

Predicting T-cell receptor specificity based on sequence similarity to previously characterized receptors

Presented by Raphael Trevizani

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- Somatic recombination
- Each chain: 3 CDRs
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2022 IEDB User Workshop

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TCR sequencing does not directly reveal the epitope recognized by a given CDR3β

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to a T-Cell	AND ANALYSIS	RESOUR	CE			
T-cell receptor: α/β units	The IEDB has just launched its updated 3D viewers! Learn more via our help article <u>here</u> .					
	Welcome		START YOUR SEARCH HERE		Epitope Analysis Resource	
Somatic recombination	The Immune Epitope Database (IEDB) is a freely available resource funded by NIAID. It catalogs experimental data on antibody and T cell epitopes studied in humans, non- human primates, and other animal species in the context of incention direction and access of any		Epitope (?)	Assay ?	T Cell Epitope Prediction (?)	
Each chain: 3 CDRs			Any Linear peptide	T Cell	Scan an antigen sequence for amino acie patterns indicative of:	
CDR3β	autoimmunity and transplantation. The IEDB also hosts tools to assist in the prediction		Exact V Ex: SIINFEKL	MHC Ligand	MHC II Binding	
 Most variable 	and analysis of epitopes.		O Non-peptidic	Outcome: Positive Negative	MHC I Processing (Proteasome,TAI MHC I Immunogenicity	
 Directly interacts with epitope 	Upcoming Events & News AAI Exhibitor Booth FOCis Exhibitor Booth Virtual User Workshop * register here May 6-10 June 21-24 Oct 26-28		Epitope Source (?) Organism Ex: influenza, peanut Find Antigen	MHC Restriction (?) (Class I) (Class II) (Cl	B Cell Epitope Prediction (2) Predict linear B cell epitopes using: Antigen Sequence Properties Predict discontinuous B cell epitopes usi antigen structure via:	
Repertoire sequencing						
Which epitope interacts with this specific TCR?	IEDB SARS-CoV-2 Epitope Analysis Videos		Ex: core, capsid, myos Find	O Ex: HLA-A*02:01 Find	Discotope ElliPro	
TCR match: searches IEDB	Summary Metrics		Host (?)	Disease (?)	Epitope Analysis Tools (?)	
for a similar CDR 36	Peptidic Epitopes	1,539,170	O Any	Any	Analyze epitope sets of:	
	Non-Peptidic Epitopes	3,146	O Human		Population Coverage	
How to find the most similar sequences?	T Cell Assays	443,509			Conservation Across Antigens	
	B Cell Assays	1,332,364	C Ex: dog camel		Clusters with Similar Sequences	
	MHC Ligand Assays	4,631,827				
	Epitope Source Organisms	4,234		Reset Search		
	Restricting Mine Aneles	23 207		Jearch		

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T-cell receptor: α/β units	The IEDB has just launched its updated 3D viewers! Learn more via our help article <u>here</u> .							
	Welcome		START YOUR SEARCH HERE		Epitope Analysis Resource			
Somatic recombination	The Immune Epitope Databa a freely available resource fund	ase (IEDB) is led by NIAID.	Epitope (?)	Assay (?)	T Cell Epitope Prediction (?)			
Each chain: 3 CDRs	It catalogs experimental data of and T cell epitopes studied in h human primates, and other anim	n antibody iumans, non- mal species	Any Linear peptide	T Cell	Scan an antigen sequence for amino acid patterns indicative of:			
CDR3β	autoimmunity and transplar also hosts tools to assist in	ase, allergy,		MHC Ligand	inding			
• Most variable	and analysis of epitopes. TCR sequence - Epitope sequence ocessing (Proteasome, TAP) munogenicity							
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Repertoire sequencing	AAI Exhibitor Booth M FOCiS Exhibitor Booth Ju <u>Virtual User Workshop</u> O * register here	lay 6-10 ine 21-24 ct 26-28	Ex: influenza, peanut Find	Class I Class II	Antigen Sequence Properties Predict discontinuous B cell epitopes using			
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	References	23,297						

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ASSIRSSYEQY

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.

Last Updated: April 24, 2022

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CDR3β

Epitope

- MHC presenting an antigen to a T-Cell
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 - \circ Most variable
 - Directly interacts with epitope
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- <u>TCRmatch: searches IEDB</u> for a similar CDR3β
- How to find the most similar sequences?

