MHC Class I and its Importance for the Immunogenicity of Novel Modalities

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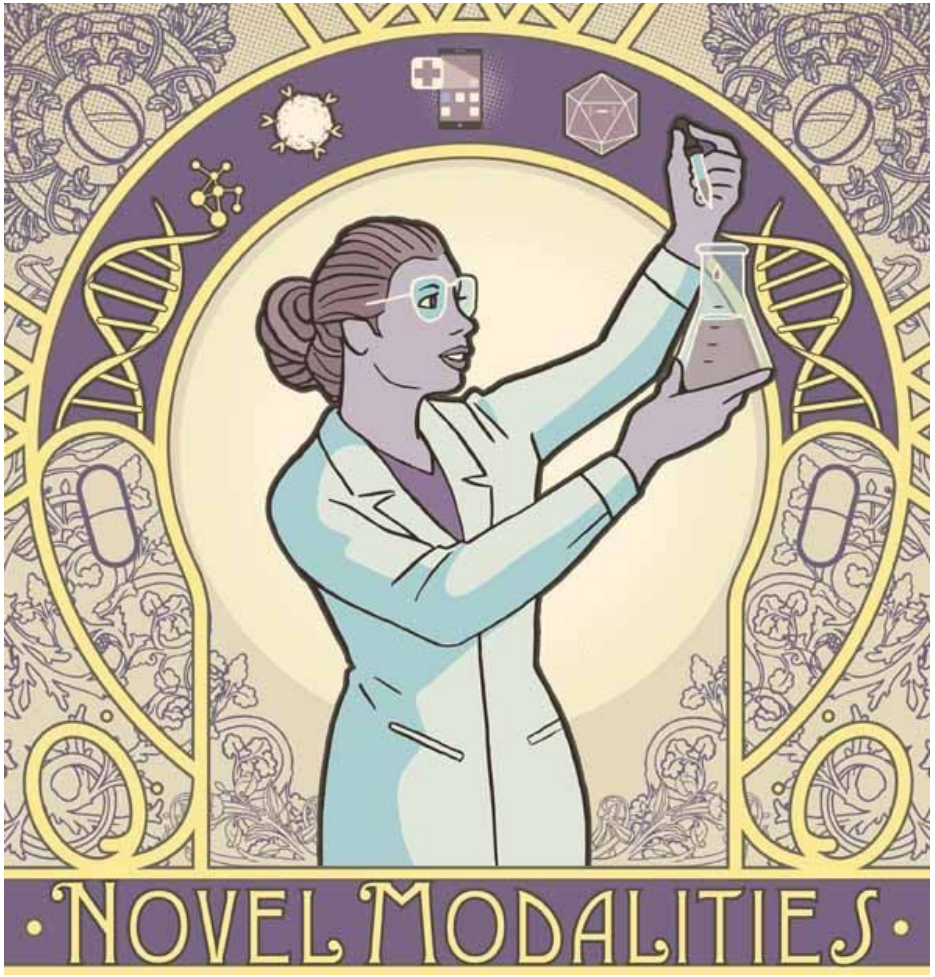
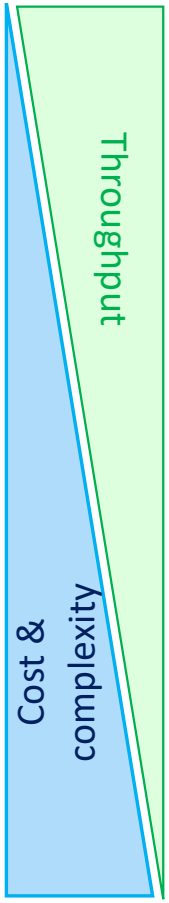
Novel modalities & immunogenicity



CLINICAL PHARMACOLOGY & THERAPEUTICS| VOLUME 114 NUMBER 3

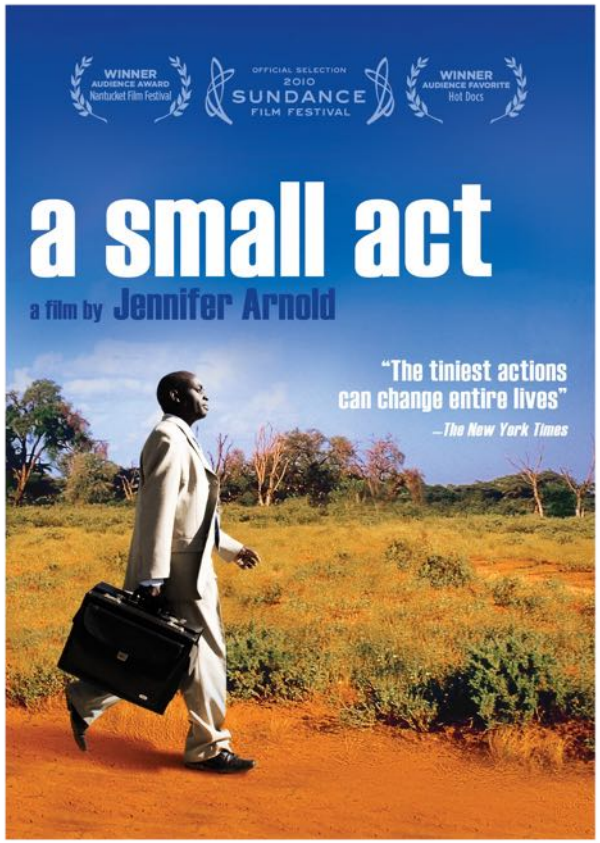
- Gene therapies, cell therapies (e.g., CAR T cells) and CRISPR Cas-based gene editors hold immense promise in treating previously intractable diseases.
- Understanding the immune response to these modalities is pivotal for improving safety and therapeutic efficacy.
- Pre-existing and induced immune responses are a key concern during the development and regulation of these emerging technologies.

Methods used to predict immunogenicity



METHOD	IMMUNE PROCESS PROBED	WHAT WE LEARN
In silico MHC-peptide binding predictions	Antigen presentation	Potential T cell epitopes
Peptide/MHC-binding assay	Antigen presentation	Measures peptide-MHC binding affinity
Human blood-derived cell-based assays (DCs as APCs; T cells as effector cells)	Depends on assay design	T cell activation measured by proliferation or cytokine production
MHC tetramer-guided epitope mapping (TGEM)	Antigen recognition	Mapping of MHC-restricted T cell epitopes
MHC-associated peptide proteomics (MAPPs) assay	Antigen processing and presentation	Identifies naturally processed and presented peptide antigens
Protein-specific T cell amplification	Antigen processing, presentation, recognition	Generation of antigen-specific T cell lines from naïve PBMC donors
HLA transgenic mice	All	Assessment of immunogenicity risk in context of human HLA

Do the methods used to predict the immunogenicity of therapeutic proteins work in the real world (a case study)



Factor VIIa

NO reports of anti-FVIIa antibodies in hemophilia patients

FVIIa variant, Vatreptacog alfa
{V158D, E296V, M298Q}

Incidence of anti-FVIIa antibodies = **11.1%**

Company Announcement

28 September 2012

novo nordisk®

Novo Nordisk discontinues development of vatreptacog alfa following analysis of phase 3 results

Novo Nordisk today announced the decision to discontinue the development of vatreptacog alfa, a fast-acting recombinant factor VIIa analogue for haemophilia patients with inhibitors. The decision follows analysis of the data from the phase 3a trial adept™2. On 9 August, Novo Nordisk announced that a few patients in the trial had developed anti-drug antibodies to vatreptacog alfa, one patient with a potentially neutralising effect.

Post-hoc assessment of Vatreptacog alfa immunogenicity

ASSAY/METHOD	RESULTS
Do mutant peptides bind HLA-II molecules with high affinity (in silico)?	Mutant peptides bind with high affinity to some but not all HLA-II variants
Do mutant peptides bind HLA-II molecules with high affinity (in vitro)?	Confirmed in silico findings
Are mutant peptides presented on HLA-II molecules (MAPPs)?	YES
Do mutant peptides that bind with high affinity elicit a T-cell response?	YES
Are there any associations with clinical outcomes?	ADA-positive patients carry HLA-II that bind to mutant peptide with high affinity

Lamberth, Reedtz-Runge, Simon, Klementyeva, Pandey, Padkjær, Pascal, León, Gudme, Buus & Sauna.
Science Transl. Med. 9: eaag1286

The immunogenicity of novel modalities

CD4 T cells are MHC-II restricted and pre-programmed for helper functions such as activation of B cells to secrete antibodies.

Antigens ingested into endocytic compartments of macrophages, dendritic cells or B cells are presented to CD4+ T cells as peptides bound to MHC II molecules.

Therapeutic proteins are almost always extracellular and immune responses are driven via the MHC II/CD4+.

Bio-analytics for assessing the immune response to protein therapies largely focus on accurate determination of anti-drug antibodies and determining whether these antibodies are neutralizing.

CD8 T cells are MHC I-restricted and pre-programmed for cytotoxic functions directly killing target cells.

Endogenously synthesized antigens in the cytosol of all cells are presented to CD8+ T cells as peptides bound to MHC I molecules.

Novel modalities elicit diverse immune responses based on the route of administration; delivery system used etc.

Bio-analytics for assessing the immune response to novel modalities cannot rely on the identification and characterization of anti-drug antibodies. These assays must be fit-for-purpose and be carefully designed for each application.

Gene therapy & immunogenicity

Luisa Jung | Nature 2021

VECTOR

AAV vector particles undergo proteasomal degradation, capsid-derived peptides are presented by MHC Class I (MHC I) and trigger $CD8^+$ cytotoxic T cells.

In an early liver-directed gene therapy trial for hemophilia B a loss of factor IX transgene expression was correlated with a $CD8^+$ T cell response against the viral capsid.

$CD8^+$ T cell responses to AAV capsid have also been observed in muscle-directed gene transfer.

TRANSGENE

A T-cell response was induced to the α-1-antitrypsin transgene product and was associated with a polymorphism present in the subject.

Gene therapy for Duchenne muscular dystrophy using three products with different transgenes, under different promoters and packaged in different AAV serotypes all showed a cytotoxic T-cell immune response against dystrophin.

CAR T cells & immunogenicity

Pre-existing and/or treatment- induced immunity to chimeric antigen receptor (CAR) constructs containing mouse- derived single-chain variable fragments are associated with treatment failure in some patients.

Novel technologies to use allogeneic CAR T cells will increase the likelihood of anti- CAR immune responses.

The presence of CAR-specific cytolytic T cells after infusion has been associated with treatment failure in some studies.

T cell-mediated anti-CAR responses have been detected in second-generation CD19-directed CAR T cells with mouse-based scFvs and, to a lesser extent, with those that use fully human CAR constructs.

In several haematological malignancies, CAR T cell therapy results in a high complete response rate to the first infusion but 30–50% of patients relapse.

Populations of cytotoxic T cells with specificity towards the CAR have been shown to expand after initial infusion but clinical responses to the second infusion are suboptimal.

CRISPR Cas-Gene editors & immunogenicity

Genetic Engineering & Biotechnology News, NOV 2022

For in vivo clinical applications of CRISPR Cas immunogenicity is a key concern.

Cas-proteins are of bacterial origin: High immunogenicity risk category per FDA Guidance.

Pre-existing antibodies to Cas9 and pre-existing T- and B-cell responses to Cas9 have been reported.

Genome editing in mouse liver was accompanied by: Increase in CD8+ T cells. Cytotoxic T cell response. Hepatocyte apoptosis. Complete elimination of genome-edited cells.

Efficient AAV CRISPR-mediated dystrophin restoration was demonstrated in canine DMD models. However, Cas9-specific immune responses were a critical barrier for successful AAV CRISPR therapy. Serum Cas9 antibody and PBMC ELISpot confirmed Cas9-specific responses in both dogs.

Cas 9 as a model for evaluating the immunogenicity of novel modalities

Pre-existing antibodies to many novel modalities makes the establishment of cut-points for identification of anti-drug antibodies much more challenging.

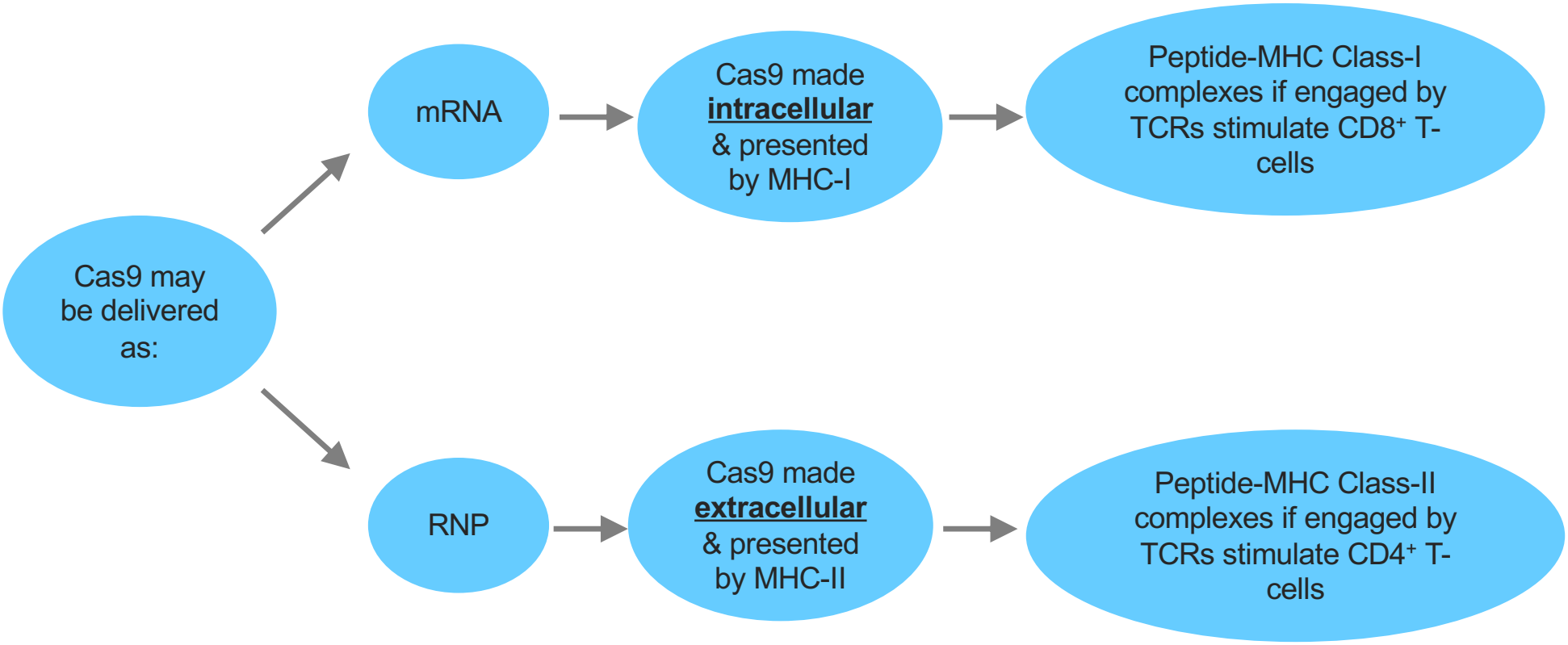
Clinical evidence suggests that many novel modalities function even in the presence of anti-drug antibodies, however the CD8+ responses present a significant barrier.

Efficient genome editing occurred in mouse liver **with pre-existing SaCas9 immunity**. HOWEVER:

Genome editing was accompanied by an increase in CD8+ T cells in the liver and a cytotoxic T cell response.

Results: Hepatocyte apoptosis, loss of recombinant AAV genomes, and complete elimination of genome-edited cells.

