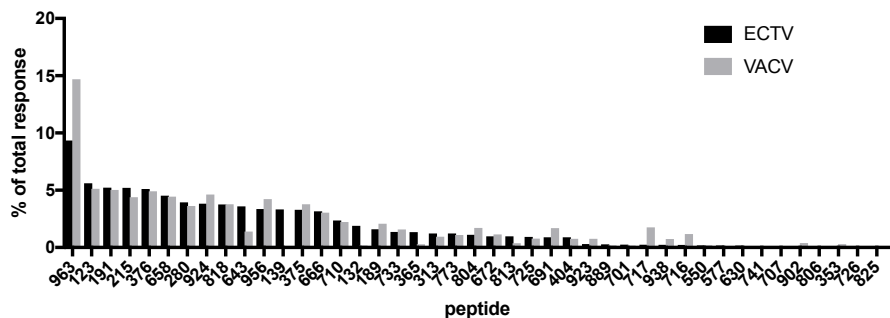


A.



B.

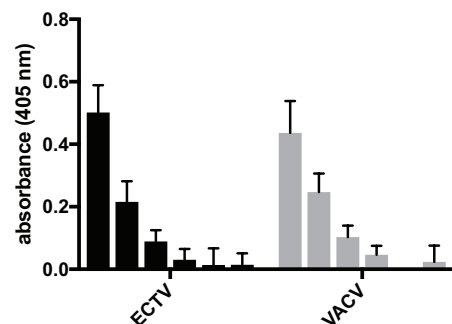


Figure S1. Analysis of peptide cross-reactivity to vaccinia virus (VACV). A. 3 Female C57Bl/6 mice were infected with either  $3 \times 10^3$  pfu ECTV via footpad injection or  $1 \times 10^5$  pfu VAVC via i.p. injection. 10 days later spleens in each group were pooled and CD4<sup>+</sup> T cells were isolated by negative bead selection and mixed with peptide-pulsed BMDCs and analyzed for IFN $\gamma$  production by ELISpot. Representative of 2 independent experiments. Peptides counts for each group were normalized to the total number of spots. B. Serum collected from each mouse in the two independent experiments in A was analyzed for levels of virus-specific IgG antibodies, with the capture virus matching the infection virus, by ELISA and background subtracted from pooled naïve serum.

