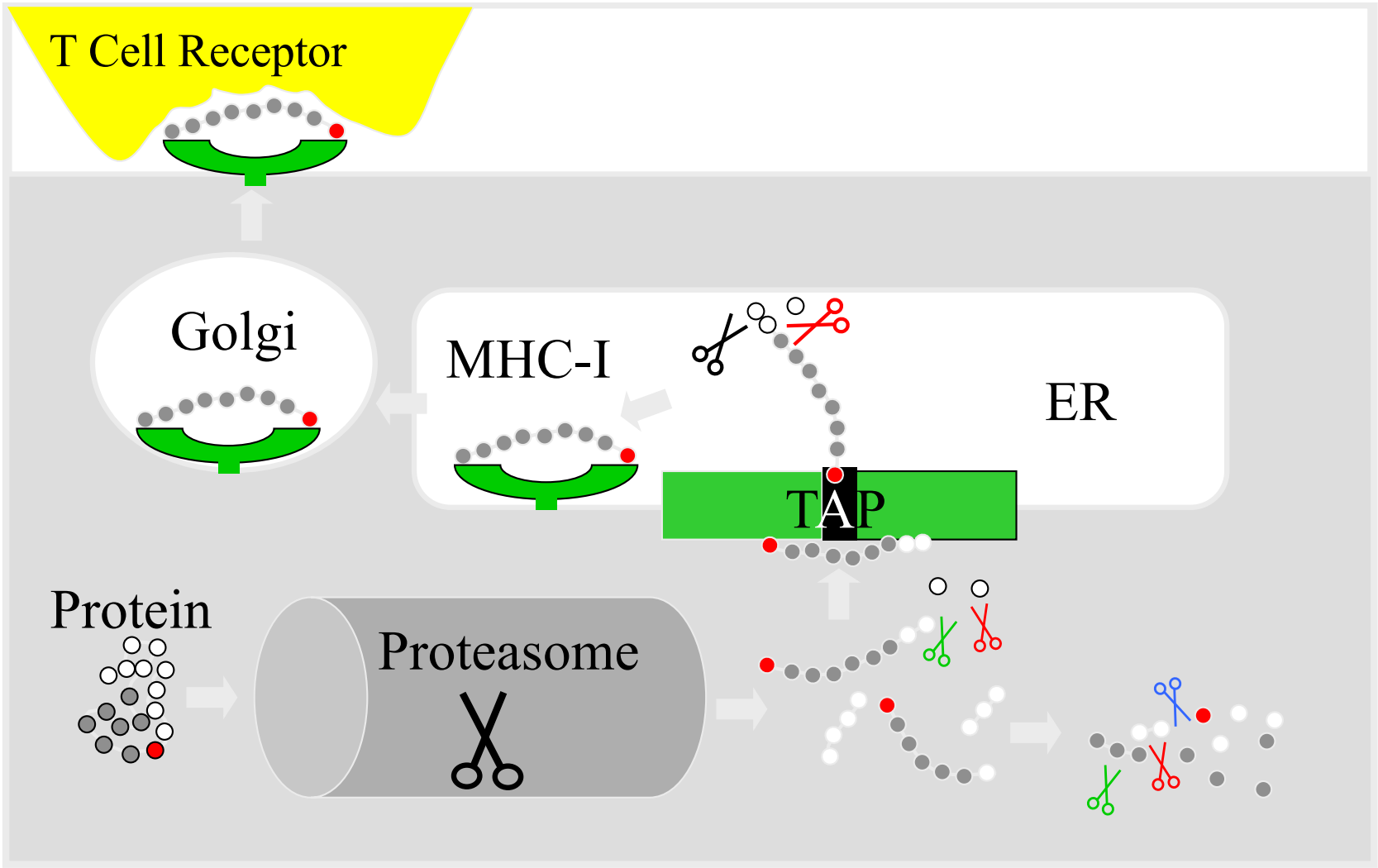
CD8+ T cell epitope recognition



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

