Clonally Expanded B Cells in Multiple Sclerosis Bind EBV EBNA1 and GlialCAM

Authors: Tobias V. Lanz[1,2,3], R. Camille Brewer[1], Peggy P. Ho[4], Jae-Seung Moon[1], Kevin M. Jude[5], Daniel Fernandez[6], Ricardo A. Fernandes[5], Alejandro M. Gomez[1], Gabriel-Stefan Nadj[1], Christopher M. Bartley[7,8], Ryan D. Schubert[9], Isobel A. Hawes[9], Sara E. Vazquez[10], Manasi Iyer[11], J. Bradley Zuchero[11], Bianca Teegen[12], Jeffrey E. Dunn[13], Christopher B. Lock[13], Lucas B. Kipp[13], Victoria C. Cotham[14], Beatrix M. Ueberheide[14], Blake T. Aftab[15], Mark S. Anderson[16], Joseph L. DeRisi[10,17], Michael R. Wilson[9], Rachael J.M. Bashford-Rogers[18], Michael Platten[2,3,19], K. Christopher Garcia[5], Lawrence Steinman[4], William H. Robinson[1,*]

Affiliations:

[1] Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, 269 Campus Drive, Stanford, CA 94305, United States, and the Geriatric Research, Education, and Clinical Centers (GRECC), VA Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304, United States

[2]Department of Neurology, Mannheim Center for Translational Neurosciences (MCTN), Medical Faculty Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

[3]Department of Neurology and National Center for Tumor Diseases, University Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany

[4]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Beckman Center for Molecular Medicine, 279 Campus Drive, Stanford, CA 94305, United States

[5]Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Beckman Center for Molecular Medicine, 279 Campus Drive, Stanford, CA 94305, United States

[6]Stanford ChEM-H Institute, Macromolecular Structure Knowledge Center, 290 Jane Stanford Way, Stanford, CA 94305, United States

[7]Hanna H. Gray Fellow, Howard Hughes Medical Institute, 4000 Jones Bridge Rd, Chevy Chase, MD 20815, United States

[8]Weill Institute for Neurosciences, Department of Psychiatry and Behavioral Sciences, University of California San Francisco, 675 Nelson Rising Ln San Francisco, CA 94158, San Francisco, United States

[9]Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, 675 Nelson Rising Ln San Francisco, CA 94158, San Francisco, United States

[10]Department of Biochemistry and Biophysics, University of California San Francisco, 1700 4th Street, San Francisco, CA 94158, United States

[11]Department of Neurosurgery, Stanford University School of Medicine, 1201 Welsh Road, Stanford, CA, United States

[12]Institute of Experimental Immunology, Euroimmun AG, Seekamp 31, 23560 Lübeck, Germany

[13]Division of Neuroimmunology, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, 213 Quarry Road, Stanford, CA, United States

[14]Department of Biochemistry and Molecular Pharmacology, NYU Perlmutter Cancer Center, and NYU Langone Health Proteomics Laboratory, Division of Advanced Research Technologies, NYU School of Medicine, 430 East 29th St, New York, NY, 10016, United States

[15]Preclinical Science and Translational Medicine, Atara Biotherapeutics, 611 Gateway Blvd South San Francisco, CA 94080, United States

[16]Department of Medicine, Diabetes Center, University of California San Francisco, 513 Parnassus Ave, San Francisco, CA 94143, United States

[17]Chan Zuckerberg Biohub, University of California San Francisco, 499 Illinois Street, San Francisco, CA 94158, United States

[18]Wellcome Centre for Human Genetics, University of Oxford, Roosevelt Dr, Headington, Oxford OX3 7BN, United Kingdom

[19]DKTK Clinical Cooperation Unit Neuroimmunology and Brain Tumor Immunology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

*Corresponding Author: William H. Robinson, Division of Immunology and Rheumatology, Department of Medicine, Stanford University School of Medicine, 269 Campus Drive, Stanford, CA 94305, United States, email: wrobins@stanford.edu

ORCID

Tobias V. Lanz, 0000-0001-7106-8801; R. Camille Brewer, 0000-0002-0342-1826; Peggy P. Ho, 0000-0002-6848-318X; Jae Seung Moon, 0000-0002-1983-465X; Kevin M. Jude, 0000-0002-3675-5136; Daniel Fernandez, 0000-0002-6221-152X; Ricardo A. Fernandes, 0000-0001-5343-3334; Alejandro M. Gomez[1], Gabriel Nadj, 0000-0002-9938-431X; Christopher M. Bartley, 0000-0002-1391-4130; Ryan D. Schubert, 0000-0002-3132-5831; Isobel A. Hawes 0000-0003-1719-0114; J. Bradly Zuchero, 0000-0002-4706-2538; Beatrix M. Ueberheide, 0000-0003-2512-0204; Blake T. Aftab, 0000-0003-4020-2718; Joseph L. DeRisi, 0000-0002-4611-9205; Michael R. Wilson, 0000-0002-8705-5084; Rachael J.M. Bashford-Rogers, 0000-0002-6838-0711; Michael Platten, 0000-0002-4746-887X; Lawrence Steinman, 0000-0002-2437-2250; William H. Robinson, 0000-0003-4385-704X

Supplementary Information

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Supplementary Table 1

	HLA-A_1	HLA-A_2	HLA-B_1	HLA-B_2	HLA-C_1	HLA-C_2
MS9	02:05	68:01	15:03	50:01	02:10	06:02
MS12	31:01	32:01	40:01	40:01	03:04	03:04
MS20	02:01	02:01	18:01	51:01	07:01	14:02
MS21	01:01	03:01	07:02	58:01	03:02	07:02
MS28	01:01	03:01	07:02	07:02	07:02	07:02
MS30	01:01	24:02	07:02	08:01	07:01	07:02
MS31	01:01	02:01	08:01	13:02	06:02	07:02
MS37	03:01	68:02	15:10	35:01	03:04	04:01
MS39	01:01	03:01	08:01	51:01	07:01	15:02

	HLA-DRB1_1	HLA-DRB1_2	HLA-DRB345_1	HLA-DRB345_2	HLA-DQA1_1	HLA-DQA1_2	HLA-DQB1_1	HLA-DQB1_2	HLA-DPA1_1	HLA-DPA1_2	HLA-DPB1_1	HLA-DPB1_2
MS9	07:01	15:01	4*01:01	5*01:01	01:02	02:01	02:02	06:02	01:03	01:03	03:01	04:01
MS12	01:01	04:04	4*01:03	null	01:01	03:01	03:02	05:01	01:03	02:01	01:01	02:01
MS20	08:01	11:01	3*02:02	null	04:02	05:05	04:02	03:01	01:03	01:03	04:01	04:02
MS21	15:01	13:02	3*01:01	5*01:01	01:02	01:02	06:02	06:09	01:03	01:03	04:01	104:01
MS28	07:01	15:01	4*01:01	5*01:01	01:02	02:01	02:02	06:02	02:01	02:01	01:01	11:01
MS30	03:01	15:01	3*01:01	5*01:01	01:02	05:01	02:01	06:02	01:03	02:01	01:01	15:01
MS31	03:01	15:01	*3*01:01*	5*01:01	01:02	05:01	02:01	06:02	01:03	01:03	03:01	03:01
MS37	01:01	08:04	null	null	01:01	05:01	03:01	05:01	01:03	01:03	02:01	04:02
MS39	03:01	07:01	*3*01:01*	4*01:03	02:01	05:01	02:01	03:03	01:03	01:03	03:01	06:01

Supplementary Table 1. Genotype of full HLA locus. HLA-DRB1*15:01 (dark red) is the main risk allele for MS, HLA-DRB1*03:01 (bright red) is a secondary risk allele for MS.