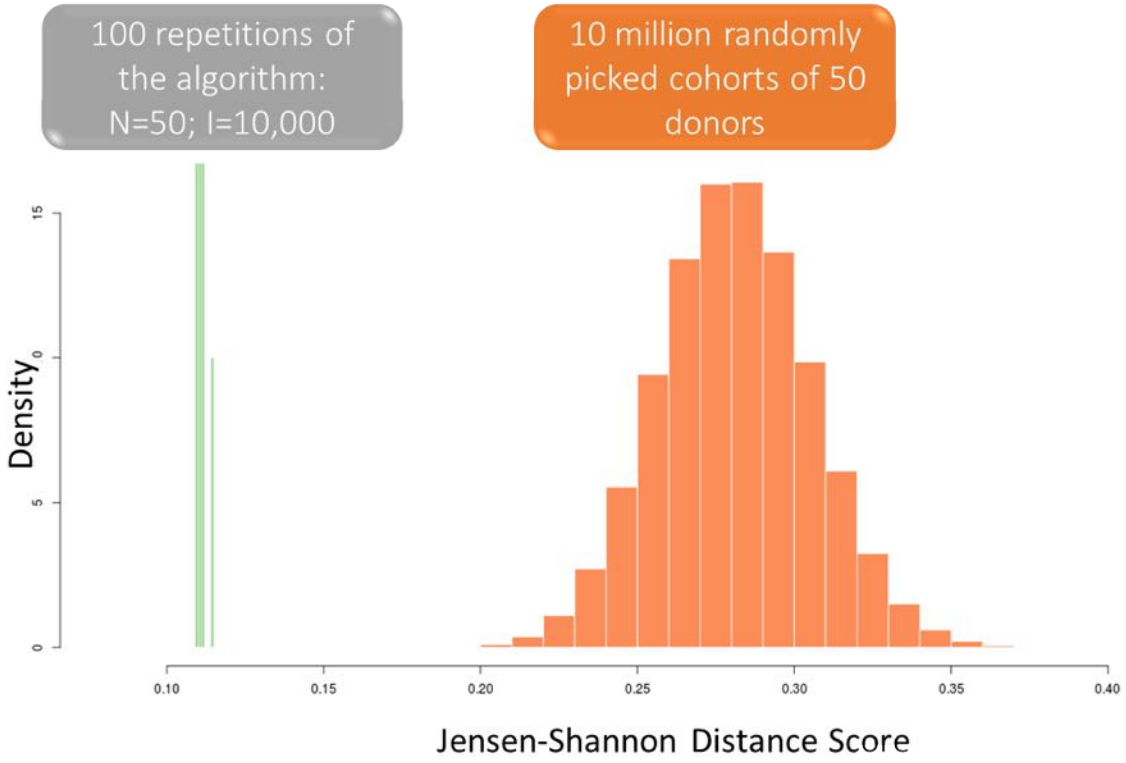
Cas 9 as a model for evaluating the immunogenicity of novel modalities



The non-trivial task of selecting a cohort of donors for ex vivo assays

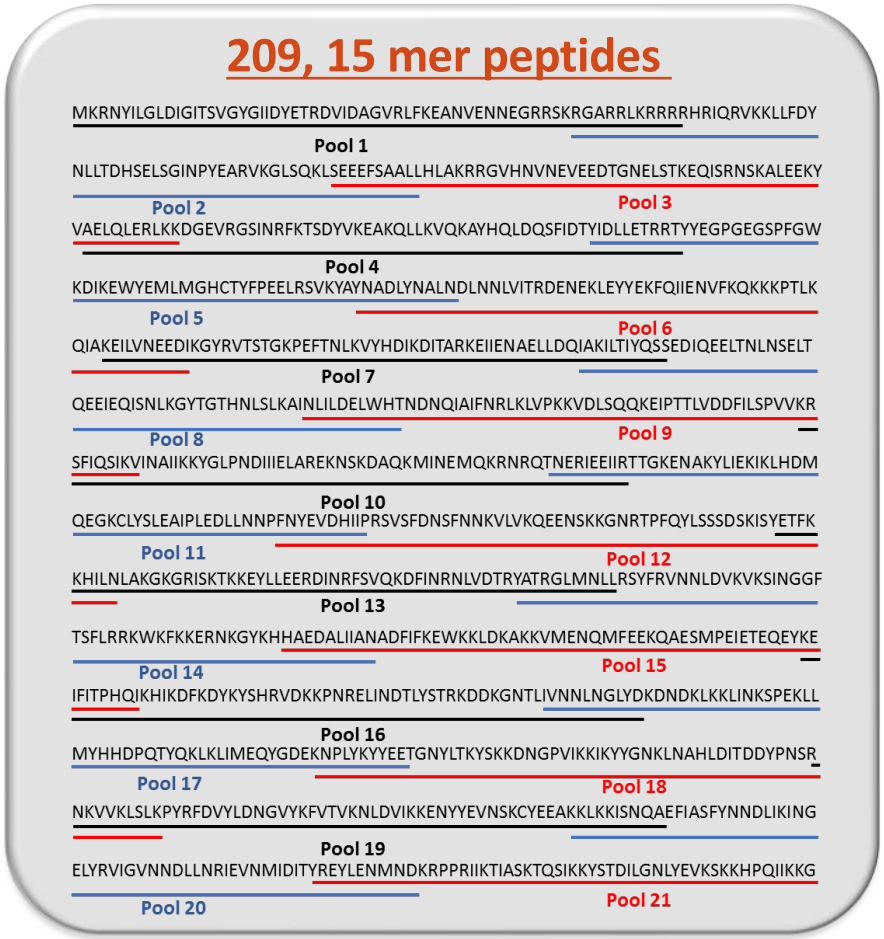
Presentation of peptides derived from the protein by the major histocompatibility complex (MHC) is a necessary (albeit not sufficient) condition for eliciting an immune response.

The MHC is polygenic: every individual contains several MHC genes
The MHC is polymorphic: The population has variants of each gene
The MHC genes are the most polymorphic genes in the human genome



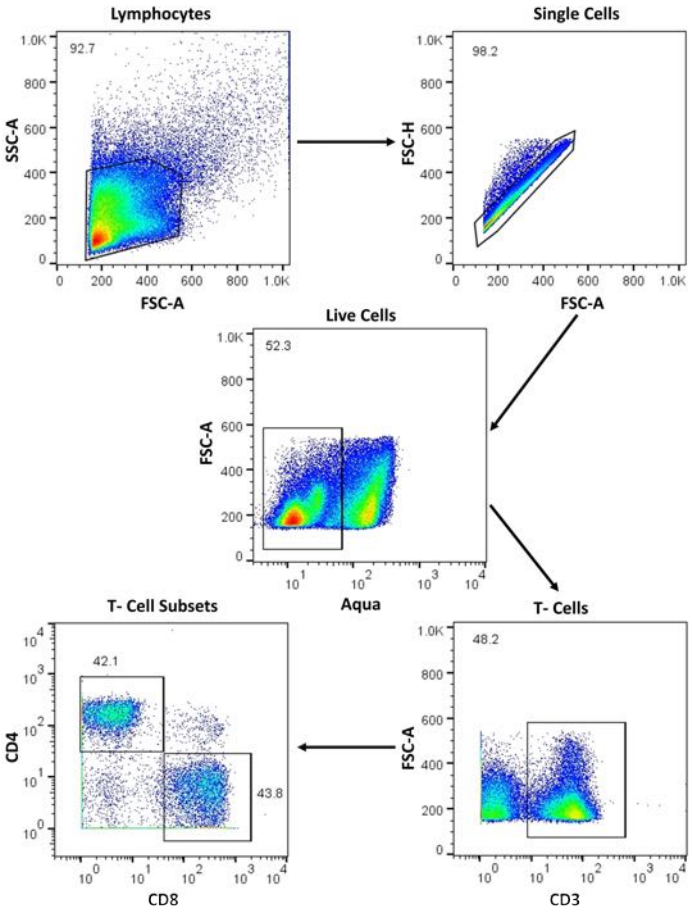
McGill, Yogurtcu, Yang, Verthelyi, & Sauna. **Front. Immunol**. 10: 2894

Identifying potential promiscuous T-cell epitopes on Cas9: The peptides and the markers



IFN-γ	Activates innate and adaptive immune responses; triggers class-switching of B-cell receptors/antibodies from IgM to IgG2
TNF-α	Associated with maturation of dendritic cells permitting antigen presentation
IL-2	Induces clonal expansion of effector T-cells primed with the antigen

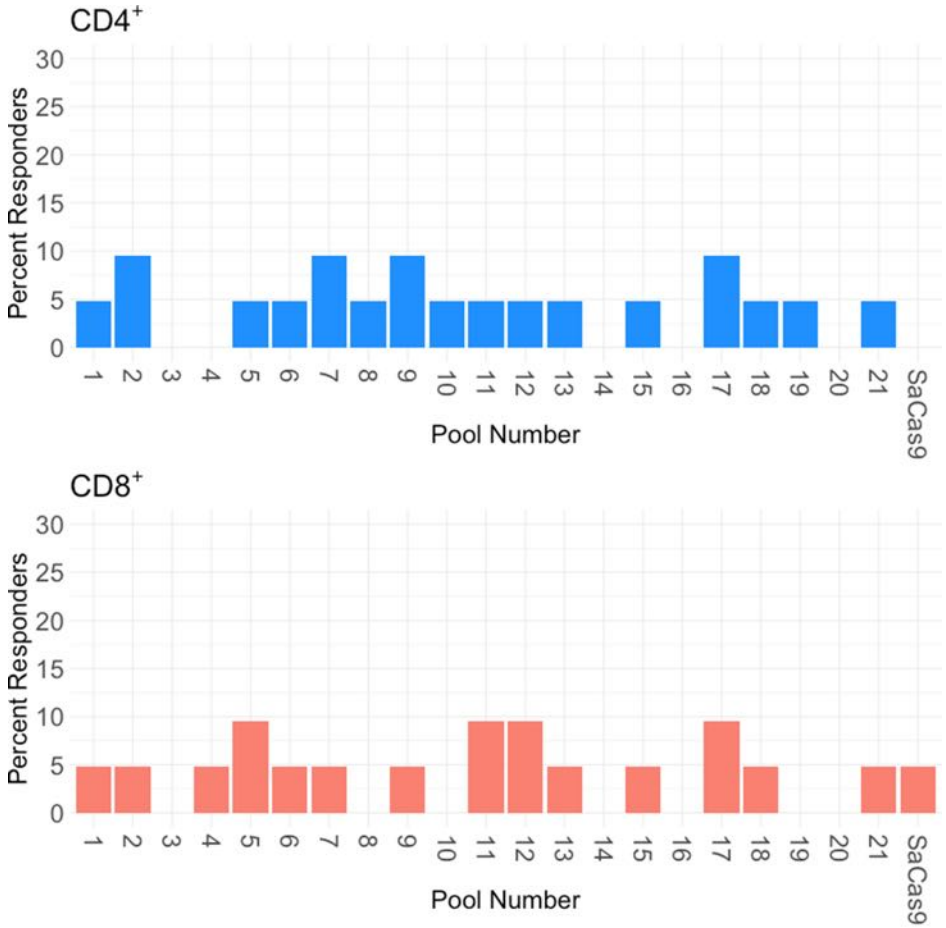
Flow cytometry-based assay to identify stimulation of CD4+ & CD8+ cells

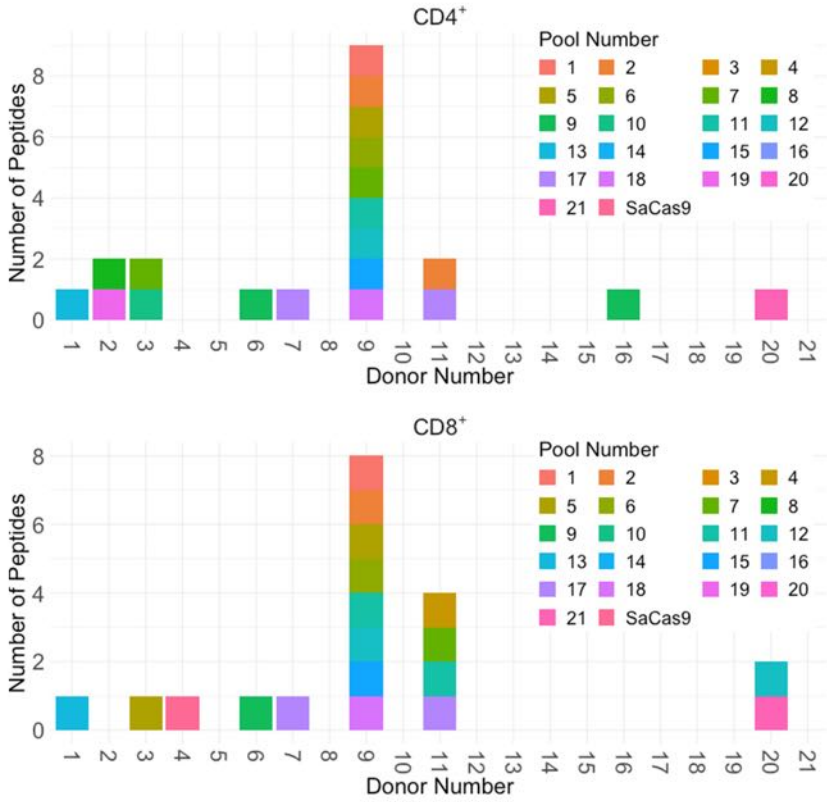


RESPONDER:

- The cell counts for each Donor/Protein/cytokine was compared to its respective unstimulated value
- The p values were **adjusted** using the Bonferroni method
- Adjusted p-values avoid spurious false-positive rates due to multiple testing

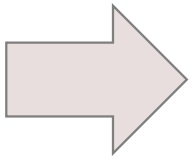
Flow cytometry-based assay to identify stimulation of CD4+ & CD8+ cells





Experimental identification of biologically relevant MHC II-restricted T-cell epitopes

- Peptide presentation (on MHC Class II) measured in an MHC-Associated Peptide Proteomics (MAPPs) assay
- Activation of CD4+ T cells measured by flow cytometry using the markers: IFN-γ, TNF-α, IL-2

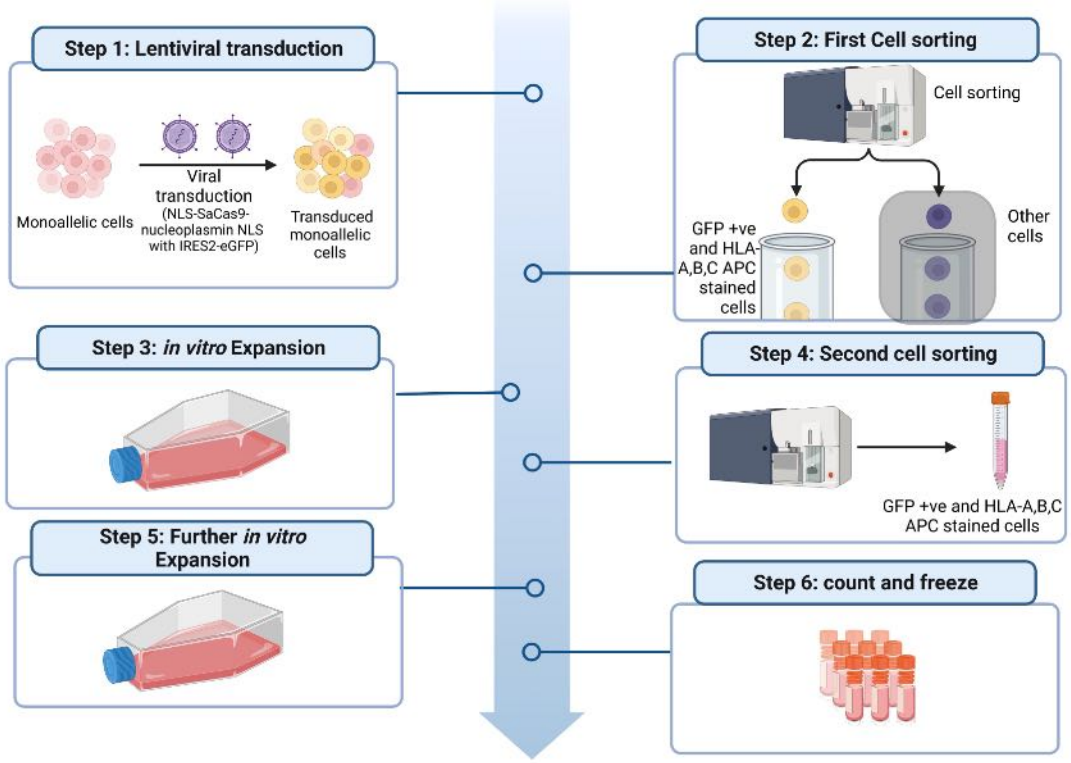


Sr #	Peptide	Position (SaCas9)
1	LFDYNLLTDHSELSGINPYEARV	71 - 93
2	SVKYAYNADLYNALNDL	246 - 262
3	NADLYNALNDLNNLVITRDENEKLE	252 - 276
4	KEILVNEEDIKGYR	301 - 314
5	LDQIAKILTIYQSSE	348 - 362
6	NLNSELTQEEIEQISNLKGYTGTHN	370 - 394
7	AINLILDELWHTNDNQIA	399 - 416
8	ILDELWHTNDNQIAIFNR	403 - 420
9	TNDNQIAIFNRLKLVPK	410 - 426
10	LVDDFILSPVVKRSFIQS	440 - 457
11	IQSIKVINAIIKKYGLPND	455 - 473
12	LPNDIIIELAREKNSKDA	470 - 487
13	EGKCLYSLEAIPLEDL	531 - 546
14	NYEVDHIIPRSVSFDNSFNN	552 - 571
15	TPFQYLSSSDSKISYE	587 - 602
16	KDDKGNTLIVNNLNGLYDKDNDKL	793 - 816
17	LLMYHHDPQTYQK	827 - 839
18	DEKNPLYKYYEETGNYLTKYS	849 - 869
19	GNYLTKYSKKDNGPV	862 - 876
20	LDNGVYKFVTVKNLDVIK	918 - 935
21	KENYYEVNSKCYEEAK	936 - 951
22	ISNQAEFIASFYNNDLIK	956 - 973