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16	L	-1	-2	-1	-3	-1	-4	-3	-4	-3	-2	-3	-2	-2	2	2	4					
17	V	-1	-2	0	-2	0	-3	-3	-3	-2	-2	-3	-3	-2	1	3	1	4				
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CS

PRIMER

pitope

Where did the BLOSUM62 alignment score matrix come from?

Sean R Eddy

Group

Publishing

Nat

2004

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Many sequence alignment programs use the BLOSUM62 score matrix to score pairs of aligned residues. Where did BLOSUM62 come from?

Back in the good old days, so many things were easier to understand. I once disassembled the engine of my 1972 MG just to see how it worked, but now I won't touch the squirrel's nest of technology that's inside my modern Honda Civic. Likewise, in the b is: early days of sequence comparison, alignment scores were straightforward stuff that anybody could tweak. The first sequence comparisons just assigned -1 per mismatch and -1 per insertion/deletion, and if you didn't like that, you could make up whatever scores you thought gave you betterlooking alignments. Those days are gone. Look inside a modern amino acid score matrix, and you'll see a squirrel's nest of 400 numbers. These highly tuned matrices, which go by industrialized acronyms like BLOSUM62 and PAM250, no longer seem to have any user serviceable parts inside. Blame probability theory.

Alignment scores are log-odds scores

What we want to know is whether two sequences are homologous (evolutionarily related) or not, so we want an alignment score that reflects that. Theory says that if you want to compare two hypotheses, a good score is a log-odds score: the loga- nator (f, f_{i}) is the likelihood of a null

ment score is the sum of individual logodds scores for each aligned residue pair. Those individual scores make up a 20×20 score matrix. The equation for calculating a score s(a,b) for aligning two residues a and

 $s(a,b) = \frac{1}{\lambda} \log \frac{p_{ab}}{f_{c}}$

The numerator (p_{ab}) is the likelihood of the hypothesis we want to test: that these two residues are correlated because they're

The definition of 'conservative substitution' in a score matrix is purely statistical. It has nothing directly to do with amino acid structure or biochemistry.

homologous. Thus, pab are the target frequencies: the probability that we expect to observe residues a and b aligned in homologous sequence alignments. The denomi-

chance $(p_{ab} > f_a f_b)$, then the odds ratio is greater than one and the score is positive. Operationally, we say that positive scores mean conservative substitutions, and negative scores indicate nonconservative substitutions. This definition of 'conservative substitution' in a score matrix is purely statistical. It has nothing directly to do with amino acid structure or biochemistry.

This explains some details in BLOSUM62 that may seem counterintuitive at first glance. For instance, tryptophan (W/W) pairs score +11, while leucine (L/L) pairs only score +4; why shouldn't all identitites get the same score? The rarer the amino acid is, the more surprising it would be to see two of them align together by chance. In the homologous alignment data that BLOSUM62 was trained on, leucine/leucine (L/L) pairs were in fact more common than tryptophan/tryptophan (W/W) pairs $(p_{tt} = 0.0371, p_{ww} = 0.0065)$, but tryptophan is a much rarer amino acid ($f_i = 0.099$, $f_w = 0.013$). Run those numbers (with BLO-SUM62's original $\lambda = 0.347$) and you get +3.8 for L/L and +10.5 for W/W, which were rounded to +4 and +11.