Supplementary Table 2

Antigen	Name in Figure	Name in Suppl. Figure	Product Name	Company	catalogue #	Lot #	residues	source	ug/ul
BALF2 = EA-p138 = DBP, Major DNA-binding protein	**BALF2**	**BALF2**	EBV Early Antigen P138	Serion	BA1363VSR6	RAB.01	mid to C-term		0.10
BALF5	**BALF5**	**BALF5_A**	Epstein-Barr Virus BALF5 Protein (Recombinant His + SUMO) (aa1-210)	LSBio	LS-G21512-50	114296	AA1-210	E. Coli	0.08
BALF5	**BALF5**	**BALF5_B**	Recombinant Epstein-Barr Virus BALF5 Protein (1-210 aa), His-SUMO-tagged	Creative Biomart	BALF5-934E	PLB4022001	AA1-210	E. Coli	0.10
BCRF1 = EBV-IL10	**BCRF1**	**BCRF1_A**	BCRF1 recombinant protein :: Viral interleukin-10 homolog (BCRF1) Recombinant Protein	MyBioSource	MBS1152507	04125	AA24-170	E.Coli	0.10
BCRF1 = EBV-IL10	**BCRF1**	**BCRF1_B**	Recombinant Viral EBV IL-10 Protein Summary	R&D Systems	915-VL-010	DTW0619041	AA26-170	E. Coli	0.10
BDLF3	**BDLF3**	**BDLF3**	Recombinant Epstein-Barr Virus BDLF3 Protein (29-186 aa)	Creative Biomart	BDLF3-2579E	PLB9022001	AA29-186	E. Coli	0.10
BFRF3 = SCP = p18	**BFRF3**	**BFRF3**	EBV Capsid Antigen P18	Serion Immunologics	BA1361VSR22	A1361R22CE	full-length	E. Coli	0.10
BHRF1 = EA-R	**BHRF1**	**BHRF1_A**	Viral BHRF1 protein	Biorbyt	orb383414		AA1-142	E. Coli	0.10
BHRF1 = EA-R	**BHRF1**	**BHRF1_B**	Recombinant Epstein-Barr virus Apoptosis regulator BHRF1(BHRF1), partial	SAB Biotech	AP74149-2	03597	AA1-142	E. Coli	0.05
BLLF1 = gp350 = gp220	**BLLF1**	**BLLF1_A**	Human BLLF1 protein	Biorbyt	orb358554	CB7834	full-length	E. Coli	0.10
BLLF1 = gp350 = gp220	**BLLF1**	**BLLF1_B**	Epstein-Barr virus (Herpesvirus 4) EBV Glycoprotein gp350 / EBV GP350 Protein (His Tag)	Sino Biological	40373-V08H-50	LC08OC2011	full-length	human cells	0.10
BLLF1 = gp350 = gp220	**BLLF1**	**BLLF1_C**	Recombinant gp350/220 (RBD/(a.a.4-450)) (EBV)	Beta Lifescience	BLIT-0568	BL5171001	AA4-450	Hek293	0.10
BLLF1 = gp350 = gp220	**BLLF1**	**BLLF1_D**	Recombinant gp350/220 (Ectodomain) (EBV)	Beta Lifescience	BLIT-0567	BL5172001	AA4-863	Hek293	0.10
BLLF1 = gp350 = gp220	**BLLF1**	**BLLF1_E**	Recombinant Epstein-Barr virus (Herpesvirus 4) EBV Glycoprotein gp350 / EBV GP350 Protein (His Tag)	Beta Lifescience	BLPSN-4871	BL17692081	AA1-490	Hek293	0.10
BLLF3	**BLLF3**	**BLLF3**	Recombinant Epstein-Barr Virus BLLF3 Protein (1-278 aa), His-SUMO-tagged	Creative Biomart	BLLF3-875E	PSB5042003	AA1-278	E. Coli	0.10
BLRF2 = p23	**BLRF2**	**BLRF2**	EBV Capsid Antigen P23	Serion Immunologics	BA1361VSR21	A1361R21HE	full-length		0.10
BMRF1 = EA-D = EA-p54	**BMRF1**	**BMRF1**	EBV Early Antigen P54	Serion Immunologics	BA1363P54VS	RMX.05	full-length		0.10
BRLF1	**BRLF1**	**BRLF1_A**	Epstein-Barr Virus BRLF1 Protein (Recombinant 10His,N-terminus + Myc,C-terminus)	LSBio	LS-G137360-50		AA352-605	E. Coli	0.10
BRLF1	**BRLF1**	**BRLF1_B**	Recombinant Epstein-Barr Virus BRLF1 Protein (352-605 aa)	Creative Biomart	BRLF1-2598E	PLB8022001	AA352-605	E. Coli	0.10
BXLF2 = gH	**BXLF2**	**BXLF2_gH**	Recombinant gH(Ectodomain) (EBV) (Strain B95-8)	Beta Lifescience	BLIT-0576	BL3703008	AA1-679	Hek293	0.10
BZLF1 = EB1 = ZEBRA	**BZLF1**	**BZLF1_A**	Recombinant Trans-activator protein BZLF1	SAB Biotech	AP71110-1	03608	full-length	E. Coli	0.07
BZLF1 = EB1 = ZEBRA	**BZLF1**	**BZLF1_B**	Epstein-Barr Virus BZLF1 Protein (Recombinant His + SUMO) (Full Length)	LSBio	LS-G21513-50	114898	full-length	E. Coli	0.07
BZLF1 = EB1 = ZEBRA	**BZLF1**	**BZLF1_C**	Epstein-Barr Virus BZLF1 Protein (Recombinant His + SUMO) (Full Length)	LSBio	LS-G21513-50	121704	full-length	E. Coli	0.10
CMV Density Gradient Purified	**CMV_Ag**	**CMV_AgB**	Cytomegalovirus Density Gradient Purified	Virusys	CV046-100	J1245027		NHDF	0.10
CMV infected Cell Extracts	**CMV_Lys**	**CMV_LysA**	Cytomegalovirus infected Cell Extracts	Virusys	CV001-1	G1242161		NHDF	0.10
CMV infected Cell Extracts	**CMV_Lys**	**CMV_LysB**	Cytomegalovirus infected Cell Extracts	Virusys	CV001-1	D1754053		NHDF	0.10
CMV purified antigen	**CMV_Ag**	**CMV_AgA**	hCMV purified antigen	The Native Antigen	CMV-HP-100	JC18		HFF	0.10
CMV Purified Glycoprotein	**CMV_GP**	**CMV_GP**	Cytomegalovirus Purified Glycoprotein	Virusys	CV216-1	A1345094		NHDF	0.10
EBNA1	**EBNA1**	**EBNA1_A**	EBV Nuclear Antigen EBNA1, P72	Serion Immunologics	BA1362VS		AA72 C-term		0.10
EBNA1	**EBNA1**	**EBNA1_B**	EBV Nuclear Antigen-1 (EBNA-1) Recombinant Protein	Advanced Biotechnologies	10-523-001		full-length	Sf-9	0.10
EBNA1	**EBNA1**	**EBNA1_C**	EBV EBNA1	Prospecbio	EBV-276	1011PEBVA1H06	AA408-641	E. Coli	0.10
EBNA1	**EBNA1**	**EBNA1_D**	EBV EBNA1, Recombinant	MyBioSource	MBS318777	2G20216	full-length	E. Coli	0.10
EBNA1	**EBNA1**	**EBNA1_E**	Recombinant EBV Nuclear Antigen protein	abcam	ab138345		full-length	E. Coli	0.04
EBNA1 (mosaic)		**EBNA1_mos**	Recombinant Nuclear antigen-1 (EBV)	Beta Lifescience	BLIT-0580	BL17632001	AA1-90 + AA408-490	E. coli	0.10
EBNA2	**EBNA2**	**EBNA2_B**	Viral EBNA2 protein	Biorbyt	orb54179	CB9312	208 N-term	Yeast	0.10
EBNA2	**EBNA2**	**EBNA2_A**	Recombinant Epstein-Barr virus Epstein-Barr nuclear antigen 2 (EBNA2), partial	Biomatik	RPC25407	03599	AA247-454	yeast	0.10
EBNA3 = EBNA-3A = BRLF3	**EBNA3A**	**EBNA3A**	Recombinant Epstein-Barr virus Epstein-Barr nuclear antigen 3 (EBNA3), partial	Biomatik	RPC25970	YA03765b1g5	AA138	E. Coli	0.10
EBNA-3C = EBNA6	**EBNA3C**	**EBNA3C**	EBNA, Native Protein	MyBioSource	MBS537124		full length	native	0.10
EBV-EA	**EBV-EA**	**EBV-EA_A**	EBV EA, Native Protein	MyBioSource	MBS5308315	16042110	full-length	P3H3	0.10
EBV-EA	**EBV-EA**	**EBV-EA_B**	EA Protein	antibodies-online inc	ABIN934554	A13012301	full-length	E. Coli	0.10
EBV-EA	**EBV-EA**	**EBV-EA_C**	EBV EA protein	MybioSource	MBS538030	605EBVEA01	AA306-390	E. Coli	0.10
EBV Lysate	**EBV_Lys**	**EBV_LysB**	Epstein-Barr Virus (EBV) Lysate	Zeptometrix	810008	311936 (sublot 520646)		Marmoset Leukocyte	0.10
EBV Density Gradient purified	**EBV_Ag**	**EBV_Ag**	Epstein-Barr Virus Density Gradient purified	Virusys	EV152-100	F1446185		P3HR1	0.10
EBV Infected Cell Extract	**EBV_Lys**	**EBV_LysA**	Epstein-Barr Virus Infected Cell Extract	Virusys	EV012-1	D175402-1		P3H3	0.10
EBV Negative Control Extract		**Ctrl_Lys_EBV**	Epstein-Barr Virus Negative Control Extract	Virusys	EV139-1	H1245003		Human B Cell	0.10
gH(DI-III)/gL/gp42	**gH_gp42**	**gH_gp42**	Recombinant gH(DI-III)/gL/gp42 (Ectodomain)(EBV) (Strain B95-8) Complex	Beta Lifescience	BLIT-0579	BL3701001	AA1-344	Hek293	0.10
gH/gp42 complex	**gH_compl**	**gH_compl**	Recombinant gH/gp42 (Ectodomain)(EBV)(Strain B95-8) Complex	Beta Lifescience	BLIT-0577	BL3721001	AA1-679	Hek293	0.10
HERV-W	**HERV-W**	**HERV-W_A**	Recombinant Human Syncytin-1(ERVW-1), partial	Cusabio	CSB-EP891578HU	YA04483b1g2	AA21-443	E. Coli	0.07
HERV-W	**HERV-W**	**HERV-W_B**	ERVWE1 (Human) Recombinant Protein (Q01)	Abnova	H00030816-Q01	H5051	AA116-215	Wheat Germ	0.08
HSV1 Infected Cell Extract	**HSV1_Lys**	**HSV1_Lys**	Herpes Simplex Virus Infected Cell Extract	Virusys	H1V016-1	C1651079			0.10
HSV-1 (MacIntyre) Density Gradient Purified	**HSV1_Ag**	**HSV1_Ag**	HSV-1 (MacIntyre) Density Gradient Purified	Virusys	H1V057-100	E1652101		Vero	0.10
HSV2 Infected Cell Extract	**HSV2_Lys**	**HSV2_Lys**	Herpes Simplex Type 2 Infected Cell Extract	Virusys	H2V017-1	D1548161		Vero	0.10
HSV-2 (G) Density Gradient Purified	**HSV2_Ag**	**HSV2_Ag**	HSV-2 (G) Density Gradient Purified	Virusys	H2V058-100	E1345151		Vero	0.10
LMP1	**LMP1**	**LMP1_A**	Recombinant Epstein-Barr virus Latent membrane protein 1(LMP1), partial	Biomatik	RPC20572	YA04259a6g5	AA185-366	Yeast	0.10
LMP1	**LMP1**	**LMP1_B**	Recombinant Epstein-Barr Virus LMP1 Protein (185-386 aa)	Creative Biomart	LMP1-872E	PLL2022001	AA185-386	E. Coli	0.10
LMP1	**LMP1**	**LMP1_C**	Recombinant Epstein-Barr virus Latent membrane protein 1(LMP1), partial	Biomatik	RPC20572	3587	AA185-366	Yeast	0.10
LMP2	**LMP2**	**LMP2_A**	Epstein-Barr Latent membrane protein 2 Recombinant Protein Product	enQuire BioReagents	QP7054-ye-200ug	1Z171101	1-148	Yeast	0.10
LMP2	**LMP2**	**LMP2_B**	Recombinant Epstein-Barr Virus LMP2 Protein (1-147 aa)	Creative Biomart	LMP2-2066E	PLL6022001	AA1-147	E. Coli	0.10
Measles Premium Antigen	**Measles_Ag**	**Measles_Ag**	Measles Premium Antigen	Serion	BA102VS	A102FCB.1			0.10
NHDF Uninfected Cell Extract		**Ctrl_Lys_NHDF_A**	NHDF Uninfected Cell Extract	Virusys	AV043-1	A1446115			0.10
NHDF uninfected cell extract		**Ctrl_Lys_NHDF_B**	NHDF uninfected cell extract	Virusys	AV043-1	C1448136		NHDF	0.10
Rubella Premium Antigen	**Rubella_Ag**	**Rubella_Ag**	Rubella Premium Antigen	Serion	BA192VS	XAH.AW			0.10
Rubella Virus Lysate	**Rubella_Lys**	**Rubella_Lys**	Rubella Virus Lysate	Zeptometrix	810048	317895 (sublot 530125)		Vero	0.10
VCA, gp125	**VCA-gp125**	**VCA-gp125_A**	Epstein-Barr Virus VCA Protein	antibodies-online inc	ABIN2129014		full-length	human	0.02
VCA, gp125	**VCA-gp125**	**VCA-gp125_B**	EBV VCA, Native Protein	MyBioSource	MBS5303600	A17102612	full-length	P3H3 cells	0.02
Vero Uninfected Cell Extract		**Ctrl_Lys_Vero**	Vero Uninfected Cell Extract	Virusys	AV042-1	A1345096		Vero	0.10
VZV Glycoprotein	**VZV_GP**	**VZV_GP**	VZV Purified Glycoproteins	Virusys	VV147-1	E1651103			0.10
VZV Lysate	**VZV_Lys**	**VZV_LysA**	Varicella Zoster Virus (VZV) Lysate	Zeptometrix	810171	311751 (sublot 519690)		Strain: Ellen CV-1	0.10
VZV Lysate	**VZV_Lys**	**VZV_LysB**	Varicella Zoster (VZV) Lysate	Zeptometrix	810168	317665 (sublot529376)		Strain: 275 CV-1	0.10
VZV Infected Cell Extract	**VZV_Lys**	**VZV_LysC**	VZV Infected Cell Extract	Virusys	VV037-1	F1345161			0.10
VZV Infected Cell Extract	**VZV_Lys**	**VZV_LysD**	VZV Infected Cell Extract	Virusys	VV037-1	F1345161		NHDF	0.10