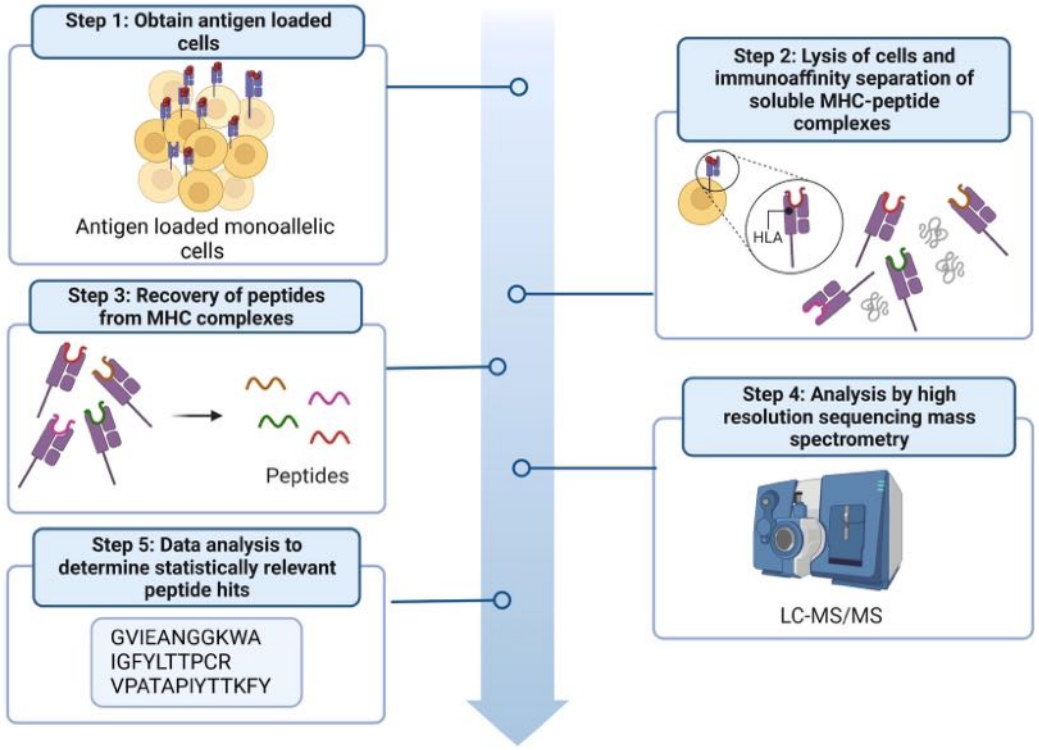
Simhadri, Hopkins, McGill, Mukherjee, Zhang & Sauna. **Nature Communications** 12: 5090

The challenge of identifying MHC I associated peptides

Monoallelic cells gift of Devin B. Keskin: ***Sarkizova et al. Nature Biotechnology 38:199-209***



Identification of Cas9 peptides presented by MHC-I



Cas9 peptides identified on MHC-I variants

Unique Peptides	Amino acid (start-end)	Donor-1	Donor-2	Donor-3	Donor-4	Donor-5	Donor-6	Donor-7	Donor-8	Donor-9	Donor-10	
		*01:01	*02:01	*11:01	*23:01	*24:02						HLA_A1
		*01:01	*02:01	*11:01	*23:01	*24:02						HLA_A2
							*35:01	*08:01	*07:02	*27:02	*44:02	HLA_B1
							*35:01	*08:01	*07:02	*27:02	*44:02	HLA_B2
EEIEQISNLKGY	378 - 389											
YLIEKIKL	519 - 526											
HIIPRSVSF	557 - 565											
SINGGFTSFLR	675 - 685											
MPEIETEQEY	741 - 750											
VYLDNGVYKF	916 - 925											
GVYKFVTVK	921 - 929											
NRIEVNMIDITY	990 - 1001											

Cas9 peptides identified on MHC-I variants

Unique Peptides	Amino acid (start-end)	Donor-1	Donor-2	Donor-3	Donor-4	Donor-5	Donor-6	Donor-7	Donor-8	Donor-9	Donor-10	
		*01:01	*02:01	*11:01	*23:01	*24:02						HLA_A1
		*01:01	*02:01	*11:01	*23:01	*24:02						HLA_A2
							*35:01	*08:01	*07:02	*27:02	*44:02	HLA_B1
							*35:01	*08:01	*07:02	*27:02	*44:02	HLA_B2
EEIEQISNLKGY	378 - 389											
YLIEKIKL	519 - 526											
HIIPRSVSF	557 - 565											
SINGGFTSFLR	675 - 685											
MPEIETEQEY	741 - 750											
VYLDNGVYKF	916 - 925											
GVYKFVTVK	921 - 929											
NRIEVNMIDITY	990 - 1001											

NetMHCpan-4.1 predictions

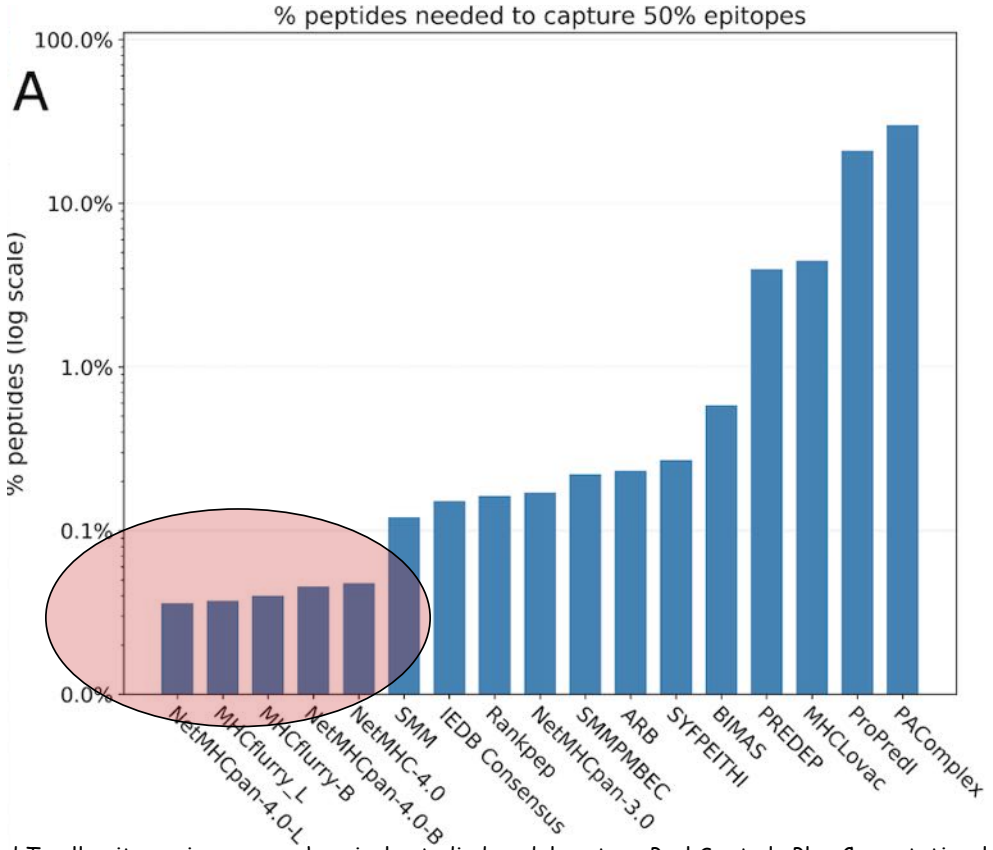
Peptide	%EL-rank	Rank (from 5220)	HLA
SINGGFTSFLR	1.031	68	HLA-A*1101
GVYKFVTVK	0.03	2	HLA-A*1101
VYLDNGVYKF	0.002	1	HLA-A*2301
VYLDNGVYKF	0.003	1	HLA-A*2402
YLIEKIKL	0.046	5	HLA-B*0801
HIIPRSVSF	0.02	1	HLA-B*0801
NRIEVNMIDITY	0.204	8	HLA-B*2702
MPEIETEQEY	0.01	1	HLA-B*3501
EEIEQISNLKGY	0.175	8	HLA-B*4402

All MS identified peptides are very strong predicted Binders, i.e within the top **~0.1%** (top <10) of the 5,220 8-12mer peptides within Cas9

How far have we come? Example from VACV

83 epitopes have been identified within 767,788 peptides (and tested MHC combinations) contained with the VACV reference proteome

The best current methods can identify >50% of these known epitopes within the top 0.025% of the entire space of peptide-MHC combinations



Benchmarking predictions of MHC class I restricted T cell epitopes in a comprehensively studied model system, Paul S. et al., Plos Computational Biology, May 2020

So MHC binding predictions clearly have value -
How are they made?

What can we learn from 4,200,000 such measurements covering more than 1000 different MHC molecules?

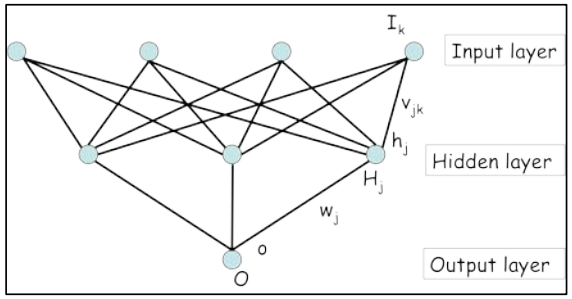
IEDB April 2023

Summary Metrics	
Peptidic Epitopes	1,612,246
Non-Peptidic Epitopes	3,188
T Cell Assays	511,679
B Cell Assays	1,403,266
MHC Ligand Assays	4,802,905
Epitope Source Organisms	4,450
Restricting MHC Alleles	1,005
References	24,670

Data interpretation (fitting mathematical models)

AADFPGIAR	0.085
AAVDLSHFL	0.169
FTFDLTALK	0.085
WVWDTWPLA	0.085
TMMRHRREL	0.085
LLPYPIAGC	0.085
LMFSTSAYL	0.735
KLNENIIRF	0.536
MRVLHLDLK	0.085
GLICGLRQL	0.196
FEFILRYGD	0.085
EFVSANLAM	0.085
RAAHRRQSV	0.085
SPLHVFVAV	0.085
RTFGKLPYR	0.085
GSLFTEQAF	0.197
SYGNANVSF	0.349
CSEVPQSGY	0.085
GSEDRDLLY	0.085
LNINKNGSF	0.430

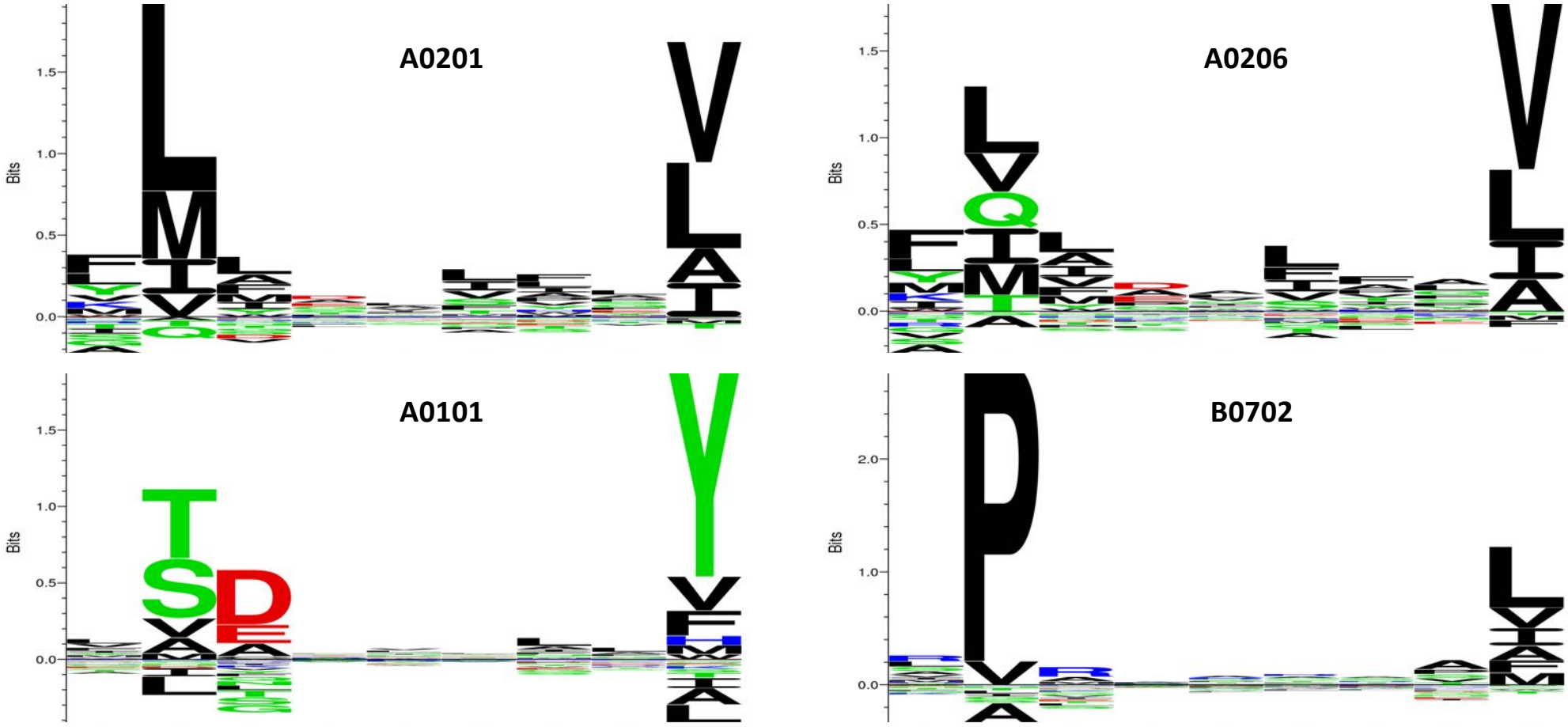
Artificial neural networks,
Support vector machines,
Similarity kernel,
Regression, ..