Another example is that BLOSUM62 awards a +1 to an apparently nonconser-

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j 1 C 9 2 S -1 4 3 T -1 1 5 4 P -8 -1 -1 7 5 A 0 1 0 -1 4 6 G 3 0 -2 -2 0 6 7 N 9 -1 0 -2 -2 0 6 9 E -4 0 -1 -1 -1 -2 -1 1 6 9 E -4 0 -1 -1 -1 -2 0 2 5 10 Q -3 0 -1 -1 -1 -2 0 2 5 11 H 3 0 -2 -2 -2 2 2 1 -1 0 0 8 12 R 9 -1 -1 -2 -1 -2 -1 1 6 13 K -3 -1 -1 -2 -1 -2 -1 2 0 2 5 14 M -1 0 -1 -2 -1 -3 -2 3 -2 0 2 0 1 0 5 13 K -3 -1 -1 -2 -1 -3 -2 3 -2 0 -2 -1 -1 5 15 I -1 -2 -1 -3 -1 -4 8 -3 -3 -3 -3 -3 -1 4 16 L 1 -2 -1 3 -1 -4 8 4 8 -2 3 -2 0 -2 1 -1 5 15 I -1 -2 -1 -3 -1 -4 8 4 8 -2 3 -2 1 3 1 4 18 F -2 -2 -2 -2 -4 -2 3 -3 -3 -3 -1 3 -3 0 0 0 0 -1 6 19 Y -2 -2 -2 -2 -4 -2 -3 -2 3 -2 -1 2 -2 -2 -1 -1 -1 -1 -1 3 7 20 W -2 -3 -2 -4 -4 -3 -2 -3 -2 -1 2 -2 -2 -3 -3 -1 3 -2 -3 -1 2 -2 -2 -2 -1 -1 -1 -1 -1 -1 3 7 20 W -2 -3 -2 -4 -4 -3 -2 -3 -2 -1 2 -2 -2 -3 -3 -1 3 -2 -3 -1 2 -2 -2 -2 -1 -1 -1 -1 -1 -1 3 7 20 W -2 -3 -2 -4 -3 -2 -3 -2 -1 2 -2 -2 -3 -3 -1 3 -2 -3 -1 2 -2 -2 -2 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1 -1	SSI	RS	S	ΥE	Q	Y							n	ot	fo	วน	n	d					→	
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18 F -2 -2 -4 -2 -3 -3 -3 -3 -1 -3 -3 0 0 0 -1 6 19 Y -2 -2 -2 -3 -2 -3 -2 -1 2 -2 -1 -1 -1 1 3 7 20 W -2 -3 -2 -3 -2 -2 -2 -1 -1 -1 1 3 7 20 W -2 -3 -2 -4 -3 -2 -2 -3 -3 1 3 7 20 W -2 -3 -2 -4 -4 -3 -2 -2 -3 -1 -3 -2 -3 1 2 11 C S T P A G N D E Q H R K M I L V F Y W i 1 2 2 4 5 </td <td>17</td> <td>L V</td> <td>-1</td> <td>-2</td> <td>0</td> <td>-2</td> <td>0</td> <td>-3</td> <td>-3</td> <td>-3</td> <td>-2</td> <td>-2</td> <td>-3</td> <td>-3</td> <td>-2</td> <td>1</td> <td>3</td> <td>1</td> <td>4</td> <td></td> <td></td> <td></td> <td></td> <td></td>	17	L V	-1	-2	0	-2	0	-3	-3	-3	-2	-2	-3	-3	-2	1	3	1	4					
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			С	S	т	Р	Δ	G	N	D	F	Q	н	R	к	м	T	T	v	F	Y	W		
			1	2	2		5	6	7	0	0	10	11	12	12	1/	15	16	17	12	10	20		

CDR3β

Epitope

Epitope

CSSIRSSYEQY -------

not found ——

CDR3β

_____ **?**

- MHC presenting an antigen to a T-Cell
- T-cell receptor: α/β units
- Somatic recombination
- Each chain: 3 CDRs
- CDR3β

 \circ Most variable

- Directly interacts with epitope
- Repertoire sequencing
- Which epitope interacts with *this specific* TCR?
- TCRmatch: searches IEDB for a similar CDR3β
- <u>How to find the most similar</u> <u>sequences?</u>

Лetric	Description
lignment Score	Alignment score divided by length of alignment
dentity Alignment	Percent identity within length of alignment
dentity Long	Percent identity within length of longer sequence
dentity Short	Percent identity within length of shorter sequence
evenshtein distance	Minimum number of edits (substitutions, insertions, and deletions) necessary to transform one sequence into another
CRdist	Similarity-weighted mismatch distance between two sequences
CRMatch (MAIT Match)	Comprehensive comparison of all possible k-mers using BLOSUM62 observed frequency matrix

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ASSSANYGYT ASSIRAAETQY











ASSSANYGYT ASSIRAAETQY

5-11 1 С 4 2 S -1 3 3 Т -1 5 2 P 4 7 1 5 Α 0 6 6 G 0 -1 7 6 0 Ν 0 -2 -2 6 8 -1 D 1 -3 5 -4 -2 Е -1 -1 -1 0 2 9 0 -4 -2 -3 0 0 2 5 10 Q 0 -1 -1 -1 -2 -2 -3 -2 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -2 -1 -1 14 Μ 0 -1 -2 -1 -2 0 -2 -1 15 -1 -1 -4 -1 -2 -4 -2 -2 -2 -1 -1 -4 2 2 16 L -1 -2 -2 0 0 -2 -2 1 17 V -2 -2 -2 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -2 -2 -2 -2 -1 3 7 19 Y -1 11 20 W W 13 14 15 16 17 18 19 20 10 11 12 1 2 3 5 6 8 9