Supplementary Table 2. Viral proteins and lysates.

Supplementary Table 3

Antigen Name	Company	AA Sequence	Pept Length	ug/ul
EBNA1_1	Sigma Aldrich	MSDEGPGTGPGNGLGEKGDT	20	0.1
EBNA1_2	Sigma Aldrich	TGPGNGLGEKGDTSGPEGSG	20	0.1
EBNA1_3	Sigma Aldrich	GEKGDTSGPEGSGGSGPQRR	20	0.1
EBNA1_4	Sigma Aldrich	GPEGSGGSGPQRRGGDNHGR	20	0.1
EBNA1_5	Sigma Aldrich	SGPQRRGGDNHGRGRGRGRG	20	0.1
EBNA1_6	Sigma Aldrich	GDNHGRGRGRGRGGGRPG	20	0.1
EBNA1_7	Sigma Aldrich	RGRGRGRGGGRPGAPGGSGS	20	0.1
EBNA1_8	Sigma Aldrich	GGGRPGAPGGSGSGPRHRDG	20	0.1
EBNA1_9	Sigma Aldrich	PGGSGSGPRHRDGVRRPQKR	20	0.1
EBNA1_10	Sigma Aldrich	PRHRDGVRRPQKRPSCIGCK	20	0.1
EBNA1_11	Sigma Aldrich	RRPQKRPSCIGCKGTHGGTG	20	0.1
EBNA1_12	Sigma Aldrich	SCIGCKGTHGGTGAGAGAGG	20	0.1
EBNA1_13	Sigma Aldrich	THGGTGAGAGAGGAGAGGAG	20	0.1
EBNA1_14	Sigma Aldrich	GAGAGGAGAGGAGAGGGAGA	20	0.1
EBNA1_15	Sigma Aldrich	GAGGAGAGGAGAGGGAGGA	20	0.1
EBNA1_16	Sigma Aldrich	GGAGAGGGAGGAGAGGAGGG	20	0.1
EBNA1_17	Sigma Aldrich	GGAGGAGGAGGAGAGGGAGA	20	0.1
EBNA1_18	Sigma Aldrich	GAGGAGAGGGAGAGGGAGGA	20	0.1
EBNA1_19	Sigma Aldrich	GGGAGAGGGAGGAGGAGAGG	20	0.1
EBNA1_20	Sigma Aldrich	GGAGGAGGAGAGGGAGAGGG	20	0.1
EBNA1_21	Sigma Aldrich	GAGAGGGAGAGGGAGGAGAG	20	0.1
EBNA1_22	Sigma Aldrich	AGAGGGAGGAGAGGGAGGAG	20	0.1
EBNA1_23	Sigma Aldrich	GGAGAGGGAGGAGAGGAGGG	20	0.1
EBNA1_24	Sigma Aldrich	GAGGAGGAGAGGGAGAGGGA	20	0.1
EBNA1_25	Sigma Aldrich	AGAGGGAGAGGGAGGAGAGG	20	0.1
EBNA1_26	Sigma Aldrich	GAGGGAGGAGAGGGAGGAGG	20	0.1
EBNA1_27	Sigma Aldrich	GAGAGGGAGGAGGAGAGGGA	20	0.1
EBNA1_28	Sigma Aldrich	AGGAGGAGAGGGAGAGGAGG	20	0.1
EBNA1_29	Sigma Aldrich	GAGGGAGAGGAGGAGAGGAG	20	0.1
EBNA1_30	Sigma Aldrich	AGGAGGAGGAGGAGAGGGAG	20	0.1
EBNA1_31	Sigma Aldrich	GGAGAGGAGAGGGAGGAGGA	20	0.1
EBNA1_32	Sigma Aldrich	AGAGGGAGGAGGAGAGGAGA	20	0.1
EBNA1_33	Sigma Aldrich	GGAGGAGAGGAGAGGAGAGG	20	0.1
EBNA1_34	Sigma Aldrich	AGGAGAGGAGAGGAGGAGGG	20	0.1
EBNA1_35	Sigma Aldrich	GAGAGGAGAGGAGGAGAGGA	20	0.1
EBNA1_36	Sigma Aldrich	GAGGAGGAGAGGAGGAGAGG	20	0.1
EBNA1_37	Sigma Aldrich	AGAGGAGGAGAGGAGGAGAG	20	0.1
EBNA1_38	Sigma Aldrich	GAGAGGAGGAGAGGGAGGAG	20	0.1
EBNA1_39	Sigma Aldrich	GGAGAGGGAGGAGAGGGAGG	20	0.1
EBNA1_40	Sigma Aldrich	GAGGAGAGGGAGGAGAGGAG	20	0.1
EBNA1_41	Sigma Aldrich	GGGAGGAGAGGAGGAGAGGA	20	0.1
EBNA1_42	Sigma Aldrich	GAGGAGGAGAGGAGGAGAGG	20	0.1
EBNA1_43	Sigma Aldrich	AGAGGAGGAGAGGAGGAGAG	20	0.1
EBNA1_44	Sigma Aldrich	GAGAGGAGGAGAGGGAGAGG	20	0.1
EBNA1_45	Sigma Aldrich	GGAGAGGGAGAGGAGAGGGG	20	0.1
EBNA1_46	Sigma Aldrich	GAGAGGAGAGGGGRGRGGSG	20	0.1
EBNA1_47	Sigma Aldrich	GAGGGGRGRGGSGGRGRGGS	20	0.1
EBNA1_48	Sigma Aldrich	GRGGSGGRGRGGSGGRGRGG	20	0.1
EBNA1_49	Sigma Aldrich	RGRGGSGGRGRGGSGGRRGR	20	0.1
EBNA1_50	Sigma Aldrich	GRGRGGSGGRRGRGRERARG	20	0.1
EBNA1_51	Sigma Aldrich	GGRRGRGRERARGGSRERAR	20	0.1
EBNA1_52	Sigma Aldrich	RERARGGSRERARGRGRGRG	20	0.1
EBNA1_53	Sigma Aldrich	SRERARGRGRGRGEKRPRSP	20	0.1
EBNA1_54	Sigma Aldrich	RGRGRGEKRPRSPSSQSSSS	20	0.1
EBNA1_55	Sigma Aldrich	KRPRSPSSQSSSSGSPPRRP	20	0.1
EBNA1_56	Sigma Aldrich	SQSSSSGSPPRRPPPGRRPF	20	0.1
EBNA1_57	Sigma Aldrich	SPPRRPPPGRRPFFHPVGEA	20	0.1
EBNA1_58	Sigma Aldrich	PGRRPFFHPVGEADYFEYHQ	20	0.1
EBNA1_59	Sigma Aldrich	HPVGEADYFEYHQEGGPDGE	20	0.1
EBNA1_60	Sigma Aldrich	YFEYHQEGGPDGEPDVPPGA	20	0.1
EBNA1_61	Sigma Aldrich	GGPDGEPDVPPGAIEQGPAD	20	0.1
EBNA1_62	Sigma Aldrich	DVPPGAIEQGPADDPGEGPS	20	0.1
EBNA1_63	Sigma Aldrich	EQGPADDPGEGPSTGPRGQG	20	0.1
EBNA1_64	Sigma Aldrich	PGEGPSTGPRGQGDGGRRKK	20	0.1
EBNA1_65	Sigma Aldrich	GPRGQGDGGRRKKGGWFGKH	20	0.1
EBNA1_66	Sigma Aldrich	GGRRKKGGWFGKHRGQGGSN	20	0.1
EBNA1_67	Sigma Aldrich	GWFGKHRGQGGSNPKFENIA	20	0.1
EBNA1_68	Sigma Aldrich	GQGGSNPKFENIAEGLRALL	20	0.1
EBNA1_69	Sigma Aldrich	KFENIAEGLRALLARSHVER	20	0.1
EBNA1_70	Sigma Aldrich	GLRALLARSHVERTTDEGTW	20	0.1
EBNA1_71	Sigma Aldrich	RSHVERTTDEGTWVAGVFVY	20	0.1
EBNA1_72	Sigma Aldrich	TDEGTWVAGVFVYGGSKTSL	20	0.1
EBNA1_73	Sigma Aldrich	AGVFVYGGSKTSLYNLRRGT	20	0.1
EBNA1_74	Sigma Aldrich	GSKTSLYNLRRGTALAIPQC	20	0.1