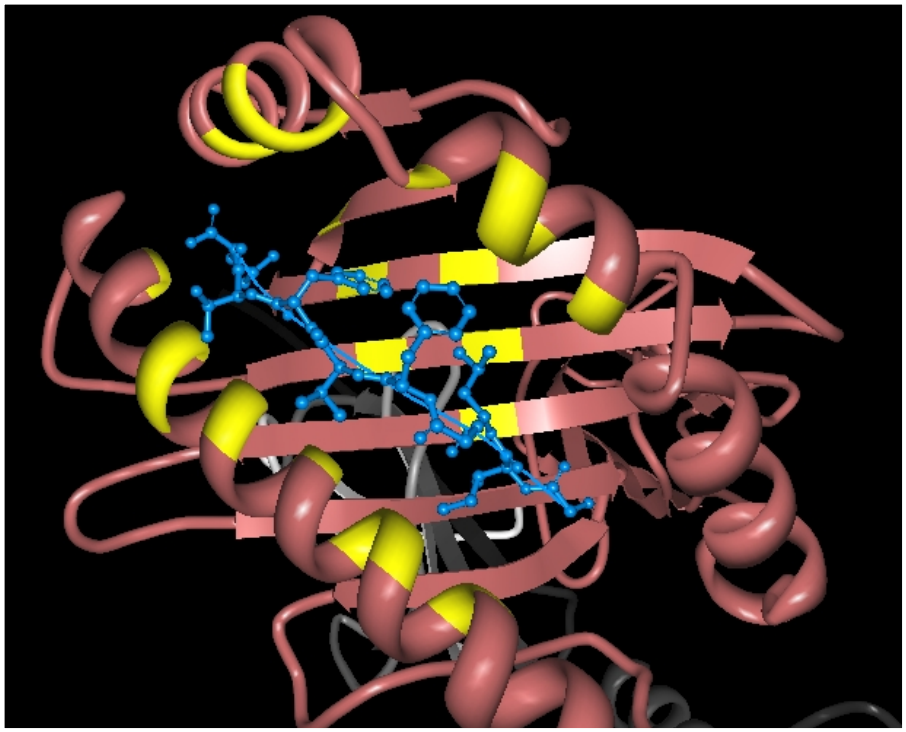


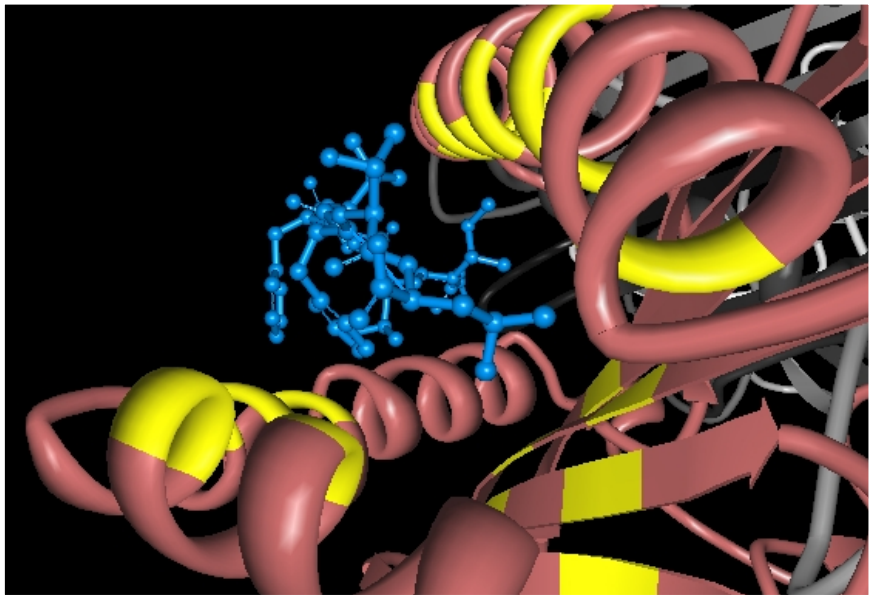
MHC I - Antigen processing and presentation pathway



