

Co-stimulatory and immune checkpoint molecules are important in the tumor microenvironment of Hodgkin-like adult T-cell leukemia/lymphoma

Mai Takeuchi,¹ Hiroaki Miyoshi,¹ Yuichiro Semba,² Kyohei Yamada,¹ Kazutaka Nakashima,¹ Kensaku Sato,¹ Takuya Furuta,¹ Mayuko Moritsubo,¹ Yusuke Ogura,¹ Ken Tanaka,¹ Teppei Imamoto,¹ Fumiko Arakawa,¹ Kei Kohno¹ and Koichi Ohshima¹

¹Department of Pathology, Kurume University School of Medicine and ²Department of Medicine and Biosystemic Science, Kyusyu University Faculty of Medicine, Fukuoka city, Fukuoka, Japan

Correspondence:

K. OHSHIMA - ohshima_kouichi@med.kurume-u.ac.jp

<https://doi.org/10.3324/haematol.2023.283163>

Table S1. Antibodies used in DSP and IHC

Targets	Methods	Clones	Dilution	Manufactures
CD30	DSP	Ber-H2	1:10	Cell Marque, Darmstadt, Germany
CD4	DSP	EPR6855	1:100	Abcam, Cambridge, UK
CD30	IHC	Ber-H2	1:100	DAKO, Glostrup, Denmark
CD4	IHC	EPR6855	1:500	Abcam, Cambridge, UK
PAX5	IHC	1EW	1:50	Leica Biosystems, Nussloch, Germany
MHC class I	IHC	EMR8-5	1:5,000	Abcam, Cambridge, UK
MHC class II	IHC	CR3/34 M0775	1:500	DAKO, Glostrup, Denmark
CD28	IHC	EPR00276	1:200	Abcam, Cambridge, UK
ICOS	IHC	D1K2T	1:50	Cell Signaling Technology, Danvers, MA, USA
TIGIT	IHC	BLR047F	1:200	Abcam, Cambridge, UK
PD-1	IHC	NAT105	1:100	Abcam, Cambridge, UK
LAG-3	IHC	11E3	1:200	Abcam, Cambridge, UK
CD80	IHC	EPR1157(2)	1:200	Abcam, Cambridge, UK
CD86	IHC	E2G8P	1:200	Cell Signaling Technology, Danvers, MA, USA

DSP, digital spatial profiling; IHC, immunohistochemistry; PAX5, paired box 5; MHC, major histocompatibility complex; ICOS, inducible T cell stimulator; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; PD-1, programmed cell death-1; LAG-3 (clone 11E3, 1:200; Abcam).