EBNA1_75	Sigma Aldrich	NLRRGTALAIPQCRLTPLSR	20	0.1
EBNA1_76	Sigma Aldrich	LAIPQCRLTPLSRLPFGMAP	20	0.1
EBNA1_77	Sigma Aldrich	LTPLSRLPFGMAPGPGPQPG	20	0.1
EBNA1_78	Sigma Aldrich	PFGMAPGPGPQPGPLRESIV	20	0.1
EBNA1_79	Sigma Aldrich	PGPQPGPLRESIVCYFMVFL	20	0.1
EBNA1_80	Sigma Aldrich	LRESIVCYFMVFLQTHIFAE	20	0.1
EBNA1_81	Sigma Aldrich	YFMVFLQTHIFAEVLKDAIK	20	0.1
EBNA1_82	Sigma Aldrich	THIFAEVLKDAIKDLVMTKP	20	0.1
EBNA1_83	Sigma Aldrich	LKDAIKDLVMTKPAPTCNIR	20	0.1
EBNA1_84	Sigma Aldrich	LVMTKPAPTCNIRVTVCSFD	20	0.1
EBNA1_85	Sigma Aldrich	PTCNIRVTVCSFDDGVDLPP	20	0.1
EBNA1_86	Sigma Aldrich	TVCSFDDGVDLPPWFPPMVE	20	0.1
EBNA1_87	Sigma Aldrich	GVDLPPWFPPMVEGAAAEGD	20	0.1
EBNA1_88	Sigma Aldrich	FPPMVEGAAAEGDDGDGDE	20	0.1
EBNA1_89	Sigma Aldrich	AAAEGDDGDGDEGGDGDEG	20	0.1
EBNA1_90	Sigma Aldrich	GDDGDEGGDGDEGEEGQE	18	0.1
BILF1_1	Genscript	LSTMAPGSTVGTLVANMTSV	20	0.1
BILF1_4	Genscript	ATEDACTKSYSAFLSGMTSL	20	0.1
BILF1_6	Genscript	SGMTSLLLLVLLILLTLAGIL	20	0.1
BILF1_7	Genscript	LVLLILLLTLAGILFIIFVRK	20	0.1
BILF1_8	Genscript	TLAGILFIIFVRKLVHRMDV	20	0.1
BILF1_9	Genscript	IIFVRKLVHRMDVWLIALLI	20	0.1
BILF1_10	Genscript	VHRMDVWLIALLIELLLWVL	20	0.1
BILF1_12	Genscript	LLLWVLGKMIQEFSSTGLCL	20	0.1
BILF1_13	Genscript	KMIQEFSSTGLCLLTQNMMF	20	0.1
BILF1_14	Genscript	STGLCLLTQNMMFLGLMCSV	20	0.1
BILF1_15	Genscript	TQNMMFLGLMCSVWTHLGMA	20	0.1
BILF1_16	Genscript	GLMCSVWTHLGMALEKTLAL	20	0.1
BILF1_17	Genscript	THLGMALEKTLALFSRTPKR	20	0.1
BILF1_18	Genscript	EKTLALFSRTPKRTSHRNVC	20	0.1
BILF1_19	Genscript	SRTPKRTSHRNVCLYLMGVF	20	0.1
BILF1_23	Genscript	ILLITMGPDANLNRGPNMCR	20	0.1
BILF1_24	Genscript	PDANLNRGPNMCREGPTKGM	20	0.1
BILF1_25	Genscript	GPNMCREGPTKGMHTAVQGL	20	0.1
BILF1_26	Genscript	GPTKGMHTAVQGLKAGCYLL	20	0.1
BILF1_30	Genscript	TVLIIWKLLRKTKPGRKPRLI	20	0.1
BILF1_31	Genscript	LLRTKFGRKPRLICNVTFTG	20	0.1
BILF1_32	Genscript	RKPRLICNVTFTGLICAFSW	20	0.1
BILF1_34	Genscript	ICAFSWFMLSLPLLFLGEAG	20	0.1
BILF1_35	Genscript	MLSLPLLFLGEAGSLGFDCT	20	0.1
BILF1_36	Genscript	FLGEAGSLGFDCTESLVARY	20	0.1
BILF1_37	Genscript	LGFDCTESLVARYTPGPAAC	20	0.1
BILF1_41	Genscript	YAWSFSHPMDSLKNQVTVTA	20	0.1
BILF1_42	Genscript	FMDSLKNQVTVTARYFRRVP	20	0.1
BILF1_43	Genscript	QVTVTARYFRRVPSQST	17	0.1
LMP1_1	Genscript	MEHDLERGPPQPRRPPRGPP	20	0.1
LMP1_2	Genscript	GPPQPRRPPRGPPLSSSLGL	20	0.1
LMP1_6	Genscript	LLFWLYIVMSDWTGGALLVL	20	0.1
LMP1_7	Genscript	VMSDWTGGALLVLYSFALML	20	0.1
LMP1_11	Genscript	IFRRDLLCPLGALCILLLMI	20	0.1
LMP1_13	Genscript	ILLLMITLLILALWNLHQQA	20	0.1
LMP1_18	Genscript	LGIWIYLLEMLWRLGATIWQ	20	0.1
LMP1_19	Genscript	LEMLWRLGATIWQLLAFFLA	20	0.1
LMP1_23	Genscript	IIALYLQQNWWTLLVDLLWL	20	0.1
LMP1_25	Genscript	VDLLWLLLFLAILIWMYHG	20	0.1
LMP1_26	Genscript	LFLAILIWMYHGQRHSDEH	20	0.1
LMP1_27	Genscript	WMYHGQRHSDEHHHDDSLP	20	0.1
LMP1_28	Genscript	RHSDEHHHDDSLPHPQQATD	20	0.1
LMP1_29	Genscript	HDDSLPHPQQATDDSGHESD	20	0.1
LMP1_30	Genscript	PQQATDDSGHESDSNSNEGR	20	0.1
LMP1_31	Genscript	SGHESDSNSNEGRHHLLVSG	20	0.1
LMP1_32	Genscript	NSNEGRHHLLVSGAGDGPPL	20	0.1
LMP1_33	Genscript	HLLVSGAGDGPPLCSQNLGA	20	0.1
LMP1_34	Genscript	GDGPPLCSQNLGAPGGGPDN	20	0.1
LMP1_35	Genscript	SQNLGAPGGGPDNGPQDPDN	20	0.1
LMP1_36	Genscript	GGGPDNGPQDPDNTDDNGPQ	20	0.1
LMP1_37	Genscript	PQDPDNTDDNGPQDPDNTDD	20	0.1
LMP1_38	Genscript	DDNGPQDPDNTDDNGPHDPL	20	0.1
LMP1_39	Genscript	PDNTDDNGPHDPLPQDPDNT	20	0.1
LMP1_40	Genscript	GPHDPLPQDPDNTDDNGPQD	20	0.1
LMP1_42	Genscript	DNGPQDPDNTDDNGPHDPLP	20	0.1
LMP1_43	Genscript	DNTDDNGPHDPLPHSPSDSA	20	0.1
LMP1_44	Genscript	PHDPLPHSPSDSAGNDGGPP	20	0.1
LMP1_45	Genscript	SPSDSAGNDGGPPQLTEEVE	20	0.1
LMP1_46	Genscript	NDGGPPQLTEEVENKGDQG	20	0.1
LMP1_47	Genscript	LTEEVENKGDQGPPLMTDG	20	0.1
LMP1_48	Genscript	KGDQGPPLMTDGGGHSHD	20	0.1
LMP1_49	Genscript	PLMTDGGGHSHDSGHGGD	20	0.1
LMP1_50	Genscript	GGHSHDSGHGGDPHLPTLL	20	0.1
LMP1_51	Genscript	GHGGDPHLPTLLLGSSGSG	20	0.1
LMP1_52	Genscript	HLPTLLLGSSGSGGDDDDPH	20	0.1
LMP1_53	Genscript	GSSGSGGDDDDPHGPVQLSY	20	0.1