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

MHC:peptide binding mode

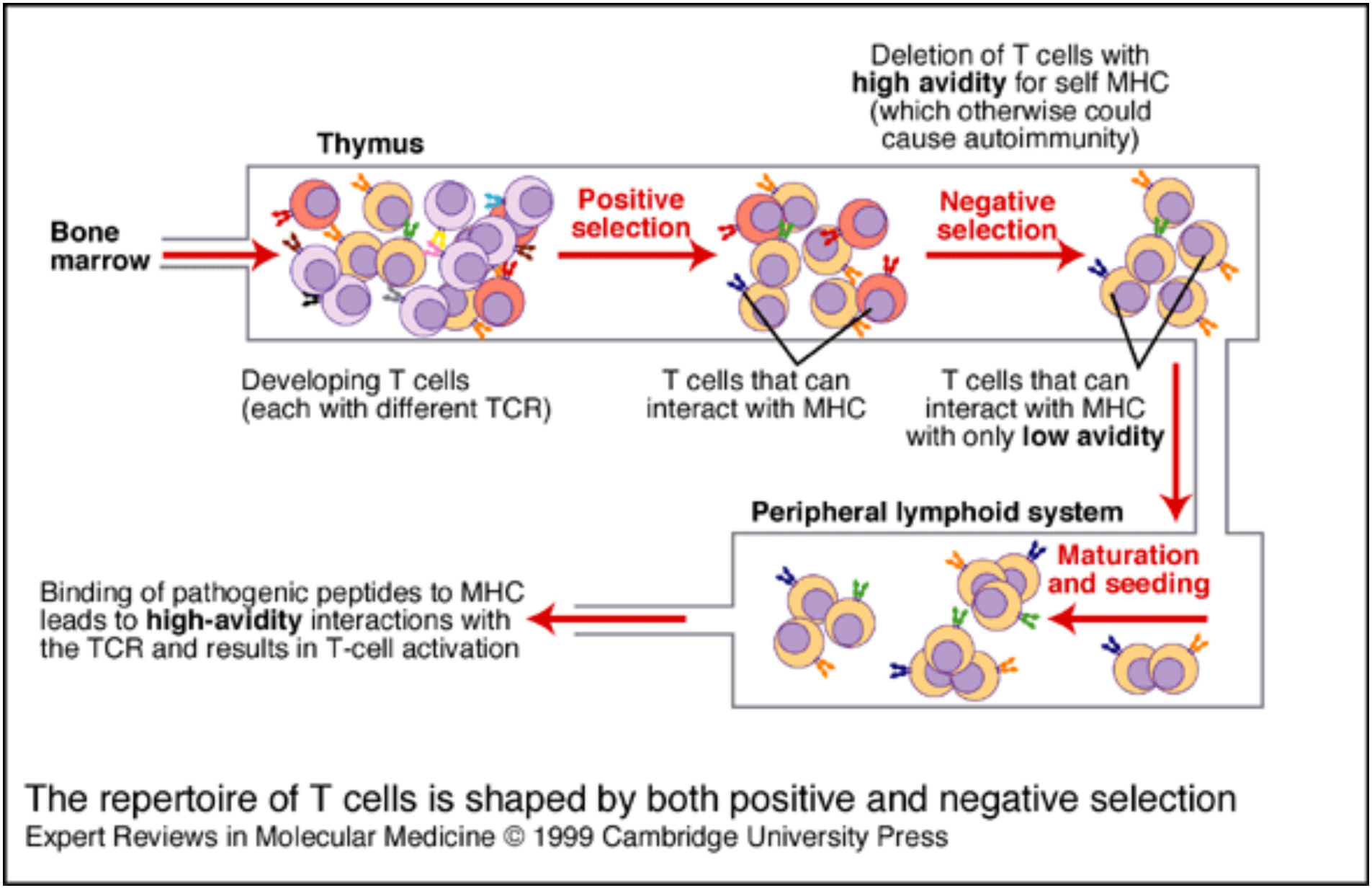




- Each human expresses up to 6 different MHC-I molecules in every cell
- >3000 MHC variants are known
- Distinct binding specificities → individual epitope repertoire

