IEDB
Immune Epitope Database & Tools

T Cell Class II Tools
Binding, Processing, Immunogenicity

tools.iedb.org

Presented by: Dr. Bjoern Peters, Professor

CD4+ T cells Recognize MHC-II-bound Epitopes

- MHC-II molecules are constitutively expressed on professional antigen-presenting cells (APCs)
- APCs take up antigens from the extracellular environment (bacteria, secreted proteins, debris from dead cells, …) and present them to CD4+ T cells
- CD4+ T cells provide ‘help’ to both CD8+ T cells and B cells, as well as having direct effector functions

Peters et al, Annual Review of Immunology, 2020

MHC Class II Molecules

- Two MHC encoded polymorphic chains (α, β), which both impact the binding motif
- Both α and β chains are variable for DP & DQ loci
  - 'HLA-DPA1*01:03/DPB1*02:01'
  - 'HLA-DQA1*01:01/DQB1*05:01'
- Only β chain is variable for DR locus
  - HLA-DRB1*01:01
- DRB3/4/5 locus is in tight linkage with DRB1

  → Often not typed, but just as important

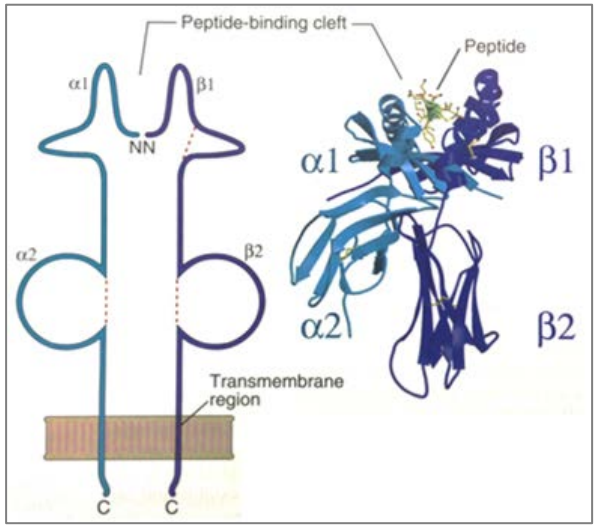
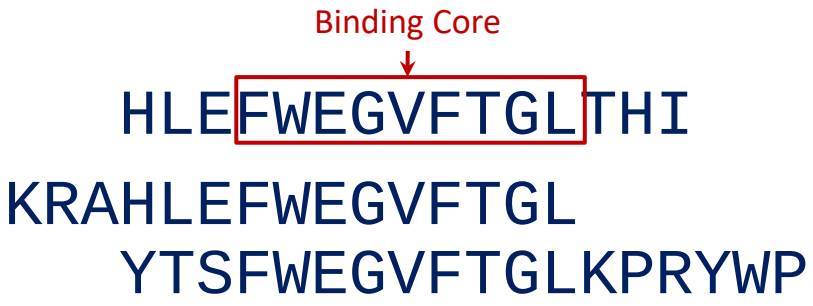


Figure Source
Cellular & Molecular Immunology, 5th Ed by Abbas and Lichtman

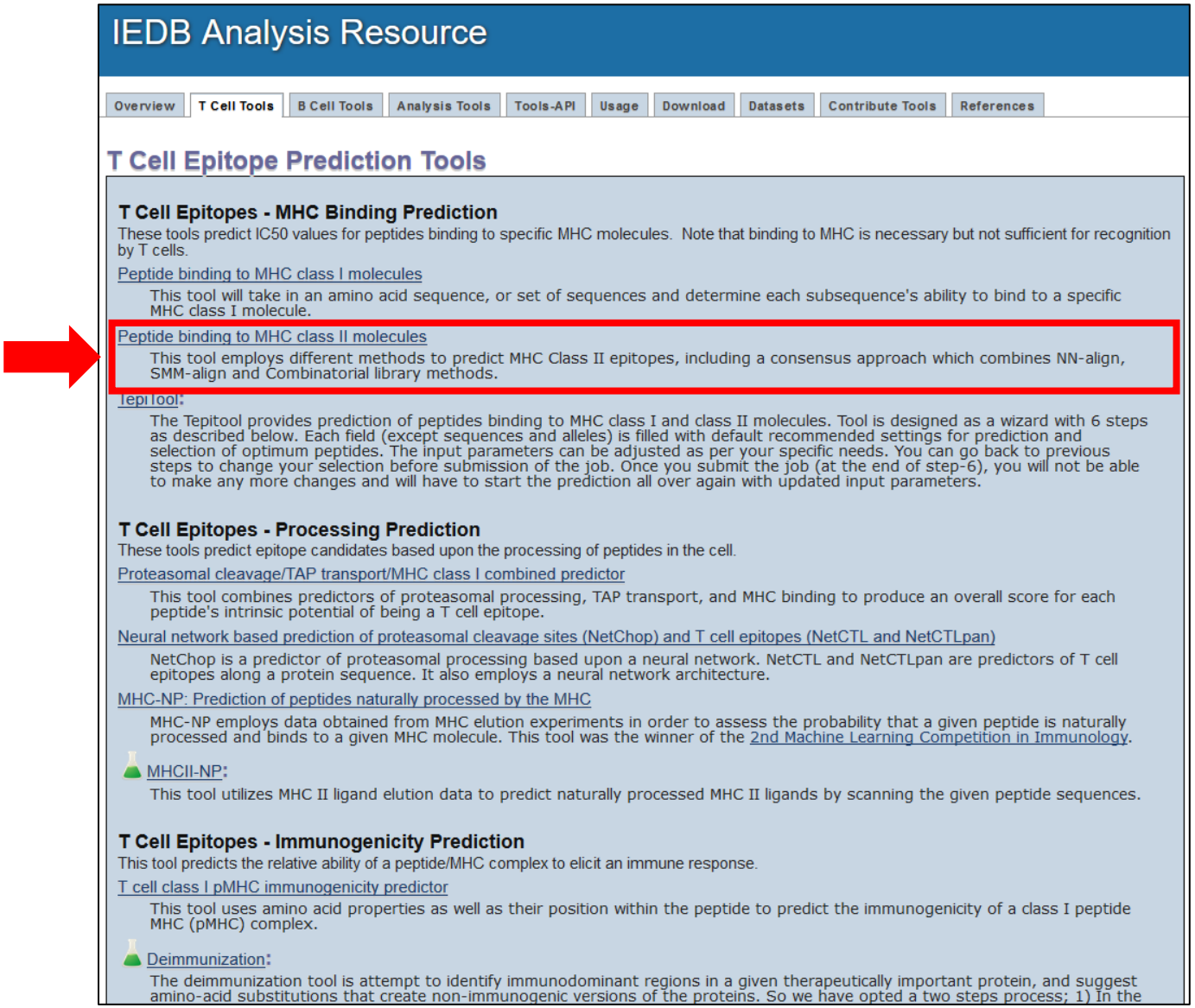
MHC Class II Peptide Binding

- Binding groove is open and can accommodate peptides (13-25 AA)
- 9 AA binding core within the peptide interacts with the binding groove of the MHC molecule



- Challenge: Correct identification of the binding core is not trivial; dissimilar-looking peptides can bind with identical affinity

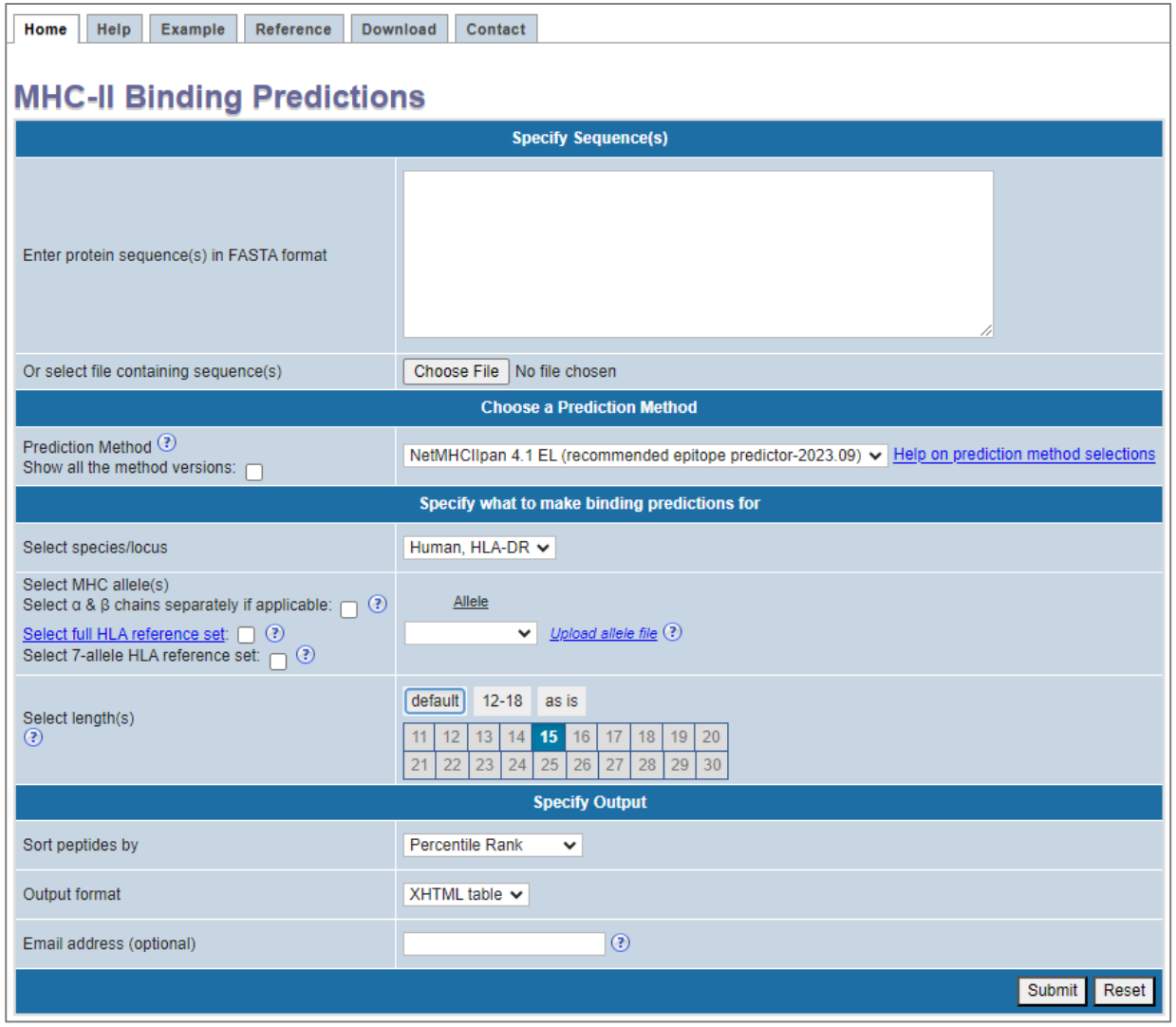
T Cell – MHC Class II Binding Prediction



tools.iedb.org/main/tcell/

MHC-II Binding Prediction Interface

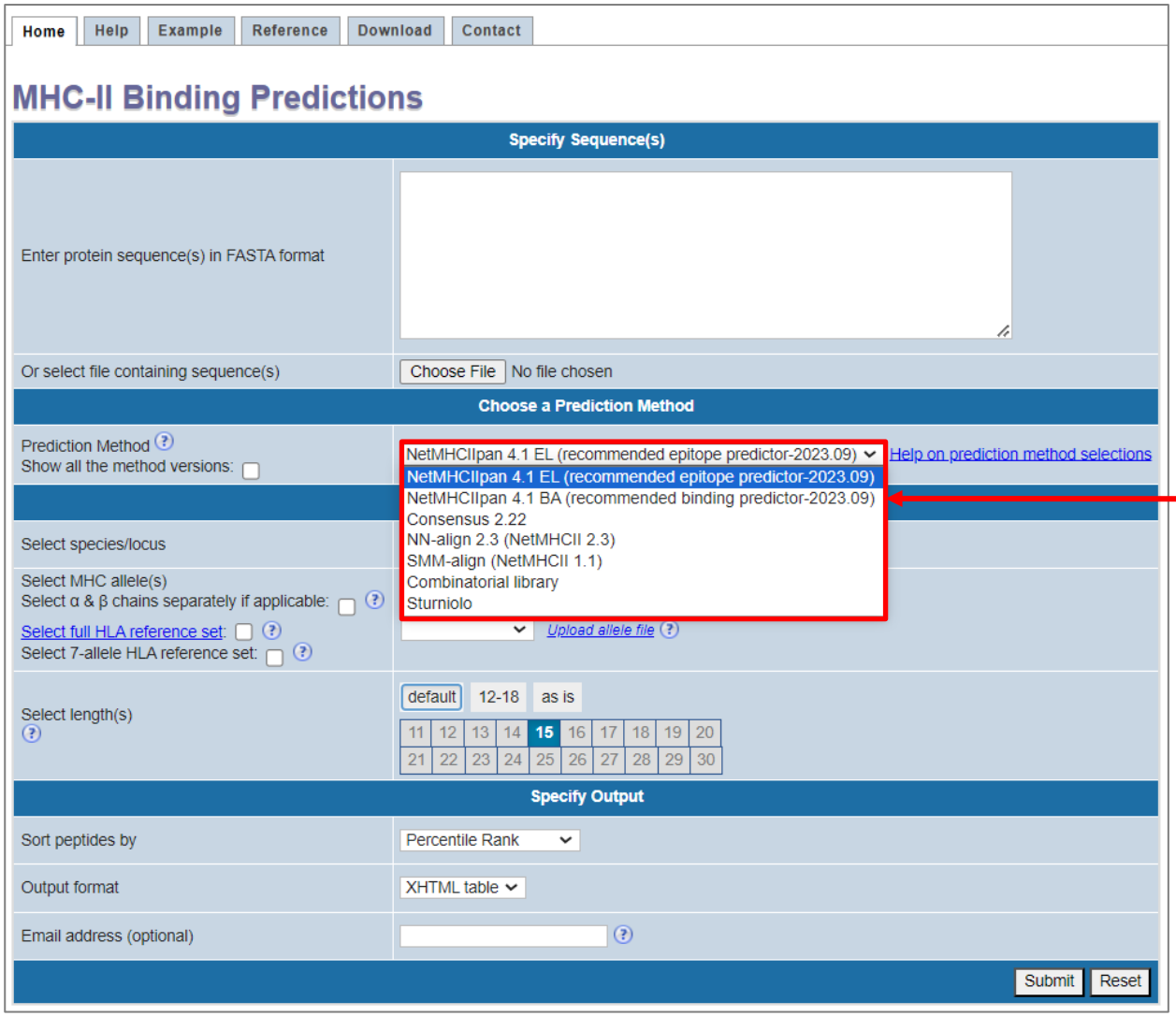
- Tool entry point layout similar to class I



tools.iedb.org/mhcii/

MHC-II Binding Prediction Interface

- Tool entry point layout similar to class I



Select prediction method

tools.iedb.org/mhcii/

MHC II Binding Prediction Methods - Benchmarking

MHC II Automated Server Benchmarks

http://tools.iedb.org/auto_bench/mhcii/weekly/

This is a live ranking of MHC II servers based on performance, which continues to be reevaluated over time. The weekly IEDB releases are automatically checked for datasets large enough to add to the benchmarks. The benchmark metrics in the table below will only be updated on releases where such new data is becoming available.

Accumulated overall ranking scores

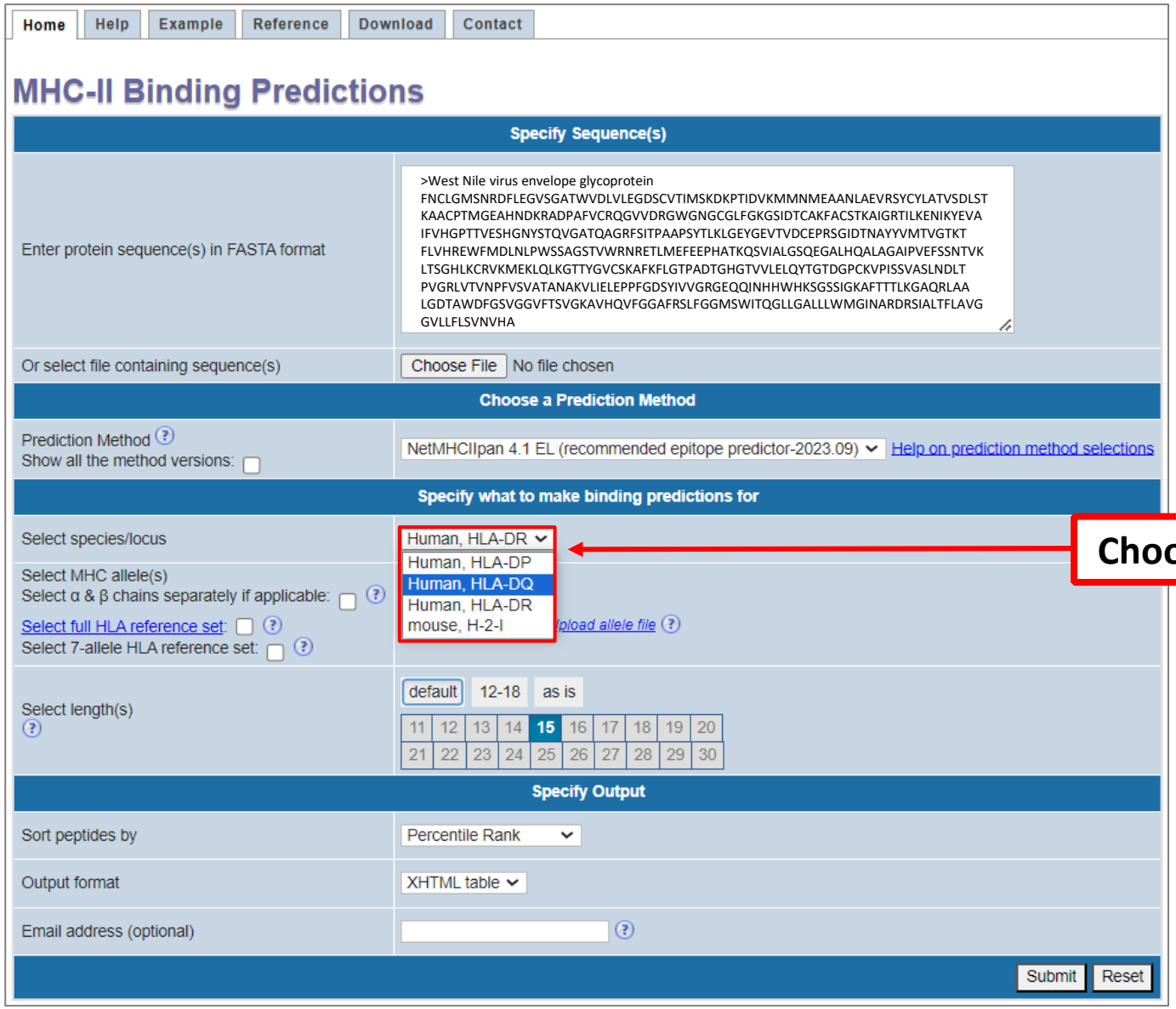
Ranking scores based on data sets submitted to the IEDB for the last at least 5 references.