LMP1_54	Genscript	DDDDPHGPVQLSYYD	15	0.1
LMP2_1	Genscript	MGSLEMVPMGAGPPSPGGDP	20	0.1
LMP2_2	Genscript	PMGAGPPSPGGDPDGYDGGN	20	0.1
LMP2_3	Genscript	SPGGDPDGYDGGNNSQYPSA	20	0.1
LMP2_4	Genscript	GYDGGNNSQYPSASGSSGNT	20	0.1
LMP2_5	Genscript	SQYPSASGSSGNTPTPNDE	20	0.1
LMP2_6	Genscript	GSSGNTPTPNDEERESNEE	20	0.1
LMP2_7	Genscript	TPPNDEERESNEEPPPYED	20	0.1
LMP2_8	Genscript	RESNEEPPPYEDPYWGNGD	20	0.1
LMP2_9	Genscript	PPPYEDPYWGNGDRHSDYQP	20	0.1
LMP2_10	Genscript	YWGNGDRHSDYQPLQTQDQS	20	0.1
LMP2_11	Genscript	HSDYQPLQTQDQSLYLGLQH	20	0.1
LMP2_12	Genscript	GTQDQSLYLGLQHDGNDGLP	20	0.1
LMP2_13	Genscript	YLGLQHDGNDGLPPPPYSPR	20	0.1
LMP2_14	Genscript	GNDGLPPPPYSPRDDSSQHI	20	0.1
LMP2_15	Genscript	PPYSPRDDSSQHIYEEAGRG	20	0.1
LMP2_16	Genscript	DSSQHIYEEAGRGSMNPVCL	20	0.1
LMP2_17	Genscript	EEAGRGSMNPVCLPVIVAPY	20	0.1
LMP2_18	Genscript	MNPVCLPVIVAPYLFWLAAI	20	0.1
LMP2_19	Genscript	VIVAPYLFWLAAIAASCFTA	20	0.1
LMP2_23	Genscript	TGLALSLLLLAAVASSYAAA	20	0.1
LMP2_24	Genscript	LLLAAVASSYAAAQRKLLTP	20	0.1
LMP2_25	Genscript	SSYAAAQRKLLTPVTVLTAV	20	0.1
LMP2_26	Genscript	RKLLTPVTVLTAVVTFFAIC	20	0.1
LMP2_28	Genscript	TFFAICLTWRIEDPPFNSLL	20	0.1
LMP2_29	Genscript	TWRIEDPPFNSLLFALLAAA	20	0.1
LMP2_30	Genscript	PFNSLLFALLAAAGLQGIY	20	0.1
LMP2_33	Genscript	LVMLVLLILAYRRRWRRLTV	20	0.1
LMP2_34	Genscript	ILAYRRRWRRLTVCGGIMFL	20	0.1
LMP2_38	Genscript	DAVLQLSPLLGAVTVVSMTL	20	0.1
LMP2_39	Genscript	PLLGAVTVVSMTLLLLAFVL	20	0.1
LMP2_40	Genscript	VVSMTLLLLAFVLWLSSPGG	20	0.1
LMP2_41	Genscript	LLAFVLWLSSPGGLGTLGAA	20	0.1
LMP2_42	Genscript	LSSPGGLGTLGAALLTLAAA	20	0.1
LMP2_44	Genscript	LTLAAALALLASLILGTLNL	20	0.1
LMP2_46	Genscript	LGTLNLTTMFLLMLLWTLVV	20	0.1
LMP2_48	Genscript	LWTLVVLLICSSCSSCPLSK	20	0.1
LMP2_49	Genscript	LICSSCSSCPLSKILLARLF	20	0.1
LMP2_50	Genscript	SCPLSKILLARLFLYALALL	20	0.1
LMP2_51	Genscript	LLARLFLYALALLLASALI	20	0.1
LMP2_53	Genscript	LASALIAGGSILQTNFKSLS	20	0.1
LMP2_54	Genscript	GGSILQTNFKSLSSTEFIPN	20	0.1
LMP2_55	Genscript	NFKSLSSTEFIPNLFCMLLL	20	0.1
LMP2_58	Genscript	VAGILFILAILTEWGSGNRT	20	0.1
LMP2_59	Genscript	LAILTEWGSGNRTYGPVFMC	20	0.1
LMP2_60	Genscript	GSGNRTYGPVFMCLGGLLTM	20	0.1
LMP2_61	Genscript	GPVFMCLGGLLTMVAGAVWL	20	0.1
LMP2_62	Genscript	GGLLTMVAGAVWLTVNSNTL	20	0.1
LMP2_63	Genscript	AGAVWLTVNSNTTLSAWILT	20	0.1
LMP2_68	Genscript	IRCCRYCCYYCLTLESEERP	20	0.1
LMP2_69	Genscript	CYYCLTLESEERPPTPYRNTV	21	0.1
BZLF1_1	Genscript	MMDPNSTSEDVKFTPDPYQV	20	0.1
BZLF1_2	Genscript	SEDVKFTPDPYQVPFVQAFD	20	0.1
BZLF1_3	Genscript	PDPYQVPFVQAFDQATRVYQ	20	0.1
BZLF1_4	Genscript	FVQAFDQATRVYQDLGGPSQ	20	0.1
BZLF1_5	Genscript	ATRVYQDLGGPSQAPLPCVL	20	0.1
BZLF1_6	Genscript	LGGPSQAPLPCVLMPVLPEP	20	0.1
BZLF1_7	Genscript	PLPCVLMPVLPEPLPQGQLT	20	0.1
BZLF1_8	Genscript	PVLPEPLPQGQLTAYHVSTA	20	0.1
BZLF1_9	Genscript	PQGQLTAYHVSTAPTGSWFS	20	0.1
BZLF1_10	Genscript	YHVSTAPTGSWFSAPQPAPE	20	0.1
BZLF1_11	Genscript	TGSWFSAPQPAPEPAYQAYA	20	0.1
BZLF1_12	Genscript	PQPAPENAYQAYAAPQLFPV	20	0.1
BZLF1_13	Genscript	AYQAYAAPQLFPVSDITQNQ	20	0.1
BZLF1_14	Genscript	PQLFPVSDITQNQQTNQAGG	20	0.1
BZLF1_15	Genscript	DITQNQQTNQAGGEAPQPGD	20	0.1
BZLF1_16	Genscript	TNQAGGEAPQPGDNSTVQTA	20	0.1
BZLF1_17	Genscript	APQPGDNSTVQTAAAVVFAC	20	0.1
BZLF1_18	Genscript	STVQTAAAVVFACPGANQGQ	20	0.1
BZLF1_19	Genscript	AVVFACPGANQGQQLADIGV	20	0.1
BZLF1_20	Genscript	GANQGQQLADIGVPQPAPVA	20	0.1
BZLF1_21	Genscript	LADIGVPQPAPVAAPARRTR	20	0.1
BZLF1_22	Genscript	QPAPVAAPARRTRKPQQPES	20	0.1
BZLF1_23	Genscript	PARRTRKPQQPESLEECDSE	20	0.1
BZLF1_24	Genscript	PQQPESLEECDSELEIKRYK	20	0.1
BZLF1_25	Genscript	EECDSELEIKRYKNRVASRK	20	0.1
BZLF1_26	Genscript	EIKRYKNRVASRKCRAKFKQ	20	0.1
BZLF1_27	Genscript	RVASRKCRAKFKQLLQHYRE	20	0.1
BZLF1_28	Genscript	RAKFKQLLQHYREVAAAKSS	20	0.1
BZLF1_29	Genscript	LQHYREVAAAKSSENDRLRL	20	0.1
BZLF1_30	Genscript	AAAKSSENDRLRLLLKQMCP	20	0.1
BZLF1_31	Genscript	NDRLRLLLKQMCPSLDVDSI	20	0.1
BZLF1_32	Genscript	LKQMCPSLDVDSIIPRTPDV	20	0.1
BZLF1_33	Genscript	LDVDSIIPRTPDVLHEDLLNF	21	0.1