ASSSANYGYT Assiraaetqy

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5-11 1 С 4 2 S -1 3 3 Т -1 5 2 P 4 7 1 5 Α 0 6 6 G 0 -1 7 6 Ν 0 0 -2 -2 6 8 -1 1 D -3 -4 -2 5 Е -1 -1 -1 0 2 9 0 -4 -2 -3 0 0 5 10 Q 0 -1 -1 -1 2 -2 -2 -3 -2 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -2 -1 -1 14 Μ 0 -1 -2 -1 -2 0 -2 -1 15 -1 -1 -4 -2 -1 -2 -2 -2 -1 -1 -4 2 2 16 L -4 -1 -2 -2 0 -2 0 -2 -2 1 17 V -2 -2 -2 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -2 -2 -1 3 7 19 Y 20 W Т Ρ Α С S G Ν W n C 14 15 16 17 18 19 20 10 11 12 13 1 2 3 Λ 6 8 9



ASSSANYGYT Assiraaetqy

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ASSSANYGYT Assiraaetqy



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5-11 1 С 4 2 S -1 3 3 Т -1 5 2 P 4 7 1 5 Α 0 6 6 G 0 -1 7 6 0 Ν 0 -2 -2 6 8 -1 D 1 -3 -4 -2 5 Е -1 -1 -1 0 2 9 0 -4 -2 -3 0 0 2 5 10 Q 0 -1 -1 -1 -2 -2 -3 -2 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -2 -1 -1 14 Μ 0 -1 -2 -1 -2 0 -2 -1 15 -1 -1 -4 -1 -2 -2 -2 -2 -1 -1 -4 -4 2 2 16 L -1 -2 -2 0 0 -2 -2 1 17 V -2 -2 -2 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -2 -2 -2 -2 -1 3 7 19 Y -1 11 20 W W 13 14 15 16 17 18 19 20 10 11 12 1 2 3 5 6 8 9



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ASSSANYGYT A**S**SIRAAETQY





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k = 1

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k = 1 ASSSANYGYT

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5-11 1 С 4 2 S -1 3 3 Т -1 5 2 P 4 7 1 5 Α 0 6 6 G 0 -1 7 6 Ν 0 0 -2 -2 6 8 -1 D 1 -3 -4 -1 -1 -2 5 9 Е -1 0 2 0 -4 -2 -3 -1 0 0 2 5 10 Q 0 -1 -1 -2 -2 -2 -3 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -2 -2 -1 -1 14 Μ 0 -1 -1 -2 0 -1 -2 15 -1 -1 -4 -1 -2 -2 -2 -2 -1 -1 -4 2 2 16 L -1 -2 -2 -2 0 -2 0 -2 1 17 V -2 -2 -4 -2 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -3 -2 -2 -2 -1 3 7 19 Y 2 -1 20 W W С 10 13 14 15 16 17 18 19 20 11 12 1 2 3 5 6 8 9



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5-11 1 С 9 4 2 S -1 3 3 Т 2 P 4 1 5 Α 0 6 6 G 0 -1 7 6 0 Ν 0 -2 -3 -2 6 8 -1 D 1 -3 -4 -2 -1 -1 5 Е -1 0 2 9 0 -4 -2 -3 -1 0 0 2 5 10 Q 0 -1 -1 -3 -2 -2 -2 -2 8 11 1 -1 0 0 Н 0 -2 -3 -2 -1 -1 -2 -1 0 12 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -1 -2 -2 -1 -1 14 Μ 0 -1 -2 0 -1 -2 15 -1 -1 -4 -1 -2 -2 -2 -2 -1 -1 -4 2 2 16 L -1 -2 -2 -2 0 -2 0 -2 1 17 V -2 -2 -2 -4 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -2 -2 -2 -2 -1 3 19 Y 2 -1 -1 -1 .2 11 20 W W С G 10 11 12 13 14 15 16 17 18 19 20 1 2 3 Δ 5 6 7 8 9