Server	2023-09-01	2023-07-28	2023-04-21	2023-03-03	2023-01-27	2022-10-28	2022-09-16	2022-09-02	2022-06-17	2022-06-10	2022-04-08	2022-04-01	2021-12-10	2021-11-05	2021-10-29	2021-07-23	2021-04-23	2021-04-16	2021-02-19	2021-01-22	2020-12-18	2020-10-30	2020-10-23	2020-08-07	2020-06-26	2020-05-01	2020-03-27	2020-03-16	2020-01-03	2019-07-02	2019-05-24	2019-03-22	2018-11-23
NetMHCIIpan-4.1 BA	85	82	70	71	70	70	76	65	65	65	65	65	67	66	65	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NetMHCIIpan-4.0 BA	76	78	68	70	68	68	70	65	66	66	63	63	63	62	61	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NetMHCIIpan-3.2	67	67	64	65	64	63	52	51	51	50	61	63	69	70	77	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NN-align 2.3	56	59	51	49	49	48	45	63	64	67	67	67	65	67	67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
NetMHCIIpan-3.1	53	54	66	56	54	55	41	47	47	41	46	46	48	50	54	58	57	58	55	58	46	49	60	61	60	64	55	64	65	65	71	84	79
Consensus IEDB method	50	58	58	59	59	61	57	66	66	68	65	66	63	62	63	66	66	71	73	69	73	76	62	60	60	58	58	61	64	66	64	64	64
NetMHCIIpan-4.1 EL	45	39	51	54	57	57	54	32	32	33	36	36	38	36	38	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SMM-align	43	42	50	50	47	48	42	55	56	52	50	47	50	51	53	49	51	43	43	43	57	61	57	57	54	56	38	41	43	39	43	49	35
NN-align	38	42	44	43	43	42	43	58	58	57	57	59	55	56	57	68	64	73	73	75	59	60	73	74	78	79	88	75	71	71	66	54	63
NetMHCIIpan-4.0 EL	27	24	47	47	50	51	48	31	31	29	34	33	37	34	38	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tepitope (Sturniolo)	26	30	39	39	41	41	37	31	27	41	36	37	41	39	29	21	24	17	18	14	21	29	27	25	27	26	33	28	26	26	29	21	47
Comblib matrices	20	14	7	4	4	4	13	17	17	15	18	16	16	16	17	10	11	8	8	7	30	38	25	25	21	10	0	0	5	5	5	10	4

Andreatta et al, Bioinformatics, 2017

- Similar to the MHC Class I benchmark set-up
- Binding affinity are best predicted with BA output; epitope selection is better using the EL output

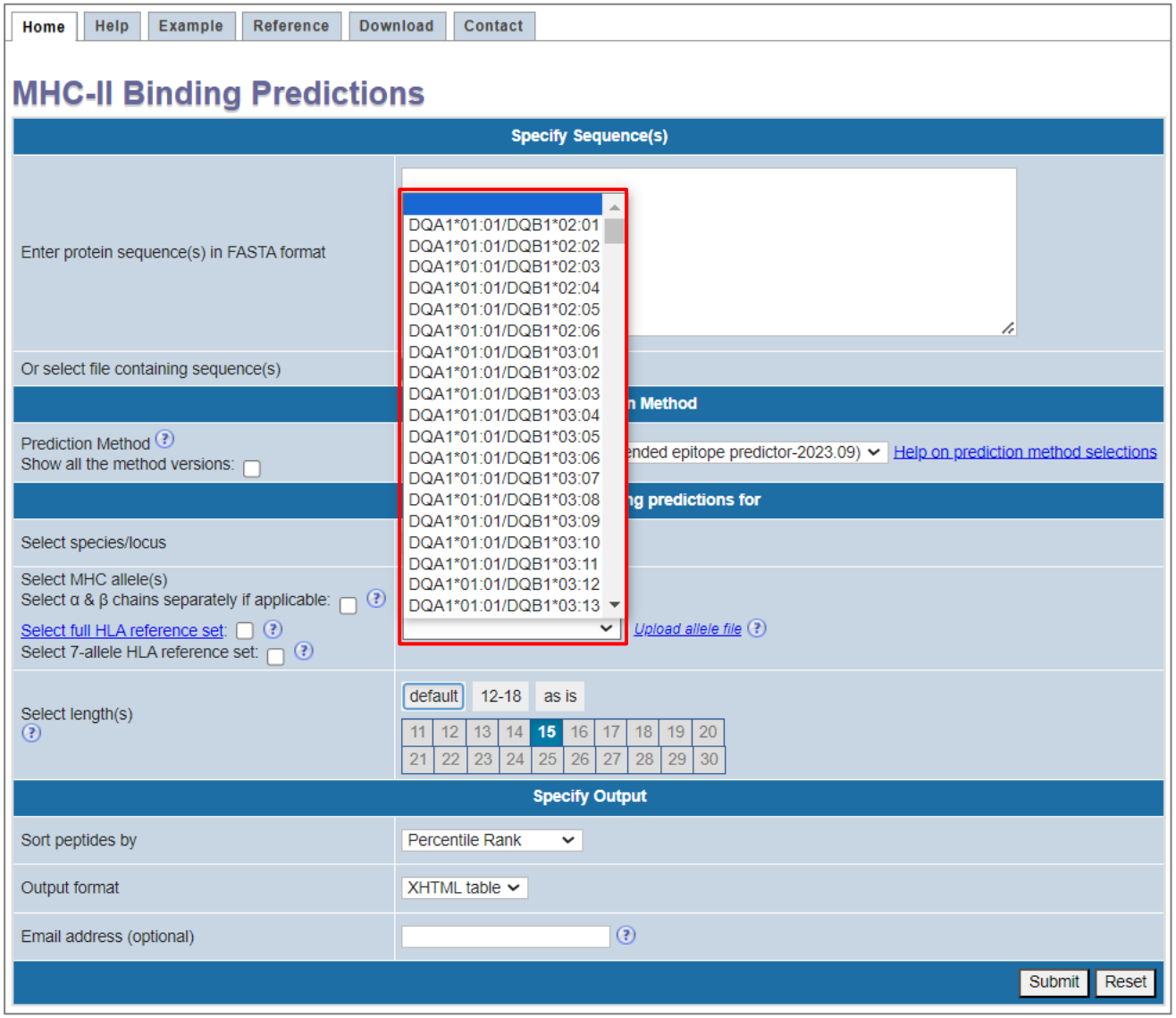
MHC-II Binding Prediction – Example



tools.iedb.org/mhcii/

Choose species & locus

Allele Selection - α and β Chains



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Allele Selection - α and β Chains

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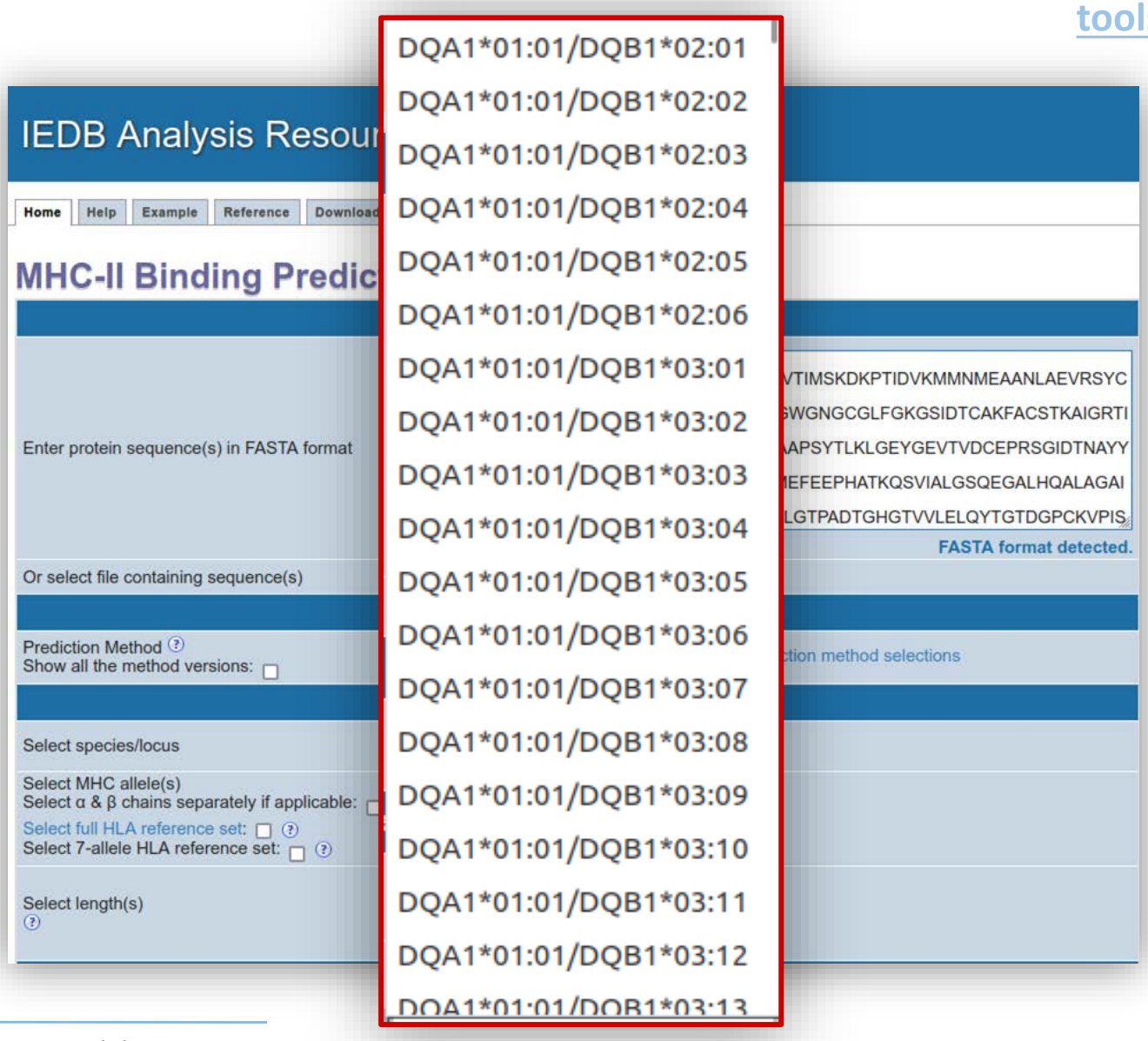
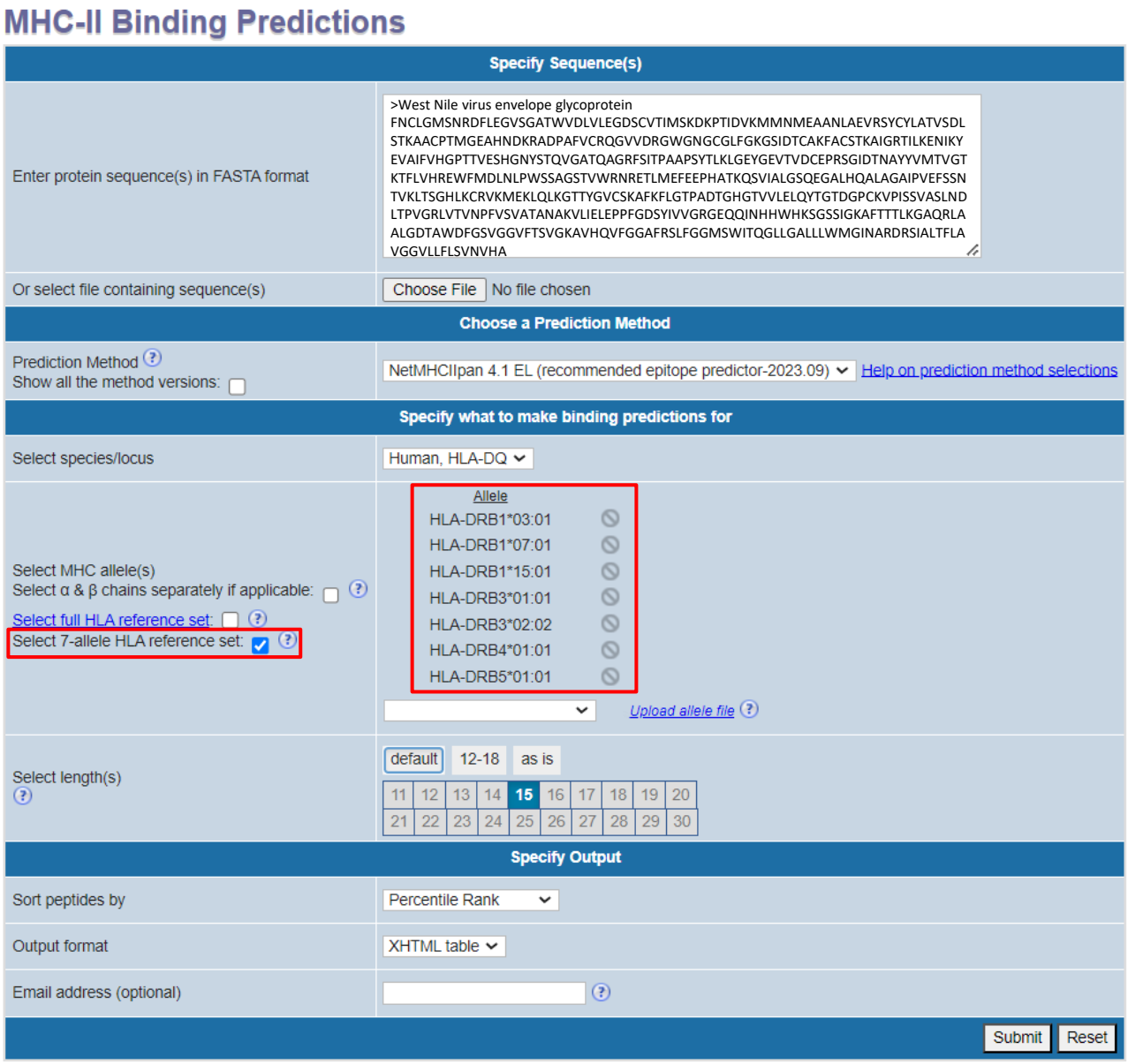


"7-Allele" Method

- Aim was to capture maximum immune response with minimum no. of peptides
- 6 peptide datasets with measured immune responses (SFCs/106 PBMCs)
- 15 or 16-mer peptide sets with 10 AA residues overlapping

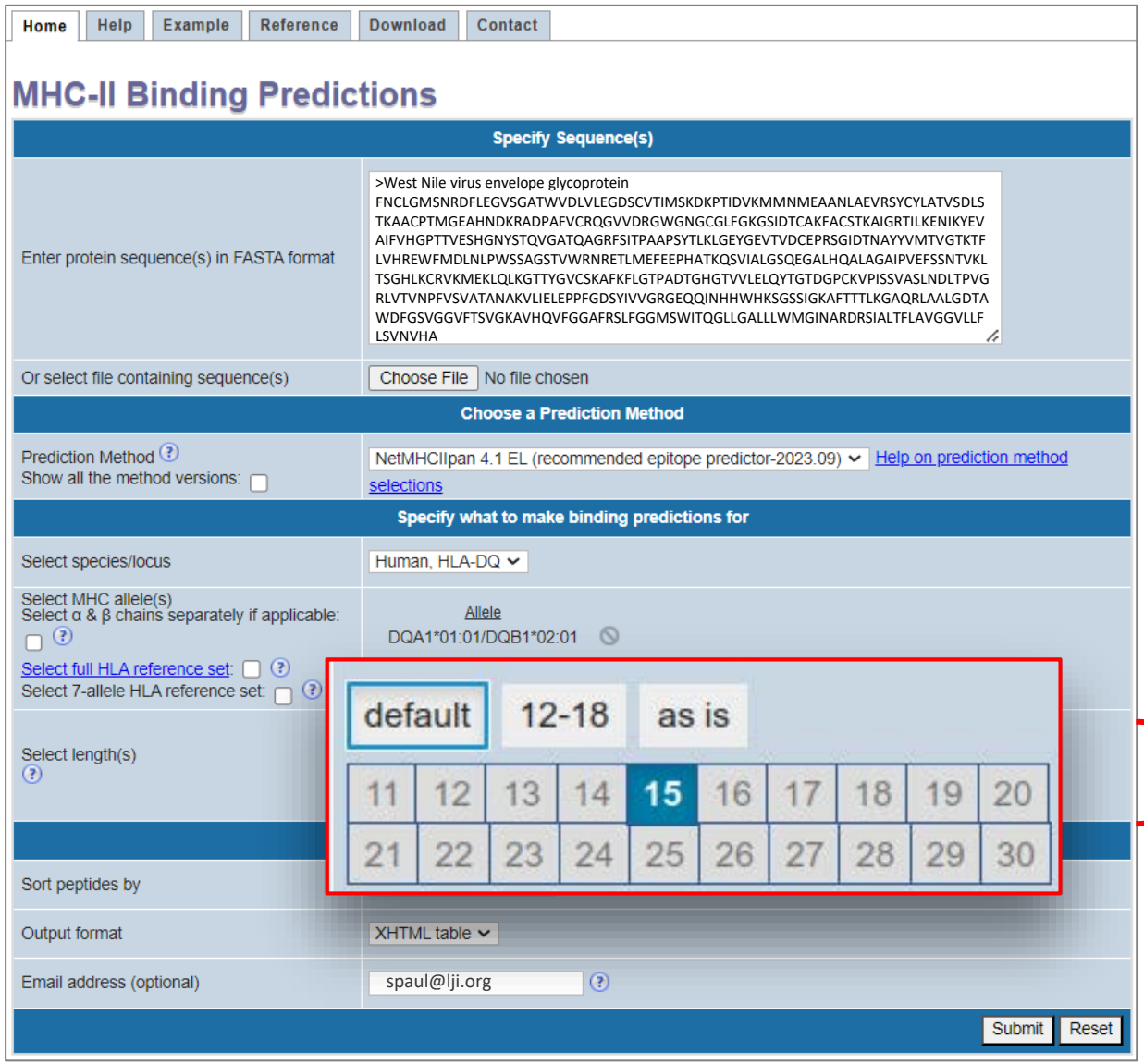
Dataset	Purpose	No. of Antigens	Total peptides	No. of donors	Reference
Der p/f (House dust mite)	Training data	4	156	20	Hinz et al., 2015, CEA
Phl p (Timothy grass)	Training data	10	425	25	Oseroff et al., 2010, JI
TB-1	Training data	4	71	18	Arlehamn et al., 2012, JI
TB-2	Training data	11	499	32	Arlehamn et al., 2016, PLoS Path
Cockroach	Validation data	6	463	19	Dillon et al., 2015, CEA
Pertussis	Validation data	9	785	23	Bancroft et al., 2016, CEA
TOTAL		**44**	**2399**	**137**	