Table S2. Significantly upregulated genes in CD4+ T cell rosettes

AARS	ATP2A5	CCDC184	CNOT9	ELK4	FUT11	HNRNPCL3	KLECD4	MCTP1	NUP98CL	PM2B	RIN3	SLC22A4	STNGB4	TRAF6	WDR66
ABHD11A	ATP9V1G1	CDC800	CNR1	ELMOD5	FXR2	HOLA1	KLEDC8B	MCU	NUPR1	POFUT9	RIPOR2	SLC3A5	STYCG2	TRAF6	WDR7C1
ABYTRAM	ATXN1	CDC68	COA5	ELF3	FYB1	HOK3B	KLHL32	MDPC	NUMBP	POGLUT9	REY1	SLC6A5	STYV1	TRAF1	WIPF3
ABLIM1	ATXN1L	CDC89	COG5	EN1	GABARAPL1	HP1B9	KLHL5	MRXN	NUMB2	PCLD4	ENAB1	SLC6A5	TAP1	TRAF3C4	WNT8A
ABTB1	BAGALT5	CDC89	COX2	ENGASE	GAGE1	HPCA	KLRC3	MESP	NVL	POLE1E	END3	SLC6A5	TAP1	TRAF3C4	WNT9B
ACBD5	BAGALT7	COL19	COL5A1	ENHO	GAGE10	HPN	KRPOX4	MESP1	GARD1	POLE2B	ENF1B	SLC6A5	TAP1	TRAF3C4	XZL1
ACSF9	BAGS8	COL5A1	COL5A5	ENTPD1	GALNT15	HPB5	KRT10	METTL5	OGT	POU5F1	ENF149	SLC6A5	TAP1	TRAF3C4	YMEK1
ACSM5	BCL2L1	COL5A1	COL5A1	EPIC1	GAL3	HSPBAP1	KRT19	MMP4	OLFM1L3	PFCS	ENF186	SLC6A5	TAP1	TRAF3C4	YPEL3
ACTA5	BCLAF1	COL5A1	COL5A5	EPST1	GALT	IC05	KRT18	MED14B	OR10C1	PFM1M	ENF187	SLC6A5	TAP1	TRAF3C4	ZEB2
ACTP3	BKRN1	CCNG2	COL4	ERP27	GALT	IDH3	KRTAP10-9	MGA7A	ORBT13	PPP1R1C	ENF206	SLC6A5	TAP1	TRAF3C4	ZBTB41
ADAMTS9	BGN	CCNG2	COL4	EPH2	GARR1	ITF7	KRTAP10-9	MIA5	ORBT14	PPP1R1	ENF207	SLC6A5	TAP1	TRAF3C4	ZBTB44
ADAMT1	BELEB1	CCNB4	CFP2	ETS1	GAST	ITTT1	KRTAP19-9	MEL1	ORBT18	PPP1R1B	EPH2A1	SLC6A5	TAP1	TRAF3C4	ZC3H4Y1
ADCK5	BICD1	CCNB5	CRLL	EYCB	GATAD5B	ITTT2	KRTAP19-4	MLL10	OBAC13	PPP1R1B	EPH2B	SLC6A5	TAP1	TRAF3C4	ZCCHC10
ADG9	BICD2	CCNB5L1	CRBRP	EYB5	GBP1	ITTT3	KRTAP19-4	MLXIP	OBAP4	PPP1R1D	EPH2E1A	SLC6A5	TAP1	TRAF3C4	ZCCHC17
ADGRB1	BICRA	CCND1	CRSTC1	EVL	GRF9	ITPA14	KRTAP19-7	MMP1	OBGQ3	PPP1R1	EPH2F	SLC6A5	TAP1	TRAF3C4	ZCCHC2
ADGRB1	BICRAL	CCND1E	CRGALINACT1	EKOC1L	GPI1	ITPA4	KRTAP19-1	MMP5	OBML1	PRACH1	EPH2G	SLC6A5	TAP1	TRAF3C4	ZCCHC7
ADO	BTD	CCND2	CHES3	EKOC5	GIMAP3	ITPA5	KRTAP19-1	MMP9	OBSD1	PRAP1	EPH2H	SLC6A5	TAP1	TRAF3C4	ZFP3
ADRB4	BTRN	CCND3	CHST2	EKOC6	GIMAP4	ITPA6	KRTAP19-3	MORNS	OBAD3	PRP1	EPH2I	SLC6A5	TAP1	TRAF3C4	ZFP65L
ADRF1	BUMED1	CCND3	CHG9B	EKTL3	GIMAP5	ITPA7	KRTAP19-2	MFRG1	OBAD5	PRM1A1	EPH2J	SLC6A5	TAP1	TRAF3C4	ZFP67
AGAP9	BMP2B	CCND3	CHS2	FAM108A	GIMAP7	ITPA8	LAMA4	MPPH1	OB9	PRKCB	EPH2K	SLC6A5	TAP1	TRAF3C4	ZFP68
AH1	BPIFA5	CCND4	CTC1	FAM117B	GIMAP8	ITPA9	LAMP1	MDFP2D	OSBP	PRKX	EPH2L	SLC6A5	TAP1	TRAF3C4	ZFP69
AIDA	BSD7	CCND4	CTHRC1	FAM138A	GIPC1	ITPA11	LAPTM5	MDFP2E	OSBP2	PRMT7	EPH2M	SLC6A5	TAP1	TRAF3C4	ZFP70
AK3	BSDP1	CCND5	CTBA	FAM138B	GTF2	ITPA12	LARGE1	MBO	OSTM1	PRMT8	EPH2N	SLC6A5	TAP1	TRAF3C4	ZFP71
AKP	BW41	CCND5	CTSS	FAM138B	GK	ITPA13	LAT	MBO1	PRY8	PRPF3	SARAF	SLC6A5	TAP1	TRAF3C4	ZFP72
AKAP1	BSDC1	CCND5	CTSW	FAM138B	GLRL	ITPA14	LRSD	MED	PRY9	PRSS2	SCARF3	SLC6A5	TAP1	TRAF3C4	ZFP73
AKAP17A	HECD19	CCND5	CUL9	FAM138B	GLPFR1	ITPA15	LRSD	MED	PRY9	PRSS2	SCARF3	SLC6A5	TAP1	TRAF3C4	ZFP74
AKNA	BFO1	CCND5	CTC1	FAM138A	GLER	ITPA16	LCK	MSTO1	PAD4	PRY7	SCN3A	SLC6A5	TAP1	TRAF3C4	ZFP75
AKR2A5	BTK	CCND5	CTPD7	FAM138B	GNPDA5	ITPA17	LRSD	MED	PAPAD1B	PRKCI	SCN3A	SLC6A5	TAP1	TRAF3C4	ZFP76
ALG13	BTN2A1	CCND7	CTP4G1	FAM178A	GOLGA1	IL17A	LITRA1	MMD4	PALLD	PERK1	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP77
ALG6	BTN2A5	CCND4	CTE1	FAM180C	GOLGA6A	IL17RA	LRNG1	MED17	PARN	PRSS8	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP78
ALG5	CLIC2B1	CCND5	CTTH1	FASLG	GOLGA6B	IL18EP	LGALS9	MYO2P3	PARP10	PRSS8	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP79
ALPK1	CLIC2F1	CCND5	CTTH4	FBI1	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP80
AM3	CLIC2B2	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP81
AMPD9	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP82
ANAPC5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP83
ANKRD10	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP84
ANKRD44	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP85
ANKRD49	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP86
ANTXR1	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP87
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP88
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP89
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP90
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP91
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP92
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP93
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP94
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP95
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP96
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP97
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP98
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP99
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP100
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP101
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP102
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP103
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP104
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP105
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP106
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP107
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP108
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP109
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP110
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP111
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP112
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP113
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP114
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP115
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP116
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP117
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP118
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP119
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP120
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP121
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP122
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP123
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP124
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP125
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP126
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP127
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP128
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP129
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP130
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP131
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP132
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP133
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP134
AP2A5	CLIC2B1	CCND5	DBP	FBI1B	GOLGA6B	IL19	LRP1L3	MYO1B	PAPPA	PRKRYN	SDCS	SLC6A5	TAP1	TRAF3C4	ZFP135
AP2A5	CLIC2B1	CCND5	DBP	FBI1B											