Machine learning

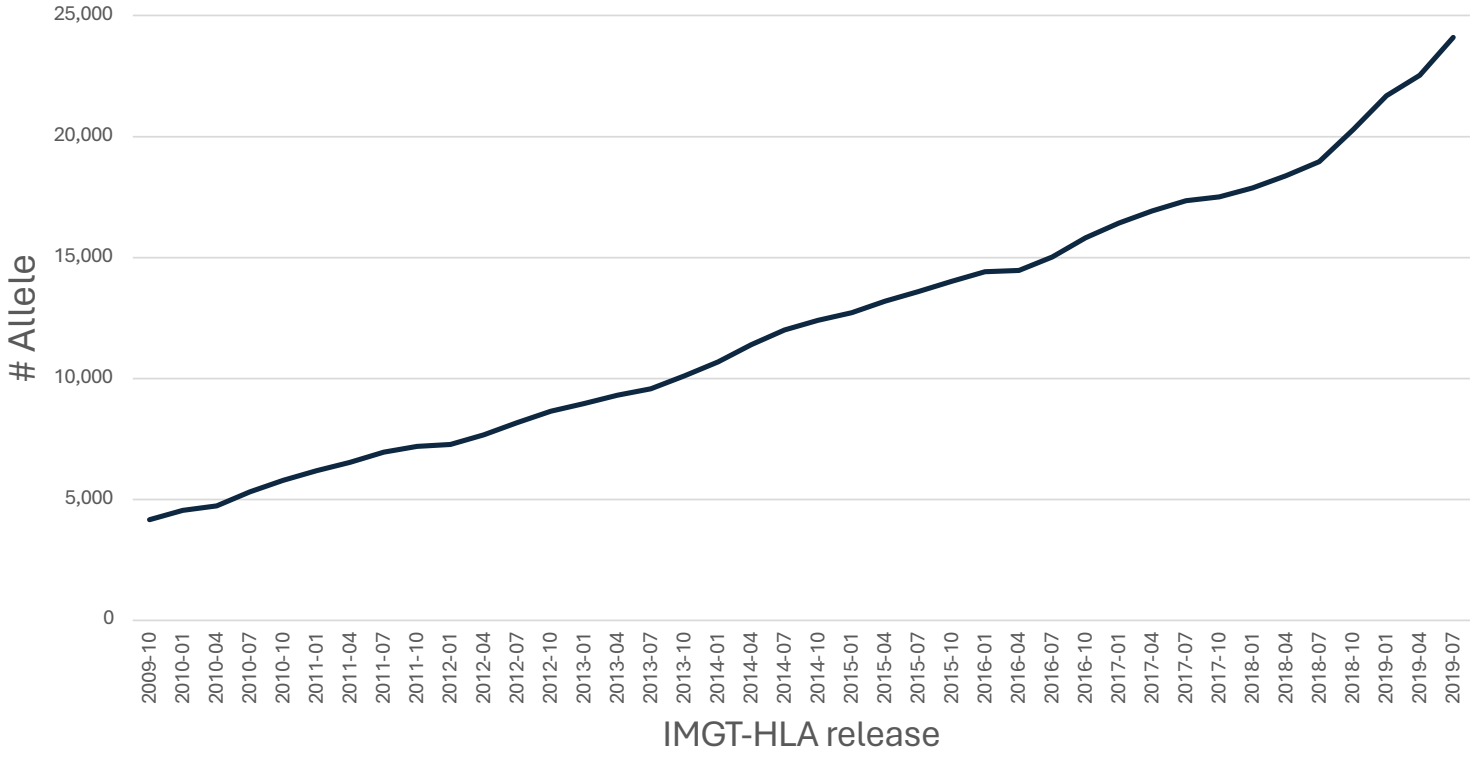
	0.036
	0.227
	0.131
	0.147
	0.338
	0.082
	0.713
	0.467
	0.044
	0.239
	0.032
	0.162
	0.126
	0.050
	0.087
	0.392
	0.181
	0.169
	0.187
	0.425

HLA specificities



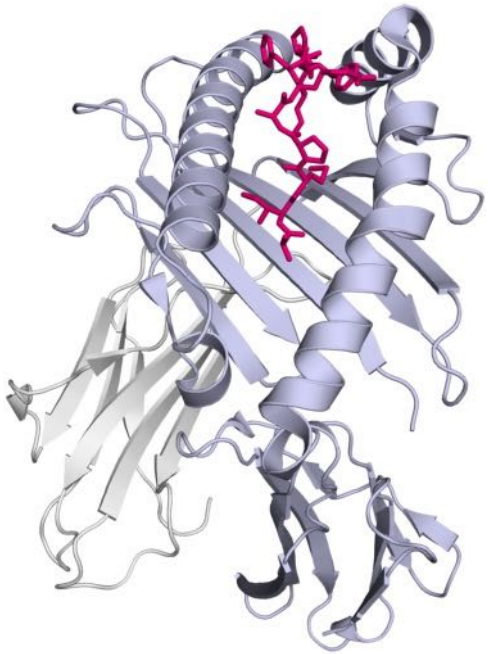
HLA polymorphism

The IMGT/HLA Sequence Database currently encompass more than 24,000 HLA alleles

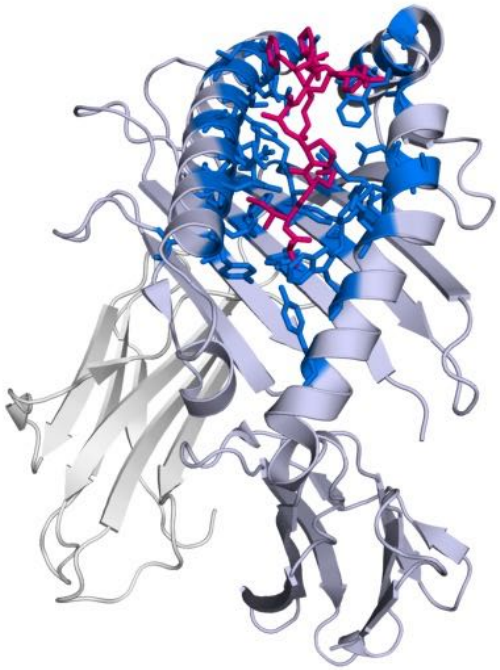


Source: https://www.ebi.ac.uk/ipd/imgt/hla/stats.html

Pan-specific prediction methods

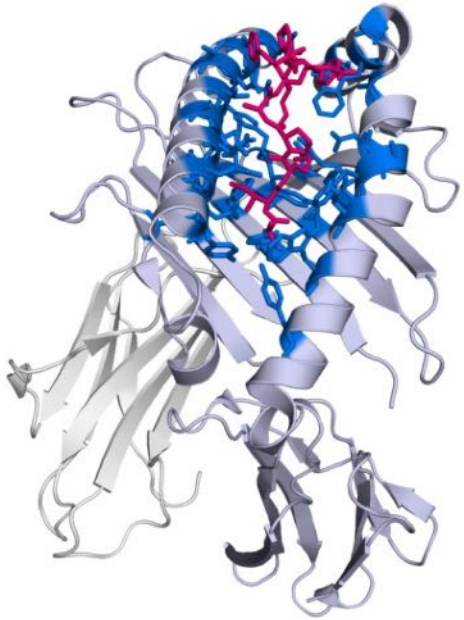


NetMHC

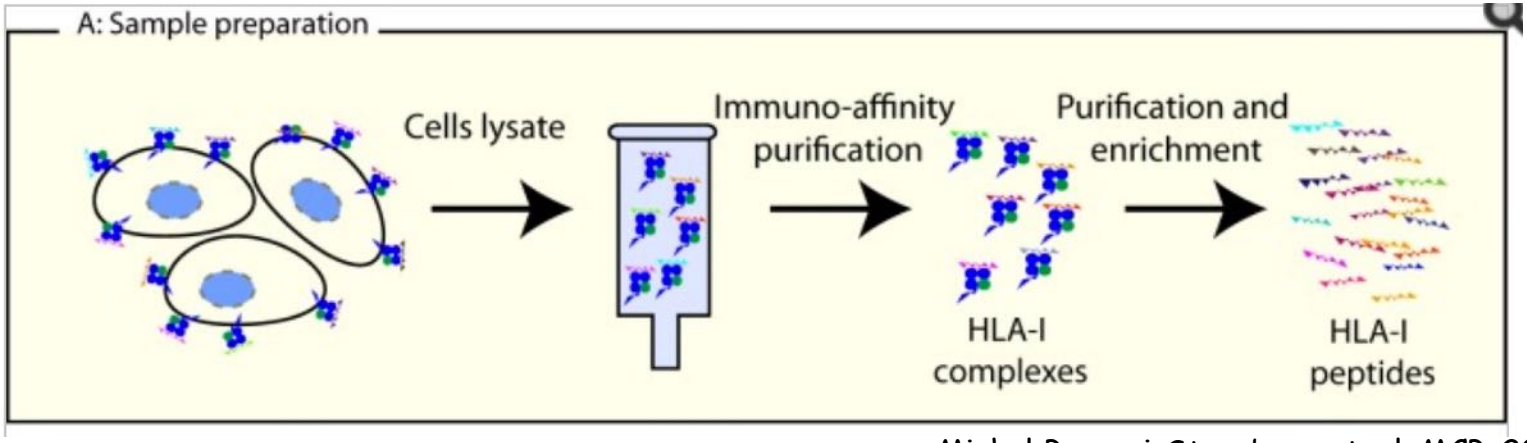


NetMHCpan

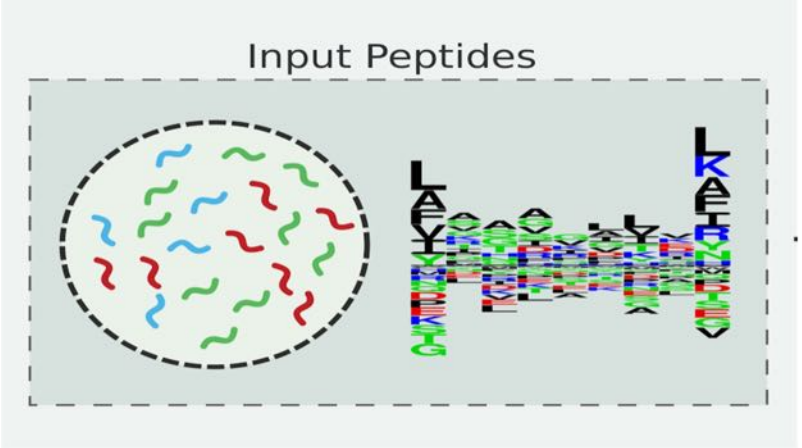
Peptide	Amino acids of HLA pockets	HLA	Aff
VVLQQHSIA	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.131751
SQVSFQQPL	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.487500
SQCQAIHNV	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.364186
LQQSTYQLV	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.582749
LQPFLQPQL	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.206700
VLAGLLGNV	YFAVLTWYGEKVHTHVDTLVRYHY	A0201	0.727865
VLAGLLGNV	YFAVWTWYGEKVHTHVDTLLRYHY	A0202	0.706274
VLAGLLGNV	YFAEWTWYGEKVHTHVDTLVRYHY	A0203	1.000000
VLAGLLGNV	YYAVLTWYGEKVHTHVDTLVRYHY	A0206	0.682619
VLAGLLGNV	YYAVWTWYRNNVQTDVDTLIRYHY	A6802	0.407855



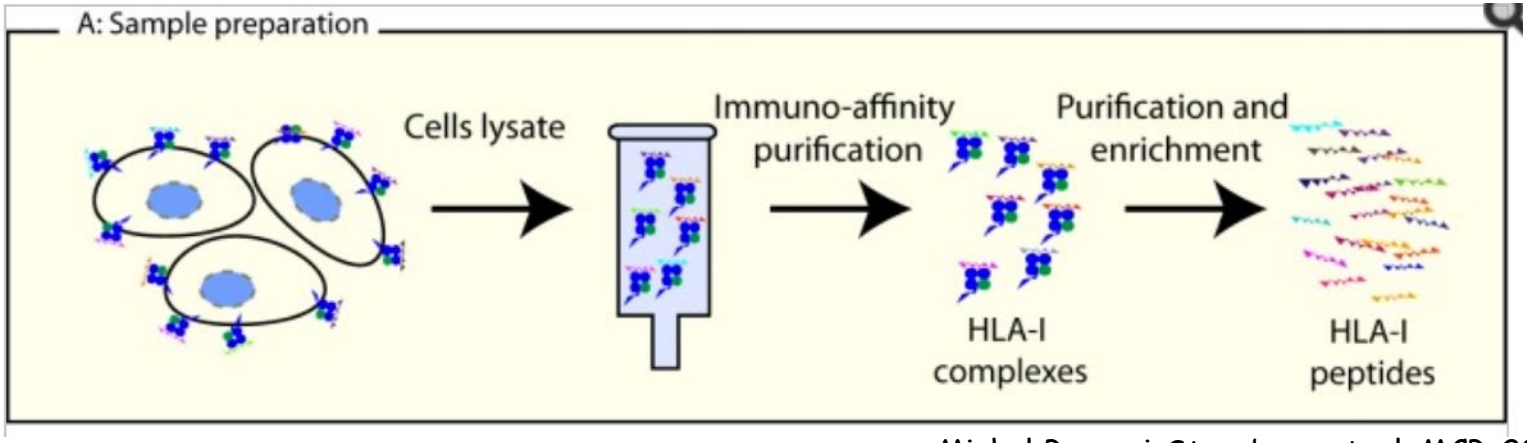
The new kid in town



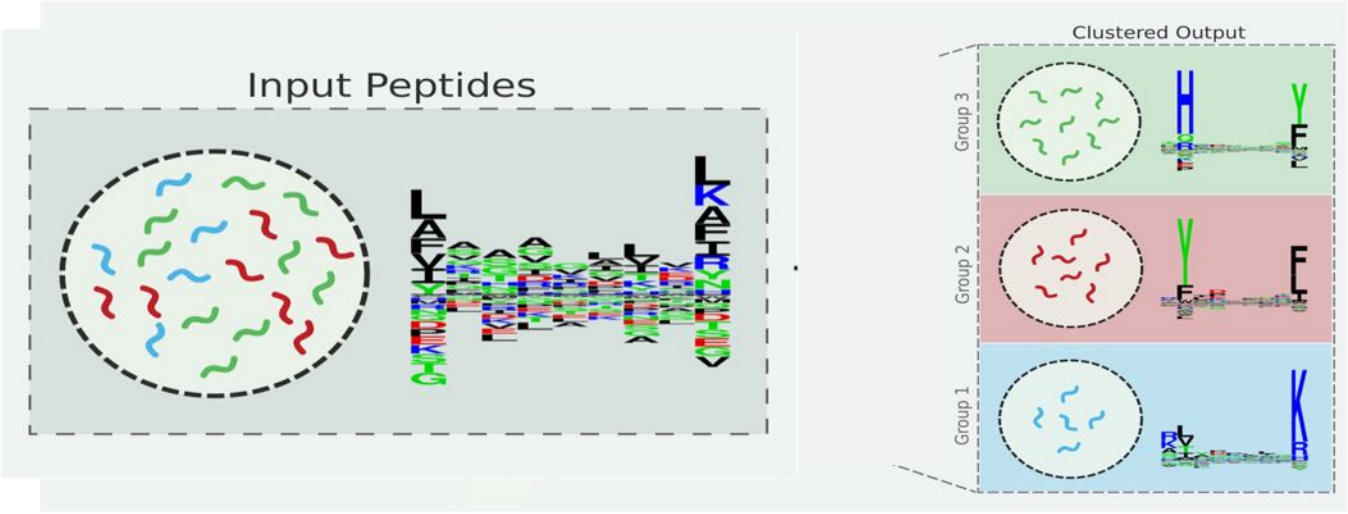
Michal Bassani-Sternberg et. al, MCP, 2015