“7-Allele” Method



MHC-II Binding Prediction – Example

tools.iedb.org/mhcii/



Length selection

MHC-II Binding Prediction – Example

MHC-II Binding Prediction Results

Input Sequences

#	Name	Sequence
1	West Nile virus envelope glycoprotein	FNCLGMSNRDFLEGVSGATWVDLVLEGDSCVTIMSKDKPTIDVKMMNMEA ANLAEVRSYCYLATVSDLSTKAACPTMGEAHNDKRADPAFVCRQGVVDRG WGNGCGLFGKGSIDTCAKFACSTKAIGRTILKENIKYEVAIFVHGPTTVE SHGNYSTQVGATQAGRFSITPAAPSYTLKLGEYGEVTVDCEPRSGIDTNA YYVMTVGTKTFLVHREWFMDLNLPWSSAGSTVWRNRETLMEFEEPHATKQ SVIALGSQEGALHQALAGAIPVEFSSNTVKLTSGHLKCRVKMEKLQLKGT TYGVCSKAFKFLGTPADTGHGTVVLELQYTGTDGPCKVPISSVASLNDLT PVGRLVTVNPFVSVATANAKVLIELEPPFGDSYIVVGRGEQQINHHWHKS GSSIGKAFTTTLKGAQRLAALGDTAWDFGSVGGVFTSVGKAVHQVFGGAF RSLFGGMSWITQGLLGALLLWMGINARDRSIALTFLAVGGVLLFLSVNVH A

Prediction method: netmhciipan_el 4.1 | High score = good binders

Download result

Citations

Allele	#	Start	End	Length	Core Sequence	Peptide Sequence	Score	Percentile Rank
HLA-DQA1*01:01/DQB1*02:01	1	306	320	15	FKFLGTPAD	SKAFKFLGTPADTGH	0.0383	1.30
HLA-DQA1*01:01/DQB1*02:01	1	132	146	15	IKYEVAIFV	KENIKYEVAIFVHGP	0.0369	1.40
HLA-DQA1*01:01/DQB1*02:01	1	236	250	15	LMEFEEPHA	RETLMEFEEPHATKQ	0.0305	2.30
HLA-DQA1*01:01/DQB1*02:01	1	305	319	15	FKFLGTPAD	CSKAFKFLGTPADTG	0.0297	2.50
HLA-DQA1*01:01/DQB1*02:01	1	357	371	15	FVSVATANA	TVNPFVSVATANAKV	0.0240	3.90
HLA-DQA1*01:01/DQB1*02:01	1	235	249	15	LMEFEEPHA	NRETLMEFEEPHATK	0.0235	4.10
HLA-DQA1*01:01/DQB1*02:01	1	131	145	15	IKYEVAIFV	LKENIKYEVAIFVHG	0.0233	4.20
HLA-DQA1*01:01/DQB1*02:01	1	237	251	15	LMEFEEPHA	ETLMEFEEPHATKQS	0.0182	7
HLA-DQA1*01:01/DQB1*02:01	1	234	248	15	LMEFEEPHA	RNRETLMEFEEPHAT	0.0181	7.10
HLA-DQA1*01:01/DQB1*02:01	1	307	321	15	FKFLGTPAD	KAFKFLGTPADTGHG	0.0176	7.60
HLA-DQA1*01:01/DQB1*02:01	1	356	370	15	FVSVATANA	VTVNPFVSVATANAK	0.0174	7.60
HLA-DQA1*01:01/DQB1*02:01	1	133	147	15	IKYEVAIFV	ENIKYEVAIFVHGPT	0.0156	9.40
HLA-DQA1*01:01/DQB1*02:01	1	304	318	15	FKFLGTPAD	VCSKAFKFLGTPADT	0.0156	9.50
HLA-DQA1*01:01/DQB1*02:01	1	233	247	15	RETLMEFEE	WRNRETLMEFEEPHA	0.0154	9.70
HLA-DQA1*01:01/DQB1*02:01	1	358	372	15	FVSVATANA	VNPFVSVATANAKVL	0.0147	11
HLA-DQA1*01:01/DQB1*02:01	1	224	238	15	SAGSTVWRN	PWSSAGSTVWRNRET	0.0142	12
HLA-DQA1*01:01/DQB1*02:01	1	130	144	15	IKYEVAIFV	ILKENIKYEVAIFVH	0.0141	12
HLA-DQA1*01:01/DQB1*02:01	1	223	237	15	SAGSTVWRN	LPWSSAGSTVWRNRE	0.0138	12
HLA-DQA1*01:01/DQB1*02:01	1	337	351	15	ISSVASLND	KVPISSVASLNDLTP	0.0135	13
HLA-DQA1*01:01/DQB1*02:01	1	43	57	15	MNMEAANLA	VKMMNMEAANLAEVR	0.0135	13

tools.iedb.org/mhcii/

Input sequence

Output
(sorted high-to-low by score)

Guidelines: Selecting Binders

- Previously, the performance of MHC-II predictions was worse than MHC-I, but this difference has decreased significantly (based on AUC values in automated benchmark)

- Previously established threshold guidelines:
  - Percentile rank ≤ **10.0** (Percentile rank on linear scale (0-100), lower value = better binder)
  - MHC binding affinity IC50 ≤ **1000nM**

- **Given the increased prediction performance, threshold can probably be made more stringent – evaluation outstanding**

Issue of Overlapping Peptides

- The tool breaks the sequence into all possible 15-mers - Peptides overlapping by 14 amino acid residues

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
1	allele	seq_n	start	end	peptide	method	percent	comblib_core	comblib	comblib	smm_align_core	smm_al	smm_al	nn_align_core	nn_a
2	HLA-DPA1*01/DPB1*0401	1	527	541	DHLEFWEGVFTGLTH	Consensus (com	2.52	FWEGVFTGL	6.9	19.59	FWEGVFTGL	310	0.62	EFWEGVFTG	3
3	HLA-DPA1*01/DPB1*0401	1	528	542	HLEFWEGVFTGLTHI	Consensus (com	2.57	FWEGVFTGL	6.9	19.59	FWEGVFTGL	302	0.58	FWEGVFTGL	4
4	HLA-DPA1*01/DPB1*0401	1	526	540	QDHLEFWEGVFTGLT	Consensus (com	2.62	FWEGVFTGL	6.9	19.59	FWEGVFTGL	310	0.62	EFWEGVFTG	4
5	HLA-DPA1*01/DPB1*0401	1	529	543	LEFWEGVFTGLTHID	Consensus (com	3.13	FWEGVFTGL	6.9	19.59	FWEGVFTGL	308	0.61	FWEGVFTGL	5
6	HLA-DPA1*01/DPB1*0401	1	525	539	CQDHLEFWEGVFTGL	Consensus (com	3.26	FWEGVFTGL	6.9	19.59	EFWEGVFTG	320	0.66	FWEGVFTGL	5
7	HLA-DPA1*01/DPB1*0401	1	39	53	AAQTFLATCINGVCW	Consensus (com	3.8	QTFLATCIN	728.23	45.84	FLATCINGV	742	3.36	FLATCINGV	6
8	HLA-DPA1*01/DPB1*0401	1	262	276	GSPITYSTYGKFLAD	Consensus (com	4.07	TYSTYGKFL	2.38	15.24	ITYSTYGKF	827	4.07	ITYSTYGKF	
9	HLA-DPA1*01/DPB1*0401	1	40	54	AQTFLATCINGVCWT	Consensus (com	4.08	QTFLATCIN	728.23	45.84	FLATCINGV	746	3.39	FLATCINGV	7
10	HLA-DPA1*01/DPB1*0401	1	263	277	SPITYSTYGKFLADG	Consensus (com	4.08	TYSTYGKFL	2.38	15.24	ITYSTYGKF	828	4.08	ITYSTYGKF	5
11	HLA-DPA1*01/DPB1*0401	1	38	52	TAAQTFLATCINGVC	Consensus (com	4.13	TAAQTFLAT	52.52	29.77	FLATCINGV	478	1.49	FLATCINGV	7
12	HLA-DPA1*01/DPB1*0401	1	37	51	STAAQTFLATCINGV	Consensus (com	4.56	TAAQTFLAT	52.52	29.77	TAAQTFLAT	464	1.41	FLATCINGV	8
13	HLA-DPA1*01/DPB1*0401	1	261	275	TGSPITYSTYGKFLA	Consensus (com	4.78	TYSTYGKFL	2.38	15.24	ITYSTYGKF	908	4.78	ITYSTYGKF	
14	HLA-DPA1*01/DPB1*0401	1	530	544	EFWEGVFTGLTHIDA	Consensus (com	5	FWEGVFTGL	6.9	19.59	FWEGVFTGL	664	2.75	FWEGVFTGL	9
15	HLA-DPA1*01/DPB1*0401	1	102	116	SDLYLVTRHADVIPV	Consensus (com	7.45	LVTRHADVI	23.49	25.43	YLVTRHADV	1194	7.45	YLVTRHADV	14
16	HLA-DPA1*01/DPB1*0401	1	41	55	QTFLATCINGVCWTV	Consensus (com	7.57	QTFLATCIN	728.23	45.84	FLATCINGV	829	4.09	FLATCINGV	16
17	HLA-DPA1*01/DPB1*0401	1	101	115	SSDLYLVTRHADVIP	Consensus (com	7.57	LVTRHADVI	23.49	25.43	YLVTRHADV	1206	7.57	YLVTRHADV	16
18	HLA-DPA1*01/DPB1*0401	1	260	274	TTGSPITYSTYGKFL	Consensus (com	7.71	TYSTYGKFL	2.38	15.24	ITYSTYGKF	1221	7.71	ITYSTYGKF	10
19	HLA-DPA1*01/DPB1*0401	1	100	114	GSSDLYLVTRHADVI	Consensus (com	7.85	GSSDLYLVT	0.74	11.33	YLVTRHADV	1183	7.34	YLVTRHADV	17
20	HLA-DPA1*01/DPB1*0401	1	531	545	FWEGVFTGLTHIDAH	Consensus (com	7.97	FWEGVFTGL	6.9	19.59	FWEGVFTGL	728	3.24	FWEGVFTGL	17
21	HLA-DPA1*01/DPB1*0401	1	103	117	DLYLVTRHADVIPVR	Consensus (com	8.57	LVTRHADVI	23.49	25.43	YLVTRHADV	1307	8.57	YLVTRHADV	16

Issue of Overlapping Peptides: Solution

- Post-processing:
  - Remove largely overlapping peptides after prediction (based on same binding core or position)

	A	B	C	D	E	G	H	I	J	K	L	M	N	O
1	allele	seq_n	start	end	peptide	percent	comblib_core	comblib	comblib	smm_align_core	smm_al	smm_al	nn_align_core	nn_a
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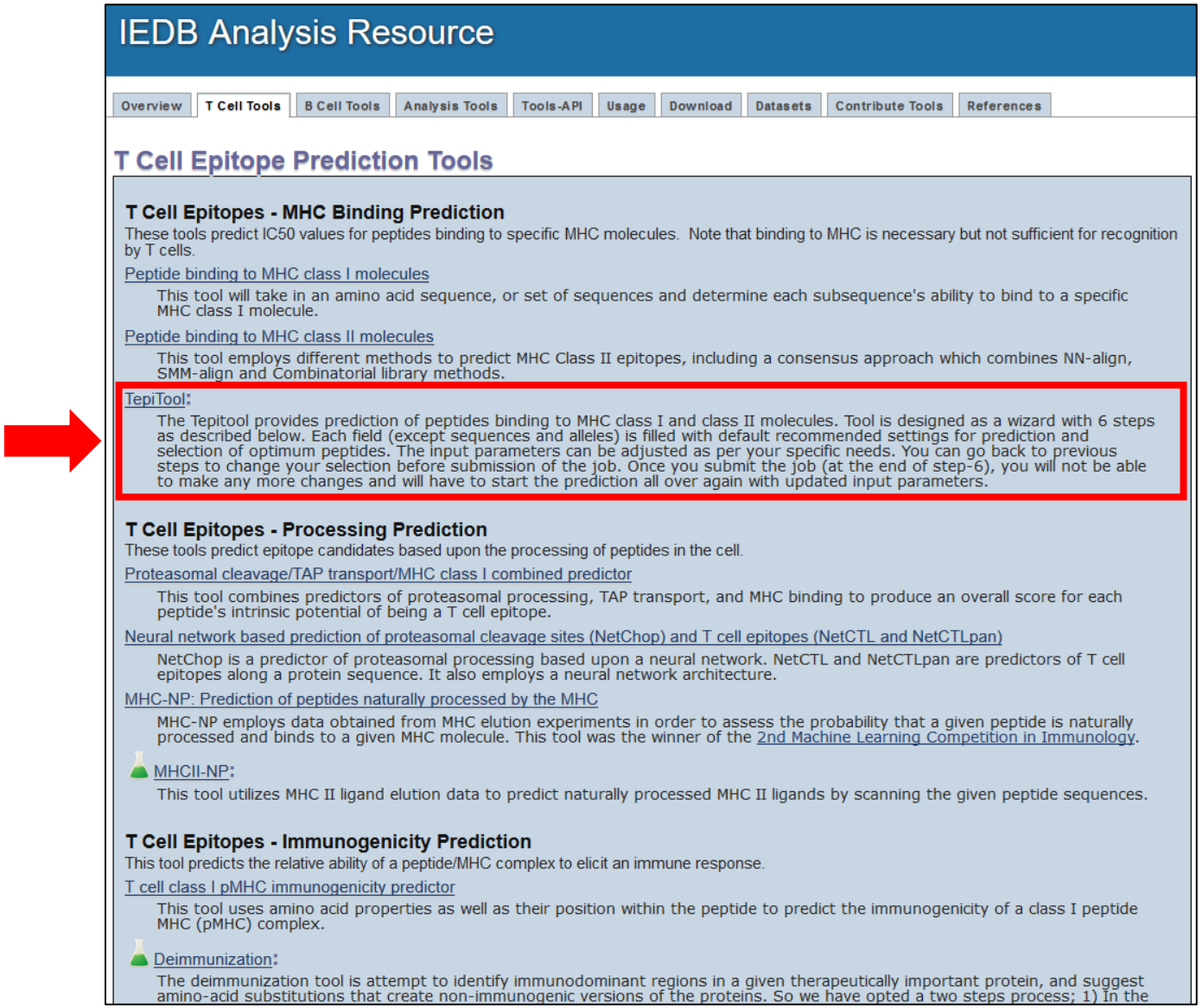
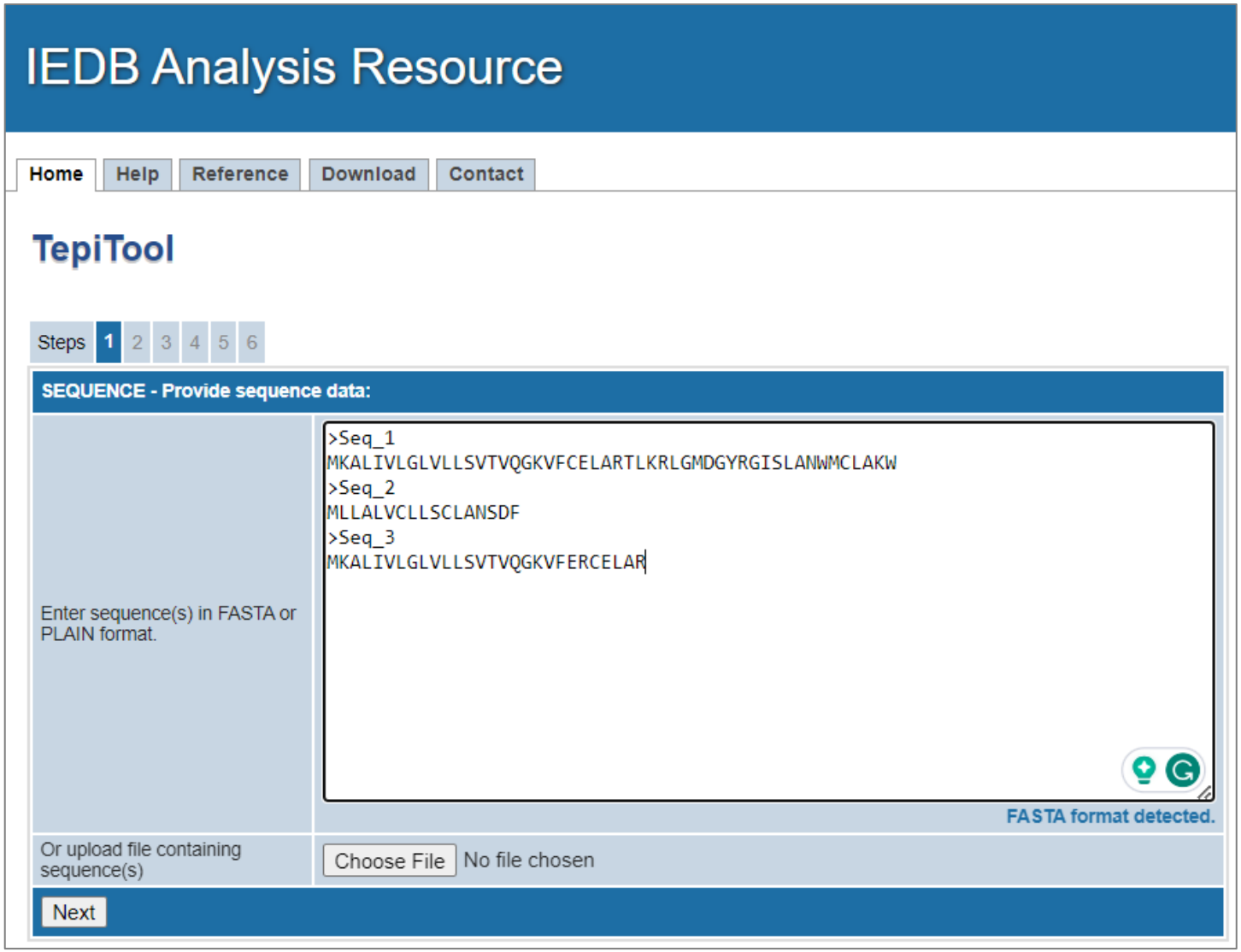