A<u>S</u>SSANYGYT AS<u>S</u>IRAAETQY



ASSSANYGYT ASSIRAAETQY



ASSSANYGYT ASSIRAAETQY

5-11 1 С 4 2 S -1 3 3 -1 5 Т 1 2 Ρ 4 1 5 0 Α 0 6 G 6 0 υ -1 7 6 Ν 0 0 -2 6 -2 8 -1 D 1 -3 -4 -2 5 Е -1 -1 -1 0 2 9 0 -4 -2 -3 -1 0 0 2 5 10 Q 0 -1 -1 -2 -2 -2 -3 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 Κ -1 0 1 -1 1 -1 -2 -2 -1 -1 14 Μ 0 -1 -1 -2 0 -1 -2 15 -1 -1 -4 -1 -2 -2 -2 -2 -1 -1 -4 2 2 16 L -1 -2 -2 -2 0 -2 0 -2 1 17 V -2 -2 -2 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -3 -2 -2 -2 -1 -2 -1 3 19 Y 2 -1 -1 11 20 W W С G 11 12 13 14 15 16 17 18 19 20 10 1 2 3 Δ 5 6 7 8 9



ASSSANYGYT AS<mark>S</mark>IRAAETQY







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5-11 1 С 4 2 S -1 3 3 Т -1 5 1 2 P 4 7 1 5 0 Α 0 6 6 G 0 0 -1 7 6 0 Ν 0 -2 -3 -2 6 8 -1 D 1 -3 -4 -1 -1 -2 5 Е -1 0 2 9 0 -4 -2 -3 -1 0 0 2 5 10 Q 0 -1 -1 -2 -2 -2 -3 -2 11 1 -1 0 0 8 Н 0 -2 -3 -2 12 -1 -1 -2 -1 0 R 0 1 0 -3 -2 2 5 13 -1 -1 -1 -1 -1 Κ 0 1 -1 1 -1 -1 -2 -1 -2 -1 -1 14 Μ 0 -2 0 -1 -1 -2 -1 4 15 -1 -2 -2 -2 -2 -1 -4 2 2 16 L -4 -1 -1 -2 -2 -2 0 -2 0 -2 1 17 V -2 -2 -2 -4 -2 -1 0 0 -1 6 18 F 0 -2 -2 -2 -2 -2 -2 -1 -2 3 19 Y 2 -1 -1 -1 11 20 W W С G 11 12 13 14 15 16 17 18 19 20 10 1 2 3 Δ 5 6 7 8 9



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ASSIRAAETQY




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(1: perfect match)

Acknowledgments

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TCRMatch: Predicting T-Cell Receptor Specificity Based on Sequence Similarity to Previously Characterized Receptors

William D. Chronister^{1†}, Austin Crinklaw^{1†}, Swapnil Mahajan¹, Randi Vita¹, Zeynep Koşaloğlu-Yalçın¹, Zhen Yan¹, Jason A. Greenbaum¹, Leon E. Jessen², Morten Nielsen^{2,3}, Scott Christley⁴, Lindsay G. Cowell⁴, Alessandro Sette^{1,5} and Bjoern Peters^{1,5*}

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The adaptive immune system in vertebrates has evolved to recognize non-self antigens, such as proteins expressed by infectious agents and mutated cancer cells. T cells play an important role in antigen recognition by expressing a diverse repertoire of antigen-specific receptors, which bind epitopes to mount targeted immune responses. Recent advances in high-throughput sequencing have enabled the routine generation of T-cell receptor (TCR) repertoire data. Identifying the specific epitopes targeted by different TCRs in these data would be valuable. To accomplish that, we took advantage of the ever-increasing number of TCRs with known epitope specificity curated in the Immune Epitope Database (IEDB) since 2004. We compared seven metrics of sequence similarity to determine their power to predict if two TCRs have the same epitope specificity. We found that a comprehensive k-mer matching approach produced the best results, which we have implemented into TCRMatch, an openly accessible tool (http://tools.iedb.org/tcrmatch/) that takes TCR β-chain CDR3 sequences as an input, identifies TCRs with a match in the IEDB, and reports the specificity of each match. We anticipate that this tool will provide new insights into T cell responses captured in receptor repertoire and single cell sequencing experiments and will facilitate the development of new strategies for

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