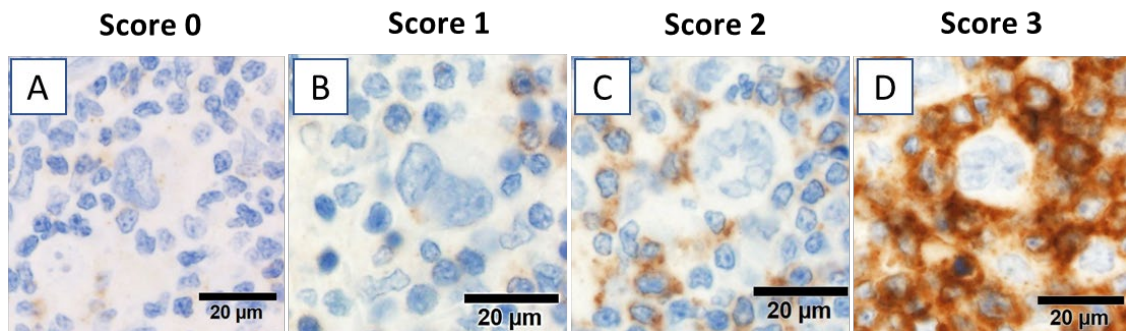


Figure S1. TIGIT scoring system

In the TIGIT scoring system¹, TIGIT expression on lymphocytes is classified into four grades (scores 0–4): no evidence of TIGIT⁺ lymphocytes (score 0) (Figure S1A), faint TIGIT⁺ lymphocytes near the HRS-like cells (score 1) (Figure S1B), moderate TIGIT⁺ lymphocytes around the HRS-like cells (score 2) (Figure S1C), and a circle of intense TIGIT⁺ lymphocytes surrounding the HRS-like cells (score 3) (Figure S1D). Cells with score 3 were defined to be positive. Microscope, Olympus BX53; original magnification, 400× for all images; scale bar: 20 µm; camera, Olympus DP53. TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; HRS, Hodgkin–Reed Sternberg.

Reference

1. Annibali O, Bianchi A, Grifoni A, et al. A novel scoring system for TIGIT expression in classic Hodgkin lymphoma. *Sci Rep.* 2021;11(1):7059.