tools.iedb.org/main/tcell/

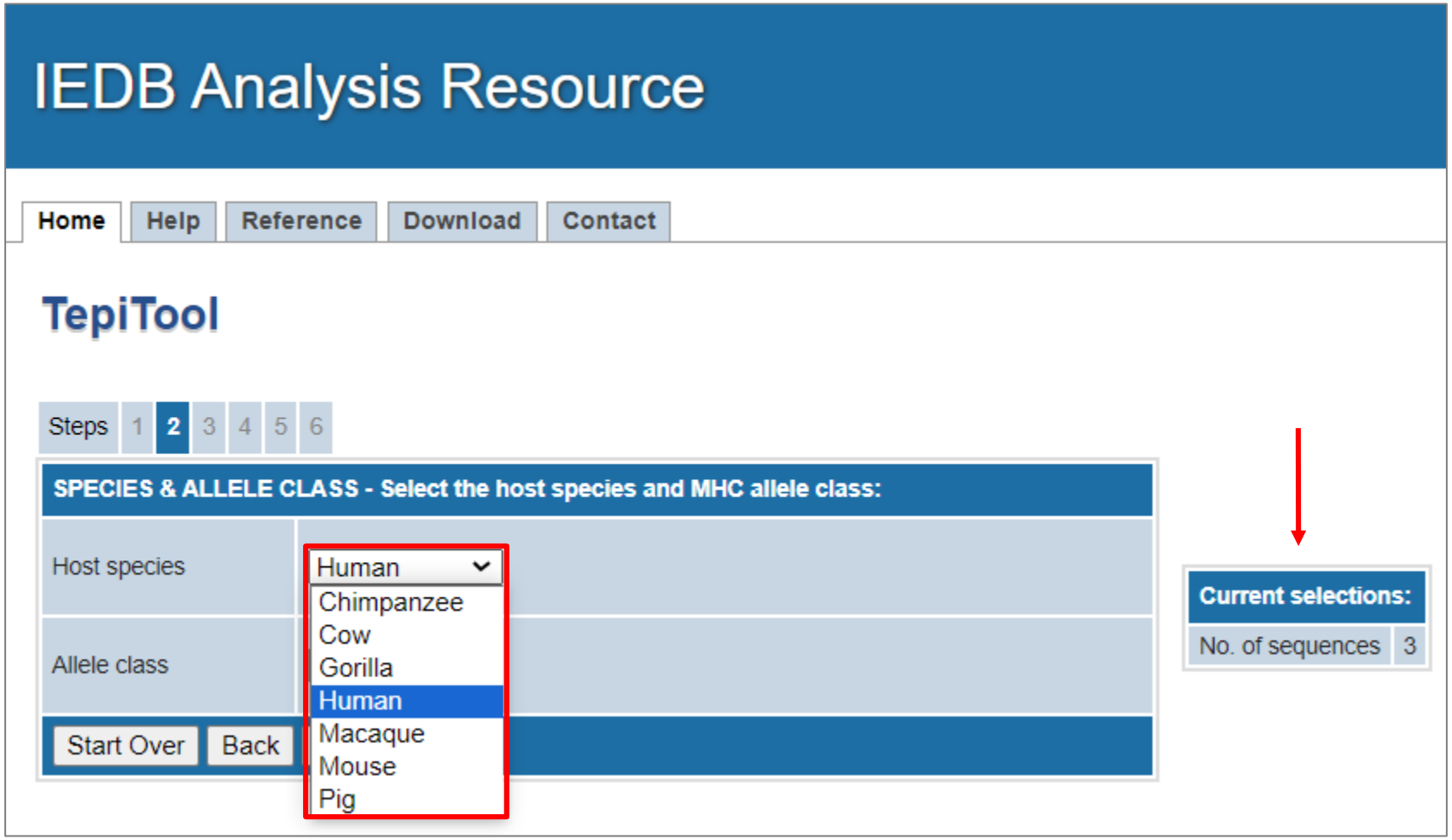
Step 1: Sequence Data

tools.iedb.org/tepitool/



Step 2: Species & Allele Class

tools.iedb.org/tepitool/



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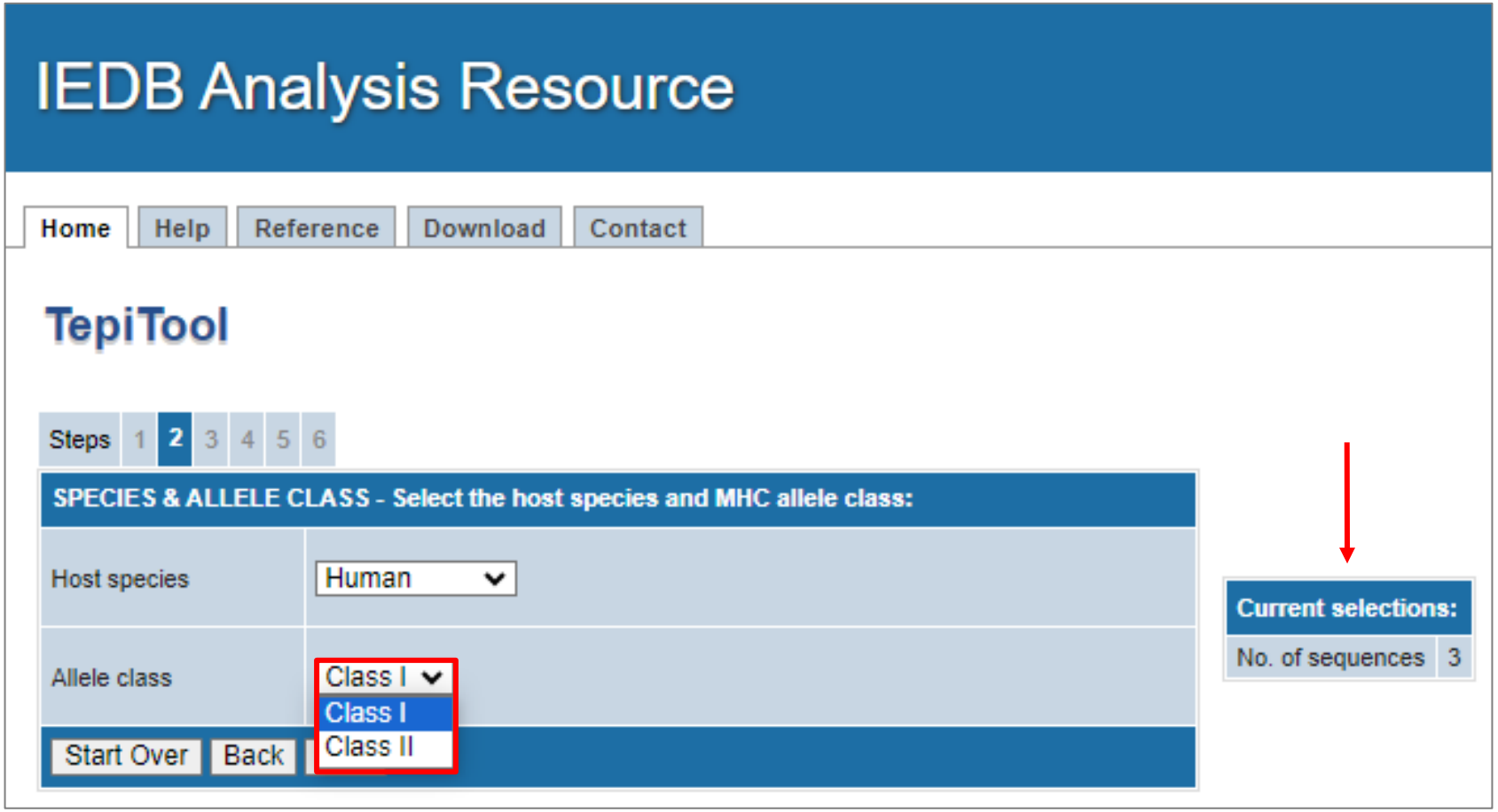
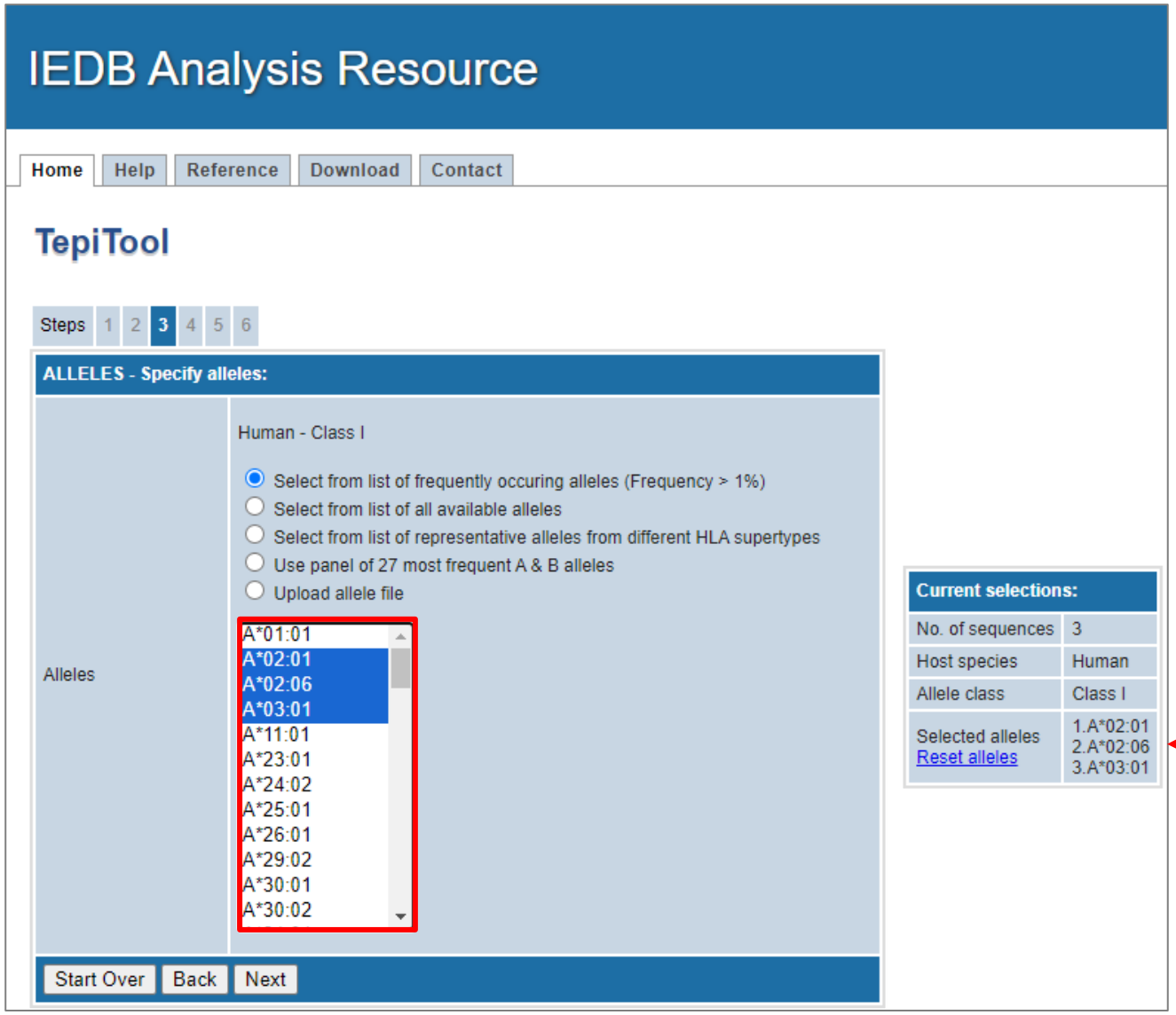
tools.iedb.org/tepitool/