Viewer: Beaver and Ponomarenko, Immunome Research, 2007

Self –reactive T cells are deleted during maturation



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

Cancer immune surveillance and escape

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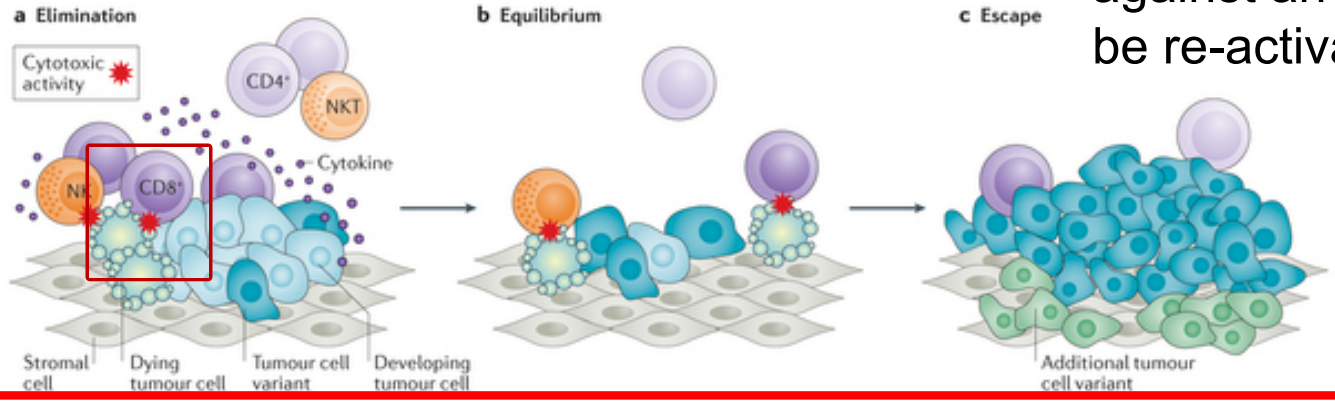
Can the immune response against an 'escaped' cancer be re-activated?



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

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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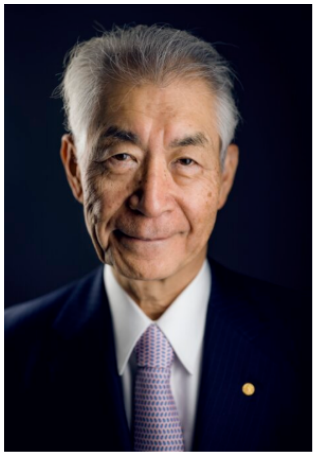
James P. Allison



© Nobel Media AB. Photo: A. Mahmoud
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.