Supplementary Table 3. Viral peptides.

Supplementary Table 4

Protein Antigen	Name in Figure	Name in Suppl. Figure	Product Name	Company	catalogue #	Lot #	residues	source	ug/ul
GlialCAM ECD	GlialCAM_ECD	GlialCAM_ECD_A	HEPACAM Protein, Human, Recombinant (ECD, His Tag)	SINO Biological	16047-H08H	LC10JL2808	AA34-240	HEK293	0.10
GlialCAM ECD	GlialCAM_ECD	GlialCAM_ECD_B	Recombinant Human HEPACAM protein	Abcam	ab151670	GR3329367-1	AA34-240	Hek293	0.10
GlialCAM ECD	GlialCAM_ECD	GlialCAM_ECD_C	Recombinant Human Hepacam	Sino Biological	16047-H08H	LC10FE2908	AA1-240	Hek293	0.10
GlialCAM ECD	GlialCAM_ECD	GlialCAM_ECD_D	Recombinant Human HEPACAM protein	Abcam	AB151670	GR3241122-1	AA34-240	Hek293	0.10
GlialCAM ICD	GlialCAM_ICD	GlialCAM_ICD_A	Hepacam intracellular region, self expression	self		batch 1	AA262-416	E. Coli	0.10
GlialCAM ICD	GlialCAM_ICD	GlialCAM_ICD_C	Hepacam intracellular region, self expression	self		batch 2	AA262-416	E. Coli	0.10
Hepacam full-length	Hepacam full-length	GlialCAM_Full_Length	HEPACAM (NM_152722) Human Recombinant Protein	OriGene	TP323693	WX02C25F	AA1-416	HEK293T	0.10

Peptide Antigen	Name in Figure	Name in Suppl. Figure	AA Sequence	Company	Peptide Length	ug/ul
GlialCAM_p315-334		GlialCAM_p315-334	DKDSPETEENPAPEPRSATE	Sigma Aldrich	20	0.10
GlialCAM_p320-339		GlialCAM_p320-339	ETEENPAPEPRSATEPGPPG	Sigma Aldrich	20	0.10
GlialCAM_p321-340		GlialCAM_p321-340	TEENPAPEPRSATEPGPPGY	Sigma Aldrich	20	0.10
GlialCAM_p327-346		GlialCAM_p327-346_A	PEPRSATEPGPPGYSVSPAV	Sigma Aldrich	20	0.10
GlialCAM_p327-346		GlialCAM_p327-346_B	PEPRSATEPGPPGYSVSPAV	Sigma Aldrich	20	0.10
GlialCAM_p333-352		GlialCAM_p333-352	TEPGPPGYSVSPAVPGRSPG	Sigma Aldrich	20	0.10
GlialCAM_p334-353		GlialCAM_p334-353_A	EPGPPGYSVSPAVPGRSPGL	Sigma Aldrich	20	0.10
GlialCAM_p334-353		GlialCAM_p334-353_B	EPGPPGYSVSPAVPGRSPGL	Sigma Aldrich	20	0.10
GlialCAM_p340-359		GlialCAM_p340-359	YSVSPAVPGRSPGLPIRSAR	Sigma Aldrich	20	0.10
GlialCAM_p341-360	GlialCAM_p341-360	GlialCAM_p341-360	SVSPAVPGRSPGLPIRSARR	Sigma Aldrich	20	0.10
GlialCAM_p346-365		GlialCAM_p346-365	VPGRSPGLPIRSARRYPRSP	Sigma Aldrich	20	0.10
GlialCAM_p348-367		GlialCAM_p348-367	GRSPGLPIRSARRYPRSPAR	Sigma Aldrich	20	0.10
GlialCAM_p352-371		GlialCAM_p352-371	GLPIRSARRYPRSPARSPAT	Sigma Aldrich	20	0.10
GlialCAM_p355-374		GlialCAM_p355-374	IRSARRYPRSPARSPATGRT	Sigma Aldrich	20	0.10
GlialCAM_p358-377		GlialCAM_p358-377	ARRYPRSPARSPATGRTHSS	Sigma Aldrich	20	0.10
GlialCAM_p362_381		GlialCAM_p362_381	PRSPARSPATGRTHSSPPRA	Sigma Aldrich	20	0.10
GlialCAM_p364-383		GlialCAM_p364-383	SPARSPATGRTHSSPPRAPS	Sigma Aldrich	20	0.10
GlialCAM_p369-388	GlialCAM_p369-388	GlialCAM_p369-388_A	PATGRTHSSPPRAPSSPGRS	Sigma Aldrich	20	0.10
GlialCAM_p369-388	GlialCAM_p369-388	GlialCAM_p369-388_B	ATGRTHSSPPRAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p370-389		GlialCAM_p370-389_A	ATGRTHSSPPRAPSSPGRSR	Genscript	20	0.10
GlialCAM_p370-389		GlialCAM_p370-389_B	ATGRTHSSPPRAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p370-389		GlialCAM_p370-389_C	ATGRTHSSPPRAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p376-395		GlialCAM_p376-395_A	SSPPRAPSSPGRSRSASRTL	Sigma Aldrich	20	0.10
GlialCAM_p376-395		GlialCAM_p376-395_B	SSPPRAPSSPGRSRSASRTL	Sigma Aldrich	20	0.10
GlialCAM_p378-389		GlialCAM_p378-389	PPRAPSSPGRSR	Genscript	12	0.10
GlialCAM_p382-401	GlialCAM_p382-401	GlialCAM_p382-401	PSSPGRSRSASRTLRTAGVH	Sigma Aldrich	20	0.10
GlialCAM_p383-402		GlialCAM_p383-402	SSPGRSRSASRTLRTAGVHI	Sigma Aldrich	20	0.10
GlialCAM_p369-388_Cit380		GlialCAM_p369-388_Cit380	ATGRTHSSPPRcAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p369-388_Cit387		GlialCAM_p369-388_Cit387	ATGRTHSSPPRAPSSPGRcSR	Sigma Aldrich	20	0.10
GlialCAM_p369-388_Cit373		GlialCAM_p369-388_Cit373	ATGRcTHSSPPRAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p369-388_Cit373/380		GlialCAM_p369-388_Cit373/380	ATGRcTHSSPPRcAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p369-388_Cit373/380/387		GlialCAM_p369-388_Cit373/380/387	ATGRcTHSSPPRcAPSSPGRcSR	Sigma Aldrich	20	0.10
GlialCAM_p370-389_pSer383/384		GlialCAM_p370-389_pSer383/384	ATGRTHSSPPRAPSpSpPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p370-389_pSer376	GlialCAM_p370-389_pSer376	GlialCAM_p370-389_pSer376	ATGRTHSpSPPRAPSSPGRSR	Genscript	20	0.10
GlialCAM_p370-389_pSer376/377	GlialCAM_p370-389_pSer376/377	GlialCAM_p370-389_pSer376/377_A	ATGRTHSpSpPPRAPSSPGRSR	Sigma Aldrich	20	0.10
GlialCAM_p370-389_pSer376/377	GlialCAM_p370-389_pSer376/377	GlialCAM_p370-389_pSer376/377_B	ATGRTHSpSpPPRAPSSPGRSR	Genscript	20	0.10
GlialCAM_p370-389_pSer377	GlialCAM_p370-389_pSer377	GlialCAM_p370-389_pSer377	ATGRTHSSpPPRAPSSPGRSR	Genscript	20	0.10
GlialCAM_p370-389_pSer377/383		GlialCAM_p370-389_pSer377/383	ATGRTHSSpPPRAPSpSPGRSR	Genscript	20	0.10

Supplementary Table 4. GlialCAM proteins and peptides.