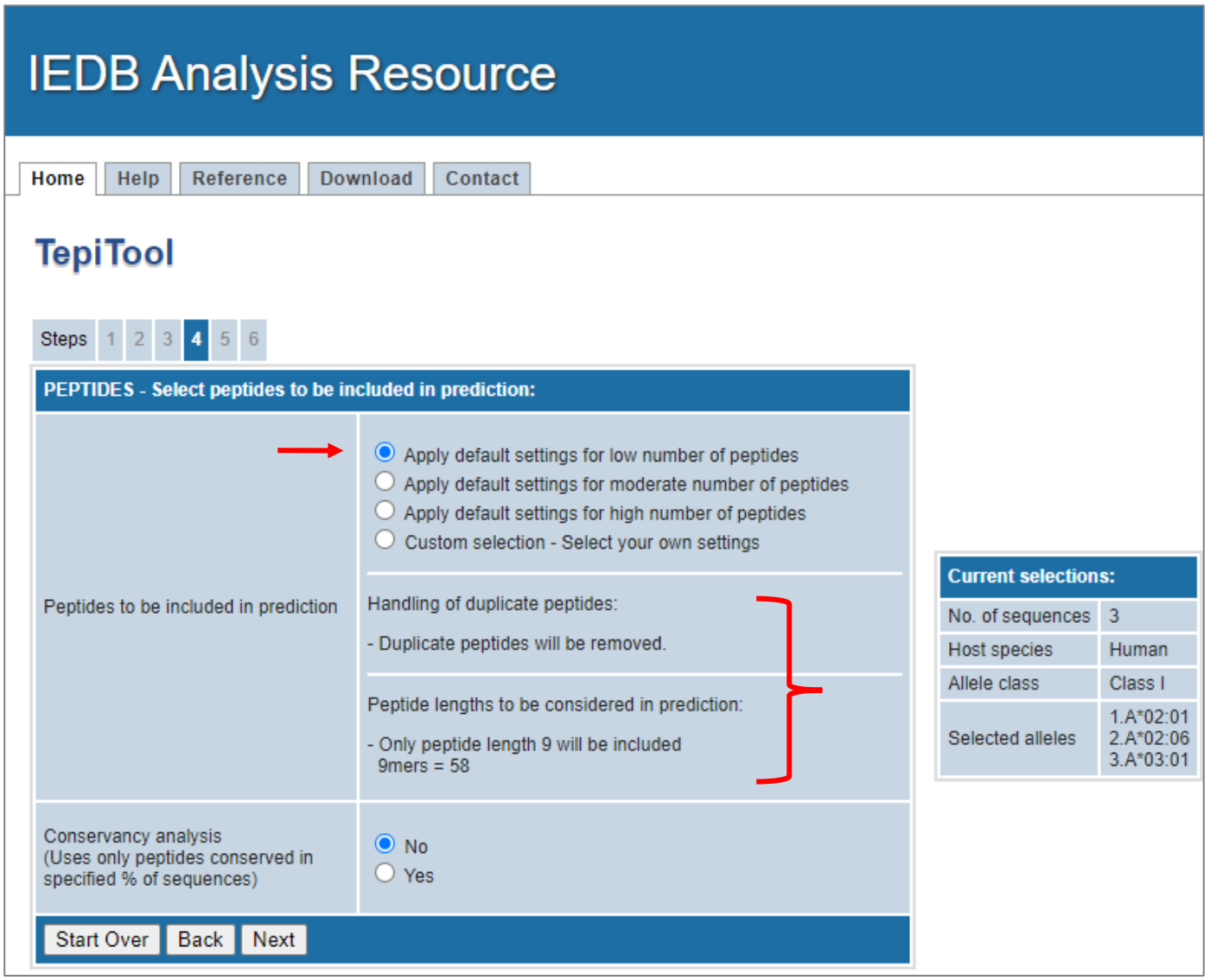
Step 3: Allele Selection

tools.iedb.org/tepitool/



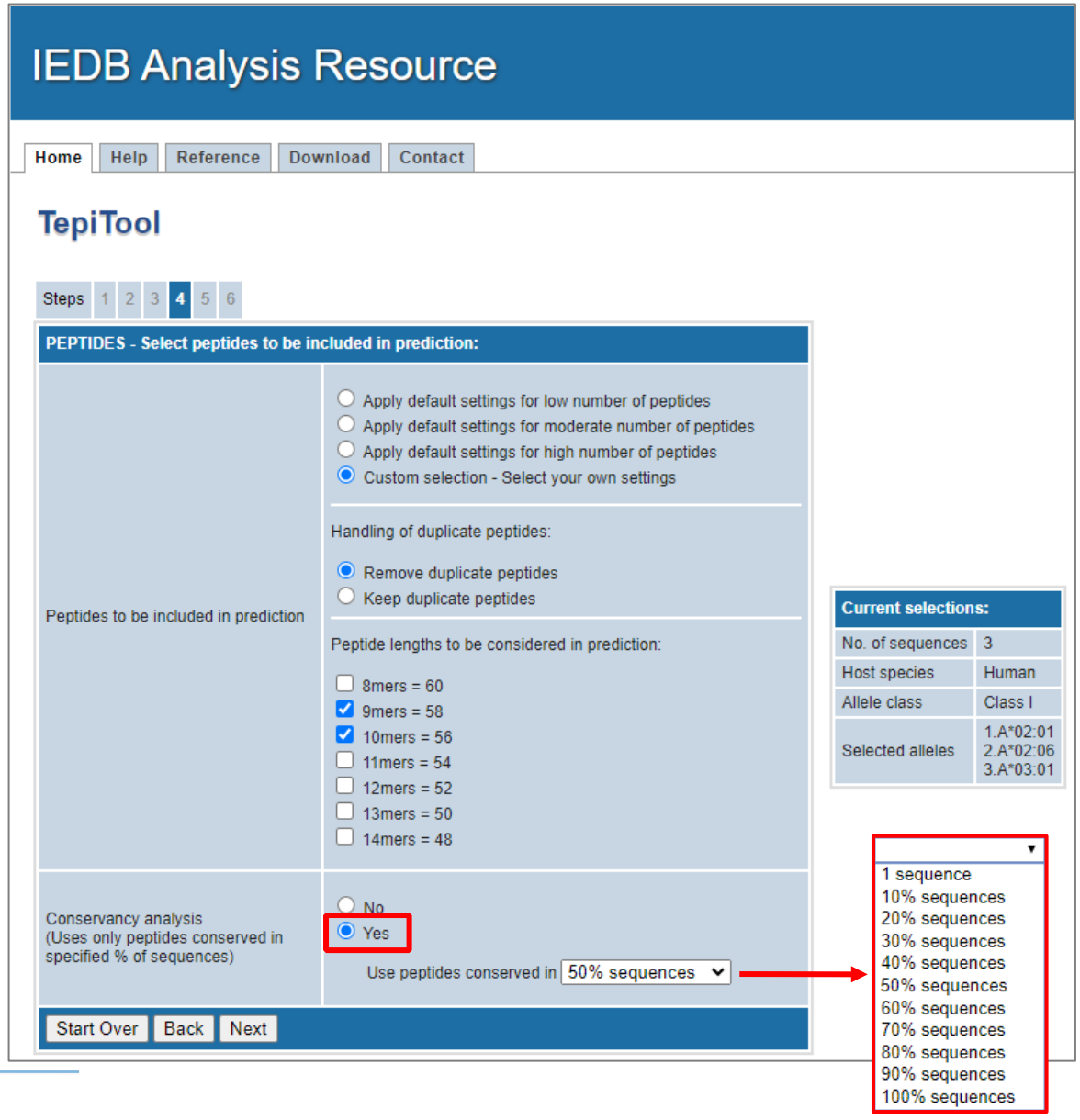
Step 4: Peptides - Class I

tools.iedb.org/tepitool/



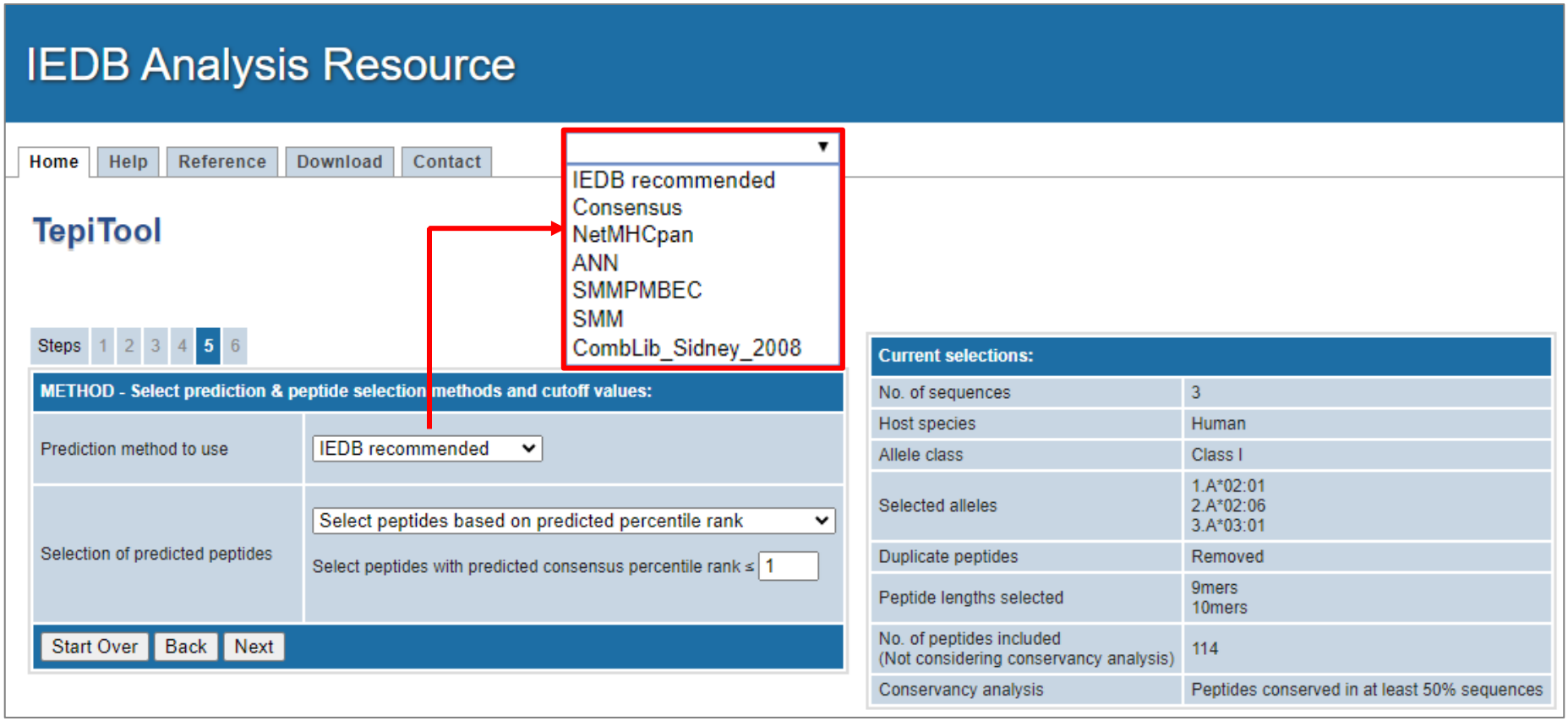
Step 4: Peptides - Class I

tools.iedb.org/tepitool/



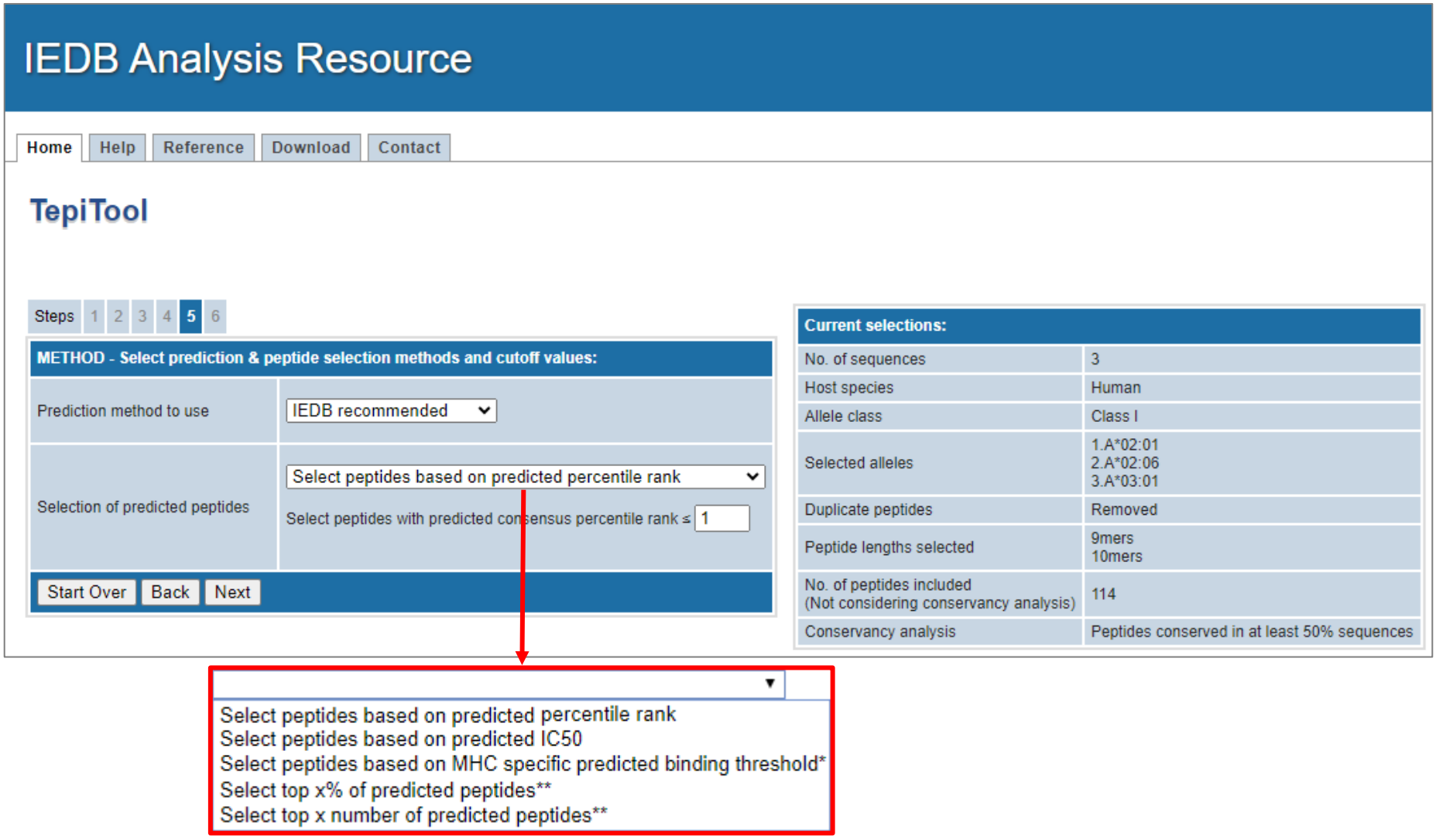
Step 5: Method - Class I

tools.iedb.org/tepitool/



Step 5: Method - Class I

tools.iedb.org/tepitool/



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- Population coverage issue: genotypic frequency is currently not working as expected
- HLA nomenclature
- Introduction and tutorials
- MHC class I binding prediction - Internal Server Error
- MHC II Epitope Prediction - "Internal Server Error"
- When can I consider an epitope as non-binder using MHC class I and II binding predictions tools?
- HLA allele frequencies and reference sets with maximal population coverage
- Selecting thresholds (cut-offs) for MHC class I and II binding predictions
- T Cell Epitopes - MHC Class II Binding Prediction Tools Description
- T Cell Epitopes - MHC Class I Binding Prediction Tools Description

Selecting thresholds (cut-offs) for MHC class I and II binding predictions

Permanently deleted user
10 months ago · Updated

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The predicted binding affinities and ranks that result from the IEDB prediction tools should be treated as ranking metrics as a way to prioritize peptides for experimental testing. There are many ways to rank the peptides. Here, we list only the latest recommendations.

MHC class I

For MHC class I T cell epitope predictions, the latest research from our group[1] shows that setting a common threshold for eluted ligand (EL) rank of ~1.1 in NetMHCPan 4.0 across all alleles results in 80% sensitivity for capturing immunogenic peptides. Allele-specific thresholds have also been established and are contained within the supplemental data of the paper. However, the increase in sensitivity and specificity is marginal unless there are relatively few alleles being considered with very divergent thresholds.

MHC class II

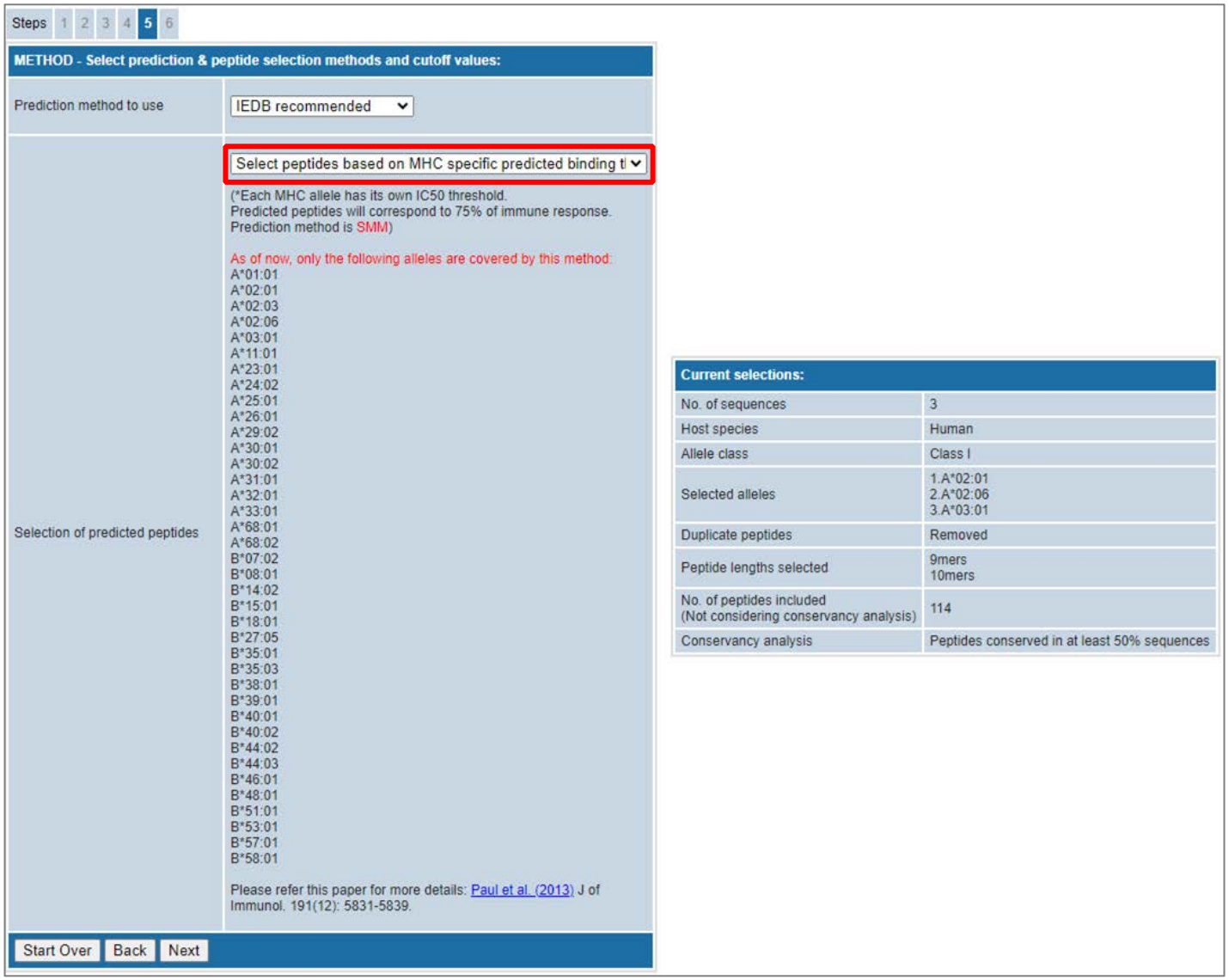
For MHC class II T cell epitope predictions, selection of predicted binders can be done based on the percentile rank or MHC binding affinity. The IEDB currently recommends making selections based on a consensus percentile rank of the top 20%[2], which captures 50% of the immune response. Alternatively, selecting peptides predicted to bind at 1,000nM is also supported by experimental data[3].