Personalized Cancer Immunotherapy

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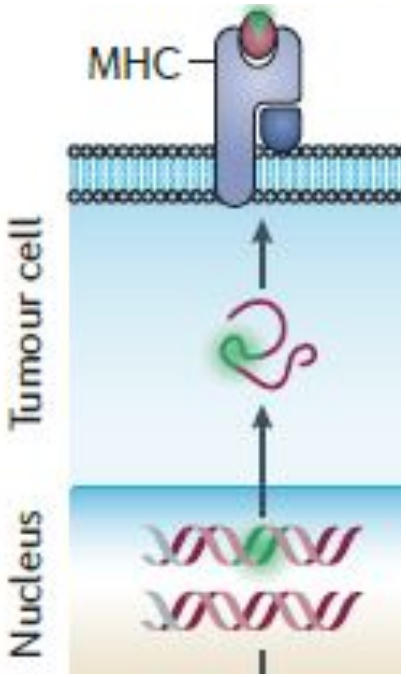
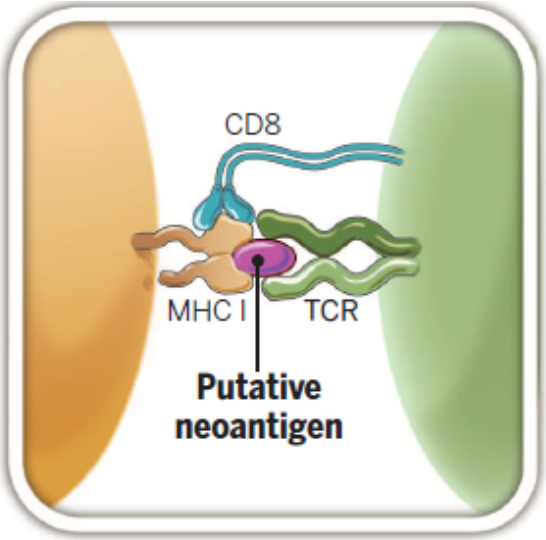
Neoepitopes (Neoantigens)



- 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

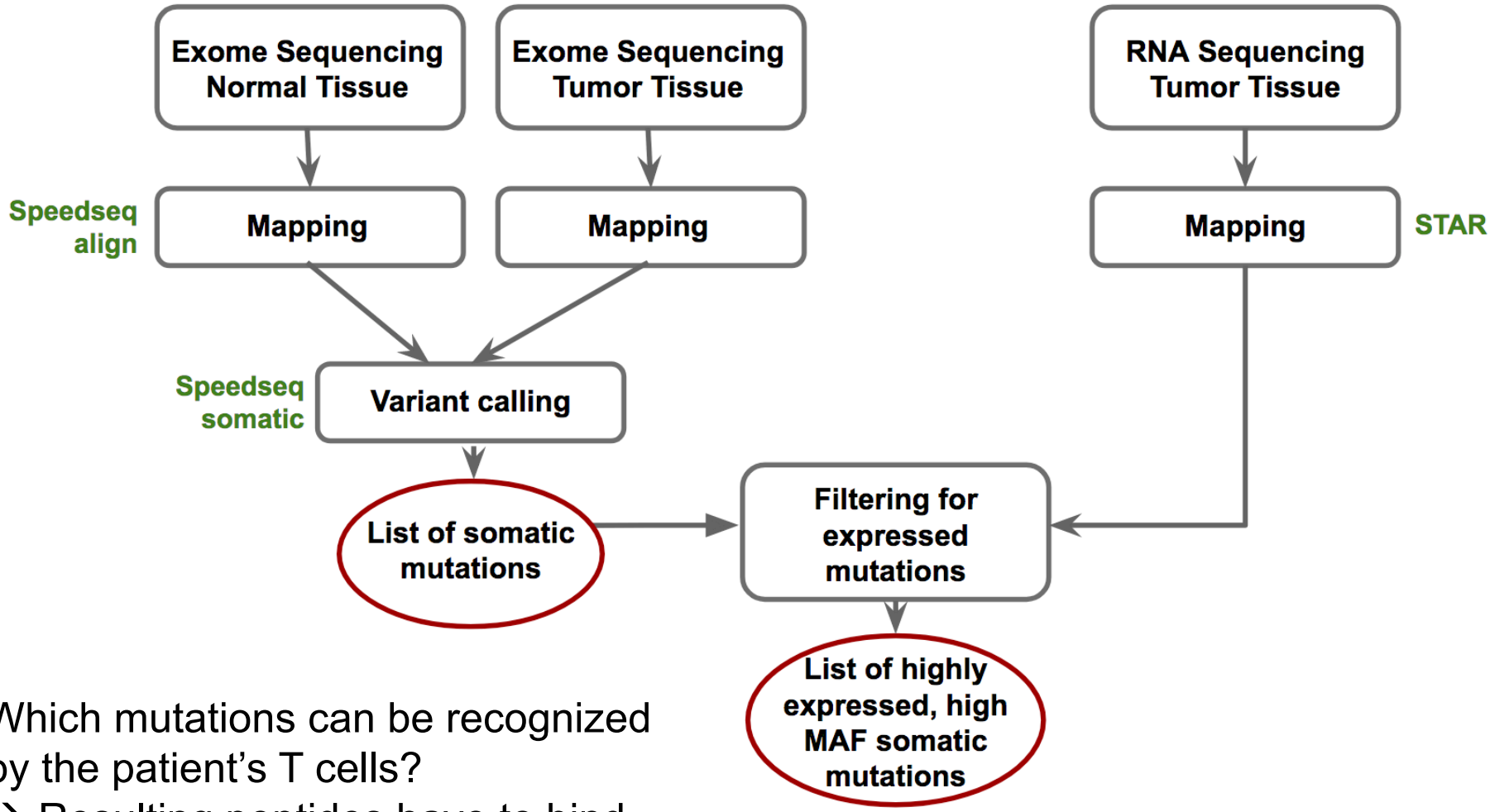
Neoepitopes are presumably recognized by tumor-infiltrating lymphocytes **(TILs)**