Supplementary Table 5

Crystallographic data collection and refinement statistics

EBNA1 peptide 386-405/MS39p2w174 Fab	
Data collection	
Beamline	SSRL BL12-2
Wavelength (Å)	0.97946
Space group	I222
Cell dimensions	
a, *b*, *c* (Å)	119.66, 137.56, 179.00
α, β, γ (°)	90.00, 90.00, 90.00
Matthews coefficient (Å^3/Da)[a]	3.7
Solvent content (%)	66.8
Anisotropy	0.72
Resolution (Å)[b]	45.14(2.19)
R_{merge}[c]	0.16(5.92)
$I / \sigma I$ ratio[d]	5.5(0.7)
Uncorrected completeness (%)[e,f]	96.1(78.0)
Spherical completeness (%)[g]	54.7(13.1)
Ellipsoidal completeness (%)[h]	92.5(72.4)
Reflections (total/unique)	51,233(3,637)
Redundancy[j]	3.2(2.0)
Refinement	
Resolution (Å)	45.14-2.50
No. reflections/test set	36,574/1,912
R_{work} / R_{free}[k]	21.1/25.2
Mean B value (Å^2)	56.4
F_{obs}-F_{calc} correlation[l]	0.90
No. atoms	
Protein	6,778
Ligand/ion	4 glycerol/1 chlorine
Water	24
B-factors	
Protein	46 (overall)
Ligand/ion	73 (glycerol)/45 (chlorine)
Water	52
Ramachandran statistics[m]	
Most favored/allowed regions (%)	100
Disallowed regions (%)	0
R.m.s. deviations	
Bond lengths (Å)	0.33
Bond angles (°)	0.55

[a]Ratio of the volume of the asymmetric unit to the molecular weight of all protein in the asymmetric unit
[b]Value in parentheses is for the highest-resolution shell: 2.24 – 2.19 Å.
[c]Reliability factor for symmetry-related reflections calculated as: $R_{merge} = \Sigma_{hkl} \Sigma j=1 \text{ to } N \mid I_{hkl} - I_{hkl}(j) \mid / \Sigma_{hkl} \Sigma j=1 \text{ to } N I_{hkl}(j)$, where N is the redundancy of the data. In parentheses, the cumulative value at the highest-resolution shell
[d]Ratio of mean intensity to the mean standard deviation of the intensity over the entire resolution range
[e]Fraction of measured reflections to possible observations at the resolution range
[f]Completeness of the uncorrected data set
[g]Completeness within the sphere that contains the ellipsoid, after removing reflections outside of the ellipsoid
[h]The amount of expected reflections within the ellipsoid that are actually measured

[j]Number of measurements of individual, symmetry unique reflections
[k]Average deviation between the observed and calculated structure factors calculated as: $R_{work} = \Sigma_{hkl} ||F_{obs}| - |F_{calc}|| / \Sigma_{hkl} |F_{obs}|$, where the F_{obs} and F_{calc} are the observed and calculated structure factor amplitudes of reflection hkl. R_{free} is equal to R_{factor} but for a randomly selected 5.0 % subset of the total reflections that were held aside throughout refinement for cross-validation
[l]Correlation coefficient between observed and calculated structure factor amplitudes
[m]According to Molprobity for non-proline and non-glycine residues

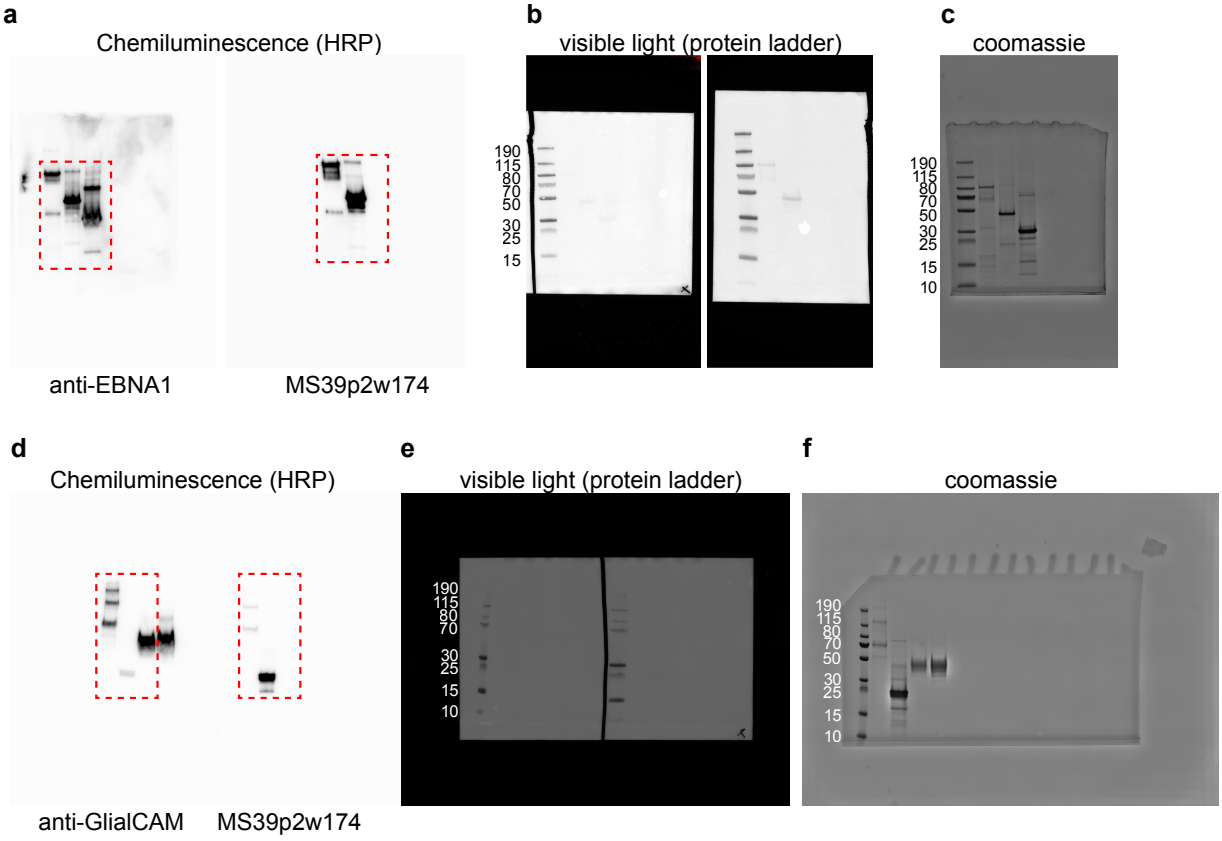
Supplementary Table 5. Crystallographic data and refinement statistics.

Supplementary Table 6

antibody	ligand	KD (M)	KD Error	kon ($M^{-1}*s^{-1}$)	kon Error	koff (s^{-1})	koff Error	*n*
MS39p2w174	EBNA1 protein	1.99E-09	6.25E-10	4.07E+04	1.61E+04	7.32E-05	1.06E-05	4
MS39p2w174 germline	EBNA1 protein	4.19E-09	7.62E-10	2.94E+04	1.65E+04	1.14E-04	4.53E-05	4
MS39p2w174	GlialCAM protein	1.91E-10	1.73E-11	2.61E+05	5.01E+04	5.00E-05	1.21E-05	3
MS39p2w174 germline	GlialCAM protein	1.05E-08	4.12E-09	4.28E+04	1.39E+04	4.12E-04	4.79E-05	3
MS39p2w174	EBNA1 AA386-405	2.67E-09	7.83E-11	2.40E+05	5.28E+03	6.40E-04	1.24E-05	4
MS39p2w174	GlialCAM AA370-389	3.02E-07	3.10E-08	7.15E+04	6.39E+03	2.16E-02	1.09E-03	4
MS39p2w174	GlialCAM AA370-389 pSer376	6.10E-09	2.69E-10	2.80E+05	1.10E+04	1.71E-03	3.40E-05	4
MS39p2w174	GlialCAM AA370-389 pSer376/377	3.73E-09	1.50E-10	3.23E+05	1.14E+04	1.20E-03	2.33E-05	4