1. Reardon et al., 2021 Mol. Cell. Proteomics (PMID 34303001)
2. Paul eg al., 2015 J. Imm. Methods (PMID 25862607)
3. Southwood et al., 1998, J. Immunology (PMID 9531296)

https://help.iedb.org/hc/en-us/articles/114094151811-Selecting-thresholds-cut-offs-for-MHC-class-I-and-II-binding-predictions

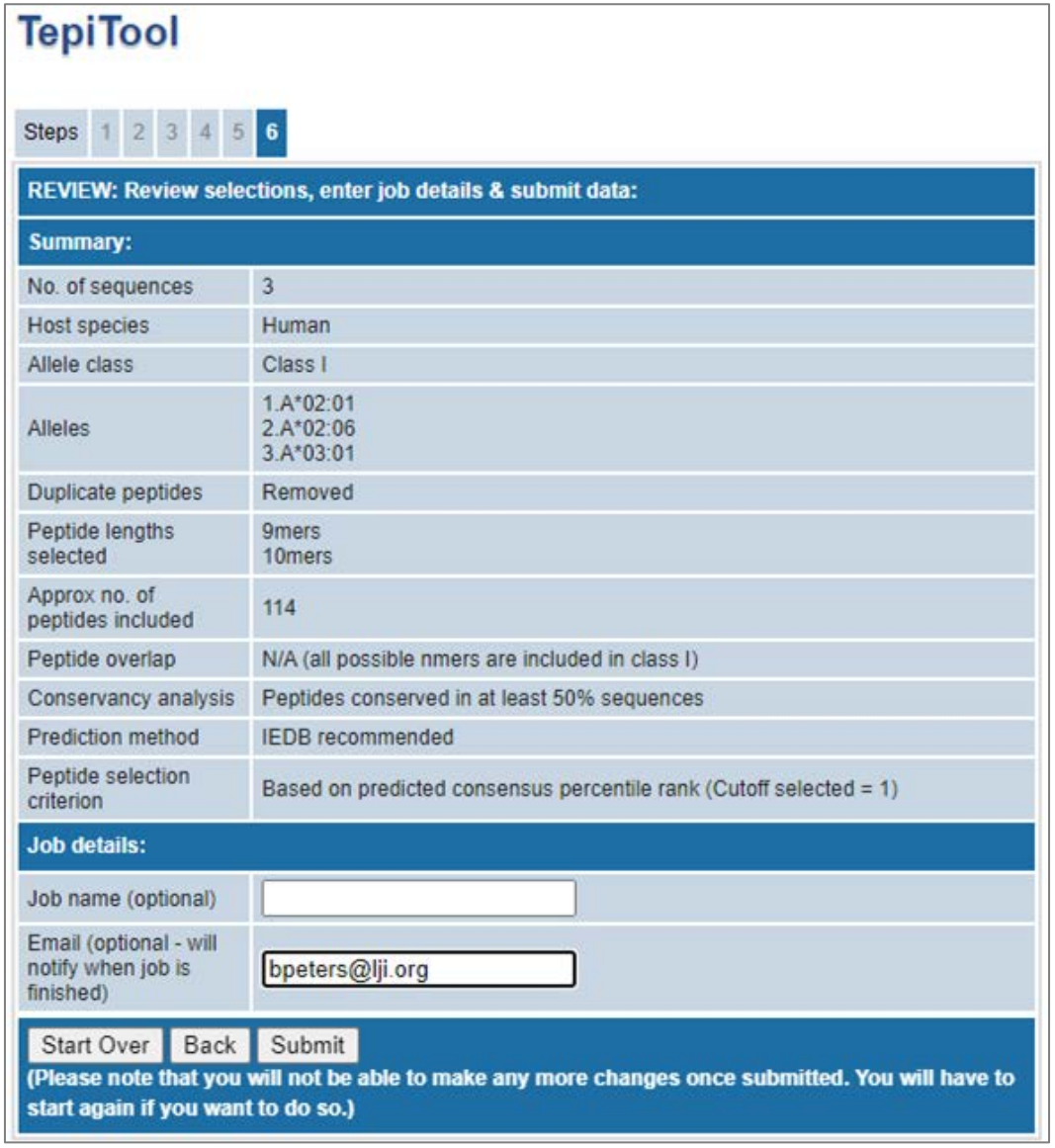
Step 5: Method - Class I

tools.iedb.org/tepitool/



Step 5: Review & Submit

tools.iedb.org/tepitool/



TepiTool

Steps 1 2 3 4 5 6

REVIEW: Review selections, enter job details & submit data:

Summary:	
No. of sequences	3
Host species	Human
Allele class	Class I
Alleles	1.A*02:01 2.A*02:06 3.A*03:01
Duplicate peptides	Removed
Peptide lengths selected	9mers 10mers
Approx no. of peptides included	114
Peptide overlap	N/A (all possible nmers are included in class I)
Conservancy analysis	Peptides conserved in at least 50% sequences
Prediction method	IEDB recommended
Peptide selection criterion	Based on predicted consensus percentile rank (Cutoff selected = 1)
Job details:	
Job name (optional)	
Email (optional - will notify when job is finished)	bpeters@lji.org

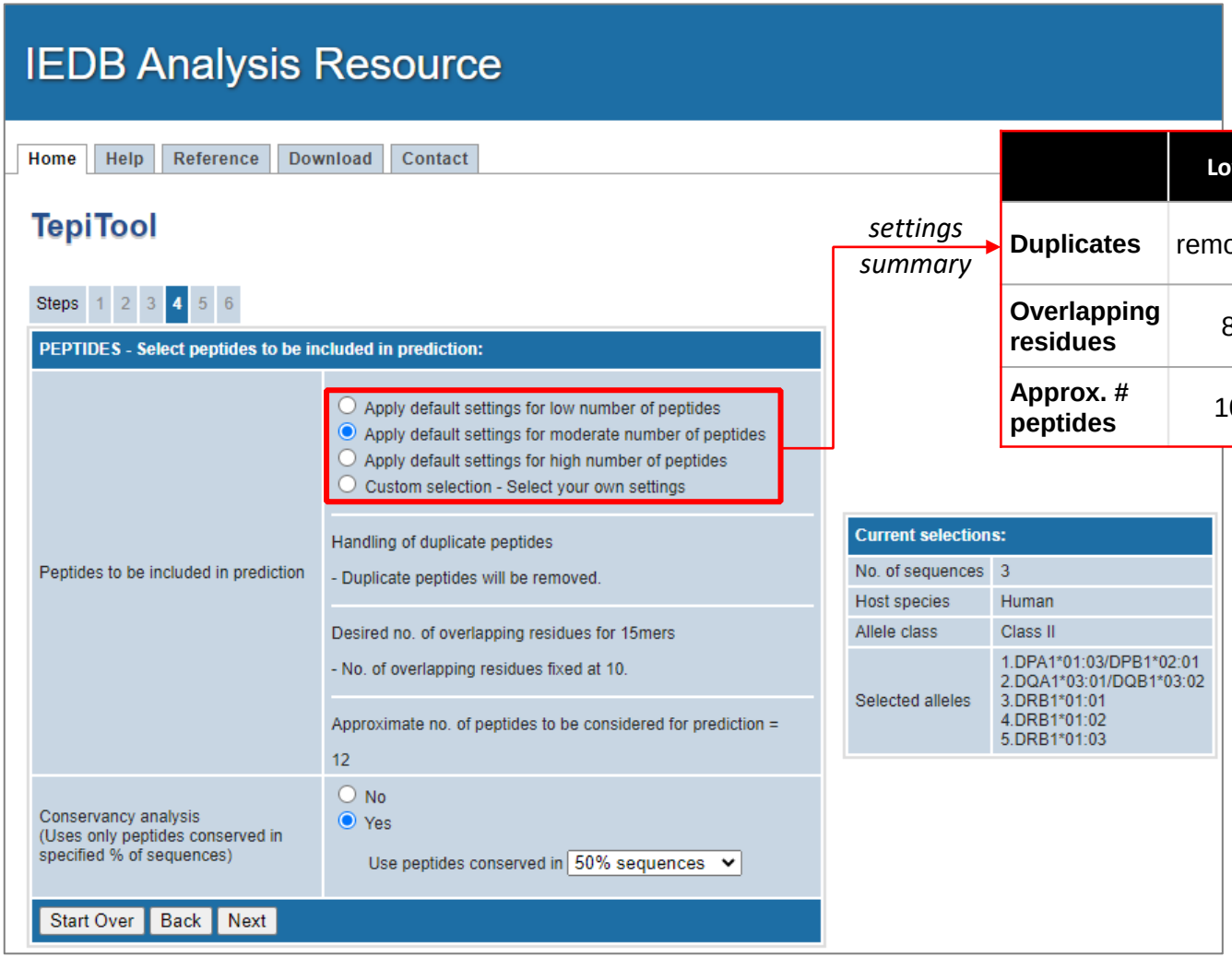
Start Over | Back | Submit

(Please note that you will not be able to make any more changes once submitted. You will have to start again if you want to do so.)

Step 4: Peptides - Class II

tools.iedb.org/tepitool/

Repeat the prediction for class II alleles

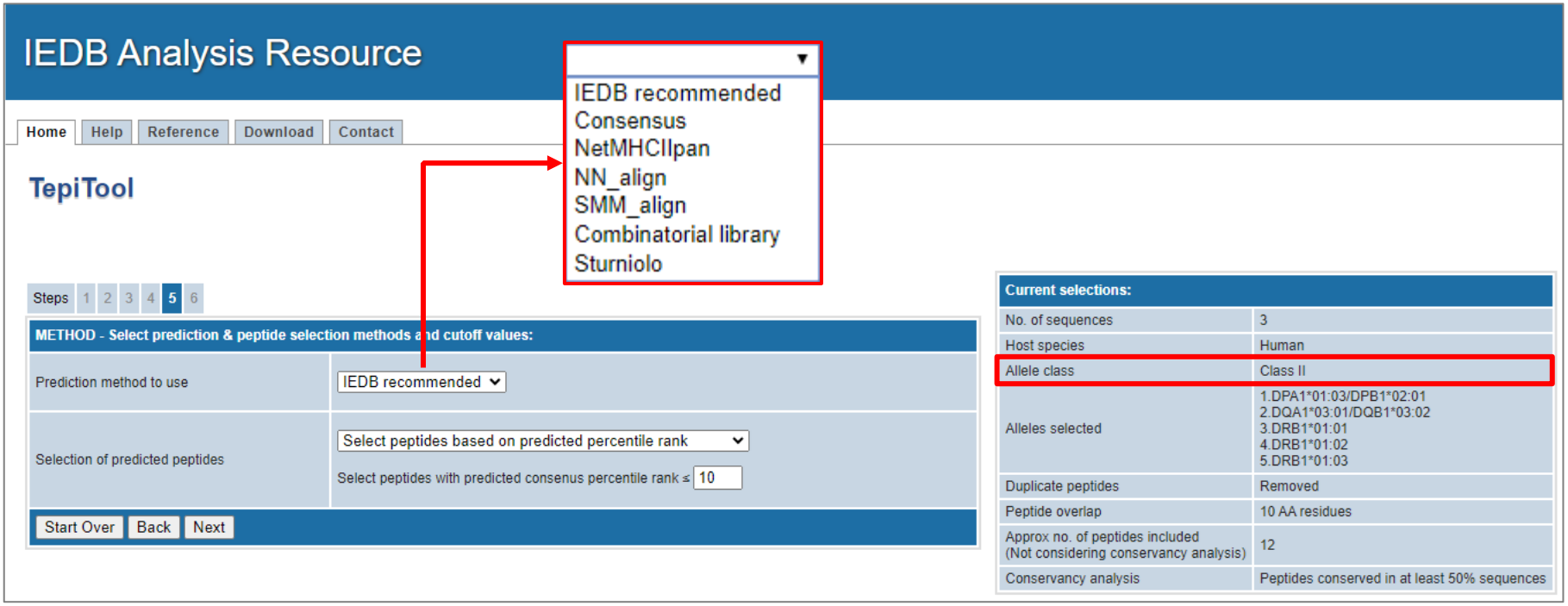


settings summary

	Low	Moderate	High	Custom
Duplicates	removed	removed	not removed	user selects
Overlapping residues	8	10	10	user selects
Approx. # peptides	10	12	14	12

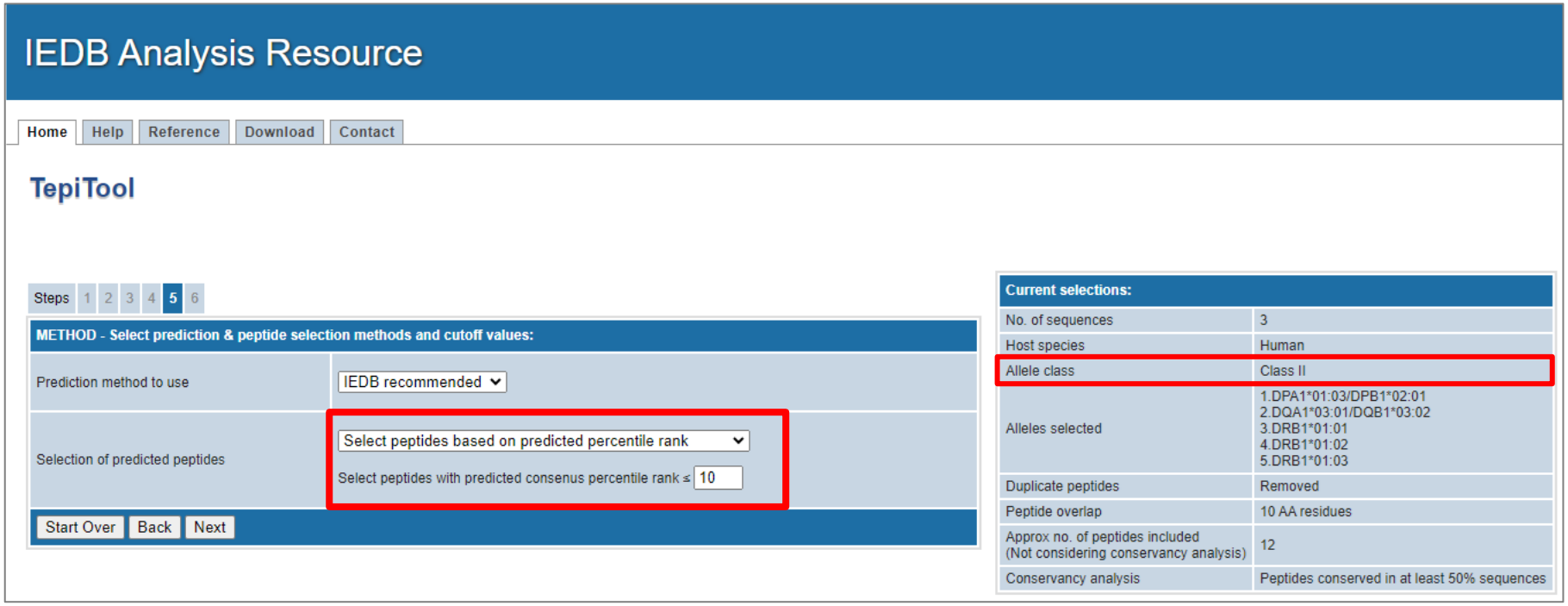
Step 5: Method - Class II

tools.iedb.org/tepitool/



Step 5: Method - Class II

tools.iedb.org/tepitool/



Step 6: Review & Submit

tools.iedb.org/tepitool/

TepiTool

Steps 1 2 3 4 5 **6**

REVIEW: Review selections, enter job details & submit data:

Summary:	
No. of sequences	3
Host species	Human
Allele class	Class II
Alleles	1.DPA1*01:03/DPB1*02:01 2.DQA1*03:01/DQB1*03:02 3.DRB1*01:01 4.DRB1*01:02 5.DRB1*01:03
Duplicate peptides	Removed
Peptide lengths selected	15mers (Only one length for class II)
Approx no. of peptides included	12
Peptide overlap	10 AA residues
Conservancy analysis	Peptides conserved in at least 50% sequences
Prediction method	IEDB recommended
Peptide selection criterion	Based on predicted consensus percentile rank (Cutoff selected = 10)
Job details:	
Job name (optional)	
Email (optional - will notify when job is finished)	bpeters@lji.org

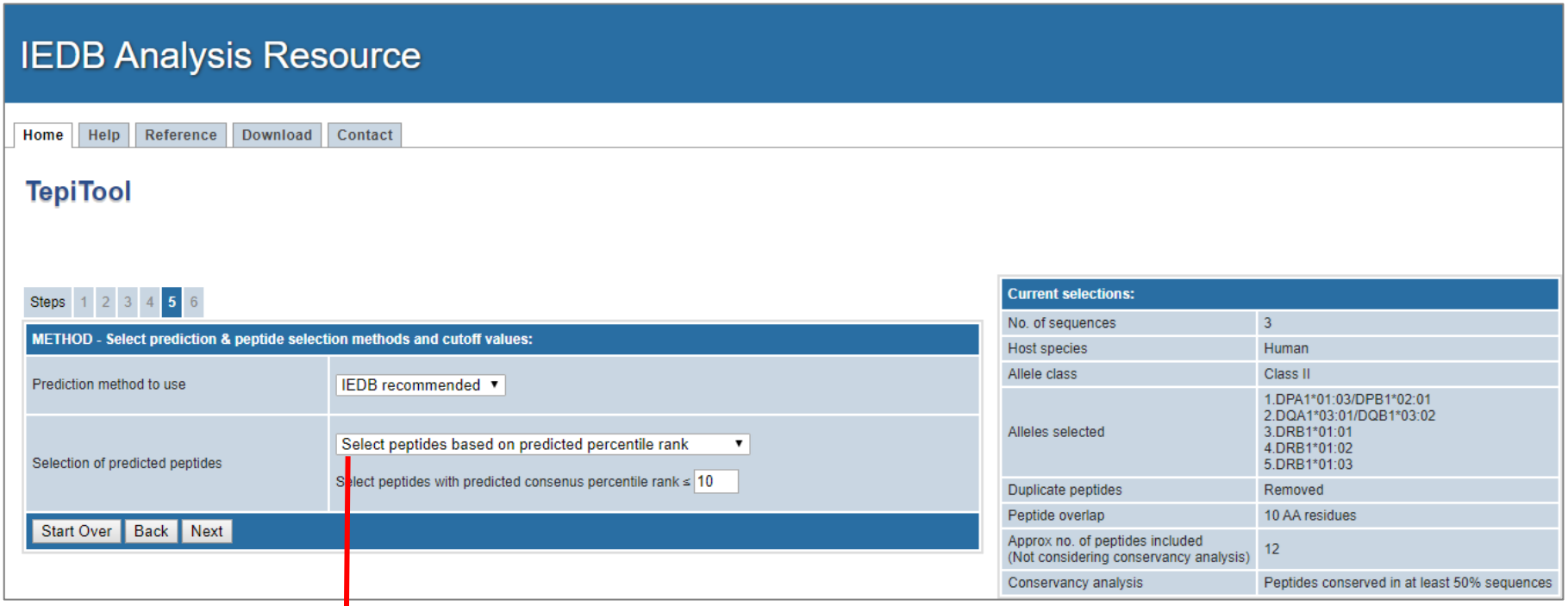
Start Over | Back | Submit

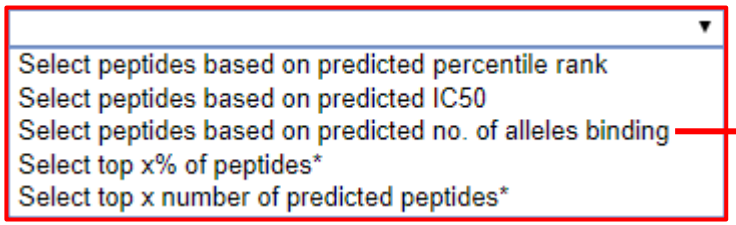
(Please note that you will not be able to make any more changes once submitted. You will have to start again if you want to do so.)