Neoepitopes are highly tumor-specific!



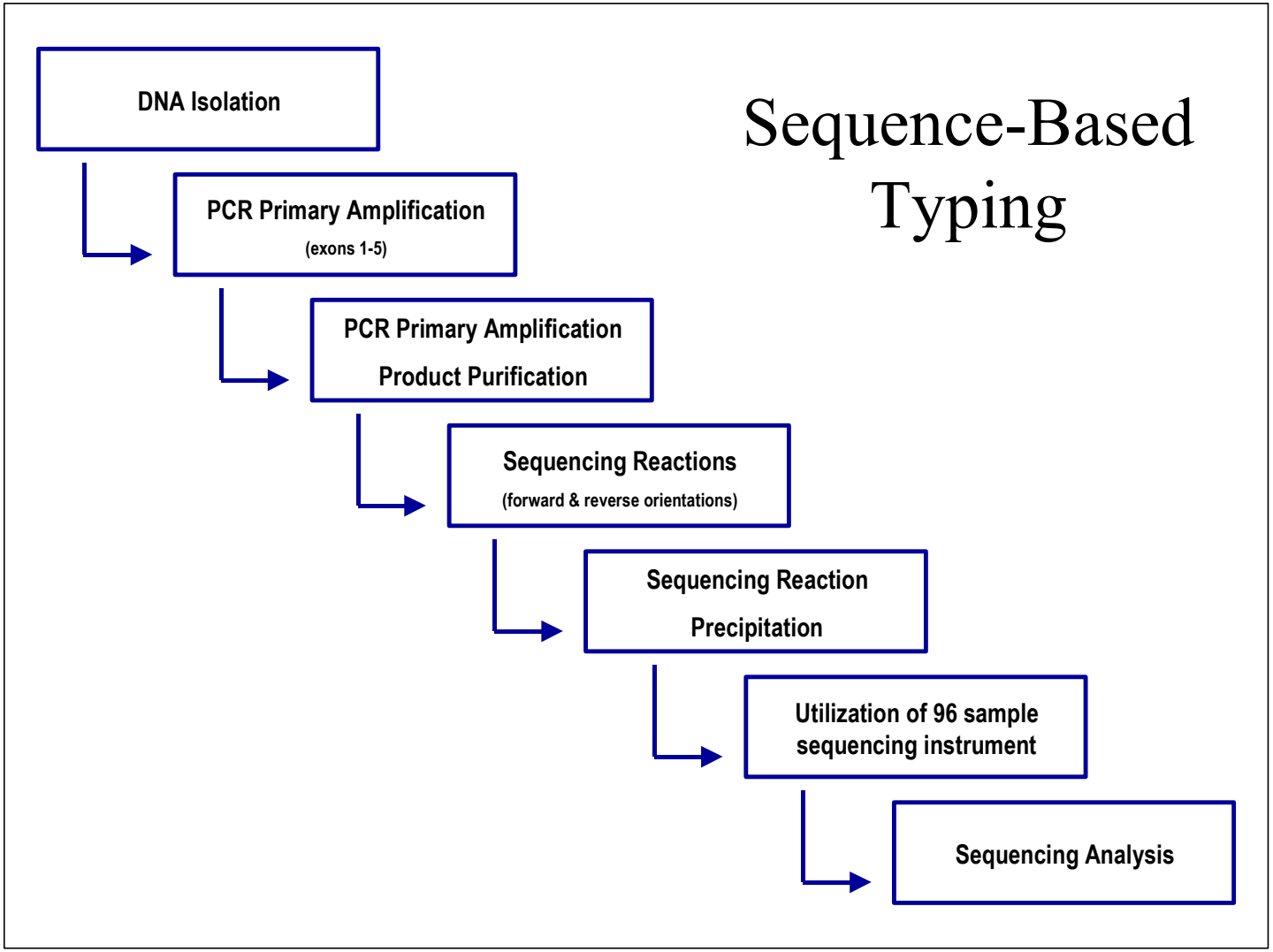
Coulie et al, Nat Rev Cancer. 2014 Feb;14(2):135-46
Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74