Supplemental Table 1- Analysis of consistent epitope hits

Protein title	Peptide #	% response	predicted strength	Peptide Sequence	Kinetics <sup>1</sup>	Function <sup>1</sup>	GI#	Accession#
EVM001	123	2.54	11.65	PMYGIESPATHEEA	E	virulence	22164608	NP_671519.1
EVM003	132	3.84	16.42	TFTSIPNHSPACLSC	N/A	N/A	22164610	NP_671521.1
EVM004	139	3.79	17.01	NIDYSGFVIETADF	E	regulation	22164611	NP_671522.1
EVM017	189	2.94	12.71	PPTCQIVKCPHPTIS	IE	unknown	22164624	NP_671535.1
EVM017	191	0.64	4.78	YKLSGSSSSTCSPEN	IE	unknown	22164624	NP_671535.1
EVM025	215	0.34	14.40	YITDIFSTPRDNATT	IE	virulence	22164630	NP_671543.1
EVM038	280	0.87	2.43	DTPRYIPSTSISSN	E	unknown	22164643	NP_671556.1
EVM044	313	3.22	5.14	LDEKYNTPCPNCKSR	E/L	unknown	22164649	NP_671562.1
EVM049	365	2.84	3.78	ERYFYAYICPANEPW	N/A	unknown	22164654	NP_671567.1
EVM049	353	0.56	1.67	SMVFEYRASTVIKGP	N/A	unknown	22164654	NP_671567.1
EVM054	376	0.56	4.82	RALKAYFTAKINEMV	IE	unknown	22164659	NP_671572.1
EVM054	375	0.28	2.21	DQLIFNSISARALKA	IE	unknown	22164659	NP_671572.1
EVM057	404	0.88	13.94	GEFQVVNPHLLRVLTL	IE	unknown	22164662	NP_671575.1
EVM082	550	2.26	15.30	NLSYITSGKNNMIRS	E	regulation	22164687	NP_671600.1
EVM084	577	0.52	11.36	MLNELGYSGYFMSPH	E	regulation	22164689	NP_671602.1
EVM090	630	0.54	1.17	DRILVYNPSTMSTPM	E/L	unknown	22164695	NP_671608.1
EVM094	643	2.22	8.57	GAIRIYKTGNPHSCK	L	structural	22164699	NP_671612.1
EVM095	658	5.22	9.87	SEYNGSQGTNPHEMIN	E	regulation	22164700	NP_671613.1
EVM097	672	4.89	2.59	YFTYLGTTINHSADA	E	regulation	22164702	NP_671615.1
EVM097	666	2.55	2.34	IHYNESKPTTIQNTG	E	regulation	22164702	NP_671615.1
EVM101	691	3.13	14.21	NLSLGKSPPLSLEYG	IE	regulation	22164706	NP_671619.1
EVM102	701	1.13	2.54	FFRPTTITANVSRGK	L	regulation	22164707	NP_671620.1
EVM106	710	4.03	5.49	SQDLSFIYRKPETNY	L	regulation	22164711	NP_671624.1
EVM106	716	3.23	1.34	GNSGRVVFAPPNIGY	L	regulation	22164711	NP_671624.1
EVM106	707	1.09	10.55	QIVDDDFISAGARNQ	L	regulation	22164711	NP_671624.1
EVM106	717	0.33	8.46	VVFAPPNIGYGRCSG	L	regulation	22164711	NP_671624.1
EVM107	733	2.52	10.29	DGSISCTTPTVTPPQ	L	structural	22164712	NP_671625.1
EVM107	726	1.83	5.61	IHITPQPVPTSTPSA	L	structural	22164712	NP_671625.1
EVM107	725	1.49	10.70	PLQPTIHITPQPVPT	L	structural	22164712	NP_671625.1
EVM109	741	2.51	13.91	TLNEYKQLYTISSSES	E/L	structural	22164714	NP_671627.1
EVM114	773	2.88	12.15	EKRFNITVSKNAEAI	IE	regulation	22164719	NP_671632.1
EVM121	804	3.04	14.20	ANRIYCNSIINIACL	L	unknown	22164727	NP_671640.1
EVM121	806	0.60	1.58	LDRTVYVFPSTSIKE	L	unknown	22164727	NP_671640.1
EVM124	813	1.99	6.99	NIFIPSVITKSGKKI	E	regulation	22164730	NP_671643.1
EVM126	818	1.69	11.17	DEYLSTTVRSNINQP	L	structural	22164732	NP_671645.1
EVM127	825	2.24	0.72	NSFTFSFSSVSPPNV	E	regulation	22164733	NP_671646.1
EVM139	889	2.71	5.32	YAPYQNSKVTIISHN	L	structural	22164745	NP_671658.1
EVM141	902	0.96	0.62	LTGYAPVSPIVIART	IE	unknown	22164747	NP_671660.1
EVM147	924	1.36	2.90	RYAFSGVAYAAAKGA	L	structural	22164753	NP_671666.1
EVM147	923	0.51	2.81	TLIVDRYAFSGVAYAY	L	structural	22164753	NP_671666.1
EVM149	938	1.95	1.67	TGVYNYFKPKDAIPV	L	structural	22164755	NP_671668.1
EVM151	956	0.64	0.87	SVFEIATPEPITDKE	IE	unknown	22164757	NP_671670.1
EVM153	963	7.43	2.23	VKNKYMWCYSQVKNR	E	regulation	22164759	NP_671672.1

<sup>1</sup> as assessed for VACV in [39]

## Supplemental Table 2- Analysis of sporadic epitope hits

Protein title	Peptide #	predicted strength	kinetics <sup>1</sup>	Peptide Sequence	GI#	Accession#	peptide start	peptide end
EVM001	124	8.05	E	VKDGFKYIDGSVSEG	22164608	NP_671519.1	216	230
EVM015	186	14.59	E	VKEENYSSPYIEHPL	22164622	NP_671533.1	126	140
EVM057	401	3.12	IE	PYDTYAGSYASNGIL	22164662	NP_671575.1	551	565
EVM060	425	8.89	N/A	VFELPVSPLAYFFK	22164665	NP_671578.1	106	120
EVM061	434	7.22	E/L	NKYPFSKIPLASLTP	22164666	NP_671579.1	151	165
EVM080	543	14.32	E	FQVFNESINYTPVD	22164685	NP_671598.1	61	75
EVM085	588	1.54	E/L	KRYPGVMYAFTTPLI	22164690	NP_671603.1	266	280
EVM086	598	2.97	N/A	TCVEQKIVAPTPSVE	22164691	NP_671604.1	621	635
EVM090	627	1.61	E/L	FRYMSSEPIIFGESS	22164695	NP_671608.1	406	420
EVM102	700	0.56	L	FTPKIFFRPTTITAN	22164707	NP_671620.1	481	495
EVM106	709	7.88	L	ELDKIYSPSNHHILL	22164711	NP_671624.1	186	200
EVM106	711	7.72	L	FIYRKPETNYIHPI	22164711	NP_671624.1	221	235
EVM106	720	8.55	L	PLSVFNPGARNARLM	22164711	NP_671624.1	546	560
EVM107	724	4.26	L	RRPIQLPQPTIHITP	22164712	NP_671625.1	66	80
H14B	988	11.96	-	LEFNTPFVFIIRHDI	22164761	NP_671541.1	346	360
serpin_C7R	25	6.11	-	MKGENVFISSASISS	22164596	NP_671680.1	11	25
serpin_C7R	31	8.30	-	MMSMYGEPFNHASVK	22164596	NP_671680.1	166	180
serpin_C7R	35	6.22	-	EEYTEAAAATCALVS	22164596	NP_671680.1	291	305

1 as assessed for VACV in [39]