Interpreting and benefitting from MS eluted ligand data sets

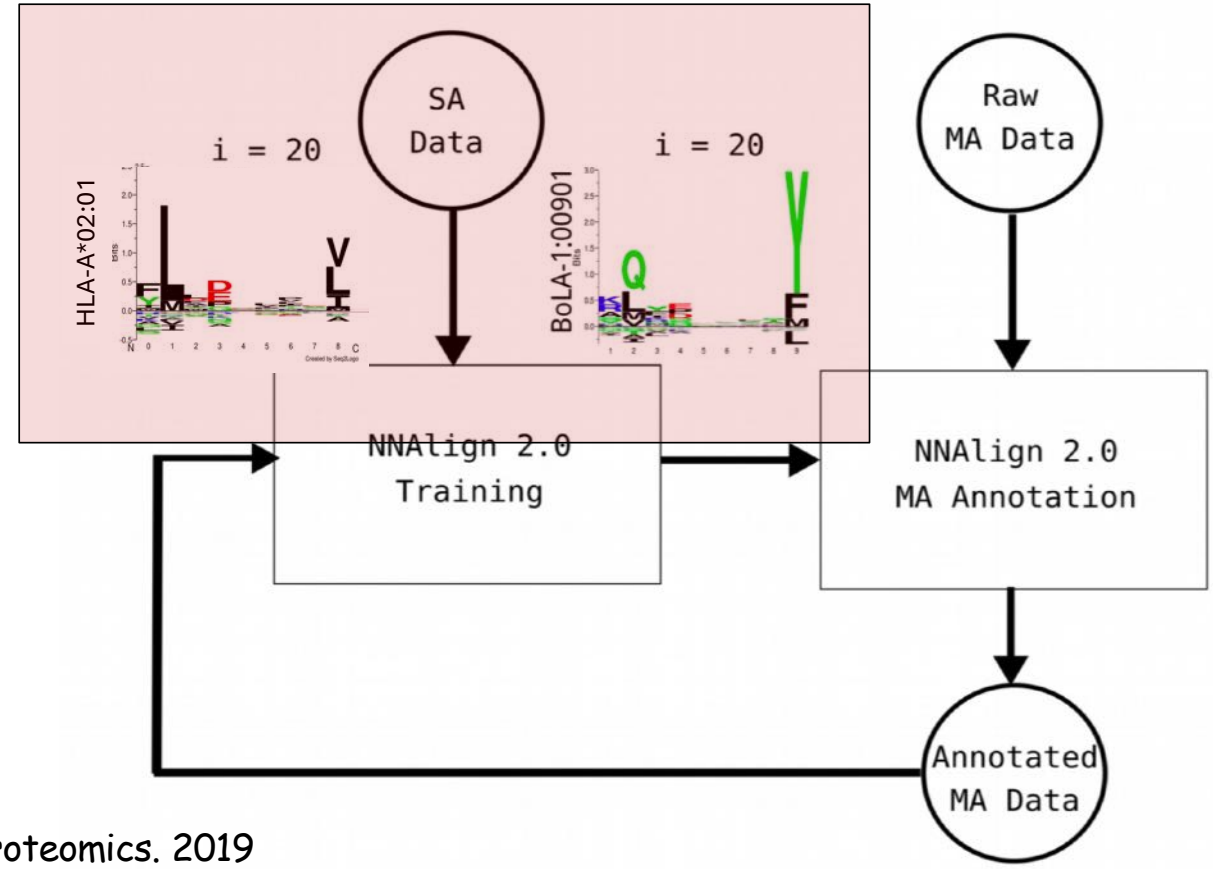


Michal Bassani-Sternberg et. al, MCP, 2015



NNAlign_MA

Train a pan-specific predictor – also covering HLA's
NOT part of training data



Alvarez el at. Mol Cell Proteomics. 2019

NNAlign_MA

Train a pan-specific predictor – also covering HLA's
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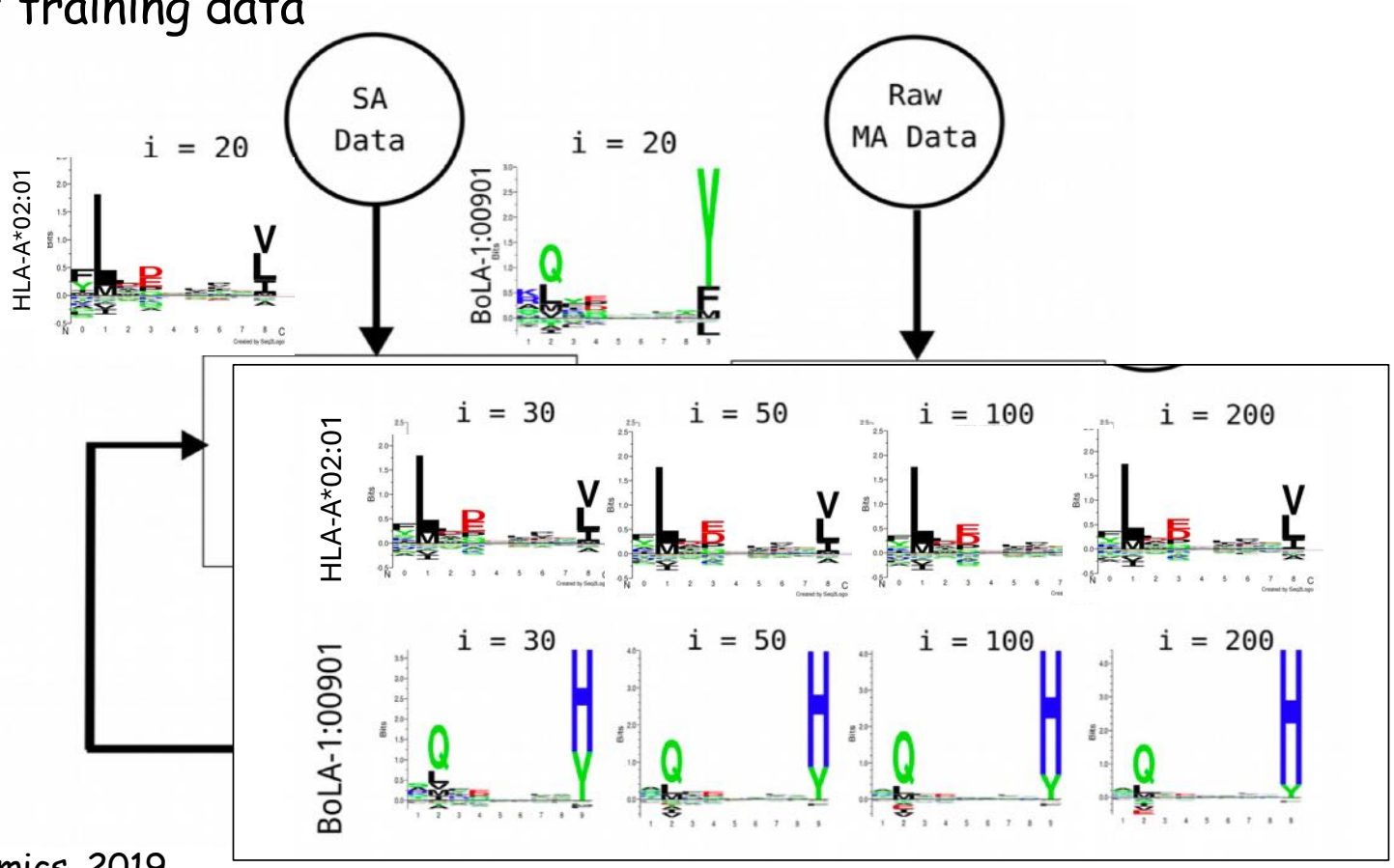
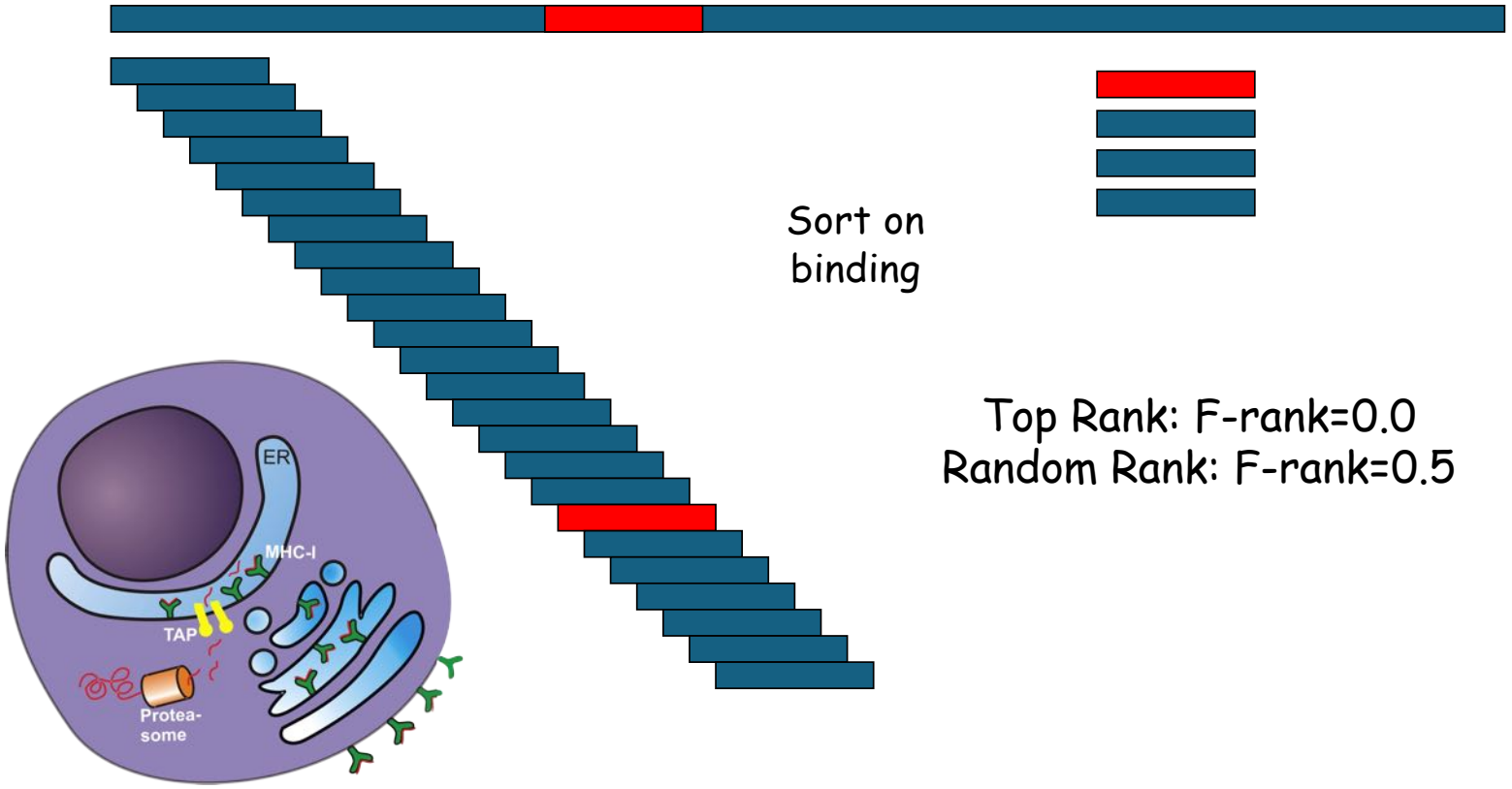


Alvarez el at. Mol Cell Proteomics. 2019

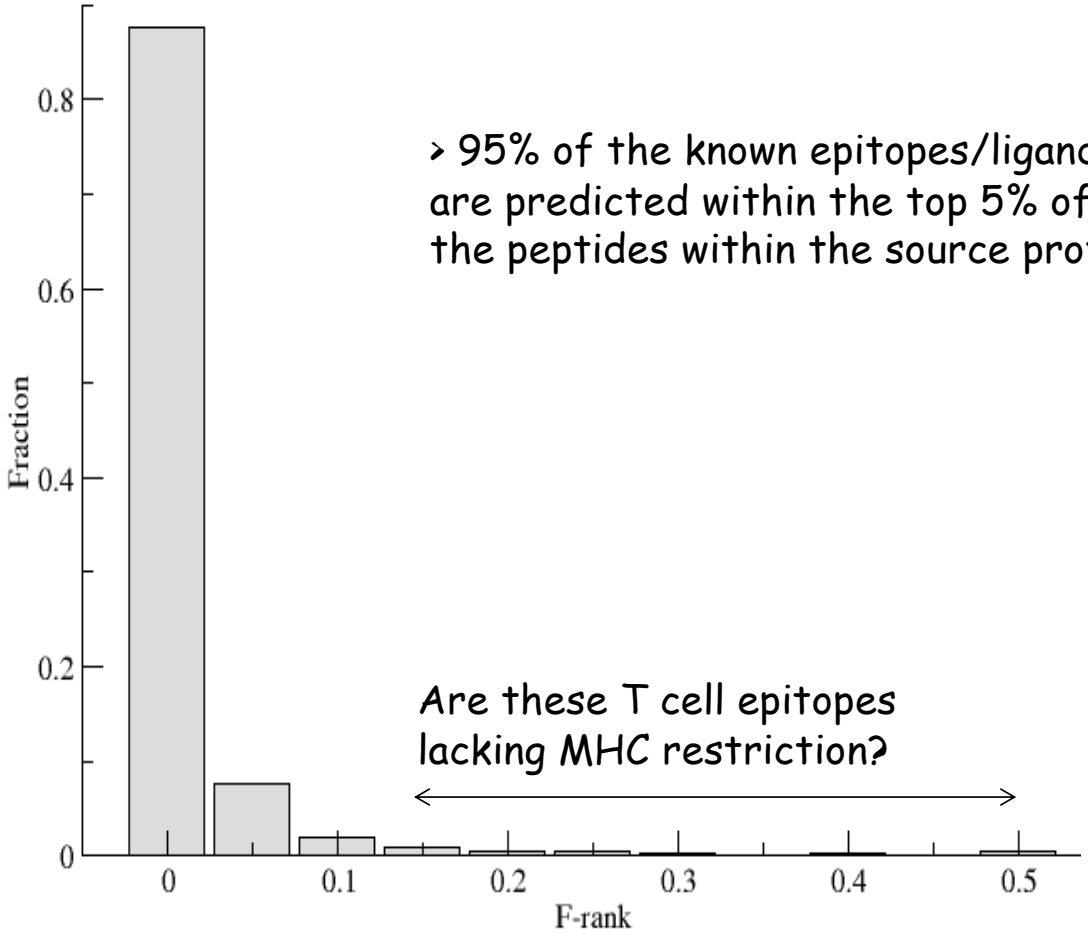
The Frank performance measure - Reproducing natures choice



Prediction accuracy

Cas9 case story

Peptide	EL_rank	Rank (from 5220)	HLA
SINGGFTSFLR	1.031	68	HLA-A*1101
GVYKFVTVK	0.03	2	HLA-A*1101
VYLDNGVYKF	0.002	1	HLA-A*2301
VYLDNGVYKF	0.003	1	HLA-A*2402
YLIEKIKL	0.046	5	HLA-B*0801
HIIPRSVSF	0.02	1	HLA-B*0801
NRIEVNMIDITY	0.204	8	HLA-B*2702
MPEIETEQEY	0.01	1	HLA-B*3501
EEIEQISNLKGY	0.175	8	HLA-B*4402



> 95% of the known epitopes/ligands are predicted within the top 5% of the peptides within the source protein

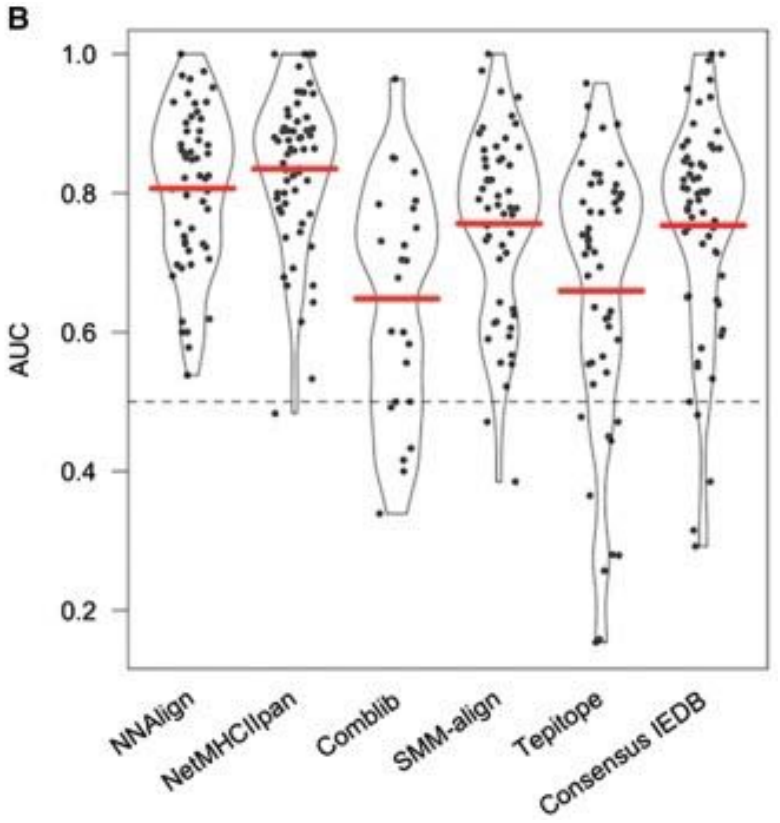
Are these T cell epitopes lacking MHC restriction?