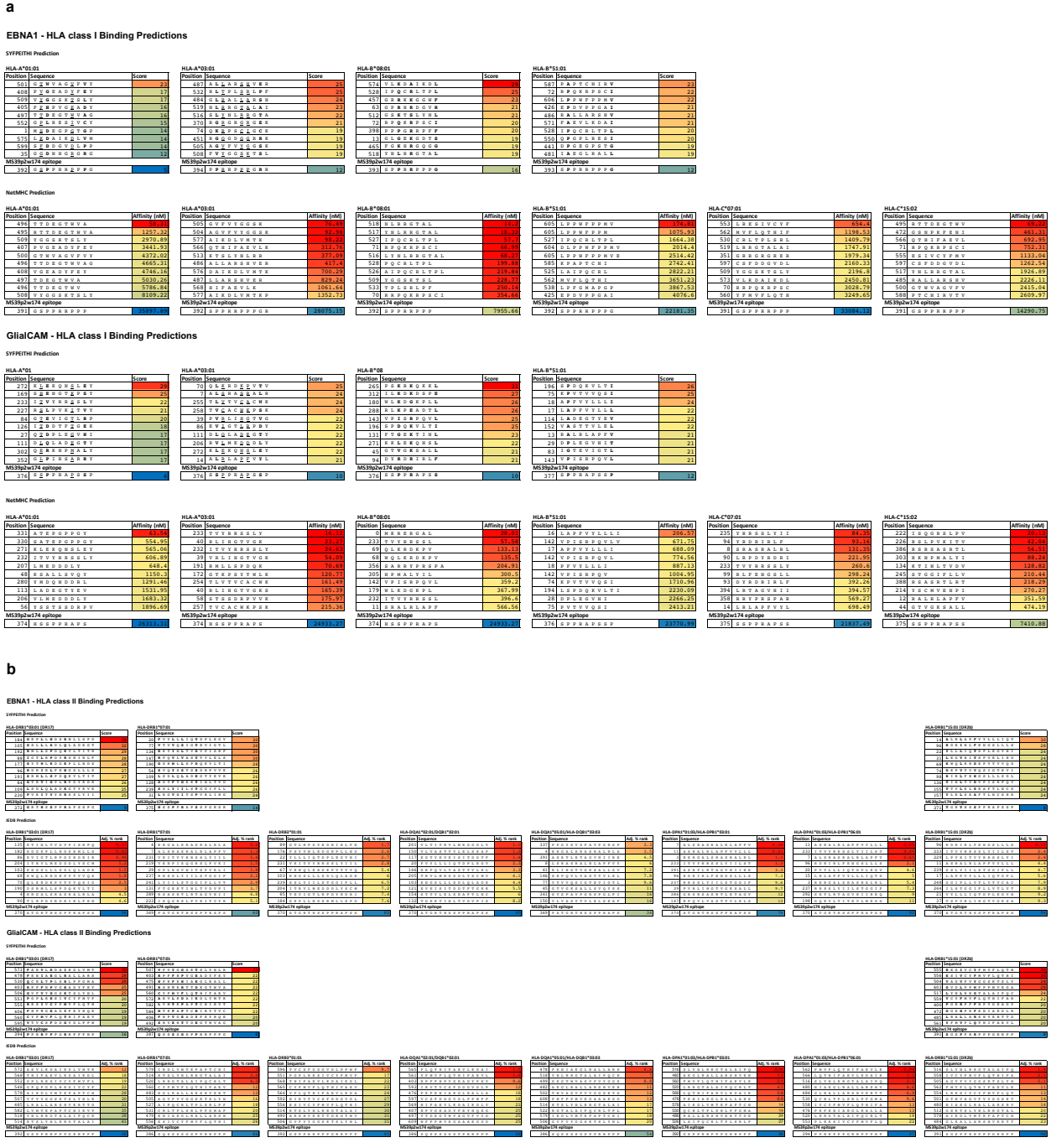
Supplementary Table 6. K_D, K_{on}, and K_{off} values for antibody-ligand pairs. Values correspond to **Fig. 2 k**,**l** (MS39p2w174 and Germline with EBNA1 protein), **Fig. 3 e**,**f** (MS39p2w174 and Germline with GlialCAM protein), and **Fig. 3 k**,**l** (MS39p2w174 with EBNA1 AA386-405, GlialCAM AA370-389, and phosphorylated GlialCAM AA370-389). Measurements are representative of at least 3 independent experiments. Values are averages of n replicate measurements in serial dilutions.

Supplementary Figure 1



Supplementary Figure 1. Raw western blot images. **a-c**, recombinant EBNA1 proteins (full-length, AA328-641, and AA408-641), corresponding to (**Fig. 2c**). **d-f**, recombinant GlialCAM proteins (full-length, ICD, and ECD), corresponding to (**Fig. 3c**). Recombinant proteins were run on three separate blots, stained with commercial anti-EBNA1 or anti-GlialCAM (**a**,**d**, left), MS39p2w174 (**a**,**d**, right), and coomassie (**c**,**f**). Red frames: cropped images used for figures.

Supplementary Figure 2.



Supplementary Figure 2. HLA binding prediction. **a**, HLA class 1 prediction and **b**, HLA class 2 prediction, each for EBNA1 peptides (top) and GlialCAM peptides (bottom). Algorithms SYFPEITHI, NetMHC, and IEDB were used. HLA genetic setup of patient MS39 was investigated as well as HLA-DRB1*15:01. Top 10 binding peptides for each protein on each allele are shown as well as the respective top peptide containing the MS39p2w174-binding epitope, together with the respective score of each prediction algorithm.

Supplementary Discussion

Patient collective and MS diagnosis

As mentioned in the main manuscript, all MS patients included in this study cohort were selected for CSF pleocytoses above 10 cells / µl. This selection was made due to technical considerations, as single-cell B cell sorting and sequencing became increasingly challenging below a threshold of 5 cells / µl and yielded significantly more BCR sequences above 10 cells / µl. CSF volumes ranged from 5-15 mL per patient. When selecting patients with high pleocytosis, we were aware of the possible misdiagnosis of neuromyelitis optica spectrum disorders (NMOSD). Special care was taken to follow the current McDonald criteria for the diagnosis of MS[1,2]. None of the patients met the diagnostic criteria for NMOSD, in particular spinal lesions spanning ≥3 segments[3]. Patients were tested for antibodies against aquaporin-4 and MOG and showed negative results. Patient MS37, who showed the highest pleocytosis of 57 cells / µl, had a spinal lesion spanning one segment in addition to several small subventricular contrast enhancing lesions. In order to avoid a misdiagnosis, her serum (and CSF) were tested repeatedly and in different laboratories for anti-aquaporin-4 and anti-MOG antibodies and always tested negative. Considering all symptoms and laboratory results, the patient did not meet criteria of NMOSD and the MS diagnosis remained. Of note, patient MS39, from whom antibody MS39p2w174 was selected, possessed 18 cells / µl, which was in the middle of the range of CSF cell counts (Extended Data Table 1).

HLA phenotype and HLA binding prediction

While our manuscript focuses on B cell biology and antibody-mediated molecular mimicry, we briefly discuss our data on human and mouse T cell reactivity against EBNA1 and GlialCAM (Extended Data Fig. 10). Patients' HLA genotypes could profoundly influence T cell reactivity to either antigen. We should point out that patient MS39, from whom antibody MS39p2w174 originated, is not a carrier of the most significant MS risk allele HLA-DRB1*15:01 (Supplementary Table 1). The patient carries HLA-DRB1*03:01, a second HLA class II risk allele for MS with lower significance. The patient did not carry any of the protective HLA class I alleles (HLA-A*02:01, HLA-B*44:02, HLA-B*38:01 and HLA-B*55:01)[4,5]. We used the prediction tools SYFPEITHI, NetMHC, and IEDB to predict binding of EBNA1 and GlialCAM peptides to the patient's molecular HLA setup, and included the main MS risk allele HLA-DRB1*15:01 (Supplementary Fig. 2). We listed the 10 highest binding peptides of EBNA1 and GlialCAM for each HLA allele as well as the highest prediction for a peptide containing the central binding motifs of antibody MS39p2w174 ($EBNA1_{AA394\text{-}400}$ and $GlialCAM_{AA377\text{-}383}$). These motifs were not predicted to presented particularly well on either HLA class I or HLA class II and were never amongst the top 10 predicted binders. However, multiple other regions of both proteins are predicted to be presented well on several alleles, with GlialCAM peptides binding slightly better to HLA class I alleles (Supplementary Fig. 2a) and EBNA1 peptides binding slightly better to HLA class II alleles (Supplementary Fig. 2b). Peptides of both proteins can be presented well on HLA-DRB1*15:01, but only EBNA1 binds tightly to HLA-DRB1*03:01. Presentation of EBNA1 on HLA-DRB1*15:01 and HLA-DRB1*03:01 might be part of the explanation how these alleles contribute to MS risk.

References

1. Thompson, A. J. *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* **17**, 162–173 (2018).
2. Polman, C. H. *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* **69**, 292–302 (2011).
3. Wingerchuk, D. M. *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* **85**, 177–189 (2015).
4. Moutsianas, L. *et al.* Class II HLA interactions modulate genetic risk for multiple sclerosis. *Nat. Genet.* **47**, 1107–1113 (2015).
5. de la Concha, E. G. *et al.* DRB1*03:01 haplotypes: differential contribution to multiple sclerosis risk and specific association with the presence of intrathecal IgM bands. *PLoS One* **7**, e31018 (2012).