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

HLA Typing: Targeted sequencing of HLA locus

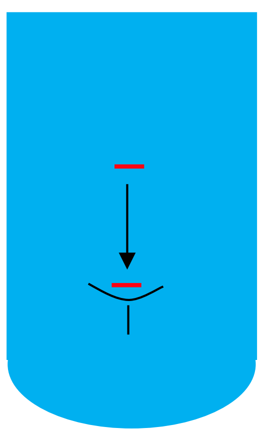


•http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/25_2_2001/highthrusbt3.htm

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
...	

$\log(IC_{50}) \sim$ 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

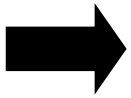
ORF 1 M G Q I V T M F E A L P H I I D E V I N I V I I V L I V I T G I K A V Y N ...
ORF 2 M G L K G P D I Y K G V Y Q F K S V E F D M S H L N L T M P N A C S A N N ...
ORF 3 M H N F C N L T S A F N K K T F D H T L M S I V S S L H L S I D G N S N Y ...
ORF 4 M S A Q S Q C R T F R G R V L D M F R T A F 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 SPLPSQAMLDLMLSPDD >Region 2 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) Select HLA allele reference set: ☐	Allele Length Upload allele file
Specify Output	
Sort peptides by	Percentile Rank
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Output format	XHTML table
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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)	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*

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

ecify Output

Sort peptides by	
Show	
Output format	
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 SPLPSQAMLDLMLSPDD >Region 2 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) 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

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 SPLPSQAMLDLMLSPDD >Region 2 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
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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.

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

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

HLA typing results:
HLA-A*02:01, HLA-A*68:01
HLA-B*07:02 , HLA-B*35:01

Workflow:

- 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 that can be presented to T cells
- Step 3: Select the top peptide for each HLA allele
- Step 4: What is the un-mutated form of the chosen peptides in the patient? What is their MHC binding affinity?
- Step 5: Are the peptides really specific for the tumor? Examine this using NCBI BLAST
- Step 6: Decide: Which peptide would you choose?

Workflow:

- 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?