Historically, MHC class II tools have poor performance and many false positive predictions

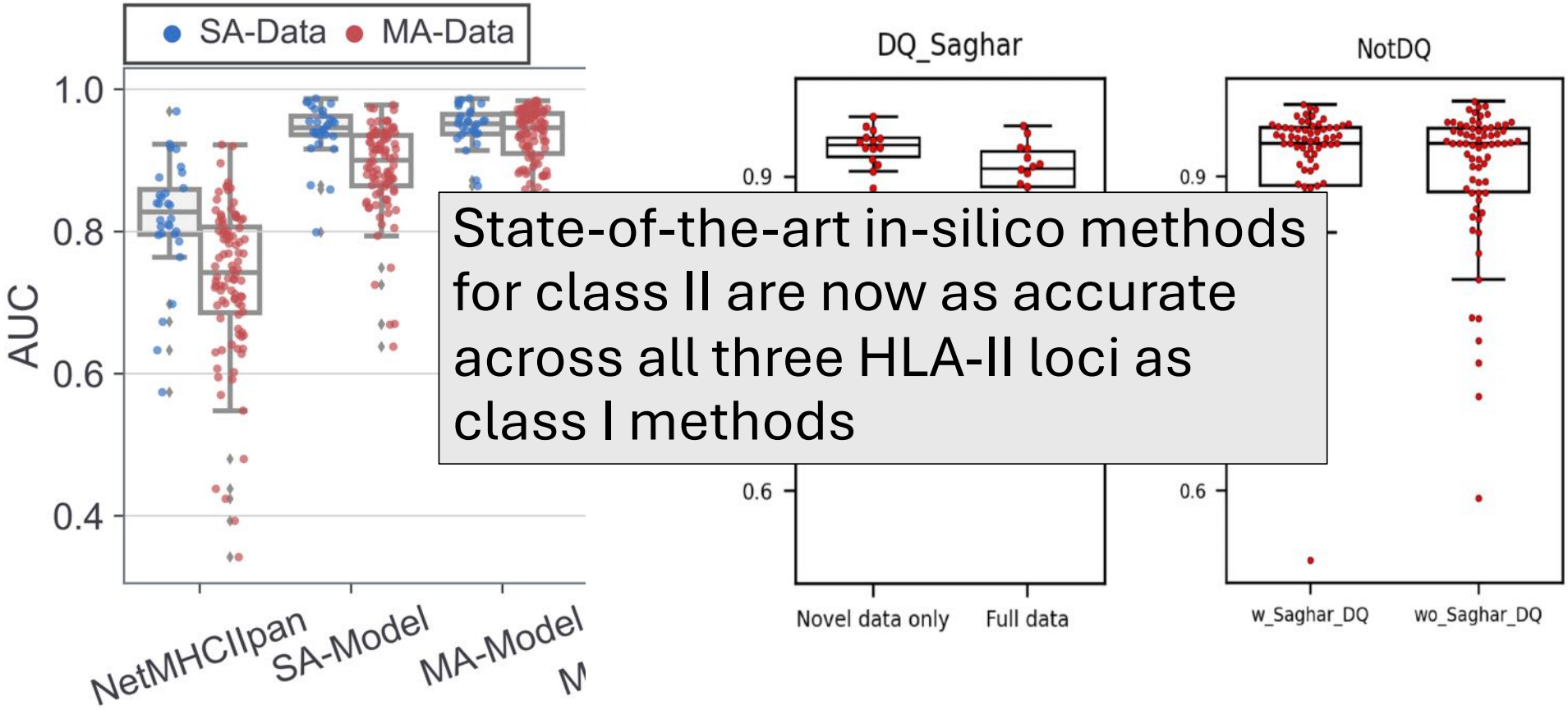
An automated benchmarking platform for MHC class II binding prediction methods

Massimo Andreatta, Thomas Trolle, Zhen Yan, Jason A Greenbaum, Bjoern Peters, Morten Nielsen ✉

Bioinformatics, Volume 34, Issue 9, 1 May 2018, Pages 1522–1528, https://doi.org/10.1093/bioinformatics/btx820



Integrating MS eluted ligand data has completely changed this



State-of-the-art in-silico methods for class II are now as accurate across all three HLA-II loci as class I methods

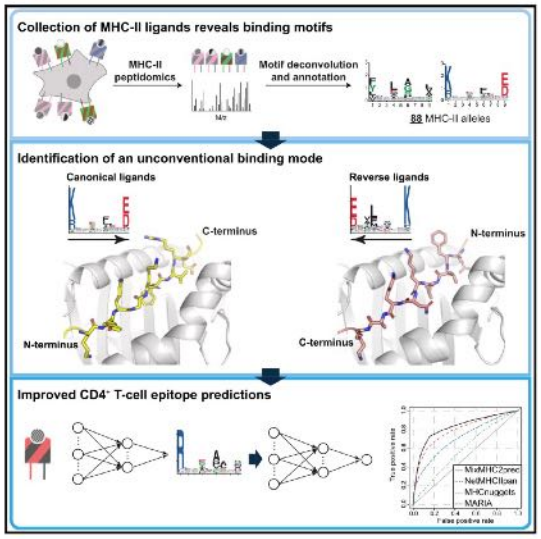
Reynisson et al. J Proteome Res. 2020 Apr 30. doi: 10.1021/acs.jproteome.9b00874.
Nilsson, Kaabinejadian et al., Commun Biol. 2023

MHC binding predictions is a done deal

Immunity

Machine learning predictions of MHC-II specificities reveal alternative binding mode of class II epitopes

Graphical abstract



Authors

Julien Racle, Philippe Guillaume, Julien Schmidt, ..., Michal Bassani-Sternberg, Alexandre Harari, David Gfeller

Completing the puzzle: Accur class II across loci using tailor learning

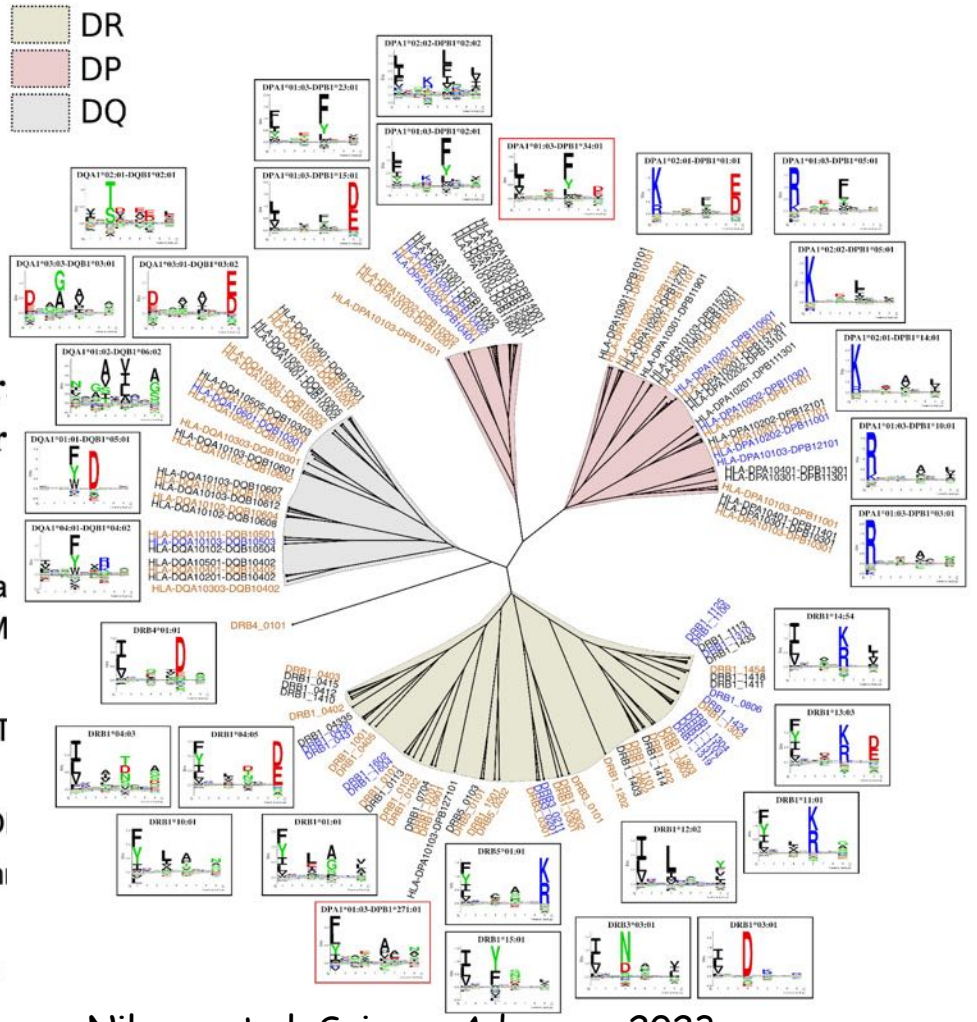
Jonas B. Nilsson[1], Saghar Kaabineja Balen[4], William H. Hildebrand[3] and M

[1] Department of Health Technology, T Denmark

[2] Pure MHC, LLC., Oklahoma City, O

[3] Department of Microbiology and Im Oklahoma City, OK, United States

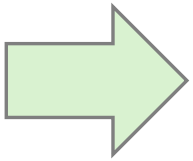
[4] Department of Hematology, Leiden



Nilsson et al, Science Advances 2023

Experimental identification of biologically relevant MHC II-restricted T-cell epitopes

- Peptide presentation (on MHC Class II) measured in an MHC-Associated Peptide Proteomics (MAPPs) assay
- Activation of CD4+ T cells measured by flow cytometry using the markers: IFN-γ, TNF-α, IL-2



Sr #	Peptide	Position (SaCas9)
1	LFDYNLLTDHSELSGINPYEARV	71 - 93
2	SVKYAYNADLYNALNDL	246 - 262
3	NADLYNALNDLNNLVITRDENEKLE	252 - 276
4	KEILVNEEDIKGYR	301 - 314
5	LDQIAKILTIYQSSE	348 - 362
6	NLNSELTQEEIEQISNLKGYTGTHN	370 - 394
7	AINLILDELWHTNDNQIA	399 - 416
8	ILDELWHTNDNQIAIFNR	403 - 420
9	TNDNQIAIFNRLKLVPK	410 - 426
10	LVDDFILSPVVKRSFIQS	440 - 457
11	IQSIKVINAIIKKYGLPND	455 - 473
12	LPNDIIIELAREKNSKDA	470 - 487
13	EGKCLYSLEAIPLEDL	531 - 546
14	NYEVDHIIPRSVSFDNSFNN	552 - 571
15	TPFQYLSSSDSKISYE	587 - 602
16	KDDKGNTLIVNNLNGLYDKDNDKL	793 - 816
17	LLMYHHDPQTYQK	827 - 839
18	DEKNPLYKYYEETGNYLTKYS	849 - 869
19	GNYLTKYSKKDNGPV	862 - 876
20	LDNGVYKFVTVKNLDVIK	918 - 935
21	KENYYEVNSKCYEEAK	936 - 951
22	ISNQAEFIASFYNNDLIK	956 - 973

Simhadri, Hopkins, McGill, Mukherjee, Zhang & Sauna. **Nature Communications** 12: 5090

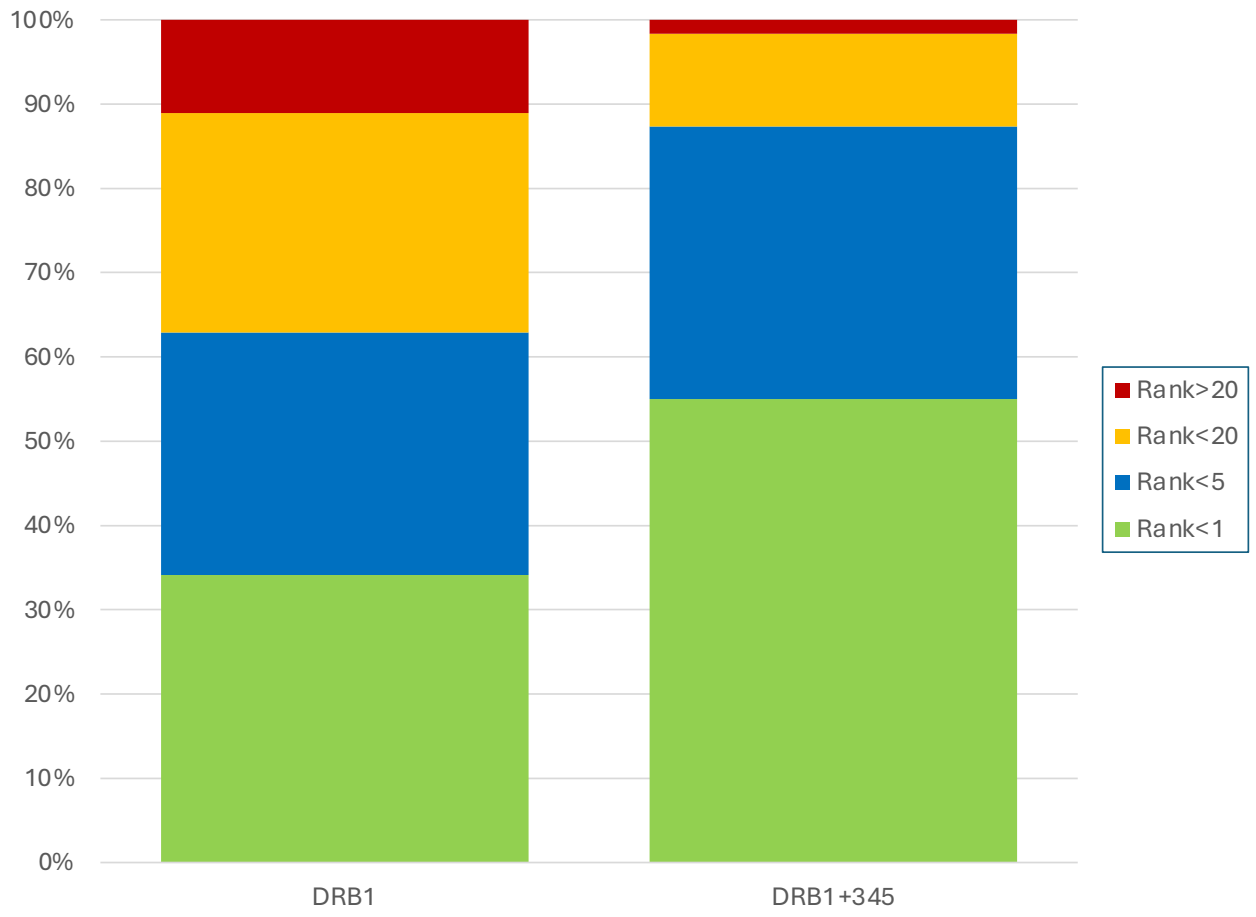
Predicting MAPPs ligands

- Donors were annotated only for DRB1
- Using HLAAssoc 1.0

https://services.healthtech.dtu.dk/services/HLAAssoc-1.0/

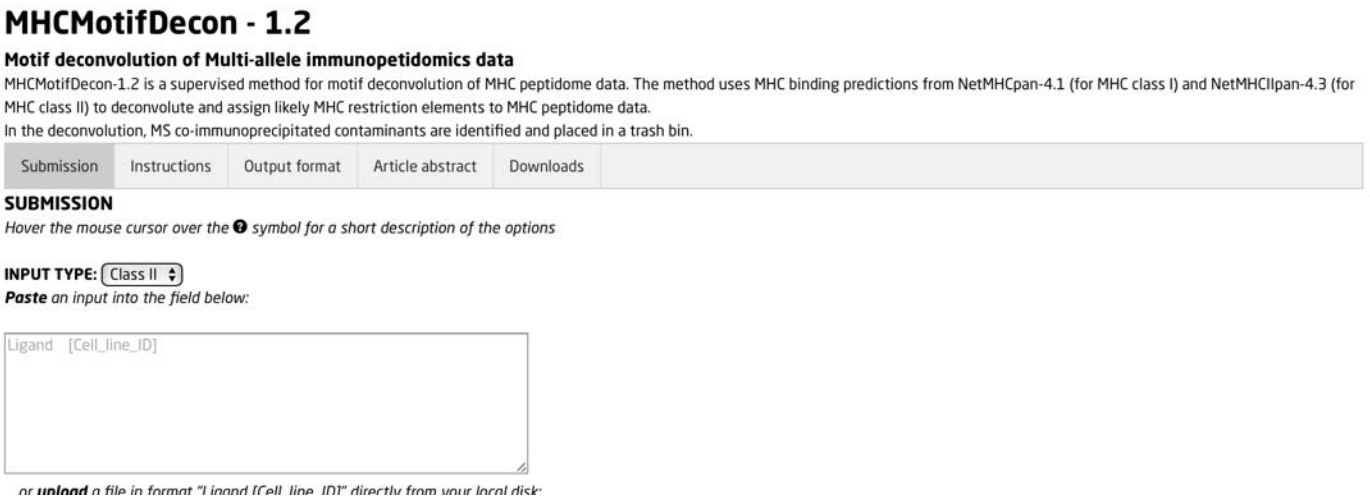
we can extent this to also cover DRB345

- DRB3,4 to 5 restrictions likely explain more than 25% of the MAPPS data



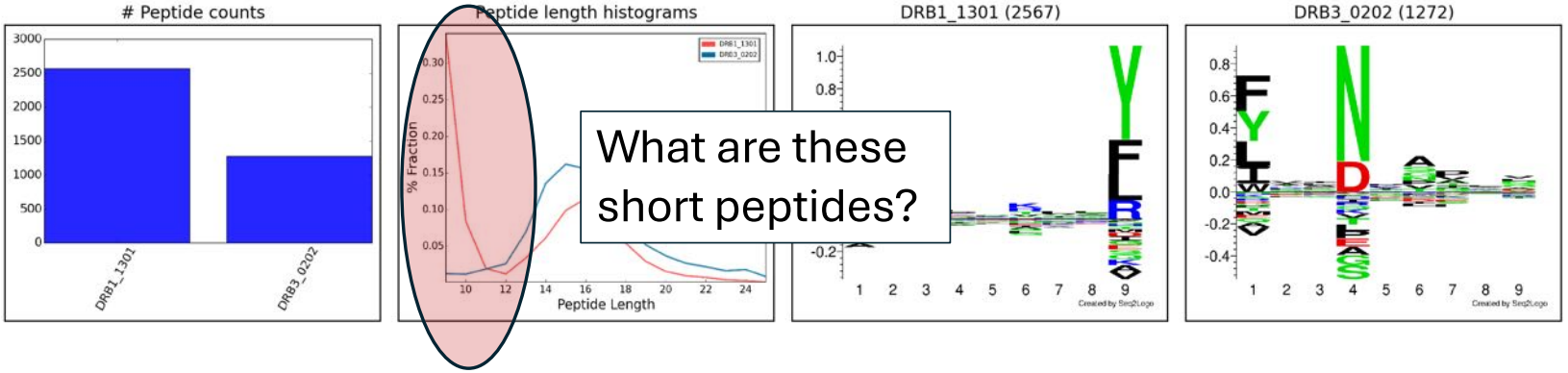
Interpretation of Immunopeptidome (MAPPs) data sets