Step 5: Method - Class II

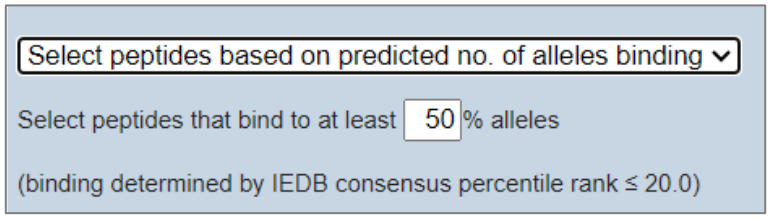
tools.iedb.org/tepitool/

Alternative Methods



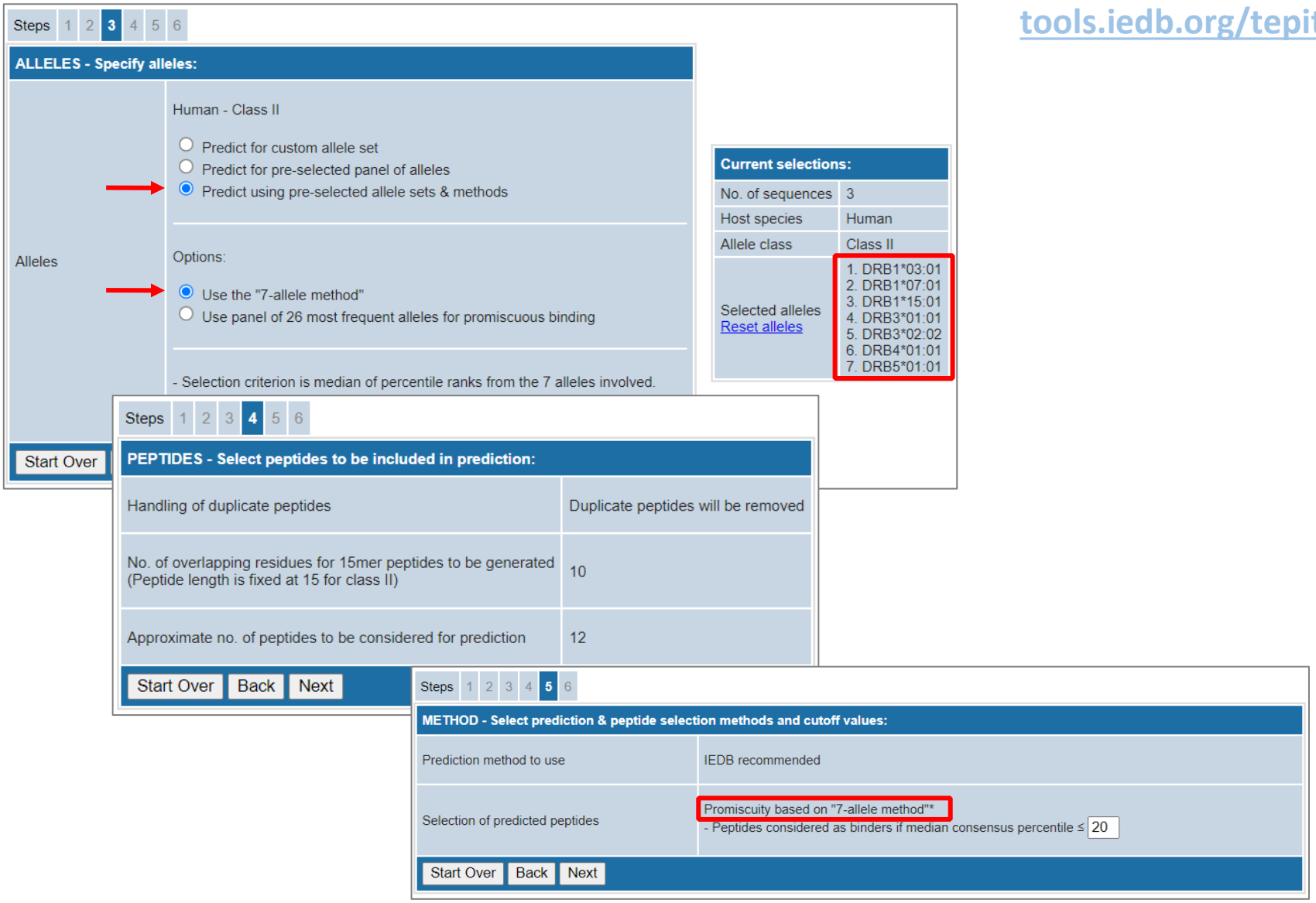


exclusive to class II



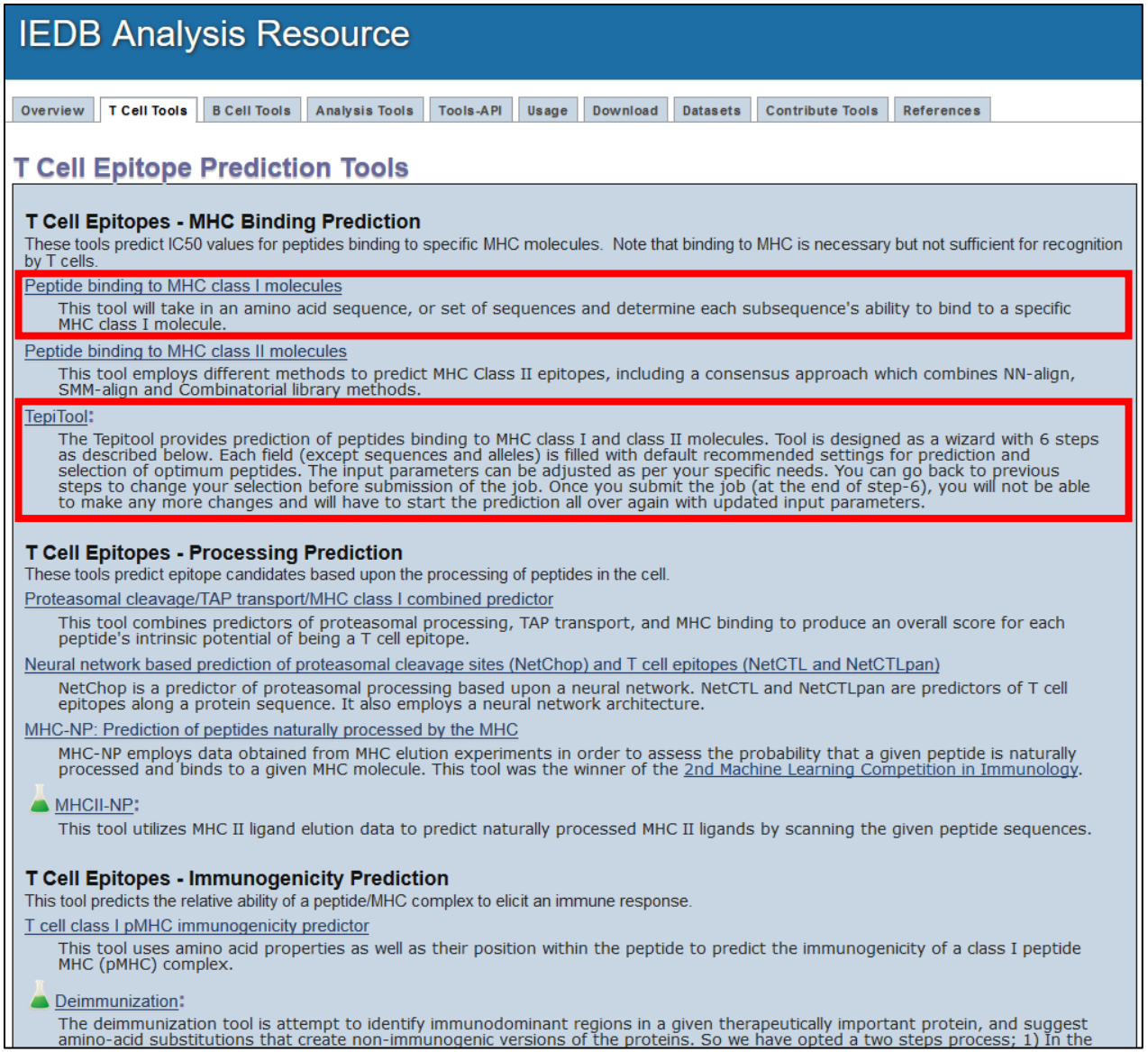
Step 3-5: Class II – 7 Allele Method

tools.iedb.org/tepitool/



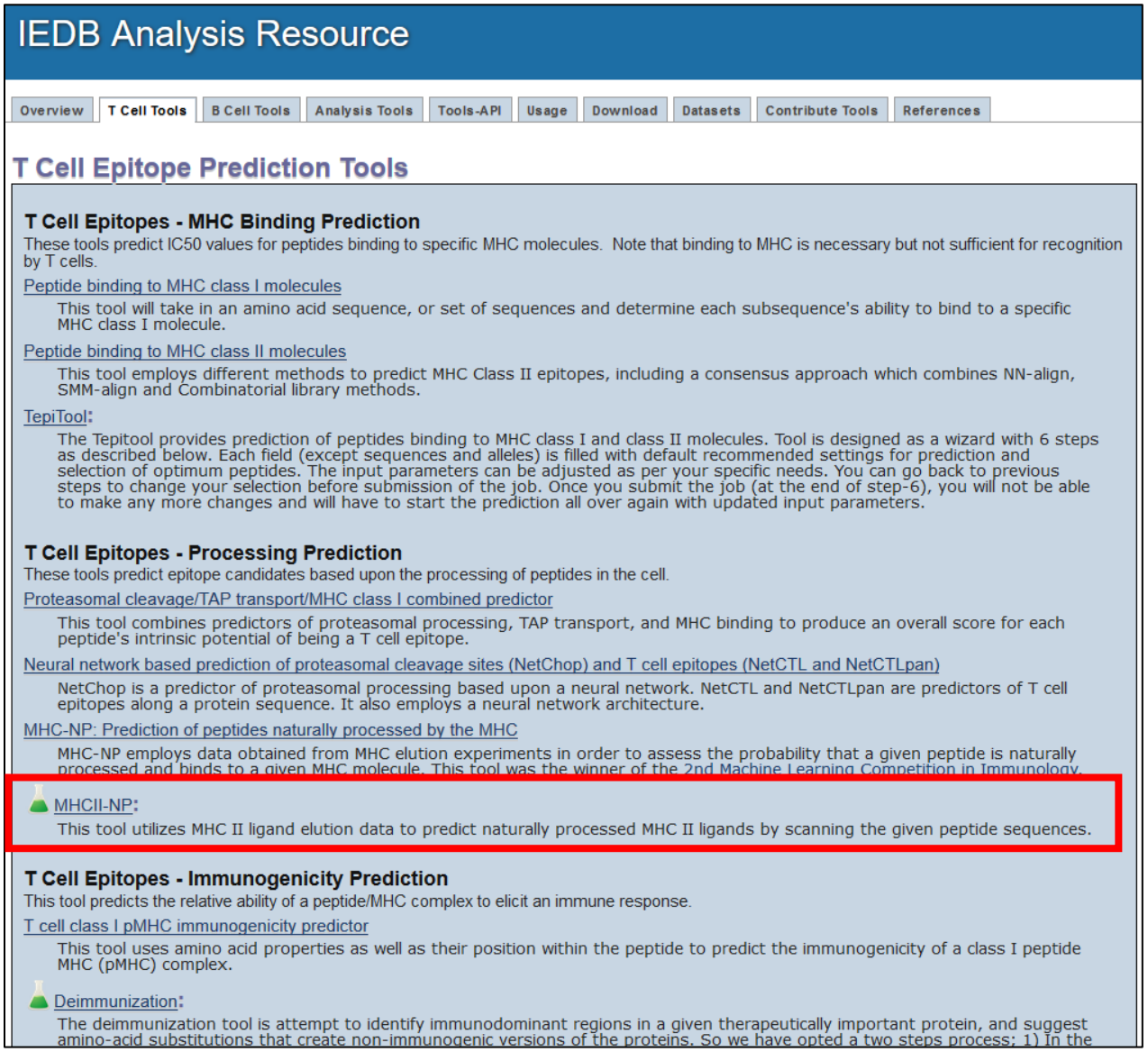
T Cell Summary

MHC Class II Binding Prediction



T Cell – MHC Class II Processing Prediction

tools.iedb.org/main/tcell/



MHC-II peptide processing

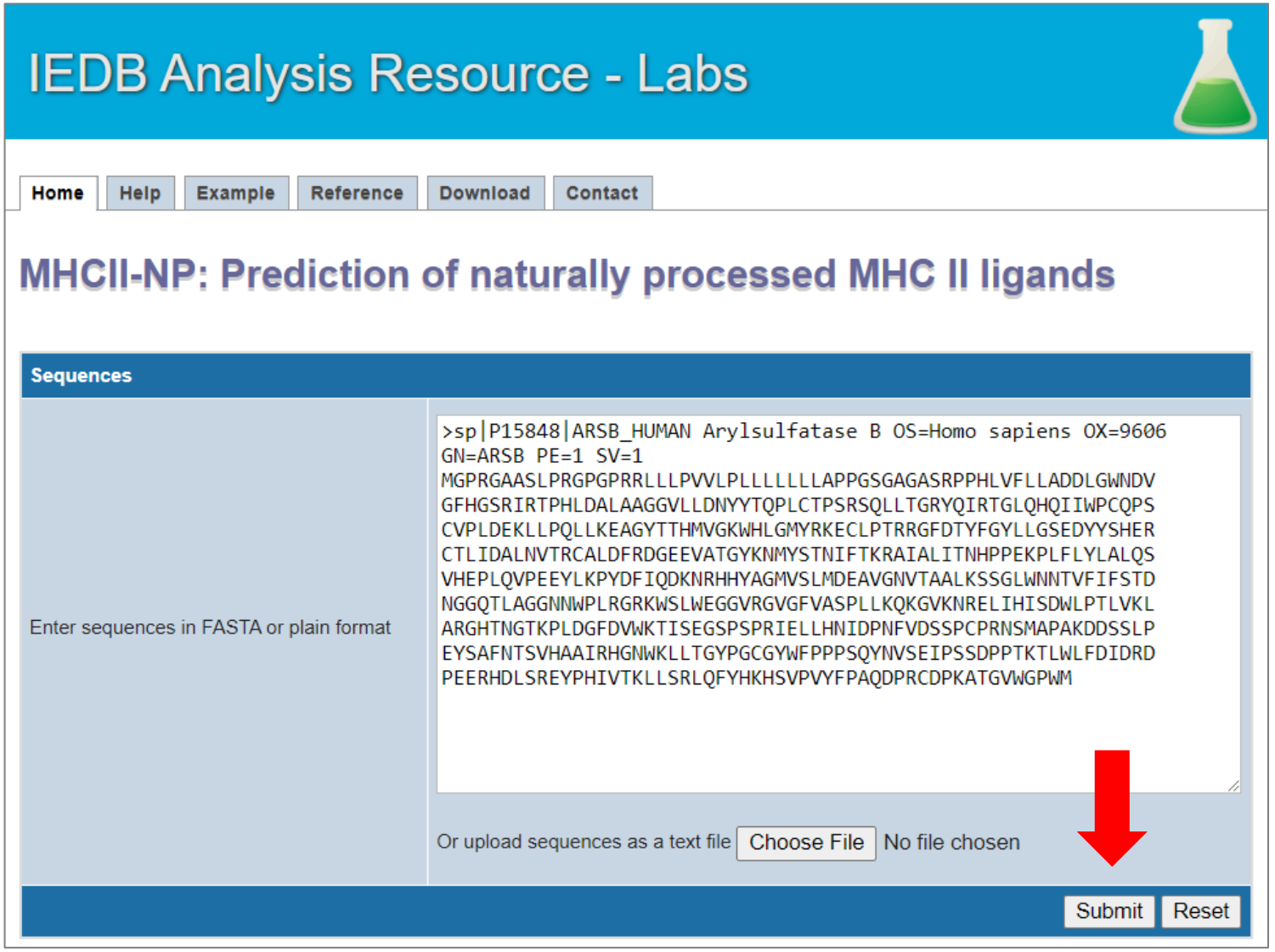
MHC-II naturally processed peptides are generated by proteases, but the ends typically flank the binding core, and don’t contribute to binding

MHCII-NP

- Predicting the naturally processed peptides for MHC class II
- Based on
  - Cleavage motif analysis at C and N terminal of peptides
  - Ligand elution data derived from IEDB
- Ligand predictions is improved markedly when combining the binding and cleavage motifs
- T cell epitope prediction is not significantly improved

MHCII-NP – Example

http://tools.iedb.org/mhciinp/



MHCII-NP – Example

http://tools.iedb.org/mhciinp/

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MHCII-NP results

Top 5 peptides per input sequence:

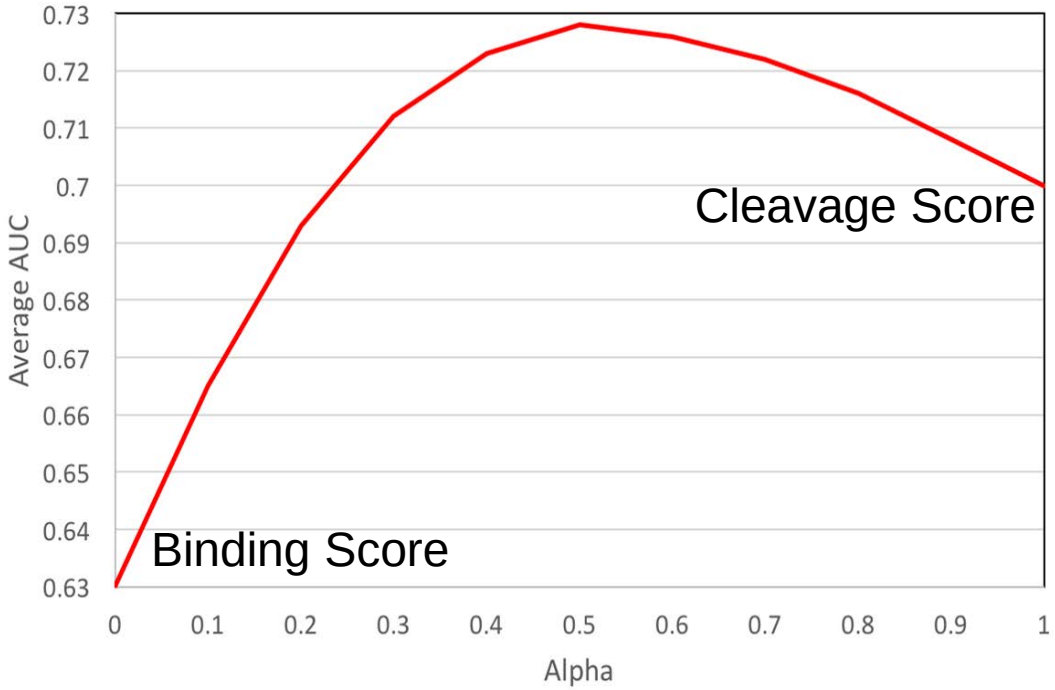
	Seq name	Peptide start	Peptide end	Peptide length	Peptide	N motif	C motif	Cleavage probability score	Cleavage probability percentile rank
1	SP|P15848|ARSB_HUMAN ARYLSULFATASE B OS=HOMO S...	510	524	15	VPVYFPAQDPRCDPK	SVP	PKA	1.75814	0.00
2	SP|P15848|ARSB_HUMAN ARYLSULFATASE B OS=HOMO S...	2	16	15	GPRGAASLPRGPGPR	MGP	PRR	1.73735	0.02
3	SP|P15848|ARSB_HUMAN ARYLSULFATASE B OS=HOMO S...	247	261	15	VPEEYLKPYDFIQDK	QVP	DKN	1.48840	0.04
4	SP|P15848|ARSB_HUMAN ARYLSULFATASE B OS=HOMO S...	384	398	15	SPSPRIELLHNIDPN	GSP	PNF	1.40420	0.05
5	SP|P15848|ARSB_HUMAN ARYLSULFATASE B OS=HOMO S...	12	26	15	GPGPRRLLLPVVLPL	RGP	PLL	1.33714	0.07

complete results (TSV)

MHCII-NP Scores

- Cleavage Score: Derived from the cleavage motif analysis in ligand elution data
- Binding Score: Derived from HLA binding affinity using 7-allele method (Paul et. al. 2015).

$$Combined\ score = \alpha \times cleavage\ \ probability\ score + (1 - \alpha) \times binding\ \ score$$



Barra et al. Genome Medicine (2018) 10:84
https://doi.org/10.1186/s13073-018-0594-6

Genome Medicine

RESEARCH Open Access

Footprints of antigen processing boost MHC class II natural ligand predictions

Carolina Barra[1†], Bruno Alvarez[1†], Sinu Paul[2], Alessandro Sette[2], Bjoern Peters[2], Massimo Andreatta[1], Søren Buus[3] and Morten Nielsen[1,4*]

Front Immunol. 2018 Aug 6;9:1795. doi: 10.3389/fimmu.2018.01795. eCollection 2018.

Determination of a Predictive Cleavage Motif for Eluted Major Histocompatibility Complex Class II Ligands.

Paul S[1], Karosiene E[1], Dhanda SK[1], Jurtz V[2], Edwards L[1], Nielsen M[2,3], Sette A[1,4], Peters B[1,4].

PMID: 30127785 PMCID: PMC6087742 DOI: 10.3389/fimmu.2018.01795

T Cell – MHC Class II Immunogenicity Prediction

T Cell Epitopes - MHC Binding Prediction

These tools predict IC50 values for peptides binding to specific MHC molecules. Note that binding to MHC is necessary but not sufficient for recognition by T cells.

Peptide binding to MHC class I molecules

This tool will take in an amino acid sequence, or set of sequences and determine each subsequence's ability to bind to a specific MHC class I molecule.

Peptide binding to MHC class II molecules

This tool employs different methods to predict MHC Class II epitopes, including a consensus approach which combines NN-align, SMM-align and Combinatorial library methods.

TepiTool:

The Tepitool provides prediction of peptides binding to MHC class I and class II molecules. Tool is designed as a wizard with 6 steps as described below. Each field (except sequences and alleles) is filled with default recommended settings for prediction and selection of optimum peptides. The input parameters can be adjusted as per your specific needs. You can go back to previous steps to change your selection before submission of the job. Once you submit the job (at the end of step-6), you will not be able to make any more changes and will have to start the prediction all over again with updated input parameters.

T Cell Epitopes - Processing Prediction

These tools predict epitope candidates based upon the processing of peptides in the cell.

Proteasomal cleavage/TAP transport/MHC class I combined predictor

This tool combines predictors of proteasomal processing, TAP transport, and MHC binding to produce an overall score for each peptide's intrinsic potential of being a T cell epitope.

Neural network based prediction of proteasomal cleavage sites (NetChop) and T cell epitopes (NetCTL and NetCTLpan)

NetChop is a predictor of proteasomal processing based upon a neural network. NetCTL and NetCTLpan are predictors of T cell epitopes along a protein sequence. It also employs a neural network architecture.

MHC-NP: Prediction of peptides naturally processed by the MHC

MHC-NP employs data obtained from MHC elution experiments in order to assess the probability that a given peptide is naturally processed and binds to a given MHC molecule. This tool was the winner of the 2nd Machine Learning Competition in Immunology.

MHCII-NP:

This tool utilizes MHC II ligand elution data to predict naturally processed MHC II ligands by scanning the given peptide sequences.

T Cell Epitopes - Immunogenicity Prediction

These tool make predictions about the relative ability of a peptide/MHC complex to elicit an immune response.

T cell class I pMHC immunogenicity predictor

This tool uses amino acid properties as well as their position within the peptide to predict the immunogenicity of a class I peptide MHC (pMHC) complex.

Deimmunization:

The deimmunization tool is attempt to identify immunodominant regions in a given therapeutically important protein, and suggest amino-acid substitutions that create non-immunogenic versions of the proteins. So we have opted a two steps process; 1) In the first step, the deimmunization tool will list all the immunogenic regions or peptides based on selected threshold. These peptides will be generated from the protein with 15mer window size and 10mer overlap. 2) In the second step, the user can select one or more peptides listed in the results and final result window will display the non-immunogenic substitution of each selected peptides. The default threshold is 8.5 (which is difference in the median of percentile rank from 26 reference alleles set for MHC class II). In the final result window, the tools will also take care of the fact that non-immunogenic substitution in the immunogenic peptides, should not create new immunogenic site in the neighboring peptides. Therefore, the result window will also display the effect of substitution on the neighboring peptides.

CD4 T cell immunogenicity prediction:

The server is developed to predict the allele independent CD4 T cell immunogenicity at population level. User can predict the T cell immunogenicity using 7-allele method (Paul et. al. 2015), immunogenicity method and combined method (IEDB recommended). The combined method predicts the final score that combines the predictions from 7-allele method and immunogenicity method.

tools.iedb.org/main/tcell/

MHC-II Restricted Immunogenicity Prediction

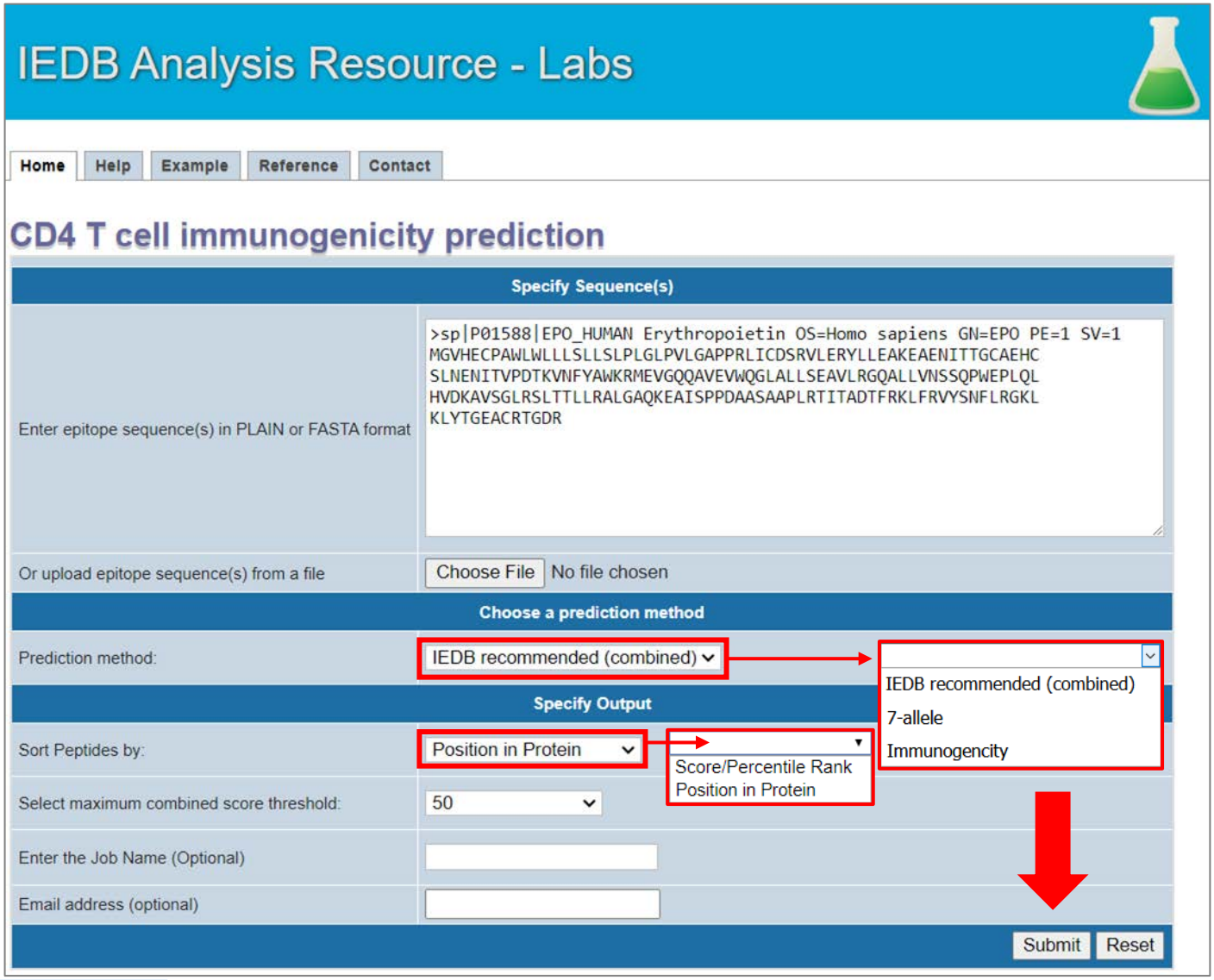
- Extracted datasets of proteins from the IEDB for which overlapping peptides were tested for immunogenicity
- Utilized these datasets to train a Neural Network to learn ‘motifs’ associated with immunogenicity independent of specific MHC alleles expressed
- Resulting score can be combined with ‘7 allele method’ quantifying MHC binding across alleles to predict overall immunogenicity

Class II Immunogenicity Prediction

- Based on Neural network model trained on
  - In house dataset for different antigens tested on different population cohorts
  - Tetramer dataset- derived from IEDB
- Validated on 57 independent studies from different groups across the world
- Implemented three approaches
  - 7-allele method (*Paul et. al. 2015*)
  - Immunogenicity predictions
  - Hybrid approach

Class II Immunogenicity Prediction – Example

http://tools.iedb.org/CD4episcore/



Class II Immunogenicity Prediction – Example

http://tools.iedb.org/CD4episcore/

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CD4 Immunogenicity prediction results

Number of proteins: 1

Number of 15mer (overlapping 10mer): 37

Threshold : 50.0%

Method : combined

Download result

Citations

Protein Number	Protein Description	Peptide	Start	End	Combined Score	Immunogenicity Score	Peptide core	Median Percentile Rank (7-allele)	HLA-DRB1:03:01	HLA-DRB1:07:01	HLA-DRB1:15:01	HLA-DRB3:01:01	HLA-DRB3:02:02	HLA-DRB4:01:01	HLA-DRB5:01:01
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	WLLLSLLSLPLGLPV	11	25	42.16452	95.0613	LLSLLSLPL	6.9	25.0	3.2	3.6	73.0	33.0	6.9	6.5
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	TKVNFYAWKRMEVGQ	71	85	47.39488	67.4872	TKVNFYAWK	34.0	52.0	22.0	15.0	71.0	30.0	65.0	34.0
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	EPLQLHVDKAVSGLR	116	130	32.55636	43.8909	LHVDKAVSG	25.0	5.4	59.0	40.0	22.0	7.0	38.0	25.0
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	VSGLRSLTTLLRALG	126	140	44.95964	86.8991	LTTLLRALG	17.0	12.0	17.0	9.3	70.0	20.0	20.0	1.3
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	SLTTLLRALGAQKEA	131	145	42.78744	69.4686	LLRALGAQK	25.0	47.0	46.0	21.0	89.0	25.0	14.0	1.6
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	PLRTITADTFRKLFR	156	170	46.18064	85.4516	LRTITADTF	20.0	6.1	47.0	40.0	8.0	20.0	20.0	20.0
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	TADTFRKLFRVYSNF	161	175	46.66984	44.6746	FRKLFRVYS	48.0	63.0	58.0	23.0	48.0	33.0	53.0	24.0
1	sp|P01588|EPO_HUMAN Erythropoietin OS=Homo sapiens GN=EPO PE=1 SV=1	RKLFRVYSNFLRGKL	166	180	13.8966	22.4415	FRVYSNFLR	8.2	53.0	8.2	0.12	27.0	4.8	26.0	1.5

Download result

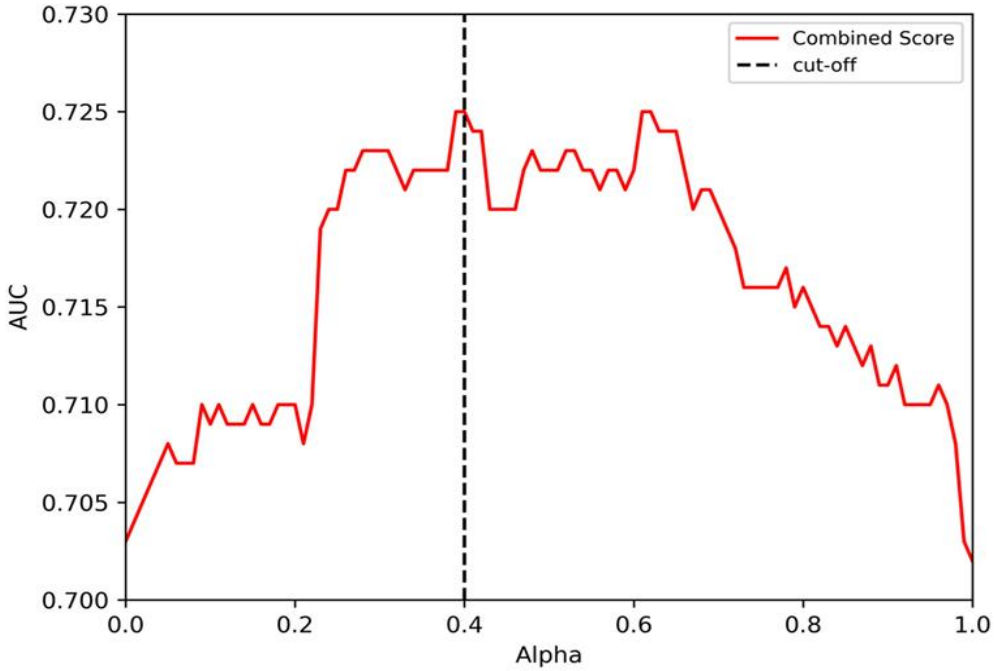
Citations

If you use CD4 T cell Immunogencity prediction tool in a manuscript, please cite following article:
Dhanda et. al.: Predicting HLA CD4 immunogenicity in human populations; *Frontiers in Immunology*, 2018, 9, 1369 Click here to read full text

Class II Immunogenicity Prediction Scores

- Immunogenicity Score: Derived from the neural network model trained on Immunogenicity data
- HLA Score: Derived from HLA binding affinity using 7-allele method (Paul et. al. 2015).

$$\text{Combined score} = \alpha \times \text{Imm score} + (1 - \alpha) \times \text{HLA score}.$$



Front Immunol. 2018 Jun 14;9:1369. doi: 10.3389/fimmu.2018.01369. eCollection 2018.

Predicting HLA CD4 Immunogenicity in Human Populations.

Dhanda SK[1], Karosiene E[1], Edwards L[1], Grifoni A[1], Paul S[1], Andreatta M[2], Weiskopf D[1], Sidney J[1], Nielsen M[2,3], Peters B[1,4], Sette A[1,4].

PMID: 29963059 PMCID: PMC6010533 DOI: 10.3389/fimmu.2018.01369

Class II Summary

- Performance of MHC II binding- and ligand elution predictions has massively improved in the last years; (thresholds have not yet been updated to reflect that)
- NetMHCIIPan 4.1 BA scores should be used for binding affinity and EL scores for ligand elution and epitope predictions
- The promiscuous nature of MHC-II binding motifs and ability to bind in different registers of a peptide allows identifying broadly reactive epitopes (→ 7 allele method)
- Tepitool implements pre-and post-processing steps for T cell epitope prediction for both class I and class II – and should be a good starting point

Both class I and II epitope predictions are constantly being re-evaluated, and all of these recommendations are subject to change