https://services.healthtech.dtu.dk/services/MHCMotifDecon-1.2/

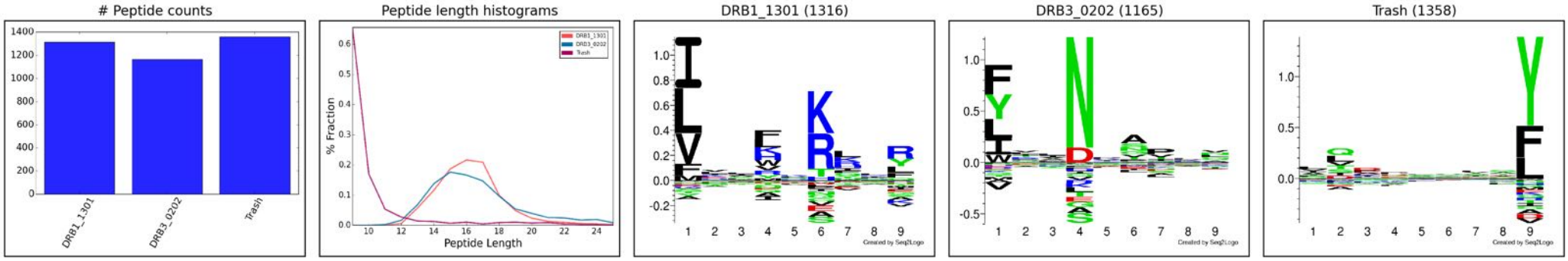


Kaabinejadian et al, Frontiers Immul, 2022

Interpretation of Immunopeptidome (MAPPs) data sets



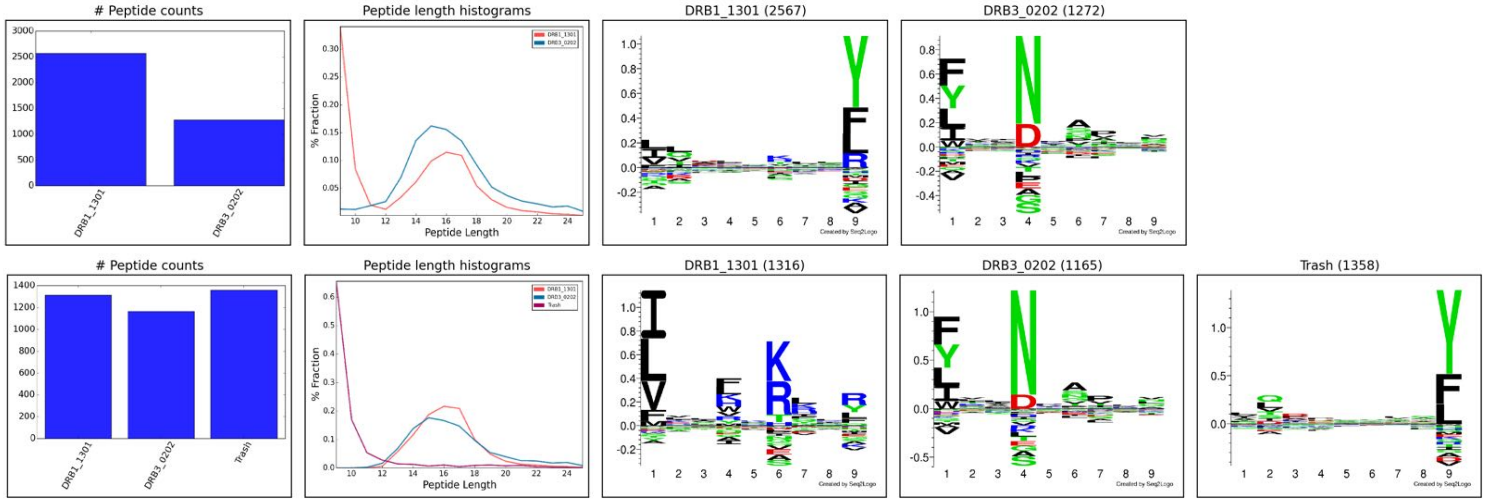
What are these short peptides?

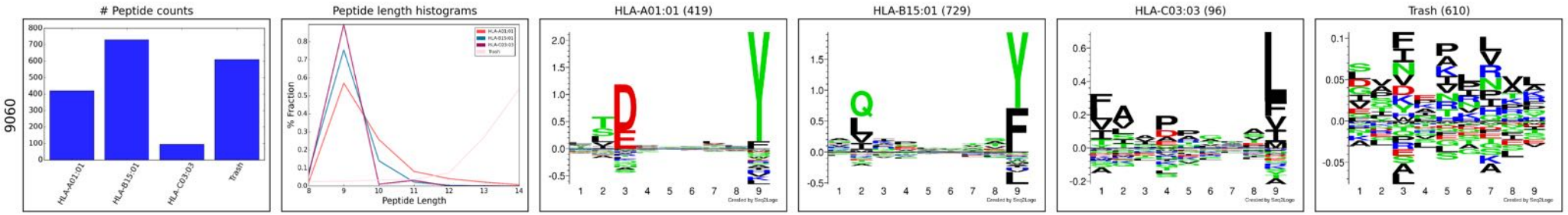


They are clearly NOT class II ligand

Kaabinejadian et al, Frontiers Immul, 2022

Interpretation of Immunopeptidome (MAPPs) data sets

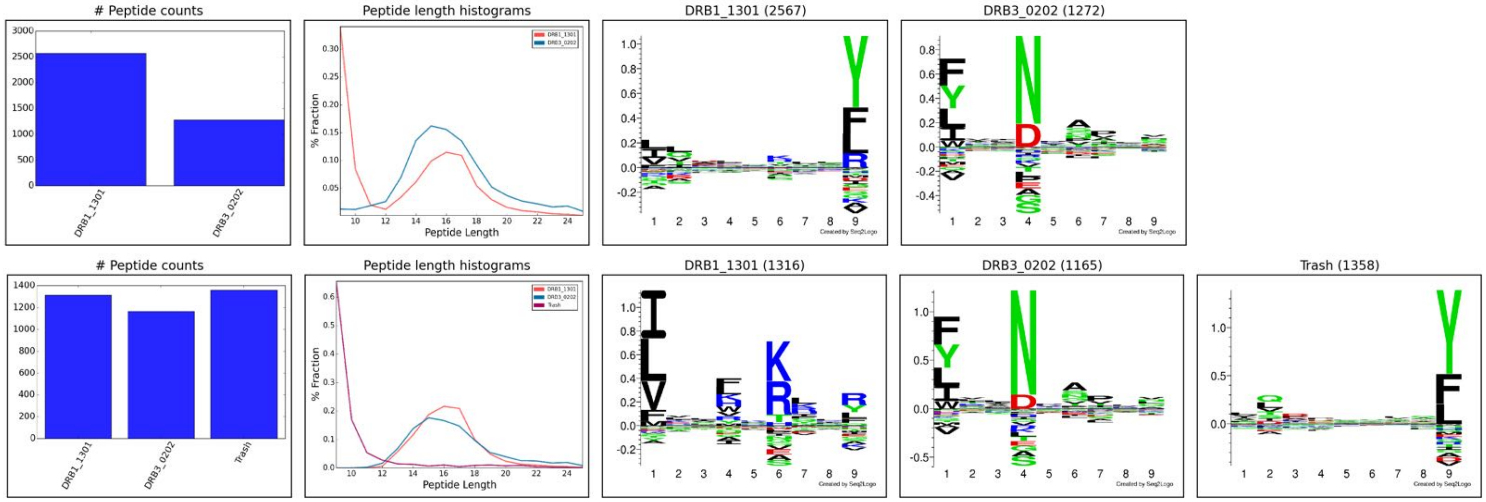


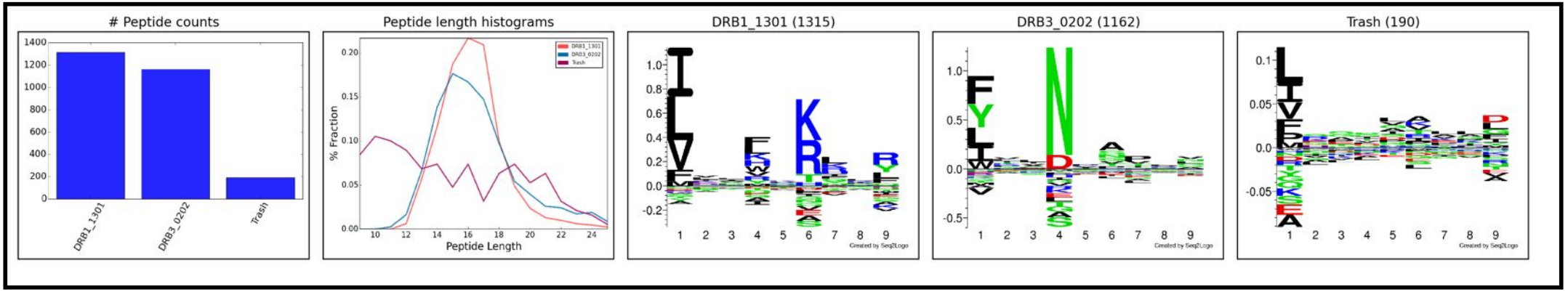


A very large proportion of the short peptides are class I restricted

Kaabinejadian et al, Frontiers Immul, 2022

Interpretation of Immunopeptidome (MAPPs) data sets

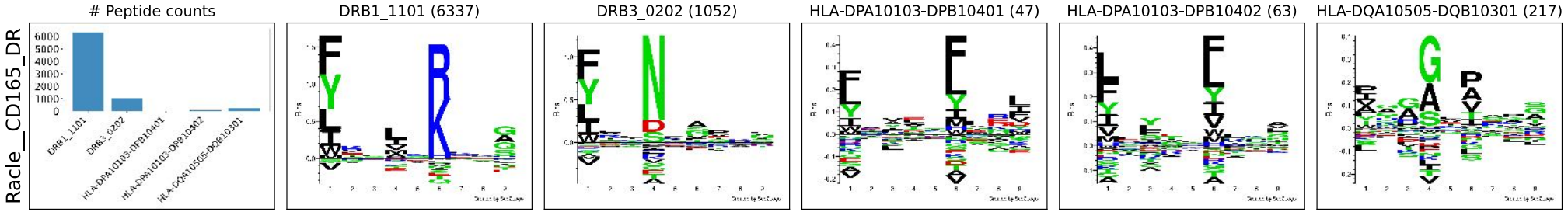




Cleaned-up motif deconvolution

Kaabinejadian et al, Frontiers Immul, 2022

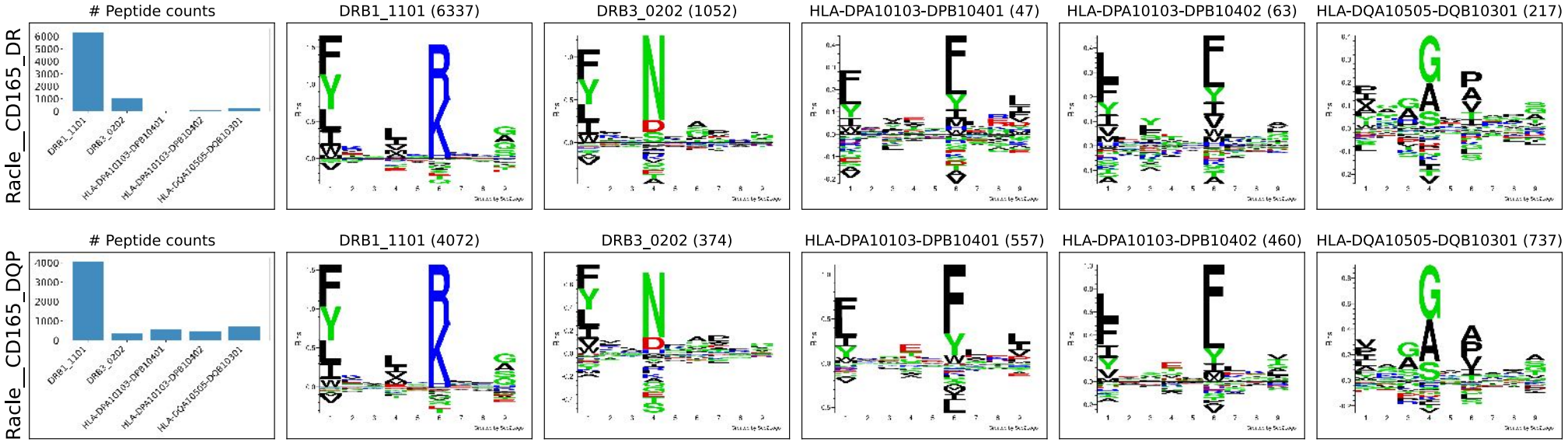
Contribution of DQ and DP in the class II peptidome - Bias in immunoprecipitation



1) Purify HLA-DR molecules with an anti-HLA-DR antibody and

Racle, J., et al. Nat Biotechnol **37**, 1283–1286 (2019)
Nilsson et al. Sci Adv. 2023

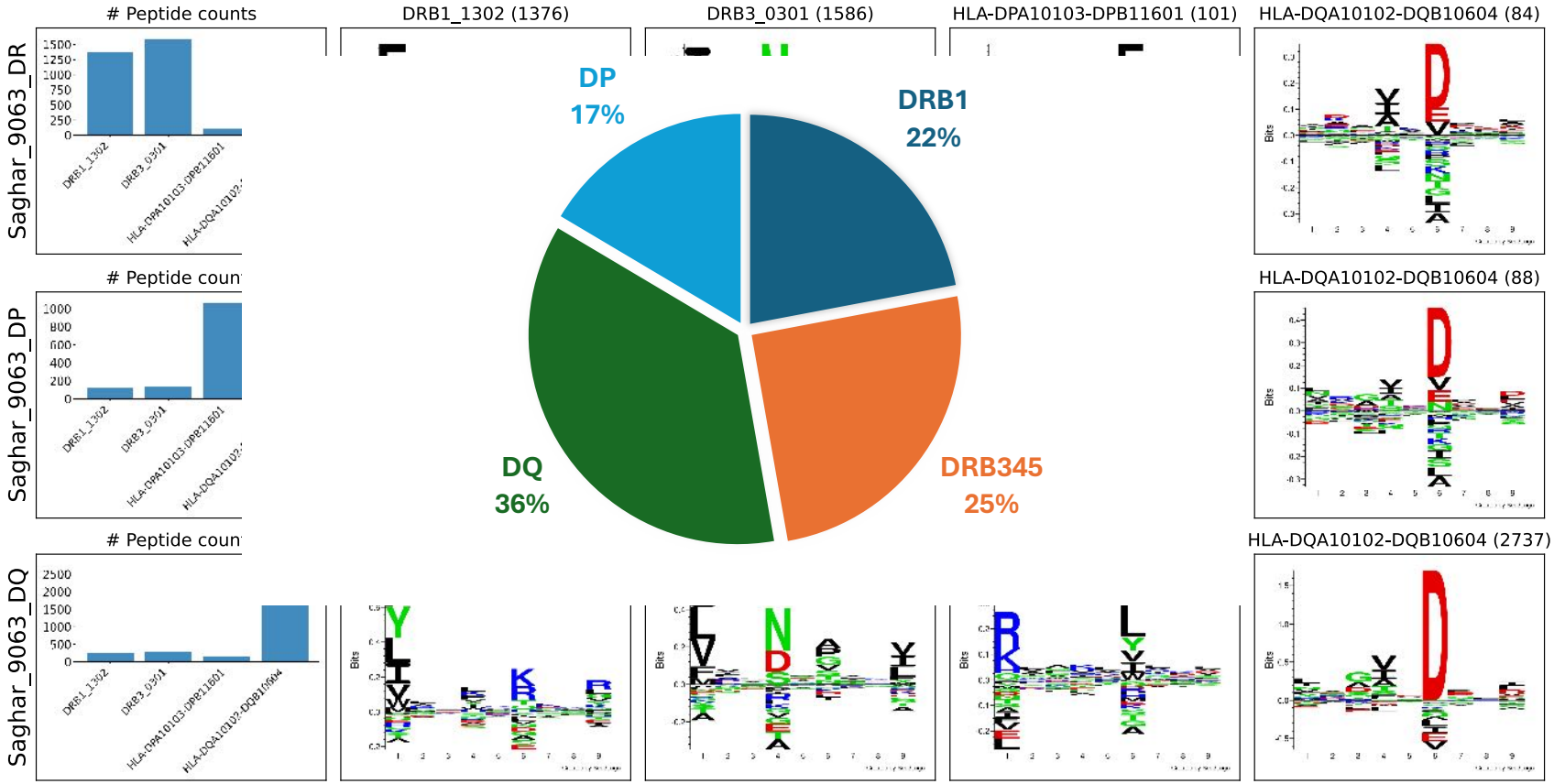
Contribution of DQ and DP in the class II peptidome - Bias in immunoprecipitation



1) Purify HLA-DR molecules with an anti-HLA-DR antibody and
2) then the remaining HLA-II molecules with a pan-HLA-II antibody

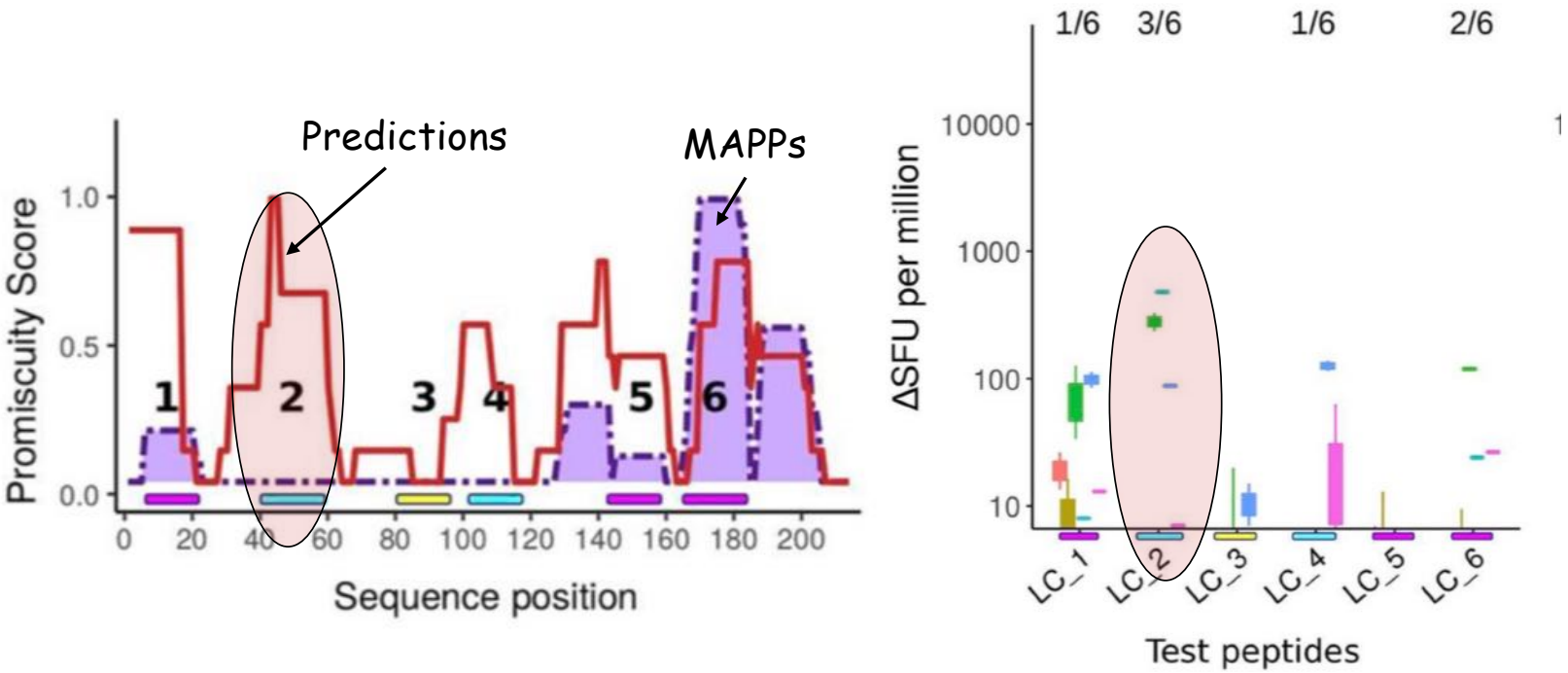
Racle, J., et al. Nat Biotechnol **37**, 1283–1286 (2019)
Nilsson et al. Sci Adv. 2023

Contribution of DRB345, DQ and DP to the class II immunopeptidome



Nilsson et al. Sci Adv. 2023

Protein drug Immunogenicity – Infliximab case-story



Barra et al., Frontiers in Immunology, 2020

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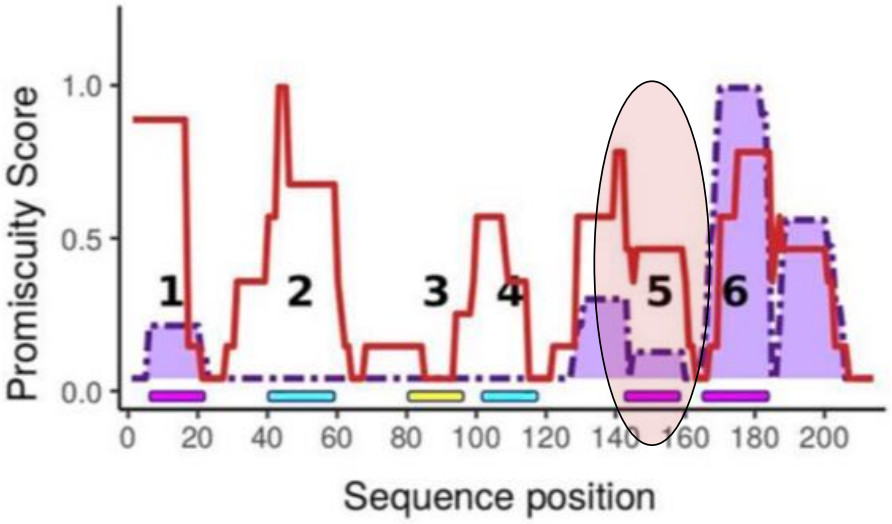
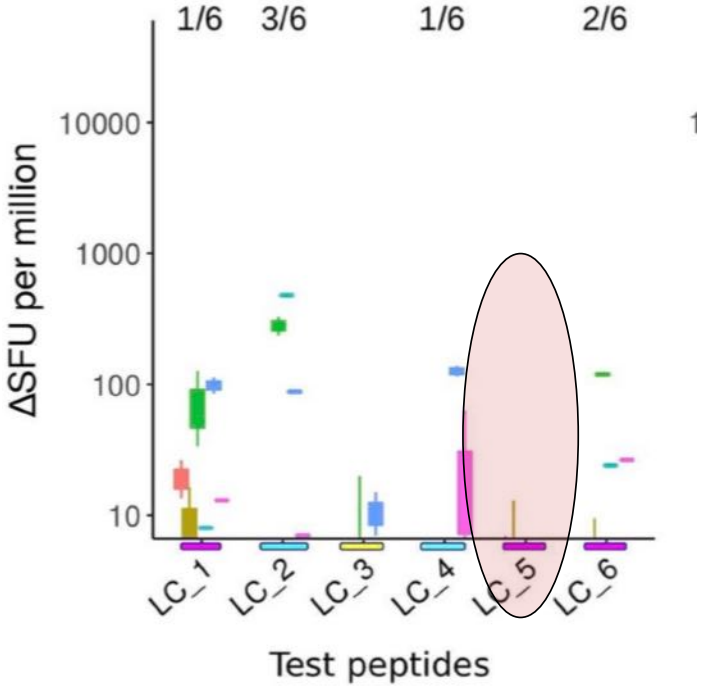
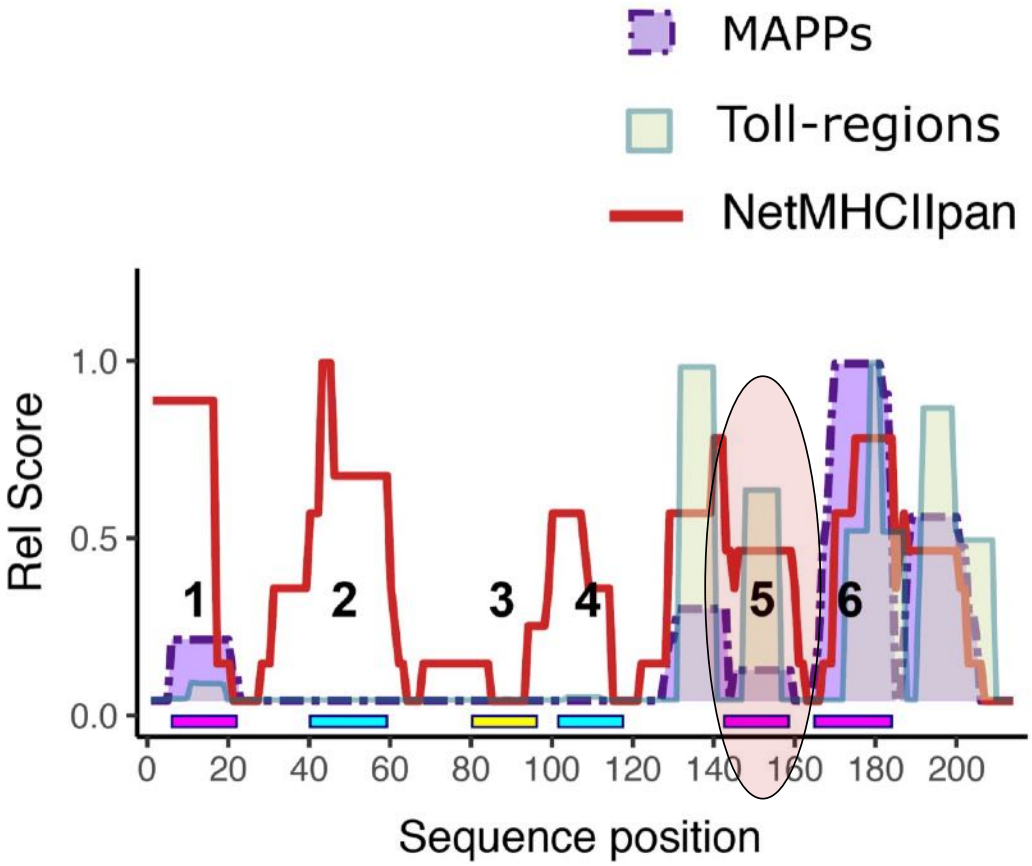




Barra et al., Frontiers in Immunology, 2020

Self-similarity and tolerance

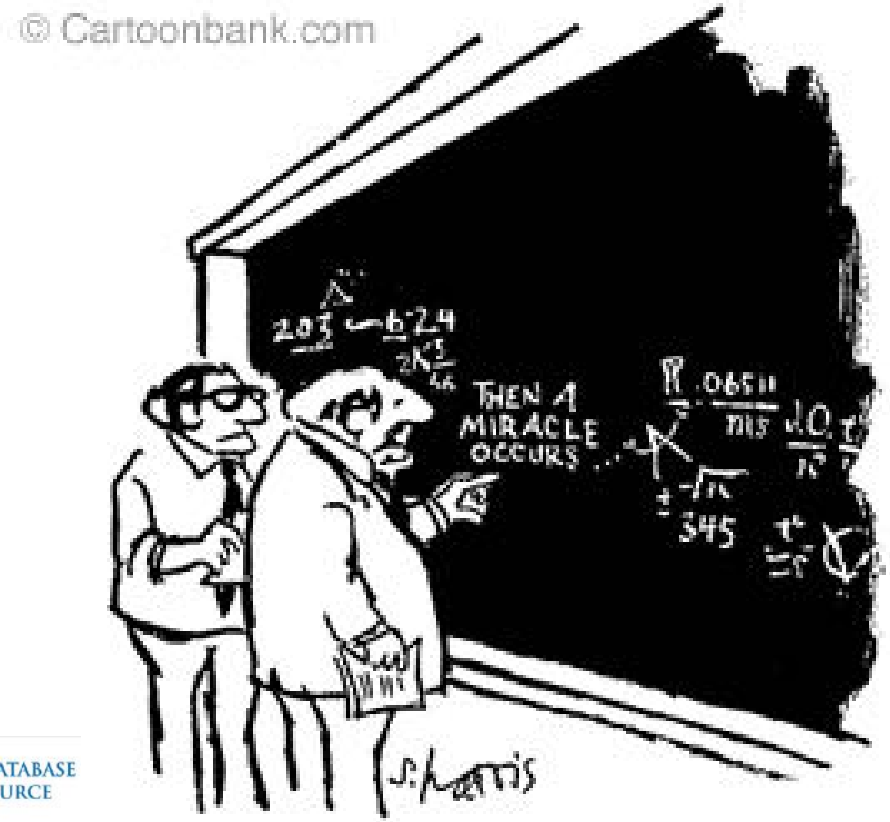


Both MAPPs and in-silico models predict antigen presentation NOT immunogenicity

CP Jacobsen et al., work in progress

Acknowledgements

- Immunological Bioinformatics group, DTU-Bioinformatics
  - PhD students, Post-docs, Colleagues
- Collaborators
  - A. Sette, B. Peters. La Jolla Institute of Allergy and Infectious Diseases: IEDB, CEDAR
  - Sofie Pattyn, ImmunXperts
  - Saghar Kaabinejadian, Pure MHC, University of Oklahoma Health Sciences Center
- Funding



Cas9 peptides identified on MHC-I variants

What is the clinical relevance of the adaptive immune response to Novel Modalities?

What assays, reagents, statistical methods (cut-point determination) do we need to evaluate immunogenicity in the clinic?

Do we need method standardization? Reference standards? Who will bell the cat? Community effort or individual?

Developing in silico tools? Mathematical models? Model Informed Drug Development (MIDD) approaches?

How do we design assays that reflect the influence of the mode of delivery on immunogenicity?

What in silico, in vitro, ex vivo and clinical assessments do we need? Should these be broad based or tailored to the gene editing approach/disease/organ?

Developing in silico tools? Going beyond peptide-MHC antigen presentation predictions. Mathematical models? Model Informed Drug Development (MIDD) approaches?